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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

DEPOMED, INC.,	)	
	)	
Plaintiff,	)	C.A. No.:3:13-CV-00571-MLC-TJB
v.	)	
	)	
PURDUE PHARMA L.P., THE P.F.	)	
LABORATORIES, INC., PURDUE	)	**SECOND AMENDED**
PHARMACEUTICALS L.P.,	)	**COMPLAINT AND DEMAND**
	)	**FOR JURY TRIAL**
Defendants.	)	
	)	

Plaintiff Depomed, Inc. ("Depomed" or "Plaintiff"), for its Complaint

against Defendants Purdue Pharma L.P., The P.F. Laboratories, Inc., and Purdue

Pharmaceuticals L.P., (collectively "Purdue" or the "Purdue Defendants") alleges

as follows:

NATURE OF THE ACTION

1.   This is an action for patent infringement arising under the patent laws

of the United States, Title 35, United States Code, for infringement of U.S. Patent

Nos. 6,340,475 and 6,635,280.

THE PARTIES

2.   Plaintiff Depomed is a corporation organized under the laws of

California, having its principal place of business at 7999 Gateway Boulevard, Suite

300 in Newark, California.

3.   Upon information and belief, Defendant Purdue Pharma L.P.

("Purdue Pharma") is a limited partnership organized and existing under the laws

of the State of Delaware, having its principal place of business at One Stamford

Forum, 201 Tresser Boulevard, Stamford, Connecticut 06901-3431 and a place of

business at 6 Cedar Brook Drive, Cranbury, New Jersey 08512. On information

and belief, Purdue Pharma is the owner of New Drug Application ("NDA") No.

22-272 for controlled-release oxycodone pain-relief medication under the brand

name OxyContin®. On information and belief, Purdue Pharma is involved in

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designing, testing, manufacturing, labeling, advertising, promoting, marketing, selling and/or distributing OxyContin® throughout the United States, including in the State of New Jersey.

4.   Upon information and belief, Defendant The P.F. Laboratories, Inc. ("P.F. Labs") is a corporation organized and existing under the laws of the State of New Jersey, having a place of business at 700 Union Boulevard, Totowa, New Jersey 07512. On information and belief, P.F. Labs is involved in the manufacture of OxyContin® in the State of New Jersey.

5.   Upon information and belief, Defendant Purdue Pharmaceuticals L.P. ("Purdue Pharmaceuticals") is a limited partnership organized and existing under the laws of the State of Delaware, having a place of business at 4701 Purdue Drive, Wilson, North Carolina 27893. On information and belief, Purdue Pharmaceuticals is involved in the manufacture of OxyContin®.

JURISDICTION AND VENUE

6.   This action arises under the patent laws of the United States, 35 U.S.C. §§ 1, *et seq.*, and this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this Court under 28 U.S.C. §§ 1391 and 1400(b).

7.   This Court has personal jurisdiction over Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals because, *inter alia*, they have each committed, or

aided, abetted, contributed to and/or participated in the commission of the tortious action of patent infringement that has led to foreseeable harm and injury to Plaintiff, which manufacture numerous drugs for sale and use throughout the United States, including New Jersey, and because they have each availed themselves of the benefits and protections of New Jersey's laws such that they should reasonably anticipate being haled into court here.

8.   On information and belief, Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals have had persistent, systematic and continuous contacts with the State of New Jersey as set forth below, and for other reasons that will be presented to the Court if jurisdiction is challenged.

9.   Each Defendant has consented to personal jurisdiction in this district on several occasions, and availed itself of the legal protections of the State of New Jersey, having asserted counterclaims in lawsuits filed in the District of New Jersey.

10.   Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals directly or through an agent, including each other, regularly do or solicit business in the State of New Jersey, engage in persistent courses of conduct in New Jersey, and/or derive substantial revenue from the development, manufacture and/or sale of pharmaceutical products that are sold in New Jersey.

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11.   Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals are, at the very least, agents of each other and/or work in concert with each other and/or other direct and indirect subsidiaries of Purdue Pharma with respect to the development, regulatory approval, marketing, sale and distribution of pharmaceutical products throughout the United States, including in the State of New Jersey.

12.   Upon information and belief, Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals share certain common officers and directors. On information and belief, Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals operate in whole or in part from one or more shared facilities in Connecticut, New Jersey, North Carolina and Rhode Island.

THE PATENTS-IN-SUIT

13.   On January 22, 2002, United States Patent No. 6,340,475 (the "'475 Patent") entitled "Extending the Duration of Drug Release Within the Stomach During the Fed Mode" was duly issued by the United States Patent and Trademark Office to Depomed as assignee of the inventors. A true and correct copy of the '475 Patent is attached as Exhibit 1.

14.   On October 21, 2003, United States Patent No. 6,635,280 (the "'280 Patent") entitled "Extending the Duration of Drug Release Within the Stomach During the Fed Mode" was duly issued by the United States Patent and Trademark

Office to Depomed as assignee of the inventors. A true and correct copy of the

'280 Patent is attached as Exhibit 2.

15.   Depomed is the owner and assignee of all right, title and interest in

and to the '475 Patent and '280 Patent (together, the "Patents-in-Suit"), including

the right to assert all causes of action arising under said patents and the right to any

remedies for infringement of them.

THE VALIDITY OF THE PATENTS-IN-SUIT

16.   Depomed filed a complaint on January 29, 2013 against Purdue for

infringement of the Patents-in-Suit through the commercial manufacture, use, offer

for sale and/or sale of the OxyContin®. On September 9, 2013, Purdue served its

invalidity contentions, purportedly identifying several pieces of alleged prior art.

Depomed responded to these contentions on September 17, 2013 pursuant to L.

Pat. R. 3.4A.

17.   Purdue was subsequently a real party in interest in an unsuccessful

attempt to invalidate the Patents-in-Suit. On January 24, 2014, Purdue filed

petitions for *inter partes* review ("IPR") of the Patents-in-Suit. Purdue's petitions

relied on references that were also asserted as alleged prior art in the pending

litigation. Purdue also requested, and was granted, a stay of the litigation pending

a final ruling on its IPR petitions. On July 10, 2014, the Patent Trial and Appeal

Board ("PTAB") instituted three separate proceedings to review the validity of the

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several claims for the Patents-in-Suit.   On July 8, 2015, after considering Purdue's

invalidity arguments, the PTAB confirmed the validity of the Patents-in-Suit,

without any need for claim amendments. On March 24, 2016, the U.S. Court of

Appeals for the Federal Circuit affirmed the PTAB's determination.

PURDUE'S INFRINGEMENT OF THE PATENTS-IN-SUIT

18.   Purdue has had knowledge of the Patents-in-Suit since at least January

29, 2013, the date that Depomed asserted the '475 and '280 Patents against Purdue

in the first complaint filed in this action.

19.   The Patents-in-Suit cover Depomed's development of its unique

polymer-based drug-delivery technology in dosage forms and methods of

administration of dosage forms designed to optimize drug delivery by allowing for

the extended release of pharmaceutical compounds. This extended release, based

on Depomed's technology, offers greater treatment efficacy and increased

treatment tolerability.

20.   Purdue submitted and received approval from the U. S. Food and

Drug Administration ("FDA") for a new drug application for OxyContin®

extended release tablets (OCR) (NDA 22-272). According to public documents,

Purdue reformulated OxyContin® with the goal of making it more difficult to

misuse and abuse OxyContin® by changing the physical and chemical properties

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of the original formulation. A copy of the FDA Advisory Committee Briefing

Document on NDA 22-272 is attached as Exhibit 3.

21.   OxyContin® falls within the scope of Depomed's patented claims.

For example, OxyContin® is an extended release oral formulation of oxycodone

hydrochloride, which is soluble in water. Purdue also represented to the FDA that

OxyContin®, which contains a specific polymer, makes the tablets difficult to

break or crush. Ex. 3 (FDA Advisory Committee Briefing Document). A primary

ingredient in the OxyContin® is polyethylene oxide (PEO), a swellable polymer,

that allows for extended release of the active ingredient oxycodone from the

dosage form. A copy of the package insert for OxyContin® is attached hereto as

Exhibit 4. To demonstrate more specifically how Purdue infringes the '475 and

'280 Patents, the below charts with representative claims of the '475 and '280

Patents are provided.

22.   OxyContin® contains all of the elements recited in at least claim 1 of

the '475 Patent and claim 1 of the '280 Patent, as exemplified below:

'475 Patent	Purdue's OxyContin®
1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising	OxyContin® is a controlled-release oral formulation of oxycodone hydrochloride, available in tablet form. Oxycodone hydrochloride is soluble in water at 1 g oxycodone hydrochloride to 6 to 7 ml of water, i.e. at about 143 ~ 167 mg/ml, which is greater than "one part by weight . . . in ten parts by weight of water." Ex. 4.
a solid polymeric matrix with said	OxyContin® contains a polymeric matrix

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drug dispersed therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20	with oxycodone hydrochloride dispersed therein at a weight ratio of drug to polymer from about 15:85 to about 80:20.
said polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during said fed mode	OxyContin® tablets swell as a result of imbibition of water to a size large enough to promote retention in the stomach during the fed mode (digestive state).
that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid	OxyContin® tablets release oxycodone hydrochloride by the dissolution and diffusion out of the polymer matrix by gastric fluid.
that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug within about eight hours after such immersion	OxyContin® tablets retain at least about 40% of oxycodone hydrochloride one hour after immersion in gastric fluid and releases substantially all of their drug content within about eight hours after immersion.
and that remains substantially intact until all of said drug is released.	OxyContin® tablets remain substantially intact until all of the drug is released.

'280 Patent	Purdue's OxyContin®
1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising	OxyContin® is a controlled-release oral formulation of oxycodone hydrochloride, available in tablet form. Oxycodone hydrochloride is soluble in water at 1 g oxycodone hydrochloride to 6 to 7 ml of water, i.e. at about 143 ~ 167 mg/ml, which is greater than "one part by weight . . . in ten parts by weight of water." Ex. 4.
one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 15:85 to 80:20,	OxyContin® contains a polymeric matrix with oxycodone hydrochloride dispersed therein at a weight ratio of drug to polymer from about 15:85 to about 80:20.
said dosage form being one that when swollen in a dimensionally unrestricted manner as a result of	OxyContin® tablets swell in a dimensionally unrestricted manner as a result of imbibition of water to a size

imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,	exceeding the pyloric diameter in the fed mode to promote retention in the stomach during the fed mode.
that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid,	OxyContin® tablets release oxycodone hydrochloride into gastric fluid by the dissolution and diffusion of oxycodone hydrochloride out of the polymer matrix by gastric fluid.
that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug after such immersion,	OxyContin® tablets retain at least about 40% of oxycodone hydrochloride one hour after immersion in gastric fluid and releases substantially all of the drug after their immersion in gastric fluid.
and that remains substantially intact until substantially all of said drug is released.	OxyContin® tablets remain substantially intact until substantially all of the drug is released.

23.   On information and belief, Purdue conducted several studies, including clinical studies, to evaluate the efficacy and toxicity of OxyContin® in subjects. On information and belief, Purdue's method of administration OxyContin® to animal and human subjects falls that within the scope of the Patents-in-Suit in connection with its efforts to obtain FDA approval for OxyContin®. More specifically, Purdue performed a method of administrating OxyContin® that contains all of the elements recited in at least claim 43 of the '280 Patent and claim 43 of the '475 Patent, as exemplified below:

'475 Patent	**Purdue's OxyContin®**
43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least	Purdue administered to a subject a controlled-release oral formulation of oxycodone hydrochloride (OxyContin®), available in tablet form. The dosage form is

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one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising	administered orally while the subject is in fed mode (digestive state). Upon information and belief, oxycodone hydrochloride has at least one ionized group in the pH range 5 through 8.
a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20,	OxyContin® contains a polymeric matrix with oxycodone hydrochloride dispersed therein at a weight ratio of drug to polymer from about 0.01:99.99 to about 80:20.
said polymeric matrix being one that: (a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,	OxyContin® contains a polymer matrix that swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during the fed mode.
(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,	OxyContin® tablets release oxycodone hydrochloride into gastric fluid by the dissolving of oxycodone hydrochloride by gastric fluid and either erosion of the matrix or diffusion of dissolved oxycodone hydrochloride out of the matrix.
(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, (d) releases substantially all of said drug within about ten hours after such immersion, and	OxyContin® tablets retain at least about 40% of oxycodone hydrochloride one hour after immersion in gastric fluid and releases substantially all of their drug content within about ten hours after immersion.
(e) remains substantially intact until all of said drug is released, thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.	OxyContin® tablets remains substantially intact until all of oxycodone hydrochloride is released, thereby extending the release rate of oxycodone hydrochloride during the fed mode while releasing substantially all of the oxycodone hydrochloride within the stomach where the oxycodone hydrochloride is maintained in an acidic environment.

'280 Patent	Purdue's OxyContin®
43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising	Purdue administered to a subject a controlled-release oral formulation of oxycodone hydrochloride (OxyContin®), available in tablet form. The dosage form is administered orally while the subject is in fed mode (digestive state). Oxycodone hydrochloride has at least one ionized group in the pH range 5 through 8.
one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20,	OxyContin® contains a polymeric matrix with oxycodone hydrochloride incorporated therein at a weight ratio of drug to polymer from about 0.01:99.99 to about 80:20.
said polymeric matrix being one that: (a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,	OxyContin® tablets swell in a dimensionally unrestricted manner as a result of imbibition of gastric fluid to a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during fed mode.
(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,	OxyContin® tablets release oxycodone hydrochloride into gastric fluid by the dissolving of oxycodone hydrochloride by gastric fluid and either erosion of the matrix or diffusion of dissolved oxycodone hydrochloride out of the matrix.
(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and (d) releases substantially all of said drug within about ten hours after such immersion, thereby extending the release rate of said drug with time during said fed mode	OxyContin® tablets retain at least about 40% of oxycodone hydrochloride one hour after immersion in gastric fluid and releases substantially all of their drug content within about ten hours after immersion in gastric fluid, thereby extending the release rate of the oxycodone hydrochloride with time during the fed mode.
while releasing substantially all of	OxyContin® tablets release substantially all

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said drug within said stomach where said drug is maintained in an acidic environment.	of oxycodone hydrochloride within the stomach where the drug is maintained in an acidic environment.

24. On information and belief, Purdue's infringement has been willful and deliberate since, at least the dates on which the PTAB and Federal Circuit confirmed the validity of the Patents-in-Suit.

25. On information and belief, Purdue continues to manufacture, use, offer for sale and sell OxyContin despite an objectively high likelihood that its actions constituted infringement of a valid patent and the objectively-defined risk was known or so obvious that it should have been known to Purdue. On information and belief, Purdue knows of or is willfully blind to the claimed invention of the Patents-in-Suit. On information and belief, Purdue also lacks an objectively reasonable defense to its infringement because it is aware that the PTAB and Federal Circuit rejected Purdue's challenges to the validity of the Patents-in-Suit based on the same prior art that it has raised in this litigation.

FIRST CAUSE OF ACTION
(Infringement of the '475 Patent)

26. Plaintiff realleges and incorporates by reference the allegations contained paragraphs 1 - 25.

27. Upon information and belief, Purdue's commercial manufacture, use, offer to sell, and/or sale of OxyContin® within the United States, or importation

of OxyContin® into the United States, and administration of OxyContin® in the United States, during the term of the '475 Patent have infringed and continue to infringe at least claims 1, 8-15, 43, 54-55, 57-58, 61-62 and 66 of the '475 Patent under 35 U.S.C. § 271 (a).

28.   Purdue's acts of making, using, importing, selling, and/or offering for sale OxyContin® have been without Depomed's permission, consent, authorization or license.

29.   Depomed has been injured by Purdue's infringing activities, and is entitled to recover money damages from Purdue Defendants adequate to compensate it for Purdue's infringement, but in no event less than a reasonable royalty together with interest and costs as fixed by the Court.

30.   Depomed will continue to suffer damages in the future unless Purdue's infringing activities are enjoined by this Court.

31.   Unless a permanent injunction is issued enjoining Purdue and their respective agents, servants, employees, representatives, affiliates, and all others acting in active concert therewith from infringing the '475 Patent, Depomed will be substantially and irreparably harmed.

32.   Purdue has been aware of the '475 Patent since at least as early as January 29, 2013 when Depomed first brought this action. Purdue is also aware

that the PTAB and Federal Circuit both rejected Purdue's challenges to the validity

of the '475 Patent.

33.   Despite this knowledge, after the date of the Federal Circuit

decision, Purdue continues its infringing activities. As a result, Purdue has acted

recklessly and continues to willfully, wantonly, and deliberately engage in acts

of infringement of the '475 Patent, warranting an award to Depomed of

enhanced damages under 35 U.S.C. § 284.

34.   This case is exceptional, and Depomed is entitled to an award of

attorneys' fees under 35 U.S.C. § 285.

<center>

SECOND CAUSE OF ACTION
(Infringement of the '280 Patent)

</center>

35.   Plaintiff realleges and incorporates by reference the allegations

contained paragraphs 1 - 34.

36.   Upon information and belief, Purdue's commercial manufacture, use,

offer to sell, and/or sale of OxyContin® within the United States, or importation

of OxyContin® into the United States, and administration of OxyContin® in the

United States, during the term of the '280 Patent, have infringed and continue to

infringe at least claims 1, 8-15, 43 and 45-46 of the '280 Patent under 35 U.S.C.

§§ 271 (a).

37.   Purdue's acts of making, using, importing, selling, and/or offering for sale OxyContin® have been without Depomed's permission, consent, authorization or license.

38.   Depomed has been injured by Purdue's infringing activities, and is entitled to recover money damages from Purdue adequate to compensate it for Purdue's infringement, but in no event less than a reasonable royalty together with interest and costs as fixed by the Court.

39.   Depomed will continue to suffer damages in the future unless Purdue's infringing activities are enjoined by this Court.

40.   Unless a permanent injunction is issued enjoining Purdue and their respective agents, servants, employees, representatives, affiliates, and all others acting in active concert therewith from infringing the '280 Patent, Depomed will be substantially and irreparably harmed.

41.   Purdue has been aware of the '280 Patent since at least as early as January 29, 2013 when Depomed first brought this action. Purdue is also aware that the PTAB and Federal Circuit both rejected Purdue's challenges to the validity of the '280 Patent.

42.   Despite this knowledge, after the date of the Federal Circuit decision, Purdue continues its infringing activities. As a result, Purdue has acted recklessly and continues to willfully, wantonly, and deliberately engage in acts

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of infringement of the '280 Patent, warranting an award to Depomed of enhanced damages under 35 U.S.C. § 284.

43.   This case is exceptional, and Depomed is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff prays for judgment against Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals and respectfully request the following relief:

a.   A judgment that the '475 and '280 Patents have been infringed by Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals;

b.   A permanent injunction enjoining Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals, their officers, agents, servants, employees, and those persons acting in active concert or participation with all or any of them from manufacturing, using, offering to sell, or selling OxyContin® within the United States, or importing OxyContin® into the United States, prior to the expiration of the '475 and '280 Patents, including any extension;

c.   A judgment and order requiring Purdue Pharma, P.F. Labs, and Purdue Pharmaceuticals to pay Depomed its damages, costs, expenses, and pre- and post-judgment interest for their infringement of the '475 and '280 Patents, and a judgment that the damages so adjudged be trebled, pursuant to 35 U.S.C. §§ 283 and 284;

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d.   A judgment and order finding that this is an exceptional case and that

Depomed be awarded its attorneys' fees incurred in this action pursuant to 35

U.S.C. § 285;

e.   A determination that Purdue's infringement of the '475 and '280

Patents has been willful, wanton, and deliberate and that Depomed is entitled to up

to treble damages;

f.   Costs and expenses in this action; and

g.   Such other and further relief as the Court deems just and appropriate.

Respectfully submitted,

DATED: February 1, 2017   By: */s/ Keith Miller*
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                                       Attorneys for Plaintiff Depomed, Inc.

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JURY DEMAND

Plaintiff hereby demands a trial by jury on all issues and claims so triable.

Respectfully submitted,

DATED: February 1, 2017   By: _/s/ Keith Miller_

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Attorneys for Plaintiff Depomed, Inc.

EXHIBIT 1

US006340475B2

(12) **United States Patent**
Shell et al.

(10) Patent No.: **US 6,340,475 B2**
(45) Date of Patent: *Jan. 22, 2002

(54) **EXTENDING THE DURATION OF DRUG RELEASE WITHIN THE STOMACH DURING THE FED MODE**

(75) Inventors: **John W. Shell**, Hillsborough; **Jenny Louie-Helm**, Union City; **Micheline Markey**, Santa Cruz, all of CA (US)

(73) Assignee: **DepoMed, Inc.**, Menlo Park, CA (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/282,233**

(22) Filed: **Mar. 29, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/870,509, filed on Jun. 6, 1997, now abandoned.

(51) **Int. Cl.[7]** **A61K 9/26**; A61K 9/14
(52) **U.S. Cl.** **424/469**; 424/464; 424/468; 424/488; 424/486; 424/487
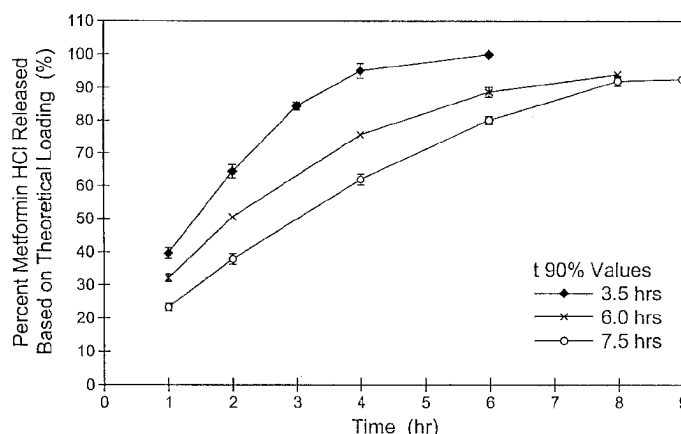(58) **Field of Search** 424/451, 457, 424/458, 464, 468, 469, 484, 485, 486, 489, 501, 502, 426

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Primary Examiner—Thurman K. Page
Assistant Examiner—Brian K. Seidleck
(74) *Attorney, Agent, or Firm*—Townsend and Townsend and Crew LLP

(57) **ABSTRACT**

Drugs are formulated as unit oral dosage forms by incorporating them into polymeric matrices comprised of hydrophilic polymers that swell upon imbibition of water to a size that is large enough to promote retention of the dosage form in the stomach during the fed mode. The oral formulation is designed for gastric retention and controlled delivery of an incorporated drug into the gastric cavity, and thus administered, the drug is released from the matrix into the gastric fluid by solution diffusion. The swollen polymeric matrix, having achieved sufficient size, remains in the gastric cavity for several hours if administered while the patient is in the fed mode, and remains intact long enough for substantially all of the drug to be released before substantial dissolution of the matrix occurs. The swelling matrix lowers the accessibility of the gastric fluid to the drug and thereby reduces the drug release rate. This process, together with diffusion retardation by selection of specific polymers, polymer molecular weights, and other variables, results in a sustained and controlled delivery rate of the drug to the gastric cavity.

89 Claims, 9 Drawing Sheets

U.S. Patent   Jan. 22, 2002   Sheet 1 of 9   **US 6,340,475 B2**

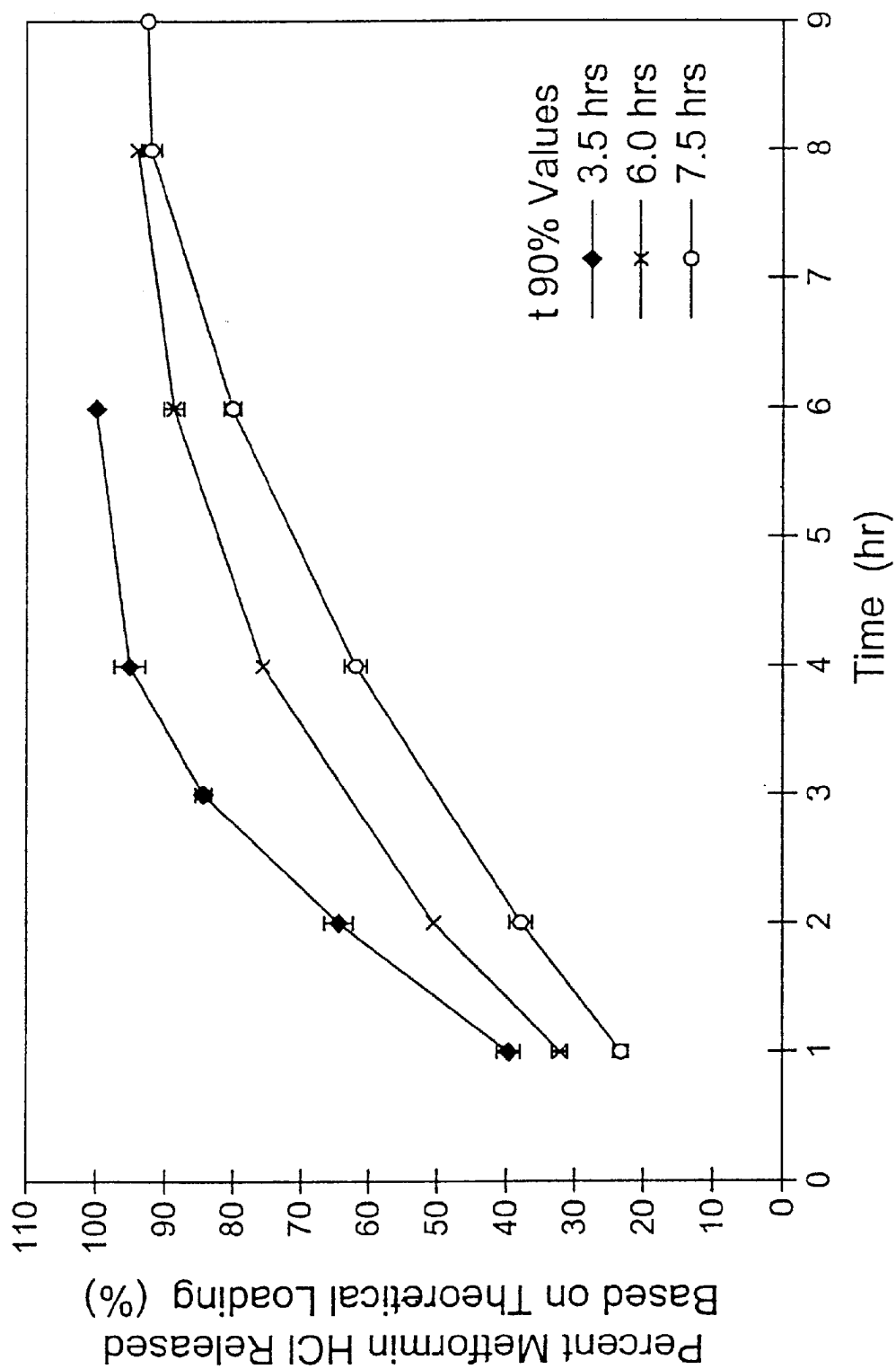Fig. 1
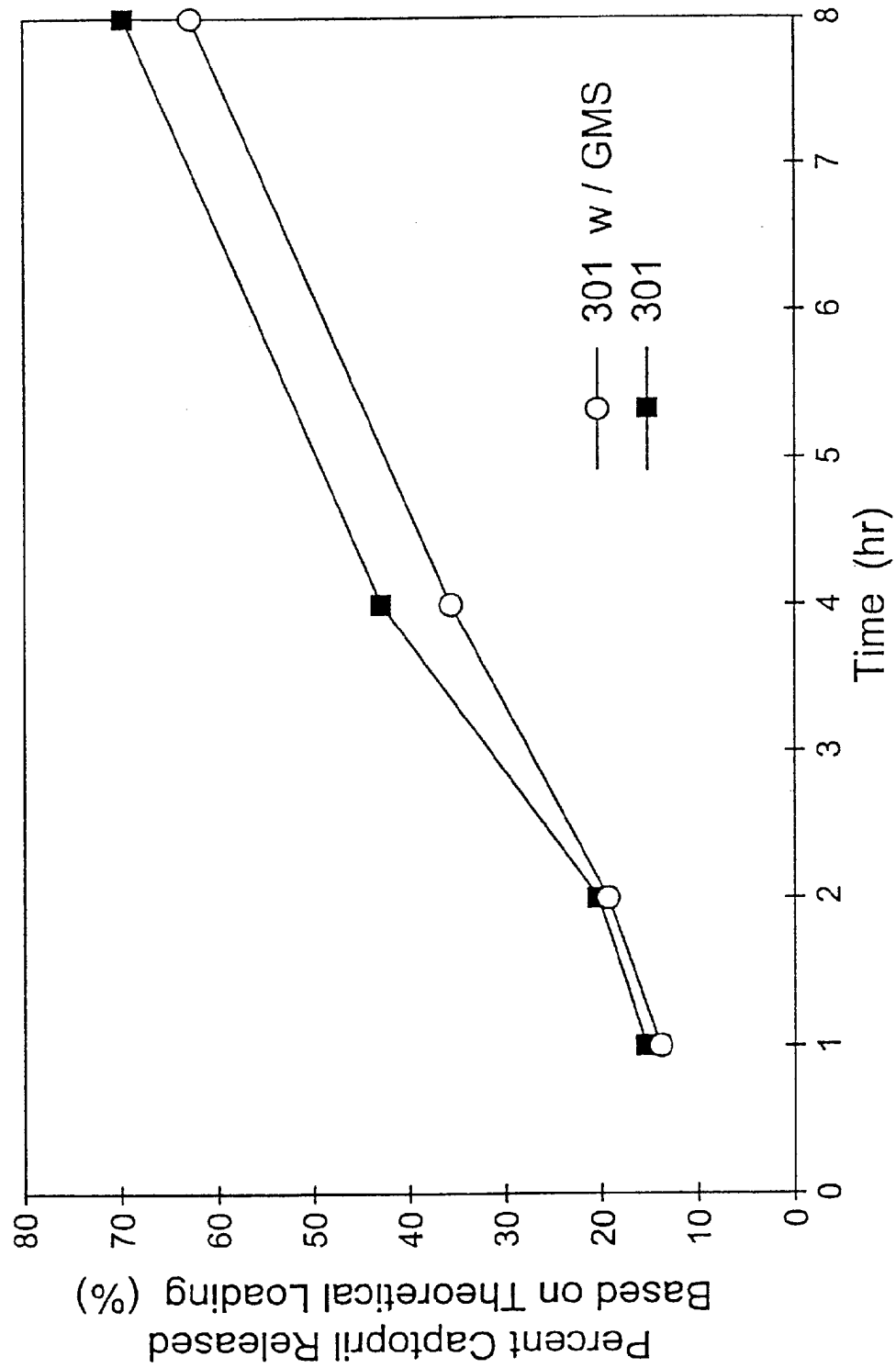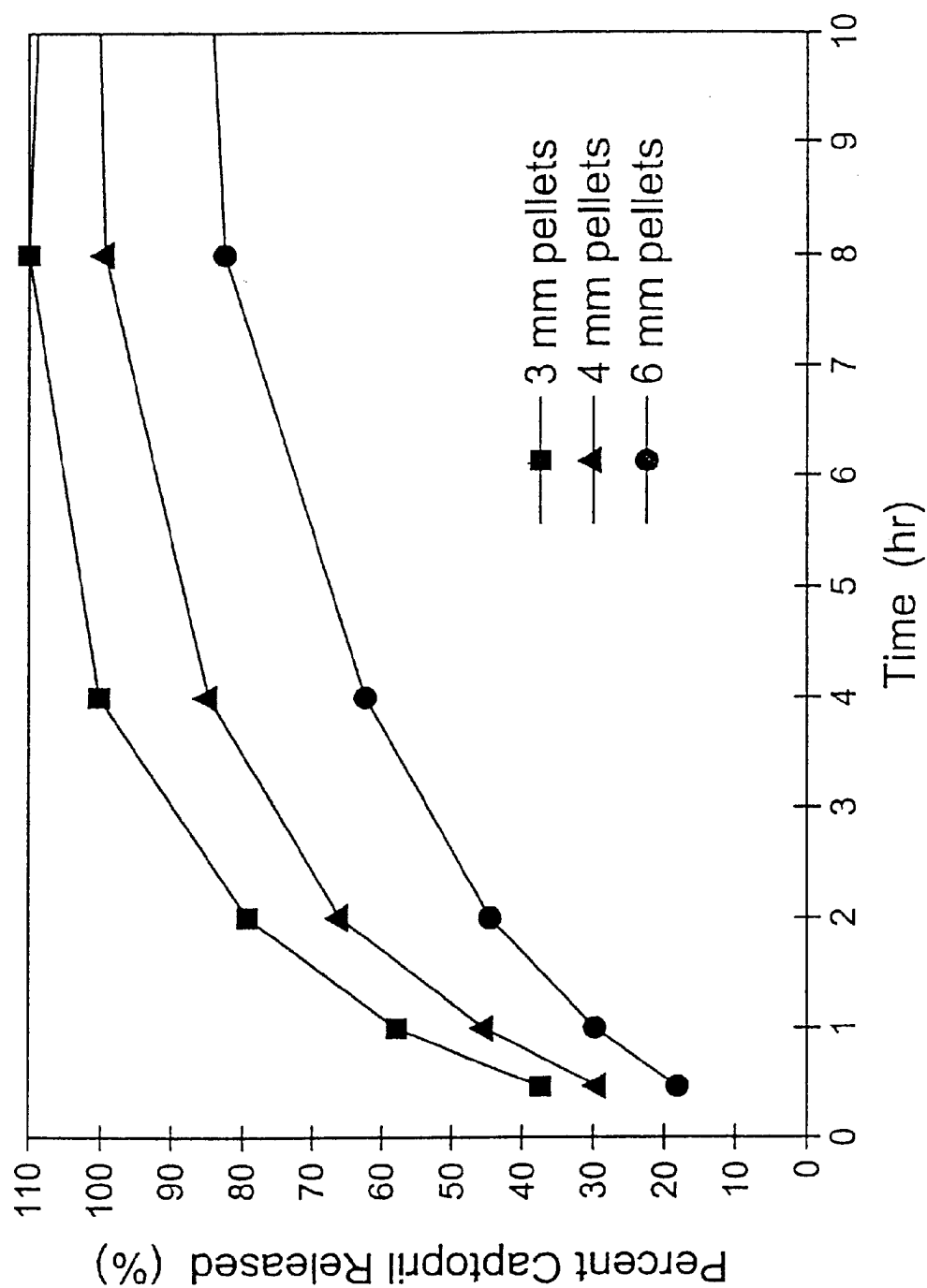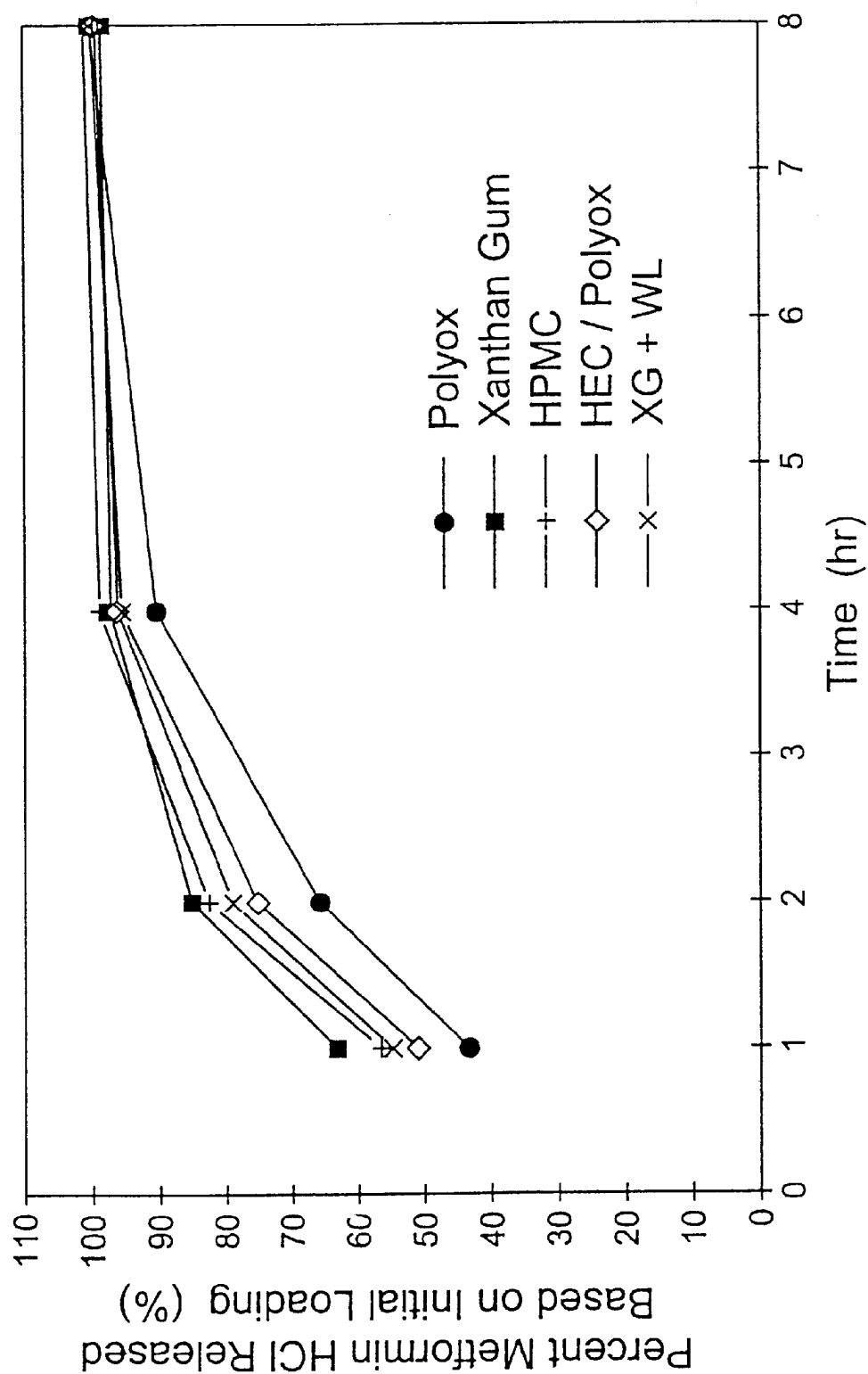
Fig. 2

Fig. 3

Fig. 4

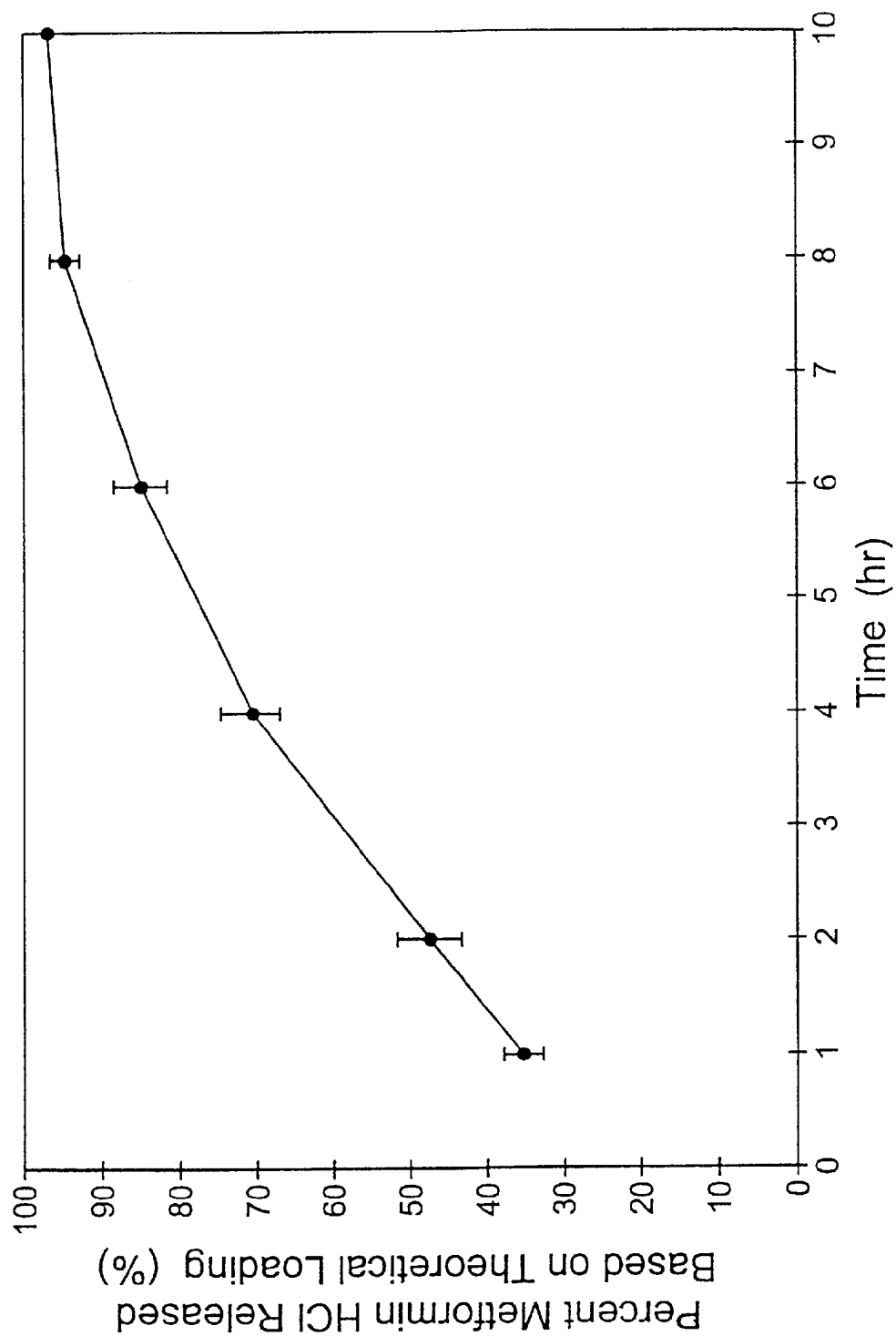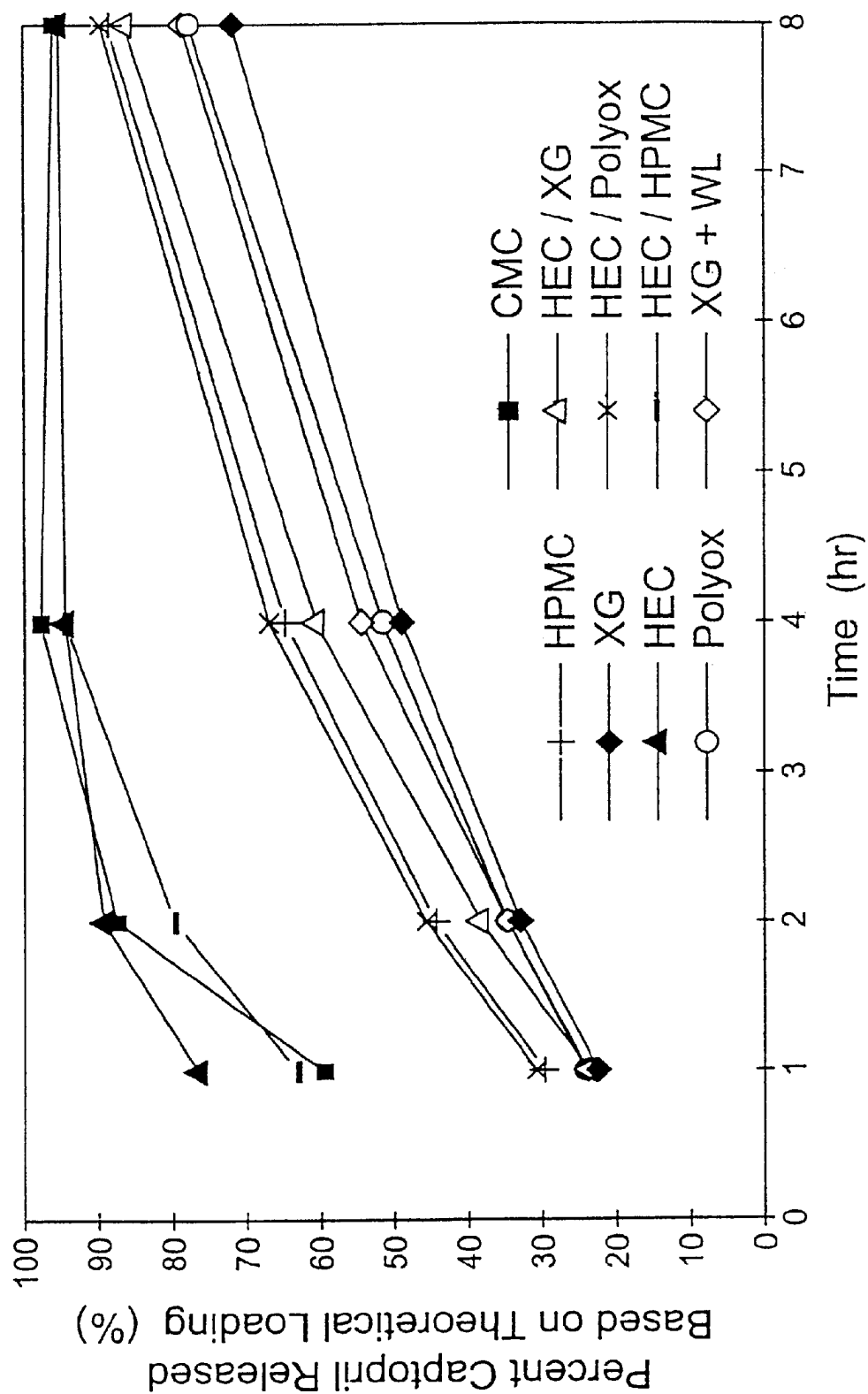**U.S. Patent**   Jan. 22, 2002   Sheet 5 of 9   US 6,340,475 B2
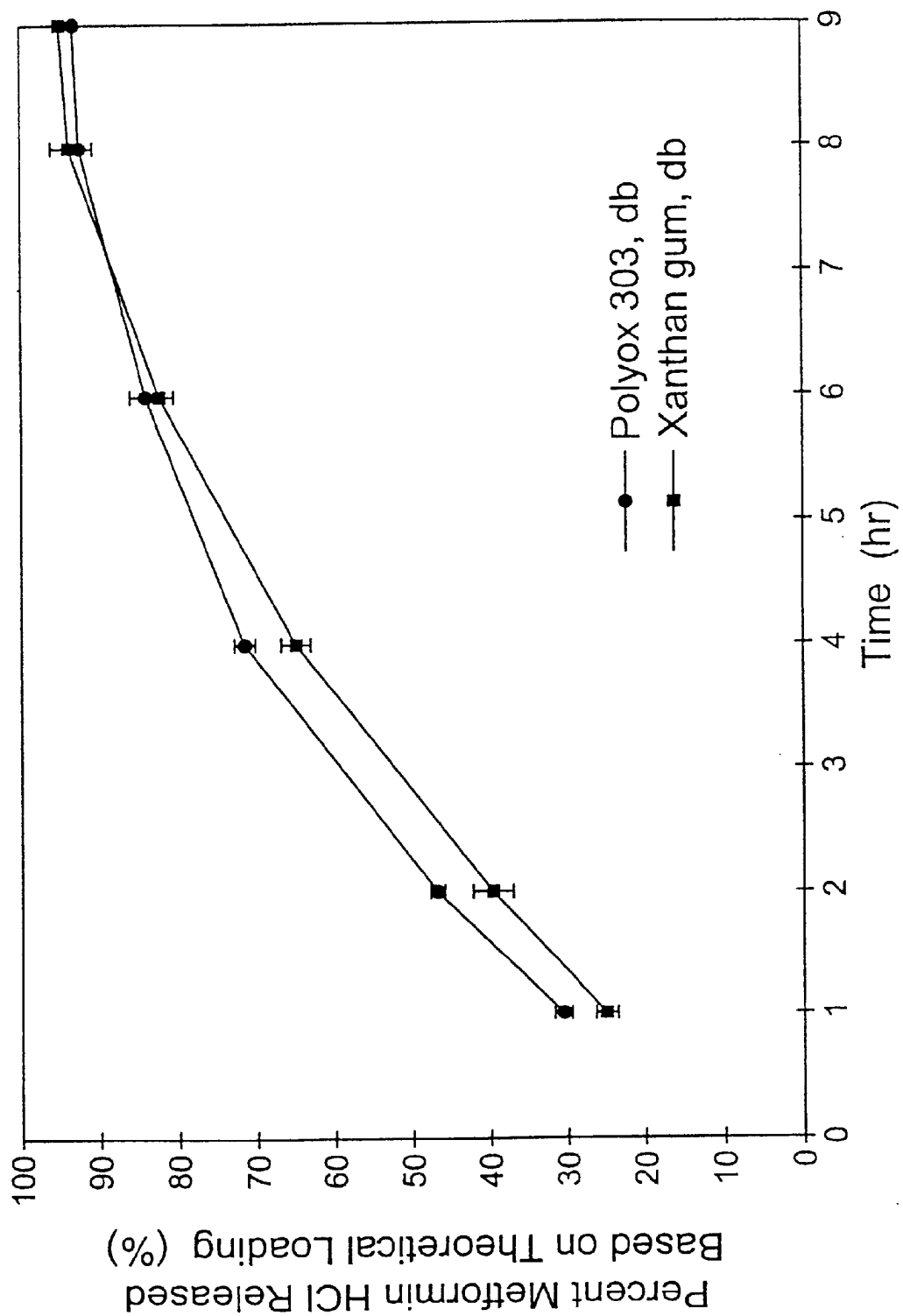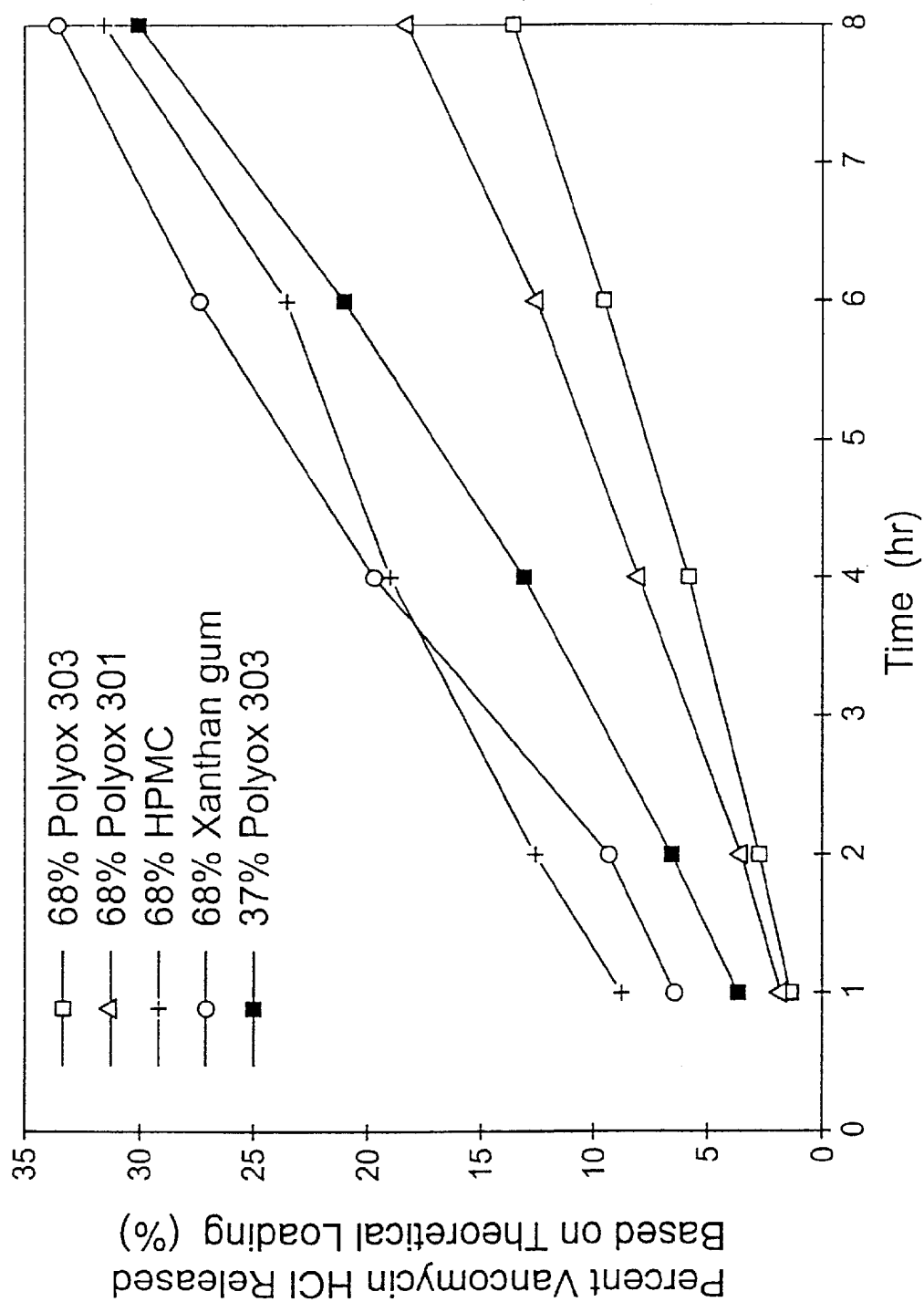

Fig. 5

Fig. 6

Fig. 7

Fig. 8

FIG 9
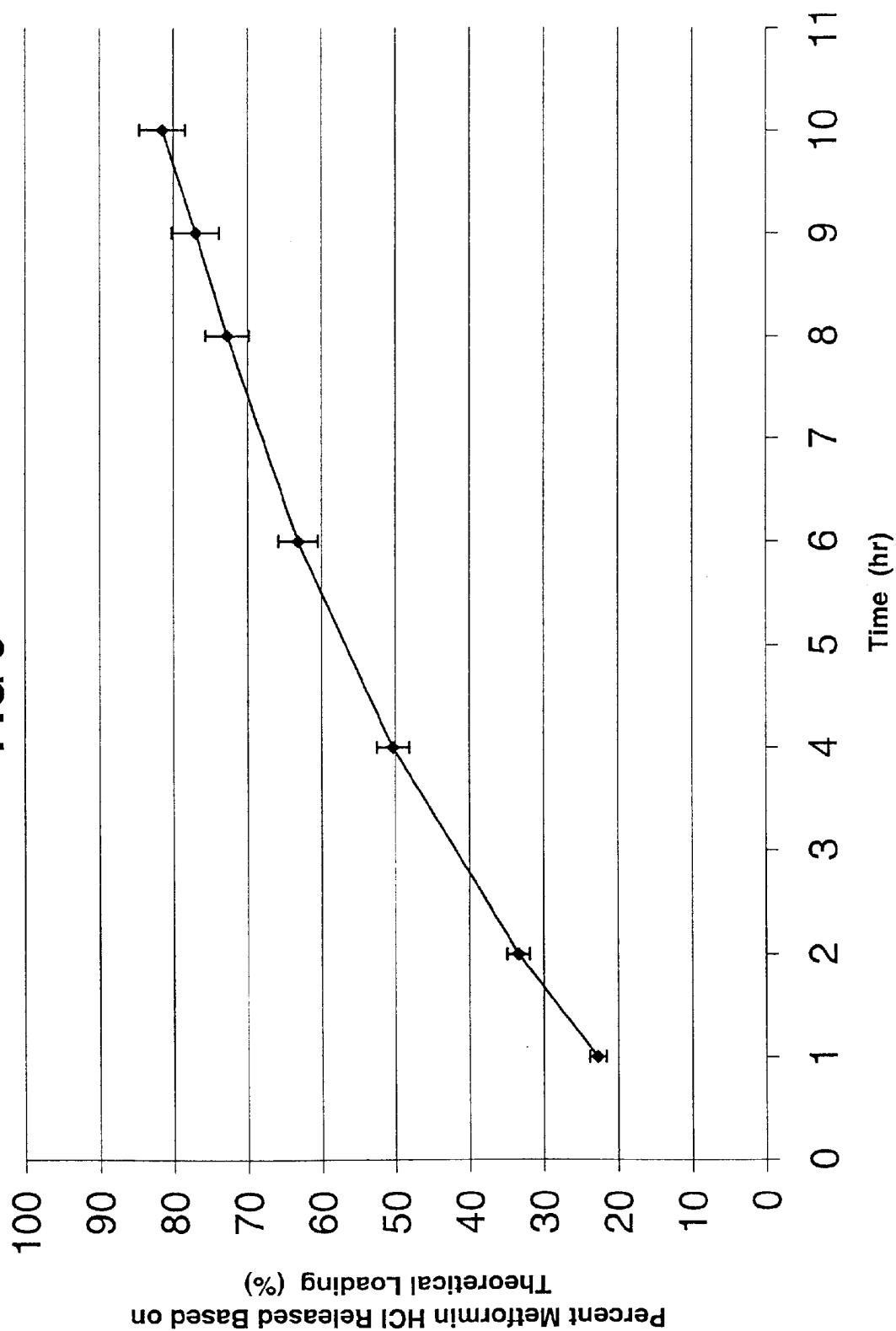
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EXTENDING THE DURATION OF DRUG RELEASE WITHIN THE STOMACH DURING THE FED MODE

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 08/870,509, filed Jun. 6, 1997 now abandoned, the entire contents of which are hereby incorporated herein by reference.

This invention is in the general field of pharmacology, and relates in particular to formulations for drugs that benefit from a prolonged time of controlled release in the stomach and upper gastrointestinal (GI) tract, and from an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. One goal in this invention is to release highly soluble drugs in a controlled manner over an extended period of time. Another goal is to extend the time of delivery into the stomach of drugs that are preferentially absorbed high in the GI tract, for purposes of achieving a greater and more prolonged therapeutic effect and thus reducing the frequency of administration required; a more efficient use of the drugs; and a more effective treatment of local stomach disorders. Another goal is to minimize both lower-tract inactivation of the drug and drug effects on the lower intestinal flora by confining the delivery and absorption of the drug to the upper GI tract.

BACKGROUND OF THE INVENTION

Drugs that are administered in the form of conventional tablets or capsules become available to body fluids at a rate that is initially very high, followed by a rapid decline. For many drugs, this delivery pattern results in a transient overdose, followed by a long period of underdosing. This is a pattern of limited clinical usefulness. The delivery pattern was improved in the 1970's with the introduction of a variety of controlled delivery systems. By providing relatively constant, controlled drug delivery, these systems avoided the overdose and the underdose effects. These improvements provided effective medication with reduced side effects, and achieved these results with reduced dosing frequency.

Many of these controlled delivery systems utilize hydrophilic, polymeric matrices that provide useful levels of control to the delivery of sparingly soluble drugs. For soluble drugs, however, and particularly for highly soluble drugs, such matrices do not provide adequate control over the drug release rate, instead resulting in a release that approximates first-order kinetics. That is, the rate of release is an inverse function of the square root of the elapsed time. With this pattern of release, most of the drug in the matrix is often released within the first hour in an aqueous medium.

One method of prolonging the release of a highly water-soluble drug is disclosed in International Patent Application Publication No. WO 96/26718, published Sep. 6, 1996 (applicant: Temple University; inventor: Kim). The method of this publication is the incorporation of the drug into a polymeric matrix to form a tablet that is administered orally. The polymer is water-swellable yet erodible in gastric fluids, and the polymer and the proportion of drug to polymer are chosen such that:

(i) the rate at which the polymer swells is equal to the rate at which the polymer erodes, so that the swelling of the polymer is continuously held in check by the erosion, and zero-order release kinetics (constant delivery rate) of the drug from the matrix are maintained;

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(ii) the release of drug from the matrix is sustained over the full erosion period of the polymer, the tablet therefore reaching complete solution at the same time that the last of the drug is released; and

(iii) release of the drug from the matrix will be extended over a period of 24 hours.

A key disclosure in WO 96/26718 is that to achieve the release of drug in this manner requires the use of a low molecular weight polymer. If, by contrast, a high molecular weight polymer is used and the swelling rate substantially exceeds the erosion rate, the lack of erosion will prolong even further the delivery of the drug residing close to the center of the tablet and even prevent it from being released. Thus, there is no disclosure in WO 96/26718 that a drug of high water solubility can be released from a high molecular weight polymer in a period of time substantially less than 24 hours, or that any advantage can be obtained by the use of a polymer that does not erode as quickly as it swells. This failure is particularly significant since even swollen tablets will not remain in the stomach beyond the duration of the fed mode, which typically lasts for only 4 to 6 hours.

For drugs of any level of solubility, the retention of the drug in a tablet or other dosage form beyond the duration of the fed mode raises a number of problems that detract from the therapeutic efficacy of the drug. These problems arise from the tendency of the tablet when the patient is no longer in the fed mode to pass from the stomach into the small intestine, and over a period of 2–4 hours to pass through the small intestine, thus reaching the colon with the drug still in the tablet. This loss of effectiveness occurs with drugs that provide their maximum benefit with minimum side effects when absorbed in the stomach and upper GI tract rather than the colon. The reasons are either favorable conditions in the stomach, unfavorable conditions in the colon, or both.

For example, most orally administered antibiotics have a potential of altering the normal flora of the gastrointestinal tract, and particularly the flora of the colon. One result of these alterations is the overgrowth of the organism *Clostridium difficile,* which is a serious adverse event since this organism releases dangerous toxins. These toxins can cause pseudomembranous colitis, a condition that has been reported as a side effect of the use of many antibiotics. In its milder forms, pseudomembranous colitis can cause mild nausea and diarrhea while in its stronger forms, it can be life-threatening or fatal. Examples of highly soluble antibiotics that pose this type of threat are amoxicillin, cefuroxime axetil, and clindamycin. Cefuroxime axetil (i.e., the axetil ester of cefuroxime), for example, becomes active when hydrolyzed to free cefuroxime, but when this occurs prior to absorption, it can be detrimental to essential bacterial flora. Hydrolysis to the active form typically occurs in the tissues into which the ester has been absorbed, but if the ester reaches the lower intestine, enzymes in the lower intestine cause the hydrolysis to occur in the intestine itself, which not only renders the drug unabsorbable but also converts the drug to the active form where its activity alters the flora. Examples of sparingly soluble antibiotics that pose the same type of threat are clarithromycin, azithromycin, ceftazidine, ciprofloxacin, and cefaclor.

A goal of the present invention is to avoid this type of alteration of the lower intestinal flora by delivering antibiotics, regardless of their level of solubility, in a manner that confines their delivery to the stomach and upper small intestine. Slow, continuous delivery from a gastric retentive system assures that both drug delivery and drug absorption are confined to the upper GI tract. More efficient delivery of antibiotics will also avoid transient overdosing which is a major cause of overgrowth of *Clostridium difficile.*

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Another example is the class of drugs that are susceptible to degradation by exposure to gastric fluid, either by enzymes or low solution pH. The swellable hydrophilic matrix of the present invention protects the yet undelivered drug during the 4 to 6 hour delivery period during which the drug is continuously released while the dosage form is retained in the stomach. One example of such a drug is topiramate, a drug that is used for the treatment of epilepsy. Topiramate is absorbed preferentially high in the GI tract and is hydrolyzed by the acidic environment of the stomach. The dosage form and delivery system of the present invention will confine the delivery of the drug to the stomach and duodenum. As the drug diffuses out of the swollen matrix, it is susceptible to the acidic environment, but the undelivered drug is protected from degradation by the polymer matrix.

Another example is the class of drugs that are known to have an absorption window high in the GI tract, but are incompletely absorbed or have a wide absorption range, intrapatient as well as interpatient. One example of such a drug is cyclosporine, a drug of low solubility that is used as an immunosuppressant to reduce organ rejection in transplant surgery. In addition to this problem, cyclosporine is in general only incompletely absorbed (on the average around 30%), and the degree of absorption is highly variable from one patient to the next (ranging from about 5% to about 89%). The variability can be attributed in part to differences among the various disease states existing in the patients to whom the drug is administered, and differences in the length of time between the transplant surgery and the administration of the drug. The variability can also however be attributed to the poor aqueous solubility of the drug and to variations in the gastric emptying, variations in the length of time required for intestinal transit between the stomach and the colon, variations in mesenteric and hepatic blood flow, variations in lymph flow, variations in intestinal secretion and fluid volume, variations in bile secretion and flow, and variations in epithelial cell turnover. All of these variations are addressed by the dosage form and delivery system of the present invention, which by confining drug delivery to the stomach reduces these differences and maximizes the absorption of the cyclosporine.

Another example is the class of drugs that are susceptible to degradation by intestinal enzymes. The degradation occurs before the drug can be absorbed through the intestinal wall, leaving only a fraction of the administered dose available for the intended therapeutic action.

An example of a highly soluble drug that is susceptible to degradation by intestinal enzymes is the pro-drug doxifluridine (5'-deoxy-5-fluouridine (dFUR)). The activity of doxifluridine depends on its activation to 5-fluorouracil by pyrimidine nucleoside phosphorylases. These enzymes are found in tumors as well as in normal tissues, with their highest activity being in the small intestine. The activity of these enzymes in tumor cells is more than twice that of normal tissues. When doxifluridine is administered orally, it can be converted to 5-fluorouracil in the intestine before it reaches the tumors. 5-Fluorouracil is much more toxic than doxifluridine and causes intestinal toxicity (nausea and diarrhea) and severe damage to the intestinal villi. A goal of the present invention is to confine the absorption of doxifluridine to the stomach and upper GI tract, thereby avoiding or reducing its conversion to 5-fluorouracil and the attendant toxicity risk. A similar result is sought for other drugs with similar susceptibilities, such as cyclosporine and digoxin.

Another class of drugs whose effectiveness suffers when the drugs are not fully absorbed high in the GI tract are those that are susceptible to inactivation by drug transporters that

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reside in lower gastrointestinal tract enterocytes. The inactivation occurs before the drug penetrates the intestinal wall, here again leaving only a fraction of the administered dose available for the intended therapeutic action. One example of a drug transporter is the p-glycoprotein efflux system, in which a p-glycoprotein acts as an absorption barrier to certain drugs that are substrates for the p-glycoprotein. The barrier acts by attaching to these drugs and transporting them drug back into the lumen, e.g., the stomach, duodenum, jejunum/ileum or colon, from which they were absorbed, or preventing them from being absorbed at all. This restriction of the drug to the interior of the GI tract is effectively an inactivation of the drug if the drug must pass out of the GI tract into the bloodstream to be effective. The p-glycoprotein efflux system is useful in many respects, such as preventing toxic compounds from entering the brain. It interferes however in some cases with the efficacy of certain drugs that would otherwise be absorbed. The p-glycoprotein concentration is lowest in the stomach and increases in concentration down the GI tract to the colon where the p-glycoprotein is most prevalent. The dosage form of the present invention will release the drug over an extended period into the upper GI tract where p-glycoprotein is lowest.

Cyclosporine is an example of a drug of low solubility that is susceptible to inactivation by the p-glycoprotein efflux system, in addition to its susceptibility to degradation by colonic bacterial enzymes. Other examples of drugs of low solubility that are susceptible to the p-glycoprotein efflux system are the anti-cancer drug paclitaxel, ciprofloxacin, and the HIV protease inhibitors saquinavir, ritonavir, and nelfinavir. All of these drugs will benefit through preserved activity by the present invention.

A still further class of drugs that suffer in effectiveness when not fully absorbed before reaching the colon are drugs that require an acidic environment for effective bioavailability. For certain drugs, the pH at a given site within the GI tract is an essential determinant of the bioavailability of the drug, since the solubility of the drug varies with pH. The stomach has a low pH and hence an acidic environment, while the small intestine has a higher pH and hence an alkaline environment. Higher bioavailability is achieved in some cases by higher solubility, which with some drugs occurs in a more acidic environment, and in other cases by keeping the drugs in a non-ionized state that is necessary for absorption, which with some drugs also occurs in a more acidic environment. Acidic drugs that have a low pK, for example, are in the neutral form that is required for absorption and are therefore preferentially absorbed in the stomach. Examples of highly soluble drugs that achieve their highest bioavailability at a low pH are esters of ampicillin. Examples of low solubility drugs that behave similarly are iron salts, digoxin, ketoconazole, fluconazole, griseofulvin, itraconazole, and micoconazole. A further goal of the present invention is therefore to maximize the bioavailability of drugs of these types by confining them to the acidic environment of the stomach while controlling their release rate to achieve an extended release profile. The invention thus improves the efficiency of iron salts in the treatment of the various forms of anemia, the efficiency of digoxin in the treatment of the heart disease, and the efficiency of ketoconazole in the treatment of systemic fungal infections such as candidiasis, canduria, blastomycosis, coccidiomycosis, histoplasmosis, chronomycosis, and pacococcidiomycosis.

The invention also improves the efficiency of drugs that have at least one ionized group in the pH range of 5 through 8. Since this is the pH range encountered in the small

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intestine and the region of the colonic junction and ionized drugs are less absorbable than neutral drugs, this invention improves the absorption of these drugs by retaining them in the stomach environment. The invention also improves the efficiency of drugs that are degradable in an acidic environment such as that of the stomach by protecting them from the acidic environment until they are released from the dosage form, thereby reducing the duration of their exposure to the acidic environment.

A still further example of drugs that lose their efficacy upon reaching the lower portions of the GI tract are drugs that are soluble in an acidic environment but insoluble in an alkaline environment. The HIV protease inhibitor nelfinavir mesylate is one example of such a drug. Portions of the drug that are undissolved cannot be absorbed. Portions that are dissolved but not yet absorbed when they pass from the stomach into the small intestine may undergo precipitation and loss of their therapeutic benefit. This is confirmed by the fact that the presence of food in the GI tract substantially increases the extent of absorption of oral nelfinavir. Peak plasma concentration and area under the plasma concentration-time curve of nelfinavir are two-fold to three-fold greater when doses are administered with or following a meal. This is presumably due, at least in part, to enhanced retention of the drug in the stomach. A further goal of the present invention is therefore to provide a means of administering these drugs that will maximize their therapeutic effectiveness by extended, controlled release into the stomach.

SUMMARY OF THE INVENTION

It has now been discovered that drugs that are highly soluble in water can be administered orally in a manner that will prolong their delivery time to spread their release rate more evenly throughout the duration of the fed mode and beyond or not as desired. This significantly reduces, and often avoids, the problems of transient overdosing caused by the initial spike in concentration entering the blood stream immediately after administration and the subsequent underdosing, and instead controls the dosage to safer and more effective levels over an extended period of time.

It has further been discovered that for drugs of high, intermediate or low solubility, the problems arising from the release of the drugs in the lower GI tract, i.e., from the failure to absorb these drugs into the blood stream prior to reaching the lower GI tract, can be mitigated as well. For all drugs regardless of solubility, therefore, this invention corrects problems such as the overgrowth of detrimental intestinal flora by drugs that are toxic to normal intestinal flora, protection of undelivered acid-labile drugs in the dosage form, chemical degradation of drugs by intestinal enzymes, loss of bioavailability of the drugs due to their leaving the acidic environment of the stomach, and chemical degradation of the drugs due to the alkaline environment of the intestinal tract. By mitigating these problems, this invention thus further improves the efficiency of the use of these drugs.

Each of the beneficial effects enumerated above is achieved by using a formulation in which the drug is dispersed in a polymeric matrix that is water-swellable rather than merely hydrophilic, that has an erosion rate that is substantially slower than its swelling rate, and that releases the drug primarily by diffusion. It has further been found that the rate of diffusion of the drug out of the matrix can be slowed by increasing the drug particle size, by the choice of polymer used in the matrix, and/or by the choice of molecular weight of the polymer. The matrix is a relatively high molecular weight polymer that swells upon

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ingestion, preferably to a size that is at least about twice its unswelled volume, and that promotes gastric retention during the fed mode. Upon swelling, the matrix may also convert over a prolonged period of time from a glassy polymer to a polymer that is rubbery in consistency, or from a crystalline polymer to a rubbery one. The penetrating fluid then causes release of the drug in a gradual and prolonged manner by the process of solution diffusion, i.e., dissolution of the drug in the penetrating fluid and diffusion of the dissolved drug back out of the matrix. The matrix itself is solid prior to administration and, once administered, remains undissolved in (i.e., is not eroded by) the gastric fluid for a period of time sufficient to permit the majority of the drug to be released by the solution diffusion process during the fed mode. The rate-limiting factor in the release of the drug is therefore controlled diffusion of the drug from the matrix rather than erosion, dissolving or chemical decomposition of the matrix.

For highly soluble drugs, the swelling of the polymeric matrix thus achieves two objectives—(i) the tablet swells to a size large enough to cause it to be retained in the stomach during the fed mode, and (ii) it retards the rate of diffusion of the highly soluble drug long enough to provide multi-hour, controlled delivery of the drug into the stomach. For drugs that are either sparingly soluble, of limited solubility, or of high solubility, and that experience any of the specific problems enumerated above upon reaching the lower GI tract prior to absorption into the bloodstream, the swelling of the polymeric matrix (i) renders the matrix sufficiently large to cause retention in the stomach during the fed mode, and (ii) localizes the release of the drug to the stomach and small intestine so that the drug will have its full effect without colonic degradation, inactivation, or loss of bioavailability.

In either of these aspects, the invention provides an effective means of using these drugs to treat local stomach disorders as well as a wide variety of disease conditions. For example, use of this invention provides more effective eradication of ulcer-causing bacteria in the gastric mucosa with soluble antibiotics. The invention also provides enhanced absorption of soluble drugs that are absorbed mostly in the stomach or high in the gastrointestinal tract, such as metformin hydrochloride or ciprofloxacin. The invention is also useful in providing a multi-hour flow of a drug past the upper part of the small intestine (the most efficient absorption site for many agents).

Details of these and other features of the invention will be apparent from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot showing the release rate of metformin hydrochloride from three different compositions of the drug in poly(ethylene oxide) matrices.

FIG. 2 is a plot showing the release rate of captopril from a poly(ethylene oxide) matrix, in accordance with this invention, both with and without glyceryl monostearate as a solubility modifier.

FIG. 3 is a plot showing the release rate of captopril from hydroxyethyl cellulose, in which the pellet size was varied.

FIG. 4 is a plot showing the release rate of metformin hydrochloride from various polymeric matrices.

FIG. 5 is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped tablet.

FIG. 6 is a plot showing the release rate of captopril from various polymeric matrices.

FIG. 7 is a plot showing further release rate studies of metformin hydrochloride from two different polymeric matrices.

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FIG. 8 is a plot showing the release rate of vancomycin hydrochloride from different polymeric matrices.

FIG. 9 is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped tablet.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

In aspects of this invention that are directed to highly soluble drugs, the drugs thus addressed are those that are characterized by the United States Pharmacopeia XXII as at least "freely soluble" in water, i. e., drugs whose solubility is greater than one part of the drug in about ten parts of water. Drugs of particular interest are those whose solubility is greater than one part in about five parts of water, and drugs of even greater interest are those whose solubility is greater than one part in about three parts of water. The parts referred to in this paragraph and throughout this specification are parts by weight.

The term "drug" is used herein to denote any chemical compound, complex or composition that is suitable for oral administration and that has a beneficial biological effect, preferably a therapeutic effect in the treatment of a disease or abnormal physiological condition. Examples of drugs of high solubility to which this invention is applicable are metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, ticlopidine hydrochloride, amoxicillin, cefuroxime axetil, cefaclor, clindamycin, doxifluridine, tramadol, fluoxitine hydrochloride, ciprofloxacin, gancyclovir, bupropion, lisinopril, and esters of ampicillin. Examples of drugs of low solubility to which this invention is applicable are cefaclor, ciprofloxacin, saguinavir, ritonavir, nelfinavir, clarithromycin, azithromycin, ceftazidine, cyclosporin, digoxin, paclitaxel, iron salts, topiramate, and ketoconazole. Other drugs suitable for use and meeting the solubility criteria described above will be apparent to those skilled in the art. Drugs of particular interest are metformin hydrochloride and sertraline hydrochloride. The drug loadings (weight percent of drug relative to total of drug and polymer) in most of these cases will be about 80% or less.

The invention is also of use with drugs that have been formulated to include additives that impart a small degree of hydrophobic character, to further retard the release rate of the drug into the gastric fluid. One example of such a release rate retardant is glyceryl monostearate. Other examples are fatty acids and salts of fatty acids, one example of which is sodium myristate. The quantities of these additives when present can vary; and in most cases, the weight ratio of additive to drug will range from about 1:20 to about 1:1, and preferably from about 1:8 to about 1:2.

The water-swellable polymer forming the matrix in accordance with this invention is any polymer that is non-toxic, that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of an incorporated drug. Examples of polymers suitable for use in this invention are cellulose polymers and their derivatives (such as for example, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyalkylene oxides, polyethylene glycols, chitosan, poly(vinyl alcohol), xanthan gum, maleic anhydride copolymers, poly(vinyl pyrrolidone), starch and starch-based polymers, poly (2-ethyl-2-oxazoline), poly (ethyleneimine), polyurethane hydrogels, and crosslinked

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polyacrylic acids and their derivatives. Further examples are copolymers of the polymers listed in the preceding sentence, including block copolymers and grafted polymers. Specific examples of copolymers are PLURONIC® and TECTONIC®, which are polyethylene oxide-polypropylene oxide block copolymers available from BASF Corporation, Chemicals Div., Wyandotte, Mich., USA.

The terms "cellulose" and "cellulosic" are used herein to denote a linear polymer of anhydroglucose. Preferred cellulosic polymers are alkyl-substituted cellulosic polymers that ultimately dissolve in the gastrointestinal (GI) tract in a predictably delayed manner. Preferred alkyl-substituted cellulose derivatives are those substituted with alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C. Particularly preferred alkyl-substituted celluloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. A presently preferred hydroxyethylcellulose is NATRASOL® 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Del., USA.

Polyalkylene oxides of greatest utility in this invention are those having the properties described above for alkyl-substituted cellulose polymers. A particularly preferred polyalkylene oxide is poly(ethylene oxide), which term is used herein to denote a linear polymer of unsubstituted ethylene oxide. Poly(ethylene oxide) polymers having molecular weights of about 4,000,000 and higher are preferred. More preferred are those with molecular weights within the range of about 4,500,000 to about 10,000,000, and even more preferred are polymers with molecular weights within the range of about 5,000,000 to about 8,000,000. Preferred poly(ethylene oxide)s are those with a weight-average molecular weight within the range of about 1×10^5 to about 1×10^7, and preferably within the range of about 9×10^5 to about 8×10^6. Poly(ethylene oxide)s are often characterized by their viscosity in solution. For purposes of this invention, a preferred viscosity range is about 50 to about 2,000,000 centipoise for a 2% aqueous solution at 20° C. Two presently preferred poly(ethylene oxide)s are POLYOX® NF, grade WSR Coagulant, molecular weight 5 million, and grade WSR 303, molecular weight 7 million, both products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Conn., USA.

Polysaccharide gums, both natural and modified (semi-synthetic) can be used. Examples are dextran, xanthan gum, gellan gum, welan gum and rhamsan gum. Xanthan gum is preferred.

Crosslinked polyacrylic acids of greatest utility are those whose properties are the same as those described above for alkyl-substituted cellulose and polyalkylene oxide polymers. Preferred crosslinked polyacrylic acids are those with a viscosity ranging from about 4,000 to about 40,000 centipoise for a 1% aqueous solution at 25° C. Three presently preferred examples are CARBOPOL® NF grades 971P, 974P and 934P (BFGoodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, USA). Further examples are polymers known as WATER LOCK®, which are starch/acrylates/acrylamide copolymers available from Grain Processing Corporation, Muscatine, Iowa, USA.

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The hydrophilicity and water swellability of these polymers cause the drug-containing matrices to swell in size in the gastric cavity due to ingress of water in order to achieve a size that will be retained in the stomach when introduced during the fed mode. These qualities also cause the matrices to become slippery, which provides resistance to peristalsis and further promotes their retention in the stomach. The release rate of a drug from the matrix is primarily dependent upon the rate of water imbibition and the rate at which the drug dissolves and diffuses from the swollen polymer, which in turn is related to the solubility and dissolution rate of the drug, the drug particle size and the drug concentration in the matrix. Also, because these polymers dissolve very slowly in gastric fluid, the matrix maintains its physical integrity over at least a substantial period of time, in many cases at least 90% and preferably over 100% of the dosing period. The particles will then slowly dissolve or decompose. Complete dissolution or decomposition may not occur until 24 hours or more after the intended dosing period ceases, although in most cases, complete dissolution or decomposition will occur within 10 to 24 hours after the dosing period.

The amount of polymer relative to the drug can vary, depending on the drug release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will be sufficient however to retain at least about 40% of the drug within the matrix one hour after ingestion (or immersion in the gastric fluid). Preferably, the amount of polymer is such that at least 50% of the drug remains in the matrix one hour after ingestion. More preferably, at least 60%, and most preferably at least 80%, of the drug remains in the matrix one hour after ingestion. In all cases, however, the drug will be substantially all released from the matrix within about ten hours, and preferably within about eight hours, after ingestion, and the polymeric matrix will remain substantially intact until all of the drug is released. The term "substantially intact" is used herein to denote a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles.

The water-swellable polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples are cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

The benefits of this invention will be achieved over a wide range of drug loadings, with the weight ratio of drug to polymer ranging in general from 0.01:99.99 to about 80:20. Preferred loadings (expressed in terms of the weight percent of drug relative to total of drug and polymer) are those within the range of 15% to 80%, more preferably within the range of 30% to 80%, and most preferably in certain cases within the range of about 30% to 70%. For certain applications, however, the benefits will be obtained with drug loadings within the range of 0.01% to 80%, and preferably 15% to 80%.

The formulations of this invention may assume the form of particles, tablets, or particles retained in capsules. A preferred formulation consists of particles consolidated into a packed mass for ingestion, even though the packed mass will separate into individual particles after ingestion. Conventional methods can be used for consolidating the particles in this manner. For example, the particles can be

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placed in gelatin capsules known in the art as "hard-filled" capsules and "soft-elastic" capsules. The compositions of these capsules and procedures for filling them are known among those skilled in drug formulations and manufacture. The encapsulating material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested.

In certain embodiments of this invention, the formulation contains an additional amount of the drug applied as a quickly dissolving coating on the outside of the particle or tablet. This coating is referred to as a "loading dose" and it is included for immediate release into the recipient's bloodstream upon ingestion of the formulation without first undergoing the diffusion process that the remainder of the drug in the formulation must pass before it is released. The "loading dose" is high enough to quickly raise the blood concentration of the drug but not high enough to produce the transient overdosing that is characteristic of highly soluble drugs that are not formulated in accordance with this invention.

One presently preferred dosage form is a size 0 gelatin capsule containing either two or three pellets of drug-impregnated polymer. For two-pellet capsules, the pellets are cylindrically shaped, 6.6 or 6.7 mm (or more generally, 6.5 to 7 mm) in diameter and 9.5 or 10.25 mm (or more generally, 9 to 12 mm) in length. For three-pellet capsules, the pellets are again cylindrically shaped, 6.6 mm in diameter and 7 mm in length. For a size 00 gelatin capsule with two pellets, the pellets are cylindrical, 7.5 mm in diameter and 11.25 mm in length. For a size 00 gelatin capsule with three pellets, the pellets are cylindrical, 7.5 mm in diameter and 7.5 mm in length. Another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 10 mm in width, and 5 to 7.5 mm in height. Still another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 7.8 mm in width, and 6.2 to 7.5 mm in height. A preferred set of dimensions is 20 mm in length, 6.7 mm in width, and 6.4 mm in height. These are merely examples; the shapes and sizes can be varied considerably.

The particulate drug/polymer mixture or drug-impregnated polymer matrix can be prepared by various conventional mixing, comminution and fabrication techniques readily apparent to those skilled in the chemistry of drug formulations. Examples of such techniques are as follows:

(1) Direct compression, using appropriate punches and dies, such as those available from Elizabeth Carbide Die Company, Inc., McKeesport, Pa., USA; the punches and dies are fitted to a suitable rotary tableting press, such as the Elizabeth-Hata single-sided Hata Auto Press machine, with either 15, 18 or 22 stations, and available from Elizabeth-Hata International, Inc., North Huntington, Pa., USA;

(2) Injection or compression molding using suitable molds fitted to a compression unit, such as those available from Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio, USA.;

(3) Granulation followed by compression; and

(4) Extrusion in the form of a paste, into a mold or to an extrudate to be cut into lengths.

When particles are made by direct compression, the addition of lubricants may be helpful and sometimes important to promote powder flow and to prevent capping of the particle (breaking off of a portion of the particle) when the pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25% to 3% by weight,

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preferably less than 1% by weight, in the powder mix), and hydrogenated vegetable oil (preferably hydrogenated and refined triglycerides of stearic and palmitic acids at about 1% to 5% by weight, most preferably about 2% by weight. Additional excipients may be added to enhance powder flowability and reduce adherence.

The term "dosage form" denotes any form of the formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular drug, including both its pharmacological characteristics and its physical characteristics such as solubility, and with the characteristics of the swellable matrix such as its permeability, and the relative amounts of the drug and polymer. In most cases, the dosage form will be such that effective results will be achieved with administration no more frequently than once every eight hours or more, preferably once every twelve hours or more, and even more preferably once every twenty-four hours or more.

As indicated above, the dosage forms of the present invention find their greatest utility when administered to a subject who is in the digestive state (also referred to as the postprandial or "fed" mode). The postprandial mode is distinguishable from the interdigestive (or "fasting") mode by their distinct patterns of gastroduodenal motor activity, which determine the gastric retention or gastric transit time of the stomach contents.

In the interdigestive mode, the fasted stomach exhibits a cyclic activity called the interdigestive migrating motor complex (IMMC). The cyclic activity occurs in four phases:

Phase I is the most quiescent, lasts 45 to 60 minutes, and develops few or no contractions.

Phase II is marked by the incidence of irregular intermittent sweeping contractions that gradually increase in magnitude.

Phase III, which lasts 5 to 15 minutes, is marked by the appearance of intense bursts of peristaltic waves involving both the stomach and the small bowel.

Phase IV is a transition period of decreasing activity which lasts until the next cycle begins.

The total cycle time is approximately 90 minutes, and thus, powerful peristaltic waves sweep out the contents of the stomach every 90 minutes during the interdigestive mode. The IMMC may function as an intestinal housekeeper, sweeping swallowed saliva, gastric secretions, and debris to the small intestine and colon, preparing the upper tract for the next meal while preventing bacterial overgrowth. Pancreatic exocrine secretion of pancreatic peptide and motilin also cycle in synchrony with these motor patterns.

The postprandial or fed mode is induced by food ingestion, and begins with a rapid and profound change in the motor pattern of the upper GI tract, the change occurring over a period of 30 seconds to one minute. The stomach generates 3–4 continuous and regular contractions per minute, similar to those of the interdigestive mode but of about half the amplitude. The change occurs almost simultaneously at all sites of the GI tract, before the stomach contents have reached the distal small intestine. Liquids and small particles flow continuously from the stomach into the intestine. Contractions of the stomach result in a sieving process that allows liquids and small particles to pass through a partially open pylorus. Indigestible particles greater than the size of the pylorus are retropelled and retained in the stomach. Particles exceeding about 1 cm in

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size are thus retained in the stomach for approximately 4 to 6 hours. The dosage form of the present invention is designed to achieve the minimal size through swelling following ingestion during the fed mode.

The following examples are offered for purposes of illustration, and are not intended to limit the invention in any manner.

EXAMPLE 1

This example illustrates the controlled-release behavior of metformin hydrochloride, a highly soluble drug (whose solubility is approximately 30%), from a polymeric matrix consisting of poly(ethylene oxide). Three different dose levels were prepared—systems designed to release 90% of their drug contents at approximately 3 hours, 6 hours, and 8 hours, respectively.

Drug and polymer, with 0.5% magnesium stearate as a tableting lubricant, were compressed into pellets measuring 7.2 mm diameter×8.8 mm length and weighing 390 mg for samples designed for 3-hour and 6-hour release, and 7.4 mm diameter×8.5 mm length and weighing 380 mg for samples designed for 8-hour release, and two pellets of a given type were incorporated into a single gelatin capsule. Thus, three different types of gelatin capsule were prepared as follows:

$t_{90\%} \cong 3$ hours	
metformin hydrochloride	250.00 mg
POLYOX ® 1105, molecular weight 900,000	138.67
magnesium stearate	1.95
Total	390.62 mg

$t_{90\%} \cong 6$ hours	
metformin hydrochloride	250.00 mg
POLYOX ® Coagulant, molecular weight 5,000,000	138.67
magnesium stearate	1.95
Total	390.62 mg

$t_{90\%} \cong 8$ hours	
metformin hydrochloride	125.00 mg
POLYOX ® 303, molecular weight 7,000,000	266.11
magnesium stearate	1.97
Total	393.08 mg

Release rate tests on each of these three formulations were performed in modified artificial gastric fluid by the following procedure.

Dissolution was performed in a USP Apparatus 2, modified to include a stainless steel cone (7/8 inch in height and 7/8 inch in diameter at the base) at the bottom of each vessel, placed directly beneath the paddle shaft to eliminate the "dead zone" effect. A paddle speed of 60 rpm and a bath temperature of 37.4° C. were used. The gelatin capsule was opened and the individual pellets and empty gelatin capsule were dropped into the dissolution vessel containing 900 mL of modified simulated gastric fluid (7 mL of hydrochloric acid and 2 g of sodium chloride in 100 mL of deionized water; the enzyme pepsin was omitted). Once the pellets had settled to the bottom of the vessel, the paddle rotation was initiated. Samples 5 mL in size were taken at specified time points, and the sample volumes were not replaced. The samples were diluted as necessary for quantitative analysis by HPLC.

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The results are shown in FIG. **1**, where the filled diamonds represent the $t_{90\%}\cong 3$ formulation, the x's represent the $t_{90\%}\cong 6$ formulation, and the open circles represent the $t_{90\%}\cong 8$ formulation. The curves show that the $t_{90\%}$ value of the first formulation was fairly close to 3.5 hours, the $t_{90\%}$ value of the second formulation was fairly close to 6.0 hours, and $t_{90\%}$ value of the third formulation was fairly close to 7.5 hours.

EXAMPLE 2

This example illustrates the controlled-release behavior of captopril from a polymeric matrix consisting of poly (ethylene oxide), both with and without glyceryl monostearate (8% by weight). The formulations used were as follows:

1. Captopril		92.50 mg
Poly(ethylene oxide) (POLYOX ® 301), molecular weight 4,000,000		407.50
Total		500.00 mg
2. Captopril		92.5 mg
glyceryl monostearate		15.0
Poly(ethylene oxide) (POLYOX ® 301), molecular weight 4,000,000		392.5
Total		500.0 mg

Each formulation was compressed into a tablet measuring 6.0 mm diameter×6.7 mm length and weighing 180 mg. Release rate tests on each of the two tablets were performed in modified simulated gastric fluid by the procedure of Example 1, except that the paddle rotation speed was 30 rpm and the tablets were dropped directly into the dissolution vessel.

The results are shown in FIG. **2**, where the filled squares represent Formulation No. 1 consisting of captopril and poly(ethylene oxide) only, and the open circles represent Formulation No. 2 which further contained glyceryl monostearate.

EXAMPLE 3

This example illustrates the controlled-release behavior of captopril from a polymeric matrix of hydroxyethyl cellulose with the inclusion of glyceryl monostearate, but at varying pellet sizes. The formulation contained 19% captopril (all percents by weight) and 4.8% glyceryl monostearate in hydroxyethyl cellulose of molecular weight within the range of 1,000,000 to 1,500,000. The pellet sizes and weights were (a) 3.3 mm diameter×3.5 mm length at 35 mg (referred to herein as 3-mm tablets), (b) 4.3 mm diameter×4.9 mm length at 75 mg (referred to herein as 4-mm tablets), and (c) 6.3 mm diameter×6.5 mm length at 187 mg (referred to herein as 6-mm tablets).

Release rate tests on each of the three tablet sizes (fifteen of the 3-mm tablets, seven of the 4-mm tablets, and three of the 6-mm tablets) were performed using the procedures of Example 1, except that a weighted watchglass was used in place of the stainless steel cone, and analyses of the samples were performed by UV/Vis. The results are shown in FIG. **3**, where the filled squares represent the 3-mm pellets, the filled triangles the 4-mm pellets, and the filled circles the 6-mm pellets. This demonstrates the variation of pellet size as a further means of varying the release pattern, the larger pellets having less surface area.

EXAMPLE 4

This example further illustrates the controlled release of metformin hydrochloride, using a higher drug loading, and

various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 4 where the results are plotted, were as follows (all percentages are by weight):

Filled circles: 79.6% metformin HCl; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.04 mm diameter×9.48 mm length; containing approximately 478 mg metformin HCl.

Filled squares: 79.6% metformin HCl; 20% xanthan gum (KELTROL® F, Kelco, Div. of Merck & Co., Inc., San Diego, Calif., USA); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.40 mm length; containing approximately 483 mg metformin HCl.

Plus signs: 79.6% metformin HCl; 20% hydroxypropyl-methyl cellulose (BENECEL® 824, Aqualon Co., Wilmington, Del., USA), viscosity (2%, 20° C.) 11,000 to 15,000 cps; 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.49 mm length; containing approximately 480 mg metformin HCl.

Open diamonds: 79.6% metformin HCl; 5% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 15% poly(ethylene oxide (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.60 mm length; containing approximately 480 mg metformin HCl.

x's: 79.6% metformin HCl, 18.05% xanthan gum (KELTROL® F); 1.99% WATER LOCKS D-223 (starch graft poly(2-propenamide-co-2-propenoic acid)), mixed sodium and aluminum salts, Grain Processing Corporation, Muscatine, Iowa, USA); 0.4% magnesium stearate. Pellet dimensions were 6.06 mm diameter×9.24 mm length; containing approximately 476 mg metformin HCl total.

EXAMPLE 5

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. **5**. The formulation was as follows (all percentages are by weight): 64% metformin HCl; 35.5% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pa., USA). The tablet dimensions were 6.48 mm diameter×7.20 mm height×19.21 mm length, and contained approximately 506 mg metformin HCl per tablet.

EXAMPLE 6

This example further illustrates the controlled release of captopril, using various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **6** where the results are plotted, were as follows (all percentages are by weight):

Plus signs: 80% captopril; 20% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20° C.) 11,000 to 15,000 cps). Pellet dimensions: 6.03 mm diameter×9.25 mm length, 2 pellets weighing 293 mg each, containing approximately 469 mg captopril total.

Filled diamonds: 80% captopril; 20% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter×9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

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Filled triangles: 80% captopril; 20% hydroxyethyl cellulose (250HX, molecular weight 1,000,000). Pellet dimensions: 6.03 mm diameter×9.53 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Open circles: 80% captopril; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter×9.59 mm length, 2 pellets weighing 301 mg each, containing approximately 482 mg captopril total.

Filled squares: 80% captopril; 20% carboxymethyl cellulose (12M31P, molecular weight 250,000). Pellet dimensions: 6.04 mm diameter×9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Open triangles: 79.93% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.04% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter×9.26 mm length, 2 pellets weighing 296 mg each, containing approximately 473 mg captopril total.

x's: 79.96% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.01% poly (ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter×9.41 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

Dashes: 80% captopril; 10% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20° C.) 11,000 to 15,000 cps). Pellet dimensions: 6.04 mm diameter×9.41 mm length, 2 pellets weighing 298 mg each, containing approximately 477 mg captopril total.

Open diamonds: 79.96% captopril; 18.05% xanthan gum (KELTROL® F); 1.99% WATERLOCK® D-223. Pellet dimensions: 6.04 mm diameter×9.16 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

EXAMPLE 7

This example presents further data on metformin hydrochloride formulations, illustrating the effect of lower drug loadings than those used in the preceding examples. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 7 where the results are plotted, were as follows (all percentages are by weight):

Filled squares: 32.5% metformin HCl; 67% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions 6.62 mm diameter×10.40 mm length, 2 pellets weighing 400 mg each, containing approximately 260 mg metformin HCl total.

Open circles: 32.5% metformin HCl; 67% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions 6.65 mm diameter×9.28 mm length; 2 pellets weighing 401 mg each, containing approximately 261 mg metformin HCl total.

EXAMPLE 8

This example illustrates the sustained release of vancomycin hydrochloride from various polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 8 where the results are plotted, were as follows (all percentages are by weight):

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Open squares: 31.5% vancomycin hydrochloride; 68% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.23 mm length, 2 pellets weighing 403 mg each, containing approximately 254 mg vancomycin hydrochloride total.

Open triangles: 31.5% vancomycin hydrochloride; 68% poly(ethylene oxide) (POLYOX® 301, molecular weight 4,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.28 mm length, 2 pellets weighing 402 mg each, containing approximately 253 mg vancomycin hydrochloride total.

x's: 31.5% vancomycin hydrochloride; 68% hydroxypropyl methylcellulose (BENECEL® 824, viscosity 11,000–15,000 cps (2% solution at 20° C.)); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.10 mm length, 2 pellets weighing 405 mg each, containing approximately 255 mg vancomycin hydrochloride total.

Open circles: 31.5% vancomycin hydrochloride; 68% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions: 6.62 mm diameter×9.77 mm length, 2 pellets weighing 401 mg each, containing approximately 253 mg vancomycin hydrochloride total.

Filled squares: 62.5% vancomycin hydrochloride; 37% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.60 mm diameter×10.01 mm length, 2 pellets weighing 409 mg each, containing approximately 511 mg vancomycin hydrochloride total.

In the prior art, vancomycin and its salts are administered by injection, due to poor absorption when administered orally. By providing for all or at least a portion of the total administered amount to be delivered by controlled delivery in the gastric retentive system of this invention, that portion so delivered is directed to the proximal portion of the small intestine, the most efficient site for absorption of this drug, resulting in an enhanced absorption from the oral dosage form of the invention.

EXAMPLE 9

This example illustrates the difference between subjects in the fed mode and subjects not in the fed mode in terms of the gastric retention of tablets of various sizes administered orally. Both Beagle dogs and human subjects were used.

Barium-containing tablets for oral administration were prepared from the following ingredients:

25% Barium Sulfate
30% PolyOx 303 (average molecular weight 7,000,000)
44.5% Hydroxypropylcellulose
0.5% Magnesium Stearate

For tests on Beagle dogs, 400-mg tablets measuring 5.8 mm diameter×5.1 mm height×15.4 mm length were prepared in a tablet press at 2,500 psi pressure, and 800-mg tablets measuring 7.9 mm diameter×5.6 mm height×19.1 mm length were prepared in a tablet press at 5,000 psi. Four beagle dogs were used, and the location of the tablets in the GI tract was followed using fluoroscopy. Two studies were initiated with the dogs. In the first study, each dog received two tablets (one 400-mg and one 800-mg) with a small amount of water after a 16-hour fast. In the second study, each dog received two tablets (one 400-mg and one 800-mg) thirty minutes after ingesting 50 grams of a standard meal. The location of the tablets (in or out of the stomach) was monitored every 30 minutes with the fluoroscope.

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The fluoroscopy revealed that tablets that were administered while the dogs were in the fasted condition were emptied from the dogs' stomachs within 90 minutes: in two of the dogs, the stomachs contained no barium tablets at 30 minutes, in a third this was true at 60 minutes, and in the fourth at 90 minutes. Tablets that were administered while the dogs were in the fed state remained in the dogs' stomach for between 4 and 5 hours.

Human tests were performed on ten normal adults of both sexes, each taking part in two trials, the first after fasting and the second after a bacon and egg breakfast of approximately 1,500 calories. The tablets used in the tests had the same composition as those used for the Beagle dogs and measured either 4 mm×4 mm or 6 mm×6 mm. The subjects were X-rayed at 30 minutes and at 1, 2, 4, 6, 8, 10, and approximately 12 hours after ingesting the tablets. In some subjects, visualization was achieved by ultrasound rather than X-rays.

Imaging revealed that in the fasted trials, the tablets left the stomach in 30 minutes to one hour after administration. In the fed trials, the tablets demonstrated multiple-hour retention in the stomach in all subjects, 80% of the contents of all tablets being retained at 4 hours. Five of the ten subjects retained the tablets for 6 hours or more, and four of these five retained them for ten hours or more.

EXAMPLE 10

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. 9. The formulation was as follows (all percentages are by weight): 48.5% metformin HCl; 49% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pa., USA). The tablet dimensions were 9.66 mm diameter×6.95 mm height×19.24 mm length, and contained approximately 506 mg metformin HCl per tablet.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that the components, additives, proportions, methods of formulation, and other parameters of the invention can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

What is claimed is:

1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20, said polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during said fed mode, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug within about eight hours after such immersion, and that remains substantially intact until all of said drug is released.

2. A dosage form of claim 1 in which the solubility of said drug in water is greater than one part by weight of said drug in five parts by weight of water.

3. A dosage form of claim 1 in which said drug is a member selected from the group consisting of metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, tramadol and ticlopidine hydrochloride.

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4. A dosage form of claim 1 in which said drug is metformin hydrochloride.

5. A dosage form of claim 1 in which said drug is sertraline hydrochloride.

6. A dosage form of claim 1 in which said drug is captopril.

7. A dosage form of claim 1 in which said drug is vancomycin hydrochloride.

8. A dosage form of claim 1 in which said polymeric matrix is formed of a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

9. A dosage form of claim 8 in which said alkyl-substituted celluloses are members selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

10. A dosage form of claim 1 in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

11. A dosage form of claim 1 in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 4,500,000 to about 10,000,000.

12. A dosage form of claim 1 in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 5,000,000 to about 8,000,000.

13. A dosage form of claim 1 in which said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said drug one hour after such immersion.

14. A dosage form of claim 1 in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said drug one hour after such immersion.

15. A dosage form of claim 1 in which said polymeric matrix upon immersion in gastric fluid retains at least about 80% of said drug one hour after such immersion.

16. A dosage form of claim 1 further comprising a member selected from the group consisting of glyceryl monostearate and sodium myristate, formulated with said drug to further retard the release of said drug to said gastric fluid.

17. A dosage form of claim 1 in which said polymeric matrix consists of two cylindrical tablets, each measuring about 9 mm to about 12 mm in length and about 6.5 mm to about 7 mm in diameter.

18. A dosage form of claim 1 in which said polymeric matrix consists of a single elongated tablet measuring about 18 mm to about 22 mm in length, about 6.5 mm to about 7.8 mm in width, and about 6.2 to 7.5 mm in height.

19. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach and doing so in a manner that substantially avoids the alteration of intestinal flora that said drug otherwise tends to cause, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

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(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal flora.

20. A method in accordance with claim 19 in which said drug is a member selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, clindamycin, clarithromycin, azithromycin, ceftazidine, and ciprofloxacin.

21. A method in accordance with claim 19 in which said drug is a highly soluble drug selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, and clindamycin.

22. A method of treating a subject suffering from infections selected from the group consisting of pneumonia, sinus bacterial infections, topical bacterial infections and staphylococcus infections, by administering to said subject a drug which is a member selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, clindamycin, clarithromycin, azithromycin, and ceftazidine, without substantially causing side effects resulting from the alteration of the intestinal flora of said subject, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal flora.

23. A method in accordance with claim 22 in which said drug is a highly soluble drug selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, and clindamycin.

24. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable by colonic bacterial enzymes residing in lower gastrointestinal tract enterocytes, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

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(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal enzymes and said drug transporters.

25. A method in accordance with claim 24 in which said drug is a member selected from the group consisting of cyclosporine, digoxin, and doxifluridine.

26. A method in accordance with claim 24 in which said drug is doxifluridine.

27. A method of treating a subject undergoing an organ transplant to suppress an immune response to said transplant, by administering cyclosporine to said subject without substantial degradation of said cyclosporine by colonic bacterial enzymes residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said cyclosporine while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said cyclosporine dispersed therein at a weight ratio of cyclosporine to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said cyclosporine one hour after such immersion in gastric fluid,

(d) releases substantially all of said cyclosporine within about ten hours after such immersion, and

(e) remains substantially intact until all of said cyclosporine is released,

thereby extending the release rate of said cyclosporine with time during said fed mode while releasing substantially all of said cyclosporine within said stomach and substantially avoiding contact of said cyclosporine with said colonic bacterial enzymes.

28. A method of treating a subject for heart disease by administering digoxin to said subject without substantial degradation of said digoxin by colonic bacterial enzymes residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said digoxin while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said digoxin dispersed therein at a weight ratio of digoxin to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

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(c) retains at least about 40% of said digoxin one hour after such immersion in gastric fluid,

(d) releases substantially all of said digoxin within about ten hours after such immersion, and

(e) remains substantially intact until all of said digoxin is released,

thereby extending the release rate of said digoxin with time during said fed mode while releasing substantially all of said digoxin within said stomach and substantially avoiding contact of said digoxin with said colonic bacterial enzymes.

29. A method of treating a subject suffering from a condition selected from the group consisting of ovarian cancer, colorectal cancer, gastric cancer, renal cancer, and breast cancer, by administering doxifluridine to said subject without substantial degradation of said doxifluridine by intestinal enzymes or substantial inactivation of said doxifluridine by drug transporters residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said doxifluridine while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said doxifluridine dispersed therein at a weight ratio of doxifluridine to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said doxifluridine one hour after such immersion in gastric fluid,

(d) releases substantially all of said doxifluridine within about ten hours after such immersion, and

(e) remains substantially intact until all of said doxifluridine is released,

thereby extending the release rate of said doxifluridine with time during said fed mode while releasing substantially all of said doxifluridine within said stomach and substantially avoiding contact of said doxifluridine with said enzymes.

30. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also susceptible to inactivation by drug transporters residing in lower gastrointestinal tract enterocytes, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said

drug within said stomach and substantially avoiding contact of said drug with said drug transporters.

31. A method in accordance with claim 30 in which said drug is a member selected from the group consisting of cyclosporine and paclitaxel.

32. A method of treating a subject undergoing an organ transplant to suppress an immune response to said transplant, by administering cyclosporine to said subject without substantial inactivation of said cyclosporine by p-glycoprotein in the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said cyclosporine while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said cyclosporine dispersed therein at a weight ratio of cyclosporine to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said cyclosporine one hour after such immersion in gastric fluid,

(d) releases substantially all of said cyclosporine within about ten hours after such immersion, and

(e) remains substantially intact until all of said cyclosporine is released,

thereby extending the release rate of said cyclosporine with time during said fed mode while releasing substantially all of said cyclosporine within said stomach and substantially avoiding inactivation of said cyclosporine by p-glycoprotein in said lower gastrointestinal tract.

33. A method of treating a subject suffering from cancer by administering paclitaxel to said subject without substantial inactivation of said paclitaxel by p-glycoprotein in the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said paclitaxel while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said paclitaxel dispersed therein at a weight ratio of paclitaxel to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said paclitaxel one hour after such immersion in gastric fluid,

(d) releases substantially all of said paclitaxel within about ten hours after such immersion, and

(e) remains substantially intact until all of said paclitaxel is released,

thereby extending the release rate of said paclitaxel with time during said fed mode while releasing substantially all of said paclitaxel within said stomach and substantially avoiding inactivation of said paclitaxel by p-glycoprotein in said lower gastrointestinal tract.

34. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach and whose bioavailability is substantially greater in an acidic

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environment than an alkaline environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

35. A method in accordance with claim 34 in which said drug is a member selected from the group consisting of esters of ampicillin, iron salts, digoxin, and ketoconazole.

36. A method in accordance with claim 34 in which said drug is a member selected from the group consisting of esters of ampicillin.

37. A method of treating a subject suffering from a bacterial infection by administering an ester of ampicillin to said subject while maintaining maximum bioavailability of said ester of ampicillin, said method comprising orally administering to said subject a dosage form of said ester of ampicillin while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said ester of ampicillin dispersed therein at a weight ratio of said ester of ampicillin to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said ester of ampicillin one hour after such immersion in gastric fluid,

(d) releases substantially all of said ester of ampicillin within about ten hours after such immersion, and

(e) remains substantially intact until all of said ester of ampicillin is released,

thereby extending the release rate of said ester of ampicillin with time during said fed mode while releasing substantially all of said ester of ampicillin within said stomach and maintaining said ester of ampicillin in the acidic environment of said stomach during said release.

38. A method of treating a subject suffering from anemia by administering iron salts to said subject while maintaining maximum bioavailability of said iron salts, said method comprising orally administering to said subject a dosage form of said iron salts while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said iron salts dispersed therein at a weight ratio of iron salts

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to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said iron salts one hour after such immersion in gastric fluid,

(d) releases substantially all of said iron salts within about ten hours after such immersion, and

(e) remains substantially intact until all of said iron salts is released,

thereby extending the release rate of said iron salts with time during said fed mode while releasing substantially all of said iron salts within said stomach where said iron salts are maintained in an acidic environment.

39. A method of treating a subject suffering from a systemic fungal infection by administering ketoconazole to said subject while maintaining maximum bioavailability of said ketoconazole, said method comprising orally administering to said subject a dosage form of said ketoconazole while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said ketoconazole dispersed therein at a weight ratio of ketoconazole to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said ketoconazole one hour after such immersion in gastric fluid,

(d) releases substantially all of said ketoconazole within about ten hours after such immersion, and

(e) remains substantially intact until all of said ketoconazole is released,

thereby extending the release rate of said ketoconazole with time during said fed mode while releasing substantially all of said ketoconazole within said stomach where said ketoconazole is maintained in an acidic environment.

40. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable in an alkaline environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix in which said drug is dispersed at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

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(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

41. A method in accordance with claim **40** in which said drug is nelfinar mesylate.

42. A method of treating a subject infected with human immunodeficiency virus by administering nelfinar mesylate to said subject without substantial degradation of said nelfinar mesylate by intestinal flora or substantial inactivation of said nelfinar mesylate by drug transporters residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said nelfinar mesylate while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said nelfinar mesylate dispersed therein at a weight ratio of nelfinar mesylate to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said nelfinar mesylate into gastric fluid by the dissolving of said nelfinar mesylate by said gastric fluid and either erosion of said matrix or diffusion of said dissolved nelfinar mesylate out of said matrix,

(c) retains at least about 40% of said nelfinar mesylate one hour after such immersion in gastric fluid,

(d) releases substantially all of said nelfinar mesylate within about ten hours after such immersion, and

(e) remains substantially intact until all of said nelfinar mesylate is released,

thereby extending the release rate of said nelfinar mesylate with time during said fed mode while releasing substantially all of said nelfinar mesylate within said stomach where said nelfinar mesylate is maintained in an acidic environment.

43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(d) releases substantially all of said drug within about ten hours after such immersion, and

(e) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

44. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable in an acidic environment, said method

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comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising a solid polymeric matrix with said drug dispersed therein at a weight ratio of drug to polymer of from about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) swells upon imbibition of gastric fluid to a size large enough to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) protects any unreleased drug in said matrix from said gastric fluid,

(d) retains at least about 40% of said drug one hour after such immersion in gastric fluid,

(e) releases substantially all of said drug within about ten hours after such immersion, and

(f) remains substantially intact until all of said drug is released,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

45. A dosage form of claim **1** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises an alkyl-substituted cellulose.

46. A dosage form of claim **1** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises hydroxypropylmethyl cellulose.

47. A dosage form of claim **1** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of from about 4,500,000 to about 10,000,000.

48. A method in accordance with claim **19** in which said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

49. A method in accordance with claim **19** in which said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of from about 4,500,000 to about 10,000,000.

50. A method in accordance with claim **19** in which said solid polymeric matrix comprises an alkyl-substituted cellulose.

51. A method in accordance with claim **19** in which said solid polymeric matrix comprises hydroxypropylmethyl cellulose.

52. A method in accordance with claim **43** in which said drug is a member selected from the group consisting of metformin hydrochloride, lisinopril, captopril, buproprion, ganciclovir, and iron salts.

53. A method in accordance with claim **43** in which said drug is metformin hydrochloride.

54. A method in accordance with claim **43** in which said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

55. A method in accordance with claim **43** in which said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of from about 4,500,000 to about 10,000,000.

56. A method in accordance with claim **43** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

57. A method in accordance with claim **43** in which said solid polymeric matrix comprises an alkyl-substituted cellulose.

58. A method in accordance with claim **43** in which said solid polymeric matrix comprises hydroxypropylmethyl cellulose.

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59. A method in accordance with claim **43** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises an alkyl-substituted cellulose.

60. A method in accordance with claim **43** in which said drug is metformin hydrochloride and said solid polymeric matrix comprises hydroxypropylmethyl cellulose.

61. A dosage form of claim **1** in which said polymeric matrix is comprised of hydroxypropylmethylcellulose.

62. A dosage form of claim **1** in which said polymeric matrix is comprised of hydroxypropylmethylcellulose with a viscosity range of 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

63. A dosage form of claim **1** in which said drug is metformin hydrochloride and said polymeric matrix is comprised of hydroxypropylmethylcellulose with a viscosity range of 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

64. A dosage form of claim **1** in which said drug is metformin hydrochloride and said polymeric matrix is comprised of an alkyl-substituted cellulose.

65. A dosage form of claim **1** in which said drug is metformin hydrochloride and said polymeric matrix is comprised of hydroxypropylmethylcellulose.

66. A method in accordance with claim **43** in which said polymeric matrix is comprised of hydroxypropylmethylcellulose with a viscosity range of 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

67. A method in accordance with claim **43** in which said drug is metformin hydrochloride and said polymeric matrix is comprised of hydroxypropylmethylcellulose with a viscosity range of 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

68. A controlled-release oral drug dosage form for releasing metformin hydrochloride, said dosage form comprising a solid polymeric matrix with said metformin hydrochloride therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20, said polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during the fed mode, that releases said metformin hydrochloride into gastric fluid by the dissolution and diffusion of said metformin hydrochloride out of said matrix by said gastric fluid, and that upon immersion in gastric fluid retains at least about 40% of said metformin hydrochloride one hour after such immersion.

69. The dosage form of claim **68**, wherein said polymeric matrix comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthum gum.

70. The dosage form of claim **69**, wherein said polymeric matrix comprises an alkyl-substituted cellulose.

71. The dosage form of claim **70**, wherein said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

72. The dosage form of claim **71**, wherein said polymeric matrix comprises hydroxypropylmethyl-cellulose.

73. The dosage form of claim **71**, wherein said polymeric matrix comprises hydroxypropylmethyl-cellulose having a viscosity ranging from 11,000 to 110,000 centipoise as measured in a 2% solution at 20 C.

74. The dosage form of claim **68**, wherein said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said metformin hydrochloride one hour after such immersion.

75. The dosage form of claim **68**, wherein said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

76. The dosage form of claim **68**, wherein said polymeric matrix comprises poly(ethylene oxide) having a molecular weight of at least about 4,000,000.

77. The dosage form of claim **68**, wherein said polymeric matrix comprises poly(ethylene oxide) having a molecular weight ranging from about 4,500,000 to about 10,000,000.

78. The dosage form of claim **68**, wherein said polymeric matrix comprises poly(ethylene oxide) having a molecular weight ranging from about 5,000,000 to about 8,000,000.

79. A controlled-release oral drug dosage form for releasing metformin hydrochloride, said dosage form comprising a solid polymeric matrix tablet with said metformin hydrochloride therein at a weight ratio of drug to polymer of from about 15:85 to about 80:20, said polymeric matrix tablet being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during the fed mode, that releases said metformin hydrochloride into gastric fluid by the dissolution and diffusion of said metformin hydrochloride out of said matrix by said gastric fluid, and that upon immersion in gastric fluid retains at least about 40% of said metformin hydrochloride one hour after such immersion.

80. The dosage form of claim **79**, wherein said polymeric matrix of said polymeric matrix tablet comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthum gum.

81. The dosage form of claim **80**, wherein said polymeric matrix comprises an alkyl-substituted cellulose.

82. The dosage form of claim **81**, wherein said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

83. The dosage form of claim **82**, wherein said polymeric matrix comprises hydroxypropylmethyl-cellulose.

84. The dosage form of claim **83**, wherein said polymeric matrix comprises hydroxypropylmethyl-cellulose having a viscosity ranging from 11,000 to 110,000 centipoise as measured in a 2% solution at 20 C.

85. The dosage form of claim **79**, wherein said polymeric matrix tablet upon immersion in gastric fluid retains at least about 50% of said metformin hydrochloride one hour after such immersion.

86. The dosage form of claim **79**, wherein said polymeric matrix tablet upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

87. The dosage form of claim **79**, wherein said polymeric matrix of said polymeric matrix tablet comprises poly (ethylene oxide) having a molecular weight of at least about 4,000,000.

88. The dosage form of claim **79**, wherein said polymeric matrix of said polymeric matrix tablet comprises poly (ethylene oxide) having a molecular weight ranging from about 4,500,000 to about 10,000,000.

89. The dosage form of claim **79**, wherein said polymeric matrix of said polymeric matrix tablet comprises poly (ethylene oxide) having a molecular weight ranging from about 5,000,000 to about 8,000,000.

*   *   *   *   *

EXHIBIT 2

US006635280B2

(12) **United States Patent**
Shell et al.

(10) Patent No.: **US 6,635,280 B2**
(45) Date of Patent: ***Oct. 21, 2003**

(54) **EXTENDING THE DURATION OF DRUG RELEASE WITHIN THE STOMACH DURING THE FED MODE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/045,823**

(22) Filed: **Nov. 6, 2001**

(65) **Prior Publication Data**

US 2003/0039688 A1 Feb. 27, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/282,233, filed on Mar. 29, 1999, now Pat. No. 6,340,475, which is a continuation-in-part of application No. 08/870,509, filed on Jun. 6, 1997, now abandoned.

(51) **Int. Cl.**[7] **A61K 9/26**; A61K 9/14
(52) **U.S. Cl.** **424/469**; 424/464; 424/468; 424/488; 424/486; 424/487
(58) **Field of Search** 424/469, 464, 424/468, 488, 486, 487

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(57) **ABSTRACT**

Drugs are formulated as unit oral dosage forms by incorporating them into polymeric matrices comprised of hydrophilic polymers that swell upon imbibition of water to a size that is large enough to promote retention of the dosage form in the stomach during the fed mode. The oral formulation is designed for gastric retention and controlled delivery of an incorporated drug into the gastric cavity, and thus administered, the drug is released from the matrix into the gastric fluid by solution diffusion. The swollen polymeric matrix, having achieved sufficient size, remains in the gastric cavity for several hours if administered while the patient is in the fed mode, and remains intact long enough for substantially all of the drug to be released before substantial dissolution of the matrix occurs. The swelling matrix lowers the accessibility of the gastric fluid to the drug and thereby reduces the drug release rate. This process, together with diffusion retardation by selection of specific polymers, polymer molecular weights, and other variables, results in a sustained and controlled delivery rate of the drug to the gastric cavity.

70 Claims, 9 Drawing Sheets
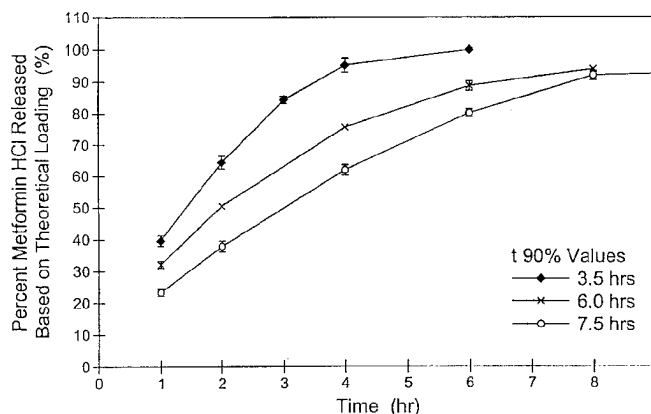
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Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

FIG 9
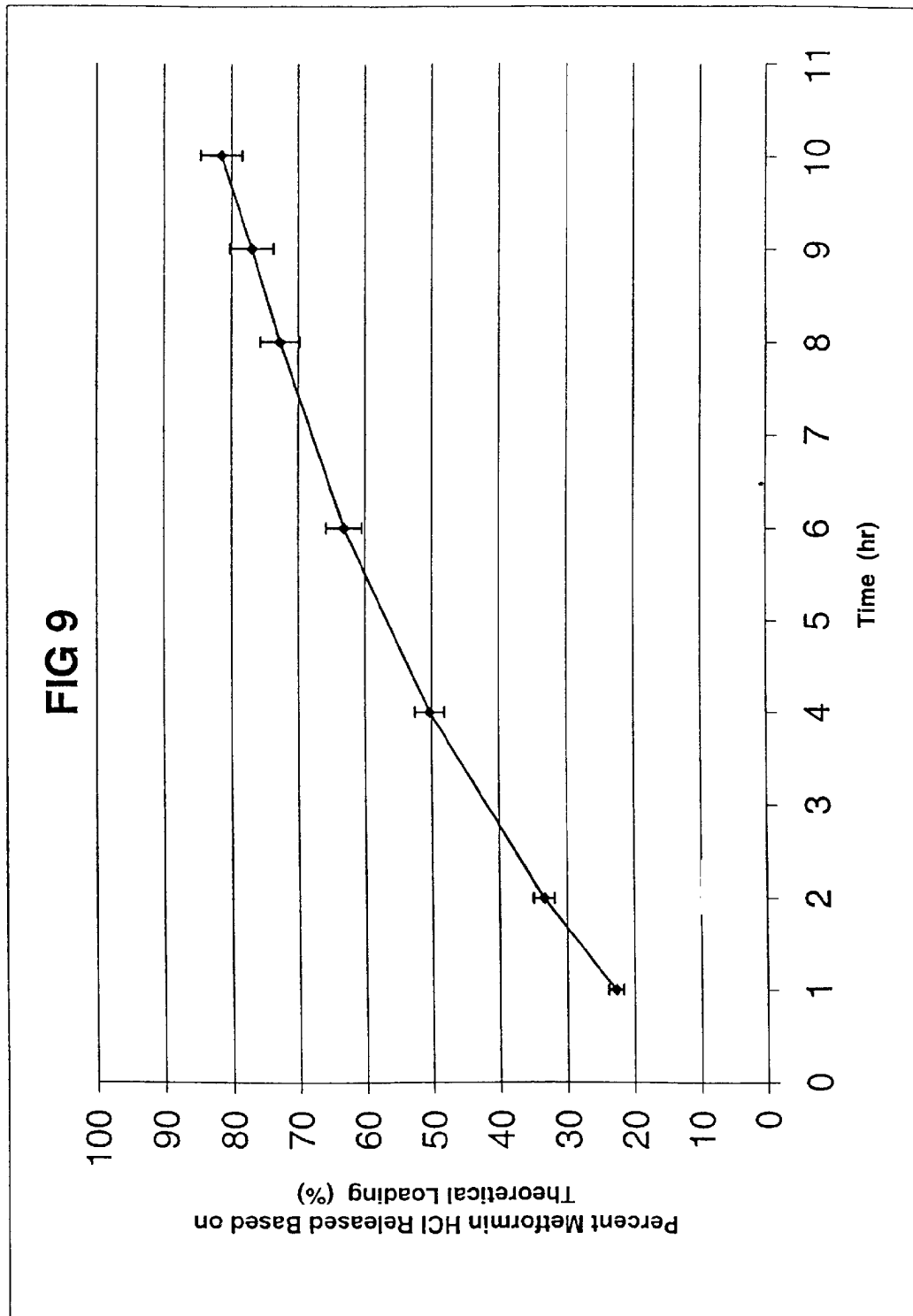
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EXTENDING THE DURATION OF DRUG RELEASE WITHIN THE STOMACH DURING THE FED MODE

CROSS-REFERENCE TO RELATED APPLICATION

This application is a con. of Ser. No. 09/282,253 filed Mar. 29, 1999, now U.S. Pat. No. 6,340,475, which is a continuation-in-part of application Ser. No. 08/870,509, filed Jun. 6, 1997, now abn the entire contents of which are hereby incorporated herein by reference.

This invention is in the general field of pharmacology, and relates in particular to formulations for drugs that benefit from a prolonged time of controlled release in the stomach and upper gastrointestinal (GI) tract, and from an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. One goal in this invention is to release highly soluble drugs in a controlled manner over an extended period of time. Another goal is to extend the time of delivery into the stomach of drugs that are preferentially absorbed high in the GI tract, for purposes of achieving a greater and more prolonged therapeutic effect and thus reducing the frequency of administration required; a more efficient use of the drugs; and a more effective treatment of local stomach disorders. Another goal is to minimize both lower-tract inactivation of the drug and drug effects on the lower intestinal flora by confining the delivery and absorption of the drug to the upper GI tract.

BACKGROUND OF THE INVENTION

Drugs that are administered in the form of conventional tablets or capsules become available to body fluids at a rate that is initially very high, followed by a rapid decline. For many drugs, this delivery pattern results in a transient overdose, followed by a long period of underdosing. This is a pattern of limited clinical usefulness. The delivery pattern was improved in the 1970's with the introduction of a variety of controlled delivery systems. By providing relatively constant, controlled drug delivery, these systems avoided the overdose and the underdose effects. These improvements provided effective medication with reduced side effects, and achieved these results with reduced dosing frequency.

Many of these controlled delivery systems utilize hydrophilic, polymeric matrices that provide useful levels of control to the delivery of sparingly soluble drugs. For soluble drugs, however, and particularly for highly soluble drugs, such matrices do not provide adequate control over the drug release rate, instead resulting in a release that approximates first-order kinetics. That is, the rate of release is an inverse function of the square root of the elapsed time. With this pattern of release, most of the drug in the matrix is often released within the first hour in an aqueous medium.

One method of prolonging the release of a highly water-soluble drug is disclosed in International Patent Application Publication No. WO 96/26718, published Sep. 6, 1996 (applicant: Temple University; inventor: Kim). The method of this publication is the incorporation of the drug into a polymeric matrix to form a tablet that is administered orally. The polymer is water-swellable yet erodible in gastric fluids, and the polymer and the proportion of drug to polymer are chosen such that:

(i) the rate at which the polymer swells is equal to the rate at which the polymer erodes, so that the swelling of the polymer is continuously held in check by the erosion, and zero-order release kinetics (constant delivery rate) of the drug from the matrix are maintained;

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(ii) the release of drug from the matrix is sustained over the full erosion period of the polymer, the tablet therefore reaching complete solution at the same time that the last of the drug is released; and

(iii) release of the drug from the matrix will be extended over a period of 24 hours.

A key disclosure in WO 96/26718 is that to achieve the release of drug in this manner requires the use of a low molecular weight polymer. If, by contrast, a high molecular weight polymer is used and the swelling rate substantially exceeds the erosion rate, the lack of erosion will prolong even further the delivery of the drug residing close to the center of the tablet and even prevent it from being released. Thus, there is no disclosure in WO 96/26718 that a drug of high water solubility can be released from a high molecular weight polymer in a period of time substantially less than 24 hours, or that any advantage can be obtained by the use of a polymer that does not erode as quickly as it swells. This failure is particularly significant since even swollen tablets will not remain in the stomach beyond the duration of the fed mode, which typically lasts for only 4 to 6 hours.

For drugs of any level of solubility, the retention of the drug in a tablet or other dosage form beyond the duration of the fed mode raises a number of problems that detract from the therapeutic efficacy of the drug. These problems arise from the tendency of the tablet when the patient is no longer in the fed mode to pass from the stomach into the small intestine, and over a period of 2–4 hours to pass through the small intestine, thus reaching the colon with the drug still in the tablet. This loss of effectiveness occurs with drugs that provide their maximum benefit with minimum side effects when absorbed in the stomach and upper GI tract rather than the colon. The reasons are either favorable conditions in the stomach, unfavorable conditions in the colon, or both.

For example, most orally administered antibiotics have a potential of altering the normal flora of the gastrointestinal tract, and particularly the flora of the colon. One result of these alterations is the overgrowth of the organism *Clostridium difficile,* which is a serious adverse event since this organism releases dangerous toxins. These toxins can cause pseudomembranous colitis, a condition that has been reported as a side effect of the use of many antibiotics. In its milder forms, pseudomembranous colitis can cause mild nausea and diarrhea while in its stronger forms, it can be life-threatening or fatal. Examples of highly soluble antibiotics that pose this type of threat are amoxicillin, cefuroxime axetil, and clindamycin. Cefuroxime axetil (i.e., the axetil ester of cefuroxime), for example, becomes active when hydrolyzed to free cefuroxime, but when this occurs prior to absorption, it can be detrimental to essential bacterial flora. Hydrolysis to the active form typically occurs in the tissues into which the ester has been absorbed, but if the ester reaches the lower intestine, enzymes in the lower intestine cause the hydrolysis to occur in the intestine itself, which not only renders the drug unabsorbable but also converts the drug to the active form where its activity alters the flora. Examples of sparingly soluble antibiotics that pose the same type of threat are clarithromycin, azithromycin, ceftazidine, ciprofloxacin, and cefaclor.

A goal of the present invention is to avoid this type of alteration of the lower intestinal flora by delivering antibiotics, regardless of their level of solubility, in a manner that confines their delivery to the stomach and upper small intestine. Slow, continuous delivery from a gastric retentive system assures that both drug delivery and drug absorption are confined to the upper GI tract. More efficient delivery of antibiotics will also avoid transient overdosing which is a major cause of overgrowth of *Clostridium difficile.*

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Another example is the class of drugs that are susceptible to degradation by exposure to gastric fluid, either by enzymes or low solution pH. The swellable hydrophilic matrix of the present invention protects the yet undelivered drug during the 4 to 6 hour delivery period during which the drug is continuously released while the dosage form is retained in the stomach. One example of such a drug is topiramate, a drug that is used for the treatment of epilepsy. Topiramate is absorbed preferentially high in the GI tract and is hydrolyzed by the acidic environment of the stomach. The dosage form and delivery system of the present invention will confine the delivery of the drug to the stomach and duodenum. As the drug diffuses out of the swollen matrix, it is susceptible to the acidic environment, but the undelivered drug is protected from degradation by the polymer matrix.

Another example is the class of drugs that are known to have an absorption window high in the GI tract, but are incompletely absorbed or have a wide absorption range, intrapatient as well as interpatient. One example of such a drug is cyclosporine, a drug of low solubility that is used as an immunosuppressant to reduce organ rejection in transplant surgery. In addition to this problem, cyclosporine is in general only incompletely absorbed (on the average around 30%), and the degree of absorption is highly variable from one patient to the next (ranging from about 5% to about 89%). The variability can be attributed in part to differences among the various disease states existing in the patients to whom the drug is administered, and differences in the length of time between the transplant surgery and the administration of the drug. The variability can also however be attributed to the poor aqueous solubility of the drug and to variations in the gastric emptying, variations in the length of time required for intestinal transit between the stomach and the colon, variations in mesenteric and hepatic blood flow, variations in lymph flow, variations in intestinal secretion and fluid volume, variations in bile secretion and flow, and variations in epithelial cell turnover. All of these variations are addressed by the dosage form and delivery system of the present invention, which by confining drug delivery to the stomach reduces these differences and maximizes the absorption of the cyclosporine.

Another example is the class of drugs that are susceptible to degradation by intestinal enzymes. The degradation occurs before the drug can be absorbed through the intestinal wall, leaving only a fraction of the administered dose available for the intended therapeutic action.

An example of a highly soluble drug that is susceptible to degradation by intestinal enzymes is the pro-drug doxifluridine (5'-deoxy-5-fluouridine (dFUR)). The activity of doxifluridine depends on its activation to 5-fluorouracil by pyrimidine nucleoside phosphorylases. These enzymes are found in tumors as well as in normal tissues, with their highest activity being in the small intestine. The activity of these enzymes in tumor cells is more than twice that of normal tissues. When doxifluridine is administered orally, it can be converted to 5-fluorouracil in the intestine before it reaches the tumors. 5-Fluorouracil is much more toxic than doxifluridine and causes intestinal toxicity (nausea and diarrhea) and severe damage to the intestinal villi. A goal of the present invention is to confine the absorption of doxifluridine to the stomach and upper GI tract, thereby avoiding or reducing its conversion to 5-fluorouracil and the attendant toxicity risk. A similar result is sought for other drugs with similar susceptibilities, such as cyclosporine and digoxin.

Another class of drugs whose effectiveness suffers when the drugs are not fully absorbed high in the GI tract are those that are susceptible to inactivation by drug transporters that

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reside in lower gastrointestinal tract enterocytes. The inactivation occurs before the drug penetrates the intestinal wall, here again leaving only a fraction of the administered dose available for the intended therapeutic action. One example of a drug transporter is the p-glycoprotein efflux system, in which a p-glycoprotein acts as an absorption barrier to certain drugs that are substrates for the p-glycoprotein. The barrier acts by attaching to these drugs and transporting them drug back into the lumen, e.g., the stomach, duodenum, jejunum/ileum or colon, from which they were absorbed, or preventing them from being absorbed at all. This restriction of the drug to the interior of the GI tract is effectively an inactivation of the drug if the drug must pass out of the GI tract into the bloodstream to be effective. The p-glycoprotein efflux system is useful in many respects, such as preventing toxic compounds from entering the brain. It interferes however in some cases with the efficacy of certain drugs that would otherwise be absorbed. The p-glycoprotein concentration is lowest in the stomach and increases in concentration down the GI tract to the colon where the p-glycoprotein is most prevalent. The dosage form of the present invention will release the drug over an extended period into the upper GI tract where p-glycoprotein is lowest.

Cyclosporine is an example of a drug of low solubility that is susceptible to inactivation by the p-glycoprotein efflux system, in addition to its susceptibility to degradation by colonic bacterial enzymes. Other examples of drugs of low solubility that are susceptible to the p-glycoprotein efflux system are the anti-cancer drug paclitaxel, ciprofloxacin, and the HIV protease inhibitors saquinavir, ritonavir, and nelfinavir. All of these drugs will benefit through preserved activity by the present invention.

A still further class of drugs that suffer in effectiveness when not fully absorbed before reaching the colon are drugs that require an acidic environment for effective bioavailability. For certain drugs, the pH at a given site within the GI tract is an essential determinant of the bioavailability of the drug, since the solubility of the drug varies with pH. The stomach has a low pH and hence an acidic environment, while the small intestine has a higher pH and hence an alkaline environment. Higher bioavailability is achieved in some cases by higher solubility, which with some drugs occurs in a more acidic environment, and in other cases by keeping the drugs in a non-ionized state that is necessary for absorption, which with some drugs also occurs in a more acidic environment. Acidic drugs that have a low pK, for example, are in the neutral form that is required for absorption and are therefore preferentially absorbed in the stomach. Examples of highly soluble drugs that achieve their highest bioavailability at a low pH are esters of ampicillin. Examples of low solubility drugs that behave similarly are iron salts, digoxin, ketoconazole, fluconazole, griseofulvin, itraconazole, and micoconazole. A further goal of the present invention is therefore to maximize the bioavailability of drugs of these types by confining them to the acidic environment of the stomach while controlling their release rate to achieve an extended release profile. The invention thus improves the efficiency of iron salts in the treatment of the various forms of anemia, the efficiency of digoxin in the treatment of the heart disease, and the efficiency of ketoconazole in the treatment of systemic fungal infections such as candidiasis, canduria, blastomycosis, coccidiomycosis, histoplasmosis, chronomycosis, and pacococcidiomycosis.

The invention also improves the efficiency of drugs that have at least one ionized group in the pH range of 5 through 8. Since this is the pH range encountered in the small

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intestine and the region of the colonic junction and ionized drugs are less absorbable than neutral drugs, this invention improves the absorption of these drugs by retaining them in the stomach environment. The invention also improves the efficiency of drugs that are degradable in an acidic environment such as that of the stomach by protecting them from the acidic environment until they are released from the dosage form, thereby reducing the duration of their exposure to the acidic environment.

A still further example of drugs that lose their efficacy upon reaching the lower portions of the GI tract are drugs that are soluble in an acidic environment but insoluble in an alkaline environment. The HIV protease inhibitor nelfinavir mesylate is one example of such a drug. Portions of the drug that are undissolved cannot be absorbed. Portions that are dissolved but not yet absorbed when they pass from the stomach into the small intestine may undergo precipitation and loss of their therapeutic benefit. This is confirmed by the fact that the presence of food in the GI tract substantially increases the extent of absorption of oral nelfinavir. Peak plasma concentration and area under the plasma concentration-time curve of nelfinavir are two-fold to three-fold greater when doses are administered with or following a meal. This is presumably due, at least in part, to enhanced retention of the drug in the stomach. A further goal of the present invention is therefore to provide a means of administering these drugs that will maximize their therapeutic effectiveness by extended, controlled release into the stomach.

SUMMARY OF THE INVENTION

It has now been discovered that drugs that are highly soluble in water can be administered orally in a manner that will prolong their delivery time to spread their release rate more evenly throughout the duration of the fed mode and beyond or not as desired. This significantly reduces, and often avoids, the problems of transient overdosing caused by the initial spike in concentration entering the blood stream immediately after administration and the subsequent underdosing, and instead controls the dosage to safer and more effective levels over an extended period of time.

It has further been discovered that for drugs of high, intermediate or low solubility, the problems arising from the release of the drugs in the lower GI tract, i.e., from the failure to absorb these drugs into the blood stream prior to reaching the lower GI tract, can be mitigated as well. For all drugs regardless of solubility, therefore, this invention corrects problems such as the overgrowth of detrimental intestinal flora by drugs that are toxic to normal intestinal flora, protection of undelivered acid-labile drugs in the dosage form, chemical degradation of drugs by intestinal enzymes, loss of bioavailability of the drugs due to their leaving the acidic environment of the stomach, and chemical degradation of the drugs due to the alkaline environment of the intestinal tract. By mitigating these problems, this invention thus further improves the efficiency of the use of these drugs.

Each of the beneficial effects enumerated above is achieved by using a formulation in which the drug is dispersed in a polymeric matrix that is water-swellable rather than merely hydrophilic, that has an erosion rate that is substantially slower than its swelling rate, and that releases the drug primarily by diffusion. It has further been found that the rate of diffusion of the drug out of the matrix can be slowed by increasing the drug particle size, by the choice of polymer used in the matrix, and/or by the choice of molecular weight of the polymer. The matrix is a relatively high molecular weight polymer that swells upon

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ingestion, preferably to a size that is at least about twice its unswelled volume, and that promotes gastric retention during the fed mode. Upon swelling, the matrix may also convert over a prolonged period of time from a glassy polymer to a polymer that is rubbery in consistency, or from a crystalline polymer to a rubbery one. The penetrating fluid then causes release of the drug in a gradual and prolonged manner by the process of solution diffusion, i.e., dissolution of the drug in the penetrating fluid and diffusion of the dissolved drug back out of the matrix. The matrix itself is solid prior to administration and, once administered, remains undissolved in (i.e., is not eroded by) the gastric fluid for a period of time sufficient to permit the majority of the drug to be released by the solution diffusion process during the fed mode. The rate-limiting factor in the release of the drug is therefore controlled diffusion of the drug from the matrix rather than erosion, dissolving or chemical decomposition of the matrix.

For highly soluble drugs, the swelling of the polymeric matrix thus achieves two objectives—(i) the tablet swells to a size large enough to cause it to be retained in the stomach during the fed mode, and (ii) it retards the rate of diffusion of the highly soluble drug long enough to provide multi-hour, controlled delivery of the drug into the stomach. For drugs that are either sparingly soluble, of limited solubility, or of high solubility, and that experience any of the specific problems enumerated above upon reaching the lower GI tract prior to absorption into the bloodstream, the swelling of the polymeric matrix (i) renders the matrix sufficiently large to cause retention in the stomach during the fed mode, and (ii) localizes the release of the drug to the stomach and small intestine so that the drug will have its full effect without colonic degradation, inactivation, or loss of bioavailability.

In either of these aspects, the invention provides an effective means of using these drugs to treat local stomach disorders as well as a wide variety of disease conditions. For example, use of this invention provides more effective eradication of ulcer-causing bacteria in the gastric mucosa with soluble antibiotics. The invention also provides enhanced absorption of soluble drugs that are absorbed mostly in the stomach or high in the gastrointestinal tract, such as metformin hydrochloride or ciprofloxacin. The invention is also useful in providing a multi-hour flow of a drug past the upper part of the small intestine (the most efficient absorption site for many agents).

Details of these and other features of the invention will be apparent from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot showing the release rate of metformin hydrochloride from three different compositions of the drug in poly(ethylene oxide) matrices.

FIG. 2 is a plot showing the release rate of captopril from a poly(ethylene oxide) matrix, in accordance with this invention, both with and without glyceryl monostearate as a solubility modifier.

FIG. 3 is a plot showing the release rate of captopril from hydroxyethyl cellulose, in which the pellet size was varied.

FIG. 4 is a plot showing the release rate of metformin hydrochloride from various polymeric matrices.

FIG. 5 is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped tablet.

FIG. 6 is a plot showing the release rate of captopril from various polymeric matrices.

FIG. 7 is a plot showing further release rate studies of metformin hydrochloride from two different polymeric matrices.

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FIG. **8** is a plot showing the release rate of vancomycin hydrochloride from different polymeric matrices.

FIG. **9** is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped tablet.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

In aspects of this invention that are directed to highly soluble drugs, the drugs thus addressed are those that are characterized by the United States Pharmacopeia XXII as at least "freely soluble" in water, i.e., drugs whose solubility is greater than one part of the drug in about ten parts of water. Drugs of particular interest are those whose solubility is greater than one part in about five parts of water, and drugs of even greater interest are those whose solubility is greater than one part in about three parts of water. The parts referred to in this paragraph and throughout this specification are parts by weight.

The term "drug" is used herein to denote any chemical compound, complex or composition that is suitable for oral administration and that has a beneficial biological effect, preferably a therapeutic effect in the treatment of a disease or abnormal physiological condition. Examples of drugs of high solubility to which this invention is applicable are metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, ticlopidine hydrochloride, amoxicillin, cefuroxime axetil, cefaclor, clindamycin, doxifluridine, tramadol, fluoxitine hydrochloride, ciprofloxacin, gancyclovir, bupropion, lisinopril, and esters of ampicillin. Examples of drugs of low solubility to which this invention is applicable are cefaclor, ciprofloxacin, saguinavir, ritonavir, nelfinavir, clarithromycin, azithiomycin, ceftazidine, cyclosporin, digoxin, paclitaxel, iron salts, topiramate, and ketoconazole. Other drugs suitable for use and meeting the solubility criteria described above will be apparent to those skilled in the art. Drugs of particular interest are metformin hydrochloride and sertraline hydrochloride. The drug loadings (weight percent of drug relative to total of drug and polymer) in most of these cases will be about 80% or less.

The invention is also of use with drugs that have been formulated to include additives that impart a small degree of hydrophobic character, to further retard the release rate of the drug into the gastric fluid. One example of such a release rate retardant is glyceryl monostearate. Other examples are fatty acids and salts of fatty acids, one example of which is sodium myristate. The quantities of these additives when present can vary; and in most cases, the weight ratio of additive to drug will range from about 1:20 to about 1:1, and preferably from about 1:8 to about 1:2.

The water-swellable polymer forming the matrix in accordance with this invention is any polymer that is non-toxic, that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of an incorporated drug. Examples of polymers suitable for use in this invention are cellulose polymers and their derivatives (such as for example, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyalkylene oxides, polyethylene glycols, chitosan, poly(vinyl alcohol), xanthan gum, maleic anhydride copolymers, poly(vinyl pyrrolidone), starch and starch-based polymers, poly (2-ethyl-2-oxazoline), poly (ethyleneimine), polyurethane hydrogels, and crosslinked

polyacrylic acids and their derivatives. Further examples are copolymers of the polymers listed in the preceding sentence, including block copolymers and grafted polymers. Specific examples of copolymers are PLURONIC® and TECTONIC®, which are polyethylene oxide-polypropylene oxide block copolymers available from BASF Corporation, Chemicals Div., Wyandotte, Mich., USA.

The terms "cellulose" and "cellulosic" are used herein to denote a linear polymer of anhydroglucose. Preferred cellulosic polymers are alkyl-substituted cellulosic polymers that ultimately dissolve in the gastrointestinal (GI) tract in a predictably delayed manner. Preferred alkyl-substituted cellulose derivatives are those substituted with alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C. Particularly preferred alkyl-substituted celluloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. A presently preferred hydroxyethylcellulose is NATRASOL® 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Del., USA.

Polyalkylene oxides of greatest utility in this invention are those having the properties described above for alkyl-substituted cellulose polymers. A particularly preferred polyalkylene oxide is poly(ethylene oxide), which term is used herein to denote a linear polymer of unsubstituted ethylene oxide. Poly(ethylene oxide) polymers having molecular weights of about 4,000,000 and higher are preferred. More preferred are those with molecular weights within the range of about 4,500,000 to about 10,000,000, and even more preferred are polymers with molecular weights within the range of about 5,000,000 to about 8,000,000. Preferred poly(ethylene oxide)s are those with a weight-average molecular weight within the range of about 1×10^5 to about 1×10^7, and preferably within the range of about 9×10^5 to about 8×10^6. Poly(ethylene oxide)s are often characterized by their viscosity in solution. For purposes of this invention, a preferred viscosity range is about 50 to about 2,000,000 centipoise for a 2% aqueous solution at 20° C. Two presently preferred poly(ethylene oxide)s are POLYOX® NF, grade WSR Coagulant, molecular weight 5 million, and grade WSR 303, molecular weight 7 million, both products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Conn., USA.

Polysaccharide gums, both natural and modified (semi-synthetic) can be used. Examples are dextran, xanthan gum, gellan gum, welan gum and rhamsan gum. Xanthan gum is preferred.

Crosslinked polyacrylic acids of greatest utility are those whose properties are the same as those described above for alkyl-substituted cellulose and polyalkylene oxide polymers. Preferred crosslinked polyacrylic acids are those with a viscosity ranging from about 4,000 to about 40,000 centipoise for a 1% aqueous solution at 25° C. Three presently preferred examples are CARBOPOL® NF grades 971P, 974P and 934P (BFGoodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, USA). Further examples are polymers known as WATER LOCK®, which are starch/acrylates/acrylamide copolymers available from Grain Processing Corporation, Muscatine, Iowa, USA.

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The hydrophilicity and water swellability of these polymers cause the drug-containing matrices to swell in size in the gastric cavity due to ingress of water in order to achieve a size that will be retained in the stomach when introduced during the fed mode. These qualities also cause the matrices to become slippery, which provides resistance to peristalsis and further promotes their retention in the stomach. The release rate of a drug from the matrix is primarily dependent upon the rate of water imbibition and the rate at which the drug dissolves and diffuses from the swollen polymer, which in turn is related to the solubility and dissolution rate of the drug, the drug particle size and the drug concentration in the matrix. Also, because these polymers dissolve very slowly in gastric fluid, the matrix maintains its physical integrity over at least a substantial period of time, in many cases at least 90% and preferably over 100% of the dosing period. The particles will then slowly dissolve or decompose. Complete dissolution or decomposition may not occur until 24 hours or more after the intended dosing period ceases, although in most cases, complete dissolution or decomposition will occur within 10 to 24 hours after the dosing period.

The amount of polymer relative to the drug can vary, depending on the drug release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will be sufficient however to retain at least about 40% of the drug within the matrix one hour after ingestion (or immersion in the gastric fluid). Preferably, the amount of polymer is such that at least 50% of the drug remains in the matrix one hour after ingestion. More preferably, at least 60%, and most preferably at least 80%, of the drug remains in the matrix one hour after ingestion. In all cases, however, the drug will be substantially all released from the matrix within about ten hours, and preferably within about eight hours, after ingestion, and the polymeric matrix will remain substantially intact until all of the drug is released. The term "substantially intact" is used herein to denote a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles.

The water-swellable polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples are cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

The benefits of this invention will be achieved over a wide range of drug loadings, with the weight ratio of drug to polymer ranging in general from 0.01:99.99 to about 80:20. Preferred loadings (expressed in terms of the weight percent of drug relative to total of drug and polymer) are those within the range of 15% to 80%, more preferably within the range of 30% to 80%, and most preferably in certain cases within the range of about 30% to 70%. For certain applications, however, the benefits will be obtained with drug loadings within the range of 0.01% to 80%, and preferably 15% to 80%.

The formulations of this invention may assume the form of particles, tablets, or particles retained in capsules. A preferred formulation consists of particles consolidated into a packed mass for ingestion, even though the packed mass will separate into individual particles after ingestion. Conventional methods can be used for consolidating the particles in this manner. For example, the particles can be placed in gelatin capsules known in the art as "hard-filled" capsules and "soft-elastic" capsules. The compositions of these capsules and procedures for filling them are known among those skilled in drug formulations and manufacture. The encapsulating material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested.

In certain embodiments of this invention, the formulation contains an additional amount of the drug applied as a quickly dissolving coating on the outside of the particle or tablet. This coating is referred to as a "loading dose" and it is included for immediate release into the recipient's bloodstream upon ingestion of the formulation without first undergoing the diffusion process that the remainder of the drug in the formulation must pass before it is released. The "loading dose" is high enough to quickly raise the blood concentration of the drug but not high enough to produce the transient overdosing that is characteristic of highly soluble drugs that are not formulated in accordance with this invention.

One presently preferred dosage form is a size 0 gelatin capsule containing either two or three pellets of drug-impregnated polymer. For two-pellet capsules, the pellets are cylindrically shaped, 6.6 or 6.7 mm (or more generally, 6.5 to 7 mm) in diameter and 9.5 or 10.25 mm (or more generally, 9 to 12 mm) in length. For three-pellet capsules, the pellets are again cylindrically shaped, 6.6 mm in diameter and 7 mm in length. For a size 00 gelatin capsule with two pellets, the pellets are cylindrical, 7.5 mm in diameter and 11.25 mm in length. For a size 00 gelatin capsule with three pellets, the pellets are cylindrical, 7.5 mm in diameter and 7.5 mm in length. Another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 10 mm in width, and 5 to 7.5 mm in height. Still another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 7.8 mm in width, and 6.2 to 7.5 mm in height. A preferred set of dimensions is 20 mm in length, 6.7 mm in width, and 6.4 mm in height. These are merely examples; the shapes and sizes can be varied considerably.

The particulate drug/polymer mixture or drug-impregnated polymer matrix can be prepared by various conventional mixing, comminution and fabrication techniques readily apparent to those skilled in the chemistry of drug formulations. Examples of such techniques are as follows:

(1) Direct compression, using appropriate punches and dies, such as those available from Elizabeth Carbide Die Company, Inc., McKeesport, Pa., USA; the punches and dies are fitted to a suitable rotary tableting press, such as the Elizabeth-Hata single-sided Hata Auto Press machine, with either 15, 18 or 22 stations, and available from Elizabeth-Hata International, Inc., North Huntington, Pa., USA;

(2) Injection or compression molding using suitable molds fitted to a compression unit, such as those available from Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio, USA.;

(3) Granulation followed by compression; and

(4) Extrusion in the form of a paste, into a mold or to an extrudate to be cut into lengths.

When particles are made by direct compression, the addition of lubricants may be helpful and sometimes important to promote powder flow and to prevent capping of the particle (breaking off of a portion of the particle) when the pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25% to 3% by weight,

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preferably less than 1% by weight, in the powder mix), and hydrogenated vegetable oil (preferably hydrogenated and refined triglycerides of stearic and palmitic acids at about 1% to 5% by weight, most preferably about 2% by weight. Additional excipients may be added to enhance powder flowability and reduce adherence.

The term "dosage form" denotes any form of the formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular drug, including both its pharmacological characteristics and its physical characteristics such as solubility, and with the characteristics of the swellable matrix such as its permeability, and the relative amounts of the drug and polymer. In most cases, the dosage form will be such that effective results will be achieved with administration no more frequently than once every eight hours or more, preferably once every twelve hours or more, and even more preferably once every twenty-four hours or more.

As indicated above, the dosage forms of the present invention find their greatest utility when administered to a subject who is in the digestive state (also referred to as the postprandial or "fed" mode). The postprandial mode is distinguishable from the interdigestive (or "fasting") mode by their distinct patterns of gastroduodenal motor activity, which determine the gastric retention or gastric transit time of the stomach contents.

In the interdigestive mode, the fasted stomach exhibits a cyclic activity called the interdigestive migrating motor complex (IMMC). The cyclic activity occurs in four phases:

Phase I is the most quiescent, lasts 45 to 60 minutes, and develops few or no contractions.

Phase II is marked by the incidence of irregular intermittent sweeping contractions that gradually increase in magnitude.

Phase III, which lasts 5 to 15 minutes, is marked by the appearance of intense bursts of peristaltic waves involving both the stomach and the small bowel.

Phase IV is a transition period of decreasing activity which lasts until the next cycle begins.

The total cycle time is approximately 90 minutes, and thus, powerful peristaltic waves sweep out the contents of the stomach every 90 minutes during the interdigestive mode. The IMMC may function as an intestinal housekeeper, sweeping swallowed saliva, gastric secretions, and debris to the small intestine and colon, preparing the upper tract for the next meal while preventing bacterial overgrowth. Pancreatic exocrine secretion of pancreatic peptide and motilin also cycle in synchrony with these motor patterns.

The postprandial or fed mode is induced by food ingestion, and begins with a rapid and profound change in the motor pattern of the upper GI tract, the change occurring over a period of 30 seconds to one minute. The stomach generates 3–4 continuous and regular contractions per minute, similar to those of the interdigestive mode but of about half the amplitude. The change occurs almost simultaneously at all sites of the GI tract, before the stomach contents have reached the distal small intestine. Liquids and small particles flow continuously from the stomach into the intestine. Contractions of the stomach result in a sieving process that allows liquids and small particles to pass through a partially open pylorus. Indigestible particles greater than the size of the pylorus are retropelled and

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retained in the stomach. Particles exceeding about 1 cm in size are thus retained in the stomach for approximately 4 to 6 hours. The dosage form of the present invention is designed to achieve the minimal size through swelling following ingestion during the fed mode.

The following examples are offered for purposes of illustration, and are not intended to limit the invention in any manner.

EXAMPLE 1

This example illustrates the controlled-release behavior of metformin hydrochloride, a highly soluble drug (whose solubility is approximately 30%), from a polymeric matrix consisting of poly(ethylene oxide). Three different dose levels were prepared—systems designed to release 90% of their drug contents at approximately 3 hours, 6 hours, and 8 hours, respectively.

Drug and polymer, with 0.5% magnesium stearate as a tableting lubricant, were compressed into pellets measuring 7.2 mm diameter×8.8 mm length and weighing 390 mg for samples designed for 3-hour and 6-hour release, and 7.4 mm diameter×8.5 mm length and weighing 380 mg for samples designed for 8-hour release, and two pellets of a given type were incorporated into a single gelatin capsule. Thus, three different types of gelatin capsule were prepared as follows:

$t_{90\%} \cong 3$ hours:	
metformin hydrochloride	250.00 mg
POLYOX ® 1105, molecular weight 900,000	138.67
magnesium stearate	1.95
Total:	390.62 mg
$t_{90\%} \cong 6$ hours:	
metformin hydrochloride	250.00 mg
POLYOX ® Coagulant, molecular weight 5,000,000	138.67
magnesium stearate	1.95
Total:	390.62 mg
$t_{90\%} \cong 8$ hours:	
metformin hydrochloride	125.00 mg
POLYOX ® 303, molecular weight 7,000,000	266.11
magnesium stearate	1.97
Total:	393.08 mg

Release rate tests on each of these three formulations were performed in modified artificial gastric fluid by the following procedure.

Dissolution was performed in a USP Apparatus 2, modified to include a stainless steel cone (⅞ inch in height and ⅞ inch in diameter at the base) at the bottom of each vessel, placed directly beneath the paddle shaft to eliminate the "dead zone" effect. A paddle speed of 60 rpm and a bath temperature of 37.4° C. were used. The gelatin capsule was opened and the individual pellets and empty gelatin capsule were dropped into the dissolution vessel containing 900 mL of modified simulated gastric fluid (7 mL of hydrochloric acid and 2 g of sodium chloride in 100 mL of deionized water; the enzyme pepsin was omitted). Once the pellets had settled to the bottom of the vessel, the paddle rotation was initiated. Samples 5 mL in size were taken at specified time points, and the sample volumes were not replaced. The samples were diluted as necessary for quantitative analysis by HPLC.

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The results are shown in FIG. **1**, where the filled diamonds represent the $t_{90\,\%} \cong 3$ formulation, the x's represent the $t_{90\,\%} \cong 6$ formulation, and the open circles represent the $t_{90\,\%} \cong 8$ formulation. The curves show that the $t_{90\,\%}$ value of the first formulation was fairly close to 3.5 hours, the $t_{90\,\%}$ value of the second formulation was fairly close to 6.0 hours, and $t_{90\%}$ value of the third formulation was fairly close to 7.5 hours.

EXAMPLE 2

This example illustrates the controlled-release behavior of captopril from a polymeric matrix consisting of poly (ethylene oxide), both with and without glyceryl monostearate (8% by weight). The formulations used were as follows:

1. Captopril		92.50 mg
Poly(ethylene oxide)(POLYOX ® 301), molecular weight 4,000,000		407.50
Total		500.00 mg
2. Captopril		92.5 mg
glyceryl monostearate		15.0
Poly(ethylene oxide)(POLYOX ® 301), molecular weight 4,000,000		392.5
Total		500.0 mg

Each formulation was compressed into a tablet measuring 6.0 mm diameter×6.7 mm length and weighing 180 mg. Release rate tests on each of the two tablets were performed in modified simulated gastric fluid by the procedure of Example 1, except that the paddle rotation speed was 30 rpm and the tablets were dropped directly into the dissolution vessel.

The results are shown in FIG. **2**, where the filled squares represent Formulation No. 1 consisting of captopril and poly(ethylene oxide) only, and the open circles represent Formulation No. 2 which further contained glyceryl monostearate.

EXAMPLE 3

This example illustrates the controlled-release behavior of captopril from a polymeric matrix of hydroxyethyl cellulose with the inclusion of glyceryl monostearate, but at varying pellet sizes. The formulation contained 19% captopril (all percents by weight) and 4.8% glyceryl monostearate in hydroxyethyl cellulose of molecular weight within the range of 1,000,000 to 1,500,000. The pellet sizes and weights were (a) 3.3 mm diameter×3.5 mm length at 35 mg (referred to herein as 3-mm tablets), (b) 4.3 mm diameter×4.9 mm length at 75 mg (referred to herein as 4-mm tablets), and (c) 6.3 mm diameter×6.5 mm length at 187 mg (referred to herein as 6-mm tablets).

Release rate tests on each of the three tablet sizes (fifteen of the 3-mm tablets, seven of the 4-mm tablets, and three of the 6-mm tablets) were performed using the procedures of Example 1, except that a weighted watchglass was used in place of the stainless steel cone, and analyses of the samples were performed by UV/Vis. The results are shown in FIG. **3**, where the filled squares represent the 3-mm pellets, the filled triangles the 4-mm pellets, and the filled circles the 6-mm pellets. This demonstrates the variation of pellet size as a further means of varying the release pattern, the larger pellets having less surface area.

EXAMPLE 4

This example further illustrates the controlled release of metformin hydrochloride, using a higher drug loading, and

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various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **4** where the results are plotted, were as follows (all percentages are by weight):

Filled circles: 79.6% metformin HCl; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.04 mm diameter×9.48 mm length; containing approximately 478 mg metformin HCl.

Filled squares: 79.6% metformin HCl; 20% xanthan gum (KELTROL® F, Kelco, Div. of Merck & Co., Inc., San Diego, Calif., USA); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.40 mm length; containing approximately 483 mg metformin HCl.

Plus signs: 79.6% metformin HCl; 20% hydroxypropylmethyl cellulose (BENECEL® 824, Aqualon Co., Wilmington, Del., USA), viscosity (2%, 20° C.) 11,000 to 15,000 cps; 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.49 mm length; containing approximately 480 mg metformin HCl.

Open diamonds: 79.6% metformin HCl; 5% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 15% poly(ethylene oxide (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter×9.60 mm length; containing approximately 480 mg metformin HCl.

x's: 79.6% metformin HCl, 18.05% xanthan gum (KELTROL®F); 1.99% WATER LOCK® D-223 (starch graft poly(2-propenamide-co-2-propenoic acid)), mixed sodium and aluminum salts, Grain Processing Corporation, Muscatine, Iowa, USA); 0.4% magnesium stearate. Pellet dimensions were 6.06 mm diameter×9.24 mm length; containing approximately 476 mg metformin HCl total.

EXAMPLE 5

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. **5**. The formulation was as follows (all percentages are by weight): 64% metformin HCl; 35.5% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pa., USA). The tablet dimensions were 6.48 mm diameter×7.20 mm height×19.21 mm length, and contained approximately 506 mg metformin HCl per tablet.

EXAMPLE 6

This example further illustrates the controlled release of captopril, using various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. **6** where the results are plotted, were as follows (all percentages are by weight):

Plus signs: 80% captopril; 20% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20° C.) 11,000 to 15,000 cps). Pellet dimensions: 6.03 mm diameter×9.25 mm length, 2 pellets weighing 293 mg each, containing approximately 469 mg captopril total.

Filled diamonds: 80% captopril; 20% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter× 9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

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Filled triangles: 80% captopril; 20% hydroxyethyl cellulose (250HX, molecular weight 1,000,000). Pellet dimensions: 6.03 mm diameter×9.53 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Open circles: 80% captopril; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter×9.59 mm length, 2 pellets weighing 301 mg each, containing approximately 482 mg captopril total.

Filled squares: 80% captopril; 20% carboxymethyl cellulose (12M31P, molecular weight 250,000). Pellet dimensions: 6.04 mm diameter×9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 478 mg captopril total.

Open triangles: 79.93% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.04% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter×9.26 mm length, 2 pellets weighing 296 mg each, containing approximately 473 mg captopril total.

x's: 79.96% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.01% poly (ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter×9.41 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

Dashes: 80% captopril; 10% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20° C.) 11,000 to 15,000 cps). Pellet dimensions: 6.04 mm diameter×9.41 mm length, 2 pellets weighing 298 mg each, containing approximately 477 mg captopril total.

Open diamonds: 79.96% captopril; 18.05% xanthan gum (KELTROL® F); 1.99% WATERLOCK® D-223. Pellet dimensions: 6.04 mm diameter® 9.16 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

EXAMPLE 7

This example presents further data on metformin hydrochloride formulations, illustrating the effect of lower drug loadings than those used in the preceding examples. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 7 where the results are plotted, were as follows (all percentages are by weight):

Filled squares: 32.5% metformin HCl; 67% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions 6.62 mm diameter×10.40 mm length, 2 pellets weighing 400 mg each, containing approximately 260 mg metformin HCl total.

Open circles: 32.5% metformin HCl; 67% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions 6.65 mm diameter×9.28 mm length; 2 pellets weighing 401 mg each, containing approximately 261 mg metformin HCl total.

EXAMPLE 8

This example illustrates the sustained release of vancomycin hydrochloride from various polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 8 where the results are plotted, were as follows (all percentages are by weight):

Open squares: 31.5% vancomycin hydrochloride; 68% poly (ethylene oxide) (POLYOX® 303, molecular weight

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7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.23 mm length, 2 pellets weighing 403 mg each, containing approximately 254 mg vancomycin hydrochloride total.

Open triangles: 31.5% vancomycin hydrochloride; 68% poly(ethylene oxide) (POLYOX® 301, molecular weight 4,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.28 mm length, 2 pellets weighing 402 mg each, containing approximately 253 mg vancomycin hydrochloride total.

x's: 31.5% vancomycin hydrochloride; 68% hydroxypropyl methylcellulose (BENECEL® 824, viscosity 11,000–15,000 cps (2% solution at 20° C.)); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter×10.10 mm length, 2 pellets weighing 405 mg each, containing approximately 255 mg vancomycin hydrochloride total.

Open circles: 31.5% vancomycin hydrochloride; 68% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions: 6.62 mm diameter×9.77 mm length, 2 pellets weighing 401 mg each, containing approximately 253 mg vancomycin hydrochloride total.

Filled squares: 62.5% vancomycin hydrochloride; 37% poly (ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.60 mm diameter×10.01 mm length, 2 pellets weighing 409 mg each, containing approximately 511 mg vancomycin hydrochloride total.

In the prior art, vancomycin and its salts are administered by injection, due to poor absorption when administered orally. By providing for all or at least a portion of the total administered amount to be delivered by controlled delivery in the gastric retentive system of this invention, that portion so delivered is directed to the proximal portion of the small intestine, the most efficient site for absorption of this drug, resulting in an enhanced absorption from the oral dosage form of the invention.

EXAMPLE 9

This example illustrates the difference between subjects in the fed mode and subjects not in the fed mode in terms of the gastric retention of tablets of various sizes administered orally. Both Beagle dogs and human subjects were used.

Barium-containing tablets for oral administration were prepared from the following ingredients:

25%	Barium Sulfate
30%	PolyOx 303 (average molecular weight 7,000,000)
44.5%	Hydroxypropylcellulose
0.5%	Magnesium Stearate

For tests on Beagle dogs, 400-mg tablets measuring 5.8 mm diameter×5.1 mm height×15.4 mm length were prepared in a tablet press at 2,500 psi pressure, and 800-mg tablets measuring 7.9 mm diameter×5.6 mm height×19.1 mm length were prepared in a tablet press at 5,000 psi. Four beagle dogs were used, and the location of the tablets in the GI tract was followed using fluoroscopy. Two studies were initiated with the dogs. In the first study, each dog received two tablets (one 400-mg and one 800-mg) with a small amount of water after a 16-hour fast. In the second study, each dog received two tablets (one 400-mg and one 800-mg) thirty minutes after ingesting 50 grams of a standard meal. The location of the tablets (in or out of the stomach) was monitored every 30 minutes with the fluoroscope.

The fluoroscopy revealed that tablets that were administered while the dogs were in the fasted condition were

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emptied from the dogs' stomachs within 90 minutes: in two of the dogs, the stomachs contained no barium tablets at 30 minutes, in a third this was true at 60 minutes, and in the fourth at 90 minutes. Tablets that were administered while the dogs were in the fed state remained in the dogs' stomach for between 4 and 5 hours.

Human tests were performed on ten normal adults of both sexes, each taking part in two trials, the first after fasting and the second after a bacon and egg breakfast of approximately 1,500 calories. The tablets used in the tests had the same composition as those used for the Beagle dogs and measured either 4 mm×4 mm or 6 mm×6 mm. The subjects were X-rayed at 30 minutes and at 1, 2, 4, 6, 8, 10, and approximately 12 hours after ingesting the tablets. In some subjects, visualization was achieved by ultrasound rather than X-rays.

Imaging revealed that in the fasted trials, the tablets left the stomach in 30 minutes to one hour after administration. In the fed trials, the tablets demonstrated multiple-hour retention in the stomach in all subjects, 80% of the contents of all tablets being retained at 4 hours. Five of the ten subjects retained the tablets for 6 hours or more, and four of these five retained them for ten hours or more.

EXAMPLE 10

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. **9**. The formulation was as follows (all percentages are by weight): 48.5% metformin HCl; 49% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pa., USA). The tablet dimensions were 9.66 mm diameter×6.95 mm height×19.24 mm length, and contained approximately 506 mg metformin HCl per tablet.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that the components, additives, proportions, methods of formulation, and other parameters of the invention can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

What is claimed is:

1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 15:85 to 80:20, said dosage form being one that when swollen in a dimensionally unrestricted manner as a result of imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug after such immersion, and that remains substantially intact until substantially all of said drug is released.

2. A dosage form in accordance with claim **1** in which the solubility of said drug in water is greater than one part by weight of said drug in five parts by weight of water.

3. A dosage form in accordance with claim **1** in which said drug is a member selected from the group consisting of metformin hydrochloride, vancomycin hydrochloride,

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captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, tramadol and ticlopidine hydrochloride.

4. A dosage form in accordance with claim **1** in which said drug is metformin hydrochloride.

5. A dosage form in accordance with claim **1** in which said drug is sertraline hydrochloride.

6. A dosage form in accordance with claim **1** in which said drug is captopril.

7. A dosage form in accordance with claim **1** in which said drug is vancomycin hydrochloride.

8. A dosage form in accordance with claim **1** in which said polymeric matrix is formed of a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

9. A dosage form in accordance with claim **8** in which said alkyl-substituted celluloses are members selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

10. A dosage form in accordance with claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight of at least about 4,000,000.

11. A dosage form in accordance with claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 4,500,000 to about 10,000,000.

12. A dosage form in accordance with claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 5,000,000 to about 8,000,000.

13. A dosage form in accordance with claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said drug one hour after such immersion.

14. A dosage form in accordance with claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said drug one hour after such immersion.

15. A dosage form in accordance with claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 80% of said drug one hour after such immersion.

16. A dosage form in accordance with claim **1** further comprising a member selected from the group consisting of glyceryl monostearate and sodium myristate, formulated with said drug to further retard the release of said drug to said gastric fluid.

17. A dosage form in accordance with claim **1** in which said polymeric matrix consists of two cylindrical tablets, each measuring about 9 mm to about 12 mm in length and about 6.5 mm to about 7 mm in diameter.

18. A dosage form in accordance with claim **1** in which said polymeric matrix consists of a single elongated tablet measuring about 18 mm to about 22 mm in length, about 6.5 mm to about 7.8 mm in width, and about 6.2 to 7.5 mm in height.

19. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also capable of altering intestinal flora in a manner detrimental to the health of said subject, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

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    (a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

    (b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

    (c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

    (d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal flora.

    20. A method in accordance with claim **19** in which said drug is a member selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, clindamycin, clarithromycin, azithromycin, ceftazidine, and ciprofloxacin.

    21. A method in accordance with claim **19** in which said drug is a highly soluble drug selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, and clindamycin.

    22. A method of treating a subject suffering from infections selected from the group consisting of pneumonia, sinus bacterial infections, topical bacterial infections and staphylococcus infections, by administering to said subject a drug which is a member selected from the group consisting of amoxicillin, cefuroxime axetil, cefaclor, clindamycin, clarithromycin, azithromycin, and ceftazidine, without substantially causing side effects resulting from the alteration of the intestinal flora of said subject, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

    (a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

    (b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

    (c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

    (d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal flora.

    23. A method in accordance with claim **22** in which said drug is a highly soluble drug selected from the group consisting of amoxiillin, cefuroxime axetil, cefaclor, and clindamycin.

    24. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable by colonic bacterial enzymes residing in lower gastrointestinal tract enterocytes, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage

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form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

    (a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

    (b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

    (c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

    (d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said intestinal enzymes and said drug transporters.

    25. A method in accordance with claim **24** in which said drug is a member selected from the group consisting of cyclosporine, digoxin, and doxifluridine.

    26. A method in accordance with claim **24** in which said drug is doxifluridine.

    27. A method of treating a subject undergoing an organ transplant to suppress an immune response to said transplant, by administering cyclosporine to said subject without substantial degradation of said cyclosporine by colonic bacterial enzymes residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said cyclosporine while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said cyclosporine incorporated therein at a weight ratio of cyclosporine to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

    (a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

    (b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

    (c) retains at least about 40% of said cyclosporine one hour after such immersion in gastric fluid, and

    (d) releases substantially all of said cyclosporine within about ten hours after such immersion,

thereby extending the release rate of said cyclosporine with time during said fed mode while releasing substantially all of said cyclosporine within said stomach and substantially avoiding contact of said cyclosporine with said colonic bacterial enzymes.

    28. A method of treating a subject for heart disease by administering digoxin to said subject without substantial degradation of said digoxin by colonic bacterial enzymes residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said digoxin while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said digoxin incorporated therein at a weight ratio of digoxin to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

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(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said digoxin one hour after such immersion in gastric fluid, and

(d) releases substantially all of said digoxin within about ten hours after such immersion,

thereby extending the release rate of said digoxin with time during said fed mode while releasing substantially all of said digoxin within said stomach and substantially avoiding contact of said digoxin with said colonic bacterial enzymes.

29. A method of treating a subject suffering from a condition selected from the group consisting of ovarian cancer, colorectal cancer, gastric cancer, renal cancer, and breast cancer, by administering doxifluridine to said subject without substantial degradation of said doxifluridine by intestinal enzymes or substantial inactivation of said doxifluridine by drug transporters residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said doxifluridine while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said doxifluridine incorporated therein at a weight ratio of doxifluridine to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said doxifluridine one hour after such immersion in gastric fluid, and

(d) releases substantially all of said doxifluridine within about ten hours after such immersion,

thereby extending the release rate of said doxifluridine with time during said fed mode while releasing substantially all of said doxifluridine within said stomach and substantially avoiding contact of said doxifluridine with said enzymes.

30. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also susceptible to inactivation by drug transporters residing in lower gastrointestinal tract enterocytes, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form one or more polymers forming comprising a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

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(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach and substantially avoiding contact of said drug with said drug transporters.

31. A method in accordance with claim 30 in which said drug is a member selected from the group consisting of cyclosporine and paclitaxel.

32. A method of treating a subject undergoing an organ transplant to suppress an immune response to said transplant, by administering cyclosporine to said subject without substantial inactivation of said cyclosporine by p-glycoprotein in the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said cyclosporine while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said cyclosporine incorporated therein at a weight ratio of cyclosporine to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said cyclosporine one hour after such immersion in gastric fluid, and

(d) releases substantially all of said cyclosporine within about ten hours after such immersion,

thereby extending the release rate of said cyclosporine with time during said fed mode while releasing substantially all of said cyclosporine within said stomach and substantially avoiding inactivation of said cyclosporine by p-glycoprotein in said lower gastrointestinal tract.

33. A method of treating a subject suffering from cancer by administering paclitaxel to said subject without substantial inactivation of said paclitaxel by p-glycoprotein in the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said paclitaxel while said subject is in a fed mode, said dosage form comprising a one or more polymers forming solid polymeric matrix with said paclitaxel incorporated therein at a weight ratio of paclitaxel to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said paclitaxel one hour after such immersion in gastric fluid, and

(d) releases substantially all of said paclitaxel within about ten hours after such immersion,

thereby extending the release rate of said paclitaxel with time during said fed mode while releasing substantially all of said paclitaxel within said stomach and substantially avoiding inactivation of said paclitaxel by p-glycoprotein in said lower gastrointestinal tract.

34. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach

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and whose bioavailability is substantially greater in an acidic environment than an alkaline environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

35. A method in accordance with claim 34 in which said drug is a member selected from the group consisting of esters of ampicillin, iron salts, digoxin, and ketoconazole.

36. A method in accordance with claim 34 in which said drug is a member selected from the group consisting of esters of ampicillin.

37. A method of treating a subject suffering from a bacterial infection by administering an ester of ampicillin to said subject while maintaining maximum bioavailability of said ester of ampicillin, said method comprising orally administering to said subject a dosage form of said ester of ampicillin while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said ester of ampicillin incorporated therein at a weight ratio of said ester of ampicillin to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said ester of ampicillin one hour after such immersion in gastric fluid, and

(d) releases substantially all of said ester of ampicillin within about ten hours after such immersion,

thereby extending the release rate of said ester of ampicillin with time during said fed mode while releasing substantially all of said ester of ampicillin within said stomach and maintaining said ester of ampicillin in the acidic environment of said stomach during said release.

38. A method of treating a subject suffering from anemia by administering iron salts to said subject while maintaining maximum bioavailability of said iron salts, said method comprising orally administering to said subject a dosage form of said iron salts while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said iron salts incorporated therein at a weight ratio of iron salts to polymer of from

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about 0.01:99.99 to about 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said iron salts one hour after such immersion in gastric fluid, and

(d) releases substantially all of said iron salts within about ten hours after such immersion,

thereby extending the release rate of said iron salts with time during said fed mode while releasing substantially all of said iron salts within said stomach where said iron salts are maintained in an acidic environment.

39. A method of treating a subject suffering from a systemic fungal infection by administering ketoconazole to said subject while maintaining maximum bioavailability of said ketoconazole, said method comprising orally administering to said subject a dosage form of said ketoconazole while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said ketoconazole incorporated therein at a weight ratio of ketoconazole to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said ketoconazole one hour after such immersion in gastric fluid, and

(d) releases substantially all of said ketoconazole within about ten hours after such immersion,

thereby extending the release rate of said ketoconazole with time during said fed mode while releasing substantially all of said ketoconazole within said stomach where said ketoconazole is maintained in an acidic environment.

40. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable in an alkaline environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix in which said drug is incorporated at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

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thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

41. A method in accordance with claim **40** in which said drug is nelfinar mesylate.

42. A method of treating a subject infected with human immunodeficiency virus by administering nelfinar mesylate to said subject without substantial degradation of said nelfinar mesylate by intestinal flora or substantial inactivation of said nelfinar mesylate by drug transporters residing in enterocytes of the lower gastrointestinal tract, said method comprising orally administering to said subject a dosage form of said nelfinar mesylate while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said nelfinar mesylate incorporated therein at a weight ratio of nelfinar mesylate to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said nelfinar mesylate into gastric fluid by the dissolving of said nelfinar mesylate by said gastric fluid and either erosion of said matrix or diffusion of said dissolved nelfinar mesylate out of said matrix,

(c) retains at least about 40% of said nelfinar mesylate one hour after such immersion in gastric fluid, and

(d) releases substantially all of said nelfinar mesylate within about ten hours after such immersion,

thereby extending the release rate of said nelfinar mesylate with time during said fed mode while releasing substantially all of said nelfinar mesylate within said stomach where said nelfinar mesylate is maintained in an acidic environment.

43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(d) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

44. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach but also degradable in an acidic environment, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said

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dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,

(c) protects any unreleased drug in said matrix from said gastric fluid,

(d) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and

(e) releases substantially all of said drug within about ten hours after such immersion,

thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

45. A dosage form in accordance with claim **1** in which said dosage form releases substantially all of said drug within about ten hours after immersion in gastric fluid.

46. A dosage form in accordance with claim **1** in which said dosage form releases substantially all of said drug within about eight hours after immersion in gastric fluid.

47. A dosage form in accordance with claim **4** in which said polymeric matrix comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

48. A dosage form in accordance with claim **4** in which said polymeric matrix comprises an alkyl-substituted cellulose.

49. A dosage form in accordance with claim **4** in which said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

50. A dosage form in accordance with claim **4** in which said polymeric matrix comprises hydroxypropylmethyl-cellulose.

51. A dosage form in accordance with claim **4** in which said polymeric matrix comprises hydroxypropylmethyl-cellulose having a viscosity ranging from 11,000 to 110,000 centipoise as measured in a 2% solution at 20° C.

52. A dosage form in accordance with claim **4** in which said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said metformin hydrochloride one hour after such immersion.

53. A dosage form in accordance with claim **4** in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

54. A dosage form in accordance with claim **4** in which said polymeric matrix comprises poly(ethylene oxide) having a molecular weight of at least about 4,000,000.

55. A dosage form in accordance with claim **4** in which said polymeric matrix comprises poly(ethylene oxide) having a molecular weight ranging from about 4,500,000 to about 10,000,000.

56. A dosage form in accordance with claim **4** in which said polymeric matrix comprises poly(ethylene oxide) hav-

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ing a molecular weight ranging from about 5,000,000 to about 8,000,000.

57. A dosage form in accordance with claim 1 in which said drug is ciprofloxacin.

58. A dosage form in accordance with claim 57 in which said polymeric matrix comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

59. A dosage form in accordance with claim 57 in which said polymeric matrix comprises an alkyl-substituted cellulose.

60. A dosage form in accordance with claim 57 in which said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

61. A dosage form in accordance with claim 57 in which said polymeric matrix comprises hydroxypropylmethyl-cellulose.

62. A dosage form in accordance with claim 57 in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

63. A dosage form in accordance with claim 57 in which said polymeric matrix comprises poly(ethylene oxide).

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64. A dosage form in accordance with claim 1 in which said drug is an iron salt.

65. A dosage form in accordance with claim 64 in which said polymeric matrix comprises a polymer selected from the group consisting of poly(ethylene oxide), cellulose, alkyl-substituted celluloses, crosslinked polyacrylic acids, and xanthan gum.

66. A dosage form in accordance with claim 64 in which said polymeric matrix comprises an alkyl-substituted cellulose.

67. A dosage form in accordance with claim 64 in which said polymeric matrix comprises an alkyl-substituted cellulose selected from the group consisting of hydroxymethyl-cellulose, hydroxyethyl-cellulose, hydroxypropyl-cellulose, hydroxypropylmethyl-cellulose, and carboxymethyl-cellulose.

68. A dosage form in accordance with claim 64 in which said polymeric matrix comprises hydroxypropylmethyl-cellulose.

69. A dosage form in accordance with claim 64 in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said metformin hydrochloride one hour after such immersion.

70. A dosage form in accordance with claim 64 in which said polymeric matrix comprises poly(ethylene oxide).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.   : 6,635,280 B2   Page 1 of 1
DATED   : October 21, 2003
INVENTOR(S)   : John W. Shell et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:
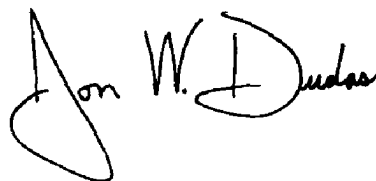
Column 27,
Line 24, delete "metformin hydrochloride", and insert -- ciprofloxacin --

Column 28,
Line 22, delete "metformin hydrochloride", and insert -- iron salts --

Signed and Sealed this

Twenty-second Day of June, 2004

JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

EXHIBIT 3

FDA U.S. Food and Drug Administration

PURDUE PHARMA L.P.

RESEARCH & DEVELOPMENT

September 24, 2009

FDA Advisory Committee Briefing Document on NDA 22-272 (reformulated OxyContin® tablets)

Summary of Briefing Document

Summary of Briefing Document

Context

OxyContin® (oxycodone HCl controlled-release, referred to as "OxyContin" through out this document) was approved by the FDA in 1995 for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. Despite bringing important benefits to patients, problems with misuse, abuse and diversion of OxyContin began to emerge in the late 1990s, sometimes with fatal consequences in both knowledgeable addicts and recreational abusers. The current OxyContin formulation has specific unforeseen vulnerabilities that allow the product to be converted easily and rapidly (e.g., between two spoons or under a coffee mug) into an essentially immediate-release form that can be ingested via multiple routes. To mitigate this problem, Purdue began development of a modified-release, single-entity, reformulation of OxyContin that is bioequivalent to the current formulation but contains a different inert excipient (polyethylene oxide).

Purdue submitted an NDA for this therapeutically equivalent reformulation of OxyContin to FDA on November 29, 2007 (referred to as "reformulated OxyContin" and "the reformulation" throughout this document). Specific elements of the original NDA 22-272 were discussed on May 5, 2008 at a combined meeting of the Anesthetic Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committees. On October 3, 2008 Purdue received a Complete Response Letter from FDA that contained requests for specific additional physicochemical testing of the reformulated tablets. On March 30, 2009 Purdue submitted these additional data to FDA. This NDA is an application for a bioequivalent reformulation of OxyContin without any request for label claims regarding the potential benefits of the   formulation   accidental misuse or abuse.

Purpose of this document

This document serves to brief members of the CDER Anesthetic Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in advance of the September 24, 2009 joint meeting on reformulated OxyContin. This meeting will be the second Advisory Committee meeting on reformulated OxyContin, and will focus on

considering whether the *in vitro* data in the March 30, 2009 NDA resubmission are sufficient to satisfy the concerns raised in FDA's October 3 2008 Complete Response Letter. Based upon guidance from FDA the scope of this document is restricted to presentation of *in vitro* data that demonstrate the physicochemical differences between the current and reformulated OxyContin tablets. Risk evaluation and mitigation strategies (REMS) for this product are not included in this document as this topic is the subject of a separate discussion with FDA.

Overview of *in vitro* experimental studies

Purdue consulted independent experts in drug abuse and tablet tampering (see **Appendix I**) to guide and supervise the design, execution, analysis and interpretation of the new *in vitro* testing program. In designing these experiments, our goals were to

- First, evaluate the performance of the reformulation in response to various forms of physical and chemical manipulation to identify the incremental improvements it offers, and

- Second, confirm that   than the current formulation under any anticipated abuser tablet manipulation scenarios.

The experimental protocols assessed both the performance and limitations of this reformulation   . These protocols encompass seven groups of studies (represented below as Studies 1 – 7) that collectively test a wide range of anticipated abuser manipulations that require different amounts of time and effort input. They   to ensure consistency and reproducibility of results. The vast majority of the experiments were performed by contracted independent third party vendors. Personnel performing the experiments were blinded to the extent possible. The scientific rigor and scale of these *in vitro* studies maps the terrain of the potential outcomes of abuse and misuse to an unprecedented level. The availability of these data in turn enables future hypothesis-driven risk evaluation and mitigation strategies.

Study 1: ▮▮▮▮▮ (b) (4)**Fractionation of Tablets**

This study was designed to survey the number of techniques that could be employed to mechanically alter OxyContin formulations. The goal of these experiments was to broadly identify and characterize for the purposes of standardization of experiments, the methods and outputs that could be used for further physicochemical testing.

Tablets of reformulated OxyContin were more resistant to physical crushing techniques to reduce particle size than current OxyContin tablets, ▮▮▮ (b) (4) ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ (b) (4) These tablets could ▮▮▮▮ when significantly more time or effort ▮▮ necessary to crush OxyContin was applied. Different particle size ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ tablets were crushed in batch and a sieving technique was employed. We were successful in defining and reproducibly ▮▮▮▮▮ (b) (4) spanning the full range of reformulated OxyContin particle sizes achievable ▮▮▮▮▮▮ :

- Band 1 = ▮▮▮▮▮
- Band 2 = ▮▮▮▮▮
- Band 3 = ▮▮▮
- Band 4 = ▮▮▮▮▮
- Band 5 = ▮▮▮▮
- Band 6 = ▮▮▮▮
- Band 7 = core powder containing oxycodone active pharmaceutical ingredient (API) and excipient ▮▮▮▮▮ ▮▮ ▮▮▮▮▮ (used as control)

Study 2: Extraction in ▮▮▮▮▮▮▮▮▮
Solutions

This study was designed to evaluate the oxycodone API release characteristics of reformulated OxyContin after small volume extraction in ▮▮▮▮▮▮▮▮▮ solutions. The goal was to determine and compare the API release kinetics for OxyContin and

reformulated OxyContin using a wide variety of solvents on a range of particle bands   (b) (4)

Experiments were performed at   (b) (4) and   (b) (4)

API release profiles for all strengths and bracketed bands 1, 4 and 6 of

) was not faster than for crushed OxyContin when carried out a   (b) (4)

the reformulation's API release profile approached that of crushed OxyContin, but was never faster.

. Overall, even the finest particle size bands of reformulated OxyContin did not release oxycodone into solution as rapidly as similarly sized particles of current formulation OxyContin tablets at room temperature.

Study 3: Dissolution in Ethanol

This study was designed to compare the performance of OxyContin and reformulated OxyContin in dissolution experiments conducted with

. The goal was to determine if and characterize how the dissolution profiles for API release differed in (b) (4)

$f2$ similarity values (50-100 concordant, <50 discordant), calculated from the mean of 6 replicate analyses, for dissolution profiles (all bands of all strengths) in   as compared to dissolution profiles in (b) (4). The values for reformulated OxyContin ranged from 29-64, while for OxyContin the values were 96, 67, and 84. For reformulated OxyContin, 12 of the 42 $f2$ values were within the 50-100. The remaining 30 $f2$ values were below 50, indicating dissimilarity. Reformulated OxyContin dissolution rates in   were slower than those seen in   (b) (4) in 28 of these 30 cases. For the remaining two discordant cases, aberrant data points at 10 minute sampling time point likely contributed to skewing of the results. The overall kinetic results show similarity of the results. Overall the API

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release kinetics of reformulated OxyContin in   (b) (4)   solution was similar to those of (b) (4) alone.

Study 4: Extraction in Advanced Solvents

This study was designed to evaluate the oxycodone API release characteristics of reformulated OxyContin after small volume extraction in   (b) (4)   The goal was to determine and compare the API release kinetics for OxyContin and reformulated   for a range of particle bands.

Three particle size bands (bands 1, 4 and 6) were tested to bracket the full range of sizes by including intact tablets, medium and fine particles.

Intact reformulated tablets maintained controlled-release properties (b) (4)   (b) (4)   and up to   (b) (4) in   Smaller particles in the (b) (4) range maintained some controlled-release in   (75% API release as compared to >90% release with crushed OxyContin), while both bands 4 and 6 (b) (4) maintain controlled-release   up   (b) (4) . API release for crushed OxyContin reaches   (b) (4)   . Repeating these experiments at   (b) (4) temperatures did not significantly alter the API release rates as compared to experiments performed at   (b) (4) for all bands studied.   was not an effective extraction solvent for reformulated or crushed current OxyContin at either   (b) (4)   (The maximum API release seen at any time point was observed with   and crushed current OxyContin at   which were measured at 29% and 23%, respectively.

Study 5: Syringability, Injectability and Extraction after Vaporization

These experiments were designed to simulate preparation for intentional misuse and abuse via intravenous and inhalation consumption. The goal of these experiments were 1) to determine how much API could be loaded and delivered via a syringe for intravenous abuse 2) to determine how much API was released after vaporization of the product.

The ability to aspirate or inject solutions of reformulated OxyContin powder was dependent on the   could not

be aspirated or expelled from a syringe, while ███████████ (b) (4) were syringable and injectable using an ████ (b) (4). The amount of API that was syringable via an ████████████ (b) (4)

(b) (4) ████████ Overall although by using (b) (4) ██████████ it was feasible to syringe or inject the material, the amount of API recovered was low and the █████████████████████, as compared to similar sample preps for OxyContin. To assess the feasibility of smoking reformulated OxyContin a ███████████ (b (b) (4) █████████████████ Simulated smoking of all strengths of reformulated OxyContin resulted in ████████ (b) (4) ██████ (b) (4) ████ (b) (4) ███████████

██████████████ Vaporization of API from reformulated OxyContin was ineffiecient. ████

Study 6: ████████████████████████████████

██████████████████████████████████████

██

Study 7: Complex Extraction with Advanced Solvents Using Liquid Phase Extraction

(b) (4)

Conclusions

Using input from FDA, the Advisory Committee and numerous experts in methods of abuse and extraction of API from pharmaceutical products, Purdue conducted seven *in vitro* studies designed to evaluate the ▨▨▨▨▨▨▨▨▨▨▨ of the reformulated tablets under a range of known and anticipated "real world" ▨▨▨▨▨▨▨ employed inadvertently by patients or well intentioned caregivers or intentionally in the setting of purposeful misuse and abuse.

These experimental results suggest that the reformulated tablets

- were superior (less susceptible to tablet manipulation) to the currently marketed formulation in many dimensions tested

- were not more susceptible to tablet manipulation than current OxyContin under any testing condition

- will be ⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4)
- will be ⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4)
⬛⬛⬛⬛⬛⬛ (b) (4)
- will be ⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4)
- will yield ⬛⬛⬛⬛ (b) (4)

Further, despite extensive testing under extreme conditions, no unexpected vulnerabilities relative to current OxyContin were identified.

In conclusion, the strengths of this reformulation relative to marketed OxyContin represent an important incremental improvement against actions ⬛⬛⬛⬛⬛⬛ (b) (4). This suggests that the reformulated tablets will be safer for patients in the context of inadvertent misuse and potentially less attractive for abuse. These data together with data demonstrating bioequivalence to the current formulation of OxyContin are sufficient to support approval of this reformulated product

Main Body of Briefing Document

Table of Contents

Introduction

This purpose of this document is to brief members the CDER Anesthetic Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in advance of the September 24, 2009 joint hearing on reformulated OxyContin. This report describes experimental work conducted in support of the March 30, 2009 NDA resubmission for reformulated OxyContin. The scope of this document was defined based upon guidance by FDA on June 2009 for Purdue to focus on presenting *in vitro* data to demonstrating the differences in physicochemical properties between the current and reformulated OxyContin.

The body of work described here (and included in the resubmission of NDA 22-272 to the FDA on March 30, 2009) updates the previous *in vitro* testing work performed by Purdue that was submitted with the original NDA 22-272 on November 29, 2007 and presented at the May 5, 2008 Advisory Committee meeting. Design of these studies was heavily influenced by the input provided from the members of the Advisory Committee, experts we have consulted, as well as recommendations from the FDA in both the October 3, 2008 Complete Response Letter and in a closed meeting on January 21, 2009.

This document is broken into several sections:

- An introduction to frame the context of the work described

- A short section describing the polyethylene oxide inert excipient in reformulated OxyContin

- Seven lengthy scientific sections covering the experimental design, results discussion of *in vitro* studies conducted

- A short section containing supplementary information on data summarizing evidence for bioequivalence, risk mitigation and the contents of the NDA 22-272 resubmission

- Discussion and conclusions, including Purdue's interpretation of results, the limitations of the experimental design and outcomes

- Glossary of terms

Three appendices accompany this document summarizing experts consulted (**Appendix I**), more detailed *in vitro* experimental methodology (**Appendix II**), and an introduction to the *in vitro* studies prepared by one of the experts who helped design and analyze the studies, Dr. Edward Cone (**Appendix III**).

The current formulation of OxyContin is referred to as "OxyContin" and the reformulated version of OxyContin is referred to as "reformulated OxyContin" and "the reformulation" throughout this document.

Developing Reformulated OxyContin

HISTORY OF OXYCONTIN

OxyContin® (oxycodone HCl controlled-release) tablets are a proprietary controlled-release oral formulation containing oxycodone as the active pharmaceutical ingredient (API). FDA approved OxyContin in1995 for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. Despite bringing important benefits to patients, problems with misuse, abuse and diversion of OxyContin began to emerge in the late 1990s, sometimes with fatal consequences to both knowledgeable addicts and recreational abusers. Inadvertent misuse by legitimate patients (medication error) and well intentioned caregivers has also occurred after chewing or crushing OxyContin tablets. The current OxyContin formulation has specific vulnerabilities that allow the product to be converted easily and rapidly (e.g., between two spoons or under a coffee mug) into an essentially immediate-release form that can be ingested via multiple routes.

EARLY DEVELOPMENT OF OXYCONTIN

Purdue evaluated several reformulation strategies for OxyContin to mitigate this problem, including different excipient matrices, novel melt extrusion multi-particulate combinations, direct compression mechanisms and inclusion of non-therapeutic active ingredient (bioavailable or not, sequestered or not). Ultimately we chose to pursue development of a modified-release, single-entity reformulation of OxyContin that bioequivalent

to the current formulation but contains a different inert excipient

(b) (4)

REFORMULATED OXYCONTIN'S EXCIPIENT: (b) (4)

(b) (4)

Reformulated OxyContin uses cured (b) (4) as a platform to manufacture tablets that retain their intended therapeutic properties while (b) (4). When hydrated, (b) (4) (b) (4) e forms a (b) (4) that retards dissolution of the API from intact, crushed, cut or ground tablets. (b) (4) levels in reformulated OxyContin range from ~108-168 mg per tablet depending on the oxycodone tablet strength (see **Table 0.1**).

Table 0.1 (b) (4) **to API ratios for all strengths of reformulated OxyContin**

Tablet strength (mg API)	Excipient (mg (b) (4))	(b) (4):API Ratio
10	138.5 mg	13.9
15	133.5 mg	8.9
20	128.5 mg	6.4
30	118.5 mg	4.0
40	108.5 mg	2.7
60	162.5 mg	2.7
80	167.5 mg	2.1

(b) (4) is included in the FDA inactive ingredient guide for oral controlled release tablets, extended release tablets, sustained release tablets and film coated sustained release tablets. The maximum amounts of (b) (4) content (57.9 mg to 543.9 mg) in products already approved by FDA is greater than those contained in any strength of reformulated OxyContin (see **Table 0.1**).

More specifically, the basic excipient used to reformulate OxyContin is (b) (4)), a high molecular weight, (b) (4), water soluble polymeric resin. The structure of (b) (4) where n is the number of oxyethylene groups. If n is less than approximately 2275, corresponding to a molecular weight of 100,000, then the materials are typically referred to as (b) (4)). The grade of (b) (4) used in all strengths of reformulated OxyContin has an approximate molecular weight o (b) (4).

(b) (4) is a white, free-flowing, hydrophilic powder with a mean molecular weight of (b) (4). It is essentially tasteless, colorless, nonionic, and non-caloric. Although described as water soluble, aqueous mixtures of (b) (4) are better referred to as (b) (4).

(b) (4) swells and imparts viscosity to aqueous solutions. These properties make it a suitable polymer for use in hydrophilic matrix controlled release systems and in controlled release tablets which are the basis for OROS push-pull pump and (b) (4) technology. It is the ability to impart (b) (4) that enables (b) (4) to function as the release rate controlling excipient in reformulated OxyContin. This property also causes the (b) (4) to (b) (4) to any aqueous solvent used to extract oxycodone from the tablets. The physical properties of (b) (4) are also what cause the reformulated OxyContin tablets to be difficult to break. (b) (4)

(b) (4)

(b) (4) is well-tolerated and has been used as an excipient in multiple widely used marketed prescription and OTC medications, including but not limited to the medications listed in **Tables 0.2** and **0.3**.

Table 0.2   Currently marketed prescription medications containing excipient

Prescription drug	API	Date approved	Indication	Manufacturer
Procardia XL	nifedipine	FDA, September 1989	vasospastic angina	Pfizer
Glucotrol XL	glipizide	FDA, April 1994	type 2 diabetes	Pfizer
DynaCirc CR	isradipine	FDA, June 1994	hypertension	Reliant
Covera HS	verapamil hydrochloride	FDA, February 1996	hypertension and angina	Pfizer
Ditropan XL	oxybutinin chloride	FDA, December 1998	urinary incontinence &	Alza
Concerta	methylphenidate	FDA, August 2000	ADHD	J&J McNeil, Alza
Proquin XR	ciprofloxacin hydrochloride	FDA, May 2005	uncomplicated urinary tract	Depomed
Glumetza ER	metformin hydrochloride	FDA, June 2005	type 2 diabetes	Depomed
Jurnista	hydromorphone hydrochloride	EMEA, August 2006	moderate to severe chronic	J&J - Janssen Cilag, Alza

Table 0.3   Currently marketed over the counter medications containing (b) (4) **excipient**

Product	API	Manufacturer
Pediatric Vicks Formula 44e Cough & Chest Congestion Relief Liquid	dextromethorphan hydrobromide, guaifenesin	Procter & Gamble
Pediatric Vicks Formula 44m Cough & Cold Relief Liquid	chlorpheniramine maleate, dextromethorphan hydrobromide	Procter & Gamble
Sudafed Nasal Decongestant Tablets	pseudoephedrine hydrochloride	McNeil Consumer
Theraflu Thin Strips Daytime Cold & Cough	dextromethorphan hydrobromide, phenylephrine hydrochloride	Novartis Consumer
Theraflu Thin Strips Nighttime Cold & Cough	diphenhydramine hydrochloride, phenylephrine hydrochloride	Novartis Consumer
Vicks Formula 44 Cough Relief Liquid	dextromethorphan hydrobromide	Procter & Gamble
Vicks Formula 44E Cough & Chest Congestion Relief Liquid	dextromethorphan hydrobromide, guaifenesin	Procter & Gamble
Vicks Formula 44M Cough, Cold & Flu Relief Liquid	acetaminophen, chlorpheniramine maleate, dextromethorphan hydrobromide	Procter & Gamble

LATE DEVELOPMENT OF REFORMULATED OXYCONTIN

Purdue submitted an NDA for reformulated OxyContin to FDA on November 29, 2007 (NDA 22-272) and was subsequently the subject of a May 5, 2008 Advisory Committee meeting that considered on proposed labeling in the application. The discussion at this meeting also covered the robustness of the *in vitro* testing presented and Purdue's risk mitigation plans. The Advisory Committee voted against approval of reformulated OxyContin, based on the concerns described below.

Purdue then received an October 3, 2008 Complete Response Letter from FDA requesting additional physicochemical testing of the reformulated tablets. After designing and completing further experimental work to address the concerns raised in the Complete Response Letter, Purdue resubmitted an updated application for NDA 22-272 on March 30, 2009. This resubmission is an application for bioequivalent reformulated OxyContin without any request for label claims regarding the potential benefits of the physicochemical properties of the new formulation against tampering or accidental misuse.

A second FDA Advisory Committee meeting will be held on September 24, 2009 with a specific focus on *in vitro* testing data to assess whether Purdue's resubmitted application is sufficient for approval.

INPUT FROM MAY 5, 2008 ADVISORY COMMITTEE

The May 5, 2008 Advisory Committee raised several important concerns about the *in vitro* data presented at that time (and included in the original NDA 22-272 submission in November 29, 2007). Purdue considered the following concerns articulated by the Advisory Committee carefully in designing the new body *in vitro* studies presented here (and included in the resubmission of NDA 22-272 on March 30, 2009):

- Correlation of the testing to "real world" abuse (particle size and equipment)

- Robustness of testing (limits of testing)

- Completeness of testing (types of tests and number of tablets)

- Quality control of testing (including blinding)

- Third party execution and auditing

INPUT FROM FDA

On January 21, 2009 FDA met with Purdue and agreed that the additional *in vitro* studies of physical and chemical manipulations that are necessary for review or approval must:

- Be designed in consultation with individuals experienced in the intentional extraction of oxycodone from OxyContin for abuse

- Be designed in consultation with experts on extraction techniques to fully assess the testing protocols and

- For the data to be interpreted upon completion by experts

- Evaluate relative rate of release of API from all strengths of crushed and milled tablets in multiple solvents (i.e., confirm that dose dumping does not occur)

- Document how altering the grinding conditions (time, type of grinder) would influence the rates of API release

- Be conducted in a blinded manner, preferably by an independent third party

- Be validated to ensure they are conducted in a reproducible and meaningful manner

INPUT FROM EXPERTS CONSULTED

Purdue also consulted with experts in drug abuse, "tampering approaches", and analytical pharmaceutics (see **Appendix I**) to design, analyze and interpret the *in vitro* studies described here. These experts provided two important types of input. First, experimental design of each protocol must include the following elements considered necessary to yield reliable scientific data:

- Testing of all dose strengths of reformulated OxyContin

- Testing methods extended to determine failure limits

- Inclusion of adequate controls for comparison to OxyContin

- Sufficient replicates for evaluation of method variability

- Method validation procedures

- Investigation of a range of conditions on outcome of results (e.g., temperature, time)

- Use of independent laboratories

- Testing under blind conditions to the extent possible

Second, the overall body of *in vitro* studies should be designed to simulate the following "tamper" techniques anticipated in the real world:

- Crushability: chewing, cutting, grinding, powdering

- Swallowing: chewed or powder (dissolution)

- Effect of co-consumption of alcohol on "dose dumping"

- Extraction (simple and complex methods)

- Injection (syringability and injectability)

- Nasal insufflation (snorting/sniffing)

- Smoking

Purdue used the above input from FDA, the Advisory Committee and other experts to design the body of *in vitro* studies described below. To date no

"gold standard" approaches have been established for this type of "tamper testing". The intent of the experiments we designed together with experts we consulted (see **Appendix I**) was to test the physical properties of reformulated OxyContin tablets under a wide range of expected "real world" tablet manipulation scenarios. These studies assessed both the strengths and limitations of this reformulation compared to the current formulation when exposed to various means of simple or complex physicochemical manipulations.

In vitro testing of reformulation's physicochemical properties

OVERVIEW OF EXPERIMENTAL STUDIES

Protocols were developed with the above input in mind and in consultation with experts in drug abuse, abuser tampering methods and analytical pharmaceutics (see **Appendix I**) in order to address the concerns raised by FDA in the October 3, 2008 Complete Response Letter. After internal validation of the protocols to ensure reproducibility and consistency across experiments, methods were standardized and transferred to third party vendors. The majority of experiments were performed by two contracted independent third party vendors (Aptuit, Kansas City, MO and Catalent Pharma Solutions, Research Triangle Park, NC). Personnel performing the experiments were blinded to the extent possible. Division of work between these two vendors was capacity-driven, with a goal to complete the experiments as expeditiously as possible. Upon completion of the studies, both independent third party vendors and internal Purdue staff performed extensive quality assurance analysis of the resulting data.

The rationale for the study designs in this report are based on two concepts: A) to experimentally standardize common and uncommon methods of misuse both simple and complex, B) to define the specific strengths of the reformulation, and C) consider the complete API release from the tablet as a final endpoint for all experiments.

The data is presented to provide a clear understanding of the performance of reformulation under simple or complex techniques of tampering that may be encountered in the "real world". The experiments test the reformulation under the following conditions:

- Extraction in small volumes of solvents encompassing ranges of pH, polarity, and temperature

- Dissolution "dose dumping" in ethanol

- Syringability

- Injectability

- Extraction after vaporization (smoking inhalation)

- Advanced cold extraction of API

- Advanced liquid-phase extraction of AP

Dr. Edward Cone, one of the external experts consulted, has written an introduction document (see **Appendix III**) to accompany the complete data package submitted to FDA describing his views on how Purdue's *in vitro* experimental studies represent "real world" scenarios of abuser and misuser manipulations (inadvertent and intentional). Dr. Cone's expertise is in chemistry and pharmacology of drugs of abuse, tablet tampering methods, drug delivery systems, pharmacokinetics, and drug testing methodologies.

To the best of our knowledge these experiments were the first of their kind in terms of scale.   These studies were designed with two goals in mind:

- First, to fully characterize the ⬛⬛⬛⬛ (b) (4) reformulated OxyContin under both common and extreme "real world" abuse and misuse (b) (4) methods

- Second, to compare the performance of OxyContin to that of reformulated OxyContin under all conditions tested

Many of the experiments had to be designed without any significant input from precedent material. Development protocols were created *de novo* to translate known and anticipated "real world" tamper protocols that were identified by consulting with drug abuse experts and studying abusers internet discussion forums on (b) (4) methods (e.g., erowid.org, blulight.ru and others) into systematic and reproducible laboratory procedures. The sequence in which these studies are presented below follow the order in which the experiments were designed and executed order as well as the presentation order of the origina (b) (4) report submitted to FDA with our NDA resubmission on March 30, 2009.

STANDARDIZATION OF PARTICLE SIZES TESTED

Typically the misuse of OxyContin involves manipulating tablets in one of several ways for the purpose of defeating the controlled-release properties (see **Appendix III**). Reducing the tablet to a powder allows immediate access to oxycodone HCl by disrupting diffusion barriers and increasing the surface area of drug particles for more efficient oxycodone extraction. Other

forms of manipulation such as solvent extraction and ▓▓▓▓▓▓▓ (b) (4)
alteration are often attempted alone or in conjunction with particle size
reduction.

Because preparation for misuse and abuse of the reformulation will most
likely involve manipulating tablets to reduce particle size, the effect of
particle size is tested throughout all manipulation scenarios. When
consulting an expert panel (see **Appendix I**) about tools used and methods
of preparation for misuse, it became apparent that while some common
approaches exist, realistically there is no limit to what will be attempted in
the "real world". For this reason, and given that one of the protective
properties of the reformulation is increased hardness of the tablet, these
"real world" techniques become subjective. In the "real world", the degree of
manipulation depends on an individual's strength, determination and
available equipment. Time, effort and available equipment are the most
impactful variables in designing an *in vitro* study that is intended to simulate
what might be attempted in the "real world".

Due to the scope of the seven studies described, continual application of
household devices in a laboratory setting became impractical. Additionally
analyst to analyst variability and the use of household tools that can not be
subjected to calibration and standardization, made it impossible to
reproducibly manipulate the tablets using these tools

To standardize this approach, we defined the limits of particle size reduction achievable by subjecting reformulated OxyContin tablets to a myriad of household devices. The upper limit (largest particle size) was generated ▇▇▇▇▇▇▇▇▇▇▇▇▇▇ a slightly indented, intact tablet. The lower limit (smallest particle size) was generated using ▇▇▇▇▇▇ ▇▇▇▇ Other successful "real world" methods ▇▇▇▇▇▇ ▇▇▇▇▇▇▇▇▇▇) generated particle sizes that fall within these limits.   To be sure that the laboratory experiments were standardized and reproducible, ▇▇▇▇▇▇▇▇▇▇▇▇ was used to create the aforementioned particle size fractions, referred to as *bands* in this report. The particle sizes were divided into ▇▇▇▇▇▇▇ ranging from intact tablets to particles smaller than ▇▇▇ plus a seventh control band ▇▇▇▇▇▇▇

- Band 1 = deformed intact tablet

- Band 2 = ▇▇▇▇▇▇▇▇▇▇

- Band 3 = ▇▇▇ (b) (4)

- Band 4 = ▇▇▇▇▇▇▇▇▇▇▇▇▇▇ (b) (4)

- Band 5 = ▇▇▇▇▇▇▇▇▇▇▇▇▇ (b) (4)

- Band 6 = ▇▇▇▇▇▇▇▇▇▇ (b) (4)

- Band 7 = core powder containing API and excipient prior to undergoing manufacturing process ▇▇▇▇▇▇▇▇ (used as control)

These distinct bands represent the full range of particle sizes likely achievable during preparation for misuse, accidental or otherwise, by the general population.

STUDY 1: (b) (4) FRACTIONATION OF TABLETS

Objective

This Study was designed to survey the number of techniques that could be employed to (b) (4) alter OxyContin formulations. The goal of these experiments were to broadly identify and characterize the methods and outputs that could be used for further (b) (4) for the purposes of standardization of experiments.

Design

Techniques that could be employed to (b) (4) reduce reformulated tablets were surveyed. These included simple or complex (b) (4) devices,

identified and tested for their ability to (b) (4) of the reformulated OxyContin tablets. Following (b) (4) fractionation, (b) (4) used to separate (b) (4) of particles generated. Each (b) (4) device produced a (b) (4) sizes that were either totally discrete or overlapping with particle ranges produced by other devices

A standardized method was developed and tested to reproduce these discrete bands for further testing in Studies 2-7. We further examine whether _____ (b) (4) of tablets with ____ (b) (4) changed the complexity and time required to create _____ (b) (4) sizes. The endpoint for these experiments was to generate and describe the discrete _____ (b) (4) bands that can be produced by multiple _____ (b) (4) l means. Data generated from these experiments include distribution curves for particle sizes generated with tablets at _____ (b) (4) and descriptive observations regarding particle size generation when _____ (b) (4). The complexity and time that was required to create each curve was recorded. Comparator data was generated for OxyContin tablets after similar manipulation. The methodology utiltized in these experiments is described in greater detail in **Appendix II**.

Results

The time or effort required to reduce the size of reformulated OxyContin tablets into small fragments or particles was dependent [   ] (b) (4) used. **Table 1.1** contains this information on devices in order of increasing
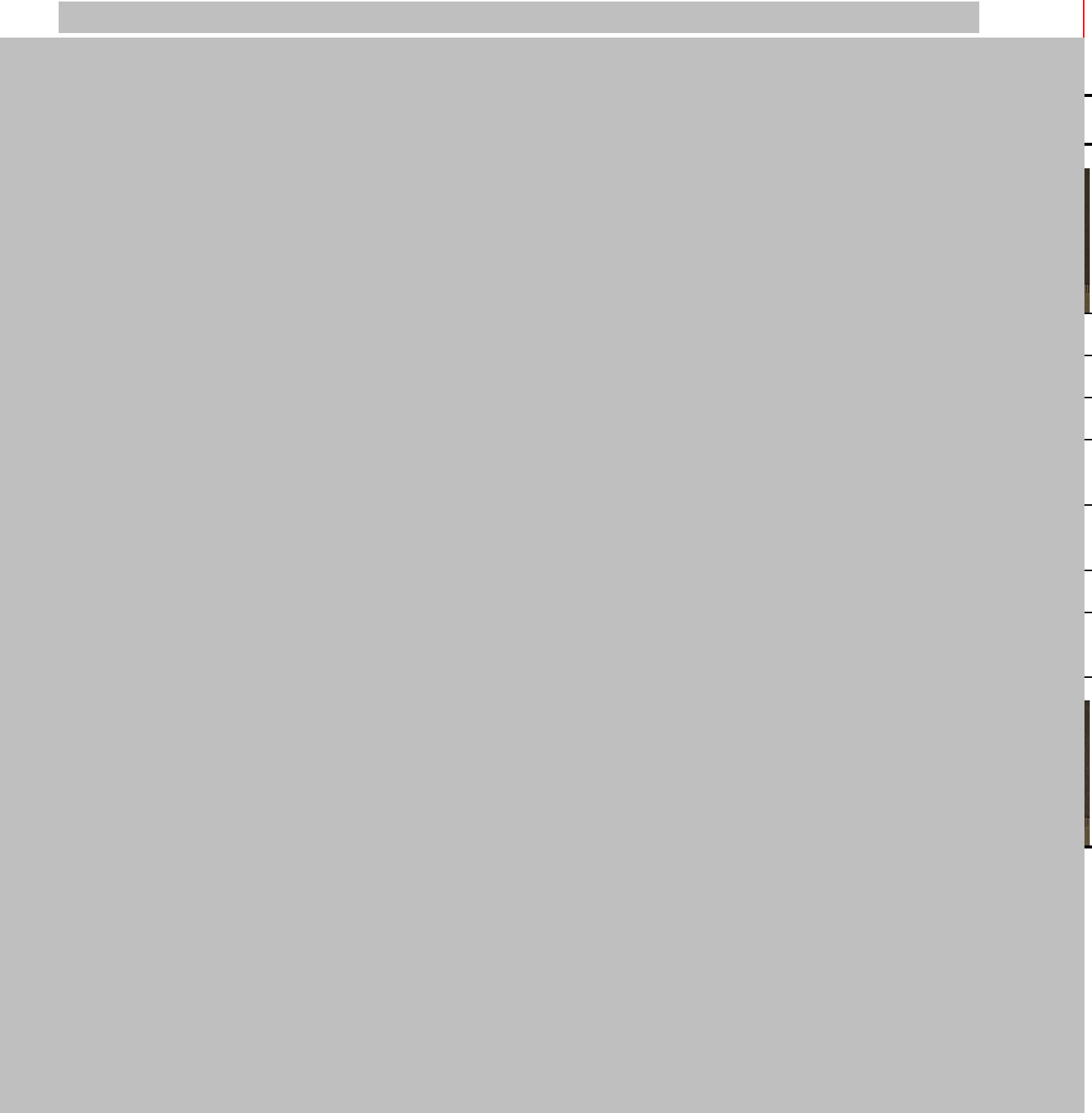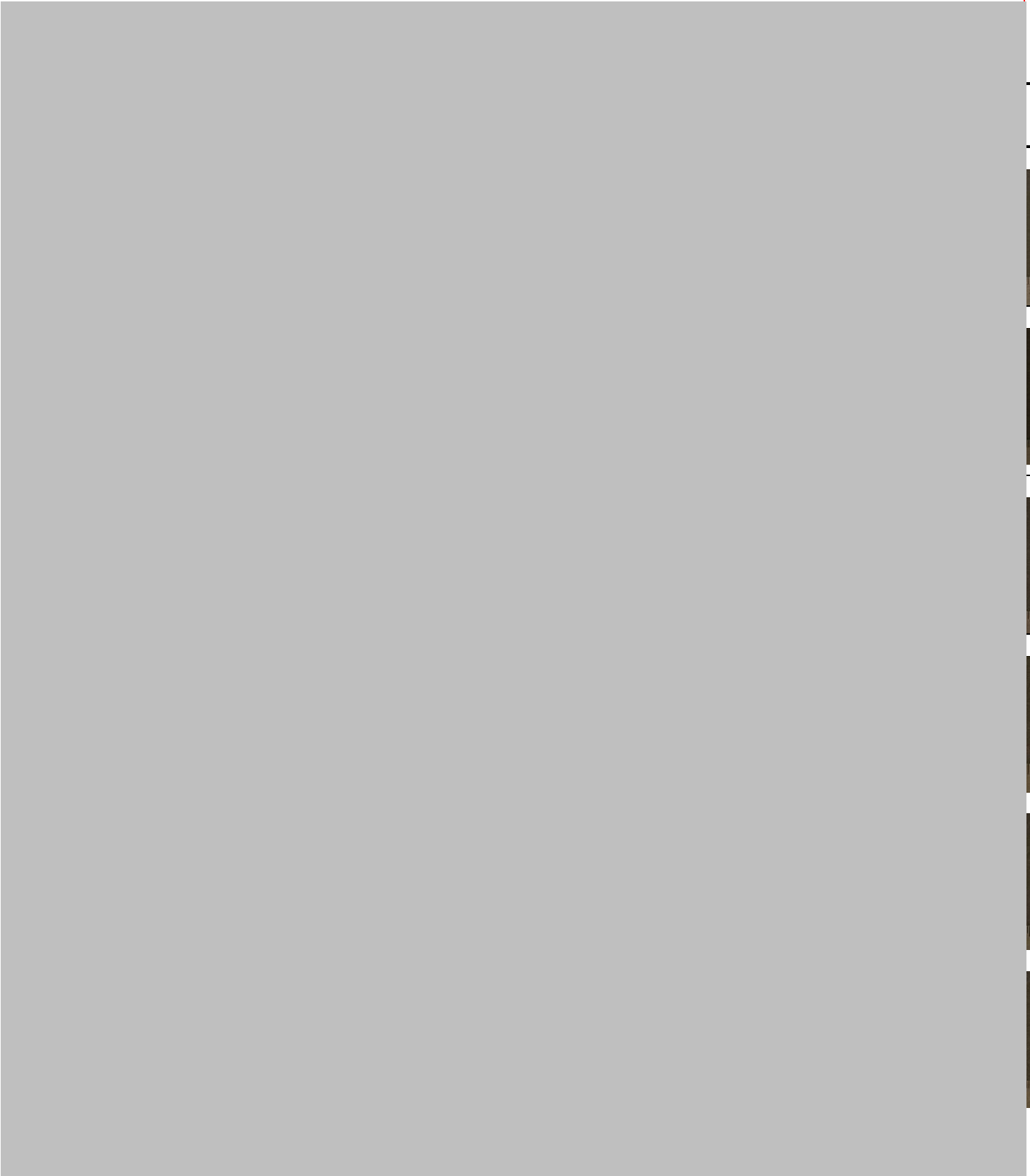
Particle sizes obtained with household techniques

Reformulated OxyContin particle sizes obtained using ▨ (b) (4) techniques ranged in size from an ▨ (b) (4) produced ▨ (b) (4) ▨ (b) (4) to ▨ (b) (4) (77% of total) when applying a ▨ (b) (4) ▨ (b) (4) - the most effective technique for ▨ (b) (4) fractionating reformulated tablets. This ▨ (b) (4) size was achieved by subjecting reformulated tablets to increasing amounts of ▨ (b) (4) until no further meaningful reduction in particle size occurs; at ▨ (b) (4) ▨ (b) (4) ▨ (b) (4) Data for end point determination using ▨ (b) (4) grinder is found in **Figure 1.1**. All other ▨ (b) (4) devices, shown in **Figure 1.2**, resulted in a range of particle sizes that fall within the limits set by the ▨.

▨

▨

▨

▨

▨ To standardize this method, particles were generated ▨ ▨ r and sieved to produce four discrete bands consisting of the following fractionated ▨ (b) (4) ▨ (b) (4) Use of a ▨ (b) (4) resulted in the most reproducible and efficient approach for the recovery of particles. We observed that an API loss upwards of 10-16% occurred when using the ▨ as opposed to 3% loss

when using [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] . The maximum API released of bands 5 or 6 do not generally reach 100% as a result of this preferential API loss.

Figure 1.1   Reformulated OxyContin – particle size results for household devices

NOTE: For illustrative purposes the figure contains smoothed curves generated from values for % weight retained (y-axis) on a series of sieves (x-axis)
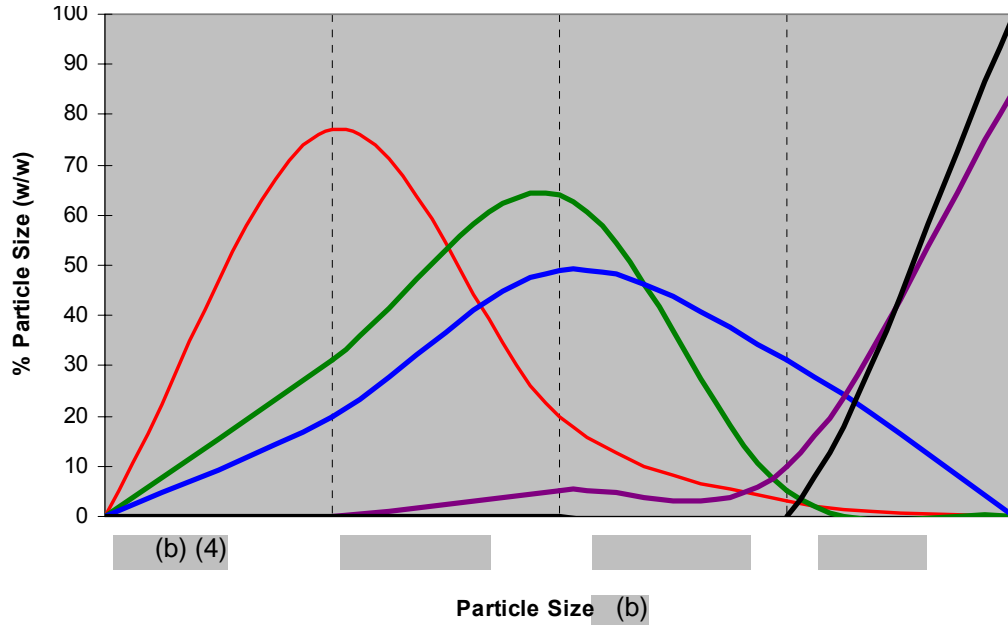
Figure 1.2   Milling results ▨▨▨▨▨▨▨▨▨ grinder

NOTE: For illustrative purposes the figure contains smoothed curves generated from values for % weight retained (y-axis) on a series of sieves (x-axis)
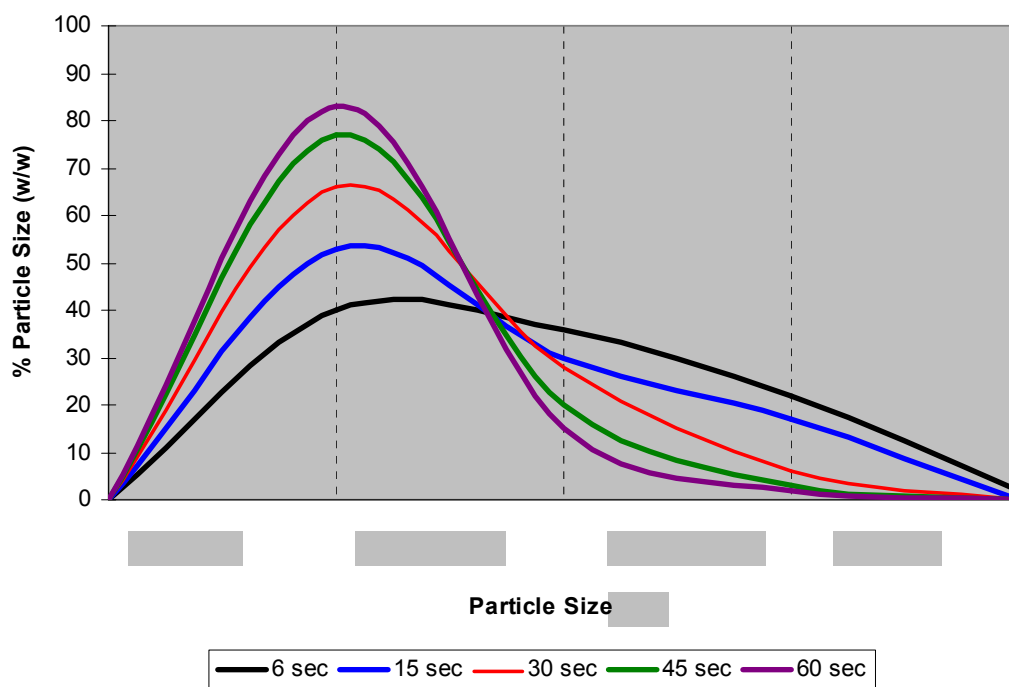
As defined in this scheme, band 1 is an (b) (4) tablet, with sligh (b) (4) (b) (4) that is caused by (b) (4) Band 7 is the finest powdered material, with 100% (b) (4). This is the (b) (4) for reformulated OxyContin. This powder consists o (b) (4) that is (b) (4) to form the reformulated OxyContin tablets. This band was used as a "positive control" in some experiments, demonstrate that API release was not dependent on any forms of mechical manipulation. This (b) (4) powder, band 7, is not available to misusers and abusers as it is an (b) (4) solely used during the (b) (4)process.

In contrast to the other bands, band 3 was obtained by grating tablets on a ⬛ no sieving step was involved in producing band 3. This approach was conceived to consider all potential particle sizes and shapes that may be available for further analysis. Analysis of samples from this band with microscopy demonstrated that the particle sizes achieved with the ⬛ ranged between ⬛ in width with a variety of long and short lengths. Because of these different (b) (4) dimensional properties, direct comparison of this band with the other bands may not result in a linear correlation for the extraction data.

⬛ used to render current OxyContin a powder; the resulting particle size was 92% (b) (4) and was

achieved within ___(b) (4)___.   Many of the other ___(b) (4)___ devices that were used were also effective in easily crushing OxyContin into powder form, including simple and readily available items such as _____.   **Figure 1.3** summarizes the relationship between ___(b) (4)___ devices and particle size reduction for OxyContin.

The premise for this strategy to standardize the particle sizes that are to be tested was that the dissolution and extraction behavior of any of the seven discrete particle size bands defined above using a _____ and sieve can be related to the same characteristics of particles that are generated by physical manipulation using ___(b) (4)___ equipment.   In other words, any ___(b) (4)___ or "real world" device would result in a range of particle sizes that can be characterized by a set of kinetic API release curves.   To standardize the experiments and to be able to perform them blindly via a third party, it was not practical or precise to use ___(b) (4)___ devices for future extraction methods.   Therefore by showing that the _____(b) (4)___ could be standardized into ___(b) (4)___r particle bands, we were able to standardize and industrialize all the experiments.

Figure 1.3   OxyContin – Particle sizes resulting from experiments with (b) (4) **tools**

NOTE: For illustrative purposes the figure contains smoothed curves generated from values for % weight retained (y-axis) on a series of sieves (x-axis)
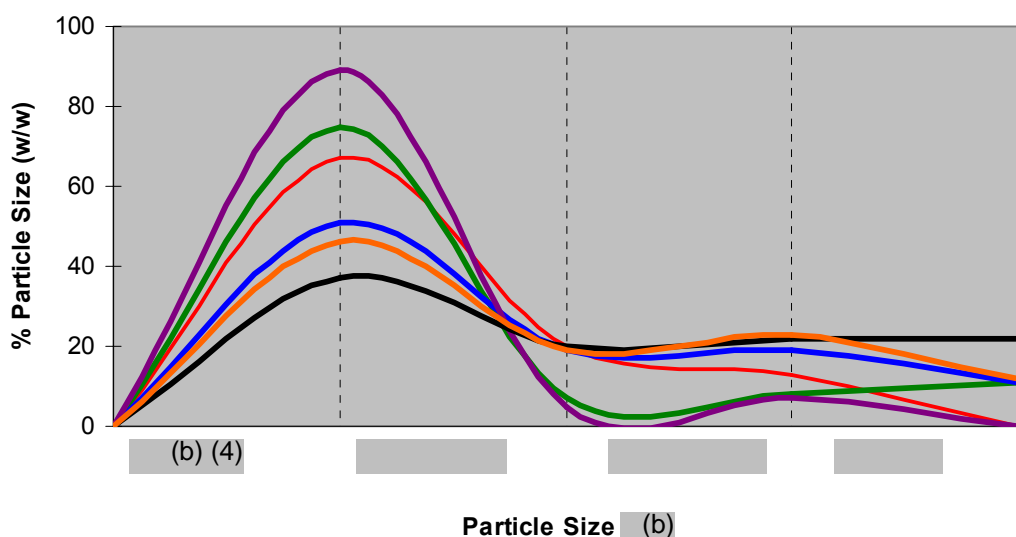
To be sure that the reformulated tablet was not preferentially vulnerable to easy crushing after (b) (4) were evaluated. Observations for each of the conditions are found in **Table 1.3**. (b) (4) of tablets was found to slightly increase the ease with which the tablets could be crushed using (b) (4) not outside of the range of particles achieved at room temperature. (b) (4) the tablets did not improve the ability to create powder from the reformulated OxyContin tablets.

Table 1.3   Effect of ▇▇▇▇ pretreatment on the subsequent effectiveness of ▇▇▇▇ tools in ▇▇▇▇ reformulated OxyContin to ▇▇▇▇

Discussion

Many commercially available ▇▇▇▇ (b) (4) tools were unable to successfully reduce the particle size of the reformulated OxyContin tablets. Although hard, the tablets are malleable and do not shatter as a nut or a peppercorn

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would when subjected to some of these devices. In addition, because the ▓▓▓▓▓ properties of the reformulation is based on its ▓▓▓▓▓ ▓▓▓▓▓, the characteristics of API release from the tablets, either as intact or in particles, differs significantly from that of crushed OxyContin powder. These ▓▓▓▓▓ properties are expected to retard the release kinetics of API from the reformulation (even when crushed into ▓▓ particles or tablet ▓▓▓▓▓) and to make it significantly more difficult to syringe, inject or smoke the material.

Reformulated OxyContin tablets were resistant to crushing and particle size reduction using readily available ▓▓▓▓▓ devices. Of the ▓▓ devices employed in this Study ▓▓▓▓▓ the particle size of reformulated tablets.   In contrast, the current formulation of OxyContin was quickly and easily rendered a fine powder using tools as simple as two spoons. Increasing amounts of time or effort were required to achieve progressively ▓▓▓▓▓ (b) (4) particle sizes of the reformulated tablets (in contrast with the binary response, intact or crushed condition, observed with the current OxyContin formulation). See **Figure 1.2** and **Figure 1.3**. The reproducible banding of particle sizes was only possible after evaluating the full range of achievable particle sizes using a wide variety of ▓▓▓▓▓ tools. This banding strategy is an effective means of standardizing experiments that may be otherwise subject to variability due to the inherent subjective nature o ▓▓▓ (b) (4) tablets with ▓▓▓ (b) (4) tools. The six particle size bands defined here were used throughout Studies 2-7.

STUDY 2: EXTRACTION IN ░░░░░░░░░░ (b) (4)

░░░░░ (b) (4) **SOLUTIONS**

Objective

This Study was designed to evaluate the oxycodone API release characteristics of reformulated OxyContin after ░░░░ (b) (4) extraction in ░░░░░░░░░ (b) (4) solutions. The goal was to determine and compare the API release kinetics for OxyContin and reformulated OxyContin using a wide variety of solvents on a range of particle bands.

Design

Study 2 was comprised of series of simple extraction protocols designed to cover a range of known and predicted methods of tampering with reformulated OxyContin. Simple extraction methods are generally employed for injection. The first step in such a process requires crushing a tablet followed by ░░░░ (b) (4) extraction in a suitable ░░░░░░░ (b) (4)

░░░░░░░░░░░░░░░░░

░░░░░░░░░░░░░░

░░░░░░░░░░░░░░░░

░░░░░░░░

Simple extraction protocols were developed to assess the difficulty of extraction, with the intent of producing a solution that could be injected or ingested via other routes of administration.

Extraction experiments were performed for all tablet strengths covering all ranges of particle size bands. Because higher temperatures facilitate faster extraction kinetics in general, all extractions were performed both a (b) (4)

(b) (4)   (b) (4) and at an elevated temperature

Multiple time points were sampled to generate a kinetic representation of API release. Data from these experiments include band-specific kinetic curves describing the release profile of API over time from all bands in multiple solvents at room temperature versus elevated temperature. It is important to re-emphasize that the endpoints for all of these experiments were defined as the time to complete release of API from the sample regardless of whether this was reformulated or current OxyContin.

Details of protocol development and experimental methodology are provided in **Appendix II**. The statistical approach to calculating the number of samples used in each experiment as well the methodology applied to determine the significance of the results are provided in **Appendix II**.

Results are separated by solvent type and presented below.

Results

(b) (4)

(b) (4)

.

(b) (4)

(b) (4), the release of API from different particle sizes of reformulated OxyContin was graded in proportion to the size of particles tested. The kinetic results should be contrasted with those

for crushed OxyContin which demonstrate a binary, immediate release
profile.   (b) (4)
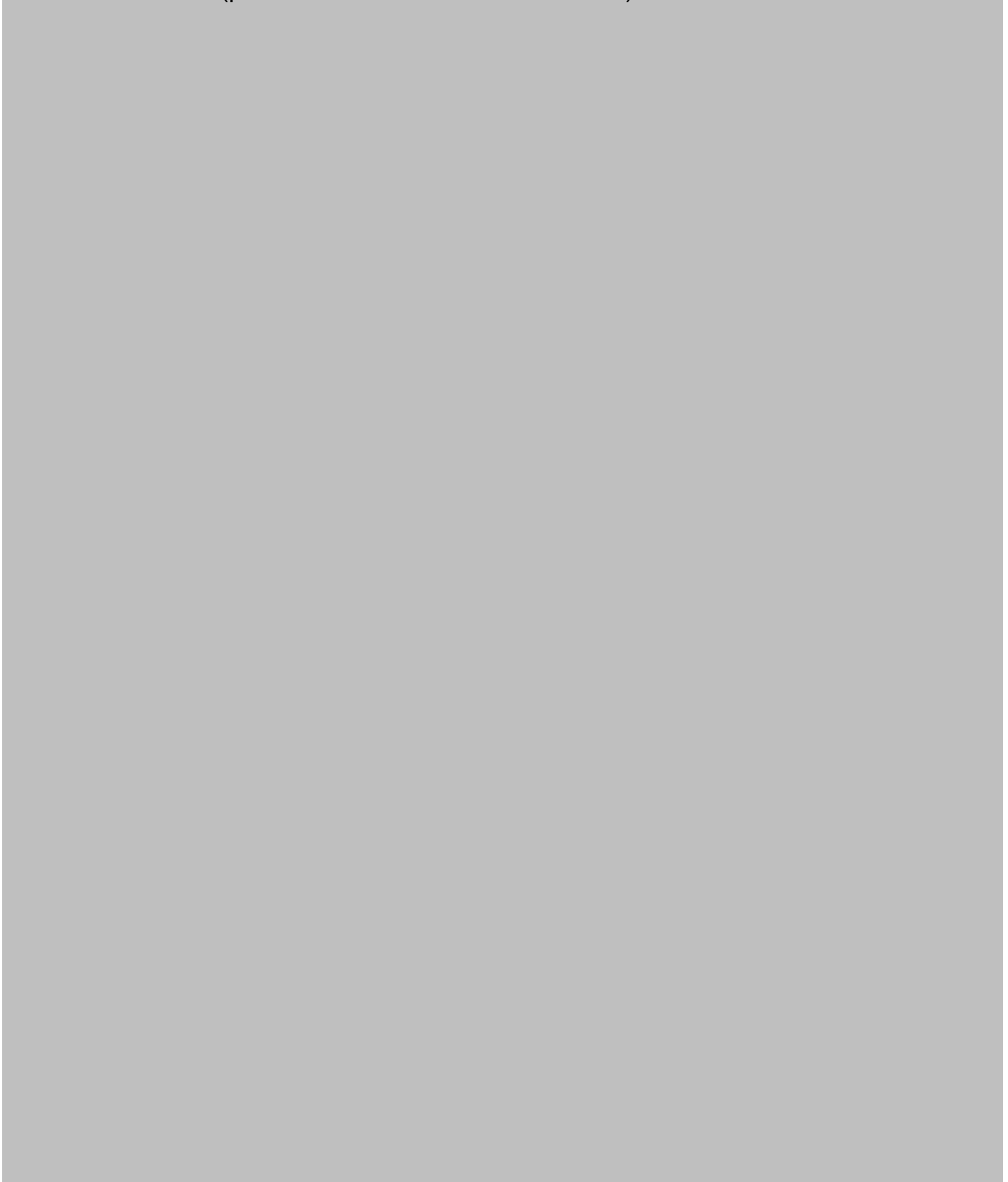
(b) (4)

(percent of label claim API extracted)

It was expected that solutions at higher temperatures would lead to faster release of API than the same solutions at room temperature. (b) (4)
(b) (4)
(b) (4)
(b) (4). Under these conditions, band 1, at all dosages tested, maintains its controlled-release property (b) (4). This API release rate was significantly slower than the release rate of (b) (4)
(b) (4) and that seen with crushed OxyContin (b) (4) (b) (4) properties of reformulated OxyContin, (b) (4)
(b) (4)

API release from band 2 (b) (4) was (b) (4) faster than that for band 1 but substantially slower than all other bands including crushed OxyContin (b) (4)
(b) (4)). Bands 2 and 6 did not reach the API release plateau (b) (4). No difference in the API release rate was observed between bands 3-5 of reformulated or crushed OxyContin. The curves reached a plateau, maximum API release, (b) (4).

Band 1 maintains its controlled-release properties (b) (4) when extracted (b) (4), (b) (4)
(b) (4)
(b) (4) To be sure that these conditions did not signify new vulnerabilities for reformulated OxyContin in contrast to (b) (4) current OxyContin, the same extractions were performed a (b) (4)

OxyContin across all strengths. ▮▮▮▮▮▮▮▮▮▮▮▮▮▮

▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮

▮▮▮   The figure shows that API release profile for ▮▮▮ OxyContin is significantly faster than that for ▮▮▮t reformulated OxyContin, band 1, (b)

▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮). At ▮▮▮▮▮▮▮ kinetics from band 1 reaches a plateau ▮▮▮▮▮▮ while intact OxyContin reaches its plateau ▮▮▮▮▮▮. As shown in these figures,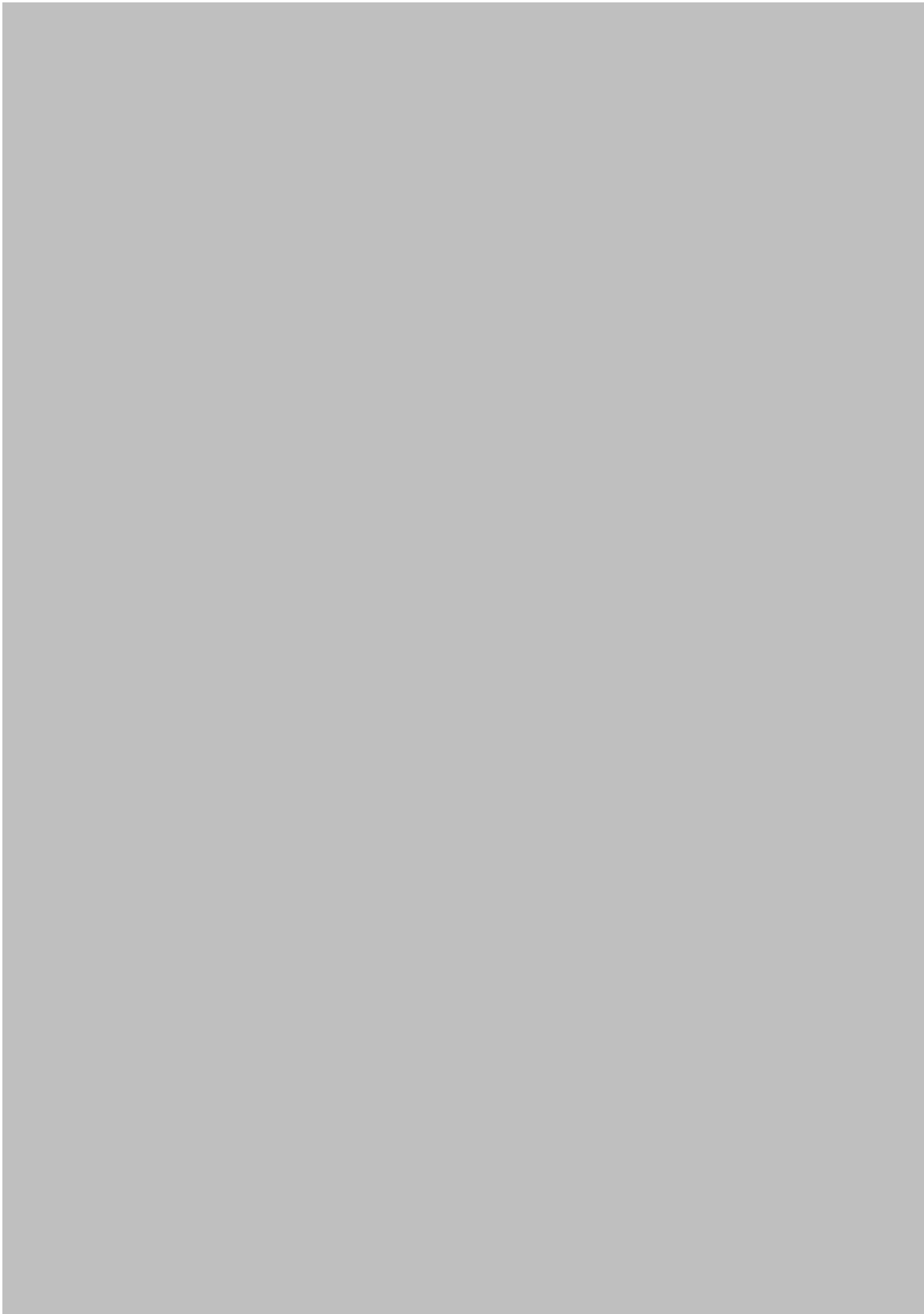 although ▮▮▮ reformulated OxyContin (band 1) releases API faster at ▮▮▮▮ when compared to API release ▮▮▮▮ the release is slower than what is seen with ▮▮▮ OxyContin extracted under the same conditions ▮▮▮▮▮ Therefore despite earlier release of API by ▮▮▮ reformulated OxyContin under these conditions, the reformulation is not vulnerable when compared to OxyContin.

(b) (4) *solvents*

Figure 2.4 presents data for bands 1, 4, 6 of reformulated OxyContin and crushed OxyContin in ▮(b) (4)▮ extractions with ▮(b) (4)▮ ▮(b) (4)▮he data was collected at 10 minutes, 60 minutes and 18 hours, in contrast to ▮(b) (4)▮ extractions ▮(b) (4)▮, only bands 1, 4 and 6 were tested for ▮(b) (4)▮ ▮(b) (4)▮ ▮(b) (4)▮ ▮(b) (4)▮

Full kinetic API release data for extraction with ▮(b) (4)▮ ▮▮ are presented in **Figure 2.4 (top panels).** For both of these solvents band 1 ▮), band 4 ▮(b) (4)▮ and band 6 ▮) maintain controlled-release properties ▮(b) (4)▮, ▮(b) (4)▮ ▮(b) (4)▮; in ▮(b) (4)▮band 1,4 and 6 release ▮ ▮(b) (4)▮ all at ▮(b) (4)▮ ▮(b) (4)▮. These results should be compared to those for crushed OxyContin which releases >90% API by ▮(b) (4)▮. In comparing ▮(b) (4)▮ ▮(b) (4)▮ as solvents, mor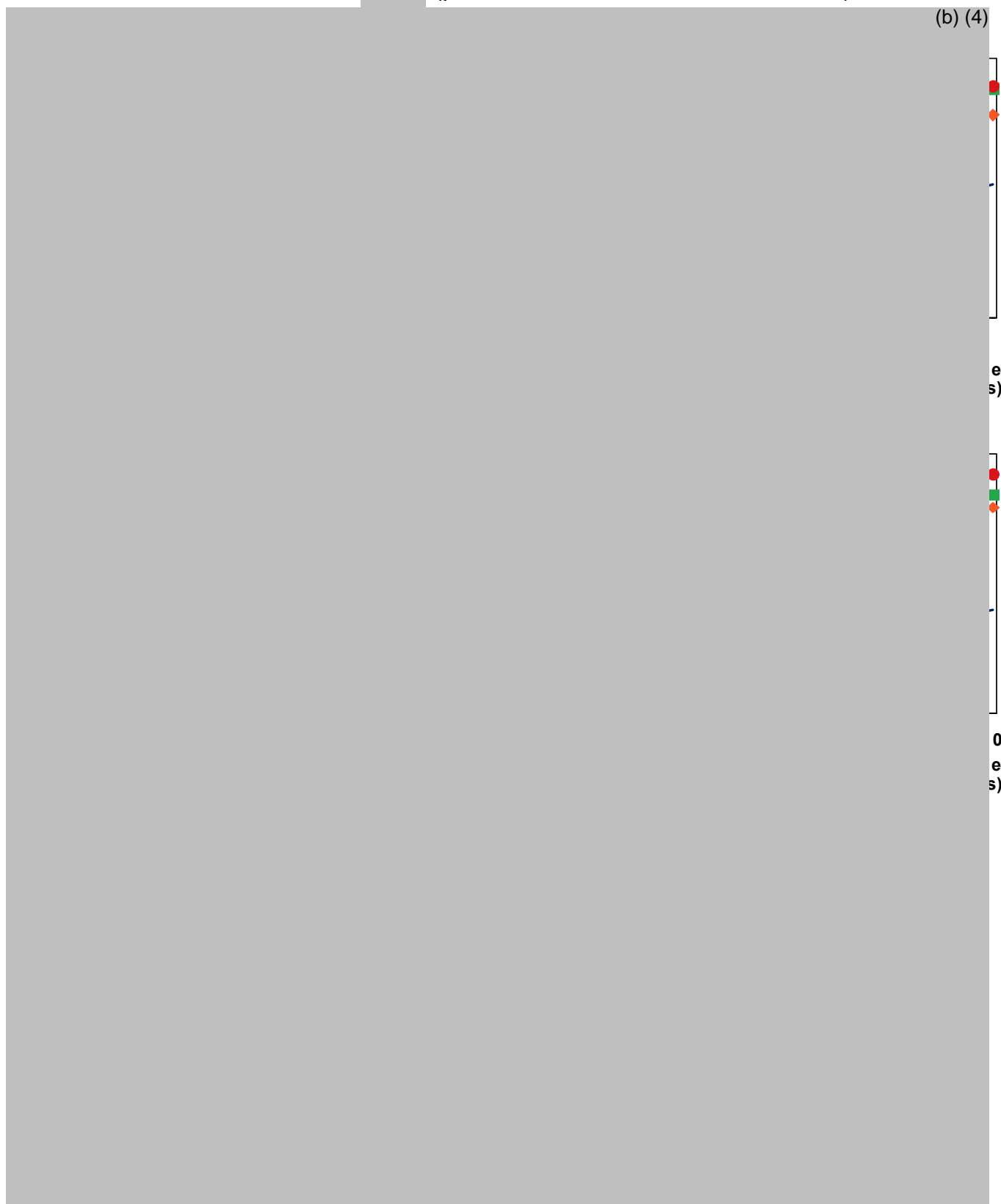e API was released from band 1 ▮(b) (4)▮ ▮ ▮(b) (4)▮ ▮(b) (4)▮ suggesting that ▮(b) (4)▮may be a slightly better solvent than ▮(b) (4)▮ ▮(b) (4)▮ and better solubility for API release from the matrix ▮(b) (4)▮

Figure 2.4   Reformulated OxyContin extraction in (b) (4) **solvents at** (b) (4) (percent of label claim API extracted)

The above experiments (████████████████ were performed at room temperature and duplicated in a ██ ████████ to examine how rates of API release could be affected by elevated temperatures. Even under ████████████ (b) (4) at ██ (b) (4) ██████ reformulated OxyContin (band 1) maintained some control release property ██████ (b) (4) at all strengths tested ████████████████████████ (b) (4) for ██████████████ (b) (4) respectively, data not shown). ██████████████████████████ (b) (4)

████████████████████████████████ (b) (4)

████████ (b) (4) ██████████████ (b) (4) in the API release rate was observed between bands 4 and 6 of reformulated and crushed current OxyContin. API release of about (b) (4) was reached as early as ████████ (b) (4). One ████████████████████████████ (b) (4) where ████████████ (b) (4) ████████ (b) (4) (data not shown).

In these set of experiments, while band 1 maintained its controlled-release properties ██████ (b) (4) when extracted with ████████████████ at 25 °C, the API release profile for band 1 extracted in the same solutions at ████████ was ██████████ (b) (4). To be sure that these conditions did not signify new vulnerabilities for (b) (4) reformulated OxyContin compared to (b) (4) current OxyContin, the same extractions were performed a ██████ for (b) (4) OxyContin. Under these conditions, only 10, 40 and 80 mg strengths (b) (4) OxyContin were tested. As previously noted, the selected strengths adequately represent the full spectrum of all six strengths of OxyContin. (b) (4) OxyContin released API significantly faster than (b) (4) reformulated OxyContin, band 1, in ████████████████████ (b) (4)

████████████████████████████████ (b) (4)

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from intact OxyContin ⬛ (b) (4)

⬛ (b) (4) from intact OxyContin) (Data not shown).

Therefore despite the fact that API is released earlier under these conditions, the reformulation is not more vulnerable than OxyContin.

Full kinetic API release data for extraction with ⬛ at ⬛ are represented in **Figure 2.4 (middle panels).** Both ⬛ extracted API from crushed OxyContin (90% API released (b) (4) ⬛ (b) (4). For reformulated OxyContin, this release rate was band-specific. As shown in **Figure 2.4**, the API release profiles of (b) (4) reformulated OxyContin (band 1) ⬛ were similar, maintaining a controlled-release profile up to the end point (⬛ (b) (4) ⬛ (b) (4)). For band 4 ⬛ (b) (4) API release rates in ⬛ were similar ⬛ (b) (4) ⬛ (b) (4) ⬛ However, more API was released at (b) (4) hours ⬛ than ⬛ (b) (4)). For band 6 ⬛ (b) (4) the ⬛ (b) (4), some control was retained ⬛ (b) (4) in but ⬛ (b) (4) of API was released at ⬛ (b) (4) in ⬛ (b) (4) data suggest that ⬛ a slightly better solvent than ⬛ for (b) (4) r particles. ⬛

⬛

Elevated temperature extraction experiments for (b) (4) solutions were performed a ⬛ ⬛ ⬛ . At this temperature only bands 1 and 4 showed controlled-release properties in both ⬛

▬▬▬▬▬▬, and ▬▬▬▬▬▬▬▬▬▬.   Band 6 had some control in API release in ▬▬▬▬▬▬▬▬▬▬ but not in ▬▬▬▬▬▬. Greater than ▬▬ API was released ▬▬▬▬▬▬. ▬▬▬▬▬▬▬▬▬▬▬▬

▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬

▬▬▬▬▬▬

▬▬▬▬▬▬ was a poor solvent for extracting API from crushed reformulated or current OxyContin (**Figure 2.4, bottom panel**). Increasing the length of time or temperature for extraction by ▬▬▬▬ did not render it a better solvent. Maximum API extracted at any time point from ▬▬▬▬▬ was from band 6 and crushed OxyContin at abou ▬▬▬▬▬▬▬▬.

▬▬▬▬ (b) (4) *solutions*

Multiple bands for all dosages of the reformulation were evaluated in extraction via ▬▬ (b) (4). Bands 1 ▬▬▬▬ (b) (4)), 4 ▬▬▬▬▬▬ and 6 ▬▬ (b) (4)) were used because these bands effectively bracket ▬▬▬▬ ▬▬▬▬▬▬▬▬▬▬▬ (b) (4) reformulation tablets. Kinetic API release data for ▬▬▬▬▬ (b) (4) solutions a ▬▬▬ are represented in **Figure 2.5**.   Bands 1, 4 and 6 of reformulated OxyContin are extracted with ▬▬▬ (b) (4) solutions and data collected at ▬▬ minutes, ▬ ▬▬▬▬▬ (b) (4)

Figure 2.5   Extraction of reformulated OxyContin in ▨(b) (4) **at**
▨(b) (4)

(percent of label claim API extracted)

Figure 2.5 (continued)

Extraction of reformulated OxyContin in (b) (4) **at** (b) (4)

(percent of label claim API extracted)
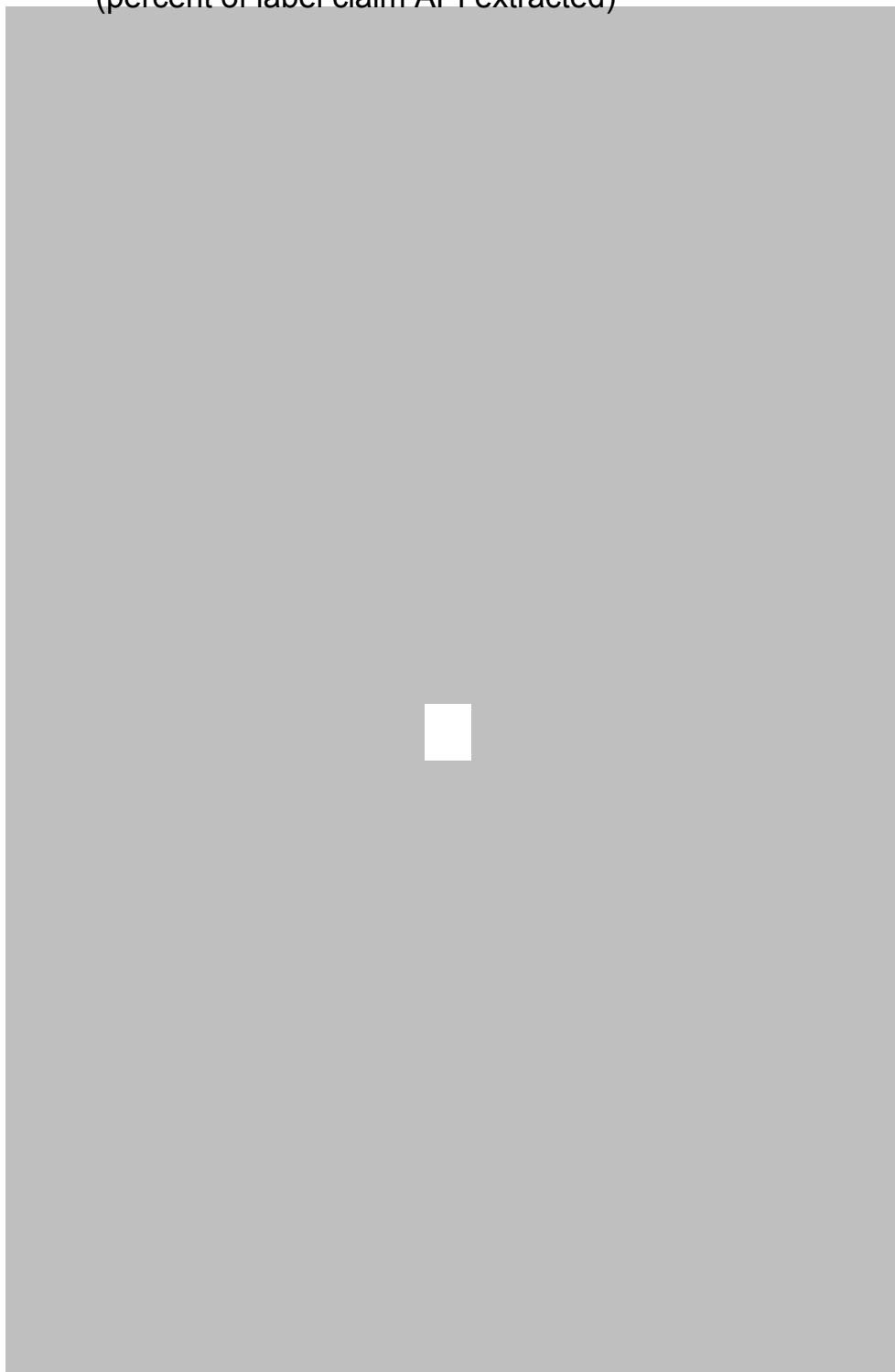
(minutes)

API release profiles are similar in _____ (b) (4). API release profiles in _____ (b) (4) was significantly slower than those seen in _____ (b) (4).

(b) (4) reformulated OxyContin (b) (4)) maintained its controlled-release properties throughout the time points. Band 4 (_____ (b) (4) and band 6 _____ (b) (4) releases _____ (b) (4) than band 1, but maintains some of the controlled-release properties _____ (b) (4). _____

_____. As the _____ a reformulated OxyContin tablet is _____ (b) (4) _____g, the rate of API release _____ (b) (4) i.e., smaller particles release API faster than larger ones. Despite this acceleration, smaller particles maintain some controlled-release properties _____ (b) (4). Even the smallest particles release API slower than crushed OxyContin _____ (b) (4) time point.

Extractions _____ were duplicated for the above _____ (b) (4) experiments to examine how rates of API release were affected. (b) (4) reformulated OxyContin (band 1), at all strengths tested, maintained some of its controlled-release properties _____ (b) (4) for al _____ (b) (4) tested.

Once the ⬛ (b) (4) ⬛ (b) (4) in the API release rates between bands 4 and 6 of reformulated or current OxyContin tablets was observed. Maximum API release plateau was reached (b) (4) ⬛ Even ⬛ ⬛ buffer was less effective in extracting API from reformulated OxyContin.

To be sure that these conditions did not signify new vulnerabilities for intact reformulated OxyContin compared to (b) (4) t current OxyContin, the same extractions were performed at ⬛ (b) (4) (10, 40 and 80 mg strengths). ⬛ (b) (4) (b) (4) OxyContin releases API significantly faster than (b) (4) reformulated OxyContin (band 1) extracted at ⬛ (b) (4) Therefore despite the fact that the baseline of API release for (b) (4) reformulated OxyContin is shifted a ⬛ the reformulated OxyContin is not more vulnerable than OxyContin.

Discussion

⬛ (b) (4)

API release rate in (b) (4) is a function of reformulated OxyContin particle size. At room temperature, the rate at which API was released is proportional to particle size ⬛ (b) (4) The ⬛ (b) (4) principle predicts that the release properties of reformulated OxyContin, even in smaller particle sizes, may be substantially different than those of crushed OxyContin which does not possess a similar physicochemical character. This ⬛ (b) (4) was demonstrated with ⬛ (b) (4) extraction of band 7, where

the uncured core powder retains some controlled release properties despite the fine particle size of the material. Furthermore because of this

the API release characteristics would be expected to correspond to the size of the particles in a graded fashion. The data shown in these experiments support this view. In contrast, current formulation OxyContin appears to show binary API release kinetics in water (performs either as a controlled-release or like an immediate-release formulation). This API release property for OxyContin is independent of the manipulation methods that may be used to reduce its particle size.   For OxyContin once the tablet is no longer whole, the release kinetics are binary. This contrasts with the reformulated OxyContin that shows more graded release characteristics.

The controlled-release properties of reformulated OxyContin were reduced

y with smaller particle sizes and in   This was expected since the increased surface area of smaller particles leads to a greater exposure area for to solvent access and with less protection from

(b) (4) and increased physicochemical degradation (b) (4) in   similarly reduce the controlled-release properties of reformulation particles.

In conclusion, API release kinetics of reformulated OxyContin extraction appears to be a graded response in proportion to particle size as compared to OxyContin that shows a binary response. Even the smallest particle sizes of reformulated OxyContin   l, thereby retaining some of their controlled-release properties when extracted

(b) (4) is a more efficient means of extracting API than (b) (4) extraction (b) (4). Under no condition tested was API release faster from the reformulation than from current OxyContin.

(b) (4) solvents may be used to extract API from reformulated OxyContin. A combination of properties unique to (b) (4) may potentially allow these solvents to extract API more effectively than (b) (4). A number of different

OxyContin. API release in (b) (4) was a function of reformulated tablet particle size and the nature of the solvent. Similar to the case with (b) (4), at room temperature the rate at which API was released was proportional to the particle sizes of the manipulated drug product. In contrast, similar to its performance in water, current OxyContin appears to have binary API release kinetics in (b) (4). Regardless of the methods attempted for (b) (4) reduction, OxyContin was reduced to the same particle ranges that behave similarly in releasing API, showing immediate-release kinetics. Reformulated OxyContin, however, shows more graded release characteristics due to the (b) (4) properties of (b) (4)

The controlled-release properties of reformulated OxyContin were reduced (b) (4) with smaller particle sizes in This was expected because the increased surface area of smaller particles lead to greater exposure to solvent with less protection from the (b) (4)

properties of (b) (4). The API release profiles in _____ and _____

_____ at _____ (b) (4) up to _____ (b) (4) were similar. At _____ _____

_____ was slightly better than _____ for extracting API from

smaller particles. _____ was a poor solvent for reformulated OxyContin.

Neither time nor temperature improved the poor extracting properties of

_____

_____ (b) (4) *solutions*

(b) (4) solutions with varying pH are also used to extract API from

reformulated OxyContin. _____ (b) (4) o _____ (b) (4) may

potentially allow these solvents to extract API more effectively than (b) (4). A

range o _____ (b) (4) were used to extract API from reformulated OxyContin.

API release in _____ solutions was a function of reformulated

OxyContin particle size and the aqueous nature and the (b) (4) of the solvent.

At _____ (b) (4), the rate at which API was released is proportional to

(b) (4) of drug particles. As was the case for (b) (4) and _____ (b) (4)

(b) (4), OxyContin appears to show a binary API release kinetics in (b) (4)

(b) (4). Regardless of the manipulation methods attempted, OxyContin

was reduced to powder fairly easily. Crushed OxyContin particles,

regardless of the method of (b) (4)r, behave with immediate-release kinetics.

Reformulated OxyContin again shows more graded release characteristics.

The controlled-release properties of reformulated OxyContin are (b) (4)

substantially with (b) (4) particle sizes and in _____ (b) (4) solutions.

This was expected since the increased surface area of (b) (4) particles

lead to greater exposure to solvent with less protection from the

4

STUDY 3: DISSOLUTION IN ETHANOL

Objective

This study was designed to compare the performance of OxyContin and reformulated OxyContin in dissolution experiments conducted with   (b) (4))   mixture of ethanol and   (b) (4)   (b) (4)   (b) (4). The goal was to determine if and characterize how the dissolution profiles for API release differed in (b) (4) versus   ethano (b) (4)

Design

Dissolution experiments are performed in standard   (b) (4) o   (b) (4) or   ethano (b) (4) (a v/v mixture of   ethanol and   (b) (4). All bands from all strengths of reformulated OxyContin were tested and multiple time points were sampled to generate a

kinetic representation of API release. Sampling was continued until no further API release was observed. Data from this experiment include a time series representation of the amount of API released.

Details of protocol development and experimental methodology are provided in **Appendix II**. The statistical approach to calculating the number of samples used in each experiment as well the methodology applied to determine the significance of the results are provided in **Appendix II**.

Results

Table 3.1 presents f2 similarity values, calculated from the mean of 6 replicate analyses, for dissolution profiles (all bands of all strengths) in   as compared to dissolution profiles   (b) (4). The values for reformulated OxyContin range from 29-64, while for OxyContin the values are 96, 67, and 84. Dissolution profiles with f2 values between 50 and 100 are considered similar while values below 50, suggesting discordance between the profiles. In the case of reformulated OxyContin, 12 of the 42 f2 values were within the 50-100 range indicating similarity between results of dissolution in (b) (4) vs.   ethano (b) (4). The remaining 30 f2 values are below 50, indicating dissimilarity. Reformulated OxyContin dissolution rates in   ethano (b) (4) are slower than those seen in (b) (4) alone in 28 of these 30 cases. This suggests that media containing ethanol has some retarding effect on the rate of oxycodone HCl API release from reformulated OxyContin.

In two instances where the f2 value is below 50, further analysis reveals that the dissolution rate of reformulated OxyContin is faster in ▓▓ ethano ▓▓ compared to ▓▓ alone. These values are presented and highlighted with red shading in **Table 3.1**. The full dissolution profiles for both of these experimental conditions (band 6 from 10 and 15 mg tablets of reformulated OxyContin) are presented in **Figure 3.1**.   In both conditions, the dissolution profile in ▓▓ and ▓▓ ethano ▓▓ converge after the ▓▓▓▓ point. For the 10 mg sample there was wide variability in the data scatter at the earlier time points. This was most likely due to sampling errors associated with sampling of the finely powdered material. One of the replicates is censored because it was measured at an impossible value of 275% API release.   In the 15 mg sample (**Figure 3.1**) one replicate at the the 10 minute time point was also abnormally high (134%). The f2 value is heavily biased by this data point, but to preserve the integrity of the data this value was not discarded.

The remaining time points in the 15 mg profile show consistency with the corresponding SGF data. Slower release rates in ▓▓ ethano ▓▓ are observed in all earlier time points. The dissolution rates of reformulated OxyContin band particles in ▓▓ ethano ▓▓ as compared to ▓▓ are consistently slower or the same.

For illustrative purposes manipulated OxyContin tablets (powdered 10, 40, 80 mg tablets) were evaluated under similar conditions. The data is presented as "OxyContin control" in **Table 3.1**. The dissolution profiles for manipulated OxyContin are similar as indicated by their f2 value (>50
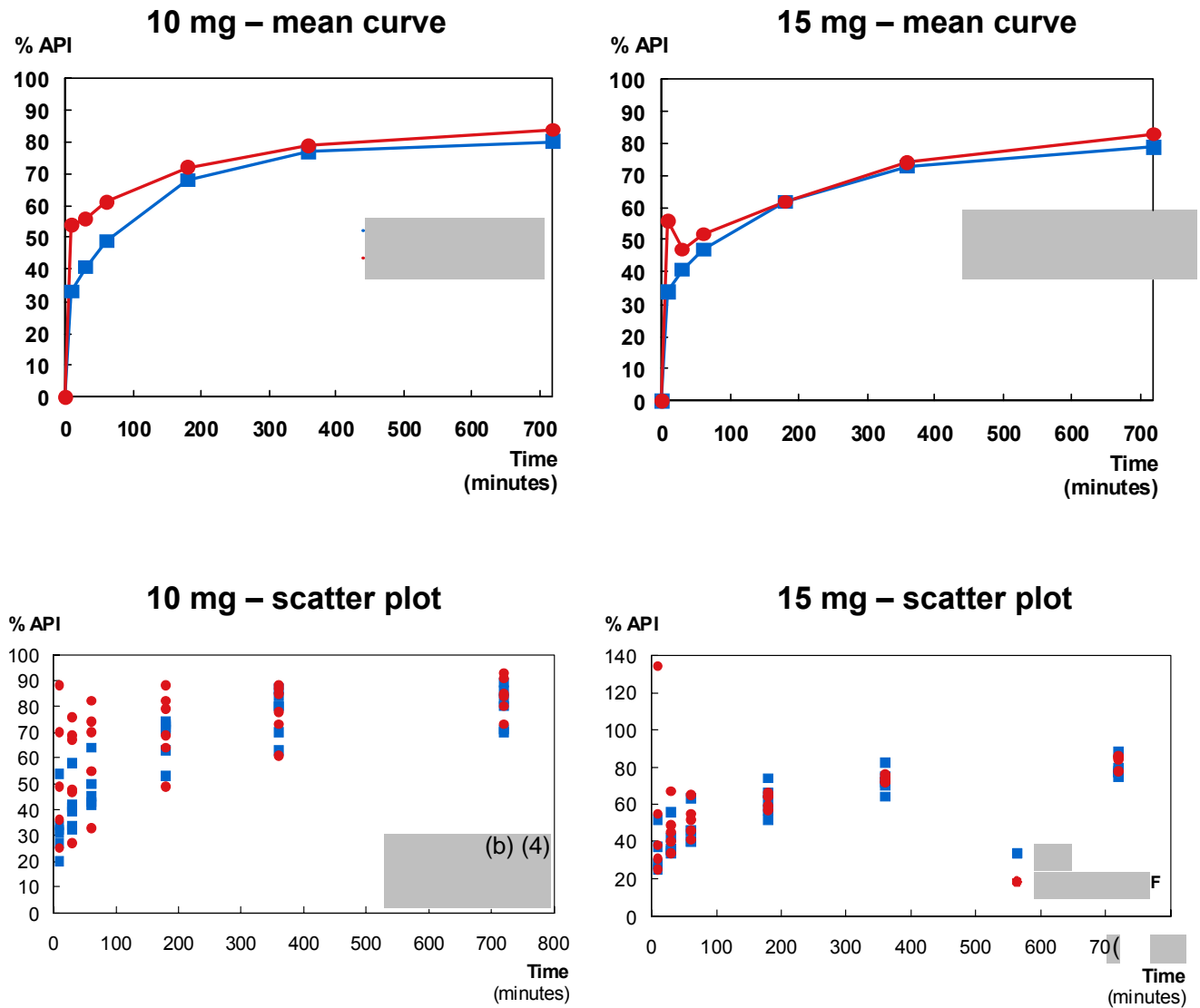
indicates similarity). The dissolution kinetic profiles for OxyContin approach that of an immediate-release formulation in both (b) (4) and ⬚⬚⬚⬚ (b) (4) (not presented).

The goal of these experiments were to evaluate the properties of reformulated OxyContin in ⬚⬚ ethanol media and compare that to its profile in (b) (4), the control media. **Table 3.1** shows that intact reformulated OxyContin is not vulnerable to "dose dumping" in ⬚⬚ ethano (b) (4) F and the baseline kinetics in (b) (4) versus ⬚⬚ ethano (b) (4) F are identical (data not shown). Similarly powdered OxyContin is not vulnerable to "dose dumping". In the absence of these findings because the baseline relationship for reformulated OxyContin relative to OxyContin was previously established, additional ethanol dissolution analysis for intact OxyContin were not performed.

Table 3.1   f2 Values for 100%   versus   ethano   dissolution results

Bands

Sample Strength	Band 1	Band 2	Band 3	Band 4	Band 5	Band 6	Band 7 (Uncured core)	OxyContin Control
10 mg	52	37	57	54	55	45		96
15 mg	45	41	38	53	49	48		
20 mg	46	36	47	51	35	64	N/A	N/A
30 mg	44	37	48	43	42	42		
40 mg	42	53	61	60	52	51		67
60 mg	47	40	44	48	31	37		N/A
80 mg	47	52	40	43	29	47	29	84

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Figure 3.1   Reformulated OxyContin (10 and 15 mg) dissolution in SGF versus ▮ ethanol in ▮ , band 6 particles
(percent of label claim API extracted)

10 mg – mean curve

15 mg – mean curve

10 mg – scatter plot

15 mg – scatter plot

Discussion

Reformulated OxyContin is not vulnerable to ethanol-induced acceleration of API release in dissolution experiments. This observation holds true regardless of particle size as supported by data shown in **Table 3.1**.

, the primary endpoints of these experiments were to examine "dose dumping" by ethanol. We have previously demonstrated that band particles from reformulated OxyContin do not show unusual or accelerated API release properties in   solutions (see Study 2,   (b) (4) solvents). Therefore we have concluded that the reformulated product, either (b) (4)t or   (b) (4) particle sizes, is not susceptible to ethanol induced accelerated release either in dissolution studies or in   (b) (4) extractions.

STUDY 4: EXTRACTION IN ADVANCED SOLVENTS

Objective

This study was designed to evaluate the oxycodone API release characteristics of reformulated OxyContin after   (b) (4) extraction in "advanced solvents"--- solvents that are not   (b) (4)

                                ]. The goal was to determine and compare the API release kinetics for OxyContin and reformulated OxyContin in "advanced solvents" for a range of particle bands.

Design

A simple extraction protocol was developed to assess the efficiency of extraction with organic solvents that are   (b) (4) . Solvents were selected by polarity and solubility criteria and to adequately cover the range of possible outcomes. Three particle bands representing   (b) (4) and   (b) (4) were selected to bracket the full range of particle sizes. Extractions were performed at different times to provide a kinetic representation of API recovery. Finally, the experiments in this study were performed both a   (b) (4) and   understand how temperature influences API release characteristics in these solvents.

Data from these experiments include band-specific recovery curves generated with multiple solvents over time at either   (b) (4) or

Comparator data was generated from crushed OxyContin tablets in identical extraction conditions.

Details of protocol development and experimental methodology are provided in **Appendix II**. The statistical approach to calculating the number of samples used in each experiment as well the methodology applied to determine the significance of the results are provided in **Appendix II**.

Results

Advanced, non-consumable solutions may be used to extract API from reformulated OxyContin tablets. Kinetic API release data for extraction in ▮▮▮ and ▮▮▮ at (b) (4) are presented in **Figure 4.1 A-B**.

Band 1 ▮▮▮ reformulated tablets) maintains controlled-release properties up to ▮▮▮ in ▮▮▮ and up to (b) (4) in ▮▮▮ Band 4 ▮▮▮ (b) (4) maintained some controlled-release in ▮▮▮ a (b) (4) ▮▮▮ (b) (4) (76% API release as compared to 98% release with crushed OxyContin), while both bands 4 and 6 (b) (4) maintain controlled-release ▮▮▮ up to (b) (4). API release for crushed OxyContin reaches >90% at (b) (4) in both ▮▮▮ and ▮▮▮

It is expected that solutions at (b) (4) temperatures would lead to faster release of API than similar solutions at (b) (4) temperature. To test this hypothesis, the above experiments were repeated in a ▮▮▮ with continuous agitation. API release rates ▮▮▮ and ▮▮▮ at ▮

▮ were similar to the API release a (b) (4) temperature for all bands studied (data not shown).

▮ was not an effective extraction solvent for reformulated or crushed current OxyContin at either (b) (4) (**Figure 4.1 C**) or ▮ ▮ ▮ was observed with band 6 of reformulated and crushed current OxyContin at (b) (4) which were measured at 29% and 23%, respectively.

Discussion

Band 1   (b) (4)   reformulated OxyContin) maintains its controlled release property up to   (b) (4)   in   and up to   (b) (4)   in   The controlled-release properties of reformulated OxyContin is maintained for the smallest particles   (b) (4)   even up to   (b) (4). Smaller particles behave as immediate-release products when extracted in   The slower API release rate observed in   for all ranges of the particles studied at   (b) (4)   temperature may be due to the aqueous properties of this solvent.   aqueous component of   is likely to induce   (b) (4)   constituent in reformulated OxyContin. This   (b) (4)   would be expected to retard the release of API.

In contrast to the reformulated product, OxyContin appears to have a binary API release kinetics. API release for crushed OxyContin reaches >90% at   (b) (4)   in both   The API release profile of   (b) (4) reformulated OxyContin in   is slightly faster at   (b) (4)   as compared to extraction in water. All other extraction conditions in advanced solvents are slower than corresponding extraction in   (b) (4)
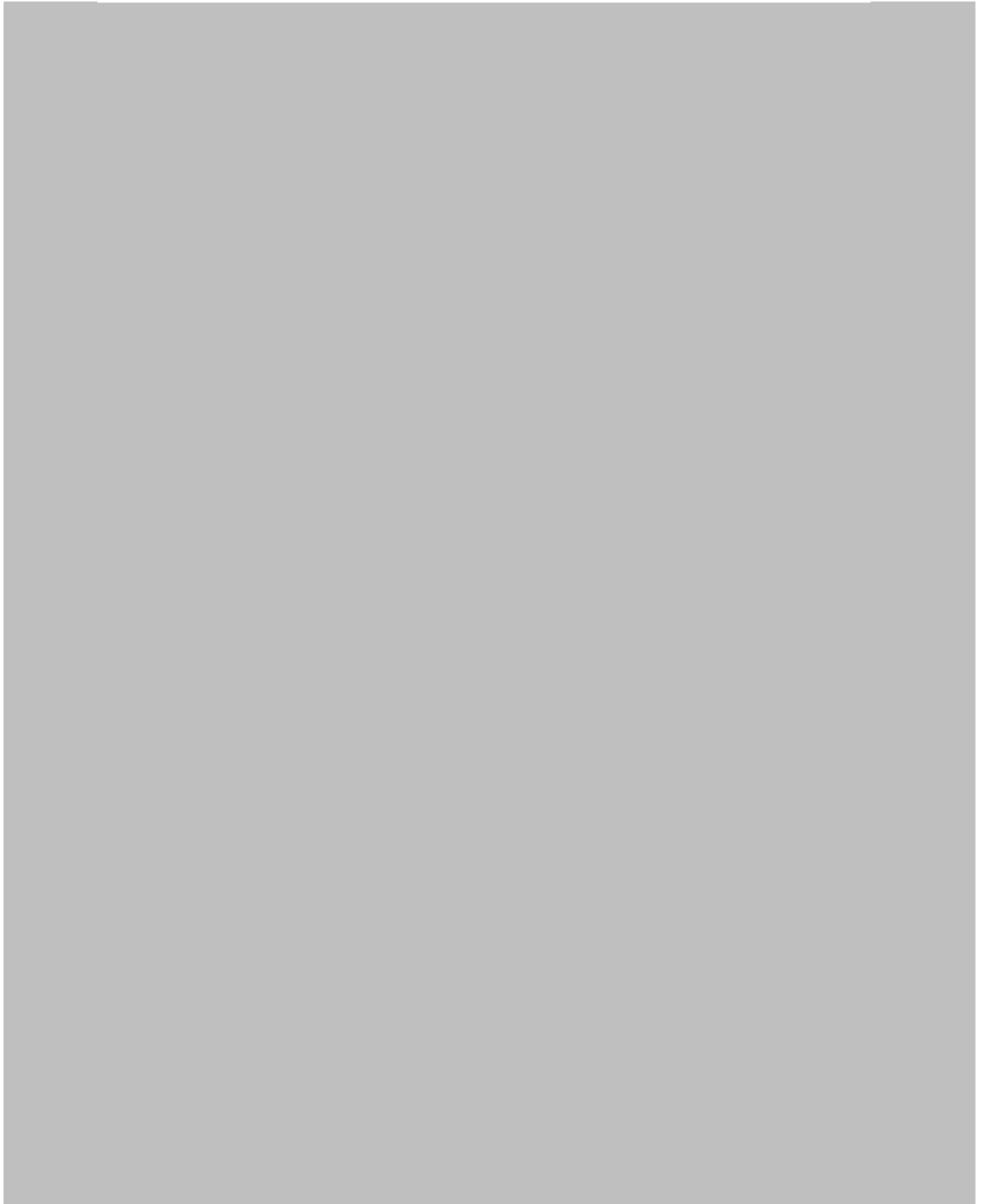

Comparison across all solvents tested (Studies 2 and 4)

The aim of Studies 2 and 4 was to better understand the strengths and limitations of reformulated OxyContin tablets in manipulation scenarios designed to extract API in a variety of solvents. Once the extraction studies were concluded the performance of each solvent was compared to the others tested.
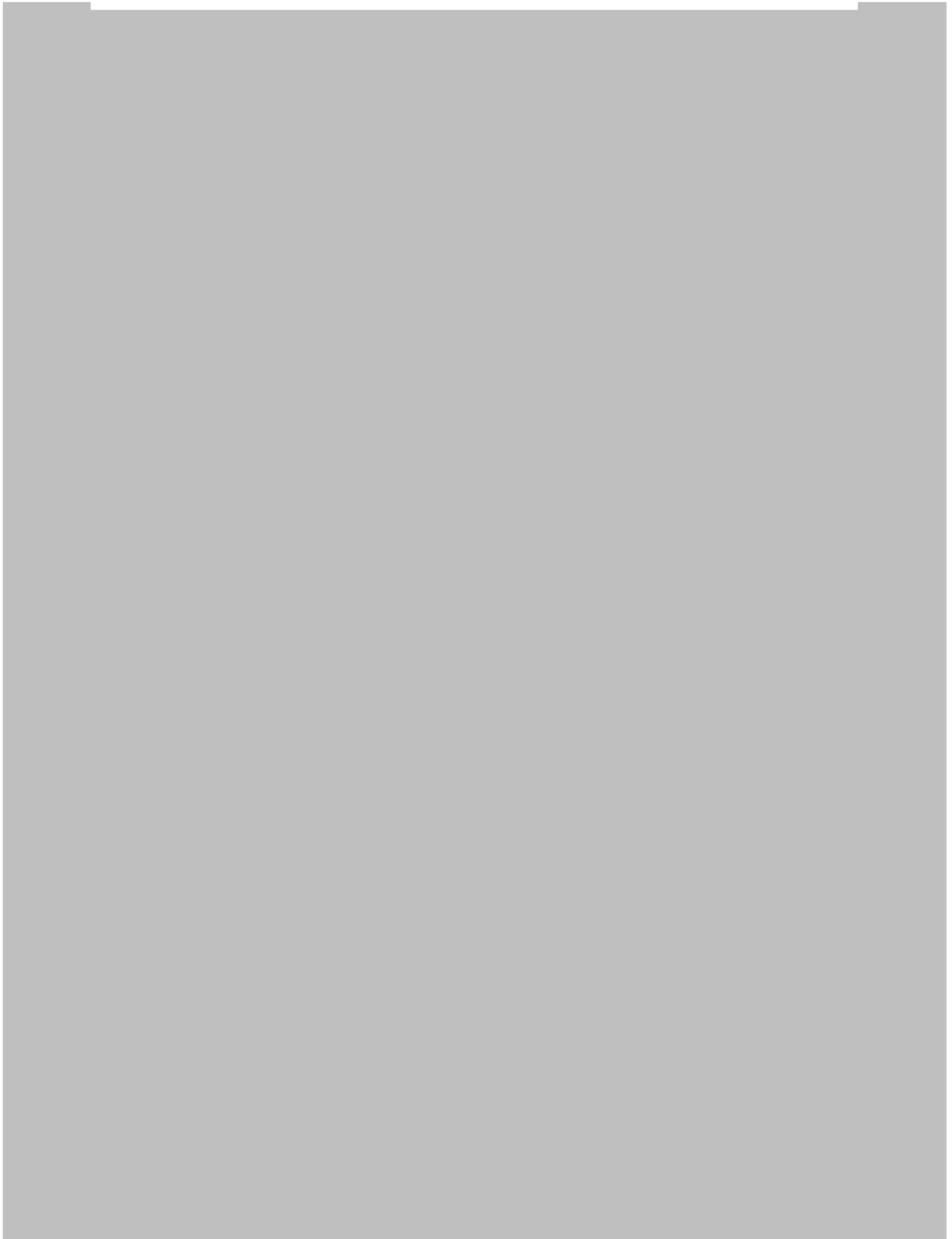
STUDY 5: SYRINGABILITY, INJECTABILITY AND EXTRACTION AFTER VAPORIZATION

Objective

These experiments were designed to simulate preparation for intentional misuse and abuse via intravenous and inhalation consumption. The goal of these experiments were 1) to determine how much API could be loaded and delivered via a syringe for intravenous abuse 2) to determine how much API is released after vaporization of the product.

Design

Intravenous use was studied in standard fashion by analyzing the rheological limits of reformulated OxyContin when aspirated into an empty syringe (syringability) and when expunged from a loaded syringe (injectability). To determine the limits of syringability and injectability, the experiments were performed after mixing a fixed volume of (b)(4)er with a (b)(4) (b)(4)) of reformulated OxyContin (b)(4) (b)(4) in these experiments because it represents the (b)(4) condition of reformulated OxyContin. Studies were conducted at both room temperature and after boiling and both syringability and injectability were assessed using a range of needle gauges.

(

An inhalation assay was designed to examine the release characteristics of API from reformulated OxyContin as a proxy for its potential to be smoked. API containing powder was dry heated to vaporization.   Vaporized API was extracted with ▓▓▓▓▓▓▓ methodology ▓▓▓▓▓▓ (b ▓▓▓▓▓▓▓▓ and heating tube apparatus. This apparatus uses standard ▓▓▓ (b ▓▓▓▓ to trap the vapors generated after heating and evaporating fine reformulated OxyContin ▓▓▓ .

Syringability

To determine the syringability of OxyContin ▓▓▓▓▓▓▓ were added to ▓▓▓▓ of reformulated OxyContin particles and the amount of API successfully aspirated into the syringe was measured. Syringability was assessed using a range of needle gauges. Because heat can alter the rheological properties of some solutions, syringability was assessed both at room temperature and after boiling. To ensure adequate API extraction prior to syringe aspiration, varying amounts of time were allowed after mixing reformulated OxyContin powder ▓▓▓▓▓ . Data obtained from this experiment include the total amount of oxycodone API and the volume that was successfully syringed. Comparator data were generated from manipulated OxyContin tablets.

Injectability

Injectability was assessed by expelling solutions of reformulated OxyContin from preloaded syringes through different gauge needles. The total volume and amount of API expelled was measured for a total ▓▓▓▓▓▓

continuous effort to inject. This time point was set with input by experts and is believed to reflect a serious effort by a motivated abuser. To determine the limits of injectability, these experiments were repeated with increasing volumes of (b) (4). To determine how heating the admixture could improve injectability, the experiments were conducted at room temperature and after heating to boiling. The endpoint in these experiments was to define the total amount of API and volume that could be injected from a preloaded syringe. Data from these injectability experiments include the total amount oxycodone API and the volume that is successfully extruded. Comparator data was generated from manipulated OxyContin tablets.

Extraction after vaporization

Inhalation (smoking) was simulated with (b) and heating tube apparatus. This apparatus uses standard (b)-(4) (b) technology to trap vapors generated after dry heating and vaporizing finely powdered reformulated OxyContin tablets. Upon completion of the experiment the (b) was removed and solvent was used to extract and to recover the total amount of trapped API. The endpoint in these experiments were vapor collection over (b) (4) to ensure that all oxycodone API was either collected or pyrolyzed. Comparator data were generated from both manipulated OxyContin tablets

Methodology for syringability, injectability and "smoking" assays were developed at Purdue. Details of protocol development and experimental methodologies for all of these studies are provided in **Appendix II**. The

statistical approach to calculating the number of samples used in each experiment as well the methodology applied to determine the significance of the results are provided in **Appendix II**.

Results

Syringability

Figure 5.1 contains mean results for each of the syringability experiments. Boxes shaded green indicate the conditions in which aspiration was unsuccessful (i.e., < 1 ml of the sample was aspirated due to viscosity). Yellow and red shaded boxes contain the amount of API (mg) extracted and the volume (ml) aspirated. Color coding was determined by the concentration of the aspirate in mg/ml, which was set as a standard based on the amount of API available in one ml when using a common insulin syringe (a realistic amount based on the type of needle and syringe most widely available to abusers). Results for 10 mg OxyContin tablets were not included due to the low strength and consequent low yield of API. Aspirates obtained for (b) (4) preparations of OxyContin 40 and 80 mg tablets contained (b) (4) The lower concentration limit (b) (4) was used as a cut off in color coding **Figure 5.1**. Yellow indicates that aspiration was successful (>1ml); however, the concentration of the aspirate was (b) (4). Red indicates successful aspiration of a liquid with concentration o (b) (4). As shown in **Figure 5.1** there are (b) (4) conditions (b) (4) temperature and (b) (4) conditions after (b) (4), for reformulated OxyContin, in which the aspirate contains equal and more than (b) (4) None resulted with a 27 gauge needle. In the remaining 135 conditions, the sample could not be aspirated or the concentration of the aspirate was (b) (4) (green boxes).

In contrast, for OxyContin 40 mg and 80 mg tablets [REDACTED] of API was available for injection even after preparing the sample in 2 mls. High viscosity prevented the aspiration of reformulated OxyContin when prepared with 2 ml of water.

Figure 5.1   Syringability results-

Volume expelled and mg of API recovered by tablet strength, syringe volume and needle gauge

(b) (4)

Figure 5.1 (continued)   Syringability results-

Volume expelled and mg of API recovered by tablet strength, syringe volume and needle gauge

Injectability

As shown in **Figure 5.2 A**, injecting a solution of material at room temperature with a 27 gauge needle allows for   to be injected. This is consistently seen regardless of the volume of the preparation. Boiling the sample before preloading the syringe, as shown in **Figure 5.2 B** increases the amount of API in the extrudate   ); in this case the sample volume is   . For all of the conditions tested, tablet strength was not shown to be a contributing factor, meaning the difficulty observed in expelling the material was not conditional on the tablet strength.

To better understand how the reformulation performs under a wide range of conditions   needles were evaluated for injectability.   Using an   resulted in a significant improvement in recovering material after injection. The amounts of preparatory volume or temperature did not result in significant differences in the amount of API expelled   once this gauge needle was used. Results for   syringe are found in **Figure 5.2 C-D**. These results can be compared to those obtained with OxyContin, which is easily expelled in all conditions delivering   label claim API through a   (b) (4).

Figure 5.2   Results for injectability
(% of API and ml of volume expelled)
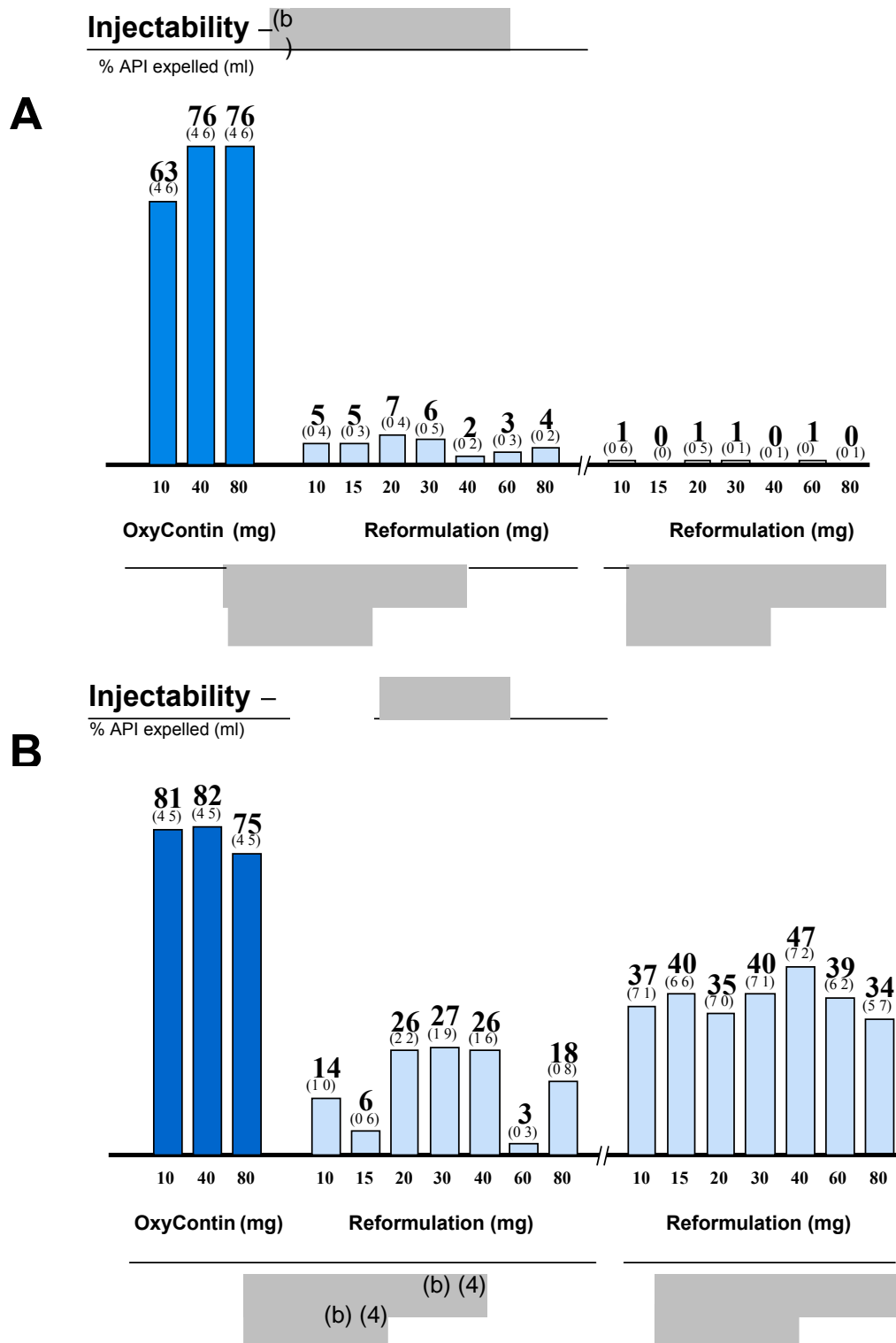
Injectability – (b)
% API expelled (ml)

A

10	40	80

OxyContin (mg)

Reformulation (mg)

Reformulation (mg)

Injectability –
% API expelled (ml)

B

OxyContin (mg)

Reformulation (mg)

Reformulation (mg)

(b) (4)

(b) (4)

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Extraction after vaporization

Figure 5.3 A-B, show the results of optimization studies performed to determine the relationship between the vaporization of API and the degradation of API through pyrolization. This figure shows that as the amount of vaporized API increases for reformulated or current OxyContin, the amount of residual API rapidly decreases. It is difficult to   because of the proximity of the vaporization and degradation temperatures   ) of oxycodone HCl, the salt form of oxycodone.   In the case of reformulated OxyContin, API can not be vaporized   possibly due to interference from the excipient. Therefore, the analysis for reformulated OxyContin was performed at   which is just below the   . As shown in **Figure 5.3 A-B**, the final amount of oxycodone HCl vaporized for both OxyContin or reformulated OxyContin is   No residual API in the analysis tube was found suggesting pyrolization of the remaining API. Using the data shown in **Figure 5.3 A-B**, the optimum analysis times were determined to be   and   (b) (4) OxyContin.

     (b) (4) e was used as a positive control. The melting point of oxycodone   (b) (4), and much of the API can be vaporized without degradation. Approximately 70% vaporization efficiency was achieved in   (b) (4) after which no API remains in the analysis tube.

Figure 5.3 C shows the amount of API recovered from vaporized samples under optimal time and temperature conditions.   As shown in this figure, ░░░░░░░░░░░░░ of all strengths of reformulated OxyContin results ░░░ ░░░░░░░░░░ after ░░░░░░░░ of heating. Results for OxyContin ░░░░░ This is likely related to the higher vaporization temperature of the salt (HCl) form of the drug. Oxycodone ░░░░░ has a lower vaporization temperature and yields a far higher vaporization efficiency of ░░░

Figure 5.3 Relationship between vaporization and pyrolization

A

Relationship between Vaporization and
Pyrolization of reformulated OxyContin tablets
(%API Recovered)
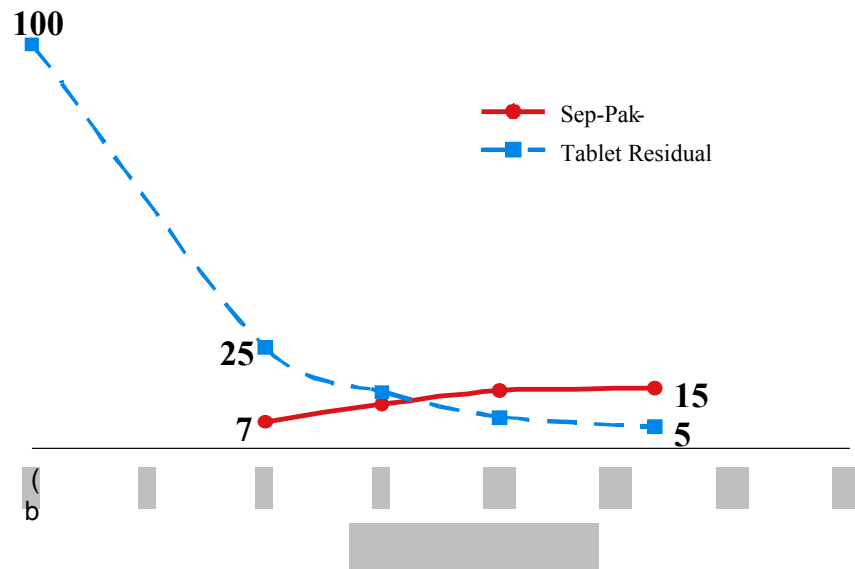
B

Relationship between Vaporization and
Pyrolization of OxyContin tablets
(%API Recovered)
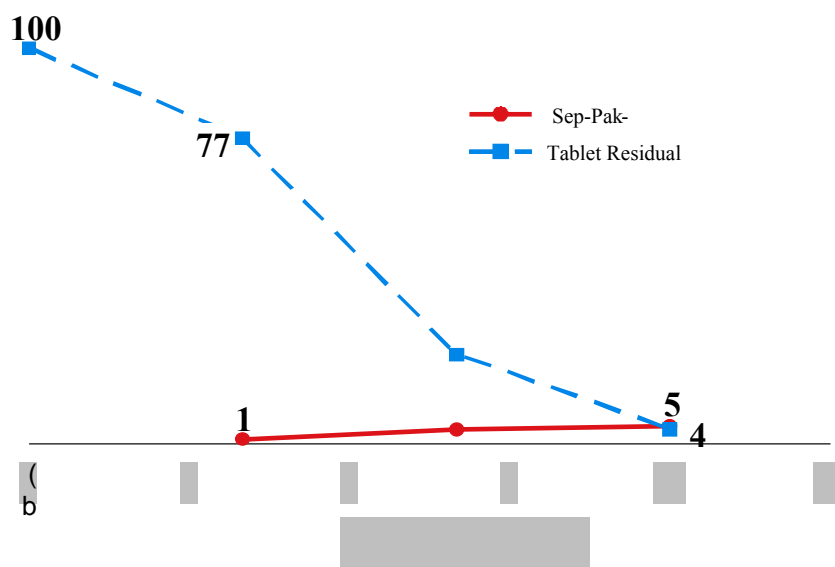
Figure 5.3 (continued)

Discussion

Syringability

Syringability preparations of reformulated OxyContin tablets result in difficult aspiration conditions and yield low drug delivery. This is due to the viscosity of polyethylene oxide after hydration.   Larger preparatory volumes are necessary to counter the viscosity of the solution. However, this is counterproductive for an abuser as the solutions become increasingly dilute.

To yield higher API,   volumes are required for injection.
Reformulated OxyContin could only be syringed with   .
Furthermore although solutions could be syringed with an
the resulting solution is highly viscous, likely deterring intravenous injection.

Injectability

Backfilling a syringe is not likely amenable to abuse due to the
      after hydration. The   renders the
preparation of reformulated OxyContin tablets   and
unattractive as a preparation for intravenous injection.   Very little API could
be pushed through a   , even with significant force. The use
of an   resulted in the extrusion of higher amounts of API.

However, large bore needles are not readily available to the general public.
Boiling aided in the amount of sample expelled.   To do this study the
syringe had to be backloaded and immediately injected with
(b) (4) solution. This would require a potential abuser to inject molten hot
material, which is undesirable and uncomfortable.

      As the temperature of a boiled solution
     (b) (4), the material becomes

STUDY 6:

(b) (4)

(b) (4)

Table 6.2

(b) (4)

STUDY 7:   (b) (4)

(b) (4)

(b) (4)

(b) (4)

Additional information

CONTENTS OF NDA 22-272 RESUBMISSION TO FDA

NDA 22-272 for reformulated OxyContin was resubmitted to FDA on March 30, 2009 and included five main elements:

- Pharmacokinetic data demonstrating bioequivalence of the current and reformulated OxyContin

- *In vitro* testing on reformulation's physicochemical properties

- Stability and other CMC data for all tablet strengths, including 60 and 80 mg strengths

- Proposed label, without reference to "tamper resistance" or improved physical properties

- Interim risk evaluation and mitigation strategy (REMS) proposal

BIOEQUIVALENCE OF REFORMULATED OXYCONTIN

Reformulated OxyContin met strict bioequivalence criteria and, as a result, is therapeutically interchangeable with the current formulation of OxyContin for patients when used as directed. Cmax mean ratio observed was 97.0 (with 90% CI limits of 93.11, 101.13) and AUCt mean ratio was 95.2 (with 90% CI limits of 92.48, 97.93) (see **Figure 8.1**, **Table 8.1**).

Figure 8.1   Pharmacokinetic data demonstrating bioequivalence of current and reformulated OxyContin
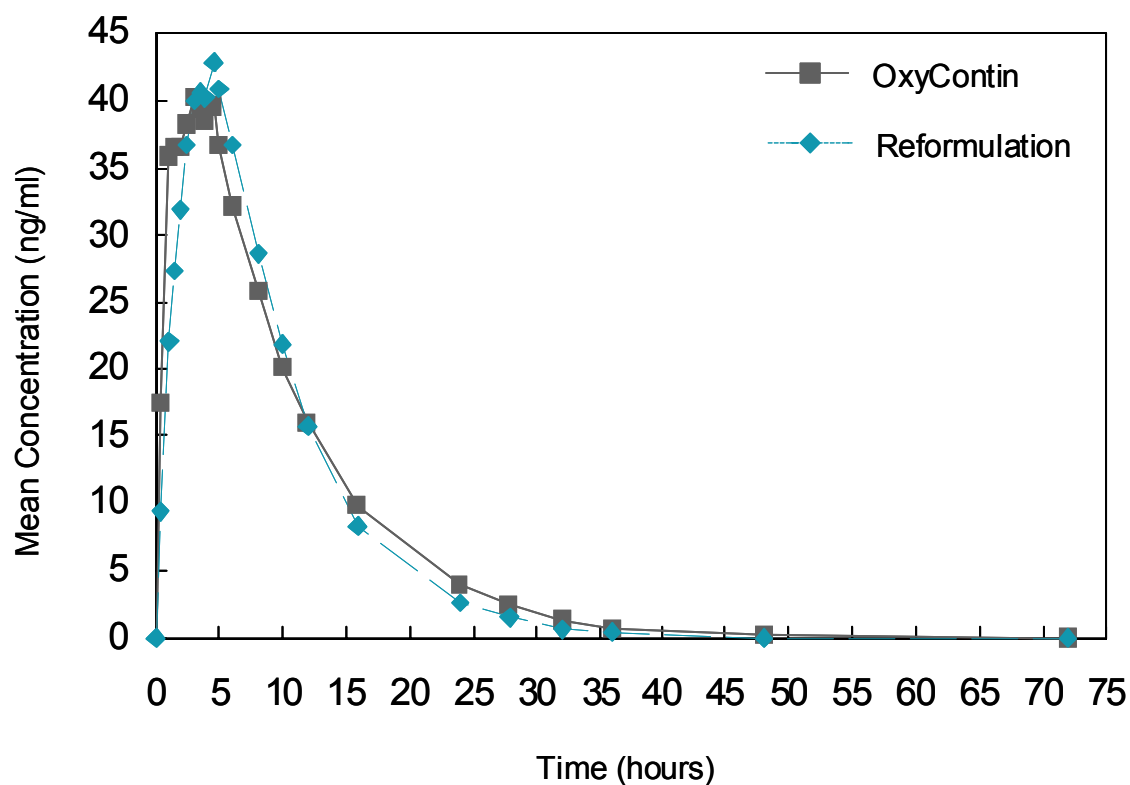
Table 8.1   Summary of pharmacokinetic results following oral administration of reformulated versus current formulation OxyContin in the fed and fasted states

Study	Dose	Condition	Cmax		AUCt	
			LS Mean Ratio	90% CI	LS Mean Ratio	90% CI
OTR1002	10 mg	Fed	105	(101.06, 108.51)	95.7	(93.85, 97.68)
OTR1003	10 mg	Fasted	102	(99.35, 105.42)	98.3	(95.20, 101.48)
OTR1004	40 mg	Fed	99.9	(95.40, 104.52)	92.6	(90.13, 95.13)
OTR1005	40 mg	Fasted	97.0	(93.11, 101.13)	95.2	(92.48, 97.93)
OTR1008	80 mg	Fed	110	(105.21, 114.47)	94.9	(92.90, 97.02)
OTR1009	80 mg	Fasted	103	(98.67, 106.66)	97.1	(94.41, 99.94)
			PK Metric	Slope	90% Conf. Interval (Power Model)	Critical Range (Power Model)
OTR1006 Dose proportionality	10-40 mg	Fasted	Cmax	1.06	(1.03, 1.09)	(0.8390, 1.1610)
			AUCt	0.963	(0.940, 0.987)	
OTR1012 Dose proportionality	40-80 mg	Fasted	Cmax	0.845	(0.771, 0.919)	(0.6781, 1.3219)
			AUCt	0.970	(0.910, 1.03)	

RISK MITIGATION

Although comprehensive preclinical work and data from *in vitro* experiments are meant to reduce the uncertainties associated with this reformulation, further risk mitigation measures are necessary to ensure that the benefits of the product continue to outweigh the risks associate with its use. Forecasting post-marketing clinical outcomes, with a high degree of precision, on the basis of *in vitro* experiments or other pre-marketing studies is not currently possible. The uncertainties inherent in predicting the outcomes associated with the introduction of a new or reformulated product into the market with only pre-approval data need to be addressed by balancing the potential risks with the product's clear benefits. This is especially important to guide us forward in the absence of relevant precedent. Therefore in parallel to developing and executing the *in vitro* experimental studies, we have engaged experts to explore and develop programs that will enable us to mitigate the risks associated with the uncertainties.

REMS have become a significant topic for discussion and development since the May 5, 2008 Advisory Committee meeting. The nature of diversion, misuse and abuse of therapeutic medications make it evident that comprehensive strategies and approaches are necessary across all opioids. Purdue has taken an active and significant role in an Industry Working Group of over 20 branded and generic companies that is driving towards creation of a collective proposal to the FDA for a class-wide REMS for modified-release and long-acting opioids. This group has been meeting regularly since April 2009 and has made significant progress. A summary of

the work from this group was presented during the May 27-28, 2009 opioid REMS open meeting.

While individual sponsors actively develop formulations that represent important incremental improvements in robustness and pursue hypothesis-driven risk mitigation approaches specific for products, many larger questions about risk need to be answered collectively by all stakeholders involved (i.e., how to measure unintended consequences, education about risks and benefits, monitor use, etc.). Purdue has independently made consistent and growing investments in a number of efforts to mitigate abuse and diversion risk, but we recognize that this is not enough.

We consider the discussion of risk management to be critically important in the overall approach to introducing a reformulation. However, based on guidance from FDA this document has not discussed risk management and rather focused on providing Advisory Committee members an overview of the *in vitro* studies conducted. The interim REMS proposal for the period before a opioid classwide RES is in place for reformulated OxyContin is the subject of a separate discussion with FDA.

Discussion

IMPLICATIONS OF *IN VITRO* TESTING RESULTS

The studies described in this document assessed the characteristics of reformulated OxyContin tablets when subjected to tampering procedures such as crushing, powdering, and extraction methods that are practiced, or may be attempted with OxyContin and other opioids.   Reformulated OxyContin was shown to be demonstrably more difficult to crush than current OxyContin and

. Given that oral abuse of OxyContin is the most common route of administration, the added hardness and hydrogelling properties of the reformulation are incremental improvements when compared to the current formulation of OxyContin, however this will require further study. Intranasal misuse also is frequently reported for OxyContin. The hydrogelling properties of reformulated OxyContin are likely to discourage abuse and misuse by this route. In order for API to be absorbed after insufflation, powdered insufflated material must be moistened in order for the active ingredient to cross the capillary barrier. Upon contact with moisture the reformulated OxyContin hydrogels, which as demonstrated by our data, is expected to retard the release of API. In comparison with current OxyContin where hydrogelling does not occur, drug release after insufflation of hydrogelled reformulated OxyContin is expected to be slower. These differences in kinetics of API release as well as the viscosity and physical appearance of hydrogelled powder will likely discourage abuse and misuse by this route. A smaller number of misusers extract OxyContin for

injection. The ability to extract oxycodone from the reformulation is more difficult and requires a greater expenditure of time or effort to prepare a solution for injection, as well willingness to inject large volumes and/or to use a large bore needle (e.g., 18 gauge, which is not commonly available). The effects of alcohol (ethanol) co-administered with reformulated OxyContin tends to retard release, rather than enhancing it as demonstrated in dissolution tests.

ANTICIPATED IMPACT ON MISUSE AND ABUSE

As mentioned above, the *in vitro* data presented in this report alone do not allow Purdue to accurately (quantitatively) predict the impact of this reformulated product on abuse and other "real world" outcomes. However, these in vitro data *do* provide the basis for a qualitative or directional prediction of these "real world" outcomes once this reformulated product is introduced to the market. For example, the *in vitro* data described below indicate that the physical properties of the reformulation will minimize or eliminate inadvertent misuse by crushing, make intravenous abuse difficult if not impossible via a common insulin syringe, render insufflation likely less attractive and yield very little API via smoking.

Despite the utility of these *in vitro* data, pre-marketing assessments whether in the lab or clinical study setting are of limited predictive value. For example, it is not possible to accurately predict unintended consequences of introducing reformulated OxyContin in terms of potential shifts to the use of other drugs (e.g. methadone, heroin). In addition, *in vitro* data cannot predict the impact of the reformulation on oral abuse of intact

tablets. Therefore, although these pre-marketing data guide us in our understanding of how certain populations may be less likely to misuse (intentionally or unintentionally) and abuse this formulation, we are unable to state with any level of certainty how the patterns will shift and if the total "denominator" of abuse will change.

In addition to insights gained regarding the improvements made by reformulating OxyContin, our *in vitro* experiments were designed to explore the limitations of the reformulation. All experimental scenarios were carried out to the point that all API or no further API was released with additional time. This means that the endpoints were specifically designed to demonstrate the time or effort necessary for the complete release of oxycodone by defeating the controlled release mechanism. We compared the physical properties of the reformulation to current OxyContin under anticipated abuser tablet manipulation scenarios. In most tablet manipulation simulations tested, the reformulated product was demonstrated to be more resistant to physicochemical tablet manipulation than the current formulation. Further, despite extensive testing we could not identify any new or unexpected vulnerabilities of the reformulation.

PURDUE'S INTENT

Our goal is to help address the ongoing public health problem of prescription opioid abuse by introducing a reformulation that is an incremental improvement for both patient and non-patients. We do not intend to use this reformulation as a basis for targeting or broadening the

patient population by suggesting enhanced safety, tamper resistance, or abuse resistance or deterrence in the absence of evidence supporting such claims. Accordingly we will:

- **Stop shipping the current formulation of OxyContin as soon as all tablet strengths (10-80 mg) of the reformulated product have been approved and are available for shipping.** Based upon our ability to maintain low levels (approximately 2-3 weeks) of original formulation inventory at the wholesaler level, we expect the transition from marketed OxyContin to reformulated OxyContin at the individual patient level to occur within approximately 6-8 weeks of shipping. Inventory of the old formulation in the pipeline will be managed to an extremely low level to minimize the availability of both formulations in the market at the same time. We expect that 90% of the current formulation will be switched within approximately two weeks. We will do this in a manner designed to minimize confusion and disruption to physicians, pharmacists and patients.

- ***Not seek label claims related to "tamper resistance," "abuse resistance," or "abuse deterrence" of the reformulated tablets.*** While small changes to the label are necessary to reflect the substitutions in tablet excipients of the reformulation and to provide new summary pharmacokinetic data, we want to avoid intentional or unintentional messaging that this reformulation offers advantages over the existing OxyContin formulation. We do not intend to use this reformulation as grounds for targeting or broadening the patient population on the basis of enhanced patient safety or resistance to tampering. In contrast to our position in May 2008, we now realize

that it is not possible to scientifically predict the impact that improvements in physical properties of any abused prescription medication will have on "real world" abuse, no matter how large the improvements ("deltas") observed via *in vitro* testing or any other pre-approval testing are. Purdue will only consider requesting "tamper resistance" labeling with the availability of supportive post-marketing epidemiological data. This data must describe and quantify the impact of the reformulation on different segments of OxyContin abuse and misuse.

- ***Retain the current OxyContin trade name.*** We intend to retain OxyContin trade name for the reformulation in order to avoid confusion on the part of the patient, pharmacist and physician regarding the nature of the product being prescribed or dispensed. Additionally, a change to the trade name would require announcements, new labeling and new promotional materials, with the associated publicity that could have the unintended potential of conveying precisely the message we are planning to avoid – that a "new and improved" formulation lacking the risks understood to be associated with OxyContin is being introduced.

Concluding remarks

Reformulated OxyContin is bioequivalent to current OxyContin, as defined by strict bioequivalence criteria. As a result, the new formulation is

therapeutically interchangeable with the current formulation for patients when used as directed.

No therapeutic product is completely immune from sophisticated tampering methods, but reformulated OxyContin tablets present a higher barrier to physicochemical tampering compared to the current formulation. The reformulation increases the amount of time or effort that misusers and abusers must expend to overcome its controlled-release mechanism to extract oxycodone API to achieve a "high". The *in vitro* experimental studies described above demonstrated this incremental improvement over the current formulation.

Our experimental results suggest that the reformulated tablets will be more difficult to accidentally misuse by crushing, more difficult or impossible to abuse intravenously using a common insulin syringe, likely less attractive to abuse via insufflation and yield very little API when smoked. Furthermore these data show that the reformulation is not more susceptible to tablet manipulation than OxyContin under any testing condition. The scientific quality and scale of these studies map the terrain of the potential outcomes of abuse and misuse to an unprecedented level, enabling future hypothesis-driven risk mitigation strategies.

We hope that this document has been helpful in briefing members of the Advisory Committee on the *in vitro* testing work that Purdue has recently completed.

Glossary of Terms

Abuse: The use of a drug in a manner detrimental to the individual or society but not meeting criteria for addiction.

"Advanced" solvents: Refers to solvents that are organic and not directly ingestible

API: active pharmaceutical ingredient.

Also referred to as **particle bands** and **particle fractions**.

Dissolution: Refers to testing designed to assess the rate of API release in a large volume of solvent   (b) (4)

Dose dumping: Refers to a phenomenon sometimes observed in other abused controlled-release prescription tablets in which accelerated release of **API** from the controlled-release mechanism is observed. In this document "dose dumping" specifically refers to accelerated release of API in ethanol solvent.

Excipient: An inactive substance added to pharmaceutical tablets as a carrier for the **API**. In the case of **reformulated OxyContin** tablets the primary excipient **PEO** is used to provide a controlled-release mechanism, and (after curing) confer the improved physical properties of crush-resistance and hydrogelling in small volumes of solvent.

Extraction: Refers to testing designed to assess the rate of API release in a small volume of solvent (30 ml).

Free-basing: The conversion of an API or illicit drug substance from its water-soluble salt form (e.g., cocaine-HCl) to its standalone basic form of an amine (usually an alkaloid natural product, e.g., "crack-cocaine").

Household Solvents: Refers to solvents that are ingestible and/or are easily obtainable (cooking oil, ethanol, water, coke and saline).

Hydrogel: Process by which particles or whole **reformulated OxyContin** tablets become highly viscous in small volumes of solvent (property conferred by the **PEO** excipient matrix).

Insulin syringe: 1 ml syringe with a 28 gauge needle. This is the most commonly available type of syringe, most likely to be used by abusers interested in abusing via intravenous route of administration.   Also referred to as a **tuburculin syringe**.

Injectability: Refers to the ability of a material to be expelled from a syringe through a needle (as it would be in an injection).

in vitro **experimental studies:** Refers to the *in vitro* experiments described in this report. These studies tested the robustness of the controlled-release mechanism of **reformulated OxyContin** tablets under scenarios of known and anticipated abuser tablet manipulations in the "real world" ("tamper testing") and was designed in response to the FDA's October 3, 2008 Complete Response Letter to Purdue.

Mechanical fractionation: Refers to mechanical reduction of tablets to smaller particles. Also referred to as **particle size reduction**.

Misuse: The exposure resulting from the use of a prescription medication in ways other than how it was prescribed, contrary to approved labeling unless taken as directed by a healthcare provider, and below the threshold of abuse.

Particle bands: (see **bands**)

Particle fractions: (see **bands**)

Particle size reduction: (see **mechanical fractionation**)

Polyethylene oxide (PEO): PEO is the main excipient of **reformulated OxyContin** tablets.

Reformulated OxyContin: Also referred to as **the reformulation**. Refers to the bioequivalent reformulation of OxyContin tablets. The currently marketed formulation is referred to throughout this document as OxyContin.

RT: Room temperature (25 ºC).

SGF: Simulated gastric fluid media.

Syringability: Refers to the ability of a material to be loaded into a syringe by withdrawing the plunger and pulling it through the needle (as it would be in preparing a syringe for an injection).

Tampering: Chemical and/or physical alteration of a prescription medication contrary to approved labeling.

Tuberculin syringe: 1 ml syringe with a 28 gauge needle. This is the most commonly available type of syringe, most likely to be used by abusers interested in abusing via intravenous route of administration.   Also referred to as an **insulin syringe.**

Vaporization: Refers to extraction of API by dry heating, simulating conditions used in abuse by an inhalation smoking route of administration.

Appendices

   I. Experts consulted external experts

  II. Detailed methodology

 III. *in vitro* testing methodology

PURDUE PHARMA L.P.

RESEARCH & DEVELOPMENT

September 24, 2009

FDA Advisory Committee Briefing Document on NDA 22-272 (reformulated OxyContin)

Appendix I:

Experts Consulted

EXPERTS CONSULTED ON MODES OF ABUSE AND MISUSE:

Sandra Comer, PhD

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Page 3 of 6

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- Senior Attending Physician & Section Chief, Division of Pain Management & Rehabilitation, Bridgeport Hospital

Bruce Burlington, MD

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- Former Deputy Director Med Affairs, FDA

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James Hill, RPh, MBA

- President, Pharmacy Strategy Group

Nathaniel P. Katz, MD, MS

- President, Analgesic Research Services

Kevin Nicholson, RPh, JD

- Vice President of Pharmacy Regulatory Affairs, National Association of Chain Drug Stores (NACDS)

John M. Pinney

- Founder and President, Pinney Associates

Bruce T. Roberts, RPh

- Executive Vice President, National Community Pharmacists Association (NCPA)

Will Rowe

- Patient Advocate

- Chief Executive Officer, American Pain Foundation

Sidney H. Schnoll, MD, PhD

- Clinical Professor of Internal Medicine and Psychiatry, Medical College of Virginia

- Vice President Pharmaceutical Risk Management Services, Pinney Associates

- Former Chairman of the Division of Substance Abuse Medicine, Medical College of Virginia

PURDUE PHARMA L.P.

RESEARCH & DEVELOPMENT

September 24, 2009

FDA Advisory Committee Briefing Document on NDA 22-272 (reformulated OxyContin)

Appendix II:

In Vitro Testing Methodology

OVERVIEW

As mentioned in the main **Briefing Document**, the seven studies described below were designed in consultation with experts in drug abuse, abuser tampering methods and analytical pharmaceutics (see **Appendix I**) in order to address the concerns raised by FDA in the October 3, 2008 Complete Response Letter. After internal validation of the protocols to ensure reproducibility and consistency across Studies, methods were standardized and transferred to contracted third party vendors.

The majority of experiments were performed by two contracted independent third party vendors (Aptuit, Kansas City, MO and Catalent Pharma Solutions, Research Triangle Park, NC). Study 1, Study 6 and Study 7 were performed in Purdue labs. Both Catalent and Aptuit met the required standards and data agreement from multiple analysts. Personnel performing the experiments were blinded to the extent possible. Division of work between these two vendors was capacity-driven, with a goal to complete the all seven Studies as expeditiously as possible. Upon completion of the studies, both an independent third party vendor (IHL Consulting Group, Loganville, GA) and internal Purdue staff performed extensive quality assurance analysis of the resulting data.

Samples in all extraction and dissolution experiments were analyzed following pre-specified HPLC conditions provided to the CROs in a separate protocol that is not covered in this document. These conditions were previously validated for the GMP analysis of reformulated OxyContin 10 – 80 mg tablets.

The methodology for each Study is summarized below. More detailed protocols than the methods described here were prepared for the CRO vendors.

STUDY 1: (b) (4) **FRACTIONATION OF TABLETS**

Table 1.1   ▮   **to API ratios for all tablet strengths of reformulated OxyContin**

Tablet strength (mg)	▮ per tablet	(b) (4) ▮ : API ratio
10	138.50	13.9
15	133.50	8.9
20	128.50	6.4
30	118.50	4.0
40	108.50	2.7
60	162.75	2.7
80	167.50	2.1

STUDY 2: EXTRACTION IN ▮▮▮ (b) (4) ▮▮▮ (b) (4) SOLUTIONS
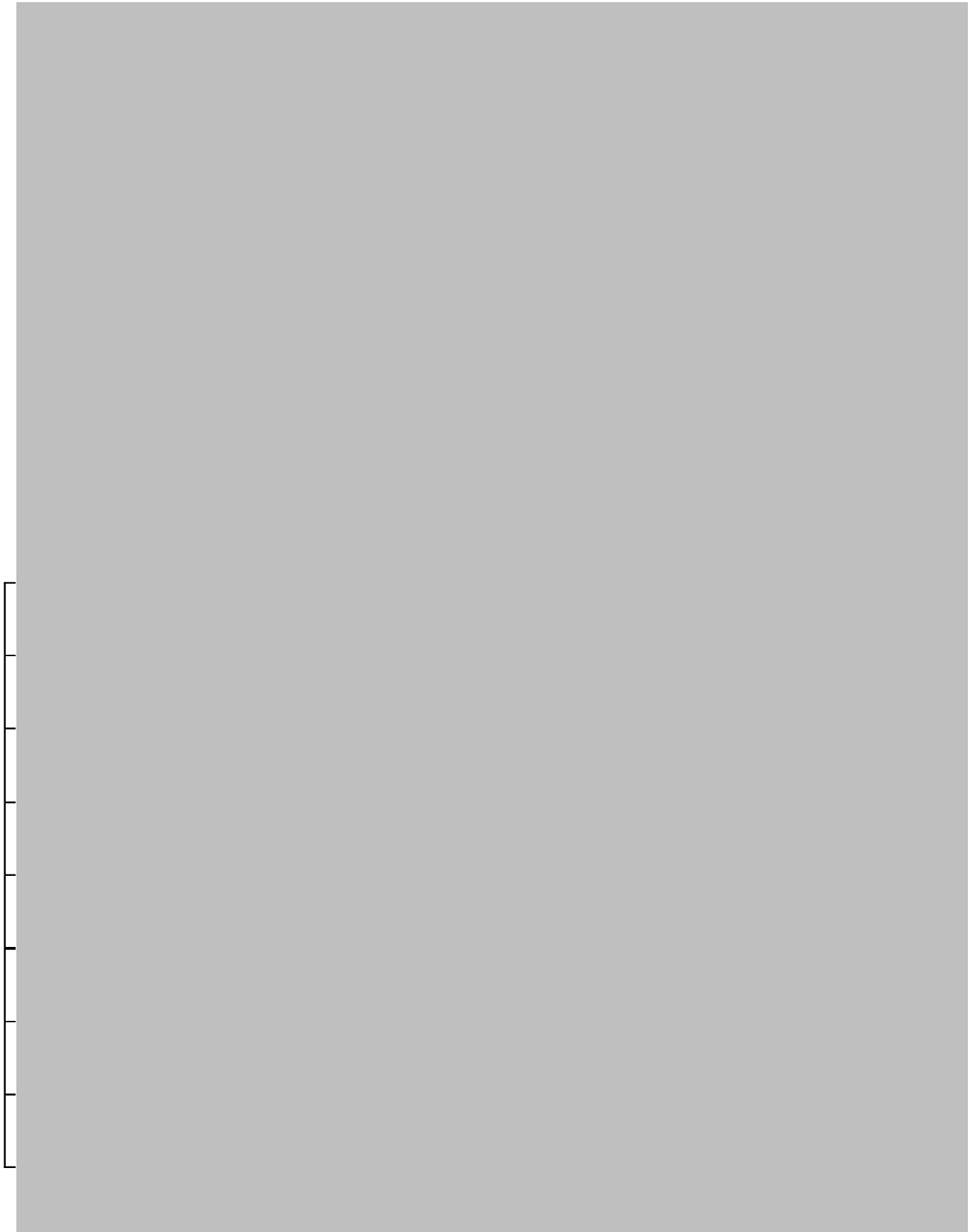
Statistical analysis

The same statistical methods were applied across all simple extraction experiments for water ████████ solvents and ████ (b) (4). The average API release across all tablet strengths for each testing condition (solvent and temperature) were plotted over time (average API release on the y-axis and time on the x-axis). A line was plotted for each particle size band within each testing condition. Significant differences between bands were assessed by comparing them using a two way analysis of variance (with fixed terms for particle band, tablet strength, and (band * strength)) followed by Duncan's multiple comparison of bands at the two sided 5% level. Individual replicates were also analyzed in this way.

STUDY 3: DISSOLUTION IN ETHANOL

The method used for the dose dumping dissolution studies was previously validated for the GMP analysis of reformulated OxyContin 10 – 80 mg tablets (not described in this document) and used in the original tamper testing experiments included in the November 29, 2009 NDA submission and discussed at the May 5, 2008 Advisory Committee meeting. In brief dissolution of tablets was carried out using USP Apparatus 1 (Baskets) at without enzymes ^{(b) (4)} maintained at ^{(b) (4)}. The dissolution vessels were covered at all times.

The number of replicates used in this study for reformulated OxyContin was determined statistically through data generated internally from dissolution of bands 2 (b) (4)), 4 ((b) (4) 5 (b) (4) and 6 (b) (4) of reformulated OxyContin 80 mg sample (n=3) in (b) (4) at (b) (4) Standard deviations of the triplicates were calculated at (b) (4) (b) (4) . The average of the 20 standard deviation was determined to be 9.0. It was decided that knowing the true mean of a particular solvent/band/time within 10% label claim was acceptable. With a standard deviation of 9.0, when the sample size is equal to 6, the 95% confidence interval for the mean is ± 9.5. Thus it was estimated that a sample size of 6 would result in the observed mean being within 10% label claim of the true mean.

The test materials used in this study are found in **Table 3.1**.

Table 3.1   Test materials for Study 3 – dissolution in ethanol

Test article	Formulation	Tablet strength (mg)
X1LY0	Reformulated OxyContin	10
X1MG0	Reformulated OxyContin	15
X1MH0	Reformulated OxyContin	20
X1MJ0	Reformulated OxyContin	30
X1LK0	Reformulated OxyContin	40
X1MK0	Reformulated OxyContin	60
X1LL0	Reformulated OxyContin	80
W1F61	Reformulated OxyContin	10
W1H71	Reformulated OxyContin	40
W1G71	Reformulated OxyContin	80
CW79D0 (core)	Reformulated OxyContin (uncured core powder)	80

Catalent Pharma Solutions, Raleigh, North Carolina, an independent contract research organization conducted this Study. Capability quality assurance in HPLC and executing the dissolution extraction procedures was performed according to separate protocols provided for the CRO. The CRO met the required standards and data agreement from multiple analysts.

Statistical analysis

The dissolution profiles of the API release in (b) (4) and   (b) (4) were compared for each tablet strength and each particle size band with the similarity factor f2 (Supac-MR:Modified Release Solid Oral Dosage Forms, FDA guidance, Sept 1997, pages 32-33). The calculation is

$$f2 = 50 \log 10\{[1+1/n \sum(R-T)^2]^{-0.5} \times 100\}$$

An f2 value of 50 or greater indicated similarity in dissolution profile. The maximum time point included for statistical analysis was chosen such that each analysis included at least three time points and only one dissolution time point after API release plateaus.

STUDY 4: EXTRACTION IN ADVANCED SOLVENTS

The sample size for reformulated OxyContin was determined statistically through data generated internally from extraction of bands 2   (b) (4) 4   (b) (4)), 5   (b) (4)) and 6   (b) (4)) of reformulated

OxyContin 80 mg sample (n=2) in ⬛ (b) (4) at (b) (4) ⬛ ⬛. Standard deviations of the duplicates were calculated at ⬛ (b) (4) extraction time. The average of the 24 standard deviation was determined to be 7.5. It was decided that knowing the true mean of a particular solvent/band/time within 10% label claim was acceptable. With a standard deviation of 7.5, when the sample size equal to 5, the 95% confidence interval for the mean is ± 9.3. Thus it was estimated that a sample size of 5 would result in the observed mean being within 10% label claim of the true mean. For OxyContin, the sample can be rendered to powder easily and the data generated is consistent, therefore, a sample size of n=3 was sufficient.

Catalent Pharma Solutions, an independent contract research organization in Raleigh, North Carolina, conducted this Study. Capability and qualification in HPLC and executing the small volume extraction procedures was performed according to separate protocols provided for the CRO.   The CRO met the required standards and data agreement from multiple analysts.

Table 4.1   Materials and conditions for Study 4 – extraction in advanced solvents

Tablet strength	Reformulated OxyContin lot number	OxyContin lot number	Testing conditions
10 mg	X1LY0	W1B71	All solvents
15 mg	X1MG0	n/a	All solvents
20 mg	X1MH0	n/a	All solvents, ,
30 mg	X1MJ0	n/a	All solvents, ,
40 mg	X1LK0	W0S71	All solvents,
60 mg	X1MK0	n/a	All solvents, ,
80 mg	X1LL0	W0Y61	All solvents, ,

Statistical analysis

Results with advance solvents were statistically analyzed in the same way as described above for small volume extractions with water, ▮(b) (4) solvents and ▮(b) (4) Average API release across all tablet strengths for each testing condition (solvent and temperature) were plotted over time (average API release on the y-axis and time on the x-axis). A line was plotted for each particle size band within each testing condition. Significant differences between bands were assessed by comparing them using a two way analysis of variance (with fixed terms for particle band, tablet strength, and (band * strength)) followed by Duncan's multiple comparison of bands at the two sided 5% level. Individual replicates were also analyzed in this way.

STUDY 5: SYRINGABILITY, INJECTABILITY AND EXTRACTION AFTER VAPORIZATION

As noted by Dr. Edward Cone in **Appendix III**,   (b) (4)) needles
are most commonly used for the purpose of abuse by intravenous injection.
For practical purposes,   needles were used for this study except
for a series of testing that was previously performed and submitted in the
original NDA. This former testing used common insulin syringes   (b) (4) ,
         (b) (4)) and a preparatory volume   (b) (4)

Aptuit, Inc., an independent contract research organization in Kansas City,
Missouri, conducted this Study. Capability and qualification for HPLC
analysis and for syringability procedures were performed under a separate
protocol prepared for the CROs (not covered in this document).

The test materials used in this study are found in **Table 5.1.**

Table 5.1   Test materials for Study 5 – syringability testing

Test article	Formulation	Tablet strength (mg)
X1LY0	Reformulated OxyContin	10
X1MG0	Reformulated OxyContin	15
X1MH0	Reformulated OxyContin	20
X1MJ0	Reformulated OxyContin	30
X1LK0	Reformulated OxyContin	40
X1MK0	Reformulated OxyContin	60
X1LL0	Reformulated OxyContin	80
W1B71	OxyContin	10
W0S71	OxyContin	40
W0Y61	OxyContin	80

Aptuit, Inc., an independent contract research organization in Kansas City, Missouri, conducted this Study.   Capability and qualification for HPLC analysis and for injectability procedures were performed under a separate protocol prepared for the CROs (not covered in this document).

The test materials used in this study are found in **Table 5.2.**

Table 5.2   Test materials for Study 5 – injectability testing

Test article	Formulation	Tablet strength (mg)
X1LY0	Reformulated OxyContin	10
X1MG0	Reformulated OxyContin	15
X1MH0	Reformulated OxyContin	20
X1MJ0	Reformulated OxyContin	30
X1LK0	Reformulated OxyContin	40
X1MK0	Reformulated OxyContin	60
X1LL0	Reformulated OxyContin	80
W1B71	OxyContin	10
W0S71	OxyContin	40
W0Y61	OxyContin	80

Aptuit, Inc., an independent contract research organization in Kansas City, Missouri, conducted this Study.   Capability and qualification for HPLC analysis and for smoking simulation procedures were performed under a separate protocol prepared for the CROs (not covered in this document).

The test materials used in this study are found in **Table 5.3.**

Table 5.3   Test materials for Study 5 – extraction after vaporization

Test article	Formulation	Tablet strength (mg)
X1LY0	Reformulated OxyContin	10
X1MG0	Reformulated OxyContin	15
X1MH0	Reformulated OxyContin	20
X1MJ0	Reformulated OxyContin	30
X1LK0	Reformulated OxyContin	40
X1MK0	Reformulated OxyContin	60
X1LL0	Reformulated OxyContin	80
W1B71	OxyContin	10
W0S71	OxyContin	40
W0Y61	OxyContin	80
Oxycodone base	Pure API	N/A
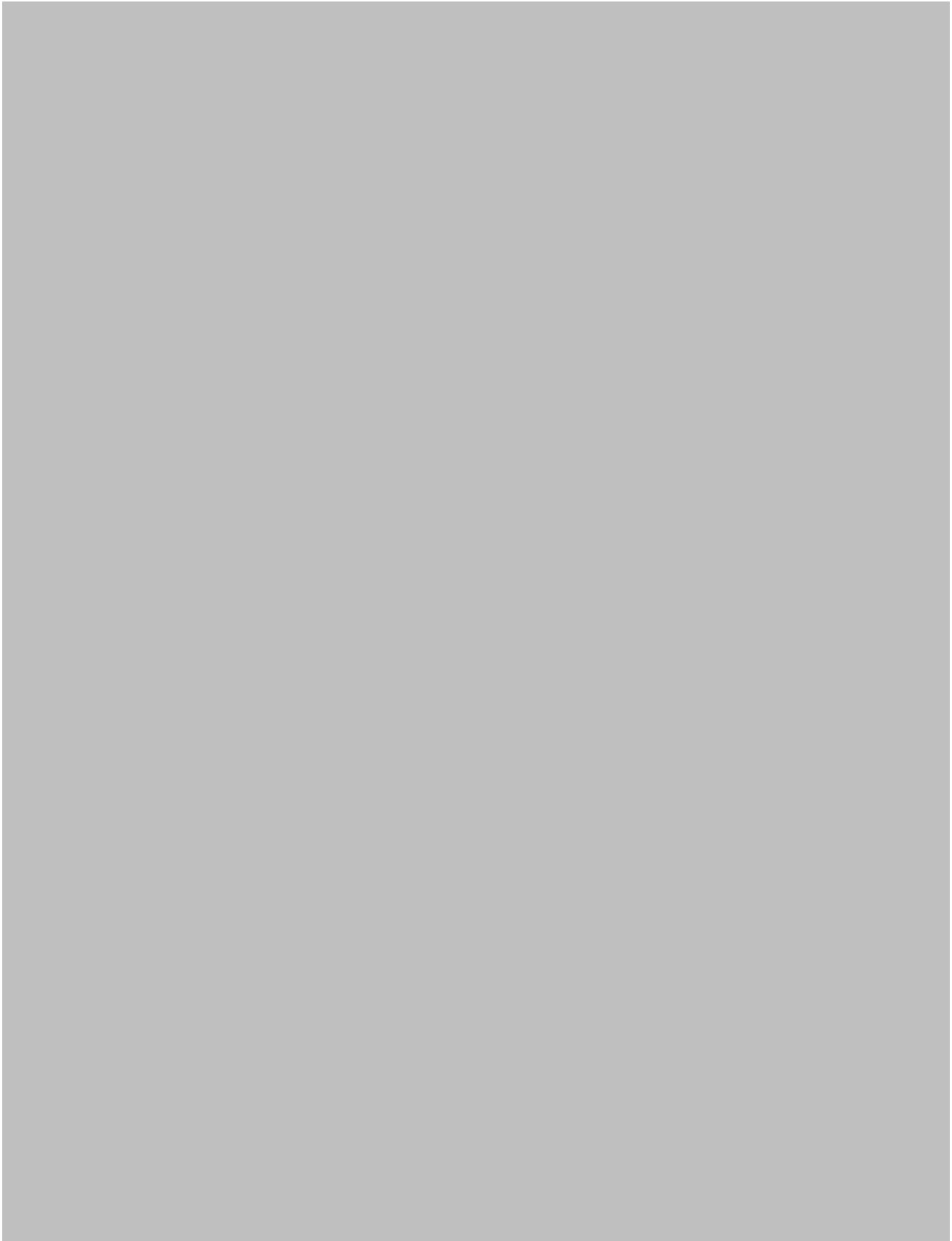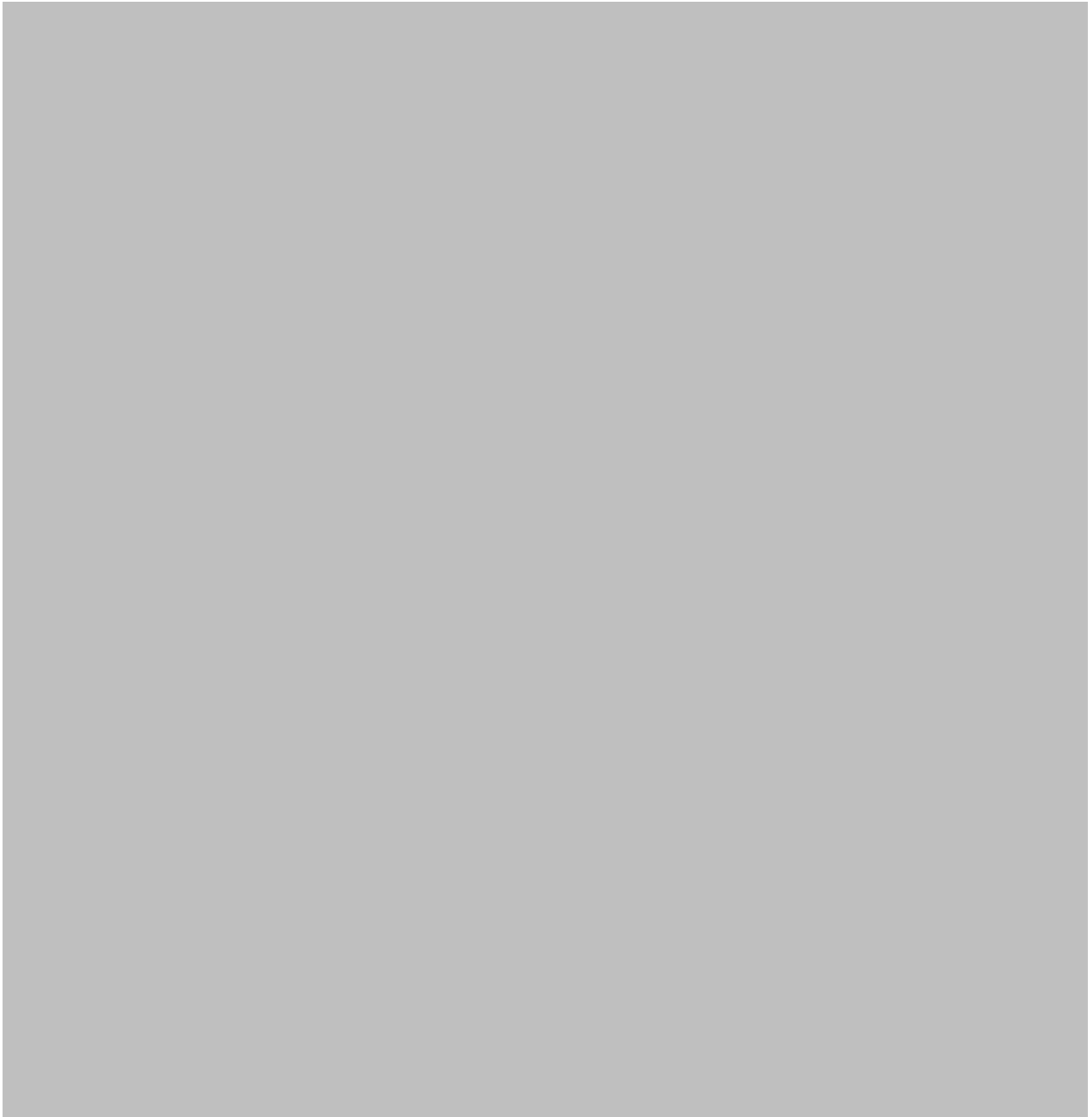
PURDUE PHARMA L.P.

RESEARCH & DEVELOPMENT

September 24, 2009

FDA Advisory Committee Briefing Document on NDA 22-272 (reformulated OxyContin)

Appendix III:

Comment on Purdue In Vitro Testing Studies Written by Dr. Edward Cone

Rational Approach to Tamper Assessment and Experimental Design: An Introduction

Edward J. Cone, Ph.D.

PinneyAssociates

March 6, 2009

Executive Summary

Although OxyContin® is used by millions of Americans for the relief of moderate to severe pain, nonmedical use, or misuse, contributes to the problem of illicit drug use. When used as intended, OxyContin®'s controlled release mechanism slowly releases oxycodone over a period of 12 hours, providing safe and effective pain relief. But cutting, crushing or chewing OxyContin® overcomes the controlled release mechanism and releases most of the oxycodone dose making it similar to an immediate release product. Crushing an OxyContin® tablet provides nonmedical users the opportunity to administer the entire dose immediately either by the oral or by the intranasal route. Crushed and powdered OxyContin® tablets also can be readily dissolved for injection, increasing the risk of overdose and death. Misuse of OxyContin® with other central nervous system depressants results in an increase in OxyContin® related deaths.

Purdue Pharma L.P. has developed a reformulation of OxyContin®, which will replace all current strengths of the current product. Reformulated OxyContin® incorporates new technology that provides significant improvements in tamper resistance. Unlike OxyContin®, which can be crushed with a spoon or other implements in a matter of seconds, the reformulation is only deformed by most manual methods, and requires electric mills or blenders for reduction to a fine powder. Even when crushed successfully, it retains a major portion of its controlled release properties. In addition, reformulated OxyContin® forms a viscous hydrogel when hydrated. It is anticipated that the gel formation will be a significant detriment to use by the intranasal route. Further, viscous gel formation occurs in small volumes of water, making it difficult if not impossible to prepare for injection. Even when successfully powdered, the reformulation continues to retain some controlled release properties. The reduced release of oxycodone from the reformulated OxyContin® tablet (compared to current OxyContin®) in water and other solvents is expected to retard tampering efforts by crushing and extraction.

Development of tamper assessment protocols for *in vitro* testing of reformulated OxyContin® was undertaken in consultation with experts experienced in drug abuse treatment and tampering methods and experts knowledgeable in extraction techniques. Scientific literature and Internet reports were reviewed for information on methods of tampering with OxyContin® and other opioid formulations. This information was used to develop a comprehensive series of laboratory-based *in vitro* assessment protocols for evaluation of the "tamper resistant" properties of reformulated OxyContin®. The scope of these protocols covered commonly known methods of tampering with oral opioid formulations as well as methods that were considered likely to be attempted by experienced tamperers. The experimental design of each protocol included the following elements considered necessary to yield reliable scientific data:

- Testing of all dose strengths of reformulated OxyContin®

- Testing methods extended to determine failure limits

- Inclusion of adequate controls for comparison to current OxyContin®

- Sufficient replicates for evaluation of method variability

- Method validation procedures

- Investigation of a range of conditions on outcome of results, e.g., temperature, time

- Use of independent laboratories

- Testing under blind conditions to the extent possible

Each protocol was developed to address at least one method or component of common tampering attempts currently employed or predicted to be employed with reformulated OxyContin®. Specifically, *in vitro* tests were designed to provide an accurate assessment of the potential for reformulated OxyContin® to be tampered with for the following types of misuse:

a. Crushability: chewing, cutting, grinding, powdering

b. Swallowing: chewed or powder (dissolution)

c. Effect of co-consumption of alcohol on "dose dumping"

d. Extraction (simple and complex methods)

e. Injection (syringeability and injectability)

f. Nasal insufflation (snorting/sniffing)

g. Smoking

The results of these assessments of reformulated OxyContin® provide detailed, valid scientific data on the strengths and weaknesses of the reformulation when subjected to current and potential future tampering attempts across a broad range of conditions.

Improvements in the tamper resistance of reformulated OxyContin® is expected to reduce, if not eliminate, some of the major health risks of current OxyContin®. These improvements in reformulated OxyContin® are expected to reduce the risk of overdose and death when crushed and consumed orally, snorted, injected or used by other routes of administration. The crush resistant characteristics of reformulated OxyContin® will also be an important safety feature when misused by legitimate patients.

1   Opioid and OxyContin® abuse

Pharmaceutical opioids are vital in the control of pain for many millions of Americans, with most patients finding significant relief, with neither severe side effects nor the emergence of abuse. Nonetheless, abuse and diversion do occur and contribute to the serious problem of illicit drug use and nonmedical use of prescription drugs both domestically and internationally. The 2007 National Survey on Drug Use and Health (NSDUH) indicated there were an estimated 19.9 million Americans aged 12 or older who were current (past month) illicit drug users, meaning they had used an illicit drug during the month prior to the survey interview *(Results from the 2007 National Survey on Drug Use and Health: National Findings)*. An estimated 6.9 million persons aged 12 years and older in the United States (US) used prescription psychotherapeutics (pain relievers, tranquilizers, stimulants, and sedatives) nonmedically at least once in the past month. Of these, 5.2 million (2.1 percent of the population aged 12 years old or older) used pain relievers, the same percentage of use as in 2006 (Figure 1). The highest rate of nonmedical use of pain relievers typically occurs in young adults. In 2007, past month use of pain relievers was 2.7 percent in youths aged 12 to 17, 4.6 percent in adults aged 18 to 25, and 1.6 percent in adults aged 26 or older.

Figure 1   Past Month Nonmedical Use of Types of Psychotherapeutic Drugs among Persons Aged 12 or Older: 2002-2007. Source: NSDUH 2007

(Results from the 2007 National Survey on Drug Use and Health: National Findings)
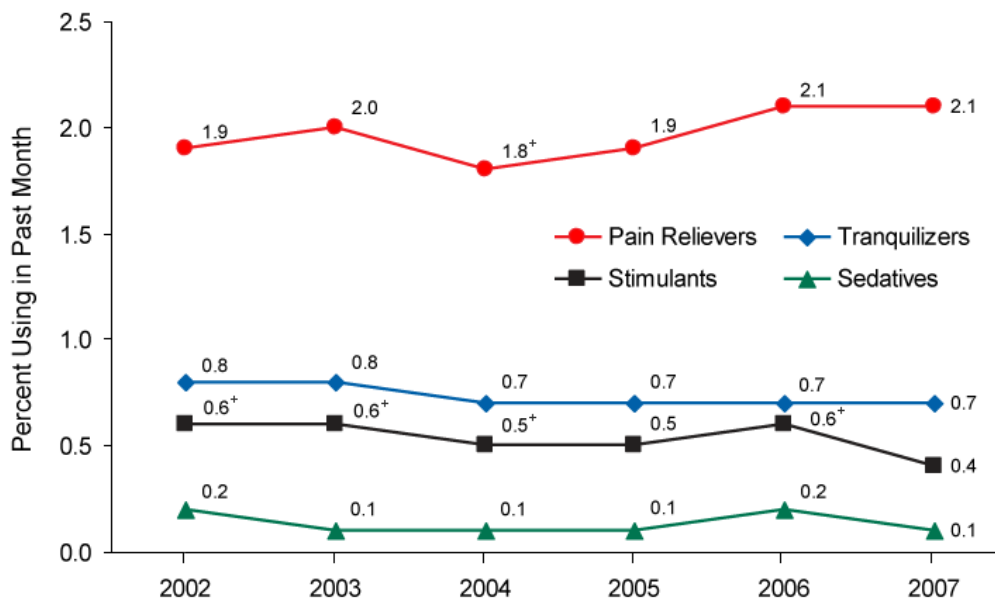
Combined NSDUH data from 2002 to 2005 (**Table 1**) indicate that 57.7 percent of persons who first used pain relievers nonmedically in the past year used hydrocodone products and 21.7 percent used oxycodone products *(National Survey on Drug Use and Health: The NSDUH Report)*. In these surveys, respondents specified that they had used hydrocodone products that included Vicodin®, Lortab®, Lorcet®/Lorcet Plus®, generic hydrocodone, and other pain relievers containing hydrocodone. Oxycodone products were reported to include Percocet®, Percodan®, Tylox®, OxyContin®, and other pain relievers containing oxycodone.

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Table 1   **Percentages Reporting Nonmedical Use of Hydrocodone and Oxycodone Products among Past Year Nonmedical Pain Reliever Initiates Aged 12 or Older, by Gender and Age Group: 2002-2005.**

Demographic Characteristic	Hydrocodone Products		Oxycodone Products	
	Percent	SE	Percent	SE
Total	57.7	1.13	21.7	0.80
Gender				
Male	61.4	1.51	22.9	1.16
Female	54.9	1.59	20.8	1.07
Age				
12 to 17	55.4	1.10	20.3	0.87
18 to 25	64.1	1.24	27.4	1.11
26 to 34	59.5	4.58	20.3	3.47
35 to 49	54.6	5.33	14.9	3.70

Source: SAMHSA, 2002-2005 NSDUHs
(National Survey on Drug Use and Health: The NSDUH Report).

Data on drug-related emergency department (ED) visits provide an indication of the physical harm that may result from drug misuse and abuse. According to Drug Abuse Warning Network (DAWN) data, of an estimated 106 million ED visits, there were nearly 1.3 million ED visits associated with drug abuse or misuse, of which approximately one half million involved nonmedical use of pharmaceuticals in 2004 *(The DAWN report: Emergency department visits involving nonmedical use of selected pharmaceuticals).* Of these visits, 31.9 percent involved opiates/opioids, 29.1 percent involved benzodiazepines, and 5.7 percent involved muscle relaxants. An estimated 158,281 ED visits involved opiates/opioids. The most frequently listed opiates/opioids were hydrocodone products (26.8% of opiates/opioids), oxycodone products (23.1%), and methadone (20.1%).

OxyContin® (controlled-release oxycodone hydrochloride) is a prescription pain reliever that first became available in 1995. It is presently available in strengths of 10, 15, 20, 30, 40, 60, and 80 milligrams of oxycodone hydrochloride. Although OxyContin® accounts for a small proportion of overall pain reliever nonmedical use, this drug is of particular concern because nonmedical use has persisted despite strong efforts to reduce diversion and abuse. Lifetime nonmedical use of OxyContin® increased in the US from 1.9 to 3.1 million persons between 2002 and 2004 *(Results from the 2004 National Survey on Drug Use and Health: National Findings)* .

2   Recreational misuse and tampering practices involving opioid formulations

The prevalence of nonmedical use, or misuse, of all prescription pharmaceuticals combined now rivals that of illicit drug use in the United States. Some abusers resort to "tampering" (i.e., physical and/or chemical alteration) with pharmaceutical formulations in attempts to achieve a bigger, faster "high" (euphoric effect). Increasing the magnitude and speed of drug onset is thought to enhance the reinforcing properties of psychoactive drugs *(College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement, Reinforcing effect as a function of infusion speed in intravenous self-administration of nicotine in rhesus monkeys)*. Tampering methods that increase the dose and speed of drug delivery primarily involve chemical and physical alteration of specific pharmaceutical products. Cone *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)* provided an extensive review of methods of pharmaceutical tampering as described and discussed on the Internet. This review provided details of tampering methods practiced with numerous types of pharmaceutical products including opioids. Perceived motives for tampering by nonmedical users were cited by Cone *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)* as enhancement of psychoactive effects, enhancement of drug availability, faster onset of effects, and elimination of undesirable excipients.

Additionally, pain patients prescribed OyxContin® may inadvertently be exposed to more rapid delivery if they attempt to adjust their dosage or save money by cutting tablets into pieces. Still other patients, or their caregivers, may crush tablets and add to applesauce or other foods if they have difficulty swallowing, and some patients might chew the product unaware of the danger of such use. Although labeling warns against all tampering, this type of use by pain patients is dangerous. A formulation that reduces the risk and/or consequences of tampering could be an important step towards improving the safety profile of OxyContin® for patients.

Through design of their composition, controlled release formulations inherently retard rapid drug release. Formulations of controlled release opioids appear desirable to those engaged in misuse and tampering because of higher doses compared to immediate release products. Overcoming these controlled release mechanisms thus becomes a goal of some nonmedical users who attempt various tampering practices.

Tampering methods range from the simple to the complex. A general hierarchy of tamper assessment procedures for oral formulations (adapted from Cone *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)*) is shown as follows:

- Crushing/powdering for oral and intranasal use
- Simple hybrid methods: crushing/powdering plus extraction (may involve use of heat or filtration in some steps)
    - Crushing/powdering, extraction
        - Aqueous/alcohol extractions: single step involving use of common household solvents, e.g., water, ethanol, household products such as vinegar
            - For direct use or further steps required, e.g., concentration

- ▪ Organic solvent extractions: single step involving use of toxic, flammable solvents, e.g., methanol, acetone, ethyl acetate
  - • Solvent removal, e.g., evaporation
  - • Solution or further steps required for use
- • Complex hybrid methods: (may involve use of heat and/or freezing in some steps)
  - o Crushing/powdering
  - o Solution in aqueous/alcoholic solvents
  - o pH adjustment (note: precipitation could be attempted at this point)
  - o Drug extraction with organic solvents, e.g., hexane, chloroform, petroleum ether, paint thinner
    - ▪ Evaporation, solution, filtration, use, or further extraction
    - ▪ Drug extraction from organic solvent into acid solution
    - ▪ pH adjustment
    - ▪ Precipitation, solution, use, or further purification for use

Detailed instructions for tampering can be found on the Internet where many tampering methods have been reported by nonmedical users. These instructions are frequently some hybrid combination of the above methods but it appears that the most commonly used approaches by drug abusers are simple. Most nonmedical users who are attempting to abuse the drug prefer tampering methods that can be accomplished immediately with household items, e.g., crushing tablets with a spoon, rapid solution with water *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)*. More motivated abusers may attempt complex hybrid methods of tampering involving physical manipulation and extraction. Complex hybrid methods of tampering most likely would be attempted by individuals with some chemistry training and access to resources not commonly found in the household, e.g., organic solvents, acids, glassware suitable for extraction. Some key observations regarding common tampering practices from the Cone review *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)* are the following:

- Increasing the speed of drug delivery is a frequent motivation for tampering.

- Abusers are adventurous and are willing to try tampering methods that may enhance speed and magnitude of drug effects.

- Numerous methods of overcoming drug/formulation barriers have become known to abusers.

- Complex tampering procedures, even if successful, are not widely utilized by abusers.

- Drug formulations that present significant barriers to tampering reduce, but do not totally eliminate misuse or abuse.

- The Internet is a prime source of information on drug tampering and offers a broad sweep of information on methods that spans from vague to highly descriptive, inaccurate to accurate, and scattered to organized.

Tampering with a controlled release product generally involves the following elements: product knowledge, information on tampering methods applicable to the product, time for experimentation, effort, resources, and motivation. Tampering methods that involve considerable time, effort and resources are used less than simple methods that can be performed in a matter of minutes.

Conceptually, a formulation "barrier" in a controlled release product makes it more difficult to convert to a form akin to an immediate release product. Elements of formulation barriers that are considered to retard tampering include:

- Difficulty in crushing/powdering
- Difficulty in extraction
- Need for specialized equipment
- Need for purification efforts to recover active and eliminate excipients
- Addition of sequestered antagonists
- Addition of aversive chemicals that only become aversive when excessive doses are taken

A barrier to tampering, consequently, increases what has been referred to as the "response cost", which can be expressed as the total work (time x effort) in addition to the financial cost of the drug and any materials needed for tampering and self-administration. In general self-administration of addictive drugs follows general economic principles whereby increasing cost (expressed by effort and/or financial expenditure) decreases the rate of self-administration and reinforcing effects *(The Economic Analysis of Substance Use and Abuse: An Integration of Economic and Behavioral Economic Research)*. Laboratory evidence of these conclusions is strong: decades of studies that have examined drug dosage level and cost demonstrated that while increasing dose is associated with increased intake, increased cost decreases intake until the cost is reached at which intake ceases ("break point") *(The Economic Analysis of Substance Use and Abuse: An Integration of Economic and Behavioral Economic Research, Similarities in animal and human drug-taking behavior)*.

The functional effect of the reformulated OxyContin® technology is to substantially increase the response cost and impair the practical ability of the drug abuser to easily extract and self-administer high doses at rapid delivery rates achieved by crushing and swallowing, nasal insufflation, and intravenous injection with currently available oxycodone formulations.

The complex of requirements for tampering, when considered as a whole, can be expressed as a "barrier" in terms of time X effort X resources. A general illustration of the "barrier" concept is shown in **Figure 2** for two products. Product A (e.g., OxyContin®) is a controlled release opioid formulation that can be converted within a few seconds with simple resources, e.g., crushing with a spoon, to an immediate release form with almost all of the active ingredient made available. Product B (e.g., reformulated OxyContin®) is a controlled release opioid formulation that requires significantly more time, resources, and skill to release only a portion of the active ingredient. The introduction of a substantially higher barrier in the Product B formulation is likely to reduce the vast majority of tampering attempts with the product.

Figure 2   Illustration of the effect of formulation barriers on likelihood of tampering.
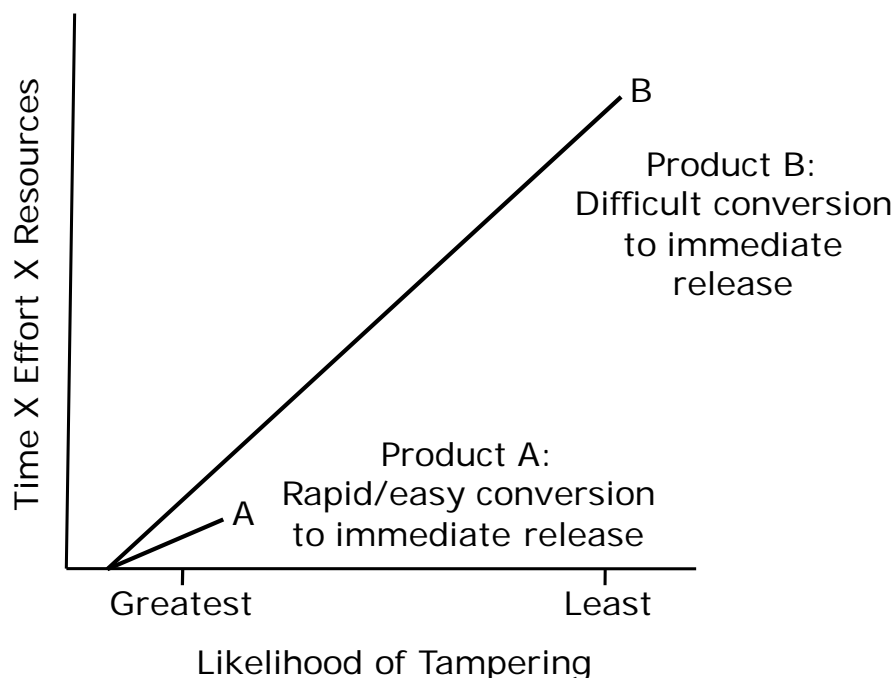
3   Tampering with OxyContin[®]

OxyContin[®] is prescribed in doses ranging from 10 to 80 mg for relief of chronic pain. When used as intended, OxyContin[®]'s controlled release mechanism slowly releases oxycodone over a period of 12 hours, providing safe and effective pain relief.   In the late 1990s OxyContin[®] became a target of misuse after the realization that breaking, crushing or chewing the tablet could release oxycodone from the controlled release matrix of the tablet. With this knowledge, nonmedical users began crushing the formulation for oral use and "snorting" (intranasal use), and dissolving the powder for intravenous injection. Amongst some legitimate medical users prescribed OxyContin[®], therapeutic misuse also occurred when patients mistakenly chewed or crushed the tablet for easy oral consumption, or cut the tablet in half to save money rather than swallowing the intact tablet as intended, posing a safety risk to these patients.

Overdoses and deaths from misuse of OxyContin® are well known. Individuals, including patients, who are non-tolerant to the effects of opioids are especially at risk of toxic overdose and death when taking the higher doses. Misuse of OxyContin® with other central nervous system depressants has exacerbated the problem and increased the death toll for this product *(Oxycodone involvement in drug abuse deaths. II. Evidence for toxic multiple drug-drug interactions).*

In addition to qualitative descriptions of tampering on the Internet, demographic studies have attempted to estimate the prevalence of OxyContin® and oxycodone nonmedical use and their reported routes of administration. Carise et al. *(Prescription OxyContin abuse among patients entering addiction treatment)* evaluated the prevalence of OxyContin® use and abuse among a population of 27,816 subjects admitted to 157 addiction treatment centers in the US from 2001-2004. Approximately 5% (N=1425) reported ever using OxyContin®. Eighty-six percent (N=1208) of OxyContin® users reported using it to "get high or get a buzz". Seventy-two percent of individuals categorized as "users" (N=1368) of OxyContin® reported their route of administration as follows:

- Oral route: 72% (N=981)
- Inhalation of crushed tablets: 11% (N=153)
- Injection of crushed tablets: 17% (N=234)

These data indicate that oral use of OxyContin® was most prevalent but did not indicate the extent to which OxyContin® is crushed or chewed for oral consumption. The authors noted that 92% (N=1242) of individuals categorized as "users" of OxyContin® reported using the medication with one or more other opioid(s) (heroin, methadone, hydromorphone, hydrocodone, and oxycodone). Only eight (0.5%) of the 1425 individuals categorized as "users" of OxyContin® reported no use of any additional drugs other than alcohol.

A study by Davis and Johnson *(Prescription opioid use, misuse, and diversion among street drug users in New York City)* of prescription opioid use, misuse and diversion among 586 street drug users in New York City identified 192 individuals who had used OxyContin®. Injection of OxyContin® was rarely reported (N=7, 3.6%), whereas snorting/sniffing was more prevalent (N=43, 22.4%).

A 2009 review of Purdue Pharma L.P.'s worldwide safety database identified a total of 1,396 oxycodone controlled release (CR) cases that described overdose, intentional drug misuse, medication error, and/or drug abuse associated with the tampering of an oxycodone CR tablet *(Reports of Tampering with OxyContin® Tablets: Postmarketing Experience (February 2009)).* The majority of the cases originated in the U.S. (N=1,346) and involved reports of drug abuse. Reports involving drug administration errors / medication errors accounted for less than 15% of the cases. The majority of the cases identified involved adults (18 years of age and older) and described crushing OxyContin® tablets for the purposes of snorting, injecting (intravenously) and / or smoking the crushed tablet (listed in descending order of frequency). One hundred and eighty two (182) of the 1,346 cases involved "chewing" OxyContin® tablets. Of these 182 cases, 125 involved reports of drug abuse. The remaining 57 cases involved medication errors or accidental exposures. Twenty two (22) of the 182 cases were associated with a fatal outcome. One hundred and three (103) cases involved adolescents (13 to < 18 years). All of the adolescent cases were associated with drug abuse, with the most common route of abuse being intranasal inhalation (snorting) in 71 of the 103 cases. Nineteen (19) of the adolescent cases were associated with a fatal outcome. Eighteen (18) cases involved "children." Thirteen (13) of the 18 children were 6 years of age or younger. Ten (10) of these 13 cases involved "chewing" an OxyContin® tablet. Two of the cases involved children of unspecified age who "chewed up" OxyContin® and died. The case outcomes for the other reports were unknown.

Internet-based estimates of prevalence of drug abuse practices have limitations that have been described elsewhere *(Ephemeral profiles of prescription drug and*

formulation tampering: Evolving pseudoscience on the Internet) but Internet-based surveys can provide information for understanding patterns and trends of drug abuse. An Internet-based survey (N=896) of nonmedical prescription opioid use in the US by Katz et al. *(Internet-based survey of nonmedical prescription opioid use in the United States)* revealed that 188 individuals had used OxyContin® nonmedically. Routes of administration reported by the 188 OxyContin® users were as follows: swallow (without chewing) (N=104, 55.5%); chew (N=64, 34.0%); snort/sniff (N=140, 74.5%); smoke (N=20, 10.6%); inject skin (N=10, 5.3%); inject vein (N=30, 16.0%); and other (N=2, 1.1%). (Note: Some individuals reported nonmedical use via multiple routes of administration, thus the total percentage exceeds 100%).

A recent survey of Erowid.org, one of the leading Internet sites that posts drug abuse experiences reported by drug abusers, provided information on tampering methods employed by OxyContin® abusers. The survey was performed of Erowid Experience Reports (accessed February, 2009) (http://www.erowid.org/experiences/exp_search.cgi) for oxycodone (only). The results of the survey provided a current "snapshot" of methods of abuse and tampering with oxycodone and OxyContin® products. The site search provided a listing of 89 reports from individuals who had used oxycodone. Individual reports from this site, in many cases, identified the oxycodone product, route(s) of administration, and in some cases, details of tampering methods that were employed. Of the 89 reports, 86 (96.6%) involved abuse while 3 (3.4%) were probable therapeutic use. Eighty-two percent of the reports identified at least one oxycodone product by name. Many of the reports identified the route(s) of administration. A summary of the routes of administration for the 86 abuse reports is shown in **Table 2**.

Table 2   Summary of Internet Survey of Reports on Erowid.Org (Experience Reports) on Abuse of OxyContin® and Other Oxycodone Products by Reported Routes of Administration (reports were accessed February, 2009)

Product	N	%Total	Oral - intact	Oral - chew	Oral - drink	Oral - cut/crushed	Oral - parachute	Intranasal	Injection	Smoke	Rectal
OxyContin®	51	59.3	11	8	1	4	1	39	6	0	1
Percocet®	12	14.0	9	4	0	0	1	2	0	1	1
Tylax®	1	1.2	0	0	1	0	0	0	0	0	0
Oxycet®	1	1.2	1	0	0	0	0	0	0	0	0
Endocet®	2	2.3	2	0	0	0	0	0	0	0	0
Roxicet®	2	2.3	1	0	0	0	0	1	0	0	0
Roxicodone®*	1	1.2	0	1	0	0	0	0	0	0	0
Unidentified	16	18.6	9	0	0	0	0	8	1	1	0
Total	86	100	33	13	2	4	2	50	7	2	2
%			38.4	15.1	2.3	4.7	2.3	58.1	8.1	2.3	2.3

Of the 51 reports of abuse of OxyContin®, intranasal (snort/sniff/insufflate) administration (N=39, 76.5%) was the most frequently described route, followed by oral (intact) (N=11, 21.6%), oral (chew) (N=8, 15.7%), injection (N=6, 11.8%), and oral (crushed) (N=4, 7.8%). There were mentions in single reports (N=1, 2.0%) of oral (drink), oral (parachute), and rectal ("plugging") administrations. Numerous methods of cutting and crushing OxyContin® and oxycodone tablets were described in these reports including use of a hammer, pill cutter, credit card, key, and pocket knife. Such detailed descriptions are invaluable in developing protocols to assess the ability of new formulations to resist real world tampering approaches.

The percent of posts on Erowid mentioning each route of administration is quite different than what has been reported for patients entering treatment programs (Prescription OxyContin abuse among patients entering addiction treatment), indicating that this may be a unique group of misusers/abusers. A prototypic example from the Erowid reports illustrates the level of detail that is often presented. One individual (Report 4, Appendix 1: Summary of Erowid.com User Experience Reports on Oxycodone) described crushing an OxyContin® tablet as, "I proceed to pound … with a hammer, leaving me

with a baggy full of white powder…" for use by insufflation. Another individual reported crushing oxycodone (unspecified product) in the following manner, "With a hammer I gently tapped each pill, causing it to crumble into smaller pieces. I then pressed the head of the hammer onto the pile of pieces and applied a gently rolling pressure so as not to lose any precious powder. With relative ease the pile of pills was transformed into a very fine mountain of powder". Another individual described preparation of OxyContin® for injection as, "He broke my 80mg tablet of Oxy into 4 similar pieces and placed them into a spoon. He then pulled 85 units of clean water into my syringe, and squirted it onto the pill. Next, he cooked the pill with a Bic until there was some bubbling and a faint trace of steam above the mix. In one motion, he crushed the cooked pill with the back of the plunger, and it squished down into the mix. Last, he placed a tic-tac sized cotton piece in the spoon, and drew up roughly 70 units of liquid oxycodone into the syringe". This same report also described the method of injection as, "I tied my right arm off with my belt, pulled it tight with my teeth, and let him spot the vein. He inserted the needle head, pulled back blood to indicate a clean vein hit, and pushed the plunger down as I let loose the tie". The effect of this injection was described as "INSTANTLY, I felt my first real head rush, and let me tell you, it was insane. All at once, the tension in my body released, and I fell back onto a pillow, and stared at the ceiling, enjoying the incredible wave of warmth that surrounded my being. It was as if God himself reached through the clouds and granted me total bliss, without any responsibilities or worries. The world was suddenly right, and all of the suffering of humans no longer mattered. I distinctly remember it as the most euphoric moment of my life".

Although there appears to be wide variability in patterns of tampering and misuse (as inferred from reported routes of administration) among different populations, the above studies and surveys suggest a pattern of tampering and nonmedical use with OxyContin® as follows: swallowing with/without chewing/crushing ≈ intranasal > injection >> smoking ≈ rectal.

4   New Oxycodone Controlled Release Formulation

Purdue Pharma has developed a reformulation of OxyContin® that will replace all current strengths of the current product. Reformulated OxyContin® incorporates new technology that provides the following improvements in tamper resistance:

- Crush resistance

- Forms a [(b) (4)] when placed in [(b) (4)] or other solvent

- Reduced active pharmaceutical ingredient (API) release in water, alcohol and other common solvents compared to OxyContin® treated similarly

These properties were incorporated into reformulated OxyContin® with the intent to improve safety and to reduce/eliminate the most commonly employed methods of tampering (formulation alterations) with current OxyContin®. The combination of these properties is expected to introduce a significant barrier to tampering with OxyContin® and substantially reduce efforts to alter the formulation for enhanced effects by the oral route (chewing/crushing), intranasal route (snorting), parenteral use (injection), and smoking. **Figure 3** illustrates this concept for current OxyContin®, which is a controlled release formulation that is easily converted by crushing to an immediate release product. The data on prevalence of route of administration of current OxyContin® is adapted from Katz et al. *(Internet-based survey of nonmedical prescription opioid use in the United States)*. The shaded bars represent the direction of the expected prevalence of abuse when reformulated OxyContin® replaces current OxyContin®. Other than abuse of the reformulation by swallowing intact (which may increase as a result of the difficulty experienced in attempted tampering efforts), tampering efforts involving chewing, crushing and extraction are expected to be substantially reduced or eliminated. Although prevalence is not known, it should be noted that therapeutic misuse (e.g., pain patient who cuts or crushes a tablet rather than swallowing intact) is a current safety risk that also should be reduced or eliminated.

Figure 3 **Expected Effect of Replacement of current OxyContin® with reformulated OxyContin® on Prevalence Rates of Tampering For Oral Use and Other Routes of Administration.**

Data are adapted from Katz et al. *(Internet-based survey of nonmedical prescription opioid use in the United States).* Shaded bars indicate the predicted direction of change in prevalence rate.
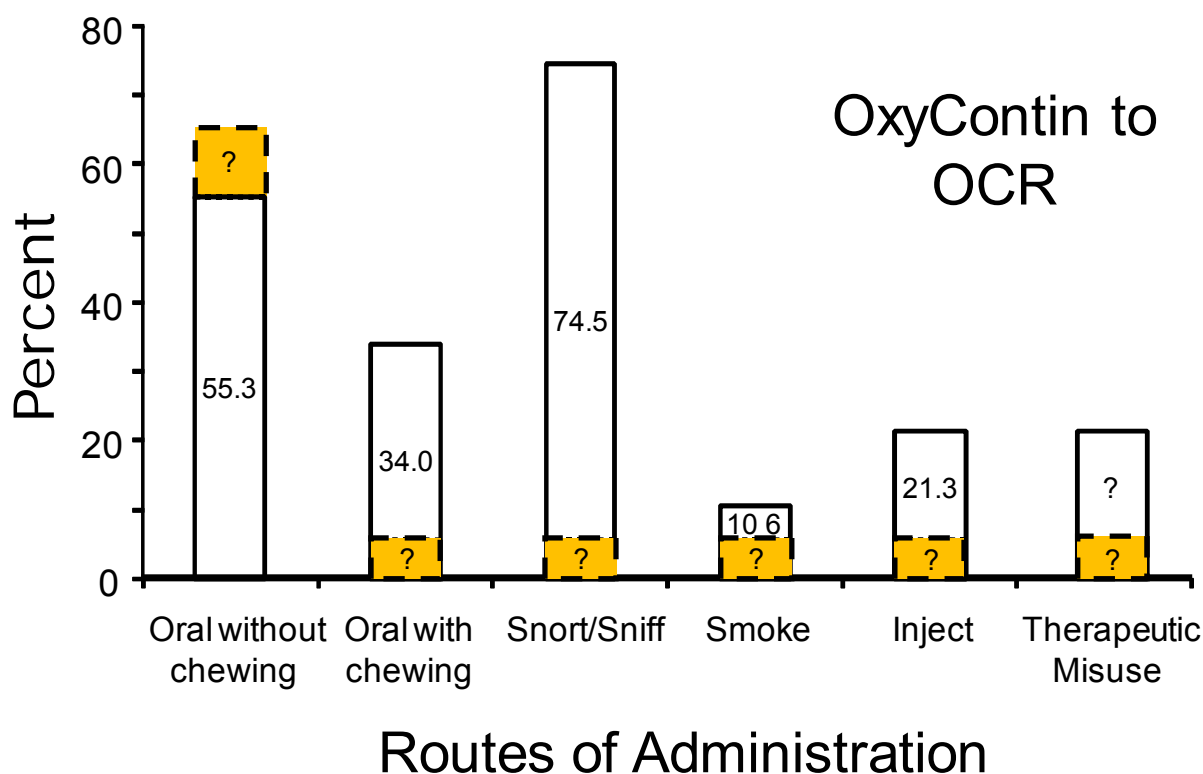
5   General Principles in Assessment of Tamper Deterrent Formulations

Designing validated laboratory methods for tamper assessment of the reformulation presents a challenge as no current standards have been established for tamper assessment of controlled release oral formulations. Protocols for tamper assessment must be developed based on known and potential methods that are considered likely to be practiced by misusers and abusers.

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Assessment of tamper deterrent formulations must take into consideration the chemical nature of the opioid active and of other actives (if present), and the physical and chemical features of the formulation as a whole. The intended therapeutic route of administration is also a key consideration in assessing tamper deterrent formulations. Products designed for different routes of administration, (e.g., oral, transdermal, sublingual), require somewhat different considerations and different assessment approaches.

In the case of oral misuse, the first consideration is the ability to chew/cut/powder the product with the resulting effect of these manipulations on drug release rate. Powdering a formulation for oral administration is quite commonly reported by individuals engaged in abuse of opioids. Powdering enables "parachuting" (e.g. encapsulation of powder in tissue paper and swallowing), and also allows the possibility of intranasal (snorting/sniffing) route, the second most common route of abuse. Further efforts including simple or complex extractions are required for use by injection routes. The smoked and rectal route for opioids should also be considered as possible alternative routes for some abusers, but these routes appears to be utilized with substantial less frequency than oral, intranasal, and intravenous use.

The simplest means of tampering is most desirable to abusers. A brief hierarchy of tamper assessment procedures follows the order (simple to difficult):

- Crushing/powdering
- Extraction: Single step
  - Common household solvents, e.g.,   (b) (4)
  ((b) (4)
  - Organic solvents, e.g.,   (b) (4)
- Extraction/precipitation

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- Extraction: Multi-step:
  - complex procedures o ▇▇▇ (b) (4) with ▇▇▇ (b) (4) into ▇▇▇ (b) (4) and further isolation steps (e.g. ▇▇▇ (b) (4)

  ▇▇▇ (b) (4)

  ▇▇▇ (b) (4)

Protocols for assessment of the "crushability" of a formulation should address the following:

- Ease of crushing/powdering
- Resource requirements
- Particle size distribution
- Extraction and dissolution characteristics of powder versus intact formulation
  - Effect of crushing on dissolution (rate of release over time)

Protocols for assessment of the "extractability" of reformulations should address the following:

- Resource requirements
- Time requirements
- Chemical training/knowledge requirements
- Hazard risks
- Toxicity risks
- Suitability for oral, intranasal, intravenous, and smoked administration

Protocols for assessment of the ability of a reformulation to be vaporized (smoked) should address the following:

- Resource requirements
- Time requirements
- Heat source and conditions
- Form of active ▇▇▇ (b) (4)

Suitable assays for drug measurement that are capable of specific and sensitive measurement of active drug (e.g., HPLC or other methods) should be utilized. All analytical methods must be validated and procedures should be conducted under blind conditions (to the extent possible). Use of independent laboratories that follow good laboratory practices to conduct tamper assessment protocols adds additional credibility to the results. Analytical results of all tamper assessment procedures should be reported in terms of extraction efficiency, recovery of active (percent dose), absolute amount of active recovered (mg), and purity (to the extent possible, dependent upon procedure).

6 Development of tamper assessment protocols for *in vitro* testing of reformulated OxyContin

The development of *in vitro* laboratory methods for tamper assessment of reformulated OxyContin[®] involved consideration of the following questions:

- What are the most common methods employed in tampering with OxyContin[®]?

- What are the most common routes of administration likely used by abusers of OxyContin[®]?

- What methods of inadvertent tampering are most commonly used by legitimate users that may result in overdose?

- What are the physico-chemical differences between OxyContin[®] and reformulated OxyContin[®]?

- What new and existing methods of tampering are most likely to be attempted with reformulated OxyContin[®]?

These questions were addressed by a) reviewing the scientific literature on methods of tampering with OxyContin[®] and other opioid formulations, b) reviewing the scientific literature on common routes of administration of oxycodone by misusers and abusers, c) reviewing Internet reports on tampering with oxycodone, d) input from an external

Expert Panel experienced in drug abuse treatment and tampering methods, and e) input from experienced individuals who are knowledgeable about extraction techniques suitable for purification of oxycodone from complex matrices and excipients. This information was used to develop a comprehensive series of laboratory-based *in vitro* assessment protocols for evaluation of the "tamper resistant" properties of reformulated OxyContin®. The experimental design of each protocol included the following elements considered necessary to yield reliable scientific data:

- Testing of all dose strengths of reformulated OxyContin®

- Testing methods extended to determine failure limits

- Inclusion of adequate controls for comparison to current OxyContin®

- Sufficient replicates for evaluation of method variability

- Method validation procedures

- Investigation of a range of conditions on outcome of results, e.g., temperature, time

- Use of independent laboratories

- Testing under blind conditions to the extent possible

The scope of these protocols covered commonly known methods of tampering with oral opioid formulations (OxyContin®, oxycodone and other opioids) as well as methods that were considered likely to be attempted by experienced tamperers. Each protocol was developed to address at least one method or component of common tampering attempts currently employed or predicted to be employed with reformulated OxyContin®. Specifically, *in vitro* tests were designed to provide an accurate assessment of the potential for reformulated OxyContin® to be tampered with for the following types of misuse:

a. Crushability: chewing, cutting, grinding, powdering

b. Swallowing: chewed or powder (dissolution)

c. Effect of co-consumption of alcohol on "dose dumping"

d. Extraction (simple and complex methods)

e. Injection (syringeability and injectability)

f. Nasal insufflation (snorting/sniffing)

g. Smoking

h. Rectal ("plugging")

i. (b) (4) isolation (for use by different routes of administration)

a. Crushability: chewing, cutting, grinding, powdering

Chewing and crushing current OxyContin® are the most common means of tampering. This approach to tampering converts OxyContin® into a (b) (4) controlled release properties of OxyContin®, with the dosage form readily available for immediate use. In this form powdered OxyContin® can be used readily by the intranasal route (snorting/sniffing) as well. Further, powdering is the first step in simple and complex extraction methods employed by injection users or by smokers of the product. Hence, assessment methods were devised to assess the difficulty of the "crushability" of reformulated OxyContin®.

Starting with the knowledge that current OxyContin® can be easily chewed or crushed in a few seconds with a (b) (4) or spoon, the potential that reformulated OxyContin® could be crushed with readily available equipment required systematic evaluation. Initial exploration of tampering methods was performed by Purdue Pharma to determine which methods would prove most successful. With input from outside experts, early evaluations included attempts at crushing reformulated OxyContin® with a variety of

(b) (4) tools (e.g.,   (b) (4) ,

                                                                    (b) (4) The

                                                        (b) (4) produced various deformations of the

tablet, but most were not successful in producing a   (b) (4) powder. Electrically powered

(b) (4) and   (b) (4) were most effective in   (b) (4) reformulated OxyContin®.

Additional studies were performed to determine the effects of time (how long was

needed to reach   (b) (4) particle size   (b) (4)?) and temperature   (b) (4)

        (b) (4)?) on powdering reformulated OxyContin®.

(b) (4)

All methods, aside from   (b) (4)g and use of   (b) (4), produced a spread of

particle sizes ranging from   (b) (4)) to   (b) (4)). Thus,

qualitatively, it was established that reformulated OxyContin® could be reduced to

varying particles sizes by use of diverse   (b) (4)instruments. However, extreme

variability in particle size production was clearly evident in all methods. This variability in

particle size depended upon the specific instrument used and the time and effort

expended.

In general, all methods, with the exception of whole, deformed tablets, produced a

(b) (4) of particle sizes. A systematic approach was needed to overcome the extreme

variability in production of different particle sizes found with different methods and different conditions. Consequently, particle size ⬜⬜⬜⬜⬜⬜ (b) (4)
selected for use in *in vitro* assessment protocols. ⬜⬜⬜⬜⬜⬜ (b) (4)

⬜⬜⬜⬜⬜⬜⬜⬜⬜⬜⬜⬜⬜⬜⬜

⬜⬜⬜⬜⬜⬜⬜⬜⬜⬜⬜ (b) (4)

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⬜⬜⬜⬜⬜⬜. Results of these studies on crushability are described in the Study 1 section of the main body of the **Briefing Document**.

b. Swallowing: chewed or powder (dissolution)

Chewing and oral consumption of powder, e.g., "parachuting" of OxyContin® is the most common means of tampering for abuse. *In vitro* studies were designed to determine if powdered reformulated OxyContin® would retain controlled release properties of the intact tablet. Dissolution experiments were designed to compare rate and extent of release of oxycodone over time in ⬜⬜⬜⬜⬜ (b) (4)). Results of the studies on dissolution are described in the section of the main **Briefing Document** on Study 3.

c. Effect of co-consumption of alcohol on "dose dumping"

The concern that co-consumption of alcohol with intact reformulated OxyContin or powdered reformulated OxyContin® would result in rapid release of oxycodone was assessed in *in vitro* dissolution experiments. Tests were conducted with 1)(b) (4), and 2) (b) (4) in which the alcohol content was (b) (4) Results of the studies on dissolution in alcohol are described are also described in the section of the main **Briefing Document** on Study 3.

d. Extraction (simple and complex methods)

A series of simple to complex extraction protocols were designed to cover a range of known and predicted methods of tampering with reformulated OxyContin®. These protocols incorporated common practices reported on the Internet by abusers who describe methods used to purify and concentrate oxycodone and other opioids from various formulations.

Simple extraction methods are generally employed for injection. The first step in such a process requires crushing an oxycodone tablet followed by _____ (b) (4) in a suitable ___ (b) (4) media. If the solution step, e.g., _____ (b) (4) __(b)(4)__r, is not successful in producing a solution suitable for injection, some abusers will resort to more elaborate means of extraction.

Simple step extractions protocols were developed to address the difficulty of extraction, primarily with the intent of producing an extract that could be injected or used by other routes of administration. The following types of extraction protocols were developed to assess relatively simple extraction methods reported or predicted to be employed by opioid tamperers. The methods are generally ranked in order of difficulty (simple to complex):

It should be noted that extractions involving organic solvents other than ethanol are not suitable for [(b) (4)] and require additional purification efforts and treatments, [(b) (4)].

A substantially smaller number of individuals who are highly motivated and have the necessary knowledge (information, skills, training), resources, and adequate drug supply, may resort to more complex purification schemes. The most difficult extraction conditions often involve methods similar to those employed in laboratory methods for purification of oxycodone. Complex tampering methods typically involve multiple steps including the following: [(b) (4)]

[(b) (4)] Further effort is then required to convert the [(b) (4)] into a usable form for drug administration.

A complex extraction protocol was developed along these lines to assess the efficiency of [(b) (4)], some the most commonly utilized [(b) (4)] solvents encountered in Internet tampering recipes for opioids. The protocol incorporated [(b) (4)] maximal extraction efficiency, as frequently advised in Internet recipes.

Results of the studies on extraction are described in the main body of the **Briefing Document** in the sections on Study 2 and Study 4.

e. Injection (syringeability and injectability)

Because reformulated OxyContin® produces a [(b) (4)] in [(b) (4)] [(b) (4)]r, no solution is available for injection when performed, as commonly reported for current OxyContin®, i.e., crushing, solution in [(b) (4)] in a spoon, and heating. It is feasible that some individuals attempting to produce a solution of oxycodone from

reformulated OxyContin® for injection will attempt use of larger volumes of water for preparation of injection solutions.

In prior experiments ████████████████████████████████████ (b) (4), ██ (b) (4), powdered reformulated OxyContin® immediately forms a ████ (b) (4) and is virtually impossible to syringe. To identify the conditions in which powdered reformulated OxyContin® could be used for intravenous injection, two protocols were designed to assess whether finely powdered reformulated OxyContin® dissolved (b) (4) ████████████████ (b) (4) could be drawn into a syringe with a needle (syringeability) or expelled (when loaded into the barrel) from a syringe with a needle. Although injection ████████████████ (b) (4) is considered unlikely to be practiced by injectors, these conditions were chosen to represent the extremes in volume that some abusers might attempt to use.

The syringeability protocol was designed to determine if (and how much) finely powdered reformulated OxyContin® when mixed with (b) (4) at either ████████ (b) (4) or ██████████ and followed by ██████ could be drawn into a syringe fitted with a needle. Needle sizes were varied from ██████████████████████), the latter being most representative of what is used by injectors. ████████ (b) (4) ██ (b) (4) are the most common type used by abusers.

The injectability protocol was designed to determine if (and how much) finely powdered reformulated OxyContin® when mixed with ██ (b) (4) r at either ██ (b) (4) temperature or ██ (b) (4) to ██ (b) (4) and loaded into the open barrel of the syringe could be expelled from the syringe through a needle. Needle sizes were varied from ████████████████ (b) (4) ██ (b) (4)

Results of the studies on syringeability and injectability are described in the main body of the **Briefing Document** in the sections on Study 5.

    f.   Nasal insufflation (snorting/sniffing)

Consideration of the physiology of the nose is important in assessing whether powdered reformulated OxyContin® is likely to be administered by the intranasal route. The nose is extremely efficient in preventing particles with a size larger than 10 μm from reaching the lungs. The high linear velocity and the bend in the airstream in the anterior nares results in impaction of a large proportion of particles that enter the nasal airway. Insoluble particles deposited in the main nasal passage are transported by mucociliary clearance to the back of the throat and swallowed. If the particle is soluble, it may readily pass into the mucosa and then be absorbed into the bloodstream. The absorption of low molecular weight drugs by the nasal mucosa appears to be primarily dependent upon diffusion processes. Consequently, absorption will be highly dependent upon drug concentration in solution, surface area, and contact time between drug and the mucosal tissue. The following drug factors appear to be important to the bioavailability of intranasal administered drugs:

- Absorption mechanisms
- Drug concentration
- Dispersion of the drug in the nasal cavity
- Contact time of drug with nasal mucosa
- Dissolution time
- Viscosity of the drug solution

Generally, snorting OxyContin® is the most frequent alternate route of administration reported by abusers *(Internet-based survey of nonmedical prescription opioid use in the United States, Prescription opioid use, misuse, and diversion among street drug users in New York City).* However, this may be the least dangerous route of administration,

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given inherent limitations on the magnitude of dosing and frequency of use, when compared to oral and intravenous administration *(Drugs and Chemicals of Concern: Oxycodone: Summary of Medical Examiner Reports on Oxycodone-Related Deaths)*. The popularity of the snorting route undoubtedly resides in the simple preparation steps involved, e.g., crushing, and the rapid onset of reported effects relative to oral administration.

Snorting OxyContin® requires crushing the tablet to a fine powder as a starting point followed by inhaling powder into the nose. Absorption of intranasally administered oxycodone by the nasal mucosa requires dissolution of the product in biofluid present in the nasal mucosa. The pH of nasal secretions ranges from 5.5 to 6.5 in normal adults. The speed of oxycodone dissolution in nasal biofluids is expected to be critical to absorption. Absorption of oxycodone by the nasal epithelium will be limited by mucociliary clearance of insoluble particles to the back of the throat where it is swallowed. Formation of a viscous gel by polyethylene oxides in reformulated OxyContin® may prolong contact time with the nasal mucosa, and thus, enhance absorption. At the same time, it is expected that gel formation will produce unpleasant sensory effects and serve as a detriment to intranasal use. For example, Internet users who attempt to snort Concerta®, a controlled release formulation of methylphenidate that contains polyethylene oxide, report that "when crushed up and snorted has been known to completely clog up the nostrils as it turns into a slime" (http://www.bluelight.ru/vb/archive/index.php/t-304858.html).

Assessment of the potential of reformulated OxyContin® use by the intranasal route can be made from the protocols that characterize the following elements essential to drug absorption from the nasal mucosa:

- Crushability, grinding and powdering potential

- Rate of dissolution

- Extraction studies in small volumes of aqueous and acidic solvents

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Results of the studies on crushing, dissolution, and extraction are described in the main body of the **Briefing Document** in the sections on Study 1, Study 2, Study 2 and Study 4.

g. Smoking

Smoking is a well-known form of drug administration, but is infrequently practiced with oxycodone. Internet accounts of smoking attempts with OxyContin® tend to follow the pattern generally described for opium and heroin, e.g., "chasing the dragon" (inhaling vapors produced by heating drug on foil). The conditions for smoked OxyContin® generally include _____ (b) (4) followed by (b) (4) the _____ (b) (4) with application of _____ (b) (4) the underside. The heat melts and _____ (b) (4). Abusers attempt to inhale the _____ (b) (4) or other _____ (b) (4). Frequently, abusers report highly unpleasant tastes and few recommend smoking oxycodone as a means of getting "high".

A protocol was designed for the assessment of the smoking potential of reformulated OxyContin®. The conditions were adopted to simulate application of intense heat to finely powdered reformulated OxyContin®. The laboratory device allowed air to pass over the heated reformulated OxyContin® _____ (b) (4) and the ____ (b) (4) collected by means of a ____ (b) (4). Initial experiments were performed to determine the optimal temperature for vaporization of reformulated OxyContin®. Results of the studies on smoking potential are described in the main body of the **Briefing Document** in the sections on Study 5.

h. Rectal ("plugging")

Rectal administration is infrequently reported as a means of administration of OxyContin®. The method generally involves a _____ (b) (4) extraction of oxycodone, followed by loading into a syringe, and insertion into the rectum for administration.

Assessment of the potential for rectal abuse of reformulated OxyContin® can be made from the protocols that characterize the following elements essential to drug absorption from the rectum:

- Crushability, grinding and powdering potential

- Extraction studies in _____ (b) (4) solvents

Results of the studies on the potential for rectal use are described are described in the main body of the **Briefing Document** in the sections on Study 1, Study 2 and Study 4

  i. _____ isolation (for use by different routes of administration)

Tampering methods reported for OxyContin® that involve routes other than oral or intranasal administration generally begin with crushing the tablet with subsequent extraction steps intended to produce concentrated solutions or residues of purified oxycodone. The motivation for many abusers, as reported on the Internet, in attempting isolation methods is not only to change the route of administration, but also to eliminate various excipients in the formulation which many abusers view as potentially harmful if used orally or injected or smoked.

Discovery of simple isolation methods that would allow recovery of relative pure drug from a formulation could result in broader tampering practices and use by additional routes of administration, somewhat akin to the "crack" cocaine epidemic. The discovery of a simple means of conversion of cocaine hydrochloride powder into "freebase"

cocaine was a significant factor in the spread of smoked cocaine abuse. The preparation of "crack" cocaine involves dissolution of cocaine hydrochloride in water and addition of a base. With cooling, insoluble cocaine base precipitates and forms "rocks" of "crack" cocaine. Another isolation procedure commonly reported on the Internet is the "cold water extraction" technique for the separation of codeine from acetaminophen *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)*. The codeine preparation is dissolved in water then chilled to precipitate insoluble acetaminophen. Filtration allows separation of codeine solution in a relatively pure form leaving insoluble acetaminophen and other excipients on the filter paper.

Results of the studies on isolation and purification are described in the main body of the **Briefing Document** in the sections on Study 6 and Study 7.

7   Safety benefits of reformulated versus current OxyContin®

The current OxyContin® formulation can be readily converted from a safe and efficacious product when used medically as intended to an immediate release product when chewed, cut, crushed or powdered. This transformation of OxyContin® can be accomplished simply in a matter of seconds. Patients who are administered crushed

OxyContin® and abusers who knowingly tamper with OxyContin® are at risk of toxic overdose and death, especially for individuals who are nontolerant to the effects of opioids.

Numerous deaths have resulted from the use, misuse, and abuse of OxyContin®. It appears that the primary route of administration in most deaths results from oral consumption. A report by the Drug Enforcement Administration (DEA) details oxycodone-related deaths over the period 2000 and 2001 from 775 medical examiners *(Drugs and Chemicals of Concern: Oxycodone: Summary of Medical Examiner Reports on Oxycodone-Related Deaths).* Of the 949 oxycodone-related deaths reported to the DEA as of February 14, 2002, OxyContin® was the verified cause in 15% of cases or the likely cause of death in 34% of cases. Of the 464 deaths (49%) linked, or most likely linked, to OxyContin®, only nine (9) deaths were associated with the presence of a "recent injection site", and only one death was associated with snorting the drug. DEA concluded that the vast majority of deaths were associated with oral consumption of the drug **(Figure 4)**.

**Figure 4   Routes of OxyContin® Administration Associated with Deaths
Reported to the United States Drug Enforcement Agency.**

*(Drugs and Chemicals of Concern: Oxycodone: Summary of Medical Examiner Reports
on Oxycodone-Related Deaths)***.**

The Majority of OxyContin Deaths (Verified,
N=146 and Likely, N=318) Were Related to
Oral Consumption

1.9%   0.2%

Total N=464

97.8%

■ Oral Consumption ■ Injection ■ Snorting
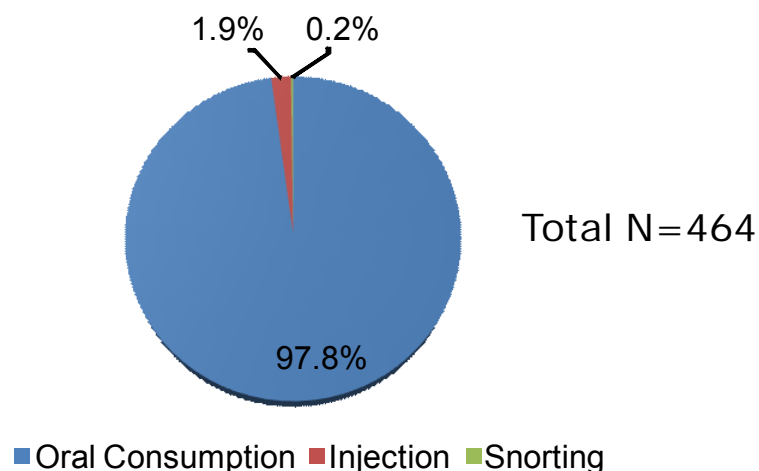
Source: Adapted from U.S. Department of Justice, Drug Enforcement Administration (DEA).
"Drugs and Chemicals of Concern: Summary of Medical Examiner Reports on Oxycodone-Related
Deaths," http://www.deadiversion.usdoj.gov/drugs_concern/oxycodone/oxycontin7.htm. Accessed
February 1, 2009.

Improvements in the tamper resistance of reformulated OxyContin® is expected to

reduce, if not eliminate, some of the major health risks of current OxyContin®. These

improvements include crush resistance, formation of viscous gels upon hydration, and

reduced drug release in water, alcohol and other common solvents. Even when

reformulated OxyContin® is successfully crushed, it retains a major portion of its

controlled release properties. These improvements in reformulated OxyContin® are

expected to reduce the risk of overdose and death when crushed and consumed orally,

snorted, injected or used by other routes of administration. The crush resistant

characteristics of reformulated OxyContin® will be an important safety feature for

patients who may want to cut the tablet to save money, inadvertently chew it, or crush

and add to applesauce to make it easier to swallow. In addition, these same

characteristics will make it more difficult for someone who is attempting to abuse reformulated OxyContin® by extracting the active ingredient to use as a bolus.

8   Summary

The evaluation of tamper resistance properties of a reformulation of OxyContin® required a full assessment of the strengths and weaknesses of the product. *In vitro* assessment methods were developed that broadly captured methods that are currently employed or predicted to be employed by abusers who seek to convert the product to an immediate release form. The current formulation of OxyContin® can be easily and quickly converted within seconds to an immediate release form by cutting or crushing the tablet. Reformulated OxyContin® has added crush resistance that could deter tampering efforts, but highly motivated individuals may resort to more elaborate attempts to remove and purify oxycodone from its matrix.

The development of tamper assessment protocols for the evaluation of reformulated OxyContin® involved substantial input from experts who are knowledgeable in the wide range of chemical and physical manipulation methods that abusers use. The emphasis in the design of these protocols for tamper assessment considered the range of possibilities that extended beyond current tampering practices with OxyContin®. Experts provided input not only on known methods of tampering with OxyContin®, but considered many other ways that an opioid formulation could potentially be altered.

All protocols were designed to push the limits of experimental conditions to failure by incorporating a broad range of   (b) (4).
Each protocol was designed to simulate components of tampering that are practiced or could be practiced by misusers in various environments (home, parties, etc). At the same time, each protocol was designed to meet the highest standards of scientific scrutiny. Analytical methods were standardized and validated. Multiple replicates of

each test were considered necessary to assess inherent variability of each process. All dose strengths of reformulated OxyContin® were evaluated and multiple controls were incorporated into each assessment. Independent laboratories performed the assessments under blind conditions to the extent possible.

The results of these assessments of reformulated OxyContin® provide detailed, valid scientific data on the strengths and weaknesses of the reformulation when subjected to current and potential future tampering attempts across a broad range of conditions.

No formulation that still allows the drug to be used therapeutically will prevent all methods of tampering that may lead to abuse. The most important aspects of these formulations are to 1) increase the safety of the product when misused by legitimate patients and 2) to make it more difficult and time consuming for abusers to extract the active ingredient to use for immediate effect. I believe that the data support these goals for reformulated OxyContin®.

Glossary of Abuse-Related Terms

(Adapted from PinneyAssociates' definitions)

Abuse: The use of a drug in a manner detrimental to the individual or society but not meeting criteria for addiction.

Note: Abuse is sometimes used as a synonym for drug abuse, substance abuse, drug addiction, chemical dependency, and substance dependency.

Addiction: Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Note: Addiction is the more widely used term for what the American Psychiatric Association (APA) and World Health Organization (WHO) refer to in their technical and diagnostic documents as "dependence."

Diversion: The removal of legitimately-manufactured controlled medications from lawful, legitimate use into illicit drug trafficking.

Note: Diversion cases involve, but are not limited to, physicians who sell prescriptions to drug dealers or abusers; pharmacists who falsify records and subsequently sell the medications; employees who steal from inventory; executives who falsify orders to cover illicit sales; prescription forgers; and individuals who commit armed robbery of pharmacies and drug distributors.

Formulation Barrier: The response cost (time, effort, resources) required to alter a prescription medication for purposes of misuse or abuse.

Misuse: The exposure resulting from the use of a prescription medication in ways other than how it was prescribed, contrary to approved labeling unless taken as directed by a healthcare provider, and below the threshold of abuse.

Nonmedical use: The use of a prescription medication in a manner inconsistent with accepted medical practice contrary to approved labeling.

Physical dependence: Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of drug and/or administration of an antagonist and is relieved by the readministration of the drug or another drug of the same pharmacologic class.

Tampering: Chemical and/or physical alteration of a prescription medication contrary to approved labeling.

Tolerance: Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. A need for markedly increased amounts of the drug to achieve intoxication or desired effects, or markedly diminished effects with continued use of the same amount of the drug.

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EXHIBIT 4

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OXYCONTIN® safely and effectively. See full prescribing information for OXYCONTIN.

OxyContin® (oxycodone hydrochloride controlled-release) Tablets   CII
Initial U.S. Approval: 1950

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE
See full prescribing information for complete boxed warning.
- **OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (9)**
- **OxyContin is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)**
- **OxyContin is NOT intended for use on an as-needed basis. (1)**
- **OxyContin 60 mg and 80 mg Tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in opioid-tolerant patients to avoid fatal respiratory depression. (2.7)**
- **Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. (2.2)**
- **OxyContin tablets must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved which can lead to rapid release and absorption of a potentially fatal dose of oxycodone. (2.1)**
- **The concomitant use with cytochrome P450 3A4 inhibitors such as macrolide antibiotics and protease inhibitors may result in an increase in oxycodone plasma concentrations and may cause potentially fatal respiratory depression. (7.2)**

---------------------------RECENT MAJOR CHANGES---------------------------
Dosage and Administration (2.1)	11/2010
Warnings and Precautions (5.6)	10/2011

---------------------------INDICATIONS AND USAGE---------------------------
OxyContin is an opioid agonist indicated for:
- Management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)
- Not for use on an as-needed basis or in the immediate post-operative period. (1)

---------------------DOSAGE AND ADMINISTRATION---------------------
- Use low initial doses in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other central nervous system (CNS) active medications. (2.2)
- For patients already receiving opioids, use standard conversion ratio estimates. (2.2)
- Tablets must be swallowed whole and are not to be cut, broken, chewed, crushed, or dissolved (risk of potentially fatal dose). (2.1)
- OxyContin tablets should be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.(2.1, 17.1)

--------------------DOSAGE FORMS AND STRENGTHS--------------------
- Controlled-Release Tablets: 10 mg, 15 mg, 20 mg , 30 mg, 40 mg, 60 mg, and 80 mg (3)

-----------------------------CONTRAINDICATIONS-----------------------------
- in patients who have significant respiratory depression (4)
- in patients who have or are suspected of having paralytic ileus (4)
- in patients who have acute or severe bronchial asthma (4)
- in patients with known hypersensitivity to oxycodone (4)

----------------------WARNINGS AND PRECAUTIONS----------------------
- Must be swallowed whole (5.1)
- May cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma. (5.2)
- Additive CNS effects are expected when used with alcohol, other opioids, or illicit drugs. (5.1, 5.3, 7.3)
- Use with caution in patients who are receiving other CNS depressants. (5.1, 5.3, 7.3)

- May cause respiratory depression. Use with extreme caution in patients at risk of respiratory depression, elderly and debilitated patients (5.4)
- May aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. (5.5)
- Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. (5.6)
- Use with caution in patients at risk for ileus. Monitor for decreased bowel motility in postoperative patients. (5.6)
- May worsen increased intracranial pressure and obscure its signs, such as level of consciousness or pupillary signs. (5.7)
- May cause hypotension. Use with caution in patients at increased risk of hypotension and in patients in circulatory shock. (5.8)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects (5.9)
- Mixed agonist/antagonist analgesics may precipitate withdrawal symptoms. (5.10)
- Use with caution in patients with biliary tract disease, including acute pancreatitis. (5.11)
- Tolerance may develop. (5.12)
- Use with caution in alcoholism; adrenocortical insufficiency; hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis. (5.13)
- May impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. (5.14)
- No approved use in the treatment of addiction. (5.15)
- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably. (5.16)

-----------------------------ADVERSE REACTIONS-----------------------------
Most common adverse reactions (>5%) are constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating.

To report Suspected Adverse Reactions, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

-----------------------------DRUG INTERACTIONS-----------------------------
- OxyContin may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. (7.1)
- The CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. (7.2)
- Concurrent use of other CNS depressants may cause respiratory depression, hypotension, and profound sedation or coma. (7.3)
- Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and may precipitate withdrawal symptoms in these patients. (7.4)

----------------------USE IN SPECIFIC POPULATIONS----------------------
- Labor and Delivery: Not recommended for use in women immediately prior to and during labor and delivery; (8.2)
- Nursing Mothers: Nursing should not be undertaken while a patient is receiving OxyContin. (8.3)
- Pediatrics: Safety and effectiveness in pediatric patients below the age of 18 have not been established. (8.4)
- Geriatrics: The initial dose may need to be reduced to 1/3 to 1/2 of the usual doses. (8.5)
- Hepatic impairment: Initiate therapy at 1/3 to 1/2 the usual doses and titrate carefully. (8.6)
- Renal impairment: Dose initiation should follow a conservative approach. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: IMPORTANCE OF PROPER PATIENT SELECTION
AND POTENTIAL FOR ABUSE

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

<div style="border:1px solid black;">

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE

OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (9)

OxyContin can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)

OxyContin is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

OxyContin is not intended for use on an as-needed basis. (1)

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer. (2.7)

OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg <u>are only for use in opioid-tolerant patients</u>, as they may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory-depressant or sedating effects of opioids. (2.7)

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. (2.2)

OxyContin <u>must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved.</u> Taking cut, broken, chewed, crushed or dissolved OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone. (2.1)

The concomitant use of OxyContin with all cytochrome P450 3A4 inhibitors such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse effects and may cause potentially fatal respiratory depression. Patients receiving

</div>

OxyContin and a CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (7.2)

1 INDICATIONS AND USAGE

OxyContin is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

<u>Limitations of Usage</u>

OxyContin is not intended for use on an as-needed basis.

OxyContin is not indicated for the management of pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is indicated for postoperative use following the immediate post-operative period only if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (see American Pain Society guidelines).

OxyContin is not indicated for pre-emptive analgesia (preoperative administration for the management of postoperative pain).

OxyContin is not indicated for rectal administration.

2 DOSAGE AND ADMINISTRATION

2.1 Safe Administration Instructions

OxyContin tablets <u>must be swallowed whole and must not be cut, broken, chewed, crushed or dissolved.</u> Taking cut, broken, chewed, crushed or dissolved OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

OxyContin tablets should be taken one tablet at a time. Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17.1)]*.

Selection of patients for treatment with OxyContin should be governed by the same principles that apply to the use of similar opioid analgesics. Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, Federation of State Medical Boards Model Policy, and the American Pain Society. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring.

2.2 Initiating Therapy with OxyContin

It is critical to initiate the dosing regimen for each patient individually. Attention should be given to:

- risk factors for abuse or addiction; including whether the patient has a previous or current substance abuse problem, a family history of substance abuse, or a history of mental illness or depression;
- the age, general condition and medical status of the patient;
- the patient's opioid exposure and opioid tolerance (if any);
- the daily dose, potency, and kind of the analgesic(s) the patient has been taking;
- the reliability of the conversion estimate used to calculate the dose of oxycodone;
- the special instructions for OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, **or total daily doses greater than 80 mg** *[see Dosage and Administration (2.7)]*; and
- the balance between pain control and adverse reactions.

Use low initial doses of OxyContin in patients who are not already opioid-tolerant *[see Dosage and Administration (2.7)]*, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications *[see Warnings and Precautions (5.1, 5.3) and Drug Interactions (7.1, 7.3)]*.

Experience indicates a reasonable starting dose of OxyContin for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg every 12 hours. Individually titrate OxyContin to a dose that provides adequate analgesia and minimizes adverse reactions while maintaining an every-twelve-hour dosing regimen.

For initiation of OxyContin therapy for patients previously taking opioids, the conversion ratios found in Table 1 are a reasonable starting point, although not verified in well-controlled, multiple-dose trials. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. A reasonable approach for converting from existing opioid therapy to OxyContin is as follows:

- Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.

- Using standard conversion ratio estimates (*see Table 1*), multiply the mg/day of each of the current opioids to be converted by their appropriate multiplication factor to obtain the equivalent total daily dose of oral oxycodone.

- Divide the calculated 24-hour oxycodone dose in half to approximate the every 12-hour dose of OxyContin.

- Round down, if necessary, to the appropriate OxyContin tablet strengths available.

- Close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 1

Multiplication Factors for Converting the Daily Dose of Current Opioids to the Daily Dose of Oral Oxycodone[1]*

| | (mg/Day Opioid x Factor = mg/Day Oral Oxycodone) | |
	Oral Opioid	Parenteral Opioid
Oxycodone	1	--
Codeine	0.15	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

2.3 Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg every 12 hours of OxyContin, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OxyContin, as there is limited documented experience with this conversion.

2.4 Hepatic Impairment

For patients with hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)]*.

2.5 Managing Expected Opioid Adverse Reactions

Most patients receiving OxyContin, especially those who are opioid-naive, will experience adverse reactions. Patients do not usually become tolerant to the constipating effects of opioids, therefore, anticipate constipation and treat aggressively and prophylactically with a stimulant laxative with or without a stool softener. If nausea persists and is unacceptable to the patient, consider treatment with antiemetics or other modalities to relieve these symptoms.

2.6 Individualization of Dosage

Once therapy is initiated, assess pain relief and other opioid effects frequently. Titrate patients to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. Increase the OxyContin dose by increasing the total daily dose, not by changing the 12-hour dosing interval. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose, each time an increase is clinically indicated.

If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Adjust the dose to obtain an appropriate balance between pain relief and opioid-related adverse reactions.

During periods of changing analgesic requirements, including initial titration, maintain frequent contact between physician, other members of the healthcare team, the patient and, with proper consent, the caregiver/family.

2.7 Special Instructions for Patients who are not Opioid Tolerant

<u>Do not begin treatment with OxyContin 60 mg and 80 mg Tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg in patients who are not already tolerant to the respiratory-depressant and sedating effects of opioids. Use of these doses in patients who are not opioid tolerant may cause fatal respiratory depression.</u> These doses are only for use in opioid-tolerant patients.

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

Instruct patients not to share or permit use by individuals other than the patient for whom OxyContin was prescribed, as such inappropriate use may have severe medical consequences, including death.

2.8 Continuation of Therapy

During chronic therapy, especially for non-cancer pain syndromes, reassess the continued need for around-the-clock opioid therapy regularly (e.g., every 6 to 12 months) as appropriate.

2.9 Cessation of Therapy

When the patient no longer requires therapy with OxyContin, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically-dependent patient.

2.10 Conversion from OxyContin to Parenteral Opioids

To avoid overdose, follow conservative dose conversion ratios. When converting from OxyContin to parenteral opioids, it is advisable to calculate an equivalent parenteral dose and then initiate treatment at half of this calculated value.

3 DOSAGE FORMS AND STRENGTHS

- 10 mg film-coated tablets (round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other)
- 15 mg film-coated tablets (round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other)
- 20 mg film-coated tablets (round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other)
- 30 mg film-coated tablets (round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other)
- 40 mg film-coated tablets (round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other)
- 60 mg film-coated tablets* (round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other)
- 80 mg film-coated tablets* (round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other)

* 60 mg and 80 mg tablets for use in opioid-tolerant patients only

4 CONTRAINDICATIONS

OxyContin is contraindicated in:

- patients who have significant respiratory depression
- patients who have or are suspected of having paralytic ileus
- patients who have acute or severe bronchial asthma
- patients who have known hypersensitivity to any of its components or the active ingredient, oxycodone.

5 WARNINGS AND PRECAUTIONS

5.1 Information Essential for Safe Administration

OxyContin tablets <u>must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved.</u> Taking cut, broken, chewed, crushed or dissolved OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

OxyContin 60 mg and 80 mg Tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg <u>are only for use in opioid-tolerant patients</u>. Use of these doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Instruct patients against use by individuals other than the patient for whom OxyContin was prescribed, as such inappropriate use may have severe medical consequences, including death.

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

5.2 CNS Depression

OxyContin may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma.

5.3 Interactions with Alcohol, CNS Depressants and Illicit Drugs

Hypotension, profound sedation, coma or respiratory depression may result if OxyContin is added to a regimen that includes other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). Therefore, use caution when deciding to initiate therapy with OxyContin in patients who are taking other CNS depressants. Take into account the types of other medications being taken, the duration of therapy with them, and the patient's response to those medicines, including the degree of tolerance that has developed to CNS depression. Consider the patient's use, if any, of alcohol and/or illicit drugs that cause CNS depression. If the decision to begin OxyContin is made, start with a lower OxyContin dose than usual *[see Drug Interactions (7.3)]*.

Consider using a lower initial dose of a CNS depressant when given to a patient currently taking OxyContin due to the potential of additive CNS depressant effects.

5.4 Respiratory Depression

Decreased respiratory drive resulting in respiratory depression is the chief hazard from the use or abuse of opioid agonists, including OxyContin. The risk of opioid-induced respiratory depression is increased, for example, in elderly *[see Use In Specific Populations (8.5)]* or debilitated patients; following large initial doses in any patient who is not tolerant to the respiratory-depressant or sedating effects of opioids; or when opioids are given in conjunction with other agents that either depress respiratory drive or consciousness.

Use OxyContin with extreme caution in patients with any of the following:
- significant chronic obstructive pulmonary disease or cor pulmonale
- other risk of substantially decreased respiratory reserve
- hypoxia
- hypercapnia
- pre-existing respiratory depression

Respiratory depression induced by opioids typically follows a pattern entailing first a shift in CO_2 responsiveness of the CNS respiratory drive center, which results in a decrease in the urge to breathe, despite the presence of hypercapnia. The increase in brain CO_2 can result in sedation that can accentuate the sedation from the opioid itself. Profound sedation, unresponsiveness, infrequent deep ("sighing") breaths or atypical snoring frequently accompany opioid-induced respiratory depression. Eventually, hypoxia ensues. In addition to further decreasing consciousness, hypoxia, along with hypercapnia, can predispose to life-threatening cardiac arrhythmias.

5.5 Seizures

Oxycodone, as with other opioids, may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Use OxyContin with caution in patients with a history of seizure disorders.

5.6 Difficulty Swallowing and Gastrointestinal Effects

There have been post-marketing reports of difficulty in swallowing OxyContin tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet OxyContin tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications.

Use caution when prescribing OxyContin for patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction.

The administration of OxyContin may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Use OxyContin with caution in patients who are at risk of developing ileus.

5.7 Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention, which can lead to an elevation of cerebrospinal fluid pressure. This effect may be exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone may produce miosis that is independent of ambient light, and altered consciousness, either of which may obscure neurologic signs associated with increased intracranial pressure in persons with head injuries.

5.8 Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Administer OxyContin with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.9 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations.

The expected clinical results with CYP3A4 inhibitors would be an increase in oxycodone plasma concentrations and possibly increased or prolonged opioid effects. The expected clinical results with CYP3A4 inducers would be a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone.

If co-administration is necessary, caution is advised when initiating OxyContin treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

5.10 Interactions with Mixed Agonist/Antagonist Opioid Analgesics

It is generally not advisable to administer mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) to a patient receiving OxyContin. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect and may precipitate withdrawal symptoms in these patients.

5.11 Use in Pancreatic/Biliary Tract Disease
Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase.

5.12 Tolerance

Tolerance to opioids is demonstrated by the need for increasing doses to maintain adequate analgesic effect (in the absence of disease progression or other external factors). If tolerance develops, or if pain severity increases, a gradual increase in dose may be required. The first sign of tolerance is usually a reduced duration of effect. Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to various opioid effects, whether the effect is desirable (e.g., analgesia) or undesirable (e.g., nausea).

5.13 Special Risk Groups

Use OxyContin with caution in the following conditions, due to increased risk of adverse reactions: alcoholism; delirium tremens; adrenocortical insufficiency; CNS depression; debilitation; kyphoscoliosis associated with respiratory compromise; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

5.14 Driving and Operating Machinery

OxyContin may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Caution patients accordingly.

5.15 Use in Addiction Treatment

OxyContin has no approved use in the treatment of addiction. Its proper usage in individuals with drug or alcohol addiction (substance dependence), either active or in remission, is for the management of pain requiring opioid analgesia.

5.16 Laboratory Monitoring

Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and use caution in interpreting results.

6 ADVERSE REACTIONS

The following adverse reactions described elsewhere in the labeling include:

- Respiratory depression *[see Boxed Warning, Warnings and Precautions (5.1, 5.4) and Overdosage (10)]*
- CNS depression *[see Warnings and Precautions (5.1, 5.2) and Overdosage (10)]*
- Hypotensive effects *[see Warning and Precautions (5.8) and Overdosage (10)]*
- Drug abuse, addiction, and dependence *[see Drug Abuse and Dependence (9.2, 9.3)]*
- Paralytic ileus *[see Warnings and Precautions (5.6)]*
- Seizures *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OxyContin was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OxyContin may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*.

The most common adverse reactions (>5%) reported by patients in clinical trials comparing OxyContin with placebo are shown in Table 2 below:

TABLE 2: Common Adverse Reactions (>5%)

Adverse Reaction	OxyContin (n=227) (%)	Placebo (n=45) (%)
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	-
Sweating	(5)	(2)

In clinical trials, the following adverse reactions were reported in patients treated with OxyContin with an incidence between 1% and 5%:

Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, gastritis, hiccups

General disorders and administration site conditions: chills, fever

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: twitching

Psychiatric disorders: abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities

Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups

Skin and subcutaneous tissue disorders: rash

Vascular disorders: postural hypotension

The following adverse reactions occurred **in less than 1% of patients** involved in clinical trials:

Blood and lymphatic system disorders: lymphadenopathy

Ear and labyrinth disorders: tinnitus

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis

General disorders and administration site conditions: withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema

Injury, poisoning and procedural complications: accidental injury

Investigations: ST depression

Metabolism and nutrition disorders: dehydration

Nervous system disorders: syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion

Psychiatric disorders: depression, agitation, depersonalization, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention

Reproductive system and breast disorders: impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of controlled-release oxycodone. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: abuse, addiction, overdose, death, amenorrhea, symptoms associated with an anaphylactic or anaphylactoid reaction, cholestasis, dental caries, increased hepatic enzymes, muscular hypertonia, hyponatremia, ileus, palpitations (in the context of withdrawal), seizures, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

7 DRUG INTERACTIONS

7.1 Neuromuscular Junction Blocking Agents

OxyContin may enhance the neuromuscular blocking action of true skeletal muscle relaxants (such as pancuronium) and produce an increased degree and/or duration of respiratory depression.

7.2 Agents Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4:
Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and C_{max} by 3.6 and 1.7 fold, respectively. Although clinical studies have not been conducted with other CYP3A4 inhibitors, the expected clinical results would be increased or prolonged opioid effects. If co-administration with OxyContin is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP450 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP3A4:

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63%, respectively. If co-administration with OxyContin is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inhibitors of CYP2D6:
Oxycodone is metabolized in part to oxymorphone via cytochrome CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not been shown to be of clinical significance during oxycodone treatment.

7.3 CNS Depressants

Start OxyContin at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other CNS depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate *[see Warnings and Precautions (5.2)]*.

7.4 Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should generally not be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as OxyContin. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and may precipitate withdrawal symptoms in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. In animal reproduction and developmental toxicology studies, no evidence of fetal harm was observed. Because animal reproduction studies

are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed.

Teratogenic Effects

The effect of oxycodone in human reproduction has not been adequately studied. Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no long-term developmental or reproductive effects in the pups *[see Nonclinical Toxicology (13.1)]*.

Non-Teratogenic Effects

Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4-times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. OxyContin is not recommended for use in women immediately prior to and during labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. Have a specific opioid antagonist, such as naloxone or nalmefene, available for reversal of opioid-induced respiratory depression in the neonate.

Neonates whose mothers have been taking opioids chronically may also exhibit withdrawal signs, either at birth and/or in the nursery, because they have developed physical dependence. This is not, however, synonymous with addiction *[see Drug Abuse and Dependence (9.3)]*. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

8.3 Nursing Mothers

Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving OxyContin. Do not initiate OxyContin therapy while nursing because of the possibility of sedation or respiratory depression in the infant.

Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.4 Pediatric Use

Safety and effectiveness of OxyContin in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, reduce the starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients. Respiratory depression is the chief risk in elderly or debilitated patients, usually the result of large initial doses in patients who are not tolerant to opioids, or when opioids are given in conjunction with other agents that depress respiration. Titrate the dose of OxyContin cautiously in these patients.

8.6 Hepatic Impairment

A study of OxyContin in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation *[see Clinical Pharmacology (12.3)]*.

8.8 Gender Differences

In pharmacokinetic studies with OxyContin, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OxyContin contains oxycodone, which is a Schedule II controlled substance with an abuse liability similar to morphine.   OxyContin, like morphine and other opioids used for analgesia, can be abused and is subject to criminal diversion.

9.2 Abuse

Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances.

With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Opioid drugs are sought by people with substance use disorders (abuse or addiction, the latter of which is also called "substance dependence") and criminals who supply them by diverting medicines out of legitimate distribution channels. OxyContin is a target for theft and diversion.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, altering or forging of prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among people with untreated substance use disorders, and criminals who divert controlled substances.

The risks of misuse and abuse should be considered when prescribing or dispensing OxyContin. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

Compromising an extended or controlled-release delivery system will result in the uncontrolled delivery of oxycodone and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions (5.1)]*. The risk of fatal overdose is further increased when oxycodone is abused concurrently with alcohol or other CNS depressants, including other opioids *[see Warnings and Precautions (5.3)]*. Abuse may occur by taking intact tablets without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

Drug addiction is characterized by compulsive abuse, repeated use for non-medical purposes, loss of control over intake, craving of psychic effects and continued abuse despite harm or risk of harm in medical, social, legal or occupational domains. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, but relapse is common.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by intentional misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin has been diverted for non-medical use.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and abuse of opioid drugs. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Physical dependence to an opioid is manifested by characteristic withdrawal signs and symptoms after abrupt discontinuation of a drug, significant dose reduction or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome in adults is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate *[see Use In Specific Populations (8.2)]*.

In general, opioids should not be abruptly discontinued *[see Dosage and Administration (2.9)]*.

10 OVERDOSAGE

Acute overdosage with OxyContin can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring and death.

It is important to take the pharmacokinetic profile of OxyContin into account when treating overdose. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects as opioid continues to be absorbed from ingested tablets.

Deaths due to overdose have been reported with abuse and misuse of whole OxyContin tablets, and with abuse and misuse by ingesting, inhaling, or injecting crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of OxyContin overdosage, primary attention should be given to the maintenance of a patent airway, and of effective ventilation (clearance of CO_2) and oxygenation, whether by spontaneous, assisted or controlled respiration. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Since the duration of action of OxyContin may exceed that of the antagonist, especially when the overdose involves intact tablets, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration. Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin, an abrupt partial or complete reversal of opioid effects may precipitate an acute abstinence (or withdrawal) syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. See the prescribing information for the specific opioid antagonist for details of its proper use.

11 DESCRIPTION

OxyContin (oxycodone hydrochloride controlled-release) is an opioid analgesic supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:
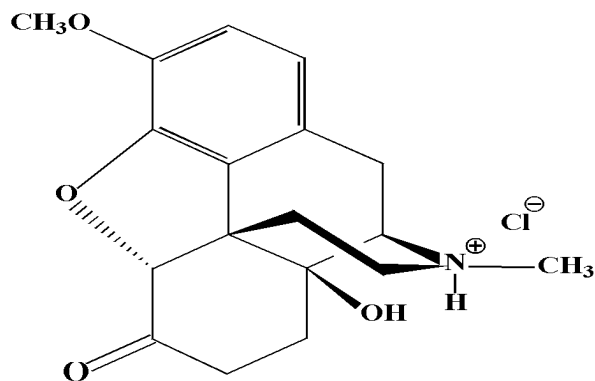
$C_{18} H_{21} NO_4 \bullet HCl$ MW 351.83

The chemical name is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7).

The 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablets contain the following inactive ingredients: butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain: hydroxypropyl cellulose.

The 15 mg tablets also contain: black iron oxide, yellow iron oxide, and red iron oxide.

The 20 mg tablets also contain: polysorbate 80 and red iron oxide.

The 30 mg tablets also contain: polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

The 40 mg tablets also contain: polysorbate 80 and yellow iron oxide.

The 60 mg tablets also contain: polysorbate 80, red iron oxide and black iron oxide.

The 80 mg tablets also contain: hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/Indigo Carmine Aluminum Lake.

12 CLINICAL PHARMACOLOGY

Oxycodone is a pure mu receptor opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, hydrocodone and oxymorphone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as

analgesia. Increasing doses of pure mu receptor agonists are associated with increasing analgesia. There is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by adverse reactions, the more serious of which may include somnolence and respiratory depression.

12.1 Mechanism of Action

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OxyContin (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. OxyContin doses of 20 mg and 30 mg produced statistically significant pain reduction compared to placebo.

Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in CO_2 tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose *[see Overdosage (10)]*.

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System

In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Concentration – Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective "drug effect", analgesia and feelings of "relaxation".

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration – Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related side effects.

The dose of OxyContin must be individualized *[see Dosage and Administration (2.6)]*, because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

12.3 Pharmacokinetics

The activity of OxyContin is primarily due to the parent drug oxycodone. OxyContin is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving OxyContin impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OxyContin is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from OxyContin to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OxyContin in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Plasma Oxycodone Concentration Over Time

Dose proportionality has been established for OxyContin 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) *(see Table 3).* Given the short elimination half-life of oxycodone, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations.

TABLE 3
Mean [% coefficient of variation]

Regimen	Dosage Form	AUC (ng•hr/mL)*	C_{max} (ng/mL)	T_{max} (hr)
Single Dose†	10 mg	136 [27]	11.5 [27]	5.11 [21]
	15 mg	196 [28]	16.8 [29]	4.59 [19]
	20 mg	248 [25]	22.7 [25]	4.63 [22]
	30 mg	377 [24]	34.6 [21]	4.61 [19]
	40 mg	497 [27]	47.4 [30]	4.40 [22]
	60 mg	705 [22]	64.6 [24]	4.15 [26]
	80 mg	908 [21]	87.1 [29]	4.27 [26]

* for single-dose AUC = AUC_{0-inf}
†data obtained while subjects received naltrexone which can enhance absorption

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin.

Distribution

Following intravenous administration, the steady-state volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk *[see Use In Specific Populations (8.3)]*.

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs *(see Drug-Drug Interactions)*.

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration in to the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and

conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Special Populations

Elderly (≥65 years)

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Gender

Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight adjusted basis. The reason for this difference is unknown *[see Use In Specific Populations (8.8)]*.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination t½ for oxycodone of 1 hour.

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination t½ for oxycodone increased by 2.3 hours.

Drug-Drug Interactions

Oxycodone is extensively metabolized by multiple metabolic pathways. CYP3A4 is the major enzyme involved in noroxycodone formation followed by CYP2B6, CYP2C9/19 and CYP2D6. Drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. For example, a published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and Cmax by 3.6 and 1.7 fold, respectively. Similarly, CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore,

may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63%, respectively.

Oxymorphone is a minor metabolite, its formation is catalyzed primarily by CYP2D6 and to a small extent by CYP2C19. The formation of oxymorphone may be blocked by a variety of drugs (such as antipsychotics, beta blockers, antidepressants, etc.) that inhibit these enzymes. However, in a study involving ten subjects using quinidine, a known inhibitor of CYP2D6, the pharmacodynamic effects of oxycodone were unchanged. The genetic expression of CYP2D6 may have some influence in the pharmacokinetic properties of oxycodone.

The in vitro drug-drug interaction studies with noroxymorphone using human liver microsomes showed no significant inhibition of CYP2D6 and CYP3A4 activities which suggests that noroxymorphone may not alter the metabolism of other drugs that are metabolized by CYP2D6 and CYP3A4, and such blockade has not been shown to be of clinical significance with oxycodone *[see Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

<u>Carcinogenesis</u>

No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.

<u>Mutagenesis</u>

Oxycodone was genotoxic in the mouse lymphoma assay at concentrations of 50 mcg/mL or greater with metabolic activation and at 400 mcg/mL or greater without metabolic activation. Clastogenicity was observed with oxycodone in the presence of metabolic activation in one chromosomal aberration assay in human lymphocytes at concentrations greater than or equal to 1250 mcg/mL at 24 but not 48 hours of exposure. In a second chromosomal aberration assay with human lymphocytes, no structural clastogenicity was observed either with or without metabolic activation; however, in the absence of metabolic activation, oxycodone increased numerical chromosomal aberrations (polyploidy). Oxycodone was not genotoxic in the following assays: Ames *S. typhimurium* and *E. coli* test with and without metabolic activation at concentrations up to 5000 µg/plate, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at concentrations up to 1500 µg/mL, and with activation after 48 hours of exposure at concentrations up to 5000 µg/mL, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels up to 48 µg/mL).

Impairment of Fertility

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to gestation day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested ($\leq$8 mg/kg/day).

14 CLINICAL STUDIES

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, OxyContin 20 mg, but not 10 mg, was statistically significant in pain reduction compared with placebo.

15 REFERENCES

1. Adapted from Foley, KM. N Engl J Med, 1985; 313:84-95

16 HOW SUPPLIED/STORAGE AND HANDLING

OxyContin (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-410-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-410-20**)

OxyContin (oxycodone hydrochloride controlled-release) Tablets 15 mg are round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-415-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-415-20**)

OxyContin (oxycodone hydrochloride controlled-release) Tablets 20 mg are round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-420-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-420-20**)

OxyContin (oxycodone hydrochloride controlled-release) Tablets 30 mg are round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-430-10**)

and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-430-20**)

OxyContin (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-440-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-440-20**)

OxyContin (oxycodone hydrochloride controlled-release) Tablets 60 mg are round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-460-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-460-20**)

OxyContin (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-480-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-480-20**)

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

See <u>MEDICATION GUIDE</u> as appended at the end of the full prescribing information

17.1 Information for Patients and Caregivers

Provide the following information to patients receiving OxyContin or their caregivers:

- Advise patients that OxyContin contains oxycodone, which is a morphine-like substance.

- Advise patients that OxyContin is designed to work properly only if swallowed whole. Taking cut, broken, chewed, crushed, or dissolved OxyContin Tablets can result in a fatal overdose.

- Advise patients that OxyContin tablets should be taken one tablet at a time.

- Advise patients not to pre-soak, lick or otherwise wet the tablet prior to placing in the mouth.

- Advise patients to take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.

- Advise patients to report adverse experiences, and episodes of increased or incident pain occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

- Advise patients not to adjust the dose of OxyContin without consulting the prescribing professional.

- Advise patients that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).

- Advise patients not to combine OxyContin with alcohol or other central nervous system depressants (e.g. sedatives, hypnotics) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.

- Advise women of childbearing potential who become, or are planning to become, pregnant to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.

- Advise patients that OxyContin is a drug with known abuse potential. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

- Advise patients that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. If tapering is appropriate, their prescriber can provide a dose schedule to gradually discontinue the medication.

- Advise patients to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

CAUTION
DEA Order Form Required.

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Purdue Pharma L.P.

Stamford, CT 06901-3431

U.S. Patent Numbers 5,508,042; 6,488,963; 7,129,248; 7,674,799; 7,674,800; 7,683,072; and 7,776,314

301734-0E

MEDICATION GUIDE

OXYCONTIN® (ox-e-KON-tin) (CII)
(oxycodone hydrochloride controlled-release)
Tablets

Read this Medication Guide before you start taking OxyContin and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about OxyContin?

- **OxyContin can cause serious side effects, including addiction or death.**

- **Do not cut, break, chew, crush, or dissolve OxyContin before swallowing. If OxyContin is taken in this way, the medicine in the tablets will be released too fast. This is dangerous. It may cause you to stop breathing, and may lead to death.**

- OxyContin is not for use to treat pain that you only have once in a while ("as needed").

- **Do not take OxyContin 60 mg or 80 mg tablets unless you are "opioid tolerant."** Opioid tolerant means that you regularly use OxyContin or another opioid medicine for your constant (around-the-clock) pain and your body is used to it.

- **Do not take more than 40 mg of OxyContin in one dose or more than 80 mg of OxyContin in one day unless you are "opioid tolerant."** This may cause you to stop breathing and may lead to death.

- **OxyContin is a federally controlled substance** (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse and abuse.** Keep OxyContin in a safe place, to keep it from being stolen. OxyContin can be a target for people who misuse or abuse prescription medicines or street drugs.

- **Never give OxyContin to anyone else, even if they have the same symptoms you have. It may harm them and even cause death.**

- Before taking OxyContin, tell your doctor if you or a family member have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental illness.

- **Do not drink alcohol while using OxyContin. Using alcohol with OxyContin may increase your risk of dangerous side effects, including death.**

- **Certain medicines can interact with OxyContin and cause you to have high levels of oxycodone in your blood. This may cause you to stop breathing and lead to death. Before taking OxyContin, tell your healthcare provider if you take an antibiotic, an antifungal medicine, or an anti-HIV medicine.**

What is OxyContin?

- OxyContin is a prescription medicine used when an opioid medicine is needed to manage moderate to severe pain that continues around-the-clock and is expected to last for a long period of time.

- It is not known if OxyContin is safe and effective in children younger than 18 years.

- OxyContin is not for use:
    - to manage pain "as needed"
    - before surgery to manage any pain from your surgery
    - to manage pain after surgery if the pain is mild and is not expected to last for a long period of time

- If you already take OxyContin, it may be used to manage your pain after surgery if:
    - it has been at least 12 to 24 hours after your surgery, and
    - your pain from surgery is expected to be moderate to severe, and last for a long period of time.

Who should not take OxyContin?

Do not take OxyContin if you:

- are allergic to any of its ingredients. See the end of this Medication Guide for a list of the ingredients in OxyContin.

- have had a severe allergic reaction to a medicine that contains oxycodone. Ask your healthcare provider if you are not sure.

- are having an asthma attack or have severe asthma, trouble breathing, or lung problems

- have a bowel blockage called paralytic ileus

What should I tell my healthcare provider before taking OxyContin?

OxyContin may not be right for you. Before taking OxyContin, tell your doctor if you:

- have trouble breathing or lung problems

- have had a head injury

- have liver or kidney problems

- have adrenal gland problems, such as Addison's disease

- have severe scoliosis that affects your breathing

- have thyroid problems

- have enlargement of your prostate or a urethral stricture

- have or had convulsions or seizures

- have a past or present drinking problem or alcoholism

- have hallucinations or other severe mental problems

- have past or present substance abuse or drug addiction

- have any other medical conditions

- are pregnant or plan to become pregnant. If you take OxyContin regularly before your baby is born, your newborn baby may have signs of withdrawal because their body has become used to the medicine. Signs of withdrawal in a newborn baby can include:

  - irritability

  - crying more than usual

  - shaking (tremors)

  - jitteriness

  - breathing faster than normal

  - diarrhea or more stools than normal

  - sneezing

  - yawning

  - vomiting

  - fever

  If you take OxyContin right before your baby is born, your baby could have breathing problems at birth.

- are breast-feeding. You should not take OxyContin if you are nursing. Some oxycodone from OxyContin passes into breast milk. A nursing baby could become very drowsy or have difficulty breathing or feeding well.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Sometimes the doses of medicines that you take with OxyContin may need to be changed if used together.

- **See "What is the most important information I should know about OxyContin?"**

- Be especially careful about taking other medicines that make you sleepy such as:
  - pain medicines
  - sleeping pills

- anxiety medicines
- antihistamines
- anti-depressants
- tranquilizers
- anti-nausea medicine

Do not take other medicines without talking to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you take OxyContin.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist.

How should I take OxyContin?

- See "What is the most important information I should know about OxyContin?"

- **Take OxyContin exactly as prescribed. Do not change your dose unless your healthcare provider tells you to**.

- **Swallow OxyContin tablets whole. Do not cut, break, chew, crush, or dissolve the tablets.**

- **In order to reduce the possibility of choking on the tablets or having difficulty swallowing the tablets:**

    o OxyContin tablets should be taken one tablet at a time.

    o Do not pre-soak, lick or otherwise wet the tablet prior to placing in your mouth.

    o Take each tablet with enough water to ensure complete swallowing immediately after placing in your mouth.

- Take OxyContin every 12 hours.

- You can take OxyContin with or without food.

- If you miss a dose, take it as soon as possible. Take your next dose 12 hours later. Do not take more than your prescribed dose of OxyContin. Call your healthcare provider if you are not sure about your dose of OxyContin or when to take it.

- **If you take more OxyContin than prescribed**, or overdose, call your local emergency number (such as 911) or your local Poison Control Center right away, or get emergency help.

- **Talk with your healthcare provider regularly about your pain** to see if you still need to take OxyContin.

What should I avoid while taking OxyContin?

- **Do not drink alcohol while using OxyContin. See "What is the most important information I should know about OxyContin?" Do not drive, operate heavy machinery, or do other dangerous activities, especially when you start taking OxyContin and when your dose is changed, until you know**

how you react to this medicine. OxyContin can make you sleepy, and also cause you to feel dizzy. Ask your healthcare provider to tell you when it is okay to do these activities.

What are the possible side effects of OxyContin?

OxyContin can cause serious side effects, including:

- **See "What is the most important information I should know about OxyContin?"**

- **OxyContin can cause serious breathing problems that can become life-threatening, especially if OxyContin is used the wrong way. Call your healthcare provider or get medical help right away if:**

  - your breathing slows down

  - you have shallow breathing (little chest movement with breathing)

  - you feel faint, dizzy, confused, or

  - you have any other unusual symptoms

  These can be signs or symptoms that you have taken too much OxyContin (overdose) or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- **Central nervous system effects, including sleepiness, dizziness, passing out, becoming unconscious, or coma.**

- **OxyContin may cause a worsening of seizures in people who already have seizures.**

- **OxyContin can cause your blood pressure to drop.** This can make you feel dizzy and faint if you get up too fast from sitting or lying down. Low blood pressure is also more likely to happen if you take other medicines that can also lower your blood pressure. Severe low blood pressure can happen if you lost blood or take certain other medicines.

- **OxyContin can cause physical dependence.** Do not stop taking OxyContin or any other opioid without talking to your healthcare provider about how to slowly stop your medicine. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction. Tell your healthcare provider if you have any of these signs or symptoms of withdrawal while slowly stopping OxyContin:

  - feel restless

  - tearing eyes

  - runny nose

  - yawning

  - sweating

  - chills or hair on your arms "standing up"

- o muscle aches, backache

- o dilated pupils of your eyes

- o feel irritable or anxious

- o nausea, loss of appetite, vomiting, diarrhea

- o increase in your blood pressure, breathing faster, or your heart beats faster

- **There is a chance of abuse or addiction with OxyContin.** The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

The most common side effects of OxyContin include:
- o constipation

- o nausea

- o drowsiness

- o dizziness

- o itching

- o vomiting

- o headache

- o dry mouth

- o weakness

- o sweating

Some of these side effects may decrease with continued use. Talk with your healthcare provider if you continue to have these side effects. These are not all the possible side effects of OxyContin. For a complete list, ask your healthcare provider or pharmacist.

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OxyContin, and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OxyContin.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.

How should I store OxyContin?

- **Keep OxyContin out of the reach of children.** Accidental overdose by a child is dangerous and can lead to death.

- Store OxyContin at 59° F to 86°F (15° C to 30° C).

- Keep OxyContin in the container it comes in.

- Keep the container tightly closed and away from light.

- After you stop taking OxyContin, flush the unused tablets down the toilet.

General information about OxyContin
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OxyContin for a condition for which it was not prescribed. Never give your OxyContin to other people even if they have the same symptoms you have.

Selling or giving away OxyContin may harm others, even causing death, and is against the law.

This Medication Guide summarizes the most important information about OxyContin. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about OxyContin that is written for health professionals. For more information about OxyContin, go to www.purduepharma.com or call 1-888-726-7535.

What are the ingredients of OxyContin?

Active ingredient: oxycodone hydrochloride
Inactive ingredients in all strengths: butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide
- The 10 mg tablets also contain: hydroxypropyl cellulose.
- The 15 mg tablets also contain: black iron oxide, yellow iron oxide, and red iron oxide.
- The 20 mg tablets also contain: polysorbate 80 and red iron oxide.
- The 30 mg tablets also contain: polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.
- The 40 mg tablets also contain: polysorbate 80 and yellow iron oxide.
- The 60 mg tablets also contain: polysorbate 80, red iron oxide and black iron oxide.
- The 80 mg tablets also contain: hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/Indigo Carmine Aluminum Lake.

Always check to make sure that the medicine you are taking is the correct one. The dosage strength and appearance of each OxyContin tablet are as follows:
- 10 mg: white-colored with "OP" on one side and "10" on the other
- 15 mg: gray-colored with "OP" on one side and "15" on the other
- 20 mg: pink-colored with "OP" on one side and "20" on the other
- 30 mg: brown-colored with "OP" on one side and "30" on the other
- 40 mg: yellow-colored with "OP" on one side and "40" on the other
- 60 mg: red-colored with "OP" on one side and "60" on the other
- 80 mg: green-colored with "OP" on one side and "80" on the other

This Medication Guide has been approved by the U.S. Food and Drug Administration.

CAUTION
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Purdue Pharma L.P.
Stamford, CT 06901-3431

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