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PURDUE PHARMA PRODUCTS L.P. and
NAAP PHARMACEUTICAL GROUP LTD.

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CLERK U.S. DISTRICT COURT
CENTRAL DIST. OF CALIF.
SANTA ANA
BY:________

DYKEMA GOSSETT LLP
333 SOUTH GRAND AVENUE
SUITE 2100
LOS ANGELES, CALIFORNIA 90071

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA
SOUTHERN DIVISION

PURDUE PHARMA PRODUCTS L.P., a Delaware limited partnership, and NAPP PHARMACEUTICAL GROUP LTD., an English limited company,

Plaintiffs,

vs.

ANCHEN PHARMACEUTICALS, INC., a California corporation,

Defendant.

Case No. **SACV10-00103 JVS (ANx)**

COMPLAINT

Plaintiffs Purdue Pharma Products L.P. and Napp Pharmaceutical Group Ltd., for their Complaint herein, aver 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.

THE PARTIES

2. Plaintiff Purdue Pharma Products L.P. ("Purdue") is a limited partnership organized and existing under the laws of the State of Delaware, having a place of business at One Stamford Forum, 201 Tresser Boulevard, Stamford, Connecticut 06901-3431. Purdue is an owner by assignment of the patents-in-suit identified in paragraph 7 below.

3. Plaintiff Napp Pharmaceutical Group Ltd. ("Napp") is a private limited company organized and existing under the laws of the United Kingdom, having a place of business at Cambridge Science Park, Milton Road, Cambridge, CB4 0GW. Napp is an owner by assignment of the patents-in-suit identified in paragraph 7 below.

4. Upon information and belief, Defendant Anchen Pharmaceuticals, Inc. ("Anchen") is a corporation organized under the laws of State of California, having a principal place of business at 9601 Jeronimo Road, Irvine, CA 92618.

JURISDICTION AND VENUE

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), and 2201.

6. Venue is proper in this Judicial District under 28 U.S.C. § 1391 and § 1400(b).

THE PATENTS-IN-SUIT

7. Purdue and Napp are the lawful owners of all right, title and interest in and to the following two United States patents, including all right to sue and to recover for past infringement thereof:

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a. United States Patent No. 5,591,452, entitled "CONTROLLED RELEASE FORMULATION" ("the '452 patent"), a copy of which is attached hereto as Exhibit A, which was duly and legally issued on January 7, 1997, naming Ronald B. Miller, Stewart T. Leslie, Sandra T. A. Malkowska, Kevin J. Smith, Walter Wimmer, Horst Winkler, Udo Hahn and Derek A. Prater as the inventors. The '452 patent is among the patents listed in the U.S. Food and Drug Administration's ("FDA") "Orange Book" (*Approved Drug Products With Therapeutic Equivalence Evaluation*) as covering Ryzolt,® a controlled-release tramadol hydrochloride pain relief medication.

b. United States Patent No. 6,326,027, entitled "CONTROLLED RELEASE FORMULATION" ("the '027 patent"), a copy of which is attached hereto as Exhibit B, which was duly and legally issued on December 4, 2001, naming Ronald Brown Miller, Sandra Therese Antoinette Malkowska, Walter Wimmer, Udo Hahn, Stewart Thomas Leslie, Kevin John Smith, Horst Winkler and Derek Allan Prater as the inventors.

ANCHEN'S ANDA

8. Upon information and belief, Anchen submitted Abbreviated New Drug Application No. 20-491 ("ANDA") to the FDA, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking approval to engage in the commercial manufacture, use or sale of tramadol hydrochloride controlled-release tablets, 100 mg, 200 mg, and 300 mg ("the Anchen Tablets"), a generic version of Ryzolt,® before the expiration of the '452 and '027 patents.

9. Upon information and belief, Anchen's ANDA contains a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that "each claim of the '452 patent...is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use or sale" of the Anchen Tablets.

10. In a letter dated December 14, 2009 addressed to Purdue, Napp, Labopharm Inc., Labopharm Europe Limited, Labopharm Canada Inc., Labopharm

(Barbados) Limited, Goodwin Procter LLP, and Davidson, Davidson & Kappel, LLC, Anchen provided "notice" with respect to the Anchen Tablets and the '452 patent under 21 U.S.C. § 355(j)(2)(B)(ii) ("Anchen's Notice Letter").

FIRST CLAIM FOR RELIEF:
PATENT INFRINGEMENT OF THE '452 PATENT

11. Anchen's submission of its ANDA was an act of infringement of the '452 patent under the United States Patent Law, 35 U.S.C. § 271(e)(2)(A).

12. Upon information and belief, the Anchen Tablets are covered by one or more claims of the '452 patent.

13. Upon information and belief, the commercial manufacture, use, sale, and/or offer for sale of the Anchen Tablets would infringe, contribute to the infringement of, and/or induce the infringement of one or more claims of the '452 patent.

14. Upon information and belief, Anchen has been aware of the existence of the '452 patent, and has no reasonable basis for believing that the Anchen Tablets will not infringe the '452 patent, thus rendering the case "exceptional," as that term is used in 35 U.S.C. § 285.

15. The acts of infringement by Anchen set forth above will cause Plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless enjoined by this Court.

SECOND CLAIM FOR RELIEF: DECLARATORY JUDGMENT OF PATENT INFRINGEMENT OF THE '027 PATENT

16. The filing of Anchen's ANDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) is a defined act sufficient to create case or controversy jurisdiction under 35 U.S.C. § 271(e)(2) to enable this Court to promptly resolve any dispute concerning infringement.

17. Additionally, upon information and belief, once the FDA grants approval of Anchen's ANDA, Anchen will undertake substantial activities directed toward engaging in infringement, contributory infringement, and active inducement of infringement of the '027 patent by making, using and undertaking substantial preparation for offering to sell, without authority from Plaintiffs, the Anchen Tablets, which are covered by one or more claims of the '027 patent.

18. Upon information and belief, Anchen has been aware of the existence of the '027 patent but, once the FDA grants approval of Anchen's ANDA, Anchen will nevertheless engage in substantial activities directed towards infringing, contributorily infringing, and actively inducing the infringement of the '027 patent. These activities will be in total disregard for Plaintiff's lawful rights under the '027 patent, thus rendering the case "exceptional," as that term is set forth in 35 U.S.C. § 285.

19. Once the FDA grants approval of Anchen's ANDA, these substantial activities engaged in by Anchen directed toward infringement, contributory infringement, and active inducement of infringement as set forth above demonstrate the existence of an actual and justiciable controversy, and, if allowed to continue and progress, will inevitably constitute infringement, contributory infringement, and active inducement of infringement of the '027 patent, will cause Plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless preliminarily and permanently enjoined by this Court.

***PURDUE V. PAR* CASE**

20. There has been prior litigation on other patents directed to controlled-release tramadol, which are related to the patents asserted here but differ in claim scope. On May 5, 2007, Plaintiffs Purdue and Napp along with Ortho-McNeil, Inc. ("Ortho") and Biovail Laboratories International, SRL ("Biovail")," filed suit against Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. (collectively "Par") in the District of Delaware, Civil Action No. 07-255-KAJ,

alleging infringement of United States Patent No. 6,254,887 ("the *Par* case"). On March 28, 2008, Plaintiffs Purdue and Napp along with Ortho and Biovail, filed an amended complaint against Par additionally seeking declaratory judgment of patent infringement of United States Patent No. 7,074,430. In response, Par denied infringement and asserted that the claims of the patents-in-suit were invalid and unenforceable due to inequitable conduct. Biovail was dismissed by consent on November 10, 2008. Ortho was dismissed for lack of standing on December 3, 2008. A five-day bench trial was held from April 16 to April 22, 2009.

21. On August 14, 2009, the District Court in *Par* issued a Judgment Order and Findings of Fact and Conclusions of Law on the asserted claims of the '887 and '430 patents that were at issue in the *Par* case. The Court found and adjudged, *inter alia*, that:

a. Par has literally infringed asserted claims 3, 13, 27, and 29 of the '887 patent, and Par's manufacture, use, and offer to sell tramadol controlled-release tablets in 100 mg, 200 mg, and 300 mg dosage strengths would infringe asserted claims 5, 7, and 11 of the '430 patent;

b. Asserted claims 3, 13, 27, and 29 of the '887 patent and asserted claims 5, 7, and 11 of the '430 patent are invalid for obviousness; and

c. The '887 patent and '430 patents are not unenforceable due to inequitable conduct.

22. On September 3, 2009, Plaintiffs Purdue and Napp filed a Notice of Appeal appealing the District Court's judgment of invalidity in the *Par* case to the U.S. Court of Appeals for the Federal Circuit. That appeal is pending.

23. The '452 and '027 patents asserted in this action are related to the patents that were the subject of the *Par* action. The '887 patent in *Par* is a divisional of the '452 patent-in-suit here. The '430 patent in *Par* is a continuation of '887, and thus also related to '452.

24. Because of the relationship among the patents in this action and in *Par*, the scope of the issues to be litigated in this case may be affected by the Federal Circuit's decision in the *Par* appeal.

RELATED MULTIDISTRICT LITIGATION

25. Since Plaintiffs initiated the *Par* action, seven other pharmaceutical companies, including Anchen, have provided "notice" to Plaintiffs of "Paragraph IV" certifications relating to seeking FDA approval of controlled-release tramadol products. At least three of those actions involve allegations of infringement of the '452 and '027 patents asserted here: *Purdue Pharma Products L.P. et al., v. Impax Laboratories Inc.,* D. Del, 08-cv-519; *Purdue Pharma Products L.P. et al., v. Handa Pharmaceuticals, LLC.,* N.D. Cal, *Purdue Pharma Products L.P. et al., v. Anchen Pharmaceuticals, Inc.*, C.D. Cal.

26. In the interest of efficiency, Plaintiffs have moved the Judicial Panel on Multidistrict Litigation ("MDL Panel") to centralize five earlier-filed actions in the United States District Court for the District of Delaware. (*In re: Tramadol Hydrochloride Extended-Release Tablets Patent Litigation*, MDL No. 2126). That motion is pending.

27. Plaintiffs intend to notify the MDL Panel about this action as a tag-along action to be included in that multidistrict litigation. If and when Plaintiffs commence suit against the remaining two ANDA-filers, Plaintiffs will seek to have those actions included in the multidistrict litigation proceeding as well.

28. Accordingly, to conserve the resources of the Court and the parties, Plaintiffs will move promptly for a stay of this action against Anchen until (1) Plaintiffs' motion requesting that the MDL Panel centralize this action with the other controlled-release tramadol cases is resolved; and (2) the earlier of (a) a final adjudication of the appeal in the *Par* case or (b) a decision by the FDA to tentatively approve the Anchen Tablets.

WHEREFORE, Plaintiffs pray for judgment:

A. Adjudging that Anchen has infringed the '452 patent, and that the commercial sale, offer for sale, and/or manufacture of the Anchen Tablets would infringe, induce infringement of, and/or contribute to the infringement of the '452 and '027 patents;

B. Adjudging, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Anchen's ANDA No. 20-491, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), to be a date not earlier than the date of expiration of the '452 and '027 patents plus any additional periods of exclusivity;

C. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 and Rule 65, Fed. R. Civ. P., Anchen, its partners, contractors, officers, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities and all other persons acting in concert, participation, or in privity with them, and their successors and assigns, from any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product that infringes the '452 or '027 patents;

D. Declaring this an exceptional case and awarding Plaintiffs their attorneys' fees, as provided by 35 U.S.C. §§ 271(e)(4) and 285; and

E. Awarding Plaintiffs such other and further relief as this Court may deem just and proper.

Dated: January 22, 2010

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Sona De

By: Craig N. Hentschel
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and NAAP PHARMACEUTICAL
GROUP LTD.

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EXHIBIT A

US005591452A

United States Patent [19]

Miller et al.

[11] **Patent Number: 5,591,452**

[45] **Date of Patent: Jan. 7, 1997**

[54] **CONTROLLED RELEASE FORMULATION**

[75] Inventors: **Ronald B. Miller**, Basel, Switzerland; **Stewart T. Leslie**, Cambridge, England; **Sandra T. A. Malkowska**, Cambridgeshire, England; **Kevin J. Smith**, Cambridge, England; **Walter Wimmer**, Limburg, Germany; **Horst Winkler**, Linter, Germany; **Udo Hahn**, Nentershausen, Germany; **Derek A. Prater**, Cambridge, England

[73] Assignee: **Euro-Celtique, S.A.**, Luxembourg, Luxembourg

[21] Appl. No.: **241,129**

[22] Filed: **May 10, 1994**

[30] **Foreign Application Priority Data**

May 10, 1993	[DE]	Germany	43 15 525.1
Nov. 23, 1993	[GB]	United Kingdom	9324045
Mar. 9, 1994	[GB]	United Kingdom	9404544
Mar. 14, 1994	[GB]	United Kingdom	9404928

[51] **Int. Cl.**^{6} **A61K 9/22**; A61K 9/26

[52] **U.S. Cl.** **424/468**; 424/470; 424/476; 424/480; 424/488; 424/494; 424/495; 424/498; 424/499; 424/502; 514/646

[58] **Field of Search** 424/468, 470, 424/476, 480, 488, 494, 495, 498, 499, 502; 514/646

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Primary Examiner—Brian M. Burn

Attorney, Agent, or Firm—Steinberg, Raskin & Davidson, P.C.

[57] **ABSTRACT**

A controlled release preparation for oral administration contains tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient.

39 Claims, 1 Drawing Sheet

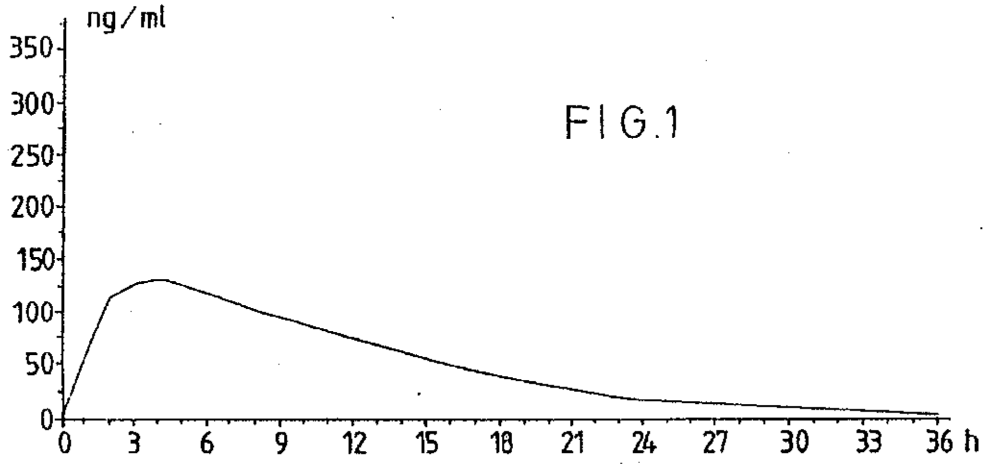
ng/ml
350
300
250
200
150
100
50
0
0
3
6
9
12
15
18
21
24
27
30
33
36 h

FIG.1

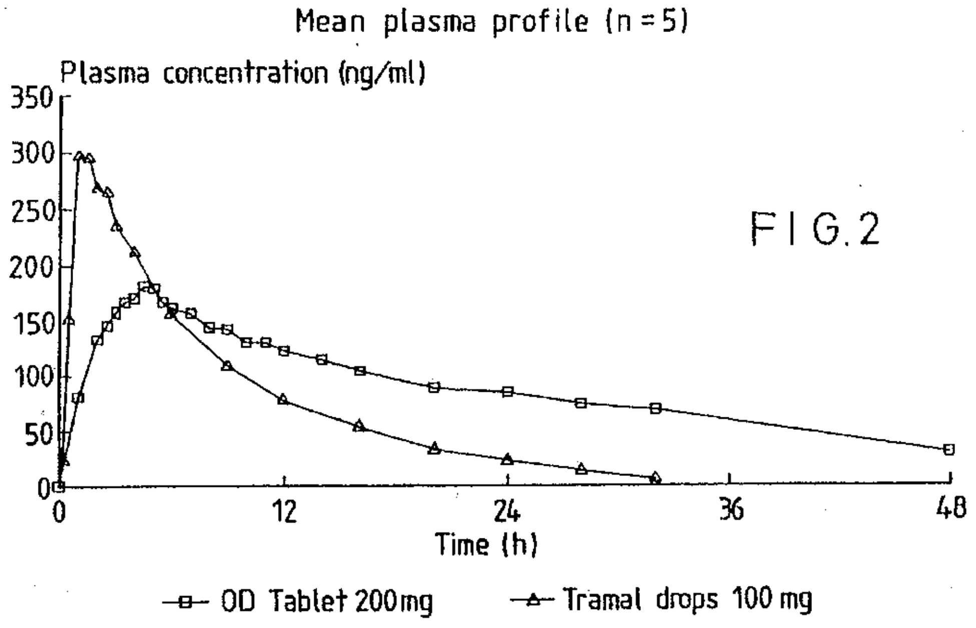
Mean plasma profile (n=5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
—□— OD Tablet 200mg
—△— Tramal drops 100 mg

FIG.2

CONTROLLED RELEASE FORMULATION

BACKGROUND OF THE INVENTION

The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, the invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

Tramadol, which has the chemical name (±)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain. Such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100

Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

A still farther preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released.

TABLE 4

TIME (H)	% RELEASED
1	0–30
2	0–40
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80

More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows;

TIME (H)	% TRAMADOL RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75

Another preferred dissolution rate in vitro upon release of the controlled release preparation for administration twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 18 hours and more than 80% (by weight) tramadol released after 24 hours.

Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and 97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferrably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing and the last (or only) downslope crossing in the plasma profile.

The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 nm.

The in vivo absorption rate is determined from measurement of plasma concentration against time using the deconvolution technique. A conventional release tramadol drop preparation (Tramal (trade mark), Grunenthal) was used as the weighting-function and the elimination half life of tramadol was taken as 7.8 hours.

The controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 800 mg, especially 100, 200, 300, 400 to 600 mg (calculated as tramadol hydrochloride) per dosage unit.

The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

Suitable materials for inclusion in a controlled release matrix include

(a) Hydrophillic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1% and 80% (by weight) of one or more hydrophillic or hydrophobic polymers.

(b) Digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25° and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

One particularly suitable controlled release matrix comprises one or more alkylcelluloses and one or more C_{12}–C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1–C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitably contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colorants, flavorants, surfactants, pH adjusters, anti-adherents and gildants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Alternatively, the controlled release preparation according to the invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

The spheronising agent may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation).

Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colorants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

Alternatively the drug may be coated onto inert non-pareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

In a further aspect the present invention provides a process for preparing a controlled release preparation according to the present invention comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix:

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,

(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally

(c) shaping and compressing the granules, and film coating, if desired; or

(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,

(e) shaping and compressing the granules, and film coating, if desired.

The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent;

(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroids are formed; and

(d) coating the spheroids with a film coat.

One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, after cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0 min, preferably 0.25 to 2.0 mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnauba wax or glyceryl monostearate, and suitably has a melting point of from 35° to 140° C., preferably 45° to 110° C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Another preferred process for the manufacture of a formulation in accordance with the invention comprises

(a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35° to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seeds; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent.

(d) optionally repeating steps (c) and possibly (b) one or more times.

This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

In this method in accordance with the invention preferably all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40° C. or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1–3 mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40° C. have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37° C. may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2 mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

The classified material is returned to the high speed mixer and processing continued. It is believed that this leads to cementation of the finer particles into particles of uniform size range.

In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g. tablets or capsules in manners known per se.

We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed on 23 Nov. 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets.

Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e.g. one or more or the standard excipients such as diluents, lubricants, binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

Suitable diluents are e.g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate. Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium. Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate. Suitable flow aids are talc colloidal anhydrous silica. Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000.

To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mold. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher

loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is further illustrated in connection with the accompanying drawings in which:

FIG. **1** is a graphical depiction of the serum levels of tramadol following administration of one tablet according to Example 2 in 12 healthy volunteers; and

FIG. **2** is a graphical depiction of the plasma profile resulting from single dose administration of the tablet of Example 8 in comparison to the administration of a commercial preparation of tramadol drops 100 mg in a trial involving five healthy male volunteers.

EXAMPLE 1

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68.0
Ethylcellulose (Surelease ® 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur. (Dehydag wax 0)	42.00
Magnesium Stearate Ph. Eur.	2.00
Purified Talc Ph. Eur.	3.00
	230.00

*Removed during processing.

Tramadol hydrochloride (100 mg) and lactose (68 mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15 mg) and water. The granules were then dried at 60° C. and passed through a 1 mm screen.

To the warmed tramadol containing granules was added molten cetostearyl alcohol (42 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

The tablets were coated with a film coat having the formulation given below.

	mg/tablet
Hydropropylmethylcellulose Ph. Eur. 15 cps (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3.87
Opaspray M-1-7111B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520
Purified Talc Ph. Eur.	0.270
Purified Water Ph. Eur.	55.52*

*Remove during processing.

EXAMPLE 2

Tables having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	58.0
Ethylcellulose USNF (Ethocel 45 CP)	15.0
Cetostearyl alcohol Ph. Eur. (Dehydag wax O)	52.0
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

A mixture of tramadol hydrochloride (100 mg), lactose (58 mg) and ethylcellulose (15 mg) was granulated while adding molten cetostearyl alcohol (52 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

EXAMPLE 3

Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.00
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur.	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

In vitro dissolution studies

In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

	WT % TRAMADOL RELEASED		
Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	—

*Measured on tablet core

In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in FIG. 1.

EXAMPLE 4 and 5

Particles having the formulations given in Table II below, were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7 kg) in the bowl of a 10 liter capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150–1000 rpm whilst applying heat until the contents of the bowl are agglomerated.

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds.

iv. Warming and mixing the classified material in the bowl of a 10 liter Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

V. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2 mm aperture sieves.

TABLE II

Example	4	5
(a) Tramadol HCl (Wt %)	50	75
(b) Hydrogenated Vegetable Oil (Wt %)	50	25

EXAMPLE 6

Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14×6 mm, (2) 16×7 mm or (3) 18.6×7.5 mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400 mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III

TABLET	MG/TABLET		
INGREDIENT	1	2	3
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Stearate	8.42	12.63	16.84

The tablets were assessed by the dissolution using Ph. Eur. Paddle Method 100 rpm, 0.1N HCl.

To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket.

The results are shown in Table IV below;

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	54	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

These results confirm the effectiveness of the tabletting in reducing the release rate.

EXAMPLE 7

Samples of the particles from Example 5 were then tabletted using a procedure similar to Example 3 and the ingredients per unit dosage amounted to:

TABLE V

TABLET INGREDIENT	MG/TABLET 4	5	6
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533
Purified Talc	7.63	11.44	15.25
Magnesium Stearate	5.16	7.63	10.17

The tablets and samples of non-compressed multiparticulates (each sample containing 400 mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below;

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	40	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved.

EXAMPLE 8

Example 4 was repeated but with the following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

The resulting multiparticulates were blended as described in Example 6 with the following;

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7.66 mg/tablet

The blend was then compressed as described in Example 6 but using 15 mm×6.5 mm normal concave capsule shaped plain/plain punches.

The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44

-continued

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
8	50
10	55
12	60
16	67
20	73
24	77

In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in FIG. 2 in comparison to the administration of a commercial preparation of Tramadol drops 100 mg.

The examples provided above are not meant to be exclusive. Many other variation of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours containing from about 50 mg to about 800 mg of tramadol or a pharmaceutically acceptable salt thereof, calculated as hydrochloride salt, in a controlled release matrix, the matrix comprising from about 1 to about 80% w/w of one or more hydrophilic or hydrophobic polymers, and having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 3 to about 95% tramadol released after 4 hours; from about 10 to about 100% after 8 hours; from about 20 to about 100% tramadol released after 12 hours; from about 30 to about 100% tramadol released after 16 hours; from about 50 to about 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight.

2. A controlled release preparation as claimed in claim 1, having an in-vitro dissolution rate (measured by the Ph. Euro Paddle method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100

3. A controlled release preparation as claimed in claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

4. A controlled release preparation as claimed in claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur.

Paddle method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	0–30
2	0–40
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80

5. A dosage form according to claim **1**, wherein said matrix comprises a cellulose ether.

6. A dosage form according to claim **5**, wherein said matrix comprises a controlled release matrix comprising at least one alkylcellulose, at least one C_{12} to C_{36}, aliphatic alcohol and, optionally at least one polyalkylglycol.

7. A dosage form as claimed in claim **6**, wherein said polyalkylglycol is polyethylene glycol.

8. A dosage form according to claim **6**, wherein said at least one C_{12} to C_{36} aliphatic alcohol is a C_{14} to C_{22} aliphatic alcohol.

9. A dosage form according to claim **6**, wherein said alkylcellulose is a C_1–C_6 alkylcellulose.

10. A dosage form according to claim **6**, wherein the dosage form contains from about 1 to about 20% w/w of said alkylcellulose.

11. A dosage form according to claim **6**, wherein said aliphatic alcohol is selected from the group consisting of lauryl alcohol, myristyl alcohol, stearyl alcohol, cetyl alcohol, cetostearyl alcohol, and mixtures thereof.

12. The dosage form of claim **11**, wherein said aliphatic alcohol is cetyl alcohol or cetostearyl alcohol.

13. A dosage form according to claim **6**, wherein said dosage form contains from about 5 to about 30% w/w of said aliphatic alcohol.

14. A dosage form according to claim **6**, wherein said dosage form contains from about 10 to about 25% w/w of said aliphatic alcohol.

15. A dosage form according to claim **1**, in the form of film coated spheroids, wherein said spheroid matrix comprises a spheronizing agent.

16. A dosage form according to claim **1**, in the form of multi-particulates wherein said matrix comprises a hydrophobic fusible carrier or diluent having a melting point from 35° to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material.

17. A dosage form according to claims **1**, which comprises a tablet formed by compressing a multiparticulate according to claim **16**.

18. A dosage form according to claim **5**, wherein said cellulose ether is an alkylcellulose.

19. A dosage form according to claim **18**, wherein said alkylcellulose is ethylcellulose.

20. A dosage form according to claim **1** which provides a t_{max} from about 3 to about 6 hours.

21. A dosage form according to claim **1** which provides a W_{50} from about 10 to about 33 hours.

22. A controlled release preparation suitable for dosing every twelve hours containing from about 50 to about 400 mg tramadol or pharaceutically acceptable salt thereof, calculated as the hydrochloride salt, in a controlled release matrix containing from about 1 to about 80% w/w of one or more hydrophilic or hydrophobic polymers, said preparation exhibiting an in vitro dissolution rate when measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 mm, such that between 5 and 50% (by weight) tramadol is released after 1 hour, between 10 and 75% (by weight) tramadol is released after 2 hours, between 20 and 95% (by weight) tramadol is released after 4 hours, between 40 and 100% (by weight) tramadol is released after 8 hours, more than 50% (by weight) tramadol is released after 12 hours, more than 70% (by weight) tramadol is released after 18 hours and more than 80% (by weight) tramadol is released after 24 hours.

23. A dosage form according to claim **22** wherein said controlled release matrix comprises a cellulose ether.

24. A dosage form according to claim **23** wherein said cellulose ether is an alkyl cellulose.

25. A dosage form according to claim **22** wherein said controlled release matrix comprises at least one C_1 to C_6, alkyl cellulose.

26. A dosage form according to claim **25**, wherein said controlled release matrix comprises at least one C_{12} to C_{36}, aliphatic alcohol.

27. A dosage form according to claim **26**, wherein said controlled release matrix further comprises at least one C_{14} to C_{22} aliphatic alcohol.

28. A dosage form according to claim **27**, wherein said controlled release matrix further comprises at least one polyalkylglycol.

29. A dosage form according to claim **28**, wherein said polyalkylglycol is polyethylene glycol.

30. A dosage form according to claim **25**, wherein said dosage form contains from about 1 to about 20% w/w of said alkyl cellulose.

31. A dosage form according to claim **29**, wherein said dosage form contains from about 2 to 15% w/w of said alkyl cellulose.

32. A dosage form according to claim **26**, wherein said aliphatic alcohol is selected from the group consisting of lauryl alcohol, myristyl alcohol, stearyl alcohol, cetyl alcohol cetostearyl alcohol, and mixtures thereof.

33. A dosage form according to claim **32**, wherein said dosage form contains from about 5 to about 30% w/w aliphatic alcohol.

34. A dosage form according to claim **32**, wherein said dosage form contains from about from 10 to 25% w/w aliphatic alcohol.

35. A dosage form according to claim **25** in the form of multiparticulate spheroid matrices, wherein said spheroid matrix comprises a spheronizing agent.

36. A dosage form according to claim **35**, wherein said spheronizing agent comprises microcrystalline cellulose.

37. A dosage form according to claim **22**, in the form of multiparticulates wherein said matrix comprises a hydrophobic fusible carrier or diluent having a melting point from 35° to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material.

38. A dosage form according to claim **22**, which provides a t_{max} from about 1.5 to about 8 hours.

39. A dosage form according to claim **22**, which provides a W_{50} from about 7 to about 16 hours.

* * * * *

EXHIBIT B

US006326027B1

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

(10) **Patent No.: US 6,326,027 B1**
(45) **Date of Patent: *Dec. 4, 2001**

(54) **CONTROLLED RELEASE FORMULATION**

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(*) 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.

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(58) **Field of Search** 424/468, 470, 424/476, 480, 488, 494, 495, 498, 499, 502; 514/646

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(57) ABSTRACT

A controlled release preparation for oral administration contains tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient.

46 Claims, 1 Drawing Sheet

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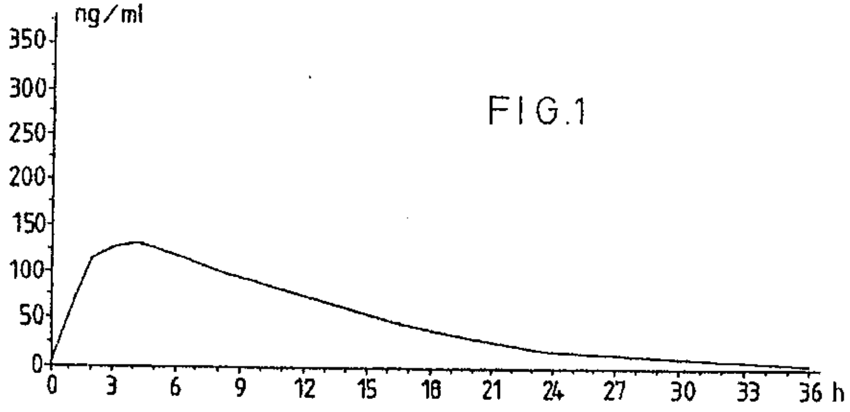
ng / ml
350
300
250
200
150
100
50
0
0
3
6
9
12
15
18
21
24
27
30
33
36 h

FIG.1

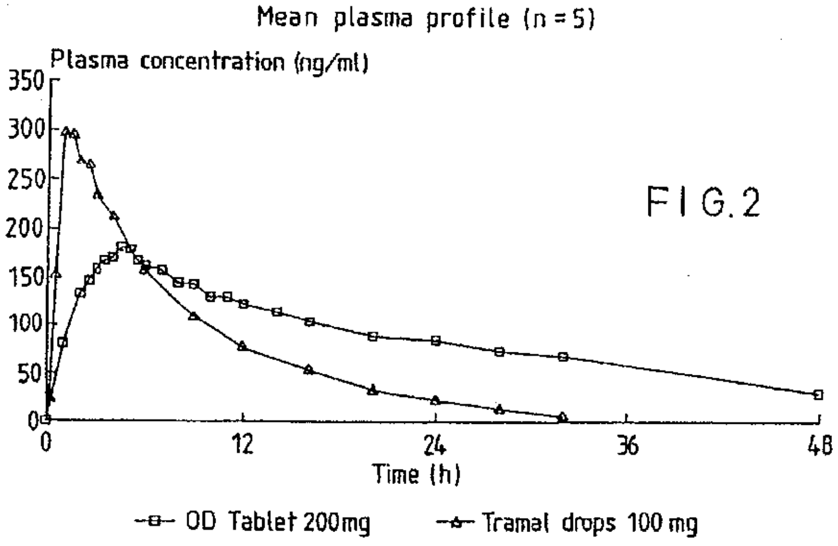
Mean plasma profile (n = 5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
OD Tablet 200mg
Tramal drops 100 mg

FIG.2

CONTROLLED RELEASE FORMULATION

This is a divisional of application Ser. No. 08/241,129, filed May 10, 1994 (now U.S. Pat. No. 5,591,452).

The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, the invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

Tramadol, which has the chemical name (±)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain; Such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt therefor for oral administration.

Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100

Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

A still further preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released.

TABLE 4

TIME (H)	% RELEASED
1	0–30
2	0–40
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80

More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows;

TIME (H)	% TRAMADOL RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75

Another preferred dissolution rate in vitro upon release of the controlled release preparation for administration twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 18 hours and more than 80% (by weight) tramadol released after 24 hours.

Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and 97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing and the last (or only) downslope crossing in the plasma profile.

The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm.

The in vitro absorption rate is determined from measurement of plasma concentration against time using the deconvolution technique. A conventional release tramadol drop preparation (Tramal (trade mark), Grunenthal) was used as the weighting-function and the elimination half life of tramadol was taken as 7.8 hours.

The controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 800 mg, especially 100, 200, 300, 400 to 600 mg (calculated as tramadol hydrochloride) per dosage unit.

The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controller release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

Suitable materials for inclusion in a controlled release matrix include

(a) Hydrophillic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1% and 80% (by weight) of one or more hydrophillic or hydrophobic polymers.

(b) Digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25 and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

One particularly suitable controlled release matrix comprises one or more alkylcelluloses and one or more C_{12}–C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1–C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitable contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colourants, flavourants, surfactants, pH adjusters, anti-adherents and glidants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Alternatively, the controlled release preparation according to the invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

The spheronising agent may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation).

Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colourants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

Alternatively the drug may be coated onto inert non-pareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

In a further aspect the present invention provides a process for preparing a controlled release preparation according to the present invention comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix, for example by

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,

(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally

(c) shaping and compressing the granules, and film coating, if desired; or

(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,

(e) shaping and compressing the granules, and film coating, if desired.

The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent;

(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroids are formed; and

(d) coating the spheroids with a film coat.

One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, after cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0 mm, preferably 0.25 to 2.0 mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnauba wax or glyceryl monostearate, and suitably has a melting point of from 35 to 140° C., preferably 45 to 110° C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Another preferred process for the manufacture of a formulation in accordance with the invention comprises

(a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seeds; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent.

(d) optionally repeating steps (c) and possibly (b) one or more times.

This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

In this method in accordance with the invention preferably all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40° C. or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1–3 mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40° C. have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37° C. may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2 mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

The classified material is returned to the high speed mixer and processing continued. It is believed that this leads to cementation of the finer particles into particles of uniform size range.

In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g. tablets or capsules in manners known per se.

We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed on Nov. 23, 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets.

Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e.g. one or more of the standard excipients such as diluents, lubricants, binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

Suitable diluents are e.g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate. Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium. Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate. Suitable flow aids are talc colloidal anhydrous silica. Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000.

To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mould. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

In order that the invention may be well understood the following examples are given by way of illustration only.

EXAMPLE 1

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68.0
Ethycellulose (Surelease ® 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur. (Dehydag wax 0)	42.00
Magnesium Stearate Ph. Eur.	2.00
Purified Talc Ph. Eur.	3.00
	230.00

*Removed during processing.

Tramadol hydrochloride (100 mg) and lactose (68 mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15 mg) and water. The granules were then dried at 60° C. and passed through a 1 mm screen.

To the warmed tramadol containing granules was added molten cetostearyl alcohol (42 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

The tablets were coated with a film coat having the formulation given below.

	mg/tablet
Hydropropylmethylcellulose Ph. Eur. 15 cps (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3.87
Opaspray M-1-7111B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520
Purified Talc Ph. Eur.	0.270
Purified Water Ph. Eur.	55.52*

*Remove during processing.

EXAMPLE 2

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	58.0
Ethylcellulose USNF (Ethocel 45 CP)	15.0
Cetostearyl alcohol Ph. Eur. (Dehydag wax O)	52.0
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

A mixture of tramadol hydrochloride (100 mg), lactose (58 mg) and ethylcellulose (15 mg) was granulated whilst adding molten cetostearyl alcohol (52 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

EXAMPLE 3

Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur.	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

In vitro Dissolution Studies

In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

	WT % TRAMADOL RELEASED		
Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	—

*Measured on tablet core

BRIEF DESCRIPTION OF DRAWING

In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in FIG. 1.

EXAMPLE 4 and 5

Particles having the formulations given in Table 11 below, were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7 kg) in the bowl of a 10 liter capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150–1000 rpm whilst applying heat until the contents of the bowl are agglomerated.

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds.

iv. Warming and mixing the classified material in the bowl of a 10 liter Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

v. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2 mm aperture sieves.

TABLE II

Example	4	5
(a) Tramadol HCl (Wt %)	50	75
(b) Hydrogenated Vegetable Oil (Wt %)	50	25

EXAMPLE 6

Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14×6 mm, (2) 16×7 mm or (3) 18.6×7.5 mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400 mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III

TABLET	MG/TABLET		
INGREDIENT	1	2	3
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Stearate	8.42	12.63	16.84

The tablets were assessed by the dissolution using PH, Eur. Paddle Method 100 rpm, 0.1 N HCl.

To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket.

The results are shown in Table IV below.

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	54	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

These results confirm the effectiveness of the tabletting in reducing the release rate.

EXAMPLE 7

Samples of the particles from Example 5 were then tabletted using a procedure similar to Example 3 and the ingredients per unit dosage amounted to:

TABLE V

TABLET	MG/TABLET		
INGREDIENT	4	5	6
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533

TABLE V-continued

TABLET INGREDIENT	MG/TABLET 4	5	6
Purified Talc	7.63	11.44	15.25
Magnesium Stearate	5.16	7.63	10.17

The tablets and samples of non-compressed multiparticles (each sample containing 400 mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below;

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	40	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved.

EXAMPLE 8

Example 4 was repeated but with the following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

The resulting multiparticulates were blended as described in Example 6 with the following:

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7.66 mg/tablet

The blend was then compressed as described in Example 6 but using 15 mm×6.5 mm normal concave capsule shaped plain/plain punches.

The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44
8	50
10	55
12	60
16	67
20	73
24	77

In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in FIG. 2 in comparison to the administration of a commercial preparation of Tramadol drops 100 mg.

What is claimed is:

1. A process for the preparation of a solid, controlled release oral dosage form, comprising incorporating a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix such that said dosage form provides a therapeutic effect for at least about 12 hours after oral administration.

2. A process according to claim 1, wherein from about 50 to about 800 mg of tramadol (calculated as tramadol hydrochloride) is incorporated in the dosage from.

3. A process according to claim 1, wherein the dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) is as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

4. A process according to claim 1, wherein the dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) is as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

5. A process according to claim 1, wherein the dissolution rate (measured by Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) is as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–40
4	3–55
8	10–65

-continued

TIME (H)	% RELEASED
12	20–75
16	30–88
24	50–100
36	>80

6. A process according to claim **1**, wherein said controlled release matrix comprises at least one C_1 to C_6 alkylcellulose, at least one C_{12} to C_{36} aliphatic alcohol and, optionally at least one polyalkylglycol.

7. A process according to claim **6**, wherein said aliphatic alcohol is a C_{14} to C_{22} aliphatic alcohol.

8. A process according to claim **6**, wherein said polyalkylglycol is polyethylene glycol.

9. A process according to claim **6**, wherein said alkylcellulose is ethylcellulose.

10. A process according to claim **1**, wherein said dosage form comprises from about 2 to 15% w/w of one or more alkylcelluloses.

11. A process according to claim **10**, wherein said dosage form comprises from about 2 to about 15% w/w of one or more alkylcelluloses.

12. A process according to claim **6**, wherein said dosage form comprises an aliphatic alcohol selected form the group consisting of lauryl alcohol, myristyl alcohol, stearyl alcohol, and mixtures thereof.

13. A process according to claim **6**, wherein said dosage form comprises an aliphatic alcohol selected form the group consisting of cetyl alcohol, cetostearyl alcohol, and mixtures thereof.

14. A process according to claim **6**, wherein said dosage form comprises from about 5 to 30% w/w of at least one aliphatic alcohol.

15. A process according to claim **14**, wherein said dosage form comprises from about 10 to about 25% w/w of at least one aliphatic alcohol.

16. A process according to claim **1**, further comprising:

(a) granulating a mixture comprising said tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses, and

(b) mixing the resultant alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols.

17. A process according to claim **1**, further comprising granulating a mixture comprising said tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one ore more C_{12-36} aliphatic alcohols.

18. A process according to claim **1**, further comprising:

(a) granulating said tramadol or a pharmaceutically acceptable salt thereof with a spheronizing agent;

(b) extruding the resultant granulate to provide an extrudate;

(c) spheronizing said extrudate to produce spheroids; and

(d) coating said spheriods with a controlled release film coat.

19. A process according to claim **1**, comprising:

(a) mechanically working in a high-speed mixer, a mixture of said tramadol or a pharmaceutically acceptable salt thereof in particulate form and a particulate, hydrophobic fusible material having a melting point from 35 to 140° C. and optionally a release control component comprising a material selected from the group consisting of water soluble fusible material, a particulate soluble organic material, a particulated soluble inorganic material and mixtures thereof, at a speed and energy input which allows said carrier or diluent to melt or soften, whereby it forms agglomerates;

(b) breaking down the larger said agglomerates to give controlled release seeds;

(c) continuing mechanically working with optionally a further addition of low percentage of said hydrophobic fusible material; and

(d) optionally repeating step (c) or steps (b) and (c) one or more times.

20. A process according to claim **1**, further comprising the step of forming a drug mixture of said tramadol or pharmaceutically acceptable salt thereof and said fusible material and mechanically working said mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles comprising said tramadol or pharmaceutically acceptable salt thereof.

21. A process according to claim **19**, further comprising compressing the resultant controlled release particles to form a tablet.

22. A process according to claim **20**, further comprising compressing the resultant controlled release particles to form a tablet.

23. A process according to claim **16** further comprising film coating said granules prepared in step (b).

24. The process according to claim **19** in which said mixture further comprises a release control component taken from the group consisting of a water soluble fusible material, a particulate soluble organic material, a particulate soluble inorganic material, a particulate insoluble organic material and a particulate insoluble inorganic material.

25. The process according to claim **19** further comprising adding an additional amount of carrier or diluent during step (c).

26. The process according to claim **1** wherein said dosage form is suitable for 12 hour administration.

27. The process according to claim **1** wherein said controlled release matrix is prepared such that said dosage form provides a therapeutic effect for about 24 hours when said dosage form in orally administered to human patients.

28. A process for the preparation of a solid, controlled release oral dosage form of tramadol, comprising incorporating a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof in a matrix comprising an effective amount of a controlled release material selected from the group consisting of hydrophilic polymers, hydrophobic polymers, fatty acids, fatty alcohols, glycerol esters of fatty acids, mineral oil, vegetable oils, waxes, polyalkylene glycols, and mixtures thereof, such that said dosage form has a dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm of between 0–50% after 1 hour; between 0–75% after 2 hours; between 3–95% after 4 hours; between 0–100% after 8 hours; between 20–100% after 12 hours; between 30–100% after 16 hours; between 50–100% after 24 hours; and greater than 80% after 36 hours; said dosage form providing a therapeutic effect for at least about 12 hours after administration.

29. The process of claim **28**, wherein said dosage form has an in vitro dissolution rate when measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, such that between 5 and 50% (by weight) tramadol is released after 1 hour, between 10 and 75% (by weight) tramadol is released after 2 hours, between 20 and 95% (by weight) tramadol is released after 4 hours, between 40 and 100% (by weight) tramadol is released after 8 hours, more than 50% (by weight) tramadol is released after 12 hours, more than 70% (by weight) tramadol is released after 18 hours and more than 80% (by weight) tramadol is released after 24 hours.

30. The process of claim **28**, wherein said dosage form provides a t_{max} at 2 to 7 hours after oral administration.

31. The process of claim **28**, wherein said dosage form provides a t_{max} at 1.5 to 8 hours after oral administration.

32. The process of claim **28**, wherein said dosage form provides a W_{50} in the range of 7 to to 16 hours when orally administered.

33. The process of claim **28**, further comprising manufacturing the dosage form as a tablet.

34. A process for the preparation of a solid, controlled release oral dosage form of tramadol suitable for dosing every 24 hours, comprising incorporation a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof in a matrix comprising an effective amount of a controlled release material comprising (a) between 1% and 80% by weight hydrophilic polymers, hydrophobic polymers, or mixtures thereof; (b) from 0–60% by weight digestible C_8–C_{50} substituted or unsubstituted hydrocarbons selected from the group consisting of fatty acids, fatty alcohols, glycerol esters of fatty acids, mineral oils, vegetable oils, waxes, and mixtures thereof; and (c) from 0–60% by weight polyalkylene glycol, such that said dosage form has a dissolution rate (measured by Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm), of between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 1005 tramadol released after 24 hours; and greater than 805 tramadol released after 36 hours, by weight, and provides a W_{50} in the range of 10 to 33 hours and a therapeutic effect for about 24 hours when orally administered to human patients.

35. The process of claim **34**, wherein said dosage form has a dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm), as set forth below:

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100.

36. The process of claim **34**, wherein said dosage form has a dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm), as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100

-continued

TIME (H)	% RELEASED
16	70–100
24	>90.

37. A process for preparation of a solid, controlled release oral dosage form, comprising incorporating a therapeutically effective amount of an opioid analgesic consisting essentially of tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix such that said dosage form provides a therapeutic effect for at least about 12 hours after oral administration.

38. The process of claim **34**, wherein said preparation provides a tmax from about 3 to about 6 hours when orally administered to human patients.

39. A process for the preparation of a solid, controlled release oral dosage form of tramadol suitable for dosing every 12 hours, comprising incorporation a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof in a matrix comprising an effective amount of a controlled release material comprising (a) between 1% and 80% by weight hydrophilic polymers, hydrophobic polymers, or mixtures thereof; (b) from 0–60% by weight digestible C_8–C_{50} substituted or unsubstituted hydrocarbons selected from the group consisting of fatty acids, fatty alcohols, glycerol esters of fatty acids, mineral oils, vegetable oils, waxes, and mixtures thereof; and (c) from 0–60% by weight polyalkylene glycol, such that said preparation contains up to 60% by weight of said polyalkylene glycol; such that said dosage form has a dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm), of between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours, between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, and provides a Tmax from about 1.5 to about 8 hours and a therapeutic effect for at least about 12 hours when orally administered to human patients.

40. The process of claim **39**, where said preparation provides a W_{50} from 7 to 16 hours.

41. A process for the preparation of a solid, controlled release oral dosage form, comprising incorporation from about 50 to about 800 mg tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix to obtain a granular product containing said tramadol; and incorporating said granular product into an orally administrable dosage form such that said dosage form provides a dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm of between 0–50% after 1 hour; between 0–75% after 2 hours; between 3–95% after 4 hours; between 10–100% after 8 hours; between 20–100% after 12 hours; between 30–100% after 16 hours; between 50–100% after 24 hours; and greater than 80% after 36 hours and provides a therapeutic effect for at least about 12 hours after oral administration.

42. The process of claim **41**, where said preparation provides a therapeutic effect for about 24 hours after oral administration.

43. The process of claim **42**, where said preparation provides a W_{50} from 7 to 16 hours.

44. The process according to claim **43**, wherein said dosage form provides Tmax from 1.5 to about 8 hours.

45. The process according to claim **44**, wherein said granular product comprises agglomerated particles.

46. The process according to claim **45**, wherein said matrix comprises an effective amount of a controlled release material comprising (a) between 1% and 80% by weight hydrophilic polymers, hydrophobic polymers, or mixtures thereof; (b) from 0–60% by weight digestible C_8–C_{50} substituted or unsubstituted hydrocarbons selected from the group consisting of fatty acids, fatty alcohols, glycerol esters of fatty acids, mineral oils, vegetable oils, waxes, and mixtures thereof; and (c) from 0–60% by weight polyalkylene glycol, such that said preparation contains up to 60% by weigh of said polyalkylene glycol; such that said dosage form has a dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm), of between 0 and 50% tramadol released after 1 hour, between 0 and 75% tramadol.

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