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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CIPHER PHARMACEUTICALS INC., GALEPHAR PHARMACEUTICAL RESEARCH, INC., RANBAXY, INC., and RANBAXY PHARMACEUTICALS, INC.,

Plaintiffs,

v.

Civil Action No. _____

ACTAVIS LABORATORIES FL, INC., ANDRX CORP., ACTAVIS, INC., and ACTAVIS PHARMA, INC.,

Defendants.

COMPLAINT

Plaintiffs Ranbaxy, Inc., Ranbaxy Pharmaceuticals, Inc. (together, "Ranbaxy"), Cipher Pharmaceuticals Inc. ("Cipher"), and Galephar Pharmaceutical Research, Inc. ("Galephar") (collectively, "Plaintiffs") for their Complaint against defendants Actavis Laboratories FL, Inc. ("ALF"), Andrx Corp. ("Andrx), Actavis, Inc. ("Actavis"), and Actavis Pharma, Inc. ("Actavis Pharma") (collectively, "Defendants"), allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the Food and Drug Laws and Patent Laws of the United States, Titles 21 and 35 of the United States Code, respectively, arising from Defendants' submission of an Abbreviated New Drug Application ("ANDA") to the Food and Drug Administration ("FDA") seeking approval to manufacture and sell a generic version of Plaintiff Ranbaxy's Absorica® (isotretinoin) capsules prior to the expiration of United States Patent No. 7,435,427 ("the '427 Patent").

THE PARTIES

2. Plaintiff Ranbaxy, Inc. ("RI") is a corporation organized and existing under the laws of the State of Delaware, having its principle place of business at 600 College Road East, Princeton, New Jersey 08540.

3. Plaintiff Ranbaxy Pharmaceuticals, Inc. ("RPI") is a corporation organized under the laws of Florida, having its principal place of business at 9431 Florida Mining Boulevard East, Jacksonville, Florida 32257.

4. Plaintiff Cipher is a corporation organized under the laws of Canada, having its principal place of business at 5650 Tomken Road, Mississauga, Ontario, Canada.

5. Plaintiff Galephar is a corporation organized under the laws of Puerto Rico, having its principal place of business at Juncos Industrial Park, Juncos, Puerto Rico 00777-3873.

6. On information and belief, ALF (formerly known as Watson Laboratories, Inc. - Florida[1]) is a corporation organized and existing under the laws of the State of Florida, having a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany,

[1] On information and belief, the entity's name was changed from Watson Laboratories, Inc. - Florida to ALF on April 21, 2014.

New Jersey 07054. On information and belief, ALF is in the business of, inter alia, developing, manufacturing, and obtaining regulatory approval of generic copies of branded pharmaceutical products throughout the United States, including within this district.

7. On information and belief, Defendant Actavis Pharma (formerly known as Watson Pharma, Inc.) is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054. On information and belief, Actavis is in the business of, inter alia, selling and distributing generic copies of branded pharmaceutical products in New Jersey and throughout the United States, including some that are manufactured by ALF and/or for which ALF is the named applicant of the approved ANDAs.

8. On information and belief, Defendant Actavis (formerly known as Watson Pharmaceuticals, Inc. ("WPI")) is a corporation organized and existing under the laws of the State of Nevada, having a principal place of business in Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054. On information and belief, Actavis is in the business of, inter alia, developing, manufacturing, obtaining regulatory approval, marketing, selling, and distributing generic copies of branded pharmaceutical products throughout the United States, including within this district, through its own actions and through the actions of its agents and subsidiaries, including at least ALF, Actavis Pharma, and Andrx.

9. On information and belief, Defendant Andrx is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 4955 Orange Drive, Davie, Florida 33314. On information and belief, Andrx is in the business of, inter alia, marketing, selling, and distributing generic copies of branded pharmaceutical

products throughout the United States, including within this district, through its own actions and through the actions of its agents and subsidiaries, including at least ALF.

10. On information and belief, WPI acquired Andrx Pharmaceuticals, Inc. on or around November 3, 2006. On information and belief, WPI renamed Andrx Pharmaceuticals, Inc. as ALF.

11. On information and belief, ALF is a wholly-owned subsidiary of Andrx, which is a wholly owned subsidiary of Actavis.

12. On information and belief, Actavis Pharma is another wholly-owned subsidiary of Actavis.

13. On information and belief, ALF, Andrx, and Actavis Pharma are within the control of Actavis for purposes of responding to discovery in this action.

14. On information and belief, ALF, Andrx, Actavis, and Actavis Pharma share certain common officers and directors and are, at the very least, agents of each other and/or work in concert with each other and/or other direct and indirect subsidiaries of Actavis with respect to the development, regulatory approval, marketing, sale and distribution of pharmaceutical products throughout the United States, including this District.

15. On information and belief, until January 23, 2013, Actavis was operating under the name of WPI. WPI organized its operations into three business segments—Global Generics, Global Brands, and ANDA Distribution—rather than by subsidiary, and reported its financial results to investors by reference to its divisions, rather than its subsidiaries. On information and belief, the name change from WPI to Actavis did not impact the organization of its operations.

16. On information and belief, until January 23, 2013, WPI's Global Generics Division, which is responsible for developing and submitting ANDAs, as well as manufacturing and marketing generic pharmaceuticals, relied on the concerted efforts of at least ALF, Actavis Pharma, and Andrx. On information and belief, the name change from WPI to Actavis did not impact the role of WPI's Global Generics Division.

17. As reported in its 2012 Annual Report on behalf of itself and its subsidiaries (collectively, "Actavis"), Actavis operates as "a leading integrated global specialty pharmaceutical company engaged in the development, manufacturing, marketing, sale and distribution of," inter alia, generic, branded generic, and brand pharmaceutical products. As described in that Annual Report, one of Actavis' business segments is "Actavis Pharma," formerly known as WPI's "Global Generics" segment, which markets a "U.S. portfolio of approximately 250 generic pharmaceutical product families." On information and belief, ALF, which is a wholly-owned subsidiary of Actavis, Inc., is part of Actavis' "Actavis Pharma" segment.

18. On information and belief, Actavis directs the activities of the other Actavis entities, including ALF, and, directly or through related companies, is responsible for sales of Actavis products to customers in New Jersey, from which Actavis, Inc. derives substantial revenue.

19. On information and belief, Defendants collaborated in the research and development of ALF's ANDA No. 205063 ("the Actavis ANDA") for isotretinoin capsules ("the Actavis ANDA Products"), continue to collaborate in seeking approval of that application by the FDA, and intend to collaborate in the commercial manufacture, marketing, offer for sale, and

sale of the Actavis ANDA Products throughout the United States, including in the State of New Jersey, in the event the FDA approves Actavis' ANDA.

20. On information and belief, ALF (formerly Watson Labs., Inc. - Florida) has submitted to the jurisdiction of this Court in prior New Jersey actions (*Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 13-3038; *Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida*, Civil Action No. 13-1669; *Depomed, Inc. v. Actavis Elizabeth LLC, et al.*, Civil Action No. 12-1358; *Warner Chilcott Co., et al. v. Watson Labs., Inc. – Florida*, Civil Action No. 11-5989; *Abbott Labs., et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 10-3241; *Mallinckrodt Inc. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 10-6424). On information and belief, ALF has availed itself of the rights, benefits, and privileges of this Court by asserting counterclaims in prior New Jersey action (*Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 13-1669).

21. On information and belief, Actavis has submitted to the jurisdiction of this Court in prior New Jersey actions (*Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 13-3038; *Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084;[2] *Depomed, Inc. v. Actavis Elizabeth LLC, et al.*, Civil Action No. 12-1358; *Noven Pharms. v. Watson Labs., Inc., et al.*, Civil Action No. 11-5997;[3] *Shire LLC, et al. v. Amneal Pharms. LLC, et al.*, Civil Action No. 11-3781; *King Pharms. Inc., et al. v. Actavis, Inc., et al.*, Civil Action No. 09-6585; *Shire LLC v. Actavis South Atlantic, LLC, et al.*, Civil Action No. 09-479; *King Pharms. Inc., et al. v. Actavis, Inc., et al.*, Civil Action No. 07-5041; *Sanofi-Aventis U.S. LLC, et al. v. Actavis Totowa LLC, et al.*, Civil Action No. 07-3142). On information and

[2] WPI submitted to the jurisdiction of this Court on July 6, 2012. WPI thereafter changed its name to Actavis Inc.

[3] WPI submitted to the jurisdiction of this Court on November 4, 2011. WPI thereafter changed its name to Actavis Inc.

belief, Actavis has availed itself of the rights, benefits, and privileges of this Court by asserting counterclaims in prior New Jersey action (*Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084).

22. On information and belief, Actavis Pharma has submitted to the jurisdiction of this Court in prior New Jersey actions (*Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 13-3038; *Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084;[4] *Abbott Labs., et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 10-3241;[5] *Teva Neuroscience, Inc., et al. v. Watson Pharma, Inc., et al.*, Civil Action No. 10-5078;[6] *Duramed Pharms. v. Watson Pharma, Inc.*, Civil Action No. 07-5941;[7] *Hoffman La-Roche Inc., et al. v. Cobalt Pharms. Inc., et al.*, Civil Action No. 07-4539).[8] On information and belief, Actavis Pharma has availed itself of the rights, benefits, and privileges of this Court by asserting counterclaims in prior New Jersey action (*Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084).

JURISDICTION AND VENUE

23. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this Court under 28 U.S.C. §§ 1391 and 1400(b).

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[4] Watson Pharma, Inc. submitted to the jurisdiction of this Court on July 6, 2012. WPI thereafter changed its name to Actavis Pharma, Inc.

[5] Watson Pharma, Inc. submitted to the jurisdiction of this Court on May 3, 2010. WPI thereafter changed its name to Actavis Pharma, Inc.

[6] Watson Pharma, Inc. submitted to the jurisdiction of this Court on December 23, 2010. WPI thereafter changed its name to Actavis Pharma, Inc.

[7] Watson Pharma, Inc. submitted to the jurisdiction of this Court on March 3, 2008. WPI thereafter changed its name to Actavis Pharma, Inc.

[8] Watson Pharma, Inc. submitted to the jurisdiction of this Court on September 1, 2011. WPI thereafter changed its name to Actavis Pharma, Inc.

24. This Court has personal jurisdiction over Defendants by virtue of, inter alia, their presence in this State, having conducted business in this State, having availed themselves of the rights and benefits of New Jersey law such that they should reasonably anticipate being haled into court in this judicial district, previously consenting to personal jurisdiction in this Court, availing themselves of the jurisdiction of this Court and having engaged in systematic and continuous contacts with the State of New Jersey through the marketing and sales of generic drugs throughout the United States, and in particular within this judicial district, through the receipt of revenue from the sales and marketing of generic drug products, including ALF products, within this judicial district, and through their intent to market and sell the Actavis ANDA Products, if approved, to residents of this judicial district.

THE PATENT-IN-SUIT

25. On October 14, 2008, the United States Patent and Trademark Office duly and legally issued the '427 Patent, entitled "Pharmaceutical Semi-Solid Composition of Isotretinoin," to Galephar as assignee of the inventors. A true and correct copy of the '427 Patent is attached as Exhibit 1. Cipher obtained an exclusive license to use the '427 patent rights from Galephar in or about January 2001. On or about November 12, 2012, Ranbaxy obtained, inter alia, an exclusive license to distribute the ABSORICA® product in the United States, its territories, possessions, and the Commonwealth of Puerto Rico.

INFRINGEMENT BY DEFENDANTS

26. RI is the owner of the approved New Drug Application No. 021- 951 (the "NDA") for isotretinoin capsules, for oral use in 10 mg, 20 mg, 30 mg, and 40 mg dosages, which are sold under the trade name ABSORICA®.

27. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, U.S. Patent No. 8,367,102 ("the '102 Patent") and the '427 Patent are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the "Orange Book"), with respect to ABSORICA® in 10 mg, 20 mg, 30 mg, and 40 mg dosages.

28. The claims of the '102 and '427 patents cover the ABSORICA® product.

29. On information and belief, Watson (now Actavis Laboratories FL, Inc.) submitted ANDA No. 205063 to the FDA, pursuant to 21 U.S.C. § 355(j), seeking approval to market isotretinoin capsules, for oral use in 10 mg, 20 mg, 30 mg, and 40 mg dosages.

30. The Actavis ANDA refers to and relies upon the ABSORICA® NDA, and contains data that, according to ALF, demonstrate the bioequivalence of the Actavis ANDA Products and ABSORICA®.

31. Plaintiffs received a letter from Watson (now Actavis Laboratories FL, Inc.) on or about September 17, 2013, stating it had included a certification in the Actavis ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that, inter alia, certain claims of the '102 and '427 Patents are either invalid or will not be infringed by the commercial manufacture, use, or sale of the Actavis ANDA Products (the "Paragraph IV Certification").

CAUSE OF ACTION
(Infringement of the '427 Patent)

32. Plaintiffs reallege and incorporate by reference the allegations contained in paragraphs 1-31.

33. Defendants have infringed at least one claim of the '427 Patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting, or causing to be submitted the Actavis ANDA, by which

Defendants seeks approval from the FDA to engage in the manufacture, use, offer to sell, sale, or importation of the Actavis ANDA Products prior to the expiration of the '427 Patent.

34. Defendants have declared their intent to manufacture, use, offer to sell, or sell in the United States or to import into the United States, the Actavis ANDA Products in the event that the FDA approves the Actavis ANDA. Accordingly, an actual and immediate controversy exists regarding Defendants' infringement of the '427 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

35. Defendants' manufacture, use, offer to sell, or sale of the Actavis ANDA Products within the United States, or importation of the Actavis ANDA Products into the United States during the term of the '427 Patent would further infringe at least one claim of the '427 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

36. Plaintiffs will be substantially and irreparably harmed if Defendants are not enjoined from infringing the '427 Patent.

37. Plaintiffs have no adequate remedy at law.

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

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that the Court enter judgment against Defendants ALF, Andrx, Actavis, and Actavis Pharma and for the following relief:

a. A judgment that Defendants have infringed at least one claim of the '427 Patent;

b. A judgment pursuant to 35 U.S.C.§ 271(e)(4)(B) and/or 35 U.S.C. § 283 for a preliminary and permanent injunction enjoining the Defendants, their officers, agents, servants, employees, and those persons acting in active concert or participation with all or any of them from: (i) manufacturing, using, offering to sell, or selling the Actavis ANDA Products within the United States, or importing the Actavis ANDA Products into the United States, prior to the expiration of the '427 Patent, and (ii) seeking, obtaining or maintaining approval of the Actavis ANDA until expiration of the '427 patent, or such other later time as the Court may determine;

c. A judgment ordering that pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 205063 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the latest of the expiration date of the '427 Patent including any extensions;

d. If any of the Defendants manufactures, uses, offers to sell, or sells the Actavis ANDA Products within the United States, or imports the Actavis ANDA Products into the United States, prior to the expiration of any of the '427 Patent, including any extensions, a judgment awarding Plaintiffs monetary relief together with interest;

e. A judgment that this is an exceptional case and that Plaintiffs be awarded their attorneys' fees incurred in this action pursuant to 35 U.S.C. § 285;

f. Costs and expenses in this action; and

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

Respectfully Submitted,

s/ Theodora McCormick
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(212) 446-4000

Attorneys for Plaintiffs

Dated: June 6, 2014

Exhibit A

US007435427B2

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

(10) **Patent No.: US 7,435,427 B2**
(45) **Date of Patent: Oct. 14, 2008**

(54) **PHARMACEUTICAL SEMI-SOLID COMPOSITION OF ISOTRETINOIN**

(75) Inventors: **Francis Vanderbist**, Beersel (BE); **Cecile Servais**, Malonne (BE); **Philippe Baudier**, Uccle (BE)

(73) Assignee: **Galephar M/F**, Marche-en-Famenne (BG)

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

(21) Appl. No.: **10/380,619**

(22) PCT Filed: **Sep. 21, 2001**

(86) PCT No.: **PCT/BE01/00163**

§ 371 (c)(1),
(2), (4) Date: **Jul. 30, 2003**

(87) PCT Pub. No.: **WO02/24172**

PCT Pub. Date: **Mar. 28, 2002**

(65) **Prior Publication Data**

US 2004/0009225 A1 Jan. 15, 2004

(51) **Int. Cl.**
A61K 47/00 (2006.01)
A61K 9/24 (2006.01)
A61K 9/14 (2006.01)

(52) **U.S. Cl.** **424/439**; 424/472; 424/484

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,464,394	A	8/1984	Bollag	
5,252,604	A *	10/1993	Nagy et al.	514/559
5,993,858	A *	11/1999	Crison et al.	424/490
6,020,003	A	2/2000	Stroh et al.	
6,248,363	B1 *	6/2001	Patel et al.	424/497
6,267,985	B1 *	7/2001	Chen et al.	424/451
6,294,192	B1	9/2001	Patel et al.	
6,383,471	B1	5/2002	Chen et al.	
6,923,988	B2	8/2005	Patel et al.	

FOREIGN PATENT DOCUMENTS

EP	A-0 184942	6/1986
WO	WO 0025772	5/2000

OTHER PUBLICATIONS

Koga K, Kawashima S, Murakami M. In vitro and in situ evidence for the contribution of Labrasol and Gelucire 44/14 on transport of cephalexin and cefoperazone by rat intestine. Eur J Pharm Biopharm. Nov. 2002; 54(3): 311-8 (see abstract).*
PCT International Preliminary Examination Report.

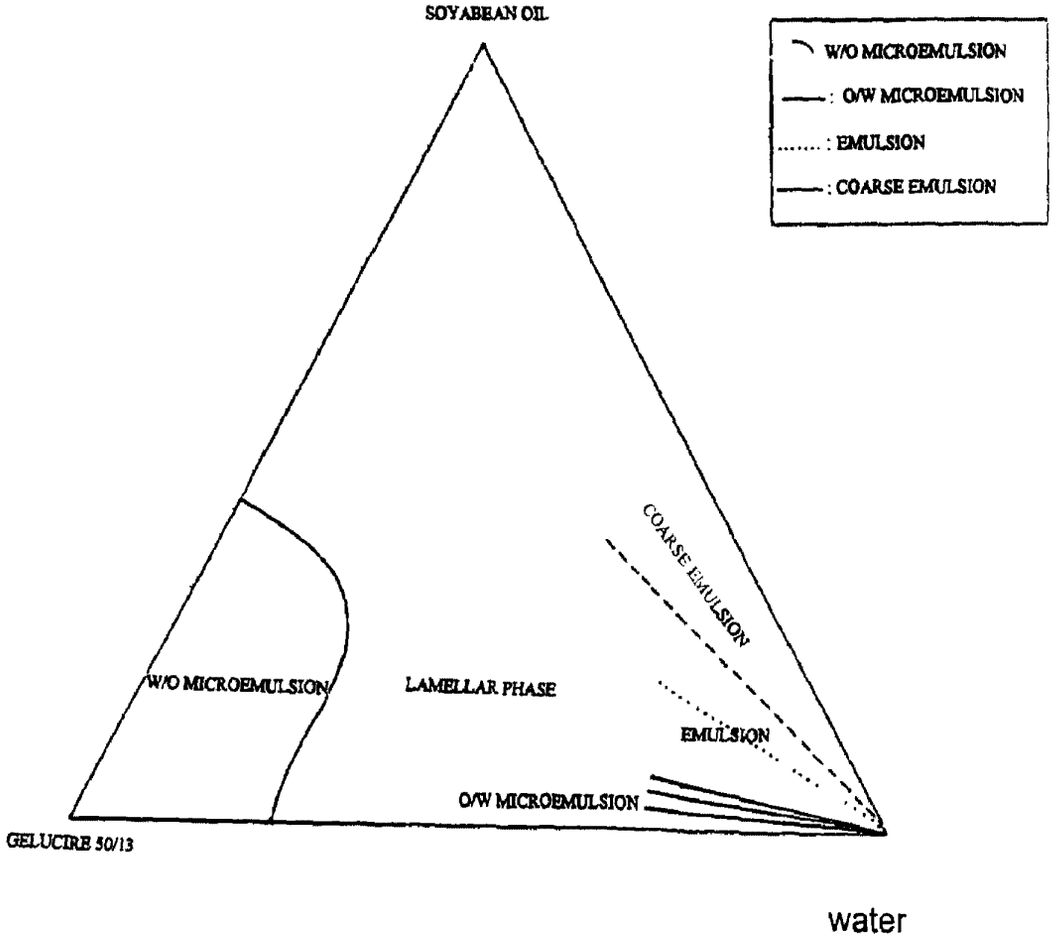
* cited by examiner

Primary Examiner—Michael G. Hartley
Assistant Examiner—Jake M. Vu
(74) *Attorney, Agent, or Firm*—William E. Beaumont

(57) **ABSTRACT**

An oral pharmaceutical composition of isotretinoin containing at least two lipidic excipients, one of them being hydrophilic (i.e. having an HLB value superior or equal to 10), the other being an oily vehicle.

18 Claims, 5 Drawing Sheets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: O/W MICROEMULSION
: EMULSION
: COARSE EMULSION
COARSE EMULSION
W/O MICROEMULSION
LAMELLAR PHASE
EMULSION
O/W MICROEMULSION
GELUCIRE 50/13
water

Figure 1

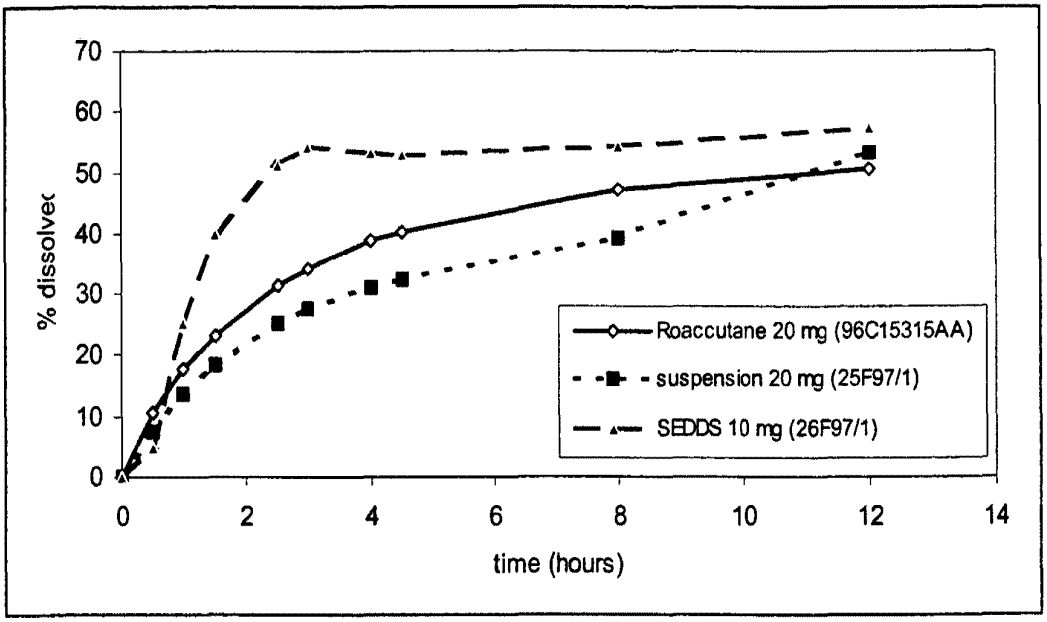


Figure 2

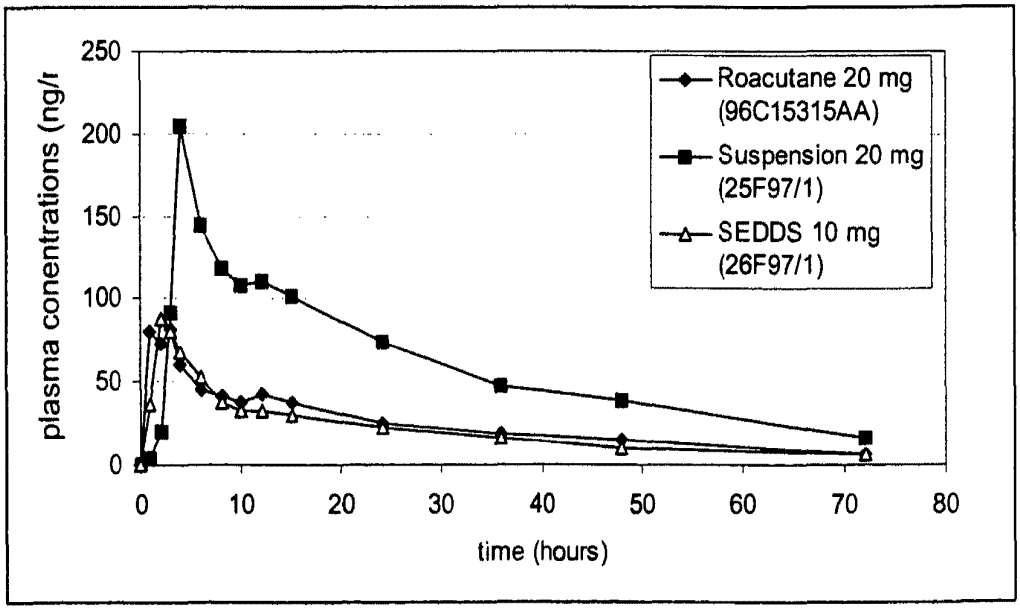


Figure 3

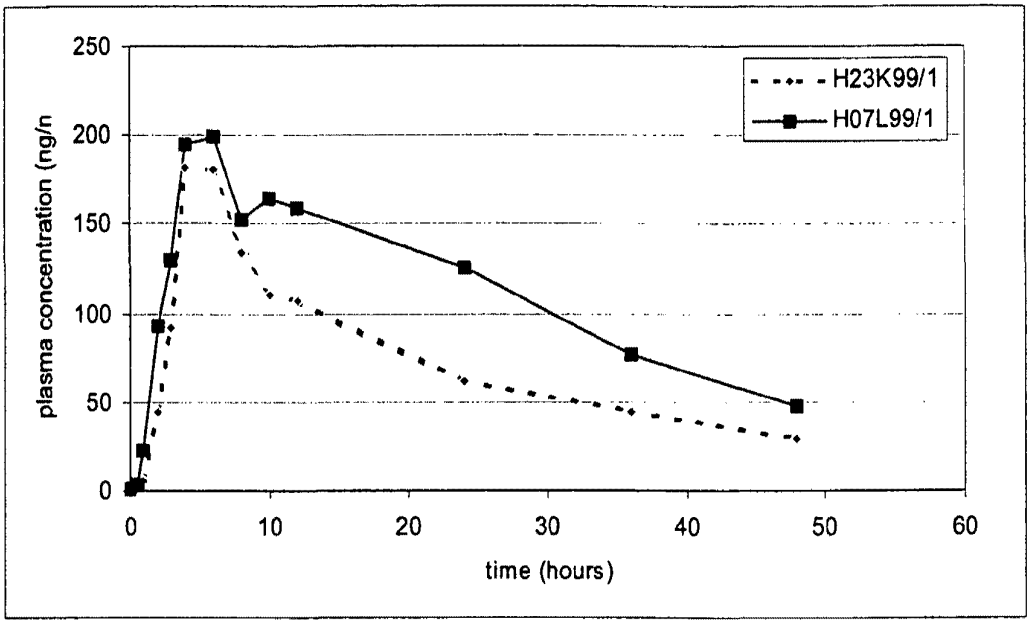


Figure 4

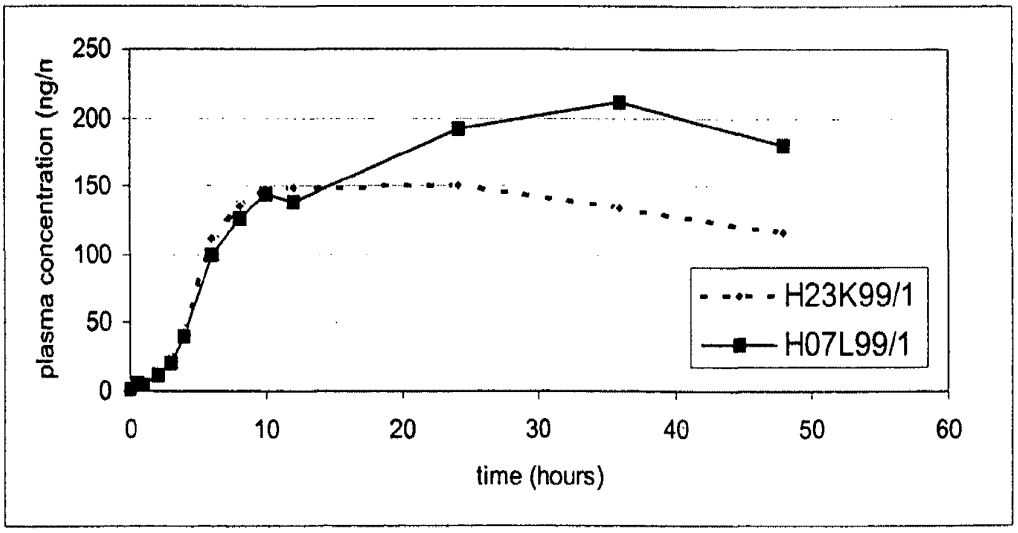
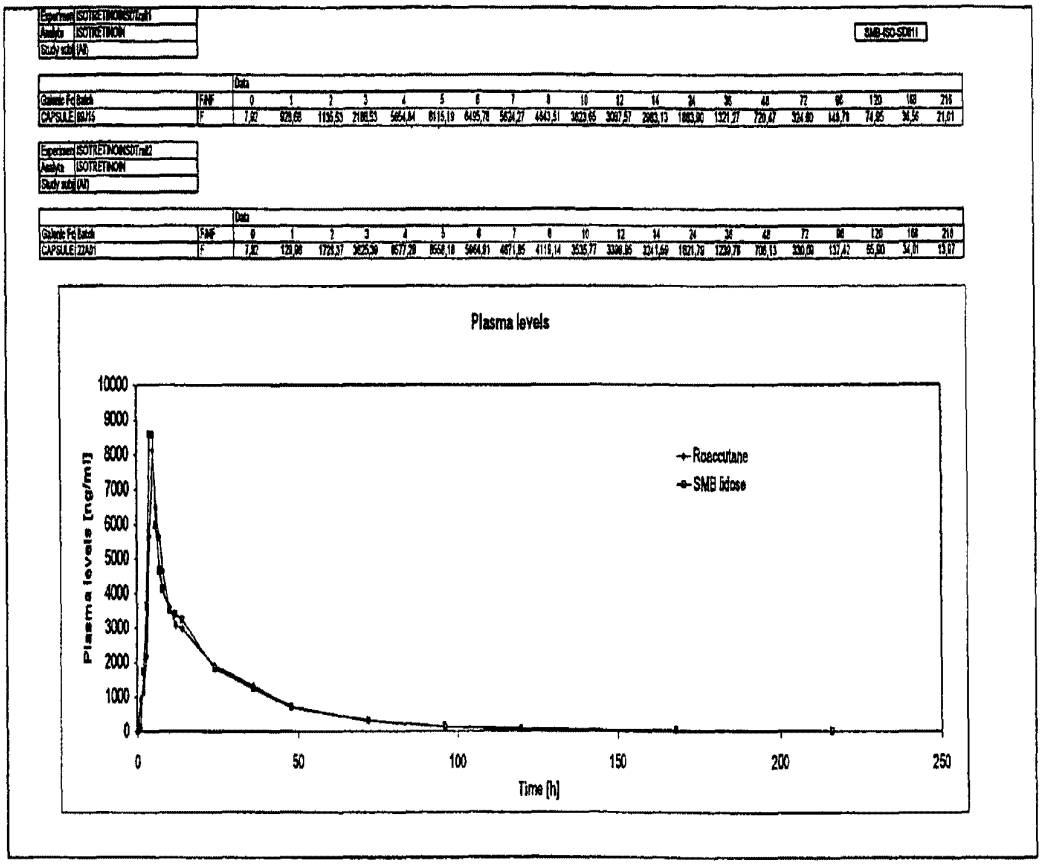


Figure 5


Plasma levels
Roaccutane
SMB Isotrex
Plasma levels [ng/ml]
Time [h]
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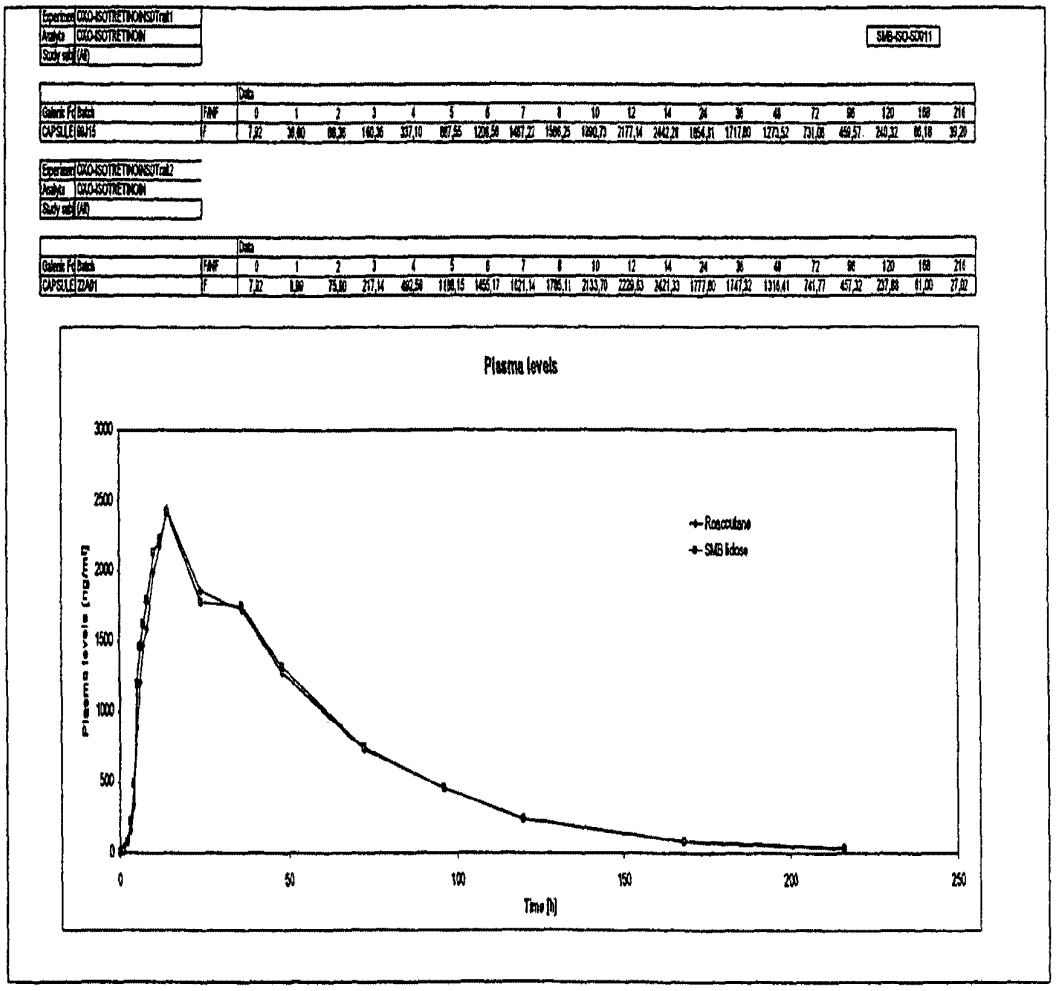
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
0
50
100
150
200
250

Figure 6


Plasma levels
Roaccutane
SMB Idose
Plasma levels (ng/ml)
Time (h)
0
500
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1500
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2500
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0
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100
150
200
250

Figure 7

PHARMACEUTICAL SEMI-SOLID COMPOSITION OF ISOTRETINOIN

The present invention relates to an oral pharmaceutical composition of isotretinoin containing at least two excipients, one of them being hydrophilic (i.e. having an HLB value superior or equal to **10**), the other being an oily vehicle.

THE PRIOR ART

Isotretinoin (13-cis retinoic acid or 13-cis vitamine A), its isomers and some of its analogs are widely known to have a therapeutical activity in the treatment of several severe skin disorders like cystic acne, hypertrophic lupus erythematosus, keratinization disorders. Some evidences have also been brought about the activity of isotretinoin in basal cell carcinoma and squamous cell carcinoma.

Unfortunately, isotretinoin is also a highly toxic drug. Indeed, although isotretinoin, which is a cis derivative, is known to be less toxic than all trans vitamine A derivatives, side effects resulting from its use such as headache, vomiting, irritation of mucosa and liver toxicity, occur frequently. Furthermore, isotretinoin is known to be highly teratogenic in both animals and humans.

In order to well understand the interest of this invention, it is important to briefly summarize the physico-chemical pharmacokinetic properties. Isotretinoin is a reddish-orange powder. It is decomposed in presence of light and atmospheric oxygen. Isotretinoin is very poorly soluble in water what mades its bioavailability quite low after an oral intake (25% in fasted conditions and 40% in fed conditions). The maximum concentration (C_{max}) is reached after 2-4 hours, while the (C_{max}) of the active metabolite, 4-oxo-isotretinoin is reached after 6 hours. The elimination half-life of isotretinoin is of 7 to 37 hours while the half life ($t_1/_2$) of the active metabolite is of 11 to 50 hours. The steady-state concentrations of isotretinoin are reached after 1 week of treatment.

Very few publications and/or patents about the pharmaceutical formulation of isotretinoin are available. The drug is available on most markets under the form of a soft gelatine capsule containing a fatty liquid formulation of isotretinoin.

The U.S. Pat. No. 4,464,394 describing for the first time the therapeutical use of isotretinoin also describes briefly some possibilities of compositions including it. It involves the use of one antioxidant agent and of one carrier like lactose, starches or polyethyleneglycols.

The EP patent 0184942 describes more specific compositions of isotretinoin involving the use of one antioxidant, one chelating agent, one pharmaceutical carrier and one suspending agent. The composition obtained is stable during time.

The U.S. Pat. No. 4,545,977 relates to improved compositions of isotretinoin wherein taurine is associated with isotretinoin to reduce the side effects thereof.

The U.S. Pat. No. 5,716,928 describes a method for increasing bioavailability and for reducing inter and intra individual variability of an orally administered hydrophobic pharmaceutical compound, which comprises orally administering the pharmaceutical compound with an essential oil or essential oil component in an amount sufficient to provide greater bioavailability of the active ingredient.

The U.S. Pat. No. 6,028,054 relates to a method for increasing bioavailability of an orally administered hydrophobic pharmaceutical compound to human, which comprises orally administering the pharmaceutical compound concurrently with a bioenhancer comprising an inhibitor of e-cytochrome P450 3A enzyme or an inhibitor of P-glycoprotein mediated membrane transport.

The U.S. Pat. No. 5,993,858 describes a self microemulsifying excipient formulation for increasing the bioavailability of a drug which includes an emulsion including an oil or other lipid material, a surfactant and an hydrophilic co-surfactant.

What is not described is a composition of isotretinoin containing at least two lipid materials, one of them being hydrophilic. The said composition may be a suspension, emulsion or microemulsion.

BRIEF DESCRIPTION OF THE INVENTION

The advent of high throughput combinatorial chemistry and efficient receptor based in vitro activity screen has resulted in molecules with poor physicochemical (ex: dissolution) properties for absorption across the gastro-intestinal tract, like isotretinoin.

It is increasingly being recognized by the pharmaceutical industry that for these molecules drug delivery systems play an important role for improving oral bioavailability.

Although the process of passive diffusion is responsible for absorption of non ionized lipophilic molecules via the transcellular pathway, specialized absorption mechanisms, first-pass metabolisms and efflux systems at the gastrointestinal wall appear to play a major role for lack of absorption and poor bioavailability for some molecules.

Isotretinoin is characterized by a low absolute bioavailability and a high inter and intra individual variability. Isotretinoin also presents a wide range of side effects among which some are severe (ocular, skin anemia, hepatic, . . .). It is consequently of a particular interest to dispose of a reliable, stable and highly bioavailable formulation of isotretinoin. Several possibilities are available to the formulator to increase the bioavailability of active ingredients (Table A).

TABLE A

I.	Use of salts, polymorphs. Precursors of the active molecule (=prodrugs)
II.	Reduction of the particles' size of the active principle and of the excipients used (by trituration, grinding, micronization, precipitation controlled by solvent, temperature or ultrasonics).
III.	Solid dispersions: Eutectic mixes Solid solutions Vitreous solutions
IV.	Recrystallization in an aqueous solution of a surfactant
V.	Modification of the microenvironment: Hydrophilization pH (acidification)
VI.	Incorporation of the active principle to lipidic systems

It has been found that a semi-solid dosage form containing isotretinoin was advantageous for obtaining a good bioavailability of the isotretinoin. A semi-solid dosage form containing isotretinoin is a form in which isotretoin is mixed with suitable melted excipients. The molten mix is then filled for example into hard gelatine capsules or other pharmaceutically acceptable capsules. At ambient temperature (temperature for example of less than 20° C.), the content of the capsule is solid while at temperature higher than 20° C. (for example at temperature greater or equal to 30° C., advantageously greater or equal to 35° C., preferably substantially at body temperature +/−37° C.), it is liquid or semi-solid (paste). The isotretinoin may be solubilized in the mix of excipients or partially solubilized. The active ingredient may also be formulated as a suspension, emulsion or microemulsion. Various lipidic excipients are available to the formulator to obtain a semi-solid formulation. Excipients compatible with hard gelatin capsule shells are: lipophilic liquid vehicles (refined

speciality oils, medium-chain triglycerides and related esters), semi-solid lipophilic vehicles, solubilizing agents, emulsifying agents and absorption enhancers. The classification of fatty excipients is based on the hydrophilicity or lipophilicity of the excipients, characterized by the hydrophilic/lipophilic balance value (HLB). Examples of lipophilic excipients are vegetable oils (peanut oil, olive oil, soyabean oil, . . .), fatty acids (stearic acid, palmitic acid, . . .), fatty alcohols, . . . Examples of hydrophilic excipients are polyethyleneglycol (PEG) with a molecular weight superior to 3,000. Examples of amphiphilic (=presenting lipophilic and hydrophilic properties) excipients are Poloxamers, Lecithin, PEG esters (Gelucire®), ...

The advantages of the semi-solid formulations of the invention are multiple for isotretinoin: protection of the active ingredient from air and humidity, possibility of increasing the dissolution rate of the molecule and hence of the bioavailability, diminution of the risk of contamination of the operator, diminution of the risk of cross contamination, no possibility of demixing under the effect of vibrational mixing during manufacturing process, facility of the production process. The choice of the nature of the formulation of course influenced the stability of the pharmaceutical form and the bioavailability of the isotretoin contained in it. Generally, a maximum bioavailability is achieved by preparing and keeping the drug in the amorphous/solubilized state in a solid dispersion or in a lipid-based formulation. For these systems, the barrier we are avoiding is the compound <<washing-out) >> of solution to a large extent into a insoluble crystalline form during the dissolution/release step in vivo.

These systems may consist of suspension, emulsion, microemulsion, self-emulsifying drug delivery systems (SEDDS®) or self-emulsifying microemulsion drug delivery system (SMEDDS®).

Microemulsions have the added advantage over suspensions such as emulsions and dispersions since thermodynamically they are more stable, that they can be manufactured with little energy input and have generally a longer shelf-life. Nevertheless, a microemulsion formulation is not a guarantee of higher bioavailability in comparison to suspension a described hereafter.

The formation of oil-in-water (O/W) and water-in-oil (W/O) microemulsions usually involves a combination of 3-5 basic compounds i.e. oil, surfactant, cosurfactant, water and electrolytes. The challenge is to select for a particular application oil(s) and surfactant(s) that are acceptable from a toxicological perspective and that allow to obtain a high bioavailability of the drug, i.e isotretoin.

The assessment of the quality of semi-solid lipid based formulations is quite difficult since the in vitro dissolution test is of little help. Indeed, the in vitro/in vivo correlation between dissolution and bioavailability is very poor for this kind of formulations. Other analytical tools are available to the formulator to try to predict the in vivo bioavailability of isotretinoin from various formulations like CACO-2 cells model, the assessment of the percentage of drug dissolved in the formulation, differential scanning calorimetry, microscopy, . . .

Nevertheless, none of them present a guarantee of in vitro/in vivo correlation and ultimately only pharmacokinetic studies on human subjects are reliable to assess the bioavailabiltiy of the drug.

DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The pharmaceutical composition of the invention is an oral semi-solid pharmaceutical composition of isotretinoin containing two lipidic excipients, one of them being hydrophilic i.e. having a HLB value of at least 10, for example equal to 10, but preferably greater than 10, such as greater or equal to 12, for example comprised between 12 and 14, and the other being an oily vehicle.

The pharmaceutical composition of the invention contains advantageously at least one hydrophilic excipient with a HLB value of at least 10 selected from the group consisting of glyceroyl macrogolglycerides, polyethyleneglycol derivatives, and mixtures thereof. Preferably, the pharmaceutical composition contains from 20 to 80% by weight of hydrophilic excipient with a HLB value of at least 10 selected from the group consisting of glyceroyl macrogolglycerides, polyethyleneglycol derivatives, and mixtures thereof.

The oily vehicle is selected from the group consisting of vegetable oils, medium chain triglycerides, fatty acid esters, amphiphilic oil, glycerol oleate derivative, and mixtures thereof. For example, the composition contains from 5 to 70% by weight of an oily vehicle selected from the group consisting of vegetable oils, medium chain triglycerides, fatty acid esters, amphiphilic oil, glycerol oleate derivative, and mixtures thereof.

According to another detail of preferred pharmaceutical compositions of the invention, the composition further contains at least one surfactant, preferably selected from the group consisting of sorbitan fatty acid esters, polysorbate derivatives, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulphate, derivatives of lecithine, propylene glycol esters, fatty acid esters of propylene glycol, fatty acid esters of glycerol, polyethylene glycol, and mixtures thereof. For example, the composition contains from 1 to 10% by weight of at least one surfactant.

Furthermore, the pharmaceutical formulation of the invention contains advantageously at least one disintegrant, preferably selected from the group consisting of povidone derivative, sodium croscarmellose and mixtures thereof.

The pharmaceutical composition of the invention may contain one or more surfactants and/or one or more disintegrants, but contains preferably one or more compounds acting as surfactants and one or more compounds acting as disintegrants.

The invention relates also to a pharmaceutical acceptable capsule containing at least one semi-solid composition of the invention, for example at least one composition of the invention as disclosed hereabove. The capsule is for example selected from the group consisting of hard gelatine capsules, soft gelatine capsules, hypromellose capsules, starch capsules.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a ternary diagram of a formulation containing only Gelucire® 50/13 and soyabean oil, the third component being water;

FIG. **2** shows the dissolution rate of a reference product (Roaccutane®-20 mg active agent), of a suspension containing 20 mg Isotretoin and of an emulsion SEDDS® containing 10 mg Isotretoin;

FIG. **3** shows an In vivo comparative pharmacokinetic profile of isotretinoin;

FIG. **4** gives the comparative pharmacokinetic profile of different formulations for isotretinoin,

FIG. **5** gives the comparative pharmacokinetic profile of different formulations for 4-oxo-isotretinoin, the active metabolite of isotretinoin and

FIGS. **6** and **7** describe the mean pharmacokinetic profile of isotretinoin and 4-oxoisotretinoin for two formulations.

DESCRIPTION OF EXAMPLES

The present invention relates thus to a semi-solid formulation of isotretinoin containing at least 2 lipidic excipients, one of them being an hydrophilic excipient (having a high HLB value namely >10) and the other an oily excipient. The molten mix of these two excipients allows to totally or partially (depending on the ratio between excipients) dissolve isotretinoin. Different kinds of formulations (SEDDS® or suspensions) of isotretinoin have been formulated. For suspensions, it was possible to dissolve a high fraction of isotretinoin in the mix of excipients and even the whole quantity of the active ingredient if the manufacturing conditions (high temperature and long time of mixing) and the formulations were optimized. Excipients particluarly suitable for the dissolution of isotretinoin were lauroyl Macrogol -32 glycerides (Gelucire® 44/14, Gattefossé) and Stearoyl Macrogol-32 glycerides (Gelucire® 50/13, Gattefossé). When those hydrophilic components are melted together with an oily vehicle, it allows to obtain very stable suspensions of isotretinoin in which an important part of the active ingredient is dissolved. A surfactant may also be added to the formulation to still improve the physical stability of the suspension. SEDDS® formulations of isotretinoin are also stable and may give an improved bioavailability of the drug.

Ternary diagrams allow to observe different areas corresponding to different physical states namely coarse emulsion, true emulsion, lamellar solution or micellar solution when the ratio between excipients changes. The behaviour of the formulation in presence of water changes when the ratio changes. One example of this ternary diagram is given in FIG. **1** for a formulation of isotretinoin containing Gelucire® 50/13 and soyabean oil.

EXAMPLES

Example 1

Effect of Different lipophilic Compounds

The effect of different lipophilic excipients was evaluated in the form of semi-solid capsules. The semi-solid capsules were made by addition of the active substance at the pre-melted lipophilic compounds followed by the filling of the liquid into hard gelatin capsule.

The active substance was incorporated into formulations, listed in table 1, consisting of glyceroyl macrogolglyceride associated with soyabean oil or derivative, medium chain triglyceride.

TABLE I

	Formulations n° (mg)				
	1	2	3	4	5
Isotretinoin	20	20	20	20	20
Labrafil ® M1944 CS	132				
Gélucire ® 50/02	198	93			
Gélucire ® 44/14		217			
Gélucire ® 50/13			76	60	60
Soya bean oil			304	320	
Mygliol ®					320

The use of stearoyl macroglyceride (Gélucire® 50/13, Gattefosse) and soyabean oil allows to obtain a formulation with a dissolution profile similar to the reference (Roaccutane® 20 mg, Roche).

The formulation with labrafil or Gelucire® 50/02 are too lipophilic to give a good dissolution in water.

In general, the use of an oily excipient can improve the absorption of lipophilic drug by increasing the solubility of the drug in the lipidic phase, but the release of the active ingredient from the formulation can be slowed down due to the high affinity of the drug for the oily phase.

The use of dispersed systems (emulsions or suspensions) instead of only lipophilic or hydrophilic vehicles, improves the absorption of the drug as well as increasing a larger contact surface.

Concerning the Gelucire®, the process of drug release varies according to the HLB of the excipient. Gelucire® with high HLB values were found to be the most favorable for a rapid release of the drug (by diffusion and erosion).

The drug release profiles of the formulations 1 to 5 were evaluated in phosphate buffer pH 7.5 with laurylsulfate and pancreatin. The percent of isotretinoin released after 4 hours is given in the following table 11.

TABLE II

	percent of isotretinoin released after 4 hours				
	Formulations n°				
	1	2	3	4	5
% released	20.1	69.1	46.0	60.3	78.1

The percent of isotretinoin released from the reference (Roaccutane ® 20 mg) after 4 hours is 55.37%

Example 2

Influence of the Ratio Oily Vehicle/Surfactive Agent on the Dissolution and Absorption of the Formulation

The study of the ratio oily vehicle/surfactive agent with the construction of a ternary diagram gives information on the dissolution profile of the formulation in water.

Stearoyl macrogolglyceride (Gelucire® 50/13) known as a drug solubilizer and emulsifying agent of different drugs (in SMEDDS® or SEDDS®) was tested in association with soyabean oil.

This component has the ability to solubilize a great part of isotretinoin in the formulation.

This is listed in table III

TABLE III

	Formulations n° (mg)					
	1	2	3	4	5	6
Isotretinoin	20	10	10	20	20	20
Soyabean oil	270	135	40	152	57	133
Gelucire ® 50/13	84	42	200	228	323	247
Filling weight	374	187	260	400	400	400
Ratio oil/Gelucire ® 50/13	3.2	3.2	0.2	0.67	0.17	0.54

In the presence of water, the behaviour of these formulations are different formulations 1 and 2: formation of coarse emulsion with large droplet sizes formulations 3 and 5: formation of micellar phase or microemulsion formulations 4 and 6: formation of emulsion with homogeneous droplet size The percentage of isotretinoin released increases generally with the percentage of Gelucire ® in the formulation (increased solubility of the active in this vehicle). For the formulation 1 (ratio oil/Gelucire ® 50/13 = 3.2) 54.9% released after 4 hours and for the formulation 3 (ratio oil/Gelucire ® 50/13: 0.2), 91.2% released after 4 hours.

Dissolution Test

For poorly soluble molecules, the prediction power of the in vitro dissolution test is weak since the in vitro/in vivo correlation is known to be poor. Nevertheless, an optimized dissolution test (using enzymes and surfactant) is of some help to assess the rate of release of the drug from the lipidic composition. It must be noted that the conditions of the dissolution (dissolution medium, speed of the paddles, temperature, . . .) test influence dramatically the results of the test and should consequently be standardized to allow comparison between various formulations.

The conditions of the solution test used for assessing the dissolution of isotretinoin were the following:

paddle apparatus

150 rpm

37° C.

buffer pH 7.5 with laurylsulfate 2.5% and pancreatin 1 g/L

FIG. **2** shows the dissolution rate of a reference product (Roaccutane®—20 mg active agent), of a suspension containing 20 mg Isotretoin and of an emulsion SEDDS® containing 10 mg Isotretoin (formulation given hereinbelow).

As the information brought by the dissolution test is poor in term of correlation with in vivo bioavailability, it is of interest to dispose of other means to predict the in vivo bioavailability.

The caco-2 cell culture system can be used for determining permeability of compounds (especially for poorly soluble compounds). The caco-2 cell model allows to measure the transport of drug from the apical to the serosal side as well as from the serosal to the apical side. This allows to determine if an efflux system is operational.

The caco-2 cells model is interesting because:

The cells used are from human origin (contrary to the models using segments of animal's guts). They are coming from an adenocarcinoma of the human colon but spontaneously differentiate into small intestine's epithelail cells. When put in culture, they form a monolayer of polarized cells expressing several enzymatic systems.

It offers a better prediction of the human intestine absorption than the animals models

The reproducibility of the test is relatively high

It allows to take samples from both apical and basolateral sides Caco-2 cells experiments have been performed with one SEDDS® and one suspension isotretinoin formulations.

Results

It was first proven that neither the active ingredient nor the excipient used in the formulations were toxic for the cells. It was also proven that the integrity of the membranes of the cells was maintained during the whole experience.

Methodology:

The formulations tested are put in solution in 250 ml of BME. Taurocholate (10 mM) was added to the solutions to better mimate the in physiological conditions. The different solutions so prepared are put in contact with Caco-2 cells at the apical or basolateral side. The cells culture inserts) are incubated for 3 hours at 37° C. and samples of 100 µl are taken every hours

The formulations tested were the following:

Formulation SEDDS® (batch number 26F97/1):

Isotretinoin: 10 mg

Gelucire® 50/13: 134 mg

Phospholipon 90®: 11 mg

Tween 80®: 71 mg

IPP®: 24 mg

Pro capsula una

Formulation suspension (batch number 25F97/1)

Isotretinoin: 20 mg

Gelucire® 50/13: 83.7 mg

Soyabean oil: 270 mg

Procapsula una

Results

Passage of formulations from apical side→basolateral side

Time minutes	SEDDS ® (26F97/1)	Suspension (25F97/1)	SEDDS ® + TC	Suspension + TC	control
60	0.7721	0.6708	0.7019	0.6469	0.0718
120	2.4096	0.8749	1.4347	0.9513	0.1836
180	2.6226	1.1311	3.2419	1.5073	0.6156

Passage of formulations from basolateral side→apical side

Time minute	SEDDS ® (26F97/1)	Suspension (25F97/1)	SEDDS ® + TC	Suspension + TC	control
60	2.0496	0.3948	8.1291	0.8713	0.0650
120	3.0844	0.9068	8.3496	1.8460	0.1131
180	4.3653	1.0763	9.7110	2.0779	0.1481

The results demonstrate that the passage of isotretinoin is superior for the SEDDS® formulation than for the suspension formulation. In order to confirm these results, a comparative pharmacokinetics study has been performed.

PK Studies

The bioavailability of SEDDS® (26F97/1) and suspension (25F97/1) isotretinoin formulations has been assessed and compared to the bioavailability of the reference (Roaccutane® 20 mg, Hoffman LaRoche) on six healthy volunteers in a single dose, three way, cross-over pharmacokinetic study). The drug was taken with food (standardized breakfast). The plasma concentration of isotretinoin and its active metabolite 4-oxo-isotretinoin were quantified using a fully validated LC/MS/MS method.

The FIG. **3** described the mean pharmacokinetic profile obtained for each formulation.

The following table gives the value of the main pharmacokinetics parameters obtained for each formulation of isotretinoin.

Formulations	AUC_{72h} (ng. h/ml)	C_{max} (ng/ml)	T_{max} (h)
Roaccutane ® 20 mg (96C15315AA)	1747.89	116.63	1.83
Suspension 20 mg (25F97/1)	4308.72	230.96	5.67
SEDDS ® 10 mg (26F97/1)	1494.64	98.36	3.00

It appears that both the SEDDS® and the suspension formulation are able to significantly increase the bioavailability of isotretinoin in comparison to the marketed reference. Indeed the ratio between AUC_{72h} of the supension 20 mg and Roaccutane® 20 mg is of 2.47. The SEDDS® 10 mg present an AUC_{72h} similar to this of Roaccutane® 20 mg what means an approximately 2-fold increase of bioavailability (ratio AUC_{72h} SEDDS® 10 mg/AUC_{72h} Roaccutane® 20 mg=0.86). Furthermore, the suspension and SEDDS® formulations both presented a lower intraindividual variability of the bioavailability as demonstrated by the values of relative standard deviations (rsd) which are of 36.0%, 22.72% and 28.18% for Roaccutane® 20 mg, suspension 20 mg and SEDDS® 10 mg respectively.

Nevertheless, the results obtained in vivo are not correlated with the results obtained on caco-2 cells since on this model the permeability of the SEDDS® formulation was much higher than the permeability of the suspension formulation while in vivo the suspension formulation gives the best results.

A second pharmacokinetic study was performed on completely different formulations (6 subjects, 2-way, fed, crossover study). Those were formulations of isotretinoin under the form of a suspension in which the ratio between Gelucire® 50/13 and soyabean oil was very different that the previous formulation of suspension

The two formulations tested were the following:

F1: suspension without surfactant (batch number H23K99/1)

Isotretinoin: 20 mg

Gelucire® 50/13: 247 mg

Soyabean oil: 133 mg

F2: suspension with surfactant (batch number H07L99/1)

Isotretinoin: 20 mg

Gelucire® 50/13: 240 mg

Soyabean oil: 130 mg

Span 80®: 20 mg

The FIG. **4** gives the comparative pharmacokinetic profile of each formulation for isotretinoin

The FIG. **5** gives the comparative pharmacokinetic profile of each formulation for 4-oxo-isotretinoin, the active metabolite of isotretinoin.

In order to confirm the first bioavailability data obtained with the present invention, a larger pharmacokinetic study has been performed.

The bioavailability of a capsule of isotretinoin 16 mg (see the formulation herebelow) from the present invention has been assessed and compared to the bioavailability of the reference (ROACCUTANE® 20 mg capsule, Roche) on 24 healthy subjects.

This study (SMB-ISO-SD011) was a single dose, two treatment, two period, two sequence, randomised, crossover and with at least 18 days wash-out between the two periods.

The subjects were healthy caucasian volunteers of both sexes (non-pregnant, non-breast-feeding), aged 18 to 50 years, non smokers or smoking less than 10 cigarettes per day.

The drugs was taken with food (a standardized breakfast).

Blood samples were collected according to the following sampling schedule: pre-dose and 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 10 h, 12 h, 14 h, 24 h, 36 h, 48 h, 72 h, 96 h, 120 h, 168 h and 216 hours post-dose.

The plasma concentration of isotretinoin and its active metabolite 4-oxo-isotretinoin were quantified using a fully validated LC/MS/MS method. The continuous variables were evaluated according to an univariate ANOVA, based on log-transformed data. The Wilcoxon non-parametric ANOVA were used where appropriate. Bioequivalence was evaluated using the Shuirman two one-sided t-test (90% Cl) and the westlake single sided confidence interval (95% CL)

The FIGS. **6** and **7** describe the mean pharmacokinetic profile of isotretinoin and 4-oxoisotretinoin for the two formulations (n=24 subjects) while the tables herebelow give the comparative main pharmacokinetic parameters.

Formulation of isotretinoin 16 mg (mg/capsule)

isotretinoin	16
stearoyl macrogol glycerides (Gelurire 50/13 ®)	192
soya bean oil refined	104
sorbitane oleate (Span 80 ®)	16

As seen, the dose of 16 mg of the formulation corresponding to the present invention gives a bioavailability similar to 20 mg of the marketed formulation, what is the evidence of the supra-bioavailability of the formulation corresponding to the present invention.

The tables hereinbelow gives the value of the main pharmacokinetics results and statistical analysis obtained for each formulation of isotretinoin and 4-oxoisotretinoin.

This study demonstrated that ROACCUTANE® 20 mg and isotretinoin 16 mg×are bioequivalent after a single oral dose administration of each product in fed conditions. Indeed, the primary parameters AUC (AUC_{∞} and AUC_{216h}) were within the predetermined confidence interval.

This study demonstrated also that Isotretinoin 16 mg has a safety profile comparable with that described in the literature for other isotretinoin preparations and similar to this of ROACCUTANE® 20 mg.

Pharmacokinetic results and statistical analysis of comparative study in 24 volunteers for isotretinoin (log-transformed data)

	Results		Bioequivalence tests Shuirman	
Parameter	ROACCUTANE ® 20 mg	Isotretinoin 16 mg	90% CI Range	Westlake 95% CL
AUC_{∞} ±	5657.09 (ng.h/ml) ±	5696.92 (ng.h/ml) ±	92-123	19.07
SD ±	2682.98 ±	1938.89 ±		
RSD	47.42	34.03		
AUC_{216h} ±	5601.36 (ng.h/ml) ±	5664.39 (ng.h/ml) ±	92-124	19.51
SD ±	2670.85 ±	1953.52 ±		
RSD	47.68	34.48		
C_{max} ±	386.68 (ng/ml) ±	441.79 (ng/ml) ±	103-140	28.81
SD ±	218.21 ±	197.43±		
RSD	56.43	44.68		
T_{max} ±	4.92 (h) ±	4.50 (h) ±	/	/
SD ±	2.22 ±	0.66±		
RSD	45.24	14.65		

Pharmacokinetic results and statistical analysis of comparative study in 24 volunteers for 4-oxoisotretinoin (log-transformed data)

	Results		Bioequivalence tests Shuirman	
Parameter	ROACCUTANE ® 20 mg	Isotretinoin 16 mg	90% CI Range	Westlake 95% CL
AUC_{∞} ±	5750.36 (ng.h/ml) ±	5769.04 (ng.h/ml) ±	92-124	19.65
SD ±	2717.38 ±	2161.97 ±		
RSD	47.26	37.48		
AUC_{216h} ±	5638.32 (ng.h/ml) ±	5712.21 (ng.h/ml) ±	92-125	20.46
SD ±	2704.73 ±	2126.61 ±		
RSD	47.80	37.23		
C_{max} ±	111.52 (ng/ml) ±	115.15 (ng/ml)	94-125	20.18
SD ±	69.62 ±	66.25 ±		
RSD	62.43	57.53		
T_{max} ±	17.83 (h) ±	16.33 (h) ±	/	/
SD ±	10.60 ±	10.11 ±		
RSD	59.43	61.88		

The invention claimed is:

1. An oral pharmaceutical composition of isotretinoin contained in a pharmaceutically acceptable capsule which comprises a semi-solid suspension containing at least two lipidic excipients, at least in an amount of about 20 to 80% of one being hydrophilic having a HLB value equal to or greater than 10 selected from the group consisting of glyceroyl macrogolglycerides, polyethylene glycol esters, and mixtures thereof; the other in an amount of about 5 to 70% and being an oily vehicle selected from the group consisting of vegetable oils, medium chain triglycerides, fatty acid esters, glycerol oleate and mixtures thereof; and an amount of about 1 to 10% of at least one additional surfactant.

2. The pharmaceutical composition of claim **1**, wherein the least one hydrophilic lipidic excipient has an HLB value of at least 12.

3. The pharmaceutical composition of claim **1**, wherein the least one hydrophilic lipidic excipient has an HLB value of at least 13.

4. The pharmaceutical composition of claim **1**, wherein the at least one additional surfactant is selected from the group consisting of sorbitan fatty acid esters, polysorbate compounds, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, lecithin, propylene glycol esters, fatty acid esters of propylene glycol, fatty acid esters of glycerol, polyethylene glycol and mixtures thereof.

5. The pharmaceutical composition of claim **1**, which further comprises at least one disintegrant.

6. The pharmaceutical composition of claim **5**, wherein at least one disintegrant is selected from the group consisting povidone, sodium croscarmellose and mixtures thereof.

7. The capsule of claim **1**, in which the pharmaceutically-acceptable capsule is selected from the group consisting of hard gelatin capsules, soft gelatin capsules, hypromellose capsules, and starch capsules.

8. The pharmaceutical composition of claim **1**, wherein the composition comprises about 10-20 mg of isotretinoin.

9. The pharmaceutical composition of claim **8**, wherein the composition comprises about 16-20 mg of isotretinoin.

10. A method of administering the pharmaceutical composition of claim **1**, which comprises administering to a human about 10-20 mg of the composition for a total daily dose.

11. The method of claim **10**, wherein the total daily dose is about 16-20 mg.

12. The pharmaceutical composition of claim **1**, wherein the composition contains about 20-80% by weight of glycer-

oyl macrogolglycerides, about 5-70% by weight of an oily vehicle and about 1-10% of an additional surfactant.

13. The oral pharmaceutical composition of claim **1**, wherein the pharmaceutically-acceptable capsule is filled by a process comprising filling into a capsule a composition prepared by mixing isotretinoin and one or more of the pre-melted lipidic excipients.

14. The oral pharmaceutical composition of claim **1**, wherein the pharmaceutically-acceptable capsule is filled by a process comprising filling into a capsule a composition prepared by mixing:

(a) isotretinoin,

(b) one or more of said hydrophilic lipidic excipients,

(c) said oily vehicle, and

(d) one or more additional ingredients selected from the group consisting of disintegrants, surfactants and combinations thereof.

15. The pharmaceutical composition of claim **1**, wherein the hydrophilic lipidic excipients further comprise an excipient having an HLB value of at least 12, and the oily vehicle is soybean oil.

16. The pharmaceutical composition of claim **1**, wherein the isotretinoin is contained within an emulsion.

17. The pharmaceutical composition of claim **1**, wherein the at least one hydrophilic lipidic excipient having an HLB value equal to or greater than 10 is glycerol macrogolglycerides.

18. The pharmaceutical composition of claim **1**, wherein the oily vehicle is a medium chain triglycerides or a mixture of medium chain triglycerides.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,435,427 B2
APPLICATION NO. : 10/380619
DATED : October 14, 2008
INVENTOR(S) : Vanderbist et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, item (86),
Please delete "PCT No.: PCT/BE01/00163"
and
replace with
-- PCT/IB00/00163 --

On the Title Page, item (86),
Please insert -- PCT/BE00/00111 --

Signed and Sealed this

Sixth Day of January, 2009

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