14 CV 6373

JUDGE WOODS

WHITE & CASE LLP
1155 Avenue of the Americas
New York, New York 10036
Telephone: (212) 819-8200
Facsimile: (202) 354-8113

Attorneys for Plaintiffs Pfizer Inc., Wyeth LLC, Wyeth Pharmaceuticals Inc., and PF Prism C.V.

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PFIZER INC., WYETH LLC, WYETH PHARMACEUTICALS INC., and PF PRISM C.V.,	)	
Plaintiffs,	)	
v.	)	**COMPLAINT**
INTELLIPHARMACEUTICS INTERNATIONAL INC., INTELLIPHARMACEUTICS CORPORATION, and INTELLIPHARMACEUTICS LTD.,	)	
Defendants.	)	

Plaintiffs Pfizer Inc., Wyeth LLC, Wyeth Pharmaceuticals Inc., and PF Prism C.V. (collectively, "Plaintiffs"), by their undersigned attorneys, for their Complaint against Defendants IntelliPharmaceutics International Inc. ("IPC International"), IntelliPharmaceutics Corporation ("IPC Corp") and IntelliPharmaceutics Ltd. ("IPC Ltd.") (collectively "IPC") allege:

NATURE OF THE ACTION

1. This is an action for patent infringement under the patent laws of the United States, Title 35 of the United States Code, arising from IPC's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to market a generic version of Plaintiff's pharmaceutical product

Pristiq® prior to the expiration of United States Patent Nos. 6,673,838 ("the '838 patent") and 8,269,040 ("the '040 patent"), which cover Pristiq® or its use.

THE PARTIES

2. Plaintiff Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, New York 10017.

3. Plaintiff Wyeth LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a place of business at 5 Giralda Farms, Madison, NJ 07940. Pfizer Inc. is the ultimate parent of Wyeth LLC.

4. Plaintiff Wyeth Pharmaceuticals Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 500 Arcola Road, Collegeville, PA 19426. Pfizer Inc. is the ultimate parent of Wyeth Pharmaceuticals Inc.

5. Plaintiff PF Prism C.V. is a Netherlands limited partnership (commanditaire vennootschap) having its registered seat in Rotterdam, the Netherlands, and registered at the Trade Register held by the Chamber of Commerce of Rotterdam, the Netherlands, under number 51840456, with main offices at Blaak 40 basement, 3011 TA, Rotterdam, Netherlands. Pfizer Inc. is the ultimate parent of PF Prism C.V.

6. On information and belief, IPC International is a Canadian corporation having a principal place of business at 30 Worcester Road, Toronto, Ontario, Canada M9W 5X2. On information and belief, IPC International is in the business of making and selling generic pharmaceutical products, which it distributes in the State of New York and throughout the United States. On information and belief, IPC International owns, directly or through its wholly owned subsidiary IPC Ltd., 100.00% of the common shares of IPC Corp. On information and

belief, IPC International has previously submitted to this Court's jurisdiction and has admitted that it is subject to the personal jurisdiction of this Court.

7. On information and belief, IPC Corp, is a Canadian corporation having a principal place of business at 30 Worcester Road, Toronto, Ontario, Canada M9W 5X2. On information and belief, IPC International is the ultimate parent of IPC Corp. On information and belief, IPC Corp. is the operating affiliate of IPC Ltd. On information and belief, IPC Corp., with the assistance and/or direction of IPC International and/or IPC Ltd. develops, manufactures, markets, offers to sell, and sells generic drug products for sale and use in the State of New York and throughout the United States. On information and belief, IPC Corp. has previously submitted to this Court's jurisdiction and has admitted that it is subject to the personal jurisdiction of this Court. IPC Corp. has purposefully availed itself of the jurisdiction of this Court by asserting counterclaims in lawsuits filed in the United States District Court for the Southern District of New York.

8. On information and belief, IPC Ltd., is a Delaware Corporation having a principal pace of business at 30 Worcester Road, Toronto, Ontario, Canada M9W 5X2. On information and belief, IPC Ltd. is a wholly owned subsidiary of IPC International. On information and belief, IPC Ltd., with the assistance and/or direction of IPC International and/or IPC Corp. develops, manufactures, markets, offers to sell, and sells generic drug products for sale and use in the State of New York and throughout the United States. On information and belief, IPC Ltd. has previously submitted to this Court's jurisdiction and has admitted that it is subject to the personal jurisdiction of this Court. IPC Ltd. has purposefully availed itself of the jurisdiction of this Court by asserting counterclaims in lawsuits filed in the United States District Court for the District of New York.

9. On information and belief, IPC Ltd., IPC Corp., and IPC International have common officers and directors and have represented to the public that they are a unitary entity.

10. On information and belief, the acts of IPC Corp. complained of herein were done at the direction of, with the authorization of, and/or with the cooperation, participation, and assistance of, and at least in part for the benefit of, IPC Ltd. and/or IPC International.

11. On information and belief, the acts of IPC Ltd. complained of herein were done at the direction of, with the authorization of, and/or with the cooperation, participation, and assistance of, and at least in part for the benefit of, IPC Corp. and/or IPC International.

12. On information and belief, the acts of IPC International, complained of herein were done at the direction of, with the authorization of, and/or with the cooperation, participation, and assistance of, and at least in part for the benefit of, IPC Ltd. and/or IPC Corp.

JURISDICTION AND VENUE

13. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

14. This Court has personal jurisdiction over IPC by virtue of, inter alia, its presence in New York, having conducted business in New York, having availed itself of the rights and benefits of New York law, previously consenting to personal jurisdiction in this Court, availing itself of the jurisdiction of this Court, and having engaged in systematic and continuous contacts with the State of New York.

15. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENTS-IN-SUIT

16. On January 6, 2004, the United States Patent and Trademark Office issued the '838 patent, entitled "Succinate Salt of O-Desmethyl-Venlafaxine." At the time of its issue, the '838 patent was assigned to Wyeth (now known as Wyeth LLC), Madison NJ, and Wyeth LLC currently holds title to the '838 patent. A copy of the '838 patent is attached hereto as Exhibit A.

17. On September 18, 2012, The United States Patent and Trademark Office issued the '040 patent, entitled "Derivatives of Venlafaxine and Methods of Preparing and Using the Same." At the time of its issue, the '040 patent was assigned to Wyeth LLC, Madison NJ, and Wyeth LLC currently holds title to the '040 patent. A copy of the '040 patent is attached hereto as Exhibit B.

PRISTIQ®

18. Pfizer Inc., itself and through its wholly owned indirect subsidiary Wyeth Pharmaceuticals, Inc., holds approved New Drug Application No. 21-992 ("the Pristiq® NDA") for O-desmethylvenlafaxine succinate extended release tablets in 50 and 100 mg dosage strengths, which are sold by Pfizer Inc. under the trade name Pristiq®.

19. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, the '838 and '040 patents are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Pristiq®.

IPC'S ANDA

20. On information and belief, IPC submitted ANDA No. 204-805 (the "IPC ANDA") to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to market O-desmethylvenlafaxine succinate extended release tablets in 50 and 100 mg dosage strengths.

The O-desmethylvenlafaxine succinate extended release tablets described in the IPC ANDA are herein referred to as the "IPC Products."

21. The IPC ANDA refers to and relies upon the Pristiq® NDA and contains data that, according to IPC, demonstrate the bioequivalence of the IPC Products and Pristiq®.

22. In a letter to Pfizer, dated June 27, 2014, IPC stated that the IPC ANDA contained a certification pursuant to 21 U.S.C. §355(j)(2)(A)(vii)(IV) (§505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act), that the '838 and the '040 patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of the IPC Products. IPC attached a memorandum to the letter, in which it claimed to give factual and legal bases for its certification.

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 6,673,838

23. Plaintiffs re-allege and incorporate by reference the allegations of paragraphs 1-22 of this Complaint.

24. IPC has infringed the '838 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the IPC ANDA, by which IPC seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale, or importation of the IPC Products prior to the expiration of the '838 patent.

25. IPC's commercial manufacture, use, offer to sell, or sale of the IPC Products within the United States, or importation of the IPC Products into the United States during the term of the '838 patent would further infringe the '838 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

26. Plaintiffs will be substantially and irreparably harmed if IPC is not enjoined from infringing the '838 patent.

27. Plaintiffs have no adequate remedy at law.

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

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 8,269,040

29. Plaintiffs re-allege and incorporate by reference the allegations of paragraphs 1-28 of this Complaint.

30. IPC has infringed the '040 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the IPC ANDA, by which IPC seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale, or importation of the IPC Products prior to the expiration of the '040 patent.

31. IPC's commercial manufacture, use, offer to sell, or sale of the IPC Products within the United States, or importation of the IPC Products into the United States during the term of the '040 patent would further infringe the '040 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

32. Plaintiffs will be substantially and irreparably harmed if IPC is not enjoined from infringing the '040 patent.

33. Plaintiffs have no adequate remedy at law.

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

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for a judgment in their favor and against IPC and respectfully request the following relief:

A. A judgment declaring that IPC has infringed the '838 patent;

B. A judgment declaring that IPC has infringed the '040 patent;

C. A judgment pursuant to 35 U.S.C. § 271(e)(4)(B) preliminarily and permanently enjoining IPC, its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from manufacturing, using, offering to sell, or selling the IPC Products within the United States, or importing the IPC Products into the United States, prior to the expiration of the '838 and '040 patents;

D. A judgment ordering that pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 204-805 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the expiration of the '838 and '040 patents, including any extensions;

E. If IPC commercially manufactures, uses, offers to sell, or sells the IPC Products within the United States, or imports the IPC Products into the United States, prior to the expiration of any of the '838 and '040 patents, including any extensions, a judgment awarding Pfizer monetary relief together with interest;

F. Attorneys' fees in this action as an exceptional case pursuant to 35 U.S.C. § 285;

G. Costs and expenses in this action; and

H. Such other relief as the Court deems just and proper.

Dated: August 11, 2014
New York, NY

Respectfully submitted,

WHITE & CASE LLP
1155 Avenue of the Americas
New York, New York 10036
Phone: (212) 819-8200
Facsimile: (212) 354-8113

By: _____
Dimitrios T. Drivas (DD 8891)
Adam Gahtan (AG 8802)
Brendan G. Woodard (BW 6194)
Ryan P. Johnson (RJ 1556)
Jayashree Mitra (JM6669)

Attorneys for Pfizer Inc., Wyeth LLC, Wyeth Pharmaceuticals Inc., and PF Prism C. V.

EXHIBIT A

US006673838B2

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

(10) **Patent No.: US 6,673,838 B2**
(45) **Date of Patent: Jan. 6, 2004**

(54) **SUCCINATE SALT OF O-DESMETHYL-VENLAFAXINE**

(75) Inventors: **Anthony F. Hadfield**, Nanuet, NY (US); **Syed M. Shah**, East Hanover, NJ (US); **Michael W. Winkley**, Campbell Hall, NY (US); **Karen W. Sutherland**, New City, NY (US); **James A. Provost**, Waltham Chase (GB); **Aeri Park**, West Lafayette, IN (US); **Rex A. Shipplett**, Wolcott, IN (US); **Brenton W. Russell**, West Lafayette, IN (US); **Beat T. Weber**, Zofingen (CH)

(73) Assignee: **Wyeth**, Madison, NJ (US)

(*) 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.: **10/073,743**

(22) Filed: **Feb. 11, 2002**

(65) **Prior Publication Data**

US 2003/0045583 A1 Mar. 6, 2003

Related U.S. Application Data

(60) Provisional application No. 60/268,214, filed on Feb. 12, 2001, and provisional application No. 60/297,963, filed on Jun. 13, 2001.

(51) **Int. Cl.**[7] **A61K 31/205**; C07C 55/00; C07C 211/00

(52) **U.S. Cl.** **514/554**; 562/590; 564/336

(58) **Field of Search** 514/554; 562/590; 564/336

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,535,186 A 8/1985 Husbands et al.

FOREIGN PATENT DOCUMENTS

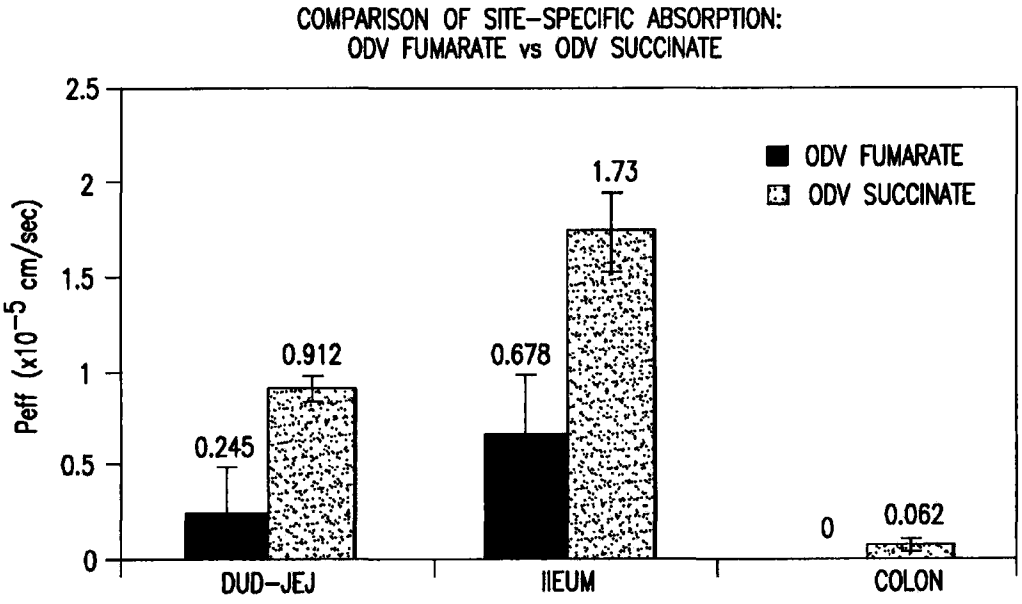
EP	0 112 669	7/1984
WO	WO 00/32555	6/2000
WO	WO 00/59851	10/2000
WO	WO 00/76955	12/2000

Primary Examiner—Samuel Barts
Assistant Examiner—Paul A. Zucker
(74) *Attorney, Agent, or Firm*—Rebecca R. Barrett

(57) **ABSTRACT**

A novel salt of O-desmethyl venlafaxine is provided, O-desmethylvenlafaxine succinate. Pharmaceutical compositions, dosage forms and methods of use are also provided.

46 Claims, 12 Drawing Sheets



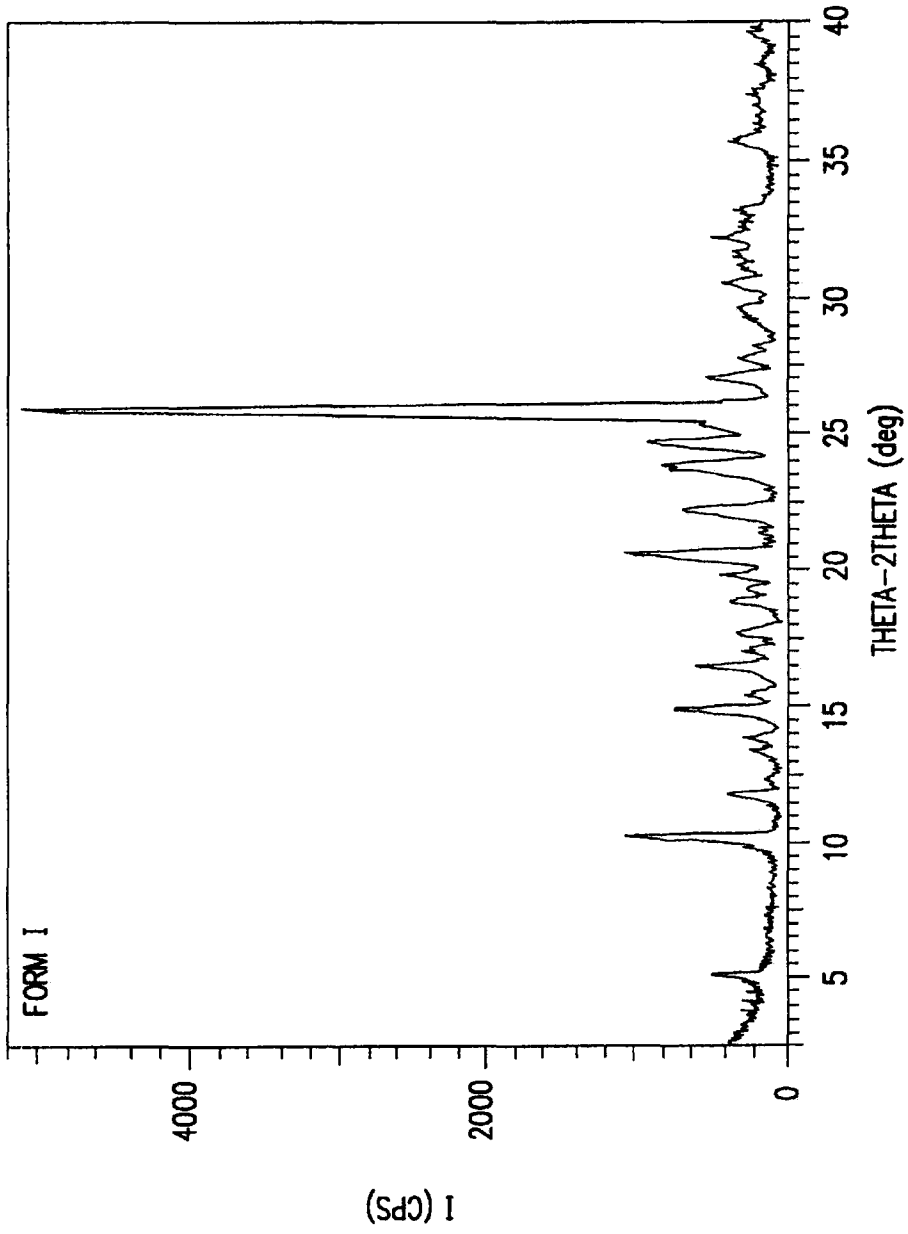


FIG. 1

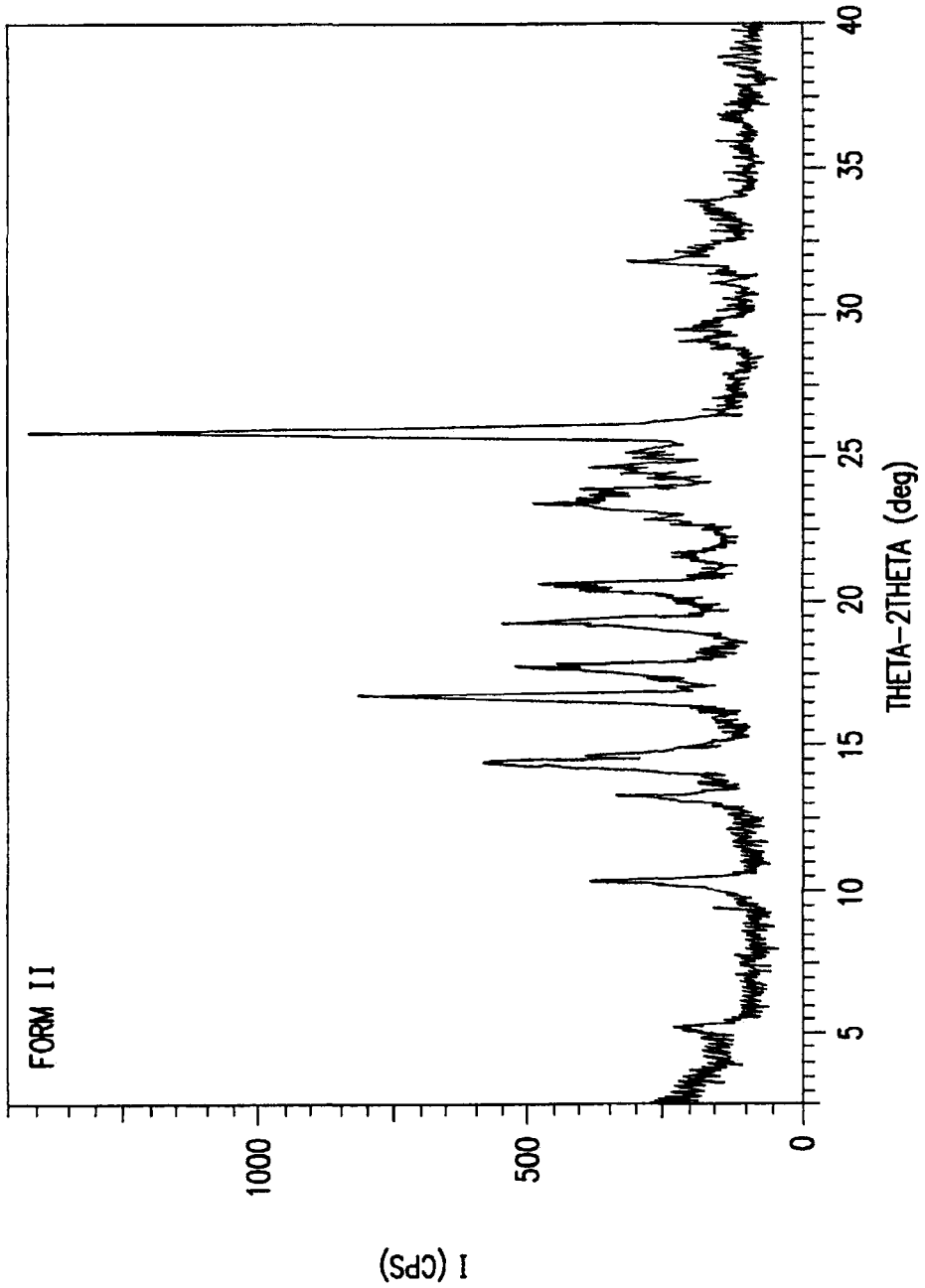


FIG.2

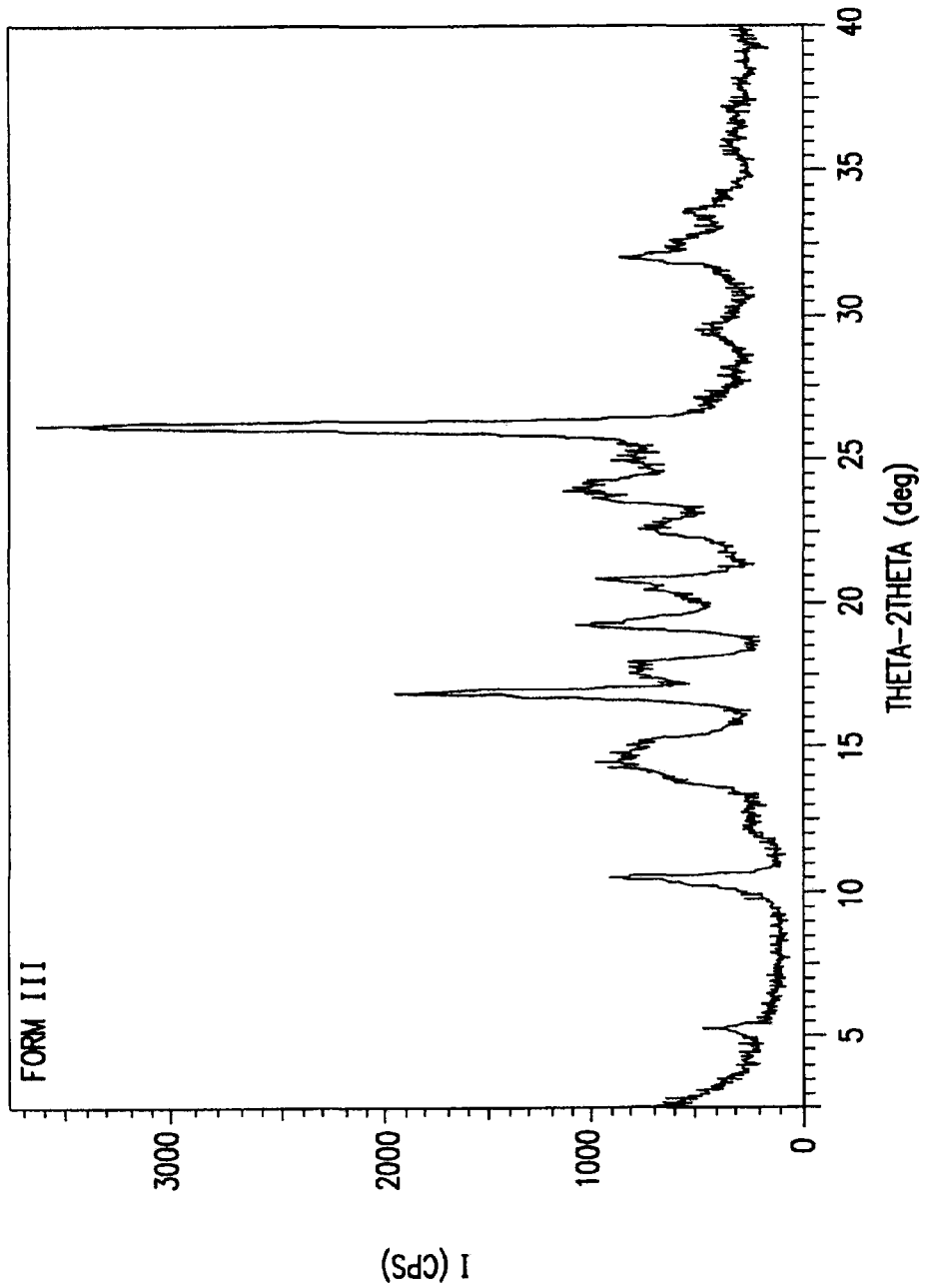

FORM III
I (CPS)
0
1000
2000
3000
5
10
15
20
25
30
35
40
THETA-2THETA (deg)

FIG.3

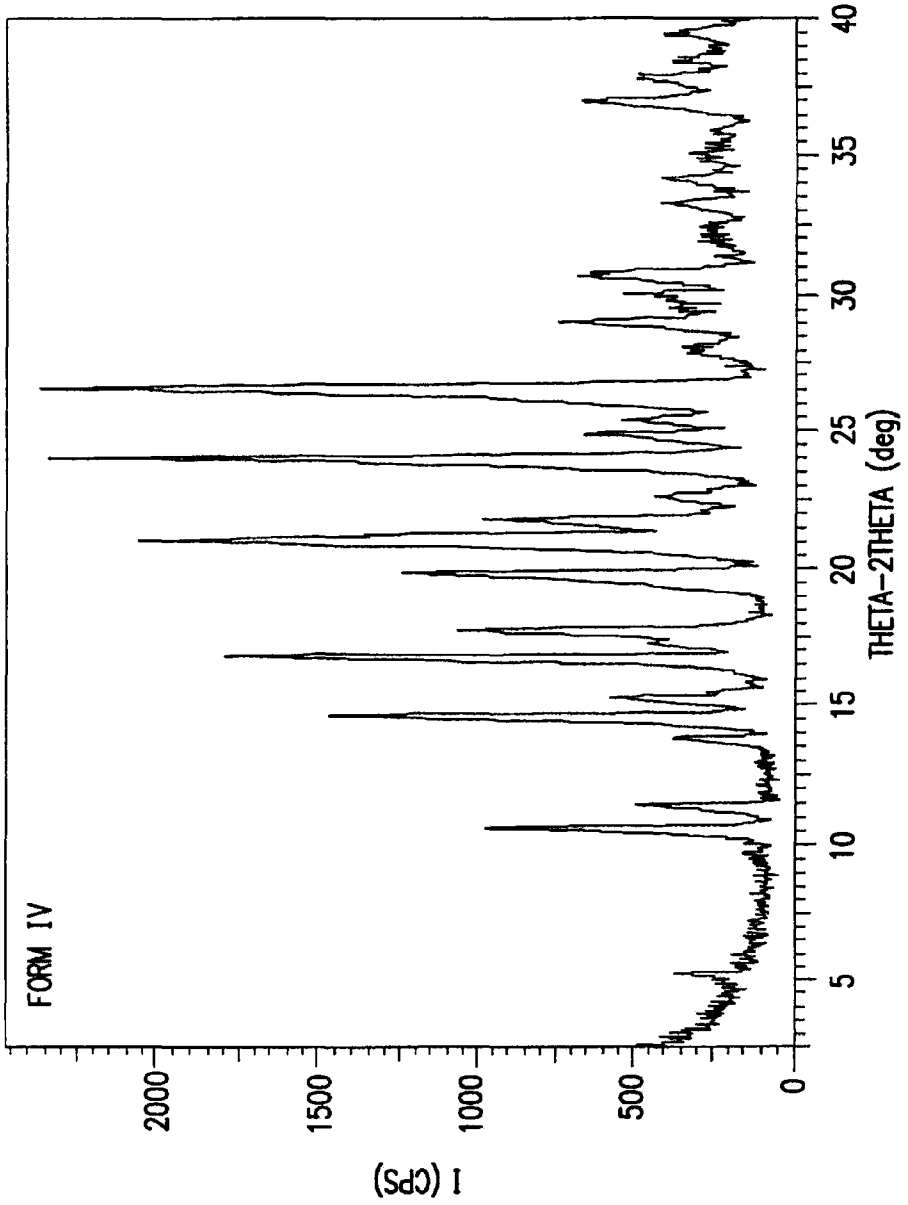

FORM IV
I (CPS)
0
500
1000
1500
2000
5
10
15
20
25
30
35
40
THETA-2THETA (deg)

FIG. 4

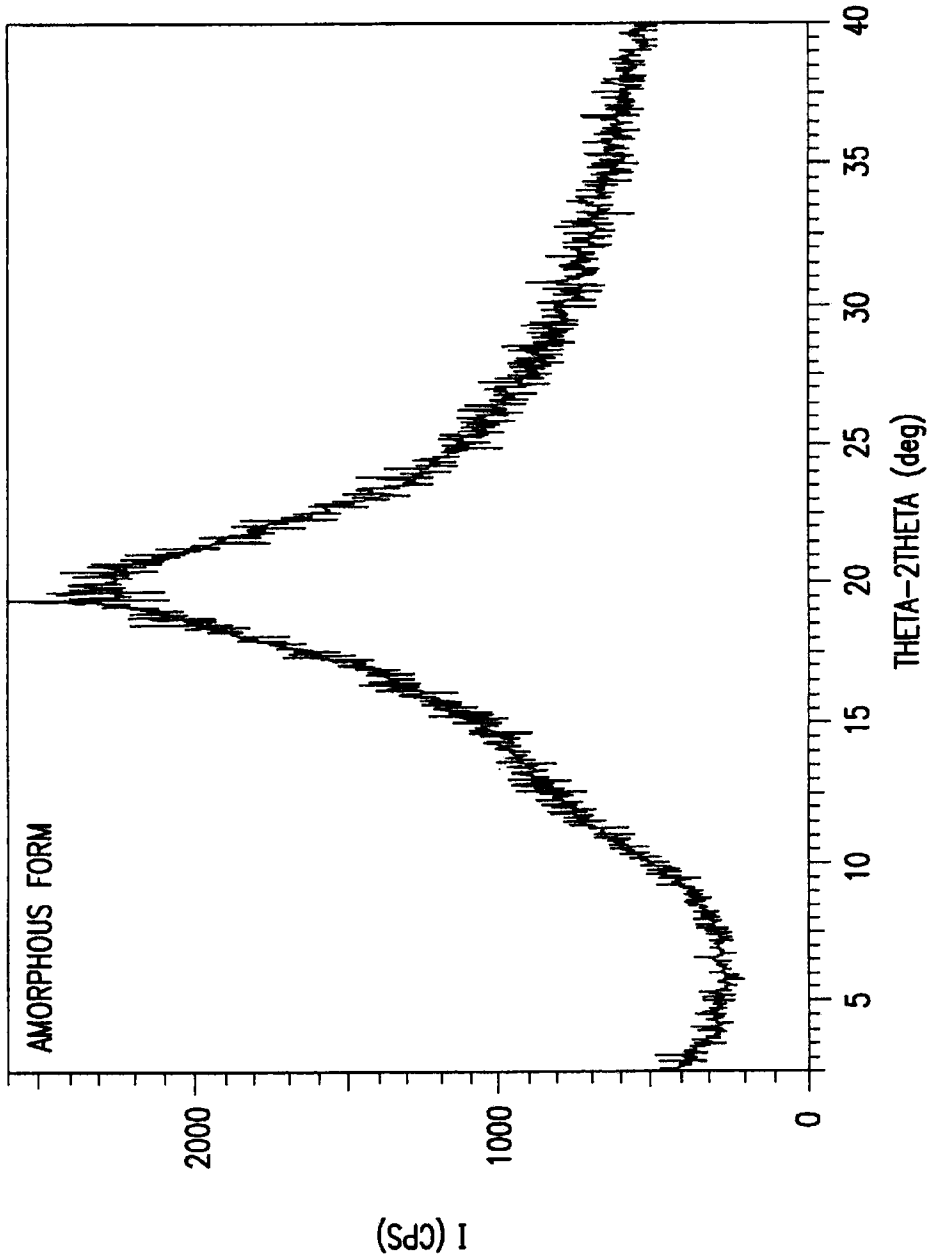

AMORPHOUS FORM
I (CPS)
2000
1000
0
5
10
15
20
25
30
35
40
THETA-2THETA (deg)

FIG.5

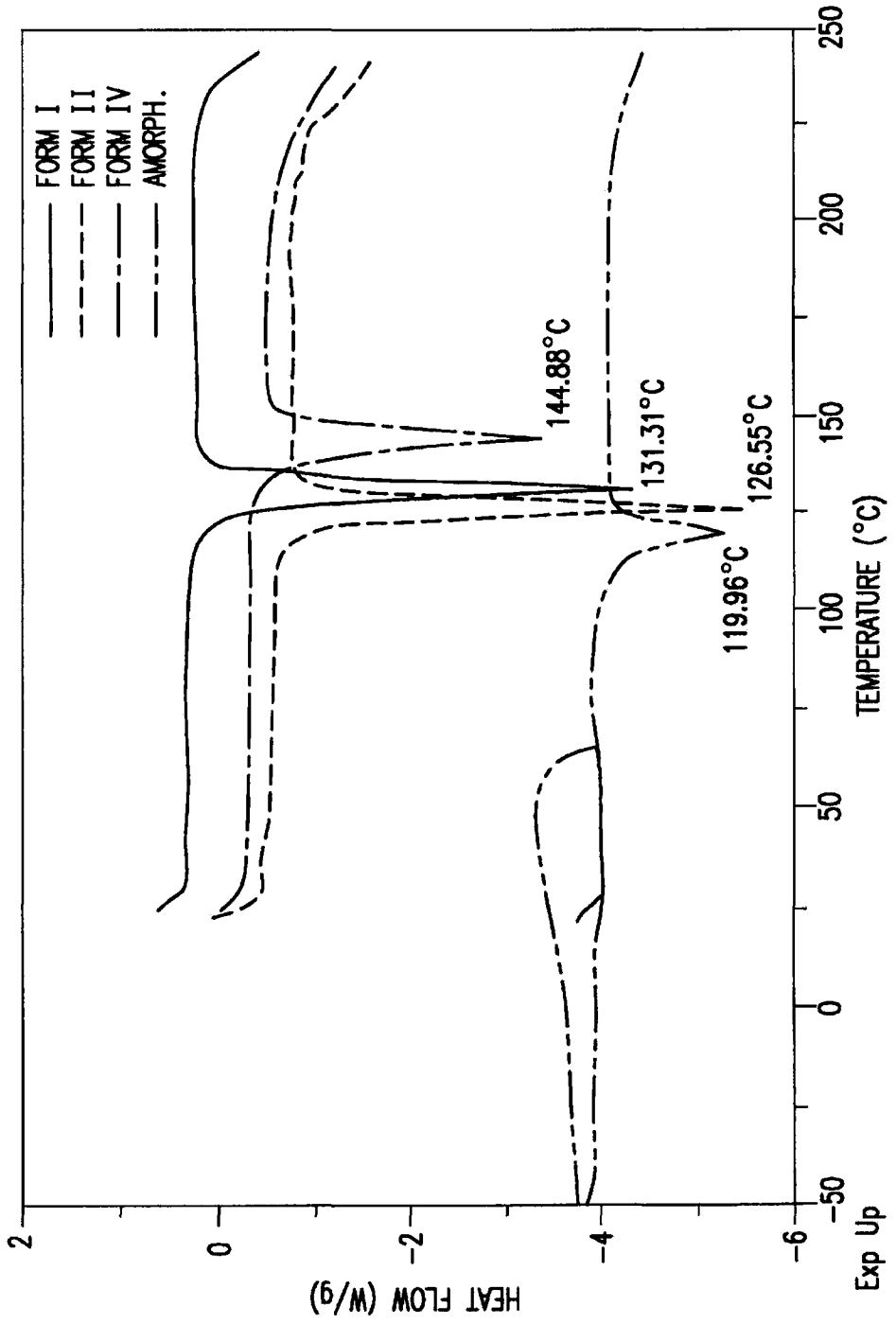

FORM I
FORM II
FORM IV
AMORPH.
144.88°C
131.31°C
126.55°C
119.96°C
HEAT FLOW (W/g)
TEMPERATURE (°C)
Exp Up
2
0
-2
-4
-6
250
200
150
100
50
0
-50

FIG.6

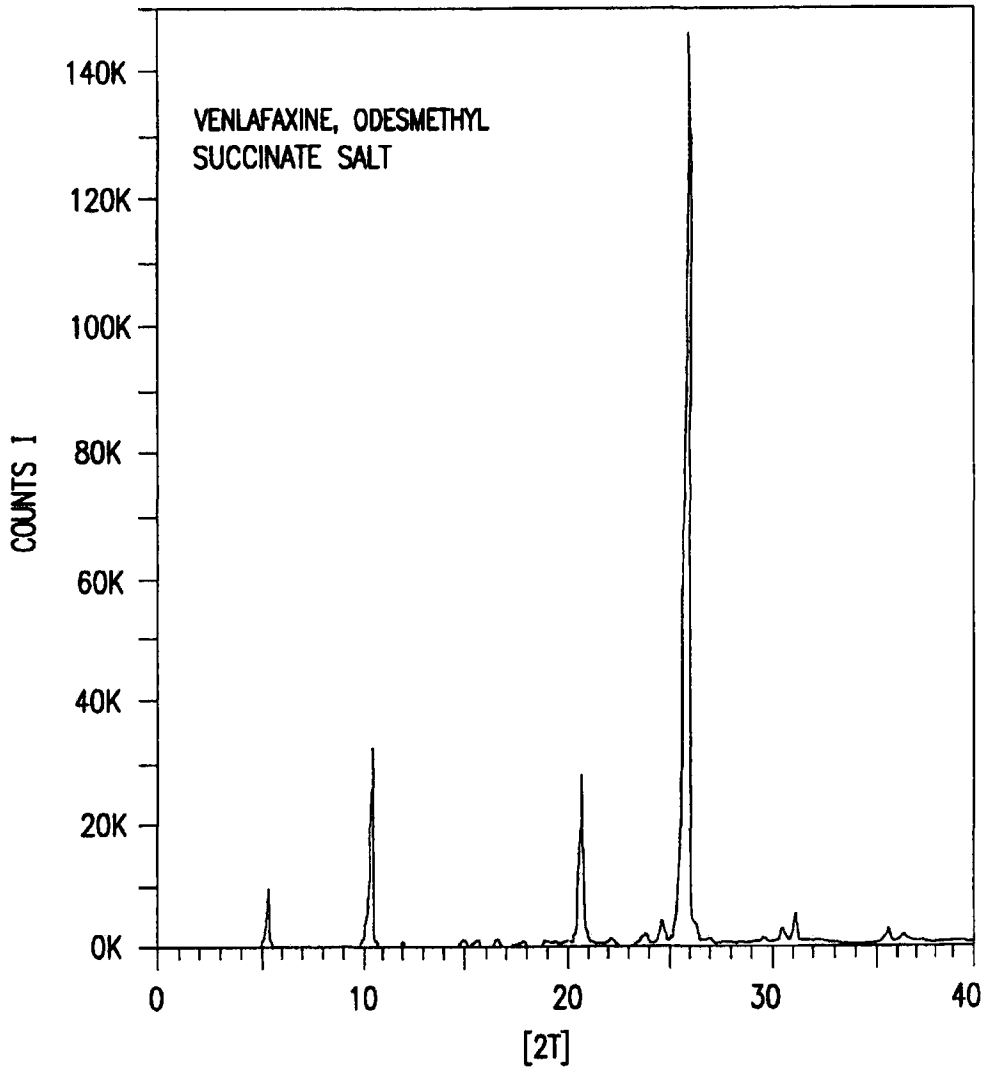

VENLAFAXINE, ODESMETHYL
SUCCINATE SALT
COUNTS 1
140K
120K
100K
80K
60K
40K
20K
0K
0
10
20
30
40
[2T]

FIG.7

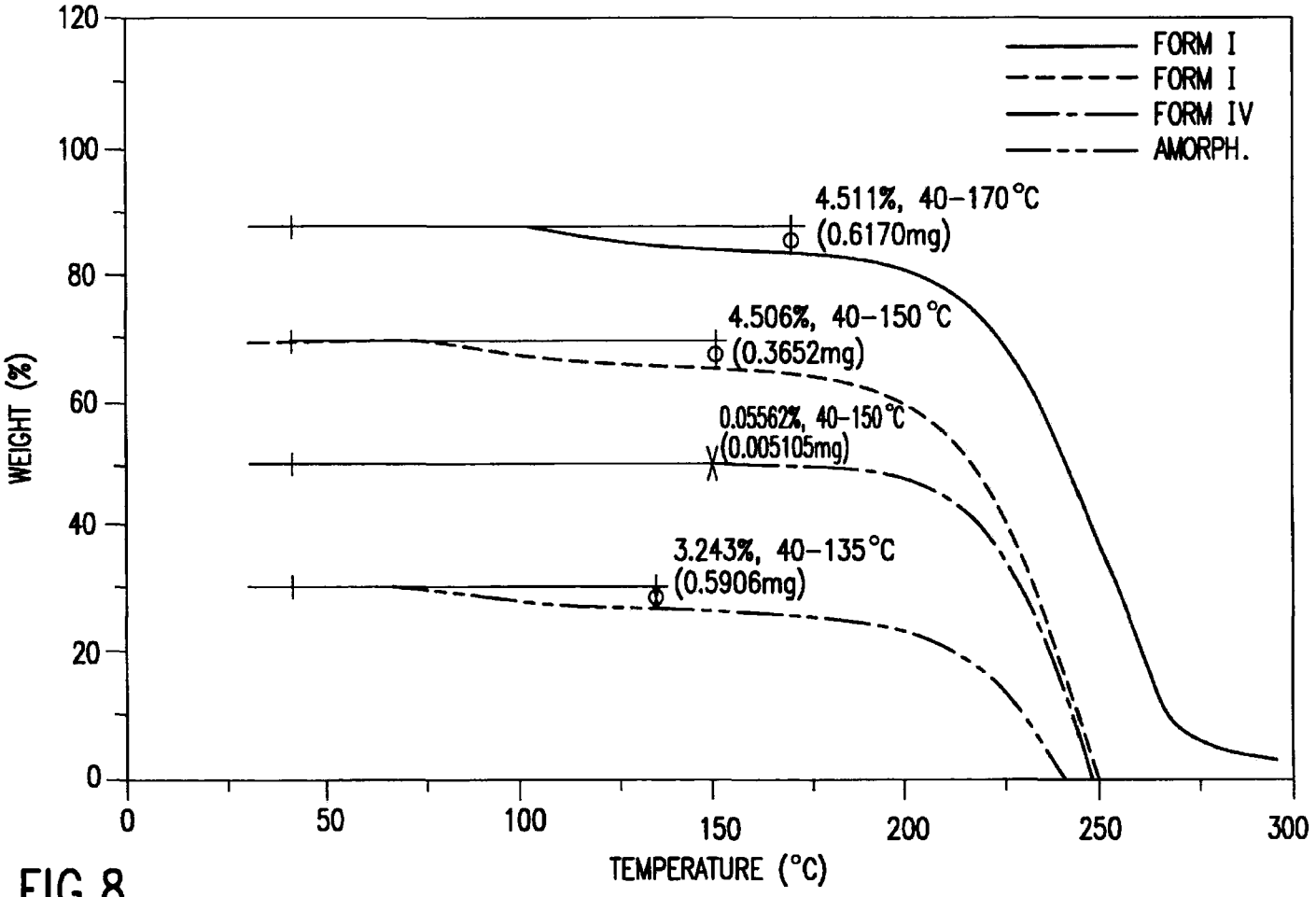

FORM I
FORM I
FORM IV
AMORPH.
4.511%, 40–170°C
(0.6170mg)
4.506%, 40–150°C
(0.3652mg)
0.05562%, 40–150°C
(0.005105mg)
3.243%, 40–135°C
(0.5906mg)
WEIGHT (%)
TEMPERATURE (°C)
120
100
80
60
40
20
0
0
50
100
150
200
250
300

FIG.8

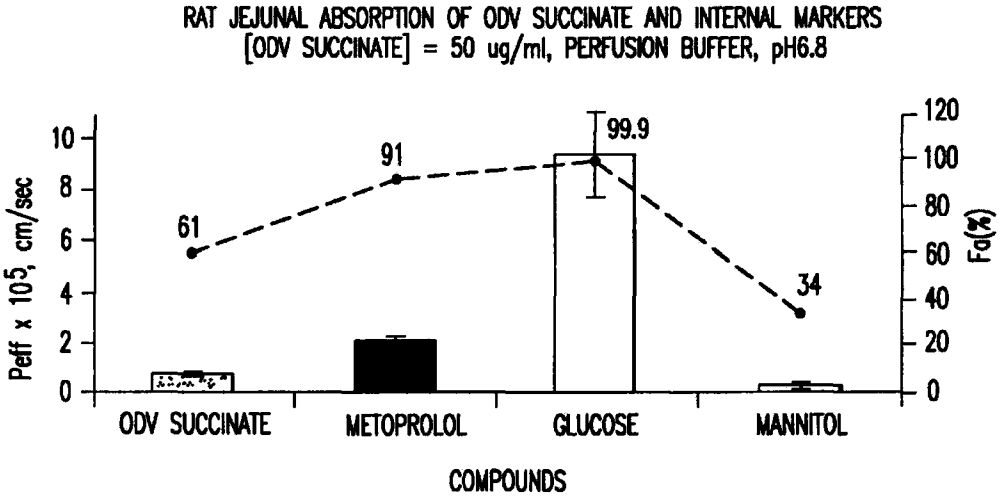

RAT JEJUNAL ABSORPTION OF ODV SUCCINATE AND INTERNAL MARKERS
[ODV SUCCINATE] = 50 ug/ml, PERFUSION BUFFER, pH6.8
Peff x 10^5, cm/sec
Fa(%)
61
91
99.9
34
ODV SUCCINATE
METOPROLOL
GLUCOSE
MANNITOL
COMPOUNDS

FIG.9

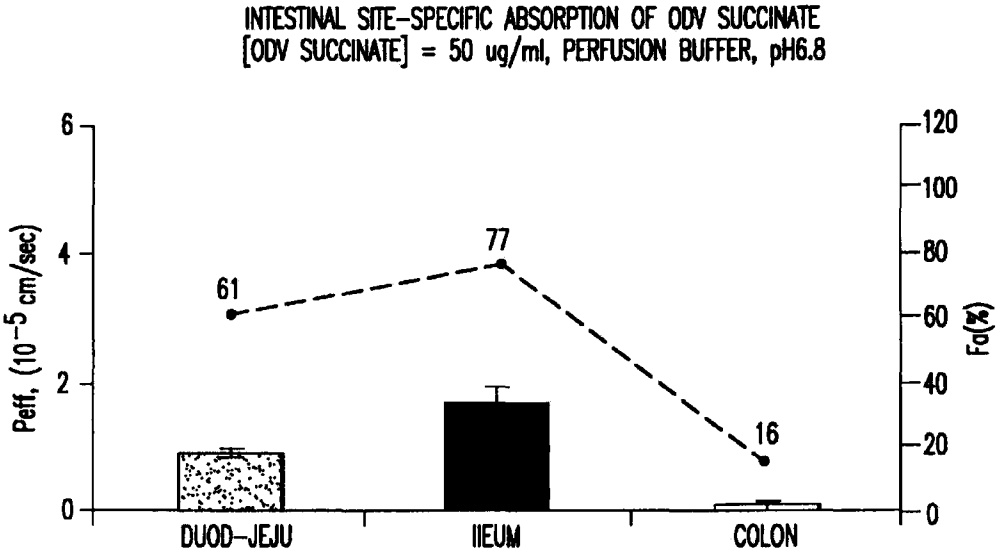

INTESTINAL SITE-SPECIFIC ABSORPTION OF ODV SUCCINATE
[ODV SUCCINATE] = 50 ug/ml, PERFUSION BUFFER, pH6.8
Peff, (10^{-5} cm/sec)
Fa(%)
61
77
16
DUOD-JEJU
IIEUM
COLON

FIG.10

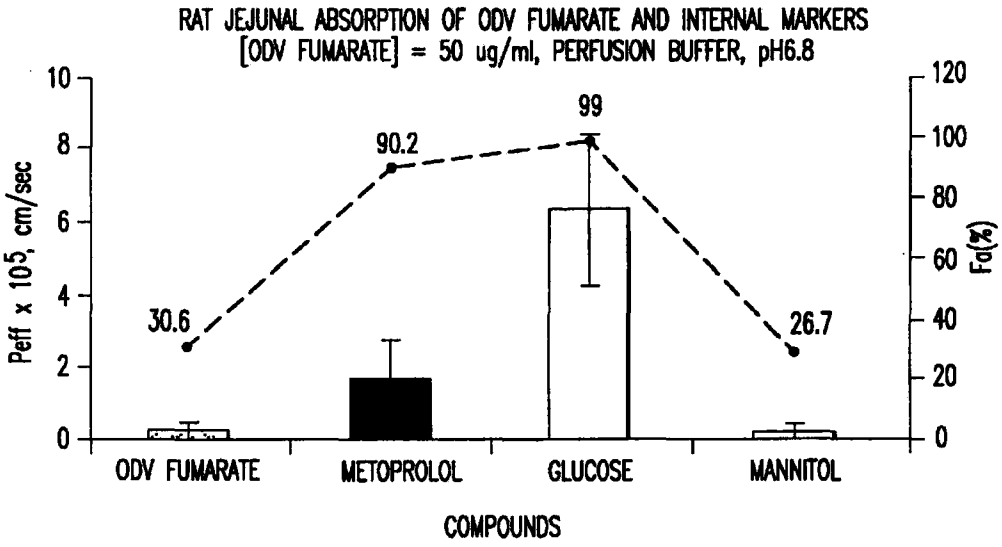

RAT JEJUNAL ABSORPTION OF ODV FUMARATE AND INTERNAL MARKERS
[ODV FUMARATE] = 50 ug/ml, PERFUSION BUFFER, pH6.8
Peff x 10^5, cm/sec
Fa(%)
30.6
90.2
99
26.7
ODV FUMARATE
METOPROLOL
GLUCOSE
MANNITOL
COMPOUNDS

FIG.11

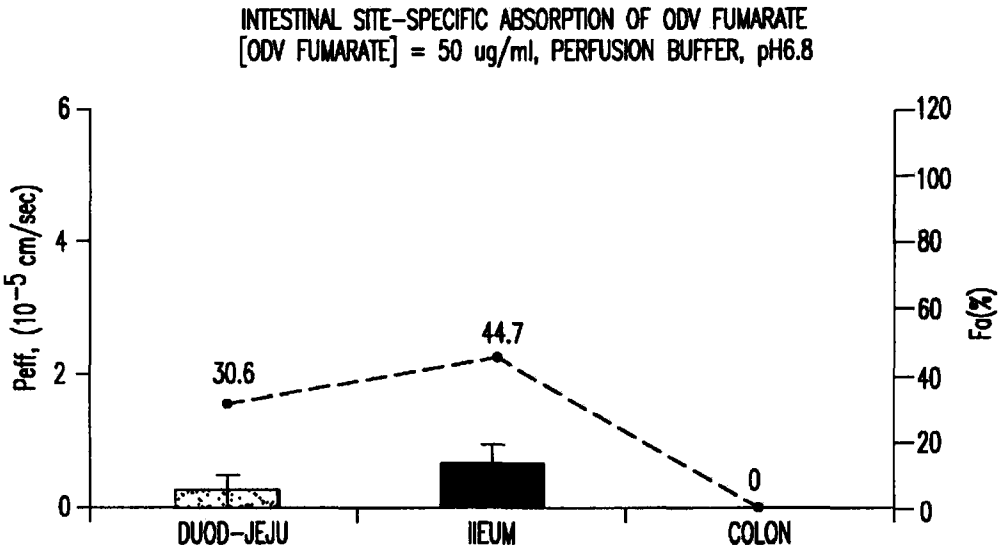

INTESTINAL SITE-SPECIFIC ABSORPTION OF ODV FUMARATE
[ODV FUMARATE] = 50 ug/ml, PERFUSION BUFFER, pH6.8
Peff, (10^-5 cm/sec)
Fa(%)
30.6
44.7
0
DUOD-JEJU
IIEUM
COLON

FIG.12

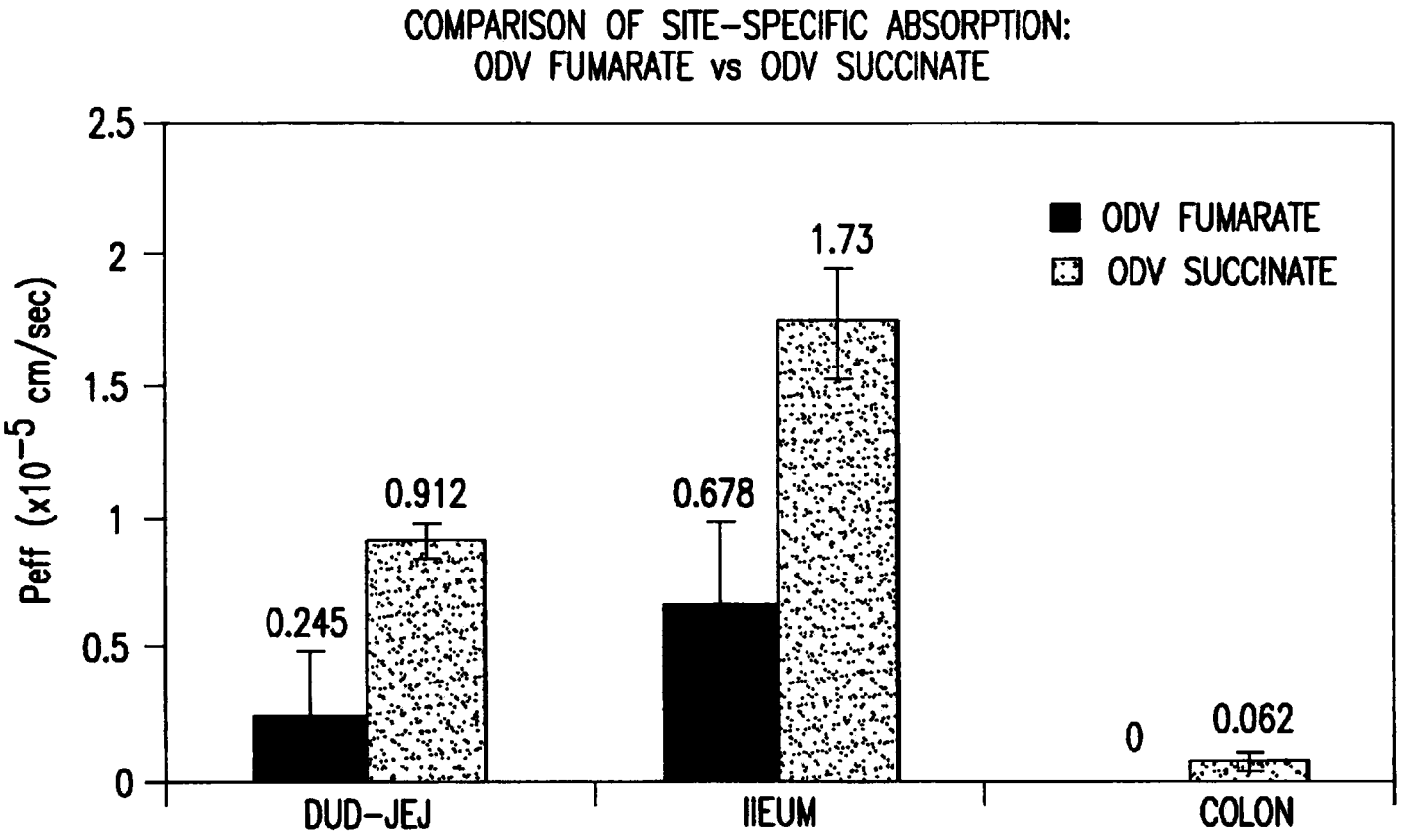

COMPARISON OF SITE-SPECIFIC ABSORPTION:
ODV FUMARATE vs ODV SUCCINATE
Peff (x10^{-5} cm/sec)
2.5
2
1.5
1
0.5
0
ODV FUMARATE
ODV SUCCINATE
0.245
0.912
0.678
1.73
0
0.062
DUD-JEJ
IIEUM
COLON

FIG.13

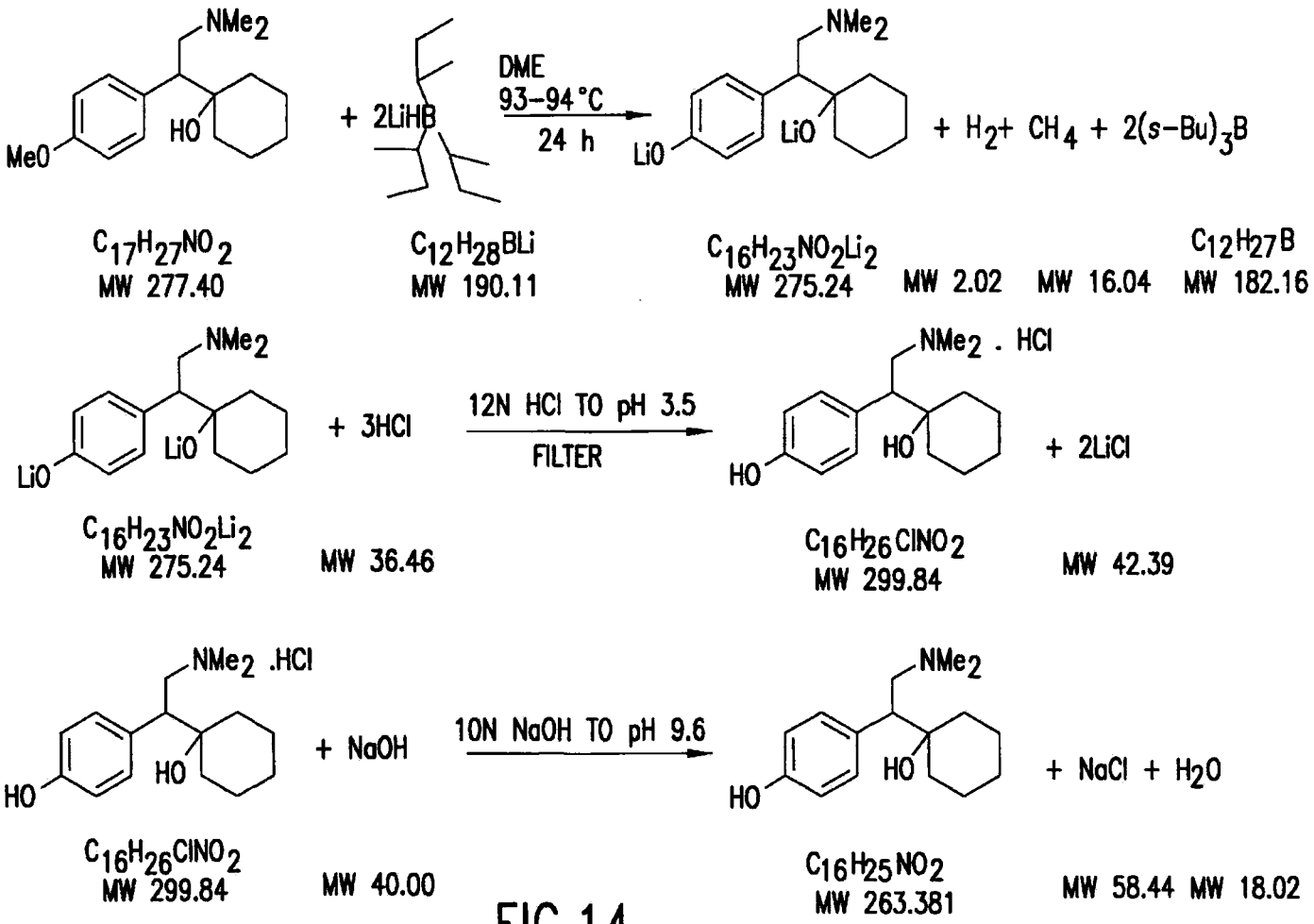

NMe2
MeO
HO
+ 2LiHB
DME
93–94 °C
24 h
LiO
LiO
+ H2+ CH4 + 2(s–Bu)3B
C17H27NO2
MW 277.40
C12H28BLi
MW 190.11
C16H23NO2Li2
MW 275.24
MW 2.02
MW 16.04
C12H27B
MW 182.16
NMe2
LiO
LiO
+ 3HCl
12N HCl TO pH 3.5
FILTER
NMe2 . HCl
HO
HO
+ 2LiCl
C16H23NO2Li2
MW 275.24
MW 36.46
C16H26ClNO2
MW 299.84
MW 42.39
NMe2 .HCl
HO
HO
+ NaOH
10N NaOH TO pH 9.6
NMe2
HO
HO
+ NaCl + H2O
C16H26ClNO2
MW 299.84
MW 40.00
C16H25NO2
MW 263.381
MW 58.44
MW 18.02

FIG.14

SUCCINATE SALT OF O-DESMETHYL-VENLAFAXINE

This application claims priority from copending provisional application(s) serial No. 60/268,214 filed on Feb. 12, 2001 and 60/297,963 filed on Jun. 13, 2001.

FIELD OF THE INVENTION

The present invention provides a novel salt of O-desmethyl-venlafaxine, O-desmethyl-venlafaxine succinate, as well as polymorphs, pharmaceutical compositions, dosage forms, and methods of use with the same.

BACKGROUND OF THE INVENTION

O-desmethyl venlafaxine is a major metabolite of venlafaxine and has been shown to inhibit norepinephrine and serotonin uptake. Klamerus, K. J. et al., "Introduction of the Composite Parameter to the Pharmacokinetics of Venlafaxine and its Active O-Desmethyl Metabolite", *J. Clin. Pharmacol.* 32:716–724 (1992). O-desmethyl-venlafaxine, chemically named 1-[2-(dimethylamino)-1-(4-phenol) ethyl]-cyclohexanol, was was exemplified as a fumarate salt in U.S. Pat. No. 4,535,186. However, the fumarate salt of O-desmethyl-venlafaxine has unsuitable physicochemical and permeability characteristics. O-desmethyl-venlafaxine is also exemplified as a free base in International Patent Publication No. WO 00/32555.

Salt formation provides a means of altering the physicochemical and resultant biological characteristics of a drug without modifying its chemical structure. A salt form can have a dramatic influence on the properties of the drug. The selection of a suitable salt is partially dictated by yield, rate and quantity of the crystalline structure. In addition, hygroscopicity, stability, solubility and the process profile of the salt form are important considerations. The identification of a salt form that exhibits a suitable combination of properties can be difficult.

Solubility is one important characteristic of a salt form that can affect its suitability for use as a drug. Where aqueous solubility is low, i.e. less than 10 mg/ml, the dissolution rate at in vivo administration can be rate limiting in the absorption process leading to poor bioavailability. Hygroscopicity is also an important characteristic. Compounds having low hygroscopicity tend to have better stability and easier processing.

SUMMARY OF THE INVENTION

The present invention provides a novel salt of O-desmethyl-venlafaxine, O-desmethyl-venlafaxine succinate (hereinafter referred to as "ODV succinate"). The novel salt of the present invention has properties which are particularly suitable for use as a drug, including improved solubility, permeability, and bioavailability. For example, ODV succinate is well absorbed in the gastrointestinal tract. Furthermore, oral administration of ODV succinate results in a lower incidence of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus than oral administration of venlafaxine. Additionally, sustained release oral formulations of ODV succinate result in a lower incidence of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus than oral administration of venlafaxine. Pharmaceutical compositions comprising ODV succinate and pharmaceutically acceptable carriers or excipients are also provided. Preferably, the pharmaceutical compositions comprise an amount of ODV succinate effective to treat the desired indication in an animal, such as a human.

In further embodiments of the present invention are provided methods of treating patients suffering from depression (include, but not limited to, major depressive disorder, bipolar disorder, and dysthymia), anxiety, panic disorder, generalized anxiety disorder, post traumatic stress disorder, premenstrual dysphoric disorder, fibromyalgia, agorophobia, attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction (including, but not limited to, premature ejaculation), borderline personality disorder, chronic fatigue syndrome, urinary incontinence, pain (including, but not limited to, migraine, chronic back pain, phantom limb pain, central pain, neuopathic pain such as diabetic neuropathy, and postherpetic neuropathy), Shy Drager syndrome, Raynaud's syndrome, Parkinson's disease, and epilepsy comprising providing to a patient an effective amount of ODV succinate. ODV succinate can also be administered to prevent relapse or recurrence of depression, to induce cognitive enhancement, to treat cognitive impairment, and in regimens for cessation of smoking or other tobacco uses. Additionally, ODV succinate can be administered to treat hypothalamic amenorrhea in depressed and non-depressed human females. These methods include administering to a patient in need thereof, an effective amount of ODV succinate or a substantially pure polymorph of ODV succinate, or mixtures thereof.

The present invention also provides four crystalline polymorphic forms of ODV succinate (hereinafter referred to as Forms I, II, III, and IV, respectively) and an amorphous form of ODV succinate. According to a preferred embodiment, the pharmaceutical composition of the present invention comprises at least about 20, 30, 40, 50, 60, 70, 80, 90, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, or 99.9% by weight of Form I, II, III, or IV or the amorphous form of ODV succinate, based upon 100% total weight of ODV succinate in the pharmaceutical composition (or the total weight of crystalline ODV succinate in the pharmaceutical composition).

Another embodiment is a method for preparing the free base of O-desemthyl-venlafaxine by demethylating venlafaxine or a salt thereof with an alkali metal salt of a trialkylborohydride.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an X-ray powder diffractogram (XRPD) of Form I of ODV succinate prepared in Example 7.

FIG. **2** is an XRPD of Form II of ODV succinate prepared in Example 8.

FIG. **3** is an XRPD of Form III of ODV succinate prepared in Example 9.

FIG. **4** is an XRPD of Form IV of ODV succinate prepared in Example 10.

FIG. **5** is an XRPD of the amorphous form of ODV succinate prepared in Example 11.

FIG. **6** are differential scanning calorimetry (DSC) analyses of Forms I, II, and IV and the amorphous form of ODV succinate from 25 to 250° C. in hermetically-sealed pans at a scan rate of 10° C./minute under a nitrogen purge.

FIG. **7** is an XRPD of Form I of the ODV succinate prepared in Example 1.

FIG. **8** are thermogravimetric analyses (TGA) of Forms I, II, and IV and the amorphous form of ODV succinate heated from 25 to 300° C. at a scan rate of 10° C./minute under a nitrogen purge.

FIG. **9** is a graph of the rat intestinal permeability coefficient (Peff) experimentally determined in Example 14 and predicted human in vivo fraction of dose absorbed (Fa (%)) for ODV succinate, metoprolol, glucose, and mannitol.

FIG. **10** is a graph of the Peff experimentally determined and Fa calculated in Example 14 for ODV succinate absorbed in the duodenum-jejunum, ileum, and colon.

FIG. **11** is a graph of Peff experimentally determined and Fa calculated in Example 14 for ODV fumarate, metoprolol, glucose, and mannitol.

FIG. **12** is a graph of the Peff experimentally determined and Fa calculated in Example 14 for ODV fumarate absorbed in the duodenum-jejunum, ileum, and colon.

FIG. **13** is a comparison of the site specific absorption of ODV fumarate versus ODV succinate in the duodenum-jejunum, ileum, and colon in Example 14.

FIG. **14** is a reaction scheme for preparing the free base of O-desmethyl-venlafaxine from venlafaxine with L-selectride.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "about" generally means within 10%, preferably within 5%, and more preferably within 1% of a given value or range. Alternatively, the term "about" means within an acceptable standard error of the mean, when considered by one of ordinary skill in the art.

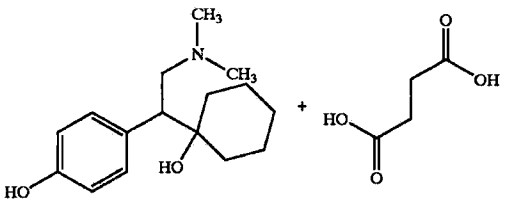
The term "monohydrate" as used herein refers to a hydrate in which one molecule of water is associated with each molecule of ODV succinate.

The term "hemihydrate" as used herein refers to a hydrate in which one molecule of water is associated with every two molecules of ODV succinate.

The term "treat" as used herein refers to preventing, amelliorating, controlling, or curing the desired symptoms or disorders.

The term "substantially the same" when used to describe X-ray powder deffraction patterns, is meant to include patterns in which peaks are within a standard deviation of ±0.2° 2θ.

The present invention relates to a novel salt of O-desmethyl-venlafaxine, O-desmethyl-venlafaxine succinate (hereinafter referred to as "ODV succinate"). ODV succinate provides optimal properties for formulation due to its high solubility, permeability, and bioavailability, and has the structural formula:



Succinic acid salts of O-desmethyl-venlafaxine exist as enantiomers and this invention includes racemic mixtures as well as stereoisomerically pure forms of the same. The term "ODV succinate" as used herein refers to racemic mixtures and stereoisomerically pure forms of ODV succinate, unless otherwise indicated.

The term "stereoisomerically pure" refers to compounds which are comprised of a greater proportion of the desired isomer than of the optical antipode. A stereoisomerically pure compound is generally made up of at least about 90% of the desired isomer, based upon 100% total weight of ODV succinate.

Succinic acid is a dicarboxylic acid and the invention therefore includes both salts in which the ratio of O-desmethyl-venlafaxine to acid (by mole) is 1:1 (i.e., a monosuccinate) and salts in which the ratio of O-desmethyl-venlafaxine to acid (by mole) is 2:1 (i.e., a bis isuccinate), as well as mixed salts, with for example an alkali metal or ammonium cation. The invention also includes mixtures of ODV succinate and the free base of O-desmethyl-venlafaxine. The crystalline polymorphs (i.e. Forms I, II, III, and IV) and the amorphous form of ODV succinate discussed below are monosuccinate salts, i.e., the molar ratio of O-desmethyl-venlafaxine to acid is 1:1. Salts of the present invention can be crystalline and may exist as more than one polymorph. Each polymorph forms another aspect of the invention. Hydrates as well as anhydrous forms of the salt are also encompassed by the invention. In particular the monohydrate form of O-desmethyl venlafaxine succinate is preferred.

ODV succinate generally has a solubility in water of greater than 30 mg/mL. Preferably, the aqueous solubility of the ODV succinate is at least 25, 30, 32, 35, 40, or 45 mg/mL at 25° C.

Succinic acid salts may be formed by contacting stoichiometric amounts of the acid with O-desmethy-venlafaxine free base. Alternatively, the acid may be used in excess, usually no more than 1.5 equivalents. Preferably the base and/or the acid are in solution, more preferably both are in solution.

The crystalline salt may be prepared by directly crystallizing from a solvent. Improved yield may be obtained by evaporation of some or all of the solvent or by crystallization at elevated temperatures followed by controlled cooling, preferably in stages. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the production process and the particle size distribution and form of the product.

Form I

Crystalline polymorph Form I of ODV succinate is a monohydrate and is stable at room temperature. Form I is physically stable up to at least about 105° C. and at 5–95% relative humidity. According to differential scanning calorimetry (DSC), Form I has an endotherm at about 131° C. (see FIG. **6**). Form I of ODV succinate has an XRPD pattern substantially identical to that shown in FIGS. **1** (ground Form I) and **7** (unground Form I). Peak locations and intensities for the XRPD pattern in FIG. **1** are provided in Table 1 below.

TABLE 1

Characteristic XRPD Peaks (expressed in degrees 2θ ± 0.2° 2θ) and Relative Intensities of Diffraction Lines for Form I of ODV Succinate

Degrees 2θ ± 0.2° 2θ	I/I_1
10.20	17
14.91	12
20.56	18
22.13	11
23.71	13
24.60	14
25.79	100

In particular, the peaks (expressed in degrees 2θ±0.2° 2θ) at 10.20, 14.91, 20.56, 22.13, 23.71, 24.60, and 25.79 are characteristic of Form I.

Form I may be prepared from the free base of O-desmethyl-venlafaxine as follows. The free base of

O-desmethyl-venlafaxine and succinic acid are dissolved in aqueous acetone. The resulting solution may optionally be filtered to remove any byproducts, such as those produced during the preparation of the free base of O-desmethyl-venlafaxine. The solution is then slowly cooled (e.g., for 3 hours or longer) to yield Form I of ODV succinate. The crystals of Form I may be recovered by any method known in the art.

Form I can also be prepared by preparing a slurry containing (a) Form I and (b) Form II, Form III, or a mixture thereof with (c) acetone, acetonitrile, a mixture of acetonitrile and water (e.g., a 9:1 mixture), or a mixture of ethanol and toluene (e.g., a 1:1 mixture) at ambient temperature.

Any crystals prepared by the aforementioned methods may be recovered by technique known to those silled in the art, such as, for example, filtration.

Form II

Crystalline polymorph Form II of ODV succinate is a monohydrate and is more thermally stable than Form III. According to DSC, Form II has an endotherm at about 127° C. (see FIG. 6). Form II of ODV succinate has an XRPD pattern substantially identical to that shown in FIG. 2. Peak locations and intensities for the XRPD pattern in FIG. 2 are provided in Table 2 below.

TABLE 2

Characteristic XRPD Peaks (expressed in degrees 2θ ± 0.2° 2θ) and Relative Intensities of Diffraction Lines for Form II of ODV Succinate

Degrees 2θ ± 0.2° 2θ	I/I_1
10.25	22
13.18	14
14.04	10
14.35	35
14.66	18
16.68	52
17.67	29
19.24	29
20.38	16
20.56	25
23.41	24
23.78	16
24.57	13
25.13	10
25.80	100
31.78	14

In particular, the peaks (expressed in degrees 2θ±0.2° 2θ) at 13.18, 14.04, 14.35, 14.66, 16.68, 17.67, 19.24, 25.13, and 31.78 are characteristic of Form II.

Form II can be prepared by rotary evaporation of Form I dissolved in acetone.

Form II can also be prepared by slow cooling of either saturated acetone or 95:5 ethanol:water solutions of Form I of ODV succinate. According to one embodiment, slow cooling is performed as follows. A mixture of the solvent and Form I of ODV succinate is prepared and heated and stirred on a hotplate (preferably set at 60–75° C.). Solvent is added until the ODV succinate is nearly all dissolved. The resulting mixture is optionally filtered (e.g., through a 0.2-μm nylon filter) into a clean vial pre-warmed, preferably on the same hotplate. The heat source is turned off, and the hotplate and vial are allowed to cool to ambient temperature. The vial is then allowed to stand at ambient temperature overnight. If no solids are generated, the vial is placed in a refrigerator for at least one day. Again, if no solids are generated, the vial is placed in a freezer for at least one day. Any solids are removed by vacuum filtration and allowed to air dry. In cases where no solid is obtained, a portion of the solvent is allowed to evaporate, and the procedure is repeated with heating and filtering.

Yet another method for preparing Form II is by precipitating Form I of ODV succinate from a solvent/anti-solvent mixture of ethanol/hexanes. Suitable solvents include those in which ODV succinate has a solubility of greater than 1 mg/mL. Suitable anti-solvents include those in which ODV succinate has low solubility, e.g., a solubility of less than 1 mg/mL. According to one embodiment, the solvent is saturated with ODV succinate. The mixture is heated, if necessary, to dissolve the ODV succinate. The mixture is filtered (e.g., through a 0.2-μm nylon filter) into a vial of cold anti-solvent (e.g., a solvent in which ODV succinate has a solubility of less than 0.1%). The resulting mixture may be placed in a freezer to increase the yield.

Form II can be prepared by slow evaporation of Form I of ODV succinate from water. For example, Form I of ODV succinate may be dissolved in water and then left in a perforated container at ambient temperature to form crystalline polymorph Form II.

Form II can be prepared by fast evaporation of Form I of ODV succinate from acetonitrile or ethanol/hexanes or ethanol/chloroform mother liquors. For example, Form I of ODV succinate may be dissolved in the solvent and then left in an open container at ambient temperature to form crystalline polymorph Form II.

Form II can be prepared by rapid cooling of an aqueous or aqueous/acetone solution of ODV succinate. Rapid cooling can be performed by any method known in the art, such as, for example, by applying a vacuum and/or an ice or ice/water bath.

Form II can also be prepared by subjecting the amorphous form of ODV succinate to 75% or greater relative humidity (e.g., at room temperature).

Any crystals prepared by the aforementioned methods may be recovered by known techniques.

Form III

Crystalline polymorph Form III of ODV succinate is a hydrate. The molar ratio of water to ODV succinate is less than 1 but more than ½ (i.e., Form III of ODV succinate is between a hemihydrate and a monohydrate). Form III of ODV succinate has an XRPD pattern substantially identical to that shown in FIG. 3. Peak locations and intensities for the XRPD pattern in FIG. 3 are provided in Table 3 below.

TABLE 3

Characteristic XRPD Peaks (expressed in degrees 2θ ± 0.2° 2θ) and Relative Intensities of Diffraction Lines for Form III of ODV Succinate

Degrees 2θ ± 0.2° 2θ	I/I_1
10.36	23
13.74	11
14.40	20
14.68	18
14.96	16
16.75	49
17.48	17
17.76	17
19.26	24
20.42	13
20.74	20
22.55	11
23.58	16
23.82	20
24.92	12
26.00	100
31.86	17
32.42	10

In particular, the peaks (expressed in degrees 2θ±0.2° 2θ) at about 13.74, 22.55, and 32.42 are characteristic of Form III.

Form III can be prepared by ball milling or cryo-grinding Form I of ODV succinate. Ball milling is performed by placing a ball in a cylinder with the ODV succinate and then shaking the cylinder. Cryo-grinding is performed by placing the ODV succinate in a cylinder and shaking the cylinder while maintaining the temperature of the cylinder at cryogenic temperatures (e.g., at <−90° C.).

Any crystals prepared by the aforementioned methods may be recovered by any known technique.

Form IV

Crystalline polymorph Form IV of ODV succinate is anhydrous. According to DSC, Form IV has an endotherm at about 145° C. (see FIG. **6**). Form IV of ODV succinate has an XRPD pattern substantially identical to that shown in FIG. **4**. Peak locations and intensities for the XRPD pattern in FIG. **4** are provided in Table 4 below.

TABLE 4

Characteristic XRPD Peaks (expressed in degrees 2θ ± 0.2° 2θ) and Relative Intensities of Diffraction Lines for Form IV of ODV Succinate

Degrees 2θ ± 0.2° 2θ	I/I_1
10.46	36
11.29	15
13.69	10
14.48	60
15.17	18
16.62	74
17.22	14
17.61	42
19.22	10
19.64	48
20.91	83
21.61	33
22.55	12
23.84	89
24.77	21
25.34	15
25.92	21
26.40	100
28.86	24
29.80	12
30.60	21
33.17	10
36.85	21
37.70	12

In particular, the peaks (expressed in degrees 2θ±0.2° 2θ) at about 11.29, 17.22, 19.64, 20.91, 21.61, 28.86, 29.80, 30.60, 36.85, and 37.70 are characteristic of Form IV.

Form IV can be prepared by slurrying equal amounts of Form I and Form II in acetonitrile at about 54° C. for several days (e.g., eight days), filtering, and heating the resulting solid for 18 hours at about 120° C. The crystals can be recovered by any method known in the art.

Amorphous Form

The amorphous form of ODV succinate has an XRPD pattern substantially identical to that shown in FIG. **5**. FIG. **5** shows an amorphous form of ODV succinate. The glass transition (T_g) onset for the amorphous form occurs at 18° C. According to DSC, the amorphous form undergoes a major endotherm at about 120° C. (see FIG. **6**). Without being bound by any theory, the inventors believe that the amorphous form was converted into a crystalline form before reaching 120° C., since amorphous forms typically do not exhibit endotherms, while crystalline forms do.

The amorphous form can be produced by forming a melt by heating Forms I, II, III, or IV, or a mixture thereof and cooling the melt to form a glass. For example, the amorphous form can be prepared by holding Forms I, II, III, or IV or a mixture thereof at about 150° C. for about 6 to about 18 minutes to form a melt and then cooling the melt to form a glass. The cooling can be done slowly or rapidly (e.g., by crash cooling).

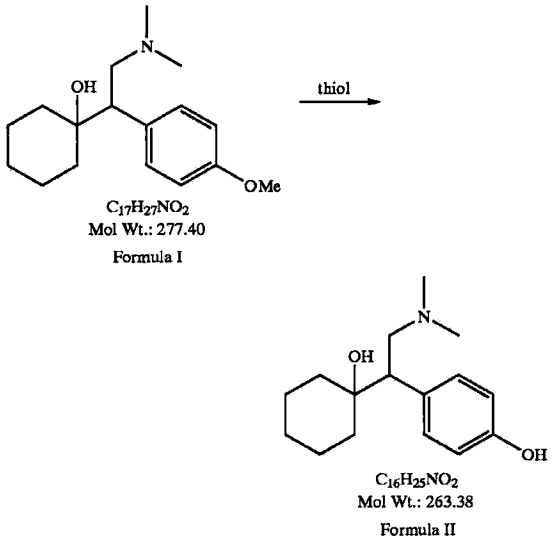
The amorphous form can be converted to Form II by placing the amorphous material in a high relative humidity environment (e.g., greater than about 50 or about 75% relative humidity).

Preparation of ODV Free Base

O-desmethyl-venlafaxine (ODV) free base may be prepared according to the general procedures outlined in U.S. Pat. No. 4,535,186.

Another method of preparing ODV free base is by demethylating a compound of Formula I (venlafaxine) to provide a compound of Formula II as described in Scheme I below.

Scheme I



$C_{17}H_{27}NO_2$
Mol Wt.: 277.40
Formula I

$C_{16}H_{25}NO_2$
Mol Wt.: 263.38
Formula II

As described in Scheme I the starting material, venlafaxine (Formula I), is demethylated. Venlafaxine may be prepared in accordance with procedures known in the art, such as those described in U.S. Pat. No. 4,535,186, which is herein incorporated by reference.

Demethylation is performed using a high molecular weight alkane, arene, or arylalkyl thiolate anion, such as straight or branched chain alkane thiolate anions having 8 to 20 carbon atoms, mono or bicyclic arene thiolate anions having 6 to 10 carbon atoms, or mono or bicyclic arylalkyl thiolate anions having 7 to 12 carbon atoms in the presence of a protic or aprotic solvent. Optionally, a base such as an alkoxide comprised of a straight or branched chain alkyl group of from 1 to 6 carbon atoms may be present to generate the thiolate anion.

Preferably the aliphatic thiol has from 10 to 20 carbon atoms and most preferably the aliphatic thiol is dodecanethiol. The aromatic thiol is preferably benzenethiol. The arylalkyl thiolate anion is preferably toluenethiol or naphthylmethanethiol.

When present, the alkoxide is preferably a lower alkoxide (methoxide, ethoxide and the like) such as sodium methoxide (sodium methylate, sodium methanolate).

The solvent is preferably a hydroxylic or ethereal solvent, and more preferably an alcohol, ethylene glycol or ether of ethylene glycol. Ethers of ethylene glycol include, but are

not limited to, ethyleneglycol monoethylether, triethyleneglycoldimethylether and polyethylene glycol. Preferably, the solvent is an inert, polar, high boiling point ether of ethylene glycol such as polyethylene glycol and most preferably PEG 400 (polyethylene glycol having a molecular weight range of from about 380–420).

The reaction is performed at a temperature of from about 150° C. to about 220° C., more preferably from about 170° C. to about 220° C., and most preferably from about 180° C. to about 200° C. The reaction is generally allowed to progress until, ideally, not more than 1% venlafaxine remains. In some aspects of the invention the reaction is complete in from about 2 hours to about 5 hours and more preferably in from about 2 to about 3.5 hours.

In preferred embodiments of this method, venlafaxine base is dissolved in polyethylene glycol 400 containing dodecanethiol and sodium methylate as a solution in methanol as the temperature is increased to from about 180° C. to about 200° C., with stirring for about 2 to about 3.5 hours.

Thereafter the reaction mixture is cooled to between about 65° C. and about 75° C. and an alcohol may be added as a diluent before neutralization to the isoelectric point (about pH 9.5 to about pH 10.0) with an appropriate neutralization agent such as hydrochloric acid. The alcoholic medium may also aid in the crystallization of the product as neutralization is initiated.

Preferably the alcohol comprises a straight or branched chain alkyl group of 1 to 6 carbon atoms, such as methanol, ethanol, isopropanol, butanol, and the like, and mixtures thereof. In some preferred embodiments of this method, the alcohol is isopropanol.

Yields of this method are greater than about 75% and generally from about 85% to greater than 90%.

Yet another method of preparing ODV free base is by demethylating venlafaxine or a salt thereof (e.g., a non-reducible salt of venlafaxine, such as the hydrochloride salt) with an alkali metal salt of a trialkylborohydride. The alkyl groups in trialkylorohydride can independently be C_1–C_6 alkyl and preferably are independently C_1–C_4 alkyl. The alkyl substituents on the trialkylborohydride can be the same or different. Suitable alkali metals include, but are not limited to, lithium, sodium, and potassium. Suitable trialkylborohydrides include, but are not limited to, selectride (tri-sec-butylborohydride) or triethylborohydride. Non-limiting examples of suitable salts include L-selectride, K-selectride, lithium triethylborohydride, and potassium triethylborohydride. Preferred salts include, but are not limited to, L-selectride and lithium triethylborohydride. A more preferred salt is L-selectride.

Generally, the demethylation process is performed in one or more of the following solvents: 1,2-dimethoxyethane, tetrahydrofuran (THF), 1,2-dethoxyethane and diglyme (bis (2-methoxyethyl) ether). The reaction is typically performed at or less than the boiling point of the solvent. Preferably, the reaction is performed at a temperature of from about 60 to about 140° C., more preferably from about 80 to about 100° C., and even more preferably from about 85 to about 95° C. The reaction is generally performed until the majority of venlafaxine has been demethylated and preferably until at least 80, 90, 95, or 99% of the venlafaxine has been demethylated. Broadly, the reaction is performed for from about 8 to about 48 hours. According to one embodiment, the reaction is performed for from about 12 to about 36 hours and preferably for about 24 hours.

The reaction results in an alkali metal salt of O-desmethyl-venlafaxine. The alkali metal salt can be converted to its free base by methods known in the art, such as neutralization with acid (e.g., to the isoelectric point).

This process for demethylating venlafaxine does not change the optical activity of the venlafaxine starting material. In other words, if the starting material is a racemic mixture of venlafaxine, the product of this demethylation process will also be a racemic mixture. If the starting material is an optically pure enantiomer, the product of this demethylation process will also be the same optically pure enantiomer.

An example of this reaction scheme for producing O-desmethyl-venlafaxine free base is shown in FIG. **14**.

This process for demethylating venlafaxine can produce the free base of ODV in substantially pure form (e.g., with <0.5, 0.4, 0.3, 0.2, 0.1, 0.09, 0.08, 0.07, 0.06, or 0.05% of impurities (w/w) (excluding inorganics) as measured by HPLC).

Demethylation with a trialkylaborohydride produces various hazardous boron containing byproducts. For example, use of L-selectride results in the formation of tris(1-methylpropyl)borane and tris(1-methylpropyl)boroxin as byproducts. These byproducts may be deactivated (or stabilized) by oxidation and, optionally, hydrolysis (of intermediate borate esters). Oxidation may be performed by reacting the boron containing byproducts with an oxidizing agent, such as hydrogen peroxide, perborates (e.g., sodium perborate), or a mixture thereof. A preferred oxidizing agent is an alkaline perborate solution (e.g., an aqueous solution containing sodium hydroxide and sodium perborate tetrahydrate). Preferably, the boron containing byproducts are added to the oxidizing agent or a solution comprising the oxidizing agent.

As described in Reviews in Contemporary Pharmacology, Volume 9(5) page 293–302 (1998), incorporated by reference in its entirety, O-desmethyl-venlafaxine has the following pharmacological profile shown in Table 5 below.

TABLE 5

	O-desmethylvenlafaxine
Effect (in vivo)	
Reversal of Reserpine-Induce Hypothermia (minimum effect; mg/kg i.p.)	3
Effect (in vitro)	
Inhibition of amine reuptake (IC50; uM)	
Norepinephrine	1.16
Serotonin	0.18
Dopamine	13.4
Affinity for Various Neuroreceptors (% inhibition at 1 uM)	
D2	6
Cholinergic	7
Adrenergic α	0
Histamine H1	0
Opiate	7

Thus, compounds, compositions and methods of the present invention can be used to treat or prevent central nervous system disorders including, but not limited to depression (including but not limited to major depressive disorder, bipolar disorder and dysthymia), fibromyalgia, anxiety, panic disorder, agorophobia, post traumatic stress disorder, premenstrual dysphoric disorder (also known as premenstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol

addiction, sexual dysfunction, (including premature ejaculation), borderline personality disorder, chronic fatigue syndrome, incontinence (including fecal incontinence, overflow incontinence, passive incontinence, reflex incontinence, stress urinary incontinence, urge incontinence, urinary exertional incontinence and urinary incontinence), pain (including but not limited to migraine, chronic back pain, phantom limb pain, central pain, neuropathic pain such as diabetic neuropathy, and postherpetic neuropathy), Shy Drager syndrome, Raynaud's syndrome, Parkinson's Disease, epilepsy, and others. Compounds and compositions of the present invention can also be used for preventing relapse or recurrence of depression; to treat cognitive impairment; for the inducement of cognitive enhancement in patient suffering from senile dementia, Alzheimer's disease, memory loss, amnesia and amnesia syndrome; and in regimens for cessation of smoking or other tobacco uses. Additionally, compounds and compositions of the present invention can be used for treating hypothalamic amenorrhea in depressed and non-depressed human females.

In some preferred embodiments of the invention, O-desmethyl-venlafaxine succinate is useful for the treatment of depression, anxiety, panic disorder, generalized anxiety disorder, post traumatic stress and premenstrual dysphoric disorder.

This invention provides methods of treating, preventing, inhibiting or alleviating each of the maladies listed above in a mammal, preferably in a human, the methods comprising administering an effective amount of a compound of the invention to a mammal in need thereof. An effective amount is an amount sufficient to prevent, inhibit, or alleviate one or more symptoms of the aforementioned conditions.

The dosage amount useful to treat, prevent, inhibit or alleviate each of the aforementioned conditions will vary with the severity of the condition to be treated and the route of administration. The dose, and dose frequency will also vary according to age, body weight, response and past medical history of the individual human patient. In generally the recommended daily dose range for the conditions described herein lie within the range of 10 mg to about 1000 mg O-desmethylvenlafaxine per day and more preferably within the range of about 15 mg to about 350 mg/day and still more preferably from about 15 mg to about 140 mg/day. In other embodiments of the invention the dosage will range from about 30 mg to about 90 mg/day. Dosage is described in terms of the free base and is adjusted accordingly for the succinate salt. In managing the patient, is generally preferred that the therapy be initiated at a lower dose and increased if necessary. Dosages for non-human patients can be adjusted accordingly by one skilled in the art.

Another embodiment of the invention is a method of lowering the incidence of nauseau, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus resulting from the oral administration of venlafaxine, O-desmethylvenlafaxine, or a salt of O-desmethylvenlafaxine other than O-desmethylvenlafaxine succinate to a patient. The method includes orally administering to a patient in need thereof a therapeutically effective amount of O-desmethylvenlafaxine succinate.

Yet another embodiment of the invention is a method of lowering the incidence of nauseauu, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus resulting from the oral administration of O-desmethylvenlafaxine succinate to a patient. The method includes orally administering to a patient in need thereof a therapeutically effective amount of a sustained release oral dosage form comprising O-desmethyl-venlafaxine succinate having a peak blood plasma level of less than about 225 ng/ml.

O-desmethylvenlafaxine succinate may also be provided in combination with venlafaxine. The dosage of venlafaxine is preferably about 75 mg to about 350 mg/day and more preferably about 75 mg to about 225 mg/day. Still more preferably the dosage of venlafaxine is about 75 mg to about 150 mg/day. The ratio of O-desmethylvenlafaxine to venlafaxine will vary from patient to patient depending upon a patient's response rate, but generally will be at least 6:1 O-desmethylvenlafaxine to venlafaxine.

Any suitable route of administration can be employed for providing the patient with an effective amount of O-desmethylvenlafaxine succinate. For example, oral, mucosal (e.g. nasal, sublingual, buccal, rectal or vaginal), parental (e.g. intravenous or intramuscular), transdermal, and subcutaneous routes can be employed. Preferred routes of administration include oral, transdermal and mucosal.

O-desmethyl venlafaxine succinate can be combined with a pharmaceutical carrier or excipient (e.g., pharmaceutically acceptable carriers and excipients) according to conventional pharmaceutical compounding technique to form a pharmaceutical composition or dosage form. Suitable pharmaceutically acceptable carriers and excipients include, but are not limited to, those described in Remington's, *The Science and Practice of Pharmacy,* (Gennaro, A. R., ed., 19th edition, 1995, Mack Pub. Co.) which is herein incorporated by reference. The phrase "pharmaceutically acceptable" refers to additives or compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to an animal, such as a mammal (e.g., a human). For oral liquid pharmaceutical compositions, pharmaceutical carriers and excipients can include, but are not limited to water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like. Oral solid pharmaceutical compositions may include, but are not limited to starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders and disintegrating agents. The pharmaceutical composition and dosage form may also include venlafaxine or a salt thereof as discussed above.

According to one embodiment, the majority of ODV succinate particles in a pharmaceutical composition or dosage form of the present invention have a particle size between 45 and 400 microns. Preferably, more than 60 or 65% of the particles have a particle size between 45 and 400 microns.

Dosage forms include, but are not limited to tablets, capsules, troches, lozenges, dispersions, suspensions, suppositories, ointments, cataplasms, pastes, powders, creams, solutions, capsules (including encapsulated spheroids), and patches. The dosage forms may also include immediate release as well as formulations adapted for controlled, sustained, extended, or delayed release. Most preferably tablets and capsules are the dosage form. Tablets and spheroids may be coated by standard aqueous and nonaqueous techniques as required.

Each dosage form generally contains from about 15 to about 350 mg of ODV succinate (as measured by the free base equivalent). More preferably, each dosage form contains from about 30 to about 200 mg of ODV succinate (as measured by the free base equivalent) and even more preferably from about 75 to about 150 mg of ODV succinate (as measured by the free base equivalent).

According to one preferred embodiment, the pharmaceutical composition is an extended release formulation, such as

that described in U.S. Pat. No. 6,274,171, which is herein incorporated by reference. For example, an extended release formulation may comprise spheroids comprised of ODV succinate, microcrystalline cellulose, and, optionally, hydroxypropylmethylcellulose. The spheroids are preferably coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

According to another preferred embodiment, the pharmaceutical composition is a sustained release formulation (e.g., in the form of a tablet). The sustained release formulation may comprise ODV succinate, a rate controlling polymer material (i.e., a material which controls the rate at which the ODV succinate is released), and, optionally, other adjuvants. Suitable rate controlling polymer materials include, but are not limited to, hydroxyalkyl cellulose, such as hydroxypropyl cellulose and hydroxypropyl methyl cellulose (HPMC); poly(ethylene) oxide; alkyl cellulose, such as ethyl cellulose and methyl cellulose; carboxymethyl cellulose; hydrophilic cellulose derivatives; and polyethylene glycol. The sustained release formulation comprises from about 30 w/w to about 50% w/w of ODV succinate and from about 25 w/w to about 70% w/w of a rate controlling polymer material. Optionally, the sustained release formulation may further comprise from about 0.5 w/w to about 10% w/w and preferably from about 2 w/w to about 10% of microcrystalline cellulose. A preferred sustained release formulation comprises from about 32 w/w to about 44% w/w of ODV succinate and from about 45 w/w to about 66% w/w of hydroxyprpopyl methylcellulose. Typically, the sustained release formulation provides sustained therapeutically effective plasma levels over at least a 16 or 20 hour period. The peak serum levels during the 16 or 20 hour period are generally up to 150 ng/ml. The sustained release formulation also shows a reduced level of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, and/or trismus.

The following examples are illustrative but are not meant to be limiting of the present invention.

EXAMPLE 1

Preparation of Form I of ODV Succinate

Acetone (2111 mL), water (667 mL) and O-desmethylvenlafaxine (250.0 g, 0.949 mol) were mixed to form a thick white suspension which was stirred at 23° C. for 0.5 hour. Succinic acid (115.5 g, 0.978 mol) was added with acetone (236 mL) and water (75 mL). The suspension was heated to 58° C. and stirred at this temperature for 30 minutes. The reaction mixture was filtered and allowed to cool to 30–34° C. The suspension was stirred at 30–31° C. for 3 hours then cooled to 0–5° C. and stirred at this temperature for a further hour. The solids were isolated by filtration and the wet cake dried at 30° C. for 12 hours (50 mm Hg) then 40° C. for 24 hours (50 mm Hg) to afford O-des-methyl-Venlafaxine succinate monohydrate as white crystals (325.5 g, 85.7%).

mp: 122.3 C and 139.6 C

^{1}H NMR (300 MHz, DMSO-d_6) 10–9 (bs, 2H), 7.00 (d, J=8.2 Hz, 2H), 6.65 (d, J=8.2 Hz, 2H), 3.4–3.2 (bs, 1H), 3.12 (dd, J=7.0, 12.2 Hz, 1H), 2.74 (t, J=8.7 Hz, 1H), 2.7–2.58 (m, 1H), 2.50 (s, 3H), 2.36 (s, 3H), 2.28 (s, 4H), 1.50–1.25 (m, 6H), 1.20–0.80 (4H). 99.40% Purity (by HPLC).

An XRPD pattern for the (unground) crystals prepared is shown in FIG. 7. Characteristic XRPD peaks are shown in Table 6 below.

TABLE 6

X-ray powder diffractogram (CuK2α)	
Angle (° 2θ)	Relative Intensity
5.285	30.6
10.435	54.6
20.680	10.4
20.850	23.2
25.660	6.6
25.955	55.5
26.125	100.0

The crystals of Form I examined in FIG. 7 were not ground, while those in FIG. 1 were ground before being examined. Without being bound by any theory, the inventors theorize that the XRPD for the unground crystals differed from that of the ground crystals due to the preferred orientation of the unground crystals.

Bulk Density: 0.369 gms/mL

Solubility in water: 32.2 mg/ml at 25° C.

The aqueous solubility (reported above) of Form I of ODV succinate was determined according to the following procedure.

Materials

Spectrophotometer—Capable of isolating a bandwidth of 2 nm or less at the wavelength of maximum absorbance, and of measuring absorbances in the 0.0 to 1.0 range with a precision of 0.01. A Cary Model 219 spectrophotometer or equivalent is suitable.

Cells—Silica, 1 cm.

Filters—0.45 micron Nylon filters which are chemical resistant or equivalent

Bottles—Glass screw top bottles having a 15 mL or greater capacity.

Shaker—A lateral shaker, wrist shaker, or a vibrator which will not generate heat is suitable.

Sample Preparation

A. For Non UV Absorbing Solvents

1. To a bottle weigh an amount of sample equivalent to approximately 1½ times the solubility.
2. Pipet 10.0 mL of water into the bottle and secure cap tightly.
3. Agitate the bottles at ambient room temperature for at least 16 hours.
4. Obtain a clear filtrate layer by either centrifugation ot filtration being careful to avoid evaporation.
5. Quantitatively transfer the solution to a volumetric flask and dilute to volume with water.
6. Blank the instrument for water.
7. Make quantitative dilutions to arrive at a suitable concentration for measurement.

B. For UV Absorbing Solvents

1. To a bottle, weigh an amount of sample equivalent to approximately 1½ times the solubility.
2. Pipet 10.0 mL of water into the bottle and secure a cap tightly.
3. Agitate the bottles at ambient room temperature for at least 16 hours.
4. Obtain a clear filtrate layer by either centrifugation or filtration being careful to avoid evaporation.
5. Evaporate an accurate amount of solvent on a steam bath and redissolve the residue, in the solvent used to prepare the standard. Quantitatively transfer to a volumetric flask with the same solvent used in preparing the standard solution.
6. Make dilutions as necessary to obtain a concentration suitable for quantitative measurement.

Procedure

1. Obtain the spectra of the sample and standard preparations between 350 and 200 nm, using water as the blank. The wavelength range may be varied depending upon the UV cut off of water.

2. Calculate the aqueous solubility with the following equation:

$$mg/mL = \frac{(As)(Ds)(Wg - Wt)(S)}{(Ar)(Dr)(V)}$$

where

As=absorbance of the sample preparation

Ds-=dilution factor of the sample preparation, mL

Wg=gross weight of the reference standard and container, mg

Wt=tare weight, mg

S=strength of the reference standard, decimal

Ar=absorbance of the reference standard preparation

Dr=dilution factor of the reference standard preparation, mL

V=amount of solvent evaporated, mL

EXAMPLE 2

Hard Gelatin Capsule Dosage Form

Ingredient	mg/capsule	% w/w
ODV succinate	116.7 (75 as free base)	39.5
Lactose Fast Flow	177.3	60.0
Magnesium Stearate	1.5	0.5
Total	295.5	100.0

The active ingredient is sieved and blended with the listed excipients. Suitably sized hard gelatin capsules are filled using suitable machinery and methods well known in the art. Other doses may be prepared by altering the fill weight and, if necessary, by changing the capsule size to suit.

EXAMPLE 3

Preparation of O-desmethyl-venlafaxine Free Base

Dodecanethiol (122 g), venlafaxine (111 g), and a methanolic solution of sodium methanolate (30%, 90 g) and PEG 400 are heated to 190° C. The methanol is distilled off and the solution is stirred for 2 hours at 190° C. Then the temperature is lowered, 2-propanol (450 g) is added and the pH is adjusted to 9.5 with aqueous HCl. The precipitate is collected by suction filtration, and the cake is washed with 2-propanol, toluene, 2-propanol and water. The wet O-desmethylvenlafaxine is dried in vacuo.

Yield: 87 g.

^{1}H-NMR: (Gemini 200, Varian, 200 MHz) (DMSO-d6) δ=9.11 (s, br, 1H; OH), 6.98 (d, br, J=8.4, 2H; arom.), 6.65 (d, br, J=8.4, 2H; arom.), 5.32 (s, br, 1H; OH), 3.00 (dd, J=12.3 and 8.5, 1H), 2.73 (dd, J=8.5 and 6.3, 1H), 2.36 (dd, J=12.3 and 6.3, 1H) 2.15 (s, 6H, 2×Me), 1.7–0.8 (m, 10H, c-hex).

EXAMPLE 4

Preparation of O-desmethyl-venlafaxine Free Base

Venlafaxine (5.6 g) and benzenethiol sodium salt (6.9 g) are charged to PEG 400 (25 g). The reaction mixture is heated to 160° C. for 5 hours. Then the temperature is lowered and water is added (60 g). The pH is adjusted to 3.5 with H_3PO_4. The organic by-products are removed by extraction with heptanes (25 g). The pH of the aqueous layer is then adjusted to 9.5 with aqueous ammonia. The precipitate is collected by suction filtration, re-slurried in water (100 g), isolated by suction filtration and dried in vacuo.

Yield 1 g.

^{1}H-NMR: (Gemini 200, Varian, 200 MHz) (DMSO-d6) δ=9.11 (s, br, 1H; OH), 6.98 (d, br, J=8.4, 2H; arom.), 6.65 (d, br, J=8.4, 2H; arom.), 5.32 (s, br, 1H; OH), 3.00 (dd, J=12.3 and 8.5, 1H), 2.73 (dd, J=8.5 and 6.3, 1H), 2.36 (dd, J=12.3 and 6.3, 1H) 2.15 (s, 6H, 2×Me), 1.7–0.8 (m, 10H, c-hex).

EXAMPLE 5

Preparation of O-desmethyl-venlafaxine Free Base

Dodecanethiol (69 g), venlafaxine (55 g), and an ethanolic solution of sodium ethanolate (21%, 82 g) are charged to a pressure vessel. The temperature is raised to 150° C. and the reaction mixture is stirred for 2 days. Then the temperature is lowered and the solution is filtered. The pH of the filtrate is adjusted to 9.5 with aqueous hydrogen chloride. The crystals are collected by suction filtration. The cake is washed with ethanol and dried in vacuo.

Yield: 42 g

^{1}H-NMR: (Gemini 200, Varian, 200 MHz) (DMSO-d6) δ=9.11 (s, br, 1H; OH), 6.98 (d, br, J=8.4, 2H; arom.), 6.65 (d, br, J=8.4, 2H; arom.), 5.32 (s, br, 1H; OH), 3.00 (dd, J=12.3 and 8.5, 1H), 2.73 (dd, J=8.5 and 6.3, 1H), 2.36 (dd, J=12.3 and 6.3, 1H), 2.15 (s, 6H, 2×Me), 1.7–0.8 (m, 10H, c-hex).

EXAMPLE 6

Preparation of O-desmethyl-venlafaxine Free Base

A 12 L multi-necked flask, equipped with a mechanical stirrer, a thermometer, a 1 L pressure equalizing dropping funnel, and a Claisen distillation head equipped with a downward condenser attached to a 5 L receiver with a vacuum take-off, was placed in a heating mantle. The system was purged with nitrogen and a nitrogen atmosphere was maintained. The distillation flask was charged with 4.00 L (4.00 mol, 5.55 molar excess) of 1 M L-selectride. The dropping funnel was charged with a solution of 200.00 g (0.720 mol) of venlafaxine base in 0.6936 kg (800 mL) of anhydrous 1,2-dimethoxyethane while maintaining the nitrogen atmosphere. The solution of venlafaxine base was added to the stirred L-selectride solution over a period of 15 minutes using rinses of 1,2-dimethoxyethane (2×400 mL, 2×0.3468 kg). Hydrogen was vented and bubbled through a dispersion tube into water. No significant temperature change occurred during the addition.

The dropping funnel was replaced with a similar 4 L funnel charged with 2.4276 kg (2800 mL) of anhydrous 1,2-dimethoxyethane. The system was again purged with nitrogen and a nitrogen atmosphere was maintained. The solution was heated and distilled at atmospheric pressure until the liquid level reached the 4 L mark and the reaction flask temperature was 84–85° C. While distilling, 2.4276 kg (2800 mL) of 1,2-dimethoxyethane was added dropwise at a rate which maintained the liquid level at the 4.00 L level until the temperature in the reaction flask reached 93–94° C. A crystalline precipitate was observed. The distillate was discarded.

The stirred slurry of crystals was cooled to 90° C., the stirrer was stopped, and the dropping funnel and distillation equipment was removed. The flask was then equipped with a reflux condenser fitted with a nitrogen inlet. The system was purged with nitrogen and a nitrogen atmosphere was maintained. The slurry was stirred and heated at reflux under a nitrogen atmosphere for about 19 hours. The initial temperature of the slurry at reflux was 94–96° C. and the final temperature was 97° C. Copious crystallization occurred. The slurry was cooled to room temperature.

12 L of distilled water in a 20 L Duran flask was purged with nitrogen to remove oxygen and carbon dioxide. The purging was repeated as necessary. This water is hereinafter referred to as "nitrogen purged distilled water".

The heating mantle was removed and replaced with an ice/water bath to bring the temperature of the reaction mixture to near room temperature. The flask was equipped with a 1000 mL pressure equalizing dropping funnel. The stirred reaction mixture was cooled with an ice/alcohol bath to obtain a temperature of 15–20° C. While the nitrogen atmosphere was maintained, the reaction mixture was quenched by dropwise addition of 0.296 kg (296 mL) of the nitrogen purged distilled water. The addition was controlled so as to maintain the temperature below 25° C. The temperature rose to 15–24° C. as a result of an exotherm. The mixture was stirred at ambient temperature for about 1 hour. A thick gel-like precipitate, which was formed initially, was converted into a crystalline precipitate during this period. While the reaction mixture was maintained in the nitrogen atmosphere, the flask was equipped with a Claisen distillation head, a downward condenser with a vacuum take-off and a 5 L receiving flask chilled in an ice/water bath. The stirred reaction mixture was distilled under pump vaccum (109–134 mm Hg) down to the 2.80 L mark at a distillation flask temperature of 25–38° C. The distillate was discarded. 3.00 kg (3000 mL) of nitrogen purged distilled water was added.

The stirred mixture was distilled under pump vacuum (113–187 mm Hg) down to 2.80 L at a distillation flask temperature of 35–50° C. to form a biphasic mixture. The distillate (Distillate A) was discarded by the Waste Treatment procedure described below. The warm biphasic mixture (35–40° C.) was transferred to a 4 L separatory funnel using rinses of 600 mL of nitrogen purged distilled water and 0.5296 kg (600 mL) of toluene. The two phases were mixed and then allowed to separate. A small quantity of solid at the interface was discarded. The aqueous layer was extracted consecutively with toluene (2×0.5196 kg, 2×600 mL) and heptane (0.5472 kg, 800 mL). The organic phases (Extract A) were discarded by the Waste Treatment procedure described below. A sufficient amount of nitrogen purged distilled water was added to the aqueous layer to achieve a volume of 3.60 L.

A 12 L multi-necked flask was equipped with a mechanical stirrer, a thermometer, and a condenser with a nitrogen inlet. The flask was purged with nitrogen and a nitrogen atmosphere was maintained in the flask.

The 3.60 L aqueous layer was transferred to the empty 12 L flask. The stirred solution was cooled under nitrogen to 10–15° C. with an ice/water bath. From a 1000 mL pressure equalizing dropping funnel, 410 mL of 12 N hydrochloric acid was added dropwise to the stirred solution while maintaining the temperature at 10–15° C. with the ice/water bath and until a pH of 3.5±0.2 was reached. A small precipitate was formed.

The resulting suspension was filtered through a Celite pad on polypropylene cloth in a 19 cm Buchner funnel into a 5 L multi-necked flask equipped with a mechanical stirrer, a thermometer, a condenser with a nitrogen inlet and a 1000 mL pressure equalizing dropping funnel. The filter pad was washed with 300 mL of nitrogen purged distilled water.

The filter funnel was removed. The system was flushed with nitrogen and again maintained in a nitrogen atmosphere. To the stirred solution, 76 mL of 10 N sodium hydroxide was added from the dropping funnel until a pH of 9.6±0.2 was reached. The resulting slurry of crystals was cooled to 5–10° C. and the slurry of crystals was maintained at 0–5° C. for about 1 hour.

The solid was collected on a polypropylene cloth in a 19 cm Buchner funnel. The filter cake was washed with 3×200 mL of nitrogen purged distilled water. The filtrate was discarded.

A 12 L multi-necked flask was equipped with a mechanical stirrer, a thermometer, and a condenser with a nitrogen inlet. The flask was purged with nitrogen and a nitrogen atmosphere was maintained in the flask. The flask was charged with 3000 mL of nitrogen purged distilled water and cooled to 15–20° C. with an ice/water bath. The solids collected on the polypropylene cloth were added to the stirred water in the flask and stirred at 15–20° C. until a smooth suspension was obtained (about 30 minutes).

The solid was collected on a polypropylene cloth in a 19 cm Buchner funnel using 600 mL of nitrogen purged distilled water to complete the transfer. The filter cake was washed with water (3×300 mL) and filtered. A dam was formed on top of the filter with a sheet of latex rubber and an aspirator vacuum was applied to the filter flask for about 5 hours. The white solid was dried in a vacuum oven under oil pump vacuum at 80° C. for about 18 hours. The solid was crushed and re-dried if necessary to constant weight. The yield was 90.7% (172.3 g) (HPLC Analysis: Strength or Purity (w/w): 98.8%, Impurities (excluding inorganics) (w/w): 0.046%, Ash (inorganics) (w/w): 0.14%).

Waste Treatment

The waste to be discarded contained byproducts, such as tris(1-methylpropyl)-borane and tris(1-methylpropyl)-boroxin. A 22 L or 50 L multi-necked flask was equipped with a mechanical stirrer, a thermometer, and a condenser with a nitrogen inlet. The flask was purged with nitrogen using a Firestone valve and a nitrogen atmosphere was maintained in the flask.

Distillate A and Extract A were combined in the flask to obtain a biphasic mixture (4.00 L with 400 mL of an aqueous bottom phase) under a nitrogen atmosphere. The stirrer was started and 600 mL of 10 N sodium hydroxide and 600 mL of water were added. A slurry of sodium perborate tetrahydrate (1.848 kg, 12.01 moles, ~3 equivalents per mole of tris(1-methylpropyl)borane) in 12 L of water was added in portions with ice/water cooling over about 20 minutes to maintain the temperature at 28–38° C. After the exotherm had subsided, the mixture was stirred at 22–23° C. under a nitrogen atmosphere for about 18 hours. The solid dissolved and two liquid phases remained.

The stirrer was stopped and the phases were allowed to separate. The upper phase was examined by gas chromatography/mass spectrometry to determine if any tris (1-methylpropyl)borane or tris(1-methylpropyl)boroxin was still detectable. If any was detected, 80 g (0.52 mol) of sodium perborate was added as a slurry in 400 mL of water and the solution was stirred at 22–23° C. for about 18 hours. Once tris(1-methylpropyl)borane and tris(1-methylpropyl) boroxin were no longer detectable in the upper phase, the aqueous phase was checked for its oxidizing capability (for example, due to peroxides and excess sodium perborate) with starch iodide paper.

The phases of the solution were then separated. The top organic layer was combined with other organic waste from the synthesis to be discarded. The aqueous layer was combined with other aqueous waste from the synthesis to be discarded.

The following procedures were used in the Examples 7–11 below.

X-Ray Powder Diffraction

XRPD analyses were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer using Cu Kα radiation. The instrument is equipped with a fine focus X-ray tube. The tube power and amperage were set at 40 kV and 40 mA, respectively. The divergence and scattering slits were at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a Nal scintillation detector. A theta-two theta continuous scan at 3°/min (0.4 s/0.02° step) from 2.5 to 40° 2θ was used. A silicon standard was analyzed each day to check the instrument alignment.

In cases where preferred orientation [vide infra] occurred during X-ray powder diffraction, the ODV succinate was sometimes placed between folded weighing paper, then ground with an agate pestle and re-analyzed by XRPD.

Thermogravimetric Analysis (TGA)

Thermogravimetric analysis was conduct on a TA Instruments 2950 thermogravimetric analyzer. The calibration standards were nickel and Alumel™. Approximately 8–20 mg of sample were placed in the pan, accurately weighed, and inserted into the TG furnace. The samples were heated under nitrogen at a rate of 10° C./min, up to a final temperature of 300° C. Weight derivative (%/° C.) was used to determine total weight loss between 40° C. and the temperature at which the derivative was zero (usually 150° C.). The results of TGA for Examples 8–12 below are shown in FIG. **8**.

Different Scanning Calorimetry

DSC analyses were carried out on a TA Instruments differential scanning calorimeter 2920. Approximately 3–5 mg of sample was placed into a DSC pan, and the weight accurately recorded. The pan was hermetically sealed. Each sample was heated under nitrogen at a rate of 10° C./min, up to final temperature of 250° C. Indium metal was used as the calibration standard. Reported DSC temperatures are at the transition maxima. The results of DSC for Examples 8, 9, 11, and 12 below are shown in FIG. **6**.

DSC Glass Transition

For studies of the glass transition temperature (T_g) of the amorphous material, the sample was heated under nitrogen at a rate of 10° C./min up to a final temperature of 250° C. The sample pan was hermetically sealed.

EXAMPLE 7

Preparation of Form I of ODV Succinate

A 5 L multi-necked flask, equipped with a stirrer, a thermometer, and a condenser, with a nitrogen inlet attached to a Firestone valve were placed in a heating mantle. The system was purged with nitrogen and a nitrogen atmosphere was maintained. 1.668 kg (2111 mL) acetone and 0.667 kg (667 mL) water were charged into the flask. The stirrer was started and 0.250 kg (0.949 mol) O-desmethyl-venlafaxine free base (prepared as described in Example 6) were added. The suspension was stirred for 30 minutes. 0.1155 kg (0.978 mol) succinic acid were added and the transfer was completed with rinses of acetone (0.186 kg, 236 mL) and water (0.075 kg, 75 mL). The suspension was stirred, warmed to 60° C. (±30° C.), and maintained at 60° C. (±3° C.) while being stirred for 30–60 minutes. A clear to cloudy solution was obtained. The mixture was then filtered through a filter comprised of polypropylene cloth with a filter paper underlay into a 5 L multi-necked flask equipped with a mechanical stirrer, a thermometer, and a condenser fitted with a vacuum outlet. The filter funnel was rinsed with warm (50–60° C.) aqueous acetone (24:76 v/v, 427 mL). The system was purged with nitrogen and the solution was cooled to 30–35° C. to induce crystallization. The stirred slurry of crystals was maintained at that temperature for about 4 hours. The stirred slurry of crystals was cooled to 0–5° C. and maintained at that temperature for about 1 hour. The crystals were collected on a polypropylene cloth filter with a filter paper underlay in a 15 cm funnel. The filter cake was washed with cold (0–5° C.) aqueous acetone (24:76 v/v, 2×300 mL) and filtered for 5 minutes. A dam was formed on top of the filter with a sheet of latex rubber. An aspirator was applied to the filter cake for 1 hour. The weight of the filter cake was about 0.351 kg. The product was dried under vacuum (50 mm Hg) at 30±5° C. for 12 hours. The product was then dried under vacuum (50 mm Hg) at 45±5° C. for 24 hours.

An XRPD of the ODV succinate is shown in FIG. 1.

Alternative Preparation of Form I of ODV Succinate

A 5 L multi-necked flask equipped with a stirrer, a thermometer, and a condenser with a nitrogen inlet attached to a Firestone valve are placed in a heating mantle. The system is purged with nitrogen and a nitrogen atmosphere was maintained. 1.651 kg (2090 mL) acetone and 0.660 kg (660 mL) water are charged into the flask. The stirrer is started and 0.250 kg (0.949 mol) O-desmethyl-venlafaxine free base (prepared as described in Example 6) are added. The suspension is stirred for 30 minutes. 0.1155 kg (0.978 mol) succinic acid are added. The suspension is stirred, warmed to 60° C. (±3° C.), and maintained at 60° C. (±3° C.) while being stirred for 30–60 minutes. The mixture is then filtered through a filter comprised of Celite on polypropylene cloth with a filter paper underlay into a 5 L multi-necked flask equipped with a mechanical stirrer, a thermometer, and a condenser fitted with a vacuum outlet. The filter funnel is rinsed with warm (50–60° C.) aqueous acetone (24:76 v/v, 427 mL). The system is purged with nitrogen and the solution is cooled to 30–35° C. to induce crystallization. The stirred slurry of crystals is maintained at that temperature for about 4 hours. The stirred slurry of crystals is cooled to 0–5° C. and maintained at that temperature for about 1 hour. The crystals are collected on a polypropylene cloth filter with a filter paper underlay in a 15 cm funnel. The filter cake is washed with cold (0–5° C.) aqueous acetone (24:76 v/v, 2×300 mL) and filtered. A dam for the filter cake is formed with a sheet of latex rubber. An aspirator is applied to the filter cake for 1 hour. The weight of the wet cake is about 0.351 kg. The product is dried under vacuum (50 mm Hg) at 30±5° C. for 12 hours. The product is then dried under vacuum (50 mm Hg) at 45±5° C. for 24 hours. The yield was 85.8% (325.2 g) (HPLC Analysis: Impurities (excluding inorganics) (w/w): 0.0%, Ash (inorganics) (w/w): 0.0%, Amount of any single impurity (w/w):<0.01%).

EXAMPLE 8

Preparation of Form II of ODV Succinate

Form II was prepared by dissolving 306.1 mg of Form I in 200 ml acetone, filtering the solution through a 0.2 um

nylon disc followed by vacuum stripping the filtrate on a rotary evaporator at ambient temperature.

An XRPD of the ODV succinate is shown in FIG. **2**.

EXAMPLE 9

Preparation of Form III of ODV Succinate

Form III was prepared using two different milling techniques. In the first technique, ball-mill grinding, 290.2 mg of Form I was measured into a stainless steel cylinder with a ball, the sealed container was placed on a Retsch Mixer and milled for five minutes at a frequency of 30/s. At the end of the cycle, a spatula was used to scrape material from the walls. The procedure was repeated three times for a total mill time of 20 minutes. In the second technique, cryo-grinding, 40.5 mg of Form I was charged to a stainless steel cylinder with a rod, the sealed container was then placed in a SPEX Freezer mill maintained at −96 degrees Celsius with liquid nitrogen. The material was milled for two minutes at a frequency of 10/s (20 impacts per second), then cooled for two minutes. The procedure was repeated two times for total mill time of six minutes.

An XRPD of the ODV succinate is shown in FIG. **3**.

EXAMPLE 10

Preparation of Form IV of ODV Succinate

Form IV was prepared in the following manner: A mixture of equal amounts of Form I and Form II was charged to a saturated, 0.2 um-filtered solution of acetonitrile-ODV succinate at 54 degrees Celsius. The mixture was agitated for a period of eight days. The slurry was filtered and the recovered solids air-dried. The solids were then charged to a 2-dram scintillating vial and heated for eighteen hours at 120° C.

An XRPD of the ODV succinate is shown in FIG. **4**.

EXAMPLE 11

Preparation of Amorphous Form of ODV Succinate

The amorphous form of ODV succinate was prepared by charging a mixture of 854.1 mg of Forms I and II to an open, 20-ml scintillating vial and then placing the vial in a 150° C. oil bath for about 18 minutes.

An XRPD of the ODV succinate is shown in FIG. **5**. According to DSC, the T_g onset occurs at 18° C.

EXAMPLE 12

Preparation of Form II of ODV Succinate

56 g of O-desmethyl-venlafaxine, 26 g of succinic acid, 112 g of acetone, and 112 g of purified water were charged into a container. The resulting slurry was heated to reflux (about 62° C.) until a solution formed. The solution was cooled slightly and 1.2 g of charcoal 2S was charged. The solution was refluxed for about 15 minutes. The solution was filtered through a Seitz filter and the filter cake was washed with 5 g of acetone. The hot solution was then charged into a bulb equipped with a reflux condenser. A vacuum was applied from the top of the condenser. The solution began to boil and crystallize. The solution was stirred. The vacuum was applied until the slurry reached 20° C. The solution was cooled with an external ice bath to 5° C. The crystals were isolated by suction filtration. The filter cake was washed with a mixture of 11 g of purified water and 45 g of acetone. Air was sucked through the cake for about 2 hours. About 70 g of ODV succinate was formed.

Alternative Preparation of Form II of ODV Succinate by Fast Crystallization

A 2 L 4-neck flask was charged with O-desmethyl-venlafaxine (75.0 g, 0.285 mol), acetone (627 mL), succinic acid (34.50 g, 0.29 mol), and water (197.5 mL). The suspension was warmed to 60° C. and filtered through a pad of Celite. The filter pad was washed with a warm mixture of acetone (97 mL) and water (30.6 mL). The filtrate was transferred to a clean 2 L flask rinsing with acetone (50 mL). The temperature of the solution was 28° C. The solution was allowed to cool and crystallization began at 23° C. The mixture was then rapidly cooled in an ice/water bath to 0–5° C. The mixture was stirred at 0–5° C. for 2 hours. The solids were isolated by filtration and washed with cold aqueous acetone (2×200 mL, 25:75 v/v water/acetone). The wet filter cake was dried in a vacuum oven at 35±5° C. (50 mm Hg) for 48 hours to yield ODV succinate monohydrate as white crystals (89.5 g, 78.7%).

^{1}H NMR (300 MHz, DMSO-d_6) 10–9 (bs, 2H), 7.00 (d, J=8.2 Hz, 2H), 6.65 (d, J=8.2 Hz, 2H), 3.4–3.2 (bs, 1H), 3.12 (dd, J=7.0, 12.2 Hz, 1H), 2.74 (t, J=8.7 Hz, 1H), 2.7–2.58 (m, 1H), 2.50 (s, 3H), 2.36 (s, 3H), 2.28 (s, 4H), 1.50–1.25 (m, 6H), 1.20–0.80 (4H).

EXAMPLE 13

Rat Jejunal Test

The rat intestine perfusion technique is a direct way to measure the regional absorption properties of a test compound in the gastrointestinal tract. Rat intestinal permeability coefficient (Peff) can be used to predict human in vivo oral absorption of passively absorbed compounds. Fagerholm, M. Johansson, and H. Lennernäs, "Comparison between permeability coefficients in rat and human jejunum", *Pharm. Res.*, 13, 1996, 1336–1342, have demonstrated a good correlation between rat Peff and human fraction of dose absorbed (Fa) for a series of compounds. Meanwhile, some other characteristics such as formulable Maximum Absorbable Dose (MAD), FDA Biopharmaceutical Classification, etc. can also be estimated.

Materials

Perfusion buffer (PB) consisted of KCl (5.4 mM), NaCl (48 mM), Na_2HPO_4 (28 mM), NaH_2PO_4 (43 mM), mannitol (35 mM), polyethylene glycol (PEG)-4000 (0.1%, w/v), glucose (10 mM). The pH was adjusted to 6.8 with NaOH and osmolarity was adjusted to 290+10 mOsm/l with 1.0 M NaCl. Before the experiment, ^{14}C-PEC-4000 (0.02 μCi/mL), 3H-mannitol (0.025 μCi/mL), metoprolol (20 μg/mL), and ODV succinate or fumarate (50 μg/mL) were added.

Rats used in this study were Charles River CD males, ranging in weight from approximately 300–350 grams.

Internal Standard Compounds

Metoprolol (a well-absorbed and passively transported compound) was used as a standard and tested simultaneously along with the ODV compounds. Glucose (a well-absorbed and actively transported compound) was used to monitor the physiological functionality of the intestinal barriers. ^{14}C-labeled PEG-4000 was used as a non-absorbable marker to describe the water flux across the intestinal wall. ^{3}H-labeled mannitol was used as a paracellularly transported marker to indicate the integrity of the intestinal tight junctions.

Analytical Methods

All chemicals were of analytical grade. After each experiment, all the analytic assays were performed

promptly. For isotope determinations, 0.5 mL of perfusate sample containing ^{14}C PEG-4000 and ^{3}H-mannitol was mixed with 5 mL of scintillation cocktail. Radioactivity was counted in a liquid scintillation counter (Wallac 1409). Glucose concentration was determined by the glucose oxidase method (Biochemistry Analyzer). Metoprolol and the ODV compounds were analyzed by HPLC-UV/Vis (HP-1100 with a diode-array detector), using a YMC AQ 120 μ, 5 μ, 150×4.6 mm column and step gradient mobile phase containing water/0.1% TFA and acetonitrile. The ODV compounds and metoroplol were detected at 226 and 272 nm UV wavelength, respectively. Blank perfusate was assayed to evaluate the interference at these chromatographic conditions.

In Situ Rat Jejunal Perfusion

The perfusions were performed in three intestinal sections of anesthetized rats: duodenum-jejunum, ileum, and colon. The lengths of the segments were approximately 10–12 cm for small intestine segments and 5–6 cm for colon segments. An inflow cannula was inserted at the proximal end and an outflow cannula was inserted at the distal end. Perfusate was pumped through the segment at 0.19 mL/min, and collected at 20, 40, 55, 70, 85 and 100 minutes.

ODV succinate or fumarate was added to the perfusion working buffer at a concentration of 50 μg/mL, which is approximately equivalent to a 200 mg human does. The disappearance rates of ODV compound, metoprolol, and glucose were determined from each collection interval by comparing to the initial compound solution remaining in the syringe at the end of the 100 minutes. This is to correct for any losses due to binding to the syringe or tubing. Meanwhile, drug concentration in perfusate samples were corrected for water influx/efflux, which was computed, based on ^{14}C-PEG-4000 concentration changes.

Data Analysis

a. Recovery and Water Flux

Recovery of ^{14}C-PEG-4000 was determined to provide information on the integrity of the perfused intestinal segment:

$$\%\ PEG_{rec}=(\Sigma PEG_{out}/\Sigma PEG_{in})*100$$

Overall ^{14}C-PEG-4000 recovery was calculated and any data for which the individual recovery fell outside of the range of 96%–103% was excluded from the data set. Values below this range would indicate tissue damage that allows passage of PEG-4000 outside of the perfused segment, while values above this range would indicate significant water movement out of the segment.

Water movement across the gut wall was determined by calculation of net water fluid:

$$\text{Net Water Flux } (NWF)=[(1-PEG_{out}/PEG_{in})*Q]/L$$

where PEG_{out} and PEG_{in} are the amount of radioactivity (dpm) of ^{14}C-PEG-4000 in inlet and outlet sides of the perfused intestinal segment, respectively; Q is the flow rate of perfusate; and L is the length of perfused segment (cm).

b. Peff Calculation

The presence of the ODV compound in the perfusate was determined by HPLC. The amount of drug present at each time point was corrected for water movement across the wall of the intestine:

$$C_{out,corr}=C_{out}*(PEG_{in}/PEG_{out})$$

where C_{out} is the concentration of drug in outlet perfusate; $C_{out,corr}$ is the concentration of drug in outlet perfusate corrected for water moving in or out of the segment, as determined by the recovery of ^{14}C-PEG-4000.

Effective intestinal permeability, Peff (cm/sec), was determined by the following equation:

$$Peff=[Q*(C_{in}-C_{out,corr})/C_{in}]/2\ \pi rL$$

where Q is the flow rate; C_{in} is the concentration of drug in inlet perfusate; 2 πrL is the inner surface area of the perfused segment, with r assumed to be 0.18 cm in the rat (see G. Amidon, H. Lennernäs, V. Shah, J. Crison. "A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability." *Pharm. Res.* 12, 1995, 413–420) and L the length of the perfused segment (cm).

c. Fraction Absorbed (Fa)

The fraction of dose absorbed, Fa, in human is currently predicted from (Fagerholm, M. ibid:

$$Fa=100*(1-e^{-(2*(\alpha*Peff,rat+\beta)*(tres/r)})$$

where α and β are the correction factors, tres is the residence time in human small intestine; and r is the radius of the human small intestine.

d. Maximum Absorbable Dose (MAD)

The maximum absorbable dose, MAD, in humans can be calculated as:

$$MAD = ka*\int_0^{} Cs*V*dt$$

$$MAD = ka*Cs*V_0*tres$$

$$=(2*Peff,\ h/r)*Cs*V_0*tres$$

where ka is a first-order absorption rate constant; tres is the residence time in a human small intestine; r is the radius of the human small intestine, and V_o is the estimated volume of fluid present in the gastrointestinal tract. See Johnson, K. C., Swindell, A. C. "Guidance in setting of drug particle size specifications to minimize variability in absorption". *Pharm. Res.* 13(2), 1996, 1795–1798).

Results

Stability in Jejunal Fluids

The stability of ODV succinate or fumarate in the solutions of blank perfusion buffer (Pβ), and jejunal fluids (perfusion buffer collected by washing the isolated jejunal segment, pH=6.8) was determined at 37° C. for up to 6 hours. The results indicated than no apparent degradation/metabolism of these two salt forms was evident under these test conditions. The results for ODV Succinate are presented in Table 7 below. Similar data was obtained for ODV fumarate.

TABLE 7

Incubation Time (hours)	Blank Perfusion Buffer[1] (ODV Succinate)	Intestinal fluid[1,2] (ODV Succinate)
0	100.0	100.0
2	99.9	99.6
3	100.3	99.8
6	99.9	100.1

[1]The data is the relative percentage remaining (%) of HPLC peak area at different time points over time zero.
[2]Total protein concentration approximately 0.2 mg/ml.

Rat Jejunal Perfusion Results

Site-specific absorption of ODV succinate

The Peff values for ODV succinate in the small intestine ($0.912\pm0.067\times10^{-5}$ cm/sec in duodenum-jejunum, $1.73\pm0.22*10^{-5}$ cm/sec in ileum) were lower than metoprolol's Peff values. The Peff value of ODV succinate in the colon was found to be $0.062\pm0.031\times10^{-5}$ cm/sec, which is about 10% of metoprolol's Peff value in the colon. The ileum segment seems to be the best absorption site for ODV

succinate. The Peff's ratio of duodenum-jejunum vs. ileum vs. colon was found to be 1.00:1.90:0.07, indicating that small intestinal sites of duodenum, jejunum, and ilcum predominate the oral absorption of this compound (μ90%) for an IR dosage form. (Dongzhou Liu, S. Ng, R. Saunders, "Effect of Polysorbate 80 on Transport of Mannitol, Glucose, and Water Flux in Rat Small Intestine", *PharmSci.*, 2, 2000; Doungzhou Liu, S. Ng, R. Saunders. "Investigating Intestinal Uptake of Zaleplon in site and Simulating/Predicting Oral Absorption in vivo", Submitted to *Pharm-Sci.* 3(4), 2001).

Based on this experimental Peff, the human in vivo Fa of ODV succinate was predicted to be in the range of 60–77% in the small intestine and a Fa of 20% in the colon, as shown in FIGS. **9** and **10** and Table 8 below. The delivery vehicle was perfusion buffer (pH=6.8). The test at each absorption site was repeated with 3 rats and the Peff values were averaged.

TABLE 8

Rat Perfusion Data of ODV Succinate (50 μg/ml)

Absorption Site	$Peff_{ODV\ Succinate}$ (10^{-5} cm/sec)	$Peff_{Meloprolol}$ (10^{-5} cm/sec)	$Peff_{ODV\ Succinate}/Peff_{Meloprolol}$	Fa (%) (predicted human in vivo)
Jejunum	0.912 ± 0.067	2.50 ± 0.11	0.37 ± 0.04	61.3 ± 2.5
Ileum	1.73 ± 0.22	3.22 ± 0.07	0.54 ± 0.07	76.6 ± 3.8
Colon	0.062 ± 0.031	0.583 ± 0.087	0.12 ± 0.07	16.4 ± 3.4

An estimated maximum absorbable dose (MAD) was generated based on the rat data. The MAD of ODV succinate in the entire gastrointestinal (GI) tract (human) was estimated to be about 8.6 grams, which is the sum of 2236 mg in the duodenum-jejunum, 5629 mg in the ileum, and 683 mg in the colon.

Site-specific absorption of ODV fumarate

The site-specific absorption of ODV fumarate was investigated under the same study conditions as ODV succinate (50 μg/ml in pH 6.8 perfusion buffer). The test at each absorption site was repeated with 3 rats (except for in the Jejunum, where only 2 rats were tested) and the Peff values were averaged. The results are shown in Table 9 below and FIGS. **11**, **12**, and **13**.

Rat Perfusion Data of ODV Fumarate (50 μg/ml)

Absorption Site	$Peff_{ODV\ Fumarate}$ (10^{-5} cm/sec)	$Peff_{Meloprolol}$ (10^{-5} cm/sec)	$Peff_{ODV\ Fumarate}/Peff_{Meloprolol}$	Fa (%) (predicted human in vivo)
Jejunum	0.245 ± 0.237	1.78 ± 0.93	0.09 ± 0.08	30.6 ± 20.0
Ileum	0.678 ± 0.295	53	0.19 ± 0.06	44.7 ± 11.4
Colon	0	11	0	0

In general, the results show that ODV fumarate was less absorbed than ODV succinate in the rat GI tract. In the small intestine, the Peff values of the fumarate salt (0.24–0.68× 10^{-5} cm/sec) were only about 27 μ40% of the succinate's Peff values. In the colon, no measurable absorption of ODV furmarate was found.

The in vivo Fa of ODV fumarate was estimated to be in the range of 33–45% in the small intestine and 0 in the colon, indicating an overall low absorption of this compound in the entire GI tract. The MAD was predicted to be about 440 mg.

The results of the site-specific intestinal absorption of ODV succinate and ODV fumarate show that ODV succinate has better absorption in the small intestine and in the colon than ODV fumarate. Several publications have demonstrated that there is high correlation between the rat perfusion model and in vivo human absorption (see e.g., Doungzhou Liu, S. Ng, R. Saunders. "Investigating Intestinal Uptake of Zaleplon in site and Simulating/Predicting Oral Absorption in vivo", Submitted to *PharmSci.* 3(4), 2001).

EXAMPLE 14

Bioavailability of O-desmethyl-venlafaxine in Beagle Dogs

Test Formulations

An intravenous solution containing 25 mg/mL of Form I of ODV succinate was prepared by mixing 3.8168 g (2.5% w/v) of the ODV succinate in a sufficient amount of water for injection, USP to obtain 100 mL of solution.

An oral solution containing 25 mg/mL of Form I of ODV succinate was prepared by mixing 3.8170 g (2.5% w/v) of the ODV succinate in a sufficient amount of water for injection, USP to obtain 100 mL of solution. Prior to administration, the oral solution (25 mg/mL) was diluted to a concentration of 7.5 mg/mL with water.

Tablets each containing the ingredients listed in the table below were prepared by the method described in Example 15 for preparing ODV Succinate Formulation #2.

Ingredient	mg per tablet	% w/w
ODV Succinate (Form I was used in the preparation)	116.70 (75.00 as free base)	39.2
HPMC 2208 USP 100, 100 SR	175.05	58.8
Magnesium Stearate	5.95	2.0
Purified Water USP	q.s.	q.s.
Total	297.70	100.0

Capsules (HGC Size 0) each containing the ingredients listed in the table below were prepared by the method described in Example 15 for preparing ODV Succinate Formulation #1.

Ingredient	mg per tablet	% w/w
ODV Succinate (Form I was used in the preparation)	116.70 (75.00 as free base)	39.5
Microcrystalline Cellulose (Avicel PH200)*	177.26	60.0
Magnesium Stearate	1.48	0.5
Total	295.44	100.0

*Available from FMC BioPolymer of Philadelphia, PA.

Study Animals

Six male beagle dogs with body weights ranging between 10.2 and 16.0 kg were used in this study. The dogs were housed and given free access to water and food.

Study Design

The six dogs were dosed in a 4 period study. In Period 1, the dogs received 1 mL of the intravenous solution. In Period 2, the dogs received 10 mL of the oral solution. In Period 3, the dogs received the tablet. In Period 4, the dogs received the capsule. There was a one week wash out period between the first two treatment periods and a one month wash out period between treatment periods 2 and 3. Between periods 3 and 4, there was a one week wash out period. For periods 1 and 2, all dogs were fasted overnight with free access to water and fed after the four-hour bleeding. For periods 3 and 4, all dogs were fed 30 minutes prior to dosing and with free access to water.

Blood Samples

In periods 1 and 2, blood samples were drawn from the jugular vein at 0 (predose), 0.05 (intravenous only) and 0.13 (intravenous only), 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 32, and 48 hours after dosing into 5 mL heparinized vacutainers and immediately placed on ice. In periods 3 and 4, blood samples were drawn from the jugular vein at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 32 hours after dosing into 5 mL heparinized vacuatiners and immediately placed on ice. Plasma was separated in a refrigerated centrifuge and stored at −70° C. Plasma samples were then assayed.

Sample Analysis

Plasma O-desmethyl-venlafaxine concentrations were determined by the HPLC method using mass spectrometric detection described in Hicks, D. R., Wolaniuk, D., Russel, A., Cavanaugh, N., Kraml, M., "A high-performance liquid chromatographic method for the simultaneous determination of venlafaxine and O-desmethylvenlafaxine in biological fluids", *Ther. Drug Monit.* 16:100–107 (1994), which is hereby incorporated by reference. Based on a 0.2 mL sample volume, the method has a limit of quantitation for O-desmethyl-venlafaxine of 5.05 ng/mL. Total O-desmethyl-venlafaxine levels were determined after incubating 0.2 mL of plasma samples in β-glucuronidase for ~18 hours. O-desmethyl-venlafaxine-glucuronide levels were determined by subtracting the O-desmethyl-venlafaxine (separate extraction procedure without the use of β-glucuronidase and analyzed by HPLC-MS) concentrations from the total O-desmethyl-venlafaxine concentrations.

Data Analysis

Noncompartmental pharmacokinetic parameters were calculated from the individual dog plasma O-desmethyl-venlafaxine and O-desmethyl-venlafaxine-glucuronide concentration-time profiles. Area under the plasma concentration-time curves ($AUC_{0-\mu}$) values were calculated by the addition of AUC_{Last} (AUC_{Last}=the linear trapezoid rule from time zero to the last measurable plasma concentration, CP_{Last}) and CP_{Last}/lambda. The values for lambda were determined from the long-linear portion of the terminal slope of the plasma O-desmethyl-venlafaxine and O-desmethyl-venlafaxine-glucuronide concentration-time profile after the intravenous dose. The half-life (t_{half}) was calculated as t_{half}=0.693/lambda. The peak plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were noted directly from the plasma concentration-time profiles.

Absolute bioavailability was determined by comparing the dose normalized $AUC_{0-\mu}$ values following the intravenous administration.

Results

All levels reported as below limit of quantitation (BLQ) were assigned a value of zero for calculation purposes. The bioanalytical results demonstrated that O-desmethyl-venlafaxine-glucuronide levels account for the major portion of total circulating O-desmethyl-venlafaxine levels after the administration of ODV succinate.

Based on the total O-desmethyl-venlafaxine levels, the absorption of O-desmethyl-venlafaxine and ODV succinate is essentially complete from the oral formulation with 121%, 103% and 76% absolute bioavailability for the oral solution, capsule, and tablet formulations, respectively.

Mean (% CV) Bioavailability Parameters of ODV Succinate (Expressed as Free ODV Levels)

	Oral Solution (75 mg)	Capsule (75 mg)	Tablet (75 mg)	Intravenous Solution (25 mg)
AUC (ng*hr/mL)	835 (33)	904 (29)	677 (23)	746 (14)
C_{max} (ng/mL)	450 (23)	465 (37)	115 (24)	—
t_{max} (hr)	0.50 (55)	0.55 (68)	2.92 (35)	—
Absolute Bioavailability (%)	37 (25)	40 (17)	31 (24)	—

Mean (% CV) Bioavailability Parameters of ODV Succinate in Beagle Dogs Expressed as ODV-glucuronide Levels

	Oral Solution (75 mg)	Capsule (75 mg)	Tablet (75 mg)	Intravenous Solution (25 mg)
AUC (ng*hr/mL)	17349 (14)	13381 (14)	11686 (18)	4814 (11)
C_{max} (ng/mL)	3917 (33)	2633 (20)	1235 (15)	856 (20)
t_{max} (hr)	2.50 (22)	1.67 (24)	3.67 (14)	2.33 (22)
Absolute Bioavailability (%)	121 (13)	95 (9)	81 (11)	—

Mean (% CV) Bioavailability Parameters of ODV Succinate in Beagle Dogs (n = 6) Expressed as Total ODV Levels

	Oral Solution (75 mg)	Capsule (75 mg)	Tablet (75 mg)	Intravenous Solution (25 mg)
AUC (ng*hr/mL)	18184 (13)	14285 (13)	12362 (18)	5560 (9)
C_{max} (ng/mL)	4026 (32)	2841 (19)	1337 (15)	N/A

-continued

Mean (% CV) Bioavailability Parameters of ODV Succinate in Beagle Dogs (n = 6) Expressed as Total ODV Levels

	Oral Solution (75 mg)	Capsule (75 mg)	Tablet (75 mg)	Intravenous Solution (25 mg)
t_{max} (hr)	2.5 (22)	1.67 (24)	3.67 (14)	N/A
Absolute Bioavailability (%)	109 (13)	86 (7)	74 (12)	—

EXAMPLE 15

18 human subjects were given 75 mg each of Effexor® XR (venlafaxine formulation) (available from Wyeth-Ayerst Pharmaceuticals of St. Davids, Pa.), ODV succinate formulation #1, and ODV succinate formulation #2 over three different periods.

ODV succinate formulation #1, which is a capsule, is shown in the table below.

ODV Succinate Formulation #1

Ingredient	mg per tablet	% w/w
ODV Succinate (Form I was used in the preparation)	113.9 (75.00 as free base)	33.5
Lactose Fast Flow	112.2	33.0
Microcrystalline Cellulose (Avicel PH200)*	112.2	33.0
Magnesium Stearate	1.7	0.5
Purified Water	q.s.	q.s.
Total	340.0	100.0

ODV succinate formulation #1 was prepared as follows. The ODV succinate was sieved through a 400 micron screen and dry mixed with lactose and microcrystalline cellulose in a high shear mixer. The resulting mixture was wet granulated in a high shear mixer with purified water and dried in an oven or fluid bed drier. The mixture was blended with magnesium stearate and encapsulated in a capsule (HGC Size 0).

ODV succinate formulation #2, which is a tablet, is shown in the table below.

ODV Succinate Formulation #2

Ingredient	mg per tablet	% w/w
ODV Succinate (Form I was used in the preparation)	113.81 (75.00 as free base)	37.94
HPMC 2208 USP 100, 100 SR	170.44	56.81
Microcrystalline Cellulose (Avicel PH200)*	7.50	2.50
Talc	6.75	2.25
Magnesium Stearate	1.50	0.50
Purified Water	q.s.	q.s.
Total	295.44	100.0

*Available from FMC BioPolymer of Philadelphia, PA.

ODV succinate formulation #2 was prepared as follows. The ODV succinate was sieved through a 400 micron screen and dry mixed with HPMC, microcrystalline cellulose, and talc in a high sheer mixer. The mixture was then wet granulated with purified water and dried in an oven or fluid bed drier. The resulting mixture was blended with HPMC and talc. Magnesium stearate was added and the mixture was again blended. The mixture was then compressed into a tablet.

All doses were administered after subjects consumed a standardized medium-fat breakfast. Blood samples were taken 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 36, 48, and 72 hours after administration. The plasma concentrations of venlefaxine and O-desmethyl-venlafaxine in each blood sample was determined by the method described in Hicks, D. R., Wolaniuk, D., Russel, A., Cavanaugh, N., Kraml, M., "A high-performance liquid chromatographic method for the simultaneous determination of venlafaxine and O-desmethylvenlafaxine in biological fluids", *Ther. Drug Monit.* 16:100–107 (1994), which is hereby incorporated by reference.

The results are shown in the table below.

Plasma Concentrations of Venlafaxine*

Formulation	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC (ng*hr/mL)
Effexor ® XR				
Mean ± Stand. Dev.	40 ± 16	5.9 ± 0.5	9.5 ± 2.4	628 ± 265
% CV	39.9%	8.0%	25.6%	42.2%
Min–Max	11–77	4–6	4.8–13.8	139–1292

*Since ODV Succinate Formulations #1 and 2 do not include venlafaxine, the plasma concentrations of venlafaxine resulting from administration of them was zero.

Plasma Concentrations of O-desmethylvenlafaxine

Formulation	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC (ng*hr/mL)
Effexor ® XR				
Mean ± Stand. Dev.	88 ± 25	9.3 ± 2.9	13.2 ± 4.0	2430 ± 647
% CV	28.9%	31.2%	30.4%	26.6%
Min–Max	37–142	6–16	7.6–24.8	1582–3835
ODV Succinate Formulation #1				
Mean ± Stand. Dev.	282 ± 57	3.1 ± 1.3	9.4 ± 1.4	3491 ± 814
% CV	20.1%	43.0%	14.7%	23.3%
Min–Max	173–399	0.5–6	6.8–11.5	1667–5086
ODV Succinate Formulation #2				
Mean ± Stand. Dev.	135 ± 54	7.3 ± 5.5	9.3 ± 1.9	3185 ± 944
% CV	39.9%	75.4%	20.5%	29.6%
Min–Max	65–279	2–28	6.1–13.7	1100–4767

The table below shows the number of human subjects who experienced various adverse effects after administration of a singled dose of ODV Succinate Formulations #1 and 2.

Without being bound to any particular theory, it is believed that adverse effects observed with Formulation #1 are related to the peak blood plasma level and/or tmax of the formulation. By flattening the curve as in sustained release formulation, Formulation #2, the peak blood plasma level is reduced and the tmax delayed. Thus, in patients, as a flattened blood plasma concentration to time profile is achieved adverse event are reduced or eliminated. Thus, a

pharmaceutical composition comprising a sustained release formulation of ODV succinate having a peak blood plasma profile of less than about 225 ng/ml will have reduced side effects such as nausea and emesis.

Adverse Effects After Administration of a Single Dose of ODV Succinate Formulations #1 and 2

Adverse Effect	ODV Succinate Formulation #1 (n = 18)	ODV Succinate Formulation #2 (n = 18)
Nauseau (VAS > 5 mm)	10	1
Nauseau (VAS > 20 mm or spontaneous)	6	1
Vomiting	2	—
Diarrhea	1	—
Abdominal Pain	—	—
Headache	2	—
Vaso-vagal Malaise	2	—
Trismus	1	—

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

It is further to be understood that values are approximate, and are provided for description.

Patents, patent applications, publications, procedures, and the like are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties. To the extent that a conflict may exist between the specification and a reference, the language of the disclosure made herein controls.

What is claimed:

1. A compound which is O-desmethyl venlafaxine succinate.

2. The compound of claim **1**, wherein the compound is a hydrate of O-desmethyl venlafaxine succinate.

3. The compound of claim **2** which is O-desmethyl venlafaxine succinate monohydrate.

4. The compound of claim **1** wherein the salt is crystalline.

5. The compound of claim **4** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.20, 14.91, 20.56, 22.13, 23.71, 24.60, and 25.79.

6. The compound of claim **4** having an endotherm at about 131° C.

7. The compound of claim **4** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **1**.

8. The compound of claim **4** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 13.18, 14.04, 14.35, 14.66, 16.68, 17.67, 19.24, 25.13, and 31.78.

9. The compound of claim **8** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.25, 13.18, 14.04, 14.35, 14.66, 16.68, 17.67, 19.24, 20.38, 20.56, 23.41, 23.78, 24.57, 25.13, 25.80, and 31.78.

10. The compound of claim **4** having an endotherm at about 127° C.

11. The compound of claim **4** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **2**.

12. The compound of claim **4** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 13.74, 22.55, and 32.42.

13. The compound of claim **12** wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.36, 13.74, 14.40, 14.68, 14.96, 16.75, 17.48, 17.76, 19.26, 20.42, 20.74, 22.55, 23.58, 23.82, 24.92, 26.00, 31.86, and 32.42.

14. The compound of claim **4** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **3**.

15. The compound of claim **4**, wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 11.29, 17.22, 19.64, 20.91, 21.61, 28.86, 29.80, 30.60, 36.85, and 37.70.

16. The compound of claim **15**, wherein the compound exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.46, 11.29, 13.69, 14.48, 15.17, 16.62, 17.22, 17.61, 19.22, 19.64, 20.91, 21.61, 22.55, 23.84, 24.77, 25.34, 25.92, 26.40, 28.86, 29.80, 30.60, 33.17, 36.85, and 37.70.

17. The compound of claim **4** having an endotherm at 145° C.

18. The compound of claim **4** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **4**.

19. The compound of claim **1** wherein the compound is amorphous.

20. The compound of claim **19** having a T_g onset at 18° C.

21. The compound of claim **1** having an X-ray powder diffraction pattern substantially the same as that shown in FIG. **5**.

22. The compound of claim **1** having a solubility in water of at least 30 mg/ml at about 25° C.

23. A pharmaceutical composition comprising O-desmethyl venlafaxine succinate and a pharmaceutically acceptable carrier or excipient.

24. The pharmaceutical composition of claim **23** further comprising venlafaxine.

25. A pharmaceutical dosage form comprising a therapeutically effective amount of O-desmethyl venlafaxine succinate and a pharmaceutically acceptable carrier or excipient.

26. An oral dosage form comprising a therapeutically effective amount of O-desmethyl venlafaxine succinate and a pharmaceutically acceptable carrier or excipient.

27. The oral dosage form of claim **26**, wherein the dosage form is a tablet or capsule.

28. The oral dosage form of claim **26**, wherein the oral dosage form is a sustained release formulation.

29. The oral dosage form of claim **26**, further comprising a rate controlling polymer material.

30. The oral dosage form of claim **29**, wherein the rate controlling polymer material is selected from hydroxyalkyl celluloses, poly(ethylene) oxides, alkyl celluloses, carboxymethyl celluloses, hydrophilic cellulose derivatives, and polyethylene glycol.

31. The oral dosage form of claim **29**, wherein the oral dosage form comprises from about 30 to about 50% by weight of O-desmethyl-venlafaxine succinate and from about 40 to about 70% by weight of the rate controlling polymer material, based upon 100% total weight of oral dosage form.

32. The oral dosage form of claim 31, wherein the oral dosage form comprises from about 32 to about 44% by weight of O-desmethyl-venlafaxine succinate and from about 45 to about 66% by weight of the rate controlling polymer material, based upon 100% total weight of oral dosage form.

33. The oral dosage form of claim 26, wherein the oral dosage form further comprises a binder.

34. The oral dosage form of claim 33, wherein the binder is microcrystalline cellulose.

35. A method of treating a patient suffering from depression comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

36. A method of treating a patient suffering from anxiety comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

37. A method of treating a patient suffering from panic disorder comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

38. A method of treating a patient suffering from generalized anxiety disorder comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

39. A method of treating a patient suffering from post traumatic stress disorder comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

40. A method of treating a patient suffering from premenstrual dysphoric disorder comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

41. A method of treating a patient suffering from a condition selected from fibromyalgia, agorophobia, attention deficit disorder, obsessive compulsory disorder, social anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, borderline personality disorder, chronic fatigue syndrome, urinary incontinence, pain, Shy Drager syndrome, Raynaud's syndrome, Parkinson's disease, and epilepsy comprising providing to a patient in need thereof an effective amount of O-desmethylvenlafaxine succinate.

42. A method of enhancing cognition or treating cognitive impairment in a patient comprising providing to a patient in need thereof an effective amount of O-desmethyl-venlafaxine succinate.

43. A method for cessation of smoking or other tobacco uses in a patient comprising providing to a patient in need thereof an effective amount of O-desmethyl-venlafaxine succinate.

44. A method for treating hypothalamic amenorrhea in a depressed or non-depressed human female comprising providing to a human female in need thereof an effective amount of O-desmethyl-venlafaxine succinate.

45. A method of lowering the incidence of nausea, vomiting, diarrhea, abdominal pain, headache, vaso-vagal malaise, or trismus resulting from the oral administration of O-desmethylvenlafaxine succinate to a patient comprising orally administering to a patient in need thereof a therapeutically effective amount of a sustained release formulation of O-desmethyl-venlafaxine succinate having a blood plasma level of no more than about 225 ng/ml.

46. A sustained release formulation comprising O-desmethyl-venlafaxine succinate and a pharmaceutically acceptable carrier or excipient, wherein the sustained release formulation provides peak serum levels of up to about 225 ng/ml.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

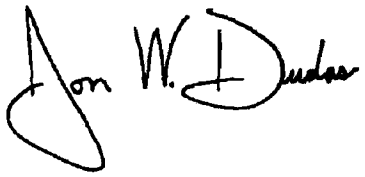
PATENT NO. : 6,673,838 B2
DATED : January 6, 2004
INVENTOR(S) : Anthony F. Hadfiedl et al.

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

Title page,
Item [75], Inventors, the names of "**Michael W. Winkley**" and "**Karen W. Sutherland**" should be deleted.

Signed and Sealed this

Eighteenth Day of May, 2004



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

EXHIBIT B


US008269040B2

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

(10) **Patent No.: US 8,269,040 B2**
(45) **Date of Patent: *Sep. 18, 2012**

(54) **DERIVATIVES OF VENLAFAXINE AND METHODS OF PREPARING AND USING THE SAME**

(75) Inventors: **Thomas P. Jerussi**, Framingham, MA (US); **Chrisantha H. Senanayake**, Shrewsbury, MA (US); **Nandkumar N. Bhongle**, Shrewsbury, MA (US)

(73) Assignee: **Wyeth LLC**, Madison, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 2666 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/720,134**

(22) Filed: **Nov. 25, 2003**

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(62) Division of application No. 09/527,442, filed on Mar. 17, 2000, now abandoned.

(60) Provisional application No. 60/127,938, filed on Apr. 6, 1999, provisional application No. 60/167,906, filed on Nov. 30, 1999.

(51) **Int. Cl.**
C07C 55/00 (2006.01)

(52) **U.S. Cl.** **562/590**

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

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Primary Examiner — Paul A Zucker

(74) *Attorney, Agent, or Firm* — Stephanie J. Monaco; Mary J. Hosley

(57) **ABSTRACT**

Methods of preparing, and compositions comprising, derivatives of venlafaxine are disclosed. Also disclosed are methods of treating and preventing diseases and disorders including, but not limited to, affective disorders such as depression, bipolar and manic disorders, attention deficit disorder, attention deficit disorder with hyperactivity, Parkinson's disease, epilepsy, cerebral function disorders, obesity and weight gain, incontinence, dementia and related disorders.

2 Claims, No Drawings

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DERIVATIVES OF VENLAFAXINE AND METHODS OF PREPARING AND USING THE SAME

This application is a division of U.S. application Ser. No. 09/527,442, filed Mar. 17, 2000, now abandoned, which claims priority to U.S. Provisional Nos. 60/127,938, filed Apr. 6, 1999, and 60/167,906, filed Nov. 30, 1999, all of which are incorporated herein in their entirety by reference.

1. FIELD OF INVENTION

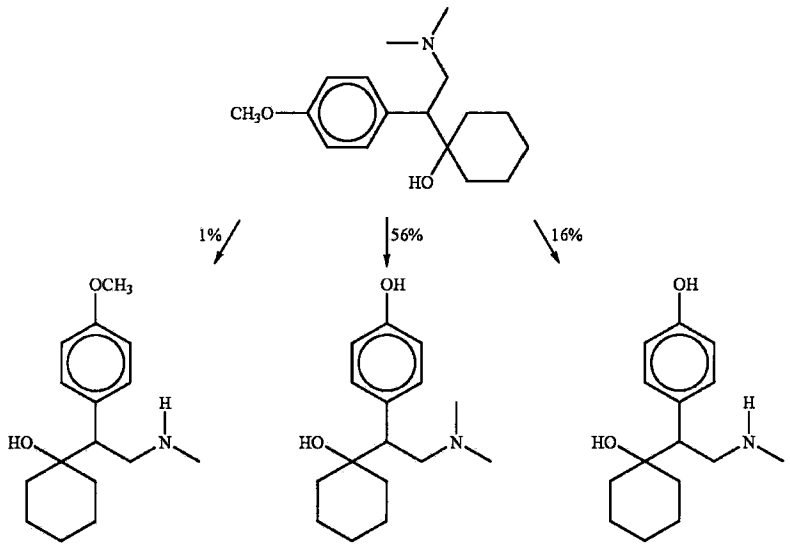
The invention relates to derivatives of racemic venlafaxine, methods of their synthesis, compositions comprising them, and methods of their use.

2. BACKGROUND OF THE INVENTION

A number of nontricyclic antidepressants have recently been developed that diminish the cardiovascular and anticholinergic liability characteristic of tricyclic antidepressants. Some of these compounds are used as anti-obesity agents and have shown promise in the treatment of cerebral function disorders such as Parkinson's disease and senile dementia. See, e.g., WO 94/00047 and WO 94/00114. The nontricyclic compound venlafaxine, chemically named (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol, is an antidepressant which has been studied extensively and which is described in, for example, U.S. Pat. No. 4,761,501 and Pento, J. T. *Drugs of the Future* 13(9):839-840 (1988). Its hydrochloride salt is currently commercially available in the United States under the trade name Effexor®. Effexor®, which is a racemic mixture of the (+) and (−) enantiomers of venlafaxine, is indicated for the treatment of depression.

Although venlafaxine contains an asymmetric carbon atom and is sold as a racemate, it has been reported that its (−) enantiomer is a more potent inhibitor of norepinephrine synaptosomal uptake while its (+) enantiomer is more selective in inhibiting serotonin uptake. Howell, S. R. et al. *Xenobiotica* 24(4):315-327 (1994). Furthermore, studies have shown that the ratio of the two isomers' metabolism varies not only among species, but between subjects as well. Klamerus, K. J. et al. *J. Clin. Pharmacol.* 32:716-724 (1992). In humans, venlafaxine is transformed by a saturable metabolic pathway into two minor metabolites, N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine, and one major metabolite, O-desmethylvenlafaxine, as shown in Scheme I(a):

Scheme I(a)



Klamerus, K. J. et al. *J. Clin. Pharmacol.* 32:716-724 (1992). In vitro studies suggest that O-desmethylvenlafaxine is a more potent inhibitor of norepinephrine and dopamine uptake than the parent compound venlafaxine. Muth, E. A. et al. *Drug Develop. Res.* 23:191-199 (1991). O-desmethylvenlafaxine has also been reported to have a half-life (t1/2) of about 10 hours, which is approximately 2.5 times as long as that of venlafaxine. Klamerus, K. J. et al. *J. Clin. Pharmacol.* 32:716-724 (1992). Studies directed at understanding the activity of O-desmethylvenlafaxine as compared to its parent have been hampered, however, by the metabolic difference between laboratory animals and man in their exposure to venlafaxine. Howell, S. R. et al. *Xenobiotica* 24(4):315-327 (1994).

Despite the benefits of venlafaxine, it has adverse effects including, but not limited to, sustained hypertension, headache, asthenia, sweating, nausea, constipation, somnolence, dry mouth, dizziness, insomnia, nervousness, anxiety, blurred or blurry vision, and abnormal ejaculation/orgasm or impotence in males. *Physicians' Desk Reference* pp. 3293-3302 (53rd ed., 1999); see also Sinclair, J. et al. *Rev. Contemp. Pharmacother.* 9:333-344 (1998). These adverse effects can significantly limit the dose level, frequency, and duration of drug therapy. It would thus be desirable to find a compound with the advantages of venlafaxine while avoiding its disadvantages.

3. SUMMARY OF THE INVENTION

This invention relates to novel pharmaceutical compositions comprising derivatives of venlafaxine such as (±)-O-desmethylvenlafaxine. The invention also relates to methods

of preparing derivatives of venlafaxine with high purity and in high yield, and to methods of treating and preventing diseases and disorders which comprise the administration of one or more derivatives of venlafaxine to a human in need of such treatment or prevention.

Methods and compositions of the invention can be used to treat or prevent depression and affective disorders such as, but not limited to, attention deficit disorder and attention deficit disorder with hyperactivity. Methods and compositions of the invention are also useful in treating obesity and weight gain in a human. The invention also encompasses the treatment of cerebral function disorders including, but not limited to, senile dementia, Parkinson's disease, epilepsy, Alzheimer's disease, amnesia/amnestic syndrome, autism and schizophrenia; disorders ameliorated by inhibition of neuronal monamine reuptake; and pain, particularly chronic pain. The invention further encompasses the treatment or prevention of obsessive-compulsive disorder, substance abuse, pre-menstrual syndrome, anxiety, eating disorders and migraines. The invention finally encompasses the treatment or prevention of incontinence in humans.

The compounds and compositions of the invention possess potent activity for treating or preventing the above-described disorders while reducing or avoiding adverse effects including, but not limited to, sustained hypertension, headache, asthenia, sweating, nausea, constipation, somnolence, dry mouth, dizziness, insomnia, nervousness, anxiety, blurred or blurry vision, and abnormal ejaculation/orgasm or impotence in males. In particular, adverse effects associated with the administration of racemic venlafaxine are reduced or avoided by the use of derivatives of venlafaxine. Compositions of the invention can also exhibit long half lives as compared to racemic venlafaxine.

Although a variety of pharmaceutical salts, solvates, clatherates and/or hydrates (including anhydrous forms) of the active ingredients disclosed herein are suitable for use in the methods and compositions of the invention, the derivatives of venlafaxine are typically prepared as hydrochloride salts, and preferably as the monohydrates.

3.1. DEFINITIONS

As used herein, the terms "venlafaxine" and "(±)-venlafaxine" mean the racemic compound (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol.

As used herein, the terms "venlafaxine derivative" and "derivative of venlafaxine" encompass, but are not limited to, human metabolites of racemic venlafaxine. In particular, the terms "venlafaxine derivative" and "derivative of venlafaxine" mean a compound selected from the group that includes, but is not limited to: (±)-N-desmethylvenlafaxine, chemically named (±)-1-[2-(methylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol; (±)-N,N-didesmethylvenlafaxine, chemically named (±)-1-[2-(amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol; (±)-O-desmethylvenlafaxine, chemically named (±)-1-[2-(dimethylamino)-1-(4-phenol)ethyl]cyclohexanol; (±)-N,O-didesmethylvenlafaxine, chemically named (±)-1-[2-(methylamino)-1-(4-phenol)ethyl]cyclohexanol; and (±)-O-desmethyl-N,N-didesmethylvenlafaxine, chemically named chemically named (±)-1-[2-(amino)-1-(4-phenol) ethyl]cyclohexanol.

As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include inorganic and organic acids such as acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, and sulfuric acids, and most particularly preferred is the hydrochloride salt.

As used herein, the term "affective disorder" includes depression, attention deficit disorder, attention deficit disorder with hyperactivity, bipolar and manic conditions, and the like. The terms "attention deficit disorder" (ADD) and "attention deficit disorder with hyperactivity" (ADDH), or attention deficit/hyperactivity disorder (AD/HD), are used herein in accordance with the accepted meanings as found in the *Diagnostic and Statistical Manual of Mental Disorders* 4th Ed., American Psychiatric Association (1997) (DSM-IV™).

As used herein, the term "a method of treating depression" means relief from the symptoms of depression which include, but are not limited to, changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, and self-deprecation. Physical changes may also be relieved, including insomnia, anorexia, weight loss, decreased energy and libido, and abnormal hormonal circadian rhythms.

As used herein, the term "a method for treating obesity or weight gain" means reduction of weight, relief from being overweight, relief from gaining weight, or relief from obesity; all of which are usually due to extensive consumption of food.

As used herein, the term "a method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake" means relief from symptoms of disease states associated with abnormal neuronal monoamine levels; such symptoms are reduced by way of neuronal monoamine reuptake inhibition. Monoamines, the reuptake of which are inhibited by the compounds or compositions of the present invention, include, but are not limited to, noradrenaline (or norepinephrine), serotonin and dopamine. Disorders treated by neuronal monoamine reuptake inhibition include, but are not limited to, Parkinson's disease and epilepsy.

As used herein, the term "method of treating Parkinson's disease" means relief from the symptoms of Parkinson's disease which include, but are not limited to, slowly increasing disability in purposeful movement, tremors, bradykinesia, rigidity, and a disturbance of posture in humans.

As used herein, the term "a method for treating cerebral function disorders" means relief from the disease states associated with cerebral function disorders involving intellectual deficits which include but are not limited to, senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbances of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome and schizophrenia. Also within the meaning of cerebral function disorders are disorders caused by cerebrovascular diseases including, but not limited to, cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like and where symptoms include disturbances of consciousness, senile dementia, coma, lowering of attention, speech disorders, and the like.

The terms "obsessive-compulsive disorder," "substance abuse," "pre-menstrual syndrome," "anxiety," "eating disorders" and "migraine" are used herein in a manner consistent with their accepted meanings in the art. See, e.g., DSM-IV™. The terms "method of treating or preventing," "method of treating" and "method of preventing" when used in connection with these disorders mean the amelioration, prevention or relief from the symptoms and/or effects associated with these disorders. Without being limited by any theory, the

treatment or prevention of certain of these disorders may be related to the activity of the active ingredient(s) as inhibitors of serotonin uptake.

As used herein, the term "a method of treating or preventing incontinence" means prevention of or relief from the symptoms of incontinence including involuntary voiding of feces or urine, and dribbling or leakage or feces or urine which may be due to one or more causes including but not limited to pathology altering sphincter control, loss of cognitive function, overdistention of the bladder, hyper-reflexia and/or involuntary urethral relaxation, weakness of the muscles associated with the bladder or neurologic abnormalities.

4. DETAILED DESCRIPTION OF THE INVENTION

This invention relates to derivatives of venlafaxine such as, but not limited to, (±)-O-desmethylvenlafaxine, (±)-N-desmethylvenlafaxine, and (±)-N,O-didesmethylvenlafaxine. This invention further relates to the synthesis of venlafaxine derivatives and to compositions (e.g., pharmaceutical compositions) comprising them. The invention also relates to novel uses of the compounds disclosed herein, which constitute improvements over the use of racemic venlafaxine as well as over the optically pure isomers of venlafaxine.

One embodiment of the invention encompasses a method of treating an affective disorder in a human which comprises administering to a human in need of such treatment a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof. Venlafaxine derivatives, preferably (±)-O-desmethylvenlafaxine, can be used to treat an affective disorder while exhibiting a longer half life than venlafaxine and/or while avoiding or reducing adverse effects that are associated with the administration of venlafaxine.

Another embodiment of the invention encompasses a method of treating weight gain or obesity in a human which comprises administering to a human in need of weight loss or obesity therapy a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, said amount being sufficient to reduce or prevent weight gain or obesity. Venlafaxine derivatives, preferably (±)-O-desmethylvenlafaxine, can be used to treat weight gain or obesity disorder while exhibiting a longer half life than venlafaxine and/or while avoiding or reducing adverse effects that are associated with the administration of venlafaxine.

Another embodiment of the invention encompasses a method of treating disorders ameliorated by neuronal monoamine reuptake inhibition in a human which comprises administering to a human a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, said amount being sufficient to treat such disorders. Disorders which are ameliorated by neuronal monoamine reuptake include, but are not limited to, Parkinson's disease, epilepsy, and depression. The derivative of venlafaxine may be used to treat such disorders while avoiding or reducing adverse effects associated with the administration of venlafaxine.

Venlafaxine derivatives, preferably (±)-O-desmethylvenlafaxine, and compositions containing them are also useful in treating cerebral function disorders. Such disorders include, but are not limited to, senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome and schizophrenia. Cerebral function disorders may be induced by factors including, but not limited to, cerebrovascular diseases such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries and the like and where symptoms include disturbances of consciousness, senile dementia, coma, lowering of attention, speech disorders and the like. Thus, the invention encompasses a method of treating cerebral function disorder in a human which comprises administering to a human in need of such therapy a therapeutically effective amount of venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof. The use of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, is intended to provide an improvement over the use of the parent drug venlafaxine. The derivatives of the invention are more potent and yet provide an overall improved therapeutic index over venlafaxine.

Another embodiment of the invention encompasses a method of treating pain, including chronic pain, in a human which comprises administering to a human in need of such therapy a therapeutically effective amount of venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, said amount being sufficient to alleviate the human's pain.

Another embodiment of the invention encompasses a method of treating an obsessive-compulsive disorder in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

Another embodiment of the invention encompasses a method of treating or preventing substance abuse in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clatlrate thereof.

Another embodiment of the invention encompasses a method of treating or preventing pre-menstrual syndrome in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

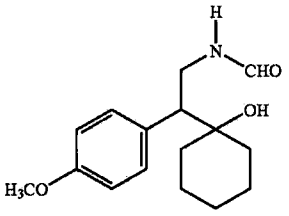
Another embodiment of the invention encompasses a method of treating anxiety in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

Another embodiment of the invention encompasses a method of treating an eating disorder in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

Another embodiment of the invention encompasses a method of treating or preventing a migraine, or migraine headaches, in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

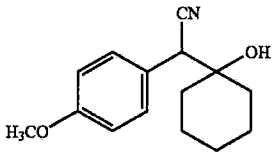
Another embodiment of the invention encompasses a method of treating or preventing incontinence in a human which comprises administering to a human in need of such therapy a therapeutically effective amount of a venlafaxine derivative, preferably (±)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof. In particular, a venlafaxine derivative can be used to treat fecal incontinence, stress urinary incontinence ("SUI"), urinary exertional incontinence, urge incontinence, reflex incontinence, passive incontinence and overflow incontinence. In a preferred embodiments the human is an elder person of an age greater than 50 or a child of an age less than 13. Further, the invention encompasses the treatment of incontinence in patients with either loss of cognitive function, sphincter control or both. The invention is particularly well suited for the treatment or prevention of fecal incontinence and stress urinary incontinence.

Another embodiment of the invention encompasses a method of preparing (±)-N-desmethylvenlafaxine which comprises contacting a compound of Formula 5:



with a reductant for a time and at a temperature sufficient to form (±)-N-desmethylvenlafaxine. A preferred reductant is $BH_3.Me_2S$.

Another embodiment of the invention encompasses a method of preparing (±)-N,N-didesmethylvenlafaxine which comprises contacting a compound of Formula 2:



with a reductant for a time and at a temperature sufficient to form (±)-N,N-didesmethylvenlafaxine. A preferred reductant is $CoCl_2/NaBH_4$.

Another embodiment of the invention encompasses a method of preparing (±)-O-desmethylvenlafaxine which comprises contacting venlafaxine with lithium diphenylphosphide for a time and at a temperature sufficient to form (±)-O-desmethylvenlafaxine.

Another embodiment of the invention encompasses substantially pure (±)-O-desmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

Another embodiment of the invention encompasses substantially pure (±)-N,O-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

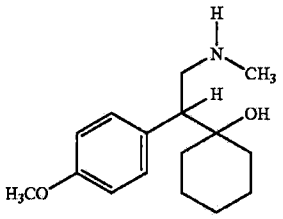
Another embodiment of the invention encompasses substantially pure (±)-O-desmethyl-N,N-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

Another embodiment of the invention encompasses (±)-N-desmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

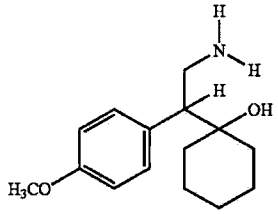
A final embodiment of the invention encompasses (±)-N,N-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

Compounds of the invention, which can be used and prepared as described herein, are shown below in Scheme I(b):

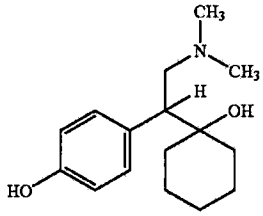
Scheme I(b)



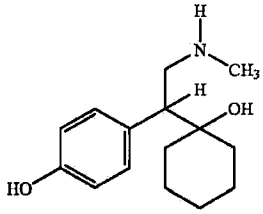
N-desmethylvenlafaxine



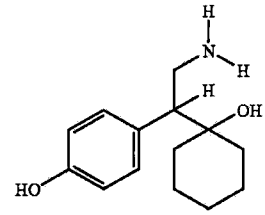
N,N-didesmethylvenlafaxine



O-desmethylvenlafaxine



N,O-didesmethylvenlafaxine

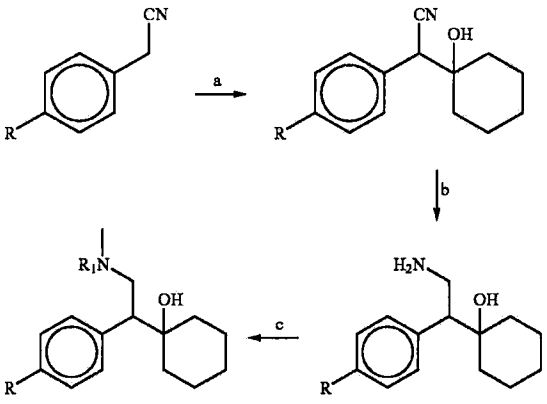


O-desmethyl-N,N-didesmethylvenlafaxine

The synthesis of some venlafaxine derivatives has been described by Yardley, J. P. et al. *J. Med. Chem.* 33:2899-2905 (1990), the disclosure of which is hereby incorporated by

reference. This method, which may be adapted for the synthesis of the compounds of this invention, is shown in Scheme II:

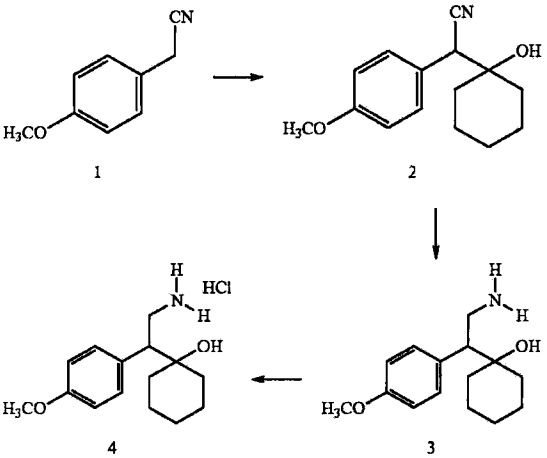
Scheme II



wherein R is methoxy or hydroxy, R_1 is hydrogen or methyl, and the reaction conditions are as follows: (a) LDA in cycloalkanone at −78° C.; (b) Rh/Al_2O_3; and (c) HCHO, HCOOH, H_2O, reflux. The final product yielded by step (c) may be isolated by any method known to those skilled in the art, including high performance liquid chromatography (HPLC). As used herein, the term "isolate" encompasses the isolation of a compound from a reaction mixture and the purification of the compound.

In a preferred method of the invention, (±)-N,N-didesmethylvenlafaxine is prepared according to the method shown in Scheme III

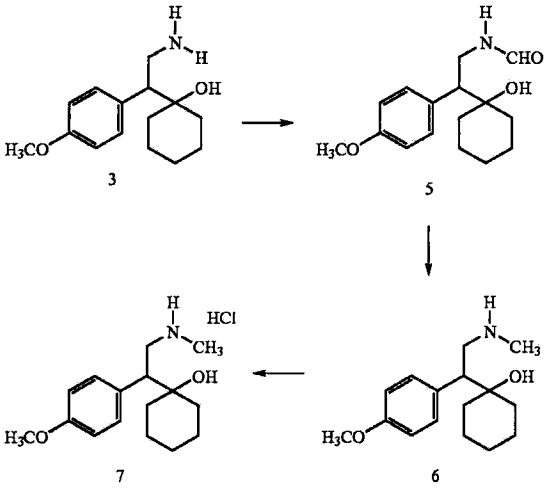
Scheme III



According to this method, cyclohexanone is reacted with compound 1 to provide compound 2. This reaction is preferably done in the presence of a catalyst such as, but not limited to, lithium diisopropylamide (LDA), and in an aprotic solvent such as, but not limited to, THF. The cyano group of compound 2 is subsequently contacted with a reductant to provide compound 3, (±)-N,N-didesmethylvenlafaxine. A preferred reductant is $CoCl_2/NaBH_4$ in methanol, although other reductants known to those skilled in the art can also be used. Salts of (±)-N,N-didesmethylvenlafaxine, such as the HCl salt (compound 4), can then be formed using reaction conditions well known in the art.

In another preferred method of the invention, (±)-N-desmethylvenlafaxine is prepared from (±)-N,N-didesmethylvenlafaxine according to the method shown in Scheme IV:

Scheme IV

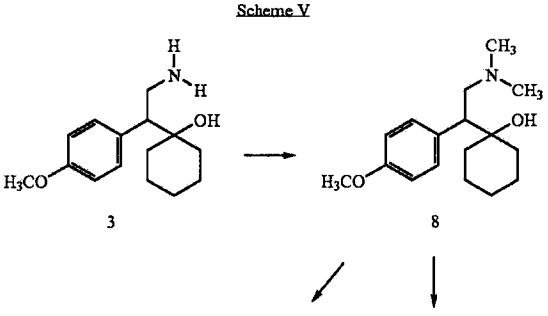


According to this method, (±)-N,N-didesmethylvenlafaxine (compound 3) is converted to compound 5 using, for example, HCO_2H in a solvent such as, but not limited to, toluene. The aldehyde of compound 5 is subsequently reduced to provide compound 6, (±)-N-desmethylvenlafaxine. A preferred reductant is $BHg_3.Me_2S$ in an aprotic solvent such as, but not limited to, THF. Salts of (±)-N-desmethylvenlafaxine, such as the HCl salt (compound 7), can then be formed using reaction conditions well known in the art.

It is also possible to prepare the compounds of the invention from racemic venlafaxine, which can be prepared according to methods disclosed, for example, by U.S. Pat. No. 4,761,501 and Pento, J. T. *Drugs of the Future* 13(9):839-840 (1988), both of which are incorporated herein by reference.

Alternative methods of preparing (±)-venlafaxine:HCl and (±)-O-desmethyl-venlafaxine are shown in Scheme V:

Scheme V



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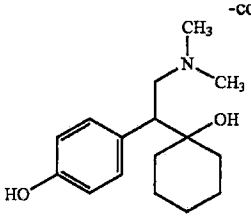

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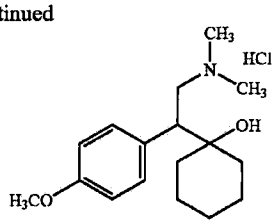

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According to Scheme V, (±)-venlafaxine (compound 8) is prepared by reacting (±)-N,N-didesmethylvenlafaxine (compound 3) with, for example, $HCHO/HCO_2H$. Compound 8 can then be converted to (±)-O-desmethylvenlafaxine (compound 13) using, for example, lithium diphenylphosphide. Alternatively, salts of (±)-venlafaxine, such as the HCl salt (compound 12), can be formed using reaction conditions well known in the art.

Utilizing derivatives of venlafaxine in the treatment and/or mitigation of the conditions described herein results in clearer dose-related definitions of efficacy, diminished adverse effects, and accordingly an improved therapeutic index as compared to venlafaxine itself.

The magnitude of a prophylactic or therapeutic dose of a venlafaxine derivative (herein also referred to as an "active ingredient"), preferably (±)-O-desmethylvenlafaxine, in the acute or chronic management of a disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to age, body weight, response, and the past medical history of the individual patient. In general, the recommended daily dose range for the conditions described herein lie within the range of from about 10 mg to about 1000 mg per day, given as a single once-a-day dose in the morning but preferably as divided doses throughout the day taken with food. Preferably, a daily dose range should be from about 50 mg to about 500 mg per day, more preferably, between about 75 mg and about 350 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 50 mg to about 75 mg, and increased if necessary up to about 250 mg to about 325 mg per day as either a single dose or divided doses, depending on the patient's global response. If a dosage is increased, it is preferably done in intervals of about 75 mg separated by at least 4 days.

Because elimination of venlafaxine derivatives from the bloodstream is dependant on renal and liver function, it is recommended that the total daily dose be reduced by at least 50% in patients with moderate hepatic impairment, and that it be reduced by 25% in patients with mild to moderate renal impairment. For patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 5% and that the dose be withheld until the dialysis treatment is completed. Because some adverse reactions have been reported for patients who took venlafaxine concurrently with, or shortly after, a monamine oxidase inhibitor, it is recommended that the venlafaxine derivatives of this invention not be administered to patients currently taking such inhibitors. In general, the concurrent administration of the compounds of this invention with other drugs, particularly other serotonin uptake inhibitors, should be done with care. See, e.g., von Moltke, L. L. et al. *Biol. Psychiatry* 41:377-380 (1997); and Sinclair, J. et al. *Rev. Contemp. Pharmacother.* 9:333-344 (1998).

The various terms "said amount being sufficient to alleviate the affective disorder," "said amount being sufficient to alleviate depression," "said amount being sufficient to alleviate attention deficit disorder," "said amount being sufficient to alleviate an obsessive-compulsive disorder", "said amount being sufficient to prevent or alleviate substance abuse", "said amount being sufficient to prevent or alleviate pre-menstrual syndrome", "said amount being sufficient to prevent or alleviate anxiety", "said amount being sufficient to prevent or alleviate an eating disorder", "said amount being sufficient to prevent or alleviate or prevent migraine", "said amount being sufficient to alleviate Parkinson's disease," "said amount being sufficient to alleviate epilepsy," "said amount being sufficient to alleviate obesity or weight gain," "an amount sufficient to achieve weight loss," "said amount being sufficient to bring about weight reduction in a human," "said amount being sufficient to alleviate pain," "said amount being sufficient to alleviate dementia," "said amount sufficient to alleviate said disorders ameliorated by inhibition of neuronal monoamine reuptake," "said amount is sufficient to alleviate cerebral function disorders" wherein said disorders are selected from the group consisting of senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome, schizophrenia, and cerebrovascular diseases, such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like, "said amount being sufficient to treat or prevent incontinence" wherein said incontinence includes but is not limited to fecal, stress, urinary, urinary exertional, urge, reflex, passive and overflow incontinence, are encompassed by the above described dosage amounts and dose frequency schedule. Similarly, amounts sufficient to alleviate each of the above disorders but insufficient to cause adverse effects associated with venlafaxine are also encompassed by the above described dosage amounts and dose frequency schedule.

Any suitable route of administration can be employed for providing the patient with a therapeutically or prophylactically effective dose of an active ingredient. For example, oral, mucosal (e.g., nasal, sublingual, buccal, rectal, vaginal), parenteral (e.g., intravenous, intramuscular), transdermal, and subcutaneous routes can be employed. Preferred routes of administration include oral, transdermal, and mucosal. Suitable dosage forms for such routes include, but are not limited to, transdermal patches, ophthalmic solutions, sprays, and aerosols. Transdermal compositions can also take the form of creams, lotions, and/or emulsions, which can be included in an appropriate adhesive for application to the skin or can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose. A preferred transdermal dosage form is a "reservoir type" or "matrix type" patch, which is applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredient. The patch can be replaced with a fresh patch when necessary to provide constant administration of the active ingredient to the patient.

Other dosage forms of the invention include, but are not limited to, tablets, caplets, troches, lozenges, dispersions, suspensions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, plasters, solutions, capsules, soft elastic gelatin capsules, and patches.

In practical use, an active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as,

for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, preferably without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets can be coated by standard aqueous or non-aqueous techniques.

In addition to the common dosage forms set out above, an active ingredient can also be administered by controlled release means or delivery devices that are well known to those of ordinary skill in the art, such as those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, the disclosures of which are incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; and 3) increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and thus can affect the occurrence of side effects.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and to gradually and continually release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various inducers, including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

This invention further encompasses lactose-free pharmaceutical compositions and dosage forms. Lactose is used as an excipient in venlafaxine formulations. See, e.g., *Physician's Desk Reference*® 3294 (53rd ed., 1999). Unlike the parent drug, however, N-demethylated derivatives of venlafaxine (e.g., (±)-N-desmethylvenlafaxine and (±)-N,N-didesmethylvenlafaxine), are secondary or primary amines and may thus decompose over time when exposed to lactose. Consequently, compositions of the invention that comprise N-demethylated derivatives of venlafaxine preferably contain little, if any, lactose or other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients which are well known in the art and are listed in the USP (XXI)/NF (XVI), which is incorporated herein by reference. In general, lactose-free compositions comprise an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g. 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, *Drug Stability: Principles & Practice,* 2d. Ed., Marcel Dekker, NY, N.Y., 1995, pp. 379-80. In effect, water and heat accelerate decomposition. Thus the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably pack-

aged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

In this regard, the invention encompasses a method of preparing a solid pharmaceutical formulation comprising an active ingredient which method comprises admixing under anhydrous or low moisture/humidity conditions the active ingredient and an excipient (e.g., lactose), wherein the ingredients are substantially free of water. The method can further comprise packaging the anhydrous or non-hygroscopic solid formulation under low moisture conditions. By using such conditions, the risk of contact with water is reduced and the degradation of the active ingredient can be prevented or substantially reduced.

Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, for example, the materials sold as AVICEL-PH-101, AVICEL-PH-1103 AVICEL RC-581, and AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa., U.S.A.). An exemplary suitable binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, and mixtures thereof. The binder/filler in pharmaceutical compositions of the present invention is typically present in about 50 to about 99 weight percent of the pharmaceutical composition.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant will produce tablets which may disintegrate in the bottle. Too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) should be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used varies based upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Typically, about 0.5 to about 15 weight percent of disintegrant, preferably about 1 to about 5 weight percent of disintegrant, can be used in the pharmaceutical composition.

Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Piano, Tex.), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), or mixtures thereof. A lubricant can optionally be added, typically in an amount of less than about 1 weight percent of the pharmaceutical composition.

Desirably, each tablet contains from about 25 mg to about 150 mg of the active ingredient and each cachet or capsule contains from about 25 mg to about 150 mg of the active ingredient. Most preferably, the tablet, cachet, or capsule contains either one of three dosages, e.g., about 25 mg, about 50 mg, or about 75 mg of active ingredient (as scored tablets, the preferable dose form).

The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

5. EXAMPLES

As discussed above, at least two different synthetic approaches may be utilized to obtain the compounds of this invention. A first is based upon the isolation of venlafaxine, followed by selective demethylation. In a second approach, the compounds are prepared directly.

5.1. Example 1

Synthesis of Venlafaxine

1-[cyano-(4-methoxyphenyl)methyl]cyclohexanol

A solution of 4-methoxybenzylnitrile (53.5 g, 0.36 mol) in 400 mL THF was cooled to −78° C. followed by slow addition of a 2.0 M THF solution of lithium diisopropylamide (200 mL, 0.40 mol) maintaining the reaction temperature below −65° C. The reaction was stirred at −78° C. for 30 minutes. Cyclohexanone (39.5 g, 0.40 mol) was added at a rate such that the reaction temperature did not rise above −65° C. After the addition reaction was stirred at −78° C. for 2 hours, then was poured into 1 L saturated aqueous NH_4Cl containing ice. The mixture was stirred for 15 minutes and was extracted with ethyl acetate (4×200 mL). Combined ethyl acetate layer was washed with water (3×100 mL), brine (1×100 mL) and dried (Na_2SO_4). Ethyl acetate was evaporated in vacuo to give colorless solid that was trichurated with hexane. The precipitate was filtered, washed with hexane, dried in vacuo to give colorless solid (72.0 g, 80.7% yield). ^1H ($CDCl_3$): 7.30 and 6.90 (q, 4H), 3.80 (s, 3H), 3.75 (s, 1H), 1.55 (m, 10H); ^{13}C ($CDCl_3$): 159.8, 130.8, 123.8, 120.0, 114.1, 72.9, 55.5, 49.5, 34.9, 25.3, 21.6.

1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol

A 3-L, three-neck flask equipped with a mechanical stirrer and a thermocouple was charged with 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol (40.0 g, 0.16 mol) and 1 L methanol. To the resulting stirred solution was added cobalt chloride (42.4 g, 0.32 mol) and the reaction was stirred until a clear dark blue solution was obtained. Sodium borohydride (62.0 g, 1.63 mol) was added in small lots maintaining the reaction temperature below 35° C. A dark black precipitate was formed along with vigorous evolution of gas as soon as sodium borohydride was added. After completion of addition the slurry was stirred at room temperature for 2 hours. TLC examination indicated complete disappearance of the starting material. The reaction was cooled in ice/water and 1 L 3N HCl was added slowly. Reaction temperature was maintained below 25° C. Reaction was stirred for 30 minutes after completion of the addition. Small amount of black precipitate was still observed. Methanol was removed in vacuo followed by extraction of the aqueous layer with ethyl acetate (3×300 mL). The aqueous layer was cooled in ice/water and was basified (pH paper) by slow addition of concentrated NH_4OH (~600 mL). Reaction temperature was maintained below 25° C. Reaction was extracted with ethyl acetate (4×200 mL). Combined ethyl acetate layer was washed with water (3×100 mL), brine (1×100 mL), and dried (Na_2SO_4). Ethyl acetate was evaporated in vacuo to give yellow gum (34.0 g, 83.6% yield). $^1H(CDCl_3)$: 7.20 and 6.85 (q, 4H), 3.80 (s, 3H), 3.20 (m, 2H), 2.70 (t, 3H), 2.35 (br s, 3H), 1.40 (m, 10H); ^{13}C ($CDCl_3$): 158.4, 132.6, 130.6, 113.7, 73.7, 56.7, 55.3, 42.4, 37.3, 34.5, 26.0, 21.9.

(±)-Venlafaxine

1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol (33.0 g, 0.13 mol) was dissolved in 88% formic acid (66.0 g, 55 mL, 1.43 mol) and water (330 mL) followed by addition of 37% aqueous formaldehyde (44.4 g, 41 mL, 1.48 mol). The resulting solution was refluxed for 20 hours, cooled to room temperature and was concentrated to 150 mL, adjusted to pH 2.0 with 3N HCl, and extracted with ethyl acetate (~6×50 mL) until pink impurity was removed. The aqueous layer was cooled in ice/water and was basified by slow addition of 50% NaOH. The aqueous layer was extracted with ethyl acetate (3×75 mL). Combined ethyl acetate layer was washed with water (3×25 mL), brine (1×25 mL) and dried (Na_2SO_4). Ethyl acetate was evaporated in vacuo to give yellow gum that turned slowly in to pale yellow solid (34.0 g, 92.6% yield). $^1H(CDCl_3)$: 7.05 and 6.80 (q, 4H), 3.80 (s, 3H), 3.30 (t, 1H), 2.95 (dd, 1H), 2.35 (s, 6H), 2.30 (dd, 1H), 1.30 (m, 10H); ^{13}C ($CDCl_3$): 158.4, 132.9, 130.3, 113.5, 74.4, 61.4, 55.3, 51.8, 45.6, 38.2, 31.3, 26.2, 21.8, 21.5. MS (277, M+).

(±)-Venlafaxine-HCl Salt

A solution of (±)-venlafaxine (1.0 g, 3.6 mmol) in 100 mL MTBE was cooled to 0° C. and 2 mL of 15% HCl in MTBE was added to it. A colorless precipitate was formed. The reaction was stirred at 0° C. for 10 minutes. Solid was filtered, washed with MTBE, dried in vacuo to give the product as colorless solid (0.700 g, 61.9% yield). ^1H ($CDCl_3$): 11.40 (s, 1H), 7.15 and 6.85 (q, 4H), 4.05 (d, 1H), 3.80 (s, 3H), 3.35 (t, 1H), 3.20 (m, 2H), 2.80 (s, 3H), 2.60 (s, 3H), 1.30 (m, 10H); ^{13}C ($CDCl_3$): 159.0, 131.4, 130.3, 114.2, 73.7, 60.4, 55.4, 52.7, 45.3, 42.8, 36.7, 31.5, 25.5, 21.7, 21.3. MS (277, M+ for free base). % purity (HPLC): 99.62.

5.2. Example 2

Synthesis of (±)-O-desmethylvenlafaxine

A solution of diphenylphosphine (3.0 g, 16.1 mmol) in 20 mL THF was cooled to −10° C. followed by slow addition of a 1.6 M THF solution of n-BuLi (12.7 mL, 20.2 mmol) at a rate such that reaction temperature did not rise above 0° C. The reaction was stirred at 0° C. for 30 minutes. A solution of (±)-venlafaxine (1.0 g, 3.6 mmol) in 10 mL THF was added slowly at 0° C. The reaction was stirred at 0° C. for 15 minutes and allowed to warm to room temperature and stirred for 1 hour. It was then refluxed overnight. The reaction was cooled to room temperature and was poured slowly into 30 mL cold 3N HCl maintaining the temperature below 15° C. After stirring for 10 minutes, the aqueous layer was extracted with ethyl acetate (3×30 mL). The aqueous layer was adjusted to pH 6.8-6.9 by slow addition of solid $NaHCO_3$. It was then saturated by adding NaCl and was extracted with ethyl acetate (6×30 mL). Combined ethyl acetate layer was dried (Na_2SO_4), ethyl acetate was evaporated in vacuo to give colorless solid. The solid was trichurated with cold ethyl acetate, filtered, washed with cold ethyl acetate to give colorless solid (0.700 g, 73.8% yield). ^1H (DMSO, d_6): 9.30 (br s, 1H), 7.10 and 6.80 (q, 4H), 5.60 (br s, 1H), 3.15 (dd, 1H), 2.88 (t, 1H), 2.50 (dd, 1H), 2.30 (s, 6H), 1.35 (m, 10H); ^{13}C (DMSO, d_6): 155.5, 131.7, 130.1, 114.4, 72.6, 60.4, 51.6, 45.3, 37.2, 32.4, 25.7, 21.2. MS: (264, M+1). % purity (HPLC): 99.9.

5.3. Example 3

Synthesis of (±)-N-desmethylvenlafaxine

To a solution of 1-[amino (4-methoxyphenyl)ethyl]cyclohexanol (1.0 g, 4.0 mmol) in 8 ml, of toluene, 96% formic acid (0.37 g, 8.0 mmol) was added and the reaction was refluxed for 4 hours. It was cooled to room temperature and poured into 40 mL saturated aqueous $NaHCO_3$. Toluene layer was separated and aqueous layer was extracted with toluene (3×15 mL). Combined toluene layer was washed with water (3×15 mL), brine (1×15 mL) and dried (Na_2SO_4). Toluene was evaporated in vacuo to give crude N-formyl compound as yellow gum (0.930 g, 83.8% yield). $^1H(CDCl_3)$: 7.95 (s, 1H), 7.15 and 6.85 (q, 4H), 5.80 (s, 1H), 4.10 (m, 1H), 3.80 (s, 3H), 3.50 (s, 1H), 2.80 (dd, 1H), 1.50 (m, 10H); ^{13}C ($CDCl_3$): 161.4, 158.8, 131.0, 130.7, 113.9, 73.0, 55.3, 54.2, 38.1, 36.1, 35.6, 25.6, 21.9, 21.8. (Impurity: 164.5, 129.0, 128.0, 125.0, 56.5, 42.0, 36.5, 35.5). MS (277, M+).

To a solution of crude N-formyl compound (0.585 g, 2.1 mmol) in 6 mL THF was added $BH_3.Me_2S$ (0.480 g, 0.63 mL of 10 M solution, 6.3 mmol) slowly at 0° C. The reaction was allowed to warm to room temperature and then was refluxed for 5 hours. It was cooled to 0° C. and 5 mL of methanol was added very carefully controlling the temperature below 10° C. The reaction was stirred for 10 minutes and volatiles were evaporated off. Residue was partitioned between 3N HCl (20 mL) and ethyl acetate (20 mL). Organic layer was separated and aqueous layer was extracted with ethyl acetate (3×15 mL). Aqueous layer was cooled to 0° C. and was basified by slow addition of conc. NH_4OH. Aqueous layer was saturated with NaCl and was extracted with ethyl acetate (3×20 mL). Combined ethyl acetate layer was dried (Na_2SO_4), ethyl acetate was evaporated in vacuo to give colorless oil (0.493 g, 88.8% yield). ^1H ($CDCl_3$): 7.15 and 6.85 (q, 4H), 3.80 (s, 3H), 3.25 (dd, 1H), 2.95 (dd, 1H), 2.82 (dd, 1H), 2.45 (s, 3H), 1.40

(m, 10H); ^{13}C ($CDCl_3$): 158.4, 133.0, 130.5, 113.7, 73.9, 55.4, 53.8, 53.0, 37.8, 36.5, 33.7, 26.0, 21.9.

(±)-N-desmethylvenlafaxine-HCl Salt

To a solution of crude (±)-N-demethylvenlafaxine (0.450 g, 1.7 mmol) in 25 mL MTBE was added 1 mL of 15% HCl in MTBE at 0° C. The resulting slurry was stirred at 0° C. for 15 minutes, filtered, solid was washed with MTBE, dried in vacuo to give the product as colorless solid (0.380 g, 74.2% yield). ^1H ($CDCl_3$): 9.10 (br d, 1H), 7.15 and 6.85 (q, 4H), 3.80 (m & s, 4H), 3.35 (dd, 1H), 3.15 (m, 1H), 2.70 (t, 3H), 1.30 (m, 10H); ^{13}C ($CDCl_3$): 159.0, 130.71, 130.4, 114.0, 74.7, 55.4, 52.8, 50.9, 37.0, 34.1, 30.9, 25.5, 21.4. % Purity (HPLC): 98.81.

5.4. Example 4

Synthesis of (±)-N,N-didesmethylvenlafaxine-HCl Salt

To a solution of 1-[amino (4-methoxyphenyl)ethyl]cyclohexanol (0.750 g, 3.0 mmol) in 75 mL MTBE was added 2 mL of 15% HCl in MTBE. The reaction was stirred at 0° C. for 15 minutes. It was then evaporated to dryness and the residue was trichurated with MTBE/hexane (6:4). Solid was filtered, washed with MTBE/hexane (6:4). The solid was suspended in cold MTBE, filtered, washed with cold MTBE, dried in vacuo to give the product as colorless solid (0.450 g, 52.3% yield). ^1H (DMSO, d_6)): 7.80 (br s, 2H), 7.20 and 6.90 (q, 4H), 4.50 (br s, 1H), 3.80 (s, 3H), 3.40 (m, 11H), 3.10 (m, 1H), 2.90 (m, 1H), 1.35 (m, 10H); ^{13}C (DMSO, d_6): 158.3, 130.7, 130.0, 113.5, 71.7, 54.9, 52.6, 36.3, 33.6, 26.8, 25.3, 21.4, 21.1. % Purity (HPLC): 99.3.

5.5. Example 5

Synthesis of (±)-O-desmethyl-N,N-didesmethylvenlafaxine

To a solution of diphenylphosphine (22.2 g, 0.12 mol) in 175 ml THF was added a 1.6 M THF solution of n-BuLi (94 mL, 0.15 mol) slowly maintaining the reaction temperature between −10° C. to 0° C. After the addition reaction was stirred at 0° C. for 30 minutes. A solution of (±)-N,N-didemethylvenlafaxine 13 (5.4 g, 0.021 mol) in 55 mL THF was added slowly at 0° C. The reaction mixture was stirred at 0° C. for 30 minutes and allowed to warm to room temperature and stirred at room temperature for 1 hour. It was then refluxed overnight. After cooling the reaction mixture to room temperature, it was poured slowly into 250 mL of 3N HCl while the temperature was maintained below 15° C. After stirring for 30 minutes, the aqueous layer was extracted with methylene chloride (3×200 mL). The aqueous layer was adjusted to pH 6.8-6.9 by slow addition of concentrated NH_4OH at 15° C. and was extracted with methylene chloride (3×100 mL). The aqueous layer was then evaporated to dryness to give a colorless solid. This colorless solid was suspended in 400 mL methylene chloride/methanol (7:3) and was stirred for 1 hour. The insolubles were filtered off, washed with methylene chloride/methanol (7:3). The filtrate was evaporated off to give colorless solid. 6.0 g of the colorless solid was chromatographed on silica gel. Elution with methylene chloride/methanol (9:1→8.5:1.5) afforded the product as a colorless solid (1.5 g_f). ^1H (DMSO, d_6): 8.1 (br s, exchangeable, 1H), 6.95 and 6.75 (q, 4H), 4.6 (m, exchangeable, 2H), 3.3 (m, 1H), 2.9 (m, 2H), 1.2 (m, 10H); ^{13}C (DMSO, d_6): 156.8, 130.5, 128.5, 115.2, 72.0, 52.1, 48.6, 36.6, 33.6, 25.6, 21.7, 21.3. % Purity (HPLC): 97.4%.

5.6. Example 6

Determination of Potency and Specificity

Several methods useful for the determination of the potency and specificity of the compounds of this invention are disclosed in the literature. See, e.g., Haskins, J. T. et al. *Euro. J. Pharmacol.* 115:139-146 (1985). Methods that have been found particularly useful are disclosed by Muth, E. A. et al. *Biochem. Pharmacol.* 35:4493-4497 (1986) and Muth, E. A. et al. *Drug Develop. Res.* 23:191-199 (1991), both of which are incorporated herein by reference.

5.6.1 Receptor Binding

Determination of receptor binding of the compounds of this invention preferably is performed by the methods disclosed by Muth et al., and using the protocols summarized below in Table I.

TABLE I

Receptor Binding Protocols

^3H-Ligand	Ligand Molarity (nM)	Specific activity (Ci/mmol)	Buffer	Time	Incubation Temp. (° C.)	Displacing agent
Spiperone	0.3	20-40	*a	10 min	37°	1 mM (+) butaclamol
WB 4101	0.5	15-30	50 mM Tris-HCl pH 7.7	30 min	25°	10 mM norepinephrine bitartrate
Quinuclindinyl benzilate	0.06	30-60	50 mM Tris-HCl pH 7.7	1 hr	25°	100 mM oxotremorine
Pyrilamine	2.0	<20	50 mM Phosphate pH 7.5	30 min	25°	10 mM chlorpheniramine maleate
Naloxone	1.3	40-60	50 nM Tris-HCl pH 7.4	30 min	0-4°	2 mM morphine

[a]50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid, 10 mM pargyline HCl, pH 7.1

The tissue homogenates used are preferably whole brain except cerebellum (histamine-1 and opiate binding), cortex (α_1 adrenergic receptor binding, monoamine uptake); and striatum (dopamine-2 and muscarinic cholinergic receptor binding).

5.6.2 Synaptosomal Uptake Studies

These studies may be performed using the modified methodology of Wood, M. D., and Wyllie, M. G. *J. Neurochem.* 37:795-797 (1981) as described in Muth et al. *Biochem. Pharmacol.* 35:4493-4497 (1986). Briefly a P2 pellet is prepared from fresh rat brain tissue by sucrose density gradient centrifugation using a vertical rotor. For uptake studies, all components are dissolved in the following buffer: 135 mM NaCl, 5 mM KCl, 1.2 mM $MgCl_2$, 2.5 mM $CaCl_2$, 10 mM glucose, 1 mM ascorbic acid, 20 mM Tris, pH 7.4, gassed with O_2 for 30 min prior to use. Various concentrations of test drug are preincubated with 0.1 μM [^{3}H]dopamine or 0.1 μM [^{3}H] norepinephrine (130,000 dpm/tube) and 0.1 μM [^{14}C]serotonin (7,500 dpm/tube) in 0.9 ml buffer for 5 min at 37° C. One-tenth milliliter of synaptosomal preparation is added to each tube and incubated for a further 4 min at 37° C. The reaction is then terminated by the addition of 2.5 ml buffer, after which the mixture was filtered under vacuum using cellulose acetate filters (0.45 μM pore size). The filters are then counted in a scintillation counter, and the results are expressed as pmoles uptake/mg protein/min. The IC_{50} values for uptake inhibition are calculated by linear regression of logit [percent of Na^+-dependent uptake] vs. long [concentration of test drug].

5.6.3. Reversal of Reserpine-Induced Hypothermia

Reversal of reserpine-induced hypothermia in male CF-1 mice (20-25 g., Charles River) may be performed according to an adaptation of the method of Askew, B. *Life Sci.* 1:725-730 (1963). Test compounds, suspended or solubilized in 0.25% Tween80® in water, are then administered i.p. at several dose levels to male mice (8/dose level) who had been treated 18 hr previously with 45.0 mg/kg reserpine s.c. A vehicle control group is run simultaneously with drug groups. Test compounds, vehicle, and reserpine are administered at a volume of 0.01 ml/g. Reserpine is solubilized by the addition of a small amount (approximately 4 drops) of concentrated acetic acid and then brought to the proper volume by the addition of distilled water. Rectal temperatures are recorded by a Yellow Springs Instruments thermistor probe at a dept of 2 cm. Measurements are taken 18 hr after reserpine pretreatment and at hourly intervals for 3 hr following administration of either test compound or vehicle.

Rectal temperatures for all time periods are subjected to a two-way analysis of variance for repeated measures with subsequent Dunnett's comparison to control values to determine the minimum effective dose (MED) for antagonizing reserpine-induced hypothermia.

5.6.4. Induction of Rat Pineal Noradrenergic Subsensitivity

Suitable rats are male Sprague-Dawley rats (250-300 g, Charles River) which should be maintained in continuous light throughout all experiments so as to attenuate the diurnal fluctuation in beta-adrenergic receptor density in the pineal gland and to maintain a consistent supersensitive response to noradrenergic agonists. Moyer, J. A. et al. *Soc. Neurosci. Abstract* 10:261 (1984). After 2 days of continuous light exposure, the rats are then injected twice daily with either saline or test compound (10 mg/kg i.p.) for 5 days (total of 9 injections). Another group of rats should receive saline injections twice daily for 4 days followed by a single injection of test compound (10 mg/kg i.p.) on the 5th day. One hour following the final injection of test compound or saline, animals are administered either 0.1% ascorbic acid (controls), or isoproterenol (2 μmol/kg i.p. in 0.1% ascorbic acid). Rats are decapitated 2.5 minutes later, the time at which preliminary experiments have shown that the isoproterenol-induced increases in cyclic AMP levels in pineal glands are maximal. Moyer, J. A. et al. *Mol. Pharmacol.* 19:187-193 (1981). Pineal glands are removed and frozen on dry ice within 30 seconds to minimize any post-decapitation increase in cAMP concentration.

Prior to radioimmunoassay for cAMP, the pineal glands are placed in 1 ml of ice-cold 2.5% perchloric acid and sonicated for approximately 15 seconds. The sonicate is then centrifuged at 49.000 g for 15 min at 4° C. and then resulting supernatant fluid is removed, neutralized with excess $CaCO_3$, and centrifuged at 12,000 g for 10 min at 4° C. The cAMP content of the neutralized extract may be measured by a standard radioimmunoassay using ^{125}I-labeled antigen and antiserum (New England Nuclear Corp., Boston, Mass.). Steiner, A. L. et al. *J. Biol. Chem.* 247:1106-1113 (1972). All unknown samples should be assayed in duplicate and compared to standard solutions of cAMP prepared in a 2.5% perchloric acid solution that had been neutralized with $CaCO_3$. Results are expressed as pmol cAMP/pineal, and statistical analyses are performed by analysis of variance with subsequent Student-Newman-Keuls tests.

5.6.5. Single Unit Electrophysiology

The firing rates of individual neurons of the locus coeruleus (LC) or dorsal raphe nucleus (DR) in the chloral-hydrate anesthetized rat are measured using single-barreled glass micro-electrodes as previously described for the L C. Haskins, J. T. et al. *Eur. J. Pharmacol.* 115:139-146 (1985). Using the stereotaxic orientation of Konig, J. F. R., and Klippel, R. A. *The rat brain: A stereotaxic atlas of the forebrain and lower parts of the brain stem* Baltimore: Williams and Wilkins (1963), the electrode tips should be lowered via a hydraulic microdrive from a point 1.00 mm above the locus coeruleus (AP 2.00 mm caudal to the interaural line and 1.03 mm lateral to midline). Drugs are administered i.v. through a lateral tail vein cannula. Only one cell should be studied in each rat in order to avoid residual drug effects.

5.7. Example 7

Oral Formulation

The pharmaceutical compositions of this invention may be administered in a variety of ways. Oral formulations are of the easiest to administer.

5.7.1. Hard Gelatin Capsule Dosage Forms

Table II provides the ingredients of suitable capsule forms of the pharmaceutical compositions of this invention.

TABLE II

Component	25 mg capsule	50 mg capsule	100 mg capsule
(±)-O-desmethyl-venlafaxine	25	50	100
Microcrystalline Cellulose	90.0	90.0	90.0
Pre-gelatinized Starch	100.3	97.8	82.8
Croscarmellose	7.0	7.0	7.0
Magnesium Stearate	0.2	0.2	0.2

The active ingredient (venlafaxine derivative) is sieved and blended with the excipients listed. The mixture is filled into suitably sized two-piece hard gelatin capsules using suitable machinery and methods well known in the art. See *Remington's Pharmaceutical Sciences,* 16th or 18th Editions, each incorporated herein in its entirety by reference thereto. Other doses may be prepared by altering the fill weight and, if necessary, by changing the capsule size to suit. Any of the stable hard gelatin capsule formulations above may be formed.

5.7.2. Compressed Tablet Dosage Forms

The ingredients of compressed tablet forms of the pharmaceutical compositions of the invention are provided in Table III.

TABLE III

Compressed Tablet Unit Dosage Forms			
Component	25 mg capsule	50 mg capsule	100 mg capsule
(±)-O-desmethyl-venlafaxine	25	50	100
Microcrystalline Cellulose	90.0	90.0	90.0
Pre-gelatinized Starch	100.3	97.8	82.8
Croscarmellose	7.0	7.0	7.0
Magnesium Stearate	0.2	0.2	0.2

The active ingredient is sieved through a suitable sieve and blended with the excipients until a uniform blend is formed. The dry blend is screened and blended with the magnesium stearate. The resulting powder blend is then compressed into tablets of desired shape and size. Tablets of other strengths may be prepared by altering the ratio of the active ingredient to the excipient(s) or modifying the table weight.

While the invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made without departing from the spirit and scope of the invention as defined in the claims. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:

1. A compound which is O-desmethylvenlafaxine succinate, wherein the compound is a hydrate of O-desmethylvenlafaxine succinate.

2. The compound of claim **1** which is O-desmethylvenlafaxine succinate monohydrate.

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