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(54) Title: SUBSTANTIALLY PURE O-DESMETHYLVENLAFAXINE AND PROCESSES FOR PREPARING IT

(57) Abstract: Methods for preparing substantially pure O-desmethylvenlafaxine are described.

SUBSTANTIALLY PURE O-DESMETHYLVENLAFAXINE AND PROCESSES FOR PREPARING IT

CROSS REFERENCE TO RELATED APPLICATIONS

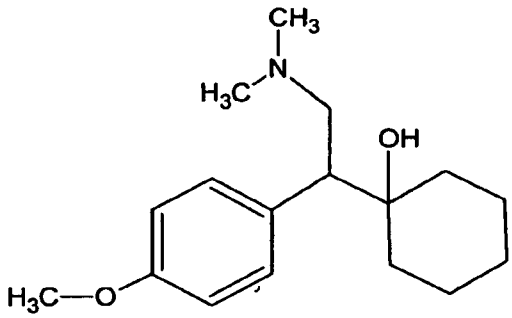
[0001] The present application claims the benefit of the following United States Provisional Patent Application Nos.: 60/792,801, filed April 17, 2006; 60/796,739, filed May 1, 2006; 60/899,166, filed February 1, 2007; 60/902,418, filed February 20, 2007; 60/872,955, filed December 4, 2006; and 60/903,988, filed February 27, 2007. The contents of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The invention encompasses substantially pure O-desmethylvenlafaxine.

BACKGROUND OF THE INVENTION

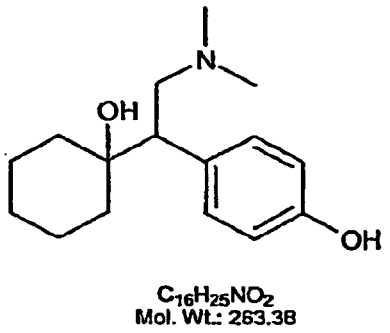
[0003] Venlafaxine, (±)-1-[2-(Dimethylamino)-1-(4-ethyoxyphenyl) ethyl] cyclo-hexanol is the first of a class of anti-depressants. Venlafaxine acts by inhibiting re-uptake of norepinephrine and serotonin, and is an alternative to the tricyclic anti-depressants and selective re-uptake inhibitors. Venlafaxine has the following chemical formula, Formula I:



Formula I

[0004] O-desmethylvenlafaxine, 4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol, is a major metabolite of venlafaxine and has been shown to inhibit norepinephrine and serotonin uptake. *See* Klamerus, K. J. et al., "Introduction of the Composite Parameter to the Pharmacokinetics of Venlafaxine and

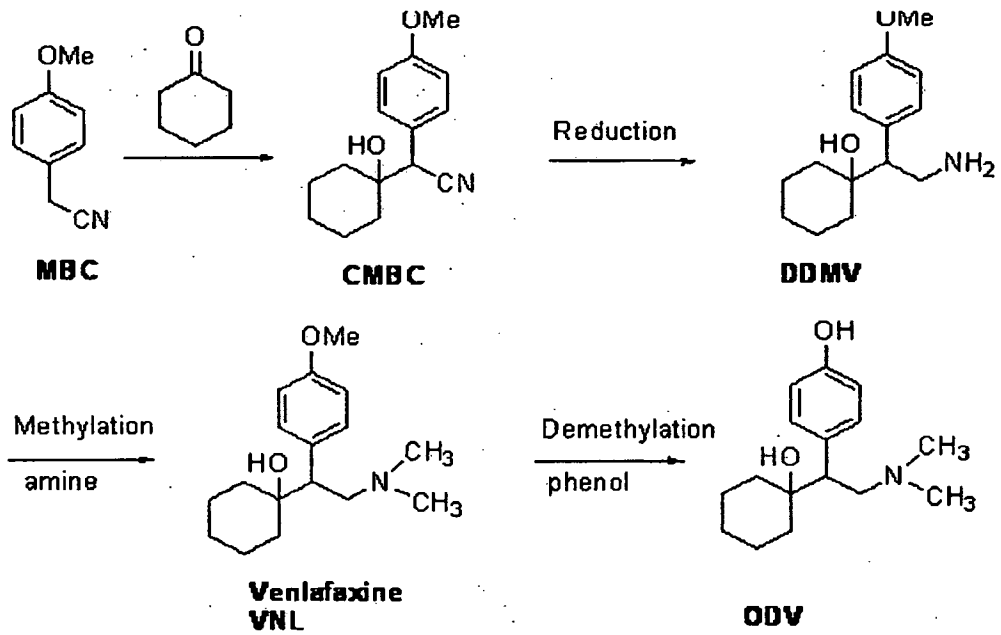
its Active O-Desmethyl Metabolite," *J. Clin. Pharmacol.* 32:716-724 (1992). O-desmethylvenlafaxine has the following chemical formula, Formula II:



Formula II

[0005] Processes for the synthesis of O-desmethylvenlafaxine, comprising a step of demethylation of the phenol group of venlafaxine, are described in U.S. patent No. 7,026,508 and 6,689,912, and in U.S. publication No. 2005/0197392, which are incorporated herein by reference.

[0006] The synthesis disclosed in the above references is performed according to the following scheme:



"MBC" refers to methyl benzyl cyanide, "CMBC" refers to cyclohexyl methylbenzyl cyanide, "DDMV" refers to didesmethyl venlafaxine, and "ODV" refers to O-desmethylvenlafaxine.

[0007] Like any synthetic compound, O-desmethylvenlafaxine can contain extraneous compounds or impurities that can come from many sources. They can be unreacted starting materials, by-products of the reaction, products of side reactions, or degradation products. Impurities in O-desmethylvenlafaxine or any active pharmaceutical ingredient (API) are undesirable and, in extreme cases, might even be harmful to a patient being treated with a dosage form containing the API.

[0008] It is also known in the art that impurities in an API may arise from degradation of the API itself, which is related to the stability of the pure API during storage, and the manufacturing process, including the chemical synthesis. Process impurities include unreacted starting materials, chemical derivatives of impurities contained in starting materials, synthetic by-products, and degradation products.

[0009] In addition to stability, which is a factor in the shelf life of the API, the purity of the API produced in the commercial manufacturing process is clearly a necessary condition for commercialization. Impurities introduced during commercial manufacturing processes must be limited to very small amounts, and are preferably substantially absent. For example, the ICH Q7A guidance for API manufacturers requires that process impurities be maintained below set limits by specifying the quality of raw materials, controlling process parameters, such as temperature, pressure, time, and stoichiometric ratios, and including purification steps, such as crystallization, distillation, and liquid-liquid extraction, in the manufacturing process.

[0010] The product mixture of a chemical reaction is rarely a single compound with sufficient purity to comply with pharmaceutical standards. Side products and by-products of the reaction and adjunct reagents used in the reaction will, in most cases, also be present in the product mixture. At certain stages during processing of an API, such as O-desmethylvenlafaxine, it must be analyzed for purity, typically, by HPLC, NMR or TLC analysis, to determine if it is suitable for continued processing and, ultimately, for use in a pharmaceutical product. The API need not be absolutely pure, as absolute purity is a theoretical ideal that is typically unattainable. Rather, purity standards are set with the intention of ensuring that an API is as free of impurities as possible, and, thus, is as safe as possible for clinical use. As discussed above, in the United States, the Food and Drug Administration guidelines recommend that the amounts of some impurities be limited to less than 0.1 percent.

[0011] Generally, side products, by-products, and adjunct reagents (collectively "impurities") are identified spectroscopically and/or with another

physical method, and then associated with a peak position, such as that in a chromatogram, or a spot on a TLC plate. (Strobel p. 953, Strobel, H.A.; Heineman, W.R., Chemical Instrumentation: A Systematic Approach, 3rd dd. (Wiley & Sons: New York 1989)). Thereafter, the impurity can be identified, e.g., by its relative position in the chromatogram, where the position in a chromatogram is conventionally measured in minutes between injection of the sample on the column and elution of the particular component through the detector. The relative position in the chromatogram is known as the "retention time."

[0012] Thus, because of its medical uses, it is desirable to obtain substantially pure O-desmethylvenlafaxine.

SUMMARY OF THE INVENTION

[0013] In one embodiment the present invention provides substantially pure O-desmethylvenlafaxine containing less than about 5% area by HPLC, more preferably less than about 3% area by HPLC, even more preferably less than about 1% area by HPLC of total impurities.

[0014] Preferably, the O-desmethylvenlafaxine contains less than about 0.7% area by HPLC of total impurities. More preferably, less than about 0.2% area by HPLC of total impurities and most preferably, the O-desmethylvenlafaxine contains less than about 0.07% area by HPLC of total impurities

[0014] In another embodiment, the present invention provides a process for preparing substantially pure O-desmethylvenlafaxine comprising: combining under reduced pressure venlafaxine, an organic solvent and a reagent selected from the group consisting of: thiophenol, sodium sulfide and C_1-C_8 alkyl thiolate, to form a mixture, heating the mixture to a temperature of about 30°C to about 220°C, and recovering O-desmethylvenlafaxine.

[0015] In another embodiment, the present invention provides a process for preparing substantially pure O-desmethylvenlafaxine comprising: combining venlafaxine, an organic solvent and C_1-C_8 alkyl thiolate or sodium sulfide to form a mixture, heating the mixture to a temperature of about 100°C to about 210°C, and recovering O-desmethylvenlafaxine.

[0016] In another embodiment, the present invention provides a process for preparing substantially pure O-desmethylvenlafaxine comprising: combining

venlafaxine and thiophenol to form a mixture, heating the mixture to a temperature of about 100°C to about 210°C, and recovering O-desmethylvenlafaxine.

[0017] In yet another embodiment, the present invention provides the use of C_1-C_8 alkyl thiolate and sodium sulfide for the demethylation of venlafaxine.

[0018] In yet another embodiment, the present invention provides a process for preparing substantially pure O-desmethylvenlafaxine comprising: preparing tridesmethyl venlafaxine as described in the co-pending application 60/849216 (which is incorporated herein by reference); converting said tridesmethyl venlafaxine to O-desmethylvenlafaxine; and recovering O-desmethylvenlafaxine.

[0019] In a further embodiment, the invention is directed to an analytical method for testing the chemical purity of O-desmethylvenlafaxine.

[0020] In another embodiment, the present invention provides a pharmaceutical composition comprising substantially pure O-desmethylvenlafaxine and a pharmaceutically acceptable excipient.

[0021] In yet another embodiment, the present invention provides a process for preparing a pharmaceutical formulation comprising mixing substantially pure O-desmethylvenlafaxine and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

[0022] As used herein, the term "substantially pure" refers to O-desmethylvenlafaxine having a purity, measured as % area HPLC, of about 95% or more. Preferably, substantially pure O-desmethylvenlafaxine has a purity of about 97% area by HPLC, more preferably of about 99% area by HPLC, even more preferably of about 99.3% area by HPLC, most preferably of about 99.8% area by HPLC.

[0023] The present invention provides O-desmethylvenlafaxine (ODV) containing less than about 5% area by HPLC, preferably less than about 3% area by HPLC, more preferably less than 1% area by HPLC, of total impurities. The term "% area by HPLC" as used herein refers to the area in an HPLC chromatogram of one or more peaks compared to the total area of all peaks in the HPLC chromatogram expressed in percent of the total area. Further the purity of O-desmethyl venlafaxine may be expressed herein as "HPLC" purity. As such, "HPLC purity", is a calculation of the area under the O-desmethyl venlafaxine peak divided by the total area under the curve in an HPLC chromatogram.

[0024] Preferably, the O-desmethylvenlafaxine contains less than about 0.7% area by HPLC of total impurities. More preferably, less than about 0.2% area by HPLC of total impurities and most preferably, the O-desmethylvenlafaxine contains less than about 0.07% area by HPLC of total impurities.

[0025] The O-desmethylvenlafaxine provided by the present invention is obtained either as a racemate or as optically pure O-desmethylvenlafaxine.

[0026] It would be apparent to any skilled artisan that further crystallizing crude O-desmethylvenlafaxine could afford higher purity.

[0027] In another embodiment, the present invention provides a process for preparing substantially pure O-desmethylvenlafaxine comprising: combining, preferably under reduced pressure, venlafaxine (VNL), an organic solvent and a reagent selected from the group consisting of: thiophenol, sodium sulfide and a C_1-C_8 alkyl thiolate, to form a mixture, preferably heating the mixture to a temperature of from about 30°C to about 220°C, preferably from about 30°C to about 100°C, and recovering substantially pure O-desmethylvenlafaxine.

[0028] As used herein, the term "reduced pressure" refers to a pressure below about 1 atmosphere, preferably to a pressure of less than 0.5 atmosphere, more preferably to a pressure of less than about 0.1 atmosphere.

[0029] The organic solvent can be selected from the group consisting of: C_3-C_7 ketones, C_3-C_7 esters, C_5-C_8 aliphatic hydrocarbons or C_6-C_{12} aromatic hydrocarbons, high boiling point solvents, C_2-C_8 ethers, chlorinated hydrocarbons, and C_2-C_8 alcohols. More preferably, the solvent is selected from the group consisting of: acetone, ethyl acetate, toluene, DMF, NMP, DMA, THF and ethanol.

[0030] As used herein, the term "high boiling point solvent" refers to a solvent having a boiling point higher than about 100°C. Preferably, the high boiling point solvent is selected from the group consisting of: toluene, dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methyl-2-pyridone, N-methyl-2-pyrrolidone, 1-methyl-2-pyrolidinone (NMP) and dimethylacetamide (DMA). More preferably, the high boiling point solvent is DMA, DMF or NMP.

[0031] Whenever NMP is used, the ratio of NMP to venlafaxine is preferably 1 to 20 (by volume), more preferably, 2 to 4 (by volume).

Whenever DMA or DMF are used, the ratio of DMA and DMF to venlafaxine is preferably at least about 1 volume, more preferably, 1 to 10 (by volume), most preferably, about 2.5 volumes.

[0032] Whenever thiophenol is used in the process, a catalyst is preferably employed in the reaction mixture. More preferably, the catalyst is a base. Most preferably, the catalyst is an alkali metal base, such as potassium carbonate.

[0033] Preferably, the substantially pure O-desmethylvenlafaxine obtained by the process above contains less than about 0.7% area by HPLC of total impurities. More preferably, less than about 0.2% area by HPLC of total impurities and most preferably, the substantially pure O-desmethylvenlafaxine obtained by the process above contains less than about 0.07% area by HPLC of total impurities.

[0034] The O-desmethylvenlafaxine may be recovered from the mixture by any method known to the skilled artisan.

[0035] Preferably, the O-desmethylvenlafaxine thus obtained is in a crystalline form, characterized by X-ray powder diffraction reflections at about: 12.1, 13.2, 15.9 and 20.4 degrees two theta ± 0.2 degrees two theta.

[0036] In another embodiment, the present invention provides a process for preparing substantially pure O-desmethylvenlafaxine comprising: combining venlafaxine, an organic solvent and a C_1-C_8 alkyl thiolate or sodium sulfide to form a mixture, heating the mixture to a temperature of about 100°C to about 210°C, preferably of about 100°C to about 190°C, more preferably of about 135°C to about 190°C, and recovering substantially pure O-desmethylvenlafaxine.

[0037] The organic solvent used is as described above.

[0038] Whenever NMP is used, the ratio of NMP to venlafaxine is preferably 1 to 20 (by volume), more preferably, 2 to 4 (by volume).

[0039] Whenever DMA or DMF are used, the ratio of DMA and DMF to venlafaxine is preferably at least about 1 volume, more preferably, 1 to 10 (by volume), most preferably, about 2.5 volumes.

[0040] Preferably, the substantially pure O-desmethylvenlafaxine obtained by the process above contains less than about 0.7% area by HPLC of total impurities. More preferably, less than about 0.2% area by HPLC of total impurities and most preferably, the O-desmethylvenlafaxine obtained by the process above contains less than about 0.07% area by HPLC of total impurities.

[0041] The O-desmethylvenlafaxine may be recovered from the mixture by any method known to the skilled artisan.

[0042] Preferably, the O-desmethylvenlafaxine thus obtained is in a crystalline form, characterized by X-ray powder diffraction reflections at about: 12.1, 13.2, 15.9 and 20.4 degrees two theta ± 0.2 degrees two theta.

[0043] In another embodiment, the present invention provides a process for preparing substantially pure O-desmethylvenlafaxine comprising: combining venlafaxine and thiophenol to form a mixture, heating the mixture to a temperature of about 100°C to about 210°C, preferably of about 100°C to about 190°C, more preferably of about 135°C to about 190°C, and recovering substantially pure O-desmethylvenlafaxine.

[0044] Optionally, the process above can be performed in the presence of a non-hydroxilic or nonethereal solvent. The solvent can be selected from the group consisting of: NMP, DMSO, DMF, DMA, carbowax, marlotherm and silicon oil. Preferably, the solvent is NMP.

[0045] Whenever NMP is used, the ratio of NMP to venlafaxine is preferably 1 to 20 (by volume), more preferably, 2 to 4 (by volume).

[0046] A catalyst is preferably employed in the reaction mixture of venlafaxine and thiophenol. More preferably, the catalyst is a base. Most preferably, the catalyst is an alkali metal base, such as potassium carbonate.

[0047] Preferably, the substantially pure O-desmethylvenlafaxine obtained by the process above, contains less than about 0.7% area by HPLC of total impurities. More preferably, less than about 0.2% area by HPLC of total impurities and most preferably, the O-desmethylvenlafaxine obtained by the process above contains less than about 0.07% area by HPLC of total impurities.

[0048] The O-desmethylvenlafaxine may be recovered from the mixture by any method known to the skilled artisan.

[0049] Preferably, the O-desmethylvenlafaxine thus obtained is in a crystalline form, characterized by X-ray powder diffraction reflections at about: 12.1, 13.2, 15.9 and 20.4 degrees two theta ± 0.2 degrees two theta.

[0050] All processes for preparing substantially pure O-desmethylvenlafaxine described above may be followed by slurrying the obtained O-desmethylvenlafaxine in a mixture of an organic solvent and water, in order to reduce salts impurities. The substantially pure O-desmethylvenlafaxine obtained by slurrying has assay purity of at least about 95%, more preferably, an assay purity of 99%. Preferably, the organic solvent/water mixture can be an alcohol/water mixture or water/acetonitrile mixture,

more preferably the alcohol/water mixture is a C_1-C_4 alcohol/water mixture, most preferably the alcohol/water mixture is an isopropanol/water mixture.

[0051] As used herein the term "assay purity" refers to a purity determined by a well known method which calculates the mass of O-desmethyl venlafaxine by comparing the area percent of the sample to the area percent of a standard.

[0052] Optionally, O-desmethylvenlafaxine is slurried in a water/IPA mixture. Preferably, the water/IPA mixture is in a ratio of 15:25 to 80:20 (by volume), more preferably the ratio is 80:20 (by volume).

[0053] The slurry is may be maintained for about 5 minutes to about 5 hours, preferably for about 30 minutes to about 4 hours, more preferably for about 1 hour to about 3 hours, most preferably for about 2 hours, at a temperature of about 20°C to about 70°C, preferably at about 20°C to about 40°C, more preferably at about room temperature, to obtain substantially pure O-desmethylvenlafaxine having an assay purity of about 95%, preferably of about 99%. The substantially pure O-desmethylvenlafaxine may be recovered from the slurry by any method known to the skilled artisan. Preferably, recovery comprises precipitation of O-desmethyl venlafaxine from an aqueous solution or suspension in water/IPA wherein the pH is adjusted to 7.5 -13.5, preferably to 7.5 to 10, more preferably to a pH of about 8. Adjusting the pH comprises adding an acid, preferably the acid is selected from HCl and an organic acid, more preferably the acid is citric acid or succinic acid, most preferably the acid is succinic acid.

[0054] In yet another embodiment, the present invention provides the use of C_1-C_8 alkyl thiolate and sodium sulfide for the demethylation of venlafaxine.

[0054] In yet another embodiment, the present invention provides a process for preparing substantially pure O-desmethylvenlafaxine comprising: preparing tridesmethyl venlafaxine (TDMV) as described in the co-pending application 60/849216, which is incorporated herein by reference; converting said tridesmethyl venlafaxine to O-desmethylvenlafaxine; and recovering substantially pure O-desmethylvenlafaxine from the reaction mixture.

[0055] A process for preparing tridesmethyl venlafaxine comprises: combining didesmethylvenlafaxine, a high boiling point solvent, and a thiolate to form a mixture, heating the mixture to a temperature of about 100°C to about 220°C, preferably of about 140°C to about 210°C, more preferably to a temperature of about

155°C to about 210°C, and optionally recovering tridesmethyl venlafaxine from the mixture.

[0056] The tridesmethyl venlafaxine obtained by the process above preferably contains less than 5% area by HPLC of total impurities.

[0057] Preferably, the high boiling point solvent is as described above.

[0058] Preferably, the thiolate is a high molecular weight thiolate or arene thiolate. More preferably, the thiolate is sodium dodecanethiolate or thiophenol. The sodium dodecanethiolate can be obtained by any method known to the skilled artisan, such as combining sodium methoxide, methanol and dodecanethiol.

[0059] Whenever thiophenol is used, a catalyst is preferably employed in the reaction mixture. More preferably, the catalyst is a base. Most preferably, the catalyst is an alkali metal base, such as potassium carbonate is the catalyst.

[0060] Preferably, the mixture is heated to a temperature of about 155°C to about 210°C.

[0061] The tridesmethyl venlafaxine may be recovered from the mixture by any method known to the skilled artisan.

[0062] The conversion of tridesmethyl venlafaxine to O-desmethylvenlafaxine can also be performed as described in the co-pending application 60/849216, which is incorporated herein by reference. This process comprises: combining a solution of tridesmethyl venlafaxine and a formaldehyde source with sodium borohydride or sodium triacetoxy borohydride to obtain a slurry and optionally recovering the O-desmethylvenlafaxine from the slurry.

[0063] Optionally, the tridesmethyl venlafaxine starting material is in a solution with an organic solvent such as a C_{1-4} alcohol.

[0064] Optionally, the process is performed under acidic conditions. Preferably, the acidic source is an organic acid, such as formic acid or an acetic acid.

[0065] Preferably, prior to combining the sodium borohydride or sodium triacetoxy borohydride, the solution is cooled to a temperature of less than about 10°C, more preferably less than about 5°C.

[0066] Substantially pure O-desmethylvenlafaxine may be further recovered from the reaction mixture by any method known to the skilled artisan. Preferably, recovering substantially pure O-desmethylvenlafaxine comprises adjusting the pH of a suspension containing crude O-desmethylvenlafaxine, for example the reaction mixture from the conversion step, to a pH of about 7.5 -13.5, obtaining substantially

pure O-desmethylvenlafaxine. Adjusting the pH of the suspension containing crude O-desmethylvenlafaxine may result or enable precipitation of substantially pure O-desmethylvenlafaxine from the suspension. The suspension containing crude O-demethylvenlafaxine may be the suspension from the reaction mixture of the conversion of tridesmethylvenlafaxine to O-desmethylvenlafaxine or a suspension in a water/C_1-C_4 alcohol mixture. The pH may be adjusted with any suitable organic or inorganic acid, preferably the pH is adjusted with citric acid or succinic acid. In recovering substantially pure O-desmethylvenlafaxine the pH is preferably adjusted to pH of about 7.5-10, more preferably to pH of about 8. Recovering the substantially pure O-desmethylvenlafaxine may further comprise filtering the obtained substantially pure O-desmethylvenlafaxine. Optionally, an anti-solvent is added to the pH adjusted suspension, wherein the anti-solvent is a water miscible solvent. Preferably, the anti-solvent is a C1-C4 alcohol, more preferably isopropanol (IPA).

[0067] Preferably, the substantially pure O-desmethylvenlafaxine obtained by the process above, contains less than about 0.7% area by HPLC of total impurities. More preferably, less than about 0.2% area by HPLC of total impurities and most preferably, the O-desmethylvenlafaxine obtained by the process above contains less than about 0.07% area by HPLC of total impurities.

[0068] The O-desmethylvenlafaxine may be recovered from the slurry by any method known to the skilled artisan.

[0069] In a further embodiment, the invention is directed to an analytical method for testing the chemical purity of O-desmethylvenlafaxine comprising combining an O-desmethylvenlafaxine sample with a mixture of acetonitrile:buffer in a ratio of about 3:7, to obtain a solution; injecting the solution onto a C-18 column, for example a Zorbax SB C-18 4.6*250mm Part No.28105-020 or similar column, followed by eluting the sample from the column at about 55 min using a mixture of acetonitrile: buffer (about 3:7) (referred to as eluent A) and a mixture of acetonitrile: buffer: trifluoroacetic acid: triethylamine (referred to as eluent B) as an eluent, and measuring the chemical purity of the relevant sample with a UV detector. Eluent B is preferably prepared by adding to a mixture of about 700 parts acetonitrile and about 300 parts buffer, about 1.6 parts trifluoroacetic acid and about 2.9 parts triethylamine and adjusting the resulting mixture to about pH 3.0, more preferably eluent B is prepared by combining about 700 ml acetonitrile, about 300 ml Buffer, about 1.6 ml trifluoroacetic acid, and 2.9 ml triethylamine and adjusting to a pH of about 3.0.

[0070] Preferably, the buffer contains about 0.4% trifluoroacetic acid, about 0.7% triethylamine and about 98.9% water having a pH of about 3.0.

[0071] Preferably, the eluent used may be a mixture of eluent A and eluent B, wherein the ratio of them varies over the time, i.e. a gradient eluent. At the time 0 minutes, the eluent contains 100% of eluent A and 0% of eluent B. At about 21 minutes, the eluent preferably contains about 100% of eluent A and about 0% of eluent B. At about 55 minutes, the eluent preferably contains about 45% of eluent A and about 55% of eluent B.

[0072] In another embodiment, the present invention provides a pharmaceutical composition comprising substantially pure O-desmethylvenlafaxine and a pharmaceutically acceptable excipient.

[0073] In yet another embodiment, the present invention provides a process for preparing a pharmaceutical formulation comprising mixing substantially pure O-desmethylvenlafaxine and a pharmaceutically acceptable carrier.

[0074] Pharmaceutical compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, bucally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups, and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration, suitable forms for administration include suppositories with hydrophilic or hydrophobic vehicle. For topical administration, the invention provides suitable transdermal delivery systems known in the art, and for nasal delivery, there are provided suitable aerosol delivery systems known in the art.

[0075] In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients or adjuvants. Selection of excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

[0076] Diluents increase the bulk of a solid pharmaceutical composition and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelitinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin,

dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol, and talc.

[0077] Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate, and starch.

[0078] The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®), and starch.

[0079] Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, and tribasic calcium phosphate.

[0080] When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and die. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and die, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the die. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor

oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

0081] Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

[0082] Solid and liquid compositions may also be died using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

[0083] In liquid pharmaceutical compositions of the present invention, the active ingredient and any other solid excipients are suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

[0084] Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol, and cetyl alcohol.

[0085] Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, and xanthan gum.

[0086] Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol, and invert sugar may be added to improve the taste.

[0087] Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole, and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

[0088] According to the present invention, a liquid composition may also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate, or sodium acetate.

[0089] Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

[0090] The solid compositions of the present invention include powders, granulates, aggregates, and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant, and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well known in the pharmaceutical arts.

[0091] Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches, and lozenges, as well as liquid syrups, suspensions, and elixirs.

[0092] The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin, and, optionally, contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

[0093] The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended, and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried, and then screened and/or milled to the desired particle size. The granulate may then be tableted or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

[0094] A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be

compacted into a slug or a sheet, and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

[0095] As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

[0096] A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

[0097] In another embodiment, the present invention provides a method of treating a patient comprising administering to a patient in need thereof a therapeutically effective amount of the above substantially pure O-desmethylvenlafaxine. Preferably, the method is treating a patient suffering from a condition which may be treated with a norepinephrine or a serotonin re-uptake inhibitor. Such patient may be suffering from depression.

[0097] Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the synthesis of the novel compound tridesmethyl venlafaxine and further its conversion to O-desmethylvenlafaxine. 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 scope of the invention.

EXAMPLES

[0098] The XRD diffraction was performed on Scintag X-ray powder diffractometer model X'TRA with a solid state detector. Copper radiation of 1.5418 Å was used. The sample holder was a round standard aluminum sample holder with rough zero

background. The scanning parameters were range: 2-40 degrees two-theta; scan mode: continuous scan; step size: 0.05 deg.; and at a rate of 5 deg/min.

HPLC method for measuring the chemical purity:

Column	Zorbax SB C-18 4.6*250mm Part No.28105-020 or equivalent column		
Buffer	0.4% trifluoroacetic acid, 0.7% triethylamine 98.9% of water (adjusted to pH=3.0).		
Eluent A:	30% Acetonitrile 70% Buffer		
Eluent B:	Prepared by adding to a mixture of 700ml Acetonitrile and 300ml buffer, 1.6ml of trifluoroacetic acid and 2.9ml of triethylamine (adjusted to pH=3.0)		
Stop time:	55 min		
Gradient of Eluent:	Time (min)	Eluent A (%)	Eluent B (%)
	0	100	0
	21	100	0
	55	45	55
Equilibration time:	10 min		
Flow:	1.0 mL/min		
Detector:	230 nm		
Injection volume:	10 μL		
Diluent:	Eluent A		
Column temperature:	25°C		

Example 1: Preparation of O-desmethylvenlafaxine in NMP

[0099] Venlafaxine (50g, 180 mmol), thiophenol (20 ml, 195 mmol), K_2CO_3 (1 g, 6 mmol), and NMP (90 ml) were charged in a 500 ml 3 necks flask equipped with stirrer, condenser and thermometer. The mixture was heated to 190°C. After 5 hours at 190°C the heating bath was removed. (less than 1.5% VNL). At 80°C IPA (300ml) was added. The solution was cooled to 0-5°C overnight. The solid was filtered under reduced pressure and washed with IPA and water. The solid was then

dried overnight at 50°C under vacuum to get pure ODV base. ODV was obtained with a purity of 97% and an Assay of 93.5%.

Example 2: Preparation of O-desmethylvenlafaxine in NMP

[0100] To one neck flask equipped with magnetic stirrer, dean stark, condenser and thermometer were added at room temperature under flow of nitrogen VNL (5g, 18.2 mmol), Na_2S Hydrate (1.58g, 12 mmol, assay >60%) and NMP (12 ml). The reaction mixture was heated to 150°C in 1 hour and kept at this temperature for 7.5 hours. Then the reaction mixture was cooled to room temperature and stirred overnight at this temperature. Afterwards Na_2S hydrate (0.71 g, 5.4 mmol, assay >60%) was added. The mixture was heated to 165°C in 1 hour and kept at this temperature for 5 hours. After this time the reaction was cooled to 40°C, IPA (30ml) and a 10% aqueous solution of citric acid (20 ml) were added slowly through a dropping funnel until light precipitation was observed (pH 10). The suspension was stirred over weekend at room temperature and the solid was filtered under reduced pressure and washed with IPA (20 ml). The solid was dried overnight in a vacuum oven at 50°C to obtain dry ODV (assay 55.2%, HPLC purity 99.11%)

Example 3: Preparation of O-desmethylvenlafaxine under pressure

[0101] A 250 ml autoclave is charged with 5g VNL (0.0182mol), 3.81g Sodium Ethanethiolate (0.0458mol, 2.5eq) and NMP (10 ml). The reaction mixture is stirred from 30°C to 220°C and 1-20 bar pressure for 4h. The mixture is then cooled to room temperature. At ambient temperature IPA (10 ml) and water (10 ml) are added. To this mixture a 10% aqueous solution of citric acid is added in order to reach pH about 12. A solid begins to precipitate and is stirred at RT for 2.5 h. The solid is then filtered under reduced pressure and washed with solvent. The wet cake is dried in a vacuum oven at 50°C to obtain pure ODV.

Example 4: Preparation of O-desmethylvenlafaxine in DMA

[0102] To a 100 ml three necks flask equipped with mechanical stirrer, thermometer and condenser were added 5g VNL (0.0182mol), 3.81g Sodium Ethanethiolate (0.0458mol, 2.5eq) and Dimethylacetamide (10 ml). The mixture was heated to 135°C for 4h, and then it was cooled to room temperature. At ambient temperature IPA (10 ml) and water (10 ml) were added. The reaction mixture was

clear. To this mixture (pH 13) a 10% aqueous solution of citric acid was added in order to reach pH 12.4. A solid began to precipitate and was stirred at RT for 2.5 h. The solid was then filtered under reduced pressure and washed with IPA. The wet cake was dried in a vacuum oven at 50°C to obtain crude ODV (assay of 78%, HPLC 99.84%).

Example 5: Preparation of O-desmethylvenlafaxine in DMA

[0103] To a 100ml three necks flask equipped with mechanical stirrer, thermometer and condenser were added 10g VNL (0.0364mol), 7.62g Sodium ethanethiolate (0.091mol, 2.5eq) and dimethylacetamide (20 ml). The mixture was heated at 110°C for 9 hours and then was cooled to room temperature. At this temperature IPA (25 ml) and water (15 ml) were added. The reaction mixture was clear. To this mixture (pH 12.43) HCl 32% was added to reach pH 10. A solid began to precipitate and was stirred at ambient temperature for 2.5 hours. The solid was then filtered and washed with IPA. The wet cake was dried in a vacuum oven at 50°C to obtain ODV crude (assay of 77.9%, HPLC 94.98%).

Example 6: Preparation of O-desmethylvenlafaxine in DMF

[0104] To a 100ml three necks flask equipped with mechanical stirrer, thermometer and condenser were added 5g VNL (0.0364mol), 3.81g Sodium ethanethiolate (0.0454mol, 2.5eq) and Dimethylformamide (10 ml). The mixture was heated to 135°C for 3 hours and 20 minutes. The solution was then cooled to room temperature.

At this temperature ethylacetate (10 ml) was added and some material precipitated. The mixture was heated back to 70°C and then cooled slowly to ambient temperature. The mixture was stirred overnight at this temperature. Then to the mixture were added IPA, brine and citric acid 10% to pH 9-10. The suspension was stirred at RT for five minutes and filtered under reduced pressure. The wet cake was washed with IPA and dried in a vacuum oven overnight at 50°C to obtain crude ODV (assay of 76.3%, HPLC 99.29%).

Example 7: Preparation of O-desmethylvenlafaxine by slurry in water/IPA

[0105] 1g of ODV (GS 1652) was stirred for 2h at ambient temperature in 5 ml of a mixture water: IPA (80:20). The slurry was stirred for 2 hours at ambient temperature and the solid was filtered under reduced pressure and washed with 2 ml

of water:IPA (80:20). The solid was dried in a vacuum oven overnight at 50°C to obtain dry pure ODV (assay of 98.7%, HPLC 99.93%)

Example 8: Preparation of O-desmethylvenlafaxine by slurry in water

[0106] To a 100 ml flask equipped with magnetic stirrer were added at room temperature wet ODV (5.65 g) previously produced and water (40 ml). The suspension was stirred at ambient temperature for 2.5 hours. The suspension was then filtered under reduced pressure and washed with water (10ml). The solid was dried in a vacuum oven overnight at 50°C to get a white pure solid ODV (assay 95%, HPLC purity 99%).

Example 9: Preparation of O-desmethylvenlafaxine in NMP

[0107] To a three necks flask equipped with mechanical stirrer, condenser and thermometer were added at room temperature under flow of nitrogen VNL (12g, 43.26 mmol), Na_2S Hydrate (6.2g, 47.69 mmol, assay >60%) and NMP (24 ml). The reaction mixture was heated to 175°C in 1 hour and kept at this temperature for 3 hours. Then the reaction mixture was cooled to 90°C. Water (36ml) and succinic acid (5g, 42.34 mmol) were added and a light precipitation was observed (pH 8.0). Diethylcarbonate (24ml) was added to the solution and the suspension was stirred at 60°C 0.5 hours. The reaction mixture was then cooled to room temperature and the solid was filtered under reduced pressure and washed with H_2O (2X20 ml). The solid was dried overnight in a vacuum oven at 50°C to obtain 9.26g (yield=79.43%) of dry pure ODV base (assay 97.7%, HPLC purity 99.34%)

Example 10: Preparation of O-desmethylvenlafaxine in NMP

[0108] To a three necks flask equipped with mechanical stirrer, condenser and thermometer were added at room temperature under flow of nitrogen VNL (12g, 43.26 mmol), Na_2S Hydrate (6.2g, 47.69 mmol, assay >60%) and NMP (24 ml). The reaction mixture was heated to 175°C in 1 hour and kept at this temperature for 3 hours. Then the reaction mixture was cooled to 90°C. Water (36ml) and succinic acid (6g 50.8 mmol) were added and a light precipitation was observed (pH 8.0). Acetonitrile (24ml) was added and the suspension was stirred at 60°C for 0.5 hour. Then the reaction mixture was cooled to room temperature, the solid was filtered under reduced pressure and washed with H_2O (2X20 ml). The solid was dried

overnight in a vacuum oven at 50°C to obtain pure dry ODV base (assay 95.8%, HPLC purity 99.47%)

Example 11: Preparation of O-desmethylvenlafaxine in NMP

[0109] To a three necks flask equipped with mechanical stirrer, condenser and thermometer were added at room temperature under flow of nitrogen VNL (12g, 43.26 mmol), Na_2S Hydrate (6.2g, 47.69 mmol, assay >60%) and NMP (24 ml). The reaction mixture was heated to 175°C in 1.5 hour and kept at this temperature for 4 hours. Then the reaction mixture was cooled to room temperature. Water (60ml) and succinic acid (5g 42.34 mmol) were added and precipitation was observed (pH 8.0).The suspension was heated to 95°C and stirred at 95°C 1 hour. Then the reaction mixture was cooled to room temperature, the solid was filtered under reduced pressure and washed with H_2O (2X20 ml). The solid was dried overnight in a vacuum oven at 50°C to obtain 11.34g of ODV base (yield=95.38%, assay 95.8%, HPLC purity 98.07%).

Example 12: Preparation of tridesmethyl venlafaxine

[0110] DDMVxHCl (10 g, 40 mmol), K_2CO_3 (6g, 44 mmol), Thiophenol (8ml, 60 mmol) and NMP (40 ml) were charged in a 250 ml flask equipped with magnetic stirrer, condenser and nitrogen inlet, and heated in a sand bath. The temperature of the bath was kept at 210°C for 5.5 hours. HPLC analysis confirmed full consumption of DDMV. TDMV was obtained with a purity of 95%.

Example 13: Preparation of substantially pure O-desmethylvenlafaxine

[0111] TDMV (0.2 g, 0.85 mmol) was dissolved in methanol. Formalin solution (0.4 ml, 5 mmol) was added and the resulting solution was cooled in an ice bath. To the cold solution, $NaBH_4$ (65 mg, 1.7 mmol) was added. After 15 min a sample was analyzed by HPLC, and determined to contain 85 % ODV in the reaction mixture.

Then to the mixture is added IPA, and citric acid 10% to pH 9-10. The suspension is stirred at RT for five minutes and filtered under reduced pressure. The wet cake is washed with IPA and dried in a vacuum oven overnight at 50°C to obtain pure ODV.

Comparative Example with WO 03/048104 example 4

[0112] NaOMe (1.3 g, 24mmol) dissolved in Methanol (3 ml) and dodecanethiol (5.83 ml=4.92 g, 24 mmol) were mixed together and placed in rotovapor under reduced pressure at 90°C. To this residue Venlafaxine (5.12 g, 18 mmol) and PEG 400 (3.7g, 0.75vol) were added. The mixture was then heated at 200°C. ($T_{internal}$=190°C). After 3 hours IPA (18ml) was added and the pH adjusted to 9.5 with aqueous HCl. The solid was filtered under reduced pressure and washed with IPA and water. The wet ODV was dried under reduced pressure to get ODV. ODV was obtained with a purity of 73.5% and an Assay of 74.2%

Comparative Example with WO 03/048104 example 2

[0113] Venlafaxine (2.8g, 10.1mmol), Benzenethiolate sodium salt (3.45g, 26mmol), and PEG 400 (12.5g, 4.5vol) were charged in a 100 ml flask with magnetic stirrer. The mixture was heated in a sand bath to 160°C. At 90°C we observed a complete dissolution. After 5 hours at 160°C the bath was removed and water (30 ml) was added. The pH was adjusted with H_3PO_4 85% to pH=3.5. The mixture was extracted with 25ml Hexane to remove organic by-products, and the aqueous phase pH was readjusted to pH 9.5 with aqueous ammonia. A solid precipitated from the reaction mixture. The solid was filtered, reslurried in water (40 ml) and filtered under reduced pressure. The solid so-obtained was dried under reduced pressure to get ODV. ODV was obtained with a purity of 95.6% and an Assay of 78.5%.

What is claimed is:

1. Substantially pure O-desmethylvenlafaxine.

2. The substantially pure O-desmethylvenlafaxine according to claim 1, wherein the amount of total impurities is less than about 5% area by HPLC.

3. The substantially pure O-desmethylvenlafaxine according to claim 2, wherein the amount of total impurities is less than about 3% area by HPLC.

4. The substantially pure O-desmethylvenlafaxine according to claim 3, wherein the amount of total impurities is less than about 1% area by HPLC.

5. The substantially pure O-desmethylvenlafaxine according to claim 4, wherein the amount of total impurities is less than about 0.7% area by HPLC.

6. The substantially pure O-desmethylvenlafaxine according to claim 5, wherein the amount of total impurities is less than about 0.2% area by HPLC.

7. The substantially pure O-desmethylvenlafaxine according to claim 6, wherein the amount of total impurities is less than about 0.07% area by HPLC.

8. A process for preparing a substantially pure O-desmethylvenlafaxine comprising:
   a) combining venlafaxine, an organic solvent and a reagent selected from the group consisting of thiophenol, sodium sulfide, and a C_1-C_8 alkyl thiolate, to form a mixture;
   b) heating the mixture; and
   c) recovering substantially pure O-desmethylvenlafaxine.

9. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 8, wherein the organic solvent is selected from the group consisting of a C_3-C_7 ketone, a C_3-C_7 ester, a C_5-C_8 aliphatic hydrocarbon, a C_6-C_{12} aromatic hydrocarbon, a high boiling point solvent, a C_2-C_8 ether, a chlorinated hydrocarbon and a C_2-C_8 alcohol.

10. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 9, wherein the high boiling point solvent is selected from the group consisting of toluene, dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methyl-2-pyridone, N-methyl-2-pyrrolidone, 1-methyl-2-pyrolidinone (NMP) and dimethylacetamide (DMA).

11. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 10, wherein the high boiling point solvent is DMA, DMF or NMP.

12. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 9, wherein the organic solvent is selected from the group consisting of acetone, ethyl acetate, toluene, DMF, NMP, DMA, THF and ethanol.

13. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 12, wherein NMP is the organic solvent and venlafaxine and NMP in the mixture are in a ratio of venlafaxine:NMP between 1:1 to 1:20 by volume.

14. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 12, wherein the organic solvent is DMF or DMA and venlafaxine and the organic solvent are in a ratio of venlafaxine:organic solvent between 1:1 to 1:10 by volume.

15. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 8 to 14, wherein when the reagent is thiophenol a catalyst is added to the mixture of step (a).

16. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 15, wherein the catalyst is a base.

17. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 16, wherein the base is an alkalimetal carbonate.

18. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 17, wherein the alkalimetal carbonate is potassium carbonate.

19. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 8 to 18, wherein the mixture is heated in step (b) to a temperature of about 100°C to about 210°C for a period of about 1 to about 12 hours.

20. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 19, wherein the mixture is heated to a temperature of about 110°C to about 190°C.

21. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 19 to 20, wherein the period is about 3 hours to about 10 hours.

22. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 8 to 21, wherein venlafaxine, the organic solvent and the reagent are combined under reduced pressure, and the mixture is heated in step (b) at a temperature of about 30°C to about 220°C.

23. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 22, wherein the pressure is less than 1 atmosphere.

24. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 8 to 23, wherein the recovering of O-desmethylvenlafaxine comprises crystallization.

25. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 24, wherein the obtained crystalline O-desmethylvenlafaxine is characterized by a powder X-ray diffraction pattern having peak reflections at about 12.1, 13.2, 15.9, and 20.4 degrees two theta ± 0.2 degrees two theta.

26. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 8 to 23, further comprising, before recovering the substantially pure O-desmethylvenlafaxine, slurrying the mixture in a solvent selected from the group consisting of water, a water/alcohol mixture and a water/acetonitrile mixture.

27. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 26, wherein the water/IPA mixture is in a ratio of 15:25 to 80:20 (by volume).

28. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 27, wherein the water/IPA mixture has a 80:20 ratio (by volume).

29. The process of preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 26 to 28, wherein the slurrying is conducted at a temperature of about 20°C to about 70°C for a period of about 5 minutes to about 5 hours.

30. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 28, wherein slurrying is conducted at about room temperature for a period of about 2 hours.

31. The process of preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 26 to 30, wherein recovering the O-desmethylvenlafaxine comprises precipitation of O-desmethylvenlafaxine from an aqueous solution or suspension in water/IPA by adjusting the pH to 7.5-13.5.

32. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 31, wherein the pH is adjusted to pH 7.5 to 10.

33. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 32, wherein the pH is adjusted to pH 8.

34. The process of preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 31 to 33, wherein adjusting the pH comprises adding an acid.

35. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 34, wherein the acid is selected from the group consisting of inorganic acids and organic acids.

36. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 35, wherein the organic acid is succinic acid.

37. A substantially pure O-desmethylvenlafaxine produced by the process of any one of claims 26 to 36.

38. The substantially pure O-desmethylvenlafaxine according to claim 37, having an assay purity of at least about 95%.

39. The substantially pure O-desmethylvenlafaxine according to claim 38, having an assay purity of at least about 99%.

40. A process for preparing a substantially pure O-desmethylvenlafaxine, comprising:
    a) combining venlafaxine and thiophenol to form a mixture;
    b) heating the mixture to a temperature of about 100°C to about 210°C; and
    c) recovering substantially pure O-desmethylvenlafaxine.

41. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 40, wherein a catalyst is added to the mixture of step (a).

42. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 41, wherein the catalyst is a base.

43. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 42, wherein the base is an alkalimetal carbonate.

44. The process of preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 40 to 43, wherein the mixture in step (a) further comprises a solvent which is a non hydroxilic or non ethereal solvent.

45. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 44, wherein the solvent is selected from the group consisting of NMP, DMSO, DMF, DMA, carbowax, marlotherm, and silicon oil.

46. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 45, wherein the solvent is NMP.

47. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 40 to 46, wherein recovering substantially pure O-desmethylvenlafaxine comprises crystallizing.

48. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 47, wherein the obtained crystalline O-desmethylvenlafaxine is characterized by a powder X-ray diffraction pattern having peak reflections at about 12.1, 13.2, 15.9, and 20.4 degrees two theta ± 0.2 degrees two theta.

49. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 40 to 48, further comprising slurrying, before recovering the O-desmethylvenlafaxine, in a solvent mixture selected from the group consisting of water, water/alcohol mixtures, and a water/acetonotrile mixture.

50. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 49, wherein the solvent mixture is a water/IPA mixture having a 80:20 ratio by volume.

51. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 50, wherein the slurrying is conducted at about 20°C to about 70°C for a period of about 5 minutes to about 5 hours .

52. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 51, wherein slurrying is conducted at about room temperature for a period of about 2 hours.

53. The process of preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 49 to 52, wherein recovering substantially pure O-desmethylvenlafaxine comprises precipitation of O-desmethylvenlafaxine from an aqueous solution or suspension in water/IPA by adjusting the pH to 7.5-13.5.

54. The process of preparing a substantially pure O-desmethylvenlafaxine according to claim 53, wherein the pH is adjusted to pH 8.

55. A substantially pure O-desmethylvenlafaxine produced by the process of any one of claims 40 to 54.

56. The substantially pure O-desmethylvenlafaxine according to claim 55, having an assay purity of at least about 99%.

57. A method of demethylating venlafaxine comprising reacting venlafaxine with a C_1-C_8 alkyl thiolate and sodium sulfide.

58. A process for preparing a substantially pure O-desmethylvenlafaxine comprising;
    a) combining didesmethylvenlafaxine, a high boiling point solvent, and a thiolate to form a mixture;
    b) heating the mixture to a temperature of about 100°C to about 220°C forming tridesmethyl venlafaxine; and
    c) converting tridesmethyl venlafaxine to O-desmethylvenlafaxine; and
    d) recovering substantially pure O-desmethylvenlafaxine.

59. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 58, wherein the thiolate is sodium dodecanethiolate or thiophenol.

60. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 59, wherein converting tridesmethyl venlafaxine to O-desmethylvenlafaxine comprises: combining a solution of tridesmethyl venlafaxine and a formaldehyde source with sodium borohydride or sodium triacetoxy borohydride to obtain a slurry; and recovering O-desmethylvenlafaxine.

61. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 60, wherein the solution of tridesmethyl venlafaxine and a formaldehyde source is cooled to a temperature of less than about 10°C prior to combining with sodium borohydride or sodium triacetoxy borohydride.

62. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 58 to 61, wherein recovering substantially pure O-desmethylvenlafaxine comprises adjusting the pH of a suspension of the obtained crude O-desmethylvenlafaxine in step c) to about pH 7.5-13.5, and further filtering the suspension.

63. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 62, wherein the pH is adjusted to about 7.5 -10.

64. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 63, wherein the pH is adjusted to about 8.

65. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 62 to 64, wherein the pH is adjusted with an acid.

66. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 65, wherein the acid is an organic acid.

67. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 66, wherein the acid is citric acid or succinic acid.

68. The process for preparing a substantially pure O-desmethylvenlafaxine according to any one of claims 62 to 67, further comprising adding a water miscible anti-solvent to the pH adjusted suspension.

69. The process for preparing a substantially pure O-desmethylvenlafaxine according to claim 68, wherein the anti-solvent is isopropanol (IPA).

70. An analytical method for testing the chemical purity of O-desmethylvenlafaxine comprising:
    a) combining an O-desmethylvenlafaxine sample with a mixture of acetonitrile: buffer in a ratio of about 3:7 (eluent A), to obtain a solution;
    b) injecting the solution onto a C-18 column;
    c) eluting the sample from the column at about 55 min using a mixture of eluent A and eluent B (a mixture of about 700 parts acetonitrile: about 300 parts buffer: about 1.6 parts trifluoroacetic acid: and about 2.9 parts triethylamine; adjusted to about pH 3.0) as an eluent; and
    d) measuring the chemical purity of the sample with a UV detector.

71. The analytical method according to claim 70, wherein the buffer contains about 0.4% trifluoroacetic acid, about 0.7% triethylamine, and about 98.9% water and has a pH of about 3.0.

72. The analytical method according to any one of claims 70 and 71, wherein the eluent is a gradient eluent which at time 0 minutes, contains 100% of eluent A and 0% of eluent B, at about 21 minutes, contains about 100% of eluent A and about 0% of eluent B, and at about 55 minutes, contains about 45% of eluent A and about 55% of eluent B.

73. A pharmaceutical composition comprising substantially pure O-desmethylvenlafaxine and a pharmaceutically acceptable excipient.

74. A process for preparing a pharmaceutical formulation comprising combining substantially pure O-desmethylvenlafaxine and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/009558

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C215/64 C07C217/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/197392 A1 (JERUSSI THOMAS P [US] ET AL) 8 September 2005 (2005-09-08) cited in the application	1-7,73, 74
Y	Scheme I(b) and Scheme II; claim 1; examples 2,5	57-69
X	WO 03/048104 A (WYETH CORP [US]) 12 June 2003 (2003-06-12) cited in the application	8-56
Y	claims 1,9-12	57-69
X	US 7 026 508 B2 (HADFIELD ANTHONY F [US] ET AL WINKLEY MICHAEL W [US] ET AL) 11 April 2006 (2006-04-11) cited in the application column 24, line 3 - line 5; examples 3-5	8-56, 70-72

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/009558

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2007/071404 A (SYNTHON BV [NL]; POSPISILIK KAREL [CZ]; THIJS LAMBERTUS [NL]) 28 June 2007 (2007-06-28) claim 1	57

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