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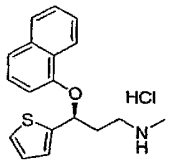
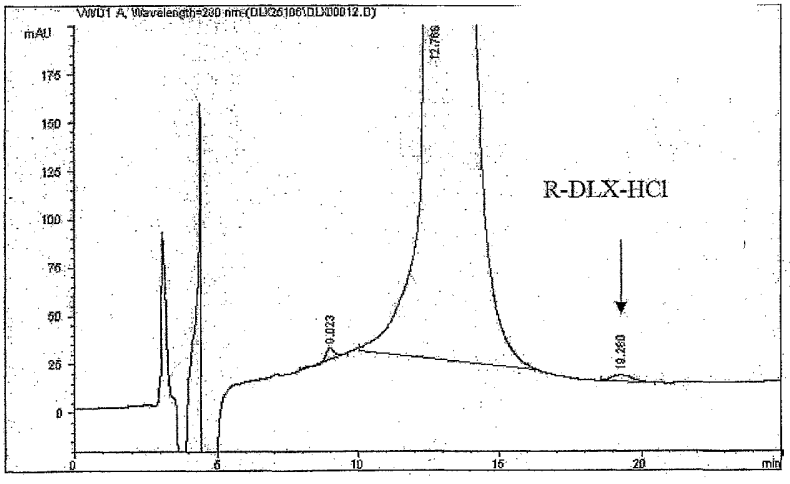
(54) Title: PURE DULOXETINE HYDROCHLORIDE



(I)

(57) Abstract: Chemically and/or enantiomerically pure duloxetine HCl and process for preparing chemically and/or enantiomerically pure duloxetine HCl are provided. (Formul I)

a chromatogram of CYMBALTA®



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PURE DULOXETINE HYDROCHLORIDE

RELATED APPLICATIONS

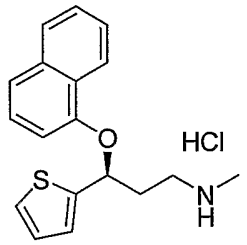
[0001] This application claims benefit of U.S. Provisional Application Nos. 60/726,502, filed October 12, 2005, 60/736,746, filed November 14, 2005, 60/661,711, filed March 14, 2005, and 60/773,593, filed February 14, 2006

FIELD OF THE INVENTION

[0002] The present invention relates to chemically and/or enantiomerically pure duloxetine hydrochloride.

BACKGROUND OF THE INVENTION

[0003] Duloxetine HCl is a dual reuptake inhibitor of the neurotransmitters serotonin and norepinephrine. It is used for the treatment of stress urinary incontinence (SUI), depression, and pain management. It is commercially available as CYMBALTA®. Duloxetine hydrochloride has the chemical name (S)-(+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine hydrochloric acid salt and the following structure.



[0004] Duloxetine, as well as processes for its preparation, is disclosed in a few published documents, such as U.S. Patent No. 5,023,269, EP Patent No. 457559, and U.S. Patent No. 6,541,668.

[0005] The conversion of duloxetine to its hydrochloride salt is described in U.S. Patent No. 5,491,243 and in Wheeler W.J., *et al, J. Label.Cpds.Radiopharm*, **1995**, *36*, 312. In both cases the reactions are performed in ethyl acetate.

[0006] Like any synthetic compound, duloxetine HCl 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 duloxetine HCl 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 of the API in which a sufficient amount of impurities is present. Furthermore, the undesired enantiomeric impurities reduce the level of the API available in the pharmaceutical composition.

[0007] 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.

[0008] 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.

[0009] 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 duloxetine hydrochloride, it must be analyzed for purity, typically, by HPLC 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. 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.

[00010] 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."

[00011] The retention time can vary about a mean value based upon the condition of the instrumentation, as well as many other factors. To mitigate the effects such variations have upon accurate identification of an impurity, practitioners use the "relative retention time" ("RRT") to identify impurities. (Strobel p. 922). The RRT of an impurity is its retention time divided by the retention time of a reference marker. It may be advantageous to select a compound other than the API that is added to, or present in, the mixture in an amount sufficiently large to be detectable and sufficiently low as not to saturate the column, and to use that compound as the reference marker for determination of the RRT.

[00012] (+)-*N*-methyl-3-(1-naphtalenyloxy)-3-(3-thienyl)propanamine is disclosed by Olsen B.A et al, as an impurity obtained in the preparation of duloxetine (J. Lib. Chrom. & Rel. Technol, **1996**, 19, 1993).

[00013] There is a need in the art for duloxetine HCl, having improved chemical and/or enantiomeric purity, compared to duloxetine HCl obtained with prior art methods. The present invention provides such a duloxetine hydrochloride, having improved chemical and/or enantiomeric purity.

SUMMARY OF THE INVENTION

[00014] In one embodiment, the present invention encompasses pharmaceutically acceptable salts of duloxetine, containing less than about 0.14 percent area by HPLC of the impurity (+)-*N*-methyl-3-(1-naphtalenyloxy)-3-(3-thienyl)propanamine (DLX-ISO3).

[00015] In another embodiment, the present invention encompasses pharmaceutically acceptable salts of duloxetine, containing less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer.

[00016] In another embodiment, the present invention encompasses pharmaceutically acceptable salts of duloxetine, containing less than about 0.14 percent area by HPLC of the impurity DLX-ISO3 and less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer.

[00017] In another embodiment, the present invention encompasses duloxetine hydrochloride (HCl), containing less than about 0.14 percent area by HPLC of the impurity DLX-ISO3.

[00018] In another embodiment, the present invention encompasses duloxetine HCl, containing less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer.

[00019] In another embodiment, the present invention encompasses duloxetine HCl, containing less than about 0.14 percent area by HPLC of the impurity DLX-ISO3 and less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer.

[00020] In another embodiment, the present invention encompasses pharmaceutical formulations comprising the chemically and/or enantiomerically pure duloxetine HCl or any other pharmaceutically acceptable salts of duloxetine, described above.

BRIEF DESCRIPTION OF THE FIGURES

[00021] Figures 1 and 2 depict HPLC chromatograms of the commercial tablet CYMBALTA®, showing a RRT of 1.20 for DLX-ISO3 and a RRT of 1.50 for the duloxetine R-enantiomer, respectively.

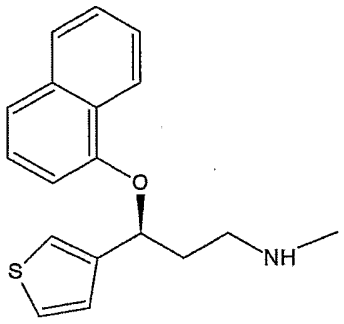
DETAILED DESCRIPTION OF THE INVENTION

[00022] As used herein the term "crystallization" refers to a process comprising heating a mixture of a starting material and a solvent to a temperature of between about 10°C below and above the reflux temperature of the solvent to obtain a solution, and cooling the solution to a temperature of about 0°C to about 30°C.

[00023] The present invention provides chemically and/or enantiomerically pure pharmaceutically acceptable salts of duloxetine

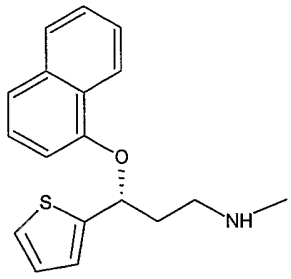
[00024] The present invention also provides chemically and/or enantiomerically pure duloxetine hydrochloride.

[00025] The chemical purity of duloxetine in the present invention relates to the level of the impurity (+)-*N*-methyl-3-(1-naphtalenyloxy)-3-(3-thienyl) propanamine, referred to herein as DLX-ISO3, and represented by the formula:



DLX-ISO3.

[00026] The enantiomeric purity in the present invention relates to the level of the R-enantiomer of duloxetine, (R)-(-)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine, represented by the formula:



[00027] As used herein, the terms "chemically pure duloxetine HCl" and "chemically pure pharmaceutically acceptable salt of duloxetine" refer to duloxetine hydrochloride/pharmaceutically acceptable salt of duloxetine, containing less than about 0.14 percent area by HPLC of the DLX-ISO3 impurity. Preferably, the level of DLX-ISO3 is less than about 0.07 percent area by HPLC, and, most preferably, is less than about 0.02 percent area by HPLC. A chemically pure duloxetine HCl/pharmaceutically acceptable salt of duloxetine in accordance with the invention may be substantially free of DLX-ISO3, such that the DLX-ISO3 is below the detection limit; i.e., the chemically pure duloxetine HCl/pharmaceutically acceptable salt of duloxetine preferably contains essentially 0.0 percent DLX-ISO3 within the error limits of the detection.

[00028] As used herein, the term "enantiomerically pure duloxetine HCl" and "enantiomerically pure pharmaceutically acceptable salt of duloxetine" refer to a

duloxetine HCl/pharmaceutically acceptable salt of duloxetine, containing less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer. Preferably, the level of the duloxetine R-enantiomer is less than about 0.03 percent area by HPLC, and, more preferably, is less than about 0.02 percent area by HPLC. An enantiomerically pure duloxetine HCl/pharmaceutically acceptable salt of duloxetine in accordance with the invention may be substantially free of the R-enantiomer, such that the R-enantiomer is below the detection limit; i.e., the enantiomerically pure duloxetine HCl/pharmaceutically acceptable salt of duloxetine preferably contains essentially 0.0 percent R-enantiomer within the error limits of the detection.

[00029] The present invention also provides a process for the preparation of the duloxetine HCl described above. This process comprises dissolving duloxetine in water or a solvent selected from the group consisting of acetone, methyl ethyl ketone (MEK), methyl t-butyl ether (MTBE), ethanol, isopropanol, and n-butanol, and mixtures thereof with water, and crystallizing duloxetine HCl. Preferably, the solvent is a mixture of acetone and water or isopropanol.

[00030] Preferably, when the solvent is in a mixture with water, the ratio (vol/vol) of the solvent and water is at least about 97:3 to about 98.25:1.75, and, more preferably, the ratio is at least about 98:2. Preferably, the ratio (vol/vol) of the starting material and the water or solvent is about 1:10. Preferably, the dissolution occurs at reflux temperature. Preferably, after cooling, the solution is maintained while stirring, for about 10 minutes to about 24 hours.

[00031] Preferably, the duloxetine HCl obtained after the crystallization contains less than about 0.14 percent area by HPLC DLX-ISO3 and less than about 0.04 percent of the R-enantiomer of duloxetine. The crystallization process may be repeated in order to increase the chemical and enantiomeric purity even further either with the same or a different solvent that was used for the first crystallization.

[00032] The present invention further provides pharmaceutical formulations comprising the duloxetine HCl or any other pharmaceutically acceptable salts of duloxetine, described above.

[00033] 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.

[00034] 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.

[00035] 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, pregelatinized 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.

[00036] 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.

[00037] 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.

[00038] 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.

[00039] 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.

[00040] 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.

[00041] 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.

[00042] 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.

[00043] 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.

[00044] 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.

[00045] Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol, and invert sugar may be added to improve the taste.

[00046] 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.

[00047] 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.

[00048] 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.

[00049] 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.

[00050] Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches, and lozenges, as well as liquid syrups, suspensions, and elixirs.

[00051] 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.

[00052] The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

[00053] 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.

[00054] 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.

[00055] 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.

[00056] 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.

[00057] 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 analysis of the duloxetine HCl and methods for preparing the duloxetine HCl of the invention.

[00058] 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

HPLC method for measuring chemical purity:

Column:	Hypersyl Gold (150 x 4.6 5μ)
Mobile phase:	(A) 63% (KH_2PO_4 (0.02M) pH-2.5): 37% (35%MeOH:10%THF)
	(B) 20% (KH_2PO_4 (0.02M) pH-2.5): 80% ACN
Gradient:	From 0 to 15 min (A) isocraticaly
	From 15 to 60 min (B) increases from 0 to 100%
Detection:	230 nm
Flow:	1 mL/min
Detection limit:	0.02%

HPLC method for measuring enantiomeric purity:

Column:	Diacel Chiral OD 250 x 4.6 5μ
Eluent:	Hexane (900mL):IPA (100mL): DEA(2mL)
Flow:	1mL/min
Detection:	230 nm
Sample conc:	0.5mg/mL
Sample vol:	100μL
Column temp:	20°C
Detection limit:	0.02%

Example 1: Purification of Duloxetine hydrochloride in acetone/water

Example 1a:

[00059] A mixture of 20 g Duloxetine hydrochloride in 204 ml acetone/water (98:2) was heated to reflux. After the compound was dissolved, the oil bath was removed, and the solution was cooled to 15°C overnight. The solid was filtered, washed with acetone, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (78 percent yield), containing DLX-ISO3 (0.21 percent) and enantiomer R (<0.03 percent)

Example 1b:

[00060] A mixture of 13 g of the previously obtained Duloxetine hydrochloride in 130 ml acetone/water (98:1.5) was heated to reflux. After the compound was dissolved, the oil bath was removed, and the solution was cooled to 10°C for 2 hours. The solid was filtered, washed with acetone, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (87 percent yield), containing DLX-ISO3 (0.15 percent) and free of enantiomer R.

Example 1c:

[00061] A mixture of 10 g of the previously obtained Duloxetine hydrochloride in 100 ml acetone/water (98:2) was heated to reflux. After the compound was dissolved, the oil bath was removed, and the solution was cooled to room temperature and stirred for 1 hour. The solid was filtered, washed with acetone, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (80 percent yield), containing DLX-ISO3 (0.07 percent), and free of enantiomer R.

Example 1d:

[00062] A mixture of 7.5 g of the previously obtained Duloxetine hydrochloride in 75 ml acetone/water (98:2) was heated to reflux. After the compound was dissolved, the oil bath was removed, and the solution was cooled to room temperature, and stirred for 2 hours. The solid was filtered, washed with acetone, and dried in a vacuum oven at 40°C for 16 hours, giving Duloxetine hydrochloride (73 percent yield), containing DLX-ISO3 (0.03 percent), and free of enantiomer R.

Example 2: Purification of Duloxetine hydrochloride in acetone/water under different conditions

Example 2a:

[00063] A mixture of 16 g Duloxetine hydrochloride (contaminated with 0.30 percent DLX-ISO3 and 0.13 percent enantiomer R) in 160 ml acetone was heated to reflux, and then 4 ml of water were added till complete dissolution. After the compound was dissolved, the oil bath was removed, and the solution was cooled to room temperature and stirred for one hour. The solid was filtered, washed with acetone, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (68 percent yield), containing DLX-ISO3 (0.10 percent) and free of enantiomer R.

Example 2b:

[00064] A mixture of 8 g of the previously obtained Duloxetine hydrochloride in 80 ml acetone was heated to reflux, and 2 ml of water were added. After the compound was dissolved, the oil bath was removed, and the solution was cooled to room temperature and stirred for half hour. The solid was filtered, washed with

acetone, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (36 percent yield), containing DLX-ISO3 (0.06 percent).

Example 2c:

[00065] A mixture of 2 g of the previously obtained Duloxetine hydrochloride in 20 ml of acetone was heated to reflux, and 0.4 ml of water were added. After the compound was dissolved, the oil bath was removed, and the solution was cooled to room temperature and stirred for three hours. The solid was filtered, washed with acetone, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (50 percent yield) free of DLX-ISO3.

Example 3: Purification of Duloxetine hydrochloride in ethyl acetate

[00066] A mixture of 2 g Duloxetine hydrochloride (contaminated with 0.46 percent DLX-ISO3 and 0.13 percent enantiomer R) in 10 ml ethyl acetate was heated to reflux, and 50 ml of ethyl acetate were added. The mixture was stirred at the same temperature for 40 minutes, followed by cooling to room temperature and stirring for two hours. The solid was filtered, washed with ethyl acetate, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (93 percent yield), containing DLX-ISO3 (0.28 percent) and 0.07 percent of enantiomer R.

[00067] Example 3 was repeated to yield Duloxetine hydrochloride, containing less than 0.14 percent DLX-ISO3.

Example 4: Purification of Duloxetine hydrochloride in IPA

Example 4a:

[00068] A mixture of 8.4 g Duloxetine hydrochloride (contaminated with 0.29 percent DLX-ISO3 and 0.17 percent enantiomer R) in 84 ml IPA was heated to reflux. The solution was stirred at the same temperature for 15 minutes, followed by cooling to room temperature and stirring for two hours. The solid was filtered, washed with IPA, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (62 percent yield), containing DLX-ISO3 (0.21 percent) and free of enantiomer R.

Example 4b:

[00069] A mixture of 8.8 g Duloxetine hydrochloride (contaminated with 0.21 percent DLX-ISO3) in 70 ml IPA was heated to reflux. The solution was stirred at the same temperature for 15 minutes, followed by cooling to room temperature and stirring for two hours. The solid was filtered, washed with IPA, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (83 percent yield), containing DLX-ISO3 (0.17 percent).

Example 4c

[00070] A mixture of 5 g Duloxetine hydrochloride (contaminated with 0.17 percent DLX-ISO3) in 40 ml IPA was heated to reflux. The solution was stirred at the same temperature for 15 minutes, followed by cooling to room temperature and stirring for two hours. The solid was filtered, washed with IPA, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (65 percent yield), containing DLX-ISO3 (0.13 percent)

Example 5: Purification of Duloxetine hydrochloride in MTBE/water:

Example 5a

[00071] A mixture of 12 g Duloxetine hydrochloride (contaminated with 0.29 percent DLX-ISO3 and 0.11 percent enantiomer) in 120 ml MTBE was heated to reflux, and 3.6 ml of water were added until complete dissolution. The two phase solution was stirred at the same temperature for 15-30 minutes, followed by cooling to room temperature and stirring overnight. The solid was filtered, washed with the same solvents, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (29 percent yield), containing DLX-ISO3 (0.16 percent) and less than 0.02 percent of enantiomer R.

Example 5b:

[00072] A mixture of 2 g Duloxetine hydrochloride (contaminated with 0.16 percent DLX-ISO3 and less than 0.03 percent of enantiomer R) in 20 ml MTBE is heated to reflux, and 0.36 ml of water are added until complete dissolution. The two phase solution is stirred at the same temperature for 15 to 30 minutes, followed by cooling to room temperature and stirring overnight. The solid is filtered, washed with

the same solvents, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (29 percent yield).

Example 6: Purification of Duloxetine hydrochloride in MEK/water:

Example 6a:

[00073] A mixture of 4 g Duloxetine hydrochloride (contaminated with 0.30 percent DLX-ISO3 and 0.17 percent enantiomer R) in 20 ml MEK was heated to reflux, and 0.6 ml of water were added until complete dissolution. The solution was stirred at the same temperature for 15-30 minutes, followed by cooling to 0° to 5°C and stirring for two hours. The solid was filtered, washed with the same solvents, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (32 percent yield), containing DLX-ISO3 (0.10 percent) and free of enantiomer R.

Example 6b:

[00074] A mixture of 0.5 g Duloxetine hydrochloride (contaminated with 0.10 percent DLX-ISO3) in 2.5 ml MEK is heated to reflux, and 0.1 ml of water are added until complete dissolution. The solution is stirred at the same temperature for 15 to 30 minutes, followed by cooling to 0° to 5°C and stirring for two hours. The solid is filtered, washed with the same solvents, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (32 percent yield).

Example 7: Purification of Duloxetine hydrochloride in water

[00075] A mixture of 2.7 g Duloxetine hydrochloride (contaminated with 0.50 percent DLX-ISO3 and 0.29 percent enantiomer R) in 27 ml water was heated to reflux. The solution was stirred at the same temperature for 10 to 15 minutes, followed by cooling to room temperature and stirring overnight. The solid was filtered, washed with water, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (61 percent yield), containing DLX-ISO3 (0.25 percent) and free of enantiomer R.

[00076] Example 7 is repeated to yield Duloxetine hydrochloride, containing less than 0.14 percent DLX-ISO3.

Example 8: Purification of Duloxetine hydrochloride in MEK

[00077] A mixture of 2 g Duloxetine hydrochloride (contaminated with 0.26 percent DLX-ISO3 and 0.17 percent enantiomer R) in 40 ml MEK was heated to reflux. The solution was stirred at the same temperature for 30 minutes, followed by cooling to 0° to 5°C and stirring for 2 hours. The solid was filtered, washed with MEK, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (60 percent yield) contaminated with DLX-ISO3 (0.21 percent) and free of enantiomer R.

[00078] Example 8 is repeated to yield Duloxetine hydrochloride, containing less than 0.14 percent DLX-ISO3.

Example 9: Purification of Duloxetine hydrochloride in acetone

Example 9a:

[00079] A mixture of 2 g Duloxetine hydrochloride (contaminated with 0.46 percent DLX-ISO3 and 0.13 percent enantiomer R) in 130 ml acetone was heated to reflux. The solution was stirred at the same temperature for one hour, followed by cooling to 27°C. The solid was filtered at the same temperature, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (59.50 percent yield), containing DLX-ISO3 (0.17 percent) and free of enantiomer R.

Example 9b:

[00080] A mixture of 1 g Duloxetine hydrochloride (contaminated with 0.17 percent DLX-ISO3) in 65 ml acetone was heated to reflux. The solution was stirred at the same temperature for one hour, followed by cooling to 27°C. The solid was filtered at the same temperature, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (59.50 percent yield).

Example 10: Purification of Duloxetine hydrochloride in n-butanol

[00081] A mixture of 2 g Duloxetine hydrochloride (contaminated with 0.26 percent DLX-ISO3 and 0.17 percent enantiomer R) in 12 ml n-butanol was heated to reflux. The solution was stirred at the same temperature for 10 minutes, followed by cooling to room temperature and stirring for 1 hour. The solid was filtered, washed with n-butanol, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine

hydrochloride (75 percent yield), containing DLX-ISO3 (0.24 percent) and 0.07 percent of enantiomer R.

[00082] Example 10 is repeated, using a solvent selected from: C_{2-5} ketones, C_{2-5} alkyl esters, C_{2-5} alkyl ethers, C_{2-4} alkanols other than n-butanol and mixtures thereof with water to yield Duloxetine hydrochloride, containing less than 0.14 percent DLX-ISO3.

Example 11: Purification of Duloxetine hydrochloride in ethanol

[00083] A mixture of 2.22 g Duloxetine hydrochloride (contaminated with 0.28 percent DLX-ISO3 and 0.50 percent enantiomer R) in 22.2 ml ethanol was heated to reflux. The solution was stirred at the same temperature for 15 minutes, followed by cooling to room temperature and stirring for 1 hour. The solid was filtered, washed with n-butanol, and dried in a vacuum oven at 45°C for 16 hours, giving Duloxetine hydrochloride (36 percent yield), containing DLX-ISO3 (0.21 percent) and free of enantiomer R.

[00084] Example 11 is repeated to yield Duloxetine hydrochloride, containing less than 0.14 percent DLX-ISO3.

Example 12: Analysis of CYMBALTA® tablets

[00085] CYMBALTA® tablets were analyzed, and found to contain 0.16 percent of the impurity (+)-*N*-methyl-3-(1-naphtalenyloxy)-3-(3-thienyl)propanamine. The tablet also contained 0.04 percent of the undesired R-enantiomer. HPLC chromatograms of a CYMBALTA® tablet are depicted in Figures 1 and 2, showing a RRT of 1.20 for DLX-ISO3 and a RRT of 1.50 for the duloxetine R-enantiomer, respectively.

Comparative Example

[00086] The procedure disclosed in US 5,491,243 was repeated as follows: to a solution of 7 g Duloxetine base in 21 ml ethyl acetate were added 0.8 ml. of concentrated HCl and stirred at room temperature. After an hour the solution was cooled to 0-5 °C and stirred for an additional two hours. The resulting solid was filtered, washed with the same solvent, and dried in a vacuum oven at 45°C for 16 hours. Duloxetine hydrochloride was obtained in 42 percent yield, containing DLX-ISO3 (0.30 percent) and 0.35 percent of enantiomer R.

[00087] While it is apparent that the invention disclosed herein is well calculated to fulfill the objects stated above, it will be appreciated that numerous modifications and embodiments may be devised by those skilled in the art. Therefore, it is intended that the appended claims cover all such modifications and embodiments as falling within the true spirit and scope of the present invention.

What is claimed:

1. Pharmaceutically acceptable salts of duloxetine, containing less than about 0.14 percent area by HPLC of the impurity (+)-*N*-methyl-3-(1-naphtalenyloxy)-3-(3-thienyl)propanamine (DLX-ISO3).
2. The pharmaceutically acceptable salts of claim 1, containing less than about 0.07 percent area by HPLC of DLX-ISO3.
3. The pharmaceutically acceptable salts of claim 2, containing less than about 0.02 percent area by HPLC of DLX-ISO3.
4. The pharmaceutically acceptable salts of claim 3, containing about 0.0 percent area by HPLC of DLX-ISO3.
5. Pharmaceutically acceptable salts of duloxetine, containing less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer.
6. The pharmaceutically acceptable salts of claim 5, containing less than about 0.03 percent area by HPLC of the duloxetine R-enantiomer.
7. The pharmaceutically acceptable salts of claim 6, containing less than about 0.02 percent area by HPLC of the duloxetine R-enantiomer.
8. The pharmaceutically acceptable salts of claim 7, containing about 0.0 percent area by HPLC of the duloxetine R-enantiomer.
9. The pharmaceutically acceptable salts of any of claims 1 to 4, containing less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer.
10. The pharmaceutically acceptable salts of claim 9, containing less than about 0.03 percent area by HPLC of the duloxetine R-enantiomer.
11. The pharmaceutically acceptable salts of claim 10, containing less than about 0.02 percent area by HPLC of the duloxetine R-enantiomer.
12. The pharmaceutically acceptable salts of claim 11, containing about 0.0 percent area by HPLC of the duloxetine R-enantiomer.
13. Duloxetine hydrochloride (HCl), containing less than about 0.14 percent area by HPLC of the impurity (+)-*N*-methyl-3-(1-naphtalenyloxy)-3-(3-thienyl)propanamine (DLX-ISO3).
14. The duloxetine HCl of claim 13, containing less than about 0.07 percent area by HPLC of DLX-ISO3.
15. The duloxetine HCl of claim 14, containing less than about 0.02 percent area by HPLC of DLX-ISO3.

16. The duloxetine HCl of claim 15, containing about 0.0 percent area by HPLC of DLX-ISO3.
17. Duloxetine HCl, containing less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer.
18. The duloxetine HCl of claim 17, containing less than about 0.03 percent area by HPLC of the duloxetine R-enantiomer.
19. The duloxetine HCl of claim 18, containing less than about 0.02 percent area by HPLC of the duloxetine R-enantiomer.
20. The duloxetine HCl of claim 19, containing about 0.0 percent area by HPLC of the duloxetine R-enantiomer.
21. The duloxetine HCl of any of claims 13 to 16, containing less than about 0.04 percent area by HPLC of the duloxetine R-enantiomer.
22. The duloxetine HCl of claim 21, containing less than about 0.03 percent area by HPLC of the duloxetine R-enantiomer.
23. The duloxetine HCl of claim 22, containing less than about 0.02 percent area by HPLC of the duloxetine R-enantiomer.
24. The duloxetine HCl of claim 23, containing about 0.0 percent area by HPLC of the duloxetine R-enantiomer.
25. A pharmaceutical formulation, comprising the pharmaceutically acceptable salts of any of claims 1 to 12.
26. A pharmaceutical formulation, comprising the duloxetine HCl of any of claims 13 to 24.

Figure 1: a chromatogram of CYMBALTA®

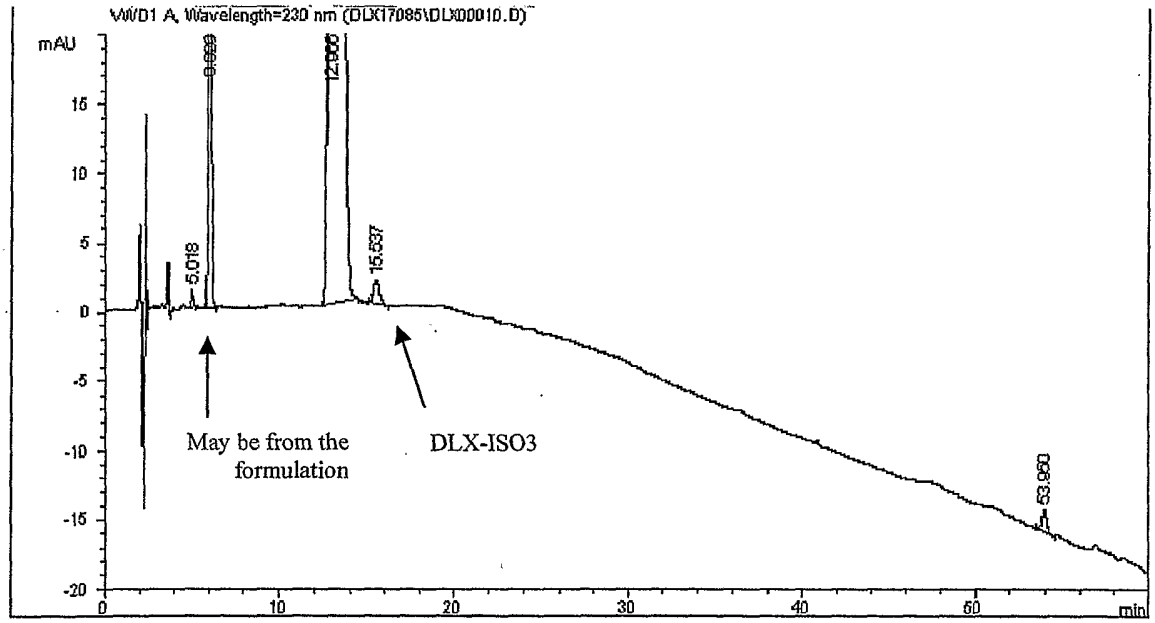
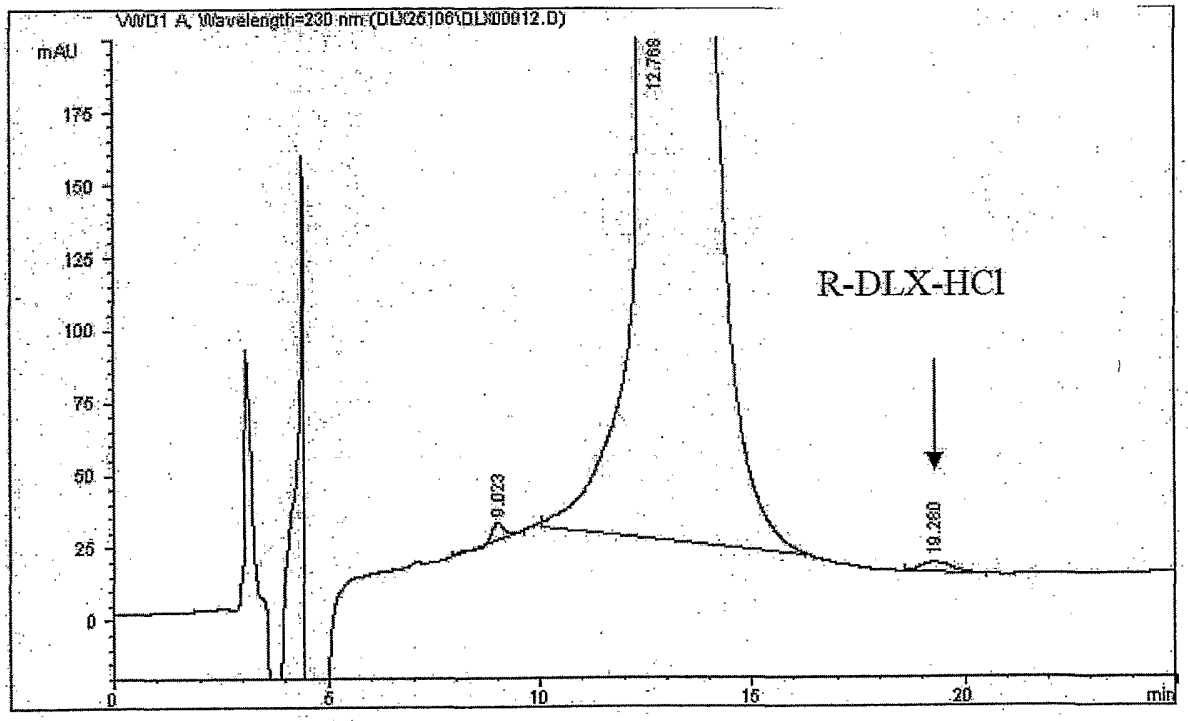


Figure 2: a chromatogram of CYMBALTA®



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009165

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D333/22 A61K31/38 A61P13/00 A61P25/24 A61P29/00

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)
C07D A61K A61P

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, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2006	24/07/2006

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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