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(54) Title: ORAL DOSAGE FORMS OF SERTRALINE HAVING CONTROLLED PARTICLE SIZE AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The present invention relates to pharmaceutical composition for oral administration comprising sertraline or pharmaceutically acceptable salts thereof in which the sertraline hydrochloride has a particle size of d?90#191 ranging from about 20 μm to about 40 μm and of d?50#191 ranging from about 5 μm to about 15 μm. The composition is bioequivalent to a reference pharmaceutical composition.

ORAL DOSAGE FORMS OF SERTRALINE HAVING CONTROLLED PARTICLE SIZE AND PROCESSES FOR THEIR PREPARATION

Technical Field of the Invention

The present invention relates to pharmaceutical compositions for oral administration that include sertraline or its pharmaceutically acceptable salts having a particle size of d_{90} ranging from about 20 μm to about 40 μm and d_{50} ranging from about 5 μm to about 15 μm and wherein the composition is bioequivalent to a reference composition. The present invention also relates to processes for their preparation.

Background of the Invention

Sertraline, or (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylenamine, is a therapeutically potent selective serotonin reuptake inhibitor. Sertraline is commercially sold as its hydrochloride salt under the trademark Zoloft® and is approved by the U.S. Food and Drug Administration for the treatment of depression, obsessive-compulsive disorder, posttraumatic stress disorder and panic disorder.

Sertraline is disclosed in U.S. 4,536,518 which describes the synthesis of certain cis-4-phenyl-1,2,3,4-tetrahydronaphthalenamine derivatives, including sertraline, and pharmaceutically acceptable salts of these compounds. Further methods of preparing sertraline are set forth in U.S. Patent Nos. 4,777,288; 4,839,104; 4,855,500; 5,463,126; 5,442,116; 5,082,970; 5,466,880; 5,196,607; 5,750,794; 5,288,916; and 6,323,500; as well as in the following published patent applications: International PCT Patent Publication No. WO 99/57089; European Patent Publication Nos. EP 997 535 A1 and EP 1 059 287 A1; and U.S. Patent Publication No. 2001-0044142 A1.

According to U.S. 5,248,699, the sertraline hydrochloride produced by the method of the U.S. 4,536,518 has a crystalline form denominated "Form II." It discloses four other polymorphs of sertraline hydrochloride designated as Forms I, III, IV, and V, and characterizes them by single crystal x-ray analysis, powder x-ray diffraction, infra-red spectroscopy, and differential scanning calorimetry. Both of the above patents also disclose certain dry solid pharmaceutical composition prepared by blending sertraline with conventional ingredients used in tablet and capsule manufacturing.

PCT application WO 03/93217 discloses a tablet of sertraline hydrochloride and the following excipients, in weight to weight percentages, wherein the tablet is prepared from an

industrial sized batch of sertraline hydrochloride Form II substantially free of sertraline hydrochloride Form I: about 20% to about 35% sertraline hydrochloride Form II, about 25% to about 40% lactose monohydrate, about 5% to about 12% croscarmellose sodium NF, about 1% to about 3% povidone, about 20% to about 40% microcrystalline cellulose and about 0.5% to about 2.5% magnesium stearate. The highly pure sertraline hydrochloride Form II used for preparing a tablet has a particle size distribution such that 100% of the particles are below 200 microns, more preferably below 100 microns and most preferably below about 50 microns.

The reduction in particle size of a drug so as to increase the surface area available for absorption is a commonly used practice in the realm of pharmaceutical sciences. A reduced particle size is known to enhance dissolution and absorption of the drug from an oral dosage form. However, such an increase in the rate and adsorption still cannot ensure that the dosage form is bioequivalent to a reference dosage form.

We have surprisingly found that pharmaceutical compositions comprising sertraline or its pharmaceutically acceptable salts, which are bioequivalent to the marketed preparation, may be prepared by controlling the particle size of sertraline, more particularly by using a finer particle size.

Summary of the Invention

In one general aspect there is provided a pharmaceutical composition for oral administration. The pharmaceutical composition includes sertraline or pharmaceutically acceptable salts, the sertraline having a particle size distribution of d_{90} of about 20 μm to about 40 μm and d_{50} of about 5 μm to about 15 μm, and one or more pharmaceutically acceptable excipients.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the one or more pharmaceutically acceptable excipients may be one or more of diluents, disintegrants, binders, glidants, and lubricants. The diluent may be one or more of powdered cellulose, microcrystalline cellulose, microfine cellulose, lactose, starch, pregelatinized starch, sugar alcohols, dextrates, dextrin, dextrose, and inorganic diluents. The sugar alcohol may be one or more of mannitol, sorbitol, and erythritol. The inorganic diluent may be one or more of calcium carbonate, calcium sulphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, potassium chloride, sodium chloride and talc.

The disintegrant may be one or more of carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, cross-linked polyvinyl pyrrolidone, sodium starch glycolate, magnesium aluminum silicate, powdered cellulose, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, polacrilin potassium, starch, pregelatinized starch, alginic acid and sodium alginate.

The binder may be one or more of gum acacia, guar gum, alginic acid, sodium alginate; carbomer, dextrin, gelatin, ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polymethacrylates, polyvinylpyrrolidone and pregelatinized starch.

The glidant may be one or more of talc, colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch and tribasic calcium phosphate. The lubricant may be one or more of magnesium stearate, calcium stearate, glyceryl monostearate, glycerylpalmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

The pharmaceutical composition may include (a) about 5% to about 70% by weight of sertraline hydrochloride, (b) about 20% to 80% by weight of a diluent, (c) about 2% to 20% by weight of a disintegrant, (d) about 1% to 20% by weight of a binder, and (e) about 0.5 % to 5% by weight of a lubricant. The pharmaceutical composition may be a tablet.

In another general aspect there is provided a process for preparing a tablet of sertraline hydrochloride. The process includes: (a) providing sertraline hydrochloride, wherein the sertraline has a particle size distribution of d_{90} of about 20 μm to about 40 μm and d_{50} of about 5 μm to about 15 μm; (b) preparing a blend comprising the sertraline hydrochloride and one or more pharmaceutically acceptable excipients; (c) optionally granulating the blend; and (d) processing the blend into a composition.

Embodiments of the process may include one or more of the following features or those described above. For example, the one or more pharmaceutically acceptable excipients may be about 20% to 80% by weight of a diluent, about 2% to 20% by weight of a disintegrant, about 1% to 20% by weight of a binder, and about 0.5 % to 5% by weight of a lubricant. The sertraline hydrochloride may be about 5% to about 70% by weight of the pharmaceutical composition.

The blend may be granulated by a granulating fluid. The granulation may be roller compaction. The blend of step (b) may be directly compressed into tablets.

In another general aspect there is provided a method for treating a disorder selected from major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder and social anxiety disorder in a patient. The method includes administering to the patient a pharmaceutical composition comprising sertraline or pharmaceutically acceptable salts thereof. The sertraline hydrochloride has a particle size distribution of d_{90} of about 20 μm to about 40 μm and d_{50} of about 5 μm to about 15 μm.

Embodiments of the process may include one o more of the following features or those described above. For example, the pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients may be about 20% to 80% by weight of a diluent, about 2% to 20% by weight of a disintegrant, about 1% to 20% by weight of a binder, and about 0.5 % to 5% by weight of a lubricant and the sertraline hydrochloride comprises about 5% to about 70% by weight of the pharmaceutical composition.

In another aspect, there is provided a pharmaceutical composition for oral administration comprising sertraline or pharmaceutically acceptable salts thereof, having a particle size distribution as follows

d_{90}: about 20 μm to about 40 μm

d_{50}: about 5 μm to about 15 μm

d_{10}: about 1 μm to 7 μm;

wherein the composition is bioequivalent to a reference composition.

In the above aspects, d_{10} may range from about 1 μm to about 7 μm.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The term "sertraline or pharmaceutically acceptable salts" as used herein includes non-salt, non-hydrated free base as well as pharmaceutically acceptable acid addition salts

and polymorphs thereof. The pharmaceutically acceptable acid addition salts may be present in the form of a hydrate or polymorph, more particularly in the form of sertraline hydrochloride form II. Sertraline or its pharmaceutically acceptable acid addition salt may be present in an amount ranging from 5% to 70% by weight of the composition.

The term "reference composition" as used herein refers to the marketed preparation of sertraline hydrochloride which is sold under the trade name ZOLOFT® by Pfizer.

The term "bioequivalent" as used herein is intended to illustrate bioequivalence of the compositions of the present invention in comparison to the reference composition. Bioequivalence studies are conducted to demonstrate equivalence in the bioavailability of the active ingredient in different formulations. The U.S. Food and Drug Administration (FDA) requires ANDA filers to show bioequivalence against the innovator's reference listed product before approval. Bioequivalence study involves statistical analysis for pharmacokinetic measures, such as area under the curve (AUC) and peak concentration (C_{max}) for a test (T) and reference (R) drug product, where T and R can vary, depending on the comparison to be performed (e.g., to-be-marketed dosage form versus clinical trial material, generic drug versus reference listed drug, drug product changed after approval versus drug product before the change).

Bioequivalence comparisons normally rely on (1) a criterion, (2) a confidence interval for the criterion, and (3) a predetermined bioequivalence limit. According to the FDA guidance, demonstration of bioequivalence involves the calculation of a 90% confidence interval for the ratio of the averages of the measures for the T and R products. To establish bioequivalence, the calculated confidence interval should fall within a limit of 80-125% for the ratio of the product averages. For a broad range of drugs, a bioequivalence limit of 80 to 125% for the ratio of the product averages has been adopted for use of a bioequivalence criterion. Generally, the bioequivalence limit of 80 to 125% is based on a clinical judgment that a test product with bioavailability measures outside this range should be denied market access.

The term "d_{90}", "d_{50}" and "d_{10}" as used herein denotes that 90%, 50% and 10%, respectively, of the particles are smaller than the specified size. The initial experiments, which we conducted using a larger particle size of sertraline, presented many problems because of the highly crystalline nature, such as capping and lamination of the tablet. In an effort to overcome such problems, it was surprisingly found that the controlled reduction of

the particle size of sertraline not only provided a solution to the above problems but also increased the compressibility of sertraline and proved instrumental in rendering the composition bioequivalent in comparison to the reference composition.

The particle size of the drug may be reduced by conventional size-reduction methods known in the art, such as the various milling techniques, more particularly air jet milling. Air jet milling is a well-proven technique that consistently produces particles in the 1-30 micron range. In such a technique the particles of sertraline to be comminuted are accelerated in a stream of compressed air and micronized in a grinding chamber by their impact against each other. The primary advantage of such a procedure is that the particle reduction occurs via particle to particle collisions with limited reduction from metal to product contact and no generation of heat.

The pharmaceutical compositions as described herein include powders, granulates, tablets and capsules. Sertraline and pharmaceutically acceptable excipients may be formulated into compositions 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 sertraline and pharmaceutically acceptable excipients such as diluents, disintegrants and binders are blended and then further mixed in the presence of a granulating fluid that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled. The granulate may then be mixed with other excipients such as a glidant and/or a lubricant, and compressed to form tablets or filled into hard gelatin capsules.

Diluents may be selected from cellulose-derived materials such as powdered cellulose, microcrystalline cellulose, microfine cellulose, and the like; lactose, starch, pregelatinized starch, sugars and sugar alcohols such as mannitol, sorbitol, erythritol and the like; dextrates, dextrin, dextrose, inorganic diluents such as calcium carbonate, calcium sulphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, potassium chloride, sodium chloride, talc and such other diluents known to the pharmaceutical industry. The diluent may be present in an amount ranging from 20% to 80% by weight of the composition.

Disintegrants which may be used include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, cross-linked polyvinyl pyrrolidone, sodium starch glycolate, magnesium aluminum silicate,

powdered cellulose, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, polacrilin potassium, pregelatinized starch, sodium alginate, starch and the like. The disintegrant may be present in an amount ranging from 2% to 20% by weight of the composition.

Binders which may be used include gums such as acacia, guar gum, alginic acid, sodium alginate; carbomer, dextrin, gelatin, ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinized starch, and the like. The binder may be present in an amount ranging from 1% to 20% by weight of the composition.

Glidants which may be used include talc, colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, tribasic calcium phosphate and the like. The glidant may be present in an amount ranging from 0.5% to 5% by weight of the composition.

Lubricants which may be used include magnesium stearate, calcium stearate, glyceryl monostearate, glycerylpalmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate and the like. The lubricant may be present in an amount ranging from 0.5% to 5% by weight of the composition.

The compositions may also include additional excipients such as flavoring agents, colors, and the like. Flavoring agents may be selected from common flavor enhancers for pharmaceutical compositions such as vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, tartaric acid and the like. Colors may be selected from the group of ferric oxide, titanium dioxide, F.D. & C. and D. & C. dyes and the like.

A tableting composition may also be prepared by dry granulation. For example, the blended composition of the sertraline and excipients, as described above, may be compacted into a sheet by a roller compactor and then comminuted into granules. The compacted granules may subsequently be compressed into tablets.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques.

The pharmaceutical composition as described herein may be a capsule containing the composition, preferably a powdered or granulated composition as described above, within either a hard or soft shell. Tablets and granules may be coated. The coating may be an

enteric coating or non-functional coating. Suitable coatings for enteric-coated compositions include cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of methacrylic acid and methyl methacrylate, and like materials. If desired, the coating may be employed with suitable plasticizers and/or extending agents. Non-functional coatings include coating compositions like Opadry® or Lustreclear® sold by Colorcon.

In one of the embodiments, pharmaceutical compositions for oral administration of sertraline hydrochloride having a particle size d_{90} ranging from about 20 μm to about 40 μm and d_{50} ranging from about 5 μm to about 15 μm may be prepared by

a) blending sertraline hydrochloride, diluent and disintegrant;

b) granulating the blend obtained in step (a) with a binder solution;

c) drying and sizing the granules;

d) blending the granules obtained in step (c) with one or more of diluents, disintegrants, lubricants and glidants;

e) compressing the blend to form tablets; and

f) optionally coating the tablets with a non-functional coating.

In another embodiment, pharmaceutical compositions for oral administration of sertraline hydrochloride having a particle size d_{90} ranging from about 20 μm to about 40 μm and d_{50} ranging from about 5 μm to about 15 μm may be prepared by

a) blending sertraline hydrochloride, diluent and disintegrant;

b) granulating the blend obtained in step (a) with water;

c) drying and sizing the granules;

d) blending the granules obtained in step (c) with one or more of diluents, disintegrants, lubricants and glidants;

e) compressing the blend to form tablets; and

f) optionally coating the tablets with a non-functional coating.

In another embodiment, pharmaceutical compositions for oral administration of sertraline hydrochloride having a particle size d_{90} ranging from about 20 μm to about 40 μm and d_{50} ranging from about 5 μm to about 15 μm may be prepared by:

a) blending sertraline hydrochloride and one or more of diluents, disintegrants and binders;

b) compacting the blend obtained in step (a) with a roller compactor;

c) sizing the compacts to form granules;

d) blending the granules obtained in step (c) with one or more of diluents, disintegrants, binders, glidants and lubricants; and

e) compressing the blend to form tablets.

In another embodiment, pharmaceutical compositions for oral administration of sertraline hydrochloride having a particle size d_{90} ranging from about 20 μm to about 40 μm and d_{50} ranging from about 5 μm to about 15 μm may be prepared by:

a) blending sertraline hydrochloride and one or more of diluents, disintegrants, binders, lubricants and glidants; and

b) compressing the blend to form tablets.

The invention described herein is further illustrated by the following examples which are provided merely for illustrative purposes and should not be construed as limiting the scope of the invention.

Example 1

Ingredients	**Qty. per tablet (in mg)**
Intragranular ingredients	
Sertraline HCl (Equivalent to 100 mg of Sertraline)	111.92#
Microcrystalline cellulose	101.08
Di calcium phosphate	32.00
Sodium starch glycolate	6.00
Hydroxypropyl cellulose	10.00
Purified water	Q.S
Extragranular ingredients	
Microcrystalline cellulose	30.00
Sodium starch glycolate	6.00
Magnesium stearate	3.00
Total	**300.00**
Opadry	9.00
Purified water	Q.S

#d_{90}=24 μm; d_{50}=10 μm; d_{10}=3.8 μm

[Particle size distribution as determined by laser beam diffraction (Malvern mastersizer)]

PROCEDURE:

1. Sertraline HCl, microcrystalline cellulose, dicalcium phosphate, and sodium starch glycolate are mixed in high shear mixer.
2. The blend obtained above is granulated using an aqueous solution of hydroxypropyl cellulose.
3. The granules are dried and milled.
4. The dried granules are blended with microcrystalline cellulose, sodium starch glycolate (only in example 1), magnesium stearate and compressed using appropriate tooling.
5. The tablets are coated using an Opadry coating mixture.

TABLE 1: Dissolution profile of tablets of Example 1 as measured in a USP type II dissolution apparatus at 70 rpm in 900 ml of pH 4.5 Acetate Buffer at a temperature of 37±0.5°C

Time (min)	% Drug Release
15	97
30	98
45	99
60	99

TABLE 2: Comparative pharmacokinetic data for tablets of Examples 1 (T) and ZOLOFT® (R)

Pharmacokinetic parameter	T/R ratio (90% confidence interval)
C_{max}	96.01 (Limit: 81.65-112.9)
AUC_{last}	99.24 (Limit: 83.82-117.5)
AUC_{α}	99.89 (Limit: 85.42-116.83)

C_{max} = Maximum plasma concentration

AUC_{last} = Area under the plasma concentration *vs.* time curve from 0 hours to the time of last sample collected

AUC_{α} = Area under the plasma concentration *vs.* time curve from 0 hours to infinity

As is evident from Table 1, the composition of Example 1 is bioequivalent to the reference composition. This demonstrates the significance of using a particle size distribution of sertraline having d_{90} ranging from about 20 μm to about 40 μm and d_{50} ranging from about 5 μm to about 15 μm in the preparation of pharmaceutical compositions.

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art may appreciate that modifications may be made to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification.

We Claim:

1. A pharmaceutical composition for oral administration comprising sertraline or pharmaceutically acceptable salts, the sertraline having a particle size distribution of d_{90} of about 20 μm to about 40 μm and d_{50} of about 5 μm to about 15 μm and one or more pharmaceutically acceptable excipients.

2. The pharmaceutical composition of claim 1, wherein the one or more pharmaceutically acceptable excipients comprise one or more of diluents, disintegrants, binders, glidants, and lubricants.

3. The pharmaceutical composition according to claim 2, wherein the diluent comprises one or more of powdered cellulose, microcrystalline cellulose, microfine cellulose, lactose, starch, pregelatinized starch, sugar alcohols, dextrates, dextrin, dextrose, and inorganic diluents.

4. The pharmaceutical composition of claim 3, wherein the sugar alcohol comprises one or more of mannitol, sorbitol, and erythritol.

5. The pharmaceutical composition according to claim 3, wherein the inorganic diluent comprises one or more of calcium carbonate, calcium sulphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, potassium chloride, sodium chloride and talc.

6. The pharmaceutical composition according to claim 1, wherein the disintegrant comprises one or more of carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, cross-linked polyvinyl pyrrolidone, sodium starch glycolate, magnesium aluminum silicate, powdered cellulose, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, polacrilin potassium, starch, pregelatinized starch, alginic acid and sodium alginate.

7. The pharmaceutical composition according to claim 1, wherein the binder comprises one or more of gum acacia, guar gum, alginic acid, sodium alginate; carbomer, dextrin, gelatin, ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polymethacrylates, polyvinylpyrrolidone and pregelatinized starch.

8. The pharmaceutical composition according to claim 1, wherein the glidant comprises one or more of talc, colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch and tribasic calcium phosphate.

9. The pharmaceutical composition according to claim 1, wherein the lubricant comprises one or more of magnesium stearate, calcium stearate, glyceryl monostearate, glycerylpalmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

10. The pharmaceutical composition according to claim 1, wherein the composition comprises

a) about 5% to about 70% by weight of sertraline hydrochloride,

b) about 20% to 80% by weight of a diluent,

c) about 2% to 20% by weight of a disintegrant,

d) about 1% to 20% by weight of a binder, and

e) about 0.5 % to 5% by weight of a lubricant.

11. The pharmaceutical composition according to claim 10, wherein the composition comprises a tablet.

12. A process for the preparation of a tablet comprising sertraline hydrochloride, the process comprising:

a) providing sertraline hydrochloride, wherein the sertraline has a particle size distribution of d_{90} of about 20 μm to about 40 μm and d_{50} of about 5 μm to about 15 μm;

b) preparing a blend comprising the sertraline hydrochloride and one or more pharmaceutically acceptable excipients;

c) optionally granulating the blend; and

d) processing the blend into a composition.

13. The process of claim 12, wherein the one or more pharmaceutically acceptable excipients comprise about 20% to 80% by weight of a diluent, about 2% to 20% by

weight of a disintegrant, about 1% to 20% by weight of a binder, and about 0.5 % to 5% by weight of a lubricant.

14. The process of claim 12, wherein the sertraline hydrochloride comprises about 5% to about 70% by weight of the pharmaceutical composition.

15. The process according to claim 12, wherein the blend is granulated by a granulating fluid.

16. The process according to claim 12, wherein the granulation comprises roller compaction.

17. The process according to claim 12, wherein the blend of step (b) is directly compressed into tablets.

18. A method for treating a disorder selected from major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder and social anxiety disorder in a patient, the method comprising administering to the patient a pharmaceutical composition comprising sertraline or pharmaceutically acceptable salts thereof, wherein the sertraline hydrochloride has a particle size distribution of d_{90} of about 20 μm to about 40 μm and d_{50} of about 5 μm to about 15 μm.

19. The method of claim 18, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

20. The method of claim 19, wherein the one or more pharmaceutically acceptable excipients comprise about 20% to 80% by weight of a diluent, about 2% to 20% by weight of a disintegrant, about 1% to 20% by weight of a binder, and about 0.5 % to 5% by weight of a lubricant and the sertraline hydrochloride comprises about 5% to about 70% by weight of the pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/28 A61K31/135 A61P25/24

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)
A61K

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, EMBASE, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/044474 A1 (CURATOLO WILLIAM J ET AL) 22 November 2001 (2001-11-22) page 1, paragraph 2 page 4, paragraph 40 page 7, paragraph 61 page 6, paragraph 55 page 9, paragraph 77 page 17; examples 3A-3C page 19; example 6A page 28; table A claims 1-5,7,21	1-3,5-20
X	WO 2004/092110 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; HER) 28 October 2004 (2004-10-28) column 1, line 21 - line 26 column 65 - column 66; example 8 column 66; tables 8-1	1-3,7,8, 12,14, 15,18,19

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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

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 2006	25/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schüle, S

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000015

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/175346 A1 (BILLOTTE ANNE ET AL) 18 September 2003 (2003-09-18) page 3, paragraph 17 page 4, paragraphs 35,38,40 page 11; example 1	1-4,6,7, 9,11,12, 14,15, 17-19
X	WO 03/093217 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; BOR) 13 November 2003 (2003-11-13) cited in the application page 15, line 7 - line 12 page 15, line 4 - line 29 page 16, line 1 - line 9 page 16; table 1	1-3, 6-15, 17-20
A	EP 1 027 888 A (PFIZER PRODUCTS INC) 16 August 2000 (2000-08-16) page 12, paragraph 91 - page 13, paragraph 92 page 19; example 7	1-20
A	US 2002/015731 A1 (APPEL LEAH E ET AL) 7 February 2002 (2002-02-07) page 13; example 3	1-20
A	US 6 517 866 B1 (AM ENDE MARY TANYA ET AL) 11 February 2003 (2003-02-11) page 60; example 4	1-20

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/000015

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 - 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/000015

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