Title: A PHARMACEUTICAL DOSAGE FORM OF CITALOPRAM

Abstract: The present invention relates to pharmaceutical dosage forms of citalopram and processes of preparation thereof. Not less than about 36% of the citalopram particles, by volume, have a particle size that is less than about 5 μm. The citalopram particles may have an average aspect ratio of less than about two.
A PHARMACEUTICAL DOSAGE FORM OF CITALOPRAM

Field of the Invention

The technical field of the present invention relates to pharmaceutical dosage forms of citalopram and processes of preparation thereof.

Background of the Invention

Citalopram is an orally administered selective serotonin reuptake inhibitor (SSRI), and is indicated for the treatment of depression. It has a chemical structure unrelated to that of other SSRI's or to tricyclic, tetracyclic and other available antidepressant agents. The compound is also being evaluated for the treatment of dementia and cerebrovascular disorders. Citalopram hydrobromide is marketed as film coated tablets by Forest Labs, in strengths equivalent to 10, 20 and 40 mg of citalopram base.

Over the years, many potential candidates in drug discovery and research have failed to emerge as drugs due to their poor biopharmaceutic properties. A major portion of these failures is due to poor solubility characteristics. Citalopram is one such example of a poorly soluble drug posing serious dissolution problems, which may affect bioavailability. Few approaches have been disclosed in the prior art addressing solutions to the solubility problems of citalopram.

U.S. Patent Application No. 2001/049450 discloses that when citalopram hydrobromide is used as a pharmaceutical agent, the particle size, particle size distribution and aspect ratio of the crystal are all important characteristics that need to be controlled within certain limits during the preparation of pharmaceutical dosage forms. This publication refers to U.S. Patent No. 4,650,884 for a process of crystallizing citalopram hydrobromide but notes that when this process is used, the result is fine crystals having a particle size of less than 5 µm being produced in a large amount (41.9% of the total amount). With such particles, the publication notes that the filtering performance is degraded and fine particles scatter and expose workers to the active ingredient. For at least this reason, the 20010049450 publication teaches using a reduced amount of smaller particle sized citalopram to produce pharmaceutical dosage forms that contain citalopram rather than the large amount of small particle sized citalopram produced using the process disclosed in the '884 patent. It further discloses that citalopram hydrobromide crystals having a smaller average aspect ratio of less
than about two can results in problems, such as poor filtering performance after crystallization and poor fluidity when crystals are being taken out. Hence, citalopram hydrobromide crystals having a particle size of less than 5 μm in a proportion of 35% at most and an average aspect ratio between two and nine are advantageous for pharmaceutical bulk.

The methods disclosed above make use of highly controlled complex crystallization processes to achieve the critical particle characteristics. Hence, there is a need for simpler, cheaper and faster processes for the preparation of pharmaceutical dosage form of citalopram. In spite of the teachings of the prior art to avoid the use of relatively large amounts of smaller particles of citalopram, the inventors have now discovered that use of a smaller particle size of citalopram in pharmaceutical dosage forms overcomes the problems of poor dissolution and erratic bioavailability while avoiding complex crystallization processes.

**Summary of the Invention**

In one general aspect there is provided a pharmaceutical dosage form that includes citalopram. Not less than about 36% of the citalopram particles, by volume, have a particle size that is less than about 5 μm.

Embodiments of the pharmaceutical dosage form may include one or more of the following features. For example, not less than about 43% of the citalopram particles, by volume, may have a particle size that is less than about 5 μm. More particularly, not less than about 50% of the citalopram particles, by volume, may have a particle size that is less than about 5 μm.

Not less than about 99% of the citalopram particles, by volume, may have a particle size that is less than about 30 μm. Not less than about 99% of the citalopram particles, by volume, may have a particle size that is less than about 22 μm.

The citalopram particles may have an average aspect ratio of less than about 2. More particularly, the citalopram particles may have an average aspect ratio of less than about 1.7. Even more particularly, the citalopram particles may have an average aspect ratio of about 1.55.

Not less than about 99% of the citalopram particles, by volume, may have a particle size that is less than about 30 μm and an average aspect ratio of less than about 2. More
particularly, not less than about 99% of the citalopram particles, by volume, may have a particle size that is less than about 22 μm and an average aspect ratio of less than about 1.7.

The pharmaceutical dosage form may be a tablet or capsule. The citalopram may be free citalopram base or its pharmaceutically acceptable salt. The pharmaceutically acceptable salt of citalopram may be citalopram hydrobromide or citalopram hydrochloride.

The pharmaceutical dosage form may further comprise one or more pharmaceutically acceptable inert excipients. The one or more pharmaceutically acceptable inert excipients may be one or more of binders, diluents, surfactants, lubricants/glidants, and coloring agents.

In another general aspect there is provided a process for the preparation of a pharmaceutical dosage form of citalopram. The process includes the steps of blending citalopram with one or more pharmaceutically acceptable inert excipient(s) to form a blend, wherein not less than about 36% of the citalopram particles, by volume, have a particle size that is less than about 5 μm; and compressing the blend or filling the blend into a pharmaceutical dosage form.

Embodiments of the process may include one or more of the following features. For example, at least a portion of the citalopram particles may be prepared by the process of micronization. The micronization may be carried out in equipment that includes one or more of a ball mill, colloid mill, grinding mill, air jet mill, roller mill, and impact mill. In particular, the micronization may be carried out in an air jet mill.

Not less than about 43% of the citalopram particles, by volume, may have a particle size that is less than about 5 μm. More particularly, not less than about 50% of the citalopram particles, by volume, may have a particle size that is less than about 5 μm. The citalopram particles may have an average aspect ratio of less than about 2.

The process may further include granulating the blend of citalopram and pharmaceutically acceptable inert excipients. The granulation may be carried out by a wet granulation or dry granulation technique. In particular, the granulation may be carried out by a wet granulation technique.

The pharmaceutical dosage form may be a tablet or a capsule, and, in particular, may be a tablet.
In another general aspect there is provided a method of treating depression in a mammal. The method includes administering to the mammal a pharmaceutical dosage form that includes not less than about 36% of the citalopram particles, by volume, having a particle size less than about 5 μm.

Embodiments may include one or more of the following features or those described above. For example, the citalopram particles may have an average aspect ratio of less than about 2. Not less than about 43% of the citalopram particles, by volume, may have a particle size that is less than about 5 μm. More particularly, not less than about 50% of the citalopram particles, by volume, may have a particle size that is less than about 5 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 inventors have now discovered that a pharmaceutical dosage form of citalopram that includes not less than about 36% citalopram particles by volume having a particle size less than about 5 μm has increased dissolution and bioavailability.

The term “citalopram” as used herein includes free citalopram base as well as any of its pharmaceutically acceptable salt thereof. Specific examples of pharmaceutically acceptable salts of citalopram include citalopram hydrobromide, citalopram hydrochloride and the like.

The term “particle size” as used herein is an average diameter upon conversion of the volume of the particles into sphere. Particle size was measured using the Malvern Mastersizer.

The term “average aspect ratio” as used herein is an average value of the major axis/minor axis of particle. Average aspect ratio was measured using image analyzer system.

The term “pharmaceutical dosage form” as used herein includes conventional solid dosage forms such as tablet, capsule and the like.
The use of smaller particle size citalopram results in an increase in the effective exposed surface to the dissolving media, aiding in solubility and increasing the bioavailability of the dosage form. Further, citalopram particles having a smaller aspect ratio facilitate processing during the production of pharmaceutical dosage forms. Citalopram of a smaller particle size may be obtained by the process of micronization.

Micronization of citalopram particles may be carried out using any of the conventionally used equipments, such as a ball mill, colloid mill, grinding mill, air jet mill, roller mill, impact mill, etc. Air jet mill is particularly suited as most of the milling in an air jet mill occurs through particle-particle collision rather than collision of the particles with the metal surfaces of the equipment. There is thus a limited generation of heat during micronization that may lead to degradation of citalopram. The process of micronization in an air jet mill involves exposing citalopram particles to streams of compressed air or gas creating a fluidized bed of citalopram particles; acceleration towards the center of the mill; and collision of the particles with each other. These impacts break the particles into smaller micron size particles. By balancing airflow force and centrifugal force, citalopram particles of desired particle size can be separated.

Alternatively, citalopram may be micronized in the presence of one or more pharmacologically inert carriers or mixed with pharmacologically inert carriers after micronization to neutralize the static charge generated during the milling process.

The term “pharmacologically inert carrier” as used herein refers to a substance that is physiologically acceptable, compatible with citalopram and other excipients in the formulation, and has a capacity to absorb citalopram on its surface. The use of carriers also prevents the reagglomeration of citalopram particles and also helps in wetting of the citalopram by the uptake of water via capillary action and thereby enhancing dissolution further.

Suitable pharmacologically inert carriers include one or more of cellulose derivatives, such as microcrystalline cellulose and carboxymethylcellulose; silicate derivatives, such as magnesium silicate, colloidal silicon dioxide, magnesium trisilicate, and magnesium aluminum silicate; and clays, such as veegum, bentonite, etc.

Greater than or equal to 99% by volume of the citalopram particles should have a particle size that is less than about 30 μm. In particular, the particle size of this volume of
particles (i.e., 99% of the particles by volume) may be less than about 22 \( \mu m \). Moreover, not less than 36% by volume of the citalopram particles should have a particle size that is less than about 5 \( \mu m \). In particular, the particle size of not less than about 43% by volume of the citalopram particles should be less than about 5 \( \mu m \). Even more particularly, the particle size of not less than about 50% by volume of the citalopram particles should be less than about 5 \( \mu m \). The average aspect ratio of the citalopram particles after size reduction should be less than about two. In particular, the average aspect ratio may be less than about 1.7 or less than about 1.55.

The pharmaceutical dosage form of citalopram may include citalopram and one or more pharmaceutically acceptable inert excipients including one or more of binders, diluents, surfactants, disintegrants, lubricants/glidants, coloring agents, and the like. The pharmaceutically acceptable inert excipients may be used intragranularly and/or extragranularly.

Suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Suitable diluents include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like.

Suitable surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include one or more of polyethoxylated fatty acids and its derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 – 150 mono dilaurate, polyethylene glycol –20 glyceryl stearate; alcohol – oil transesterification products, for example, polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example, polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monomcaprylate; mono and diglycerides for example, glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example, polyethylene...
glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example, sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as “poloxamer”; ionic surfactants, for example, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like.

Suitable disintegrants include one or more of cross-linked polyvinylpyrrolidone, croscarmellose sodium and the like.

Suitable lubricants/glidsants include one or more of colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like.

Suitable coloring agents include any FDA approved colors for oral use.

The pharmaceutical dosage form of citalopram may optionally be coated with functional and/or non-functional layers comprising film-forming polymers, if desired.

Suitable film-forming polymers include one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate; waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit ® RL and RS; and the like. Alternatively, commercially available coating compositions may be used for the coating, including film-forming polymers marketed under various trade names, such as, Opadry®.

The pharmaceutical dosage form of citalopram may be prepared by processes known in the prior art, e.g. by comminuting, mixing, granulation, drying, sizing, filling, compressing, molding, spraying, immersing, coating, drying etc.

The pharmaceutical dosage form of citalopram may be prepared by blending citalopram and intragranular inert excipient(s); granulating with granulating fluid or solution/dispersion of binder; drying and sizing the granules; blending with extragranular pharmaceutically inert excipient(s); lubricating the blend; compressing the blend into suitable sized tablets; and, optionally, coating the tablets with film-forming polymers.
The pharmaceutical dosage form of citalopram may also be prepared by blending citalopram and intragranular inert excipient(s); dry granulating the blend by roller compaction or slugging; sizing the granules; blending with extragranular excipient(s); lubricating the blend; compressing the blend into suitable sized tablets; and, optionally, coating with film-forming polymers.

The pharmaceutical dosage form of citalopram may also be prepared by blending citalopram and inert excipient(s); lubricating the blend; directly compressing the blend into suitable sized tablets; and, optionally, coating with film-forming polymers.

Suitable solvents used for granulation or coating processes include one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water, and the like.

The following examples further exemplify the invention and are not intended to limit the scope of the invention.

**EXAMPLES 1-2**

**I. Composition**

**Table 1**

Composition of citalopram hydrobromide tablet

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight (mg)/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example 1</td>
</tr>
<tr>
<td><strong>Intragranular</strong></td>
<td></td>
</tr>
<tr>
<td>Micronized citalopram hydrobromide</td>
<td>50.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>25.0</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>80.0</td>
</tr>
<tr>
<td>Starch</td>
<td>70.0</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>5.0</td>
</tr>
<tr>
<td>Cross-linked polyvinylpyrrolidone</td>
<td>9.0</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s</td>
</tr>
<tr>
<td><strong>Extragranular</strong></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>53.0</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>5.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Procedure:

1. Micronized citalopram hydrobromide (with more than 99% of the particles, by
   volume, having particle size less than about 22 μm and more than 50% of the
   particles, by volume, having particle size less than about 5 μm; and an average
   aspect ratio of about 1.55), intragranular microcrystalline cellulose, lactose
   monohydrate and croscarmellose sodium were blended in a mixer granulator and
   granulated with purified water.

2. Granules of step 1 were dried and sieved through suitable sized sieves.

3. Granules of step 2 were blended with extra granular microcrystalline cellulose and
   croscarmellose sodium.

4. Blend of step 3 was lubricated by blending with magnesium stearate and
   compressed into tablets using suitable tooling.

5. Opadry was dissolved in water to prepare the coating composition.

6. Tablets of step 4 were coated with the coating composition of step 5 using
   conventional coating technique.

II. In vitro dissolution study

Comparative in vitro release of citalopram hydrobromide from citalopram tablets as
per composition of Examples 1 and 2, and the marketed Celexa® (40mg) tablets were studied
in 800 ml HCl buffer media (pH 1.5) using USP I dissolution apparatus, at a basket speed of
50 rpm. The results of the study are given in Table 2.
Table 2

*In vitro* release of citalopram hydrobromide tablets prepared according to Examples 1 and 2, and Celexa® tablets

<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>Cumulative percentage (%) release of citalopram hydrobromide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example 1</td>
</tr>
<tr>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td>30</td>
<td>97</td>
</tr>
<tr>
<td>45</td>
<td>97</td>
</tr>
</tbody>
</table>

III. *In vivo* bioequivalence study

*In vivo* performance of citalopram tablets prepared as per the composition of Example 1 (T) was evaluated with respect to the Celexa® tablets (R) in 12 healthy male volunteers under fasted conditions. The study protocol followed was an open randomized, two treatment, two sequence, two period, cross over study with a wash out period of at least 28 days. Blood samples were collected at appropriate time intervals over a period of 336 hours and citalopram content was analyzed using a validated in-house HPLC method. Pharmacokinetic parameters $C_{\text{max}}$ (Maximum plasma concentration), $T_{\text{max}}$ (Time to attain maximum plasma concentration), AUC$_{0-4}$ (Area under the plasma concentration vs time curve from 0 hours to the time of last sample collected) and AUC$_{0-\infty}$ (Area under the plasma concentration vs. time curve from 0 hours to infinity) were calculated from the data obtained. Statistical analysis was carried out at 90% interval using “SAS” software package. The results of the study are given in Table 3.

Table 3

Comparative pharmacokinetic data for tablets of Example 1 (T) and Celexa® tablet (R)

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>AUC$_{0-4}$ (µg/ml.h)</th>
<th>AUC$_{0-\infty}$ (µg/ml.h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets of Example 1 (T)</td>
<td>3.18</td>
<td>60.26</td>
<td>1921.78</td>
<td>2376.46</td>
</tr>
<tr>
<td>Celexa® (40mg) tablets (R)</td>
<td>4.77</td>
<td>54.76</td>
<td>2094.69</td>
<td>2446.64</td>
</tr>
<tr>
<td>T/R ratio (90% confidence interval)</td>
<td>-</td>
<td>113.25 (Limit: 101.81-125.97)</td>
<td>95.60 (Limit: 80.72-113.23)</td>
<td>101.73 (Limit: 84.06-123-11)</td>
</tr>
</tbody>
</table>
The *in vitro* and *in vivo* performance of the pharmaceutical dosage forms of the present invention; clearly indicate the importance of controlling size and average aspect ratio of citalopram particles, used in the preparation of dosage forms.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.
We claim:

1. A pharmaceutical dosage form comprising citalopram, wherein not less than about 36% of the citalopram particles, by volume, have a particle size that is less than about 5 μm.

2. The pharmaceutical dosage form according to claim 1, wherein not less than about 43% of the citalopram particles, by volume, have a particle size that is less than about 5 μm.

3. The pharmaceutical dosage form according to claim 1, wherein not less than about 50% of the citalopram particles, by volume, have a particle size that is less than about 5 μm.

4. The pharmaceutical dosage form according to claim 1, wherein not less than about 99% of the citalopram particles, by volume, have a particle size that is less than about 30 μm.

5. The pharmaceutical dosage form according to claim 4, wherein not less than about 99% of the citalopram particles, by volume, have a particle size that is less than about 22 μm.

6. The pharmaceutical dosage form according to claim 1, wherein the citalopram particles have an average aspect ratio of less than about 2.

7. The pharmaceutical dosage form according to claim 6, wherein the citalopram particles have an average aspect ratio of less than about 1.7.

8. The pharmaceutical dosage form according to claim 7, wherein the citalopram particles have an average aspect ratio of about 1.55.

9. The pharmaceutical dosage form according to claim 1, wherein not less than about 99% of the citalopram particles, by volume, have a particle size that is less than about 30 μm and an average aspect ratio of less than about 2.

10. The pharmaceutical dosage form according to claim 9, wherein not less than about 99% of the citalopram particles, by volume, have a particle size that is less than about 22 μm and an average aspect ratio of less than about 1.7.
11. The pharmaceutical dosage form according to claim 1, wherein the pharmaceutical dosage form comprises a tablet or capsule.

12. The pharmaceutical dosage form according to claim 11, wherein the pharmaceutical dosage form comprises a tablet.

13. The pharmaceutical dosage form according to claim 1, wherein the citalopram comprises free citalopram base or its pharmaceutically acceptable salt.

14. The pharmaceutical dosage form according to claim 13, wherein the pharmaceutically acceptable salt of citalopram comprises citalopram hydrobromide or citalopram hydrochloride.

15. The pharmaceutical dosage form according to claim 14, wherein the pharmaceutically acceptable salt of citalopram comprises citalopram hydrobromide.

16. The pharmaceutical dosage form according to claim 1, wherein the pharmaceutical dosage form further comprises one or more pharmaceutically acceptable inert excipients.

17. The pharmaceutical dosage form according to claim 16, wherein the one or more pharmaceutically acceptable inert excipients comprise one or more of binders, diluents, surfactants, lubricants/ glidants, and coloring agents.

18. A process for the preparation of a pharmaceutical dosage form of citalopram comprising the steps of:

   blending citalopram with one or more pharmaceutically acceptable inert excipient(s) to form a blend, wherein not less than about 36% of the citalopram particles, by volume, have a particle size that is less than about 5 μm; and

   compressing the blend or filling the blend into a pharmaceutical dosage form.

19. The process according to claim 18, wherein not less than about 43% of the citalopram particles, by volume, have a particle size that is less than about 5 μm.

20. The process according to claim 18, wherein not less than about 50% of the citalopram particles, by volume, have a particle size that is less than about 5 μm.
21. The process according to claim 18, wherein at least a portion of the citalopram particles are prepared by the process of micronization.

22. The process according to claim 21, wherein the micronization is carried out in equipment comprising one or more of a ball mill, colloid mill, grinding mill, air jet mill, roller mill, and impact mill.

23. The process according to claim 22, wherein the micronization is carried out in an air jet mill.

24. The process according to claim 18, wherein the citalopram particles have an average aspect ratio of less than about 2.

25. The process according to claim 18, further comprising granulating the blend of citalopram and pharmaceutically acceptable inert excipients.

26. The process according to claim 25, wherein the granulation is carried out by a wet granulation or dry granulation technique.

27. The process according to claim 26, wherein the granulation is carried out by a wet granulation technique.

28. The process according to claim 18, wherein the pharmaceutical dosage form comprises a tablet or a capsule.

29. The process according to claim 28, wherein the pharmaceutical dosage form comprises a tablet.

30. A method of treating depression in a mammal, the method comprising administering to the mammal a pharmaceutical dosage form comprising not less than about 36% of the citalopram particles, by volume, having a particle size less than about 5 µm.

31. The method according to claim 30, wherein not less than about 43% of the citalopram particles, by volume, have a particle size that is less than about 5 µm.

32. The process according to claim 30, wherein not less than about 50% of the citalopram particles, by volume, have a particle size that is less than about 5 µm.
33. The method according to claim 30, wherein the citalopram particles have an average aspect ratio of less than about 2.