Abstract:
The present invention refers to a granule for the preparation of pharmaceutical compositions comprising a core comprising quetiapine or a pharmaceutically acceptable salt thereof as active ingredient and a binder agent, and a coating layer comprising a lubricant agent. In addition, this invention provides new solid pharmaceutical compositions containing quetiapine as well as process for their preparation.
PHARMACEUTICAL COMPOSITIONS CONTAINING QUETIAPINE FUMARATE

FIELD OF THE INVENTION

The present invention relates to new pharmaceutical compositions for the oral administration of Quetiapine or a pharmaceutically acceptable salt thereof and to a process for its manufacture.

BACKGROUND OF THE INVENTION

Quetiapine is a compound of formula (I):

![Chemical Structure](image)

which has been employed as an antipsychotic or neuroleptic agent in the treatment of schizophrenia and bipolar mania, due to its antidopaminergic activity.

Quetiapine is currently marketed as a hemifumarate salt in the form of tablets of several doses of 25 mg, 100 mg, 200 mg and 300 mg for the administration two or three times per day. However, previously described formulations of quetiapine have certain drawbacks derived from the poor dissolution properties of this medicament and the uncontrolled release profile provided by said formulations. For example, document WO2005/041935 describes Quetiapine formulations which do not provide a constant or substantially constant level of quetiapine, such that the patient can, at certain time intervals, receive therapeutic amounts of quetiapine exceeding the recommended doses, whereas at other times the amount may be below the therapeutically effective limits.

Patent applications WO97/45124 and WO2005/041935 describe modified-release pharmaceutical compositions containing Quetiapine, i.e. they slowly release the active ingredient in long time intervals. For example patent WO2005/041935 describes
solid dosage pharmaceutical compositions comprising a matrix formed by means of melted waxes, whereas application WO97/45124 describes the use of matrices with a gelling agent. However, in the later application, the use of water-soluble active ingredients, such as quetiapine or its pharmaceutically acceptable salts, combined with gelling agents such as hydroxypropylmethylcelluloses, can give rise to a phenomenon known as dumping in which the release of the active ingredient is delayed but once it starts the release occurs at very high rates.

Patent EP1218009 describes the preparation of granules containing Quetiapine and a freely or very water-soluble binder for their use in suspensions or solutions. Patent application WO03/039516 relates to methods for improving the dissolution of poorly dispersible medicaments among them Quetiapine is included. The dissolution is improved by means of preparing granules in which a floating agent is added to the medicament. However, there is no indication about the release profile of these medicaments in the granulate formulations.

For all these reasons, there is still a need for developing pharmaceutical compositions which incorporate Quetiapine or one of its pharmaceutically acceptable salts or methods for preparing said compositions with an improved physical stability which allows their marketing without the active ingredient release properties being affected.

BRIEF DESCRIPTION OF THE INVENTION

The aim of the present invention is to provide pharmaceutical compositions containing quetiapine or a pharmaceutically acceptable salt thereof for oral administration having an improved dissolution profile and an improved physical stability without affecting the release profile of said active ingredient. In addition, it is an aim of the present invention to provide a process for preparing said pharmaceutical compositions, particularly tablets, by means of a process that can be applied at an industrial level with low energy costs and which does not subject the active ingredient to aggressive formulation conditions which can entail the loss of stability of the product.

The authors of the present invention have found that the use of granules containing quetiapine or a pharmaceutically acceptable salt thereof coated with a lubricating agent allows preparing oral pharmaceutical compositions, particularly in the form of tablets, with improved physical stability without affecting the dissolution
properties of the oral compositions, making them suitable for therapeutic use.

Accordingly, a first aspect of the present invention is a granule which comprises:

a) a core comprising quetiapine or a pharmaceutically acceptable salt thereof and a binder agent; and
b) a coating layer comprising a lubricant agent.

In a particular embodiment of the invention, the core may further comprise a diluent agent and/or a disintegrant agent. In another particular embodiment said granule is for the preparation of pharmaceutical compositions.

A second aspect of the present invention is a process for preparing granules as defined above comprising:

a) providing quetiapine or a pharmaceutically acceptable salt thereof and, optionally, mixing it with a disintegrant agent and/or a diluent agent;
b) adding to the quetiapine or to the mixture obtained in step a) a binder agent;
c) adding a solvent to the mixture obtained in step b), or optionally, adding a solution or suspension containing a binder and a solvent to the quetiapine or to the mixture obtained in step a), thus suppressing step b);
d) wet granulating the mixture obtained in step c);
e) drying the granules obtained in step d);
f) sieving the dried granules obtained in step e); and
g) coating the granules with a lubricant agent.

In another aspect, the present invention refers to the use of granules as defined above for the elaboration of pharmaceutical compositions.

Another aspect of the invention relates to a pharmaceutical composition comprising a set of granules as defined above, optionally in combination with one or more pharmaceutically acceptable excipients. In a particular embodiment, the pharmaceutical composition is in the form of a tablet.

Further, in another aspect the invention refers to an immediate release tablet which comprises a set of granules as defined above wherein the quantity of the lubricant agent in the coating layer of the granule is between 5 and 10% by weight with respect to the total weight of the granule.

Still in another aspect the invention relates to a sustained release tablet which comprises a set of granules as defined above wherein the quantity of the lubricant agent in the coating layer of the granule is between 15 and 25% by weight with respect to the
total weight of the granule.

Finally, another aspect of the invention is a process for the preparation of an immediate or sustained release tablet as defined above comprising:

a) preparing granules as defined above;

b) optionally mixing the granules obtained in step a) with one or more pharmaceutically acceptable excipients;

c) tableting the granules obtained in step a) or in its case the mixture obtained in step b); and

d) coating the tablet obtained in step c).

DETAILED DESCRIPTION OF THE INVENTION

In the context of the present invention, by the term "granule" it is understood a structure comprising a core, which comprises quetiapine as the active ingredient and a binder agent, said core being coated by a layer comprising a lubricant agent.

In a particular embodiment of the invention, the core of the granule may comprise at least one diluent agent and/or a disintegant agent.

The expression "set of granules" refers to granules in such an amount that a pharmaceutical composition can be prepared.

Unless otherwise indicated, "quetiapine" is understood to be the compound quetiapine or a pharmaceutically acceptable salt thereof, preferably quetiapine fumarate with a 2:1 stoichiometry, also known as quetiapine hemifumarate. Quetiapine may be incorporated in the granule in crystalline form either as a free compound or as a solvate. For example, in the case of using quetiapine fumarate, it can be incorporated in any of the several polymorphic forms described in patent applications WO99/06381, WO03/080065 and WO2004/078735 which are herewith incorporated by reference.

Quetiapine is preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. Purity levels for the drug substance are preferably above 50%, more preferably above 70%, most preferably above 90%. In a preferred embodiment it is above 95% of the compound of formula (I), or of its salts, solvates or prodrugs.

In a particular embodiment of the invention, the binder agent included in the
core of the granule is selected from povidone, corn starch, hydroxypropylcellulose and copovidone. Advantageously, the use of povidone K-25 as a binder is preferred. The amount of binder agent to be added to the core may vary between 1 and 15% by weight with respect to the total weight of the granule.

The diluent agent optionally included in the core is preferably selected from microcrystalline cellulose, lactose monohydrate and dibasic calcium phosphate. Advantageously, the use of microcrystalline cellulose as a diluent agent is particularly preferred. The amount of the diluent agent to be optionally added to the core may vary between 10 and 40% by weight with respect to the total weight of the granule.

The disintegrant agent optionally included in the core of the granule is preferably selected from sodium starch glycolate, crospovidone and sodium croscarmellose. Advantageously, sodium starch glycolate type A, known with the commercial name Primogel®, as a disintegrant agent is particularly preferred. The amount of disintegrant agent to be optionally added to the core may vary between 3 and 20% by weight with respect to the total weight of the granule.

For coating the core of the granule, a lubricating agent selected from the glyceryl behenate, glyceryl palmitostearate and macrogol group can be used. Advantageously, glyceryl behenate as a lubricating agent is particularly preferred. The amount of lubricant agent to be used for preparing the coating layer may vary between 5 and 25% by weight with respect to the total weight of the granule.

In a particular embodiment of the invention, the granule comprises a core containing quetiapine hemifumarate combined with microcrystalline cellulose as a diluent agent, sodium starch glycolate (Primogel®) as a disintegrant agent and Povidone (PVP K25) as a binder, said core being coated with a layer comprising glyceryl behenate as a lubricating agent.

The granules described above can be prepared by any method known in the state of the art. However, in a particular embodiment, said granules are prepared by wet granulation of quetiapine with a binder and optionally with a diluent agent and/or a disintegrant agent, followed by a coating process which allows the lubricant agent to coat the core of each granule. Accordingly, the process for preparing the granules as described above comprises the steps of:

a) providing quetiapine or a pharmaceutically acceptable salt thereof and, optionally mixing it with a disintegrant agent and/or a diluent agent;
b) adding to the quetiapine or to the mixture obtained in step a) a binder agent;
c) adding a solvent to the mixture obtained in step b), or optionally, adding a
solution or suspension containing a binder and a solvent to the quetiapine or
to the mixture obtained in step a), thus suppressing step b);
d) wet granulating the mixture obtained in step c);
e) drying the granules obtained in step d);
f) sieving the dried granules obtained in step e); and
g) coating the granules with a lubricant agent.

The first step consists of providing quetiapine or a pharmaceutically acceptable
salt thereof and optionally mixing the active ingredient quetiapine with a disintegrant
and/or a diluent.

Quetiapine or a pharmaceutically acceptable salt thereof, such as fumarate, can
be prepared according to the method described in patent application WO2005/014590,
which is incorporated herein as a reference. In a particular embodiment, the amount of
quetiapine in the granules is comprised between 20 and 80% of the total weight of the
granule, preferably between 40 and 80%.

The amount of disintegrant to be optionally added is comprised between 3% and
20% by weight with respect to the total weight of the granule. Preferably, between 5% and
15% is added, more preferably between 7% and 12% of the total weight of the
granule. The amount of diluent to be optionally added is comprised between 10% and
40% by weight with respect to the total weight of the granule, preferably between 15% and
25% of the total weight of the granule.

In the second step, the amount of binder to be added to the quetiapine or to the
mixture obtained in step a) is comprised between 1% and 15% by weight with respect to
the total weight of the granule.

In the third step, a solvent is added in an amount comprised between 25% and
65% by weight with respect to the weight of the mixture to be granulated, which will
serve to carry out the wet mixture. Alternatively, the binder agent can be previously
dissolved or suspended in said solvent and then added to the quetiapine or to the
mixture obtained in step a) thus suppressing step b). As solvents for preparing the wet
mixture, water, hydroalcoholic mixtures and alcohols can be used, being preferred the
use of water as a solvent for the granulation of the mixture. This solvent is later
eliminated from the composition by means of a drying step.

Then, in the fourth step, the wet granulation is performed. The granules can be produced by a known granulation method such as rolling granulation, fluidized-bed granulation, stirring granulation and the like. Additionally, suitable equipment for this type of processing can be used, for example, the granulation can be carried out in a low shear mixer or a high shear mixer. However, a low shear granulation will be preferably used since pharmaceutical compositions with a faster dissolution profile are obtained.

Once the wet granules are obtained, they are subjected to a drying process to eliminate the solvent. This step can be carried out for example in a fluid bed dryer. The granules are subjected to a temperature comprised between 40°C and 90°C, preferably between 60°C and 80°C, for the time period necessary to obtain granules with a moisture content less than 5%, preferably less than 3%.

Subsequently, the dried granules are calibrated by sieving or milling.

Finally, the sieved or milled granules are coated with a lubricating agent. The coating process can be carried out by mixing the granules with the lubricating agent by any process known by a skilled person.

Surprisingly, the inventors have discovered that the amount of lubricating agent used for coating the granules allows controlling the rate of release of the active ingredient. Thus, the use of a lubricating agent as described above for coating the core of the granules in a proportion between 5% and 10% by weight with respect to the total weight of the granule allows preparing immediate release compositions. On the contrary, the use of the coating lubricating in a proportion between 15% and 25% by weight with respect to the total weight of the granule allows preparing sustained release compositions.

By "immediate release" it is understood a release form in which greater than or equal to about 50% or more, preferably about 75% of quetiapine is released within two hours of administration, preferably within one hour of administration.

By "sustained release" it is understood a release form in which quetiapine is released at such a rate that blood (e.g. plasma) levels are maintained within a therapeutic range but below toxic levels for at least 8 hours, preferably at least about 12 hours after administration.

Accordingly, a set of granules as defined above can be used for the elaboration of pharmaceutical compositions with different release profiles. Examples of these
pharmaceutical compositions include any solid (tablets, pills, capsules, etc.) or liquid (solutions, suspensions or emulsions) composition for oral administration. In an embodiment of the invention, the pharmaceutical composition is an immediate release composition. In another embodiment, the pharmaceutical composition is a sustained release composition.

Suitable dose forms for oral administration may further contain conventional excipients known in the art such as binding agents, for example syrup, acacia, cellulose derivatives (i.e. hydroxypropylcellulose, carboxymethylcellulose, etc.) gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or mannitol; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, crospovidone, sodium starch glycolate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulfate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may for example be prepared by wet or dry granulation and optionally coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

The mentioned compositions will be prepared using standard methods such as those described or referred to in the Spanish and US Pharmacopoeias and similar reference texts.

In a preferred embodiment of the invention, the pharmaceutical composition is in the form of a tablet. The excipients used for preparing tablets may comprise between 0.25% and 5% by weight with respect to the total weight of the tablet of one or more lubricating agents, between 5% and 20% by weight of one or more disintegrants, between 20% and 50% by weight of one or more diluents and between 0.1% and 0.5% by weight of a glidant.

As disintegrant, low-substituted hydroxypropylcellulose, hydroxyethylcellulose, crospovidone, croscarmellose, starch, sodium carboxymethyl starch, casein derivatives or mixture thereof can be used.

As lubricating agent, magnesium stearate, calcium stearate, glyceryl palmitostearate, talcum, stearic acid, glyceryl behenate, sodium lauryl sulfate, sodium
stearyl fumarate or mixtures thereof can be used. A stearate will preferably be used, still more preferably, magnesium stearate.

As diluent, a saccharide (monosaccharide or oligosaccharide, polysaccharides) and/or their oxidized and/or reduced forms; lactose in its anhydrous, monohydrate, agglomerated or spray forms; mannitol; cellulose powder, microcrystalline cellulose, silicified microcrystalline cellulose or chemically modified cellulose derivatives, such as hydroxypropylcellulose, hydroxypropylmethylcellulose; starch, sucrose, pharmaceutically acceptable inorganic compounds such as dibasic calcium phosphate, calcium or magnesium carbonates, magnesium oxide, or mixtures thereof can be used.

Additionally, previously prepared coprocessed diluents can be used such as Cellactose®, coprocessed lactose and cellulose powder, or Microcellac®, coprocessed lactose and microcrystalline cellulose, among others.

Preferably, cellulose will be used, more preferably, microcrystalline cellulose.

As glidant, anhydrous or hydrated colloidal silica, magnesium trisilicate or talc can be used.

The authors of the present invention have been able to prove that when quetiapine or one of its pharmaceutically acceptable salts are mixed with the necessary excipients and are compressed directly with no other type of processing (e.g., granulation, etc.), the use of the direct compression method gives rise to very adherent tablets. It has also been proved that when quetiapine granules which are not coated with a lubricating agent are prepared, the obtained tablets are still adherent.

However, upon coating each granule with a lubricating agent, adhesions are minimized or disappear, providing tablets with a regular surface.

An additional aspect of the invention refers to an immediate release tablet which comprises a set of granules as described previously wherein the quantity of lubricant agent in the coating layer of each granule is between 5% and 10% by weight with respect to the total weight of the granule. Further another aspect of the invention relates to a sustained release tablet which comprises a set of granules as described previously wherein the quantity of lubricant agent in the coating layer of each granule is between 15% and 25% by weight with respect to the total weight of the granule.

Finally, another aspect of the present invention consists of providing a process for preparing an immediate or sustained release tablet as defined above which comprises:
1. preparing a set of granules according to the process previously described;
2. optionally mixing the granules obtained in step 1) with one or more
   pharmaceutically acceptable excipients;
3. tableting the granules obtained in step 1) or in its case the mixture obtained in
   step 2); and
4. coating the tablet obtained in step 3).

Step 1) comprises all the steps a) to g) previously described in the preparation of
the granules of the invention. In the case of preparing an immediate release tablet, the
amount of lubricating agent to be used for coating the core of the granules may vary
between 5% and 10% by weight with respect to the total weight of the granule.
However, in the case of preparing a sustained release tablet, the amount of lubricating
agent to be used for coating the core of the granules may vary between 15% and 25% by
weight with respect to the total weight of the granule.

The excipients optionally used in step 2) for preparing tablets may comprise
between 0.25% and 5% by weight with respect to the total weight of the tablet of one or
more lubricating agents, between 5% and 20% by weight of one or more disintegrants,
between 20% and 50% by weight of one or more diluents and between 0.1% and 0.5%
by weight of a glidant.

The tableting process of step 3) can be carried out by any method known in the
state of the art for preparing tablets, including for example direct compression, double
compression, granulation etc. Finally, the tablet is coated with a conventional or enteric
coating material or a polymeric coating material. For example, a mixture of
hypromellose, titanium dioxide and macrogol in purified water can be used.

The pharmaceutical compositions of this invention may be used with other drugs
to provide a combination therapy. The other drugs may form part of the same
composition, or be provided as a separate composition for administration at the same
time or at different time.

In the following, the present invention is further illustrated by examples. They
should in no case be interpreted as a limitation of the scope of the invention as defined
in the claims.

Examples
Example 1. Preparation of quetiapine tablets
Quantitative composition: % by weight

Quetiapine hemifumarate 37
Lactose monohydrate 18
Microcrystalline Cellulose (Avicel PH102) 18
Povidone (K-25) 3
Na starch glycolate type A (Primojel) 15
Glyceryl behenate 5
Anhydrous colloidal silica (Aerosil) 0.3
Magnesium stearate 1
Purified water* 26*

Coating dispersion 3**

* solvent which disappears during the manufacturing process.
** dry residue

Detailed description of the manufacturing process:

Quetiapine hemifumarate is mixed with povidone and 50% of the total sodium starch glycolate. The mixture is granulated in a low shear mixer with purified water, dried and sieved. The obtained granules are coated with glyceryl behenate by mixing. The coated granules are mixed with the remaining 50% of sodium starch glycolate, together with microcrystalline cellulose, lactose and aerosil and finally with magnesium stearate. The obtained mixture is compressed and the tablets are coated with a coating dispersion formed by traditional coating agents.

Example 2. Preparation of quetiapine tablets
Quantitative composition: % by weight

Quetiapine hemifumarate 37
Lactose monohydrate 20
Detailed Description of the manufacturing process:

Quetiapine hemifumarate is mixed with povidone, 50% of the total sodium starch glycolate and 50% of the total microcrystalline cellulose. The mixture is granulated in a low shear mixer with purified water, dried and sieved. The obtained granules are coated with glycercyl behenate by mixing. The coated granules are mixed with the remaining 50% of microcrystalline cellulose and sodium starch glycolate, together with lactose and aerosil and finally with magnesium stearate. The obtained mixture is compressed and the tablets are coated with a coating dispersion formed by traditional coating agents.

Example 3. Preparation of quetiapine tablets

Quantitative composition: % by weight

<table>
<thead>
<tr>
<th>Material</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine hemifumarate</td>
<td>37</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>22</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel PH 102)</td>
<td>22</td>
</tr>
<tr>
<td>Povidone (K-25)</td>
<td>3</td>
</tr>
<tr>
<td>Na starch glycolate type A (Primojel)</td>
<td>7</td>
</tr>
<tr>
<td>Glycercyl behenate</td>
<td>5</td>
</tr>
<tr>
<td>Anhydrous colloidal silica (Aerosil)</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Detailed Description of the manufacturing process:

Quetiapine hemifumarate is mixed with povidone, 50% of the total sodium starch glycolate and 50% of the total microcrystalline cellulose. The mixture is granulated in a low shear mixer with purified water, dried and sieved. The obtained granules are coated with glyceryl behenate by mixing. The coated granules are mixed with the remaining 50% of microcrystalline cellulose and sodium starch glycolate, together with lactose and aerosil and finally with magnesium stearate. The obtained mixture is compressed and the tablets are coated with a coating dispersion formed by traditional coating agents.

Example 4. Preparation of quetiapine tablets and measure of their dissolution profiles

Quantitative composition: % by weight

<table>
<thead>
<tr>
<th>Component</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine hemifumarate</td>
<td>58</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>16</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel PH102)</td>
<td>16</td>
</tr>
<tr>
<td>Povidone (K-25)</td>
<td>5</td>
</tr>
<tr>
<td>Na starch glycolate type A (Primojel)</td>
<td>5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
</tr>
<tr>
<td>Purified water*</td>
<td>38* (Meth. A)</td>
</tr>
<tr>
<td></td>
<td>43* (Meth. B)</td>
</tr>
</tbody>
</table>

* solvent which disappears during the manufacturing process.
wherein the granulation is carried out using a high shear mixer (Method A) and other
wherein a low shear mixer is used (Method B).

The dissolution profiles of the obtained tablets were determined in hydrochloric acid (900 ml, Ph. Eur. paddle apparatus, 50 rpm). The obtained results are indicated in the following table:

<table>
<thead>
<tr>
<th>TIME (minutes)</th>
<th>Method A</th>
<th>Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>37</td>
<td>97</td>
</tr>
<tr>
<td>30</td>
<td>72</td>
<td>101</td>
</tr>
<tr>
<td>45</td>
<td>90</td>
<td>101</td>
</tr>
<tr>
<td>60</td>
<td>99</td>
<td>103</td>
</tr>
</tbody>
</table>

By using a low shear mixer during the granulation process, a faster dissolution profile is obtained, allowing a total dissolution of the tablet at least 30 minutes before than the tablet containing granules manufactured with a high shear mixer.

Example 5. Adhesion properties of quetiapine formulations

Quantitative composition: Formula A (%) Formula B (%)
Quetiapine hemifumarate 38 38
Lactose monohydrate 20 18
Microcrystalline cellulose (Avicel PH102) 21 19
Dibasic calcium phosphate 1 1
Povidone (K-25) 3 3
Na starch glycolate type A (Primojel) 15 15
Glyceryl behenate — 5
Magnesium stearate 1 1
Purified water* 28* 28*

* solvent which disappears during the manufacturing process.

Formulas A and B were manufactured following the method described in
Example 1. The difference between both formulas is in the coating of the obtained granules; in formula B the granules are coated with glyceryl behenate by mixing, while in formula A the granules are not coated. Adherent compounds are obtained in the compression of formula A; the coating of the granules with glyceryl behenate solves the adhesion problems in the tablets.

Example 6. Comparative example. Dissolution profiles of quetiapine formulation of example 2 (28.78 mg quetiapine hemifumarate equivalent to 25 mg quetiapine base) and commercial formulation Seroquel (25 mg quetiapine base).

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>(%) percentage by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granule</td>
<td></td>
</tr>
<tr>
<td>Quetiapine hemifumarate</td>
<td>37</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>20</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>20</td>
</tr>
<tr>
<td>Calcium Hydrogen Phosphate dihydrate (Emcompress)</td>
<td>8.5</td>
</tr>
<tr>
<td>Povidone (K-25)</td>
<td>3</td>
</tr>
<tr>
<td>Na starch glycolate type A (Primojel)</td>
<td>11</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>5</td>
</tr>
<tr>
<td>Anhydrous colloidal silica (Aerosil)</td>
<td>0.3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
</tr>
<tr>
<td>Tablet coating</td>
<td>3*</td>
</tr>
</tbody>
</table>

* Qualitative composition of the coating of tablet obtained in example 2: lactose monohydrate, hypromelose, titanium dioxide, macrogol 4000 and red iron oxide.

** Qualitative composition of the coating of tablets Seroquel: hypromelose, titanium dioxide, macrogol 400, red iron oxide, yellow iron oxide.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Time (min)</th>
<th>Example 2 (25 mg)</th>
<th>Seroquel (25 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>pH 7.4</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>
In addition to these results, dissolution assay on purified water medium has also showed that the dissolution of quetiapine from tablets described in Example 2 is 86.6% after 10 min, in front of 80.6% quetiapine dissolved in the case of Seroquel.

The results have pointed out that coating the core of the granules with a lubricating agent, such as glyceryl behenate, allows obtaining formulations with an improved dissolution profile with respect to quetiapine commercial formulations.
CLAIMS

1. A granule which comprises:
   a) a core comprising quetiapine or a pharmaceutically acceptable salt thereof as active ingredient and a binder agent; and
   b) a coating layer comprising a lubricant agent.

2. The granule according to claim 1 wherein the core further comprises a diluent agent and/or a disintegrant agent.

3. The granule according to claims 1 or 2 wherein the binder agent is selected from the group comprising povidone, corn starch, hydroxypropylcellulose and copovidone, in particular wherein the binder agent is povidone K-25.

4. The granule according to anyone of claims 2 to 3 wherein the diluent agent is selected from the group comprising microcrystalline cellulose, lactose monohydrate and dibasic calcium phosphate, in particular wherein the diluent agent is microcrystalline cellulose.

5. The granule according to anyone of claims 2 to 4 wherein the disintegrant agent is selected from the group comprising sodium glycolate starch, crospovidone and sodium croscarmellose, in particular wherein the disintegrant agent is sodium starch glycolate type A (Primojel®).

6. The granule according to anyone of claims 1 to 5 wherein the lubricant agent is selected from the group comprising glyceryl behenate, glyceryl palmitoestearate and macrogol, in particular wherein the lubricant agent is glyceryl behenate.

7. The granule according to anyone of claims 1 to 6 wherein the active ingredient is quetiapine hemifumarate.

8. The granule according to anyone of claims 1 to 7 comprising:
   a) a core comprising quetiapine hemifumarate, microcrystalline cellulose, sodium starch glycolate and povidone; and
   b) a coating layer comprising glyceryl behenate.

9. The granule according to anyone of claims 1 to 8 wherein the quantity of lubricant agent is in a proportion between 5 and 25% by weight with respect to the total weight of the granule.

10. The granule according to anyone of claims 1 to 9 for the preparation of pharmaceutical compositions.
11. A process for the preparation of granules as defined in anyone of claims 1 to 10 comprising:
   a) providing quetiapine or a pharmaceutically acceptable salt thereof and, optionally, mixing it with a disintegrant agent and/or a diluent agent;
   b) adding to the quetiapine or to the mixture obtained in step a) a binder agent;
   c) adding a solvent to the mixture obtained in step b) or, optionally, adding a solution or suspension containing a binder and a solvent to the quetiapine or to the mixture obtained in step a), thus suppressing step b);
   d) wet granulating the mixture obtained in step c);
   e) drying the granules obtained in step d);
   f) sieving the dried granules obtained in step e); and
   g) coating the granules with a lubricant agent.

12. The process according to claim 11 wherein the solvent used in step c) is water, a hydroalcoholic mixture or one or more alcohols.

13. The process according to claims 11 or 12 wherein the wet granulating is carried out in a low shear mixer.

14. The process according to anyone of claims 11 to 13 wherein the drying step e) provides granules with a humidity content lower than 5%, preferably lower than 3%.

15. Use of granules as defined in anyone of claims 1 to 10 for the elaboration of pharmaceutical compositions.

16. A pharmaceutical composition comprising a set of granules as defined in anyone of claims 1 to 10, optionally in combination with one or more pharmaceutically acceptable excipients.

17. The composition according to claim 16 which is an immediate release composition.

18. The composition according to claim 16 which is a sustained release composition.

19. The pharmaceutical composition according to anyone of claims 16 to 18 in the form of a tablet.

20. An immediate release tablet which comprises a set of granules as defined in anyone of claims 1 to 10 wherein the quantity of the lubricant agent in the coating layer of the granule is between 5 and 10% by weight with respect to the total weight of the granule.
21. A sustained release tablet which comprises a set of granules as defined in anyone of claims 1 to 10 wherein the quantity of the lubricant agent in the coating layer of the granule is between 15 and 25% by weight with respect to the total weight of the granule.

22. A process for the preparation of a tablet as defined in any of claims 19 to 21 comprising:
   a) preparing granules as defined in claims 11 to 14;
   b) optionally mixing the granules obtained in step 1) with one or more pharmaceutically acceptable excipients;
   c) tableting the granules obtained in step a) or in its case the mixture obtained in step b); and
   d) coating the tablet obtained in step c).
INTERNATIONAL SEARCH REPORT

PCT/EP2008/051753

A CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/16

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, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further special documents are listed in the continuation of Box C

See patent family annex

T1 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

Date of the actual completion of the international search

15 April 2008

Date of mailing of the international search report

22/04/2008

Name and mailing address of the ISA/Authorized officer

European Patent Office, P B 5818 Patentlaan 2 NL - 2280 H Wassenaar NL Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

S. von Eggelkraut-G.
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