A pharmaceutical composition comprising ziprasidone free base or ziprasidone hydrochloride and the method for their preparation.

A new pharmaceutical compositions are provided containing ziprasidone and the method for their preparation. The pharmaceutical composition according to the invention contains ziprasidone hydrochloride in the form of micronized particles, wherein average particle size can be characterized by volume weighted mean $D_{4.3}$, which is less than 2 $\mu m$ or by Sauter diameter $D_{3.2}$, which is less than 1 $\mu m$. 

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Pharmaceutical compositions comprising ziprasidone free base or ziprasidone hydrochloride and the method for their preparation

The subject matter of the invention are pharmaceutical compositions comprising ziprasidone free base or ziprasidone hydrochloride and the method for their preparation.

Ziprasidone free base is a compound with the chemical formula as follows:

![Chemical structure of ziprasidone free base]

Ziprasidone is typically administered as hydrochloride acid addition salt, hydrochloride or monohydrate of this salt with the chemical formula:

![Chemical structure of ziprasidone hydrochloride]

The method for preparation of ziprasidone hydrochloride was presented in the US patent specification No. US 4,831,031, where also its application as a neuroleptic agent useful *inter alia* in the treatment of schizophrenia was disclosed.

Ziprasidone free base and ziprasidone hydrochloride are hereinafter collectively referred to as "ziprasidone" for convenience.

Ziprasidone belongs to the class II of Biopharmaceutical Classification System (BCS), which indicates that the active ingredient is poorly soluble in water but highly permeable across biological barriers. Therefore, the factor having a decisive influence on bioavailability of the drugs belonging to this class is their solubility.

The size of active ingredient crystals is a parameter which helps to control the solubility. The size of active ingredient crystals directly influences its absorption rate.
into the organism. This is particularly essential for ziprasidone, which is a highly active
drug characterized by narrow therapeutic range.
As it was disclosed in patent No. PL 196 867 B ziprasidone is administered orally as
hydrochloride acid addition salt. The drug containing ziprasidone in form of
ziprasidone hydrochloride monohydrate is characterized with high permeability
through biological barriers but it is poorly soluble in water, what negatively affects its
bioavailability.
The formulation of pharmaceutical compositions containing active ingredients poorly
soluble in water is difficult. The adequate preparation of pharmaceutical composition
allows for increase of drug solubility what results in improvement of bioavailability.
The use of various methods for preparation of pharmaceutical compositions containing
active ingredients poorly soluble in water is known in the pharmaceutical industry
It was disclosed in the international patent application No. WO 2006/024944 A that
implementation of polymers in the pharmaceutical composition improves solubility of
the drugs which are poorly soluble. This effect is achieved as a result of partial coating
of the drug particles with polymer that preferably contains hydrophilic and
hydrophobic groups. The polymer used in this invention was Hydroxypropyl
Methylcellulose Acetate Succinate (HMPCAS) which contains low amount of carboxylic
acid groups.
In turn, it was disclosed in the international patent application No. WO 2007/027273 A
that the use of surface stabilizers such as hydroxypropyl methylcellulose, gelatin or
sodium lauryl sulfate in pharmaceutical compositions allows for obtaining composition
that in FAST (on an empty stomach) and FED (during or after the meal) studies has
comparable pharmacokinetics. The method for preparation of this composition
consists in contact of ziprasidone with at least one surface stabilizer in suitable
conditions and for suitable time in order to receive ziprasidone particles of size lower
than 2,000 nm. Emulsion polymerization processes, precipitation or supercritical
extraction provide suitable conditions. The use of technologically advanced methods
for preparation of the composition is expensive and may be problematic in the large-
scale processes.
The similar solution was presented in the US patent application No. US 2008/0305161 where a ziprasidone depot formulation (pharmaceutical composition with prolonged action) for intramuscular and hypodermic administration is in the form of nanoparticles. The composition contains at least two surfactants, i.e. cetylpiridine chloride, gelatin, casein, phosphatides, etc.

There are also other methods for improvement of ziprasidone solubility such as use of cyclodextrins in pharmaceutical compositions described in the patent No. PL 189 324 B.

In turn, in the patent No. PL 195 209 B the pharmaceutical composition was disclosed that contains crystalline ziprasidone free base or crystalline ziprasidone hydrochloride in form of particles of size at most 85 µm, preferably particles of average size between 5-50 µm. Apart from ziprasidone the composition contains known pharmaceutically acceptable excipients, such as carboxymethyl cellulose, pregelatinized starch and others. The pharmaceutical composition is in a form of capsules and that is why the granulate volume is an important parameter that determines capsule size and patient comfort of medication administration. In the patent No. PL 195 209 B pharmaceutical compositions were disclosed that contain relatively low amount of active ingredient in the granulate (about 23% according to Example 3 (a)). Thus, a large capsule has to be used for relatively small drug dose. Such solution makes it necessary to use large capsules which can house the proper dosage unit which in turn can be uncomfortable for the patients when taking the drug.

The purpose of the present invention is to provide new pharmaceutical compositions containing ziprasidone and the method for their preparation.

As a result of work on pharmaceutical composition containing ziprasidone it was unexpectedly noticed that the use of ziprasidone in micronized form, adequately crosslinked polymer and disintegrant guarantees development of pharmaceutical composition with desired release profile parameters.

The term "adequately crosslinked polymer" refers to the polymer that forms hydrogel...
in aqueous environment and, while surrounding particles of the active ingredient, creates suitable environment favoring dissolution of ziprasidone.

During research and development work on optimal drug formulation it was observed that ziprasidone in micronized form with the average particle size $D_{[4.3]}$ below 2 µm is dissolved worse than the larger particles. This observation is surprising as usually particles of a small size due to a larger solvent accessible surface area are more readily dissolved than the larger particles. Thus, it was necessary to find the excipients which could increase rate of micronized ziprasidone dissolution.

As a result of work on development of pharmaceutical composition containing ziprasidone hydrochloride it was surprisingly found out that crospovidone perfectly meets above-mentioned requirements.

Crospovidone (polyvinylpyrrolidine) is a substance insoluble in water and is usually used in pharmaceutical compositions as a disintegrant.

Because of use of the micronized ziprasidone hydrochloride in the pharmaceutical composition according to the invention, crospovidone of average particle size within the range of 5-10 microns and large specific surface area about 2.0-2.5 $m^2/g$ was advantageously used (an example of crospovidone of this type is known under the trade name Polyplasdone INF-IO, ISP). This polyvinylpyrrolidine has very high capillary activity what results in the increase of amount of water provided to the system, which in turn facilitates increase in substance dissolution rate. Moreover, during compression of crospovidone with other ingredients of the pharmaceutical composition they are significantly concentrated and intermolecular interactions are generated.

Crospovidone when in contact with water forms a loose gel which surrounds ziprasidone particles and creates a local environment that facilitates dissolution of ziprasidone hydrochloride. Additionally, this phenomenon prevents ziprasidone particles from floating to the surface of acceptor fluid, forming agglomerates or adhering of substance particles to the vessel walls. Elimination of those phenomena increases contact surface area of ziprasidone and acceptor fluid and, as a consequence, the pharmaceutical drug availability is increased.
Because of the tendency of crospovidone to form loose gels in aqueous environment the use of disintegrant is advantageous. It is especially preferable to use modern compounds belonging to the group of the so-called superdisintegrants. In the pharmaceutical composition according to the invention sodium carboxymethyl starch with sodium content in the range of 2.8-4.2% was used (it is known under the trade name Ultraamylopectin of type A, JRS Pharma).

The generally used pharmaceutically acceptable auxiliary substances such as lactose monohydrate (known under the trade name Flowlac-100), microcrystalline cellulose (known under the trade name Avicel PH101) and magnesium stearate are used besides the carrier for preparation of the pharmaceutical composition according to the invention.

The pharmaceutical composition according to the invention contains ziprasidone hydrochloride in the form of micronized particles, wherein average particle size can be characterized by volume weighted mean D[4.3], which is less than 2 µm or by Sauter diameter D[3.2], which is less than 1 µm.

The term "average particle size" expressed by D[4.3] parameter lower than 2 µm or D[3.2] parameter lower than 1 µm, measured by means of a method of particle size laser measurement by Malvern, means that the particles size of 90% is lower than 5 µm.

During research and development work on optimal drug form a great difference between aqueous solubility of ziprasidone free base and ziprasidone hydrochloride was observed. This phenomenon is compliant with data available on substances of low solubility, whose addition salts are dissolved to a larger extent -Table 1.

Table 1. Comparison of ziprasidone hydrochloride and ziprasidone free base solubility in water at 37°C.

<table>
<thead>
<tr>
<th>Solubility in water at 37 °C</th>
<th>Ziprasidone free base</th>
<th>Ziprasidone hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0005 mg/ml</td>
<td>0.24 mg/ml</td>
<td></td>
</tr>
</tbody>
</table>
However, it was surprisingly noticed that in the case of acetate buffer solution of pH 4.5, containing acetyl groups, reverse phenomenon is observed; solubility of ziprasidone base is much higher than solubility of ziprasidone hydrochloride which is presented in Table 2 and in Fig. 1.

Table 2. Comparison of ziprasidone hydrochloride and ziprasidone free base solubility in the solution containing acetyl groups and phosphate groups and at 37°C.

<table>
<thead>
<tr>
<th>Solubility in acetate buffer solution of pH 4.5 at 37 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone free base</td>
</tr>
<tr>
<td>0.16 mg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solubility in phosphate buffer solution of pH 4.5 at 37 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone free base</td>
</tr>
<tr>
<td>0.006 mg/ml</td>
</tr>
</tbody>
</table>

Physicochemical properties of both substances, i.e. ziprasidone hydrochloride and ziprasidone free base, significantly differ from each other (Table 3). Thus, it is obvious for persons skilled in the art that substances of such different physicochemical properties need quite different approach when developing the optimal pharmaceutical composition.

Table 3. Comparison of physicochemical properties of ziprasidone hydrochloride and ziprasidone free base.

<table>
<thead>
<tr>
<th>Physicochemical parameter</th>
<th>Ziprasidone free base</th>
<th>Ziprasidone hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>C_{22}H_{21}ClN_{4}OS</td>
<td>C_{21}H_{22}Cl_{2}N_{4}OS</td>
</tr>
<tr>
<td>Molecular mass</td>
<td>412.94 g/mol</td>
<td>449.40 g/mol</td>
</tr>
<tr>
<td>Solubility in water at 20 °C</td>
<td>&gt; 0.0005 mg/ml</td>
<td>0.17 mg/ml</td>
</tr>
</tbody>
</table>
When developing the optimal drug formulation an appropriate excipients was searched for, which could provide suitable amount of acetyl groups, forming the environment facilitating ziprasidone dissolution. It turned out unexpectedly during the investigations that the use of a polymer, polyacrylic acid of specific linear crosslinking, allows for obtaining pharmaceutical composition of the desired release profile.

In the pharmaceutical composition according to the invention, polymer, polyacrylic acid (known as carbopol), was advantageously used. The polymer is characterized with high content of acetyl groups originating from residues of the solvent, ethyl acetate (max. residue level of the solvent ethyl acetate is 0.5%), which is used during synthesis of this polymer. The viscosity of the polymer is within the range 29,400-39,400 cp (viscosity measured for 0.5% w/w aqueous solution at 25°C, according to the European Pharmacopoeia). This type of carbopol is available under the trade name Carbopol 974P, Noveon.

It may seem surprising for persons skilled in the art of development of technologies of drug form preparation that polymer, polyacrylic acid, was used in order to increase the dissolution rate, as conventionally this polymer is used in slow release formulations because it forms hydrogels which gradually release an active ingredient to the solution. However, in case of ziprasidone free base, during investigations of pharmaceutical availability carbopol, on the one hand, forms hydrophilic matrix surrounding particles of active ingredient and on the other hand, it provides suitable microenvironment containing acetyl groups that facilitate dissolution of the drug.

Because polyacrylic acid forms hydrogel of high viscosity it is preferable to use disintegrant. It is especially preferable to use new compounds belonging to the group of the so-called superdisintegrants. In the pharmaceutical composition according to the invention sodium carboxymethyl starch with sodium content in the range 2.8-4.2% (known inter alia under the trade name Ultraamylopectin of type A, JRS Pharma) was used.

<table>
<thead>
<tr>
<th>Melting point</th>
<th>&gt; 300°C</th>
<th>224°C</th>
</tr>
</thead>
</table>
The generally used pharmaceutically acceptable excipients such as lactose (known under the trade name Flowlac-100), microcrystalline cellulose (known under the trade name Avicel PH101) and magnesium stearate are used besides the carrier for preparation of the pharmaceutical composition according to the invention. The pharmaceutical composition according to the invention contains ziprasidone free base in the form of micronized particles, wherein average particle size can be characterized by volume weighted mean D[4.3], which is less than 2 µm or by Sauter diameter D[3.2], which is less than 1 µm. The term "average particle size" expressed by D [4.3] parameter lower than 2 µm or D [3.2] parameter lower than 1 µm, measured by means of a method of particles size laser measurement by Malvern, means that the particles size of 90% is lower than 5 µm. The method of investigation of drug pharmaceutical availability was chosen based on the methodology published in the FDA internet service (http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm). The method comprises investigation of therapeutic substance release from the drug form with the help of apparatus II (blade apparatus) with the rotational speed of 75 rpm. As the acceptor fluid 0.05M phosphate buffer solution of pH 7.5 containing 2% of sodium lauryl sulfate and pancreatin was added. The addition of pancreatin reduces the influence of hard gelatin capsule on degradation time and release rate of therapeutic substance. Additionally, in order to avoid floating of the drug onto the acceptor fluid surface capsules were placed in sinkers. The investigation of pharmaceutical availability consists of two stages. During the first stage the capsules are macerated for 15 minutes in 700 ml of 0.05M phosphate buffer solution containing 0.5% w/w pancreatin. In the second stage 200 ml of phosphate buffer solution of pH 7.5 and containing 9% w/w of sodium lauryl sulfate is added. The amount of the dissolved ziprasidone can be determined using any common method, e.g. UV/Vis spectroscopic method, by comparing absorbance of investigated and standard solution in 1 cm layer at the wavelength of 319 nm in relation to acceptor fluid as a reference.
It is typical of the pharmaceutical composition according to the invention that if the dosage form is placed in the apparatus II according to the Ph. Eur. (blade apparatus) containing 0.05M phosphate buffer solution of pH 7.5 as acceptor fluid with 1% sodium lauryl sulfate and with pancreatin, equipped with blades stirring with speed equal to 75 rpm, at least 75% of ziprasidone contained in the dosage form is dissolved within 30 minutes.

It is obvious for persons skilled in the art that when developing the optimal technology of drug form preparation specific problems may occur in the case of substances in the form of micronized particles. The micronized substance tends to form large compact agglomerates which remain intact during mixing with excipients and during encapsulation. As a result, the granulate is not homogeneous, which negatively affects uniformity of dosage units. Moreover, the substance is not fully accessible for acceptor fluid, which can result in decrease of substance solubility and in limiting the drug bioavailability. Moreover, micronized ziprasidone has high bulk volume, which makes technological processes difficult and it can easily form dust. Additionally, high bulk volume of the granulate containing micronized ziprasidone makes it necessary to use very large capsules that can house the proper dosage unit. This may be uncomfortable for the patients taking the drug.

Unexpectedly, it was found out that the use of roller compaction method for granulate preparation for production of pharmaceutical composition containing micronized ziprasidone causes that bulk volume of the granulate is significantly lowered, flow properties are improved, the phenomenon of dusting and losses due to adhesion of active ingredient to the production devices are eliminated.

The use of roller compaction technique of micronized ziprasidone with at least one crosslinked polymer as a carrier allows for effective compression of ziprasidone particles and for obtaining granulate of high integration of the active ingredient with the carrier.

The method for preparation of pharmaceutical composition containing ziprasidone hydrochloride according to the invention is characterized by the following stages:
a. the active ingredient (micronized ziprasidone) is subjected to granulation with at least one pharmaceutically acceptable carrier,
b. obtained granules are calibrated,
c. calibrated granulate is mixed with excipients,
d. the granulate is subjected to encapsulation.

Preferably, the granulation process is conducted dry with use of roller compaction method.
The pharmaceutical composition according to the invention obtained in this way is characterized by high concentration of ziprasidone up to 60% w/w of the active ingredient in the granulate. As a result, a smaller capsule size for high doses of the preparation can be used and thus increasing patient’s comfort in taking the drug.

This invention is illustrated with the following examples that do not limit the invention in any way:

**Example 1**

In the below described examples the powder for compaction containing 3.0 kg of substances mentioned in the following tables was prepared in the 20-L bin blender by Zanchetta. Dry granulation process was conducted in the roller compactor by Alexanderwerk WP 150 Pharma. During the process the pressing force of 8 kN/cm² and sieve of 1.0 mm diameter were used for milling of the “ribbons” formed.
The proportional granulate content was used for doses 20 and 40 mg as well as for 60 and 80 mg.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Composition No. 1 mg / tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone hydrochloride (A)</td>
<td>45.3</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>5.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>11.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>11.0</td>
</tr>
<tr>
<td>Sodium carboxymethyl starch of type A</td>
<td>2.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0</td>
</tr>
</tbody>
</table>

10
Example 2.

The following example illustrates influence of compaction process on the active ingredient release rate.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Composition No. 1*</th>
<th>Composition No. 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone hydrochloride (A)</td>
<td>45.3</td>
<td></td>
</tr>
<tr>
<td>Crospovidone</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Sodium carboxymethyl starch of type A</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>75.8</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Prepared according to the scheme presented in Fig. 2
** Prepared according to the scheme presented in Fig. 4

Based on the results presented in Fig. 5, it can be concluded that the use of compacting process for preparation of pharmaceutical composition according to the invention allows for obtaining the desired release profile.

Example 3.

The following example illustrates the influence of the polymer type used in the composition on active ingredient release rate.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Composition No. 1*</th>
<th>Composition No. 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone hydrochloride</td>
<td>45.3</td>
<td></td>
</tr>
<tr>
<td>Carbopol 974P</td>
<td>-</td>
<td>5.0</td>
</tr>
<tr>
<td>Polyplosdone INF-10</td>
<td>5.0</td>
<td>-</td>
</tr>
<tr>
<td>Lactose Flowlac-100</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose Avicel PH101</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Ultraamylopectin of type A</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>75.8</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Composition prepared according to the scheme presented in Fig. 2
Based on the results presented in Fig. 6, it may be concluded that in the pharmaceutical composition only the use of crospovidone as a pharmaceutically acceptable carrier of high capillary activity being able to form loose gel in aqueous environment allows for obtaining the desired release profile.

In the below described examples, the powder for compaction containing 3.0 kg of substances mentioned in the following tables was prepared in the 20-L bin blender, by Zanchetta. Dry granulation process was conducted in the roller compactor by Alexanderwerk WP 150 Pharma. During the process the pressing force of 8 kLM/cm² and sieve of 1.0 mm diameter were used for milling of the "ribbons" formed. The proportional granulate content was used for doses 20 and 40 mg as well as for 60 and 80 mg.

Example 4.
The following example illustrates the influence of the polymer type used in the composition according to the invention.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Composition No. 4</th>
<th>Composition No. 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone hydrochloride</td>
<td>-</td>
<td>40.00</td>
</tr>
<tr>
<td>Methocel K100M Premium</td>
<td>-</td>
<td>6.85</td>
</tr>
<tr>
<td>Carbopol 974P</td>
<td>6.85</td>
<td>-</td>
</tr>
<tr>
<td>Lactose Flowlac-100</td>
<td>9.15</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose Avicel PH101</td>
<td>9.15</td>
<td></td>
</tr>
<tr>
<td>Ultraamylopectin of type A</td>
<td>2.50</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>68.40</strong></td>
<td></td>
</tr>
</tbody>
</table>

Example 5.
The following example illustrates the comparison of ziprasidone release rate from the pharmaceutical composition containing ziprasidone free base and ziprasidone hydrochloride.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Composition No. 4*</th>
<th>Composition No. 6*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone free base</td>
<td>40.00</td>
<td>-</td>
</tr>
</tbody>
</table>
According to the results presented in Fig. 9, the use of carbopol leads to obtaining the pharmaceutical composition consistent with the desired release profile only for ziprasidone free base.

**Example 6.**

The following example illustrates the influence of compacting process on ziprasidone release rate.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Composition No. 4*</th>
<th>Composition No. 7**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone free base</td>
<td>40.00 mg / tablet</td>
<td></td>
</tr>
<tr>
<td>Carbopol 974P</td>
<td>6.85</td>
<td></td>
</tr>
<tr>
<td>Lactose Flowlac-100</td>
<td>9.15</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose Avicel PH101</td>
<td>9.15</td>
<td></td>
</tr>
<tr>
<td>Ultraamylopectin of type A</td>
<td>2.50</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>68.40</strong></td>
<td><strong>73.70</strong></td>
</tr>
</tbody>
</table>

* Composition prepared according to the scheme presented in Fig. 7

**Example 7.**

The following example illustrates the influence of active ingredient particles size on ziprasidone release rate.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Composition No. 7**</th>
<th>Composition No. 8**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone free base (A)</td>
<td>40.00 mg / tablet</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone free base (B)</td>
<td>-</td>
<td>40.00 mg / tablet</td>
</tr>
<tr>
<td>Carbopol 974P</td>
<td>6.85</td>
<td></td>
</tr>
</tbody>
</table>
substance of average particle size $D_{4.3}^{4.3}$ below 2 $\mu$m ($D_{[2,3]}^{2,3}$ below 1 $\mu$m)
(B) substance of average particle size $D_{4.3}^{4.3}$ about 20 $\mu$m
** * Composition prepared according to the scheme presented in Fig. 10

Example 8.

The following example illustrates the influence of granulate particle size on active ingredient release profile from the capsules.

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Composition No. 9**</th>
<th>Composition No. 10**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone free base</td>
<td>80.00</td>
<td></td>
</tr>
<tr>
<td>Carbopol 974P</td>
<td>13.70</td>
<td></td>
</tr>
<tr>
<td>Lactose Flowlac-100</td>
<td>18.30</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose Avicel PH101</td>
<td>18.30</td>
<td></td>
</tr>
<tr>
<td>Ultraamylopectin of type A</td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td>**Total</td>
<td>136.80</td>
<td></td>
</tr>
</tbody>
</table>

** * Composition prepared according to the scheme presented in Fig. 9
Composition No. 10 -granulate particle size: $D_{[v,0.9]}^{v,0.9}$ - 97 $\mu$m
Composition No. 9 -granulate particle size: $D_{[v,0.9]}^{v,0.9}$ - 170 $\mu$m
The subject matter of the invention is visualized in the figures, in which:

**Fig. 1.** Comparison of ziprasidone hydrochloride and ziprasidone free base solubility within the pH range of 1 to 7.5.

**Fig. 2** presents the flow chart of preparation of composition No. 1

**Fig. 3** presents obtained release profiles of the active ingredient

**Fig. 4** presents the flow chart of preparation of composition No. 2

**Fig. 5** presents obtained release profiles of the active ingredient from the composition No. 1 and composition No. 2

**Fig. 6** presents the comparison of release profiles of the active ingredient from composition No. 1 and composition No. 3

**Fig. 7** presents the flow chart of preparation of composition No. 4 and composition No. 5

**Fig. 8** presents the comparison of ziprasidone release profiles from compositions No. 4 and composition No. 5

**Fig. 9** presents the comparison of ziprasidone release profiles from compositions No. 4 and composition No. 6

**Fig. 10** presents the flow chart of preparation of composition No. 7

**Fig. 11** presents the comparison of ziprasidone release profiles from compositions No. 4 and composition No. 7

**Fig. 12** presents the comparison of ziprasidone release profiles from compositions No. 7 and composition No. 8

**Fig. 13** presents the comparison of ziprasidone release profiles from compositions No. 9 and composition No. 10.
Claims

1. The pharmaceutical composition containing ziprasidone as an active ingredient and pharmaceutically acceptable carrier, wherein the active ingredient is ziprasidone in micronized form and pharmaceutically acceptable carrier is a substance of high capillary activity able to form gel in aqueous environment.

2. The pharmaceutical composition according to claim 1 wherein said active ingredient is ziprasidone hydrochloride in micronized form.

3. The pharmaceutical composition according to claim 2 wherein ziprasidone hydrochloride in micronized form has the average particle size D[4.3] below 2 µm (D[2.3] below 1 µm).

4. The pharmaceutical composition according to claim 2 wherein the substance of high capillary activity able to form loose gel in the aqueous environment is crospovidone.

5. The pharmaceutical composition according to claim 2 wherein pharmaceutically acceptable carrier is disintegrant belonging to the group of superdisintegrants.

6. The pharmaceutical composition according to claim 5 wherein ultraamylopectin of type A is used as disintegrant.

7. The pharmaceutical agent according to claim 2 wherein in case of placing the dosage form in the apparatus II according to the Ph. Eur. (paddleapparatus) containing 0.05M phosphate buffer solution of pH 7.5 as acceptor fluid with 1% sodium lauryl sulfate and with pancreatin, equipped with paddlesstirring with speed equal to 75 rpm, at least 75% of ziprasidone contained in the dosage form is dissolved within 30 minutes.

8. The pharmaceutical agent according to claim 2 wherein ziprasidone accounts for max. 60% w/w of the granulate.

9. The method for preparation of pharmaceutical composition containing ziprasidone hydrochloride as an active ingredient wherein said method consists of the following stages:
a. the active ingredient (micronized ziprasidone) is subjected to granulation with at least one pharmaceutically acceptable carrier,
b. obtained granules are recalibrated,
c. normalized granulate is mixed with the excipients,
d. the granulate is subjected to encapsulation.

10. The method according to claim 9 wherein the granulation process is dry granulation process (dry blending).

11. The method according to claim 10 wherein roller compaction is used as dry granulation method.

12. The method according to claim 9 wherein obtained granules are calibrated by milling - sieving.

13. The method according to claim 9 wherein the excipient used is lubricant, preferably magnesium stearate.

14. The pharmaceutical composition according to claim 1 wherein ziprasidone free base in micronized form is used as an active ingredient.

15. The pharmaceutical composition according to claim 14 wherein ziprasidone free base in micronized form has average particle size $D_{4.3}$ below 2 µm ($D_{2.3}$ below 1 µm).

16. The pharmaceutical composition according to claim 14 wherein the substance of high capillary activity is able to form gel in aqueous environment and contains suitable amount of acetyl groups.

17. The pharmaceutical composition according to claim 16 wherein the substance containing the suitable amount of acetyl groups is carbopol.

18. The pharmaceutical composition according to claim 14 wherein the pharmaceutically acceptable carrier used is disintegrant belonging to the group of superdisintegrants.

19. The pharmaceutical composition according to claim 18 wherein the disintegrant used is ultraamylopectin of type A.

20. The pharmaceutical agent according to claim 14 wherein in case of placing the dosage form in the apparatus II according to the Ph. Eur. (paddle apparatus)
containing 0.05M phosphate buffer solution of pH 7.5 as acceptor fluid with 1% sodium lauryl sulfate and with pancreatin, equipped with paddles stirring with speed equal to 75 rpm, at least 75% of ziprasidone contained in the dosage form is dissolved within 30 minutes.

21. The pharmaceutical agent according to claim 14 wherein ziprasidone accounts for min. 40% w/w of the granulate.

22. The method for preparation of pharmaceutical composition containing ziprasidone free base as an active ingredient wherein said method consists of the following stages:
   a. the active ingredient (ziprasidone free base) is subjected to granulation with at least one pharmaceutically acceptable carrier,
   b. obtained granules arecalibrated,
   c. calibrated granulate is mixed with theescipients ,
   d. the granulate is subjected to encapsulation.

23. The method according to claim 22 wherein the granulation process is dry granulation process.

24. The method according to claim 23 wherein roller compaction is used as dry granulation method.

25. The method according to claim 22 wherein obtained granules are calibrated by milling - sieving.

26. The method according to claim 22 wherein the excipient used is lubricant, preferably magnesium stearate.
Fig. 1. Comparison of ziprasidone hydrochloride and ziprasidone free base solubility within the pH range of 1 to 7.5.

[legend]
ZPR HCl
ZPR free base

0.1 M HCl / 37°C
acetate buffer pH 4.5 / 37°C
phosphate buffer pH 4.5 / 37°C
phosphate buffer pH 6.8 / 37°C
phosphate buffer pH 7.5 / 37°C
water / 37°C
water / 20°C
Fig 2. The flow chart of preparation of composition No. 1

1. Ziprasidone
2. Polypylasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamyllopectin of type A

1. Ziprasidone
2. Polypylasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamyllopectin of type A

3. Magnesium stearate

1. Ziprasidone
2. Polypylasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamyllopectin of type A

Fig 3. The release profile of the active ingredient from the composition No. 1

[legend]
X-axis: Time [min]
Y-axis: Amount of substance released [%]
Fig 4. The flow chart of preparation of composition No. 2

1. Ziprasidone
2. Polyplasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A

3. Magnesium stearate

- sieving and mixing

1. Ziprasidone
2. Polyplasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A

- mixing

1. Ziprasidone
2. Polyplasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A
6. Magnesium stearate

- encapsulation
**Fig 5.** The comparison of the release profiles of the active ingredient from the composition No. 1 and composition No. 2

![Graph showing release profiles for Comp. No. 1 and Comp. No. 2.]

*Legend*

composition No. 1

composition No. 2

X-axis: Time [min]

Y-axis: Amount of substance released [%]
**Fig 6.** The comparison of the release profiles of the active ingredient from the composition No. 1 and composition No. 3

[Chart showing release profiles over time for Comp. No. 1 and Comp. No. 3]

*Legend*

- composition No. 1
- composition No. 3

X-axis: Time [min]

Y-axis: Amount of substance released [%]
Fig 7. The flow chart of preparation of composition No. 4 and composition No. 5

1. Ziprasidone
2. Polysoladone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A

3. Magnesium stearate

1. Ziprasidone
2. Polysoladone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A

sieving and mixing

mixing

encapsulation

1. Ziprasidone
2. Polysoladone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A
6. Magnesium stearate
Fig 8. The comparison of the release profiles of the active ingredient from the composition No. 4 and composition No. 5.

[legend]
composition No. 4
composition No. 5
X-axis: Time [min]
Y-axis: Amount of substance released [%]
**Fig 9.** The comparison of ziprasidone release profiles from the composition No. 4 and composition No. 6

[legend]
composition No. 4
composition No. 6
X-axis: Time [min]
Y-axis: Amount of substance released [%]
Fig 10. The flow chart of preparation of composition No. 7

1. Ziprasidone
2. Polyplasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A

sieving
and
mixing

1. Ziprasidone
2. Polyplasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A

compacting
and
milling

3. Magnesium stearate

mixing

1. Ziprasidone
2. Polyplasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A

encapsulation

1. Ziprasidone
2. Polyplasdone INF-10
3. Flowlac 100
4. Avicel PH101
5. Ultraamylopectin of type A
6. Magnesium stearate
Fig. 11 The comparison of ziprasidone release profiles from the composition No. 4 and composition No. 7

[legend]
composition No. 4
composition No. 7
X-axis: Time [min]
Y-axis: Amount of substance released [%]
Fig 12. The comparison of ziprasidone release profiles from the composition No. 7 and composition No. 8

[legend]
- composition No. 7
- composition No. 8

X-axis: Time [min]
Y-axis: Amount of substance released [%]
Fig 13. The comparison of ziprasidone release profiles from the composition No. 9 and composition No. 10

[legend]

composition No. 9
composition No. 10
X-axis: Time [min]
Y-axis: Amount of substance released [%]
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K31/496
ADD.

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 database consulted during the international search (name of database and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No</th>
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Further documents are listed in the continuation of Box C

See patent family annex

Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

12 May 2010

Date of mailing of the international search report

02/06/2010

Name and mailing address of the ISA
European Patent Office, P O Box 801883, 2280 CH-CH, Switzerland
Tel (+41-22) 333-2222, Fax (+41-22) 333-2222

Authorized officer
Schüle, Stefanie

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