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(71) Applicant *(for all designated States except US)*: **ZENTIVA, A.S.** [CZ/CZ]; U kabelovny 130, 102 37 Praha 10 (CZ).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VLADOVICOVA, Beata** [SK/SK]; Vazska 1, 920 01 Hlohovec (SK). **LEHOCKY, Mikulas** [SK/SK]; Zeleznicna 16, 920 01 Hlohovec (SK). **KORMANOVA, Viera** [SK/SK]; Slnecna 3, 920 01 Hlohovec (SK). **HUBINOVA, Viera** [SK/SK]; SNP 21/E, 920 01 Hlohovec (SK).

(74) Agents: **JIROTKOVA, Ivana** et al.; Rott, Ruzicka & Guttmann, Nad Stolou 12, 170 00 Praha 7 (CZ).

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(54) Title: A PHARMACEUTICAL COMPOSITION CONTAINING OLANZAPINE AS THE ACTIVE AGENT AND A PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: A pharmaceutical composition containing, as the active agent, olanzapine and further a filler and auxiliary substances, in the form of tablet obtainable by direct tabletting, the core of the tablet containing olanzapine in an amount of 0.5 to 20 w.% and a pharmaceutically acceptable filler in an amount of 35 to 99 w.%, preferably up to 95 w.%, with the particle sizes ranging from 10 to 1000 μm, preferably from 50 to 400 μm, the core being optionally coated, in which case the coating contains 1 to 10 w.% of polyethyleneglycol after drying. The pharmaceutically acceptable filler is selected from the series of microcrystalline cellulose, lactose, the polyalcohols mannitol or sorbitol, calcium hydrogenphosphate, and a combination of microcrystalline cellulose with a mono- or oligosaccharide or polyalcohol. A process for the preparation of tablets is also disclosed.

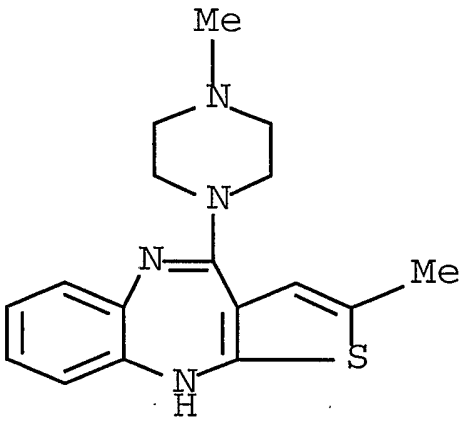
A pharmaceutical composition containing olanzapine as the active agent and a process for the preparation thereof

Technical Field

The invention concerns a tablet containing the active agent olanzapine, prepared via direct tabletting and a method of its preparation.

Background Art

Olanzapine, a compound with the chemical name 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b] [1,5] benzodiazepine, of formula I



I

belongs to the group of antipsychotic agents that are used to treat schizophrenia.

Olanzapine was described in patent EP 456 436, where pharmaceutical formulations of the compound were also mentioned in general. The patent lists a number of auxiliary substances that can be used for preparation of the pharmaceutical formulation. According to the patent, the tablet is prepared via granulation of a mixture of olanzapine, microcrystalline cellulose, magnesium stearate and starch using povidone as the binder. The granulate is further tabletted.

Further information about the medical form of olanzapine is presented in patent EP 733 367 B. It is a coated tablet that contains lactose, hydroxypropyl cellulose, microcrystalline cellulose in the core and hydroxypropylmethyl cellulose (HPMC) in the isolation layer of the coating and a subsequent coating with a suspension. For coating, the isolation layer is important according to the patent, which is supposed to prevent change of the tablet's color, which is a problem specifically for olanzapine. According to the patent, polyethyleneglycol is not suitable for the coating being supposed to prevent the color change.

The tablet according to patent EP 733 367 B is prepared via a wet granulation technique, drying and tabletting. The patent suggests (page 4) that the applicant believes that an insufficiently homogenous mixture (non-uniformity of doses) is formed in direct tabletting and recommends wet granulation in a high-shear granulation device.

The wet granulation method, especially with high shear, as suggested in the mentioned document, usually indeed provides better homogeneity and hence uniformity of the composition of individual tablets. On the other hand, it has also negative implications. First of all, the active agent is exposed to temperature stress under wet conditions. That can lead to a number of decomposition reactions and eventually to lower purity of the product.

Wet granulation can also result in a color change of the tablet, which is subsequently solved using a suitable coating.

Another problem can include change of the crystalline form of the active agent, which can also often occur when the substance is heated under wet conditions. The change of the crystalline form can result in a change of biological availability of the active agent in the pharmaceutical formulation, which, in the worst case, eventually leads to loss of activity. Particularly with olanzapine, for which a number of crystalline forms and several types of solvates have been described, the risk of conversion to another crystalline form is especially high.

It seems to be desirable, therefore, to overcome the problem of insufficient dose uniformity during direct tabletting, so that this most gentle method can be used for olanzapine. Such a composition is solved by the present invention.

Disclosure of Invention

A pharmaceutical composition, containing olanzapine as the active agent, and further a filler and auxiliary substances, in the form of a tablet obtainable by direct tabletting, the essence of which is that the core of the tablet contains olanzapine in an amount of 0.5 to 20 w.% and a pharmaceutically acceptable filler in an amount of 35 to 99 w.% with the particle sizes ranging from 10 to 1000 μm, the core being optionally coated, in which case the coating contains 1 to 10 w.% of polyethyleneglycol after drying.

The pharmaceutical preparation according to the invention preferably contains a pharmaceutically acceptable filler in an amount of 60 to 95 w.% and has a particle size of preferably from 50 to 400 μm. The content of the active agent olanzapine is preferably 2 up to 10%.

The pharmaceutically acceptable filler is selected from the series of microcrystalline cellulose, lactose, the polyalcohols mannitol or sorbitol, calcium hydrogenphosphate and a combination of microcrystalline cellulose with a mono- or oligosaccharide or polyalcohol.

The pharmaceutically acceptable filler in this definition of the invention means such a bulk substance, which is used as a filler in pharmaceutical practice. It is, therefore, primarily free of any health risk and has appropriate physical properties for this function. A list of acceptable fillers and their properties can be found in various types of pharmaceutical publications; one can recommend for example the Handbook of Pharmaceutical Excipients, which is published by the American Pharmaceutical Association.

The invention also solves a process for the preparation of a tablet containing the active agent olanzapine, comprising mixing a mixture of olanzapine and the filler in a homogenization device; optionally adding a substance modifying the flow

properties of the tabletting blend and an anti-adhesive substance in the subsequent step and, after homogenization, the mixture is tabletted.

Detailed description of the invention

Tablets obtainable by direct tabletting have numerous advantages compared to tablets which have to be obtained via alternative methods.

Preparation of the tabletting blend is technologically simple; it is limited only to steps that are not energetically demanding or time-consuming. The preparation of the tabletting blend does not involve stress procedures such as introduction of a moistening agent into the mixture of the active agent and auxiliary substances and dry granulation via compacting the mixture of the active agent and auxiliary agents for preparation of the tabletting blend.

Compression of the tabletting blend prepared by dry mixing allows for preparation of cores and/or tablets having satisfactory parameters and the presented method of preparation and selection of auxiliary substances according to the invention also ensure good stability of the preparation and the required physical properties of the pharmaceutical formulation.

The technique of direct tabletting is not only simple, but primarily the most gentle of all the methods. Therefore, it represents further progress compared to the previously described techniques of wet granulation, which is associated with introduction of a moistening agent, and of dry granulation, which is associated with compacting and, therefore, using high pressures, which can subsequently cause problems concerning release of the drug into the patient's organism. Such problems can lead to the situation when a significant part of the drug is not utilized at all.

However, for application of direct tabletting such a mixture of the active agent and auxiliary substances has to be found that can be tabletted without any further treatment, producing a tablet that meets all the requirements. The tablet of the pharmaceutical preparation has to be sufficiently hard so that it withstands various types of stress during transport. However, it must also disintegrate fast enough upon

contact with water so that it can release the active agent into the solution before it passes through the upper part of the patient's digestive system. The value of hardness of the tablet and that of dissolution of the active-agent are therefore two variables that work more or less directly against each other and the conditions have always to be optimized.

Another problem of direct tabletting can include variation of the dosage sizes in the individual tablets; the problem therefore resides in uniformity of doses. As specified above, this problem was expected during preparation of an olanzapine tablet (EP 0 733 367 B). Accordingly, dry mixing does not have to be sufficiently effective. This was the reason why only wet granulation, most preferably in a high-shear granulation device, has been applied so far.

In the technique of direct tabletting, homogeneity and, therefore, also uniformity of dosage are influenced by the percentual content of the active agent. While the advantageous properties of the tablet described in the previous paragraph (sufficient hardness and speed of release of the active-agent) can be better achieved at lower concentrations of the active agent, uniformity of dosage is, on the contrary, better at higher concentrations of the active agent. The expected problems with uniformity of dosage in patent EP 0 733 367 B can be so interpreted that there was an expectation that there would not be possible to find such a formulation that would simultaneously meet both contradicting requirements at the desired reasonable concentration of olanzapine.

For the olanzapine pharmaceutical preparation according to the invention, the filler is important, or rather its share in the tablet's core and the size of the particles that form it.

It has turned out that an olanzapine tablet that meets both the requirements concerning hardness and speed of release of the active-agent release and those concerning homogeneity (uniformity) of individual doses contains 0.5 to 20 w.% of the active agent in the form of olanzapine and a pharmaceutically acceptable filler in an amount of 35 to 99 w.% with particle sizes ranging from 10 to 1000 μm, preferably from 50 to 400 μm.

It further turns out that such tablet, wherein a higher excess of the filler between 3 to 100 fold the volume of the active agent, displays better properties.

The most advantageous ratios between the active agent and the filler are 1 : 5 to 30, particularly between 1 : 10 to 25.

In a preferable embodiment, the content of the active agent in the tablet's core ranges from 2 to 10 w.%.

In a preferable embodiment, it is possible to select the filler from the series of microcrystalline cellulose, lactose, the polyalcohols mannitol or sorbitol, calcium hydrogenphosphate and a combination of microcrystalline cellulose with a mono- or oligosaccharide or polyalcohol.

Anhydrous spray-dried lactose with the particle sizes ranging from 10 to 250 μm, preferably from 150 to 250 μm, lactose hydrate compact with the particle sizes ranging from 10 to 200 μm, a polyalcohol selected from the series of mannitol or sorbitol compacted with the particle sizes ranging from 10 to 400 μm, preferably from 200 to 400 μm or a combination of microcrystalline cellulose with lactose, preferably anhydrous spray-dried lactose, in the weight ratio 1 : 2 to 2 : 1, or a combination of microcrystalline cellulose with a polyalcohol, preferably compacted, in the ratio 1 : 2, have turned to be preferable fillers.

Microcrystalline cellulose turns to be a particularly advantageous filler for these purposes is. It has good flow properties. The tablets have acceptable strength and disintegration properties because microcrystalline cellulose in the pressing ensures preservation of capillary orifices, through which water, inhibiting the effect of bonding forces, gets in. They ensure very good stability of the preparation. For the formulation of the invention, quality of selected microcrystalline cellulose is essential. Particle size of commercially available cellulose for pharmaceutical use ranges from about 1 to 1000 μm. For direct tabletting of olanzapine, cellulose within the range from 10 to 1000 μm can be used; it is advantageous to use particles with

sizes ranging from 90 to 360 μm, the size 180 μm appearing to be the most preferable one.

In another embodiment, the tabletting blend contains substances improving its flow properties. Colloidal silica (silica colloidalis anhydrica) is the most preferable substance for the described mixture, preferably in an amount of 0.1 to 10 %, particularly preferably from 0.1 to 4 %. These substances are important for preventing variation of the tablet's weight caused by undesirable flow of the solid mixture through the hopper into the high-performance tabletting machine.

In a further embodiment, the tabletting blend contains anti-adhesive substances, facilitating the tabletting process. Magnesium stearate is the most preferable substance for the described mixture, preferably in an amount of 0.1 to 10 %, especially preferably 0.5 to 4 %.
From the above mixtures, it is possible to prepare the tabletting blend, or tablets, via dry process, by dry mixing and direct tabletting.

The tablets according to the invention ensure reproducibility of the production process.

Advantageously, the preparation of the tabletting blend is not energetically demanding or time-consuming.

The above described process of preparation of a tabletting blend and solid pharmaceutical formulations containing olanzapine by direct tabletting via dry mixing and selection of auxiliary substances according to the invention provide for preparation of a tabletting blend and solid pharmaceutical formulations with excellent physical parameters.

Examples

Example 1

Filler: microcrystalline cellulose

Olanzapine 10 mg tablets

Starting substances	**weight in g**
Olanzapinum (Olanzapine)	0.01000 g
Cellulosum microcrystallinum (microcrystalline cellulose), size 180 μm	0.17710 g
Silicii dioxidum colloidale (colloid silicon dioxide)	0.00100 g
Magnesii stearas (magnesium stearate)	0.00190 g
Total weight of tabl. in g	**0.19000 g**

Description of technology of preparation of the tabletting blend (dry method, direct tabletting):

1. Mixing I: the active agent and microcrystalline cellulose are mixed in a homogenization device for 15 minutes.
2. Mixing II: substances for the final preparation are added - silicii dioxidum colloidale and magnesii stearas and the mixture is mixed in a homogenization device for 15 minutes.
3. Tabletting

Two important variables were determined in tablets prepared via this method. They were break resistance, which is necessary for preserving tablets intact during transport, and speed of releasing the active agent into the dissolution medium, which indicate availability of the medicament for the patient's organism. Both variables were measured using standard methods.

The tablets prepared via the method showed break resistance of at least 60N, which indicates that they will not be damaged under common transportation conditions.
The content of thus obtained tablets of olanzapine 10 mg conformed to the limit 9.5 – 10.5 mg.

During the active-agent-release test, more than 85 % of the total content was released within 30 minutes. The result is in very good agreement with the already registered and marketed preparation Zyprexa of Eli Lilly.

It turns out, therefore, that tablets prepared via this new method are with respect to their properties in agreement with products obtained by known, standard methods.

Olanzapine 20 mg, 15 mg, 7.5 mg, 5 mg, 2.5 mg was obtained by the same method.

Composition:

Olanzapine 20 mg tablets

Starting substances	**weight in g**
Olanzapinum	0.02000 g
Cellulosum microcrystallinum, size 180 μm	0.35420 g
Silicii dioxidum colloidale	0.00200 g
Magnesii stearas	0.00380 g
Total weight of tabl. in g	**0.38000 g**

Olanzapine 15 mg tablets

Starting substances	**weight in g**
Olanzapinum	0.01500 g
Cellulosum microcrystallinum, size 180 μm	0.26565 g
Silicii dioxidum colloidale	0.00150 g
Magnesii stearas	0.00285 g
Total weight of tabl. in g	**0.28500 g**

Olanzapine 7.5 mg tablets

Starting substances	**weight in g**
Olanzapinum	0.007500 g
Cellulosum microcrystallinum, size 180 μm	0.132825 g
Silicii dioxidum colloidale	0.000750 g

Magnesii stearas	0.001425 g
Total weight of tabl. in g	**0.142500 g**

Olanzapine 5 mg tablets

Starting substances	**weight in g**
Olanzapinum	0.00500 g
Cellulosum microcrystallinum, size 180 μm	0.08855 g
Silicii dioxidum colloidale	0.00050 g
Magnesii stearas	0.00095 g
Total weight of tabl. in g	**0.09500 g**

Olanzapine 2.5 mg tablets

Starting substances	**weight in g**
Olanzapinum	0.002500 g
Cellulosum microcrystallinum, size 180 μm	0.091050 g
Silicii dioxidum colloidale	0.000500 g
Magnesii stearas	0.000950 g
Total weight of tabl. in g	**0.095000 g**

Composition uniformity of tablets was tested in tablets olanzapine 2.5 mg (Table 1) (requirement 2.375 to 2.625 mg)

Table 1

Tablet No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Content /mg/	2.472	2.455	2.467	2.469	2.431	2.520	2.441	2.452	2.458	2.462

Based on the presented results, we can conclude that composition uniformity of thus obtained tablets is acceptable and that homogeneous tablets can be produced by the present method.

Example 2

Combination microcrystalline cellulose and mannitol

Olanzapine 10 mg tablets

Starting substances	**weight in g**
Olanzapinum	0.01000 g
Cellulosum microcrystallinum, size 180 μm	0.10000 g
Mannitol (Pearlitol 400 DC), size 360 μm	0.07710 g
Silicii dioxidum colloidale	0.00100 g
Magnesii stearas	0.00190 g
Total weight of tabl. in g	**0.19000 g**

The tablet was produced by the method according to Example 1.

Example 3

A combination of microcrystalline cellulose and anhydrous lactose was used.

Olanzapine 10 mg tablets

Starting substances	**weight in g**
Olanzapinum	0.01000 g
Cellulosum microcrystallinum, size 180 μm	0.08855 g
Lactose anhydrous DCL 21, size 250 μm	0.08855 g
Silicii dioxidum colloidale	0.00100 g
Magnesii stearas	0.00190 g
Total weight of tabl. in g	**0.19000 g**

Processing made according to Example 1.

Example 4

Mannitol was used as the filler.
Olanzapine 10 mg tablets

Starting substances	**weight in g**
Olanzapinum	0.01000 g

Mannitol, (Pearlitol 400 DC), size 360 μm	0.17710 g
Silicii dioxidum colloidale	0.00100 g
Magnesii stearas	0.00190 g
Total weight of tabl. in g	**0.19000 g**

Processing made according to Example 1.

Example 5

Coated tablets

Olanzapine 10 mg **coated tablets**

Starting substances	**weight in g**
Olanzapinum	0.01000 g
Cellulosum microcrystallinum, size 180 μm	0.17710 g
Silicii dioxidum colloidale	0.00100 g
Magnesii stearas	0.00190 g
Total weight of the nucleus in g	**0.19000 g**
Sepifilm White	0.01000 g
Polyethylenglycolum (polyethyleneglycol)	0.00050 g
Aqua purificata (purified water)	0.03500 g
Total weight of coated tabl. in **g**	**0.20050 g**

Processing was made according to Example 1.

CLAIMS

1. A pharmaceutical composition containing, as the active agent, olanzapine and further a filler and auxiliary substances, in the form of tablet obtainable by direct tabletting, characterized in that the core of the tablet contains olanzapine in an amount of 0.5 to 20 w.% and a pharmaceutically acceptable filler in an amount of 35 to 99 w.% with the particle sizes ranging from 10 to 1000 μm, the core being optionally coated, in which case the coating contains 1 to 10 w.% of polyethyleneglycol after drying.

2. The pharmaceutical preparation according to claim 1, characterized in that the ratio of the filler to the active agent is 3 to 100 : 1, more preferably 5 to 30 :1, the preferably 10 to 25 :1.

3. The pharmaceutical composition according to claim 1 or 2, characterized in that it contains a pharmaceutically acceptable filler in an amount of 60 to 95 w.%.

4. The pharmaceutical composition according to any of the preceding claims, characterized in that pharmaceutically acceptable filler has particle sizes from 50 to 400 μm.

5. The pharmaceutical composition according to claim 1 or 2, characterized in that the content of the active agent is 2 to 10 w.%.

6. The pharmaceutical composition according to any of the preceding claims, characterized in that it contains a pharmaceutically acceptable filler selected from the series of microcrystalline cellulose, lactose, the polyalcohols mannitol or sorbitol, calcium hydrogenphosphate and a combination of microcrystalline cellulose with a mono- or oligosaccharide or polyalcohol.

7. The pharmaceutical composition according to claim 6, characterized in that it contains a filler selected from the series of microcrystalline cellulose with the particle sizes ranging from 10 to 1000 μm, preferably from 90 to 360 μm, most preferably 180 μm, or anhydrous spray-dried lactose with the particle sizes

ranging from 10 to 250 μm, preferably from 150 to 250 μm, or lactose hydrate compact with the particle sizes ranging from 10 to 200 μm or a polyalcohol selected from the series of mannitol or sorbitol compacted with the particle sizes ranging from 10 to 400 μm, preferably from 200 to 400 μm, or a combination of microcrystalline cellulose with lactose with the above defined particle size, the lactose being preferably anhydrous spray-dried lactose in the weight ratio 1 : 2 to 2 : 1, or a combination of microcrystalline cellulose with a polyalcohol, preferably compacted, in the ratio 1 : 2.

8. The pharmaceutical composition according to claim 7, characterized in that microcrystalline cellulose is selected as the filler.

9. The pharmaceutical composition according to any of the preceding claims, characterized in that it additionally contains a substance adjusting flow properties of the tabletting blend and an anti-adhesive substance.

10. The pharmaceutical composition according to claim 9, characterized in that it contains 0.1 to 10 w.%, preferably 0.1 to 4 w.%, of the substance adjusting flow properties of the tabletting blend, preferably colloidal silicon dioxide.

11. The pharmaceutical composition according to claim 9, characterized in that it contains 0.1 to 10 w.%, preferably 0.5 to 4 w.%, of the anti-adhesive substance, preferably magnesium stearate.

12. A process for the preparation of the tablet containing olanzapine as the active agent according to claims 1 to 11, characterized in that a mixture of olanzapine and the filler is mixed in a homogenization device, optionally a substance modifying the flow properties of the tabletting blend and an anti-adhesive substance are added in the subsequent step and, after homogenization, the mixture is tabletted.