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A61K AO,

Applicant:
SYNTHON B.V., Microweg 22, NL-6545 CM Nijmegen (NL).

Inventors:
Bakker-Holmdahl, Lisa; Synthron B.V., Microweg 22, NL-6545 CM Nijmegen (NL).
De Haan, Frans Henri Nicolaas; Synthron B.V., Microweg 22, NL-6545 CM Nijmegen (NL).
Mrupani, Deepak; Synthron B.V., Microweg 22, NL-6545 CM Nijmegen (NL).

Designated States (unless otherwise indicated, for every kind of national protection available):

Abstract:
The present invention relates to a directly compressible orodispersible tablet composition comprising aripiprazole, lactose, at least one superdisintegrant and at least one additional compressible diluent, and not comprising an alcoholic sugar or a metal silicate.

Designated Agent:
MENDFVTI-GIL, Maria Dolores; SYNTHON BV, P.O. Box 7071, NL-6503 GN Nijmegen (NL).
ORODISPERSIBLE PHARMACEUTICAL COMPOSITIONS COMPRISING ARIPIPRAZOLE

The present invention relates to pharmaceutically useful orodispersible tablet compositions that contain aripiprazole and pharmaceutically acceptable excipients.

BACKGROUND OF THE INVENTION

Aripiprazole, or chemically 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril, is a compound of the formula (1).

It is a pharmaceutically active substance useful for treatment of, i.a., schizophrenia and bipolar disorder. In all pharmaceutical products discussed in more detail below, aripiprazole is present as the free base.

Solid state free base of aripiprazole was prepared in US 5006528. In an article of Aoki (Study on Crystal Transformation of Aripiprazole, The Fourth Japan-Korea Symposium on Separation Technology, p.937 ff (1996)), this solid state form was designated as Type I aripiprazole and identified as an anhydrate. Aoki also teaches that the Type I aripiprazole may be converted into a Type II aripiprazole by heating at 130-140°C for 15 hours. This product is also an anhydrate. When both Type I and Type II aripiprazole were recrystallized from an alcoholic solvent containing water up to 20%, the product was an aripiprazole hydrate labeled as Type III by Aoki.
WO 03/26659 (EP 1330249) teaches that Type I and Type II aripiprazole are significantly hygroscopic. In an effort to find a form of aripiprazole having reduced hygroscopicity and better processing qualities, seven crystalline forms (Form A-Form G) were described.

More recently techniques for crystallizing Type II aripiprazole directly from a solution were disclosed in WO 2006/097343; similarly, WO2005/058835 also purports to have directly crystallized Type II aripiprazole. Furthermore, a crystallization process for making Form B aripiprazole has been disclosed in WO 2006/053781.

PCT application WO 2006/053780 discloses crystalline alcohohates of aripiprazole.

Other solvates of aripiprazole have been disclosed in WO 2005/009990.

Aripiprazole (base) is commercially marketed, e.g., under brand name Abilify by Otsuka (in cooperation with Bristol-Myers-Squibb), in various pharmaceutical products: in tablets (of 2mg, 5mg, 10mg, 15mg, 20mg, 30 mg strengths), orodispersible tablets (of 10mg, 15 mg and 30 mg strengths), in peroral solution (1mg/ml), or in injection solution (9.75 mg/ml).

The orodispersible (orally disintegrating) tablets, which the present invention relates to, have certain importance in treatment of patients having problems of swallowing or for immediate medication.

The marketed Abilify orodispersible tablets comprise aripiprazole in combination with the following inactive ingredients: calcium silicate, croscarmellose sodium, crospovidone, silicon dioxide, xylitol, microcrystalline cellulose, aspartame, acesulfame potassium, vanilla flavour, tartaric acid, magnesium stearate and colourants (Red or yellow iron oxide).

The quantitative composition and manufacturing process for making these tablets are not publicly available. However, tablets with the same qualitative composition as the marketed Abilify tablets were disclosed in Examples in EP 1145711 and WO 03/030868.
process described therein comprises mixing the part of the components together, granulate them by a roller-compacting and cutting process, mixing the obtained granulate with the remaining components and compressing the mixture into tablets. Such complicated process is apparently necessary because otherwise the components would not have desired compacting properties.

Similarly, WO 2013/100878 teaches an orodispersible composition of aripiprazole characterized by a presence of a diluent and disintegrant in a certain ratio, which is preferably 1:1 to 20:1. No example of a suitable diluent/disintegrant combination has been provided. Such compositions have to be twice compacted in special compacting steps before compressing them into tablets.

Accordingly, there is an objective need for alternate tablet composition of aripiprazole, which can be formulated into suitable orodispersible tablets by a simpler method, preferably by a direct compression of all components, without the need of a pre-compacting step.

**BRIEF DESCRIPTION OF THE PRESENT INVENTION**

In a first aspect, the present invention provides a directly compressible orodispersible tablet composition comprising aripiprazole, lactose, at least one superdisintegrant and at least one additional compressible diluent, and not comprising an alcoholic sugar or a metal silicate.

In a particular embodiment, the amount of lactose is from about 50 to about 80 weight %, preferably from about 60 to about 70 weight %.

In a particular embodiment, the amount of a superdisintegrant is from about 5 to about 15 weight %.

In a more particular embodiment, the superdisintegrant is selected from modified starch, crosslinked polyvinylpyrrolidone, modified cellulose, crosslinked alginic acid,
xanthan gum or crosslinked polyacrylate and preferably is selected from the group consisting of sodium croscarmellose, crospovidone, sodium starch glycollate and combination thereof.

In a particular embodiment, the compressible diluent is microcrystalline cellulose, hydroxypropylcellulose, silicified cellulose, compressible calcium phosphate, starch and combination thereof.

In a particular embodiment, the composition further comprises at least one auxiliary component and at least one lubricant.

In another aspect, the present invention provides an orodispersible tablet comprising aripiprazole, lactose, at least one superdisintegrant and at least one additional compressible diluent obtainable by the direct compression of a mixture of all components.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to a directly compressible orodispersible tablet composition comprising aripiprazole.

"Directly compressible", as used in the disclosure and claims, is a composition characterized by such selection of components that a physical mixture thereof may be, after homogenization, compressed into a tablet sufficiently hard to sustain normal conditions of treatment.

The "orodispersible", in accordance with common meaning, is such composition of tablets, which can disintegrate or dissolve in the mouth, wherein the active substance may be absorbed by oral tissues without a need to enter stomach. The orodispersible tablets disintegrate within 3 minutes or less in a disintegration test as described in the European Pharmacopeia.

The "composition" within the present invention is a pharmaceutical composition.

Accordingly, it may comprise only components that are pharmaceutically acceptable.
"Aripiprazole", as used within the disclosure and claims related to the present invention, means the free base of the compound of formula (1). It is a well known compound available on the market or obtainable according to processes known in the art.

Several basic concepts are known for preparing orodispensible tablets. The first one is based on freeze drying of a solution resulting in a shaped wafer comprising the dose amount of the drug. The basic disadvantage of these drug forms is that a solution must be made first and the process is expensive and time consuming. The resulted forms are very soft and hygroscopic and must be kept in a special moisture resistant packaging. The second concept is based on using special grades of sugars in a combination with superdisintegrants, which are compounds able to absorb water upon rapid swelling resulting in disintegration of the compressed composition. In another concept, the rapid disintegration results from the presence of an effervescent combination comprising a bicarbonate and a weak acid.

It is a common disadvantage of many orodispensible tablet forms known in the art that such forms are often hygroscopic and friable. In particular, effervescent compositions are susceptible for moisture attack.

In literature, the concept based on the presence of a superdisintegrant in a combination with a sugar appears to be useful for making aripiprazole-comprising orodispensible compositions; the same concept has been used in EP 1145711 and WO 03/030868. The main characteristic of the technical solution disclosed therein is in that two superdisintegrants (croscarmellose and crospovidone) and a dispersing agent (calcium silicate) are combined with a suitable sugar alcohol (xylitol). Further, the composition comprises a distributing agent (fumed silica), and a binder (microcrystalline cellulose). As apparent from the examples, the aripiprazole-comprising orodispensible tablets disclosed in EP 1145711 and WO 03/030868 can only be prepared by a complicated process, comprising a pre-formulation step of blending the active ingredient, the dispersing agent, distributing agent and parts of the
superdisintegrant(s) and the binder in a suitable mixer, compacting the blended mixture in a roller compactor or in a slugger and breaking the compacts or slugs by passing through a sieve forming an intragranulate. The intragranulate is then mixed with remaining extragranular excipients to form a final blend which is compressed into tablets by a tablet press. While a direct compression is mentioned as a possible approach for making the orodispersible compositions in these documents, no suitable example of such directly compressible composition of aripiprazole has been provided.

It has now been found that orodispersible tablets comprising aripiprazole may be prepared by a direct compression, i.e. by a compression of a mixture of the active components with excipients, which were not subjected in advance to a special pre-treatment except that of providing particles of the desired particle size (such as milling and/or sieving), in particular to any treatment resulting in combining more than two kinds of excipients into a compactate.

Thus, the present invention provides a directly compressible tablet composition of aripiprazole that is orodispersible, i.e. useful for making orodispersible tablets. In its broadest aspect, the tablet composition comprises aripiprazole, lactose, at least one superdisintegrant and at least one compressible diluent not comprising an alcoholic sugar or a metal silicate. When comparing the qualitative composition of the invention with that of EP 1145711 and WO 03/030868, lactose replaces xylitol, which has negative impact on the overall hardness of the resulted tablet in case of direct compression. Additionally, the tablet composition of the present invention does not comprise metal silicate, such as calcium silicate, which is not useful in direct compression process due to its low flowability. In essence, the replacement of metal silicate and alcoholic sugar that formed essential part of the composition of the orodispersible tablets of the prior art by a compressible lactose improves the tabletting properties of the composition while maintaining the orodispersible character of the resulting
tablets. This improvement results to a composition, which may be directly compressed into an orodispersible tablet without a need of any pre-formulation step, in particular that of compaction of at least part of the composition. By no doubt, the direct compression process, by which the composition of the present invention may be formulated into tablets, is simpler and cheaper than the dry granulation process of the prior art.

The aripiprazole useful in making the compositions of the present invention is in solid form that may be amorphous or crystalline. The crystalline aripiprazole include any particular crystalline form, including mixtures of such forms, regardless the form is an anhydrate, a hydrate, or a solvate. The amorphous aripiprazole includes adducts or co-precipitates of aripiprazole with various adjuvants.

The preferred solid state form of aripiprazole for making compositions of the present invention is a crystalline aripiprazole. In some embodiments, Crystalline Type II polymorph as defined in the above mentioned article of Aoki, is preferred. This polymorph is characterized by the XRPD pattern comprising signals at 5.4, 10.0, 10.7, 11.1, 11.6, 12.6, 14.2, 15.1, 15.6, 15.9, 16.2, 18.5, 18.9, 19.8, 20.0, 20.4, 20.7, 21.8, 22.2, 23.1, 23.3, 24.4, 25.0, 25.3, 26.0, 26.5, 27.0, 27.6, 28.4, 29.5, 30.2, 30.6, 31.0, 31.6, 32.1 ± 0.2 degrees two theta, when measured at copper Ka radiation.

As known in the art, aripiprazole may be provided in particles of various particle size and particle size distribution. It is preferred that aripiprazole is used in compositions of the present invention as a particulate product of the particle size value d90 of between about 15 and about 100 micrometers, preferably between about 35 and about 80 micrometers (as determined by a laser diffraction method).

The compositions of the present inventions preferably comprise from 5 to 15 weight % of aripiprazole, calculated on the total mass of the composition.
Lactose, for purposes of the present invention, is preferably a directly-compressible lactose, i.e. lactose having good flow and compressibility properties. From these aspects, spray-dried lactose is the preferred type of lactose for use in compositions of the present invention. Spray-dried lactose is prepared by spraying a suspension of alpha-form of lactose monohydrate in a saturated aqueous solution of lactose in water. Spray-dried lactose has, in general, spherical particles and contains approx. 85% of alpha-monohydrate crystals and 15% of amorphous lactose.

As an alternative, anhydrous beta-lactose, a coprocessed mixture of beta-lactose with lactitol or a coprocessed mixture of lactose monohydrate and maize starch may be used as the "lactose" for purpose of the present invention.

In a particular embodiment, the amount of lactose is from about 50 to about 80 weight %, preferably from about 60 to about 70 weight%, calculated on the total mass of the composition.

For clarity, the amount of lactose corresponds to the weighed amount of the lactose, i.e. including water eventually present in the material charged in making the composition.

Particle size distribution of the lactose has a certain effect on tabletting properties. Accordingly, lactose is preferably used as a particulate product having the particle size value d90 of about 150-300 micrometers (as determined by laser diffraction process).

In a particular embodiment, the amount of a superdisintegrant is from about 5 to about 15 weight %.

The superdisintegrant useful in compositions of the present invention is preferably modified starch, crosslinked polyvinylpyrrolidone, modified cellulose, crosslinked alginic acid, xanthan gum, or crosslinked polyacrylate, and combinations thereof. In particular, the superdisintegrant is selected, alone or in combination, from the group consisting of sodium croscarmellose, crospovidone, and sodium starch glycollate. Combination of two or more
superdisintegrants is in some embodiments advantageous, particularly a combination of a
swelling and a non-swelling superdisintegrant. In accordance with the invention, the
superdisintegrant should be compressible.

The composition may further comprise at least one diluent, which is typically a directly
compressible diluent. Accordingly, calcium silicate or any other silicate is not present in the
composition as they suffer from low flowability. Suitable compressible diluents for purposes
of the present invention comprise microcrystalline cellulose, hydroxypropylcellulose,
silicified cellulose, compressible calcium phosphate, starch and combination thereof. The
most preferred compressible diluent is microcrystalline cellulose. Typically, the composition
of the invention comprises 10-25 weight % of the compressible diluent.

In compositions comprising both lactose monohydrate and cellulose, the marketed
Cellactose, which is a co-processed product of both components in the ratio 75 : 25 (w/w),
may be used as the single excipient.

Apart of these basic components, the composition of the present invention may
comprise auxiliary components, which improve organoleptic properties. Such components
comprise, e.g., flavours, taste masking agents, taste enhancers, sweeteners or colourants. The
choice is not specifically limited except to those having proven suitability in making tablet
compositions.

As common in the art, the composition also comprises at least one lubricant. Lubricants
include, but are not limited to, magnesium stearate, calcium stearate, sodium stearyl
fumarate, stearic acid, zinc stearate or talc.

In a preferred embodiment, the final composition has less than 2% of water, determined
as loss on drying at 105°C.

The composition of the present invention is useful in making pharmaceutical
orodispersible aripiprazole tablets. For said purpose, the composition of the present invention
is compressed into a form of a tablet. The present invention accordingly provides an orodispersible tablet comprising the tablet composition disclosed above.

The present invention accordingly provides an orodispersible tablet comprising aripiprazole, lactose, at least one superdisintegrant and at least one compressible diluent, obtainable by the compression of a mixture of all components. As to the qualitative and quantitative limitations of the components, they have been discussed above within the disclosure of the composition of the invention.

The orodispersible tablet of the present invention is obtainable by a simple process comprising the steps of making the above tablet composition by blending aripiprazole, lactose, at least one superdisintegrant, at least one compressible diluent, at least one auxiliary component and at least one lubricant to form a lubricated blend, and of compressing the blend into tablets in a tablet press. No specific order of mixing the components in a suitable mixer/homogenizer is prescribed except of the fact that lubricant is preferably added to the homogenized mixture as the last component. In case of need or desire, any of the components may be milled, screened or sieved prior to the mixing step to obtain a population of particles of the desired particle size distribution and desired flowability. Preferably the final composition to be tabletted is characterized by a flowability higher than 12 g/s, when passing through a 25 mm orifice, and/or higher than 7 g/s, when passing through a 15 mm orifice. The homogenization is carried out at ambient temperature, without special precaution as to aerial oxygen and humidity. The final lubricated blend may be sieved prior to compression to remove lumps.

The lubricated blend may be compressed on conventional tablet press, advantageously at the compression force of about 4 kN. The hardness of the compressed tablets should advantageously be higher than 15N, advantageously between 19 and 27 N.
Orodispersibility of the tablet may be tested by a conventional pharmacopoeial test for disintegration in a basket-rack assembly, in water. Typically, the disintegration time is less than 2 minutes, advantageously less than 1 minute.

Each tablet represents a unit dosage form, which suitably contains between 1 and 50 mg, preferably between 2 and 30 mg of the drug substance. Advantageously, the unit dosage form comprises 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg of aripiprazole. Such unit dosage form is suitable for administration 1-5 times daily, depending on the therapy and stage of the therapy.

A plurality of tablets may be packed in a suitable package material, which advantageously protects them against light and moisture; blisters made from aluminium and/or hard polymer (i.e. PVC/PE/PVDC or PVC/PVDC) are examples of such package materials.

The tablet of the present invention may be used for any therapeutic or prophylactic treatment approved for aripiprazole-comprising medicaments. For instance, it may be used for the treatment of schizophrenia and bipolar disorder.

The invention will be further illustrated by way of the following non-limiting examples.
EXAMPLES

Example 1 - Formulation and process for making 15mg orodispersible tablets comprising aripiprazole

Formulation:

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<tr>
<th>Ingredients</th>
<th>Amount</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(%)</td>
</tr>
<tr>
<td>Aripiprazole d90= 53μm</td>
<td>8.33</td>
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<tr>
<td>Lactose monohydrate</td>
<td>60.50</td>
</tr>
<tr>
<td>Iron oxide yellow</td>
<td>0.10</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>15.00</td>
</tr>
<tr>
<td>Tartaric acid</td>
<td>2.00</td>
</tr>
<tr>
<td>Silica colloidal anhydrous</td>
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</tr>
<tr>
<td>Crospovidone XL.</td>
<td>4.00</td>
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<tr>
<td>Croscarmellose sodium</td>
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</tr>
<tr>
<td>Vanillin</td>
<td>0.50</td>
</tr>
<tr>
<td>Acesulfam K</td>
<td>1.71</td>
</tr>
<tr>
<td>Aspartame</td>
<td>1.71</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.75</td>
</tr>
<tr>
<td>Total mass:</td>
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</table>

Process:

Microcrystalline cellulose and iron oxide are mixed in a first container.
Aripiprazole and lactose are mixed in a second container.
Colloidal silica, croscarmellose sodium and crospovidone are mixed in a third container.
A bin mixer is charged with tartaric acid, vanilla flavour, acesulfame K and aspartame, the contents of the three containers are added upon stirring and the mixture is mixed for 30 minutes.

Magnesium stearate is added and the mixture is mixed for 3 minutes.

The mixture is compressed to 8 mm rounded flat tablets comprising 15 mg aripiprazole per tablet.
CLAIMS

1. A directly compressible orodispersible tablet composition comprising aripiprazole, lactose, at least one superdisintegrant and at least one additional compressible diluent, and not comprising an alcoholic sugar or a metal silicate.

2. The composition according to claim 1, comprising from 5 to 15 weight % of aripiprazole, calculated on the total mass of the composition.

3. The composition according to claim 1 or 2, wherein the amount of lactose is from about 50 to about 80 weight % calculated on the total mass of the composition.

4. The composition according to claim 1 to 3, wherein the amount of lactose is from about 60 to about 70 weight % calculated on the total mass of the composition.

5. The composition according to claim 1 to 4, wherein the amount of superdisintegrant is from about 5 to about 15 weight % calculated on the total mass of the composition.

6. The composition according to any one of claims 1 to 5, wherein lactose is a spray-dried lactose.

7. The composition according to any one of claims 1 to 6, wherein the superdisintegrant is selected from modified starch, crosslinked polyvinylpyrrolidone, modified cellulose, crosslinked alginic acid, xanthan gum, or crosslinked polyacrylate.

8. The composition according to any one of claims 1 to 7, wherein the superdisintegrant is selected from the group consisting of sodium croscarmellose, crospovidone, sodium starch glycollate and combination thereof.

9. The composition according to any one of claims 1 to 8, wherein the compressible diluent is microcrystalline cellulose, hydroxypropylcellulose, silicified cellulose, compressible calcium phosphate, starch and combination thereof.

10. The composition according to any one of claims 1 to 9, further comprising at least one auxiliary component and at least one lubricant.
11. The composition according to any one of claims 1 to 10, compressed into a form of a tablet.

12. An orodispersible tablet comprising aripiprazole, lactose, at least one superdisintegrant and at least one additional compressible diluent obtainable by the direct compression of a mixture of all components.

13. The tablet according to claim 12 comprising from about 1 to about 50 mg of aripiprazole.
**INTERNATIONAL SEARCH REPORT**

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K47/26 A61K31/497

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 data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
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<td>WO 2008/034628 AI (KRKA T0VARNA ZDRAVIL D NOVO [SI] ; MERSLAVIC MARJ0 [SI] ; GOJAK URSKA) 27 March 2008 (2008-03-27) page 1, paragraph 1 page 9, line 3, paragraph 2 page 9, line 2, paragraph 4 page 21, paragraph 3 page 22; example 16 page 23; examples 17, 18</td>
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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

E: earlier application or patent but published on or after the international filing date

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Date of the actual completion of the international search

27 February 2014

Date of mailing of the international search report

06/03/2014

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040;
Fax: (+31-70) 340-3016

Authorized officer

Toulacius, C
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<td>WO 2009/043844 A2 (LESVI LABORATORIOS SL [ES]; UBEDA PEREZ CARMEN [ES]; DÍEZ MARTÍN IGNAC) 9 April 2009 (2009-04-09) page 1, lines 4-7 page 9, line 26 examples 1-6</td>
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