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(54) **Title**: PROCESS FOR PRODUCING ARIPIPRAZOLE IN ANHYDROUS TYPE I CRYSTALS

(57) **Abstract**: Disclosed herein is an improved process for the preparation of anpiprazole in anhydrous Type I crystals, substantially free of other polymorphic forms of aripiprazole *via* improved drying technique.

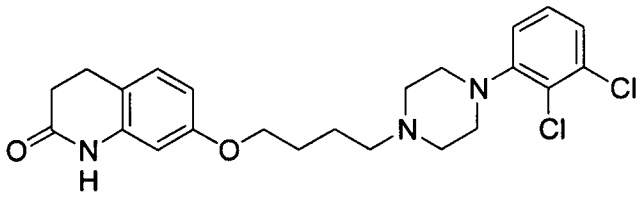
PROCESS FOR PRODUCING ARIPIPRAZOLE IN ANHYDROUS TYPE I CRYSTALS

FIELD OF THE INVENTION

The present invention relates to an improved and commercially viable process for the preparation of aripiprazole in anhydrous Type I crystals, which is substantially free of other polymorphic forms of aripiprazole *via* improved drying technique.

BACKGROUND OF THE INVENTION

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril (Aripiprazole) of the Formula I is an atypical antipsychotic agent useful for the treatment of schizophrenia.



Formula I

Schizophrenia is a common type of psychosis characterized by the symptoms like delusions, hallucination, excitations and the like. Schizophrenia generally occurs between the age of 16–25 years and affects one percent individuals worldwide. It is considered as more prevalent than alzheimer's disease, multiple sclerosis, insulin-dependent diabetes and muscular dystrophy. Schizophrenia is the most common type of psychosis caused by an excessive neurotransmission activity of the dopaminergic nervous system in the central nervous system.

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril (Aripiprazole) is generically disclosed in US4,734,416 and specifically in US5,006,528 patents. Solid state aripiprazole was first disclosed in US5,006,528 by a two-fold recrystallization of crude aripiprazole from ethanol resulting in colorless flake crystals having a melting point of 139-139.5°C. The main disadvantage of the process is that US'528 patent is silent about the recrystallization condition and drying step necessary for the preparation of pure aripiprazole.

In an article of Aoki (Study on Crystal Transformation of Aripiprazole, The Fourth Japan-Korea Symposium on Separation Technology, Oct 6-8 1996, p. 937-940, aripiprazole recrystallized from ethanol solution was designated as "anhydrous Type I" having melting point 140°C. Further, 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 an anhydrous having a melting point of 150°C. When both Type I and Type II crystals of aripiprazole were recrystallized from an alcoholic solvent containing water up to 20%, the product was an aripiprazole hydrate labeled as Type III by Aoki. Type III aripiprazole can be converted into Type I by heating at 80°C. The process disclosed in the said article is not commercially viable on an industrial scale for the preparation of aripiprazole in anhydrous Type I, as the specific conditions used for the crystallization and drying to obtain pure Type I crystals are not disclosed. Moreover, according to the teachings of the said article, aripiprazole obtained is contaminated with other polymorphic forms, thus require extra step(s) to obtain the pure polymorphic form of aripiprazole. This in-turn makes the process lengthy and costly, thus industrially less viable.

WO03/26659 discloses various polymorphic forms of aripiprazole *viz* Hydrate A, Anhydrous Crystal B, C, D, E, F and G. Anhydrous Crystal B is the preferred crystalline form, and is non-hygroscopic in nature *i.e.* absorbs less than 0.4% water in 24 hours inside a dessicator set at a temperature of 60°C and a humidity of 100%. Anhydrous Crystal B is prepared by heating the Hydrate Form A preferably at 90-120°C for 3-50 hours or by heating the Type I /Type II crystals at 90-120°C. The process is cumbersome, as drying condition used for the preparation of Anhydrous Crystal B from Hydrate A is of longer duration such as 3-50 hours, which not only affect the distribution of crystalline forms and/or crystalline purity but also causes crystalline transformation from one crystalline form to another, which results in the contamination of other polymorphic forms, thus affect the polymorphic purity of the pure aripiprazole API.

The above mentioned documents disclose diverse processes for the preparation of aripiprazole in anhydrous Type I, but due to one more reasons they are not particularly convenient and amenable to commercial scale-up for preparing aripiprazole in anhydrous Type I. However, the methods of the prior art are rather difficult to reproduce and often do not lead to obtaining the anticipated pure

anhydrous Type I. Thus, there is an unmet need for a simple, cost-effective process for the preparation of aripiprazole anhydrous Type I, which overcomes the drawbacks of various prior art disclosed processes, e.g., longer drying hours, contamination of other polymorphic forms, which make the processes neither cost effective nor amenable to scale up for industrial scale production.

Polymorphism has a direct impact on the process-ability of drug substance and the quality of final product. Drugs that crystallize in different forms exhibit a wide range of chemical and physical properties including different melting points and spectral properties. The crystalline form of drugs is particularly important since the dissolution rates, bioavailability, chemical reactivity and physical stability of even a chemically pure solid state drug can vary with the particular crystalline form of the drug. Owing to the reason that-polymorphic forms can vary in their chemical and physical properties, regulatory authorities often require that efforts should be made to identify all polymorphic forms, e.g., crystalline, amorphous, solvated forms, etc. of the drug substances. In addition, there are no "standard" procedures that can be used to prepare pure polymorphic forms of a substance. Therefore, methods for the reproducible production of substantially pure polymorphic form of the drugs are therefore very much in demand.

During the production of an API in the final step, one or more unit operations such as heating, drying and exposure to solvent may provide favorable conditions for a change in the polymorphic form or contamination by unwanted form. Considering the impact of polymorphism on drug performance, the applicant has developed an industrially feasible and commercially viable process for the preparation of substantially pure aripiprazole in anhydrous Type I without allowing other crystalline forms of aripiprazole, to co exist.

OBJECT AND SUMMARY OF THE INVENTION

According to one embodiment of the present invention, there is provided an improved and commercially viable process for the preparation of aripiprazole in anhydrous Type I crystals, which are substantially free from the contamination of other polymorphic forms of aripiprazole.

In accordance with another embodiment, the present invention encompasses a process for preparing aripiprazole in anhydrous Type I crystals, the process comprising drying wet crystals of aripiprazole in a preheated oven at suitable

temperature ranging from 90-110°C for 2-12 hours, wherein wet crystals of aripiprazole is obtained by crystallizing crude aripiprazole in alcoholic solvent selected from the group comprising of methanol, ethanol, *n*-propanol, *iso*-propanol, *n*-butanol, *iso*-butanol, or mixture thereof with water, heating the resulting mixture followed by cooling.

In accordance with yet another embodiment, the present invention relates to aripiprazole in anhydrous Type I, possess the relative particle size distribution as having D(0.1) not more than 50 μm, D(0.5) not more than 100 μm and D(0.9) not more than 200 μm.

In accordance with yet further embodiment, the present invention relates to aripiprazole in anhydrous Type I crystals, which shows hygroscopicity having moisture content greater than 0.4% after placing the drug substance for 24 hours in a desiccator set at a temperature of 60°C and a humidity level of 100%.

DETAILED DESCRIPTION OF THE INVENTION

According to one embodiment of the present invention, there is provided an improved and commercially viable process for the preparation of aripiprazole in anhydrous Type I crystals, which is substantially free from the contamination of other polymorphic forms of aripiprazole preferably free from the contamination of Anhydrous Crystal D and Hydrate A.

As used herein, aripiprazole in anhydrous Type I crystals are characterized by x-ray diffraction peaks at 8.8, 10.5, 11.0, 12.1, 14.9, 15.7, 16.6, 17.7, 20.3, 22.0, 26.6, 27.1, 28.2, 28.8 and 29.7±0.2 degree 2-theta. Typically the anhydrous Type I crystals have single melting endoderm at about 139-141°C preferably between 139-140°C.

A polymorphic form is 'substantially free' of other polymorphic forms, if it contains less than 10% by weight of other polymorphic, preferably less than 5% by weight of other polymorphic form, more preferably less than 2% by weight of other polymorphic form, even more preferably less than 1% by weight of other polymorphic form and most preferably less than 0.5% by weight of other polymorphic form as measured by XPRD or DSC, preferably XPRD.

In accordance with another embodiment, the present invention encompasses a process for preparing aripiprazole in anhydrous Type I crystals, the process comprising drying wet crystals of aripiprazole in a preheated oven at suitable temperature ranging from 90-110°C for 2-12 hours. The wet crystals of aripiprazole

obtained are uniformly spread on drying tray so as to form a uniform distribution of the crystals. Uniform distribution of the crystal is necessary for uniform drying of the crystals, as uniform distribution not only reduces the drying time but also reduces the contamination of other polymorphic forms preferably aripiprazole anhydrous crystal D and Hydrate A.

Further drying in a preheated oven refers to heating of the crystals in an oven at a desired temperature ranging between 90-110°C, preferably between 95-105°C more preferably between 100-105°C optionally under reduced pressure. Small variation in the oven temperature may have a significant effect on the time required for the formation of other polymorphic forms such as aripiprazole anhydrous crystal D crystal and Hydrate A. Preheating is important, because otherwise exposure of crystals in the oven for longer duration of time not only increases the drying hours but also leads to the contamination of other polymorphic forms such as aripiprazole anhydrous crystal D and Hydrate A. Further, drying time may vary from 2-12 hours, preferably between 3-10 hours.

The wet crystals of aripiprazole according to the present invention are obtained by dissolving crude aripiprazole in an alcoholic solvent selected from the group comprising of methanol, ethanol, *n*-propanol, *iso*-propanol, *n*-butanol, *iso*-butanol, or mixture thereof with water, heating the resulting mixture at a temperature between about 60-120°C, preferably between 70-100°C, more preferably between 80-90°C followed by cooling. The purification effect may be enhanced by using a surface active material during the crystallization as such material may absorb various impurity on its surface. Any conventional material, for instance activated carbon, hyflo etc. may be used for this purpose. Similarly, the rate of cooling during crystallization is particularly important and in general may affect the particle size of the formed crystals. The isolation of the wet crystals is carried out by any conventional methods or method reported in the prior art. In general, the wet solid is isolated by filtration or centrifugation.

In accordance with yet another embodiment, the present invention relates to the particle size distribution of aripiprazole in anhydrous Type I crystals having D(0.1) not more than 50 μm, not more than 150 μm and D(0.9) not more than 300 μm. The term "particle size distribution" as used herein refers to the relative percentages by weight or volume of each of the different size fractions of a particulate matter. The

term D(0.1) defines a size, where 10 volume percent of the particles have sizes less than the specified value. The term D(0.5) defines a size, where 50 volume percent of the particles have sizes less than the specified value. The term D(0.9) as used herein is defined as a size of particles, where 90 volume percent of the particles have sizes less than the value given.

In accordance with yet further embodiment, the present invention relates to aripiprazole in anhydrous Type I crystals, which shows hygroscopicity having moisture content greater than 0.4% after placing the drug substance for 24 hours in a desiccator set at a temperature of 60°C and a humidity level of 100%. Well-known methods such as the Karl Fischer method or method known in the prior art such as WO03/026659 are used.

ANALYTICAL METHOD

1 g of the sample was accurately weighed in a weighing bottle (diameter 5 cm), covered with kimwipes and left to rest in a 60 C/100% RH environment (water/dessicator). 24 Hours later, the weighing bottle was removed, transferred to an environment of a room temperature and about 30% RH (magnesium chloride hexahydrate saturated water solution/dessicator) and left to rest for 24 hours and the water content of the sample was measured by the Karl Fischer method.

Aripiprazole anhydrous Type I crystals obtained according to present invention were left for 24 hours inside a dessicator set at a temperature of 60°C and humidity level of 100%, exhibit hygroscopicity exceeding 0.4% as shown in Table 1.

Table 1

Batch No.	**Initial moisture content (%)**	**Moisture content after 24hrs (%)**
Sample 1	0.07	2.01
Sample 2	0.08	1.55
Sample 3	0.10	2.01

The present invention is more particularly described and explained by the following examples. It is to be understood, however, that the present invention is not limited to these examples and various changes and modifications may be made without departing from the scope of the present invention.

Example 1

Preparation of crude 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril

7-(4-Bromobutoxy)-1,2,3,4-tetrahydroquinolin-2-one (50 g) was taken in acetonitrile (500 ml) at 25-30°C. To this potassium carbonate (67.2 g) and 1-(2,3-dichlorophenyl) piperazine hydrochloride (44.9 g) were added under stirring. The reaction mixture was refluxed at 80-85°C for 8 hours. The reaction mass was cooled to room temperature, filtered and the resulting solid was washed with acetonitrile. To the resulting solid, water was added and was stirred. The solid was filtered off, washed with water and dried under vacuum at 75-80°C for 15 hours to obtain title compound.

Example 2

Preparation of aripiprazole anhydrous Type I using isopropyl alcohol and water

Crude aripiprazole (30 g) was taken in isopropyl alcohol (600 ml) and was heated to 80-85°C. Water (90 ml) was added at the same temperature. Activated carbon was added and the mixture was stirred for 30 minutes at the same temperature. The resulting hot solution was filtered and the bed was washed with hot isopropyl alcohol. The resulting filtrate was cooled to 25-30°C for 4 hours. The resulting solid was filtered, washed with isopropyl alcohol and dried under suction for 1 hour. The resulting wet solid was dried in preheated oven maintained at 100-105°C for 6 hours to obtain title compound.

Yield: 87-89% HPLC Purity: 99.89

Anhydrous crystal D: Below detectable limit (BDL) at limit of detection 1%.

Hydrate A: Below detectable limit (BDL) at limit of detection 1%.

Particle size distribution: d_{10}=15.83μ, d_{50}=60.12μ, d_{90}=144.99μ

Example 3

Preparation of aripiprazole anhydrous Type I using ethanol and water

Crude aripiprazole (15 g) was taken in ethanol (300 ml) and water (45 ml) and was heated to 80-85°C for 1-2 hours. The resulting mixture was cooled to 25-30°C within 4 hours and stirred for 3 hours. The resulting solid was filtered and dried under suction for 1 hour. The resulting wet solid was dried in preheated oven maintained at 100-105°C for 3 hours to obtain title compound.

Yield: 90% HPLC Purity: 99.9%

Anhydrous crystal D: Below detectable limit (BDL) at limit of detection 1%.

Hydrate A: Below detectable limit (BDL) at limit of detection 1%.

Particle size distribution: d_{10}=22.01μ, d_{50}=105.10μ, d_{90}=232.97μ

Example 4

Preparation of aripiprazole anhydrous Type I using n-butanol and water

Crude aripiprazole (15 g) was taken in n-butanol (300 ml) and water (45 ml) and was heated to 80-85°C for 1 hours. The resulting mixture was cooled to 25-30°C within 4 hours and stirred for 3 hours. The resulting solid was filtered and dried under suction for 1 hour. The resulting wet solid was dried in preheated oven maintained at 100-105°C for 3 hours to obtain title compound.

Yield: 84.6% HPLC Purity: 99.9%

Anhydrous crystal D: Below detectable limit (BDL) at limit of detection 1%.

Hydrate A: Below detectable limit (BDL) at limit of detection 1%.

Particle size distribution: d_{10}=8.81μ, d_{50}=37.81μ, d_{90}=113.03μ

Certain modification and improvements of the disclosed invention will occur to those skilled in the art without departing from the scope of invention, which is limited only by the appended claims.

We claim:

1. An improved process for the preparation of aripiprazole in anhydrous Type I crystals substantially free from the contamination of other polymorphic forms of aripiprazole, the process comprising drying wet crystals of aripiprazole in a preheated oven at temperature between 95-110°C for 2-12 hrs.
2. The process according to claim 1, wherein the aripiprazole anhydrous Type I crystals are substantially free from the contamination of Anhydrous Crystal D and Hydrate A.
3. The process according to claim 1, characterized in that the crystallization of crude aripiprazole is carried out in alcoholic solvent with water, heating the resulting mixture followed by cooling to obtain wet crystals.
4. The process according to claim 3, wherein the alcoholic solvent is selected from the group comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, or mixture thereof.
5. The process according to claim 3, wherein the resulting mixture is heated at a temperature between about 60-120°C.
6. The process according to claim 3, wherein the resulting mixture is cooled at a temperature between 25-30°C.
7. The process according to claim 1, wherein the drying is carried out between 3-10 hours.
8. Aripiprazole anhydrous Type I crystals prepared according to claim 1, showed hygroscopicity having moisture content greater than 0.4% after placing the drug substance for 24 hours inside in a desiccator maintained at a temperature of 60°C and a humidity level of 100%.
9. Aripiprazole anhydrous Type I crystals having particle size distribution D(0.1) not more than 50 μm, D(0.5) not more than 150 μm and D(0.9) not more than 300 μm.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/227
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)
C07D

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2008/001188 A2 (CADILA PHARMACEUTICALS LTD [IN] CADILA PHARMACEUTICALS LTD [IN]; MODI) 3 January 2008 (2008-01-03) page 12	1-9
A	WO 03/026659 A1 (OTSUKA PHARMA CO LTD [JP]; BANDO TAKUJI [JP]; AOKI SATOSHI [JP]; KAWAS) 3 April 2003 (2003-04-03) the whole document	1-9
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A	US 2007/203150 A1 (BANDO TAKUJI [JP] ET AL) 30 August 2007 (2007-08-30) page 15 - page 16; examples 1-10	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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