Abstract:
Disclosed is a process for preparing aripiprazole polymorph hydrate A, form B and type II. Also provided is a process for preparing aripiprazole polymorph having an average particle size less than 100 µm using a specific solvent system and reaction condition for inducing precipitation.
FIELD OF THE INVENTION

The present invention relates to an industrially advantageous and efficient process for the preparation of aripiprazole polymorph having particle size less than 100 µm. Specifically, the present invention relates to processes for the preparation of aripiprazole hydrate A, anhydrous crystal B and crystalline aripiprazole Type II.

BACKGROUND OF THE INVENTION

Aripiprazole, chemically known as 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril, of formula

![Chemical structure of aripiprazole]

is a drug useful and approved for treating schizophrenia, which is a serious mental illness characterized by a disintegration of the process of thinking and of emotional responsiveness. Schizophrenia most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with significant social or occupational dysfunction. Onset of symptoms typically occurs in young adulthood, with around 1.5% lifetime prevalence of the population affected. Diagnosis is based on the patient's self-reported experiences and observed behavior. No laboratory test for schizophrenia currently exists. It is more prevalent than Alzheimer's disease, multiple sclerosis, insulin-dependent diabetes and muscular dystrophy. Early diagnosis and treatment can lead to significantly improved recovery and outcome. Moreover, early therapeutic intervention can avert costly hospitalization.

Aripiprazole has been approved by the FDA for the treatment of schizophrenia in 2, 5, 10, 15, 20 and 30 mg tablets for oral administration and is currently marketed under the brand name of Abilify®. The commercially marketed product contains the aripiprazole as the free base; i.e., not as an aripiprazole salt.

Aripiprazole and related compounds were first disclosed in US patent 5,006,528 (herein referred as US '528). It discloses various salts of aripiprazole and their preparation. The patent discloses double re-crystallization of crude aripiprazole from ethanol resulting in colorless crystals having a melting point 139-139.5°C.

Like any other pharmaceutical solids, aripiprazole also exist in different polymorphic forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more
crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice.

Polymorphism of aripiprazole has been disclosed in an article, Study on Crystal Transformation of Aripiprazole, presented at the Fourth Japan-Korea Symposium on Separation Technology, p. 937 (1996). According to this reference, aripiprazole anhydride crystals may exist as Type-I, Type-II and Type-III crystals. This article designate aripiprazole crystal prepared by US '528 as Type I aripiprazole and identified as an anhydrite. It discloses that anhydride crystals of aripiprazole can be prepared by re-crystallization of aripiprazole from ethanol or by heating aripiprazole hydrate (Type-III) at a temperature of 80 °C. Type-II aripiprazole crystals can be prepared by heating Type-I crystals at 130 °C to 140 °C for 15 hours. This process of heating is not easily applied to an industrial scale preparation of anhydride aripiprazole Type-II.

US patent application publication 2004/0058935 discloses several polymorphic forms of aripiprazole namely hydrate A, crystal B, type C, D, E, F & G and processes for their preparation. In application, it is disclosed that hydrate A is useful intermediate for preparation of anhydrate forms. Aripiprazole hydrate A is prepared by milling conventional aripiprazole hydrate.

Aripiprazole anhydrous form B (also known as crystal B), which seems to be preferred crystalline form, is low hygroscopic and is a stable crystalline form. Aripiprazole form B is prepared by heating aripiprazole hydrate A at 90-125 0 C for about 3 to 50 hours. Aripiprazole form B is also prepared by heating conventional hygroscopic aripiprazole anhydrous crystals or conventional aripiprazole hydrate at 100 °C or 120 °C for 3 to 50 hours.

It is observed on our hand that process described above does not show consistent results. Major disadvantage of the process is that although form B is low hygroscopic but unsuitable for the milling, whenever, milling is attempted in order to obtain smaller particle size, the milled substance tends to convert to other polymorph, thus it is prepared in above application from hydrated A, which is in turn prepared by milling. Also milling of aripiprazole hydrate is undesirable, as a broad particle size distribution will be obtained and chances to conversion to other polymorphs are high. Therefore, processes described for hydrate A as well as crystal form B are not suitable from industrial point of view. This US application is silent about method of preparation of crystalline aripiprazole Type II and moreover disclosed processes produce mixture of polymorphs.

There are several other processes for preparation of hydrate A, form B and Type II of aripiprazole known in art which have one or more disadvantages, some are described herein.

US patent 7,507,823 discloses a process for synthesis of aripiprazole hydrate A by providing a mixture of unprocessed aripiprazole in a solvent and mixture of supercritical fluid, optionally along
with modifier, with water into a particle formation vessel to produces crystalline aripiprazole hydrate. The process involves use of supercritical fluid which requires elevated pressure and is thus not suitable for industrial scale manufacturing.

US patent 7,642,353 discloses a process for preparation of aripiprazole form B by dissolving aripiprazole in a suitable solvents like 1-propanol, 2-propanol, 1-butanol, ethyl acetate, acetonitrile and mixture thereof at reflux temperature, adding seed crystals of aripiprazole form B to the solution, cooling the mixture and isolating crystals of aripiprazole form B. Process requires seeding with aripiprazole form B and silent about the mode to get seeding material.

US patent 7,655,798 discloses a process for preparation of aripiprazole Type II by dissolving aripiprazole in a solvent selected from 2-propanol, dimethylsulfoxide or mixture there and optionally further adding ethyl acetate. Patent discloses that use of iso-propanol during crystallization of aripiprazole may results in Type I or Type II depending on conditions. Higher crystallization temperature favors Type II while lower temperature favors Type I. Process require strict condition of temperature for the formation of aripiprazole Type II, therefore not advisable to employ for industrial synthesis.

US patent application publication 2005/0152981 discloses a process for preparation of aripiprazole hydrate by mixing jet stream of a solution of aripiprazole in an organic solvent with a jet stream of anti-solvent to create high turbulence at their point of impact to produce slurry of crystals of aripiprazole monohydrate. The process involves use of special machine for producing jet streams of two solutions and also requires special knowledge of instrument to provide sufficient linear velocity of streams to achieve high intensity micromixing prior to nucleation. Thus, complex procedural requirements for operating machine and need of special machine add to the cost of final API i.e. aripiprazole, making the process unsuitable from the commercial point of view.

US patent application publication 2005/0277650 discloses a process for aripiprazole hydrate by dissolving aripiprazole in a aqueous, organic solvent at elevated temperature, adding seed crystals of aripiprazole hydrate to the solution, cooling the mixture, and isolating crystals of aripiprazole hydrate. Process requires seeding with aripiprazole hydrate and silent about the mode of getting seed of aripiprazole hydrate crystals.

US patent application publication 2006/0142299 discloses a process for preparation of aripiprazole form B by refluxing aripiprazole hemi-ethanolate or methanolate in ethyl acetate followed by cooling and isolation of flake-like crystals. Process needs isolation of aripiprazole alcoholate and then conversion to desired polymorph, thus adds an extra step to the process.
US patent application publication 2009/0198059 discloses a process for preparation of aripiprazole form B by basification of aripiprazole acid salt with base in a mixture of water and organic ester solvent subsequently separating the layers and concentrating organic layer followed by cooling to isolate aripiprazole form B. Process requires neutralization of aripiprazole salt and then conversion to form B, thus makes the process lengthy and unsuitable to employ for industrial synthesis.

US patent application publication 2009/0247542 discloses a process of preparation of aripiprazole Type II which is referred therein as form J by suspending/ dissolving aripiprazole in ketonic solvents. In examples, methyl ethyl ketone and acetone have been used as solvent for preparation of Form J. Particularly when solvent is methyl ethyl ketone, recrystallization is carried out, but when solvent is acetone then aripiprazole is suspended and form J is prepared by acetone digestion.

PCT publication WO 2008/059518 discloses a process for preparation of crystalline anhydrous aripiprazole by refluxing aripiprazole in an organic solvent selected from alcohols, esters, acetic acid, tetrahydrofuran or mixture thereof followed by cooling to isolate wet compound. The wet solid is then heated in an organic solvent such as dichloromethane, optionally charcoaldised, and seeded with crystalline anhydrous aripiprazole to give the desired product. Process requires isolation of product and then again heating in an organic solvent. Process also needs seeding with anhydrous aripiprazole to give crystalline anhydrous aripiprazole.

A recent PCT publication WO 2010/106551 discloses a process for preparation of anhydrous aripiprazole form B by heating aripiprazole in an alcoholic solvent till complete dissolution followed by cooling, centrifugation and drying. The obtained dry material is sieved using sifter of 40 mesh size without crushing, separating out sieve tops and further drying the sieved material. Process requires sieving of material to get the desired material but sieving is performed by using sifter of 40 mesh size (400 micron) which results in larger particle of aripiprazole. Another disadvantage is that the amount of energy used to sieve the sample is arbitrarily determined.

Different polymorphs exhibit different physicochemical properties such as solubility, dissolution rate, bioavailability and chemical and physical stabilities. So, polymorphism has become a topic of great interest for pharmaceutical industries as it has the potential to significantly affect the physical properties of a compound. In addition to this, process for preparing such polymorph should be robust and efficient in producing commercial quantity of crystalline compounds. This question arises because sometimes the most suitable polymorph is difficult to produce. Further particle size of the drug molecule also affects its physicochemical properties and in case of aripiprazole it is especially important for effective formulation. So, it is of greatest importance for pharmaceutical
industry to ensure reliable, robust, cost effective as well as efficient process for synthesis of crystalline aripiprazole of desired particle size.

Most of prior art processes for preparation of aripiprazole hydrate A and form B either require special conditions such as seeding, milling or require special equipment which makes the final product costly and eventually makes the process not attractive for industrial production. Also some of the processes do not yield reproducible results, are lengthy and do not provide consistency in particle size of aripiprazole produced. In addition to above, prior art methods for the preparation of crystalline type II also necessitate the optimization of experimental conditions such as temperature along with that of the selection of solvents, require heating procedure and does not give reproducible results and/or result in mixture of polymorphs. Numerous factors effect crystallization conditions, and they are well known to one of skill in the art.

In view of above, it is desirable to develop an alternate, economically advantageous process, which avoids the use of special techniques such as jet stream, milling; long term heat treatment for the synthesis of aripiprazole hydrate A as well as crystal form B and crystalline aripiprazole Type-II of lower particle size, which proved to be helpful in maintaining polymorphic integrity, because unwanted polymorphic transformation can lead to difficulties during formulation and storage. Moreover, new process to prepare aripiprazole polymorphs provides opportunities to improve the characteristics of pharmaceutical product. Accordingly, there is a need in the art for processes which minimize or eliminate the amount of polymorphic transformation in the resulting aripiprazole.

Thus, the present invention provides an easy, industrially advantageous and efficient process for the preparation of polymorphs of aripiprazole, mainly hydrate A, anhydrous form B and crystalline aripiprazole Type II with desired particle size which does not involve use of special equipment or milling, and avoids need for heat treatment or heat conversion or long-term exposure to high temperatures.

**OBJECTIVE OF THE INVENTION**

The principal and foremost objective of the present invention is to provide an industrially advantageous and efficient process for preparation of aripiprazole polymorph having particle size less than 100 µm.

Another objective of the present invention is to provide a process for the preparation of crystalline aripiprazole mainly hydrate A, form B and Type II.

Another objective of the present invention is to provide a process for the preparation of crystalline aripiprazole having particle size less than 100 µm without the use of special techniques.
Another objective of the present invention is to provide a process for the preparation of crystalline aripiprazole having particle size less than 100 μm which avoids process of milling.

Another objective of the present invention is to provide a process for the preparation of aripiprazole hydrate A having particle size less than 100 μm.

Another objective of the present invention is to provide a process for the preparation of aripiprazole form B having particle size less than 100 μm.

Still another objective of present invention is to provide a process for the preparation of crystalline aripiprazole Type-II, which does not require long-term exposure to high temperatures.

Yet another objective of present invention is to provide an efficient process, which produces pure hydrate A, form B and crystalline aripiprazole Type II consistently.

SUMMARY OF THE INVENTION

The present invention provides an improved, industrial advantageous and efficient process for the preparation of aripiprazole polymorph, specifically aripiprazole hydrate A, form B and Type II.

According to one embodiment, present invention provides a process for the preparation of aripiprazole hydrate A, comprising the steps of:

a) providing a solution of aripiprazole in alcoholic solvent or mixture thereof with water;

b) mixing solution of step a) with a second solvent;

c) optionally, adding water to the mixture of step b);

d) inducing precipitation of aripiprazole hydrate A; and

e) isolating aripiprazole hydrate A there from.

According to another embodiment, present invention provides a process for preparation of aripiprazole crystal form B, comprising the steps of:

a) dissolving aripiprazole in a suitable solvent;

b) mixing solution of step a) with a second solvent;

c) inducing precipitation of aripiprazole crystal form B; and

d) isolating aripiprazole crystal form B there from.

According to yet another embodiment, present invention provides crystalline aripiprazole having particle size less than 100 μm.

According to one embodiment, present invention provides a process for the preparation of crystalline aripiprazole Type II, comprising the steps of:

a) providing a mixture of aripiprazole in a suitable solvent;

b) heating the mixture to 50 °C to reflux temperature of solvent till dissolution;

c) preparing a suspension of seed crystals of crystalline aripiprazole type II in hydrocarbon solvent;
d). admixing the solution of step b) with suspension of step c);
e). stirring the mixture at 5 °C to ambient temperature for time sufficient for conversion to crystalline aripiprazole type II;
f). cooling the mixture to 0 to 5 °C; and
g). isolating crystalline aripiprazole Type II.

According to another embodiment, present invention provides a process for the preparation of crystalline aripiprazole Type II, comprising the steps of:
a). providing a mixture of aripiprazole in a suitable solvent;
b). heating the mixture to 50 °C to reflux temperature of solvent till dissolution;
c). admixing the solution of step b) with a suitable hydrocarbon solvent;
d). stirring the mixture at 5 °C to ambient temperature for time sufficient for conversion to crystalline aripiprazole type II;
e). cooling the mixture to 0 to 5 °C; and
f). isolating crystalline aripiprazole Type II.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1: shows X-ray diffraction pattern of crystalline aripiprazole Type II as given in Japan-Korea Symposium on Separation Technology, p. 937 (1996)

Figure 2: shows X-ray diffraction pattern of crystalline aripiprazole Type II prepared according to present invention

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term, "d₉₀" refers to the particle size at which 90% of the particles have the same or a smaller particle size.

As used herein, the term "dmean" refers to average particle diameter by mass.

As used herein "Type II" of aripiprazole means a crystalline aripiprazole substance having X-ray diffraction pattern that substantially corresponds to that of Type II product as defined in an article, "7th Japanese Korea Symposium on Separation Technology, p. 937 (1996) " and given as figure 1.

As used herein "Substantially corresponds" means it cover differences or variations in the pattern that would not be understood by a person skilled in the art to represent a difference in crystal structure, but rather differences in techniques, sample preparation and instrument etc.

As used herein "ambient temperature" means temperature of the surrounding. It means any suitable temperature found in a laboratory or other working quarter, and is generally not below about 15 °C and not above about 30 °C.
Accordingly, present invention provides an industrially advantageous and efficient process for the
preparation of aripiprazole polymorph. Specifically present invention provides process for the
preparation of aripiprazole hydrate A and form B having particle size less than 100 µm.

According to one embodiment, the present invention provides a process for preparation of
aripiprazole hydrate form A.

Generally, the process involves dissolution of aripiprazole in a suitable alcoholic solvent or mixture
thereof with water at a temperature of 60 °C to reflux temperature of the solvent for 10 minutes to 8
hours, preferably till complete dissolution. The solution can be optionally, filtered to remove any
insoluble particles, if present, in the solution. Suitable solvent can be selected amongst alcohol such
as methanol, ethanol, propanol, isopropanol, n-butanol, isobutanol and the like or mixture thereof or
in mixture with water. Usually dissolution can be carried out at 60 °C to 100 °C for 10 minutes to 6
hours. Thereafter, second solvent can be added to the resulting solution at 40 to 90 °C, preferably 60
to 80 °C. Second solvent includes C₃₋₈ nitriles such as acetonitrile, propionitrile; aliphatic ketones
such as acetone, methyl ethyl ketone; aliphatic or cyclic ether such as isopropyl ether, 1,2-diethoxy
ethane, 1,2-dimethoxy ethane, tetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, methyl tert-
butyl ether, dibutyl ether, diphenyl ether and the like or mixture thereof or in mixture with water.
The resulting product can be isolated from the mixture by inducing precipitation.

Alternatively, a solution of aripiprazole is provided in alcoholic solvent followed by addition of
second solvent to the resulting solution. Thereafter, resulting solution can be optionally cooled to a
temperature of -30 to 30 °C followed by addition of water to the solution and then inducing the
precipitation of hydrate A.

In an alternate way, aripiprazole hydrate A crystal can be prepared by adding mixture of second
solvent with water to the solution of aripiprazole in a suitable alcoholic solvent.

In yet another alternate way, aripiprazole hydrate A crystal can be prepared by crystallizing
aripiprazole from a solvent mixture containing a suitable alcoholic solvent, second solvent or
mixture thereof and water.

The desired product can be isolated from the solution of aripiprazole, alcoholic solvent, optionally
water, and second solvent, prepared by any of the method described by the present invention, by
inducing precipitation of hydrate A. The precipitation can be initiated by lowering the temperature
to fasten the precipitation of hydrate A. The temperature of solution can be lowered immediately by
adding pre-cooled second solvent to the solution of aripiprazole (in alcoholic solvent or in mixture
with water) or two solution can be mixed in reversed order i.e. aripiprazole solution can be added to
the pre cooled second solvent to fasten the precipitation of hydrate A. Second solvent can be cooled
to a temperature of less than ambient temperature, preferably -40 °C to 25 °C prior to mixing with
aripiprazole solution. In another way, reaction mixture after the addition of second solvent can be
cooled fastly to form aripiprazole hydrate A.

Cooling of the solution can be done along with optional stirring to -40 to 25 °C for few minutes to
several hours, preferably -10 to 10 °C for 10 minutes to 6 hours, preferably till complete
precipitation of the product. Aripiprazole hydrate A thus formed by process of present invention can be
isolated by the suitable techniques known in the art such as filtration, centrifugation, decantation
and the like.

According to another embodiment, present invention provides a process for the preparation of
aripiprazole crystal form B.

Generally, the process involves dissolution of aripiprazole in a suitable solvent at a temperature of
60 °C to reflux temperature of the solvent for 10 minutes to 6 hours, preferably till complete
dissolution. Suitable solvent can be selected amongst ketone such as acetone, ethyl methyl ketone,
diethyl ketone, methyl isobutyl ketone; aliphatic alcohol such as methanol, ethanol, n-propanol, n-
butanol, isobutanol and the like or mixture thereof. Usually the dissolution can be carried out 60 to
90 °C for 30 minutes to 2 hours. Thereafter, aripiprazole solution thus formed is mixed with a
second solvent. The mixing of the two solutions can be carried out in any order, aripiprazole
solution can be added to the second solvent or second solvent can be added to solution of
aripiprazole in suitable solvent. Alternatively, two solutions can be mixed simultaneously.

Second solvent includes ketones such as acetone, ethyl methyl ketone, diethyl ketone, methyl
isobutyl ketone; aliphatic ether such as isopropyl ether, diethyl ether, methyl tert-butyl ether, di-n-
butyl ether, diphenyl ether; aliphatic alcohols such as ethanol, n-propanol, isopropanol, n-butanol,
isobutanol and the like or mixture thereof, provided second solvent is different from the solvent used
for the dissolution of aripiprazole. After the mixing of the two solutions, aripiprazole crystal form B
can be isolated from the resulting solution by inducing precipitation by any suitable method.

Precipitation can be induced from the solution by reducing the temperature of the solution or by
concentrating the solution by evaporation followed by cooling.

Preferably, aripiprazole crystal form B can be isolated from the resulting solution by reducing the
temperature of solution. The solution can be cooled -40 to 60 °C and/or stirred for few minutes to
several hours, preferably -5 to 10 °C for 10 to 60 minutes, preferably till complete precipitation of
the product takes place. In another way, pre cooled second solvent can be added to the solution of
aripiprazole in suitable solvent or reverse addition can be carried out to shorten the cooling time and
to fasten the precipitation, this makes the solution to cool immediately and results aripiprazole of
lower particle size as compared to undisturbed cooling of the solution. Second solvent can be cooled to a temperature of less than ambient temperature, preferably -40 °C to 25 °C prior to mixing with aripiprazole solution. Crystal form B of aripiprazole can be isolated from resulting mixture by suitable techniques such as filtration, centrifugation and the like.

Alternatively, aripiprazole crystal form B can be isolated from the resulting solution by concentrating the solution. The solution can be concentrated by the partial or complete removal of the solvents from the solution. Thereafter, the resulting residue can be cooled to -40 to 60 °C and/or stirred for few minutes to several hours, preferably -5 to 10 °C for 10 to 60 minutes, preferably till complete precipitation of product takes place. Crystal form B of aripiprazole can be isolated from resulting mixture by suitable techniques such as filtration, centrifugation and the like.

The rate of cooling used in processes of the present invention is not particularly limited but in general can be used to affect the particle size of the formed crystals. A faster rate of cooling generally leads to smaller crystals where as gradual cooling rate; i.e., allowing the solution to cool without special cooling leads to larger crystals.

The final temperature after cooling may also affect particle size, yield and/or purity of the product. Solution can be stirred at high speed or slow speed. It may affect the nature of the product obtained from the solution. Stirring speed of the solution can be 60 to 3000 revolution per minutes (rpm) or more; preferably more than 200 rpm. Solution can be stirred without making any special emphasis on speed of revolution of solution.

As it is evident from the process for preparation of aripiprazole i.e. hydrate A and crystal form B, the order and manner of adding the solvents to aripiprazole does not affect the nature of the final product but cooling rate can make an impact on particle size. The amount of solvent added to each stage may depend on several factors such as amount of aripiprazole to be crystallized and/or purity of starting aripiprazole. It is found by the present inventor that the specific solvent system used in the present invention, proved to be highly advantageous in yielding the aripiprazole hydrate A and crystal form B of particular particle size.

Crystalline polymorph of aripiprazole both hydrate A and crystal form B thus isolated by the processes of present invention yield aripiprazole having particle size less than 100 μm. A common particle size distribution of aripiprazole prepared by the present invention falls within the range 35 to 85 μm. It is found that the crystalline aripiprazole particles formed by the process of present invention are in the desired size/population whereas milling to obtain a desired smaller size is not preferred because it tends to cause and/or increase hygroscopicity of aripiprazole.
Aripiprazole hydrate A as well as crystal form B can be incorporated into pharmaceutical composition in the form of particles having a particle size of 100 µm or less. For increasing rate of dissolution, it is normally desired that aripiprazole have an average particle size of less than 100 µm, or 50 µm or less. Similarly, the population of particles typically has a SD of not greater than 100 µm, more typically not greater than 50 µm.

According to another embodiment, present invention provides an improved, efficient and industrially advantageous process for the preparation of crystalline aripiprazole type-II by providing a mixture of aripiprazole in a suitable solvent followed by addition of hydrocarbon solvent. Generally, the process involves heating of mixture of aripiprazole in a suitable solvent at a temperature of 50 °C to reflux temperature of solvent till complete dissolution. Mixture of aripiprazole in suitable solvent can be provided by various means which is not particularly limited. The temperature for the dissolution also depends on volume and nature of solvent used. The temperature at which aripiprazole is dissolved in a suitable solvent may range from 50 °C to reflux temperature of the solvent. Preferably the dissolution can be carried out above 55 °C.

Alternatively, aripiprazole can be synthesized in a suitable solvent and reaction mixture containing aripiprazole solution can be used for further crystallization process to prepare crystalline aripiprazole Type II.

Solvent employed for dissolution can be selected from solvent in which aripiprazole is having more solubility. Preferably solvent can be selected from ethers such as tetrahydrofuran; ketones such as acetone; nitriles such as acetonitrile and the like or mixture thereof or mixture with water.

The concentration of aripiprazole solution may be varied according to the solvent used, and its volume and temperature of dissolution. The volume of solvent used can vary from 1 to 45 ml for 1 gm of starting aripiprazole; preferably 2 to 40 ml of solvent can be used for 1 gm of solvent. More preferably, 2 to 35 ml of solvent can be used for the dissolution of 1 gm of starting aripiprazole.

The solution of aripiprazole in a suitable solvent is then combined with second solvent in which aripiprazole is insoluble or is less soluble. Second solvent is preferably hydrocarbon solvent such as n-hexane, n-heptane, cyclohexane and the like or mixture thereof. Hydrocarbon solvent can be added to the solution of aripiprazole or solution of aripiprazole can be added to hydrocarbon solvent.

The amount of hydrocarbon solvent can vary depending upon the nature of solvent and it is not particularly limited. Preferably, 1 to 45 ml of hydrocarbon solvent can be added to the solution with respect to 1 gm of starting aripiprazole, more preferably 2 to 40 ml of hydrocarbon solvent is used for the process with respect to 1 gm of starting aripiprazole.
Hydrocarbon solvent can be optionally chilled prior to mixing with solution of aripiprazole in order to induce fast crystallization. Preferably hydrocarbon solvent can be cooled to a temperature of -10 to 15 °C, most preferably 0 to 5 °C. Use of chilled hydrocarbon solvent for the preparation of crystalline aripiprazole type II has been found to beneficial in terms of high yield of crystalline aripiprazole type II.

In an alternate way, crystallization can be induced or aided by adding small amount of seed crystal of aripiprazole Type II. Seeding material can be added prior to mixing with hydrocarbon solvent or after the mixing the initial solution with hydrocarbon solvent or it can be added along with hydrocarbon solvent. Usually, seeding can be carried out at a temperature of 50 to 60 °C, preferably at temperature where seed crystals do not dissolve in resulting mixture.

Preferably, seed crystals can be first suspended in hydrocarbon solvent and then resulting suspension is mixed with a solution of aripiprazole in a suitable solvent. Suspension of seed crystal of aripiprazole Type II in hydrocarbon solvent can be added to solution of aripiprazole or a solution of aripiprazole can be added to the suspension of seed crystals in hydrocarbon solvent. Preferably suspension of seed crystals in hydrocarbon solvent can be optionally chilled prior to mixing with solution of aripiprazole. Preferably suspension can be cooled to a temperature of -10 to 15 °C, most preferably 0 to 5 °C.

The amount of seed crystal can vary from 0.2% to 10 % by weight of starting aripiprazole, preferably 0.4 % to 8 %, more preferably 0.5 to 5 % by weight of starting aripiprazole.

The mixture comprising aripiprazole, first solvent and hydrocarbon solvent with or without seeding can be stirred at a temperature of 5 °C to ambient temperature till complete formation of crystalline aripiprazole Type II take place. Preferably, mixture can be stirred at a temperature of 5 to 30 °C for 30 minutes to 30 hours. The mixture can be first stirred at a temperature of 20-30 °C and then can be optionally cooled to temperature of 0 to 15 °C. Preferably mixture can be cooled to a temperature of 0 to 5 °C. Resulting product i.e. aripiprazole Type II can be isolated from the mixture using a suitable techniques known in art such as filtration, centrifugation, decantation and the like. Preferably filtration of crystalline aripiprazole type II can be carried out at a temperature of 0- 10 °C, more preferably at a temperature of 0- 5 °C.

Isolated aripiprazole Type II can be optionally washed with suitable solvent selected from hydrocarbon solvent such as n-heptane, n-hexane, cyclohexane and the like or mixture thereof. Aripiprazole Type II thus obtained by the process of present invention can be dried using suitable techniques known in the art.
Starting material, aripiprazole, used for preparation of hydrate A, crystal form B and Type II of present invention, can be of any polymorphic form for example an isolated or un-isolated crude product arising from the synthesis of aripiprazole or an aripiprazole product already crystallized such as the hydrate form A, Type I, Type II, Type III or Form B to G or form XII, compound 2, form C, anhydrate, hydrate, solvate and mixture thereof as made by the techniques disclosed in the art, including hydrated and solvated forms. Starting material can be amorphous or crystalline or solvate of aripiprazole.

The main advantage of the present invention is that it provides a process for preparation of crystalline aripiprazole hydrate A, crystal form B and Type II which circumvent the adherence of aripiprazole to equipment by avoiding milling and also circumvent the need of special handling techniques to maintain the equipment and does not require thermal treatment at a temperature higher than 100 °C which can decompose the product. Present invention provides a new solvent system for synthesis of aripiprazole hydrate A as well crystal form B that directly yield the product with a particle size less than 100 µm without need of milling or special equipment such as jet stream.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of aripiprazole hydrate A

A suspension of aripiprazole (100 g) in a mixture of ethanol (1600 ml) and water (400 ml) was heated to reflux till complete dissolution. The solution was filtered to remove suspended particles. Acetone (1500 ml) was added to resulting filtrate at 75-78 °C. The reaction mass was cooled under stirring and the temperature was brought down 0-5 °C. The reaction mass was stirred for 60 minutes at 0-5 °C. The solid thus precipitated was filtered and dried below 50 °C for 2 hours to give title compound having particle size diameter of $d_{90} = 48.42 \mu m$.

Example 2: Preparation of aripiprazole hydrate A

A suspension of aripiprazole (100 g) in ethanol (2000 ml) was heated to 75-78 °C till complete dissolution. The solution was filtered to remove suspended particles. Acetone (1500 ml) was added to resulting filtrate at 75-78 °C. The reaction mass was cooled under stirring and the temperature was brought down 10-15 °C. Demineralised water (600ml) was added to the reaction mixture and cooled to 0-5 °C, stirred for 60 minutes. The precipitated solid was filtered and dried below 50 °C to give title compound having particle size diameter of $d_{90} = 55 \mu m$. 

13
Example 3: Preparation of aripiprazole hydrate A
A suspension of aripiprazole (100 g) in a mixture of ethanol (1600 ml) and water (400 ml) was heated to reflux till complete dissolution. The solution was filtered to remove suspended particles. Diisopropyl ether (1500 ml) was added to the resulting filtrate at 70-75 °C. The reaction mass was rapidly cooled under stirring and temperature was brought down 0-5 °C. The reaction mixture was stirred for 60 minutes. The precipitated solid was filtered and dried to give title compound having particle size diameter of \( d_{90} = 45 \mu \text{m} \).

Example 4: Preparation of aripiprazole hydrate A
A suspension of aripiprazole (100 g) in ethanol (2000 ml) was heated to reflux and solution was filtered to remove suspended particles. Diisopropyl ether (1500 ml) was added to resulting filtrate at 70-75°C. Reaction mixture was cooled under rapid stirring of around 200 rpm and the temperature was brought down 10-15 °C. Demineralised water (600 ml) was added to the reaction mixture and cooled to 0-5 °C. The mixture was stirred for 60 minutes. The solid thus precipitated was filtered and dried below 50 °C for 2 hours to give title compound having particle size diameter of \( d_{90} = 50.2 \mu \text{m} \).

Example 5: Preparation of aripiprazole crystal form B
A suspension of aripiprazole (10 g) in acetone (200 ml) was heated to reflux till complete dissolution. Cold isopropyl ether (150 ml, -5 to 0 °C) was added to the resulting solution at a temperature of 60-65 °C. The reaction mixture was cooled to 0 to 5 °C and stirred for 1 hour. Product thus obtained was filtered and dried under vacuum to give 8.88 g of the title compound having particle size diameter of \( d_{90} = 50 \mu \text{m} \), and \( d_{\text{mean}} = 26 \mu \text{m} \).

Example 6: Preparation of aripiprazole crystal form B
A suspension of aripiprazole (10 g) in acetone (200 ml) was heated to reflux till complete dissolution. The reaction mixture was poured into cold isopropyl ether (150 ml) and stirred for 1 hour at 0 to 5 °C. Product thus obtained was filtered and dried under vacuum to give 8.52 g of the title compound having particle size diameter of \( d_{90} = 62 \mu \text{m} \), and \( d_{\text{mean}} = 34 \mu \text{m} \).

Example 7: Preparation of aripiprazole crystal form B
A suspension of aripiprazole (5 g) in acetone (100 ml) was heated to reflux till complete dissolution. The hot reaction mixture was added into cold isopropyl ether (75 ml, 0 to -5 °C) and then cooled to 0-5 °C. Reaction mixture was stirred for 1 hour followed by distillation of solvent (approximately 80 %) under vacuum at below 35 °C. Resulting reaction mixture was cooled to 0-5 °C and stirred for 1 hour. The product thus crystallized was filtered, washed with isopropyl ether (50 ml) and dried at
95-100 °C to give 4.62 g of the title compound having particle size diameter of \( d_{90} = 79 \mu \eta \), and \( d_{\text{mean}} = 45 \mu \eta \).

**Example 8: Preparation of aripiprazole crystal form B**

A suspension of aripiprazole (10 g) in ethanol (200 ml) was heated to reflux till complete dissolution. Isopropyl ether (150 ml) was added to the reaction mixture and the reaction mass was cooled to 15-20 °C. The reaction mixture was stirred for 1 hour, filtered and dried under vacuum at 95-100 °C to give 9.32 g of the title compound having particle size diameter of \( d_{90} = 90 \mu \eta \), and \( d_{\text{mean}} = 52 \mu \eta \).

**Example 9: Preparation of aripiprazole crystal form B**

A suspension of aripiprazole (10 g) in ethanol (200 ml) was heated to reflux till complete dissolution. Isopropyl ether (150 ml) was added to the reaction mixture at 80-85 °C and reaction mass was cooled to 0-5 °C. Reaction mixture was stirred for 1 hour, filtered and dried to give 9.05 g of the title compound having particle size diameter of \( d_{90} = 55 \mu \eta \), and \( d_{\text{mean}} = 37 \mu \eta \).

**Example 10: Preparation of aripiprazole crystal form B**

A suspension of aripiprazole (20 g) in ethanol (400 ml) was heated to reflux till complete dissolution. Acetone (300 ml) was added to the reaction mixture and cooled to 0-5 °C. The reaction mixture was stirred for 1 hour, filtered and dried at 70-80 °C to give 17.1 g of the title compound having particle size diameter of \( d_{90} = 66 \mu \eta \), and \( d_{\text{mean}} = 39 \mu \eta \).

**Example 11: Preparation of aripiprazole crystal form B**

A suspension of aripiprazole (20 g) in acetone (300 ml) was heated to reflux till complete dissolution. Ethanol (300 ml) was added to the reaction mixture and cooled to 0-5 °C. The reaction mixture was stirred for 1 hour, filtered and dried at 70-80 °C to give 16.33 g of the title compound having particle size diameter of \( d_{90} = 82 \mu \eta \), and \( d_{\text{mean}} = 47 \mu \eta \).

**Example 12: Preparation of aripiprazole crystal form B**

A suspension of aripiprazole (10 g) in ethanol (200 ml) was heated to reflux till complete dissolution. Reaction mixture was added into cold acetone (150 ml) and cooled to 0 to 5 °C and stirred for 1 hour. The resulting solid was filtered and dried to give 7.88 g of the title compound having particle size diameter of \( d_{90} = 68 \mu \eta \), and \( d_{\text{mean}} = 37 \mu \eta \).

**Example 13: Preparation of aripiprazole crystal form B**

A suspension of aripiprazole (100 g) in a ethanol (1500 ml) was heated to reflux till complete dissolution. The solution was filtered hot through a candle filter and poured into cold particle free methyl tertiary butyl ether (3000 ml) at -50 to -30 °C. The reaction mass was stirred at -30 to -15 °C for 3 hours. Resulting solid was filtered and suck dried for 30 minutes. The wet solid was initially
dried for 3 hours at 50-55 °C then dried at 78-85 °C for approx 48 hour to give title compound having particle size diameter of $d_{90} = 47 \, \mu m$.

**Example 14: Preparation of aripiprazole Type II**

Aripiprazole (5 g) was dissolved in acetonitrile (150 ml) at 80-82 ºC. Chilled n-heptane (150 ml) containing seeds of Type II crystals (0.1 g) was added to the above solution and stirred for 1 hour. Mixture was further stirred at room temperature for 24 hours. Thereafter the reaction mass was cooled to 0 to 5 ºC and stirred for 60 minutes. Product thus formed was filtered, washed with chilled n-heptane and dried under vacuum to give 4.4 g of title compound.

**Example 15: Preparation of aripiprazole Type II**

Aripiprazole (5 g) was dissolved in acetonitrile (150 ml) at 80-82 ºC. Above solution was added to chilled suspension of seeds of Type II crystals (0.1 g) in n-heptane (150 ml) and stirred for 1 hour. Mixture was further stirred at 20-25 ºC for 24 hours. Thereafter the reaction mass was cooled to 0 to 5 ºC and stirred for 60 minutes. Product thus formed was filtered, washed with chilled n-heptane and dried under vacuum at 80-85 ºC to give 4.1 g of title compound.

**Example 16: Preparation of aripiprazole Type II**

Aripiprazole (5 g) was dissolved in tetrahydrofuran (10 ml) at 60-65ºC. Above solution was added to a chilled suspension containing seeds of Type II crystals (0.1 g) in n-heptane (10 ml) and stirred for 1 hour. Mixture was further stirred at 20-25 ºC for 24 hours. Thereafter the reaction mass was cooled to 0 to 5 ºC and stirred for 30 minutes. Product thus formed was filtered, washed with chilled n-heptane and dried under vacuum at 80-85 ºC to give 3.8 g of title compound.

**Example 17: Preparation of aripiprazole Type II**

Aripiprazole (5 g) was dissolved in acetone (110 ml) at 50-55ºC. Above solution was added to chilled n-heptane (110 ml) containing seeds of Type II crystals (0.1 g) and stirred for 1 hour. Mixture was further stirred at room temperature for 24 hours. Thereafter the reaction mass was cooled to 0 to 5 ºC and stirred for one hour. Product thus formed was filtered, washed with chilled n-heptane and dried under vacuum at 80-85 ºC to give 4.2 g of title compound.

**Example 18: Preparation of aripiprazole Type II**

Aripiprazole (5 g) was dissolved in acetonitrile (200 ml) at reflux temperature and the hot solution was poured into chilled cyclohexane (100 ml) containing seeds of aripiprazole Type II crystals (0.1 g). The reaction mass was stirred at 25-30 ºC. The reaction mass was then cooled to 0-5 ºC and stirred for 60 minutes. Product thus formed was filtered, washed with n- heptane (25 ml) and dried under vacuum for 12 hours to give 4.3 g of title compound.
Example 19: Preparation of aripiprazole Type II
Aripiprazole (5 g) was dissolved in acetonitrile (200 ml) at reflux temperature and n-heptane (100 ml) was added to the solution followed by seeds of aripiprazole Type II crystals. Resulting mixture was stirred at 25-30 °C. The reaction mass was then cooled to 0-5 °C and stirred for 60 minutes. Product thus formed was filtered, washed with n-heptane (25 ml) and dried under vacuum for 12 hours to give 4.4 g of title compound.

Example 20: Preparation of aripiprazole Type II
Aripiprazole (50 g) was dissolved in acetone (1.25 L) at 50-60 °C and solution was filtered to remove suspended particles. Particle free n-heptane (175 ml) was slowly added to the above solution and was stirred then slowly cooled to 20-25 °C till complete formation of Type II crystals. Thereafter the reaction mass was cooled to 0 to 5 °C and stirred for 3 hours. Resulting product was filtered, washed with chilled n-heptane and dried under vacuum at 80-85 °C for 12 hours to give 44 g of title compound.

Example 21: Preparation of aripiprazole Type II
Aripiprazole (50 g) was dissolved in acetone (1.25 L) at 50-60 °C. n-Heptane (1.25 L) was added to the above solution followed by addition of seeds of Type II crystals (1 g). Reaction mass was cooled to 20-25 °C and stirred till complete formation of Type II crystals. Thereafter the reaction mass was cooled to 0 to 5 °C and stirred for 3 hours. Product thus formed was filtered, washed with chilled n-heptane and dried under vacuum at 80-85 °C for 12 hours to give 41.5 g of title compound.

Example 22: Preparation of aripiprazole Type II
Aripiprazole (50 g) was dissolved in acetone (1.25 L) at 50-60 °C. The hot resulting solution was poured into n-heptane (1.25 L) containing seeds of Type II crystals and was stirred at 20-25 °C for 24 hours. Thereafter the reaction mass was cooled to 0 to 5 °C and stirred for 3 hours. Product thus formed was filtered, washed with chilled n-heptane and dried under vacuum at 80-85 °C to give 42.2 g of title compound.

Example 23: Preparation of aripiprazole Type II
Aripiprazole (50 g) was dissolved in a mixture of acetone (1.0 L) and water (0.25 L) at 60-65 °C. Resulting solution was poured into n-heptane (1.0 L) containing seeds of Type II crystals and the stirred at 20-25 °C for 24 hours. Thereafter the reaction mass was cooled to 0 to 5 °C and stirred for 3 hours. Resulting solid was filtered, washed with chilled n-heptane and dried under vacuum at 80-85 °C to give 42.2 g of title compound.
WE CLAIM:

1) A process for the preparation crystalline aripiprazole hydrate A, comprising the steps of:
   a) providing a solution of aripiprazole in alcoholic solvent or mixture thereof with water;
   b) mixing solution of step a) with a second solvent;
   c) optionally, adding water to the solution;
   d) inducing precipitation of aripiprazole hydrate A; and
   e) isolating aripiprazole hydrate A therefrom.

2) The process according to claim 1, wherein in step a) alcoholic solvent is selected methanol, ethanol, propanol, isopropanol, n-butanol, isobutanol and the like or mixture thereof.

3) The process according to claim 1, wherein in step b) second solvent is selected from nitriles, aliphatic or cyclic ether, ketone or mixture thereof or in mixture with water.

4) The process according to claim 1, wherein in step b) second solvent is selected from acetonitrile, propionitrile, isopropyl ether, 1,2-diethoxy ethane, 1,2-dimethoxy ethane, tetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, methyl tert-butyl ether, dibutyl ether, diphenyl ether, acetone, methyl ethyl ketone or mixture thereof or in mixture with water.

5) The process according to claim 1, wherein precipitation is induced by adding pre cooled second solvent to the solution of step a).

6) The process according to claim 1, wherein precipitation is induced by adding solution of step a) to pre cooled second solvent.

7) The process according to claim 1, wherein precipitation is induced by lowering the temperature of solution of step b) or step c).

8) A process for the preparation of aripiprazole crystal form B, comprising the steps of:
   a). dissolving aripiprazole in a suitable solvent;
   b). mixing solution of step a) with a second solvent;
   c). inducing precipitation of aripiprazole crystal form B; and
   d). isolating aripiprazole crystal form B therefrom.

   provided second solvent in step b) is different from suitable solvent in step a)

9) The process according to claim 8, wherein in step a) suitable solvent is selected from ketone such as acetone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone; aliphatic alcohol such as methanol, ethanol, n-propanol, n-butanol, isobutanol and the like or mixture thereof.

10) The process according to claim 8, wherein in step b) second solvent is selected from ketones, aliphatic ethers, aliphatic alcohols and the like or mixture thereof.
11) The process according to claim 8, wherein in step b) second solvent is selected from acetone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone, as isopropyl ether, diethyl ether, methyl tert-butyl ether, di-n-butyl ether, diphenyl ether, ethanol, n-propanol, isopropanol, n-butanol, isobutanol and the like or mixture thereof.

12) The process according to claim 8, wherein precipitation is induced by adding pre cooled second solvent to the solution of step a) or by adding solution of step a) to pre cooled second solvent.

13) The process according to claim 8, wherein precipitation is induced by lowering the temperature of solution of step b).

14) The process according to any of the proceeding claims, aripiprazole is having particle size less than 100 µm.

15) A process for the preparation of crystalline aripiprazole Type II, comprising the steps of:
   a). providing a mixture of aripiprazole in a suitable solvent;
   b). heating the mixture to 50 °C to reflux temperature of solvent till dissolution;
   c). preparing a suspension of seed crystals of crystalline aripiprazole type II in hydrocarbon solvent;
   d). admixing the solution of step b) with suspension of step c);
   e). stirring the mixture at 5 °C to ambient temperature for time sufficient for conversion to crystalline aripiprazole type II;
   f). cooling the mixture to 0 to 5 °C; and
   g). isolating crystalline aripiprazole Type II.

16) The process according to claim 15, wherein in step a) solvent is selected from ethers such as tetrahydrofuran; ketones such as acetone; nitriles such as acetonitrile and the like or mixture thereof or mixture with water.

17) The process according to claim 15, wherein in step c) hydrocarbon solvent is selected from n-hexane, n-heptane, cyclohexane and the like or mixture thereof.
# INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/IN2011/000830

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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)

WPI, CNPAT, EPDOC, CNKI, CA, ISI Web of Knowledge: Aripiprazole, polymorph, crystal, crystalline form, hydrate

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Further documents are listed in the continuation of Box C. See patent family annex.

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Name and mailing address of the ISA/CN

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