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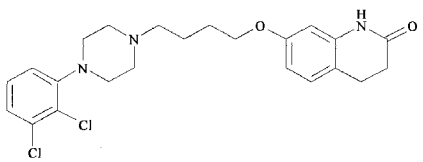
(54) **Title**: A PROCESS FOR THE MANUFACTURE OF PURE ANHYDROUS ARIPIPRAZOLE FORM B



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(57) **Abstract**: The present invention relates to a novel, industrially viable and cost effective process for manufacturing of substantially pure anhydrous Form B of 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-di-hydrocarbostyril also known as Aripiprazole. (I)

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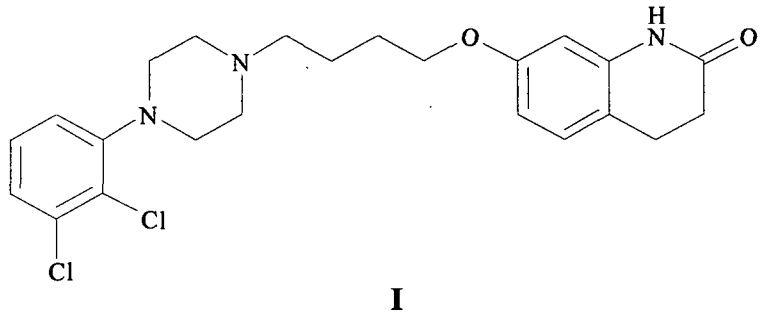
A PROCESS FOR THE MANUFACTURE OF PURE ANHYDROUS ARIPIPRAZOLE FORM B

FIELD OF THE INVENTION

The present invention relates to a novel, industrially viable and cost effective process for manufacturing a substantially pure anhydrous Form B of 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-carbostyril also known as Aripiprazole.



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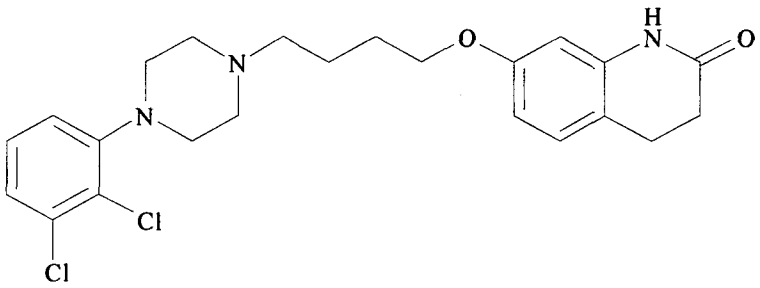
BACKGROUND OF THE INVENTION

Aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-carbostyril of formula I is a psychotropic drug available in the brand name of Abilify® and is useful for the treatment of schizophrenia. Schizophrenia is a common type of psychosis characterized by delusions, hallucinations and extensive withdrawal from others. 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.



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This drug was disclosed in US 4,734,416 patent and further described in US 5,006,528. This patent describes the preparation of solid Aripiprazole by a two-fold recrystallization of crude Aripiprazole from ethanol resulting in colorless flake crystals having a melting point of 139-139.5°C. According to Example 1 of Japanese Unexamined Patent Publication No. 191256/1990, Aripiprazole anhydride crystals are manufactured for example by reacting 7-(4-bromobutoxy)-3,4-dihydro-carbostyril with 1-(2,3-di-chlorophenylpiperidine and recrystallizing the resulting raw Aripiprazole anhydride with ethanol. Also, according to the Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (Oct. 6-8, 1996), Aripiprazole anhydride crystals are manufactured by heating Aripiprazole hydrate at 80°C. However, the Aripiprazole anhydride crystals obtained by the aforementioned methods have the disadvantage of being significantly hygroscopic.

The hygroscopicity of these crystals makes them difficult to handle during process and formulation. If it is exposed to moisture, the anhydrous form can take on water and convert to a hydrate form. This presents several disadvantages like less bio-availability and less dissoluble than the anhydrous forms of Aripiprazole.

The Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (Oct. 6-8, 1996) state that, Aripiprazole anhydride crystals exist as type-I crystals and type-II crystals; the type-I crystals of Aripiprazole anhydride can be prepared by recrystallizing from an ethanol solution of Aripiprazole, or by heating Aripiprazole hydrate at 80°C.; and the type-II crystals of Aripiprazole anhydride can be prepared by heating the type-I crystals of Aripiprazole anhydride at 130 to 140°C for 15 hours.

There are number of patents which disclose the preparation of anhydrous form B of Aripiprazole. Aripiprazole form B obtained by most of these processes have almost the same XRD pattern but in case of DSC some has two endothermic peaks or some has three endothermic peaks which indicates that it is not a pure polymorph Form B it is contaminated by other form or a solvate form.

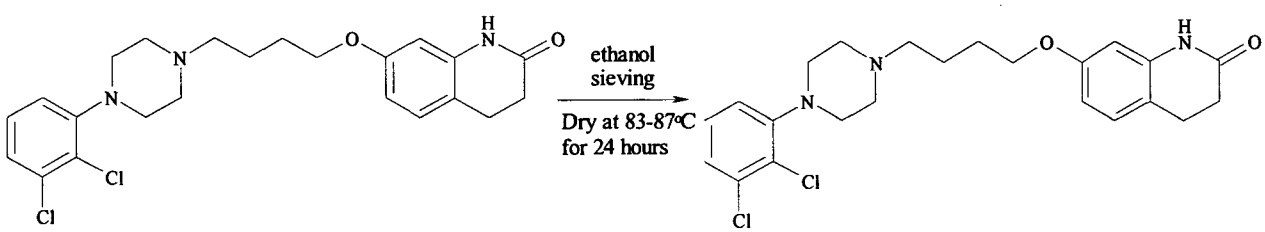
Therefore, there is still a continued need to develop a process for the manufacture of anhydrous Aripiprazole, which gives a single peak endotherm at DSC. The present inventors after a lot of experimentation succeeded to develop a robust and reproducible process which gives a single endothermic peak in the range of 138-140°C by DSC.

SUMMARY OF THE INVENTION

The principal aspect of the present invention is to provide a process for the preparation of anhydrous Aripiprazole form B which gives a single endothermic peak in the range of 138-140°C by DSC, which comprises:

a) heating Aripiprazole in an alcoholic solvent to make a clear solution;
b) cooling the contents at a temperature over a period of time;
c) centrifuging the product and washing with an alcoholic solvent to obtain wet material;
d) drying the obtained wet material under vacuum;
e) sieving the obtained dry material without crushing and separating out the sieve tops;
f) further drying the sieved material.

This invention can be illustrated by the scheme given below:



Anhydrous Crystalline Form-B

Another aspect of the present invention is to provide anhydrous Aripiprazole form B having a single endothermic peak in the range of 138-140°C by DSC.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a differential scanning calorimetry thermogram of the Anhydrous Aripiprazole Form B.
FIG. 2 is a powder x-ray diffraction diagram of the Anhydrous Aripiprazole Form B.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of anhydrous Aripiprazole form B having a single endothermic peak in the range of 138-140°C by DSC.

In an embodiment of the invention, mixing of Aripiprazole in step (a) is carried out in a suitable alcoholic solvent selected from the group consisting of methanol, n-propanol, ethanol, isobutanol, n-butanol and the like by heating to the reflux temperature of the solvent. In the present invention Aripiprazole in step (a) is preferably mixed in ethanol and heated to reflux temperature (78-80°C) to make a clear solution.

In another embodiment of the invention, cooling of contents in step (b) is carried out at a suitable temperature in the range of 0-10°C; preferably in the range of 0-5°C over a period 30 minutes to 90 minutes and maintained for one hour.

In another embodiment of the invention, centrifuging and washing is carried out in step (c) with a suitable chilled alcoholic solvent selected from the group consisting of methanol, n-propanol, ethanol, isobutanol, n-butanol and the like; and mixtures thereof, preferably with ethanol.

In another embodiment of the invention, drying is carried out in step (d) under vacuum at a suitable temperature in the range of 40-45°C; preferably in the range of 43-47°C.

In another embodiment of the invention, sieving in step (e) is carried out by using sifter (40 mesh) without crushing and further separating out the sieve tops.

In yet another embodiment of the invention, drying in step (f) is carried out at a suitable temperature in the range of 80-90°C preferably 83-87°C by hot water circulation under vacuum to obtain anhydrous Aripiprazole Form B having a single endothermic peak in the range of 138-140°C by DSC.

The starting material, Aripiprazole can be prepared by the process mentioned in product patent US 5,006,528 or by other processes available in the prior art.

In yet another embodiment of the invention, Anhydrous Aripiprazole Form B has a powder x-ray diffraction spectrum which is substantially the same as the powder x-ray diffraction spectrum shown in fig.2. Specifically, they have characteristic peaks at d-spacing [Å] 8.00849, 7.33222, 6.16414, 5.949, 5.33806, 4.58549, 4.35752, 4.02380, 3.15271, 2.83466. They exhibit an endothermic peak which is substantially the same as given in Fig.1 i.e. about 138.5°C in differential scanning calorimetry.

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art would appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification.

The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

EXAMPLES:

Example 1: Preparation of Anhydrous Crystalline Aripiprazole Form B

Aripiprazole (10 Kg) was mixed with ethanol (220 L) and heated to reflux at 78-80°C to make a clear solution. The contents were cooled to 0-5°C over a period and maintained for some

time. The product was centrifuged and washed with chilled ethanol (20 L). The obtained wet material was dried under vacuum at 43-47°C. The obtained dry material was sieved using sifter (40 mesh) without crushing and separated out the sieve tops. The sieved material was again dried at 83-87°C (bath temperature) under vacuum till the LOD is complies (LOD limit: NMT 0.5%w/w).

Dry Weight = 9.12 Kg
Yield = 91.2 %

We Claim:

1. A process for the preparation of anhydrous Aripiprazole form B having a single endothermic peak in the range of 138-140°C by DSC comprising:
    a) heating Aripiprazole in an alcoholic solvent to make a clear solution;
    b) cooling the content at a temperature over a period of time;
    c) centrifuging the product and washing with an alcoholic solvent to obtain wet material;
    d) drying the obtained wet material under vacuum;
    e) sieving the obtained dry material without crushing and separating out the sieve tops; and
    f) further drying the sieved material.
2. A process according to claim 1, wherein the alcoholic solvent is selected from the group consisting of methanol, n-propanol, ethanol, isobutanol, n-butanol, and the mixtures thereof.
3. A process according to claim 2, wherein the alcoholic solvent is ethanol.
4. A process according to claim 1, wherein the content in step (b) is cooled to a temperature in the range of 0-10°C.
5. A process according to claim 4, wherein the content in step (b) is cooled to a temperature at 0-5°C.
6. A process according to claim 1, wherein the vacuum drying in step (d) is carried out at a temperature in the range of 40-50°C.
7. A process according to claim 1, wherein the sieving in step (e) is carried out by using sifter (40 mesh).
8. A process according to claim 1, wherein, the drying is carried out in step (f) at a temperature in the range of 80-90°C.

9. Anhydrous Aripiprazole having a single endothermic peak in the range of 138-140°C by DSC.
10. Anhydrous Aripiprazole having a single endothermic peak in the range of 138-140°C by DSC, substantially as in figure 1.

FIG. 1 is a differential scanning calorimetry thermogram of the Anhydrous Aripiprazole Form B.

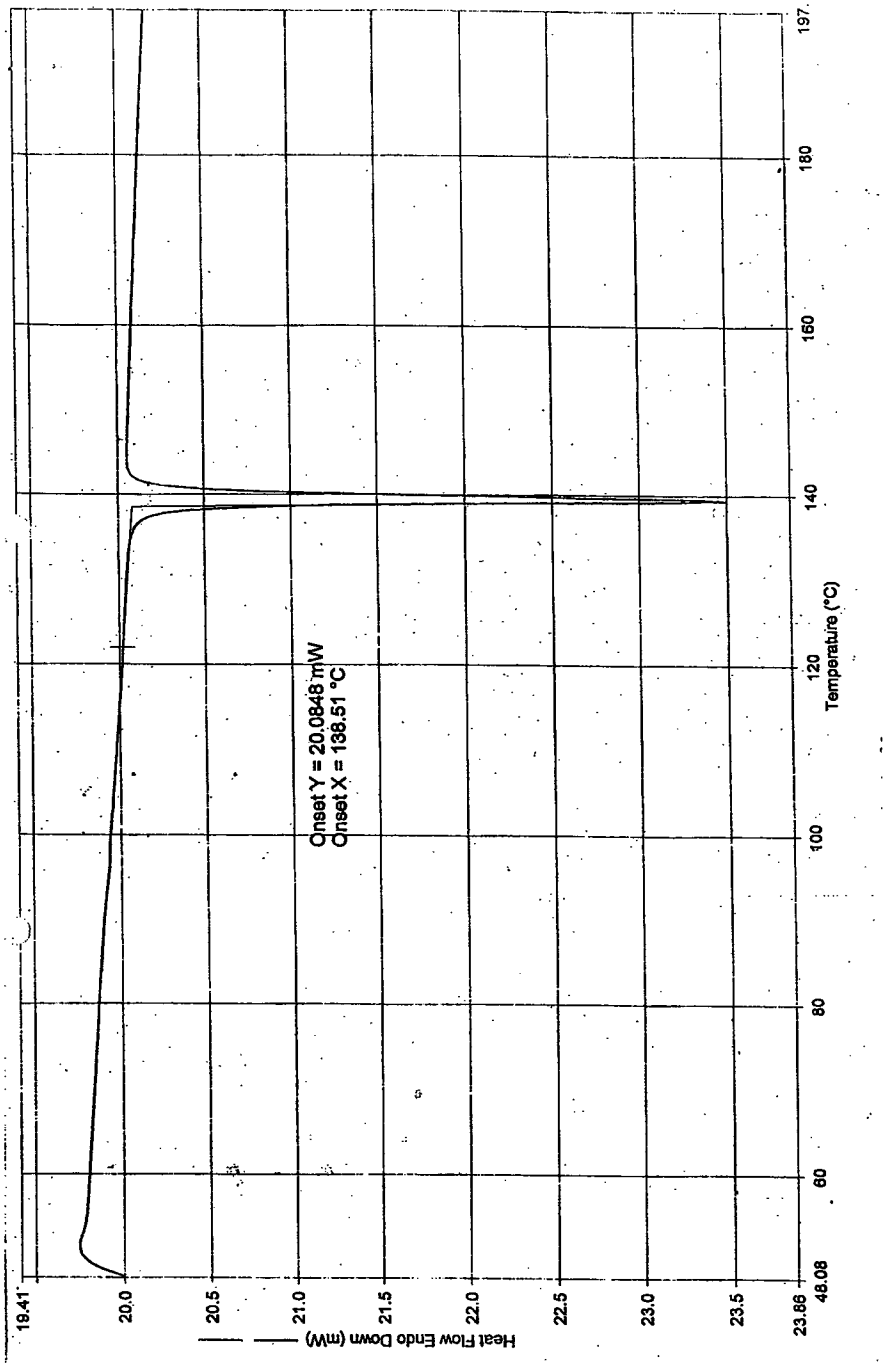
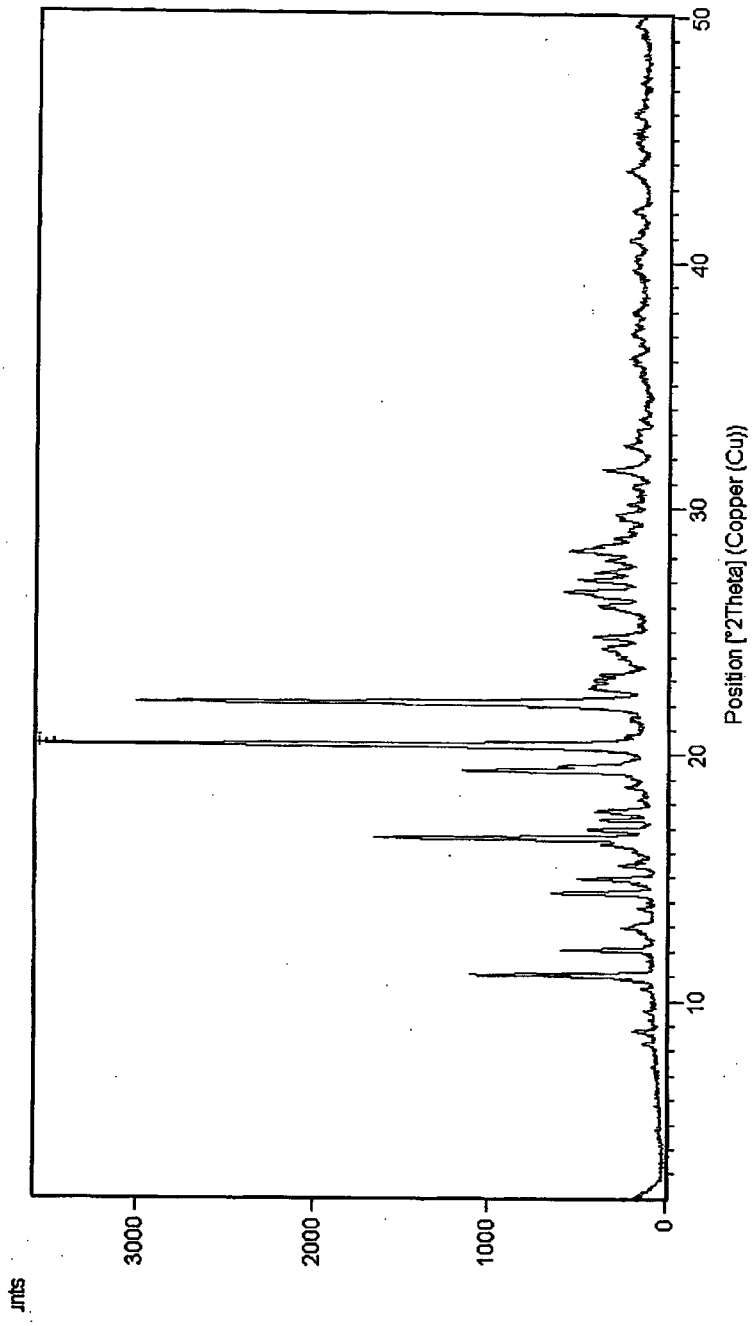



FIG. 2 is a powder x-ray diffraction diagram of the Anhydrous Aripiprazole Form B.