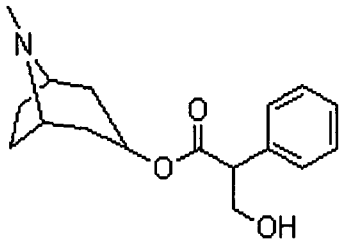
This application claims priority to Indian patent application numbered IN 5520/CHE/2012 filed on Dec 31, 2012 the contents of which are incorporated by reference in their entirety.

FIELD OF THE INVENTION:

The present invention relates to crystalline polymorph form of Atropine sulfate and process for the preparation thereof.

BACKGROUND OF THE INVENTION:

Atropine, an anticholinergic agent (muscarinic antagonist), Atropine, a naturally occurring belladonna alkaloid, is a racemic mixture of equal parts of d- and l-hyoscyamine, whose activity is due almost entirely to the levo isomer of the drug. Chemically, atropine is designated as 1αH, 5αH-Tropan-3-α-ol (±) –tropate and it is structurally represented as below



Atropine

Atropine is first disclosed in US2276677 and marketed as Atropine Sulfate under the brand name of AtroPen It is indicated for the treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides.

IN133779 patent discloses the process for the preparation of Atropine in pure form, wherein by heating for short time (1 hour to 2 hours) hyoscyamine in a suitable organic solvent such as ethyl alcohol or n-butyl alcohol, or in a suitable organic base such as pyridine or diethylamine or in organic solvent like ethyl alcohol or benzene containing the organic base such as pyridine or diethylamine yields Atropine and crystallized from acetone which is then converted to its pharmaceutically acceptable salts.

Journal of Pharmacy and Pharmacology (1954), 6; 256-8 discloses crystallization of atropine sulfate stereoisomer from ethanol.

Computational Biology and Chemistry 28 (2004) 375–385 discloses X-ray structural analysis of atropine.

OBJECT AND SUMMARY OF THE INVENTION:

The principle object of the present invention is to provide crystalline polymorph of Atropine Sulfate.

Another object of the present invention relates to process for the preparation of crystalline polymorph of Atropine Sulfate.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1 illustrates X-ray powder diffraction pattern of crystalline polymorph of Atropine Sulfate.

Figure 2 illustrates DSC thermogram of crystalline polymorph of Atropine Sulfate.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention provides crystalline Atropine Sulfate. The present invention further relates to process for the preparation of crystalline Atropine sulfate.

In one embodiment the present invention provided crystalline Atropine Sulfate is characterized by the Powder X-ray diffraction having peaks at about 5.51, 5.92, 6.67, 10.67, 11.32, 11.80, 13.24, 13.91, 14.95, 15.60 and 16.41 (±) 0.2 degree 2θ values.

In another embodiment the present invention provided crystalline Atropine Sulfate which is further characterized by the Powder X-ray diffraction having peaks at about 5.51, 5.92, 6.67, 10.67, 11.32, 11.80, 13.24, 13.91, 14.95, 15.60, 16.41, 23.67, 24.52, 26.19, 26.56, 27.31, 28.30, 28.95, 30.01and 30.40 (±) 0.2 degree 2θ values.

In yet another embodiment, the crystalline Atropine Sulfate of the present invention is characterized by powder X-ray diffraction as depicted in by Figure 1.

In yet another embodiment, the crystalline Atropine Sulfate is of the present invention is characterized by a differential scanning calorimeter (DSC) as depicted in Figure 2.

In yet another embodiment, the crystalline Atropine Sulfate of the present invention as represented by fig. 2 has an endotherm peak at 199.43°C.

In yet another embodiment, the crystalline Atropine Sulfate of the present invention is a hydrate.

Yet another embodiment the present invention provides a process for the preparation of crystalline Atropine sulfate comprising the steps of:

a) dissolving Atropine in an organic solvent,
b) adding sulfuric acid solution prepared by adding sulfuric acid in dichloromethane, acetone and water,
c) heating the reaction mixture; and
d) isolating the crystalline Atropine sulfate.

According to the present invention, Atropine base is dissolved in an organic solvent such as dichloromethane. Separately, sulfuric acid is taken in acetone, dichloromethane mixture and added water. This sulphuric acid solution is added to atropine base and after addition is completed, the solution is heated to reflux at temperature 40-42°C for 3 hours. After the reaction completes, the reaction mixture is cooled and the cake is washed from dichloromethane followed by washing with acetone for twice. The resultant compound is dried under reduced pressure to obtain atropine sulfate.

In yet another embodiment, crystalline Atropine Sulfate obtained by following the process according to the present invention is a monohydrate.

The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention in any way.

Experimental procedure:

Example 1: Preparation of tropinone

In a round bottom flask charge water 1000 ml, 500 gm of 2, 5-dimethoxy tetrahydrofuran (3.783 mol) and 10 ml conc. The reaction mixture was heated to 85-90°C for 2 hrs. After 2 hours the reaction mixture was allowed to cool to 25-30°C and further chilled the reaction mass to -5 to-10°C. In the above reaction mass 553 g of 1, 3 acetone dicarboxylic acid (3.783 mol) was added under stirring at -5 to 0°C and 1000 ml water was added and chilled to -5 to 0°C. In the reaction mass 440 g of aq. mono methyl amine (40% solution) (5.67 mol) was added drop wise at temp. -5 to 0°C (**Caution: Exotherm was observed during addition of monomethyl amine**). Raise the temp. of reaction mixture to 5 to 10 °C and added portion wise 54.2 g of sodium bicarbonate to get pH 7 to 8. After the addition of sodium bicarbonate is completed, flushed the reaction mass with 500 ml of water. The temperature of the reaction mixture was raised to 20-25 °C. The progress of reaction was monitored by GC (unreacted 2,5-dimethoxy tetrahydrofuran is <5%). After completion of reaction extracted the reaction mass with 6× 2.5 litre dichloromethane. The combine dichloromethane layer and distilled the solvent at bath temp. 50-55°C to get crude tropinone. The crude tropinone was distilled under vacuum (~15 mbar) and oil temp. 125-130°C and vapour temp. 105-110°C to get 250 g of pure tropinone (GC purity >95%).

Yield = 250 g (0.5 w/w)

Theoretical yield = (1.05 w/w)

Molar yield = 47.6 %

Example 2: Preparation of Tropine

In a cleaned autoclave reactor, charged the methanol 960 mL, 240 g tropinone (1.72 mol.) and water 240 mL water at 25-30°C. Charged 48 g of Raney Nickel catalyst KALCAT-4061 (20% w/w with respect to tropinone). Stirred the reaction mass at rpm 800. The reaction mass was flushed with nitrogen followed by hydrogen. Heated the reaction

mixture to 60-65°C and maintained the pressure 8 to 10 Kg/ cm2. The progress of reaction was monitored by GC. After 6 hours, draw the sample and check the unreacted tropinone content (Limit: unreacted tropinone content <1%). Cool the autoclave to 25-30 °C and take out the material. Flushed the autoclave with methanol 120 ml. Filter the reaction mass through celite bed under nitrogen atmosphere to remove the spent catalyst and washed the catalyst with methanol. The combined mother liquor was concentrated under reduced pressure at bath temperature of 60-70°C. After complete distillation of solvent, the oily mass was swapped with 2×250 ml of n-heptane to obtain an oily mass (water content not more than 2%).

(Caution: The Raney Nickel is pyrophoric material, handle it carefully)

Yield = 192 g (0.8 w/w)

Theoretical yield = (1.01 w/w)

Molar yield = 79.2%

Example 3: Preparation of α Formyl methyl phenyl acetate

In a round bottom flask, charge 400 g methyl phenyl acetate (2.66 mol) and 1.6 litre ethylformate under stirring at 25°C-30 °C. Chill the reaction mixture to 0 to -5 °C. Mixed 1012 g titanium tetra chloride (5.33 mol.) in to 800 ml dichloromethane and added drop wise over a period of 2 hour at temp. 0 to -5 °C (Note: The addition of TiCl4 solution is exothermic, hence controlled addition of TiCl4 is required). After complete addition of TiCl4 solution, 673 g of triethyl amine (6.66 mol.) was added drop wise at a temperature of about 0 to -5 °C over a period of 2 hours. Slowly raised the temperature of reaction mixture to 20-25°C and stirred for 3 hours. After 3 hours draw the sample and check the unreacted methyl phenyl acetate content (Limit: unreacted methyl phenyl acetate <5%). After completion of reaction, chill the reaction mixture to 5 to 10 °C. In the reaction mass 4000 ml of water was added and 2000 ml DCM was added. Stirred for 15 min and then separated the organic layer. The aqueous layer was extracted with 800 ml dichloromethane. The combine organic layer was washed with 2 liters of brine solution. The organic layer was distilled under reduced pressure and bath temperature 45-50°C to get 427.5 g of product as a viscous dark brown oil.

Yield = 427.5 g (1.067 w/w)

Theoretical yield = (1.187 w/w)

Molar yield = 90.0%

Example 4: Preparation of α-formyl phenyl acetic acid tropine ester

Charge the toluene 1200 ml into round bottom flask and further charged the 2.64 g sodium methoxide (0.0488 mol.) at 25 to 23°C. Heated the reaction mass to 109-115°C and distilled 400 mL toluene. 200 g tropine (1.418 mol.) was mixed 1200 ml toluene and 387.7 g α-formyl methyl phenyl acetate (2.127 mol.) was mixed with 1200 ml toluene. The tropine solution and α-formyl methyl phenyl acetate solution were added drop wise over a period of two hour simultaneously and solvent was distilled out. After complete addition 1000 ml of fresh toluene was added drop wise and simultaneously distilled the toluene. After maintaining for 3 hours, check the unreacted tropine by GC (Limit of unreacted tropine is not more than 5%). Distilled the toluene to get ~1000 ml of slurry and then reaction mass was cooled to 25-30°C and stirred for 12 hours. The product was isolated by filtration and and washed with 400 mL acetone. The cake was dried under reduced pressure at temperature 60-65 °C for 6 hours to get LOD not more than 1%.

Yield = 268 g (1.34 w/w)

Theoretical yield = (2.035 w/w)

Molar yield = 65.8%

Example 5: Preparation of Atropine base

200 g (0.696 mol) of α-Formyl phenyl acetic acid tropine ester was suspended into 2000 ml dichloromethane (5 vol.) and methanol 200 ml (1 vol.) at 20-25. The reaction mixture was chilled to 0 to 5 °C. 18.53 g (0.487 mol.) of sodium borohydride was added portion wise over a period of 1 hour at temperature 0 to 5°C. The frothing was observed during the addition of sodium borohydride. Stir the reaction mixture for 3 hours at 10-20°C. The progress of reaction was monitored by HPLC (Limit of unreacted aldehyde is 0.5%).

After completion of reaction, added 1000 ml of water, stir for 30 min. and separated the organic layer. Aqueous layer was extracted with 400 ml DCM. The combine organic extracts was washed with 1000 mL water. In the organic layer 10 g of activated carbon was added at 20-25°C stirred for 30 min and filter through the celite bed. The organic layer was distilled at bath temp. 55-60°C to get a slurry. In the slurry 1000 ml of n-heptane was added and stir for 1 hour at 20-25°C and filter. Washed the wet cake with 100 ml n-heptane. The wet cake was charged into flak and 500 ml acetone was added. The reaction mass was heated to 55-60°C to get a clear solution and maintained for 30 min. In the clear solution 500 ml of n-heptane was added at 55-60°C. The reaction mass was allowed to cool to 5-10°C and stirred for 2 hour. Filter the solid and washed the cake with 200 ml 1:1 mixture of acetone and n-heptane to get a crude Atropine base.

The crude Atropine base was charged into flak and 400 mL acetone was added. The reaction mass was heated to 50-55°C to get a clear solution and maintained for 30 min. In the clear solution 400 mL of n-heptane was added at 55-60°C. The reaction mass was allowed to cool to 25-30°C and stirred for 2 hour and further chill the reaction mass to 5 to 10 °C. Filter the solid and washed the cake with 200 ml 1:1 mixture of acetone and n-heptane to get a pure Atropine base. Purified base was dried under 60 mm Hg pressure and temp. 65-70°C for 6 hours to get LOD < 1%.

Yield = 100 g (0.50 w/w)

Theoretical yield = (1.004 w/w)

Molar yield = 49.8 %

Example 6: Preparation of Atropine sulfate mono hydrate

Charge 90 g of atropine base (0.3114 mol.) and 1080 mL of dichloromethane into a round bottom flask and stirred to get a clear solution at 25-30°C. In another conical flask weigh 13.7 g of sulfuric acid (0.140 mol) was mixed with 135 mL acetone, 90 dichloromethane and 2.8 g water (0.1557 mol.) to get a clear solution. The sulfuric acid solution was added drop wise into a clear solution of atropine base under stirring over a period of 30 min. at temp. 29-32°C. After complete addition of sulfuric acid, reaction mixture was heated to reflux at temp. 40-42°C for 3 hours. Cool the reaction mass to 25-30°C and filter. The

cake was charged into flask and added 1080 mL dichloromethane and stirred for 30 min. at 29-32°C. Filter the solid and cake was charged again into flask and added 900 ml acetone and stirred for 30 min. at 29-32°C. Filter the solid and cake was again charged into flask and added 900 ml acetone and stirred for 30 min. at 29-32°C. Filter the solid and washed the cake with 180 ml acetone. The solid was dried under reduced pressure at temp. 70-75°C for ~35 hours to get LOD < 0.5%.

Yield = 85 g (w/w 6.2 w.r.t. sulfuric acid)
Theoretical yield = (7.09 w/w)
Molar yield = 87 %