PROCESS FOR THE PREPARATION OF PAROXETINE HYDROCHLORIDE

The present invention relates to a process for the preparation of a pharmaceutically active compound, and to the use of the so-prepared compound in therapy. In particular this invention is concerned with a new process for the preparation of a paroxetine chloride propan-2-ol solvate and its use to prepare a crystalline anhydrate form of paroxetine hydrochloride.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-)*trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt for the treatment and prophylaxis of *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

Paroxetine hydrochloride has been described in the literature as a crystalline hemihydrate (see EP-A-0223403 of Beecham Group) and as various crystalline anhydrate forms (see WO96/24595 of SmithKline Beecham). WO96/24595 describes the preparation of the form A anhydrate via an intermediate solvate with an organic solvent such as propan-2-ol.

When prepared conventionally (crystallisation from anhydrous propan-2-ol), paroxetine hydrochloride propan-2-ol solvate has very poor stirring properties, and is very difficult to isolate, wash, and dry. It is also very difficult to desolvate by heat treatment under vacuum. In WO96/24595, the problem that conventional drying techniques were incapable of efficient removal of solvent was addressed by providing an additional displacement stage before the product was finally dried.

The present invention is based on the finding that crystallisation of paroxetine hydrochloride from a mixture of propan-2-ol and a co-solvent produces an improved crystalline form which is much easier to stir, filter, wash and dry. Surprisingly it has also been found that it is easier to remove solvent of crystallisation by heat treatment.

Accordingly the present invention provides a process for the preparation of paroxetine hydrochloride propan-2-ol solvate which comprises forming a solution of paroxetine hydrochloride in a mixture of propan-2-ol and an effective co-solvent, and crystallising paroxetine hydrochloride propan-2-ol solvate from the solution.

Typically an effective cosolvent is one which will form a clear solution when added to a solution of paroxetine hydrochloride in propan-2-ol and which does not form a competing solvate during crystallisation. Suitable cosolvents include toluene, heptane and hexane. Surprisingly toluene has been found to be particularly useful despite the fact that a toluene solvate of paroxetine hydrochloride can exist.

The cosolvent mixture may formed before addition of paroxetine hydrochloride, or by addition of a cosolvent to a solution of paroxetine hydrochloride in propan-2-ol, or by addition of propan-2-ol to a solution of paroxetine hydrochloride in an effective cosolvent. In a preferred procedure, the final stage of the preparation of paroxetine hydrochloride is carried out in an effective cosolvent, to which propan-2-ol may be added for crystallisation in accordance with the invention. For example when toluene is used as the cosolvent it can be used conveniently in the preceding manufacturing step. After washing and acidification, only partial evaporation is necessary, followed by addition of propan-2-ol and crystallisation.

Crystallisation may be initiated by conventional procedures such as cooling a heated solution, or removing solvent by evaporation or heating. It may be advantageous to add seeds of crystalline paroxetine hydrochloride propan-2-ol solvate prepared by the procedure of this invention or by the procedure of WO96/24595.

A crystalline anhydrate of paroxetine hydrochloride may be formed by heating the propan-2-ol solvate to remove bound propan-2-ol. The resultant product desirably contains less than 2% of the solvated solvent, preferably less than 1%, more preferably less than 0.5%, and most preferably less than 0.1%. Advantageously the crystalline product is the Form A anhydrate of paroxetine hydrochloride.

The crystalline paroxetine hydrochloride product of this invention may be formulated for therapy as described in EP-A-0223403 or WO96/00477.

Therapeutic uses of the paroxetine product of this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the disorders comprising paroxetine hydrochloride anhydrate prepared by this invention and a pharmaceutically acceptable carrier;

the use of paroxetine hydrochloride anhydrate prepared by the process of this invention to manufacture a medicament for the treatment or prophylaxis of the disorders; and

a method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine hydrochloride anhydrate prepared by this invention to a person suffering from one or more of the disorders.

The invention is illustrated by the following Examples:

Example 1

Paroxetine hydrochloride hemihydrate (160 g) was suspended in a mixture of toluene (250 mil) and isopropanol (1000 ml) and heated to boiling. Solvent was removed by distillation and replaced by fresh isopropanol (3 x 500 ml). The boiling point was then 81.2°C. Further solvent was removed by distillation until the volume was about 1000 ml. The well stirred mixture was allowed to cool to about 70°C, then hexane (500 ml) was added slowly to give a clear solution at 57°C. Seeds of paroxetine hydrochloride isopropanol solvate were added, and as the crystallisation proceeded the temperature increased to 60°C. Stirring was continued until the temperature had fallen to about 30°C, then the product was collected, washed on the filter with hexane (2 x 500 ml) and dried in vacuo at ambient temperature.

Yield 171 g isopropanol content by NMR:10.5% wt/wt

Example 2

(-)-Trans-4-(4-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-1-phenoxycarbonylpiperidine (90 g) is heated with potassium hydroxide (8.5 g) in toluene (1500 ml) at reflux for 3 hours, cooled, washed with hot water, acidified with hydrochloric acid, and distilled to approximately one quarter volume under vacuum. Hot propan-2-ol (2000 ml) is added and the mixture cooled slowly with vigorous stirring until the temperature reaches 20°C. After stirring for a further 2 hours, the

product is filtered, washed with propan-2-ol, and dried under vacuum, to give paroxetine hydrochloride propan-2-ol solvate.

Example 3

Paroxetine hydrochloride hemihydrate (122 g) was suspended in toluene (1000 ml) and heated to reflux for 2 hours under Dean & Stark apparatus to remove water. The toluene solution was concentrated to approximately 250 ml volume at which point it was still mobile and easy to stir. Warm propan-2-ol was added (1300 ml at about 50°C) and the reaction mixture stirred vigorously; the mixture crystallised slowly but did not become unstirrable. After about 30 minutes a further quantity of propan-2-ol (300 ml) and n-heptane (300 ml) was added, and the mixture was cooled to ambient temperature (approximately 20°C), stirred for a further 30 minutes, filtered and dried.

One part of the product was dried under vacuum at approximately 20°C to give paroxetine hydrochloride propan-2-ol solvate with a composition ratio of approximately 1:1.

Another part was dried under vacuum at a final temperature of 65°C to give paroxetine hydrochloride containing approximately 1.6% propan-2-ol. By comparison, a conventionally prepared sample of solvate heated overnight in a vacuum oven at 70°C for 24 hours contained 4.1% propan-2-ol.

Example 4

Paroxetine hydrochloride hemihydrate (50 g) was heated to reflux with stirring in toluene (500 ml) and the water removed using a Dean and Stark apparatus. The solution was allowed to cool to about 40°C, diluted with isopropanol (200 ml), and allowed to crystallize at ambient temperature. The product was collected, washed with toluene and dried at 40°C to give paroxetine hydrochloride isopropanol solvate.

Yield 23 g



Claims

1. A process for the preparation of paroxetine hydrochloride propan-2-ol solvate which comprises forming a solution of paroxetine hydrochloride in a mixture of propan-2-ol and an effective co-solvent, and crystallising paroxetine hydrochloride propan-2-ol solvate from the solution.

2. A process according to claim 1 wherein the cosolvent comprises toluene, heptane or hexane.

3. A process according to claim 1 or 2 wherein the final stage of the preparation of paroxetine hydrochloride is carried out in the cosolvent, to which propan-2-ol is subsequently added for crystallisation.

4. A process for the preparation of a crystalline anhydrate of paroxetine hydrochloride which comprises heating a propan-2-ol solvate , obtained using the process of any one of the preceding claims, to remove bound propan-2-ol.

5. A pharmaceutical composition for treatment or prophylaxis of the disorders comprising paroxetine hydrochloride anhydrate prepared by the process of claim 4 and a pharmaceutically acceptable carrier.

6. The use of paroxetine hydrochloride anhydrate prepared by the process of claim 4 to manufacture a medicament for the treatment or prophylaxis of the disorders.

7. A method of treating the disorders which comprises administering an effective or prophylactic amount of paroxetine hydrochloride anhydrate prepared by the process of claim 4 to a person suffering from one or more of the disorders.