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(54) Title: PAROXETINE ASCORBATE

(57) Abstract

Paroxetine ascorbate is useful in the treatment of certain CNS disorders.

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PAROXETINE ASCORBATE

The present invention relates to a novel compound, to processes for preparing it and to its use in treating medical disorders.

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.

We have now surprisingly discovered a novel salt of paroxetine which may be used as an alternative to the currently marketed hydrochloride, or as an intermediate in the preparation of the hydrochloride.

According to the present invention there is provided paroxetine ascorbate.

In one aspect the novel salt of this invention is provided in non-crystalline form, which may a solid or an oil. The oil is preferably absorbed on a solid carrier, especially a carrier that is usable as a component of a pharmaceutical composition

In another aspect the novel salt of this invention is provided in crystalline form. When the crystalline form exists as more than one polymorph, each polymorph forms another aspect of this invention.

Paroxetine ascorbate may be prepared by contacting stoichiometric amounts of ascorbic acid and paroxetine free base. Preferably either the acid or base is in solution, more preferably both are in solution. Elevated temperature may be used to bring the acid into solution, but good yields of the salt are obtained by evaporation of some or all of the solvent or by controlled cooling, preferably in stages. Most commonly used solvents are suitable for mobilizing paroxetine free base, for example toluene, alcohols such as

methanol, ethanol, propan-2-ol, esters such as ethyl acetate, ketones such as acetone and butanone, halogenated hydrocarbons such as dichloromethane, and ethers such as tetrahydrofuran and diethyl ether, but solvents in which ascorbic acid is very insoluble are preferably avoided. Suitable solvents for ascorbic acid include water and lower alcohols.

The salt may be isolated in solid form by conventional means from a solution thereof obtained as above. For example, the non-crystalline salt may be prepared by precipitation, spray drying, and freeze drying of solutions, or vacuum drying of oils, or solidification of melts obtained from reaction of the free base and the acid. The crystalline salt may be prepared by crystallization or recrystallization from appropriate solvents.

When the salt is obtained as a solvate, by association with the solvent in which it is dissolved, such solvate forms a further aspect of this invention. Solvates may be returned to the unsolvated salt by heating, for example by oven-drying, or by treatment with a displacement solvent which does not form a solvate.

Prior to the isolation of the paroxetine salt, water may be removed by azeotropic distillation to avoid the formation of hydrates or to obtain the product in anhydrous form. In that case, suitable solvents for the solution of the salt are those which form an azeotrope with water such as toluene and propan-2-ol. It should also be appreciated that mixtures of solvents can also be used to aid the azeotropic removal of water.

More generally, crystallization may be carried out from any solvent which allows formation of the desired crystal structure, using seeds of the desired structure where necessary or desirable. When polymorphs exist, individual polymorphs are preferably crystallized directly from a solution of the salt, although recrystallizing a solution of one polymorph using seeds of another polymorph may also be carried out.

Paroxetine free base may be prepared according to the procedures generally outlined in US Patent No 4,007,196 and EP-B-0 223403. Ascorbic acid is commercially available.

The compounds of this invention may be used to treat and prevent the following disorders:

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
Substance Abuse	

These disorders are herein after referred to as "the Disorders".

The present invention further provides a method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a salt of the invention to a sufferer in need thereof.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of the Disorders which comprises an admixture of a salt of the invention with a pharmaceutically acceptable carrier.

The present invention also provides the use of a salt of the invention for treating and/or preventing the Disorders.

The present invention also provides the use of a salt of the invention in the manufacture of a medicament for treating and/or preventing the Disorders.

Most suitably the present invention is applied to the treatment of depression, OCD and panic.

The compositions of this invention are usually adapted for oral administration, but formulations for dissolution for parental administration are also within the scope of this invention.

The composition is usually presented as a unit dose composition containing from 1 to 200mg of active ingredient calculated on a free base basis, more usually from 5 to 100mg, for example 10 to 50mg such as 10, 12.5, 15, 20, 25, 30 or 40mg by a human patient. Most preferably unit doses contain 20mg of active ingredient calculated on a free base basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400mg of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

Preferred unit dosage forms include tablets or capsules.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilized in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Specific examples of pharmaceutical compositions include those described EP-B-0-223403, and US 4,007,196 in which the products of the present invention may be used as the active ingredients.

The following Examples illustrate the present invention:

Example 1: Preparation of paroxetine ascorbate

A 1.28 mol solution of paroxetine base in toluene (5 ml, 6.38 mmol) was added to a solution of ascorbic acid (1.12g, 6.38 mmol) in methanol (15 ml). The solvent was removed *in vacuo*, the residual oil was diluted with toluene (15 ml) and the solvent removed *in vacuo*. Trituration with diethyl ether (*c.* 15 ml) and filtration under nitrogen

gave a pale yellow solid which was washed with diethyl ether (2 × 10 ml), dried in a vacuum desiccator for 3 hours.

Yield 2.99g.

IR nujol mull:

Bands at 1716, 1603, 1510, 1465, 1377, 1224, 1186, 1136, 1037, 930, 831, 722, 540 cm^{-1}.

Example 2: preparation of tablets

INGREDIENTS	**20 mg Tablet**	**30mg Tablet**
Paroxetine ascorbate	20.00 mg (based on free base)	30.0 mg (based on free base)
Dicalcium Phosphate (DCP)	83.34 mg	125.0 mg
Microcrystalline Cellulose	50.67 mg	76.0 mg
Sodium Starch Glycollate	8.34 mg	12.5 mg
Magnesium Stearate	1.67 mg	2.5 mg

Commercial source of the ingredients

Dicalcium Phosphate Dihydrate	-	Emcompress or Ditab*
Microcrystalline Cellulose	-	Avicel PH 102*
Sodium Starch Glycollate	-	Explotab.*

* Tradenames

Method

1. Pass DCP through a screen and weigh it into a Planetary mixer.
2. Add 30 mesh Paroxetine Ascorbate to the bowl.
3. Add 20 mesh Avicel and Explotab and mix all the powders for 10 minutes.
4. Add magnesium stearate and mix for 5 minutes.

Tablet into Pentagonal Tablets using the following punches:

30 mg Tablet	9.5 mm	Circumcircle
20 mg Tablet	8.25 mm	Circumcircle

The tablets are made satisfactorily on a single punch or a Rotary press.

Example 3: preparation of tablets

INGREDIENTS	**10 mg Tablet**	**20 mg Tablet**	**30mg Tablet**
Paroxetine ascorbate	10 mg (as on free base)	20 mg (as on free base)	30 mg (as on free base)
Sodium Starch Glycollate	2.98 mg	5.95 mg	8.93 mg
Granular Dicalcium Phosphate (DITAB) or Dicafos	158.88 mg	317.75 mg	476.63 mg
Magnesium Stearate	1.75 mg	3.50 mg	5.25 mg

Method

1. Paroxetine ascorbate, Sodium Starch Glycollate and Dicalcium Phosphate Dihydrate are screened and mixed together in a suitable mixer.

(Planetary, Cuble or High Energy Shear mixer.)

2. Add Magnesium Stearate and compress it into a tablet using a single punch or Rotary Tablet machine.

CLAIMS

1. Paroxetine ascorbate.

2. A compound according to claim 1 in non-crystalline form.

3. A compound according to claim 1 in crystalline form.

4. A process for the preparation of a compound as claimed in claim 1 or 2 by precipitation, spray drying or freeze drying a solution of paroxetine ascorbate, or by vacuum drying of oils of paroxetine ascorbate, or solidification of melts of paroxetine ascorbate.

5. A process for the preparation of a compound as claimed in claim 1 or 3 by crystallization or re-crystallization from a solution of paroxetine ascorbate.

6. A process according to claim 4 or 5 in which the solution, oil or melt of paroxetine ascorbate is prepared by treating paroxetine free base with ascorbic acid.

7. A method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of paroxetine ascorbate to a sufferer in need thereof.