PAROXETINE 10-CAMPHORSULFONATE FOR TREATMENT OF CNS DISORDERS

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 a paroxetine camphor 10-sulfonate. 10-camphorsulfonic acid exists in enantiomeric forms and this invention includes salts with both D-(+)-10-camphorsulfonic acid and (1R)-(-)-10-camphorsulfonic acid and racemic mixtures of both salts.

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 camphor-10-sulfonates may be prepared by contacting stoichiometric amounts of the acid and paroxetine free base. Preferably either the acid or base is in solution, more preferably both are in solution. Elevated temperature can 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 mobilising 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 camphor-10-sulfonic acids are very insoluble are preferably avoided. Suitable solvents for camphor-10-sulfonic acids include water, alcohols, ethyl acetate and acetic acid.

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. D-10-camphorsulfonic acid and L-10-camphorsulfonic acid are 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 crystalline paroxetine D-(+)-10-camphorsulfonate

A solution of paroxetine base in toluene (5 ml, 6.38 mmol) was added to a solution of D(+)-10-camphorsulfonic acid (1.48 g, 6.38 mmol) in methanol (20 ml). The mixture was allowed to stand at room temperature for 20 min. and the solvent was removed *in vacuo*. The residue was diluted with toluene (20 ml) and the solvent removed *in vacuo*.

Trituration with diethyl ether (*c.* 50 ml) and filtration under nitrogen gave a white solid which was washed with diethyl ether (2 × 20 ml) and dried in a vacuum desiccator.

Yield 3.50g.

Example 2: Larger scale preparation of crystalline salt.

A solution of paroxetine base in toluene (75 ml, 95.7 mmol) was added to a solution of D(+)-10-camphorsulfonic acid (22.2 g, 95.7 mmol) in methanol (300 ml). The solvent was removed *in vacuo*, the residue diluted with toluene (100 ml), and the solvent removed *in vacuo*. Trituration with diethyl ether (*c.* 350 ml) gave a white solid which was filtered, washed with diethyl ether (2 × 100 ml) and vacuum dried.

Yield 54.46g

^{1}H NMR ($CDCl_3$) showed a ratio between D(+)-10-camphorsulfonic acid and paroxetine of 1:1.

m. p. 109°C (phase change).

IR nujol mull:

Bands at 1740, 1501, 1464, 1376, 1183, 1034, 828, 768, 601, 515 cm^{-1}.

X-ray diffractogram major peaks ($CuK_{2\alpha}$):

Angle [°2θ]	Rel.Int [%]
5.965	39.9
6.400	56.5
6.665	36.8
11.880	44.0

13.765	31.5
15.055	29.1
16.200	38.4
16.945	68.0
17.970	39.2
19.360	28.5
20.825	32.8
21.630	43.0
22.270	36.8
23.365	21.2
24.255	100.0
25.190	75.4
27.105	35.1
29.720	15.5
30.360	18.6
32.360	15.7
32.800	14.9

Example 3: Preparation of crystalline paroxetine (1R)-(-)-10-camphorsulfonate

A solution of paroxetine base in toluene (5 ml, 6.38 mmol) was added to a solution of (1R)-(-)-10-camphorsulfonic acid (1.48 g, 6.38 mmol) in methanol (20 ml). The mixture was allowed to stand at room temperature for 20 minutes and the solvent was then removed *in vacuo*. The residual solid was diluted with toluene (20 ml) and the solvent removed *in vacuo*. Trituration with diethyl ether (*c*. 50 ml) and filtration under nitrogen gave a white solid which was washed with diethyl ether (2 × 20 ml) and dried at reduced pressure.

Yield 3.18g.

Example 4: Larger scale preparation of crystalline salt.

A solution of paroxetine base in toluene (66 ml, 84.16 mmol) was added to a solution of (1R)-(-)-10-camphorsulfonic acid (19.5g, 83.94 mmol) in methanol (200 ml). The mixture was allowed to stand at ambient temperature for 40 min. and then the solvent was removed by evaporation. The residual solid was triturated with diethyl ether (*c.* 350 ml), stirred at ambient temperature for 16 hours and filtered to give a white solid which was washed with diethyl ether (2 × 100 ml) and dried at reduced pressure.

Yield 43.77g

^{1}H NMR ($CDCl_3$) showed a ratio between (1R)-(-)-10-camphorsulfonic acid and paroxetine of 1:1.

m. p. 136 - 139°C.

IR nujol mull:

Bands at 1736, 1604, 1503, 1462, 1376, 1278, 1194, 1037, 827, 670, 602, 538 cm^{-1}.

X-ray diffractogram major peaks ($CuK_{2\alpha}$):

Angle [°2θ]	Rel.Int [%]
6.105	19.0
6.645	14.2
13.615	10.0
15.715	17.0
16.785	100.0
17.175	53.2
17.735	16.7
19.205	10.5
19.550	18.9
20.050	13.6
20.430	13.0
21.200	25.5
21.760	14.3
22.270	16.4
23.350	13.2
24.345	42.7
24.905	19.8
25.160	26.1
25.925	19.4
29.015	10.8
30.860	10.6

Example 5: preparation of tablets

INGREDIENTS	20 mg Tablet	30mg Tablet

Paroxetine 10-camphorsulfonate	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 10-camphorsulfonate 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 6: preparation of tablets

INGREDIENTS	10 mg Tablet	20 mg Tablet	30mg Tablet
Paroxetine 10-camphorsulfonate	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 10-camphorsulfonate, 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. A paroxetine 10-camphorsulfonate.

2. Paroxetine (D)-(+)-10-camphorsulfonate.

3. Paroxetine (1R)-(-)-10-camphorsulfonate.

4. A compound according to claim 1, 2 or 3 in non-crystalline form.

5. A compound according to claim 1, 2 or 3 in crystalline form.

6. A process for the preparation of a compound as claimed in claim 1, 2, 3 or 4 by precipitation, spray drying or freeze drying a solution of a paroxetine 10-camphorsulfonate, or by vacuum drying of oils of paroxetine10-camphorsulfonate, or solidification of melts of a paroxetine 10-camphorsulfonate.

7. A process for the preparation of a compound as claimed in claim 1, 2, 3 or 5 by crystallization or re-crystallization from a solution of a paroxetine 10-camphorsulfonate.

8. A process according to claim 6 or 7 in which the solution, oil or melt of a paroxetine 10-camphorsulfonate is prepared by treating paroxetine free base with 10-camphorsulfonic acid.

9. A method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a paroxetine 10-camphorsulfonate to a sufferer in need thereof.