CRYSTALLINE FORM OF PAROXETINE

The present invention relates to new pharmaceutically active compounds, and in particular to a novel crystalline form of paroxetine.

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.

In the literature this compound is usually isolated as an acid salt, especially the hydrochloride. Paroxetine is approved for human use as the hydrochloride salt, and has been proposed 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).

Paroxetine free base has hitherto been disclosed in the literature only as an oil, and so the free base has not itself been considered for therapeutic use, preference being given to crystalline forms which can be more easily purified and processed into dosage forms.

The present invention provides paroxetine free base in crystalline form, and the use of crystalline paroxetine free base as a therapeutic agent.

Crystalline paroxetine free base is characterised by a sharp band in the infra-red spectrum (nujol mull) at about 3330 cm^{-1}, which is not present in the infra-red spectrum of the liquid form. Samples have been prepared by Applicant which have a melting point in the range 45 to 47°C.

Paroxetine free base may be prepared by crystallisation from a solution in an organic solvent such as propan-2-ol. Crystallisation is an effective method of removing impurities and/or solvent.

A further aspect of the invention thus provides paroxetine free base which is substantially pure, for example at least 98%, preferably at least 99%, more preferably at least 99.5% pure.

A still further aspect of the invention provides paroxetine free base which is substantially free of solvent, for example containing less than 2%, preferably less than 1%, more preferably less than 0.5%, most preferably less than 0.1% solvent.

A suitable solution of the free base may be prepared by addition of a base such as triethylamine to a solution of a crystalline paroxetine salt especially the hydrochloride. Alternatively the solution may be prepared by basifying a solution of an amorphous paroxetine hydrochloride or a crystalline anhydrate or hydrated form of paroxetine hydrochloride.

The preparation of the free base and the maleic acid salt are described in Example 2 of US 4007196. The acetate salt may also be used. Procedures for forming suitable salts are described in EP-A-0223403.

Additionally the paroxetine free base may be prepared in solution by adding a base such as potassium hydroxide to a solution of a N-protected paroxetine compound such as N-phenoxycarbonyl paroxetine.

Crystallisation of paroxetine free base from solution may be initiated by conventional means such as addition of a non-solvent, evaporation of solvent, cooling a saturated solution, adding nuclei or seeds to or scraping the sides of a vessel containing a supersaturated solution of the free base or free base in the form of an oil.

Crystallisation is preferably carried out using seeds of the crystalline paroxetine free base. The seeds may be prepared by routine methods from solutions as described above.

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

The amount of paroxetine used is adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from 10 to 100 mg paroxetine (as measured in terms of the free base). More preferable the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 50mg. The most preferred amount of paroxetine in a unit dose is 20mg.

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 a product according to the invention and a pharmaceutically acceptable carrier;

the use of a product according to the 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 a product according to the invention to a person suffering from one or more of the disorders.

The invention is illustrated by the following Examples:

Example 1. Preparation of crystalline paroxetine free base.

Paroxetine hydrochloride (50 g) was dissolved in dichloromethane (250 ml) by addition of triethylamine (67.6 g) and was stirred at 20C for 12 hours. Solid triethylamine hydrochloride was filtered off and the filtrate washed twice with water (2 x 200 ml), dried with anhydrous magnesium sulfate, and evaporated to a viscous oil, removing as much solvent as possible. Propan-2-ol (165 ml) was added and the mixture warmed and stirred until a homogenous solution was formed. The solution was cooled to -10C and the side

of the vessel scratched to initiate seeding. After 12 hours, the product was filtered, washed with propan-2-ol (50 ml at -10C), and dried under vacuum.

Example 2

A solution of paroxetine free base (obtained from 80g of paroxetine hydrochloride hemihydrate) in propan-2-ol was evaporated under vacuum to remove the solvent. About 13 g of the residual oil was seeded with crystals of paroxetine free base and left to stand for 18 hours, whereupon a white crystalline solid formed.

Purity by HPLC 98.04%

Residual propan-2-ol <0.1% wt/wt

Melting point 45-47°C

IR data (Nujol mull) cm^{-1}

3331	**1488**	**934**	**653**
3053	**1330**	**920**	**620**
2812	**1284**	**888**	**592**
2749	**1187**	**849**	**572**
2734	**1144**	**828**	**541**
1630	**1112**	**801**	**528**
1605	**1102**	**777**	**490**
1510	**1038**	**760**	**470**
1503	**976**	**722**	**456**

XRD data, CuKα radiation, scanned from 3.5 to 35 degrees

Angle (degrees 2θ)	relative intensity (%)
4.1	24.7
6.1	1.1
8.2	0.5
13.2	12.3
13.6	2.3
14.4	8.9
15.5	19.0
16.1	54.1
16.6	19.5
18.0	77.3
19.9	83.5
20.8	41.0
21.1	33.8
22.3	100.0
22.8	39.6
23.5	14.1
23.9	21.0
24.5	26.8
25.6	19.2
26.3	7.2
27.4	43.0
28.0	8.4
29.2	10.7
30.5	14.6
31.1	4.6
32.1	2.5
32.9	6.2
33.8	7.0

Solid State NMR data (ppm)

~160 broad
155.2
149.5
142.5
140.5
129.6
115.7
107.6
102.6
99.2
70.8
52.7
48.6
46.5
45.3
35.1

Example 3

Paroxetine mesylate (10.0 g) was added to water (100 ml) and the mixture was stirred until a complete solution was observed. Ethyl acetate (100 ml) was added, followed by aqueous sodium hydroxide solution (10% by wt, 20 ml) and the two phase mixture stirred vigorously for 5 minutes. The layers were allowed to settle and the organic layer was separated and washed with water (100 ml). The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure with water bath heating at 40°C, until no more solvent came off, to give a pale orange-brown viscous oil.

The product was analysed by ^{1}H nmr ($CDCl_3$) and found to be consistent with paroxetine free base containing ethyl acetate, 5.6% wt/wt.

The viscous oil was seeded with crystalline paroxetine free base and allowed to stand at 21°C for 24 hours to give paroxetine free base as a crystalline solid. The product was dried under vacuum at 21°C for 6 hours.

Weight of product: 7.5 g. Ethyl acetate content 0.8% wt/wt.

The product was dried for a further 3 hours under vacuum at 21°C to give paroxetine free base containing ethyl acetate, 0.2% wt/wt (by ^{1}H nmr).

HPLC analysis: 98.7%.

Example 4

Aqueous sodium hydroxide solution (20% by wt, 20 ml) was added to a stirred suspension of paroxetine hydrochloride propan-2-ol solvate (10.0 g) in a mixture of ethyl acetate (100 ml) and water (100 ml) and the mixture stirred vigorously for 5 minutes. The layers were allowed to settle and the organic layer was seperated and washed with water (100 ml). The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure with water bath heating at 40°C for 30 minutes, when solvent removal appeared to be complete, to give a pale brown viscous oil.

The product was analysed by ^1H nmr ($CDCl_3$) and found to be consistent with paroxetine free base containing ethyl acetate, 5.5% wt/wt.

The product was seeded with crystalline paroxetine free base and allowed to stand at 21°C for 24 hours to give a pale brown crystalline solid. The product was dried under vacuum at 21°C for 6 hours.

Weight of product: 8.1 g. Ethyl acetate, 0.8% wt/wt (by ^1H nmr)

The product was dried for a further 3 hours under vacuum at 21°C to give paroxetine free base containing ethyl acetate, 0.2% wt/wt (by ^1H nmr).

Example 5

Paroxetine acetate (10.0 g) was added to water (100 ml) and the mixture was stirred until a complete solution was observed. Ethyl acetate (100 ml) was added followed by aqueous sodium hydroxide solution (10% by wt, 20 ml) and the two phase mixture stirred vigorously for 5 minutes. The layers were allowed to settle and the organic layer was separated and washed with water (100 ml). The organic layer was dried over magnesium sulfate, filtered, and the filtrate evaporated under reduced pressure with water bath heating at 40°C, until solvent removal appeared to be complete, to give a colourless viscous oil.

The product was analysed by ^1H nmr ($CDCl_3$) and found to be consistent with paroxetine free base containing ethyl acetate, 5.9% wt/wt.

The viscous oil was seeded with crystalline paroxetine free base and allowed to stand at 21°C for 24 hours. The crystalline product was dried under vacuum at 21°C for 6 hours.

Weight of product: 8.2 g. Ethyl acetate content 0.8% wt/wt (by 1H nmr).

The product was dried for a further 3 hours under vacuum at 21°C to give paroxetine free base containing ethyl acetate, 0.2% wt/wt (by ^1H nmr).

HPLC analysis: 99.2%.

Example 6

A mixture of paroxetine free base (2.0 g) and heptane 50 ml was stirred and warmed to 55°C under a nitrogen atmosphere. The resulting clear solution was decanted from a small amount of insoluble residue and cooled to 21°C under a nitrogen atmosphere with stirring over a period of 30 minutes. The mixture was cooled to 0°C with stirring continued for 10 minutes, and the resulting white crystalline solid collected by filtration and washed with cold heptane (5 ml at 0°C). The product was dried under vacuum at 21°C for 4 hours to give paroxetine free base as a free flowing white crystalline solid.

Weight of product 1.0g. Heptane content < 0.1% wt/wt (by ^{1}H nmr).
HPLC analysis: 99.6%.

IR (nujol mull): Major bands at 3328, 3051, 2811, 1627, 1603, 1509, 1502, 1489, 1329, 1283, 1248, 1218, 1188, 1159, 1143, 1113, 1101, 1038, 1027, 976, 934, 919, 888, 849, 828, 801, 776, 760, 722, 652, 621, 592, 574, 542, 527, 490, 471, 458 cm^{-1}.

X-Ray Powder Diffractogram:
Major peaks at:

Angle (degrees 2 theta)	Relative Intensity (%)
4.1	53.6
8.2	1.5
12.4	2.0
13.2	10.1
14.5	7.2
15.5	7.4
16.1	39.2
16.7	13.7
18.1	64.5
19.9	4.34
20.3	22.4
20.9	37.1
21.2	20.4
22.4	100.0
22.9	17.8
23.5	4.6
24.0	17.7

24.7	13.0
25.7	26.2
26.0	8.6
26.4	6.4
27.5	50.2
28.4	6.3
29.2	18.2
30.5	17.0
31.1	8.0
31.7	7.7
32.1	6.7
33.0	8.6
33.9	9.9

Example 7

A mixture of paroxetine free base (1.1 g) and hexane (25 ml) was stirred and warmed to 55°C under a nitrogen atmosphere. The resulting clear solution was decanted from a small amount of insoluble residue and then cooled to -5°C with stirring under a nitrogen atmosphere. After stirring at -5°C for 10 minutes a crystalline product was collected by filtration washed with cold hexane (5 ml at –5°C) and dried under vacuum at 21°C for 4 hours to give paroxetine free base as a free-flowing white crystalline solid.

Weight of product 0.52 g. Hexane content < 0.1% (by ^{1}H nmr).
HPLC analysis: 98.2%.

Example 8

Paroxetine mesylate (3.0 g) was added to water (35 ml) and the mixture was stirred until a complete solution was observed. Ethyl acetate (35 ml) was added, followed by aqueous sodium hydroxide solution (10% by wt, 7.5 ml) and the two phase mixture stirred vigorously for 5 minutes. The layers were allowed to settle and the organic layer was separated and washed with water (35 ml). The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure with water bath heating at 40°C for 30 minutes to give a pale orange-brown viscous oil. Heptane (55 ml) was added to the residue and the mixture stirred and warmed to 55°C under a nitrogen atmosphere. The resulting clear solution was

decanted from a small amount of insoluble residue and then cooled to -5°C with stirring under a nitrogen atmosphere. After stirring at -5°C for 10 minutes a crystalline product was collected by filtration washed with cold heptane (10 ml at -5°C) and dried under vacuum at 21°C for 4 hours to give paroxetine base as a free-flowing white crystalline solid.

Weight of product 1.1 g. Heptane content < 0.1% wt/wt (by ^{1}H nmr). No ethyl acetate observed by ^{1}H nmr.
HPLC analysis: 99.2%.

Example 9

A conical flask equipped with a magnetic stirring bar was charged with paroxetine acetate (40.4 g), water (400 ml) and ethyl acetate (300 ml). The mixture was stirred until all of the paroxetine acetate had dissolved and then 60 g of a 10 wt % aqueous sodium hydroxide solution was added. The suspension was stirred for a further 30 minutes. The resulting layers were separated and the aqueous layer was extracted with ethyl acetate (1 x 100 ml). The combined organic layers were washed with water (2 x 200 ml), dried over sodium sulfate and concentrated by evaporation at reduced pressure to afford an oil which upon standing slowly crystallised to yield crystalline paroxetine base.

Yield = 32.9 g

IR (Attenuated total reflection): *3331, 1628, 1605, 1500, 1488, 1466, 1439, 1395, 1329, 1283, 1246, 1219, 1185, 1159, 1143, 1113, 1102, 1036, 1027, 1015, 976, 947, 934, 920, 889, 848, 827, 815, 801, 776, 760, 722, 652, 621, 592, 572 cm^{-1}.*

CLAIMS

1. Paroxetine free base in crystalline form.

2. Crystalline paroxetine free base which is characterised by a sharp band in the infra-red spectrum (nujol mull) at about 3330 cm -1.

3. Paroxetine free base in substantially pure form.

4. Paroxetine free base which is substantially solvent-free.

5. A pharmaceutical composition comprising a product according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier.

6. Use of a product according to any one of claims 1 to 4 to manufacture a medicament for the treatment of depression.

7. A method of treating depression which comprises administering an effective amount of a product according to any one of claims 1 to 4 to a person suffering from depression.

8. A process for preparing a product according to any one of claims 1 to 4 which comprises crystallising paroxetine free base from an oil or a solution.