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The present invention is concerned with duloxetine free base in crystalline form, and also novel polymorphic forms thereof.



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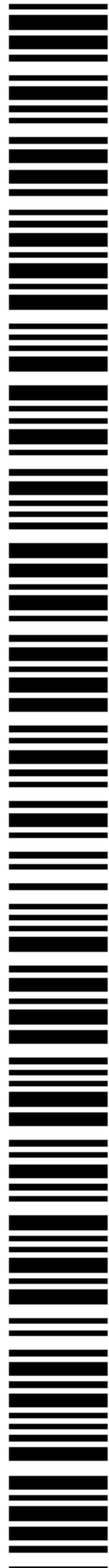
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(54) Title: CRYSTALLINE FORMS OF DULOXETINE FREE BASE

(57) Abstract: The present invention is concerned with duloxetine free base in crystalline form, and also novel polymorphic forms thereof.



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CRYSTALLINE FORMS OF DULOXETINE FREE BASE

The present invention is concerned with duloxetine free base in crystalline form, and also novel polymorphic forms thereof.

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is a dual serotonin and norepinephrine reuptake inhibitor. (+)Duloxetine has particular therapeutic utility as an anti-depressant.

Duloxetine, and the preparation thereof, is described in US patents 5023269 and 4956388, and also Tetrahedron Letters, 31, (49), 7101-04, 1990. Seven different routes of synthesis have also been reported in Drugs of the Future 2000, 25(9) 907-916. These syntheses have involved either a resolution of a key intermediate or a stereospecific reduction of a keto group to the alcohol.

Isolation of duloxetine free base in crystalline form has not, however, been achieved by any of the processes described in the reported literature and patents.

There is now provided by the present invention, however, duloxetine free base in crystalline form.

The present invention further provides processes of preparing three different polymorphic forms of duloxetine, herein designated Forms A, B and C respectively, and these three polymorphic forms represent further embodiments of the present invention. As used herein, the term "duloxetine" preferably designates (+) duloxetine.

According to the present invention, there is provided crystalline duloxetine free base, Form A, having an X-ray diffraction pattern, or substantially the same X-ray diffraction pattern, as shown in Figure 1. More particularly, crystalline duloxetine free base Form A according to the present invention can be characterised as having an X-ray diffraction pattern with characteristic peaks (2θ): 9.70, 10.88, 13.03, 15.61, 19.19, 19.55, 19.88, 21.94, 22.16, 26.95 and 27.76°.

Further characterising data for crystalline duloxetine free base Form A according to the present invention as obtained by X-ray diffraction is shown in following table 1.

Table 1

Peak No.	2 θ (deg)	FWHM (deg)	d (Å)	Intensity (Counts)	I/I ₀
1	9.700	0.212	9.1103	1107	27
2	10.880	0.188	8.1248	1372	34
3	12.050	0.165	7.3384	643	16
4	12.290	0.188	7.1956	721	18
5	13.030	0.294	6.7886	1548	38
6	13.910	0.129	6.3610	431	11
7	15.610	0.235	5.6719	2432	59
8	17.300	0.188	5.1214	652	16
9	17.770	0.318	4.9870	443	11
10	18.410	0.118	4.8151	599	15
11	19.030	0.153	4.6596	2632	64
12	19.190	0.235	4.6211	3098	75
13	19.550	0.176	4.5368	2429	59
14	19.880	0.235	4.4622	4143	100
15	20.170	0.165	4.3987	1332	33
16	20.910	0.271	4.2447	1119	27
17	21.200	0.200	4.1873	1127	28
18	21.940	0.271	4.0477	3684	89
19	22.160	0.200	4.0080	3494	85
20	22.730	0.106	3.9088	584	15
21	23.290	0.165	3.8160	713	18
22	23.420	0.129	3.7951	673	17
23	23.660	0.165	3.7572	718	18
24	24.350	0.235	3.6523	2351	57
25	24.810	0.224	3.5856	969	24
26	25.280	0.129	3.5200	950	23
27	25.460	0.188	3.4955	1042	26

28	26.070	0.106	3.4151	533	13
29	26.950	0.247	3.3055	1527	37
30	27.360	0.188	3.2569	1078	27
31	27.760	0.247	3.2109	1653	40
32	28.700	0.118	3.1078	638	16
33	29.460	0.318	3.0293	916	23
34	29.930	0.365	2.9828	1118	27
35	30.970	0.106	2.8850	763	19
36	31.130	0.188	2.8705	769	19
37	31.590	0.294	2.8298	1038	26
38	33.170	0.129	2.6985	575	14
39	33.520	0.106	2.6711	646	16
40	33.700	0.176	2.6573	668	17
41	33.940	0.118	2.6390	626	16
42	34.860	0.306	2.5715	685	17
43	36.370	0.118	2.4681	816	20
44	36.740	0.271	2.4441	1052	26
45	37.150	0.118	2.4180	954	24
46	37.330	0.118	2.4068	953	23
47	39.710	0.165	2.2679	806	20
48	40.090	0.176	2.2472	738	18
49	40.700	0.118	2.2149	658	16
50	41.050	0.153	2.1969	766	19
51	41.610	0.106	2.1686	883	22
52	41.690	0.141	2.1646	962	24
53	42.290	0.118	2.1353	770	19
54	42.420	0.129	2.1290	818	20
55	42.720	0.165	2.1148	692	17

According to the present invention, there is provided crystalline duloxetine free base, Form B, having an X-ray diffraction pattern, or substantially the same X-ray diffraction pattern, as shown in Figure 2. More particularly, crystalline duloxetine free base Form B according to the present invention can be characterised as having an X-ray diffraction pattern with characteristic peaks (2θ): 4.98, 9.96, 11.18, 12.58, 15.32, 18.98, 20.04, 20.62, 22.32, 22.44, 27.28 and 30.30°.

Further characterising data for crystalline duloxetine free base Form B according to the present invention as obtained by X-ray diffraction is shown in following table 2.

Table 2

Peak No.	2θ (deg)	FWHM (deg)	d (Å)	Intensity (Counts)	I/I ₀
1	4.980	0.188	17.7294	915	17
2	9.960	0.212	8.8731	1269	23
3	11.180	0.235	7.9074	2278	41
4	11.580	0.212	7.6352	749	14
5	12.580	0.259	7.0304	1131	21
6	14.580	0.259	6.0702	576	11
7	15.320	0.282	5.7786	1767	32
8	17.860	0.118	4.9621	640	12
9	17.980	0.141	4.9293	690	13
10	18.980	0.353	4.6717	3036	55
11	20.040	0.235	4.4270	5583	100
12	20.620	0.282	4.3037	1716	31
13	21.000	0.306	4.2267	1383	25
14	22.320	0.306	3.9796	4190	76
15	22.440	0.141	3.9586	3576	65
16	23.220	0.141	3.8274	1435	26
17	23.340	0.188	3.8080	1498	27
18	23.840	0.259	3.7292	1382	25

19	24.560	0.118	3.6215	726	13
20	25.000	0.165	3.5588	1010	19
21	25.160	0.400	3.5365	1089	20
22	27.280	0.400	3.2663	2364	43
23	27.760	0.306	3.2109	1996	36
24	30.300	0.329	2.9473	2574	47
25	30.880	0.118	2.8932	944	17
26	31.140	0.118	2.8696	921	17
27	31.840	0.141	2.8081	985	18
28	32.000	0.165	2.7945	1003	18
29	32.180	0.118	2.7792	822	15
30	36.760	0.212	2.4428	871	16
31	37.120	0.118	2.4199	1095	20
32	37.420	0.306	2.4012	1360	25
33	38.380	0.141	2.3433	860	16
34	38.560	0.259	2.3328	890	16

According to the present invention, there is provided crystalline duloxetine free base, Form C, having an X-ray diffraction pattern, or substantially the same X-ray diffraction pattern, as shown in Figure 3. More particularly, crystalline duloxetine free base Form C according to the present invention can be characterised as having an X-ray diffraction pattern with characteristic peaks (2θ): 12.23, 13.49, 16.90, 18.28, 20.37, 22.61, 27.22, 27.40 and 30.65°.

Further characterising data for crystalline duloxetine free base Form C according to the present invention as obtained by X-ray diffraction is shown in following table 3.

Table 3

Peak No.	2θ (deg)	FWHM (deg)	d (Å)	Intensity (Counts)	I/I ₀
1	11.160	0.306	7.9215	1911	51

2	12.230	0.318	7.2308	919	25
3	12.570	0.224	7.0360	872	23
4	13.490	0.400	6.5581	1419	38
5	15.050	0.341	5.8817	640	17
6	16.900	0.282	5.2417	850	23
7	18.280	0.400	4.8490	1717	46
8	18.840	0.388	4.7061	1646	44
9	19.500	0.106	4.5483	941	25
10	19.660	0.129	4.5117	1141	30
11	20.370	0.424	4.3560	3573	94
12	20.810	0.271	4.2649	1890	50
13	21.710	0.106	4.0900	637	17
14	22.610	0.424	3.9292	3808	100
15	23.080	0.212	3.8503	1206	32
16	23.850	0.247	3.7277	725	20
17	25.140	0.318	3.5393	958	26
18	25.570	0.318	3.4807	1065	28
19	27.220	0.141	3.2733	1534	41
20	27.400	0.400	3.2522	1778	47
21	27.830	0.129	3.2030	786	21
22	28.030	0.129	3.1806	704	19
23	28.440	0.224	3.1356	696	19
24	29.730	0.153	3.0024	696	19
25	30.180	0.129	2.9587	989	26
26	30.650	0.471	2.9144	1636	43
27	32.340	0.129	2.7658	746	20
28	32.530	0.224	2.7501	836	22
29	34.420	0.200	2.6033	708	19
30	34.900	0.118	2.5686	760	20
31	35.080	0.188	2.5558	787	21
32	36.730	0.235	2.4447	815	22

33	36.990	0.106	2.4281	785	21
34	37.230	0.271	2.4130	812	22
35	40.430	0.106	2.2291	796	21
36	40.600	0.176	2.2202	813	22
37	42.970	0.306	2.1030	1057	28

There is also provided by the present invention a pharmaceutically acceptable salt of duloxetine, which pharmaceutically acceptable salt is prepared from duloxetine free base in crystalline form as provided by the present invention. Preferred pharmaceutically acceptable salts of duloxetine as provided by the present invention include duloxetine hydrochloride and duloxetine oxalate, especially duloxetine hydrochloride.

A pharmaceutically acceptable salt of duloxetine as provided by the present invention is preferably at least about 99.5% w/w pure.

Crystalline duloxetine free base as provided by the present invention can in turn be prepared from salts of duloxetine, such as the oxalate salt, hydrochloride salt, di-p-toluyll tartarate salt, or any other suitable salt. According to the present invention, there is further provided a process of preparing crystalline duloxetine free base, which process comprises dissolving or suspending a salt of duloxetine in a suitable medium, such as water, neutralizing with a suitable base, such as an alkali metal hydroxide, typically sodium hydroxide, extracting the thus formed duloxetine free base into a suitable solvent, replacing the solvent with a non-solvent, and thus isolating duloxetine free base in crystalline form.

It is also possible to interconvert distinct polymorphic forms of crystalline duloxetine free base as provided by the present invention. There is, therefore, further provided by the present invention an interconversion process, whereby a second polymorphic form of crystalline duloxetine free base is prepared from a distinct first polymorphic form of crystalline duloxetine free base. Suitably, the first polymorphic form of crystalline duloxetine free base which is employed as the starting material is dissolved or suspended in a suitable lower alcohol solvent, preferably methanol, and the second polymorphic form is re-crystallized therefrom. Preferably, this interconversion process is employed for the preparation of crystalline duloxetine free base Form B from Form A substantially as hereinafter described in further detail.

The preparation of crystalline duloxetine free base according to the present invention is advantageous in that crystalline duloxetine free base can be employed as a useful intermediate in the preparation of highly pure pharmaceutically acceptable salts of duloxetine, in particular duloxetine oxalate or hydrochloride. Pharmaceutically acceptable salts of duloxetine prepared from crystalline duloxetine free base can exhibit beneficial properties, for example, duloxetine hydrochloride prepared from crystalline duloxetine free base as provided by the present invention is more resistant to degradation than duloxetine hydrochloride prepared by conventional methods known from the prior art.

According to the present invention there is further provided a process of preparing crystalline duloxetine free base Form A, which process comprises suspending or dissolving a duloxetine salt, such as the hydrochloride or di-p-toluyyl tartarate salt of duloxetine, in water, neutralizing with a base, such as an alkali metal hydroxide, typically sodium hydroxide, extracting into a substantially water immiscible solvent, such as dichloromethane, concentrating the substantially water immiscible solvent, replacing the substantially water immiscible solvent with acetone and thus isolating duloxetine free base Form A in crystalline form. Crystalline duloxetine free base Form A is characterized by powder x-ray diffraction substantially as shown in Figure 1.

According to the present invention there is further provided a process of preparing crystalline duloxetine free base Form B, which process comprises dissolving or suspending a first polymorphic form of crystalline duloxetine free base, typically duloxetine free base Form A, in a suitable lower alcohol solvent, preferably methanol, and recrystallizing duloxetine free base Form B therefrom. Crystalline duloxetine free base Form B is characterized by powder x-ray diffraction substantially as shown in Figure 2.

According to the present invention there is further provided a process of preparing crystalline duloxetine free base Form C, which process comprises suspending or dissolving a duloxetine salt, such as the hydrochloride or di-p-toluyyl tartarate salt of duloxetine, in water, neutralizing with a base, such as an alkali metal hydroxide, typically sodium hydroxide, extracting into a substantially water immiscible solvent, such as dichloromethane, concentrating the substantially water immiscible solvent, replacing the substantially water immiscible solvent with isopropanol and thus isolating duloxetine free base Form C in crystalline form. Crystalline duloxetine free base Form C is characterized by powder x-ray diffraction substantially as shown in Figure 3.

There is also provided by the present invention a process of preparing a pharmaceutically acceptable salt of duloxetine, which process comprises dissolving or suspending crystalline duloxetine free base as provided by the present invention in a water miscible solvent, such as acetone, adding a pharmaceutically acceptable acid thereto required to form the pharmaceutically acceptable salt, and isolating the required pharmaceutically acceptable salt of duloxetine in crystalline form. Any of polymorphic forms A, B or C of crystalline duloxetine free base as provided by the present invention can be employed as crystalline duloxetine free base starting material for the above process of preparing a pharmaceutically acceptable salt of duloxetine.

Suitable acid addition salts which can be prepared from crystalline duloxetine free base according to the present invention include those formed with pharmaceutically acceptable organic or inorganic acids and are well known to those of skill in the art. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as paratoluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonates, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts. Preferred pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as oxalic acid and maleic acid. A particularly preferred acid addition salt is the hydrochloride.

As noted above, duloxetine is a dual serotonin and norepinephrine reuptake inhibitor. The present invention further provides a pharmaceutically acceptable formulation for administering to a patient, including humans, suffering from, or susceptible to, a disease state

prevented, ameliorated or eliminated by the administration of a serotonin and / or norepinephrine reuptake inhibitor, which formulation comprises a therapeutically effective amount of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

As used herein, the term "therapeutically effective amount" means an amount of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, which is capable of preventing, ameliorating or eliminating a disease state for which administration of a serotonin and / or norepinephrine reuptake inhibitor is indicated.

By "pharmaceutically acceptable formulation" it is meant that the carrier, diluent or excipient is compatible with crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, and not deleterious to a recipient thereof.

Pharmaceutical formulations as provided by the present invention can be prepared by known procedures using well known and readily available ingredients. In preparation of formulations as provided by the present invention, crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, can be mixed with a carrier, diluent or excipient therefor. Formulations as provided by the present invention can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol, ointments containing, for example, up to 10% by weight of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders. In particular, capsules are suitable formulations for use in accordance with the present invention, which can typically include

coated non pareil seeds substantially as hereinafter illustrated in further detail by reference to the Examples.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained or delayed release of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, after administration to the patient by employing procedures well known in the art.

The formulations are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described,. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

There is also provided by the present invention crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, for use in therapy.

The present invention further provides crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of a serotonin and / or norepinephrine reuptake inhibitor as described herein.

The present invention also provides a method of treating a disease state prevented, ameliorated or eliminated by the administration of a serotonin and / or norepinephrine reuptake inhibitor in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described.

A variety of physiologic functions have been shown to be subject to influence by brain serotoninergic and norepinephrinergic neural systems. As such, crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, of the present invention, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, has utility in the treatment of a variety of disorders in mammals associated with these neural systems such as obesity, depression, alcoholism, pain, loss of memory, anxiety and smoking. In particular, crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, has utility in the treatment of depression.

In a preferred aspect of the present invention, therefore, there is provided crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, for use in the manufacture of a medicament for the treatment of depression.

In a preferred aspect of the present invention, therefore, there is also provided a method of treating depression in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described.

The particular dose of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, administered according to this invention will of course be determined by the particular

circumstances surrounding the case, the route of administration, the particular condition being treated, and similar considerations. Crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described, can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes. A typical daily dose will contain from about 0.01 mg/kg to about 20 mg/kg of crystalline duloxetine free base, optionally as any of Forms A, B or C, substantially as hereinbefore described, of the present invention, or a pharmaceutically acceptable salt of duloxetine as provided by the present invention substantially as hereinbefore described,. Preferred daily doses will be about 0.05 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg.

The present invention will now be further illustrated by the Figures and following Examples, which do not limit the scope of the invention in any way.

Figure 1 is a powder X-ray diffraction pattern for crystalline duloxetine free base Form A.

Figure 2 is a powder X-ray diffraction pattern for crystalline duloxetine free base Form B.

Figure 3 is a powder X-ray diffraction pattern for crystalline duloxetine free base Form C.

The above referred to X-ray diffraction patterns were obtained on a Rigaku Miniflex X-ray Diffractometer equipped with a Cu K α source and a scintillation counter detector. The scan speed was 2 degrees per minute and the range was from 3 to 45 degrees.

Examples

Reference Example - Preparation of duloxetine (-)-di-p-toluyl tartarate

1. Racemic Duloxetine (100gm) was added to methanol (200ml).
2. (-) Di-p-Toluoyl-L-Tartaric acid (130gm) was added lotwise at 25-30°C.
3. The contents were heated to 60-65°C and maintained for 1 hour at 60-65°C.
4. Methanol was completely distilled under vacuum at 45-50°C.

5. Acetone (1.5lit) was added to the residue and stirred for 3 hours at 25-30°C.
6. The solids were filtered, washed with acetone (100ml) and dried under vacuum at 45-50°C to give the title compound (80gm).

Example 1

Preparation of duloxetine free base (Form A)

1. To Duloxetine (-) Di-p-toluytl tartarate (100gm), prepared by the above Reference Example, was charged water (1lit), followed by stirring at 25-30°C for 15 minutes.
2. Slowly, lye solution (8gm sodium hydroxide in 50ml water) was added and stirred for 10-15 minutes at 25-30°C.
3. The mixture was extracted twice with methylene chloride (500ml).
4. Combined methylene chloride layers were washed with water (100ml).
5. Methylene chloride was distilled out under vacuum at a temperature less than 40°C, and stripped off with acetone (50ml).
6. The residue was stirred with acetone (1lit) at room temperature for 1 hour.
7. The solids were filtered and dried under vacuum at 50-55°C to obtain duloxetine base Form A (25gm).

Example 2

Preparation of duloxetine free base (Form B)

1. Duloxetine free base Form A (10g) was dissolved in methanol (250ml) at 55-60°C.
2. The solution was cooled to room temperature.
3. The solution was stirred at room temperature for 1 hour.
4. The solids were filtered and washed with methanol (10ml).
5. The solids were dried under vacuum at 50-55°C to give duloxetine free base Form B (7gm).

Example 3

Preparation of duloxetine free base (Form C)

1. To Duloxetine (-) Di-p-toluyyl tartarate (100gm), prepared by the above Reference Example, was charged water (1lit), followed by stirring at 25-30°C for 15 minutes.
2. Slowly, lye solution (8gm sodium hydroxide in 50ml water) was added and stirred for 10-15 minutes at 25-30°C.
3. The mixture was extracted twice with methylene chloride (500ml).
4. Combined methylene chloride layers were washed with water (100ml).
5. Methylene chloride was distilled out under vacuum at a temperature less than 40°C, and stripped off with isopropanol (50ml).
6. The residue was stirred with isopropanol (500 ml) at room temperature for 1 hour.
7. The solids were filtered and dried under vacuum at 50-55°C to obtain duloxetine free base Form C (25gm).

Example 4

Preparation of duloxetine hydrochloride

1. Duloxetine free base Form A (25gm) and acetone (250ml) were stirred for 15 minutes at 25-30°C
2. The pH of the mixture was adjusted to 2.0-3.0 using 20% isopropanolic HCl at 25-30°C.
3. The solids were filtered, washed with acetone (100ml) and dried under vacuum at 50-55°C to give duloxetine hydrochloride (25gm).

Example 5

Preparation of duloxetine hydrochloride

In a manner analogous to Example 4, duloxetine free base Form B was converted to duloxetine hydrochloride.

Example 6

Duloxetine Capsules (Duloxetine base according to the present invention) – 60 mg

Sr. No	Ingredients	Qty (mg/capsule)
I.	Drug Loading	
1.	Duloxetine	60 mg
2.	Non pareil seeds	110 – 140 mg
3.	Hydroxy propyl methyl cellulose	2.0 – 4.0
4.	Talc	1.5 – 2.8
5.	Colloidal Silicon Dioxide	0.5 – 1.5
6.	Isopropyl Alcohol	q.s
7.	Methylene chloride	q.s
II.	Seal Coating	
1.	Hydroxy propyl methyl cellulose	7 – 10
2.	Propylene Glycol	2 – 4
3.	Talc	2 - 4
4.	Isopropyl Alcohol	q.s
5.	Methylene chloride	q.s
III.	Eudragit Coating	
1.	Eudragit L 100 - 55	10 – 20
2.	Talc	4 – 8
3.	Titanium dioxide	2 – 5
4.	Triethyl citrate	1.5 – 3.0
5.	Sodium hydroxide	0.1 – 0.5
6.	Purified water	q.s

Manufacturing process – Drug loading in glatt GPCG 1.1 by bottom spray.

Example 7

Duloxetine Capsules (Duloxetine base according to the present invention) – 60 mg

Sr. No	Ingredients	Qty (mg/capsule)
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I.	Drug Loading	
1.	Duloxetine	60 mg
2.	Non pareil seeds	110- 140
3.	Hydroxy propyl methyl cellulose	2.0-4.0
4.	Talc	1.5 – 2.5
5.	Colloidal Silicon Dioxide	0.5 – 1.5
6.	Mannitol	60 mg
II.	Seal Coating	
1.	Hydroxy propyl methyl cellulose	7 – 10
2.	Mannitol	3.0 - 9.0
3.	Talc	3.5 - 4.5
4.	Propylene Glycol	1.5 - 2.5
5.	Purified water	q.s
III.	Eudragit Coating	
1.	Eudragit	9 – 11
2.	Talc	2.0 – 4.0
3.	Titanium dioxide	1.0 – 3.0
4.	Tiethyl citrate	1.0-3.0
5.	Sodium hydroxide	0.1-0.3
6.	Purified water	q.s

Manufacturing process – Drug loading in rotar coater.

Example 8

Duloxetine Hydrochloride Capsules (Duloxetine hydrochloride as provided according to the present invention) – 60 mg

Sr. No	Ingredients	Qty (mg/capsule)
I.	Drug Loading	
1.	Duloxetine Hydrochloride	60 mg

2.	Non pareil seeds	110 – 140 mg
3.	Hydroxy propyl methyl cellulose	2.0 – 4.0
4.	Talc	1.5 – 2.8
5.	Colloidal Silicon Dioxide	0.5 – 1.5
6.	Isopropyl Alcohol	q.s
7.	Methylene chloride	q.s
II.	Seal Coating	
1.	Hydroxy propyl methyl cellulose	7 – 10
2.	Propylene Glycol	2 – 4
3.	Talc	2 - 4
4.	Isopropyl Alcohol	q.s
5.	Methylene chloride	q.s
III.	Eudragit Coating	
1.	Eudragit L 100 - 55	10 – 20
2.	Talc	4 – 8
3.	Titanium dioxide	2 – 5
4.	Tiethyl citrate	1.5 – 3.0
5.	Sodium hydroxide	0.1 – 0.5
6.	Purified water	q.s

Manufacturing process – Drug loading in glatt GPCG 1.1 by bottom spray.

Example 9

Duloxetine Hydrochloride Capsules (Duloxetine hydrochloride as provided according to the present invention) – 60 mg

Sr. No	Ingredients	Qty (mg/capsule)
I.	Drug Loading	
1.	Duloxetine Hydrochloride	60 mg
2.	Non pareil seeds	110- 140

3.	Hydroxy propyl methyl cellulose	2.0-4.0
4.	Talc	1.5 – 2.5
5.	Colloidal Silicon Dioxide	0.5 – 1.5
6.	Mannitol	60 mg
II.	Seal Coating	
1.	Hydroxy propyl methyl cellulose	7 – 10
2.	Mannitol	3.0 - 9.0
3.	Talc	3.5 - 4.5
4.	Propylene Glycol	1.5 - 2.5
5.	Purified water	q.s
III.	Eudragit Coating	
1.	Eudragit	9 – 11
2.	Talc	2.0 – 4.0
3.	Titanium dioxide	1.0 – 3.0
4.	Tiethyl citrate	1.0-3.0
5.	Sodium hydroxide	0.1-0.3
6.	Purified water	q.s

Manufacturing process – Drug loading in rotar coater.

Example 10

Forced degradation study on duloxetine hydrochloride produced according to the prior art (Preparation 2, US 5,491,243) and duloxetine hydrochloride produced from crystalline duloxetine free base according to the present invention

STRESS CONDITION	DULOXETINE HCl (from prior art)			DULOXETINE HCl (from free base)		
	Description	SMI	Total imp	Description	SMI	Total imp
1. Heat /UV						
a) Before exposure to heat or light	White powder	0.20%	0.48%	White powder	0.05%	0.11%
b) 45°C	Cream coloured powder	0.19%	0.65%	White powder	0.07%	0.12%
c) 60°C	Light pink coloured powder	0.19%	0.70%	White powder	0.07%	0.12%
d) UV	Light brown coloured powder	0.19%	0.66%	Cream coloured powder	0.06%	0.11%

“SMI” - Single maximum impurity

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE
PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS

1. Duloxetine free base in crystalline form.
2. Crystalline duloxetine free base, Form A, having an X-ray diffraction pattern as shown in Figure 1.
3. Crystalline duloxetine free base, Form A, characterised as having an X-ray diffraction pattern with characteristic peaks (2θ): 9.70, 10.88, 13.03, 15.61, 19.19, 19.55, 19.88, 21.94, 22.16, 26.95 and 27.76°.
4. Crystalline duloxetine free base, Form B, having an X-ray diffraction pattern as shown in Figure 2.
5. Crystalline duloxetine free base, Form B, characterised as having an X-ray diffraction pattern with characteristic peaks (2θ): 4.98, 9.96, 11.18, 12.58, 15.32, 18.98, 20.04, 20.62, 22.32, 22.44, 27.28 and 30.30°.
6. Crystalline duloxetine free base, Form C, having an X-ray diffraction pattern as shown in Figure 3.
7. Crystalline duloxetine free base, Form C, characterised as having an X-ray diffraction pattern with characteristic peaks (2θ): 12.23, 13.49, 16.90, 18.28, 20.37, 22.61, 27.22, 27.40 and 30.65°.
8. A process of preparing crystalline duloxetine free base according to any one of claims 1 to 7, the process comprising converting a duloxetine salt to crystalline duloxetine free base.
9. A process according to claim 8, wherein the salt is selected from the group consisting of duloxetine oxalate, duloxetine hydrochloride and duloxetine di-p-toluyyl tartarate salt.

10. A process of preparing crystalline duloxetine free base according to any one of claims 1 to 7, which process comprises dissolving or suspending a salt of duloxetine in a suitable medium, neutralizing with a suitable base, extracting the thus formed duloxetine free base into a suitable solvent, replacing the solvent with a non-solvent, and thus isolating duloxetine free base in crystalline form.
11. A process according to claim 10, wherein said medium comprises water.
12. A process according to claim 10 or 11, wherein said base comprises an alkali metal hydroxide.
13. A process according to claim 12, wherein said alkali metal hydroxide is sodium hydroxide.
14. A polymorph interconversion process for preparing crystalline duloxetine free base according to any one of claims 1 to 7, which process comprises converting a distinct first polymorphic form of crystalline duloxetine free base to a second polymorphic form of crystalline duloxetine free base.
15. A process according to claim 14, wherein the first polymorphic form of crystalline duloxetine free base employed as the starting material of the interconversion process is dissolved in a suitable C₁₋₃ alcohol solvent, and the second polymorphic form is re-crystallized therefrom.
16. A process according to claim 15, wherein said C₁₋₃ alcohol solvent is methanol.
17. A process according to any one of claims 14 to 16, wherein crystalline duloxetine free base Form A is converted to crystalline duloxetine free base Form B.
18. A process of preparing crystalline duloxetine free base Form A according to claim 2 or 3, which process comprises suspending or dissolving a duloxetine salt in water, neutralizing with a base, extracting into a substantially water immiscible solvent,

concentrating the substantially water immiscible solvent, replacing the substantially water immiscible solvent with acetone and thus isolating duloxetine free base Form A in crystalline form.

19. A process according to claim 18, wherein said duloxetine salt is duloxetine hydrochloride or duloxetine di-p-toluy l tartarate.

20. A process according to claim 18 or 19, wherein said base is an alkali metal hydroxide.

21. A process according to claim 20, wherein said alkali metal hydroxide is sodium hydroxide.

22. A process according to any one of claims 18 to 21, wherein said water immiscible solvent is dichloromethane.

23. A process of preparing crystalline duloxetine free base Form B according to claim 4 or 5, which process comprises dissolving or suspending duloxetine free base Form A in a C₁₋₃ alcohol solvent and recrystallizing duloxetine free base Form B therefrom.

24. A process according to claim 23, wherein said C₁₋₃ alcohol solvent is methanol.

25. A process of preparing crystalline duloxetine free base Form C according to claim 6 or 7, which process comprises suspending or dissolving a duloxetine salt in water, neutralizing with a base, extracting into a substantially water immiscible solvent, concentrating the substantially water immiscible solvent, replacing the substantially water immiscible solvent with isopropanol and thus isolating duloxetine free base Form C in crystalline form.

26. A process according to claim 25, wherein said duloxetine salt is duloxetine hydrochloride or duloxetine di-p-toluy l tartarate.

27. A process according to claim 25 or 26, wherein said base is an alkali metal hydroxide.

28. A process according to claim 27, wherein said alkali metal hydroxide is sodium hydroxide.

29. A process according to any one of claims 25 to 28, wherein said water immiscible solvent is dichloromethane.

30. A process of preparing a pharmaceutically acceptable salt of duloxetine, which process comprises dissolving or suspending crystalline duloxetine free base according to any one of claims 1 to 7 in a water miscible solvent, adding a pharmaceutically acceptable acid thereto required to form the pharmaceutically acceptable salt, and isolating the required pharmaceutically acceptable salt of duloxetine in crystalline form.

31. A process according to claim 30, wherein said crystalline duloxetine free base is Form A.

32. A process according to claim 30, wherein said crystalline duloxetine free base is Form B.

33. A process according to claim 30, wherein said crystalline duloxetine free base is Form C.

34. A process according to any one of claims 30 to 33, wherein said water miscible solvent is acetone.

35. A process according to any one of claims 30 to 34, wherein said salt is duloxetine oxalate.

36. A process according to any one of claims 30 to 34, wherein said salt is duloxetine hydrochloride.

37. A pharmaceutically acceptable formulation for administering to a patient, including humans, suffering from, or susceptible to, obesity, depression, alcoholism, pain, loss of

memory, anxiety or smoking, which formulation comprises a therapeutically effective amount of crystalline duloxetine free base according to any one of claims 1 to 7 together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

38. Crystalline duloxetine free base according to any one of claims 1 to 7 for use in the treatment of obesity, depression, alcoholism, pain, loss of memory, anxiety or smoking.

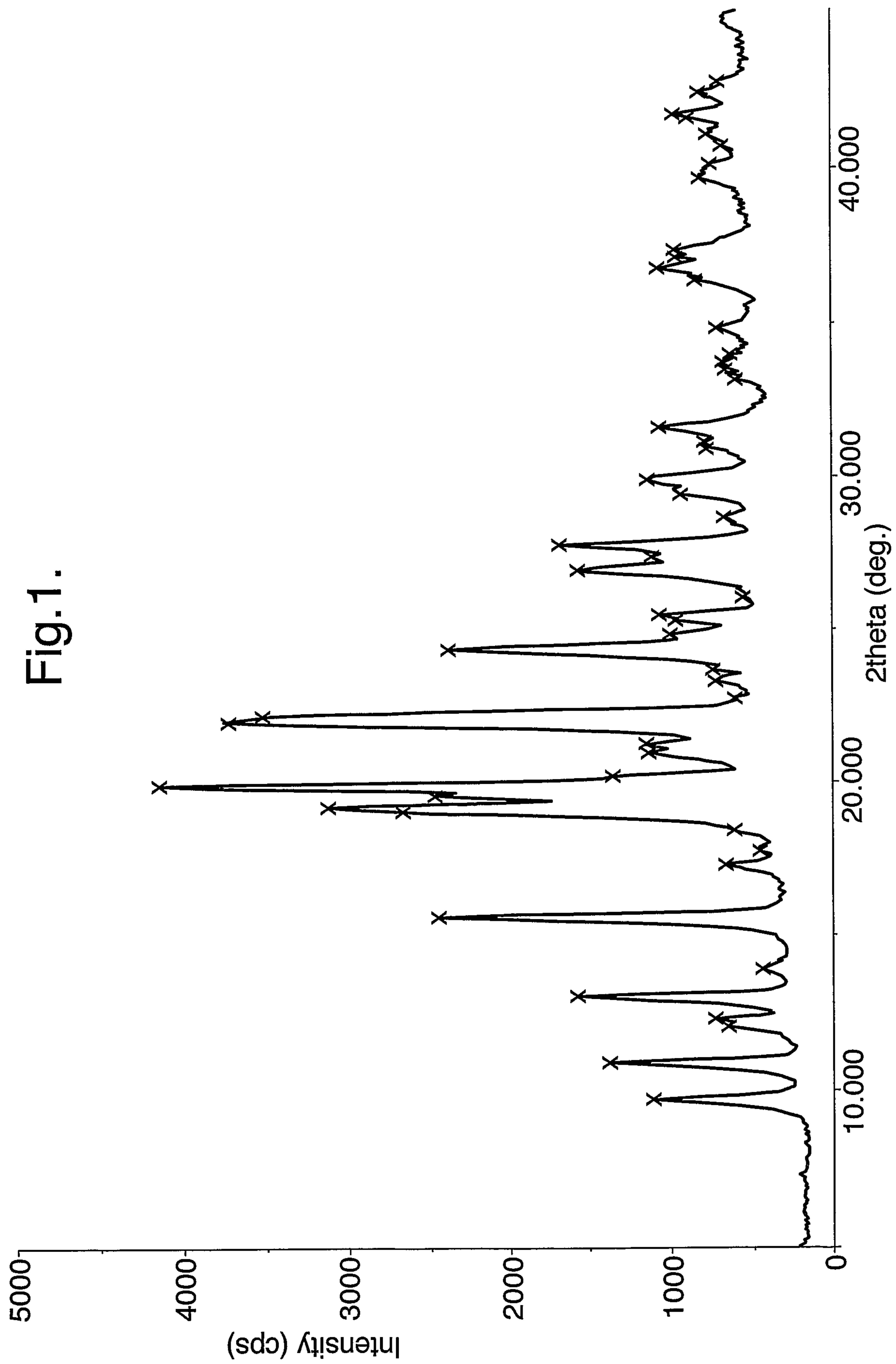
39. Crystalline duloxetine free base according to any one of claims 1 to 7 for use in the manufacture of a medicament for the treatment of obesity, depression, alcoholism, pain, loss of memory, anxiety or smoking.

40. Crystalline duloxetine free base according to any one of claims 1 to 7 for use in the manufacture of a medicament for the treatment of depression.

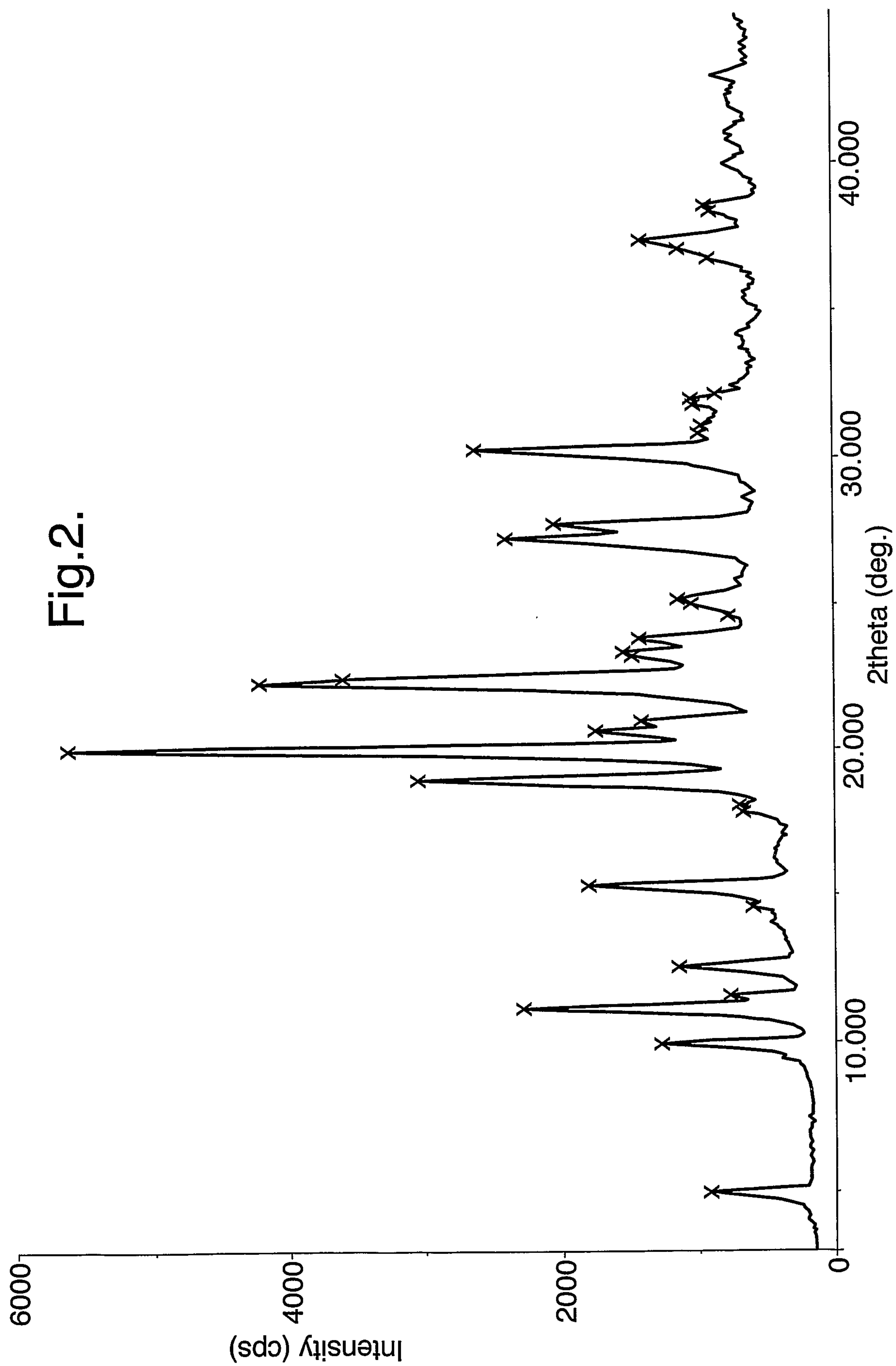
41. A use of crystalline duloxetine free base according to any one of claims 1 to 7 for the treatment of obesity, depression, alcoholism, pain, loss of memory, anxiety or smoking.

42. A use of crystalline duloxetine free base according to any one of claims 1 to 7 for the treatment of depression.

1/3



2/3



3/3

