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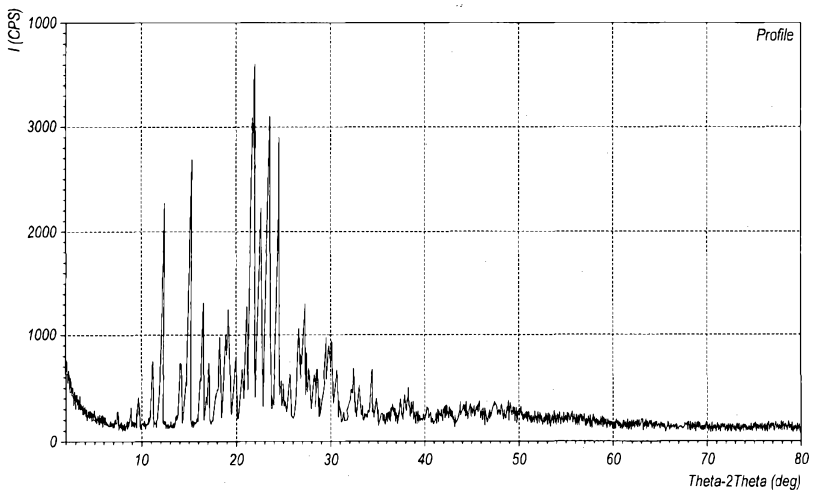
(54) Title: CRYSTALLINE DULOXETINE HYDROCHLORIDE



(57) Abstract: Crystalline duloxetine hydrochloride, compositions containing the same and methods for the production thereof.

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CRYSTALLINE DULOXETINE HYDROCHLORIDE

The present invention relates to crystalline duloxetine hydrochloride, to compositions containing the same and to methods for the formation thereof.

Duloxetine hydrochloride is a potent dual reuptake inhibitor of serotonin and norepinephrine possessing comparable affinities in binding to serotonin and norepinephrine transport sites. Duloxetine hydrochloride has, therefore, been implicated in the treatment of various diseases related to these effects. For example, duloxetine hydrochloride is the active ingredient of the antidepressant drug Cymbalta™. It is also used to target pain related to diabetic neuropathy and stress urinary incontinence.

Preparation of duloxetine hydrochloride has been disclosed elsewhere, for example in US 5,023,269. Crystalline forms of the free base of duloxetine and their preparation have been reported in WO2005/108386. The amorphous form of duloxetine hydrochloride salt together with its preparation has been reported in WO2005/019199.

There is no generally applicable method for preparing a crystalline form of an amorphous drug. For example, it is impossible to know without experimentation whether any crystalline form of a given compound exists. Even once it has been found that a drug can be crystallised, extensive experimentation is usually required before a repeatable and quantifiable process is identified from which the crystalline form can be isolated. In this respect, several independently variable conditions, such as the nature of solvent, concentration of solvent and temperature, must be correctly identified in order to elucidate a suitable process. Indeed, to date, there have been no reports describing isolation or production of crystalline duloxetine hydrochloride.

It is, therefore, an object of the present invention to provide crystalline forms of duloxetine hydrochloride together with methods for the production thereof.

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Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

Summary of the Invention

According to a first aspect the present invention provides a method for the preparation of crystalline duloxetine hydrochloride which exhibits an X-ray diffraction pattern comprising peaks expressed in degrees two-theta at 11.99 ± 0.2, 14.78 ± 0.2, 21.44 ± 0.2, 22.16 ± 0.2, 23.12 ± 0.2 and 24.12 ± 0.2, the method comprising:-

(a) dissolving duloxetine in a first organic solvent to form a first solution;

(b) combining the first solution with a second organic solvent solution comprising HCl to form a second solution;

(c) allowing duloxetine hydrochloride to crystallize out from the solution; and

(d) collecting the crystallized duloxetine hydrochloride,

wherein the first organic solvent is an aromatic hydrocarbon.

The degree of error is preferably ± 0.1.

Preferably the crystalline duloxetine hydrochloride exhibits an X-ray diffraction pattern comprising peaks expressed in degrees two-theta at approximately 11.02 ± 0.2, 11.99 ± 0.2, 13.94 ± 0.2, 14.78 ± 0.2, 16.19 ± 0.2, 16.87 ± 0.2, 18.0 ± 0.2, 18.8 ± 0.2, 19.77 ± 0.2, 20.84 ± 0.2, 21.44 ± 0.2, 22.16 ± 0.2, 23.12 ± 0.2, 24.12 ± 0.2, 26.34 ± 0.2, 26.76 ± 0.2, 27.0 ± 0.2, 27.45 ± 0.2, 29.24 ± 0.2, 29.58 ± 0.2, 29.92 ± 0.2, 30.4 ± 0.2, 32.2 ± 0.2, 32.82 ± 0.2 and 34.17 ± 0.2. The degree of error is preferably ± 0.1.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

There is also provided by the present invention, crystalline duloxetine hydrochloride which exhibits an X-ray diffraction pattern substantially the same as shown in figure 1.

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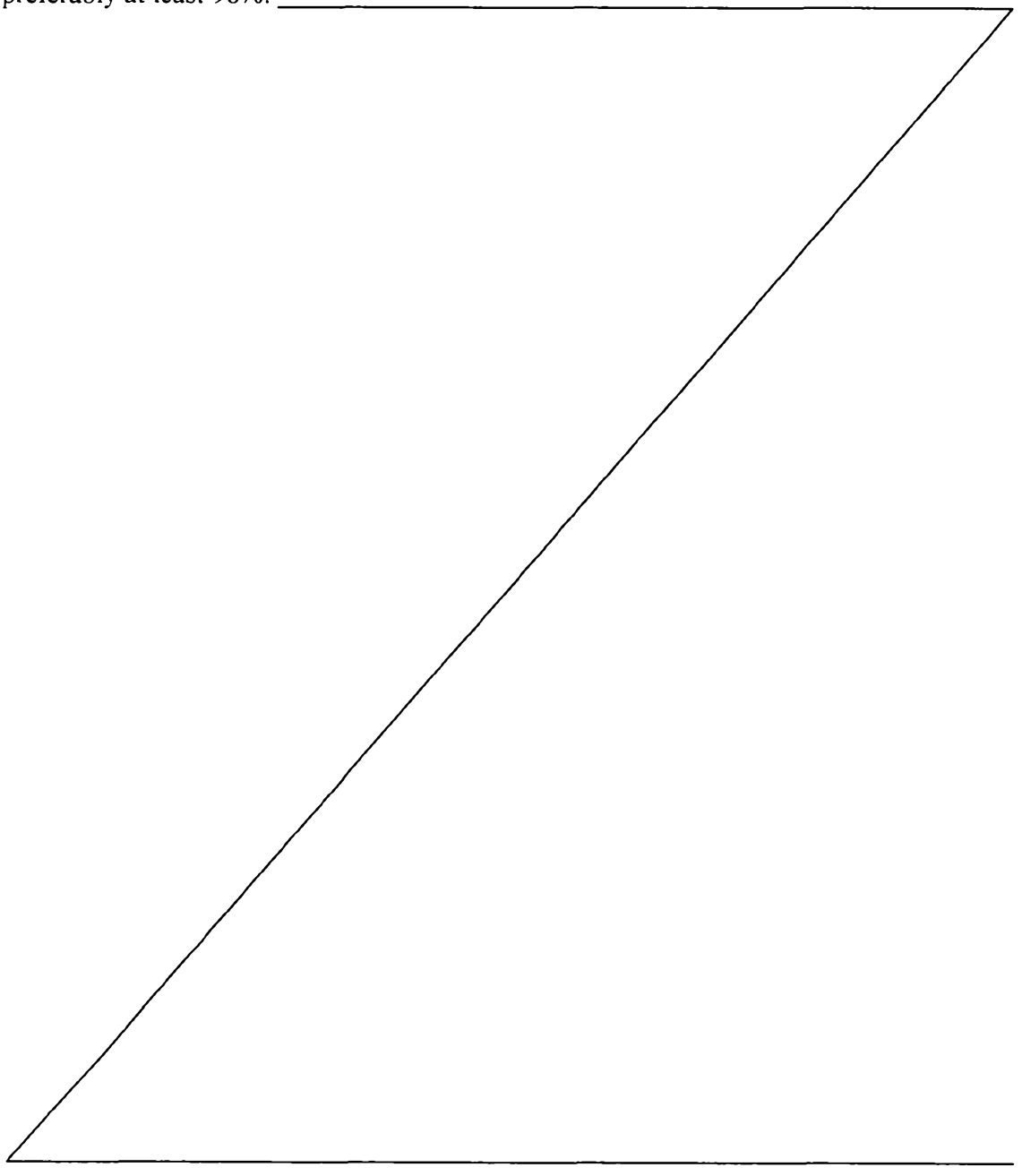
According to a second aspect the present invention provides crystalline duloxetine hydrochloride prepared by a method according to the first aspect, which has a purity of at least 95%.

According to a third aspect the present invention provides crystalline duloxetine hydrochloride prepared by a method according to the first aspect, which has an optical purity of at least 95%.

Preferably, the crystalline duloxetine hydrochloride has a purity of at least 95%, more preferably at least 98%.



Preferably, the first organic solvent is an aromatic hydrocarbon, more preferably toluene.

In preferred embodiments, the second organic solvent is an alcohol, more preferably a straight or branched C_1 to C_6 alcohol, further preferably ethanol.

Preferably, the duloxetine is dissolved in the first organic solvent in a ratio of about 40ml first organic solvent for about every 3g of duloxetine.

In preferred aspects, the second organic solvent comprises about 20% HCl.

It is also preferred that the first solution is added to the second organic solvent at around 0°C. The first solution is preferably added to the second organic solvent with stirring.

In order to maximize crystallization, the duloxetine hydrochloride may be allowed to crystallize out from the solution during a period of cooling at around 0°C to around 10°C. Preferably, the duloxetine hydrochloride is allowed to crystallize out from the solution during a period of about 10 hours.

Preferably, the crystallized duloxetine hydrochloride is collected by filtration. The collected crystallized duloxetine hydrochloride is preferably washed and then dried.

In preferred embodiments, the collected crystallized duloxetine hydrochloride is washed with an aromatic hydrocarbon, more preferably toluene.

Preferably, the collected crystalline duloxetine hydrochloride is dried under vacuum.

Preferably, the method comprising the following additional steps for the preparation of duloxetine for use in step (a):-

(i) placing duloxetine oxalate into a solution of a third organic solvent and water;

(ii) adding aqueous ammonia solution for dissolving the duloxetine oxalate;

(iii) isolating a separated organic layer;

(iv) washing the organic layer with saturated brine;

(v) drying the organic layer; and

(vi) removing the solvents from the organic layer.

Preferably, the third organic solvent is a C_1 to C_6 ester, more preferably ethyl acetate.

The duloxetine oxalate is preferably placed into a solution of the third organic solvent and water at a ratio of about 300ml third organic solvent and water solution for about every 39g of duloxetine oxalate.

Preferably, the solution of a third organic solvent and water contains about 1ml third organic solvent for about every 1ml water.

The aqueous ammonia is preferably added under stirring.

Preferably, an aqueous layer is isolated and then washed with the third organic solvent.

According to a further aspect of the present invention, there is provided crystalline duloxetine hydrochloride prepared by any of the methods above.

Preferably, the crystalline duloxetine hydrochloride has a purity of at least 95%, more preferably at least 98%.

Accordingly, the present invention describes a novel crystalline form of duloxetine hydrochloride and a process to prepare it.

It is anticipated that the crystalline form of duloxetine hydrochloride disclosed herein will be useful in the treatment of a variety of diseases which are prevented, ameliorated or eliminated by the administration of a serotonin and/or norepinephrine reuptake inhibitor. Examples of such diseases include depression, pain related to

diabetic neuropathy and stress urinary incontinence, obesity, alcoholism, loss of memory, anxiety and smoking.

According to another aspect of the present invention, there is therefore provided a pharmaceutical composition comprising crystalline duloxetine hydrochloride as described herein.

According to a further aspect, there is provided a composition for treating a disease which is prevented, ameliorated or eliminated by the administration of a serotonin and/or norepinephrine reuptake inhibitor, the composition comprising crystalline duloxetine hydrochloride as described herein.

Preferably, the disease is selected from depression, pain related to diabetic neuropathy and stress urinary incontinence, obesity, alcoholism, loss of memory, anxiety and smoking.

There is also provided a method of treating a disease which is prevented, ameliorated or eliminated by the administration of a serotonin and/or norepinephrine reuptake inhibitor, the method comprising administering to a patient a therapeutically effective amount of crystalline duloxetine hydrochloride as described herein, or of the pharmaceutical composition as described herein.

Preferably, the disease is selected from depression, pain related to diabetic neuropathy and stress urinary incontinence, obesity, alcoholism, loss of memory, anxiety and smoking.

By a therapeutically effective amount, it is meant an amount which is capable of preventing, ameliorating or eliminating the diseases mentioned herein.

The crystalline duloxetine hydrochloride can be mixed with a carrier, diluent or excipient therefor, all of which are well known in the art. For example, suitable carriers may include pills, powders, lozenges, sachets, cachets, elixirs, suspensions,

emulsions, solutions, syrups, aerosols, ointments, soft and hard gelatine capsules, suppositories, sterile injectable solutions and sterile packaged powders.

There are many advantages to providing a crystalline form of duloxetine hydrochloride compared to an amorphous form. A crystalline form of the drug can be easily purified by crystallisation and recrystallisation. Compared to other methods of purification, it is also cheaper and more convenient to perform crystallisation on a large scale. Furthermore, a crystalline form may be more stable than an amorphous form.

An example of the present invention will now be described in detail with reference the accompanying figure, in which:-

Figure 1 shows the XRD spectrum for the crystalline form of the present invention; and

Figure 2 shows TGA and DTA thermograms for the crystalline form of the present invention.

Duloxetine oxalate salt was initially prepared following the procedure given in EP 273658. Duloxetine was then freed from the oxalic acid and converted directly to its hydrochloride salt by the introduction of hydrochloride in organic solvent.

The isolated crystalline duloxetine hydrochloride was fully characterized by DSC, solid carbon-13 NMR and X-ray powder diffraction.

Crystallization

Example 1

Free duloxetine preparation:

Duloxetine oxalate (38.7g) was placed into 300ml of an ethyl acetate/water (1:1) mixture. Aqueous ammonium solution was added to dissolve the solid completely under stirring. The separated aqueous layer was washed with ethyl acetate twice. The

combined organic solution was then washed with saturated brine, and dried with anhydrous sodium sulphate. The free duloxetine (26g) was obtained as an oil by removing the solvents from the filtrate solution.

Crystallization of duloxetine hydrochloride:

The free oily duloxetine (3g) was added to toluene (40ml), then an ethanol solution (2ml) containing 20%HCl was added at 0°C. The resultant solution was then stirred for an extra half hour and kept at 0-10°C for 10 hours. The product crystallized out and was collected by filtration, washed with more toluene and dried (1.7g, 53%yield, m.p. 154-158°C). Its purity was determined to be 98.9% by HPLC, and its optical purity was 99.4% (chiral column HPLC). The DTA result shown m.p. was 169.2°C. The crystalline form, designated as Form II, was thus obtained.

Table 1: The XRD spectrum for the crystalline form obtained according to the example above.

2theta (degree)	I/I_0	d(A)
11.021	16	8.021
11.993	54	7.373
13.936	18	6.349
14.780	73	5.988
16.192	32	5.469
16.868	15	5.251
17.997	25	4.924
18.792	30	4.718
19.765	16	4.488
20.842	31	4.258
21.444	100	4.140
22.159	58	4.008
23.120	84	3.843
24.122	71	3.686
26.341	24	3.380

26.760	19	3.328
27.000	31	3.299
27.448	12	3.246
29.240	19	3.051
29.580	19	3.017
29.920	21	2.983
30.398	12	2.938
32.200	14	2.777
32.820	10	2.726
34.165	14	2.622

Table 2: TGA/DTA parameters

Detector	DTG-60H
Sample Weight	7.698mg
Temperature Rate	10°C
Hold Temperature	300°C
Hold Time	0 min

CLAIMS

1. A method for the preparation of crystalline duloxetine hydrochloride which exhibits an X-ray diffraction pattern comprising peaks expressed in degrees two-theta at 11.99 ± 0.2, 14.78 ± 0.2, 21.44 ± 0.2, 22.16 ± 0.2, 23.12 ± 0.2 and 24.12 ± 0.2, the method comprising:-

(a) dissolving duloxetine in a first organic solvent to form a first solution;

(b) combining the first solution with a second organic solvent solution comprising HCl to form a second solution;

(c) allowing duloxetine hydrochloride to crystallize out from the solution; and

(d) collecting the crystallized duloxetine hydrochloride,

wherein the first organic solvent is an aromatic hydrocarbon.

2. A method according to claim 1, wherein the crystalline duloxetine hydrochloride exhibits an X-ray diffraction pattern expressed in degrees two-that at 11.02 ± 0.2, 11.99 ± 0.2, 13.94 ± 0.2, 14.78 ± 0.2, 16.19 ± 0.2, 16.87 ± 0.2, 18.0 ± 0.2, 18.8 ± 0.2, 19.77 ± 0.2, 20.84 ± 0.2, 21.44 ± 0.2, 22.16 ± 0.2, 23.12 ± 0.2, 24.12 ± 0.2, 26.34 ± 0.2, 26.76 ± 0.2, 27.0 ± 0.2, 27.45 ± 0.2, 29.24 ± 0.2, 29.58 ± 0.2, 29.92 ± 0.2, 30.4 ± 0.2, 32.2 ± 0.2, 32.82 ± 0.2 and 34.17 ± 0.2.

3. A method according to claim 1 or 2, wherein the crystalline duloxetine hydrochloride exhibits an X-ray diffraction pattern substantially the same as shown in figure 1.

4. A method according to any of claims 1 to 3, wherein the first organic solvent is toluene.

5. A method according to any of claims 1 to 4, wherein the second organic solvent is an alcohol.

6. A method according to claim 5, wherein the second organic solvent is ethanol.

7. A method according to any of claims 1 to 6, wherein the duloxetine is dissolved in the first organic solvent in a ratio of about 40ml first organic solvent for every 3g of duloxetine.

8. A method according to any of claims 1 to 7, wherein the second organic solvent comprises about 20% HCl.

9. A method according to any of claims 1 to 8, wherein the first solution is added to the second organic solvent at around 0°C.

10. A method according to any of claims 1 to 9, wherein the first solution is added to the second organic solvent with stirring.

11. A method according to any of claims 1 to 10, wherein the duloxetine hydrochloride is allowed to crystallize out from the solution during a period of cooling at 0°C to 10°C.

12. A method according to any of claims 1 to 11, wherein the duloxetine hydrochloride is allowed to crystallize out from the solution during a period of about 10 hours.

13. A method according to any of claims 1 to 12, wherein the crystallized duloxetine hydrochloride is collected by filtration.

14. A method according to any of claims 1 to 13, wherein the collected crystallized duloxetine hydrochloride is washed and then dried.

15. A method according to claim 14, wherein the collected crystallized duloxetine hydrochloride is washed with an aromatic hydrocarbon.

16. A method according to claim 14 or 15, wherein the collected crystallized duloxetine hydrochloride is washed with toluene.

17. A method according to any of claims 1 to 16, comprising the following additional steps for the preparation of duloxetine for use in step (a):-

(i) placing duloxetine oxalate into a solution of a third organic solvent and water;

(ii) adding aqueous ammonia solution for dissolving the duloxetine oxalate;

(iii) isolating a separated organic layer;

(iv) washing the organic layer with saturated brine;

(v) drying the organic layer; and

(vi) removing the solvents from the organic layer.

18. A method according to claim 17, wherein the third organic solvent is a C_1 to C_6 ester.

19. A method according to claim 18, wherein the third organic solvent is ethyl acetate.

20. A method according to any of claims 17 to 19, wherein duloxetine oxalate is placed into a solution of the third organic solvent and water at a ratio of about 300ml third organic solvent and water solution for every 39g of duloxetine oxalate.

21. A method according to any of claims 17 to 20, wherein the solution of a third organic solvent and water contains about 1ml third organic solvent for every 1ml water.

22. A method according to any of claims 17 to 20, wherein the aqueous ammonia is added under stirring.

23. A method according to any of claims 17 to 22, wherein an isolated aqueous layer is washed with the third organic solvent.

24. A method according to any of claims 17 to 23, wherein the organic layer is dried with anhydrous sodium sulphate.

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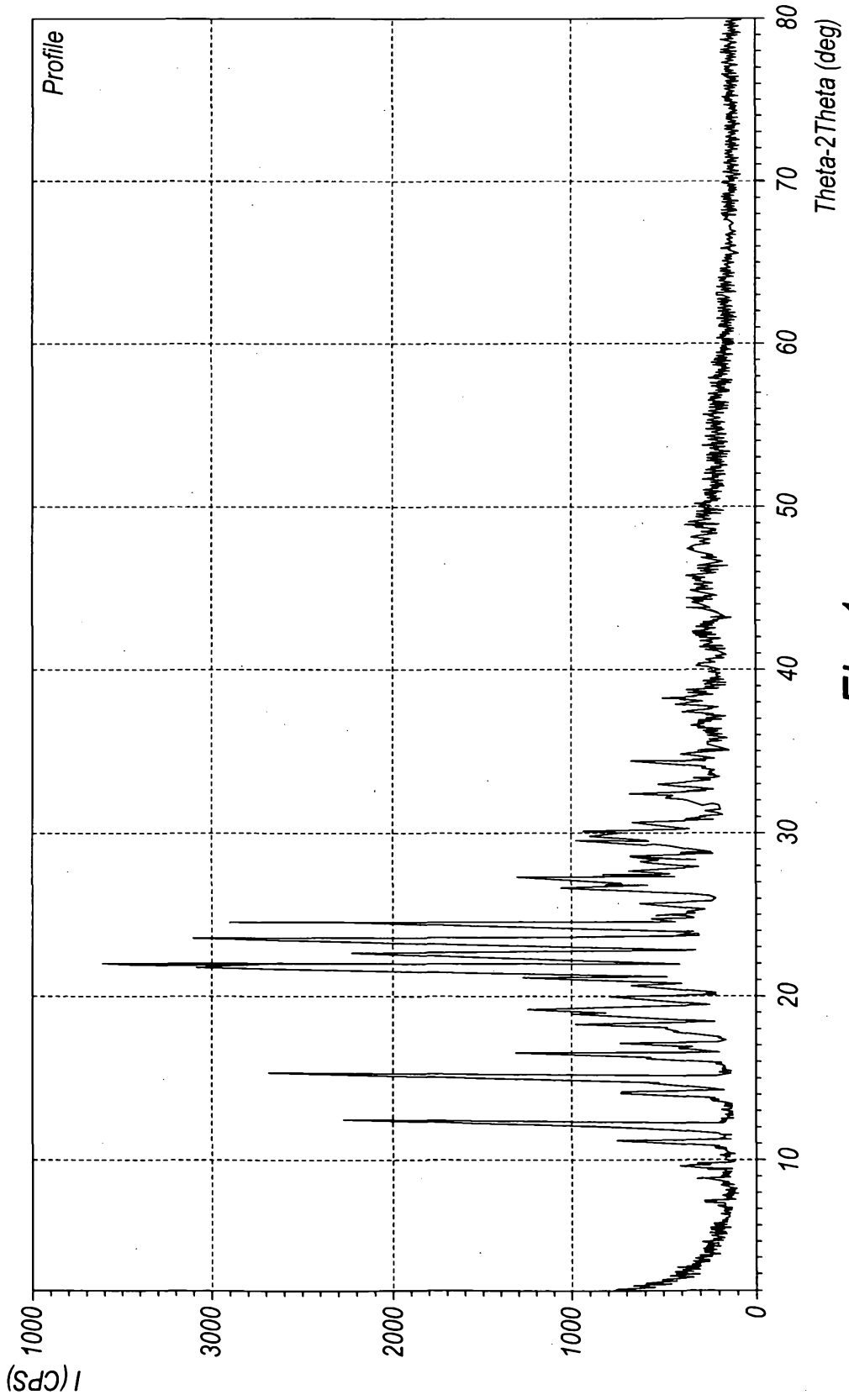
25. Crystalline duloxetine hydrochloride prepared by a method according to any of claims 1 to 24, which has a purity of at least 95%.

26. Crystalline duloxetine hydrochloride according to claim 25, which has a purity of at least 98%.

27. Crystalline duloxetine hydrochloride prepared by a method according to any of claims 1 to 24, which has an optical purity of at least 95%.

28. Crystalline duloxetine hydrochloride according to claim 31, which has an optical purity of at least 98%.

29. A method according to claim 1; or crystalline duloxetine hydrochloride according to claims 25 or 27, substantially as herein described with reference to any one or more of the examples but excluding comparative examples.


Profile
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Theta-2Theta (deg)

Fig. 1

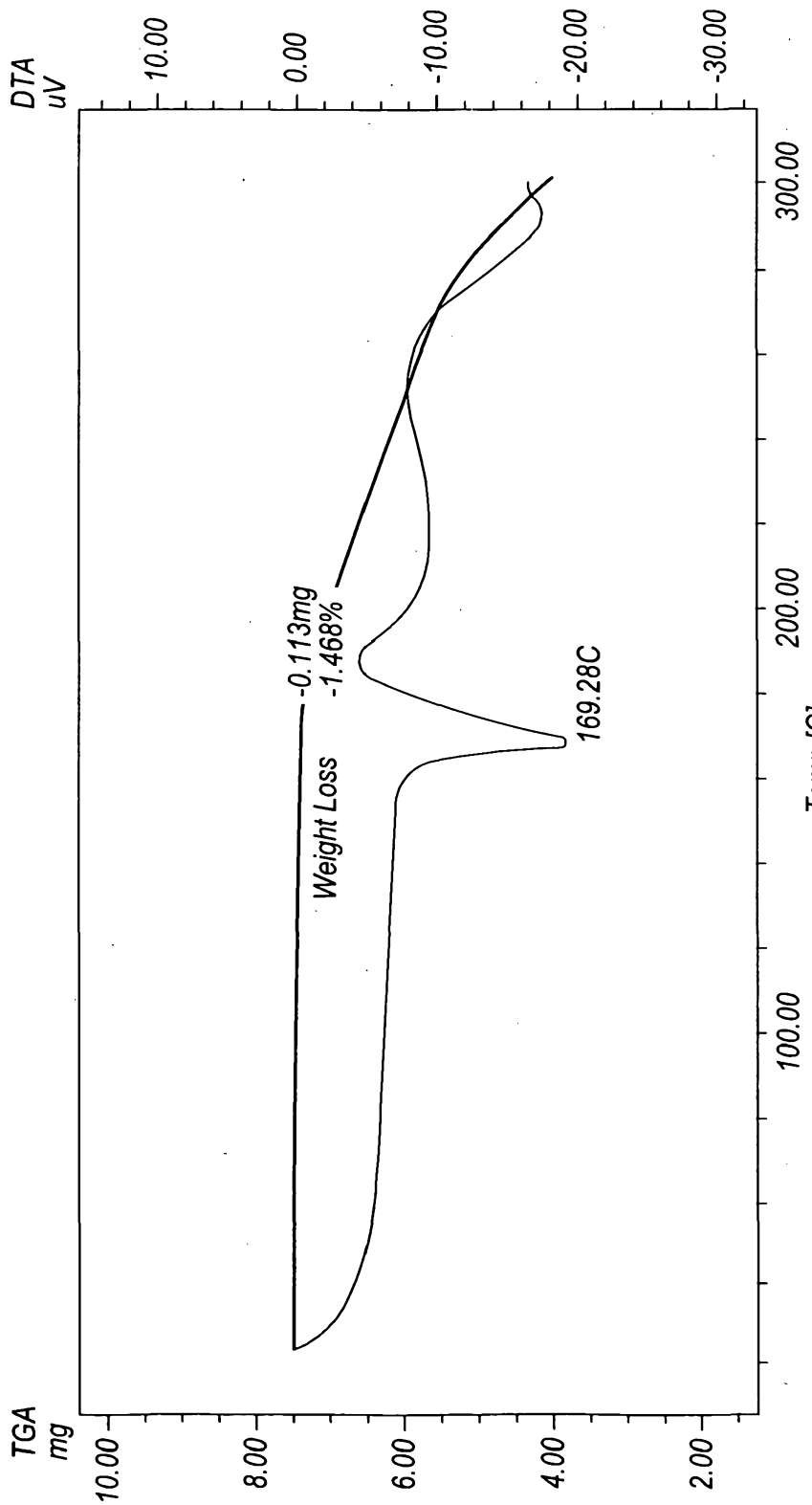
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Fig.2