

A NOVEL PHARMACEUTICAL SALT OF 1-BENZYL-4-[(5,6-DIMETHOXY-1-INDANONE)-2-YL] METHYL PIPERIDINE (DONEPEZIL)**Related Applications**

This application claims priority from US application Serial No.10/879816 filed on 29th June 2004.

Cross Reference to Related Applications

This application is continuation-in-part of U.S. Application Serial No. 10/365,717 filed February 12,2003 now US 6,649,765, which is entirely incorporated herein by reference.

Technical Field:

The present invention relates to a novel oxalate salt of 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl] 5 methyl piperidine commonly known as Donepezil (I) and its polymorphic forms and method of preparation thereof.

Background and Prior art:

The process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl] methyl piperidine has been described in JP A-64-79151 (US-4895841, EP 296560).

Japanese patent application, publication No. A-64-79151 (US-4895841, EP 296560) discloses certain salts of Donepezil, 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl] methyl piperidine and in particular the hydrochloride salt having an excellent action as a prophylactic and a therapeutic agent for senile dementia, and in particular as a prophylactic and therapeutic agent for Alzheimer's disease and an industrial process for producing the same.

Summary of the Invention :

The present invention describes the oxalate salt of 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl] 5 methyl piperidine commonly known as Donepezil (I) and its polymorphic forms and method of preparation thereof.

The said method of preparation of Donepezil oxalate comprises dissolving donepezil base in a first solvent to make a first solution; dissolving oxalic acid in a second solvent to make a second solution; combining said first solution and said second solution to make a reaction mixture; and isolating from said reaction mixture a donepezil oxalate (product).

The present invention further relates to a method of preparation of polymorphs of the said donepezil oxalate salt, wherein the said process comprises; dissolving said donepezil product in a third solvent to make a second reaction mixture; and isolating from said second reaction mixture a donepezil polymorph. The said isolating step comprises mixing said second reaction mixture with an anti-solvent; whereby said donepezil polymorph precipitates from said second reaction.

The powder X-ray diffraction pattern of oxalate form I crystals is shown in Fig. 1.

The infrared absorption spectrum for the same polymorphic form, as recorded in potassium bromide, is shown in Fig. 4.

The powder X-ray diffraction pattern of oxalate form II crystals is shown in Fig. 2.

The infrared absorption spectrum for the same polymorphic form, as recorded in potassium bromide, is shown in Fig. 5.

The powder X-ray diffraction pattern of oxalate form III crystals is shown in Fig. 3.

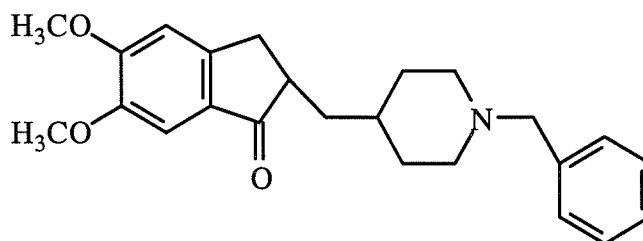
The infrared absorption spectrum for the same polymorphic form, as recorded in potassium bromide, is shown in Fig. 6.

Further, pharmaceutical compositions comprising therapeutically effective amount of the novel oxalate salt of Donepezil or its polymorphic form is also envisaged as part of this invention.

A method of treating Senile dementia of Alzheimer's disease, the method comprising administering to a warm blooded animal an effective amount of a product-by-process composition of matter comprising novel oxalate salt of Donepezil or its polymorphic forms is also envisaged as part of this invention.

Detailed Description:

The compound Donepezil, {(1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl] methyl piperidine)}, hereinafter is referred as Compound R.



Compound (R)

It has been discovered that compound (R) can be formed into a novel oxalate salt. The novel salt can be prepared by an efficient, economic and reproducible process and

particularly suited to large-scale preparation. The oxalate salt is therefore surprisingly amenable to large scale pharmaceutical processing and formulation.

The present invention also relates to three novel polymorphic forms (I, II and III) of Donepezil oxalate, which are characterized by powder X-ray diffraction and / or infrared absorption peaks recorded in potassium bromide.

Polymorphic crystals of compound (R) oxalate are hereafter referred as Oxalate form (I), Oxalate form (II) and Oxalate form (III).

The oxalate provides a melting point in the range of from 170 to 180° C, such as 175 to 180° C, for Oxalate form (I), Oxalate form (II); a melting point in the range of from 95 to 96°C for Oxalate form (III).

The present invention encompasses the oxalate salts isolated in a purified form.

Also, the invention provides the oxalate salts in a pharmaceutically acceptable form, especially in bulk form; such form having good flow properties, especially good bulk flow properties.

The invention also provides a process for the preparation of the oxalate, in which 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl] methyl piperidine (compound R) is preferably dispersed or dissolved in a suitable solvent and reacted with oxalic acid; and thereafter the oxalate formed is recovered by filtration.

A suitable solvent is an alkanol, for example propan-2-ol, or a hydrocarbon, such as toluene, a ketone, such as acetone, an ester, such as ethyl acetate, an ether such as tetrahydrofuran, a nitrile such as acetonitrile, a halogenated hydrocarbon such as dichloromethane.

The concentration of compound (R) is preferably in the range of from 3 to 25 % weight / volume, more preferably in the range of from 5 to 20 %. The concentration of oxalic acid solution is preferably in the range of from 3 to 50 % weight / volume.

The reaction is usually carried out at ambient temperature or at an elevated temperature, although any convenient temperature that provides the required product may be employed. A preferred temperature is in the range of about 20 to about 120°C, such as 40°C to 90°C, or more preferably about 70°C.

X-ray powder diffraction pattern has been obtained on D 8 –Advance, Bruker AXE, Germany, diffractometer equipped with scintillation detector using Copper K_α (λ = 1.5406 Å) radiation with scanning range between 2-50 θ (theta) at scanning speed of 2°/min.

Brief description of the drawings:

Fig. 1 shows a powder X-ray diffraction pattern for Oxalate form (I) crystals.

Fig. 2 shows a powder X-ray diffraction pattern for Oxalate form (II) crystals.

Fig. 3 shows a powder X-ray diffraction pattern for Oxalate form (III) crystals.

Fig. 4 shows an infrared absorption spectrum for Oxalate form (I) crystals.

Fig. 5 shows an infrared absorption spectrum for Oxalate form (II) crystals.

Fig. 6 shows an infrared absorption spectrum for Oxalate form (III) crystals.

Oxalate form (I) crystals

The powder X-ray diffraction pattern of oxalate form I crystals is shown in Fig. 1.

The infrared absorption spectrum for the same polymorphic form, as recorded in potassium bromide, is shown in Fig. 4.

Oxalate form (II) crystals

The powder X-ray diffraction pattern of oxalate form II crystals is shown in Fig. 2.

The infrared absorption spectrum for the same polymorphic form, as recorded in potassium bromide, is shown in Fig. 5.

Oxalate form (III) crystals

The powder X-ray diffraction pattern of oxalate form III crystals is shown in Fig. 3.

The infrared absorption spectrum for the same polymorphic form, as recorded in potassium bromide, is shown in Fig. 6.

The designations of x-ray diffraction angles, x-ray intensities and infrared ("IR") wave values are approximate; the numerical values here disclosed are therefore intended to encompass a range of approximately ± 0.3 about each stated value. Thus, for example, the term "IR values ... as follows; 407.0, 466.7, 499.5" is intended to encompass IR values of a range of from 406.7 to 407.3; and a range of from 466.4 to 467.0; and a range of from 499.2 to 499.8. Similarly, claim terms incorporating parameters illustrated by the Figures do not require exact equality in physical characteristics; a variation of approximately ± 0.3 about each value along the parameters shown in each Figure is to be expected.

Detail processes for preparing the novel oxalate salts are given below, where in, Donepezil base is prepared by a process as described in US 6,649,765 B1; this document is incorporated here by reference.

In a preferred embodiment, Donepezil oxalate is made by a process which comprises:

- (a) dissolving donepezil base in a first solvent to make a first solution;
- (b) dissolving oxalic acid in a second solvent to make a second solution;

- (c) combining said first solution and said second solution to make a reaction mixture; and
- (d) isolating from said reaction mixture a donepezil Oxalate.

The said first solvent is ethyl acetate.

The said second solvent is selected from the group consisting: of acetone, propane-2-ol and methanol.

The said isolating step comprises evaporating said first solvent and said second solvent.

The said process further comprising; (e) dissolving said donepezil product in a third solvent to make a second reaction mixture; and (f) isolating from said second reaction mixture a donepezil polymorph.

The said third solvent is selected from the group consisting of: water, methanol and ethanol.

The said third solvent comprises methanol and said isolating step comprises evaporating said third solvent from said second reaction mixture.

The said isolating step comprises mixing said second reaction mixture with an anti-solvent; whereby said donepezil polymorph precipitates from said second reaction.

The said anti-solvent is selected from the group consisting of: diethyl ether, di-isopropyl ether, acetone, propan-2-ol, n-hexane, and toluene.

The said third solvent is selected from the group consisting of: dimethyl formamide and dichloromethane.

The said third solvent comprises dimethyl formamide and said isolating step comprises evaporating said third solvent from said second reaction mixture.

The said isolating step comprises: mixing said second reaction mixture with an anti-solvent; whereby said donepezil polymorph precipitates from said second reaction.

The said anti-solvent is selected from the group consisting of: toluene and ethyl acetate.

The said third solvent comprises methanol and is held at a temperature of about 40 °C to about 60 °C, and said isolating step comprises evaporating said third solvent from said second reaction mixture.

The said reaction mixture is held at a temperature of about 25 °C and said isolating step comprises evaporating said third solvent from said second reaction mixture.

We discuss below eighteen Examples. The Examples first teach various methods to prepare donepezil oxalate. The Examples then teach various ways to process donepezil oxalate to make each of the three polymorphic forms of it. Here is a “Table of Contents” for the Examples which follow below:

Preparing donepezil oxalate:

Example 1: Process for preparing Donepezil oxalate by addition of oxalic acid in acetone to Donepezil base in ethyl acetate.

Example 2: Process for preparing Donepezil oxalate by addition of oxalic acid in Propan-2-ol to Donepezil base in ethyl acetate.

Example 3: Process for preparing Donepezil oxalate by addition of oxalic acid in methanol to Donepezil base in ethyl acetate.

Modifying donepezil oxalate to make polymorph oxalate form (I) crystals

Example 4: Dissolving Donepezil oxalate in Methanol, followed by addition of Diethyl ether.

Example 5: Dissolving Donepezil oxalate in Methanol, followed by addition of Diisopropyl ether.

Example 6: Dissolving Donepezil oxalate in Ethanol, followed by addition of Diisopropyl ether.

Example 7: Dissolving Donepezil oxalate in Acetone, followed by addition of water.

Example 8: Dissolving Donepezil oxalate in Water, followed by addition of propan-2-ol.

Example 9: Dissolving Donepezil oxalate in Ethanol, followed by addition of n-hexane.

Example 10: Dissolving Donepezil oxalate in Methanol and cooling below 10° C.

Example 11: Dissolving Donepezil oxalate in Methanol, followed by addition of Toluene.

Example 12: Dissolving Donepezil oxalate in water, followed by addition of Acetonitrile.

Example 13: Dissolving Donepezil oxalate in Tetrahydrofuran, followed by addition of diisopropyl ether.

The above- mentioned Examples teach that the donepezil oxalate salt is dissolved in the respective solvents by heating at 40 to 60° C.

Modifying donepezil oxalate to make polymorph oxalate form (II) crystals :

Example 14: Dissolving Donepezil oxalate in Dichloromethane, followed by addition of toluene.

Example 15: Dissolving Donepezil oxalate in Dimethyl formamide and cooling below 10° C.

Example 16: Dissolving Donepezil oxalate in Dichloromethane, followed by addition of Ethyl acetate.

The above mentioned Examples teach that the donepezil oxalate salt is dissolved in the respective solvents by heating at 40 to 60° C.

Modifying donepezil oxalate to make polymorph oxalate form (III) crystals :

Example 17: Dissolving Donepezil oxalate in water and kept at room temperature (RT) for 72 hrs.

Example 18: Dissolving Donepezil oxalate in Methanol-water mixture kept at RT for 72 hrs.

The above- mentioned Examples teach that the donepezil oxalate salt is dissolved in respective solvents by heating at 40 to 60° C.

The oxalate form (I) polymorphic form is identifiable by a characteristic powder X-ray diffraction. These peaks in the powder X-ray diffraction pattern are roughly as follows:

Sr. No	Diffraction Angle ($2\theta^\circ$)	Intensity % (I/I ₀)
1.	5.92	17.0
2.	8.47	73.4
3.	10.30	13.8
4.	11.04	3.0
5.	11.89	100.0
6.	13.07	3.5
7.	13.74	14.0
8.	14.17	13.2
9.	15.00	4.4
10.	15.94	14.1
11.	16.88	21.2
12.	17.25	14.6
13.	17.67	7.3
14.	18.16	13.9
15.	18.90	5.3
16.	19.40	9.9
17.	19.67	13.5
18.	20.77	5.2
19.	21.29	7.8
20.	22.02	57.0
21.	23.23	13.4
22.	23.63	21.5
23.	23.98	24.7
24.	24.79	6.5
25.	26.26	7.9
26.	26.55	11.3
27.	27.70	4.8
28.	28.43	6.5
29.	29.03	5.6
30.	32.01	3.3
31.	33.35	4.1
32.	34.53	5.3
33.	36.55	3.0
34.	37.31	3.7
35.	41.35	3.9

For the same polymorph, the wave numbers (cm^{-1}) of infrared absorption spectra recorded in potassium bromide are approximately as follows:

3010.7, 2931.6, 2842.9, 2540.1, 2362.6, 2335.6, 1695.3, 1596.9, 1498.6, 1460.0, 1363.6, 1313.4, 1265.2, 1218.9, 1191.9, 1116.7, 1035.7, 1008.7, 931.6, 852.5, 812.0, 759.9, 707.8, 599.8, 559.3, 499.5, 466.7 and 407.0.

The oxalate form (II) polymorphic form is identifiable by a characteristic powder X-ray diffraction. These peaks in the powder X-ray diffraction pattern are approximately as follows:

Sr. No	Diffraction Angle ($2\theta^\circ$)	Intensity % (I/I ₀)
1.	10.264	13.6
2.	11.872	10.5
3.	12.634	3.2
4.	13.515	100
5.	14.815	9.8
6.	15.506	36.1
7.	16.219	16.5
8.	16.790	15.2
9.	17.498	1.9
10.	17.979	9.2
11.	18.402	14.0
12.	19.214	15.0
13.	19.953	8.0
14.	20.471	22.2
15.	21.047	2.5
16.	21.656	5.2
17.	22.199	29.0
18.	22.860	19.9
19.	23.681	17.9
20.	24.123	12.5
21.	24.954	5.6
22.	25.282	3.5
23.	25.951	3.3
24.	26.552	15.4
25.	27.097	12.0

26.	28.691	4.9
27.	29.791	7.0
28.	30.186	6.4
29.	31.283	6.9
30.	32.402	4.8
31.	34.892	5.7
32.	35.446	3.5
33.	43.329	3.2

For the same polymorph, the wave numbers (cm^{-1}) of infrared absorption spectra recorded in potassium bromide are approximately as follows:

418.5, 439.7, 459.0, 497.6, 559.3, 588.2, 669.3, 704.0, 719.4, 754.1, 806.2, 862.1, 941.2, 1012.6, 1037.6, 1066.6, 1120.6, 1151.4, 1188.1, 1220.9, 1249.8, 1265.2, 1315.4, 1361.7, 1386.7, 1404.1, 1421.4, 1438.8, 1454.2, 1469.7, 1502.4, 1554.5, 1591.2, 1631.7, 1693.4, 2327.9, 2360.7, 2542.0, 2839.0, 2929.7, and 3010.7.

The Oxalate form (III) polymorphic form is identifiable by a characteristic powder X-ray diffraction. These peaks in the powder X-ray diffraction pattern are approximately as follows:

Sr. No	Diffraction Angle ($2\theta^\circ$)	Intensity % (I/I ₀)
1.	6.968	31.5
2.	9.939	19.0
3.	10.454	10.2
4.	11.032	11.8
5.	13.104	8.4
6.	13.970	3.6
7.	15.788	100
8.	16.668	5.6
9.	18.314	4.5
10.	19.651	7.8
11.	19.994	6.0
12.	21.644	23.6

13.	21.992	28.5
14.	22.702	10.0
15.	23.312	28.6
16.	24.266	25.8
17.	24.978	3.5
18.	25.926	16.3
19.	26.788	14.5
20.	28.216	3.8
21.	28.779	16.2
22.	29.268	4.2
23.	30.101	3.5
24.	30.741	4.3
25.	31.977	7.5
26.	35.240	3.2
27.	36.274	4.8
28.	40.222	4.4

For the same polymorph, the wave numbers (cm^{-1}) of infrared absorption spectra recorded in potassium bromide are approximately as follows:

405, 432, 445.5, 470.6, 503.4, 561.2, 588.2, 607.5, 650, 705.9, 756, 769.5, 785.0, 800.4, 821.6, 864.1, 900.7, 923.8, 947.0, 968.2, 989.4, 1010.6, 1039.6, 1066.6, 1078.1, 1118.6, 1126.4, 1157.2, 1220.9, 1267.1, 1290.3, 1319.2, 1367.4, 1406.0, 1438.8, 1458.1, 1498.6, 1602.7, 1670.2, 1705.0, 1724.2, 2422.4, 2547.8, 2624.9, 2742.6, 2839.0, 2925.8, 2950.9, 3004.9, 3300, 3369.4, and 3571.9.

Examples

Examples 1 to 3: Production of donepezil oxalate.

Examples 4 to 13: Production of Polymorphic crystals of Oxalate form (I).

Examples 14 to 16: Production of Polymorphic crystals of Oxalate form (II).

Examples 17 to 18 Production of Polymorphic crystals of Oxalate form (III).

The present invention will now be described in more detail with reference to the following examples. It is needless to say that the technical scope of the present invention is not limited to these examples.

Example 1

To Donepezil base (obtained after benzylation; benzylation is known in the art, and is taught by, *e.g.*, US 6,649,765) (10 gms.) in ethyl acetate (200 ml) was added oxalic acid (5 gms dissolved in 100 ml acetone) slowly with stirring. After addition the reaction mass was concentrated in vacuum. The solid separated was filtered and washed with acetone and dried at 60° C afforded the title compound with a yield of 12 gms (90.2%) and melting point 176-77 ° C.

Example 2

To Donepezil base (obtained after benzylation) (10 gms.) in ethyl acetate (200 ml) was added oxalic acid (5 gms dissolved in 100 ml propan-2-ol) slowly with stirring. After addition the reaction mass was concentrated in vacuum. The solid separated was filtered and washed with acetone and dried at 60° C afforded the title compound with a yield of 12.5 gms (96.9%) and melting point 176-78° C

Example 3

To Donepezil base (obtained after benzylation) (10 gms.) in ethyl acetate (200 ml) was added oxalic acid (5 gms dissolved in 100 ml Methanol) slowly with stirring. After addition the reaction mass was concentrated in vacuum. To the residue was added 50 ml propan-2-ol. The solid separated was filtered and washed with propan-2-ol and dried at 70° C afforded the title compound with a yield of 12 gms, 90.2%.

Example 4

Donepezil oxalate (any form) 5 gms was dissolved in Methanol 50 ml under heating at 50° C. Under stirring, at room temperature 50 ml diethyl ether was added. Stirring was

continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.5 gms (90%) and melting point 177-78° C.

Example 5

Donepezil oxalate (any form) 5 gms was dissolved in Methanol 50 ml under heating at 50° C. Under stirring, at room temperature 50 ml diisopropyl ether was added. Stirring was continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.0 gms (80%) and melting point 177-78° C.

Example 6

Donepezil oxalate (any form) 5 gms was dissolved in Ethanol 50 ml under heating at 50° C. Under stirring, at room temperature 50 ml diethyl ether was added. Stirring was continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.2 gms (84%) and melting point 176-78° C.

Example 7

Donepezil oxalate (any form) 5 gms was dissolved in water 50 ml at room temperature. Under stirring, at 50° C 100 ml acetone was added. Stirring was continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.1 gms (82%) and melting point 177-78° C.

Example 8

Donepezil oxalate (any form) 5 gms was dissolved in water 50 ml at room temperature. Under stirring, at 50° C 100 ml propan-2-ol was added. Stirring was continued for 2 hour after the separation of the crystals at 15° C. Filtration of the crystals and drying at

60° C afforded the title compound with a yield of 4.6 gms (92%) and melting point 176-78° C.

Example 9

Donepezil oxalate (any form) 5 gms was dissolved in ethanol 50 ml under heating at 50° C. Under stirring, at 50° C 50 ml n-hexane was added. Stirring was continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.4 gms (88%) and melting point 177-78° C.

Example 10

Donepezil oxalate (any form) 5 gms was dissolved in methanol 25 ml under heating at 50° C. Stirring was continued for 1 hour with gradual cooling. Stirring was further continued for 1 hour after the separation of the crystals at room temperature. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.0 gms (80%) and melting point 177-78° C.

Example 11

Donepezil oxalate (any form) 5 gms was dissolved in methanol 50 ml under heating at 50° C. Under stirring, at 50° C 100 ml toluene was added. Stirring was continued for 1 hour with gradual cooling. Stirring was further continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.4 gms (88%) and melting point 177-78° C.

Example 12

Donepezil oxalate (any form) 5 gms was dissolved in water 50 ml at room temperature. Under stirring, at 50° C 100 ml acetonitrile was added. Stirring was continued for 2 hour with gradual cooling. Stirring was further continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.0 gms (80%) and melting point 176-78° C.

Example 13

Donepezil oxalate (any form) 5 gms was dissolved in tetrahydrofuran 50 ml under heating at 50°C. Under stirring, at 40° C 100 ml diisopropyl ether was added. Stirring was continued for 1 hour after the separation of the crystals at 15° C. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.2 gms (86%) and melting point 177-78° C.

Example 14

Donepezil oxalate (any form) 5 gms was dissolved in dichloromethane 50 ml under heating at 50° C. Under stirring, at 40° C 100 ml toluene was added. Stirring was continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.2 gms (86%) and melting point 177-78° C.

Example 15

Donepezil oxalate (any form) 5 gms was dissolved in dimethyl formamide 25 ml under heating at 50° C. Stirring was continued for 1 hour with gradual cooling. Stirring was further continued for 1 hour after the separation of the crystals at room temperature. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 3.9 gms (78%) and melting point 176-78° C.

Example 16

Donepezil oxalate (any form) 5 gms was dissolved in dichloromethane 50 ml under heating at 50° C. Under stirring, at 40° C 100 ml ethyl acetate was added. Stirring was continued for 1 hour with gradual cooling. Stirring was further continued for 1 hour after the separation of the crystals. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.2 gms (86%) and melting point 176-78° C.

Example 17

Donepezil oxalate (any form) 5 gms was dissolved in water 60 ml under heating at 50° C. The reaction mass was kept for 72 hrs at RT. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.1 gms (82 %) and melting point 95.4-96° C. Water content 12.2% (By KF).

Example 18

Donepezil oxalate (any form) 5 gms was dissolved in mixture of water 50 ml and 10 ml methanol under heating at 50° C. The reaction mass was kept for 72 hrs at RT. Filtration of the crystals and drying at 60° C afforded the title compound with a yield of 4.0 gms (80 %) and melting point 95.5-96° C. Water content 12.4% (By KF).

Given our teachings herein, one of skill in the art will without undue experimentation be able to make variations and modifications of the forgoing. Thus, while we discuss numerous specific examples here, we intend the scope of our patent to be defined not by any specific example(s) provided here, but by the appended claims.

Note that in the claims, we use the word “a” to mean at least one (*i.e.*, perhaps more than one). Thus, for example, the claim phrase, “a compound selected from the group consisting of A, B and C” encompasses at least one of the enumerated compounds, and also encompasses combinations of more than one of these enumerated compounds (e.g., A and C together).

We Claim :

1. A composition of matter comprising Donepezil oxalate.
2. The composition of matter of claim 1, said composition of matter in a physical form having a physical characteristic selected from the group consisting of: a powder X-ray diffraction pattern as shown in Figure 1; a powder X-ray diffraction pattern as shown in Figure 2; a powder X-ray diffraction pattern as shown in Figure 3; an infrared absorption spectrum as shown in Figure 4; an infrared absorption spectrum as shown in Figure 5; and an infrared absorption spectrum as shown in Figure 6.
3. The composition of matter of claim 2, said physical form having a physical characteristic comprising: a powder X-ray diffraction pattern as shown in Figure 1, and an infrared absorption spectrum as shown in Figure 4.
4. The composition of matter of claim 2, said physical form having a physical characteristic comprising: a powder X-ray diffraction pattern as shown in Figure 2, and an infrared absorption spectrum as shown in Figure 5.
5. The composition of matter of claim 2, said physical form having a physical characteristic comprising: a powder X-ray diffraction pattern as shown in Figure 3, and an infrared absorption spectrum as shown in Figure 6.
6. A composition of matter made by a process comprising:
 - (a) dissolving Donepezil base in a first solvent to make a first solution;
 - (b) dissolving oxalic acid in a second solvent to make a second solution;
 - (c) combining said first solution and said second solution to make a reaction mixture; and
 - (d) isolating from said reaction mixture a Donepezil product.

7. The composition of matter of claim 6, said first solvent comprising ethyl acetate.
8. The composition of matter of claim 6, said second solvent selected from the group consisting of: acetone, propan-2-ol and methanol
9. The composition of matter of claim 6, said isolating step comprising evaporating said first solvent and said second solvent.
10. The composition of matter of claim 6, said process further comprising:
 - (e) dissolving said Donepezil product in a third solvent to make a second reaction mixture; and
 - (f) isolating from said second reaction mixture a Donepezil polymorph.
11. The composition of matter of claim 10, said third solvent selected from the group consisting of: water, methanol and ethanol.
12. The composition of matter of claim 11, said third solvent comprising methanol and said isolating step comprising evaporating said third solvent from said second reaction mixture.
13. The composition of matter of claim 10, said isolating step comprising: mixing said second reaction mixture with an anti-solvent; whereby said Donepezil polymorph precipitates from said second reaction.
14. The composition of matter of claim 13, said anti-solvent selected from the group consisting of: diethyl ether, di-isopropyl ether, acetone, propan-2-ol, n-hexane, and toluene.
15. The composition of matter of claim 10, said third solvent selected from the group consisting of: dimethyl formamide and dichloromethane.

16. The composition of matter of claim 15, said third solvent comprising dimethyl formamide and said isolating step comprising evaporating said third solvent from said second reaction mixture.
17. The composition of matter of claim 15, said isolating step comprising: mixing said second reaction mixture with an anti-solvent; whereby said Donepezil polymorph precipitates from said second reaction.
18. The composition of matter of claim 17, said anti-solvent selected from the group consisting of: toluene and ethyl acetate.
19. The composition of matter of claim 11, said third solvent comprising aqueous methanol, said reaction mixture held at a temperature of about 40 °C to about 60°C, and said isolating step comprising evaporating said third solvent from said second reaction mixture.
20. The composition of matter of claim 12, said reaction mixture held at a temperature of about 25 °C and said isolating step comprising evaporating said third solvent from said second reaction mixture.
21. A pharmaceutical composition comprising the said novel oxalate salt or polymorphs as prepared by process claimed in any of the above claims.
22. A method of treating senile dementia of Alzheimer's disease, the said method comprising administering to a warm blooded animal an effective amount of a product –by-process composition of matter comprising the said novel oxalate salt or polymorphic forms of Donepezil wherein the said novel oxalate salt or polymorphic forms of Donepezil are manufactured by the process as claimed in any of the claims 1 to 20.