Disclosed herein novel crystalline polymorphic forms of 1-benzyl-4-(5,6-dimethoxy-1-indanone-2-yl)methylpiperidine (Donepezil) base having higher stability. Said polymorphic forms are designated as Form D and E and characterized by employing analytical tools such as infrared absorption spectrum, X-ray powder diffraction pattern, thermo gravimetric analysis (TGA), differential scanning calorimetry (DSC) and/or melting point. The present invention also disclosed a process for preparing said polymorphic forms. Further an improved process for preparing polymorphic form B of 1-benzyl-4-(5,6-dimethoxy-1-indanone-2-yl)methylpiperidine (Donepezil) base is also disclosed.
NOVEL POLYMORPHIC FORMS OF 1-BENZYL-4-[(5,6-DIMETHOXY-1-INDANONE)-2-YL]METHYL PIPERIDINE [DONEPEZIL] AND PROCESS FOR PREPARING THE SAME

Field of the Invention

This invention, in general relates to the novel crystalline polymorphic forms of 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl]methyl piperidine (Donepezil). More particularly, the present invention provides a novel and stable crystalline form of Donepezil designated as Form D and Form E and the process for preparing the same.

Background of the Invention

1-Benzyl-4-(5,6-dimethoxy-1-indanone-2-yl)methylpiperidine (Donepezil) represented by the formula 1, is a new drug and has acetylcholinesterase inhibitory action, due to which it is used in the treatment of mild to moderate cases of SDAT (Senile Dementia of Alzheimers Type) as well as preventing and improving various cerebrovascular disorder associated with cerebral apoplexy (cerebral hemorrhage and cerebral infarction), head injury, logopathy, hypobulia, emotional disorders, memorization disorders, paranoid hallucinatory states, abnormal behavior associated with sequelae of encephalitis, cerebral paralysis etc.

(1)

Many pharmaceutically active compounds have been found to exist in more than one polymorphic form, such as one or more crystalline forms, an amorphous form, and/or sometimes one or more solvated forms. Frequently it is found that the different forms have different physical or chemical properties, such as solubility, hygroscopicity, etc., or have properties that render some form easier to formulate into a pharmaceutical product. In addition, certain forms can have a greater stability than other forms, as shown by a decreased tendency to spontaneously convert into a different polymorphic form.
Donepezil and its pharmaceutically acceptable salts were first disclosed in US patent no. 4,895,841. After the US 4,895,841 many processes for preparing Donepezil Hydrochloride and its polymorphic forms are disclosed in the different US patents e.g. 5,100,901; 5,606,064; 5,985,864; 6,140,321 and 6,252,081. In above-mentioned patents pharmaceutically acceptable salt forms of Donepezil are produced by first producing Donepezil, which is a free base, followed by the conversion of base into a salt by employing appropriate conditions. In other words, Donepezil base is used as a precursor for the production of Donepezil hydrochloride. Donepezil freebase is in itself a pharmaceutical agent in addition to being a precursor for production of Donepezil hydrochloride.

US patent no. 6,245,911 had claimed three polymorphic forms of Donepezil base i.e. Form A, Form B and Form C and their process of preparation. US'911 purify the crude Donepezil base by crystallizing the same in different solvents. Donepezil base is obtained after the reduction of compound III of scheme 1.

US'911 states that Donepezil base crystals have physical properties which allow it to occur in a non-sticky form, and which therefore enable excellent filtration after crystallization and facilitate facile recovery of the cake by scraping.
Some of the methods used for obtaining the three novel crystalline forms of Donepezil base described in US'911 are cumbersome.

It is important to evaluate the new polymorphs of Donepezil base, which may have higher stability and handling properties than reported polymorphic forms. Also, the stability of Donepezil base against heat and humidity during storage period is very essential, therefore a more stable polymorph of Donepezil base is desirable. There is also a need for improved production processes for crystalline Donepezil base known in prior art, devoid of the limitations of the processes known in the art.

**Summary of the Invention**

It is a principal aspect of the present invention to provide novel crystalline polymorphic forms of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine (Donepezil) base, designated as Polymorphic forms D and E having higher stability and easy to handle than the polymorphic forms known in the prior arts.

It is another aspect of the present invention is to provide a process for preparing said polymorphic forms D and E of donepezil base employing selective solvent system and process parameters.

It is yet another aspect of the present invention to provide an improved process to produce the polymorphic form B of donepezil base employing selective solvent system and temperature parameters.

It is further aspect of the present invention to provide novel crystalline polymorphs of the donepezil base, referred hereinafter as Form D and as Form E characterized by employing analytical tools such as infrared absorption spectrum, X-ray powder diffraction pattern, thermo gravimetric analysis (TGA), differential scanning calorimetry (DSC) and/or melting point.

In accordance with one preferred embodiment of the present invention, there is provided a novel and stable crystalline polymorphic form D of donepezil base characterized by
having an X-ray powder diffraction pattern at 4.8, 9.7, 16.9, 17.6, 17.9, 21.1 ± 0.2° 2Θ values.

In accordance with yet other preferred embodiment of the present invention, there is provided a novel and stable crystalline polymorphic form D of donepezil base characterized by having an X-ray powder diffraction pattern at 4.8, 9.7, 12.9, 16.8, 16.9, 17.6, 17.9, 18.4, 18.7, 19.3, 19.7, 20.7, 21.1, 23.1, 24.3, 25.0, 25.1, 26.0, 29.2 ± 0.2° 2Θ values.

In accordance with yet other preferred embodiment of the present invention, there is provided a novel and stable crystalline polymorphic form D of donepezil base characterized by an infrared spectroscopy having absorption bands (cm⁻¹) at 2913, 2795, 2750, 1696, 1592, 1501, 1312, 1265, 1120, 1038 and 739.

In accordance with still other preferred embodiment of the present invention, there is provided a novel and stable crystalline polymorphic form D of donepezil base characterized an infrared spectroscopy having absorption bands (cm⁻¹) at 3374, 3067, 3009, 2913, 2841, 2795, 2750, 2723, 1696, 1606, 1592, 1501, 1480, 1458, 1429, 1361, 1340, 1312, 1265, 1226, 1203, 1190, 1147, 1120, 1108, 1072, 1038, 975, 886, 856, 839, 811, 785, 739, 698, 652, 561 and 463.

In accordance with yet another embodiment of present invention, there is provided a process for preparing crystalline polymorphic form D of donepezil base, wherein the process comprises contacting donepezil in mixture of water and an organic solvent, cooling the resultant reaction mixture, isolating the solid material to get final product.

In accordance with yet another embodiment of the present invention there is provided a process for preparing crystalline polymorphic form D of donepezil base, wherein the process comprises contacting donepezil base in a solvent system, stirring the resultant mixture and isolating the solid material to get final product.

In accordance with yet another embodiment of present invention, there is provided a process for preparing crystalline polymorphic form D of donepezil base, wherein the
process comprises contacting donepezil base in mixture of water and an organic solvent selected preferably from alcohol or cyclic ether, stirring the resultant mixture and isolating the solid material to get final product.

In accordance with yet another embodiment of present invention, there is provided a process for preparing crystalline polymorphic form D of donepezil base, wherein the process comprises contacting donepezil base in mixture of water and solvent preferably selected from alcohol or cyclic ether, heating with stirring the resultant mixture at 40 to 60°C and cooling the resultant reaction mixture slowly at room temperature, isolating the solid material to get final product.

In accordance with yet another embodiment of present invention, there is provided a process for preparing crystalline polymorphic form D of donepezil base, wherein the process comprises contacting donepezil base in methanol, heating with stirring the resultant mixture at 30 to 45°C, followed by slow addition of water, thereafter cooling the resultant reaction mixture and isolating the solid material to get the final product.

In accordance with yet another embodiment of present invention, there is provided a process for preparing crystalline polymorphic form D of donepezil base, wherein the process comprises contacting donepezil base in solvent selected from alcohols having C1-C4 carbon chain, heating with stirring the resultant mixture at 40 to 60°C and cooling the resultant reaction mixture slowly at room temperature, isolating the solid material to get final product.

In accordance with one other preferred embodiment of the present invention, there is provided a novel and stable crystalline polymorphic form E of donepezil base characterized by having an X-ray powder diffraction pattern at 4.9, 5.7, 12.3, 13.0, 13.3, 16.9, 17.0, 17.7, 17.9, 19.7, 21.1 and 24.2 ± 0.2° 2θ values.

In accordance with further preferred embodiment of the present invention, there is provided a novel and stable crystalline polymorphic form E of donepezil base characterized by having an X-ray powder diffraction pattern at 4.9, 5.7, 9.8, 12.3, 16.7,
16.9, 17.0, 17.7, 17.9, 19.3, 19.7, 20.7, 21.1, 21.6, 21.9, 22.9, 23.2, 23.4, 24.2, and 25.2 ± 0.2° 2θ values.

In accordance with one other preferred embodiment of the present invention, there is provided a novel and stable crystalline polymorphic form E of donepezil base characterized by an infra red spectroscopy having absorption bands (cm⁻¹) at 2919, 2795, 2751, 1696, 1592, 1501, 1312, 1266, 1129, 1038 and 739.

In accordance with one other preferred embodiment of the present invention, there is provided a novel and stable crystalline polymorphic form E of donepezil base characterized by an infra red spectroscopy having absorption bands (cm⁻¹) at 3366, 3058, 3010, 2919, 2844, 2795, 2751, 1696, 1592, 1501, 1458, 1362, 1312, 1266, 1129, 1038, 976, 857, 811, 739, 698, 561 and 462.

In accordance with yet another embodiment of present invention, there is provided a process for preparing crystalline polymorphic form E of donepezil base, wherein the process comprises contacting donepezil base in mixture of an organic solvent, adding antisolvent into the resultant mixture and stirring the same at O°C to room temperature, isolating the solid material to get final product.

In accordance with yet another embodiment of present invention, there is provided a process for preparing crystalline polymorphic form E of donepezil base, wherein the process comprises contacting donepezil base in solvent selected preferably from ketone and hydrocarbon, adding antisolvent preferably selected from ether into the resultant mixture and stirring the same at O°C to room temperature, isolating the solid material to get final product.

In accordance with yet another embodiment of present invention, there is provided an improved process for preparing crystalline polymorphic form B of donepezil base employing a selective solvent system, wherein the process comprises contacting Donepezil in an organic solvent selected from any alkyl acetate heating the resultant mixture at 30 to 60°C to make clear solution followed by cooling with stirring. Optionally adding an
antisolvent to the resultant solution and, isolating the solid material to get final product, wherein said antisolvent is selected from non-polar hydrocarbon or ether.

In accordance with yet another embodiment of present invention, there is provided an improved process for preparing crystalline polymorphic form B of donepezil base employing a selective solvent system, wherein the process comprises contacting said donepezil base in an organic solvent selected from alcohol heating the resultant mixture at 30 to 60°C to make clear solution followed by cooling with stirring, adding an antisolvent to the resultant solution and isolating the solid material to get final product, wherein said antisolvent is selected non-polar hydrocarbon or water.

In accordance with yet another embodiment of present invention, there is provided an improved process for preparing crystalline polymorphic form B of donepezil base employing a selective solvent system, wherein the process comprises contacting donepezil in methanol, heating the reaction mixture at 30-45°C, followed by slow addition of water, rapid cooling of the reaction mixture and isolating the solid material to get the final product.

**Brief Description of the Drawing**

Further aspects of the present invention together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of preferred embodiments of the invention which are shown in the accompanying drawing figures, wherein:

Fig. 1 shows a characteristic X-ray powder diffraction pattern for crystalline Form D of Donepezil.

Fig. 2 shows a characteristic infrared absorption spectrum of crystalline Form D of Donepezil in potassium bromide. [Vertical axis: Transmission (%); horizontal axis: wave number (cm⁻¹)].

Fig. 3 shows Thermo gravimetric analysis of crystalline Form D of Donepezil.

Fig. 4 shows DSC thermogram of crystalline Form D of Donepezil.

Fig. 5 shows a characteristic X-ray powder diffraction pattern for crystalline Form E of Donepezil.
Fig. 6 shows a characteristic infrared absorption spectrum of crystalline Form E of Donepezil in potassium bromide. [Vertical axis: Transmission (%); horizontal axis: wave number (cm⁻¹)].

Fig. 7 shows Thermo gravimetric analysis of crystalline Form E of Donepezil.

Fig. 8 shows DSC thermogram of crystalline Form E of Donepezil.

Description of Invention

The present invention describes the novel and stable Donepezil crystalline Form D and crystalline Form E. Crystalline Form D and crystalline Form E of Donepezil differ from prior art forms in their physical properties, spectral data and methods of preparation and characterized by their X-ray powder diffraction patterns, thermo gravimetric analysis (TGA), differential scanning calorimetry (DSC) and/or by their infra red absorption spectrum (IR).

X-ray powder Diffraction

Crystalline Form D and Form E of Donepezil are characterized by their X-ray powder diffraction pattern. Thus the X-ray diffraction patterns of crystalline Form D and Form E of Donepezil are measured on a PANalytical X'Pert Pro diffractometer with Cu radiation and expressed in terms of 2Θ d-spacings and relative intensities.

Methodology

Continuous Θ/2Θ coupled scan: 5.01° to 45.00° in 2Θ scan rate of 3°/min.

Infrared absorption spectrometer (IR)

Methodology

Infrared measurements are made on Thermo Nicolet FT IR spectrometer using KBr pellets having the characteristic absorption bands expressed in reciprocal centimeter.

Thermo Gravimetric analysis (TGA)

Methodology
TGA thermograms are recorded on TGA Q50 with a ramp of 5°C/min.

**Differential Scanning Calorimetry (DSC)**

**Methodology**

DSC thermograms are recorded on DSC Q100 equilibrated at 250°C and with a ramp of 5°C/min.

Crystalline Form D of Donepezil is characterized by powder X-ray diffraction pattern as shown in Fig. 1 with major peaks shown in Table 1, which lists the 2θ d-spacings and relative intensities.

<table>
<thead>
<tr>
<th>2θ</th>
<th>d-spacing [Å]</th>
<th>Relative Intensity [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.89</td>
<td>18.03</td>
<td>27.11</td>
</tr>
<tr>
<td>9.78</td>
<td>9.03</td>
<td>14.87</td>
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<tr>
<td>12.97</td>
<td>6.82</td>
<td>14.71</td>
</tr>
<tr>
<td>16.87</td>
<td>5.25</td>
<td>35.19</td>
</tr>
<tr>
<td>16.98</td>
<td>5.22</td>
<td>36.50</td>
</tr>
<tr>
<td>17.67</td>
<td>5.01</td>
<td>41.71</td>
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<tr>
<td>17.93</td>
<td>4.94</td>
<td>100.00</td>
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<tr>
<td>18.42</td>
<td>4.81</td>
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<td>18.70</td>
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<tr>
<td>19.33</td>
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<td>19.70</td>
<td>4.50</td>
<td>29.98</td>
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<tr>
<td>20.75</td>
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<td>23.12</td>
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<td>25.93</td>
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<td>3.82</td>
<td>22.72</td>
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<td>24.30</td>
<td>3.66</td>
<td>19.92</td>
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<td>25.06</td>
<td>3.54</td>
<td>16.96</td>
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<td>25.17</td>
<td>3.53</td>
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<td>26.08</td>
<td>3.41</td>
<td>16.47</td>
</tr>
<tr>
<td>29.22</td>
<td>3.05</td>
<td>13.03</td>
</tr>
</tbody>
</table>

Crystalline Form D of Donepezil base is further characterized by IR with absorption bands at 3374, 3067, 3009, 2913, 2841, 2795, 2750, 2723, 1696, 1606, 1592, 1501, 1480, 1458, 1429, 1361, 1340, 1312, 1265, 1226, 1203, 1190, 1147, 1120, 1108, 1072, 1038, 975, 886, 856, 839, 811, 785, 739, 698, 652, 561 and 463 cm⁻¹ as depicted in Fig. 2.

Crystalline Form D is having the melting point of 93.6°C analyzed by its DSC analysis data as shown in Fig. 4.
Crystalline Form E of Donepezil is characterized by powder X-ray diffraction pattern as shown in Fig. 5 with major peaks shown in Table 2, which lists the 2θ d-spacings and relative intensities.

<table>
<thead>
<tr>
<th>2θ</th>
<th>d-spacing [Å]</th>
<th>Relative Intensity [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.93</td>
<td>17.91</td>
<td>21.77</td>
</tr>
<tr>
<td>5.79</td>
<td>15.24</td>
<td>48.45</td>
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<tr>
<td>9.82</td>
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</tr>
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<td>13.00</td>
<td>6.80</td>
<td>19.03</td>
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<tr>
<td>13.36</td>
<td>6.62</td>
<td>17.43</td>
</tr>
<tr>
<td>16.73</td>
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<td>16.90</td>
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<tr>
<td>17.02</td>
<td>5.20</td>
<td>62.98</td>
</tr>
<tr>
<td>17.72</td>
<td>5.00</td>
<td>66.59</td>
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<td>4.93</td>
<td>100.00</td>
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<tr>
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</tr>
<tr>
<td>19.73</td>
<td>4.49</td>
<td>47.09</td>
</tr>
<tr>
<td>20.79</td>
<td>4.26</td>
<td>32.93</td>
</tr>
<tr>
<td>21.19</td>
<td>4.18</td>
<td>44.32</td>
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<tr>
<td>25.20</td>
<td>3.53</td>
<td>21.14</td>
</tr>
</tbody>
</table>

Crystalline Form E is having the melting point of 93.1-94.0°C, which is further analyzed by its DSC analysis data as shown in Fig. 8.

The Donepezil free base used herein according to the present invention for the preparation of crystalline Form B, D and E, wherein said base is prepared by the procedure known in the literature, preferably by reacting compound II with benzylating agent, in presence of a base in solvent (Scheme 2). The reaction is carried out optionally in the presence of phase
transfer catalyst and followed by precipitation in alcohol to get solid material as compound I. The resultant precipitated material can be collected by a usual filtration method such as gravity filtration, filtration under suction, centrifugation etc. The base used herein is selected from the group comprising any inorganic or organic bases. The inorganic base is selected from the group comprising carbonates or bicarbonates of alkali metal like potassium, sodium, lithium, preferably potassium carbonate. The organic base is selected from the group comprising triethyl amine, pyridine, iV-methyl morpholine, A,iV-dimethyl benzyl amine, picoline or lutidine. The benzylating agent used herein is from the group comprising benzyl bromide, benzyl chloride, benzyl iodide, benzyl mesylate or benzyl tosylate.

The phase transfer catalyst used herein is selected from the group comprising ammonium based phase transfer reagent, phosphonium based phase transfer reagent, crown ethers or polyethylene glycols for example tetrabutylammonium iodide, tetrabutylammonium bromide, tetrabutylammonium hydrogen sulfate, benzyl triethylammonium chloride, benzyl tributylammonium chloride, tetramethylammonium chloride, tetrabutylphosphonium chloride, dibenzo-18-crown-6, PEG-200 or PEG-400, preferably tetrabutylammonium iodide (TBAI) or PEG-200. The solvent used is selected from the group comprising ethers such as diethyl ether, dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran; chlorinated hydrocarbons such as methylene chloride; esters such as ethyl acetate and isopropyl acetate; ketones such as acetone, methyl ethyl ketone (MEK) and methyl isobutyl ketone (MIBK); alcohols such as methanol, ethanol, propanol.
and isopropanol; acetonitrile; dimethylformamide; dimethyl sulfoxide; 1,2-dimethoxyethane; 1-V-methylpyrrolidone; sulpholane; water or mixture thereof. The benzylolation reaction is carried out at a temperature range from about 0°C to 100°C, for example from about 0°C to about 80°C, preferably from about 25°C to about 60°C. The primary use of phase transfer catalyst in benzylolation reaction is to reduce the reaction time for completion. It also reduces the by product formation during the reaction, which credited to the enhancement in the yield as well as purity of 1-benzyl-4-[(5,6-dimethoxy-1-indenon-2-yl)methyl]piperidine (I).

The present invention provides the process for the preparation of donepezil crystalline Form D, which comprises dissolving donepezil base in a mixture of water and organic solvent or in organic solvent alone at 40-60°C to get the clear solution. The reaction mixture is stirred at 0°C to room temperature preferably at room temperature to get the crystalline donepezil base form D. The organic solvent used herein is selected from the group comprising alcohol and cyclic ether. The alcohol used herein is selected from the group comprising alcohols having C1-C4 carbon chain preferably methanol, ethanol, isopropyl alcohol, n-propyl alcohol, t-butyl alcohol or n-butyl alcohol more preferably ethanol. The cyclic ether used herein is selected from the group comprising tetrahydrofuran, 1,4-dioxane, preferably tetrahydrofuran. The donepezil base is used either in the form of oil or any form present in the literature.

The novel polymorphic form D according to the present invention is free flowing crystalline and can thus be collected very easily in a shorter time, thus exhibiting excellent physical properties in handling and production efficiency. The crystalline material thus collected by filtration can be made completely free of residual solvent easily by a usual drying methods such as spontaneous drying, drying under reduced pressure, heating drying, heating drying under reduced pressure etc.

The present invention provides the process for the preparation of crystalline donepezil base Form E, which comprises dissolving donepezil base in a mixture of ketone and hydrocarbon at room temperature to get the clear solution. Ether is added to the reaction mixture and stirred at 0°C to room temperature preferably at 0°C to get the crystalline donepezil base form E. The crystalline form E is further dried under vacuum at 40°C. The
ketone used herein is selected from the group comprising acetone, methyl ethyl ketone or methyl isobutyl ketone, preferably acetone. The hydrocarbon used herein selected from the group comprising hexane, cyclohexane or heptane, preferably hexane. The ether used herein is selected from the group comprising diethyl ether or diisopropyl ether, preferably diisopropyl ether. The donepezil base is used either in the form of oil or any form present in the literature.

The present invention also provides an improved process for the preparation of crystalline Form B of donepezil base, which comprises dissolving donepezil base in a solvent at a temperature of 30-60°C, preferably 50-55°C and then cooled to 10-30°C, preferably 25-30°C. Optionally anti solvent is added to the reaction mixture at a temperature of 10-30°C preferably 25-30°C and stirred followed by cooling to a temperature range of 0-15°C. The solid material is filtered and dried under vacuum at 45-50°C. Donepezil used herein can be oil, or as a solid. Solvent used herein is selected from the group comprising acetate preferably ethyl acetate; alcohol preferably methanol and anti solvent used herein is selected from the group comprising non-polar hydrocarbon such as hexane, cyclohexane, heptane; ether such as diisopropyl ether, diethyl ether, preferably hexane or diisopropyl ether or water.

According to this invention, contacting donepezil base in methanol at 30-45°C, followed by the addition of water. The temperature of nucleation and the rate of crystallization are the critical variable parameters that control the formation of Form D and Form B. According to this, if the rate of crystallization is fast, the form B is formed whereas the rate of crystallization is slow then form D is formed.

The following non-limiting examples illustrate specific embodiments of the present invention. They are, however, not intended to be limiting the scope of present invention in any way.

Example 1
A compound of formula II (5.0gm) was dissolved in ethyl acetate (75ml) and followed by the addition of aqueous potassium carbonate (2.8gm in 5ml water) and polyethylene glycol (0.1ml) at 45-50°C. The benzyl chloride (2.8gm) was added and reaction mixture was
heated. After completion of the reaction, reaction mixture was cooled. Water (50ml) was added and stirred. The layers were separated and organic layer was evaporated to dryness to get residue. The obtained residue was dissolved in isopropyl alcohol (20ml) and stirred to get the precipitates. The precipitated material was filtered and dried in vacuum at 45-50°C to afford 5.4-5.6 gm of Donepezil base form D.

Example 2

Donepezil Base (Oil) (1.0gm) was dissolved in mixture of isopropyl alcohol (3.0ml) and water (1.0ml) at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried under vacuum at 45-50°C to afford donepezil base form D. Yield 0.80-0.85 gm.

Example 3

Donepezil Base (Oil) (1.0gm) was dissolved in a mixture of ethanol (3.0ml) and water (1.0ml) at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried under vacuum at 45-50°C to afford donepezil base form D. Yield 0.80-0.85 gm.

Example 4

Donepezil Base (Oil) (1.0gm) was dissolved in a mixture of methanol (2.0ml) and water (1.0ml) at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried under vacuum at 45-50°C to afford donepezil base form D. Yield 0.70-0.75 gm.

Example 5

Donepezil Base (Oil) (1.0gm) was dissolved in ethanol (4.0ml) and at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried under vacuum at 45-50°C to afford donepezil base form D. Yield 0.80-0.85 gm.

Example 6

Donepezil Base (Oil) (1.0gm) was dissolved in THF (4.0ml) and at 40-45°C. Reaction mixture was cooled and stirred. The water (40 ml) was added and stirred for 8 hr. The
solid material was filtered and dried under vacuum at 45-50°C to afford donepezil base form D. Yield 0.80-0.85 gm.

Example 7

Process for preparing Form D from Form B of Donepezil base:
Donepezil Base form B (1.0gm) was dissolved in a mixture of isopropyl alcohol (3.0ml) and water (1.0ml) at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried in vacuum at 45-50°C to afford form D. Yield 0.80-0.85 gm.

Example 8

Donepezil Base form B (1.0gm) was dissolved in a mixture of ethanol (3.0ml) and water (1.0ml) at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried in vacuum at 45-50°C to afford form D. Yield 0.80-0.85 gm.

Example 9

Donepezil Base form B (1.0gm) was dissolved in a mixture of methanol (2.0ml) and water (1.0ml) at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried in vacuum at 45-50°C to afford form D. Yield 0.70-0.75 gm.

Example 10

Donepezil Base (1.0 gm) was dissolved in methanol (3.0 ml) at 40-45°C. Water (3.0 ml) was added slowly to the reaction mixture. The reaction mixture was cooled slowly to room temperature in 2 hr with stirring to get solid material. The solid was filtered and dried at 50-55°C in vacuum to afford Form D. Yield 0.80-0.85 gm.

Example 11

Donepezil Base form B (1.0gm) was dissolved in ethanol (3.0ml) and at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried in vacuum at 45-50°C to afford form D. Yield 0.80 gm.
Example 12
Donepezil Base form B (1.0 gm) was dissolved in isopropyl alcohol (4.0ml) and at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried at 45-50°C in vacuum to afford form D; Yield 0.80-0.85 gm.

Example 13
Process for preparing Form E of Donepezil base
Donepezil Base (oil) (1.0 gm) was dissolved in acetone (5.0 ml) and hexane (2.0 ml). Diisopropyl ether (15.0 ml) was added. Reaction mixture was cooled and stirred. The solid material was filtered and dried at 45-50°C in vacuum to afford form E. Yield 0.80-0.82 gm.

Example 14
Process for preparing Form B of Donepezil base:
Donepezil Base (1.0 gm) was dissolved in ethyl acetate (4.0ml) and at 55-60°C. Reaction mixture was cooled and stirred. The solid material was filtered and dried at 45-50°C in vacuum to afford form B. Yield 0.75-0.80 gm.

Example 15
Donepezil Base (1.0 gm) was dissolved in ethyl acetate (4.0ml) and at 55-60°C. Reaction mixture was cooled and stirred. Diisopropyl ether was added to the reaction mixture and cooled to 10°C and stirred. The solid material was filtered and dried at 45-50°C in vacuum to afford form B. Yield 0.80-0.83 gm.

Example 16
Donepezil Base (1.0 gm) was dissolved in ethyl acetate (4.0ml) and at 55-60°C. Reaction mixture was cooled and stirred. Hexane was added to the reaction mixture and cooled to 10°C and stirred. The solid material was filtered and dried at 45-50°C in vacuum to afford Form B. Yield 0.80-0.85 gm.

Example 17
Donepezil Base (1.0 gm) was dissolved in methanol (2.0ml) and at 40-45°C. Reaction mixture was cooled and stirred. Hexane was added to the reaction mixture and cooled to 10°C and stirred. The solid material was filtered and dried at 45-50°C in vacuum to afford Form B. Yield 0.80-0.85 gm

Example 18
Donepezil Base (1.0 gm) was dissolved in methanol (2.0ml) and at 40-45°C. Reaction mixture was cooled to room temperature and stirred. Water (2.0 ml) was added to the reaction mixture and stirred. The solid material was filtered and dried at 50-55°C in vacuum to afford Form B. Yield 0.80-0.85 gm.

Example 19
Donepezil Base (1.0 gm) was dissolved in methanol (3.0 ml) and at 40-45°C. Water (3.0 ml) was added to the reaction mixture. The reaction mixture was fast cooled to room temperature and stirred to get solid material. The solid was filtered and dried at 50-55°C in vacuum to afford Form B. Yield 0.80-0.85 gm.

Certain modifications and improvements of the disclosed invention will occur to those skilled in the art without departing from the scope of invention, which is limited only by the appended claims.
We Claim:
1. Novel crystalline polymorphic forms of l-benzyl-4-(5,6-dimethoxy-l-
indanon-2-yl)methylpiperidine base, designated as Form D and E.

2. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-
indanon-2-yl)methylpiperidine base according to claim 1, designated as Form D

3. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-
indanon-2-yl)methylpiperidine base according to claim 2, wherein said polymorphic form
D is characterized by having an X-ray powder diffraction pattern at 4.8, 9.7, 16.9, 17.6, 17.9, 21.1 ± 0.2° 2Θvalues.

4. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-
indanon-2-yl)methylpiperidine base according to claim 3, wherein said polymorphic form
D is characterized by having an X-ray powder diffraction pattern at 4.8, 9.7, 12.9, 16.8, 16.9, 17.6, 17.9, 18.4, 18.7, 19.3, 19.7, 20.7, 21.1, 23.1, 23.2, 24.3, 25.0, 25.1, 26.0, 29.2 ±
0.2° 2Θvalues.

5. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-
indanon-2-yl)methylpiperidine base according to claim 4, wherein said X-ray powder
diffraction pattern is as depicted in Figure 1.

6. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-
indanon-2-yl)methylpiperidine base according to claim 2, wherein said polymorphic form
D is characterized by an infra red spectroscopy having absorption bands (cm⁻¹) at 2913, 2795, 2750, 1696, 1592, 1501, 1312, 1265, 1120, 1038 and 739.

7. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-
indanon-2-yl)methylpiperidine base according to claim 6, wherein said polymorphic form
D is characterized by an infrared spectroscopy having absorption bands (cm⁻¹) at 3374, 3067, 3009, 2913, 2841, 2795, 2750, 2723, 1696, 1606, 1592, 1501, 1480, 1458, 1429, 1361, 1340, 1312, 1265, 1226, 1203, 1190, 1147, 1120, 1108, 1072, 1038, 975, 886, 856, 839, 811, 785, 739, 698, 652, 561 and 463.
8. The crystalline polymorphic form of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base according to claim 7, wherein said infra red spectroscopy absorption bands (cm⁻¹) are as depicted in Figure 2.

9. A process for preparing crystalline polymorphic form D of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base comprising:
   (a) contacting 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base in a mixture of water and an organic solvent;
   (b) heating the reaction mixture at 40-60°C and stirring the same;
   (c) cooling the reaction mixture;
   (d) isolating the polymorphic form D of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base from the mixture.

10. The process according to claim 9, wherein said 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base is used in the form of oil or solid.

11. The process according to claim 9, wherein said organic solvent selected from alcohol or cyclic ether.

12. The process according to claim 11, wherein said alcohol is selected from C₁-C₄ alcohol.

13. The process according to claim 12, wherein said alcohol is preferably methanol and ethanol.

14. The process according to claim 11, wherein said cyclic ether is selected from tetrahydrofuran and dioxane.

15. The process according to claim 14, wherein said cyclic ether is preferably tetrahydrofuran.
16. A process for preparing crystalline polymorphic form D of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base comprising:
   (a) contacting 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base in an organic solvent;
   (b) heating the reaction mixture at 40-60°C and stirring the same;
   (c) cooling the reaction mixture;
   (d) isolating the polymorphic form D of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base from the mixture.

17. The process according to claim 16, wherein said 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base is used in the form of oil or solid.

18. The process according to claim 16, wherein said organic solvent selected from C₁-C₄ alcohol.

19. The process according to claim 18, wherein said alcohol is preferably methanol or ethanol.

20. A process for preparing crystalline 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base form D comprising:
   (a) contacting 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base in methanol;
   (b) heating the resultant mixture at 30 to 45°C;
   (c) adding water to the reaction solution;
   (d) cooling the reaction mixture to room temperature slowly;
   (e) isolating the polymorphic form D of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine from the resultant.

21. The process according to claim 20, wherein said 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base is in the form of oil or solid.

22. The crystalline polymorphic form of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base according to claim 1, designated as Form E.
23. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base according to claim 22, wherein said polymorphic form E is characterized by having an X-ray powder diffraction pattern at 4.9, 5.7, 12.3, 13.0, 13.3, 16.9, 17.0, 17.7, 17.9, 19.7, 21.1 and 24.2 ± 0.2° 2Θ values.

24. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base according to claim 23, wherein said polymorphic form E is characterized by having an X-ray powder diffraction pattern at 4.9, 5.7, 9.8, 12.3, 16.7, 16.9, 17.0, 17.7, 17.9, 19.3, 19.7, 20.7, 21.1, 21.6, 21.9, 22.9, 23.2, 23.4, 24.2, and 25.2 ± 0.2° 2Θ values.

25. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base according to claim 24, wherein said X-ray powder diffraction pattern is as depicted in Figure 5.

26. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base according to claim 22, wherein said polymorphic form E is characterized by an infra red spectroscopy having absorption bands (cm⁻¹) at 2919, 2795, 2751, 1696, 1592, 1501, 1312, 1266, 1129, 1038 and 739.

27. The crystalline polymorphic form of l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base according to claim 26, wherein said polymorphic form E is characterized by an infra red spectroscopy having absorption bands (cm⁻¹) at 3366, 3058, 3010, 2919, 2844, 2795, 2751, 1696, 1592, 1501, 1458, 1362, 1312, 1266, 1129, 1038, 976, 857, 811, 739, 698, 561 and 462.

28. A process for preparing the crystalline polymorphic form E of l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base comprising:

(a) contacting l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base in a mixture of organic solvents;
(b) adding antisolvent into the resultant mixture and stirring the same;
(c) isolating the polymorphic form E of 1-benzyl-4-(5,6-dimethoxy-1-
indanon-2-yl)methylpiperidine base from the mixture.

29. The process according to claim 28, wherein said 1-benzyl-4-(5,6-
dimethoxy-1-indanon-2-yl)methylpiperidine base is used in the form of oil or solid.

30. The process according to claim 28, wherein said mixture of solvents comprises an organic solvent selected from ketone or hydrocarbon.

31. The process according to claim 30, wherein said ketone is selected from acetone, methyl ethyl ketone or methyl isobutyl ketone.

32. The process according to claim 31, wherein said ketone is preferably acetone.

33. The process according to claim 30, wherein said hydrocarbon is selected from hexane, cyclohexane or heptane.

34. The process according to claim 33, wherein said hydrocarbon is preferably hexane.

35. The process according to claim 28, wherein said antisolvent is selected from any ether.

36. The process according to claim 35, wherein said ether is selected from diethyl ether or diisopropyl ether.

37. The process according to claim 36, wherein said ether is preferably diisopropyl ether.

38. A process for preparing crystalline 1-benzyl-4-(5,6-dimethoxy-1-indanon-
2-yl)methylpiperidine base form B comprising:
(a) contacting 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base in an alkyl acetate;
(b) heating the resultant mixture at 30 to 60°C;
(c) cooling the reaction mixture;
(d) adding optionally antisolvent to the reaction solution;
(e) isolating the polymorphic form B of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine from the resultant.

39. The process according to claim 38, wherein said 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base is in the form of oil or solid.

40. The process according to claim 38, wherein the alkyl acetate is preferably ethyl acetate.

41. The process according to claim 38, wherein the antisolvent is selected from the group comprising non-polar hydrocarbon or ether.

42. The process according to claim 41, wherein the non-polar hydrocarbon is selected from pentane, hexane, cyclohexane or heptane.

43. The process according to claim 41, wherein ether is selected from diisopropyl ether or diethyl ether.

44. A process for preparing crystalline 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base form B comprising:
(a) contacting 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine base in methanol;
(b) heating the resultant mixture at 30 to 60°C;
(c) cooling the reaction mixture;
(d) adding antisolvent to the reaction solution;
(e) isolating the polymorphic form B of 1-benzyl-4-(5,6-dimethoxy-1-indanon-2-yl)methylpiperidine from the resultant.
45. The process according to claim 44, wherein said l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base is in the form of oil or solid.

46. The process according to claim 44, wherein the antisolvent is selected from the group comprising non-polar hydrocarbon or water.

47. The process according to claim 46, wherein the non-polar hydrocarbon is selected from pentane, hexane, cyclohexane or heptane.

48. A process for preparing crystalline l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base form B comprising:
   (a) contacting l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base in methanol;
   (b) heating the resultant mixture at 30 to 45°C;
   (c) adding water to the reaction solution;
   (d) cooling the reaction mixture to room temperature immediately;
   (e) isolating the polymorphic form B of l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine from the resultant.

49. The process according to claim 48, wherein said l-benzyl-4-(5,6-dimethoxy-l-indanon-2-yl)methylpiperidine base is in the form of oil or solid.
TGA

Weight (%) vs Temperature (°C)

0.1488%
(0.01254 mg)
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**INV.** C07D211/32

**B. FIELDS SEARCHED**

**Min. doc. searched (classification system followed by classification symbols)**

C07D

**Documentation searched other than min. doc. to the extent such documents are included in the fields searched**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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**D. Further documents are listed in the continuation of Box C**

* " Special categories of cited documents
  1A* document defining the general state of the art which is not considered to be of particular relevance
  1E* earlier document but published on or after the international filing date
  1L* document which may throw doubts on priority claim(s) or Which is cited to establish the publication date of another citation or other special reason (as specified)
  1O* document referring to an oral disclosure, use exhibition or other means
  1P* document published prior to the international filing date but later than the priority date claimed
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  1X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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**Date of the actual completion of the international search**

26 June 2007

**Date of mailing of the International search report**

28/08/2007

**Name and mailing address of the ISA/**

European Patent Office, PB 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

**Authorized officer**

Usuell i, Ambrogio
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically.

3. Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a).

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos. 1(part), 2-21

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest

☐ No protest accompanied the payment of additional search fees
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