Abstract:

Disclosed herein discloses a crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone and process for preparing the same and use thereof. The present invention also provides a process for producing 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone employing the crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone to obtain pure and better yield.
CRystalline Form of 2-Chloro-3-[4-(4-Chlorophenyl) Cyclohexyl]-1,4-Napthoquinone, Process for the Same and Use for Producing 2-[4-(4-Chlorophenyl)Cyclohexyl]-3-hydroxy-1,4-napthoquinone

Field of the Invention

This invention, in general relates to a process for producing 2-[4-(4-chlorophenyl)-cyclohexyl]-3-hydroxy-1,4-naphthoquinone (Atovaquone). More particularly the present invention provides a crystalline form of 2-chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone, process for preparing the same and employing the same for producing 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

Background of the Invention

Atovaquone is an antiprotozoal agent for oral administration, chemically known as trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-napthalenedione as represented by Formula I:

![Formula I]

Atovaquone is a unique naphthoquinone with broad-spectrum antiprotozoal activity. It is effective for the treatment and prevention of Pneumocystis carinii pneumonia (PCP), a common parasitic lung infection of immunocompromised patients. It is not only used for the treatment of PCP, but also displays potent activity as an antimalarial agent, and has been used in the treatment of toxoplasmosis and babesiosis. Atovaquone is marketed under the brand name of MEPRON® oral suspension containing about 750mg of Atovaquone.

Atovaquone and its pharmaceutically acceptable salts are first disclosed in US Patent No 5,053,432 (the ’432 patent). The patent further discloses a process for the
preparation of trans compound of atovaquone. The specific process for the preparation of atovaquone is schematically represented in scheme-I as follows:

**Scheme-I**

The '432 patent discloses the process for the preparation of atovaquone, wherein 2-chloro-1,4-naphthoquinone of formula-II is condensed with 4-(4-chlorophenyl)cyclohexane-1-carboxylic acid of formula-III in the presence of silver nitrate and ammonium persulphate in a mixture of acetonitrile, sulpholane and water solvent system in the ratio of 1.0: 3.0: 8.0 to give 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone compound of formula-IV which is further subjected to hydrolysis in the presence of boiling methanol and aqueous KOH followed by recrystallization in acetonitrile to give atovaquone of compound of formula-I.

US Patent No 4,981,874 (the '874 patent) discloses a process for the preparation of atovaquone, wherein 2-chloro-1,4-naphthoquinone of formula-II is condensed with 4-(4-chlorophenyl)cyclohexane-1-carboxylic acid of formula-III in the presence of silver nitrate in a mixture of acetonitrile and water solvent system in the ratio of 5.0:6.0 to give 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4] naphthoquinone compound of formula-IV which is further subjected to hydrolysis in
the presence of boiling methanol and aqueous KOH followed by recrystallization in acetonitrile to give atovaquone compound of formula-I.

In the prior art processes 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone is obtained in low yield less than about 37%. In addition, the process requires a number of purification steps in different solvent mixtures to give the desired quality of the product.

Hence, the existing processes produce atovaquone having low purity and involve tedious work up to isolate the required product. A large number of purification steps result in low yield of the final product and makes the process more time consuming and not viable for commercial scale up.

Tetrahedron Letters 39 (1998) 7629-7632 discloses a process for the preparation of atovaquone which is schematically represented in scheme-H as follows:

According to the above scheme, the process for the preparation of atovaquone includes condensing 2-chloro-1,4-naphthoquinone compound of formula-II with 4-(4-chlorophenyl)cyclohexane-oxalate acid compound of formula-V in the presence of the
phase transfer catalyst Adogen®464, oxidant ammonium persulphate in a mixture of
dichloromethane, acetonitrile and water in the ratio of 1:1:2 to give 2-Chloro-3-[4-(4-
chlorophenyl)cyclohexyl][1,4] naphthoquinone in 43% yield and an additional side
product with 38% yield. Subsequently, 2-Chloro-3-[4-(4-
chlorophenyl)cyclohexyl][1,4] naphthoquinone is converted to atovaquone upon
treatment with potassium hydroxide in methanol at reflux followed by recrystallization in hot acetonitrile.

The additional side product formed along with the compound of formula-I in
the process requires repeated crystallizations to remove the additional side product
from the final product, thereby resulting in low yield at final stage.

In light of the foregoing processes, there exists a need to develop an alternate,
simple and commercially viable process for producing atovaquone. In addition, the
process should produce fewer side products thereby requiring fewer purification steps
and resulting in high yield of the final product.

Object and Summary of the Invention

It is an object of the present invention to provide a crystalline form of 2-
chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4] naphthoquinone and process thereof.

It is another object of the present invention to provide an improved process for
producing 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone
employing the crystalline form of 2-chloro-3-[4-(4-chlorophenyl) cyclohexyl]
[1,4]naphthoquinone.

It is yet another object of the present invention to provide a cost effective,
commercially viable and easily scalable process for producing 2-[4-(4-
chlorophenyl)cyclohexyl]-3-hydroxy- 1,4- naphthoquinone.

It is still another object of the present invention to provide an improved
process for the preparation of 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-
naphthoquinone, wherein the process produces fewer side products and requires
minimal purification steps to obtain 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-
naphthoquinone with high purity.

The above and other objects of the present invention are further attained and
supported by the following embodiments described herein. However, the scope of the
invention is not restricted to the described embodiments herein after.
In accordance with one preferred embodiment of the present invention, there is provided a crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone, wherein said crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone is characterized by an X-ray powder diffraction pattern having peaks at about 7.14, 9.91, 14.45, 14.90, 16.23, 17.81, 19.93, 21.56, 25.23, 25.51, 26.74 ± 0.2 °.

In accordance with another embodiment of the present invention, there is provided a compound 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone prepared by hydrolyzing the 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone in the presence of an alkali earth metal hydroxide and a solvent to give 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone, wherein the 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone is characterized by having purity more than 99.0%, preferably more than 99.5%.

In accordance with another embodiment of the present invention, there is provided a process for preparing crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone, wherein the process comprises of condensing 2-chloro-[1,4] naphthoquinone with 4-(4-chlorophenyl)-cyclohexane carboxylic acid in the presence of silver nitrate and a persulphate in a solvent mixture to give 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone, wherein the solvent mixture comprises acetonitrile, water and sulpholane in the ratio of 1.0: 1.0: 0.1 to 0.5.

In accordance with still another embodiment of the present invention, wherein the process further comprises of purifying the 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone by employing a solvent to obtain pure crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone.

In accordance with still another embodiment of the present invention, there is provided a process for preparing 2-[4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone, the process comprises of condensing 2-chloro-[1,4] naphthoquinone with 4-(4-chlorophenyl)-cyclohexane carboxylic acid in the presence of silver nitrate and a persulphate in a solvent mixture to give 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl][1,4]naphthoquinone, and hydrolyzing the 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl][1,4] naphthoquinone in the presence of an alkali earth
metal hydroxide and a solvent to give 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-
1,4- naphthoquinone, wherein the solvent mixture used for the condensation
comprises acetonitrile, water and sulpholane in the ratio 1.0: 1.0: 0.1 to 0.5.

In accordance with yet another embodiment of the present invention, the
solvent used in hydrolyzing the 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl]
[1,4]naphthoquinone is mixture of water and alcohol. The alcohol solvent is selected
from methanol, ethanol and isopropyl alcohol, preferably methanol.

In accordance with still another embodiment of the present invention, wherein
the process further comprises of purifying the 2-[4-(4-chlorophenyl)cyclohexyl]-3-
hydroxy-1,4- naphthoquinone employing a solvent to obtain pure 2-[4-(4-
chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

In accordance with still another embodiment of the present invention, wherein
the process further comprises of micronizing the pure 2-[4-(4-
chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone to obtain micronized 2-[4-
(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone having particle size
distribution d_{90} less than 10 micrometer, preferably between 3.0 - 10 micrometer.

**Brief Description of the Drawings**

Further objects 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 the X-ray diffraction pattern of 2-[4-(4-
chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone (Atovaquone) obtained as
per the present invention.

Fig. 2 shows the X-ray diffraction pattern of 2-Chloro-3-[4-(4-
chlorophenyl)cyclohexyl] [1,4]naphthoquinone compound of formula-IV obtained as
per the present invention.

**Detailed Description of the Invention**

While this specification concludes with claims particularly pointing out and
distinctly claiming that, which is regarded as the invention, it is anticipated that the
invention can be more readily understood through reading the following detailed
description of the invention and study of the included examples.
The present invention discloses a crystalline form of 2-chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone. The crystalline form of 2-chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone is characterized by X-ray powder diffraction pattern.

Further, the present invention describes an improved process for the preparation of 2-chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone. In addition, the 2-chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone is employed for the preparation of 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

**Powder X-ray Diffraction (PXRD)**

The crystalline form of 2-chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone of the present invention is characterized by its X-ray powder diffraction pattern. Thus, the X-ray diffraction pattern of said crystalline form of the invention was measured on PANalytical, X'Pert PRO powder diffractometer equipped with goniometer of θ/θ configuration and X'Celerator detector. The Cu-anode X-ray tube was operated at 40 KV and 30 mA. The experiments were conducted over the 2Θ range of 2.0°-50.0°, 0.030° step size and 50 seconds step time.

The crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone is characterized by an X-ray powder diffraction pattern as shown in Figure 2 having peaks at about 7.14, 9.91, 14.45, 14.90, 16.23, 17.81, 19.93, 21.56, 25.23, 25.51, 26.74 ± 0.2 Θ°.

According to the present invention, the improved process for the preparation of crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone of formula IV, wherein the process involves condensing 2-chloro-[1,4]naphthoquinone of formula (III) with 4-(4-chlorophenyl)-cyclohexane carboxylic acid of formula (II) in the presence of free radical initiators and an oxidant in a solvent mixture to give crude 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone of formula (IV) as shown in the following scheme:
According to the present invention, the process further comprises hydrolyzing 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone using an alkali earth metal hydroxide in presence of a suitable solvent to give 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone of formula I.

According to the present invention, the free radical initiator used in the condensation reaction is selected from sodium persulphate, ammonium persulphate, more preferably sodium persulphate and the oxidant is preferably silver nitrate.

According to the present invention, the solvent mixture used in the condensation of 2-chloro-[1,4]naphthoquinone of Formula-III with 4-(4-chlorophenyl)-cyclohexane carboxylic acid of Formula-II to obtain 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone compound of formula-IV is selected from water miscible organic solvent, water or mixtures thereof. The water miscible organic solvent is selected from acetonitrile, acetone, dimethylformamide, dimethylsulfoxide, sulpholane. The solvent mixture is preferably a mixture of acetonitrile, sulpholane and water.

According to a preferred embodiment of the present invention, condensation reaction is carried out in a solvent mixture containing acetonitrile, water and sulpholane in the ratio 1.0: 1.0: 0.1 to 0.5, preferably in the ratio 1.0: 1.0: 0.25.
The solvent ratio is very critical in this condensation step and results in formation of desired isomer predominantly as compared to the prior art process. In addition, complete conversion of the reactants occurs, thereby resulting in formation of fewer amounts of impurities. The process thus requires fewer purification steps to get desired quality and yield of 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone.

According to the present invention, the alkali earth metal hydroxide employed in the hydrolysis reaction is selected from sodium hydroxide, potassium hydroxide and preferably potassium hydroxide. The solvent employed in the hydrolysis step is preferably a mixture of water and alcohol, wherein the alcohol is selected from methanol, ethanol or isopropyl alcohol, preferably methanol.

According to the present invention, 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4] naphthoquinone compound of formula-IV is subjected to further purification employing a solvent. The solvent is selected from the group comprising alcohol, chlorinated hydrocarbons or mixtures thereof. The alcohol solvent is selected from methanol, ethanol, and isopropyl alcohol. The chlorinated hydrocarbon is selected from dichloromethane, dichloroethane, chloroform.

The purified 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone contains the desired isomer and impurities within limits. The purified 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone is subjected to hydrolysis in the presence of alkali earth metal hydroxides in a solvent to give 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone of compound formula (I).

According to the present invention, the above isolated 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone of compound formula (I) is further purified in a suitable solvent, preferably acetonitrile to give pure 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone of compound formula (I). The pure 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone so obtained is having the purity more than 99.0%, preferably more than 99.5% and all the impurities less than 0.1%. USP reference standard material and 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone obtained by the present invention were analyzed by HPLC.

The solvent ratio is very critical in this condensation step and results in formation of desired isomer predominantly as compared to the prior art process. In addition, complete conversion of the reactants occurs, thereby resulting in formation of fewer amounts of impurities. The process thus requires fewer purification steps to get desired quality and yield of 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone.

According to the present invention, the alkali earth metal hydroxide employed in the hydrolysis reaction is selected from sodium hydroxide, potassium hydroxide and preferably potassium hydroxide. The solvent employed in the hydrolysis step is preferably a mixture of water and alcohol, wherein the alcohol is selected from methanol, ethanol or isopropyl alcohol, preferably methanol.

According to the present invention, 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4] naphthoquinone compound of formula-IV is subjected to further purification employing a solvent. The solvent is selected from the group comprising alcohol, chlorinated hydrocarbons or mixtures thereof. The alcohol solvent is selected from methanol, ethanol, and isopropyl alcohol. The chlorinated hydrocarbon is selected from dichloromethane, dichloroethane, chloroform.

The purified 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone contains the desired isomer and impurities within limits. The purified 2-Chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4]naphthoquinone is subjected to hydrolysis in the presence of alkali earth metal hydroxides in a solvent to give 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone of compound formula (I).

According to the present invention, the above isolated 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone of compound formula (I) is further purified in a suitable solvent, preferably acetonitrile to give pure 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone of compound formula (I). The pure 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone so obtained is having the purity more than 99.0%, preferably more than 99.5% and all the impurities less than 0.1%. USP reference standard material and 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone obtained by the present invention were analyzed by HPLC.
According to the present invention, 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone is subjected to micronization to get a particle size distribution with \( d_{50} \) less than 10.0 micrometer, preferably more than 3.0 micrometer, more preferably \( d_{50} \) between 4.0 to 6.0 micrometer.

The disclosed process provides good conversion of reactants and formation of fewer impurities, thereby yielding the 2-chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4] naphthoquinone with high purity. In addition fewer purification steps are required to obtain pure crystalline form of 2-chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4] naphthoquinone. Furthermore, 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone obtained is having purity more than 99.0% and all the impurities less than 0.1%.

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

**Example-1**

**Preparation of 2-chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4] naphthoquinone**

A mixture of 2-chloro-[1,4]naphthoquinone (100.85g), acetonitrile (2000ml), DM water (2000ml), 4-(4-chlorophenyl)-cyclohexane carboxylic acid (100g), silver nitrate (26.8g) and sulpholane (500ml) was heated to 70-75\(^\circ\)C. Sodium persulphate solution (500ml) was added to the mixture and the mixture cooled to 25\(^\circ\)C. Toluene (1000ml) was added to the reaction mass, filtered and the layers were separated. Subsequently, toluene (200ml) was again added to the resulting reaction mass, the layers separated and washed with 10\% sodium chloride solution (1000ml X 2). Toluene was distilled off completely under vacuum. Acetonitrile (1000 ml) was added to the obtained residue, heated to reflux for over 15-30 min and cooled to 25\(^\circ\)C. The solid was filtered and washed with acetonitrile (100ml X 2). Dichloromethane (500ml) was added to the obtained wet material, stirred and methanol (750ml) was added. The solid was filtered, washed with methanol (100ml X 2) and dried under vacuum till LOD is <1.0%w/w to get 2-chloro-3-[4-(4-chlorophenyl)cyclohexyl][1,4] naphthoquinone.

Yield: 34g.
Example-2
Preparation of 2-chloro-3-[4-(4-chlorophenyl)cyclohexyl]-[1,4]naphthoquinone

To a mixture of 2-chloro-[1,4]naphthoquinone (100.85g), acetonitrile (2000ml), DM water (2000ml), 4-(4-chlorophenyl)-cyclohexanecarboxylic acid (100g), silver nitrate (26.8g) and sulpholane (500ml). The mixture was heated to 65-70°C and sodium persulphate solution is added (247.3 gm 500ml water). The resulting mixture was stirred for 2-3 hrs at 65-70°C and cooled to 5-10°C. The resultant mass was filtered and residual sticky solid was extracted with toluene (1500ml) to remove inorganic material. The toluene layer washed with 10% sodium chloride solution (1000ml X 2) and toluene was removed by distillation completely under vacuum. Acetonitrile (1000 ml) was added to the obtained residue, heated to reflux for over 15-30 min and cooled to 25°C. The solid was filtered and washed with acetonitrile (100ml X 2). Dichloromethane (500ml) was added to the obtained wet material, stirred and methanol (750ml) was added. The solid was filtered, washed with methanol (100ml X 2) and dried under vacuum till LOD is <1.0%w/w to get 2-chloro-3-[4-(4-chlorophenyl)cyclohexyl]-[1,4]naphthoquinone.

Yield: 37g.

Example-3
Preparation of 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone

To a mixture of 2-chloro-3-[4-(4-chlorophenyl)cyclohexyl]-[1,4]naphthoquinone (100g) and methanol (1800ml), potassium hydroxide solution (50.97 gm in 900ml) was added and heated to reflux for 300-360 min. The reaction mass was cooled to 25°C and toluene (1000ml) was added.

The aqueous layer was separated, filtered and washed with methanol: water in the ratio 2:1 (200ml). The pH of the filtrate and washing was adjusted to 5.0-5.5 by HCl solution (~250ml). The solid was filtered and water (1000ml) was added to the wet material. The resultant solid was filtered and washed with water (500ml). Acetonitrile (8500ml) was added to the wet material, heated to reflux for about 30min and slowly cooled to 20-25°C. The solid was filtered, washed with acetonitrile (200ml) and dried under vacuum till LOD is <0.5%w/w to get 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone.
Yield: 75g.

HPLC analysis for various samples obtained using the above mentioned process was performed, the results of which are mentioned in Table 1.

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<th>S. No.</th>
<th>Specification</th>
<th>USP (Limit)</th>
<th>Matrix Sample</th>
<th>USP Ref. Std.</th>
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<tr>
<td>01</td>
<td>Related comp. A (Cis isomer)</td>
<td>NMT 1.0 %</td>
<td>0.01</td>
<td>BDL</td>
</tr>
<tr>
<td>02</td>
<td>Impurity at RRT 0.63</td>
<td>NMT 0.50%</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>03</td>
<td>Impurity at RRT 0.89</td>
<td>NMT 0.30 %</td>
<td>BDL</td>
<td>BDL</td>
</tr>
<tr>
<td>04</td>
<td>Impurity at RRT 1.8</td>
<td>NMT 0.50 %</td>
<td>BDL</td>
<td>BDL</td>
</tr>
<tr>
<td>05</td>
<td>Any other unknown impurity</td>
<td>NMT 0.20 %</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>06</td>
<td>Total other unknown impurity</td>
<td>NMT 1.0 %</td>
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</tr>
<tr>
<td>07</td>
<td>Total impurity</td>
<td>NMT 1.5 %</td>
<td>0.14</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Example-4**

Micronization of 2-r4-(4-chlorophenyl)cyclohexyl1-3-hydroxy-1,4-naphthoquinone
2-r4-(4-chlorophenyl)cyclohexyl 1-3-hydroxy-1,4-naphthoquinone was micronized to obtain a target d90 between 10µm to 3µm. The particle size obtained in the above examples dso (0.5) of the feed stock was 25.45 µm with a d90(0.9) of 52.58 µm. This was micronized and material produced with partial size dso(0.5) of 1.9µm with a d90(0.9) of 4.4µm.

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. A crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [l,4]naphthoquinone, wherein said crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [l,4]naphthoquinone is characterized by an X-ray powder diffraction pattern having peaks at about 7.14, 9.91, 14.45, 14.90, 16.23, 17.81, 19.93, 21.56, 25.23, 25.51, 26.74 ± 0.2 θ°.

2. The crystalline form according to claim 1, wherein said crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [l,4]naphthoquinone is having a substantially similar X-ray powder diffraction pattern as depicted in Figure 2.

3. The crystalline form according to claim 1, wherein said crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [l,4]naphthoquinone is employed to prepare 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone by hydrolyzing the 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [l,4]naphthoquinone in the presence of an alkali earth metal hydroxide and a solvent to give 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4- naphthoquinone.

4. The crystalline form according to claim 3, wherein the solvent is a mixture of water and alcohol.

5. The crystalline form according to claim 1, wherein said crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [l,4]naphthoquinone is characterized by having purity more than 99.0%, preferably more than 99.5%.

6. A process for preparing crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [l,4]naphthoquinone comprising condensing 2-chloro-[1,4] naphthoquinone with 4-(4-chlorophenyl)-cyclohexane carboxylic acid in the presence of silver nitrate and a persulphate in a solvent mixture to give 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl][l,4]naphthoquinone, wherein the solvent mixture comprises acetonitrile, water and sulpholane in the ratio of 1.0: 1.0: 0.1 to 0.5.

7. The process according to claim 6, wherein the ratio of acetonitrile, water and sulpholane in the solvent mixture is 1.0: 1.0: 0.1 to 0.25.

8. The process according to claim 6, wherein the persulphate is selected from ammonium persulphate or sodium persulphate.

9. The process according to claim 6, wherein the process further comprising purifying 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl]
[1,4]naphthoquinone by employing a solvent to obtain pure crystalline form of 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl] [1,4]naphthoquinone.

10. The process according to claim 9, wherein the solvent is selected from a group comprising alcohol, chlorinated solvents or mixtures thereof.

11. The process according to claim 10, wherein the alcohol is selected from methanol, ethanol and isopropyl alcohol.

12. The process according to claim 10, wherein the chlorinated solvent is selected from dichloromethane, dichloroethane or mixtures thereof.

13. A process for preparing 2-[4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone, the process comprising:

a) condensing 2-chloro-[1,4] naphthoquinone with 4-(4-chlorophenyl)-cyclohexane carboxylic acid in the presence of silver nitrate and a persulphate in a solvent mixture to give 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl][1,4]naphthoquinone, wherein the solvent mixture comprises acetonitrile, water and sulpholane in the ratio 1.0: 1.0: 0.1 to 0.5; and

b) hydrolyzing the 2-Chloro-3-[4-(4-chlorophenyl) cyclohexyl][1,4] naphthoquinone in the presence of an alkali earth metal hydroxide and a solvent to give 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

14. The process according to claim 13, wherein the ratio of acetonitrile, water and sulpholane in the solvent mixture is 1.0: 1.0: 0.1 to 0.25.

15. The process according to claim 13, wherein the persulphate is selected from ammonium persulphate or sodium persulphate.

16. The crystalline form according to claim 13, wherein the solvent employed in step (b) is a mixture of water and alcohol.

17. The process according to claim 13, the process further comprising purifying 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone employing a solvent to obtain pure 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

18. The process according to claim 17, wherein the solvent is preferably acetonitrile.
19. The process according to claim 17, wherein the process further comprising micronizing the pure 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone to obtain micronized 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone having particle size distribution \( d_{90} \) less than 10 micrometer, preferably between 3.0 - 10 micrometer.

20. A compound 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone prepared according to claim 13, wherein the 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone is characterized by having purity more than 99.0% and preferably more than 99.5%.