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(54) Title: CYCLODEXTRIN COMPLEXES OF ATOVAQUONE

(57) Abstract: The present invention relates to an inclusion complex of Atovaquone or its pharmaceutically acceptable salts and cyclodextrin or its derivatives, wherein the molar ratio of atovaquone to cyclodextrin in the inclusion complex ranges from about 1:2 to about 1:5.



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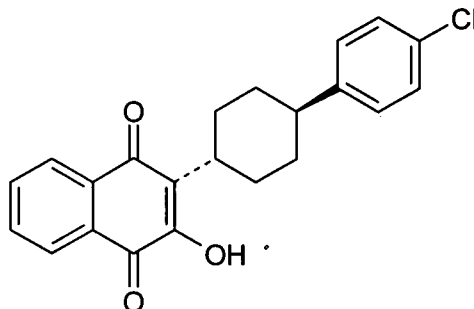
CYCLODEXTRIN COMPLEXES OF ATOVAQUONE

FIELD OF THE INVENTION

The present invention relates to an inclusion complex of *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione a compound of formula I with cyclodextrins, a method for their preparation and pharmaceutical compositions containing these complexes for therapeutic use.

BACKGROUND OF THE INVENTION

The compound of formula I, commonly known as atovaquone, is an antiprotozoal agent used in the treatment and/or prophylaxis of *Pneumocystis carinii* pneumonia. Further uses of atovaquone as a therapeutic agent for *toxoplasmosis* and *cryptosporidiosis* are disclosed in European Patent application nos. EP 0445141 and EP0496729, respectively.



Atovaquone is a yellow crystalline solid that is practically insoluble in water. The efficacy of atovaquone as a therapeutic agent is limited because of its oral bioavailability, which may be ascribed to its poor aqueous solubility.

Conventional means of improving bioavailability by reducing particle size of atovaquone, and therefore surface area available for dissolution, have been reported to be disadvantageous. A particular problem reported is that conventional processes of particle size reduction, such as air jet milling, were incapable of reducing the particle size of atovaquone below 6 microns. Further reduction was found to cause fracture of the crystal structure of atovaquone, thereby leading to oozing of a red dye when such milled material was suspended in an aqueous vehicle. Therefore, conventional methodologies such as size reduction for increasing the dissolution and improving bioavailability are not suitable for atovaquone.

Other techniques to increase the dissolution and thereby its bioavailability include microfluidization technique using a microfluidizer to reduce the particle size. United States Patent No: 6,649,659 discloses microfluidized particles of atovaquone having mean particle size in the range 0.1 to 3 microns, produced using a microfluidizer, and compositions thereof. But, the process of microfluidization is complicated, results in longer processing time and further the equipment and its maintenance costs are very high.

Hence, there is a need for alternative methods to increase aqueous solubility of atovaquone which in turn would lead to increased bioavailability.

We have now found an inclusion complex of atovaquone with cyclodextrins and that such an inclusion complex provides an enhanced aqueous solubility and dissolution and a more bioavailable form of atovaquone.

OBJECTS OF THE INVENTION

It is therefore an object of the present invention to provide atovaquone with increased solubility thereby providing it in a more bioavailable form.

It is another object of the present invention to increase the solubility of atovaquone by preparing inclusion complex of atovaquone and cyclodextrin.

It is further object of the present invention to provide a pharmaceutical composition comprising an inclusion complex of atovaquone-cyclodextrin and pharmaceutically acceptable excipients, wherein the pharmaceutical composition is suitable for oral administration.

SUMMARY OF THE INVENTION

In one aspect of the present invention, there is provided an inclusion complex of Atovaquone or its pharmaceutically acceptable salts and cyclodextrin or its derivatives, wherein the molar ratio of atovaquone to cyclodextrin in the inclusion complex ranges from about 1:2 to about 1:5.

In another aspect of the present invention there is provided a process of preparing inclusion complex of atovaquone and cyclodextrin.

In yet another aspect of the present invention there is provided a pharmaceutical composition comprising an inclusion complex of atovaquone and cyclodextrin; and pharmaceutically acceptable excipients, wherein the pharmaceutical composition is suitable for oral administration.

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DETAILED DESCRIPTION OF THE INVENTION

10 The present invention provides an inclusion complex of Atovaquone or its pharmaceutically acceptable salts and cyclodextrin or its derivatives, wherein the molar ratio of atovaquone to cyclodextrin in the inclusion complex ranges from about 1:2 to about 1:5.

15 The inclusion complex of atovaquone-cyclodextrin of the present invention contains atovaquone or its pharmaceutically acceptable salts. The suitable bases that form physiologically acceptable salts of atovaquone include inorganic base salts such as alkali metal (e.g. sodium and potassium) salts and alkaline earth metal (e.g. calcium salts; organic base salts e.g. phenylethylbenzylamine, dibenzylethylenediamine, ethanolamine and diethanolamine salts; and amino acid salts e.g. lysine and arginine.

20 The term "complex" or "inclusion complex" as used herein refers to a complex that is formed between atovaquone and the cyclodextrin wherein the atovaquone molecules are located inside the cyclodextrin cavities. There is no covalent bonding between atovaquone and cyclodextrin, the attraction being generally due to van der Waals forces. The inclusion complex that is produced in the present invention is in a powder form.

25 Cyclodextrins are a group of structurally related saccharides which are formed by enzymatic cyclization of starch by a group of amylases termed glycosyltransferases. Cyclodextrins are cyclic oligosaccharides, consisting of (alpha-1,4)-linked alpha-D-glucopyranose units, with a lipophilic central cavity and a hydrophilic outer surface. The cyclodextrins that may be used in the inclusion complex of the present invention may be selected from alpha-cyclodextrin, beta-cyclodextrin and
30 gamma-cyclodextrin consisting of 6, 7 and 8 glucopyranose units, respectively and their derivatives. Examples of cyclodextrin derivatives that may be used include hydroxypropyl derivatives of alpha-, beta- and gamma-cyclodextrin, sulfoalkylether cyclodextrins such as sulfobutylether beta-cyclodextrin, alkylated cyclodextrins such as the randomly methylated beta-

cyclodextrin, and various branched cyclodextrins such as glucosyl- and maltosyl beta-cyclodextrin, and the like, and mixtures thereof. The preferred cyclodextrin that can be used in the inclusion complex is beta-cyclodextrin (β -cyclodextrin).

- 5 The ratio of atovaquone to cyclodextrin in the inclusion complex of the present invention varies from about 1:1 to about 1:5; preferably from about 1:2 to about 1:5.

In a preferred embodiment, the ratio of atovaquone to beta-cyclodextrin in the inclusion complex of the present invention varies from about 1:1 to about 1:5; preferably from about 1:2 to about
10 1:5.

In one embodiment of the present invention, the atovaquone-cyclodextrin complex is prepared by dissolving cyclodextrin and atovaquone in an aqueous medium comprising a volatile amine, and drying.

15 In another embodiment of the present invention, the atovaquone-cyclodextrin is prepared by dissolving cyclodextrin and atovaquone in aqueous medium comprising a water miscible organic solvent and a volatile amine and drying.

- 20 The inclusion complex of atovaquone with cyclodextrins prepared as per the process of the present invention, possess high aqueous solubility, and provide rapid absorption, enhanced bioavailability and better tolerability.

The aqueous medium for dissolution of the cyclodextrin for forming the inclusion complex may
25 be selected from water (water for injection) or an aqueous system comprising a major proportion of water.

The water miscible organic solvents that may be used in preparing atovaquone-cyclodextrin inclusion complexes include monohydric alcohols like methanol, ethanol, 1-propanol, 2-propanol;
30 ketones like acetone, 2-butanone; ethers like dihydrofuran; nitriles like acetonitrile, and the like.

The volatile amines that may be used in preparing atovaquone-cyclodextrin inclusion complexes include methyl amine, ethyl amine, dimethyl amine, trimethyl amine, ammonia and the like. Preferably, the volatile amine that is used is ammonia solution (liquor ammonia), used in a

concentration of about 23% to about 25%. The ratio of volatile amine to the water miscible organic solvent that is used in the preparation of the atovaquone-cyclodextrin complex of the invention is about 1:10.

- 5 The inclusion complex formed may be suitably dried using methods like flash evaporation, spray drying or freeze drying or any suitable methods known in the art.

In a preferred embodiment, the atovaquone-cyclodextrin inclusion complex was prepared by dissolving β -cyclodextrin in demineralized water at 60⁰ C to 65⁰ C. Atovaquone, liquor ammonia
10 and 2-propanol was added to the cyclodextrin solution, to obtain a clear reddish solution. The solution was then flash dried under vacuum at 85⁰ C to 90⁰C to obtain a yellowish powder containing atovaquone-cyclodextrin complex.

In another embodiment, the present invention provides a pharmaceutical composition of
15 atovaquone comprising: an inclusion complex of atovaquone-cyclodextrin prepared according to the present invention; and pharmaceutically acceptable excipients, wherein the pharmaceutical composition is suitable for oral administration.

The dissolution test that is recommended for atovaquone and Proguanil hydrochloride tablets by
20 Food and Drug Administration (FDA) was adopted for performing in-vitro dissolution studies of atovaquone-cyclodextrin complex. The dissolution test comprises a U.S.P Type II, paddle with peak vessels in a dissolution medium of pH 8.0 potassium dihydrogen phosphate buffer and 40% isopropanol, in a volume of 900 ml and samples analyzed at an interval of 15, 30, and 60 minutes. The atovaquone-cyclodextrin complexes of the present invention were found to dissolve in less
25 than 2 hours, preferably in less than 1 hour when subjected to invitro dissolution test as described above for atovaquone and proguanil hydrochloride tablets.

The atovaquone-cyclodextrin complex of the present invention may be formulated into various pharmaceutical dosage forms for administration to the humans. To prepare pharmaceutical
30 compositions containing the inclusion complex of the present invention, an effective amount of atovaquone-cyclodextrin is combined with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical formulations include those suitable for oral and parenteral (including subcutaneous, intradermal, intramuscular and intravenous) administration as well as by naso-

gastric tube. Preferable pharmaceutical compositions suitable for oral administrations include solid dosage forms such as tablets, granules, pellets, capsules, sachets, suspensions and solutions. Most preferably, the inclusion complex may be formulated as an oral suspension. The composition formulated as oral suspension may include additives or excipients selected from suspending agents, viscosity modifiers, sweetening agents, flavors, colorants, antioxidants, chelating agents, surfactants, wetting agents, antifoaming agents, pH modifiers, acidifiers, preservatives, cosolvents, and mixtures thereof.

The following examples are provided only for the purpose of illustrating the invention, and in no way they may be construed as a limitation to the scope of the invention.

EXAMPLES

EXAMPLE 1

Preparation of atovaquone- β -cyclodextrin complex

To a stirred mixture of β -cyclodextrin in demineralized water at 60-65°C was added atovaquone. Liquor ammonia was then added, followed by 2-propanol, and a clear reddish solution was obtained. The solution was then flash dried under vacuum at 85-90°C to obtain a yellowish powder of the atovaquone-cyclodextrin complex. The mole ratio of atovaquone to β -cyclodextrin used in the preparation of complexes are 1:1, 1:2 and 1:3 and are shown in Tables 1-3 below:

Table 1 : Atovaquone - β -cyclodextrin (1:1)

Materials	Unit	Quantity	Mole
Atovaquone	g	0.50	1.00
β -cyclodextrin (on anhyd. Basis)	g	1.55	1.00
Ammonia solution (23-25%)	ml	1.00	-
2-Propanol	ml	10.00	-
Demineralised Water	ml	25.00	-

Table 2 : Atovaquone - β -cyclodextrin (1:2)

Materials	Unit	Quantity	Mole
Atovaquone	g	0.50	1.00
β -cyclodextrin (on anhyd. Basis)	g	3.10	2.00
Ammonia solution (23-25%)	ml	1.00	-
2-Propanol	ml	10.00	-
Demineralised Water	ml	25.00	-

Table 3: Atovaquone - β -cyclodextrin (1:3)

Materials	Unit	Qty	Mole
Atovaquone	gm	0.50	1.00
β -cyclodextrin (on anhyd. Basis)	gm	4.65	3.00
Ammonia solution (23-25%)	ml	1.00	-
2-Propanol	ml	10.00	-
Demineralised Water	ml	25.00	-

EXAMPLE 2

In-vitro dissolution profile of Atovaquone - β -cyclodextrin complexes

The atovaquone- β -cyclodextrin complex in a powder form and microfluidized atovaquone (commercially available as MEPRON®) oral suspension equivalent to 750 mg of atovaquone was taken in 900ml of pH 8 sodium phosphate buffer containing 0.5% Sodium lauryl sulfate (SLS) in a United States Pharmacopoeia type II dissolution apparatus and stirred at a speed of 50rpm. The samples were analyzed at an interval of 0, 15, 30, 45 and 60 minute for the %drug dissolved using High Performance Liquid chromatography (HPLC). The results are recorded in Table 4 below.

Table 4

Time (min)	Medium: 900ml, pH 8.0 Sodium Phosphate Buffer with 0.5% SLS, USP II, 50 rpm			
	% Drug dissolved			
	Atv- β -CD(1:1)	Atv- β -CD (1:2)	Atv- β -CD (1:3)	Microfluidized Atovaquone (MEPRON)
0	0.00	0.00	0.00	0.00
15	2.06	56.87	59.18	27.9
30	2.87	62.62	65.38	32.73
45	3.68	63.03	67.91	34.93
60	3.02	62.45	70.41	34.55

The data clearly demonstrates that atovaquone- β -cyclodextrin complexes (1:2 and 1:3) have higher % dissolution of the atovaquone when compared with microfluidized atovaquone.

The drug dissolution profiles of atovaquone - β -cyclodextrin complex (Atv- β -CD) was also compared with microfluidized atovaquone (commercially available as MEPRON®) and unmilled atovaquone, in 900ml of pH 8 sodium phosphate buffer containing 40% 2-propanol, in a United

States Pharmacopoeia (USP) type II dissolution apparatus, at a speed of 50rpm. The results are recorded in Table 5 below.

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Table 5

Time (min)	Medium: 900ml, pH 8.0 Sodium Phosphate Buffer with 40% 2-propanol,		
	% Drug dissolved		
	Atovaquone	atovaquone - β -cyclodextrin (1:3)	Microfluidized Atovaquone (MEPRON)
0	0.00	0.00	0.00
15	51.60	84.80	44.94
30	55.59	99.59	50.32
45	58.50	102.31	51.71
60	59.50	102.74	52.77

10

The data clearly demonstrates that atovaquone- β -cyclodextrin complex (1:3) when subjected to the USP test as above, the atovaquone dissolves within 1 hour into the dissolution medium.

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We claim:

1. An inclusion complex of Atovaquone or its pharmaceutically acceptable salts and cyclodextrin or its derivatives, wherein the molar ratio of atovaquone to cyclodextrin in the inclusion complex ranges from about 1:2 to about 1:5.
2. An inclusion complex of Atovaquone as in claim 1, wherein the said cyclodextrin is selected from the group consisting of alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin and their derivatives.
3. An inclusion complex of atovaquone as in claim 1, wherein the inclusion complex is in a powder form.
4. An inclusion complex as in claim 1, wherein the complex is prepared by dissolving cyclodextrin, atovaquone in an aqueous medium comprising a volatile amine, and drying.
5. An inclusion complex as in claim 1, wherein the complex is prepared by dissolving cyclodextrin, atovaquone in an aqueous medium comprising a water miscible organic solvent and a volatile amine, and drying.
6. The process as in claim 4 or 5, wherein the volatile amine is ammonia.
7. The process as in claim 5, wherein the water miscible organic solvent is 2-propanol.
8. The process as in claim 4 or 5, wherein the drying is carried out by flash evaporation, spray drying or by freeze drying.
9. A pharmaceutical composition of atovaquone comprising an inclusion complex of atovaquone-cyclodextrin as in claim 1 and pharmaceutically acceptable excipients, wherein the pharmaceutical composition is suitable for oral administration.
10. A pharmaceutical composition as in claim 9, wherein the composition is in the form of granules, pellets, tablets, capsules, sachets, suspensions, solutions suitable for oral administration.