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(54) Title: AQUEOUS ORAL FORMULATIONS OF RISPERIDONE

(57) Abstract: The present invention relates to stable aqueous solution of risperidone or salts thereof for oral administration. The invention also relates to processes for preparation of such formulations.

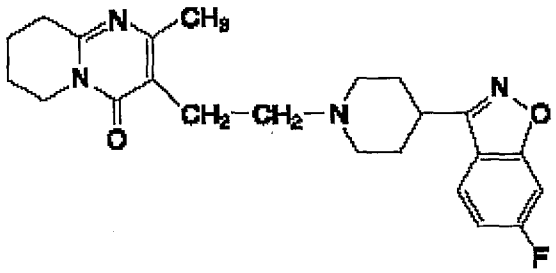
AQUEOUS ORAL FORMULATIONS OF RISPERIDONE

Field of the Invention

The present invention relates to stable aqueous solution of risperidone or salts thereof for oral administration. The invention also relates to processes for preparation of such formulations.

Background of the Invention

Risperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one of formula 1. Risperidone is indicated for the treatment of schizophrenia. It is also indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.



FORMULA I

U.S. Patent No. 4,804,663 discloses a pharmaceutical composition for treating psychotic diseases, comprising an inert carrier and a pharmaceutically effective amount of risperidone as an active ingredient.

U.S. Patent Nos. 5,453,425 and 5,616,587 disclose aqueous solutions for oral administration containing water, risperidone or its acid addition salt and preservative. The

pH of the solution was maintained between the ranges of about 2 to 6. This solution is essentially free of sorbitol.

U.S. Patent No. RE39181 discloses aqueous solution suitable for oral and parenteral administration comprising water, risperidone or a pharmaceutically acceptable acid addition salt thereof. The solution comprises a buffer to maintain the pH in the range of 2 to 6 and is essentially free of sorbitol.

European Patent Application No. 1,534,288 discloses an aqueous solution containing water; a therapeutically effective amount of risperidone or a pharmaceutically acceptable free base or acid addition salt; one or more polyhydric alcohols; and one or more buffering agents configured to maintain the pH in the range of about 3 to about 4.

European Patent Application No. 1,757,294 discloses aqueous risperidone solution for oral administration substantially free from sorbitol, and comprises a buffering system selected from the citric acid/ disodium phosphate, disodium phosphate/monosodium phosphate and monopotassium phosphate/sodium hydroxide group, and the solution pH is adjusted between 6.0 and 7.5. Further solution contains one or more preservatives, effective in the pH range between 6.0 and 7.5.

European Patent Application No. 1,739,086 discloses stable aqueous solution of risperidone, for oral administration, which contains amino acids as regulators and stabilizing agents and celluloses as agents that increase the viscosity of the solution, which also excludes the use of polyhydric alcohols.

PCT Application No. WO 2006129160 discloses buffer free stable oral solution composition comprising risperidone and benzoic acid or sorbic acid as preservative and process for the preparation of the same.

Summary of the Invention

In one general aspect there is provided an aqueous solution for oral administration comprising a therapeutically effective amount of risperidone or a pharmaceutically acceptable acid addition salt thereof, and one or more cyclodextrins or derivatives thereof.

The aqueous solubility of risperidone may be enhanced by the addition of a pharmaceutically acceptable cyclodextrins or a derivative thereof to an aqueous solution.

Embodiments of the solution may include one or more of the following features. For example, the solution may further include one or more pharmaceutically acceptable additives. The one or more pharmaceutically acceptable additives may be one or more of chelating agents, sweetening agents, flavouring substances, viscosity regulating agents, preservatives, buffering agents and the like.

In another general aspect there is provided an aqueous solution for oral administration comprising a therapeutically effective amount of risperidone or a pharmaceutically acceptable acid addition salt thereof and one or more cyclodextrins or derivatives thereof, wherein the pH of the solution is about 6.5 and above.

The pH of the solution is about 7.5. The pH of the solution may be adjusted by addition of buffering agents.

Embodiments of the solution may include one or more of the following features. For example, the solution may further include one or more pharmaceutically acceptable additives. The one or more pharmaceutically acceptable additives may be one or more of chelating agents, sweetening agents, flavouring substances, viscosity regulating agents, preservatives, buffering agents, and the like.

In yet another general aspect there is provided a process for the preparation of an aqueous solution of risperidone, the process comprising mixing water, a therapeutically effective amount of risperidone or a pharmaceutically acceptable acid addition salt thereof, one or more cyclodextrins or derivatives thereof; and one or more buffering agents to maintain the pH of the solution in the range of about 6.5 and above.

Embodiments of the solution may include one or more of the following features. For example, the solution may further include one or more pharmaceutically acceptable additives. The one or more pharmaceutically acceptable additives may be one or more of chelating agents, sweetening agents, flavouring substances, viscosity regulating agents, preservatives, buffering agents, and the like.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The present invention provides an aqueous solution for oral administration comprising a therapeutically effective amount of risperidone or a pharmaceutically acceptable acid addition salt thereof and one or more cyclodextrins or derivatives thereof, characterised in that the pH of the solution is about 6.5 and above.

The term "therapeutically effective amount" as used herein refers to the quantity of a compound or composition according to the invention necessary to prevent, cure or at least partially arrest the symptoms of the disorder and its complications. Amounts effective to achieve this goal will, of course, depend on the severity of the disease and the weight and general state of the patient. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of the pharmaceutical composition, and animal models may be used to determine effective dosages for treatment of particular disorders. Various considerations are described, for example, in Gilman et al., eds., 1900,

"Goodman and Gilman's: The Pharmaceutical Bases of Therapeutics," 8th ed., Pergamon Press; and Remington's Pharmaceutical Sciences," 1990, 17th ed., Mack Publishing Co., Easton, Pa., each of which is hereby incorporated by reference.

The pharmaceutically acceptable acid addition salts include one or more salts of risperidone with inorganic acids such as hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methane-sulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

The cyclodextrin or derivatives thereof that may be used include β-cyclodextrin, α-cyclodextrin, γ-cyclodextrin, hydroxypropyl-α-cyclodextrin, hydroxypropyl-β-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin, 2-hydroxypropyl-gamma-cyclodextrin and the like.

The solution may further include one or more pharmaceutically acceptable additives such as chelating agents, sweetening agents, flavoring substances, viscosity regulating agents, preservatives, buffering agents and the like additives.

Examples of chelating agents include one or more of edetic acid and its salts, Disodium EDTA and the like. Chelating agents help to stabilize the product during storage.

The bitter taste of risperidone may be masked by the presence of one or more sweetening agents such as sodium saccharin, potassium saccharin, calcium saccharin, neotame, acesulfame potassium or sodium cyclamate.

Examples of flavors include all FDA approved flavors suitable for oral use such as vanilla, cherry, raspberry, strawberry and the like.

Suitable viscosity regulating agents may include one or more of hydroxypropyl methylcellulose, hydroxypropylcellulose and the like.

The preservatives prevent the growth of micro-organisms in the formulation and may be one or more of methylparaben or salt thereof, propylparaben or salt thereof, benzoic acid, sorbic acid, benzylalkonium chloride and the like.

The oral solution according to the present invention has a pH of about 6.5 and above. For example, the pH of the solution may be 7.5. The pH of the solution may be adjusted by addition of buffering agents.

The buffering agents that may be used include an acid-base combination or base alone. The acid may be one or more of succinic, tartaric, lactic or citric acid and the base may be one or more of potassium hydroxide, sodium hydroxide or disodium hydrogen phosphate, monosodium phosphate, monopotassium phosphate and the like.

The risperidone oral solution may be prepared by the processes known in the art for preparation of oral solution. In particular, it may be prepared by dissolving risperidone in purified water and adding hydroxypropyl-β-cyclodextrin to the above solution; dissolving sodium methyl paraben and sodium propyl paraben in purified water and adding to the above solution; dissolving disodium EDTA in hot water and adding to the above solution; dissolving sodium saccharine in purified water and adding to the above solution; and adjusting pH of the solution with a buffering agent and making up the volume.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Examples:

Table 1and 2 provides composition of batches of the present invention.

Table 1 - Risperidone Solution using Sodium Saccharine as the sweetener

Sr.No	Ingredients	Qty/100 ml	Qty/500 ml
1	Risperidone	100 mg	500 mg
2	Malic acid	100 mg	500 mg
3	Hydroxypropyl-β-cyclodextrin	913.5 mg	4.56 gm
4	Sodium Methyl Paraben	0.18 gm	0.9 gm
5	Sodium Propyl Paraben	0.02 gm	0.1 gm
6	Disodium EDTA	10 mg	50 mg
7	Potassium Hydroxide	0.101 gm	0.505 gm
8	Sodium Saccharine	250 mg	1.25 gm
9	Purified Water	QS to 100 ml	QS to 500 ml

Procedure-

Malic acid was dissolved in purified water. Risperidone was dissolved in the above solution under stirring. Hydroxypropyl-β-cyclodextrin was added to the above solution and stirred for 2 hours. Sodium methyl paraben and sodium propyl paraben were dissolved in purified water and this solution was added to the above solution containing risperidone. Disodium EDTA was dissolved in hot purified water and added to the above solution. Sodium saccharine was dissolved in purified water and added to the above solution. The pH of the solution at this stage was 4.4 and was adjusted to 7.5 using 2.5% potassium hydroxide solution, followed by volume make up with purified water. The above solution was then filtered through Millipore prefilter under vacuum and filled into suitable containers.

Table 2: Risperidone Solution using Neotame as the sweetener.

Sr.No	Ingredients	Qty/100 ml	Qty/500 ml
1	Risperidone	100 mg	500 mg
2	Malic acid	100 mg	500 mg
3	Hydroxypropyl-β-cyclodextrin	913.5 mg	4.56 gm
4	Sodium Methyl Paraben	0.18 gm	0.9 gm
5	Sodium Propyl Paraben	0.02 gm	0.1 gm
6	Disodium EDTA	10 mg	50 mg
7	Potassium Hydroxide	0.101 gm	0.505 gm
8	Neotame	5 mg	25 mg
9	Purified Water	QS to 100 ml	QS to 500 ml

Procedure-

Malic acid was dissolved in purified water. Risperidone was dissolved in the above solution under stirring. Hydroxypropyl-β-cyclodextrin was added to the above solution and stirred for 2 hours. Sodium methyl paraben and sodium propyl paraben were dissolved in purified water and this solution was added to the above solution containing risperidone. Disodium EDTA was dissolved in hot purified water and added to the above solution. Neotame was dissolved in purified water and added to the above solution. The pH of the solution at this stage was 4.4 and was adjusted to 7.5 using 2.5% potassium hydroxide solution, followed by volume make up with purified water. The above solution was then filtered through Millipore prefilter under vacuum and filled into suitable containers.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. An aqueous solution for oral administration comprising a therapeutically effective amount of risperidone or a pharmaceutically acceptable acid addition salt thereof, and one or more cyclodextrins or derivatives thereof.

2. The aqueous solution according to claim 1, wherein the acid addition salt is selected from one or more of salts of risperidone with inorganic acids comprising hydrochloric, hydrobromic, sulfuric, nitric, and phosphoric acids; or organic acids comprising acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, and citric acids.

3. The aqueous solution according to claim 1, wherein the cyclodextrin comprises one or more of β-cyclodextrin, α-cyclodextrin, γ-cyclodextrin, hydroxypropyl-α-cyclodextrin, hydroxypropyl-β-cyclodextrin, 2-hydroxy propyl-beta-cyclodextrin, and 2-hydroxypropyl-gamma-cyclodextrin.

4. The aqueous solution according to claim 3, wherein the cyclodextrin comprises hydroxypropyl-beta-cyclodextrin.

5. The aqueous solution according to claim 1, wherein the solution further comprises one or more pharmaceutically acceptable additives.

6. The aqueous solution according to claim 5, wherein the pharmaceutically acceptable additives comprise one or more of chelating agents, sweetening agents, flavouring substances, viscosity regulating agents, preservatives, and buffering agents.

7. The aqueous solution according to claim 6, wherein the chelating agent comprises one or more of edetic acid and its salts, and Disodium EDTA..

8. The aqueous solution according to claim 6, wherein the sweetening agent comprises one or more of sodium saccharin, potassium saccharin, calcium saccharin, neotame, acesulfame potassium, and sodium cyclamate.

9. The aqueous solution according to claim 6, wherein the flavouring agent comprises one or more of vanilla, cherry, raspberry, and strawberry.

10. The aqueous solution according to claim 6, wherein the viscosity regulating agent comprises one or more of hydroxypropyl methylcellulose, and hydroxypropylcellulose.

11. The aqueous solution according to claim 6, wherein the preservative comprises one or more of benzoic acid, sorbic acid, methyl paraben or salts thereof, propyl paraben or salts thereof, benzyl alcohol and benzylalkonium chloride.

12. The aqueous solution according to claim 6, wherein the buffering agent comprises one or more of succinic, tartaric, lactic acid or citric acid, potassium hydroxide, sodium hydroxide or disodium hydrogen phosphate, monosodium phosphate, and monopotassium phosphate.

13. The aqueous solution according to claim 1, wherein the pH of the solution is about 6.5 and above.

14. The aqueous solution according to claim 13, wherein the pH of the solution is about 7.5.

15. An aqueous solution for oral administration comprising a therapeutically effective amount of risperidone or a pharmaceutically acceptable acid addition salt thereof and one or more cyclodextrins or derivatives thereof, wherein the pH of the solution is about 6.5 and above.

16. The aqueous solution according to claim 15, wherein the pH of the solution is about 7.5.

17. The aqueous solution according to claim 15, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin.

18. The aqueous solution according to claim 15, wherein the solution further comprises one or more pharmaceutically acceptable additives.

19. The aqueous solution according to claim 18, wherein the pharmaceutically acceptable additives comprise one or more of chelating agents, sweetening agents, flavouring substances, viscosity regulating agents, preservatives, and buffering agents.

20. The aqueous solution according to claim 19, wherein the buffering agent comprises one or more of succinic, tartaric, lactic acid or citric acid, potassium hydroxide, sodium hydroxide or disodium hydrogen phosphate, monosodium phosphate, and monopotassium phosphate.

21. A process for the preparation of an aqueous solution of risperidone, the process comprising:

mixing water, a therapeutically effective amount of risperidone or a pharmaceutically acceptable acid addition salt thereof, one or more cyclodextrins or derivatives thereof; and one or more buffering agents to maintain the pH of the solution in the range of about 6.5 and above.