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(54) Title: WATER SOLUBLE PHARMACEUTICAL COMPOSITION

(57) Abstract: The present invention relates to a water soluble pharmaceutical composition comprising levetiracetam, and use of said composition in the treatment of partial seizures, myoclonic seizures and tonic-clonic seizures of patients diagnosed with epilepsy.

WATER SOLUBLE PHARMACEUTICAL COMPOSITION

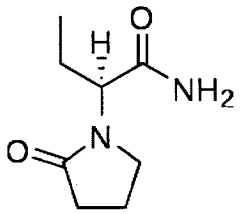
Field of the Invention

The present invention relates to a water soluble pharmaceutical composition comprising levetiracetam, and use of said composition in the treatment of partial seizures, myoclonic seizures and tonic-clonic seizures of patients diagnosed with epilepsy.

Background of the Invention

Epilepsy is a neurological disorder-disease which emerges as a result of an abnormal electrochemical discharge induced by neurons in the brain. It results from excessive and uncontrolled emission of electricity related to the brain operation. It frequently causes temporary loss of consciousness.

Levetiracetam (Formula I), which is described in the patent numbered US 4,943,639, is a derivative of pyrrolidon ((S)-(-)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide)) and it does not have chemical resemblance to known antiepileptic drugs.



(I)

Levetiracetam is supplied in tablet, delayed release tablet, solution forms and forms for injection under KEPPRA® trade mark. KEPPRA® is used in partial onset seizures of adult patients and pediatric patients older than 4 years; and as an add-on-therapy in myoclonic seizures of adolescent patients older than 12 years with juvenile myoclonic epilepsy and adult patients. It is also used as monotherapy in the treatment of partial onset seizures with or without secondary generalization of recently diagnosed patients aged 16 years and older.

In the prior art, the pharmaceutical compositions comprising levetiracetam are prepared in tablet, solution and parenteral forms.

Tablet or capsule dosage forms comprising levetiracetam are disclosed in the patent numbered EP 1,810,676.

However, use of tablet dosage forms poses problems for patients having swallowing problems, for instance children, elderly patients and handicapped patients or for those who do not want to swallow these dosage forms and therefore, they are not preferred by most patients.

Solution dosage forms, on the other hand, are not preferred due to the reasons that they make the adaptation of patients to the therapy difficult as they cause uncontrolled dose intake, unpleasant taste, difficulty of use, and they have more inconvenient shelf life compared with solid dosage forms.

When the prior art is taken into consideration, there is need for compositions comprising levetiracetam which have fast dissolution and effects as well as having long shelf life and being user-friendly and appropriate for patients with swallowing difficulties.

Detailed Explanation of the Invention

Therapeutically advantageous water soluble compositions comprising levetiracetam which are user-friendly and have fast dissolution and/or dispersion have been found in scope of the present invention.

The characteristic feature of the present invention is being water soluble compositions which hold the advantages of both tablet and suspension forms and eliminating the problems encountered in these dosage forms.

A characteristic feature of the compositions in scope of the present invention is their being in single dose solid dosage form and in water soluble form.

The term "water soluble" used in the text comprises effervescent tablets, effervescent granules, effervescent powders, water soluble tablets, water soluble powders and/or water soluble granules.

The term "single dose solid dosage forms" used in the text comprises the composition comprising one dose of the active agent to be in solid dosage form for instance water soluble tablets, effervescent tablets or water soluble powder or granules stored as being filled in a suitable dosage pack.

The levetiracetam compositions of the present invention formulated in water soluble form would have high stability as they will be in solid form during storage. No stability problem is experienced which may result from long-term contact with water since they dissolve in water

immediately before use. Water soluble compositions of the present invention are stored in separate dosage forms comprising unit dose. Thus, each dose is freshly prepared before use.

Levetiracetam comprised in the composition of the present invention can be in free base form, pharmaceutically acceptable salt, racemate, solvate, hydrate, different polymorphic form and amorphous form thereof, preferably in free base form.

The compositions of the present invention comprises high amount of levetiracetam as being more than 200 mg per dosage form. The ratio of the active agent in total composition is in the range of 0.1% to 60%, preferably in the range of 10% to 50% by weight.

According to an aspect, the present invention provides a method which includes delivering effective amounts of levetiracetam to a patient in need of treatment and treating partial seizures, myoclonic seizures and tonic-clonic seizures of patients.

In another aspect, the present invention comprises use of compositions of the invention in prevention of seizures of patients diagnosed with epilepsy; in reducing the number of seizures or in the treatment of the disease.

In another aspect, the present invention comprises preparation of the compositions of the invention as a medicament composition which is effective in the treatment of partial seizures, myoclonic seizures and tonic-clonic seizures of patients diagnosed with epilepsy.

The pharmaceutical compositions pertaining to the present invention comprises levetiracetam as the active agent and one or more excipients selected from the group comprising pH adjusters, stabilizing agents, diluents, binders, coating materials developed to provide various release characteristics, disintegrants, anti-adhesive agents, plasticizers, rate control agents, filling substances, effervescent couples, flavoring agents, lubricants, glidants, coloring agents, aqueous or non-aqueous solvents or combinations thereof.

The water soluble compositions of the present invention preferably comprise at least one pharmaceutically acceptable diluent, at least one binder, at least one lubricant, at least one sweetener, at least one flavoring agent and optionally at least one effervescent couple.

The pharmaceutically acceptable binders pertaining to the present invention can be selected from a group comprising ethyl cellulose, hydroxyethyl cellulose, methyl cellulose, hydroxymethyl cellulose, mannitol, sorbitol, xylitol, lactitol, maltitol, sugar, maltodextrin,

hydroxypropyl cellulose, gelatine, hypromellose, magnesium aluminum silicate, polyethylene oxide, povidone and water or combinations thereof.

The pharmaceutically acceptable diluents pertaining to the present invention can be selected from a group comprising starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, xylitol, lactitol, maltitol, sugar, maltodextrin or combinations thereof.

The pharmaceutically acceptable lubricants pertaining to the present invention can be selected from a group comprising magnesium stearate, polyethylene glycol 4000, polyethylene glycol 6000, sodium lauryl sulphate, starch, talc or combinations thereof.

The pharmaceutically acceptable flavoring agents can be selected from a group comprising sour cherry flavor, grapefruit flavor, grape flavor, pear flavor, orange flavor, apricot flavor or combinations thereof.

A significant problem encountered in oral solutions of levetiracetam is that this substance has a quite bitter taste and its taste lingers in users after use. The inventors have used at least 0.5% sweetener in the water soluble compositions comprising high amounts of active agent they prepared in order to prevent this problem.

In another aspect, the present invention characterized by comprising at least one pharmaceutically acceptable sweetener in the range of 0.5% to 20%, preferably in the range of 0.5% to 10%, more preferably in the range of 1% to 4% by weight.

The pharmaceutically acceptable sweeteners pertaining to the present invention can be selected from a group comprising acesulfame potassium, acesulfame, aspartame, fructose, dextrose, glucose, lactitol, maltitol, xylitol, sorbitol, maltose, saccharine, saccharine sodium, sodium cyclamate, sucralose, sucrose or combinations thereof.

In another aspect, the present invention characterized by comprising aspartame in the range of 0.5% to 20%, preferably in the range of 0.5% to 10%, more preferably in the range of 1% to 4% by weight.

The inventors have observed that bitter taste problem of levetiracetam is entirely eliminated and no negative feeling of bitter taste remains in patients in the case that a sugar derivative binder is used along with the sweetener in the range of 0.5% to 20% by weight in the compositions.

According to this, another characteristic feature of the invention is to comprise preferably a sugar derivative binder such as at least one binder selected from the group comprising mannitol, sorbitol, xylitol, lactitol, maltitol, sugar and/or maltodextrin in the range of 1% to 20% by weight, more preferably sorbitol.

Another characteristic feature of the invention is that the ratio of the sweetener and the sugar derivative binder is in the range of 1:20 to 20:1, preferably in the range of 1:10 to 10:1, more preferably in the range of 1:3 to 3:1; for example 1:1, 1:2, 1:3, 2:1, 2:3, 3:1, 3:2.

The pharmaceutical compositions of the present invention can be produced by any methods in the prior art, for instance by wet granulation method.

Said production method basically comprises the following steps:

a) Preparation of granulation solution by mixing at least one pharmaceutically acceptable binder and the solution,
b) Dry mixing of levetiracetam on an effective amount and at least one pharmaceutically acceptable diluent, at least one sweetener and optionally at least one effervescent couple and another excipient,
c) Wet granulation of the dry mixture obtained in the second step with the granulation solution obtained in the first step,
d) Drying and sieving the granules,
e) Optionally adding at least one pharmaceutically acceptable lubricant and flavoring agent into the dry granules,
f) Turning the final granules into suitable dosage forms.

The compositions of the present invention can be produced by one of the methods of dry granulation and dry mixing. In the case that the selected production method is dry blending, levetiracetam and pharmaceutically acceptable excipients are mixed; at least one pharmaceutically acceptable sweetener, at least one pharmaceutically acceptable flavoring agent and at least one pharmaceutically acceptable lubricant is added into the mixture. The final mixture is turned into a suitable dosage form.

Optionally, tablets are compressed of the water soluble compositions of the present invention. Compression force to compress tablets in the compositions of the present invention is in the range of 10 to 150 kN, preferably in the range of 20 to 150 kN, more preferably in the range

of 30 to 150 kN. It has been observed that the tablets prepared by imposing this compression force do not undergo deformation in course of tube/blister filling and carrying.

The compositions according to the present invention can optionally be formulated in effervescent form. Effervescent formulations are especially beneficial for patients with swallowing difficulties and in pediatrics.

In an aspect, the present invention provides a pharmaceutical composition comprising an effective amount of levetiracetam along with pharmaceutically acceptable excipients.

In another aspect, the effervescent compositions comprise levetiracetam as the active agent and at least one effervescent couple that is composed of an acidic and a basic agent in order to provide water solubility. The acidic agent reacts with the basic agent and lead to carbon dioxide production. Therefore, a solution that can be easily taken by patients who do not like swallowing tablets or who have swallowing difficulties is obtained by dissolving and/or dispersing the pharmaceutical composition of the invention in an aqueous media like drinking water.

One characteristic feature of the present invention is that the percentage of the acidic agent of the effervescent couple in the total weight of the composition is in the range of 15% to 75%, preferably in the range of 25% to 60% by weight while the percentage of the basic agent of the effervescent couple in the total weight of the composition is in the range of 0.1% to 35%, preferably in the range of 10% to 25% by weight.

In another aspect, one characteristic feature of the present invention is that the ratio of the acidic agent of the effervescent couple to the basic agent is in the range of 1.6:1 to 3.5:1, preferably in the range of 2:1 to 2.9:1 by weight.

It was observed that the dissolution profile is improved and the formulation is dissolved in water at room temperature in less than 5 minutes when these characteristics are provided.

The pharmaceutically acceptable acidic agent of the present invention can be selected from a group comprising other organic acids like citric acid and acetic acid, tartaric acid, fumaric acid, adipic acid, malic acid or combinations thereof. According to the present invention, it is preferred to be used citric acid anhydrous as the acidic agent.

The pharmaceutically acceptable basic agent pertaining to the present invention can be selected from a group comprising potassium carbonate, potassium bicarbonate, potassium

citrate, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate or combinations thereof. According to the present invention, it is preferred to be used sodium hydrogen carbonate as the basic agent.

In another aspect, a characteristic feature of the effervescent compositions of the present invention is that said compositions comprise;

a) levetiracetam in the range of 10% to 50% by weight,
b) at least one acidic agent in the range of 25% to 60% by weight,
c) at least one basic agent in the range of 10% to 25% weight,
d) at least one diluent in the range of 1% to 10% by weight,
e) at least one binder in the range of 1% to 20%,
f) at least one sweetener in the range of 0.5 to 20% and optionally,
g) at least one more pharmaceutically acceptable excipient in the range of 1 to 50%.

The production method preferred for effervescent compositions of the present invention, on the other hand, is as follows:

a) Preparation of the granulation solution prepared by mixing at least one pharmaceutically acceptable binder and the solution,
b) Dry mixing of levetiracetam on an effective amount and at least one pharmaceutically acceptable diluent, at least one sweetener and at least one effervescent couple,
c) Wet granulation of the dry mixture obtained in the second step with the granulation solution obtained in the first step,
d) Drying and sieving the granules,
e) Optionally adding at least one pharmaceutically acceptable lubricant and flavoring agent into the dry granules obtained,
f) Turning the final granules into suitable dosage forms.

The inventors have found that the desiccation temperature of the granules plays a significant role for the final product to attain to sufficient dissolution in the effervescent compositions produced by wet granulation method given above. Suitable desiccation temperature for the active agent granules obtained following the granulation is in the range of 20°C to 80 °C, preferably in the range of 20°C to 70 °C, more preferably in the range of 20°C to 60 °C.

The pharmaceutical compositions and preparation methods for said compositions of the present invention can be explained with, but not limited to, the examples below.

Example 1. Water soluble granule composition comprising levetiracetam

Content	% of amount in unit dose		
Levetiracetam	45	45	40
Binder	10	5	5
Diluent	40	35	48
Sweetener	5	10	5
Lubricant	2	2	2
Other excipients	10	3	0
Total tablet weight	100	100	100

The method for preparation of the water soluble composition comprising levetiracetam which is going to be produced according to the formulation given above can comprise granulating the active agent and the excipients with aqueous binder solution; adding sweetener and lubricant into the granules obtained; then mixing the blend, and optionally filling sachets. Optionally, tablets can be compressed of the granules obtained.

Example 2. Effervescent tablet composition comprising levetiracetam

Content	% of amount in unit dose		
Levetiracetam	40.00	15.00	30.00
Acidic agent	39.00	50.00	40.00
Basic Agent	15.00	20.00	20.00
Diluent	3.00	5.00	4.00
Binder	1.50	3.00	1.50
Sweetener	1.50	1.50	3.00
Other excipients	0.00	5.50	1.50
Total tablet weight	100	100	100

The mixture composed of levetiracetam, the acidic agent, the basic agent, the diluent and other excipients according to the formulation given above is granulated with the granulation solution obtained by mixing the binder and the pharmaceutically acceptable solvent; the granules are dried at 55°C. The final mixture is obtained after the other excipients are added and optionally tablets are compressed of the obtained mixture.

CLAIMS

1. A pharmaceutical composition comprising levetiracetam characterized in that said composition is in single dose solid dosage form and in water soluble form.
2. The pharmaceutical composition according to claim 1 characterized in that the percentage of levetiracetam in total composition is in the range of 0.1% to 60% by weight.
3. The pharmaceutical composition according to claim 2 characterized in that the percentage of levetiracetam in total composition is in the range of 10% to 50% by weight.
4. The pharmaceutical composition according to claims 1 to 3 characterized in that said composition is in effervescent tablet, effervescent granule, effervescent powder, water soluble tablet, water soluble powder and/or water soluble granule form.
5. The pharmaceutical composition according to claims 1 to 4 characterized in that said composition comprises at least one pharmaceutically acceptable excipient selected from the group comprising pH adjusters, stabilizing agents, diluents, binders, coating materials developed to provide various release characteristics, disintegrants, anti-adhesive agents, plasticizers, rate control agents, filling substances, effervescent couples, flavoring agents, lubricants, glidants, coloring agents, aqueous or non-aqueous solvents or combinations thereof.
6. The pharmaceutical composition according to claim 5 characterized in that said composition comprises at least one pharmaceutically acceptable diluent, at least one binder, at least one lubricant, at least one sweetener, at least one flavoring agent and optionally at least one effervescent couple.
7. The pharmaceutical composition according to claim 6 characterized in that said composition comprises at least one pharmaceutically acceptable sweetener at least in the range of 0.5% by weight.
8. The pharmaceutical composition according to claim 7 characterized in that said composition comprises at least one pharmaceutically acceptable sweetener in the range of 0.5% to 20 % by weight.
9. The pharmaceutical composition according to claim 8, characterized in that said composition comprises at least one pharmaceutically acceptable sweetener in the range of 0.5% to 10 % by weight.

10. The pharmaceutical composition according to claim 9 characterized in that said composition comprises at least one pharmaceutically acceptable sweetener in the range of 0.5% to 4 % by weight.
11. The pharmaceutical composition according to claim 6 characterized in that said composition comprises at least one binder selected from the group comprising mannitol, sorbitol, xylitol, lactitol, maltitol, sugar and/or maltodextrin.
12. The pharmaceutical composition according to claim 11 characterized in that said binder is sorbitol.
13. The pharmaceutical composition according to claims 7 to 12 characterized in that the ratio of the sweetener to the binder is in the range of 1:20 to 20:1.
14. The pharmaceutical composition according to any one of the preceding claims characterized in that said composition is in effervescent tablet, effervescent granule and/or effervescent powder form.
15. The pharmaceutical composition according to claim 14 characterized in that said composition comprises at least one pharmaceutically acceptable effervescent couple, at least one binder, at least one flavoring agent, at least one diluent, at least one lubricant, at least one sweetener and other pharmaceutically acceptable excipients.
16. The pharmaceutical composition according to claim 15 characterized in that the effervescent couple used is composed of the combination of an acidic agent and a basic agent.
17. The pharmaceutical composition according to claim 16 characterized in that the percentage of the acidic agent comprised in the effervescent couple in total composition is in the range of 15% to 75% by weight.
18. The pharmaceutical composition according to claim 17 characterized in that the percentage of the acidic agent comprised in the effervescent couple in total composition is in the range of 25% to 60% by weight.
19. The pharmaceutical composition according to claim 18 characterized in that the percentage of the basic agent comprised in the effervescent couple in total composition is in the range of 0.1% to 35% by weight.
20. The pharmaceutical composition according to claim 19 characterized in that the percentage of the basic agent comprised in the effervescent couple in total composition is in the range of 10% to 25% by weight.
21. The pharmaceutical composition according to claims 16 to 20 characterized in that the ratio of the acidic agent to the basic agent used is in the range of 1.6:1 to 3.5:1.

22. The pharmaceutical composition according to claim 21 characterized in that the ratio of the acidic agent to the basic agent used is in the range of 2:1 to 2.9:1.
23. The pharmaceutical composition according to claims 14 to 21 characterized in that the acidic agent used is selected from a group comprising citric acid, acetic acid, tartaric acid, fumaric acid, adipic acid, malic acid or combinations thereof.
24. The pharmaceutical composition according to claim 23 characterized in that the acidic agent used is citric acid anhydrous.
25. The pharmaceutical composition according to claims 14 to 24 characterized in that the basic agent used is selected from a group comprising potassium carbonate, potassium bicarbonate, potassium citrate, potassium hydroxide, sodium carbonate and sodium hydrogen carbonate or combinations thereof.
26. The pharmaceutical composition according to claim 25 characterized in that the basic agent used is sodium hydrogen carbonate.
27. The pharmaceutical composition according to claims 14 to 26 characterized in that said composition comprises;
    a. levetiracetam in the range of 10% to 50% by weight,
    b. at least one acidic agent in the range of 25% to 60% by weight,
    c. at least one basic agent in the range of 10% to 25% weight,
    d. at least one diluent in the range of 1% to 10% by weight,
    e. at least one binder in the range of 1% to 20%,
    f. at least one sweetener in the range of 0.5% to 20%, and optionally,
    g. at least one more pharmaceutically acceptable excipients in the range of 1% to 50%.
28. The pharmaceutical composition according to claim 1 characterized in that said composition is produced by one of the methods of dry mixing, dry granulation or wet granulation.