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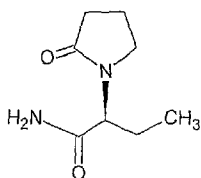
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(I)

(57) Abstract: Present invention relates to an improved process for the purification of Levetiracetam of formula (I).

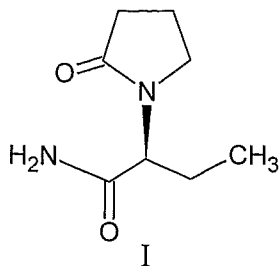


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A PROCESS FOR THE PURIFICATION OF LEVETIRACETAM

FIELD OF THE INVENTION

Present invention relates to an improved process for the purification of Levetiracetam of formula (I).



BACKGROUND OF THE INVENTION

Levetiracetam (I) is a 2-oxo-1-pyrrolidine derivative which is chemically known as (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, having molecular formula $C_8H_{14}N_2O_2$ and molecular weight 170.21. The current pharmaceutical product containing this drug is being sold by UCB using the tradename Keppra[®] in the form of tablets and solution.

Levetiracetam (I) is useful in the treatment of epilepsy, hypertonia, motion sickness and hyperkinesia. Levetiracetam acts as N-Type calcium Channel (Ca (v) 2.2) Blockers.

Levetiracetam (I) is first disclosed in US Patent No. 4,696,943 which also discusses its process for preparation wherein Levetiracetam (I) is prepared by condensation of (S)-2-aminobutanamide hydrochloride with 4-halobutyryl halide. However, this patent remains silent about purity and yield of final product. Moreover, it has been observed by present inventors that Levetiracetam as prepared by this process always contains more than 0.1% impurity of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid and (S)-2-aminobutanamide hydrochloride.

Another process for the preparation of Levetiracetam is disclosed in GB 2,225,322 wherein Levetiracetam is prepared by hydrogenolysis of (S) α -ethyl-[2-(methylthio) ethyl] -2-oxo-1-pyrrolidineacetamide by means of a desulphurizing agent such as Raney Nickel or $\text{NaBH}_4/\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ followed by recrystallization with ethyl acetate. This process is difficult to control at an industrial scale and also requires specifically designed reactor equipment and extraordinary handling precautions. Moreover, this process is also silent about yield and purity of the final product.

US Patent No. 6,858,740 which discloses process for the preparation of Levetiracetam (I) by asymmetric hydrogenation in the presence of rhodium or ruthenium catalysts. A disadvantage of this process is that racemisation may occur during ammonolysis. Moreover, this process is less preferred with respect to economical value because of the use of costly reagent such as rhodium. Moreover, this process is also silent about impurity and residual solvent level in the final product.

US Application No. 20040259933 which discloses a process wherein Levetiracetam is prepared by reaction of (S)-2-aminobutanamide hydrochloride with 4-halobutyryl halide in solvents like acetonitrile, methyl tertiary butyl ether followed by recrystallization in ethyl acetate. The major drawback of this process is use of acetonitrile which has higher boiling range and methyl tertiary butyl ether which is highly prone to catch fire. Moreover, this process does not specify the impurity level of (S)-2-aminobutanamide hydrochloride in the final product.

The solvent used in the purification of a drug substance cannot completely be removed by practical manufacturing techniques, which are employed in the production. Therefore, in the preparation of drug substance wherein plural steps are serially carried out till the final step, each solvent used in each step may possibly remain in a residual amount in the drug substance. Further, residual solvents in the drug substance usually cannot be useful for the therapeutic benefits of the drug substance, and contrarily, there may be caused a problem of

safety of a patient according to the kinds of residual solvents and a concentration thereof. In terms of improving and increasing the safety of drugs, "Impurities: guideline for residual solvents", ICH harmonized tripartite guideline, 17 Jul. 1997 was made in International Conference on Harmonization of technical requirements for registration of a pharmaceuticals for human use (ICH). This guideline is applied to the drugs, which are already on market, and it is very important to prepare a drug substance complying with this guideline in terms of safety of drugs.

Since a solvent may play an important role in increasing the yield rate or in determination of physical properties of drug substance such as crystal form, purity, solubility, etc., even if such a solvent is known to be toxic, there may be many cases that the use thereof in the purification of drug substance cannot be avoided in terms of risk-benefits. In such cases, this guideline decrees that a concentration of a residual solvent in the drug substance should be not more than a limit which is toxicologically acceptable.

Thus Levetiracetam is prepared according to any of the process, the residual solvents concentration thereof should be not more than as defined in the above-mentioned guideline "Impurities: Guideline for residual solvents".

It is therefore, a need to develop a process for the purification of Levetiracetam which results in high purity with less amount of residual solvent content preferably well below the level as per the ICH guideline without any quantitative yield loss. It is also a need to overcome the disadvantages associated with prior art purification processes which does not gives pure Levetiracetam with controlled quantitative level of impurities such as (S) -2-amino butyramide hydrochloride, (S)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid.

OBJECT OF THE INVENTION

It is therefore an object of the present invention is to provide process for the purification of substantially impure Levetiracetam.

Another object of the present invention is to provide process for the purification of substantially impure Levetiracetam which is operationally simple, easy to handle and applicable at an industrial scale.

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Another object of the present invention is to provide process for the purification of substantially impure Levetiracetam which gives Levetiracetam (I) with greater yield and purity.

- 10 Another object of the present invention is to provide process for the purification of substantially impure Levetiracetam which gives Levetiracetam (I) having at least 99.5 % purity.

- 15 Another object of the present invention is to provide process for the purification of substantially impure Levetiracetam which gives Levetiracetam (I) having less than 0.1 % impurity of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid or (S) -2-amino butyramide hydrochloride.

- 20 Another object of the present invention is to provide process for the purification of substantially impure Levetiracetam which gives Levetiracetam (I) containing controlled level of residual solvents as per ICH guidelines.

- 25 Another object of the present invention is to provide Levetiracetam (I) containing residual solvent content of dichloromethane of not more than 600 ppm.

Another object of the present invention is to provide Levetiracetam (I) containing residual solvent content of methyl tertiary butyl ether of not more than 5000 ppm.

Another object of the present invention is to provide Levetiracetam (I) containing residual solvent content of ethyl acetate of not more than 5000 ppm.

Another object of the present invention is to provide Levetiracetam (I) having impurity of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid less than 0.1 %.

Another object of the present invention is to provide Levetiracetam (I) having impurity of (S)-2-amino butyramide hydrochloride less than 0.1 %.

10 Yet another object of the present invention is to provide process for the purification of Levetiracetam comprising steps of:

- (i) treating substantially impure Levetiracetam with acetic acid and activated carbon in a suitable organic solvent,
- (ii) stirring and filtering the mixture obtained in step (i)
- 15 (iii) evaporating the filtrate of step (ii) to obtain a residue
- (iv) adding ester solvent to the residue obtained in step (iii) to obtain solution
- (v) refluxing and cooling the solution obtained in step (iv)
- (vi) filtering and drying a solid obtained in step (v) to obtain Levetiracetam (I) having purity at least 99.5 %.

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Yet another object of the present invention is to provide process for the purification of Levetiracetam comprising steps of:

- (i) treating substantially impure Levetiracetam with acetic acid and activated carbon in a dichloromethane,
- 25 (ii) stirring and filtering the mixture obtained in step (i)
- (iii) evaporating the filtrate of step (ii) to obtain a residue
- (iv) adding ethyl acetate to the residue obtained in step (iii) to obtain solution
- (v) refluxing and cooling the solution obtained in step (iv)

- (vi) filtering and drying a solid obtained in step (v) to obtain Levetiracetam (I) having purity at least 99.5 %.

Yet another object of the present invention is to provide process for the purification of

5 Levetiracetam comprising steps of:

- (i) treating substantially impure Levetiracetam with acetic acid and activated carbon in a methyl tertiary butyl ether,
- (ii) stirring and filtering the mixture obtained in step (i)
- (iii) evaporating the filtrate of step (ii) to obtain a residue
- 10 (iv) adding ethyl acetate to the residue obtained in step (iii) to obtain solution
- (v) refluxing and cooling the solution obtained in step (iv)
- (vi) filtering and drying a solid obtained in step (v) to obtain Levetiracetam (I) having purity at least 99.5 %.

15 **SUMMARY OF THE INVENTION**

The present invention provides process for the purification of Levetiracetam comprising steps of:

- (i) treating substantially impure Levetiracetam with acetic acid and activated carbon in a suitable organic solvent,
- 20 (ii) stirring and filtering the mixture obtained in step (i)
- (iii) evaporating the filtrate of step (ii) to obtain a residue
- (iv) adding ester solvent to the residue obtained in step (iii) to obtain solution
- (v) refluxing and cooling the solution obtained in step (iv)
- (vi) filtering and drying a solid obtained in step (v) to obtain Levetiracetam (I) having
- 25 purity at least 99.5 %.

DETAIL DESCRIPTION OF THE INVENTION

For the purpose of this specification, the meaning of the term “substantially impure Levetiracetam” used as starting material hereinabove that include Levetiracetam is crude, any form, or hydrate, solvate or their mixtures, or having purity less than 99.5%.

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For the purpose of this specification, the meaning of the term “treating” as used hereinabove includes suspending, dissolving, washing, mixing, adding, accumulating and totaling in any of the suitable organic solvent as described herein below at any of the temperature in between 25 °C to refluxing temperature.

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For the purpose of this specification, the meaning of the term “refluxing” as used hereinabove includes heating and stirring a solution at refluxing temperature of appropriate ester solvent.

15 The term “activated carbon” as used hereinabove includes activated charcoal or activated coal which is a material with an exceptionally high surface area.

The term “suitable organic solvent” as used hereinabove includes chlorinated or ether solvents such as dichloromethane, ethylene dichloride, chloroform, carbon tetrachloride, 20 methyl tertiary butyl ether, ethyl methyl ether, dimethyl ether, diethyl ether, diphenyl ether, diisopropyl ether, cyclic ether and the like or mixture thereof. The most preferred solvents are dichloromethane and methyl tertiary butyl ether.

The term “ester solvent” as used hereinabove includes ethyl acetate, butyl acetate, propyl 25 acetate and the like or mixture thereof. The most preferred solvent is ethyl acetate.

In the process of step (i) as described hereinabove instead of acetic acid, organic acid such as formic acid, maleic acid, citric acid, succinic acid and the like or mixtures thereof may be used.

The process of step (ii) as described hereinabove involves stirring the mixture for half to two hour.

- 5 The process of step (ii) as described hereinabove also involves filtering the mixture through hyflobed followed by washing with a suitable organic solvent at any of the temperature between 25 °C to refluxing temperature.

- 10 The process of step (iii) as described hereinabove involves evaporating the filtrate under reduced pressure at temperature 40 °C to 60 °C.

The process of step (iv) as described hereinabove involves adding ester solvent at any of the temperature between 10 °C to 40 °C.

- 15 The process of step (v) as described hereinabove also involves stirring for half an hour to one hour at refluxing temperature.

- 20 The process of step (v) as described hereinabove also involves cooling at first temperature of 20 °C to 30 °C followed by at second temperature of 10 °C to -15 °C and maintained at this temperature for one to three hours.

The process of step (vi) as described hereinabove involves filtering and washing the solid with ester solvent at any of the temperature between 10 °C to -10 °C.

- 25 The process of step (vi) as described hereinabove involves drying the solid under reduced or atmospheric pressure at the temperature between 45 °C to 65 °C.

Levetiracetam (I) obtained according to present invention contains less than 0.1 % of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid.

Levetiracetam (I) obtained according to present invention contains less than 0.1 % of (S) -2-amino butyramide hydrochloride.

- 5 Levetiracetam (I) obtained according to present invention contains residual dichloromethane of not more than 600 ppm.

Levetiracetam (I) obtained according to present invention contains residual methyl tertiary butyl ether of not more than 5000 ppm.

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Levetiracetam (I) obtained according to present invention contains residual ethyl acetate of not more than 5000 ppm.

- 15 All compounds are isolated from reaction mass by conventional isolation procedure such as filtration, centrifugation, washing the wet cake, crystallization and drying or by evaporation of solvent.

- 20 The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

Example 1

- 25 Glacial acetic acid (7 ml to 9 ml) and activated charcoal (7 gm to 9 gm) was added to the stirred mixture of substantially impure Levetiracetam (70 gm to 90 gm) and dichloromethane (350 ml to 450 ml) at ambient temperature respectively. The mixture was stirred for 30 minute to 2 hours and filtered through hyflo bed and washed with dichloromethane (350 ml to 450 ml). The filtrate was concentrated under reduced pressure at 40-60°C to get an oily residue. Ethyl acetate (300ml to 400 ml) was added to this residue and refluxed for further 15

minute to one hour. The mixture layer was cooled at first temperature of 15 to 35°C and then at second temperature of 15 to -15°C and maintained for 30 minute to 3 hour to obtain a solid. The solid was filtered at temperature of 15 to -15°C and washed by pre-cooled ethyl acetate (70 ml to 90 ml). The solid product was vacuum dried to get Levetiracetam (I) (55 gm-75gm).

Purity ~ 99.6 % (by HPLC)

Content of impurity of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid ~ 0.05 % (by HPLC)

Content of impurity of (S) -2-amino butyramide hydrochloride ~ 0.09 % (by HPLC)

Example 2

Glacial acetic acid (7 ml to 12 ml) and activated charcoal (7 gm to 12 gm) was added to the stirred mixture of substantially impure Levetiracetam (70 gm to 110 gm) and methyl tertiary butyl ether at ambient temperature respectively. The mixture was stirred for 30 minute to 2 hours and filtered through hyflo bed and washed with methyl tertiary butyl ether. The filtrate was concentrated under reduced pressure at suitable temperature to get an oily residue. Ethyl acetate (300ml to 400 ml) was added to this residue and refluxed for further 15 minute to one hour. The mixture layer was cooled at first temperature of 15 to 35°C and then at second temperature of 15 to -15°C and maintained for 30 minute to 3 hour to obtain a solid. The solid was filtered at temperature of 15 to -15°C and washed by pre-cooled ethyl acetate (70 ml to 90 ml). The solid product was vacuum dried to get Levetiracetam (I) (55 gm-75gm).

Purity ~ 99.6 % (by HPLC)

Content of impurity of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid ~ 0.05 % (by HPLC)

Content of impurity of (S) -2-amino butyramide hydrochloride ~ 0.09 % (by HPLC)

CLAIMS

1. A process for the purification of Levetiracetam comprising steps of:
 - (i) treating substantially impure Levetiracetam with acetic acid and activated
5 carbon in a suitable organic solvent,
 - (ii) stirring and filtering the mixture obtained in step (i)
 - (iii) evaporating the filtrate of step (ii) to obtain a residue
 - (iv) adding ester solvent to the residue obtained in step (iii) to obtain solution
 - (v) refluxing and cooling the solution obtained in step (iv)
 - 10 (vi) filtering and drying a solid obtained in step (v) to obtain Levetiracetam (I)
having purity at least 99.5 %.
2. The process according to claim 1, wherein a suitable organic solvent used is selected
15 from the group consisting of dichloromethane, ethylene dichloride, chloroform, carbon
tetrachloride, methyl tertiary butyl ether, ethyl methyl ether, dimethyl ether, diethyl ether,
diphenyl ether, diisopropyl ether, cyclic ether or mixture thereof.
3. The process according to claim 1, wherein an ester solvent used is selected from the
20 group consisting of ethyl acetate, butyl acetate, propyl acetate or mixture thereof.
4. A process for the purification of Levetiracetam comprising steps of:
 - (i) treating substantially impure Levetiracetam with acetic acid and activated
carbon in a dichloromethane,
 - (ii) stirring and filtering the mixture obtained in step (i)
 - 25 (iii) evaporating the filtrate of step (ii) to obtain a residue
 - (iv) adding ethyl acetate to the residue obtained in step (iii) to obtain solution
 - (v) refluxing and cooling the solution obtained in step (iv)
 - (vi) filtering and drying a solid obtained in step (v) to obtain Levetiracetam (I)
having purity at least 99.5 %.

5. A process for the purification of Levetiracetam comprising steps of:
- (i) treating substantially impure Levetiracetam with acetic acid and activated carbon in a methyl tertiary butyl ether,
 - 5 (ii) stirring and filtering the mixture obtained in step (i)
 - (iii) evaporating the filtrate of step (ii) to obtain a residue
 - (iv) adding ethyl acetate to the residue obtained in step (iii) to obtain solution
 - (v) refluxing and cooling the solution obtained in step (iv)
 - 10 (vi) filtering and drying a solid obtained in step (v) to obtain Levetiracetam (I) having purity at least 99.5 %.
6. Levetiracetam having impurity of (S) -2-amino butyramide hydrochloride less than 0.1%.
7. Levetiracetam having impurity of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid less
15 than 0.1 %.
8. Levetiracetam having residual solvent content of dichloromethane not more than 600ppm.
- 20 9. Levetiracetam having residual solvent content of methyl tertiary butyl ether not more than 5000 ppm.
10. Levetiracetam having residual solvent content of ethyl acetate not more than 5000 ppm.