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(54) **Title:** A METHOD FOR THE PURIFICATION OF LEVETIRACETAM

(57) **Abstract:** The present invention relates to an improved process for the preparation of Levetiracetam of formula (I). More particularly, the present invention relates to a method for the purification of crude Levetiracetam using a solvent mixture of ethyl acetate and water.(I).

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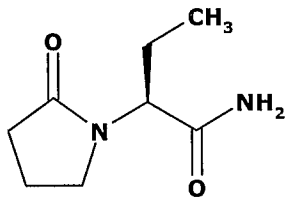
A METHOD FOR THE PURIFICATION OF LEVETIRACETAM

Field of the Invention

The present invention relates to an improved process for the preparation of Levetiracetam of formula (I). More particularly, the present invention relates to a method for the purification of crude Levetiracetam using a solvent mixture of ethyl acetate and water.



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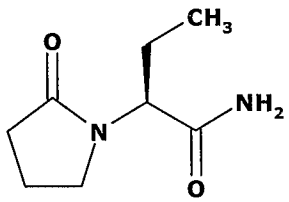
Background of the Invention

Levetiracetam which is chemically known as (-)-(*S*)-alpha-Ethyl-2-oxo-1-pyrrolidineacetamide is a Calcium Channel blocker and has the following structural formula:



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Levetiracetam is an anti-epileptic drug indicated as adjunctive treatment of partial onset seizures in adults with epilepsy and it is marketed as Keppra ® by UCB.

Levetiracetam is known from U. S. Patent Nos. 4696943, 4837223, 4943639, which disclosed the preparation of levetiracetam by reacting (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid successively with alkylhaloformate and with ammonia. (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid, in turn was obtained by the chemical

resolution of racemic (±)-alpha-ethyl-2-oxo-1- pyrrolidineacetic acid. According to these US patents crude Levetiracetam is purified with ethyl acetate.

WO 2004 / 069796 (Teva Pharmaceutical Industries Ltd.) disclosed a process for making Levetiracetam of high chemical purity, i.e., having less than 0.2 % impurities in the crude product and less than 0.1 % impurities in the crystallized product. This PCT application further claimed the purification step in which the crude Levetiracetam crystallized or re-crystallized from an organic solvent or a mixture of organic solvents to obtain purified Levetiracetam. Organic solvents such as ethanol, ethyl acetate, toluene, methylethyl ketone, tetrahydrofuran, isopropyl alcohol, dichloromethane, methanol, nitromethane, hexane, and methyl tertbutyl ether are used in the purification step of Levetiracetam.

WO 2005 / 023763 (Ranbaxy Laboratories Ltd.) disclosed a process for preparing pure Levetiracetam having optical purity more than 99.8%. The process includes obtaining a solution of crude Levetiracetam in one or more solvents; removing un-dissolved material; and recovering the pure levetiracetam having optical purity more than 99.8% from the solution thereof by the removal of the solvent. For obtaining a solution of crude Levetiracetam solvents used such as one or more of acetone, methyl ethyl ketone, methyl isobutyl ketone, acetonitrile, toluene, methylene chloride, ethylene dichloride, diethyl ether, diisopropyl ether, dioxane and tetrahydrofuran. For removal of un-dissolved material solvents used such as one or more of ethyl acetate, isobutyl acetate, isopropyl acetate, hexane, cyclohexane, toluene, heptane, octane, diethyl ether, diisopropyl ether.

U. S. Patent No. 6713635 disclosed a purification process of Levetiracetam, which is obtained by asymmetric hydrogenation, was dissolved in water and extracted with ethyl acetate. The organic phase was then back extracted with water and the aqueous phase evaporated to afford a pale yellow solid was dissolved in acetone and heated to reflux for one hour. The solution was allowed to cool down slowly to 0°C at a rate of 5 to10 °C/hr. The crystals were filtered, washed with acetone and dried to give a white solid.

U. S. Patent No. 6713635 disclosed the process for the extraction of Levetiracetam using water and ethyl acetate. In this patent aqueous layer is separated and then concentrated and finally purified by crystallizing the Levetiracetam in acetone.

Since none of the prior art reference disclosed or claimed the use of aqueous organic solvent for the purification of the compound of formula (I), we focused our research to develop an improved and efficient process for the purification of the compound of formula (I) in commercial scale using a mixture of ethyl acetate and water, which helps to reduce the organic solvent volume significantly in the purification step and reduce the cost of production substantially. The disclosed process has advantages over the processes described in the above-mentioned prior art references.

Objectives of the Invention

The main objective of the present invention is to provide a method for the purification of compound of formula (I) in good yield and high chemical purity.

Another objective of the present invention is to provide a method for the purification of compound of formula (I), which would be easy to implement on commercial scale and economically viable.

Summary of the Invention

Accordingly, the present invention provides a method for the purification of Levetiracetam of formula (I) having purity more than 99.90%. The process includes obtaining a solution of crude Levetiracetam in aqueous organic solvents and recovering the pure Levetiracetam having purity more than 99.90% from the solution thereof. More particularly, the present invention provides a method for yielding highly purified Levetiracetam (I) using aqueous ethyl acetate as solvent mixture.

Description of the Invention

In an embodiment of the present invention, the purification is performed in an aqueous organic solvent. The aqueous organic solvent is selected from the group consisting of methyl acetate and water, ethyl acetate and water, butyl acetate and water; the most preferred aqueous solvent for this reaction is ethyl acetate and water.

In another embodiment of the present invention, the purification method is preferably performed at a temperature of about 20° C to 80° C. Most preferably the reaction step is performed at a temperature of about 20°C to 60°C.

In yet another embodiment of the present invention the starting material of this invention is prepared according to the literature available in the prior art.

Crude Levetiracetam is prepared according to the procedure mentioned in US 4,943,639. The purification stage has been incorporated in order to obtain better and consistent quality of the final product.

The present invention is illustrated with the following example, which should not be construed for limiting the scope of the invention.

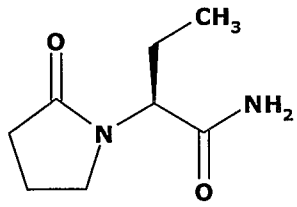
Example 1: Preparation of Pure Levetiracetam

Crude Levetiracetam (15 g), ethyl acetate (150 mL) and water (2.5 mL) were taken in a reaction vessel and heated the reaction mass to 50 °C to 55°C to get a clear solution. The clear solution was filtered through hi-flow bed and collected the clear filtrate into reaction vessel and concentrated the reaction mass till reaction mass attained 4 to 5 volumes. The concentrated mass was cooled 20°C to 25°C, filtered the product, washed with ethyl acetate (15 ml) and dried the material under vaccum to get the highly pure Levetiracetam. The yield of the Levetiracetam was found 12 g (w/w 80%) and the chromatographic purity was 99.98 %.

We Claim:

(1) A method for the purification of Levetiracetam of formula (I), by treating crude Levetiracetam in an aqueous organic solvent.

(2) A method as claimed in claim no.1, wherein said method comprising the steps of;
(a) dissolving or suspending crude Levetiracetam in an aqueous organic solvent;
(b) optionally distilling the solution as obtained in step (a); and
(c) isolating purified Levetiracetam of formula (I)



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(3) A method as claimed in claim no.1, wherein the said purification is carried out in an aqueous organic solvent, which is selected from the group comprising of methyl acetate and water, ethyl acetate and water, butyl acetate and water and the like; most preferably ethyl acetate and water.

(4) A method as claimed in claim no.1, wherein the said purification is performed at a temperature in the range of 20^0C to 80^0 C; most preferably 20° C to 60° C.

(5) A method as claimed in claim no.1, wherein the purity of Levetiracetam of formula (I) is more than 99.90 %.