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(54) Title: CONTROLLED RELEASE COMPOSITION COMPRISING LEVETIRACETAM

(57) Abstract: The present invention relates to a controlled release pharmaceutical composition comprising levetiracetam.



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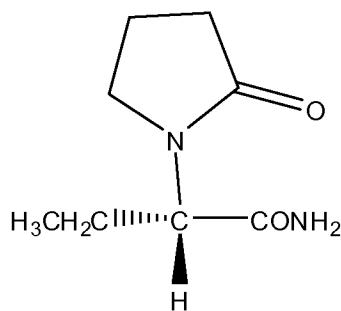
Controlled release composition comprising levetiracetam

Field of the Invention

The present invention relates to a controlled release pharmaceutical composition comprising
5 levetiracetam.

Description of the background art

Levetiracetam is disclosed as a protective agent for the treatment and the prevention of
10 hypoxic and ischemic type aggressions of the central nervous system in the European patent
No. EP 0 162 036 A and has the following formula.



The chemical name of levetiracetam, a single enantiomer, is (-)-(S)- α -ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is C₈H₁₄N₂O₂ and its molecular weight is 170.21.
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Levetiracetam is marketed under the registered trademark Keppra®. Levetiracetam is available as 250 mg, 500 mg, 750 mg and 1000 mg tablets and as a clear, colorless, grape-flavored liquid (100 mg/ml) for oral administration. Recently, an extended release formulation has been made available under the trade name KEPPRA XR™, which contains 500 mg or
20 750 mg of levetiracetam.

Levetiracetam has a relatively low order of toxicity and a relatively high therapeutic index. The twice daily dosing regimen for immediate-release levetiracetam tablets is well tolerated but with few incidences of neuropsychiatric adverse events like somnolence, fatigue, coordination difficulties and behavioral abnormalities. These adverse events are proportionate to the drug plasma level.
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The prior art records few documents describing controlled release levetiracetam formulations.

WO 2001/51033 provides for a solid pharmaceutical compound that can be administered orally, permitting controlled release of at least one active substance which can be levetiracetam consisting of a homogeneous mixture comprising active substance, at least one matrix excipient between 5 and 95% by weight; at least one entero-soluble polymer
5 between 2 % and 50 % by weight and at least one alkalinizing agent soluble in a aqueous phase under conditions of physiological pH, of at least 0.5 to 50% by weight in relation to the total weight of the compound.

WO 2003/101428 provides a pharmaceutical composition, which has a delayed active
10 substance (which can be levetiracetam) release and can be obtained by means of a special compacting method for which organic solvents and water are not required. Said pharmaceutical composition preferably exists in the form of individual active substance compartments or breaks down into compartments of this type when brought into contact with aqueous media.

15 PCT application WO 2006/088864 discloses a controlled release formulation of levetiracetam, which comprises an immediate release component and a modified release component, such that the immediate release component comprises a first population of levetiracetam and the modified release component preferably comprises a second population
20 of levetiracetam and a controlled release constituent

The PCT application WO 2006/080029 discloses an extended release tablet with the core containing levetiracetam and water dispersible rate controlling polymer and further teaches that the tablet core is optionally coated with a combination of water non-dispersible and/or
25 water dispersible polymer.

WO 2006/123357 exemplifies once-daily oral matrix based extended release pharmaceutical compositions of levetiracetam, comprising a rate-controlling agent which is coated using a coating selected from an active ingredient permeable coating surrounding the unit dosage
30 form, and an active ingredient impermeable coating covering one or more surfaces but not all the surfaces of the unit dosage form.

Another PCT application WO2008/062446 relates to extended release pharmaceutical compositions of levetiracetam, which exhibits no adverse food effect. The extended release
35 tablet of levetiracetam is with a core comprising of levetiracetam and water dispersible rate controlling polymer, and the tablet core is optionally functional coated comprising a

combination of water non-dispersible and/or water dispersible polymer. It provides extended therapeutically effective plasma levels over a twenty four hour period with diminished incidences of neuropsychiatric adverse events by eliminating the troughs and peaks of drug concentration in a patient's blood plasma.

5

WO2008/006528 describes a controlled release pharmaceutical formulation comprising levetiracetam and at least one hydrophilic matrix agent or a combination of hydrophilic and lipophilic or inert matrix agents providing controlled release.

10

WO2008/113901 describes controlled release formulation of levetiracetam comprising a core of levetiracetam, water soluble polymer and a lubricant, and outer water semi-permeable layer.

15

WO2009/069089 is concerned with a controlled release pharmaceutical composition which comprises an immediate release core comprising of levetiracetam; and a release rate-controlling membrane coating of hydrophobic polymer(s).

20

WO2009/087675 describes an extended release pharmaceutical composition comprising levetiracetam comprising levetiracetam wherein the extended release is achieved by coating the tablet core with a rate controlling composition. Said coated rate controlling composition comprises one or more hydrophilic agents and one or more hydrophobic agents.

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Although pharmaceutical compositions comprising levetiracetam exist, there is still a need for controlled release formulation with improved properties.

Summary of the invention

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The aspects, advantageous features and preferred embodiments of the present invention summarized in the following items, respectively alone or in combination, further contribute to solving the object of the invention:

1. A controlled release pharmaceutical composition, comprising levetiracetam and from 30 % to 40 % by weight of at least one lipophilic matrix agent.

2. The controlled release pharmaceutical composition according to item 1, wherein lipophilic matrix agent is selected from the group consisting of waxes, fatty acids, fatty alcohols, fatty acids esters, glycerides and mixtures thereof.
- 5 3. The controlled release pharmaceutical composition according to item 1 or 2, wherein said lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate.
4. The controlled release pharmaceutical composition according to any one of items 1 to 3, further comprising a lubricant.
- 10 5. The controlled release pharmaceutical composition according to item 4, comprising from 0.1 % to 4 % by weight of a lubricant.
- 15 6. The controlled release pharmaceutical composition according to item 4 or 5, wherein said lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate.
- 20 7. The controlled release tablet according to any one of items 1 to 6 comprising levetiracetam,
from 30 % to 40 % by weight of lipophilic matrix agent, wherein said lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate, and
from 0.1 % to 4 % by weight of lubricant, wherein said lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate,
25 magnesium stearate and sodium stearyl fumarate.
- 30 8. The controlled release tablet to any one of items 1 to 7 comprising
from 55 % to 70 % by weight of levetiracetam,
from 30 % to 40 % by weight of lipophilic matrix agent, wherein said lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate, and
30 from 0.1 % to 4 % by weight of lubricant, wherein said lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate.
- 35 9. The controlled release pharmaceutical composition according to any one of items 1 to 8, wherein a pharmaceutical composition is in the form of a tablet.

10. The controlled release pharmaceutical composition according to item 9, wherein said tablet further comprises a coating.

Description of further advantages and preferred embodiments of the invention

In the following, the present invention will be described in more detail by preferred embodiments and examples while referring to the attached drawings, noting, however, that these embodiments, examples and drawings are presented for illustrative purposes only and shall not limit the invention in any way.

According to one aspect the present invention discloses an easy to make robust controlled release pharmaceutical formulation for oral administration comprising levetiracetam as active ingredient and lipophilic matrix agent enabling controlled release.

Fig. 1 shows cumulative amount of drug released (%) from pharmaceutical formulation obtained in Example 1 plotted versus time (h); and analyzed under test 1, 2 and 3 conditions.

Fig. 2 shows cumulative amount of drug released (%) from pharmaceutical formulation described in Comparative example 1 plotted versus time (h); and analyzed under tests 1, 2 and 3 conditions.

Fig. 3 shows cumulative amount of drug released (%) from pharmaceutical formulations obtained in Example 1 and Comparative example 2 plotted versus time (h); and analyzed under test 4 conditions.

The term "controlled release pharmaceutical composition", as referred to herein, is defined to mean oral pharmaceutical compositions which when administered releases the active medicament at a relatively constant rate and provide plasma concentrations of the active medicament that remain substantially invariant with time within the therapeutic range of the active medicament over a 24-hour period and encompasses "prolonged release", "extended release", "modified release", "delayed release" and "sustained release" compositions. The compositions according to the present invention deliver a therapeutically effective amount of levetiracetam to a patient for 24 hours following a once-daily administration. The term "therapeutically effective amount" intends to describe an amount of the active agent which stops or reduces the progress of the condition to be treated or which otherwise completely or partly cures or acts palliatively on the condition.

The term "by weight", as referred to herein, is defined to mean with respect to total weight of pharmaceutical composition in question.

The term "coating" as used herein refers to a layer which completely covers an object and is applied by film coating. By contrast, a compartment according to the invention can be in the form of a layer, wherein the layer can e.g. have the form of a disc and is applied by compaction.

Controlled drug delivery systems frequently offer significant benefit in comparison with immediate release dosage forms from the efficiency and safety viewpoint. They enable maintaining a desired blood level of a drug over a longer period of time resulting in increased patient compliance by reducing the number of daily administrations and consequently less fluctuation in drug plasma concentration, all together contributing to reduced side effects and improved efficacy of the therapy.

Controlled release of a pharmaceutical composition may be achieved by different manners. Previously described in the art controlled release was mostly obtained using a hydrophilic matrix agent or a combination of hydrophilic and lipophilic or inert matrix agents. More commonly, the controlled release was obtained using a coating comprising a combination of water non-dispersible and/or water dispersible polymer.

Surprisingly, it has been found that the controlled release of the present invention is achieved by using a lipophilic matrix agent without applying a rate controlling coating. The present invention thus provides an advantage for preparing a uniform controlled release pharmaceutical formulation, as the repeatability of coating process is technologically difficult to achieve. Furthermore, the present invention particularly provides a very simple process for preparing pharmaceutical dosage forms.

Oral controlled release formulation faces substantial changes in gastrointestinal conditions during its passage along gastrointestinal tract, *i.e.* change in pH and composition of gastrointestinal fluids (ionic strength, presence / absence of food, presence / absence of other liquids, solvents, such as alcohol, surfactants, *etc.*), change in mechanical exposure (abrasion) due to change in gastrointestinal motility and migrating myoelectrical complex (MMC). The conditions in gastrointestinal tract are subjected to high intra subject and even more inter subject variability. Additionally, various disease states like Crohn's disease, alcoholism, microbiological infections dramatically influence the conditions in gastrointestinal tract. Considering this facts, controlled release formulation with robust drug release profile which is not susceptible to changes in gastrointestinal tract is required to provide a desired

release profile that assures optimal therapeutic efficacy of a drug. If the drug release profile from the formulation is subjected to changes in gastrointestinal conditions the drug release can be faster (dose dumping) or slower than intended. In both cases, severe consequences for a patient can occur including reduced therapeutic efficacy due to too low drug concentration or toxic effect due to overdosing.

The presence of alcohol may have a profound influence on release of active ingredient, e.g. slower release of levetiracetam can result in lower therapeutic efficacy what is of special importance in the treatment of alcohol dependence and in treatment of patients with epilepsy which abuse alcohol more frequently. Faster release of levetiracetam on the other hand might increase a risk of toxic effect due to overdosing. Recently, levetiracetam was tested for the treatment of alcohol dependence and co-occurring anxiety disorder. It was shown that levetiracetam can be effective in alcohol dependence treatment (The American Journal of Drug and Alcohol Abuse, 34: 683–691, 2008, The American Journal of Drug and Alcohol Abuse, 34: 441–447, 2008. From safety and efficacy viewpoint it is therefore crucial to develop a controlled release formulation comprising levetiracetam characterized by a robust drug release profile independent of changes in gastrointestinal conditions and presence of alcohol.

Unexpectedly, the release of levetiracetam from matrix tablet formulation according to the present invention is insensitive to various *in vivo* relevant dissolution testing media as well as different hydrodynamic conditions. In particular, a controlled release pharmaceutical formulation according to the present invention shows excellent robustness regarding the influence of alcohol. The levetiracetam release profile of controlled release pharmaceutical formulation according to present invention is not affected by the presence of alcohol.

In certain embodiment, the pharmaceutical composition of the present invention comprises levetiracetam and from 30 % to 40 % by weight of at least one lipophilic matrix agent.

In a preferred embodiment, the pharmaceutical composition of the present invention comprises from 45 % to 90 % by weight of levetiracetam; more preferably from 50 % to 80 % by weight of levetiracetam and most preferably from 55 % to 70 % by weight of levetiracetam or a pharmaceutically acceptable salt thereof.

Lipophilic matrix agents provide several advantages, ranging from good stability at varying pH values and moisture levels to safe applications. Use of lipophilic matrix agents is

particularly advantageous for drugs with high water solubility (such as levetiracetam) as restrictions of controlled drug release due to rapid diffusion of the dissolved drug through the hydrophilic gel network, that might occur when hydrophilic matrix system is used, is avoided.

- 5 Suitable lipophilic matrix agents include, but are not limited to waxes (such as for example white wax, bees wax, carnauba wax and the like), fatty acids (such as for example stearic, palmitic, lauric acid and the like), fatty alcohols (such as for example cetyl, cetostearyl, stearyl alcohol and the like), fatty acids esters (such as for example monostearates of propylene glycol, monostearates of sucrose, sucrose distearate and the like), glycerides
10 (such as for example monoglycerides, diglycerides, triglycerides: palmitin, stearin, behenic, laurin, myristin, hydrogenated vegetable oil (such as for example hydrogenated castor oil, hydrogenated cottonseed oils), glyceryl behenate and the like) and mixtures thereof. Preferably lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate.
- 15 In a preferred embodiment lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate.

In another preferred embodiment, the pharmaceutical composition of the present invention might further comprise a lubricant.

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In another preferred embodiment, pharmaceutical composition of the present invention comprises from 0.1 % to 4 % by weight of a lubricant, more preferably from 0.5 % to 3 % by weight of a lubricant.

- 25 Various suitable lubricants include but are not limited to stearic acid, talc, hydrogenated vegetable oil (e.g. hydrogenated castor oil), sodium lauryl sulphate, glyceryl behenate, polyethylene glycol, magnesium stearate and sodium stearyl fumarate. In a preferred embodiment lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate,
30 more preferably lubricant is magnesium stearate and/or hydrogenated castor oil.

- In another preferred embodiment, the same excipient material can be used as lipophilic matrix agent and as a lubricant (e.g. hydrogenated castor oil, glyceryl behenate), making the pharmaceutical composition of the present invention more convenient and appropriate for
35 industrial production.

In another preferred embodiment, the controlled release tablet according to present invention comprises

levetiracetam,

from 30 % to 40 % by weight of lipophilic matrix agent, wherein said lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate, and

from 0.1 % to 4 % of lubricant, wherein said lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate.

In another preferred embodiment, the controlled release tablet according to present invention comprises

from 55 % to 70 % by weight of levetiracetam,

from 30 % to 40 % by weight of lipophilic matrix agent, wherein said lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate, and

from 0.1 % to 4 % by weight of lubricant, wherein said lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate.

The pharmaceutical composition according to present invention may optionally further comprise other excipients which are commonly used in the art and known to any person skilled in the art. These include, but are not limited to binders, fillers, glidants, antiadhesive agents and the like.

Various useful binders include but are not limited to hydroxypropylcellulose (Klucel™-LF), hydroxypropyl methylcellulose (Methocel™), polyvinylpyrrolidone (PVP-K25, PVP-K29, PVP-K30), powdered acacia, gelatin, guar gum, carbomer (e.g. carbopol), methylcellulose, polymethacrylates, and starch.

Various useful fillers include but are not limited to starches, lactose, mannitol, cellulose derivatives and the like. Different grades of lactose include but are not limited to lactose monohydrate and lactose anhydrous. Different grades of starches included but are not limited to maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch. Different cellulose compounds that can be used include microcrystalline cellulose and powdered cellulose. Examples of microcrystalline cellulose products include but are not limited to Avicel™ PH 101, PH102, PH301, PH302 and PH-F20, microcrystalline cellulose 114, and microcrystalline cellulose 112.

Various useful glidants include but are not limited to starches, colloidal silicon dioxide and talc.

- 5 Various useful antiadhesive agents include but are not limited to colloidal silicon dioxide and talc.

A pharmaceutical compositions according to the present invention is preferably in solid form, including tablets, capsules, caplets, lozenges and sachets. Tablets may be suitably coated
10 (film coated tablets, pills). Capsule formulations may cover both soft and hard capsules. A pharmaceutical compositions according to the present invention is preferably in the form of tablet, more preferably coated tablet with appropriate film coating material.

The coating can be selected from the group of ready to form dispersion such as OPADRY.
15 The coating dispersion comprises hydrophilic film forming polymer (such as for example low viscosity HPMC, HPC, PVA (polyvinylalcohol) and the like), plastificators (e.g. PEG), colorants and may optionally include other excipients such as antitacking agents.

Any method for film coating, known in the field of the pharmaceutical technology, may be
20 used.

A levetiracetam pharmaceutical composition according to present invention can be prepared by processes well known to those skilled in the art. For example, levetiracetam tablets according to present invention can be prepared by wet granulation, dry granulation, melt
25 granulation, direct compression and the like.

Preferably, the core of the tablets of the present invention is formulated with levetiracetam, at least one lipophilic matrix agent and a lubricant. More preferably the core of the tablets of the present invention is formulated with levetiracetam, hydrogenated castor oil and/or glyceryl
30 behenate as lipophilic matrix agent and magnesium stearate, hydrogenated castor oil or glyceryl behenate as lubricant.

A pharmaceutical composition of the present invention comprises preferably 500, 750 or 1000 mg of levetiracetam as the respective dose.

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The present invention can thus provide a pharmaceutical composition that is not susceptible to ethanol. As it is evident from Table 1 and Figures 1 and 2 the difference between the amount of levetiracetam released under Test 1 conditions (simulating influence of alcohol) compared to the amount released under normal physiological conditions (Test 2) is significantly smaller for pharmaceutical formulation according to present invention compared to the composition of Comparative example 1. In other words, the amount of levetiracetam released from pharmaceutical formulation according to present invention is less affected by the presence of ethanol compared to pharmaceutical formulation described in Comparative example 1. The release of levetiracetam is slower in the presence of ethanol in the case of pharmaceutical formulation described in Comparative example 1.

Furthermore pharmaceutical composition according to present invention is very robust to the influence of mechanical forces that can occur when tablet passes the gastrointestinal tract as it can be seen from the results in Table 2 and Figure 1. Only minor differences in the release of levetiracetam are observed when the pharmaceutical composition according to present invention is subjected to test conditions that simulate the situation in gastrointestinal tract with intense mechanical stress like transfer of matrix tablet through pylorus, presence of food or MMC, compared to the results obtained under test conditions that mimic physiologically normal conditions (*i.e.* results under Test 3 conditions compared with results under Test 2).

Excellent robustness regarding the influence of alcohol of the pharmaceutical composition according to present invention is further supported by the results presented in Figure 3. The pharmaceutical formulation obtained in Comparative example 2 (that contains inert matrix agent in addition to lipophilic matrix agent) shows considerable susceptibility to the presence of ethanol as it exhibits a burst release of levetiracetam. The pharmaceutical composition according to present invention, however, retains its controlled release properties when subjected to the same conditions (*i.e.* Test 4 conditions).

Examples

Example 1:

Core	Function	mg	%
Levetiracetam	Active	500.00	62.50
Castor oil, hydrogenated	Lipophilic matrix agent	284.00	35.50
Castor oil, hydrogenated	Lubricant	16.00	2.00

		800.00	100.00
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The tablets were prepared by wet granulation where levetiracetam is granulated with dispersion of hydrogenated castor oil in acetone.

Preparation of granulation liquid: hydrogenated castor oil was dispersed in acetone and the dispersion was mixed on a magnetic stirrer for 4 h.

Levetiracetam, previously sieved, was granulated with acetone dispersion. The granulate was dried in vacuum dryer and afterwards sieved through a proper sieve. Finally, hydrogenated castor oil was added to dry and sieved granulate and homogenously blended and compressed into 800 mg tablets.

Example 2:

Core	Function	mg	%
Levetiracetam	Active	500.00	62.50
Castor oil, hydrogenated	Lipophilic matrix agent	284.00	35.50
Magnesium stearate	Lubricant	16.00	2.00
		800.00	100.00

Direct compression was used as manufacturing procedure for preparation of the tablets.

Levetiracetam and hydrogenated castor oil were homogenously blended and sieved.

Magnesium stearate was added to a mixture, homogenously blended and compressed into tablets, 800 mg.

Example 3:

Core	Function	mg	%
Levetiracetam	Active	500.00	62.50
Glyceryl behenate	Lipophilic matrix agent	284.00	35.50
Glyceryl behenate	Lubricant	16.00	2.00
		800.00	100.00

Hot melt granulation was used as manufacturing procedure for preparation of the tablets.

Glyceryl behenate was melted. Previously sieved levetiracetam was granulated with the melt.

Granulate was sieved through appropriate sieve. Powdered glyceryl behenate was added to granulate, homogenously blended and compressed into tablets, 800 mg.

Comparative example 1:

Reference product KEPPRA XR 500 mg levetiracetam tablets with following qualitative composition were comparatively evaluated.

Keppra XR	Function
Levetiracetam	Active
Hypromellose	Hydrophilic matrix agent
Polyethyleneglicol 6000	Lubricant
Anhydrous colloidal silica	Glidant
Magnesium stearate	Lubricant
Polyvinyl alcohol – partially hydrolized, Titanium dioxide, Macrogol PEG 3350, Talc	Film coating

Comparative example 2:

Core	Function	mg	%
Levetiracetam	Active	500.00	50.00
Eudragit RS 30D	Inert matrix agent	800.00 of dispersion (240 mg of dry polymer)	24.00
Dibutyl sebacate	Plastificator	48.00	4.80
Castor oil, hydrogenated	Lipophilic matrix agent	197.00	19.70
Anhydrous colloidal silica	Glidant	5.00	0.50
Magnesium stearate	Lubricant	10.00	1.00
		1000.00	100.00

5

Fluid bed granulation was selected as manufacturing procedure for preparation of the tablets. Dispersion of Eudragit RS 30D and dibutyl sebacate were mixed for 1h and afterwards sprayed on levetiracetam in fluid bed granulator. Dry granulate was sieved through appropriate sieve. Hydrogenated castor oil and anhydrous colloidal silica were added to granulate, the mixture was sieved and homogenized. Magnesium stearate was added to a mixture, homogenously blended and compressed into tablets, 1000 mg.

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Dissolution tests

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Tablets of present invention as well as tablets from Comparative examples 1, 2 were subjected to dissolution tests that simulate different conditions in human gastrointestinal tract. The solubility of levetiracetam is good, and it is pH independent, therefore in particular

extreme conditions that can occur in gastrointestinal tract can affect the release of levetiracetam from tablets. Four different tests were chosen for evaluation of levetiracetam extended release matrix tablets to prove robustness.

5 **Test 1:** Apparatus 1 (basket method), 100 rpm in 43 % ethanol media; sampling times: 1, 2, 4, 8, 12 h. Test simulates the influence of alcohol on release of levetiracetam from matrix tablet after simultaneous consumption of ethanol and levetiracetam matrix tablet.

10 **Test 2:** Apparatus 1 (basket method), 100 rpm in potassium phosphate buffer pH 6.0; sampling times: 1, 2, 4, 6, 8, 12 h. This test mimic physiologically normal conditions under which the levetiracetam is released from the tablet.

15 **Test 3:** Apparatus 1 (basket method); 100 rpm, after 30 minutes tablets were transferred to plastic tubes containing 5 ml of media and 10 glass beads with density 2.5 g/cm^3 and diameter 10 mm. The tablets were then shaken for 10 minutes on laboratory shaker in 300 rotations per minute. After this manipulation, tablets were transferred back to baskets and dissolution test continued. Media used was water; sampling times: 30 min, 1, 2, 4, 6, 12 h. This test describes situation in gastrointestinal tract with intense mechanical stress like transfer of matrix tablet through pylorus, presence of food or MMC.

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Test 4: Apparatus 3 (reciprocating cylinder), 25 dpm, tablets tested in 43 % of alcohol media; sampling times: 30 min, 1, 2, 4, 8, 14 h.

The results are shown in Figures 1 and 2 and 3 and in Tables 1 and 2.

25

Table 1: Relative difference (%) in amount of levetiracetam released for various time points between Test 2 and Test 1 conditions.

t (h)	Example 1	Comparative example 1
1	3.8	10.4
2	5.4	11.1
4	6.4	10.7
8	6.7	5.3

30 **Table 2:** Relative difference (%) in amount of levetiracetam released for various time points between Test 3 and Test 2 conditions.

t (h)	Example 1	Comparative example 1
1	2.2	1.2
2	2.7	2.6
4	1.1	2.2
12	1.8	1.5

It is evident from Table 1 and Figures 1 and 2 that pharmaceutical formulation of present invention was less susceptible to ethanol (Test 1) compared to pharmaceutical formulation described in Comparative example 1 since the difference between the amount of levetiracetam released under Test 1 conditions compared to the amount released under normal physiological conditions (Test 2) was significantly smaller for pharmaceutical formulation obtained in Example 1. In other words, the amount of levetiracetam released from pharmaceutical formulation obtained in Example 1 was less affected by the presence of ethanol compared to pharmaceutical formulation described in Comparative example 1. The release of levetiracetam was slower in the presence of ethanol in the case of pharmaceutical formulation described in Comparative example 1.

Results in Table 2 and Figure 1 (comparison of results under Test 3 conditions with results under normal physiological conditions (Test 2)) show that pharmaceutical formulation of present invention showed excellent robustness to the influence of mechanical forces that can occur when tablet passes the gastrointestinal tract.

The pharmaceutical formulation obtained in Comparative example 2 showed considerable susceptibility to the presence of ethanol as it is evident from Figure 3. Said formulation exhibits burst release and the controlled release property of matrix tablet is diminished which consequently leads to therapeutic efficacy and safety issues. Test 4 showed further advantage in robustness of pharmaceutical composition of present invention.

Claims

1. A controlled release pharmaceutical composition, comprising levetiracetam and from 30 % to 40 % by weight of at least one lipophilic matrix agent.
2. The controlled release pharmaceutical composition according to claim 1, wherein lipophilic matrix agent is selected from the group consisting of waxes, fatty acids, fatty alcohols, fatty acids esters, glycerides and mixtures thereof.
3. The controlled release pharmaceutical composition according to claim 1 or 2, wherein said lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate.
4. The controlled release pharmaceutical composition according to any one of claims 1 to 3, further comprising a lubricant.
5. The controlled release pharmaceutical composition according to claim 4, comprising from 0.1 % to 4 % by weight of a lubricant.
6. The controlled release pharmaceutical composition according to claim 4 or 5, wherein said lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate.
7. The controlled release tablet according to any one of claims 1 to 6 comprising levetiracetam, from 30 % to 40 % by weight of lipophilic matrix agent, wherein said lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate, and from 0.1 % to 4 % by weight of lubricant, wherein said lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate.
8. The controlled release tablet to any one of claims 1 to 7 comprising from 55 % to 70 % by weight of levetiracetam, from 30 % to 40 % by weight of lipophilic matrix agent, wherein said lipophilic matrix agent is hydrogenated castor oil and/or glyceryl behenate, and

from 0.1 % to 4 % by weight of lubricant, wherein said lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate.

- 5 9. The controlled release pharmaceutical composition according to any one of claims 1 to 8, wherein a pharmaceutical composition is in the form of a tablet.
10. The controlled release pharmaceutical composition according to claim 9, wherein said tablet further comprises a coating.

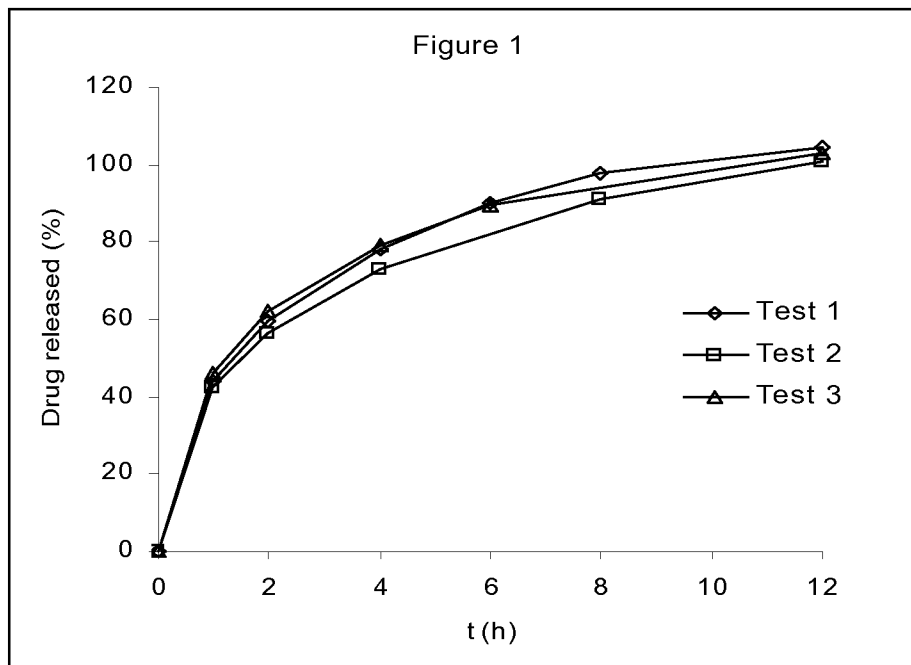
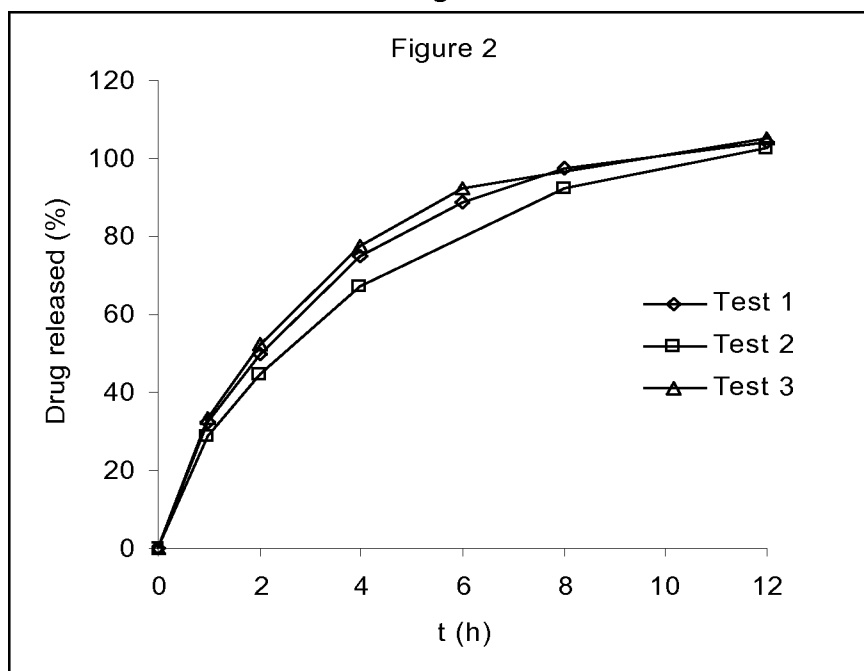
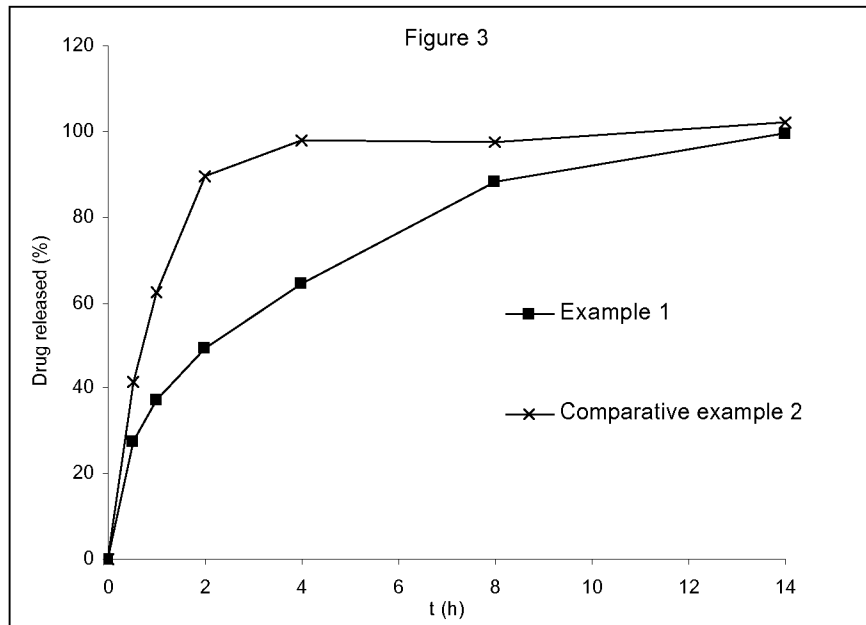
Fig. 1**Fig. 2**

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/063620

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/28 A61K9/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/123357 A (SUN PHARMACEUTICAL IND LTD [IN]; ZALA YASHORAJ RUPSIH [IN]; DHARMADHI) 23 November 2006 (2006-11-23) page 2, line 25 - line 34 page 3, line 19 - line 27 page 7, line 21 - page 8, line 14 page 13, line 1 - line 3 example 1	1-10
X	WO 2009/087675 A (ALEMBIC LTD [IN]; KSHIRSAGAR RAJESH [IN]; RAO ASHWIN [IN]; KATHIRIYA A) 16 July 2009 (2009-07-16) example 2 * abstract	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

9 November 2010

Date of mailing of the international search report

17/11/2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/063620

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006123357 A	23-11-2006	EP 1909770 A2 US 2009123541 A1	16-04-2008 14-05-2009
WO 2009087675 A	16-07-2009	AU 2008346118 A1 CA 2709521 A1 EP 2229153 A2 KR 20100103629 A	16-07-2009 16-07-2009 22-09-2010 27-09-2010