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(54) Title: PHARMACEUTICAL FORMULATIONS OF LACOSAMIDE

(57) Abstract: The present invention relates to a pharmaceutical formulation comprising lacosamide or a pharmaceutically acceptable salt thereof in the form of a tablet comprising sodium stearyl fumarate. Particularly, the formulation is obtained by means of dry granulation.



PHARMACEUTICAL FORMULATIONS OF LACOSAMIDE

Field of Invention

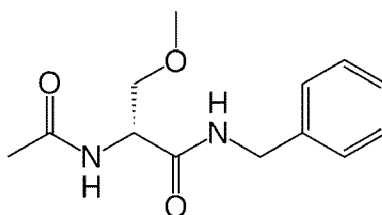
- 5 The present invention relates to a pharmaceutical formulation comprising lacosamide or a pharmaceutically acceptable salt thereof in the form of a tablet comprising sodium stearyl fumarate. Particularly, the formulation is obtained by means of dry granulation.

Background of Invention

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Lacosamide is an aminoacid derivative with an anticonvulsant activity useful in the adjunctive treatment of partial-onset seizures with or without secondary generalization in adults with epilepsy. It is also called as erlosamide or harkoseride. Its chemical name is (2R)-2-(Acetylamino)-3-methoxy-N-(phenylmethyl) propanamide and its chemical

15 structure is shown in the Formula 1.



Formula 1

- 20 The precise mechanism of antiepileptic effects of lacosamide in humans remains to be fully elucidated. In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. Inactivation of sodium channels is important to control of abnormal neuronal activity
- 25 in the brain of epilepsy patient, and it can occur via fast or slow mechanism. While traditional sodium channel blocking antiepileptics (e.g., Lamotrigine, Carbamazepine, Oxcarbazepine or Phenytoin) act primarily via fast inactivation, lacosamide acts by selectively enhancing slow inactivation of voltage-gated sodium channels to control and stabilise the neural network in the brain.

30

Lacosamide is sparingly soluble in water and it has low flowability, which makes the tableting process difficult at the high amount of active substance in tablets.

There is lacosamide immediate release formulation licensed in the US and Europe in the form of immediate release tablets, oral solutions and intravenous injection solutions under the brand name Vimpat® by UCB. Vimpat® IR tablet has crospovidone as disintegrant agent, microcrystalline cellulose, HPC (low substituted) and HPC as filler and binder, silicified microcrystalline cellulose as glidant, colloidal silicon dioxide as filler, magnesium stearate as lubricant and a non-functional coating. It may be taken with or without food. The initial dose should be 50 mg twice daily (100 mg per day). Vimpat® IR tablet is prepared by wet granulation. To overcome poor flowability of lacosamide, wet granulation comprising HPC (including low substituted HPC) is selected.

Lacosamide can be increased at weekly intervals by 100 mg/day given as two divided doses up to the recommended maintenance dose of 200 to 400 mg/day, based on individual patient response and tolerability. The currently commercially available tablets are available in strengths of 50, 100, 150 and 200 mg of lacosamide.

PCT application WO 2010/060624 A2 Ratiopharm GMBH, 27.11.2008, provides preparation of lacosamide containing tablets wherein the tablets produced by means of dry granulation and direct compression to overcome poor flowability of lacosamide.

In this present invention, the solution to the flowability problem is producing granules that contain sodium stearyl fumarate as a hydrophilic lubricant instead of magnesium stearate which has some known drawbacks by means of dry granulation.

In addition, croscarmellose is used as a super-disintegrant which is not previously used in prior art to further improve the process.

Description of the invention

The present invention provides a pharmaceutical tablet formulation comprising lacosamide or a pharmaceutically acceptable salt to eliminate process problems as flowability and ensure rapid disintegration for desired drug dissolution characteristics.

The present invention provides a pharmaceutical formulation in the form of a tablet comprising a therapeutically effective amount of lacosamide or a pharmaceutically acceptable salt and at least one hydrophilic lubricant.

The present invention further provides a pharmaceutical tablet formulation to ensure a rapid disintegration and desired drug dissolution characteristic at the high dose (200mg or more) level of lacosamide that has flowability-problem.

5 In one aspect, the advantages of the formulations producing by dry granulation are well known by the skilled person in the art and such techniques were already studied for the lacosamide. However, the major difficulties of the development on dry granulation process are compressibility and flowability. Most of the directly compressible materials can accommodate only 30-40 % of the poorly compressible active ingredients which brings
10 compressibility and also flowability problems.

The object of this invention is to produce dry granules comprising at least one hydrophilic lubricant to overcome compressibility and also flowability problems.

15 According to another embodiment of the present invention is to provide a pharmaceutical formulation comprising lacosamide or a pharmaceutically acceptable salt thereof in the form of a tablet obtained by means of dry granulation.

According to another object of the present invention is to provide a pharmaceutical
20 formulation wherein lacosamide or a pharmaceutically acceptable salt thereof is present in an amount of about 5 to 80 % by weight of total composition, preferably it is about 20 to 50 % by weight of total composition.

In one aspect, the present invention relates to a lacosamide containing pharmaceutical
25 composition does not comprise magnesium stearate. Magnesium stearate is a metal derivative lubricant. It has anti-adhesive and flow enhancement properties by ensuring uniformity of tablets. Besides this advantageous, its hydrophobic properties increase the process time with prolonged mixing. Because of this increase in time, lubricant forms a hydrophobic film around the active agent and retards the dissolution by retarding wetting
30 of active agent.

According to one embodiment, the pharmaceutical formulation comprises at least one hydrophilic lubricant which is selected from the group comprising sodium stearyl fumarate, polyethylene glycol, sodium benzoate or a proper mixture thereof.

35

Accordingly, said pharmaceutical formulation does not comprise magnesium stearate.

In this invention, sodium stearyl fumarate is selected as a suitable lubricant in tableting. Due to hydrophilic property of sodium stearyl fumarate, formulation does not have the disadvantages of magnesium stearate in respect of tablet strength, disintegration and dissolution.

The amount of sodium stearyl fumarate is present in an amount of 0.01 to 10 % by weight of total composition; preferably it is 0.1 to 5% by weight of total composition.

In one embodiment, said hydrophilic lubricant is preferably sodium stearyl fumarate to overcome compressibility and flowability problem. The ratio of lacosamide to sodium stearyl fumarate is in the range of 10 to 60 (w/w), preferably 20 to 30(w/w).

In this present invention, flowability test is performed by Erweka Gt Powder Tester instrument with cone diameter in 10 mm with a sample of 150 ml. The results shows that average angle of repose is between 41 to 45 degree.

In another aspect, the pharmaceutical formulation further comprises super-disintegrant to further improve the disintegration and dissolution of formulation.

As used herein, the term "super-disintegrant" is defined as the pharmaceutical ingredient that provides improved disintegration and dissolution. According to this embodiment, the term "super-disintegrant" is defined as croscarmellose sodium, sodium carboxymethyl starch, sodium starch glycolate, soy polysaccharide, cross-linked alginic acid, gellan gum, xanthan gum, calcium silicate or ion exchange resins preferably croscarmellose sodium.

The main embodiment of the present invention is to provide a pharmaceutical formulation comprising lacosamide or a pharmaceutically acceptable salt thereof in the form of a tablet comprising croscarmellose as a super-disintegrant which is not previously used in prior art.

According to this embodiment, the present invention relates to a pharmaceutical composition comprising lacosamide or a pharmaceutically acceptable salt thereof in the form of a tablet comprising croscarmellose sodium is in the range of 0.1 - 10% ,

preferably 2 - 7%, and the ratio of lacosamide to croscarmellose sodium is in the range of 5 to 50(w/w) , preferably 2 to 10(w/w).

The advantage of the formulation with croscarmellose is to further improve disintegration and dissolution lacosamide by increasing the effect of sodium stearyl fumarate without using magnesium stearate that cause undesirable dissolution profile.

In another embodiment, the pharmaceutical formulation according to any of the preceding claims, wherein the ratio of croscarmellose sodium to sodium stearyl fumarate is in the range of preferably 1 to 10(w/w) and more preferably 2 to 5(w/w).

Suitable glidants may include but not limited to colloidal silicon dioxide, talc, aluminium silicate and the like and mixtures thereof, preferably colloidal silicon dioxide.

Suitable binders may include but not limited to polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate and their copolymers, cellulose derivatives such as hydroxypropyl methyl cellulose, carboxy methyl cellulose, methyl cellulose, microcrystalline cellulose, gelatin, polyvinylalcohol, carrageenan, guar gum and the like and mixtures thereof; preferably polyvinylpyrrolidone - polyvinyl acetate copolymers.

Coating material may include but not limited to hydroxypropyl methyl cellulose (HPMC), polyethyleneglycol (PEG), polyvinylpyrrolidone (PVP), vinylpyrrolidone-vinyl acetate copolymer (PVP- PVAc) and polyvinyl alcohol and all OpadryTM derivatives and pigments, titanium dioxide, dyes and iron oxide and talc or mixtures thereof.

According to another embodiment, the formulation wherein minimum 85% of lacosamide by weight relative to the total weight of said formulation is released within 15 minutes when measured in 900ml_ of 0.1 N HCl at 50 rpm named as USP Apparatus II (Paddle).

The pharmaceutical formulation consists of;

- a) about 5 to 60% by weight of lacosamide
- b) about 0.1 to 10% by weight of croscarmellose sodium
- c) about 2 to 15% by weight of crospovidone
- d) about 0.25 to 5% by weight polyvinylpyrrolidone - polyvinyl acetate copolymer
- e) about 0.01 to 1% by weight colloidal silicon dioxide

- f) about 10 to 60% by weight microcrystalline cellulose
- g) about 0.1 to 5% by weight sodium stearyl fumarate
- h) about 0.4 to 5% by weight coating

5 The pharmaceutical formulation is processed by means of dry granulation

According to another embodiment, a method for preparing a pharmaceutical formulation according to any of the preceding claims, comprising the steps of

- 10 a) sieving lacosamide, 50% of sodium stearyl fumarate, 50% of crospovidone, 50% of colloidal silicon dioxide and all other excipients and mixing the resulting mixture,
- b) passing the mixture through a compactor or pressing into a slug briquette.
- c) powders or slug briquetted tablets are crushed and sieved.
- 15 d) adding 50% of sodium stearyl fumarate, 50% of crospovidone, 50% of colloidal silicon dioxide and mixing the resulting mixture,
- e) pressing resultant mixture,

According to another embodiment, a method according to any of the preceding claims, wherein the compaction is carried out in a roller compactor and the rolling force is 180 to

20 190 kN

Example 1: immediate release tablet

Ingredients	% amount (mg)
lacosamide	40 %
croscarmellose sodium	5.0 %
crospovidone	8.0 %
kollidon VA 64	2.0 %
colloidal silicon dioxide	0.4 %
microcrystalline Cellulose (AvicelPh 112)	43.1 %
sodium stearyl fumarate	1.5 %
Opadry 200F (coating)	3.0 %

25 The production of the formulation is carried out as follows: 50% of sodium stearyl fumarate and all excipients other than colloidal silicon dioxide and lacosamide are weighed and pre-mixed for 10 min. Mixed powder passed through the compactor or

pressed in slug briquettes. Powders or slug briquetted tablets are crushed and sieved. Colloidal silicon dioxide and other part of sodium stearyl fumarate are added and mixed for 5 minutes. Then, they are pressed and the tablets are coated preferably with OPADRY 200F.

5 For this example the average angle of repose has been found to be 44.2 degree.

With this invention, a pharmaceutical tablet formulation comprising lacosamide or a pharmaceutically acceptable salt thereof eliminating any flowability and process related problems and bringing additional advantages. Method described above both serves both
10 improved dissolution and disintegration and eliminates the need of magnesium stearate.

CLAIMS

1. A pharmaceutical formulation in the form of a tablet comprising a therapeutically effective amount of lacosamide or a pharmaceutically acceptable salt, sodium stearyl fumarate and at least one excipient..
5
2. The pharmaceutical formulation according to claim 3, wherein the amount of sodium stearyl fumarate is present in an amount of 0.01 to 10% by weight of total composition; preferably it is 0.1 to 5% by weight of total composition.
10
3. The pharmaceutical formulation according to claims 1 to 5, wherein the ratio of lacosamide to sodium stearyl fumarate is in the range of 1 to 100 (w/w), preferably 20 to 30 (w/w).
4. The pharmaceutical formulation according to claim 1, further comprising super - disintegrant.
15
5. The pharmaceutical formulation according to claim 7, wherein said super - disintegrant is selected from the group comprising croscarmellose sodium, sodium carboxymethyl starch, sodium starch glycolate, soy polysaccharide, cross-linked alginic acid, gellan gum, xanthan gum, calcium silicate or ion exchange resins or mixtures thereof.
20
6. The pharmaceutical formulation according to claim 8, wherein said super - disintegrant is croscarmellose sodium.
25
7. The pharmaceutical formulation according to any of the preceding claims, wherein croscarmellose sodium is in the range of 0.1 - 10% , preferably 2 - 7%
8. The pharmaceutical formulation according to any of the preceding claims, wherein the ratio of lacosamide to croscarmellose sodium is in the range of 5 to 50 (w/w), preferably 2 to 10 (w/w).
30
9. The pharmaceutical formulation according to any of the preceding claims, wherein the ratio of croscarmellose sodium to sodium stearyl fumarate is in the range of preferably 1 to 10 (w/w) and more preferably 2 to 5 (w/w).
35

10. A pharmaceutical formulation according to any of the preceding claims, wherein said formulation does not comprise magnesium stearate.

11. The pharmaceutical formulation according to any preceding claim consisting of;

- 5 a) 5 to 60% by weight of lacosamide
 b) 0.1 to 10% by weight of croscarmellose sodium
 c) 2 to 15% by weight of crospovidone
 d) 0.25 to 5% by weight polyvinylpyrrolidone - polyvinyl acetate copolymer
 e) 0.01 to 1% by weight colloidal silicon dioxide
10 f) 10 to 60% by weight microcrystalline cellulose
 g) 0.1 to 5% by weight sodium stearyl fumarate
 h) 0.4 to 5% by weight coating

12. The pharmaceutical formulation according to any preceding claim comprising;

- 15 a) 40% by weight of lacosamide
 b) 5.0 % by weight of croscarmellose sodium
 c) 8.0 % by weight of crospovidone
 d) 2.0 % by weight polyvinylpyrrolidone - polyvinyl acetate copolymer
 e) 0.4 % by weight colloidal silicon dioxide
20 f) 43.1 % by weight microcrystalline cellulose
 g) 1.5 % by weight sodium stearyl fumarate
 h) 3.0 % by weight coating

13. The formulation according to any of the preceding claims, wherein minimum 85%
25 of lacosamide by weight relative to the total weight of said formulation is released
 within 15 minutes when measured according to USP Apparatus II (Paddle) method
 in 900ml of 0.1 N HCl at 50rpm.

14. A pharmaceutical formulation according to any of the preceding claims, wherein
30 said formulation is processed by means of dry granulation.

15. The method for preparing the pharmaceutical formulation according to claim 14 to
17, comprising the steps of

- 35 a) Sieving lacosamide, 50% of sodium stearyl fumarate, 50% of
 crospovidone, 50% of colloidal silicon dioxide and all other excipients and
 mixing the resulting mixture,

- b) Passing the mixture through a compactor or pressing into a slug briquette.
- c) Powders or slug briquetted tablets are crushed and sieved.
- d) adding 50% of sodium stearyl fumarate, 50% of crospovidone, 50% of colloidal silicon dioxide and mixing the resulting mixture,
- 5 e) pressing resultant mixture,

16. The method according to claim 17 and 18, wherein the compaction is carried out in a roller compactor and the rolling force is 180 to 190 kN.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/059324

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/00 A61K9/20 A61K31/165 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 practicable, search terms used) EPO-Internal , WPI Data, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	page 116 - page 120; examples 12-14 -----	15, 16
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
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INTERNATIONAL SEARCH REPORT

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