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(54) Title: MUCOADHESIVE TABLET OF PREGABALIN

(57) Abstract: The present invention relates to a mucoadhesive tablet comprising pregabalin with at least one mucoadhesive excipient, at least one swelling agent and at least one gelling agent, wherein the mucoadhesive tablet maintains gastric retention for the time period during which the drug is released into the stomach. Further it relates to a process for the preparation of the mucoadhesive tablet.

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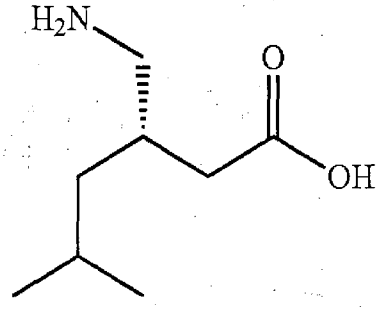
## FIELD OF THE INVENTION

The present invention relates to a mucoadhesive tablet comprising pregabalin with pharmaceutically acceptable excipients, wherein the mucoadhesive tablet maintains gastric retention for the time period during which the drug is released into the stomach. Further it relates to a process for the preparation of the mucoadhesive tablet.

## BACKGROUND OF THE INVENTION

Pregabalin is an analogue of the physiologically important endogenous neurotransmitter [gamma]-amino butyric acid (GABA), which is involved in the regulation of neural processes.

The IUPAC name of pregabalin [INN] is (S)-3-(aminomethyl)-5-methyl hexanoic acid. The chemical structure of pregabalin is shown in formula below:




Pregabalin is disclosed in U.S. Patent Nos. 6,197,819 and 5,563,175, which describe its use in the treatment of seizure disorders. U.S. Patent No. 6,117,906 discloses the use of pregabalin in treating anxiety, while U.S. Patent No. 6,001,876 discloses its use in treating pain.

Currently, pregabalin is available as conventional immediate-release capsules marketed by CP Pharms/Pfizer under the brand name Lyrica®. The marketed product Lyrica® Capsules requires two or three times a day dosing.

In order to improve patient compliance and to reduce the severity and frequency of side effects by reducing peak blood levels along with an increase in drug efficacy by increasing minimum plasma concentration, a once-daily tablet is desirable.

The development of a suitable once-daily formulation is rendered more difficult by the fact that pregabalin cannot be absorbed in the entire gastrointestinal tract (GIT). Pregabalin is only absorbed in the upper sections of the gut. It is therefore desirable to have a dosage form which has a longer retention time in the upper GIT and which, during that time, releases the active agent continuously over a longer period of time.

The U.S. Publication Application No. 2007/0269511 discloses a pregabalin formulation containing matrix forming agent and a swelling agent, wherein the matrix forming agent is polyvinyl acetate and polyvinylpyrrolidone, and the swelling agent is cross-linked polyvinylpyrrolidone.

The U.S. Publication Application No. 2010/0255067 describes pharmaceutical compositions comprising pregabalin, a hydrophobic release controlling agent, and other pharmaceutically acceptable excipients.

The U.S. Publication Application No. 2013/149253 describes oral dosage form for the modified release of pregabalin, comprising pregabalin in a matrix comprising a swelling agent, a matrix former and a buoyancy agent or alternatively a sedimentation agent.

Therefore, a mucoadhesive tablet that retains in the upper parts of the gastrointestinal tract would be an ideal dosage form for pregabalin. The objective of the present invention is to develop a mucoadhesive tablet of pregabalin.

## OBJECTS OF THE INVENTION

The primary object of the invention is to provide a mucoadhesive tablet comprising pregabalin with pharmaceutically acceptable excipients, wherein the mucoadhesive tablet maintains gastric retention for the time period during which the drug is released into the stomach.

Another object of the invention is to provide a mucoadhesive tablet comprising pregabalin with at least mucoadhesive excipient, at least one swelling agent and at least one gelling agent, wherein the mucoadhesive tablet maintains gastric retention for the time period during which the drug is released into the stomach.

Another object of the invention is to provide a process for the preparation of a mucoadhesive tablet of pregabalin.

## SUMMARY OF THE INVENTION

In a first embodiment, the invention relates to a mucoadhesive tablet comprising pregabalin with pharmaceutically acceptable excipients, wherein the mucoadhesive tablet maintains gastric retention for the time period during which the drug is released into the stomach.

In another embodiment, the invention relates to a mucoadhesive tablet comprising pregabalin with at least mucoadhesive excipient, at least one swelling agent and at

least one gelling agent, wherein the mucoadhesive tablet maintains gastric retention for the time period during which the drug is released into the stomach.

In a preferred embodiment, the invention relates to a mucoadhesive tablet comprising pregabalin with polyethylene oxide (PEO) as mucoadhesive excipient, cross-linked homopolymers of 1-vinyl-pyrrolidin-2-one (Crospovidone) as swelling agent, and sodium alginate as gelling agent.

In a preferred embodiment, the invention relates to a mucoadhesive tablet comprising pregabalin with tragacanth as mucoadhesive excipient, sodium starch glycolate as swelling agent, and polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol such as carbomers (carbopols) as gelling agent.

In another embodiment, the invention relates to a process for the preparation of a mucoadhesive tablet of pregabalin, preferably direct compression method.

## DETAILED DESCRIPTION

The present invention relates to a mucoadhesive tablet comprising pregabalin with pharmaceutically acceptable excipients, wherein the mucoadhesive tablet maintains gastric retention for the time period during which the drug is released into the stomach.

The "mucoadhesive tablet" remains in the patient's stomach following oral administration, which is substantially longer than the average residence time of a corresponding immediate release dosage form.

The present invention may employ any pharmaceutically acceptable form of pregabalin, including its free form (zwitter ion), and its pharmaceutically acceptable complexes, acid addition salts, base addition salts solvates, hydrates, and polymorphs.

The present invention relates to a mucoadhesive tablet comprising pregabalin with at least mucoadhesive excipient, at least one swelling agent and at least one gelling agent, wherein the mucoadhesive tablet maintains gastric retention for the time period during which the drug is released into the stomach.

The "mucoadhesive excipient" of the present invention includes polyethylene glycol (PEG 8000), Tragacanth, polymethacrylate derivatives (Eudragit), polyethylene oxide (PEO) or combinations or copolymers thereof.

The mucoadhesive excipient is generally used in an amount ranging from about 5% to about 20% by weight of the tablet composition.

The "swelling agent" of the present invention includes croscarmellose sodium, sodium starch glycolate (SSG), microcrystalline cellulose (MCC), starch, cross-linked homopolymers of 1-vinyl-pyrrolidin-2-one (Crospovidone) or combinations or copolymers thereof.

The swelling agent absorbs water from the gastric fluid and thereby the tablet expands in size larger than the pylorus. The swelling agent is generally used in an amount ranging from about 5% to about 30% by weight of the tablet composition.

The "gelling agent" of the present invention includes polyvinyl pyrrolidone (PVP), polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol such

as carbomers (carbopols), alginates, preferably sodium alginate, hydroxyalkyl cellulose, especially hydroxyethyl cellulose (HEC), xanthan gum or combinations or copolymers thereof.

The gelling agent includes excipient that forms a gel when in contact with gastric fluid and thereby modulates the drug release characteristics of the tablet. The gelling agent is generally used in an amount ranging from about 0.5% to about 40% by weight of the tablet composition.

In addition to the above-mentioned ingredients, the mucoadhesive tablet may also comprise further pharmaceutically acceptable excipients such as diluents, binders, rate-controlling agents, lubricants, wetting agent, glidants and coating excipients.

The mucoadhesive tablet of pregabalin is designed for once-daily administration and achieves bioequivalence with immediate release dosage form of pregabalin that is taken two- or three-times daily.

In another embodiment, the invention relates to a process for the preparation of a mucoadhesive tablet of pregabalin. It can be prepared by routine tableting method including direct compression, granulation and pelletization methods. Preferably, the process for the preparation is direct compression method.

In order to further illustrate the present invention, the following examples are provided for the purpose of clarity of understanding. However, it is not intended in any way to limit the scope of present invention and it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the scope of the invention.

**Example 1: Mucoadhesive Tablet by Direct Compression approach**

| | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Pregabalin | 25-30% | 25-30% | 25-30% | 25-30% | 25-30% |
| **Mucoadhesive Excipient** | | | | | |
| PEG 8000 | 5-20% | - | - | - | - |
| Tragacanth | - | 5-20% | - | - | - |
| Eudragit (polymethacrylate derivatives) | - | - | 5-20% | - | - |
| polyethylene oxide | - | - | - | 5-20% | 5-20% |
| **Swelling agents** | | | | | |
| Croscarmellose sodium | 5-20% | - | - | - | - |
| Sodium starch glycolate | - | 5-20% | - | - | - |
| MCC (commercially available grade (PH-102 / PH-200) | 5-30% | 5-30% | 5-30% | 5-30% | 5-30% |
| Starch | - | - | 5-20% | - | - |
| Crospovidone | - | - | - | 5-20% | 5-20% |
| **Gelling agents** | | | | | |
| PVP | 10-40% | - | - | - | - |
| Carbopol 934/940 | - | 10-40% | - | - | - |
| Xanthan gum | - | - | 10-40% | - | - |
| Sodium Alginate | - | - | - | 10-40% | - |
| HEC | - | - | - | - | 10-40% |
| Magnesium Stearate/ SSF | 0.5-2% | 0.5-2% | 0.5-2% | 0.5-2% | 0.5-2% |
| Sub Total (mg) | | | | | |
| Film Coat (Optional) | 2-4% | 2-4% | 2-4% | 2-4% | 2-4% |
| Total (mg) | | | | | |

The mucoadhesive tablet of the present invention is prepared by Direct Compression method in the procedural steps as described below.

**Manufacturing Process:**

(i) Sift all ingredients through appropriate sieves,

(ii) Blend the sifted ingredients for an appropriate time,

(iii) Compressed the blend into tablets

(iv) Optionally film coat the compressed tablets.

**Dissolution Studies of Mucoadhesive tablet formulation (F3) as representative example:**

| **Dissolution Media** | **0.06 N HCL / Paddle / 900 ml / 50 rpm** |
|---|---|
| **Time (Hr)** | |
| **1** | 17 |
| **2** | 27 |
| **3** | 35 |
| **4** | 41 |
| **5** | 47 |
| **6** | 52 |
| **8** | 61 |
| **10** | 69 |
| **12** | 76 |

**We claim:**

1. A mucoadhesive tablet comprising pregabalin with pharmaceutically acceptable excipients, wherein the mucoadhesive tablet substantially maintains gastric retention for the time period during which the drug is released into the stomach.

2. The mucoadhesive tablet according to claim 1, wherein the mucoadhesive tablet comprises pregabalin with at least one mucoadhesive excipient, at least one swelling agent and at least one gelling agent.

3. The mucoadhesive tablet according to claim 2, wherein the mucoadhesive excipient is selected from the group of polyethylene glycol (PEG 8000), tragacanth, polymethacrylate derivatives (Eudragit), polyethylene oxide (PEO) or combinations or copolymers thereof.

4. The mucoadhesive tablet according to claim 2, wherein the swelling agent is selected from the group of croscarmellose sodium, sodium starch glycolate (SSG), microcrystalline cellulose (MCC), starch, cross-linked homopolymers of 1-vinyl-pyrrolidin-2-one (Crospovidone) or combinations or copolymers thereof.

5. The mucoadhesive tablet according to claim 2, wherein the gelling agent is selected from the group of polyvinyl pyrrolidone (PVP), polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol such as carbomers (carbopols), alginates, preferably sodium alginate, hydroxy alkyl cellulose, especially hydroxy ethyl cellulose (HEC), xanthan gum or combinations or copolymers thereof.

6. The mucoadhesive tablet according to claim 1, wherein the mucoadhesive tablet is a once-daily administration and achieves bioequivalence with immediate release dosage form of pregabalin that is taken two- or three-times daily.

7. The mucoadhesive tablet according to claim 1, wherein the mucoadhesive tablet is prepared by direct compression method.

8. The mucoadhesive tablet according to claim 1, wherein the mucoadhesive tablet comprises pregabalin, polyethylene oxide (PEO), cross-linked homopolymers of 1-vinyl-pyrrolidin-2-one (Crospovidone), sodium alginate, and optionally other pharmaceutically acceptable excipients.

9. The mucoadhesive tablet according to claim 1, wherein the mucoadhesive tablet comprises pregabalin, polyethylene oxide, Crospovidone, sodium alginate, and optionally other pharmaceutically acceptable excipients.

10. The mucoadhesive tablet according to claim 1, wherein the mucoadhesive tablet comprises pregabalin, tragacanth, sodium starch glycolate, carbomers, and optionally other pharmaceutically acceptable excipients.