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Title: SUSTAINED RELEASE TABLET COMPRISING PREGABALIN THROUGH TWO-PHASE RELEASE-CONTROLLING SYSTEM

Abstract: The present invention provides a sustained release tablet having two-phase release-controlling system, which consists of a first release-controlling phase comprising pregabalin or its salt and hydroxypropyl methylcellulose; and a second release-controlling phase comprising polyethylene oxide as a swelling polymer, the first release-controlling phase being homogeneously dispersed in the second release-controlling phase.
Description

Title of Invention: SUSTAINED RELEASE TABLET COMPRISING PREGABALIN THROUGH TWO-PHASE RELEASE-CONTROLLING SYSTEM

Technical Field

The present invention relates to a sustained release tablet having two-phase release-controlling system, which consists of a first release-controlling phase comprising pregabalin or its salt and hydroxypropyl methylcellulose; and a second release-controlling phase comprising polyethylene oxide as a swelling polymer, the first release-controlling phase being homogeneously dispersed in the second release-controlling phase.

Background Art

Pregabalin, chemically known as (S)-(+) 3-aminomethyl-5-methylhexanoic acid, binds to the alpha-2-delta subunit of calcium channels and is related to the endogenous inhibitory neurotransmitter γ-aminobutyric acid (GABA), which is involved in the regulation of brain neuronal activity. Pregabalin is useful for treating epilepsy, neuropathic pain, fibromyalgia, etc. Pregabalin is being marketed as an immediate release (IR) formulation, e.g., capsules containing 75 mg, 150 mg, or 300 mg and is usually administered to patients twice a day.

The conversion of drugs administered more than twice a day into a form for once-a-day administration can improve patients' drug compliance; reduce any side effects originated from maximum blood concentration exceeding the desired effective blood concentration and/or sudden increase of blood concentration; and increase the maintenance time of effective blood concentration, thereby increasing pharmacological effects. However, there are some problems in designing a pregabalin-containing formulation for once a day administration. Because pregabalin is absorbed through L-amino acid transport system, it does not exhibit uniform gastrointestinal absorptions. And also, because the absorption of pregabalin takes place in the upper small intestine where most of L-amino acid transporters reside, an average absorption window thereof is less than 6 hours (Su T-Z, Feng MR, Weber ML: Mediation of highly concentrative uptake of pregabalin by L-type amino acid transport in Chinese hamster ovary and Caco-2 cells. J Pharmacol Exp Ther 2005, 313:1406-1415). Therefore, it is very difficult to design pregabalin-containing formulations for once-a-day administration, which can show a release profile equivalent to the formulation for twice-a-day administration, according to conventional technologies for sustained release formations.

Gastro-retentive drug delivery systems may be considered as one of the methods for
designing a sustained release formulation for pregabalin. The gastro-retentive drug delivery systems are classified into three systems, i.e., an expansion-by-swelling system, a floating or buoyant system, and a bioadhesive system. As a gastro-retentive drug delivery system, WO 2007/052125 has disclosed a sustained release formulation for once daily oral administration comprising pregabalin, a matrix forming agent, and a swelling agent. However, since the formulation disclosed in WO 2007/052125 is designed for inducing the gastro-retention by simple swelling, individual variations in the absorption of pregabalin (especially, time to reach maximum plasma concentration, Tmax) is very high according to patients' respective gastrointestinal conditions, e.g., according to patients' respective gastrointestinal motilities. And also, there cannot be excluded the possibility to pass through the pylorus depending on patients' gastrointestinal conditions, thereby resulting in not showing sustained release patterns. In addition, there is a disadvantage that matrix hardness of the formulation becomes decreased at the time of about 24 hours.

WO 2006/078811 has been disclosed a controlled release formulation of gabapentin and pregabalin, comprising an immediate release component, a sustained release component, and a delayed release component. However, since the formulation is not a gastro-retentive form, there is a problem that it releases pregabalin not only in the upper small intestine (major absorption site of pregabalin), but also in other gastrointestinal sites such as the stomach and the lower small intestine.

Disclosure of Invention

Technical Problem

The present inventors performed various researches for developing a sustained release formulation comprising pregabalin having limited absorption window as an active ingredient. Especially, the present inventors carried out various researches for designing a sustained release formulation in a gastro-retentive form, which exhibits a controlled release profile capable of minimizing individual variations. We newly designed a two-phase release-controlling system, in which a first release-controlling phase for both controlling the release of pregabalin and promoting floatability is homogeneously dispersed in a second release-controlling phase having both swellability and floatability. We found that the two-phase release-controlling system can stably show both 'swellability' and 'floatability'; and thus accomplish effective gastro-retention, which make it possible to minimize the individual variations originated from e.g., different gastrointestinal motilities.

Therefore, it is an object of the present invention to provide a sustained release formulation comprising pregabalin or its salt through two-phase release-controlling system.
Solution to Problem

[8] In accordance with an aspect of the present invention, there is provided a sustained release tablet having two-phase release-controlling system, which consists of a first release-controlling phase comprising pregabalin or its salt and hydroxypropyl methylcellulose; and a second release-controlling phase comprising polyethylene oxide as a swelling polymer, the first release-controlling phase being homogeneously dispersed in the second release-controlling phase.

[9] In the first release-controlling phase, the polyethylene oxide may have an average molecular weight ranging from 100,000 to 7,000,000; and be present in an amount ranging from 10 to 70 % by weight, based on the total weight of the tablet.

[10] In the first release-controlling phase, the hydroxypropyl methylcellulose may have a viscosity ranging from 100 to 150,000 centipoises; and be present in an amount ranging from 5 to 40 % by weight, based on the total weight of the tablet.

[11] The first release-controlling phase may further comprise hydroxypropyl cellulose as a binder; and the second release-controlling phase may further comprise crospovidone or sodium starch glycolate as a supplemental floating agent.

[12] In an embodiment, a time to reach maximum plasma concentration (Tmax) may range from 4 to 8 hours after oral administration of the sustained release tablet of the present invention. In another embodiment, the sustained release tablet of the present invention may be magnified to 12 mm of size when contacting with water. In still another embodiment, the sustained release tablet of the present invention may be floated within 30 minutes after contact with water and the resultant floating state may be maintained for at least 12 hours.

[13] In accordance with another of the present invention, there is provided a process for preparing a sustained release tablet having two-phase release-controlling system, the process comprising (a) granulating a mixture of pregabalin or its salt and hydroxypropyl methylcellulose; and (b) mixing the granules obtained in the step (a) with polyethylene oxide and a pharmaceutically acceptable excipient, followed by compressing the resulting mixture.

[14] In the process of the present invention, the granulating may be performed using a binder solution.

Advantageous Effects of Invention

[15] The sustained release tablet according to the present invention can effectively control the release of pregabalin along with showing controlled and prolonged release profiles (i.e., without showing initial sudden release thereof) at the time of oral administration. In the sustained release tablet of the present invention, the release of pregabalin is controlled in the first release-controlling phase; and then the released pregabalin from
the first release-controlling phase is further controlled during the pass through the second release-controlling phase. That is, in the sustained release tablet of the present invention, the release of pregabalin is controlled by two phase release-controlling system. The sustained release tablet according to the present invention may be administered once a day by controlling the release mechanism of pregabalin having limited absorption window. Especially, the polymer in the first release-controlling phase can enhance floatability effectively and thus ensure both 'swellability' and 'floatability' which increases the shape-maintenance time as well as floating-maintenance time after contact with water, thereby minimizing individual variations in the absorption of pregabalin (especially, time to reach maximum plasma concentration, Tmax) originated from different gastrointestinal motilities. And also, it is possible to control a maximum blood concentration (Cmax) and a bioavailability by controlling the release time and/or the gastro-retentive characteristics through varying amounts of the polymer in the first and/or second release-controlling phase(s).

**Brief Description of Drawings**

[16] FIG. 1 shows the appearances of the sustained release tablet prepared according to the present invention and the sustained release tablet of Comparative Example 1, which were obtained 6 hours after initiating the dissolution test. A: the sustained release tablet prepared according to the present invention, B: the sustained release tablet of Comparative Example 1.

[17] FIG. 2 shows the results of pharmacokinetic studies of the sustained release tablets prepared according to the present invention (Examples 5, 13, and 20) and the comparative formulation.

[18] FIG. 3 shows the results of pharmacokinetic studies of the sustained release tablets prepared according to the present invention (Examples 23, 28, and 31) and the comparative formulation.

**Best Mode for Carrying out the Invention**

[19] The present invention provides a sustained release tablet having two-phase release-controlling system, which consists of a first release-controlling phase comprising pregabalin or its salt and hydroxypropyl methylcellulose; and a second release-controlling phase comprising polyethylene oxide as a swelling polymer, the first release-controlling phase being homogeneously dispersed in the second release-controlling phase.

[20] The sustained release tablet according to the present invention is a gastro-retentive drug delivery system, wherein the drug (i.e., pregabalin) is continuously released while it is staying in the stomach for a predetermined time after oral administration, thereby maximizing the absorption of pregabalin in the upper small intestine. In the sustained
release tablet of the present invention, the release of pregabalin is controlled in the first release-controlling phase; and then the released pregabalin from the first release-controlling phase is further controlled during the pass through the second release-controlling phase. That is, in the sustained release tablet of the present invention, the release of pregabalin is controlled by two phase release-controlling system. And also, the polymer in the first release-controlling phase can enhance floatability effectively and thus ensure both 'swellability' and 'floatability' which increases the shape-maintenance time as well as floating-maintenance time after contact with water, thereby minimizing individual variations in the absorption of pregabalin (especially, time to reach maximum plasma concentration, T\text{max}) originated from different gastrointestinal motilities. In addition, it is possible to control a maximum blood concentration (C\text{max}) and a bioavailability by controlling the release time and/or the gastro-retentive characteristics through varying amounts of the polymer in the first and/or second release-controlling phase(s). Therefore, the sustained release tablet according to the present invention may be administered once a day by controlling the release mechanism of pregabalin having limited absorption window.

The first release-controlling phase comprises hydroxypropyl methylcellulose, so as to control the release of pregabalin and improve floatability. The hydroxypropyl methylcellulose expands on contact with water to form a matrix, thereby controlling the release of pregabalin; and improves floatability based on its own low density. The hydroxypropyl methylcellulose used in the sustained release tablet of the present invention may have a viscosity ranging from 100 to 150,000 centipoises, preferably 400 to 100,000 centipoises. The hydroxypropyl methylcellulose may be present in an amount ranging from 10 to 70 \% by weight, based on the total weight of the tablet. When the hydroxypropyl methylcellulose is used in an amount below 10 \%, dissolution of the active ingredient may be too fast to show a desired sustained release pattern. When the hydroxypropyl methylcellulose is used in an amount above 70 \%, dissolution of the active ingredient may become slow due to thick matrix formation, which results in showing a drug concentration below an appropriate therapeutic concentration. The first release-controlling phase may further comprise a binder conventionally used in the field of pharmaceutics, preferably hydroxypropyl cellulose. An amount of the binder is not limited. That is, the binder may be used in an amount sufficient for forming the first release-controlling phase, for example the first release-controlling phase in a granular form.

The second release-controlling phase comprises polyethylene oxide as a swelling polymer, so as to improve both swellability and floatability for increasing the gastro-retention time. The polyethylene oxide may have an average molecular weight ranging from 100,000 to 7,000,000, preferably 4,000,000 to 7,000,000. The polyethylene oxide
may be present in an amount ranging from 5 to 40 % by weight, based on the total weight of the tablet. When the polyethylene oxide is used in an amount below 5 %, sufficient swelling may not be shown. When the polyethylene oxide is used in an amount above 40 %, it may be difficult to control a release of the drug.

The second release-controlling phase may comprise one or more excipient conventionally used in the field of pharmaceutics, such as a diluent, a lubricant, etc. For example, the diluent includes microcrystalline cellulose, lactose, etc.; and the lubricant includes magnesium stearate, zinc stearate, colloidal silicon dioxide, etc. And also, the second release-controlling phase may further comprise crospovidone or sodium starch glycolate as a supplemental floating agent. If necessary, the second release-controlling phase may further comprise hydroxypropyl methylcellulose as an erosion-preventing agent, in order to prevent potential erosion after swelling.

The sustained release tablet according to the present invention may be coated with a conventional film coating agent.

In an embodiment, a time to reach maximum plasma concentration (Tmax) may range from 4 to 8 hours after oral administration of the sustained release tablet of the present invention. In another embodiment, the sustained release tablet of the present invention may be magnified to 12 mm of size when contacting with water. In still another embodiment, the sustained release tablet of the present invention may be floated within 30 minutes after contact with water and the resultant floating state may be maintained for at least 12 hours. In still another embodiment, when an in vitro dissolution test of the sustained release tablet of the present invention is carried out according to the Korean Pharmacopeia or the US Pharmacopeia, the active ingredient (i.e., pregabalin) is released in an amount below 30% within 1 hour, in an amount (cumulative dissolution rate) ranging 20 to 75% within 4 to 6 hours; and an amount (cumulative dissolution rate) above 75% within 12 hours.

The present invention also provides a process for preparing a sustained release tablet having two-phase release-controlling system. The sustained release tablet having two-phase release-controlling system according to the present invention may be prepared by providing a first release-controlling phase, typically a first release-controlling phase in a granular form, and then compressing the first release-controlling phase with the remaining components. For example, the process for preparing a sustained release tablet having two-phase release-controlling system may comprise (a) granulating a mixture of pregabalin or its salt and hydroxypropyl methylcellulose; and (b) mixing the granules obtained in the step (a) with polyethylene oxide and a pharmaceutically acceptable excipient, followed by compressing the resulting mixture.

The granulating may be performed using a binder solution. In an embodiment, the step (a) may be performed by granulating a mixture of pregabalin (or its salt) and hy-
droxypropyl methylcellulose in a wet granulator (e.g., High Shear Mixer or One-pot), using a binder solution (e.g., an aqueous ethanol solution of hydroxypropyl cellulose), to form a first release-controlling phase. The obtained first release-controlling phase is mixed with components of the second release-controlling phase, i.e., polyethylene oxide and a pharmaceutically acceptable excipient, followed by compressing the resulting mixture. The pharmaceutically acceptable excipient includes a diluent, a lubricant (such as magnesium stearate, zinc stearate, colloidal silicon dioxide, etc.), etc. And also, the components of the second release-controlling phase may further comprise crospovidone or sodium starch glycolate as a supplemental floating agent; and/or hydroxypropyl methylcellulose as an erosion-preventing agent. The process of the present invention may further comprise coating with a conventional film coating agent.

The present invention will be described in further detail with reference to the following examples and experimental examples. These examples and experimental examples are for illustrative purposes only and are not intended to limit the scope of the present invention.

Examples 1 to 34

Sustained release tablets were prepared according to the components and amounts shown in Tables 1 to 5. The amounts of Tables 1 to 5 represent the weight (mg) of each component per one tablet. Pregabalin and hydroxypropyl methylcellulose (Metolose™ 90SH-100,000cps SR, Shinetsu) were charged in a high speed mixer and then a binder solution (prepared by dissolving hydroxypropyl cellulose (HPC JF) in a 50% ethanol solution) was added thereto. The mixer was rotated at 250 rpm for 3 minutes to give granules. The resulting granules were dried and then sieved with a milling machine. The obtained granules were mixed with polyethylene oxide (Polyox 301 and/or Polyox 303), along with a supplementary floating agent (crospovidone or sodium starch glycolate), a diluent (hydroxypropyl cellulose or microcrystalline cellulose), or a lubricant (colloidal silicon dioxide) for 5 minutes. Magnesium stearate was additionally mixed with the mixture for 3 minutes, followed by compressing to obtain sustained release tablets.
<table>
<thead>
<tr>
<th>Components</th>
<th>Example (mg per one tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>First release-controlling phase</strong></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>350</td>
</tr>
<tr>
<td><strong>Second release-controlling phase</strong></td>
<td></td>
</tr>
<tr>
<td>Polyethylene oxide (Polyox 301)</td>
<td>100</td>
</tr>
<tr>
<td>Polyethylene oxide (Polyox 303)</td>
<td>-</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>-</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>-</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>795</td>
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![Table 2]

<table>
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<th>Components</th>
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<td>10</td>
</tr>
<tr>
<td><strong>First release-controlling phase</strong></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>250</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>25</td>
</tr>
<tr>
<td><strong>Second release-controlling phase</strong></td>
<td></td>
</tr>
<tr>
<td>Polyethylene oxide (Polyox 301)</td>
<td>100</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (100,000 cps)</td>
<td>100</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (400 cps)</td>
<td>-</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>-</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>-</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>-</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>845</td>
</tr>
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</table>

![Table 3]

<table>
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<th>Components</th>
<th>Example (mg per one tablet)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td><strong>First release-controlling phase</strong></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>150</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>15</td>
</tr>
<tr>
<td><strong>Second release-controlling phase</strong></td>
<td></td>
</tr>
<tr>
<td>Polyethylene oxide (Polyox 301)</td>
<td>100</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (100,000 cps)</td>
<td>-</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>-</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>585</td>
</tr>
</tbody>
</table>

![Table 4]
Comparative Example 1

Pregabalin (300 g), Kollidon SR (256 g), Plasdone XL (280 g), Polyox N60K NF (224 g), and Carbopol 71G (56.5 g) were mixed for 5 minutes. Magnesium stearate (5.5 g) was additionally mixed with the mixture for 3 minutes, followed by compressing to obtain tablets.

Experimental Example 1: *In vitro* dissolution test

The dissolution tests of the tablets prepared in Examples 1 to 34 were performed according to the 'Dissolution Test 2 (Paddle Method)' of the Korean Pharmacopoeia. 900 ml of a 0.06N HCl solution was used as a dissolution medium and the dissolution test was performed at 37 ± 0.5 °C and at the paddle rotation speed of 50 rpm. An aliquot was taken from the dissolution medium at the time of 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 minutes, respectively. Each aliquot was analyzed with HPLC (at 210 nm) to calculate the dissolution rates. The results are presented in Tables 6 to 10. As shown in Tables 6 to 10, the tablets prepared according to the present invention showed excellent sustained release dissolution patterns.
### Table 6

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Example (Dissolution rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>0.5</td>
<td>9.2</td>
</tr>
<tr>
<td>1</td>
<td>16.1</td>
</tr>
<tr>
<td>2</td>
<td>25.5</td>
</tr>
<tr>
<td>3</td>
<td>36.6</td>
</tr>
<tr>
<td>4</td>
<td>46.2</td>
</tr>
<tr>
<td>6</td>
<td>58.5</td>
</tr>
<tr>
<td>8</td>
<td>66.5</td>
</tr>
<tr>
<td>12</td>
<td>85.5</td>
</tr>
<tr>
<td>16</td>
<td>100.6</td>
</tr>
<tr>
<td>24</td>
<td>101.4</td>
</tr>
</tbody>
</table>

### Table 7

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Example (Dissolution rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>0.5</td>
<td>8.2</td>
</tr>
<tr>
<td>1</td>
<td>13.1</td>
</tr>
<tr>
<td>2</td>
<td>21.3</td>
</tr>
<tr>
<td>3</td>
<td>28.3</td>
</tr>
<tr>
<td>4</td>
<td>34.8</td>
</tr>
<tr>
<td>6</td>
<td>47.1</td>
</tr>
<tr>
<td>8</td>
<td>57.5</td>
</tr>
<tr>
<td>12</td>
<td>74.9</td>
</tr>
<tr>
<td>16</td>
<td>87.4</td>
</tr>
<tr>
<td>24</td>
<td>103.0</td>
</tr>
</tbody>
</table>

### Table 8

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Example (Dissolution rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td>0.5</td>
<td>10.2</td>
</tr>
<tr>
<td>1</td>
<td>15.5</td>
</tr>
<tr>
<td>2</td>
<td>24.8</td>
</tr>
<tr>
<td>3</td>
<td>33.2</td>
</tr>
<tr>
<td>4</td>
<td>40.7</td>
</tr>
<tr>
<td>6</td>
<td>54.1</td>
</tr>
<tr>
<td>8</td>
<td>66.1</td>
</tr>
<tr>
<td>12</td>
<td>84.1</td>
</tr>
<tr>
<td>16</td>
<td>95.3</td>
</tr>
<tr>
<td>24</td>
<td>102.8</td>
</tr>
<tr>
<td>Time (hr)</td>
<td>Example</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>0.5</td>
<td>12.9</td>
</tr>
<tr>
<td>1</td>
<td>19.1</td>
</tr>
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<td>30.1</td>
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<tr>
<td>3</td>
<td>39.3</td>
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<td>4</td>
<td>47.1</td>
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<td>6</td>
<td>58.7</td>
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<tr>
<td>8</td>
<td>68.9</td>
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<tr>
<td>12</td>
<td>83.9</td>
</tr>
<tr>
<td>16</td>
<td>95.4</td>
</tr>
<tr>
<td>24</td>
<td>107.9</td>
</tr>
</tbody>
</table>

Experimental Example 2: Measurement of floating-initiation times and floating-maintenance times

The dissolution tests of the tablets prepared in the above Examples were performed according to the 'Dissolution Test 2 (Paddle Method)' of the Korean Pharmacopeia. 900 ml of a 0.06N HCl solution was used as a dissolution medium and the dissolution test was performed at 37 ± 0.5 °C and at the paddle rotation speed of 50 rpm. The floating lag times were measured and then the floating-maintenance times were measured until 24 hours. The results are presented in Tables 11 to 13. As shown in Tables 11 to 13, the tablets prepared according to the present invention initiated floating within 30 minutes; and each floating was maintained for at least 24 hours.
Floating lag time: 3 - 6 min. 18 - 20 min. 8 - 10 min.
Floating-maintenance time: 24 hours 24 hours 24 hours

Experimental Example 3: Measurement of swelling size

The dissolution tests of the tablets prepared in the above Examples were performed according to the 'Dissolution Test 2 (Paddle Method)' of the Korean Pharmacopeia. 900 ml of a 0.06 N HCl solution was used as a dissolution medium and the dissolution test was performed at 37 ± 0.5 °C and at the paddle rotation speed of 50 rpm. Each tablet was recovered 24 hours after initiating the dissolution test and then the size thereof was measured. The results are presented in Tables 14 to 16. As shown in Tables 14 to 16, the sizes of the tablets prepared according to the present invention were increased to above 12 mm, the size of which allows for gastro-retention.

<table>
<thead>
<tr>
<th>Tablet size</th>
<th>Example 5</th>
<th>Example 13</th>
<th>Example 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 X 20 mm</td>
<td>32 X 22 mm</td>
<td>25 X 15 mm</td>
<td></td>
</tr>
</tbody>
</table>

Experimental Example 4: Comparison of tablet size and water-contents

The dissolution tests of the tablets prepared in Examples 5, 13, 20, and Comparative Example 1 were performed according to the 'Dissolution Test 2 (Paddle Method)' of the Korean Pharmacopeia. 900 ml of a 0.06 N HCl solution was used as a dissolution medium and the dissolution test was performed at 37 ± 0.5 °C and at the paddle rotation speed of 50 rpm. Each tablet was recovered 6 hours after initiating the dissolution test and then the picture was taken. And also, each tablet was recovered 2, 6, and 24 hours after initiating the dissolution test and then the dissolution medium was removed for about 1 minute. Each size change was measured and each weigh change was obtained by measuring the water content thereof. The results are presented in
As shown in Table 17, the tablets prepared in Examples 5, 13, and 20 showed more excellent properties in size change and water contents, in comparison with the tablet of Comparative Example 1. These results shows that the tablets of the present invention can increase the gastro-retention time and thus effectively control the drug release. And also, as shown in FIG. 1, the tablet prepared according to the present invention (the tablet of Example 5) was homogeneously swelled with forming a firm matrix, while the tablet of Comparative Example 1 was crushed to pieces, not forming a firm matrix.

**Experimental Example 5: Measurement of dissolution rate according to rotation speed**

The dissolution tests of the tablets prepared in Example 5 and Comparative Example 1 were performed according to the 'Dissolution Test 2 (Paddle Method)' of the Korean Pharmacopeia. 900 ml of a 0.06N HCl solution was used as a dissolution medium and the dissolution test was performed at 37 ± 0.5 °C and at the paddle rotation speeds of 50 rpm and 200 rpm, respectively. An aliquot was taken from the dissolution medium at the time of 1, 2, 3, 4, and 6 hours, respectively. Each aliquot was analyzed with HPLC (at 210 nm) to calculate the dissolution rates. The results are presented in Table 18.
As shown in Table 18, the tablet of Example 5 showed small differences in the dissolution rate when the rotation speed of the paddle was increased. In contrast, the dissolution rate, especially the initial dissolution rate, was remarkably increased in the tablet of Comparative Example 1, when the rotation speed of the paddle was increased. These results show that the tablets of the present invention is less affected by the rotation speed of the paddle than the sustained release tablet known in the prior art; and thus that the tablets of the present invention is less affected by gastrointestinal motility, thereby minimizing individual variations.

**Experimental Example 6: Comparative pharmacokinetic evaluation**

The comparative pharmacokinetic evaluations on the tablets prepared in Example 5 and Comparative Example 1 were performed using beagle dogs. Beagle dogs (body weight: about 10 kg) fasted for 12 hours were divided into 2 groups, each group having 4 dogs (i.e. n=4). The dogs were provided with a single mixed feed consisting of solid food and liquid nutrients. 1 hour after the feeding, the dogs of each group were orally administered with the tablet of Example 5 and the tablet of Comparative Example 1, respectively. The blood (about 0.5 mL) was collected using a heparin-treated injector, at the time of 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after the administration. The collected blood was centrifuged at 10,000 rpm for 1 minutes, and then the separated serum was stored at -20 °C for analysis. The concentration of pregabalin in the serum was analyzed with LC/MS/MS. The pharmacokinetic parameters obtained from the blood concentration profiles are presented in Table 19 below.

As shown in Table 19, the tablet of Comparative Example 1 showed larger variations than the tablet of Example 5. Especially, the time to reach maximum plasma concentration (Tmax) of the tablet of Example 5 was only from 4 to 8 hours, while Tmax of the tablet of Comparative Example 1 was from 1.5 to 12 hours. These results show that the tablet of the present invention is less affected by gastrointestinal motility, thereby minimizing individual variations.

**Experimental Example 7: Pharmacokinetic study**
The pharmacokinetic studies on the tablets prepared in Examples 5, 13, 20, 23, 28, and 31 were performed using beagle dogs, according to the same method as in Example 6. The commercially available Lyrica™ Capsule 150 mg (Pfizer Inc.) and Lyrica™ Capsule 75 mg (Pfizer Inc.) were used as a comparative formulation. The concentration of pregabalin in the serum was analyzed with LC/MS/MS. The blood concentration profiles are shown in FIGs. 2 and 3; and the pharmacokinetic parameters obtained therefrom are presented in Tables 20 and 21 below.

As shown in FIG. 2 and Table 20, the absorptions of the sustained release tablets of Examples 5, 13, and 20 were more delayed, in comparison with the immediate release tablet of the comparative formulation (Lyrica™ Capsule 150 mg). And also, the tablets of Examples 5, 13, and 20 showed delayed Tmax values, unlike the comparative formulation for twice-a-day administration; and about 2.0 times, 1.9 times, and 1.5 times higher AUC_{0-24hr} than the comparative formulation, respectively. Similarly, as shown in FIG. 3 and Table 21, the absorptions of the sustained release tablets of Examples 23, 28, and 31 were more delayed, in comparison with the immediate release tablet of the comparative formulation (Lyrica™ Capsule 75 mg). And also, the tablets of Examples 23, 28, and 31 showed delayed Tmax values; and about 2.1 times, 2.0 times, and 1.5 times higher AUC_{0-24hr} than the comparative formulation, respectively. Considering that pregabalin is absorbed in the upper small intestine, the sustained release tablet of the present invention can stay in the stomach for longer period than the comparative formulation; and the amount absorbed can be controlled. And also, it can be seen that, even when the dose is changed, the resulting tablet can stay in the stomach for long period; and therefore allow for sustained release of pregabalin.
Claims

[Claim 1] A sustained release tablet having two-phase release-controlling system, which consists of a first release-controlling phase comprising pregabalin or its salt and hydroxypropyl methylcellulose; and a second release-controlling phase comprising polyethylene oxide as a swelling polymer, the first release-controlling phase being homogeneously dispersed in the second release-controlling phase.

[Claim 2] The sustained release tablet according to claim 1, wherein the hydroxypropyl methylcellulose in the first release-controlling phase has a viscosity ranging from 100 to 150,000 centipoises.

[Claim 3] The sustained release tablet according to claim 2, wherein the hydroxypropyl methylcellulose is present in an amount ranging from 10 to 70 % by weight, based on the total weight of the tablet.

[Claim 4] The sustained release tablet according to claim 1, wherein the polyethylene oxide in the second release-controlling phase has an average molecular weight ranging from 100,000 to 7,000,000.

[Claim 5] The sustained release tablet according to claim 4, wherein the polyethylene oxide is present in an amount ranging from 5 to 40 % by weight, based on the total weight of the tablet.

[Claim 6] The sustained release tablet according to claim 1, wherein the first release-controlling phase further comprises hydroxypropyl cellulose as a binder.

[Claim 7] The sustained release tablet according to claim 1, wherein the second release-controlling phase further comprises crospovidone or sodium starch glycolate as a supplemental floating agent.

[Claim 8] The sustained release tablet according to any one of claims 1 to 7, wherein a time to reach maximum plasma concentration (Tmax) ranges from 4 to 8 hours after oral administration.

[Claim 9] The sustained release tablet according to any one of claims 1 to 7, wherein the tablet is magnified to 12 mm of size when contacting with water.

[Claim 10] The sustained release tablet according to any one of claims 1 to 7, wherein the tablet is floated within 30 minutes after contact with water and the resultant floating state is maintained for at least 12 hours.

[Claim 11] A process for preparing a sustained release tablet having two-phase release-controlling system, the process comprising (a) granulating a mixture of pregabalin or its salt and hydroxypropyl methylcellulose;
and (b) mixing the granules obtained in the step (a) with polyethylene oxide and a pharmaceutically acceptable excipient, followed by compressing the resulting mixture.

[Claim 12] The process for preparing a sustained release tablet having two-phase release-controlling system according to claim 11, wherein the granulating is performed using a binder solution.
A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/22(2006.01)i, A61K 9/20(2006.01)l, A61K 31/197(2006.01)l, A61K 47/38(2006.01)l

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 9/22; A61K 9/00; A61K 47/34; A61K 9/20; A61K 47/30; A61K 31/197

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: pregabalin, sustained-release, controlled-release, hydroxypropylmethylcellulose, polyethylene oxide, swelling, floating

c. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search
20 NOVEMBER 2012 (20.11.2012)

Date of mailing of the international search report
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## INTERNATIONAL SEARCH REPORT

### Information on patent family members

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