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(54) Title: SAFE CONTROLLED RELEASE PREPARATION COMPOSITION CONTAINING ZOLPIDEM OR ITS SALT

(57) Abstract: The present invention relates to a controlled release preparation comprising Zolpidem or its salt. More particularly, it relates to a pharmaceutical composition comprising a immediately-acting part rapidly releasing a drug and delayed sustained-release pellets delaying drug release for a time of passing stomach by the enteric coating, which is characterized by timed dual release and can prevent side effects due to sudden drug release of the sustained release pellets.



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Safe controlled release preparation composition containing zolpidem or its salt

Technical Field

5 The present invention relates to a safe controlled release preparation comprising zolpidem or its salt.

Background Art

Zolpidem is a sedative-hypnotic drug, which has a bioavailability of about 70%
10 when orally administered as a common formulation and shows linear vital dynamics in the dose range of 5 to 10 mg, reaching the maximum blood level at 0.5 to 3 hours after administration. However, it has very short half life of average 2.4 hours and thus, the medical duration is less than 6 hours. Because of such a short duration effective time, Stilnox[®], commercially available, has defects in that it cannot maintain sleep for a
15 sufficient period of time.

European Patent No. EP 1194132 discloses a sustained-release preparation for releasing zolpidem or its salt over a predetermined period of time by two-phase dissolution profile to overcome the above-described defects. That is, the patent is directed to a pharmaceutical composition comprising the first phase for immediate
20 releasing of the drug after oral administration and the second phase for sustained releasing of the drug to induce sufficient sleep. Particularly, it discloses (i) capsules comprising at least one intermediate drug releasing tablets and at least one delayed drug releasing tablets, (ii) capsules comprising a mixture of delayed drug releasing pellets

and immediate drug releasing pellets, (iii) tablets comprising matrix of the drug surrounding delayed drug releasing coating pellet comprising the drug, (iv) multi-layered tablets, or (v) multi-coated tablets. The above-described invention has been completed by defining the drug release profile in 0.01M hydrochloric acid solution according to the dissolution test of European Pharmacopeia.

The above technique is characterized in that it has pH-independent drug release mode and the drug release profile defined under the acidic condition is also shown under the pH 6.8 of the small intestines. That is, since the drug release is pH-independent, though the drug release is defined under the acidic condition, it can be applied in the conditions of the living body without particular problems. However, in case of the pH-independent sustained-release preparation prepared by the above known method, there may occur change in the dissolution rate due to non-uniformity in the manufacture lot and exposure to severe environment including heat or humidity during storage and distribution.

Particularly, as compared to the sustained-release tablet in the matrix form, the sustained-release preparation prepared by forming a coating onto pellets comprising an active ingredient has its drug release sensitively affected by the amount of the coating and working conditions. Also, according to the size and the surface condition of the used pellets as well as the amount of the coating, variation in drug release is inevitably induced. That is, during the process for preparing sustained-release pellets by a fluid bed coating apparatus, differences in the particle size and the surface condition between pellets affect perfection of the coating as well as the thickness of the coating applied on the pellets, which directly affect the drug release. With the same coating amount, as

the size of the pellet is increased, the thickness of the coating is reduced and the drug release is accelerated. In case of the pellets with rough surface, the surface area is increased and thus, the perfection of the coating can be trouble. In spite of the difficulties in the preparation, the sustained-release preparation in the pellet form is preferred, as compared to the preparation in the matrix form, because the drug release from the pellet form is seldom affected by the movement of the stomach and intestines. In order to overcome the variation in the drug release between pellets due to the differences in particle size and the surface condition, which inevitably occur during the preparing process, generally, effort to accomplish homogeneous mixing has been made.

Though the above-described problems can be solved by homogenous mixing, due to impacts and scratches of pellets occurring in the capsule filling process, the sustained-release coating can be damaged. Also, the designed drug release mode can be changed over time due to contact with heat and humidity during storage and distribution of end product. Particularly, when water is contained in the sustained-release pellet, due to loss of the sustained-release property as well as deformation of the coating for controlling the drug release, sudden rapid drug release can be occurred at the early stage. In order to solve this problem, many techniques and methods for providing a protection coating to the sustained-release pellet have been disclosed. Generally, such protection coating comprises mainly pH-independent polymer that does not affect the dissolution rate and optionally a colorant to increase marketability.

The zolpidem and its salt are psychotropic medicines and it is very important to maintain the sustained-release of the drug in providing a sustained-release preparation, as compared to other medicines. Thus, in the above-described preparation process,

variation of drug release between pellets due to difference in particle size and surface condition of pellets and sudden drug release caused by damage of pellets in the capsule filling process and harsh circumstances during storage and distribution can lead severe side effects in patients, as compared to other drugs. In order to prevent the side-effects caused by sudden drug release in specific circumstances in the sustained-release preparation of zolpidem or its salt, it is preferably to delay or inhibit drug release in specific circumstances.

Disclosure of Invention

10

Technical problem

It is an object of the present invention to provide a preparation that can express rapidly zolpidem (or its salt), a sedative-hypnotic drug, while can maintain the stable and sustained release of zolpidem, that can reduce significantly the possibility of sudden release of drug, resulted from the variation between pellets which may occur in the prior art and resulted from the damage and the deformation of pellets which may occur in the filling process and during storage and distribution, and in the ultimate that can reduce remarkably the possibility of side-effects in patients.

20

Technical solution

The present invention relates to a controlled release preparation composition comprising zolpidem or its salt and more particularly, a controlled release preparation

composition comprising:

(1) a immediately-acting part comprising zolpidem or its salt as an active ingredient, and

(2) a delayed sustained-release pellet comprising zolpidem or its salt as an
5 active ingredient and showing inhibited drug release in 0.01 Mol/L hydrochloric acid solution.

The drug of present invention comprises zolpidem or its pharmaceutically acceptable salt. The most preferable salt is in the hemitartrate form, which is commercially available under the trade name of Stilnox. In the present invention, the
10 hemitartrate of zolpidem that is readily purchased in the market is used but the present invention is not limited thereto.

In the composition according to the present invention, the immediately-acting part may be in the forms of granule, pellet or coating. In case of coating, for example, the drug may be applied on the surface of the delayed sustained-release pellet. The
15 immediately-acting part may be prepared using spherical seeds, and it can be exemplified as pellets having a layer containing the drug formed on the surface of the spherical seed. The method for preparing the immediately-acting part may employ the granulation, pellet preparation and coating method commonly used in the pharmaceutical fields. If needed, a pH-independent polymer may be added to form a
20 protection coating, or a binding agent or a disintegrant may be used. As the spherical seeds, pH-independent polymers, binding agent and disintegrant, those commonly used in the pharmaceutical fields may be used without any limit. Their composition and amount may vary according to the method. According to the present invention, the

composition and the preparation method of the immediately-acting part are not particularly limited and preferably, the immediately-acting part is defined as having a dissolution rate of 75% or more, as measured in 900 mL of 0.01 Mol/L hydrochloric acid solution at 100 rpm for 30 minutes by the paddle method in the dissolution test
5 according to the Korea Pharmacopeia general test methods.

In the composition according to the present invention, preferably, the delayed sustained-release pellet has a dissolution rate of 10% or less, as measured in 900 mL of 0.01 Mol/L hydrochloric acid solution at 100 rpm for 2 hours and a dissolution rate of 45% or less and 70% or more, as measured in 900 mL of pH 6.8 phosphate buffer for 2
10 hours and 8 hours respectively, according to the dissolution test (paddle method) according of the Korea Pharmacopoeia.

In the composition according to the present invention, the drug content of immediately-acting part is preferably 0.3 to 4 times of the drug content of the delayed sustained-release pellet.

15 The delayed sustained-release pellet may have the following configurations.

In the first configuration, the delayed sustained-release pellet comprises:

(a) a core of a water-soluble or water-swellaable inactive material;

(b) as a first layer, the layer containing an active ingredient, formed on the surface of the core;

20 (c) as a second layer, the layer containing a polymer for controlling release of the active ingredient, formed on the surface of the first layer; and

(d) as a third layer, the layer containing a polymer for protecting the pellet under an acid condition, formed on the surface of the second layer. Here, it may further

comprise a layer comprising a water-insoluble polymer between the core and the first layer.

In the second configuration, the delayed sustained-release pellet includes:

- 5 (a) a core of a water-soluble or water-swellaable inactive material;
- (b) as a first layer, the layer containing an active ingredient, formed on the surface of the core; and
- (c) as a second layer, the layer containing a polymer for controlling release of the active ingredient and a polymer for protecting the pellet under an acid condition,
- 10 formed on the surface of the first layer. Here, it may further comprise a layer comprising a water-insoluble polymer between the core and the first layer.

The term "water-soluble or water-swellaable" in the "core of a water-soluble or water-swellaable inactive material" means that the material is substantially soluble or

15 swellaable in water.

The term "water-insoluble" in the first layer of water-insoluble polymer formed on the surface of the core" means that the polymer is substantially insoluble in water.

The term "polymer for controlling release of the active ingredient" means a polymer that is effective in controlling the release of the active ingredient. The layer for

20 controlling the release of the active ingredient can accomplish the control of drug release more effectively by forming a multi-layered structure with different types and compositional ratios of the polymers.

The term "polymer for controlling the release of the active ingredient and

polymer for protecting the pellet under an acidic condition” means that two or more polymers are mixed to protect the pellet under an acidic condition while controlling the release of the active ingredient.

The composition according to the present invention is not limited to the above-
5 described configurations, but any controlled release preparation including both a immediately-acting part of zolpidem or its salt and delayed sustained-release pellets for preventing sudden drug release by inhibiting drug release under an acidic condition.

As to the compositional ratio of the components, preferably, the active
ingredient and the core are used in a weight ratio of 1:1 to 1:30, the active ingredient
10 and the polymer for controlling release are used in a weight ratio of 1:0.1 to 1:10.0, and the active ingredient and the polymer for protecting the pellet under an acidic condition are used in a weight ratio to of 1:0.1 to 1:10.0.

In the layer further formed between the core and the first layer, that is the layer
comprising the water-insoluble polymer, the active ingredient and the water-insoluble
15 polymer are used in a weight ratio of 1:0.3 to 1:5.0.

In practice, materials, which can be used as the core of the water-soluble or
water-swellaable inactive material, include sucrose/starch spheres (Sugar Spheres NF),
sucrose crystals, or spheres prepared using typical excipient, for example,
microcrystalline cellulose and lactose by exclusion and drying. Any seeds known and
20 commonly used in pharmaceutical fields can be used in the present invention.
Preferably, the seeds have a particle size of 300 to 1,000 μm .

The active ingredient contained in the pellet comprises zolpidem or its
pharmaceutically acceptable salt, and zolpidem hemitartrate is preferable since it is

readily commercially available.

The layer comprising the active ingredient may be formed of the active ingredient alone or in combination with a polymer in order to form the layer effectively. Here, usable examples of the polymer include polyvinylpyrrolidone (PVP);
5 polyalkylene glycol, for example, polyethylene glycol; gelatin; polyvinyl alcohol; starch and a derivative thereof; cellulose derivative, for example, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, carboxyethylcellulose and carboxymethylhydroxyethyl cellulose; acrylic acid polymer,
10 methacrylic acid polymer or methacrylate polymer(Eudragits), hydroxypropylmethylcellulose phthalate and pharmaceutically acceptable polymer. The above-described components can be used alone or as a mixture of two or more thereof.

As the polymer for controlling release of the active ingredient in the
15 composition of the present invention, a water-insoluble polymer can be used alone, or in combination with a water-soluble polymer according to the intended profile of drug release. The usable examples of the water-insoluble polymer include ethylcellulose, polymer of methacrylic acid and methacrylate (Eudragits), polyethylene, polyamide, poly(ethylene-vinyl acetate), cellulose nitrate, silicone, poly(lactide-co-glycolide) and
20 commercially available Surelease, but are not limited thereto. Any water-insoluble polymers that are commonly used in the pharmaceutical fields can be used in the present invention. The above-described components can be used alone or as a mixture of two or more thereof. Concrete examples of the water-soluble polymer added for

release control include polyethylene glycol, polyethylene oxide, gelatin, starch, dextran sulfate, sucrose, carboxymethylcellulose, chitosan, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, arabinogalactan, polyvinyl alcohol, polyacrylic acid, polyvinylpyrrolidone, arabia gum and sodium alginate, but are not limited thereto. Any water-soluble polymers which are commonly used in the pharmaceutical fields can be used in the present invention. The above-described components can be used alone or as a mixture of two or more thereof. For perfect formation of the release-controlling layer, a plasticizer which is commonly used in the pharmaceutical fields may be added. The amount of the water-insoluble polymer forming the coating and the ratio to the water-soluble polymer adding thereto may vary according to types and properties of the polymers to satisfy the requirements of the controlled release preparation.

The polymer for protecting the pellet under an acidic condition includes enteric coating materials, that is enteric polymers, known and commonly used in the pharmaceutical fields, which can inhibit the collapse of pellets under acidic conditions of pH 1.2 but allow the collapse over pH 5.5. Concrete examples include hydroxypropylmethyl cellulose phthalate (HPMCP), hydroxypropylmethyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP) and copolymer of methacrylic acid and methyl methacrylate ester (Eudragits), but are not limited thereto. The above described components may be used alone or as a mixture of two or more thereof. For perfect formation of the enteric coating, a pharmaceutically acceptable plasticizer may be added.

Moreover, concrete examples of the water-insoluble polymers in the layer

additionally formed between the core and the first layer, that is, the layer comprising the water-insoluble polymer include ethylcellulose, copolymers of metachrylic acid and methacrylate (Eudragits), polyethylene, polyamide, poly(ethylene-vinyl acetate), cellulose nitrate, silicone, poly(lactide-co-glycolide) and commercially available
5 Surelease, but are not limited thereto. The above-described components may be used alone or as a mixture of two or more thereof.

The capsule filling process is performed by mixing the immediately-acting part and the delayed sustained-release pellet in the ratio of 0.3:1 to 4:1 based on the drug content, and then by filling the mixture into the capsule using capsule filling apparatus
10 commonly used in the pharmaceutical fields. If needed, a lubricant such as talc or magnesium stearate may be added.

In the study of sustained-release pellet comprising zolpidem or its salt, the present inventors have found that by filling in a capsule the immediately-acting part which immediately releases the drug in the stomach of acidic condition, along with the
15 delayed sustained-release pellets showing sustained-release when reaching the intestines without releasing the drug in the stomach, it is possible to minimize the side-effects in patients caused by sudden drug release. Based on the finding, the present invention has been completed. More particularly, in the first phase the drug is released immediately after oral administration of the composition and undergoes systemic
20 absorption to induce rapid sleep of patients, as disclosed in European Patent No. EP 1194132, and in the second phase the sustained-release pellets having the enteric coating slowly releases the drug when arrive in the intestines after passing time while the sudden drug release in the stomach is inhibited by the coating, whereby the patient

can sleep for a sufficient period of time. Unlike EP 1194132, in which the drug release test of the preparation was performed under an acidic condition, the present invention is characterized to define the drug release profile not only under the acidic condition, but also under pH 6.8 environment, because the composition of the present invention has

5 pH-dependent delayed drug release mode. According to the prior art, the sudden drug release caused by the variation of coating thickness and coating perfection among pellets is inhibited by homogeneous mixing. However, according to the present invention, such defects are effectively overcome by addition of the enteric coating, and the sudden drug release caused by damage and deformation of pellets which may occur

10 in the filling process and during storage and distribution can be also prevented.

The composition according to the present invention is characterized by timed dual release, which comprises both the immediately-acting part for immediately releasing a drug and the delayed sustained-release pellets for delaying the drug release by the enteric coating. That is, the delayed sustained-release pellet is protected by the

15 enteric coating, and thereby, does not release the drug for passing time until it passes the stomach after oral administration. Therefore, it is possible to effectively prevent the side effects caused by unexpected sudden drug release that may often occur in the general sustained-release pellets.

20

Best Mode

Now, the present invention is described in detail by the following examples, however, the present invention is not limited thereto.

Example 1: Preparation of immediately-acting pellet

600 g of sugar spheres of 500 to 710 μm was placed in a fluid bed coating apparatus and flown while spraying the solution of 45.0 g of zolpidem hemitartrate and 5.0 g of hydroxypropylmethylcellulose dissolved in 3.0 kg of purified water to prepare immediately-acting pellets.

5

Example 2: Preparation of immediately-acting pellet

600 g of sugar spheres of 500 to 710 μm was placed in a fluid bed coating apparatus and flown while spraying the solution of 45.0 g of zolpidem hemitartrate and 5.0 g of hydroxypropylmethylcellulose dissolved in 3.0 kg of purified water and then
10 the solution of 30.0 g of hydroxypropylmethylcellulose dissolved in 1.0 kg of purified water to prepare immediately-acting pellets with a protection coating.

Example 3: Preparation of delayed sustained-release pellet

500 g of immediately-acting pellet prepared by the same procedures with Example 1 except using 355 to 500 μm sugar spheres, was placed in a fluid bed coating
15 apparatus and flown while spraying the suspension of 100.0 g of Surelease (solid content of 25.0 g) and 50.0 g of hydroxypropylmethylcellulose in 500 g of purified water on the pellets to form a coating in a weight ratio to the immediately-acting pellet of 6%. Then, the suspension of 100.0g of Surelease (solid content of 25.0 g) and 25.0 g of hydroxypropylmethylcellulose in 250 g of purified water was sprayed on the pellets
20 to form a coating in a weight ratio to the immediately-acting pellet of 6% and the suspension of 200.0 g of Surelease (solid content of 50.0 g) and 25.0 g of hydroxypropylmethylcellulose in 250 g of purified water was sprayed on the pellets to form a coating in a weight ratio to the immediately-acting pellet of 4%. Thus, the

sustained-release pellets are formed. Next, the suspension of 450 g of Eudragit L30-D55 in 4.0 kg of purified water was sprayed on the pellets to form a coating in a weight ratio to the sustained-release pellet of 15% and thus, the delayed sustained-release pellets are formed.

5 **Example 4: Preparation of delayed sustained-release pellet**

600 g of 355 to 500 μ m sugar spheres were placed in a fluid bed coating apparatus and flown while spraying the suspension of 320.0 g of Surelease (solid content of 80.0 g) in 400 g of purified water to form a coating in a weight ratio to the sugar spheres of 12%. Then, 600 g of the prepared pellets was used to prepare
10 immediately-acting pellets according to the procedures disclosed in Example 1. 500 g of the prepared immediately-acting pellets was placed in a fluid bed coating apparatus and flown while spraying the suspension of 100.0 g of Surelease (solid content of 25.0 g) and 50.0 g of hydroxypropylmethylcellulose in 500 g of purified water to form a coating in a weight ratio to the immediately-acting pellet of 6%. Then, the suspension
15 of 100.0 g of Surelease (solid content of 25.0 g) and 25.0 g of hydroxypropylmethylcellulose in 250 g of purified water was sprayed on the pellets to form a coating in a weight ratio to the immediately-acting pellet of 6% and the suspension of 200.0 g of Surelease (solid content of 50.0 g) and 25.0 g of in 250 g of purified water on the pellets to form a coating in a weight ratio to the immediately-
20 acting pellet of 4%. Thus, the sustained release pellets were prepared. Next, the suspension of 450 g of Eudragit L30-D55 in 4.0 kg of purified water was sprayed on the pellets to form a coating in a weight ratio to the sustained-release pellet of 15% and thus, the delayed sustained-release pellets were prepared.

Example 5: Preparation of capsule

78.6 g and 86.5 g of the pellets prepared in Example 1 and Example 3 were mixed with 1.6 g of talc and filled into No. 2 capsule to the content of 209 mg (zolpidem hemitartrate of 12.5 mg) to prepare the sustained-release preparation.

5

Example 6: Preparation of capsule

83.3 g and 86.5 g of the pellets prepared in Example 2 and Example 4 were mixed with 1.6 g of talc and filled into No. 2 capsule to the content of 214 mg (zolpidem hemitartrate of 12.5 mg) to prepare the sustained-release preparation.

10

Example 7: Preparation of delayed sustained-release pellet

500 g of the immediately-acting pellets prepared by the same procedures with Example 1 except using 355 to 500 μm sugar spheres, was placed in a fluid bed coating apparatus and flown while spraying a mixture of the suspension of 300.0 g of Surelease (solid content of 75.0 g) and 150.0 g of hydroxypropylmethylcellulose in 1.5 kg of purified water with the suspension of 450 g of Eudragit L30-D55 in 4.0 kg of purified water to form a coating in a weight ratio to the immediately-acting pellet of 25%. Thus, delayed sustained-release pellets were prepared.

15

Example 8: Preparation of capsule

78.6 g and 81.3 g of pellets prepared in Example 1 and Example 7 were mixed with 1.6 g of talc and filled into No. 2 capsule to the content of 199 mg (zolpidem hemitartrate of 12.5 mg) to prepare the sustained-release preparation.

20

Dissolution test 1: Dissolution test of immediately-acting pellet

The pellets corresponding to 12.5 mg of zolpidem hemitartrate were precisely weighted and subjected to dissolution test at 100 rpm in 900 mL of 0.01 Mol/L hydrochloric acid solution according to a dissolution test (paddle method) of Korea Pharmacopeia. After 30 minutes, the dissolution sample was taken.

5

Dissolution test 2: Acid resistant test of delayed sustained-release pellet

The pellets corresponding to 12.5 mg of zolpidem hemitartrate were precisely weighted and subjected to dissolution test at 100 rpm in 900 mL of 0.01 Mol/L hydrochloric acid solution according to a dissolution test (paddle method) of Korea Pharmacopeia 100 rpm. After 2 hours, the dissolution sample was taken.

10

Dissolution test 3: Dissolution test of delayed sustained-release pellet

The pellets corresponding to 12.5 mg of zolpidem hemitartrate were precisely weighted and subjected to dissolution test at 100 rpm in 900 mL of pH 6.8 phosphate buffer according to a dissolution test (paddle method) of Korea Pharmacopeia. After 2 hours and 8 hours, the dissolution sample was taken, respectively.

15

Dissolution test 4: dissolution test of capsules

6 capsules were taken from each group of capsules prepared in Examples 5, 6 and 8 and subjected to a dissolution test (paddle method) of Korea Pharmacopeia at 100 rpm in 900 mL of 0.01 Mol/L hydrochloric acid solution. After 30 minutes, the dissolution sample was taken from the solution of 900 mL and after 2 hours and 8 hours, the dissolution sample was taken from 900 mL of the solution of pH 6.8 phosphate buffer.

20

Analysis of zolpidem and calculation of dissolution rate

20 mg of standard zolpidem hemitartrate was placed in 200 mL flask and purified water was added thereto for dissolution. 10 mL of the solution was decanted, and placed in 100 mL flask. Purified water added thereto to prepare a standard solution. Each of the sampled solutions for dissolution test was filtered through 0.45 μm membrane filter paper and the filtrate was measured for UV absorbance at 254 nm to calculate the dissolution rate.

Dissolution rate = $[\text{At}/\text{As}] \times [9/10] \times [\text{reference weight (mg)}/20] \times \text{reference purity (\%)}$

At: absorbance of the tested sample

As: absorbance of the standard solution

[Table 1]

Dissolution test

	0.01 Mol/L hydrochloric acid solution		pH 6.8 phosphate buffer	
	30 minutes	2 hours	2 hours	8hours
Example 1	84.2%	-	-	-
Example 2	86.5%	-	-	-
Example 3	-	Less than 5%	23.6%	78.8%
Example 4	-	Less than 5%	27.3%	89.2%
Example 5	46.2%	-	63.4%	89.0%
Example 6	47.3%	-	66.2%	95.3%
Example 7	-	Less than 5%	24.5%	80.2%
Example 8	47.5%	-	64.5%	91.2%

Industrial Applicability

The present invention relates to a safe controlled release preparation comprising zolpidem or its salt. By the preparation according to the present invention, it is possible to accomplish both the immediately-acting release in the early stage and sustained release after several hours later and significantly reduce possibility of side effects in patients caused by sudden drug release which may result from damage and deformation in pellet occurring during the filling process or storage and distribution process resulting. Therefore, while effectively inhibiting side effects due to the unexpected sudden release of the delayed sustained-release pellet contained in general sustained-release pellets, it is possible to rapidly induce sleep, stably control drug release and maintain continuous sleep by single administration. Also, by using the preparation composition according to the present invention, it is possible to prevent misuse of the drug.

15

CLAIMS

1. A controlled release preparation composition comprising:

(1) a immediately-acting part comprising zolpidem or its salt as an active ingredient, and

5 (2) a delayed sustained-release pellet comprising zolpidem or its salt as an active ingredient and showing inhibited drug release in 0.01 Mol/L hydrochloric acid solution.

2. The composition according to claim 1, wherein the immediately-acting part
10 has a dissolution rate of 75% or more, as measured at 100 rpm for 30 minutes in 900 mL of 0.01 Mol/L hydrochloric acid solution by the dissolution test according to paddle method of Korea Pharmacopoeia.

3. The composition according to claim 1, wherein the delayed sustained-release
15 pellet has a dissolution rate of 10% or less, as measured at 100 rpm for 2 hours in 900 mL of 0.01 Mol/L hydrochloric acid solution by a dissolution test according to paddle method of Korea Pharmacopoeia, and a dissolution rate of 45% or less and 70% or more, as measured in 900 mL of pH 6.8 phosphate buffer for 2 hours and 8 hours, respectively.

20 4. The composition according to claim 1, wherein the immediately-acting part and the delayed sustained-release pellet are in the ratio of 0.3:1 to 4:1 based on the drug content.

5. The composition according to claim 1, wherein the salt of zolpidem is zolpidem hemitartrate.

6. The composition according to claim 1, wherein the delayed sustained-release pellet comprises:

- (a) a core of a water-soluble or water-swellaable inactive material;
- (b) as a first layer, the layer containing an active ingredient formed on the surface of the core;
- (c) as a second layer, the layer containing a polymer for controlling release of the active ingredient, formed on the surface of the first layer; and
- (d) as a third layer, the layer containing a polymer for protecting the pellet under an acid condition, formed on the surface of the second layer.

7. The composition according to claim 6, wherein the delayed sustained-release pellet further comprises a layer comprising a water-insoluble polymer between the core and the first layer.

8. The composition according to claim 1, wherein the delayed sustained-release pellet comprises:

- (a) a core of a water-soluble or water-swellaable inactive material;
- (b) as a first layer, the layer containing an active ingredient, formed on the surface of the core; and
- (c) as a second layer, the layer containing a polymer for controlling release of

the active ingredient and a polymer for protecting the pellet under an acid condition, formed on the surface of the first layer.

9. The composition according to claim 8, wherein the delayed sustained-release
5 pellet further comprises a layer comprising a water-insoluble polymer between the core and the first layer.

10. The composition according to claim 6 or 8, wherein the active ingredient and the core are in a weight ratio of 1:1 to 1:30, the active ingredient and the polymer
10 for controlling release are in a weight ratio of 1:0.1 to 1:10.0, and the active ingredient and the polymer for protecting the pellet under an acidic condition are in a weight ratio to of 1:0.1 to 1:10.0.

11. The composition according to claim 7 or 9, wherein the active ingredient
15 and the water-insoluble polymer are in a weight ratio of 1:0.3 to 1:5.0.

12. The composition according to claim 6 or 8, wherein the polymer for controlling release of the active ingredient is a water-insoluble polymer alone or a combination of a water-insoluble polymer and a water-soluble polymer.

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13. The composition according to claim 12, wherein the water-insoluble polymer is at least one selected from the group consisting of ethylcellulose, polymer of methacrylic acid and methacrylate (Eudragits), polyethylene, polyamide, poly(ethylene-

vinyl acetate), cellulose nitrate, silicone, poly(lactide-co-glycolide) and Surelease, and
the water-soluble polymer is at least one selected from the group consisting of
polyethylene glycol, polyethylene oxide, gelatin, starch, dextran sulfate, sucrose,
carboxymethylcellulose, chitosan, hydroxyethylcellulose,
5 hydroxypropylmethylcellulose, methylcellulose, arabinogalactan, polyvinyl alcohol,
polyacrylic acid, polyvinylpyrrolidone, arabia gum and sodium alginate.

14. The composition according to claim 6 or 8, wherein the polymer for
protecting the pellet under an acidic condition is an enteric polymer.

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15. The composition according to claim 14, wherein the enteric polymer is at
least one selected from the group consisting of hydroxypropylmethyl cellulose phthalate
(HPMCP), hydroxypropylmethyl cellulose acetate succinate (HPMCAS), cellulose
acetate phthalate (CAP) and copolymer of methacrylic acid and methyl methacrylate
15 ester.

16. The composition according to claim 7 or 9, wherein the water-insoluble
polymer is at least one selected from the group consisting of ethylcellulose, polymer of
methacrylic acid and methacrylate(Eudragits), polyethylene, polyamide, poly(ethylene-
20 vinylacetate), cellulose nitrate, silicone, poly(lactide-co-glycolide) and Surelease.

17. The composition according to claim 6 or 8, wherein the layer containing
the active ingredient further comprises a polymer.

18. The composition according to claim 17, wherein the polymer is at least one selected from the group consisting of polyvinylpyrrolidone (PVP); polyalkylene glycol; gelatin; polyvinyl alcohol; starch and a derivative thereof; cellulose derivative; acrylate
5 polymer; and Hydroxypropylmethylcellulose phthalate.

19. The composition according to claim 1, wherein the immediately-acting part is in the form of granules, pellets or a coating applied on the delayed sustained-release pellets.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2007/001146**A. CLASSIFICATION OF SUBJECT MATTER****A61K 9/52(2006.01)i**

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)

IPC 8 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Unity models and applications for Unity Models since 1975

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

eKIPASS, STN(Caplus), Pubmed

* Key words: zolpidem, controlled-release, slow-release, HCl, phosphate, polymer, pellet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/045589 A1 (ELAN PHARMACEUTICALS, INC.) 03 June 2004 See abstract, page 12 -15, examples 1 - 18, Figs. 1-6, and claims.	1- 19
A	WO 2000/033835 A1 (SANOFI-SYNTHELABO) 15 June 2000 See the whole document.	1- 19
A	EP 1194132 B1 (SANOFI-SYNTHELABO) 16 June 2004 See the whole document.	1- 19
A	US 6228398 B1 (ELAN CORPORAYION, PLC) 08 May 2001 See the whole document.	1 - 19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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

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Information on patent family members

International application No.

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