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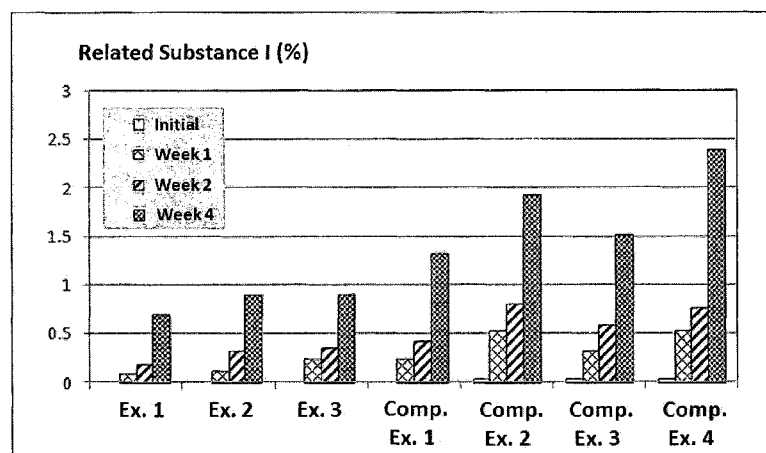
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(54) Title: GRANULE COMPRISING SILODOSIN, AND PHARMACEUTICAL COMPOSITION AND FORMULATION COMPRISING SAME

FIG. 1



(57) Abstract: The present invention relates to a granule comprising silodosin; alkaline inorganic salt as a stabilizer; and a pharmaceutically acceptable excipient. The present invention shows that the inventive granules exhibit improved stability for silodosin, and reduction in unwanted reaction of silidosin with other excipients. Thus, the granule comprising silidosin of the present invention can be used for the development of a composition or formulation with a variety of dissolution characteristics, without any influence to the stability of silodosin. Also, owing to the decreased adverse effects which may result from degradation products of silodosin, it can be utilized as a safer therapeutic agent for prostatic hypertrophy.

DESCRIPTION

GRANULE COMPRISING SILODOSIN, AND PHARMACEUTICAL COMPOSITION AND FORMULATION COMPRISING SAME

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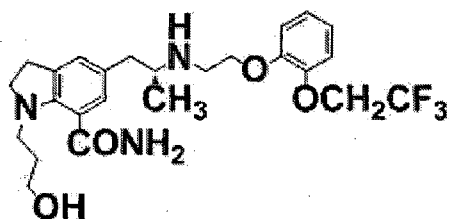
FIELD OF THE INVENTION

The present invention relates to a granule comprising silodosin, and a pharmaceutical composition and a formulation comprising same. More particularly, it relates to a granule comprising silodosin showing improved storage stability, and a pharmaceutical composition and a formulation comprising same.

BACKGROUND OF THE INVENTION

Prostatic hypertrophy is a disease showing high incidence in elderly males, and it is estimated that 70% of males in their 60s are suffering from this disease. Due to a recent accelerated ageing of populations, the number of patients with prostatic hypertrophy is increasing rapidly, leading to an increased interest in its therapy. The main treatment methods for prostatic hypertrophy include drug therapy and surgical therapy. Surgical therapies may include laparotomy with prostatic resection, transurethral resection of the prostate (TUR-P), hyperthermic therapy, laser therapy and stent placement therapy, while drug therapies may include $\alpha 1$ -adrenergic receptor blockers, anti-androgen drugs and herbal medicine.

More particularly, silodosin is an $\alpha 1$ -adrenergic receptor antagonist as presented in the formula I below (chemical name: 1-(3-hydroxypropyl)-5-[(2R)-2-(2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino)propyl]-2,3-dihydro-1H-indole-7-carboxamide). Owing to selective inhibition of urethral smooth muscle contraction, it decreases pressure inside urethra without significantly affecting blood pressure. Also, owing to the selectivity for the $\alpha 1$ -adrenergic receptor subtype, it is very useful in the treatment of urination difficulties and the like, associated with prostatic hypertrophy.



(I)

Silodosin is being sold worldwide with a variety of trade names such as Urief[®], Thrupas[®], Rapaflo[®], Silodyx[®], etc.

5 However, it is known that silodosin is apt to produce various related substances by reactions with a variety of excipients in a pharmaceutical formulation. In particular, silodosin is known to decrease dissolution characteristics by a reaction with lactose. More specifically, Korean Patent No. 10-1072909 discloses that silodosin produces a variety of related substances by reactions with pharmaceutical excipients including
10 lactose, and that D-mannitol can be used as an excipient to improve its stability. However, even with D-mannitol, some degradation products cannot be avoided, and thus, there is a need for the development of a new composition to improve the stability of silodosin.

15 Therefore, the present inventors have endeavored to improve the stability of silodosin, and found that preparing a granule using alkaline inorganic salt as a stabilizer results in the improvement of its storage stability, dissolution rate and bioavailability.

SUMMARY OF THE INVENTION

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It is an object of the present invention to provide a new silodosin preparation which shows improved stability.

In accordance with one embodiment of the present invention, there is provided a granule comprising: silodosin; an alkaline inorganic salt as a stabilizer; and a
25 pharmaceutically acceptable excipient.

In accordance with another embodiment of the present invention, there is provided a pharmaceutical composition comprising the above granule and a pharmaceutically acceptable additive.

In accordance with another embodiment of the present invention, there is

provided a pharmaceutical formulation prepared by using the above granule or the above pharmaceutical composition.

The present invention shows that the inventive granules exhibit improved stability for silodosin, and reduction in unwanted reaction of silodosin with other excipients. Thus, the granule comprising silodosin of the present invention can be used for the development of a composition or formulation with a variety of dissolution characteristics, without any influence to the stability of silodosin. Also, owing to the decreased adverse effects which may result from degradation products of silodosin, it can be utilized as a safer therapeutic agent for prostatic hypertrophy.

BRIEF DESCRIPTION OF THE DRAWING

The above and other objects and features of the present invention will become apparent from the following descriptions of the invention, when taken in conjunction with the accompanying drawings:

Fig. 1 is a graph showing the stability of silodosin according to the type of a stabilizer (the amount of related substance I production);

Fig. 2 is a graph showing the stability of silodosin according to the type of a stabilizer (the amount of total related substance production);

Fig. 3 is a graph showing the stability of silodosin according to the content of a stabilizer (the amount of related substance I production);

Fig. 4 is a graph showing the stability of silodosin according to the content of a stabilizer (the amount of total related substance production);

Fig. 5 is a graph showing the dissolution rate of silodosin according to the content of a stabilizer;

Fig. 6 is a graph showing the stability of silodosin according to the combination of various excipients and stabilizers (the amount of related substance I production);

Fig. 7 is a graph showing the stability of silodosin according to the combination of various excipients and stabilizers (the amount of total related substance production);

Fig. 8 is a graph showing the dissolution rate of silodosin according to the type of an excipient;

Fig. 9 is a graph showing the dissolution rate of silodosin according to the difference in preparation method; and

Fig. 10 is a graph comparing the pharmacokinetics of silodosin according to the difference in preparation method.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a granule comprising silodosin; an alkaline inorganic salt as a stabilizer; and a pharmaceutically acceptable excipient.

10

The present invention can improve the stability of silodosin by preparing a granule using an alkaline inorganic salt as a stabilizer. In addition, the present invention can minimize interactions between silodosin and various pharmaceutical excipients employed in the preparation process of the granule, by preparing the granule using an alkaline inorganic salt as a stabilizer.

15

Silodosin employed as an active ingredient in a granule according to the present invention is a compound represented by the formula I, with a chemical name of: 1-(3-hydroxypropyl)-5-[(2R)-2-(2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino)propyl]-2,3-dihydro-1H-indole-7-carboxamide. Owing to selective inhibition of urethral smooth muscle contraction, it decreases inner pressure of urethra without significantly affecting blood pressure. Also, owing to the selectivity for the α_1 -adrenergic receptor subtype, it is very useful in the treatment of urination difficulties and the like, associated with prostatic hypertrophy.

20

Daily standard dose of silodosin for adults is 1 to 16 mg, which can be administered in an amount of 1 mg, 2 mg, 4 mg, 8 mg, or 16 mg per day.

25

An alkaline inorganic salt employed as a stabilizer in a granule according to the present invention can be selected from the group consisting of oxides, hydroxides, carbonates and phosphates of sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium. In one embodiment, the alkaline inorganic salt can be selected from the group consisting of alkaline metal or alkaline earth metal oxide,

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hydroxide, carbonate, and phosphate. In another embodiment, the alkaline inorganic salt can be calcium carbonate (CaCO_3), magnesium carbonate (MgCO_3), sodium hydrogen carbonate (NaHCO_3), or a mixture thereof.

With respect to the stability of silodosin, a stabilizer can be employed in an amount ranging from 0.05 to 33 parts by weight, preferably 0.1 to 10 parts by weight based on 1 part by weight of silodosin. When the amount of a stabilizer is less than the aforementioned lower limit of the range, the aimed stabilizing effect on silodosin cannot be achieved, while there is a problem that the dissolution rate of silodosin decreases when it exceeds the aforementioned upper limit of the range.

The aforementioned stabilizer can significantly improve the stability of silodosin as compared to antioxidants (e.g., butylated hydroxyanisole (BHA) or butylated hydroxytoluene (BHT)) or other stabilizers (e.g., meglumine) which are conventionally known to improve the stability of a drug.

An excipient that can be used in a granule according to the present invention, for example, can be at least one selected from the group consisting of a pharmaceutically acceptable diluent, a disintegrant, a plasticizer and a lubricant.

The diluent can be selected from the group consisting of cellulose powders, microcrystalline cellulose, silicified microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, xylitol, lactose, dextrose, maltose, sucrose, glucose, fructose, maltodextrin, and a mixture thereof, but are not limited thereto. The diluent can be employed in an amount ranging from 1 to 99% by weight, preferably 5 to 95% by weight based on the total weight of the granule.

The disintegrant can be a component that shows stable disintegration, selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, starch, alginic acid or its sodium salt, and a mixture thereof, but are not limited thereto. The disintegrant can be employed in an amount ranging from 1 to 70% by weight, preferably 2 to 50% by weight based on the total weight of the granule.

Examples of the plasticizer may include polyoxyalkylene (e.g., BASF Pluronics, UCC Carboxaxes, PEGs), ether-capped polyoxyalkylene (e.g., polyoxyethylene lauryl ether), ester-capped polyoxyalkylene (e.g., polyoxyethylene stearate), sorbitan stearate,

phosphatide, alkyl amine, glycerin, polyethylene oxide, carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, sodium lauryl sulfate, aryl (C₆-C₁₀) sulfate salt, etc., but are not limited thereto. The plasticizer can be employed in an amount ranging from 0.01 to 10% by weight based on the total weight of the granule.

5 Examples of the lubricant may include stearic acid, magnesium stearate, calcium stearate, talc, sodium stearyl fumarate, silicon dioxide (SiO₂), etc., but are not limited thereto. The lubricant can be employed in an amount ranging from 0.01 to 10% by weight based on the total weight of the granule.

10 A granule according to the present invention can be prepared by granulation processes widely known in the pharmaceutical industry, e.g., a dry granulation process or a wet granulation process.

Preferably, a granule according to the present invention can be prepared by a wet granulation process using a mixing granulator or fluidized bed granulator. In the
15 pharmaceutical industry, a wet granulation process is generally known to be disadvantageous as compared to a dry granulation process in terms of instability of the drug. However, a granule according to the present invention shows excellent stability, dissolution rate, and bioavailability owing to the effect of the aforementioned stabilizer, although it is prepared by a wet granulation process.

20

The present invention also provides a pharmaceutical composition comprising the aforementioned granule and a pharmaceutically acceptable additive. The additive can be a diluent, a disintegrant, a humectant, a binder or a lubricant. The diluent, disintegrant and lubricant are the same as described above. Examples of the humectant
25 may include polyoxyalkylene (e.g., BASF Pluronic, UCC Carboxaxes, PEGs), ether-capped polyoxyalkylene (e.g., polyoxyethylene lauryl ether), ester-capped polyoxyalkylene (e.g., polyoxyethylene stearate), sorbitan stearate, phosphatide, alkyl amine, glycerin, polyethylene oxide, carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, sodium lauryl sulfate, aryl (C₆-C₁₀) sulfate salt, etc., but are not
30 limited thereto. The humectant can be employed in an amount ranging from 0.01 to 10% by weight based on the total weight of the composition. In addition, the binder can be selected from the group consisting of hydroxypropyl cellulose, hypromellose,

polyvinyl pyrrolidone, copovidone, macrogol, silicate derivatives such as light anhydrous silicic acid, synthetic calcium aluminum silicate or magnesium metasilicate aluminate (magnesium aluminum silicate), phosphates such as calcium phosphate dihydrate, carbonates such as calcium carbonate, and a mixture thereof, but are not limited thereto. The binder can be employed in an amount ranging from 0.3 to 30% by weight, preferably 1 to 20% by weight based on the total weight of the composition.

Furthermore, the present invention provides a pharmaceutical formulation prepared by using the aforementioned granule or aforementioned pharmaceutical composition. A pharmaceutical formulation of the present invention can be a formulation for oral administration, such as a tablet or capsule.

For example, in case of a tablet, the aforementioned granule or pharmaceutical composition can be manufactured into a tablet by a tablet compression process using conventional rotary press, etc.; and preferably into a coated tablet by a light-shielded coating process.

In addition, in case of a capsule, the aforementioned granules or pharmaceutical composition can be manufactured into a capsule by filling it into a capsule using a conventional capsule filler. Preferably, the capsule may be a hard capsule made of HPMC, gelatin, etc.

In case of a capsule, various excipients disclosed in the literature, (*Modern pharmaceuticals, General Consideration in the Design of Hard Gelatin Capsule Formulation*, p470, 1989), can be used. More particularly, magnesium stearate as a lubricant, and a surfactant (e.g., sodium lauryl sulfate (SLS)), to prevent dissolution decrease caused by hydrophobic nature of magnesium stearate, can be used.

Meanwhile, the present invention provides a method for preparing the aforementioned granule comprising:

mixing silodosin, an alkaline inorganic salt as a stabilizer, and a pharmaceutically acceptable excipient, to prepare a granule by a dry granulation process or wet granulation process.

In addition, the present invention provides a method for preparing a pharmaceutical composition or pharmaceutical formulation, comprising the steps of:

(a) mixing silodosin, an alkaline inorganic salt as a stabilizer, and a pharmaceutically acceptable excipient, to prepare a granule by a dry granulation process or wet granulation process; and

5 (b) adding a pharmaceutically acceptable additive to the granule of step (a) to obtain a formulation.

The following Examples are intended to further illustrate the present invention without limiting its scope.

10 **Examples 1 to 3: Preparation of silodosin formulations comprising a stabilizer**

According to the compositions shown in Table 1, granules comprising silodosin were prepared by a dry granulation method, which were then filled into capsules.

15 Specifically, silodosin (Dongwoo Syntech Ltd., Korea) as an active ingredient; lactose as an excipient; pregelatinized starch as a disintegrant; and calcium carbonate (CaCO_3), magnesium carbonate (MgCO_3) or sodium hydrogen carbonate (NaHCO_3), respectively as a stabilizer, were mixed using High Speed Mixer (Sejong, Korea; Agitator 126 ± 10 rpm, Chopper 3000 ± 300 rpm, kneading time 2 ± 1 min). The
20 mixture was dried to reach a water content of $2.0 \pm 0.5\%$, using a fluidized bed dryer (air supply temperature $50 \pm 10^\circ\text{C}$), followed by adding sodium stearyl fumarate (Pruv[®]) as a lubricant and sodium lauryl sulfate (SLS) as a surfactant thereto, and post-mixing them with a column blender to obtain granules. Thereafter, the granules comprising silodosin were filled into No. 3 gelatin capsule using a capsule filler (SF-100, Bosch,
25 Germany) to prepare capsule formulations.

Comparative Examples 1 to 4: Preparation of silodosin formulations with different stabilizers

30 According to the compositions shown in Table 1, capsule formulations of Comparative Examples 1 to 3 were prepared by repeating the procedure of Example 1, except for using butylated hydroxyanisole (BHA) or butylated hydroxytoluene (BHT) as

antioxidants, or meglumine as another stabilizer, instead of the stabilizer used in Example 1. Meanwhile, in case of Comparative Example 4, a capsule formulation was prepared without using a stabilizer or antioxidant.

5 [Table 1]

	Ex. 1	Ex. 2	Ex. 3	Comp. Ex. 1	Comp. Ex. 2	Comp. Ex. 3	Comp. Ex. 4
Silodosin	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Lactose	130.0	130.0	130.0	130.0	130.0	130.0	130.0
Pregelatinized starch	36.0	36.0	36.0	36.0	36.0	36.0	36.0
Calcium Carbonate	2.0	-	-	-	-	-	-
Magnesium Carbonate	-	2.0	-	-	-	-	-
Sodium Hydrogen Carbonate	-	-	2.0	-	-	-	-
BHA	-	-	-	2.0	-	-	-
BHT	-	-	-	-	2.0	-	-
Meglumine	-	-	-	-	-	2.0	-
Pruv	1.8	1.8	1.8	1.8	1.8	1.8	1.8
SLS	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Total weight (mg)	174.0	174.0	174.0	174.0	174.0	174.0	172.0

Experimental Example 1: Storage stability of the formulations according to the type of a stabilizer

10 The formulations of Examples 1 to 3 and Comparative Examples 1 to 4 were placed in sealed HDPE bottles and stored under the condition of about 60 °C. Then, the amount of related substances was measured as described below, at week 1, 2, and 4.

<Analysis method>

15 About 50 mg of silodosin (standard preparation) was taken and placed into a 100 mL flask, and methanol was added up to a marked line. After accurately taking 1 mL of this solution, methanol was added thereto to reach the final volume of 100 mL, which was then filtered through a 0.45 μm membrane filter to obtain a standard solution. Separately, after taking the contents of capsules of Examples 1 to 3 and Comparative
20 Examples 1 to 4 in the amounts which correspond to 50 mg of silodosin, methanol was

added thereto to reach the final volume of 100 mL each, which were then filtered with a 0.45 µm membrane filter to obtain sample solutions.

10 µL each of the standard solution and the sample solutions was examined using liquid chromatography under the following conditions.

5

<HPLC measurement conditions>

- Detector: UV-absorption detector (absorbance at 225 nm)

- Column: a column filled with octadecyl silylated silica gel (25 cm × 4.6 mm, 5 µm), or the like

10 - Flow rate: adjusted to keep the peak retention time of silodosin to about 12-15 minutes

- Column temperature: 40 °C

- Mobile phase:

15 A: 3.9 g of sodium dihydrogen phosphate dihydrate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$) was dissolved in 1000 mL of DW, and adjusted to pH 3.4 with diluted phosphoric acid (1 → 10mL; prepared by diluting 1 mL of phosphoric acid to 10 mL of total volume with D.W.);

B: acetonitrile

- Mobile phase conditions

Time (min)	A(%)	B(%)
0 - 15	75	25
15 - 35	17 → 50	25 → 50
35 - 45	50	50

20 The amounts of related substances (related substance I and total related substances) produced in the formulations of Examples 1 to 3 and Comparative Examples 1 to 4 are shown in Table 2 and Figs. 1 and 2.

[Table 2]

		Ex. 1	Ex. 2	Ex. 3	Comp. Ex. 1	Comp. Ex. 2	Comp. Ex. 3	Comp. Ex. 4
Related substance I	Initial	0	0	0	0	0.02	0.03	0.02
	Week 1	0.08	0.11	0.23	0.24	0.52	0.31	0.53
	Week 2	0.18	0.32	0.35	0.41	0.8	0.58	0.76
	Week 4	0.69	0.89	0.90	1.32	1.93	1.52	2.4
Total Related Substances	Initial	0	0	0	0	0.02	0.03	0.03
	Week 1	0.1	0.19	0.28	0.9	0.83	0.44	1.21

	Week 2	0.21	0.33	0.46	1.2	1.76	0.73	1.82
	Week 4	0.88	0.98	0.98	2.07	2.44	1.92	3.07

As shown in Table 2 and Figs. 1 and 2, the peaks of related substances at RRT (relative peak retention time) of 1.34 relative to the peak area of main ingredient were measured at initial preparation, and at week 1, 2, and 4, sequentially. In the formulations of Examples 1 to 3, in which alkaline inorganic salt, such as calcium carbonate, magnesium carbonate or sodium hydrogen carbonate was used as a stabilizer, the amount of related substance was significantly smaller than Comparative Example 4, in which no stabilizers or antioxidants was used. In addition, in the formulations of Examples 1 to 3, the amount of related substance production was significantly smaller than Comparative Examples 1 to 3, in which BHA, BHT, or meglumine was used. These results indicate that the stability of silodosin can be improved by using an alkaline inorganic salt (e.g., calcium carbonate, magnesium carbonate or sodium hydrogen carbonate) as a stabilizer. In particular, among the alkaline inorganic salts, calcium carbonate was the most preferred as a stabilizer.

Examples 4 to 9: Preparation of silodosin formulations with various contents of a stabilizer

In order to compare the stability of silodosin formulations according to the content of a stabilizer, capsule formulations employing various amounts of calcium carbonate were prepared according to the compositions of Table 3. The capsules were prepared by the method described in Examples 1 to 3.

[Table 3]

	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9
Silodosin	4.0	4.0	4.0	4.0	4.0	4.0
Lactose	131.9	131.6	122.0	92.0	52.0	0.0
Pregelatinized starch	36.0	36.0	36.0	36.0	36.0	36.0
Calcium Carbonate	0.1	0.4	10.0	40.0	80.0	132.0
Pruv	1.8	1.8	1.8	1.8	1.8	1.8
SLS	0.2	0.2	0.2	0.2	0.2	0.2
Total weight (mg)	174.0	174.0	174.0	174.0	174.0	174.0
Content of a Stabilizer based on 1 part by weight of Silodosin	0.025	0.1	2.5	10	20	33

(part by weight)						
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Experimental Example 2: Storage stability of the formulations according to the content of a stabilizer

5 Using the capsule formulations of Examples 4 to 9, the amount of related substance was measured by the same method as Experimental Example 1. The results are shown in Table 4 and Figs. 3 and 4.

[Table 4]

		Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9
Related substance I	Initial	0	0	0	0	0	0
	Week 1	0.45	0.09	0.08	0.05	0.03	0.02
	Week 2	0.68	0.18	0.17	0.16	0.14	0.09
	Week 4	1.56	0.72	0.59	0.57	0.49	0.38
Total Related Substances	Initial	0.02	0	0	0	0	0
	Week 1	1.09	0.13	0.1	0.06	0.05	0.03
	Week 2	1.57	0.28	0.2	0.11	0.23	0.18
	Week 4	2.74	0.92	0.79	0.73	0.65	0.46

10 By comparing the results of the Table 4 and Figs. 3 and 4 with those of Experimental Example 1, it was found that the capsule formulations of the present invention which comprise an alkaline inorganic salt as a stabilizer (Examples 4 to 9) had significantly superior storage stability as compared to the capsule formulations which do not comprise the stabilizer (Comparative Examples 1 to 4).

15 In particular, it was shown that the amount of related substances decreased as the content of a stabilizer increased, which indicates that employing a sufficient amount of stabilizer is preferable in terms of stability of the product.

20 Meanwhile, in the formulation of Example 4, which employs a stabilizer in an amount of 0.025 part by weight based on 1 part by weight of silodosin, larger amount of related substances was produced as compared to Examples 5 to 9, which employ a stabilizer in an amount of at least 0.1 part by weight. This indicates that it is preferable to use a stabilizer in an amount of at least 0.1 part by weight based on 1 part by weight of silodosin, in order to maximize the stabilizing effect of the stabilizer on the formulation comprising silodosin.

Experimental Example 3: Dissolution test of silodosin according to the content of a stabilizer

Using capsule formulations of Examples 4 to 9, dissolution test was carried out at 50 rpm in 900 mL of 0.1N HCl solution by a sinker in USP paddle. The results are shown in Table 5 and Fig. 5.

[Table 5]

<i>In vitro</i> dissolution				
	5 min	10 min	15 min	30 min
Ex. 4	49.2%	90.0%	92.5%	97.5%
Ex. 5	47.4%	89.2%	91.9%	96.9%
Ex. 6	44.8%	87.5%	90.7%	95.3%
Ex. 7	42.0%	83.5%	88.1%	90.6%
Ex. 8	20.3%	45.1%	49.0%	50.3%
Ex. 9	10.5%	19.5%	20.1%	21.3%

As shown in Table 5 and Fig. 5, the formulations of Examples 8 and 9, which employ a stabilizer in an amount of 20 and 33 parts by weight based on 1 part by weight of silodosin, were shown to have lower dissolution rates than the formulations which employ a stabilizer in an amount of 10 parts by weight or less. The results indicate that it is preferable to employ a stabilizer in an amount of 10 parts by weight or less, in terms of the dissolution rate of silodosin.

Examples 10 to 13: Preparation of silodosin formulations comprising various excipients and stabilizers

Silodosin is known to generate a number of degradation products by reactions with a variety of excipients. In order to determine whether the stabilizer of the present invention can inhibit the reactions of silodosin with various excipients, capsule formulations were prepared using various excipients, according to the compositions of Table 6. The capsules were prepared by the methods described in Examples 1 to 3.

Comparative Examples 5 to 8: Preparation of silodosin formulation which does not comprise a stabilizer

In accordance with the compositions of Table 6, capsule formulations of Comparative Examples 5 to 8 were prepared by repeating the procedure described in Examples 10 to 13, except that no stabilizer was used.

5 [Table 6]

	Ex. 10	Ex. 11	Ex. 12	Ex. 13	Comp. Ex. 5	Comp. Ex. 6	Comp. Ex. 7	Comp. Ex. 8
Silodosin	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Calcium Carbonate	2.0	2.0	2.0	2.0	-	-	-	-
D-mannitol	130.0	-	-	-	130.0	-	-	-
Xylitol	-	130.0	-	-	-	130.0	-	-
Sorbitol	-	-	130.0	-	-	-	130.0	-
Avicel	-	-	-	130.0	-	-	-	130.0
Pregelatinized starch	36.0	36.0	36.0	36.0	36.0	36.0	36.0	36.0
Pruv	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
SLS	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Total weight	174.0	174.0	174.0	174.0	172.0	172.0	172.0	172.0

Experimental Example 4: Storage stability of the formulation according to the combination of various excipients and stabilizers

10 Using the capsule formulations of Examples 10 to 13 and Comparative Examples 5 to 8, the amount of related substance was measured by the same method as Experimental Example 1. The results are shown in Table 7 and Figs. 6 and 7.

[Table 7]

		Ex. 10	Ex. 11	Ex. 12	Ex. 13	Comp. Ex. 5	Comp. Ex. 6	Comp. Ex. 7	Comp. Ex. 8
Related substance I	Initial	0	0.01	0.01	0.02	0.02	0	0.01	0.03
	Week 1	0.07	0.13	0.13	0.2	0.21	0.28	0.036	0.99
	Week 2	0.29	0.36	0.34	0.45	0.64	0.78	0.92	2.36
	Week 4	0.83	0.89	0.81	0.92	1.23	1.83	1.79	6.7
Total Related Substances	Initial	0	0.01	0.01	0.02	0.2	0	0.01	0.03
	Week 1	0.13	0.16	0.17	0.22	0.34	0.42	0.44	1.41
	Week 2	0.39	0.42	0.41	0.49	0.85	1.01	1.12	2.82
	Week 4	0.92	1	1.07	1.2	1.75	1.93	1.98	7.16

As shown in the Table 7 and Figs. 6 and 7, it was found that the formulations of Examples 10 to 13, which used an alkaline inorganic salt as a stabilizer had significantly superior stability as compared to Comparative Examples 5 to 8, which did not use stabilizers, although there were small differences in the amount of the production of related substances according to the type of excipients.

These results indicate that the stabilizer of the present invention can improve the stability of silodosin by inhibiting the reaction of silodosin with various excipients.

Experimental Example 5: Dissolution test of silodosin according to the type of an excipient

In order to compare the dissolution rates of silodosin according to the type of excipients, dissolution test of the capsule formulations of Examples 10 to 13 comprising various excipients, was carried out at 50 rpm in 900 mL of 0.1N HCl solution by a sinker in USP paddle. The results are shown in Table 8 and Fig. 8. In Fig. 8, the dissolution rate of Example 1 is also illustrated for comparison.

[Table 8]

<i>In vitro</i> dissolution				
	5 min	10 min	15 min	30 min
Ex. 10	40.2%	84.8%	91.9%	97.4%
Ex. 11	43.7%	89.2%	94.2%	98.7%
Ex. 12	49.1%	90.4%	93.5%	98.8%
Ex. 13	44.0%	85.6%	93.9%	97.9%

As shown in Table 8 and Fig. 8, it was found that the formulations prepared by a wet granulation process showed excellent dissolution rates even with various excipients.

Comparative Example 9: Preparation of silodosin formulation by a different preparation method

A capsule formulation was prepared according to the same composition as Example 1, by directly filling the mixture into a capsule without a granulation process.

Example 6: Dissolution test of silodosin according to the preparation method

Using the capsule formulations of Example 1 and Comparative Example 9, which were prepared by different preparation methods, dissolution test was carried out at 50 rpm in 900 mL of 0.1N HCl solution by a sinker in USP paddle. The results are shown in Table 9 and Fig. 9.

[Table 9]

<i>In vitro</i> dissolution				
	5 min	10 min	15 min	30 min
Ex. 1	48.7%	88.2%	92.3%	97.2%
Comp. Ex. 9	23.4%	46.2%	51.4%	55.2%

As shown in the Table 9 and Fig. 9, the formulation of Example 1, which comprises a granule prepared by a wet granulation process, showed significantly superior dissolution rate as compared to Comparative Example 9, which was not granulated. This result indicates that preparation of the granule by a wet granulation process is preferable in terms of dissolution rate.

Experimental Example 7: Pharmacokinetic comparison of silodosin

Male rats (Sprague-Dawley, Sprague-Dawley Inc., U.S.A.) (n = 4) were divided into two groups, and capsules of Example 1 and Comparative Example 9 were administered to a first and second group, respectively, by a double-blind method. Then, drug concentrations in the blood over time were analyzed using WinNonlin[®], a program of Phoenix[®] Inc., and their pharmacokinetic parameter results are shown in Table 10 and Fig. 10.

[Table 10]

Parameter	Silodosin	
	Ex. 1	Comp. Ex. 9
AUC ₀₋₁₂ (ng·hr/mL)	42.7 ± 7.6	26.8 ± 8.4
C _{max} (ng/mL)	30.2 ± 4.1	13.7 ± 3.7
T _{max} (hr)	0.6 ± 0.1	0.8 ± 0.2

As shown in Table 10 and Fig. 10, the capsule of Example 1, which comprises a granule prepared by a wet granulation process, was shown to have at least about two-fold higher C_{max} and AUC as compared to the capsule of Comparative Example 9, which

was not granulated. Therefore, it has been determined that a wet granulation process of silodosin results in improved stability, and increased bioavailability of the drug by maximizing the drug concentration in a particular organ, thereby increasing the therapeutic effect of the drug.

WHAT IS CLAIMED IS:

1. A granule comprising:
silodosin;
5 an alkaline inorganic salt as a stabilizer; and
a pharmaceutically acceptable excipient.
2. The granule of claim 1, wherein the alkaline inorganic salt is at least one
selected from the group consisting of oxides, hydroxides, carbonates and phosphates of
10 sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum
and lithium.
3. The granule of claim 1, wherein the alkaline inorganic salt is calcium
carbonate (CaCO_3), magnesium carbonate (MgCO_3), sodium hydrogen carbonate
15 (NaHCO_3), or a mixture thereof.
4. The granule of claim 1, wherein the alkaline inorganic salt is employed in
an amount ranging from 0.05 to 33 parts by weight based on 1 part by weight of
silodosin.
20
5. The granule of claim 1, wherein the pharmaceutically acceptable excipient
is at least one selected from the group consisting of a diluent, a disintegrant, a
plasticizer and a lubricant.
- 25 6. The granule of claim 1, wherein the granule is prepared by a wet
granulation process.
7. A pharmaceutical composition comprising the granule of claim 1 and a
pharmaceutically acceptable additive.
30

8. The composition of claim 7, wherein the pharmaceutically acceptable additive is a diluent, a disintegrant, a humectant, a binder or a lubricant.

9. A pharmaceutical formulation prepared by using:
5 a granule of any one of claims 1 to 6; or
a pharmaceutical composition of claim 7 or 8.

10. The pharmaceutical formulation of claim 9, wherein the pharmaceutical formulation is a tablet or capsule

FIG. 1

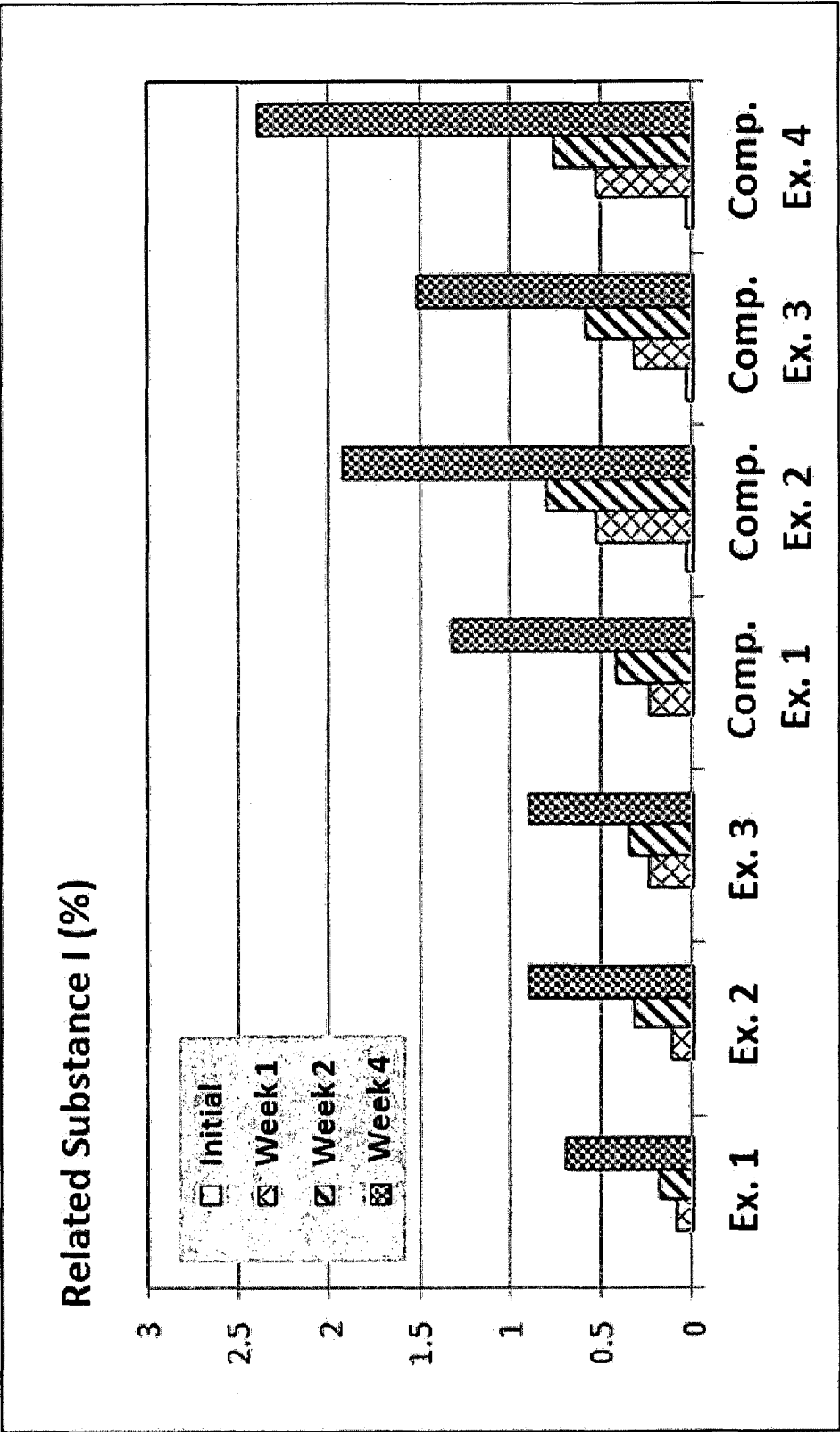


FIG. 2

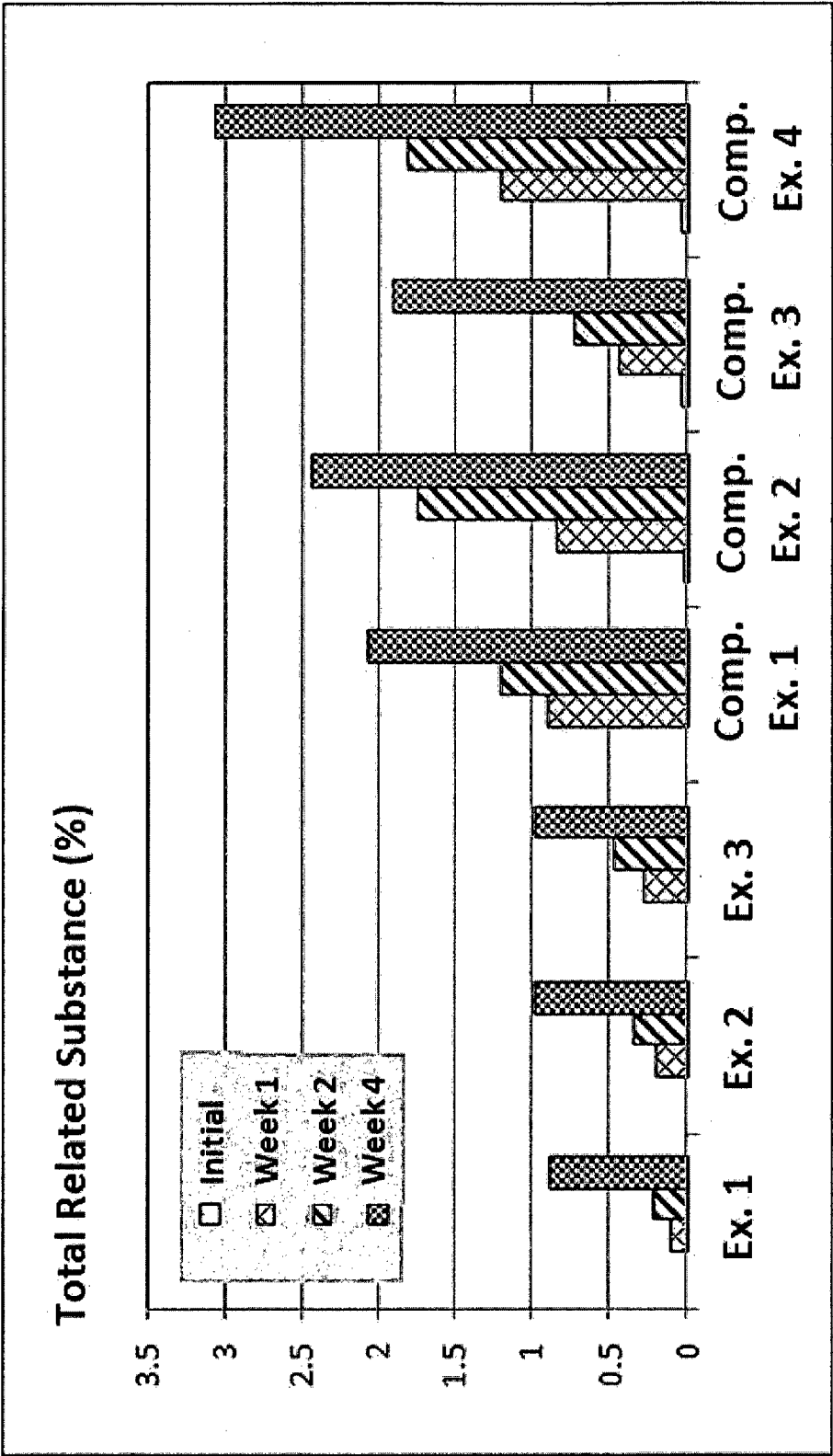


FIG. 3

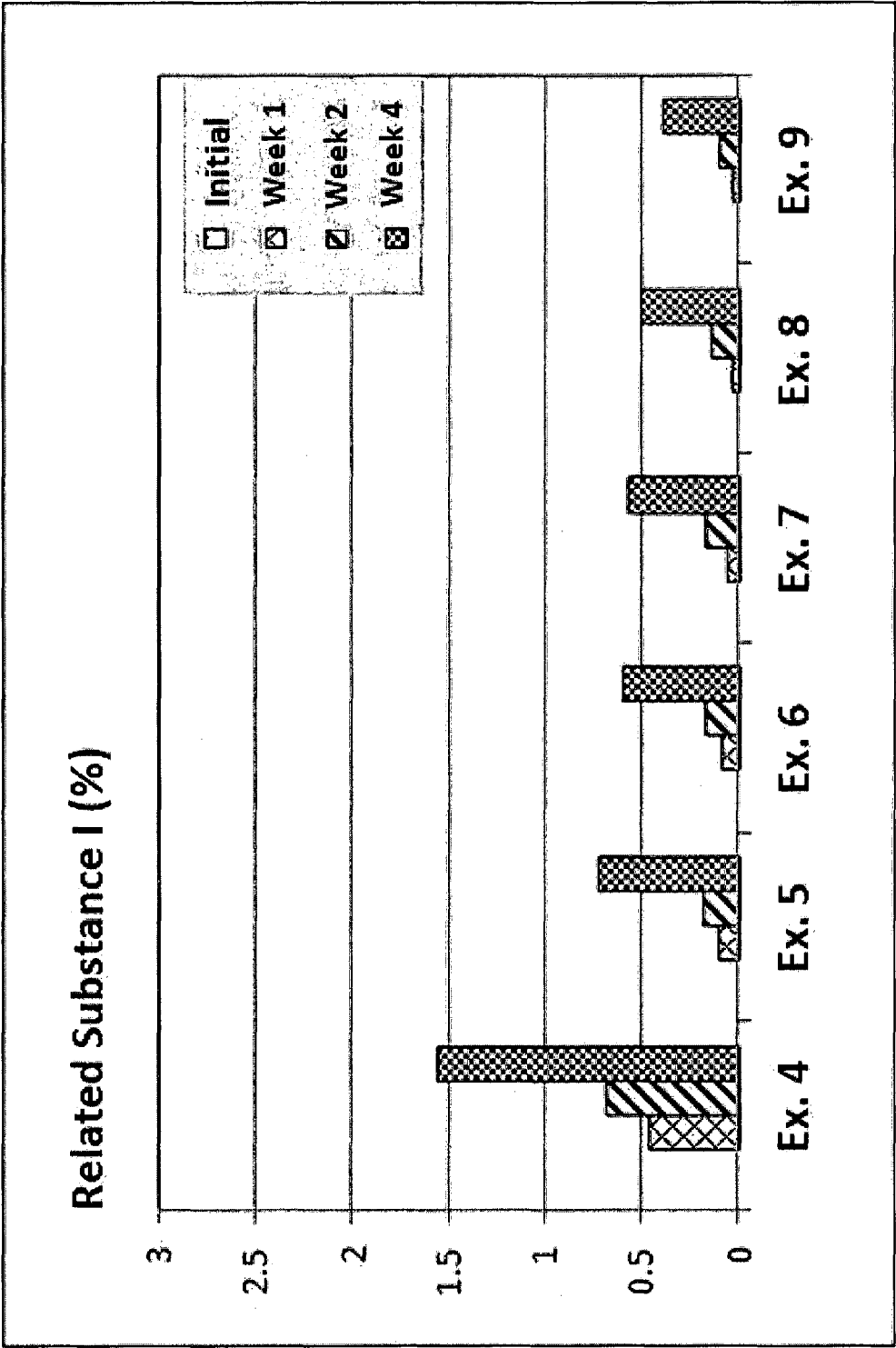


FIG. 4

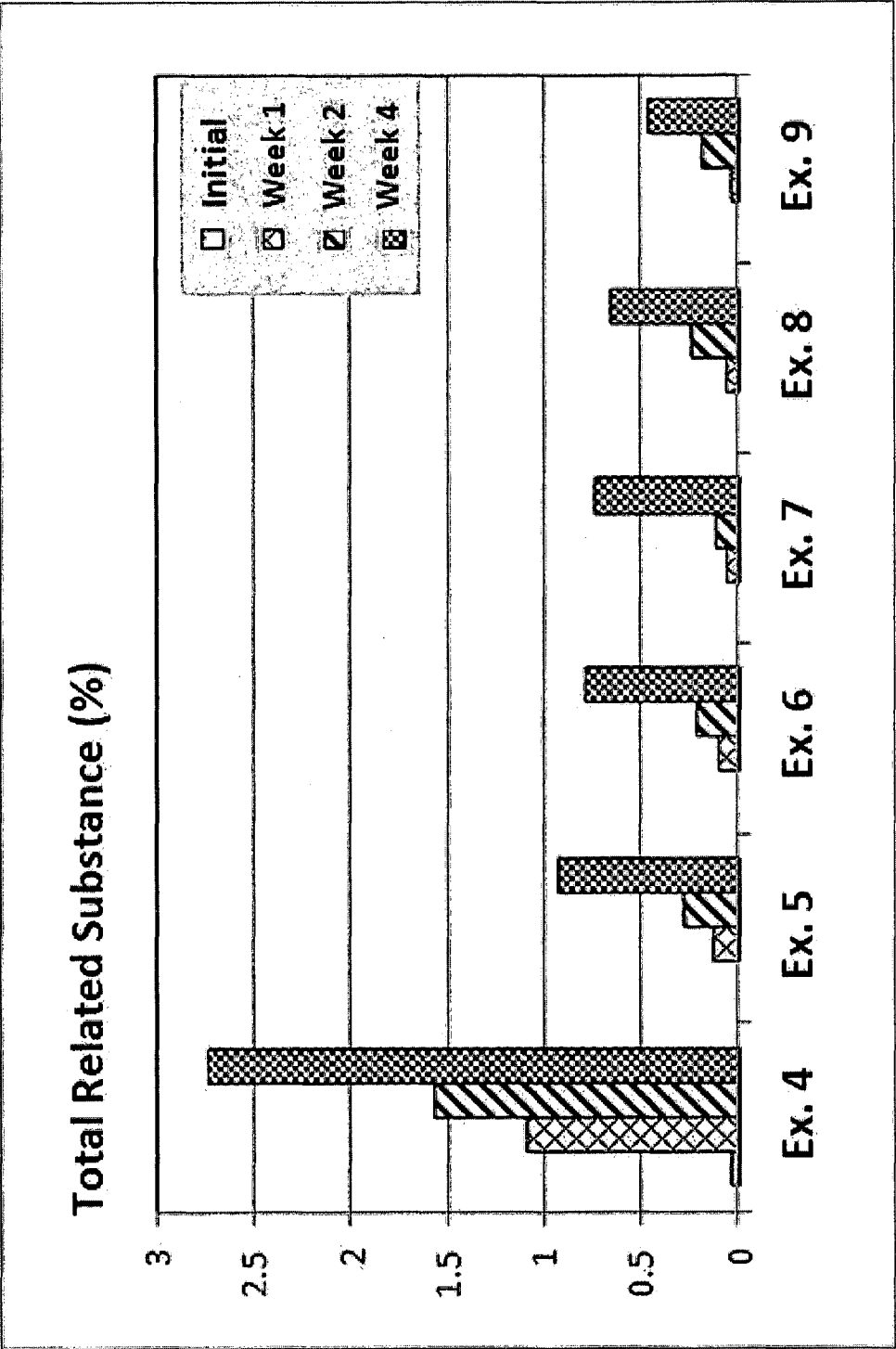


FIG. 5

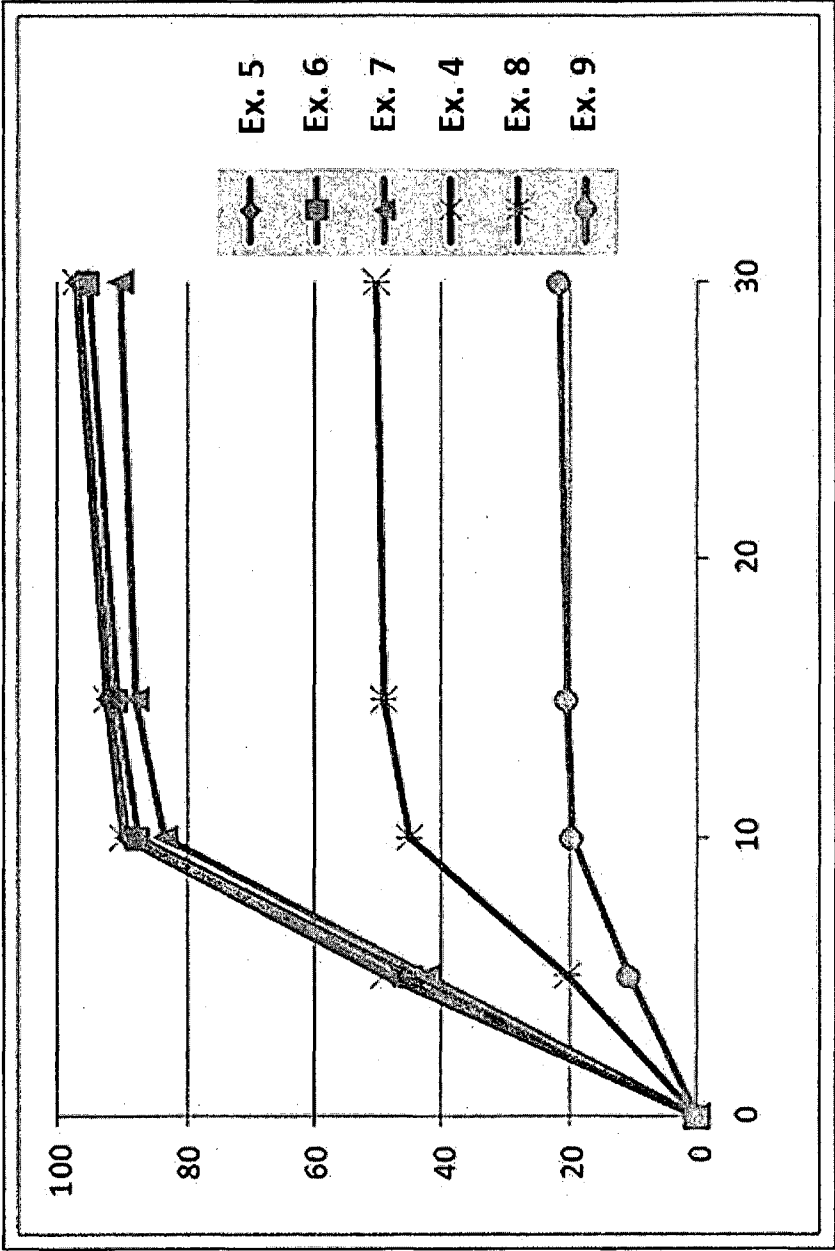


FIG. 6

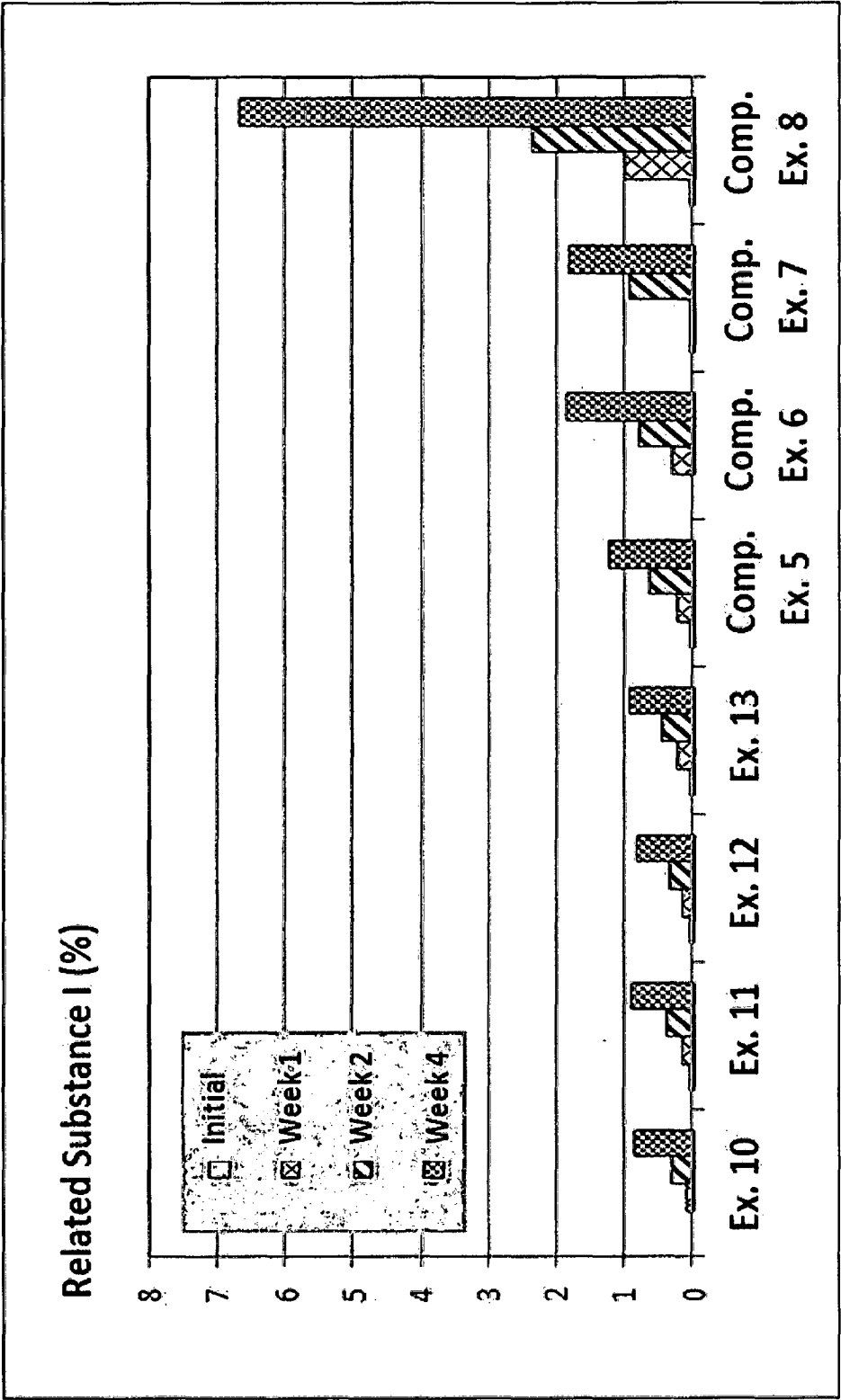


FIG. 7

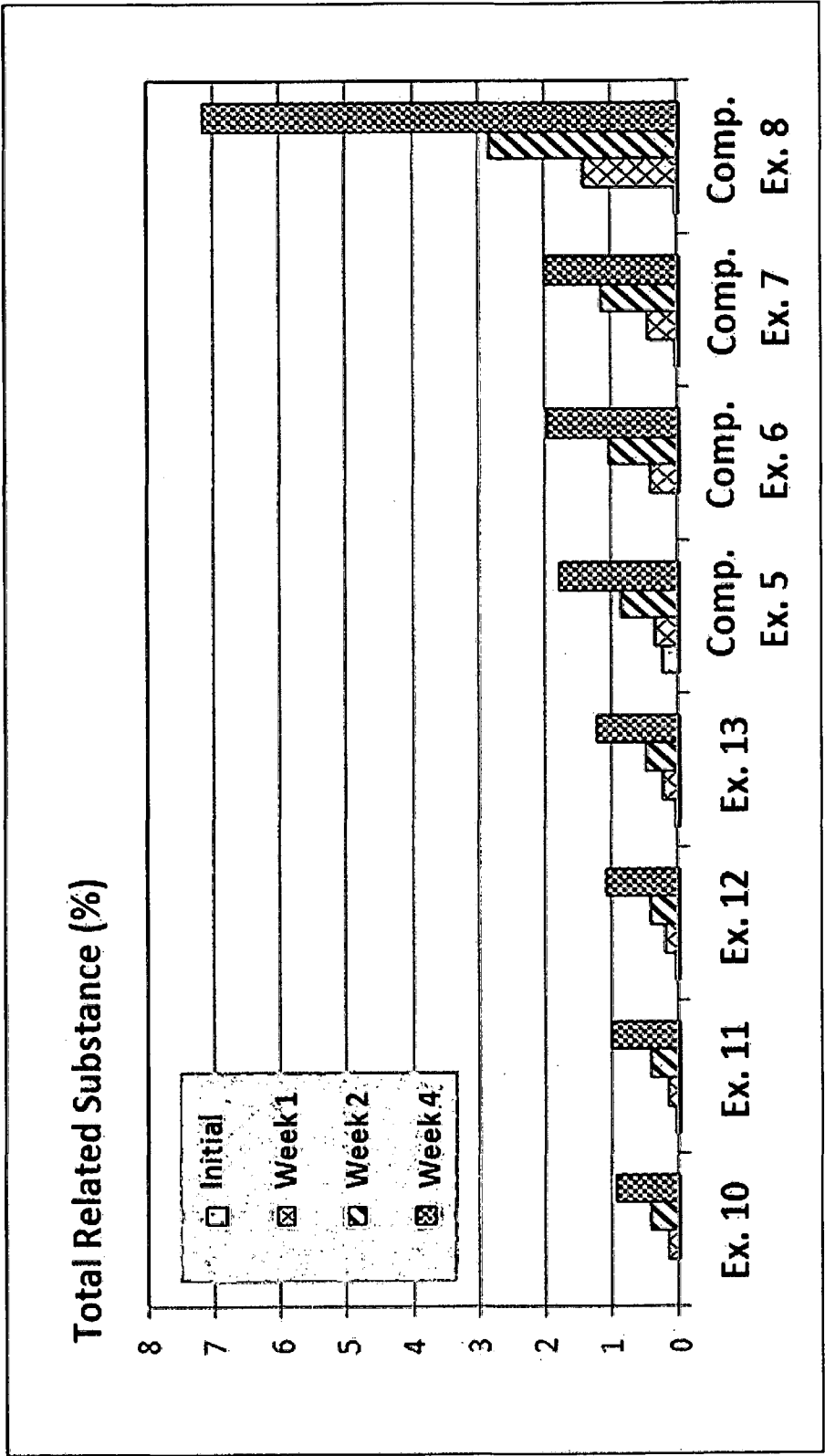
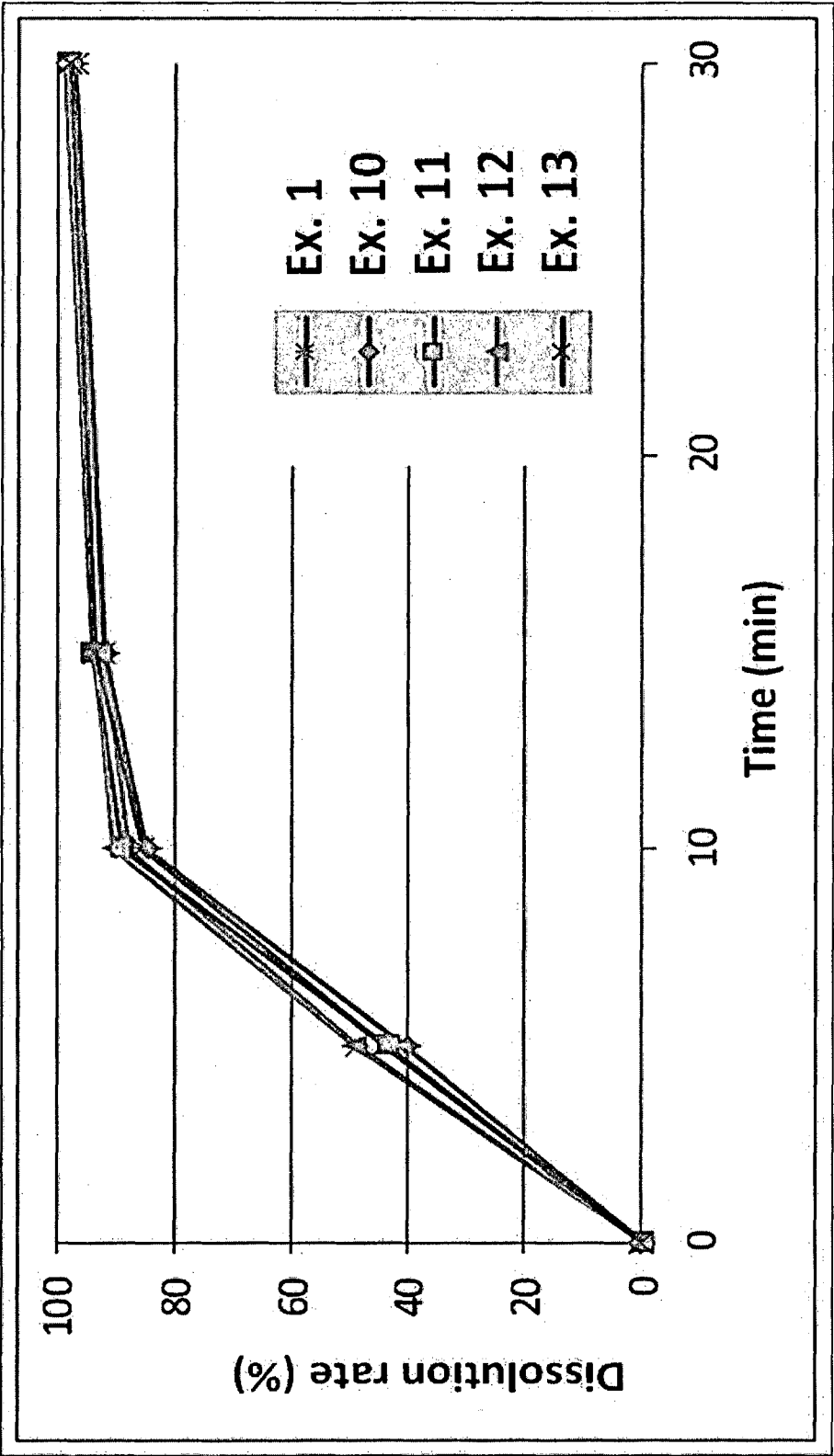
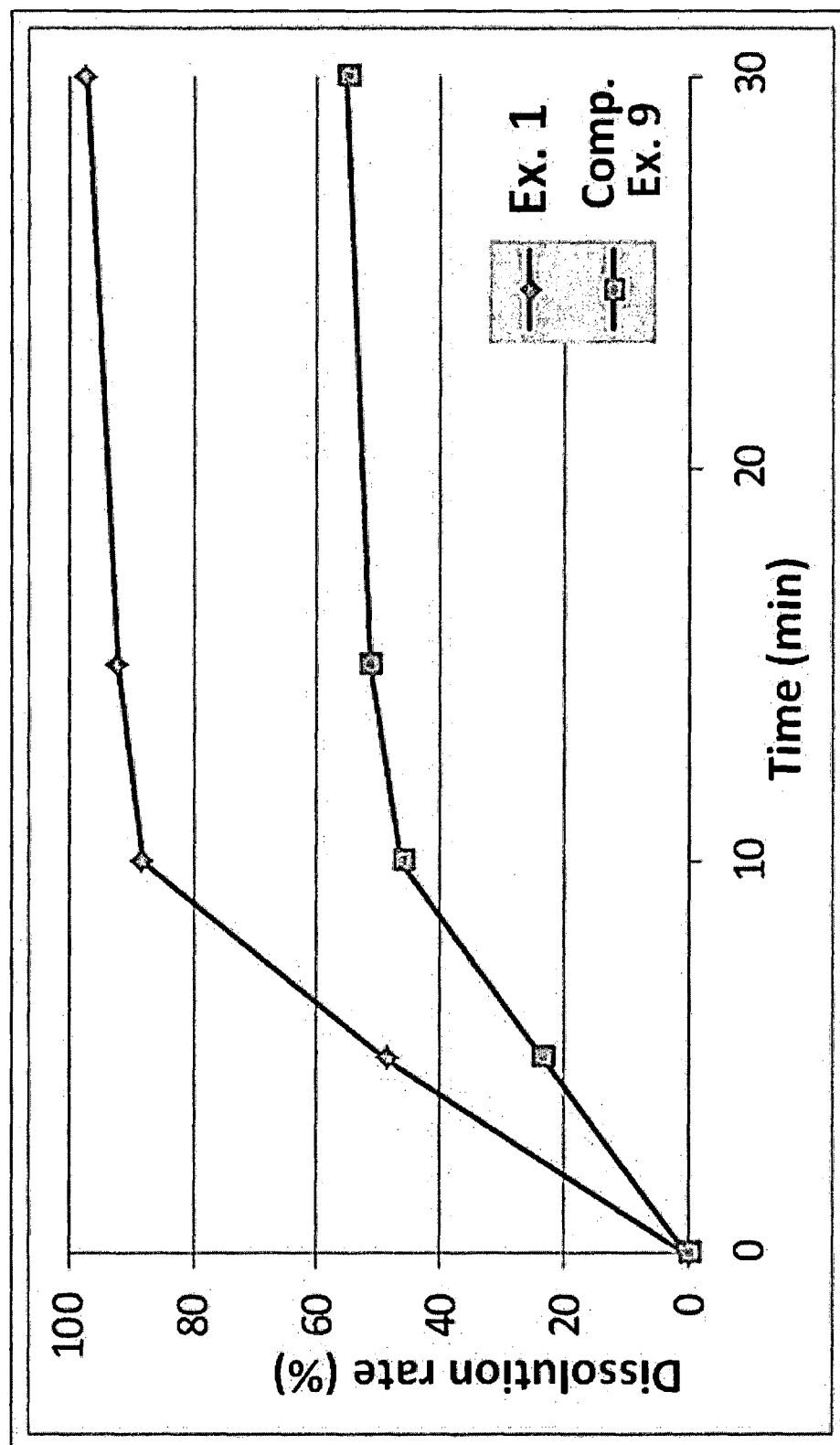


FIG. 8



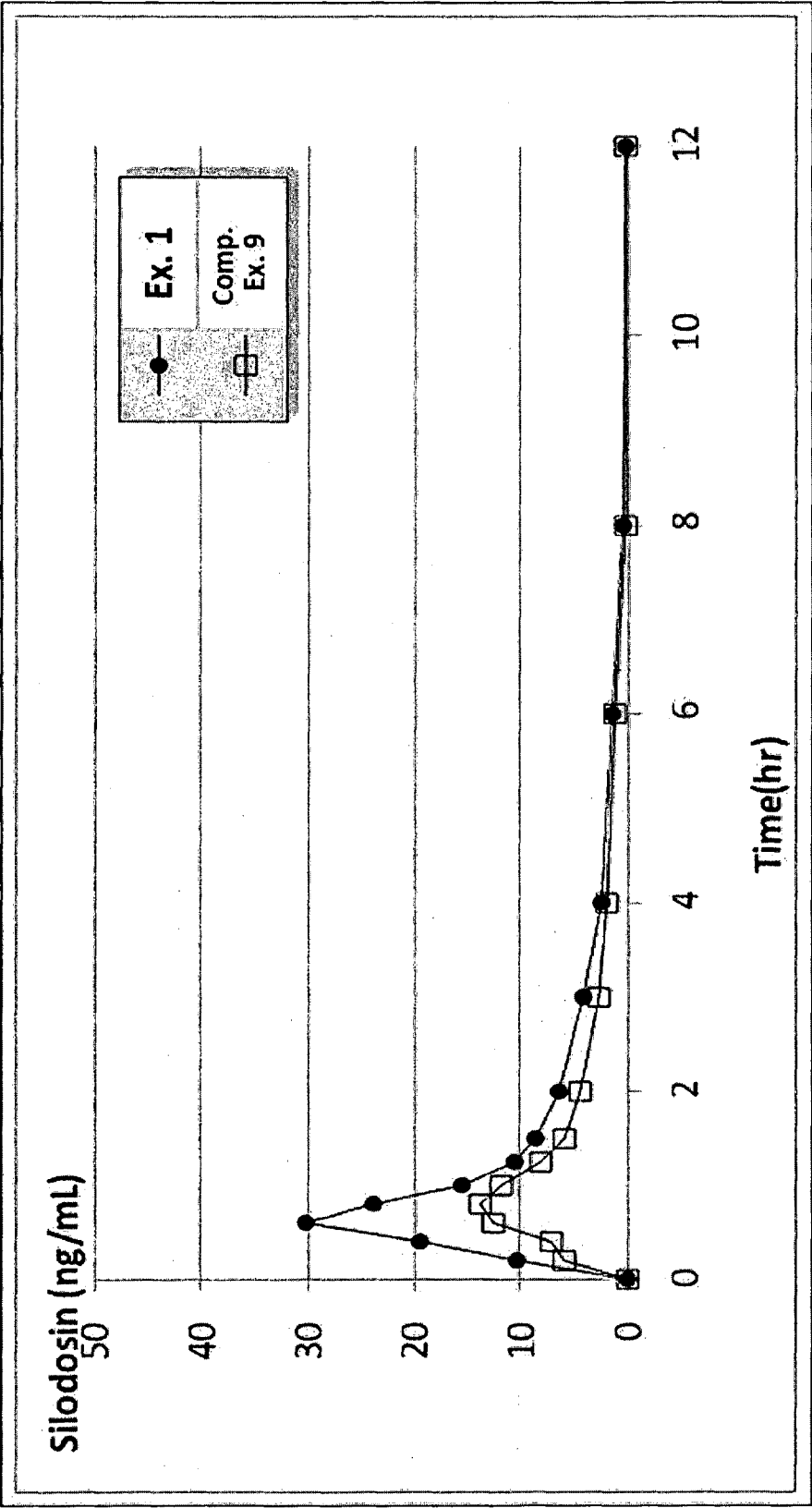
9/10

FIG. 9



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FIG. 10



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2015/003376**A. CLASSIFICATION OF SUBJECT MATTER****A61K 47/02(2006.01)i, A61K 9/20(2006.01)i, A61K 9/48(2006.01)i, A61K 31/404(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)

A61K 47/02; A61K 9/20; A61K 031/405; A61K 9/16; A61K 31/4045; A61K 033/22; A61P 13/00; A61K 9/48

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: granule, silodosin, alkaline inorganic salt, stabilizer, additive, excipient

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014-006635 A2 (HETERO RESEARCH FOUNDATION) 09 January 2014 See abstract; page 6, lines 12-16, page 7, lines 6-8, page 12, lines 3-8; claims 1, 4, 7, 10-11.	1-10
Y	US 2003-0166705 A1 (NITTA, HIROO et al.) 04 September 2003 See abstract; paragraphs [0007], [0031], [0038], [0067]; claims 1, 6-7; table 1.	1-10
A	WO 2012-000926 A1 (RATIOPHARM GMBH) 05 January 2012 See abstract; claims 1-2, 7, 12.	1-10
A	US 2012-0064154 A1 (NAGANUMA, TSUYOSHI et al.) 15 March 2012 See abstract; paragraphs [0016], [0022]; claim 19.	1-10
A	WO 2012-010669 A2 (RATIOPHARM GMBH) 26 January 2012 See abstract; claims 1, 5-7, 10-12.	1-10

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

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA/KR

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International application No.

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