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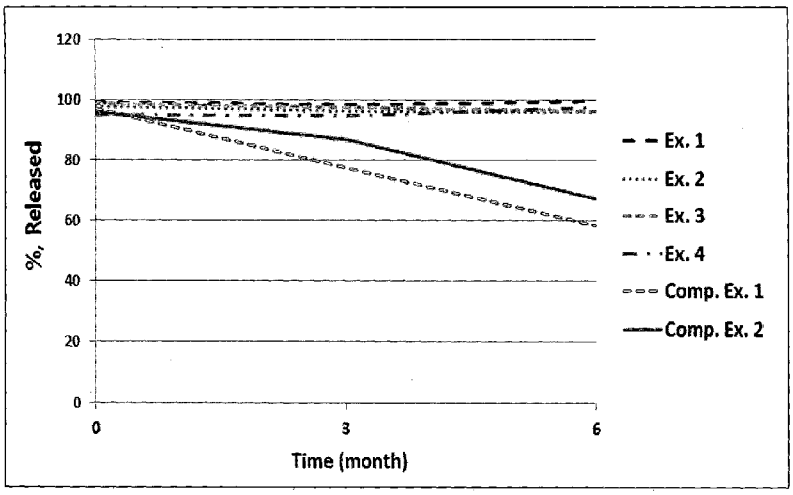
(54) Title: COMPOSITION FOR A SELF-EMULSIFYING DRUG DELIVERY SYSTEM COMPRISING DUTASTERIDE

FIG. 1



(57) Abstract: The present invention relates to a composition for a self-emulsifying drug delivery system comprising dutasteride, an oil, and a PEG-40 hydrogenated castor oil as a surfactant. The composition has following characteristics: 1) the size of formulation can be reduced by decreasing the amount of excipient, resulting in convenient drug ingestion; and 2) the composition can be emulsified in a stable emulsion state in an aqueous solution, so as to exhibit good drug dissolution stability after a long-term storage, as well as good bioavailability. The composition in accordance with the present invention can be utilized for the treatment or prevention of benign prostatic hyperplasia, prostate cancer or androgenetic alopecia.

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COMPOSITION FOR A SELF-EMULSIFYING DRUG DELIVERY SYSTEM COMPRISING DUTASTERIDE

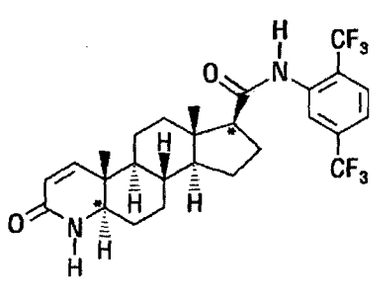
FIELD OF THE INVENTION

The present invention relates to a composition for a self-emulsifying drug delivery system comprising dutasteride. More particularly, the present invention relates to a composition for a self-emulsifying drug delivery system comprising dutasteride, an oil, and a PEG-40 hydrogenated castor oil as a surfactant.

BACKGROUND OF THE INVENTION

An azasteroid compound is one of the important pharmaceutical active compounds. Among the azasteroid compounds, dutasteride (chemical name: 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl-4-aza-5-α-androst-1-en-3-one), as represented by formula 1 below, is a 5-α reductase inhibitor, and is known to be useful in the treatment of benign prostatic hyperplasia, prostate cancer, and androgenetic alopecia (*see* U.S. Pat. No. 5565467).

Formula 1



U.S. Patent Application Publication No. 2009/0069364 discloses that the solubilities of dutasteride in ethanol, isopropanol, Capmul MCM NF, and propylene glycol are 4.4 g/100 g, 3.06 g/100 g, 2.75 g/100 g and 1.34 g/100 g,

respectively.

Dutasteride is currently being sold in the market with the product name of AVODART®. It can be prepared by dissolving 0.5 mg of dutasteride in 349.5 mg of a mixture of mono- and di-glyceride oil of caprylic/capric acid and butylated hydroxy toluene (BHT), and then filling the resultant into a soft capsule, which is used as a therapeutic agent for benign prostatic hyperplasia, prostate cancer or androgenetic alopecia. However, the amount of the excipient that makes up the product is relatively far greater than the active ingredient, leading to a large size of the resulting soft capsule and making it difficult to ingest such capsule.

To solve this problem, the present inventors have developed a self-emulsifying drug delivery system less bulky than AVODART®, yet with excellent bioavailability. However, there was a problem in that HCO-50 (a PEG-50 hydrogenated castor oil), a hydrogenated castor oil employed as a surfactant, caused delay in disintegration of dutasteride when stored for a long time under a particular condition, thereby decreasing dissolution stability of dutasteride.

Thus, the present inventors endeavored to improve dissolution stability of dutasteride, and found that, by employing a hydrogenated castor oil with appropriate degree of substitution, the initial dissolution rate of dutasteride can be maintained even when stored for a long time under a particular condition.

SUMMARY OF THE INVENTION

Therefore, it is an object of the present invention to provide a composition for a self-emulsifying drug delivery system comprising dutasteride showing good bioavailability even with a small amount of an excipient, and good dissolution stability even when stored for a long time under a particular condition.

In accordance with one object of the present invention, there is provided a composition for a self-emulsifying drug delivery system, which comprises (a) dutasteride in an amount of 0.1 to 1 weight%; (b) an oil in an amount of 50 to 95 weight%; and (c) a PEG-40 hydrogenated castor oil as a surfactant in an amount of 4 to 40 weight%.

The composition of the present invention has the following characteristics:

1) the size of formulation can be reduced by decreasing the amount of excipient, resulting in convenient drug ingestion; and

2) the composition can be emulsified in a stable emulsion state in an aqueous solution, so as to exhibit good drug dissolution stability after a long-term storage, as well as good bioavailability.

Therefore, the composition of the present invention can be utilized for the treatment or prevention of benign prostatic hyperplasia, prostate cancer or androgenetic alopecia.

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 shows the results of measurement of the dissolution rates (at 45 minutes) of the compositions of Examples 1 to 4 and Comparative Examples 1 and 2 at initial point and after 3 and 6 month storages under 40°C, 75% Relative Humidity (RH).

Fig. 2 shows the comparative results of the dissolution rates (at 45 minutes) for the compositions of Example 1 and Comparative Examples 1 and 2 after a 6-month storage under 40°C, 75% RH.

Fig. 3 shows the comparative results of the dissolution deviations (%)

for the compositions of Example 1 and Comparative Example 1 at 15, 30, 45 and 60 minutes, after a 6-month storage under 40°C, 75% RH.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a composition for a self-emulsifying drug delivery system, which comprises dutasteride, an oil, and a surfactant. The composition of the present invention is characterized by self-emulsification when mixed with water, to form an emulsion.

In one embodiment of the present invention, a composition of the present invention comprises:

(a) dutasteride in an amount of 0.1 to 1 weight%;

(b) an oil in an amount of 50 to 95 weight%; and

(c) a PEG-40 hydrogenated castor oil as a surfactant in an amount of 4 to 40 weight% based on the total weight of the composition.

In another embodiment of the present invention, a composition of the present invention comprises:

(a) dutasteride in an amount of 0.1 to 1 weight%;

(b) an oil in an amount of 59 to 95 weight%; and

(c) a PEG-40 hydrogenated castor oil as a surfactant in an amount of 4 to 40 weight% based on the total weight of the composition.

Preferably, a composition of the present invention may comprise dutasteride in an amount of 0.3 to 0.6 weight%, an oil in an amount of 70 to 85 weight%, and a PEG-40 hydrogenated castor oil as a surfactant in an amount of 4 to 40 weight% based on the total weight of the composition.

Preferably, a composition of the present invention may comprise dutasteride in an amount of 0.3 to 0.6 weight%, an oil in an amount of 70 to 85 weight%, and a PEG-40 hydrogenated castor oil as a surfactant in an amount of 14 to 28 weight% based on the total weight of the composition.

(a) Dutasteride

Dutasteride utilized as an active ingredient in a composition for the self-emulsifying drug delivery system of the present invention can be comprised in an amount of 0.1 to 1 weight%, preferably 0.3 to 0.6 weight% based on the total weight of the composition. The amount of dutasteride should be 0.1 weight% or more so as to reduce the amount of excipient and the mass of the resulting capsule, thereby allowing a medication to be conveniently taken by patients. On the other hand, the amount of dutasteride should be 1 weight% or less for easy dissolution of the active ingredient and easy preparation of soft capsules. Further, a single dose of dutasteride is fixed as 0.5 mg.

(b) Oil

For the composition of the present invention, such pharmaceutically acceptable oils that mix well with a surfactant, become emulsified in water to form a stable emulsion, and have sufficient solubility for dutasteride, can be used. Oil examples that can be utilized in the present invention may include:

① mono-, di- or mono/di-glycerides of a fatty acid, preferably mono- or di-glycerides of caprylic/capric acid (product name: Capmul MCM);

② triglycerides of a fatty acid, preferably medium grade triglycerides of a fatty acid, e.g., fractionated coconut oil (product name: Capriole);

③ esters of a fatty acid with a monovalent alkanol, preferably esters of a fatty acid having 8 to 20 carbons with a monovalent alkanol having 2 to 3 carbons, e.g., isopropyl myristate, isopropyl palmitate, ethyl linoleate or ethyl oleate; and

④ free a fatty acids, preferably oleic acid or linoleic acid in a liquid phase.

In the composition of the present invention, an oil can be comprised in an amount of 50 to 95 weight%, preferably 70 to 85 weight% based on the total weight of the composition. The amount of oil should be 50 weight% or more to prevent precipitation formation by sufficiently dissolving the main

component. On the other hand, the amount of oil should be 95 weight% or less to maintain the emulsifying capability of the formulation by using a proper amount of surfactant.

(c) Surfactant: PEG-40 hydrogenated castor oil

A surfactant utilized in the composition of the present invention plays a role of stably emulsifying the oil component in water to form an emulsion. Hydrogenated castor oil (HCO) utilized in the composition of the present invention is a non-ionic surfactant with extremely high stability, which is known to have almost no stimulation or hemolytic property. The hydrogenated castor oil, which is characterized by having a significantly large molecular weight as compared to other non-ionic surfactants to which ethylene oxide is added, is excellent as a solubilizing agent for dissolving a lipid-soluble substance in water. The hydrogenated castor oils can be divided into several groups with different grades as shown in Table 1, according to the degree of substituted ethoxylation per PEG unit.

Table 1

INCI names
PEG-10 hydrogenated castor oil
PEG-20 hydrogenated castor oil
PEG-30 hydrogenated castor oil
PEG-40 hydrogenated castor oil
PEG-50 hydrogenated castor oil
PEG-60 hydrogenated castor oil

According to the experimental results of the present invention, a soft capsule formulation containing a PEG-40 hydrogenated castor oil (e.g., NIKKOL HCO-40 or Cremophor RH40) has superior dissolution stability compared to a soft capsule formulation containing PEG-60 hydrogenated castor oil (e.g., NIKKOL HCO-60) or a PEG-50 hydrogenated castor oil (e.g., NIKKOL HCO-50). Also, it was found that a soft capsule formulation containing a PEG-40 hydrogenated castor oil has superior capability of emulsion formation compared to a soft capsule formulation containing a PEG-

30 hydrogenated castor oil (e.g., NIKKOL HCO-30) or a PEG-20 hydrogenated castor oil (e.g., NIKKOL HCO-20).

HCO-40 utilized as a surfactant in a composition of the present invention can be comprised in an amount of 4 to 40 weight%, preferably 17 to 33 weight% or 14 to 28 weight%, based on the total weight of the composition. The amount of the surfactant should be 4 weight% or more to achieve a desired emulsion formation, while it should be less than 40 weight% to exhibit good emulsion formation relative to the amount of the surfactant added.

The ratio of components (dutasteride: oil: surfactant) in a composition of the present invention can be, in the weight ratio, 1:100-500:1-100, 1:100-400:1-90, 1:100-350:1-85, 1:100-300:1-80 or 1:100-200:1-70, preferably 1:160:60.

The composition of the present invention can further comprise a property stabilizer selected from the group consisting of water, ethanol, glycine, propylene glycol, polyethylene glycol, diethylene glycol monoethyl ether, dimethyl isosorbide, cetyl alcohol and a mixture thereof. Preferably, the property stabilizer can be water, ethanol or glycine. And, the composition of the present invention can further contain one or more other pharmaceutically acceptable additives.

The composition of the present invention can be appropriately administered once or several times so that dutasteride may be administered in an amount of generally known daily dosage (e.g., common dosage for adults is 0.5 mg Q.D.).

The composition of the present invention, as a pharmaceutical composition, can be effectively utilized in the prevention or treatment of benign prostatic hyperplasia, prostate cancer or androgenetic alopecia.

Meanwhile, the present invention provides a capsule formulation containing the aforementioned composition for the self-emulsifying drug delivery system. The capsule formulation can be prepared by filling the composition of the present invention in a capsule, preferably, in a soft capsule.

The total amount of filling material in a capsule formulation according to the present invention can be 90 mg to 150 mg, preferably, 100 mg to 120 mg. Owing to the lighter weight of its filling material compared to commercially available AVODART® (350 mg, size of 6 oblong), a capsule formulation according to the present invention can be prepared in the shape and size of 2 oval (oval #2) or 3 oval (oval #3), 3 oblong (oblong #3), etc. The volumes according to the oval number and oblong number are well known in the industry of pharmacy. For example, 2 oval, 3 oval, and 3 oblong are equivalent to 0.092 to 0.142 ml, 0.148 to 0.185 ml, and 0.142 to 0.185 ml, respectively. Owing to its small volume (weight) of the soft capsule as compared to commercially available formulations, the capsule formulation according to the present invention can be taken by patients more conveniently.

When compared with the commercially available AVODART®, prepared by dissolving 0.5 mg of dutasteride in 349.5 mg of mono- and di-glyceride oil of caprylic/capric acid and having a large volume, the composition of the present invention, even when prepared by dissolving 0.5 mg of dutasteride in 110 mg of a mixture of an oil and a surfactant, not only shows equivalent drug absorption rate by forming a stable emulsion in an aqueous solution, but shows superior dissolution stability when the PEG-40 hydrogenated castor oil is used as a surfactant.

[Examples]

Hereinafter, the present invention is described more specifically by the following examples, but these are provided only for illustration purposes and the present invention is not limited thereto.

Examples 1 to 4: Preparation of soft capsule formulations containing a PEG-40 hydrogenated castor oil as a surfactant

As shown in Table 2 below, dutasteride was dissolved in Capmul MCM

oil, and then a PEG-40 hydrogenated castor oil, such as Cremophor RH40 (BASF) or HCO-40 (NIKKOL), was added as a surfactant to obtain a preliminary concentrated solution of a self-emulsifying emulsion (self-emulsifying emulsion solution).

The prepared preliminary concentrated solution of the self-emulsifying emulsion was filled in a soft capsule to obtain a capsule formulation. Specifically, using generally known components for a soft capsule including gelatin, plasticizer, and the like (43 mg of bovine gelatin, 19 mg of glycerine and glycine of 0.5 mg), a film composition was made by a general film preparation method. Then, using a soft capsule filler (Bochang Press, Korea), the prepared preliminary concentrated solution of the self-emulsifying emulsion was filled into a soft capsule by a conventional filling method, with a shape of 2 round and a ribbon thickness of 0.65 mm, which was then trimmed and dried to prepare a soft capsule formulation.

Table 2

	mg/unit	Ex. 1	Ex. 2	Ex. 3	Ex. 4
Filling material	dutasteride	0.5	0.5	0.5	0.5
	Capmul MCM NF	80	90	80	90
	Cremophor RH40 (BASF)	30	20	-	-
	HCO-40 (NIKKOL)	-	-	30	20
Soft capsule film	bovine gelatin	43	43	43	43
	glycerin	19	19	19	19
	glycine	0.5	0.5	0.5	0.5
	purified water	aa	aa	aa	aa

* aa: appropriate amount

Comparative Examples 1 to 4: Preparation of soft capsule formulations comprising a PEG-60, PEG-50, PEG-30 or PEG-20 hydrogenated castor oil as a surfactant

As shown in Table 3 below, except for the usage of HCO-60 (NIKKOL), HCO-50 (NIKKOL), HCO-30 (NIKKOL), or HCO-20 (KIKKOL) instead of

Cremophor RH40 (BASF), the procedure in Example 1 was repeated to prepare soft capsule formulations of Comparative Examples 1 to 4.

Table 3

	mg/unit	Comp. Ex.1	Comp. Ex.2	Comp. Ex. 3	Comp. Ex. 4
Filling material	dutasteride	0.5	0.5	0.5	0.5
	Capmul MCM NF	80	80	80	80
	HCO-60 (NIKKOL)	30	-	-	-
	HCO-50 (NIKKOL)	-	30	-	-
	HCO-30 (NIKKOL)	-	-	30	-
	HCO-20 (NIKKOL)	-	-	-	30
Soft capsule film	bovine gelatin	43	43	43	43
	glycerin	19	19	19	19
	glycine	0.5	0.5	0.5	0.5
	purified water	aa	aa	aa	aa

* aa: appropriate amount

Experimental Example 1: Comparison of particle sizes of compositions for a self-emulsifying drug delivery system

The preliminary concentrated solutions of self-emulsifying emulsion prepared in Examples 1 to 4 and Comparative Examples 1 to 4 were diluted by 100-fold with distilled water and their particle size was measured based on Photon Cross Correlation Spectroscopy (PCCS) principle, optically observing particle flow in a fluid, using a particle measuring instrument (Nanophox, Sympatec, Germany). The results are shown in Table 4.

Table 4

	Particle size (nm)
Ex. 1	18.2 ± 1.5
Ex. 2	22.5 ± 2.3
Ex. 3	16.3 ± 2.2
Ex. 4	24.9 ± 1.1
Comp. Ex. 1	20.1 ± 1.7
Comp. Ex. 2	25.8 ± 2.9
Comp. Ex. 3	171.7 ± 21.3
Comp. Ex. 4	248.8 ± 30.4

As shown in Table 4, the compositions of Examples 1 to 4 and Comparative Examples 1 and 2 formed emulsions with a small particle size of 100 nm or less, while the compositions of Comparative Examples 3 and 4 formed emulsions with a large particle size, indicating that their drug absorption would not be easy. These results indicate that, although the hydrogenated castor oils of PEG-30 grade or lower have low HLB values, making it easy to dissolve the main component, they are not suitable for a formulation of the present invention because they do not form emulsions having a small particle size.

Experimental Example 2: Evaluation of dissolution stability

In order to examine the dissolution stability of the soft capsules prepared above, the soft capsules prepared in Examples 1 to 4 and Comparative Examples 1 and 2 were packed in HDPE bottles containing 1g each of silica gel, and were stored under 40°C, 75% RH, and then dissolution test was carried out at initial point, and after 3 and 6 month storages. The dissolution test was carried out in accordance with the conditions below, followed by analysis with HPLC (HITACHI, Model 2000, JAPAN).

<HPLC Conditions>

Column: Zorbax SB-phenyl (4.6 mm X 15 mm, 3.5 μm)

Flow rate: 1.0 ml/minute

Column temperature: 40°C

Eluent: acetonitrile: purified water = 6: 4 (v/v)

Injection volume: 100 μL

Wavelength: 210 nm

<Dissolution test conditions>

Method: Dissolution test methods (second method), Korean Pharmacopoeia, 8th ed.

Test solution: purified water

Test fluid temperature: 37.5°C

Stirring rate: 50 rpm

The results are shown in Tables 5 and 6 and Figs. 1 to 3. Table 5 shows the dissolution results at initial point and after 3 and 6 month storages (at 45 minutes). Table 6 shows the dissolution results after a 6 month storage. Fig. 1 is a chart illustrating the results of Table 5. Fig. 2 shows the dissolution results after a 6 month storage (at 45 minutes). Fig. 3 shows the dissolution deviations at each timings after a 6 month storage.

Table 5

Dissolution results (at 45 minutes)

	Initial	3 months	6 months
Ex. 1	99.1	98.4	99.6
Ex. 2	97.9	96.3	95.8
Ex. 3	98.7	97.8	96.3
Ex. 4	95.2	94.8	97.7
Comp. Ex. 1	97.3	77.5	58.4
Comp. Ex. 2	96.1	87.1	67.3

Table 6

Dissolution results after 6 months

	Ex. 1	Comp. Ex. 1	Comp. Ex. 2
5 minutes	8.4	0.0	0.0
15 minutes	85.6	33.4	38.5
30 minutes	90.2	42.9	55.2
45 minutes	99.6	58.4	67.3
60 minutes	98.3	68.2	73.2

As shown in the results of Tables 5 and 6, and Fig. 1 and 2, when compositions containing PEG-60 hydrogenated castor oil or PEG-50 hydrogenated castor oil as a surfactant were tested after a 6 month storage under accelerated conditions, delayed dissolution of soft capsules was observed.

This is considered to be caused by the promotion of gelatin bridging by a PEG-60 or PEG-50 hydrogenated castor oil due to their different degree of substituted ethoxylation, leading to the delay in disintegration of soft capsules. On the other hand, the formulations of the present invention which used a PEG-40 hydrogenated castor oil were found to show no gelatin bridging, thereby exhibiting significantly faster dissolution at early stages.

These results indicate that, by using a PEG-40 hydrogenated castor oil, dissolution stability can be maintained even after a long-term storage, leading to a consistent drug efficacy.

In addition, six samples each from the formulations of Example 1 and Comparative Example 1 were stored for 6 months under 40°C, 75% RH and the dissolution rates were measured after 15, 30, 45, and 60 minutes to calculate dissolution deviations (%) between individual samples. It was found that the formulations of the present invention which used a PEG-40 hydrogenated castor oil exhibited relatively smaller dissolution deviations as compared with the formulations containing a PEG-60 hydrogenated castor oil (*see* Fig. 3).

These results indicate that, by using a PEG-40 hydrogenated castor oil as a surfactant, deviations between samples can be reduced, resulting in uniform drug efficacies.

WHAT IS CLAIMED IS:

1. A composition for a self-emulsifying drug delivery system, which comprises:

(a) dutasteride in an amount of 0.1 to 1 weight%;

(b) an oil in an amount of 50 to 95 weight%; and

(c) a PEG-40 hydrogenated castor oil as a surfactant in an amount of 4 to 40 weight%.

2. The composition of claim 1, which comprises:

(a) the dutasteride in an amount of 0.3 to 0.6 weight%;

(b) the oil in an amount of 70 to 85 weight%; and

(c) the PEG-40 hydrogenated castor oil in an amount of 14 to 28 weight%.

3. The composition of claim 1, wherein the oil is selected from the group consisting of mono-, di- or mono/di-glycerides of a fatty acid, triglycerides of a fatty acid, esters of a fatty acid with a monovalent alkanol, and free fatty acids.

4. The composition of claim 1, which is utilized in the prevention or treatment of benign prostatic hyperplasia, prostate cancer or androgenetic alopecia.

5. An oral capsule formulation comprising the composition of any one of claims 1 to 4.

6. The oral capsule formulation of claim 5, wherein the capsule is a soft capsule.

7. The oral capsule formulation of claim 5, wherein the total amount of

the filling material in the capsule is 90 mg to 150 mg.

8. The oral capsule formulation of claim 6, wherein the soft capsule has a shape and size of 2 oval to 3 oval.

9. The oral capsule formulation of claim 6, wherein the soft capsule has a shape and size of 3 oblong.

FIG. 1

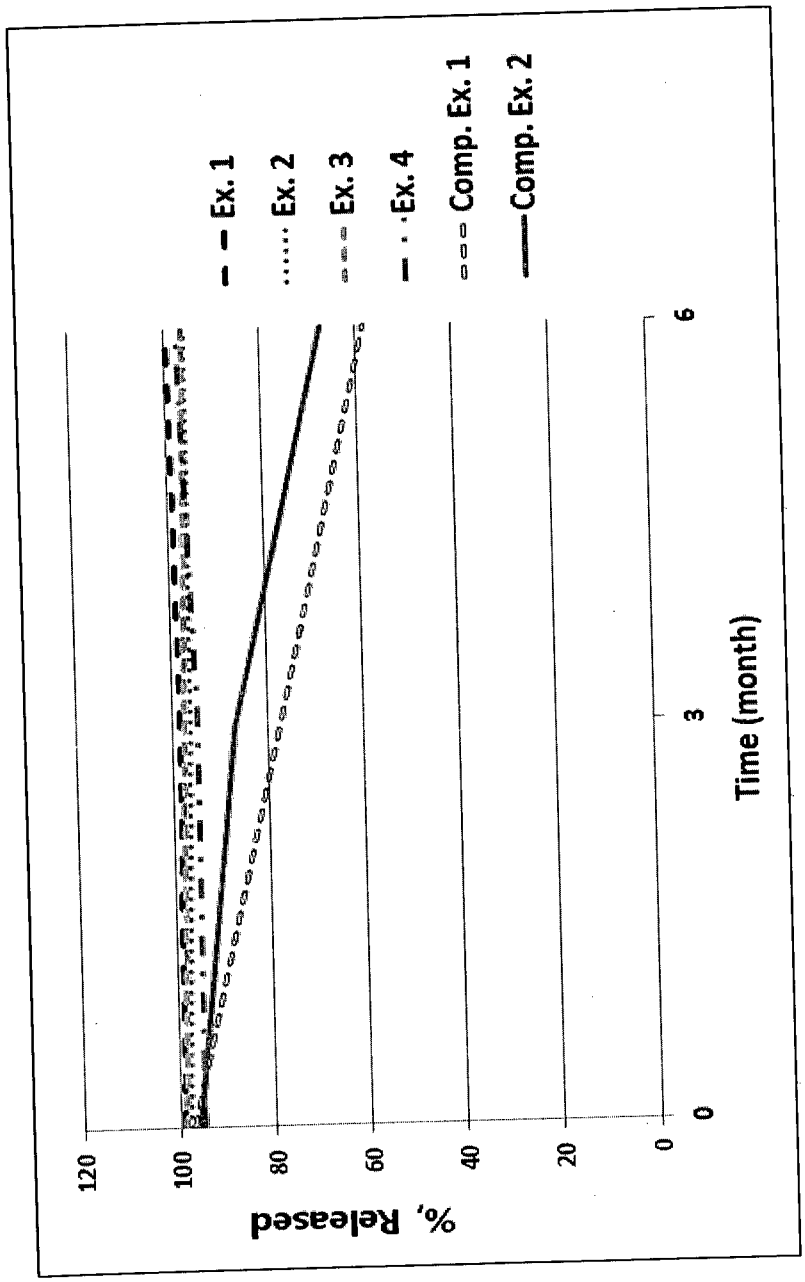

Ex. 1
Ex. 2
Ex. 3
Ex. 4
Comp. Ex. 1
Comp. Ex. 2
% Released
120
100
80
60
40
20
0
0
3
6
Time (month)

FIG. 2

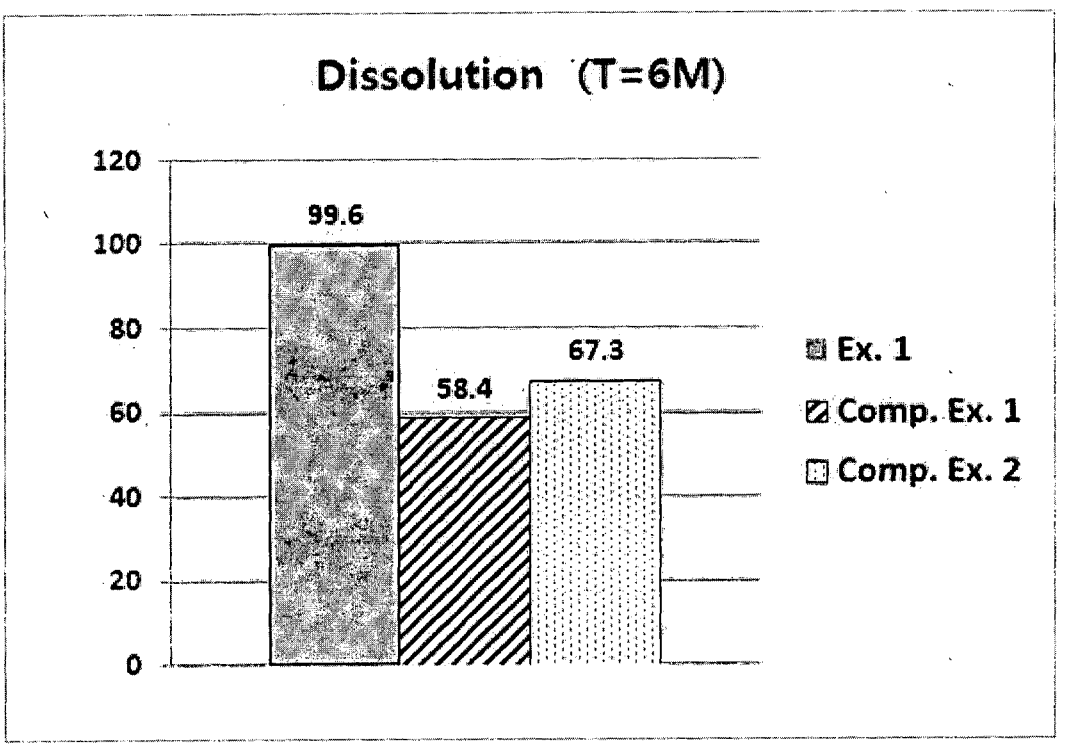
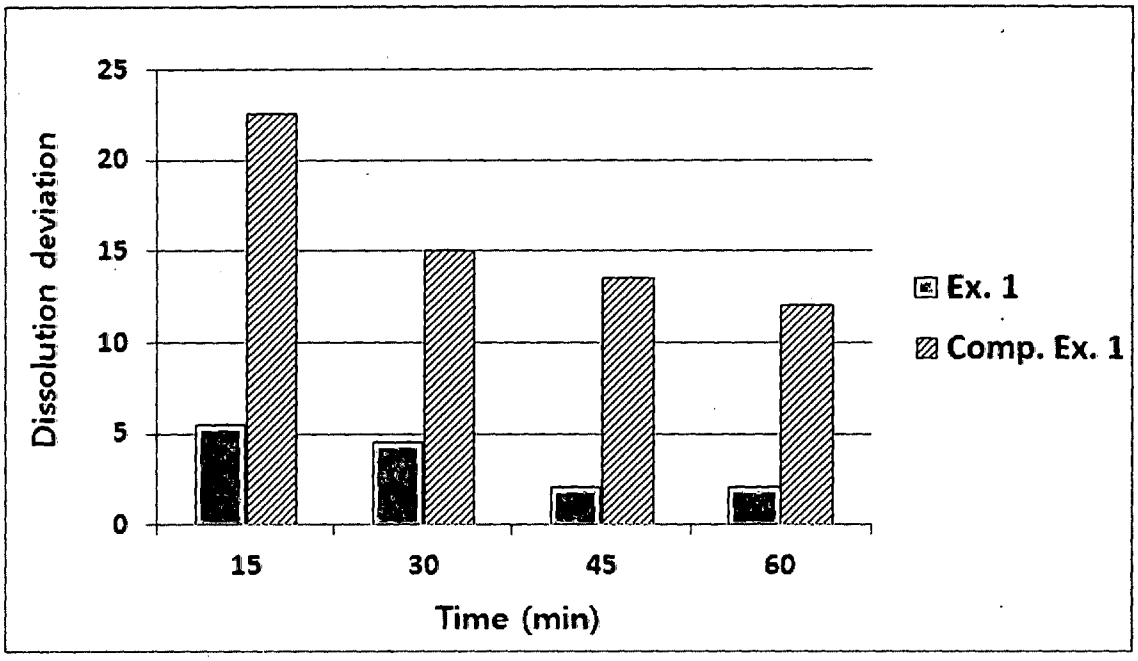

Dissolution (T=6M)
120
100
80
60
40
20
0
99.6
58.4
67.3
Ex. 1
Comp. Ex. 1
Comp. Ex. 2

FIG. 3


Dissolution deviation
25
20
15
10
5
0
15
30
45
60
Time (min)
Ex. 1
Comp. Ex. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2015/005186

A. CLASSIFICATION OF SUBJECT MATTER

A61K 47/44(2006.01)i, A61K 9/48(2006.01)i, A61K 31/58(2006.01)i, A61P 13/08(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 47/44; A61K 31/58; A61K 31/56; A61K 9/48; A61P 13/08

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:dutasteride, self-emulsifying drug delivery system, oil, surfactant, HCO-40, cremophore, fatty acid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	G.-H. Choo et al., "Formulation and in vivo evaluation of a self-microemulsifying drug delivery system of dutasteride", Drug Res., 2013, vol.63, pp.203-209 See abstract; page 204, 'Optimization of the formulation dutasteride-loaded SMEDDS'; tables 1-2; fig. 4.	1-9
Y	KR 10-2004-0015746 A (PFIZER PRODUCTS INC.) 19 February 2004 See abstract; page 5, lines 10-22.	1-9
A	KR 10-2013-0086551 A (HANMI PHARM. CO., LTD.) 02 August 2013 See abstract; claims 1-12; examples 1-8.	1-9
A	K. Sarpal et al., "Self-emulsifying drug delivery systems: A strategy to improve oral bioavailability", Current Research & Information on Pharmaceuticals Sciences, 2010, vol.11, no.3, pp.42-49. See the whole document.	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2015 (18.09.2015)	**18 September 2015 (18.09.2015)**

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2015/005186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 10-2004-0015746 A	19/02/2004	CA 2455288 A1	03/01/2003
		CN 1635911 A	06/07/2005
		CN 1635911 C	06/07/2005
		EP 1453544 A2	08/09/2004
		JP 2005-500314 A	06/01/2005
		WO 03-000295 A2	03/01/2003
		WO 2003-000295 A3	27/05/2004
KR 10-2013-0086551 A	02/08/2013	None	