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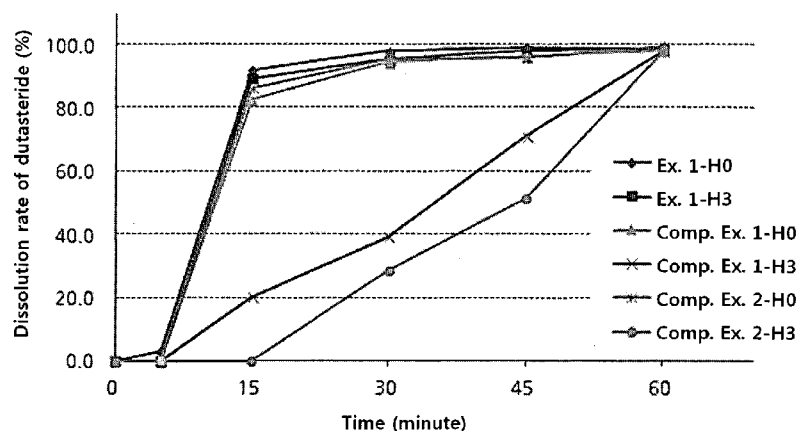
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(54) Title: ORAL SOFT CAPSULE FORMULATION COMPRISING DUTASTERIDE



(57) Abstract: The present invention relates to an oral soft capsule formulation comprising: (1) a filling material comprising dutasteride; and (2) a soft capsule film containing succinylated gelatin, a plasticizer, and a cross-linking inhibitor. The inventive soft capsule formulation can maintain superior drug dissolution stability, disintegration time and sealability of formulation, regardless of packaging and storage and storage conditions; and thus can be effectively used in the treatment of benign prostatic hyperplasia, prostate cancer, and male pattern alopecia.

DESCRIPTION

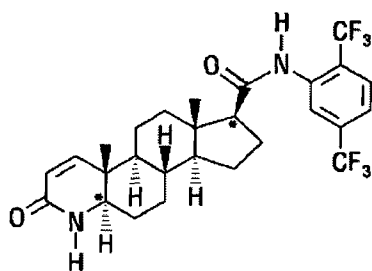
ORAL SOFT CAPSULE FORMULATION COMPRISING DUTASTERIDE

FIELD OF THE INVENTION

The present invention relates to an oral soft capsule formulation comprising dutasteride, and more specifically to an oral soft capsule formulation with improved dissolution stability of dutasteride.

BACKGROUND OF THE INVENTION

Dutasteride (chemical formula: 17β -N-(2,5-bis(trifluoromethyl))phenylcarbamoyl-4-aza-5- α -androst-1-en-3-one), as represented by formula (I) below, is a dual 5- α reductase inhibitor that inhibits conversion of testosterone to dihydrotestosterone (DHT). Dutasteride is known to be useful in the treatment of benign prostatic hyperplasia, prostate cancer, and male pattern alopecia (*see* U.S. Pat. No. 5565467):



Self-emulsifying drug delivery systems are being widely used in the process of formulating a drug having low solubility such as dutasteride in order to improve bioavailability of the drug. In this connection, KR Pat. No. 10-1055412 discloses a method for improving the solubility of dutasteride by using a self-emulsifying drug delivery system; and KR. Pat. Laid-open Publication No. 10-2005-0030282 discloses a self-emulsifying drug delivery system as a method of solubilization for improving absorption rate of poorly water-soluble simvastatin by increasing its dissolution rate.

As such, considerable research efforts have been devoted to the methods of solubilization of poorly water-soluble drugs; however, attempts for increasing dissolution rate by improving formulation types for such drugs, which is equally important, have not been made sufficiently.

5 A formulation type is one of the most important factors in the field of pharmaceuticals because application sites and indication may vary with a type of formulation even if same active ingredients are used, and it may also affect pharmacokinetic factors such as absorption rate, etc.

10 The inventors of the present invention have conducted a research on formulation of dutasteride, and discovered that certain storage conditions caused a reduction in solubility and delay in dissolution of dutasteride even when dutasteride was solubilized by using a self-emulsifying drug delivery system. Gelatin used for making of soft capsules are known to slow down dissolution of a drug due to formation of cross-links among amino acids; however, this phenomenon does not
15 take place in all formulations, but it rather varies depending on the material which is in contact with the gelatins. Specifically, in a soft capsule containing dutasteride, interaction between gelatin and dutasteride promotes cross-linking among amino acids, which causes delay in dissolution. It is thus evident that there is a great need for a novel method which could redress such problems.

SUMMARY OF THE INVENTION

20 Therefore, it is an object of the present invention to provide an oral soft capsule formulation, as a self-emulsifying drug delivery system, with improved bioavailability and dissolution stability of dutasteride, and sealability of capsule formulation.

25 In accordance with one object of the present invention, there is provided an oral soft capsule formulation comprising: (1) a filling material comprising dutasteride; and (2) a soft capsule film containing succinylated gelatin, a plasticizer, and a cross-linking inhibitor.
30

The oral soft capsule formulation of the present invention filled with dutasteride optimizes the dissolution of dutasteride, and thus can maintain good bioavailability due to consistent dissolution stability, regardless of storage or

packaging conditions. Also, the formulation uses suitable materials to improve dissolution stability and sealability of the capsule formulation.

BRIEF DESCRIPTION OF THE DRAWING

5

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

Fig. 1 shows the comparison of the dissolution profiles of the formulations of Examples 1-H0 and 1-H3, and Comparative Examples 1-H0, 1-H3, 2-H0 and 2-H3.

Fig. 2 shows the comparison of the disintegration times (initial) of the formulations of Example 1 and Comparative Examples 1 and 2 according to the thickness of the film of the formulation.

Fig. 3 shows the comparison of the disintegration times (after storage for one month) of the formulations of Example 1 and Comparative Examples 1 and 2 according to the thickness of the film of the formulation.

Fig. 4A demonstrates a method of cutting a capsule for sealing rate measurement; and Fig. 4B is a picture showing: an upper junction part (DL0), a lower junction part (DL1) and the thickness of the film (DL2).

Fig. 5 shows the sealing rate (in upper junction part) of the formulations of Example 1 and Comparative Examples 1 and 2 according to the thickness of the film of the formulation.

Fig. 6 shows the sealing rate (in lower junction part) of the formulations of Example 1 and Comparative Examples 1 and 2 according to the thickness of the film of the formulation.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an oral soft capsule formulation comprising: (1) a filling material comprising dutasteride; and (2) a soft capsule film containing succinylated gelatin, a plasticizer, and a cross-linking inhibitor.

The present invention is explained in detail hereinafter.

(1) Filling material

5 The soft capsule formulation according to the present invention comprises dutasteride as an active ingredient. The filling material is preferably an emulsion using a self-emulsifying drug delivery system in order to improve dissolution rate of dutasteride. The filling material may further comprise, besides dutasteride, other ingredients to establish a self-emulsifying drug delivery system. Examples of the
10 other ingredients include a solvent, a surfactant, a stabilizer, and the like. The solvent may be polysorbates including polysorbate 20, 40, 60, and 80; propylene glycol; vegetable oils containing 10 to 20% of ethanol (*e.g.*, peanut oil, safflower oil, olive oil, etc.); glyceryl caprylate/caprate; methyl cellulose; stearyl monoester of glycerol; monounsaturated fatty acid ester of glycerol; or a mixture thereof. The
15 surfactant may be polysorbates including polysorbate 20, 40, 60, and 80; sorbitan fatty acid esters (*e.g.*, Span[®] 20, 40, 60, 65, 80, 85); castor oils such as polyoxyl castor oil; substituted castor oils such as Cremophor[®] or hydrogenated Cremophor[®]; polyoxyethylene-polyoxypropylene copolymers; mono- or di-glycerides of caprylic/capric acid; polyoxyethylene-polyoxypropylene block copolymer; and the
20 like; preferably poloxamer 407, but not limited thereto. Also, the stabilizer may be 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 water, ethanol or glycine. In addition, the emulsion may further comprise other pharmaceutically acceptable additive.

25 Dutasteride may be comprised in an amount of 0.1 to 1 wt% based on the total weight of the filling material. Also, the solvent may be comprised in an amount of 50 to 93 wt% based on the total weight of the filling material; the surfactant in an amount of 5 to 40 wt% based on the total weight of the filling material; and the stabilizer in an amount of 1 to 10 wt% based on the total weight of
30 the filling material, but not limited thereto.

(2) Soft capsule film

The film of the soft capsule according to the present invention comprises the following ingredients as its materials.

(a) Succinylated gelatin

5 Gelatin, which is commonly used as a main ingredient in conventional soft capsules, interacts with dutasteride and promotes cross-linking among amino acids, thereby causing a delay in dissolution of dutasteride. On the contrary, succinylated gelatin does not allow amino acids to form cross-links, and thus can improve dissolution of dutasteride. The succinylated gelatin may be obtained by
10 subjecting gelatin to an alkaline treatment, followed by a reaction with anhydrous succinic acid. As a result, an amino group ($-\text{NH}_3^+$) of gelatin undergoes a succinylation, and is substituted with a carboxyl group ($-\text{COOH}$). The succinylated gelatin may be used in an amount of 50 to 90 wt%, preferably 60 to 75 wt%, based on the total weight of the soft capsule film.

15 A soft capsule formulation comprising the succinylated gelatin of the present invention shows excellent dissolution stability of dutasteride as compared with those of gelatins from pig- or bovine-origin, and it also has advantages in quality maintenance during manufacturing process owing to small changes in sealability and disintegration time of soft capsule formulation in accordance with the thickness
20 of the film.

(b) Plasticizer

In the soft capsule of the present invention, a plasticizer is used to allow the succinylated gelatin to have elasticity so as to prevent hardening of the succinylated
25 gelatin and to remain soft and pliable. Examples of the plasticizer include glycerine, sorbitol, mannitol, propylene glycol, polyethylene glycol, sugar alcohol, monosaccharide, disaccharide, oligosaccharide, etc. and two or more of the plasticizer may be used in combination. The plasticizer may be used in an amount of about 5 to 45 wt%, preferably about 20 to 40 wt%, more preferably about 20 to
30 37 wt%, based on the total weight of the soft capsule film.

(c) Cross-linking inhibitor

Generally, a cross-linking inhibitor is used to prevent gelatins from forming

cross-links. In the present invention, the cross-linking inhibitor prevents the formation of cross-links by interacting with the part of the succinylated gelatins unsubstituted with carboxyl group. Examples of the cross-linking inhibitor may include glycine, citric acid, etc., and two or more of the cross-linking inhibitor may be used in combination. The cross-linking inhibitor may be used in an amount of about 0.5 to 5 wt% based on the total weight of the soft capsule film. When the cross-linking inhibitor is used within said range, desirable sealability and disintegration time of the formulation may be obtained.

The film of the soft capsule of the present invention employing the aforementioned three components improves sealability of the formulation and disintegration time of the drug.

In the preparation of the soft capsule formulation, the thickness of the film is one of the most important parameters which affect product qualities such as disintegration time of the drug and the sealability of the formulation. In consideration of dissolution rate of the drug, disintegration time and the sealability of the formulation, the thickness of the soft capsule formulation comprising dutasteride is preferably about 0.6 mm to 0.8 mm, or about 0.65 mm to 0.75 mm.

However, it may be nearly impossible to completely eliminate the deviation in the thickness of the film no matter how precise the formulation process is, and thus there is a problem of deviation in disintegration time of drug and sealability of formulation.

On the contrary, the soft capsule of the present invention maintains consistency in disintegration time despite having varied film thicknesses, *i.e.*, having deviation in the thickness of the film during the manufacturing process. In one embodiment, the soft capsule of the present invention releases at least 85% of dutasteride as an active ingredient within 15 minutes, and this property is maintained regardless of the type of packaging or the duration of storage. In another embodiment, the oral soft capsule formulation of the present invention releases at least 90% of dutasteride within 30 minutes, and this property is maintained regardless of the packaging type or the duration of storage.

Also, the soft capsule of the present invention shows good sealability of the formulation despite having varied film thicknesses, *i.e.*, having deviation in the

thickness of the film during the manufacturing process. Thus, the soft capsule formulation of the present invention can be stored and distributed without getting damaged.

Moreover, the oral soft capsule of the present invention exhibits good dissolution stability against time, and thus can be effectively used in the treatment of benign prostatic hyperplasia, prostate cancer, and male pattern alopecia.

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.

Example 1 and Comparative Examples 1 and 2: Preparation of soft capsule formulations having various types of gelatin

<Preparation of filling material>

In accordance with the amounts listed in Table 1 below, dutasteride (Dr. Reddy's Laboratories Ltd.) was dissolved in Capmul[®] MCM oil (Abitech), and the rest of the ingredients were sequentially dissolved so as to obtain a self-emulsifying system.

<Preparation of soft capsule film>

In accordance with the amounts listed in Table 1 below, glycerine, glycine, and distilled water were placed in a gelatin tank, and then uniformly suspended by using a homo mixer. One of succinylated gelatin (Geltech, 200 Bloom), bovine gelatin (Geltech, 165 Bloom), and pig gelatin (Rousselot, 175 Bloom) and distilled water were added to be wetted.

The filling material thus prepared was filled into a soft capsule in accordance with the conventional method described in the General Preparation Chapter of the Korean Pharmacopoeia by using a soft gelatin encapsulation machine (BCM-GB, Bochang Co., Ltd.) to prepare soft capsule formulations of Example 1 and Comparative Examples 1 and 2. During this process, gelatin sheets in the

solid state were adjusted before the soft gelatin encapsulation process to maintain the film thickness at 0.8 mm.

[Table 1]

Component	Ingredient	Amount (mg/formulation)		
		Example 1	Comp. Ex. 1	Comp. Ex. 2
Filling material	Dutasteride	0.5	0.5	0.5
	Capmul [®] MCM	100	100	100
	Poloxamer 407	10	10	10
	Distilled water	3	3	3
Soft capsule film	Succinylated gelatin	43.0	-	-
	Bovine gelatin	-	43.0	-
	Pig gelatin	-	-	43.0
	Glycerine	19.0	19.0	19.0
	Glycine	0.5	0.5	0.5
	Distilled water	q.s.	q.s.	q.s.
Total		176.0	176.0	176.0

5

Experimental Example 1: Evaluation of dissolution stability according to gelatin types

Each of soft capsules obtained in Example 1 and Comparative Examples 1 and 2 were stored under 40°C and 70% RH according to Tables 2, 3, and 4 below.

10

[Table 2]

	Ex. 1-H0	Ex. 1-H1	Ex. 1-H3	Ex. 1-P0	Ex. 1-P1	Ex. 1-P3
Sample used	Ex. 1	Ex. 1	Ex. 1	Ex. 1	Ex. 1	Ex. 1
Packaging condition	HDPE bottle	HDPE bottle	HDPE bottle	PTP laminated PVDC-Alu	PTP laminated PVDC-Alu	PTP laminated PVDC-Alu
Storage duration (month)	0	1	3	0	1	3

[Table 3]

	Comp. Ex. 1-H0	Comp. Ex. 1-H1	Comp. Ex. 1-H3	Comp. Ex. 1-P0	Comp. Ex. 1-P1	Comp. Ex. 1-P3
Sample used	Comp. Ex. 1	Comp. Ex. 1	Comp. Ex. 1	Comp. Ex. 1	Comp. Ex. 1	Comp. Ex. 1

Packaging condition	HDPE bottle	HDPE bottle	HDPE bottle	PTP laminated PVDC-Alu	PTP laminated PVDC-Alu	PTP laminated PVDC-Alu
Storage duration (month)	0	1	3	0	1	3

[Table 4]

	Comp. Ex. 2-H0	Comp. Ex. 2-H1	Comp. Ex. 2-H3	Comp. Ex. 2-P0	Comp. Ex. 2-P1	Comp. Ex. 2-P3
Sample used	Comp. Ex. 2	Comp. Ex. 2	Comp. Ex. 2	Comp. Ex. 2	Comp. Ex. 2	Comp. Ex. 2
Packaging condition	HDPE bottle	HDPE bottle	HDPE bottle	PTP laminated PVDC-Alu	PTP laminated PVDC-Alu	PTP laminated PVDC-Alu
Storage duration (month)	0	1	3	0	1	3

As shown in Tables above, PVDC-Alu refers to a blister pack which consists of a lidding seal of polyvinylidene chloride (PVDC) and a backing of aluminum foil. Also, Example 1-H0 refers to the sample in which the soft capsule of Example 1 was packaged in a high-density polyethylene (HDPE) bottle and stored for 0 month; Example 1-H1 refers to the sample in which the soft capsule of Example 1 was packaged in an HDPE bottle and stored for 1 month; Example 1-H3 refers to the sample in which the soft capsule of Example 1 was packaged in an HDPE bottle and stored for 3 months; Example 1-P0 refers to the sample in which the soft capsule of Example 1 was packaged in a press through package (PTP) and stored for 0 month; Example 1-P1 refers to the sample in which the soft capsule of Example 1 was packaged in a PTP and stored for 1 month; and Example 1-P3 refers to the sample in which the soft capsule of Example 1 was packaged in a PTP and stored for 3 months. The samples of Comparative Examples 1 and 2 were named in the same manner as Example 1.

The soft capsule samples were subjected to the dissolution test using 2% SLS dissolved in 0.1 N HCl solution (900 mL) as an eluent at a rate of 50 rpm, as described in Dissolution Apparatus 2 (paddle) of the United States Pharmacopeia. The dissolution rates of the samples were analyzed by collecting the samples at 5,

15, 30, 45 and 60 minutes after the test and measuring them. The results are shown in Tables 5 to 7, and Fig. 1.

[Table 5]

Sampling time (min)	Ex. 1-H0	Ex. 1-H1	Ex. 1-H3	Ex. 1-P0	Ex. 1-P1	Ex. 1-P3
5	3.0	0.0	0.0	5.0	0.0	1.7
15	92.2	91.8	89.5	92.8	92.4	90.8
30	98.0	96.5	95.4	97.2	98.1	96.4
45	99.1	98.1	98.2	97.8	98.2	96.5
60	98.8	98.6	98.5	98.1	98.1	97.5

5

[Table 6]

Sampling time (min)	Comp. Ex. 1-H0	Comp. Ex. 1-H1	Comp. Ex. 1-H3	Comp. Ex. 1-P0	Comp. Ex. 1-P1	Comp. Ex. 1-P3
5	0.0	0.0	0.0	0.0	0.0	0.0
15	82.7	43.5	20.2	88.5	61.5	0.0
30	94.5	70.3	39.1	89.8	83.2	77.6
45	96.4	89.4	71.1	94.5	96.4	96.3
60	98.4	97.9	98.2	97.9	98.2	98.4

[Table 7]

Sampling time (min)	Comp. Ex. 2-H0	Comp. Ex. 2-H1	Comp. Ex. 2-H3	Comp. Ex. 2-P0	Comp. Ex. 2-P1	Comp. Ex. 2-P3
5	0.0	0.0	0.0	0.0	0.0	0.0
15	86.5	38.1	0.0	84.5	0.8	1.8
30	95.7	60.2	28.4	93.4	72.8	42.0
45	96.2	82.4	51.6	97.2	90.5	65.4
60	99.4	97.9	98.0	97.9	98.1	97.2

10 As shown in Tables 5 to 7 and Fig. 1, Example 1 having succinylated gelatin as the soft capsule material exhibited consistent dissolution rates regardless of the type of packaging or duration of storage. On the other hand, Comparative Examples 1 and 2 having pig gelatin or bovine gelatin as the soft capsule material showed, although there were some differences depending on the type of packaging,
15 a reduction in dissolution rate as time passes.

Examples 1-1 to 1-5, Comparative Examples 1-1 to 1-5, and Comparative Examples 2-1 to 2-5: Preparation of soft capsule formulations having various types of gelatin and various thickness of soft capsule film

In order to evaluate the effect of the type of gelatin on the soft capsules having various film thicknesses, the film thickness of the soft capsule formulations obtained in Example 1 and Comparative Examples 1 and 2 was varied according to Table 8 below. The film thickness was adjusted to 0.6, 0.65, 0.7, 0.75, and 0.8 mm by changing the thickness of gelatin sheets before the soft gelatin encapsulation process. Soft capsule formulations having various thicknesses were prepared and named Examples 1-1 to 1-5, Comparative Examples 1-1 to 1-5 and 2-1 to 2-5. Example 1-1 refers to a formulation of Example 1 having the film thickness of 0.6 mm; Example 1-2 refers to a formulation of Example 1 having the film thickness of 0.65 mm; Example 1-3 refers to a formulation of Example 1 having the film thickness of 0.7 mm; Example 1-4 refers to a formulation of Example 1 having the film thickness of 0.75 mm; and Example 1-5 refers to a formulation of Example 1 having the film thickness of 0.8 mm. Likewise, each of Comparative Examples 1-1 to 1-5 and 2-1 to 2-5 has the thicknesses as indicated in Table 8 below.

[Table 8]

	Ex. 1-1	Ex. 1-2	Ex. 1-3	Ex. 1-4	Ex. 1-5
Formulation	Example 1				
Film thickness(mm)	0.6	0.65	0.7	0.75	0.8
	Comp. Ex. 1-1	Comp. Ex. 1-2	Comp. Ex. 1-3	Comp. Ex. 1-4	Comp. Ex. 1-5
Formulation	Comparative Example 1				
Film thickness(mm)	0.6	0.65	0.7	0.75	0.8
	Comp. Ex. 2-1	Comp. Ex. 2-2	Comp. Ex. 2-3	Comp. Ex. 2-4	Comp. Ex. 2-5
Formulation	Comparative Example 2				
Film thickness(mm)	0.6	0.65	0.7	0.75	0.8

Experimental Example 2: Evaluation of disintegration time according to gelatin types and thickness of film

Soft capsule formulations of Examples 1-1 to 1-5, Comparative Examples 1-1 to 1-5 and 2-1 to 2-5, which have various gelatin types and thicknesses of film, were each packaged in an HDPE bottle and stored under 40°C and 70%, and then disintegration time of each formulation was evaluated according to the disintegration test method described in the Korean Pharmacopoeia. Specifically, samples were decided as disintegrated and disintegration time was determined when there was no sample residue remaining in a glass tube or there remained some sample in a glass tube yet it was a soft material without having a distinct circle shape, or it was a fragment of insoluble coating or coating film. The results are shown in Tables 9 to 11 and Figs. 2 and 3.

[Table 9]

		Ex. 1-1	Ex. 1-2	Ex. 1-3	Ex. 1-4	Ex. 1-5
Film thickness (mm)		0.6	0.65	0.7	0.75	0.8
Disintegration time (initial)	1 st trial	2.8	3.5	3.5	3.8	4.6
	2 nd trial	2.6	4.2	3.2	4.0	4.8
	3 rd trial	3.2	3.0	4.0	4.2	4.4
	Avg (min)	2.87	3.57	3.57	4.0	4.6
Disintegration time (after storage for 1 month)	1 st trial	3.0	3.8	4.8	5.0	10.0
	2 nd trial	3.6	6.5	6.0	6.2	12.5
	3 rd trial	4.8	3.5	4.0	6.8	14.8
	Avg (min)	3.8	4.6	4.93	6.0	12.43

[Table 10]

		Comp. Ex. 1-1	Comp. Ex. 1-2	Comp. Ex. 1-3	Comp. Ex. 1-4	Comp. Ex. 1-5
Film thickness (mm)		0.6	0.65	0.7	0.75	0.8
Disintegration time (initial)	1 st trial	1.0	3.0	3.6	4.8	12.6
	2 nd trial	3.2	2.8	3.8	5.2	10.8
	3 rd trial	2.2	2.4	3.2	8.0	9.6
	Avg (min)	2.13	2.73	3.53	6.00	11.00
Disintegration time (after storage for 1 month)	1 st trial	9.0	15.0	14.3	16.2	20.5
	2 nd trial	8.0	10.3	16.5	20.6	16.8
	3 rd trial	8.8	11.6	17.0	17.4	14.0
	Avg (min)	8.60	12.30	15.93	18.07	17.10

[Table 11]

	Comp. Ex. 2-1	Comp. Ex. 2-2	Comp. Ex. 2-3	Comp. Ex. 2-4	Comp. Ex. 2-5
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Film thickness (mm)		0.6	0.65	0.7	0.75	0.8
Disintegration time (initial)	1 st trial	1.5	3.6	4.0	6.0	13.2
	2 nd trial	3.5	3.2	4.0	8.6	8.0
	3 rd trial	2.0	4.0	4.2	9.0	9.2
	Avg (min)	2.33	3.60	4.07	7.87	10.13
Disintegration time (after storage for 1 month)	1 st trial	10.8	16.4	16.5	16.0	18.5
	2 nd trial	8.5	13.5	14.8	18.0	16.4
	3 rd trial	12.0	10.8	15.0	18.5	20.0
	Avg (min)	10.43	13.57	15.43	17.50	18.30

As shown in Tables 9 to 11 above, Examples 1-1 to 1-5 containing succinylated gelatin exhibited small changes in disintegration time among formulations with various film thicknesses for both the initial and after storage for one month. Contrarily, Comparative Examples 1-1 to 1-5 and 2-1 to 2-5 containing either bovine or pig gelatin resulted in a large difference in disintegration time depending on the film thickness of the formulation.

In the preparation of the soft capsule formulation, the thickness of the film is one of the most important parameters which affect product qualities, and thus it is advantageous to have a broader tolerable range of such parameter during the preparation process. It can be shown that consistency in disintegration time is maintained in a larger range of film thickness when succinylated gelatin is used as a film material as compared with other types of gelatin. That is to say, the deviation of the thickness, which might occur during the preparation process, does not greatly affect the product qualities when succinylated gelatin is used as a film material.

Experimental Example 3: Evaluation of sealability of soft capsule according to gelatin types and thickness of film

In a soft capsule formulation, sealability is an important factor which is directly related to product quality. Generally, a film of a soft capsule is formed by sealing two sheets; so if sealing is not formed appropriately, the film is easily damaged during the storage and distribution of the formulation. Also, the sealability may change significantly when there is a deviation of film thickness in the preparation of formulation. Thus, it is an important task in the field of pharmaceuticals to maintain a desirable sealability of a soft capsule formulation regardless of its film thickness.

Accordingly, sealability of soft capsules having various gelatin types and film thicknesses was evaluated so as to examine the effect of gelatin types on sealabilities of soft capsules having various film thicknesses.

Specifically, a midsection of the soft capsule formulations of Examples 1-1 to 1-5, Comparative Examples 1-1 to 1-5 and 2-1 to 2-5 which have various gelatin types and thicknesses of film was cut (*see* Fig. 4A), and the filling materials were removed therefrom. Then, the thickness of the film (DL2) and the thickness of the thinnest parts of the film, *i.e.*, in an upper junction part (DL0) and a lower junction part (DL1), were measured (*see* Fig. 4B), and sealability of the upper and lower junction parts were measured using the equations below:

- Sealing rate (upper part) (%) = (DL0 / DL2) x 100
- Sealing rate (lower part) (%) = (DL1 / DL2) x 100

The sealing rate measurements are shown in Tables 12 to 14 and Figs. 5 and 6.

[Table 12]

	Ex. 1-1	Ex. 1-2	Ex. 1-3	Ex. 1-4	Ex. 1-5
Film thickness (mm)	0.6	0.65	0.7	0.75	0.8
Sealing rate of upper part (%)	55.8	72.3	80.4	88.6	90.2
Sealing rate of lower part (%)	74.6	81.7	94.5	93.5	95.6

[Table 13]

	Comp. Ex. 1-1	Comp. Ex. 1-2	Comp. Ex. 1-3	Comp. Ex. 1-4	Comp. Ex. 1-5
Film thickness (mm)	0.6	0.65	0.7	0.75	0.8
Sealing rate of upper part (%)	31.6	48.6	78.3	79.4	81.7
Sealing rate of lower part (%)	50.8	59.6	80.1	86.2	92.5

[Table 14]

	Comp. Ex. 2-1	Comp. Ex. 2-2	Comp. Ex. 2-3	Comp. Ex. 2-4	Comp. Ex. 2-5
Film thickness (mm)	0.6	0.65	0.7	0.75	0.8

Sealing rate of upper part (%)	28.5	53	72.4	83.5	86.3
Sealing rate of lower part (%)	53.6	70	77.8	89.4	94.5

As can be seen in Tables above and Figs., Examples 1-1 to 1-5 containing succinylated gelatin exhibited small changes in sealing rate among formulations with various film thicknesses. Contrarily, Comparative Examples 1-1 to 1-5 and 2-1 to 2-5 containing either bovine or pig gelatin resulted in a large difference in sealing rate depending on the thicknesses of the film.

In the preparation of a soft capsule formulation, the thickness of the film is one of the most important parameters which affect product qualities, and thus it is advantageous to have a broader range of such parameter during the preparation process. It can be shown that consistency in sealing rate is maintained in a larger range of film thickness when succinylated gelatin is used as a film material as compared with other types of gelatin. That is to say, the deviation of the thickness, which might occur during the preparation process, does not greatly affect the product qualities when succinylated gelatin is used as a film material.

Examples 2 to 5: Preparation of soft capsule formulations having various amounts of cross-linking inhibitor

In order to evaluate the effect of the cross-linking inhibitor on the soft capsule formulations, soft capsule formulations with various amounts of cross-linking inhibitor, (*i.e.*, glycine) were prepared according to Table 15 below.

[Table 15]

Component	Ingredient	Amount (mg/formulation)				
		Ex. 2	Ex. 3	Ex. 1	Ex. 4	Ex. 5
Filling material	Dutasteride	0.5	0.5	0.5	0.5	0.5
	Capmul [®] MCM	100	100	100	100	100
	Poloxamer 407	10	10	10	10	10
	Distilled water	3	3	3	3	3
Soft capsule film	Succinylated gelatin	43.0	43.0	43.0	43.0	43.0
	Glycerine	19.0	19.0	19.0	19.0	19.0
	Glycine	0.1	0.3	0.5	2.0	5.0
	Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.

Total	175.6	175.8	176.0	177.5	180.5
Amount of glycine in the soft capsule film (%)	0.16	0.48	0.80	3.13	7.46

Experimental Example 4: Evaluation of disintegration time according to amounts of cross-linking inhibitor

Soft capsule formulations of Examples 1 to 5 were separately packaged in an HDPE bottle and stored for one month under 40°C and 70% RH, and then disintegration time of each formulation was evaluated according to the method described in Experimental Example 2. The results are shown in Table 16 below.

[Table 16]

Disintegration time		Ex. 2	Ex. 3	Ex. 1	Ex. 4	Ex. 5
Initial	1 st trial	5.2	4.0	4.6	4.0	2.5
	2 nd trial	3.5	5.0	4.8	3.8	3.8
	3 rd trial	4.2	3.8	4.4	3.8	3.6
	Avg (min)	4.3	4.3	4.6	3.9	3.3
After storage for 1 month	1 st trial	16.6	9.5	5.4	4.0	3.6
	2 nd trial	10.2	13.5	3.8	3.0	1.8
	3 rd trial	9.0	6.8	3.8	6.2	2.0
	Avg (min)	11.9	9.9	4.3	4.4	2.5

As shown in Table 16 above, Examples 2 and 3 which contained glycine as a cross-linking inhibitor in amounts of, respectively, 0.1 mg (0.16 wt%) and 0.3 mg (0.48 wt%) showed a considerable increase in disintegration time due to insufficient inhibitory activity against the formation of cross-links when stored under accelerated conditions for 1 month. Thus, it can be concluded that the amount of glycine as the cross-linking inhibitor is preferably at least 0.50 wt%, based on the total weight of the soft capsule film, for maintaining consistency in disintegration time against storage time.

Experimental Example 5: Evaluation of sealability of soft capsules according to amounts of cross-linking inhibitor

The following test was conducted in order to evaluate the effects of the amounts of cross-linking inhibitor on sealability of soft capsules. For precise measurement, soft capsules of Examples 1 to 5 with the film thickness of 0.8 mm were prepared. Then, sealing rates of the upper and lower junctions were measured according to the method as described in Experimental Example 3. The sealing rate measurements are shown in Table 17 below.

[Table 17]

Sealing rate (%)	Ex. 2	Ex. 3	Ex. 1	Ex. 4	Ex. 5
Upper part	92.4	89.5	90.2	73.6	36.8
Lower part	92.8	94.1	95.6	86.1	65.4

As shown in Table 17 above, the sealing rates decreased as the amount of glycine as the cross-linking inhibitor increased because glycine negatively affected the properties of the capsule film. Particularly, the sealing rate of Example 5 containing glycine in an amount of 7.46 wt% significantly decreased as compared with those of Examples 1 to 4 containing glycine in amounts of 0.16 to 3.13 wt%. Thus, in consideration of sealing rate, the amount of glycine to be used is preferably 5 wt% at most.

Examples 6 to 9: Preparation of soft capsule formulations having various amounts of succinylated gelatin

In order to evaluate the effect of the succinylated gelatin on the soft capsule formulations, soft capsule formulations were prepared based on Example 1, varying the amount of succinylated gelatin according to Table 18 below.

[Table 18]

Component	Ingredient	Amount (mg/formulation)				
		Ex. 6	Ex. 7	Ex. 1	Ex. 8	Ex. 9
Filling material	Dutasteride	0.5	0.5	0.5	0.5	0.5
	Capmul® MCM	100	100	100	100	100
	Poloxamer 407	10	10	10	10	10
	Distilled water	3	3	3	3	3
Soft capsule	Succinylated gelatin	23.0	33.0	43.0	53.0	63.0
	Glycerine	19.0	19.0	19.0	19.0	19.0

film	Glycine	0.5	0.5	0.5	0.5	• 0.5
	Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.
Total amount		156.0	166.0	176.0	186.0	196.0
Amount of gelatin in the soft capsule film (%)		54.12	62.86	68.80	73.10	76.36
Amount of glycine in the soft capsule film (%)		1.18	0.95	0.80	0.69	0.61

Experimental Example 6: Evaluation of disintegration time according to amounts of succinylated gelatin

Soft capsule formulations of Examples 1 and 6 to 9 were separately packaged in an HDPE bottle and stored for one month under 40°C and 70% RH, and then disintegration time of each formulation was evaluated according to the method described in Experimental Example 2. The results are shown in Table 19 below.

[Table 19]

Disintegration time		Ex. 6	Ex. 7	Ex. 1	Ex. 8	Ex. 9
Initial	1 st trial	1.8	4.0	4.6	4.5	10.6
	2 nd trial	3.2	5.6	4.8	8.5	5.6
	3 rd trial	3.0	1.6	4.4	5.2	9.5
	Avg (min)	2.7	3.7	4.6	6.1	8.6
After storage for 1 month	1 st trial	3.0	6.0	5.4	6.0	16.0
	2 nd trial	3.2	6.2	3.8	6.5	14.5
	3 rd trial	1.5	4.0	3.8	8.2	14.2
	Avg (min)	2.6	5.4	4.3	6.9	14.9

As shown in Table 19 above, the formulation of Example 9 which contained succinylated gelatin in an amount of 76.36 wt% showed a considerable increase in disintegration time when stored under the accelerated conditions for 1 month despite the fact that the amount of glycine as the cross-linking inhibitor was within the preferable amount range, *i.e.*, 0.50 to 5.0 wt%. Thus, it can be concluded that the amount of the succinylated gelatin to be used is preferably 75 wt% at most, based on the total weight of the soft capsule film, for maintaining consistency in disintegration time against storage time.

Experimental Example 7: Evaluation of sealability of soft capsules according to amounts of succinylated gelatin

The following test was conducted in order to evaluate the effects of the amounts of succinylated gelatin on sealability of soft capsules. For precise measurement, soft capsules of Examples 1 and 6 to 9 with the film thickness of 0.8 mm were prepared. Then, sealing rates of the upper and lower junction parts were measured according to the method as described in Experimental Example 3. The sealing rate measurements are shown in Table 20 below.

[Table 20]

Sealing rate (%)	Ex. 6	Ex. 7	Ex. 1	Ex. 8	Ex. 9
Upper part	26.5	79.2	90.2	89.5	91.8
Lower part	56.8	90.6	95.6	96.8	95.5

As shown in Table 20 above, the sealing rates of the formulations of Examples 1 and 7 to 9 which contained succinylated gelatin in amounts of at least 62.86 wt% were good; whereas the sealing rate of the formulation of Example 6 which contained succinylated gelatin in an amount of 54.12 wt% was significantly low. Accordingly, in consideration of sealing rate, the amount of the succinylated gelatin to be used is preferably at least 60 wt%.

What is claimed is:

1. An oral soft capsule formulation comprising:
 - (1) a filling material comprising dutasteride; and
 - (2) a soft capsule film containing succinylated gelatin, a plasticizer, and a cross-linking inhibitor.
2. The oral soft capsule formulation of claim 1, wherein the filling material is an emulsion.
3. The oral soft capsule formulation of claim 1, wherein the filling material contains a solvent selected from the group consisting of polysorbates, propylene glycol, vegetable oils containing 10 to 20% of ethanol, glyceryl caprylate/caprate, methyl cellulose, stearyl monoester of glycerol, monounsaturated fatty acid ester of glycerol, and a mixture thereof.
4. The oral soft capsule formulation of claim 1, wherein the filling material contains a surfactant selected from the group consisting of polysorbates, sorbitan fatty acid esters, castor oils, substituted castor oils, polyoxyethylene-polyoxypropylene copolymers, mono- or di-glycerides of caprylic/capric acid, polyoxyethylene-polyoxypropylene block copolymer, and a mixture thereof.
5. The oral soft capsule formulation of claim 1, wherein the filling material contains a 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.
6. The oral soft capsule formulation of claim 1, wherein the succinylated gelatin is comprised in an amount of 60 to 75 wt%, based on the total weight of the soft capsule film.
7. The oral soft capsule formulation of claim 1, wherein the plasticizer is selected from the group consisting of glycerine, sorbitol, mannitol, propylene glycol,

polyethylene glycol, sugar alcohol, monosaccharide, disaccharide, oligosaccharide, and a mixture thereof.

8. The oral soft capsule formulation of claim 1, wherein the plasticizer is comprised in an amount of 5 to 45 wt%, based on the total weight of the soft capsule film.
9. The oral soft capsule formulation of claim 1, wherein the cross-linking inhibitor is selected from the group consisting of glycine, citric acid, and a mixture thereof.
10. The oral soft capsule formulation of claim 1, wherein the cross-linking inhibitor is comprised in an amount of 0.5 to 5 wt%, based on the total weight of the soft capsule film.
11. The oral soft capsule formulation of claim 1, wherein the soft capsule releases at least 85% of dutasteride within 15 minutes.
12. The oral soft capsule formulation of claim 11, wherein the soft capsule releases at least 90% of dutasteride within 30 minutes.

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Fig. 1

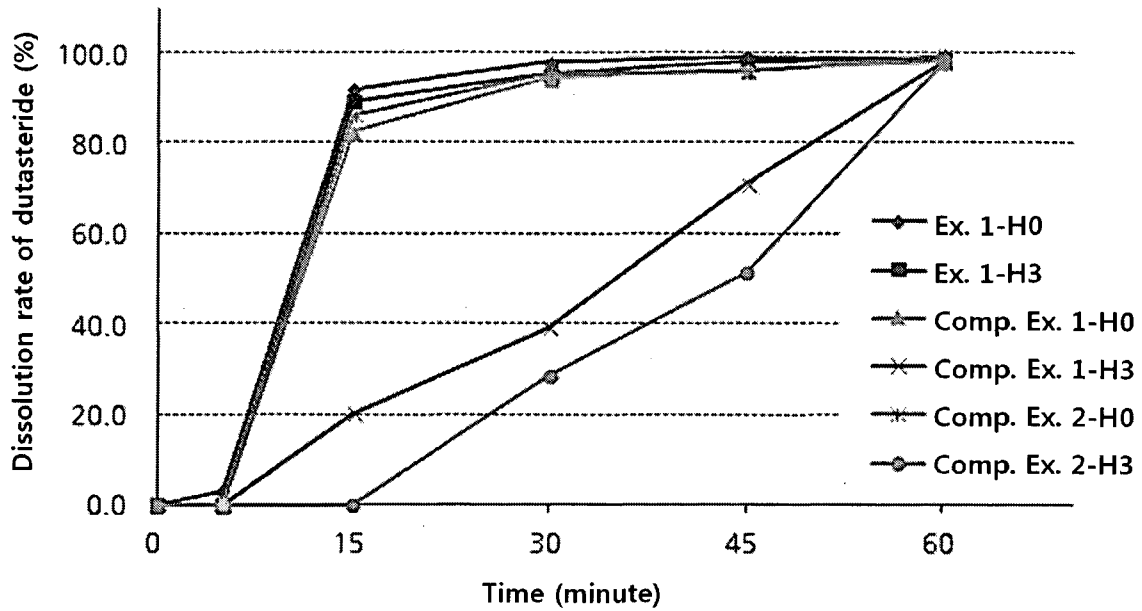
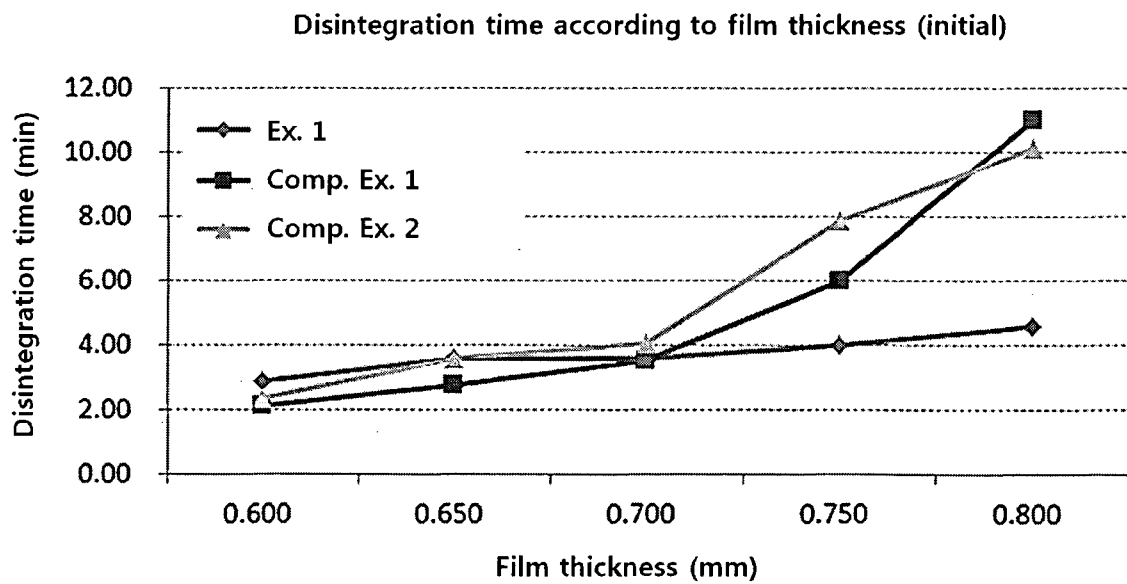
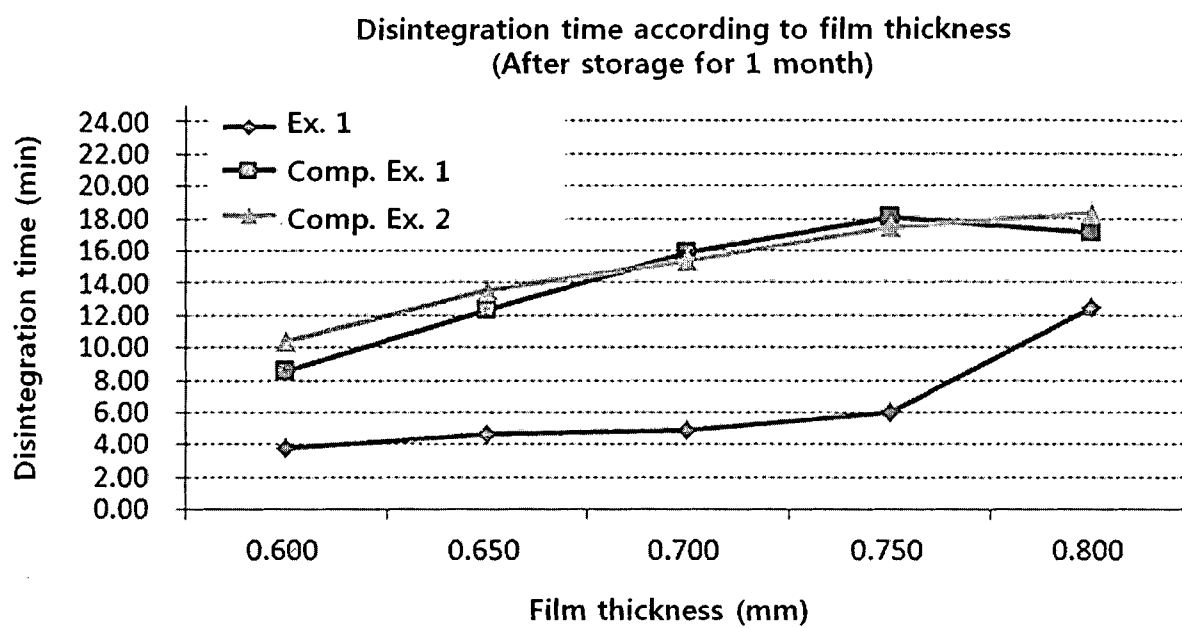


Fig. 2



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Fig. 3



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Fig. 4A

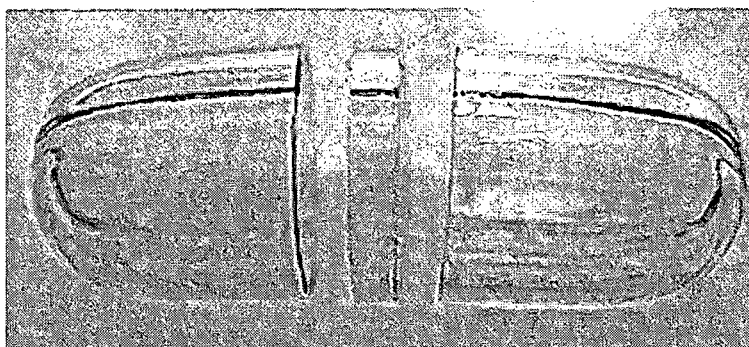
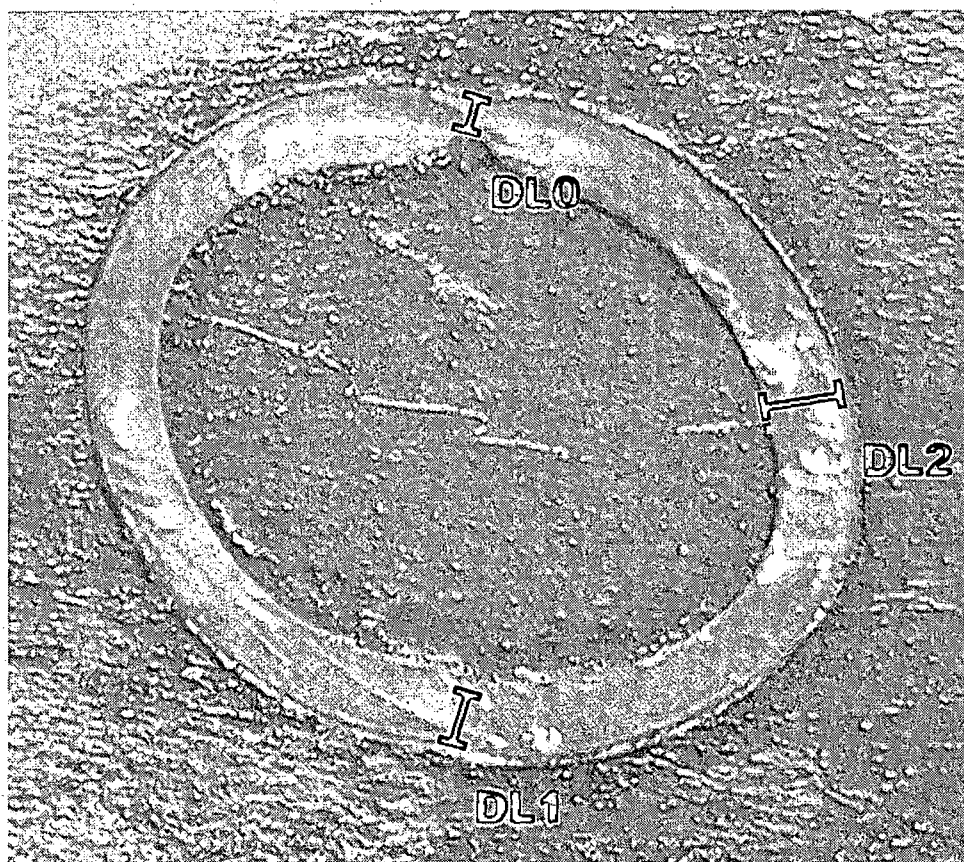


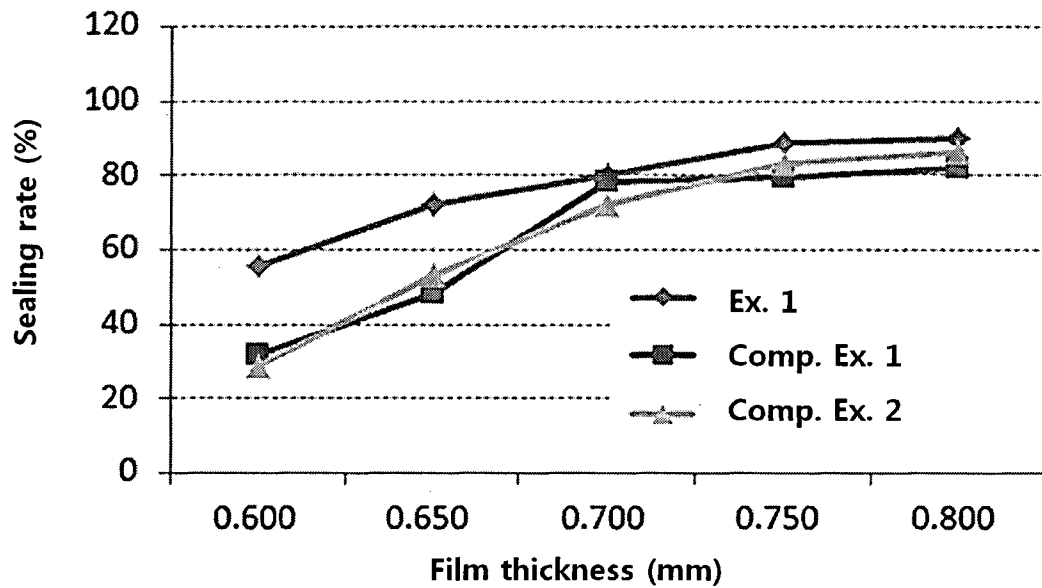
Fig. 4B



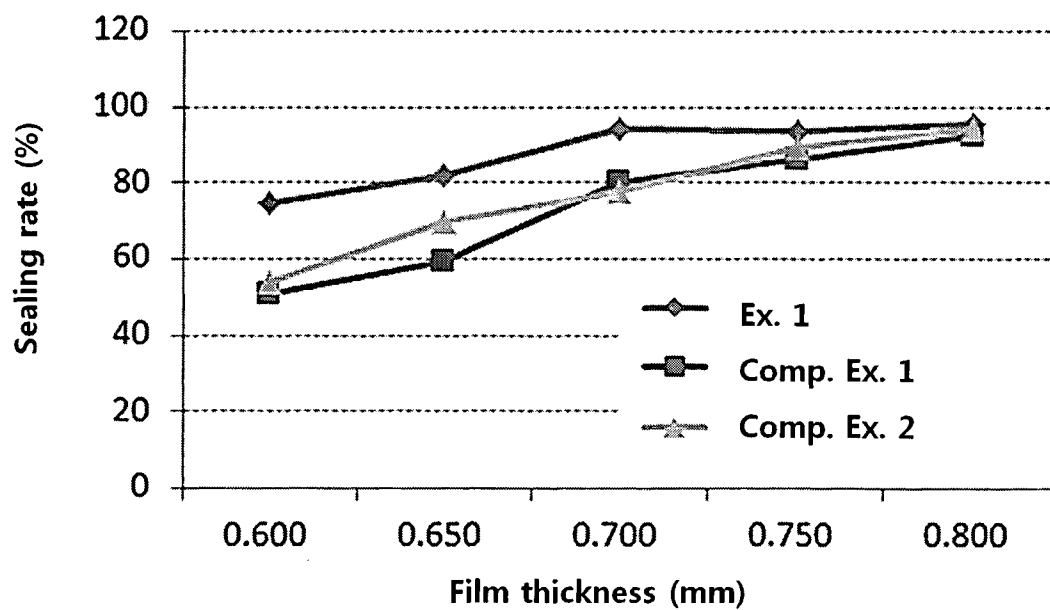
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Fig. 5

Sealing rate according to film thickness
(upper junction part)

**Fig. 6**

Sealing rate according to film thickness
(lower junction part)



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2014/005753**A. CLASSIFICATION OF SUBJECT MATTER****A61K 9/48(2006.01)i, A61K 31/58(2006.01)i, A61P 35/00(2006.01)i, A61P 17/14(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 9/48; A61K 31/58; A01N 43/42; A61K 9/107; A61K ; A61K 31/473; A61K 31/56; A61K 31/44; A61P 35/00; A61P 17/14

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: soft gelatin capsule, succinylated gelatin, dutasteride, cross-linking inhibitor, glycine, citric acid**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010-092596 A1 (GENEPHARM INDIA PRIVATE LIMITED) 19 August 2010 See pages 5-7, 9, 14; claims 1-2.	1-12
Y	WO 03-103582 A2 (IVAX CORPORATION et al.) 18 December 2003 See abstract; paragraphs [0021], [0024], [0037], [0042]; and table J.	1-12
A	WO 2010-124039 A1 (GLAXOSMITHKLINE LLC) 28 October 2010 See abstract; and claim 1.	1-12
A	US 5874106 A (ADESUNLOYE, A. T. et al.) 23 February 1999 See abstract; and claims 1, 7-8.	1-12
A	KR 10-1055412 B1 (BCWORLD PHARM. CO., LTD.) 8 August 2011 See abstract; and claim 1.	1-12

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

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Date of the actual completion of the international search

08 October 2014 (08.10.2014)

Date of mailing of the international search report

08 October 2014 (08.10.2014)

Name and mailing address of the ISA/KR

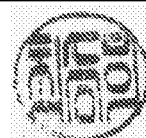
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2014/005753

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