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Independent part
of tamsulosin

FIG. 1

Independent part of tadalafil

Independent part of tamsulosin

Abstract: Disclosed are a capsule composite formulation for preventing or treating erectile dysfunction and benign prostatic hyperplasia comprising tadalafil and tamsulosin, and a method of preparing the same. The capsule composite formulation of the present invention enables the complete separation of the two pharmaceutically active ingredients and minimizes reactivity between the active ingredients, and thus provides excellent product stability over time, thereby maximizing the therapeutic effects thereof.
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DESCRIPTION

PHARMACEUTICAL CAPSULE COMPOSITE FORMULATION
COMPRISING TADALAFIL AND TAMSULOSIN

FIELD OF THE INVENTION

The present invention relates, in general, to a capsule composite formulation containing tadalafil and tamsulosin for preventing or treating erectile dysfunction and benign prostatic hyperplasia, and a method of manufacturing the same.

BACKGROUND OF THE INVENTION

Erectile dysfunction and benign prostatic hyperplasia are diseases common to males in their 50's or older. Erectile dysfunction is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis during sexual performance due to various causes including cardiovascular diseases, diabetes, hormonal deficiency, etc. Benign prostatic hyperplasia is an increase in size of the prostate which causes dysuresia, with the concomitant or consequent onset of complications such as urinary infection, urolithiasis, hematuria, renal failure, etc.

Tadalafil is a substance belonging to phosphodiesterase 5 (PDE 5) inhibitors such as sildenafil and vardenafil. Tadalafil has a half life at least 3 times longer than sildenafil and vardenafil. Tadalafil was originally developed by Icos Corporation. Eli Lilly and Company currently offers Cialis®, a treatment for erectile dysfunction containing tadalafil, and Adcirca®, a treatment for pulmonary arterial hypertension, on the market. Cialis® was approved in 2011 by the FDA as a treatment for benign prostatic hyperplasia.

Tamsulosin is an alpha blocker effective in the treatment of symptoms of benign prostatic hyperplasia, chronic prostatitis, and chronic abdominal pain. In addition, tamsulosin is also effective in the treatment of urolithiasis via the skeletal muscle relaxation mechanism by blocking alpha. Tamsulosin was first developed
by Yamanouchi Phannaceutical Co., Ltd. in 1996, and various products containing tamsulosin hydrochloride are known (Korean Patent Laid-open Publication No. 2006-105976, etc.).

Erectile dysfunction and benign prostatic hyperplasia may occur alone and independent of each other. However, erectile dysfunction and benign prostatic hyperplasia are likely to occur in the same patient, and, according to a study, 8.5 patients out of 10 erectile dysfunction patients in Korea also had prostate gland diseases. Accordingly, there is a need for the development of a therapeutic method to treat the two diseases simultaneously with excellent stability and efficacy.

In particular, although the action mechanism of tadalafil differs from that of tamsulosin, they are both effective in the treatment of benign prostatic hyperplasia. Therefore, a more excellent therapeutic effect may be obtained by administering both tadalafil and tamsulosin simultaneously or at intervals as a combined therapy, and also adverse effects due to long term administration may be alleviated by reducing the dosage of each individual drug. However, the combined therapy, which requires administration of at least two drugs as individual units may deteriorate drug compliance, and thus may cause much inconvenience to patients who are under continuous medication. In addition, the combined therapy also causes much inconvenience to patients who continuously manage their social activities by requiring them to carry with them and administer several individual drug units.

Accordingly, there is an urgent need for the development of a composite formulation (also called as a combination drug) containing at least two active ingredients necessitating a combined therapy. However, the development of a composite formulation containing at least two active ingredients raises problems as follows. First, the composite formulation requires that the different active ingredients to be used therein be easily and freely combined but unexpected difficulties may occur due to various problems caused by the pharmacokinetic and pharmaceutical characteristics of the drugs. Second, the amount of a composition containing the active ingredients and a pharmaceutically acceptable excipient should be in the range suitable as a medicine. Therefore, when the amount of active ingredients to be combined is excessive or too little it may be a difficult to prepare them into a composition with an appropriate mass. Third, in
manufacturing a combination drug, the dissolution rate and stability of the composite formulation may be deteriorated by the interaction between the different active ingredients of the composite formulation, thus making it difficult to develop a fixed composite formulation for administration in a physicochemically stable form. The composite formulation may be manufactured in the form of a double-layered or a triple-layered tablet to separate each active ingredient into each separate layer. However, the above method will require a special manufacturing facility such as a tableting machine for preparing double-layered or triple-layered tablets, and also interactions may occur among the ingredients in neighboring regions of the tablets. In the contemporary art, it has not been possible to establish a perfect separation between ingredients.

Accordingly, there has been a need for the development of a novel composite formulation with excellent medication convenience and stability, while being capable of providing the effects of preventing and treating erectile dysfunction and benign prostatic hyperplasia.

**SUMMARY OF THE INVENTION**

Accordingly, an object of the present invention is to provide a composite formulation with excellent medication convenience, dissolution rate and stability, while being capable of providing the effects of preventing and treating both erectile dysfunction and benign prostatic hyperplasia.

In order to accomplish the above object(s), the present invention provides a capsule composite formulation for preventing or treating erectile dysfunction and benign prostatic hyperplasia comprising: an independent part of tadalafil containing tadalafil or a pharmaceutically acceptable salt thereof; and an independent part of tamsulosin containing tamsulosin or a pharmaceutically acceptable salt thereof, in a separate state.

In order to accomplish another object, the present invention also provides a method of manufacturing the above capsule composite formulation, comprising: a) mixing tadalafil or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable additive, and granulating the mixture, or tableting the
granules thus obtained into a tablet; b) mixing tamsulosin or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable additive, and granulating the mixture, or tableting the granules thus obtained into a tablet; and c) filling into a hard capsule the tadalafil granules or tablets prepared in step a), and the tamsulosin granules or tablets prepared in step b), in a separate state.

The capsule composite formulation of the present invention is prepared by efficiently filling a pharmaceutical composition into the limited internal capacity of a capsule. Therefore, the capsule composite formulation of the present invention has advantages in that it can provide high-dose active ingredients into a small sized capsule, thereby having high productivity and providing patients with improved convenience in taking the medicine. Additionally, the capsule composite formulation of the present invention has an excellent dissolution rate because the pharmaceutically active ingredients within the capsule are separated, thus having a low impact on the dissolution rate between the pharmaceutically active ingredients. Furthermore, the capsule composite formulation of the present invention has minimal reactivity between active ingredients, thus providing excellent product stability over time and is capable of maximizing the therapeutic effect of the pharmaceutically active ingredients.

**BRIEF DESCRIPTION OF THE DRAWINGS**

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 is a diagram of a capsule composite formulation prepared according to an exemplary embodiment of the present invention;

FIG. 2 and FIG. 3 respectively show the results of a dissolution test for tadalafil and tamsulosin conducted according to Test Example 1;

FIG. 4 and FIG. 5 respectively show the individual impurities and total impurities of tadalafil according to Test Example 2; and

FIG. 6 and FIG. 7 respectively show the individual impurities and total impurities of tamsulosin according to Test Example 2.
The present invention is described in further detail below.

The term, "a composite formulation" used herein, refers to a formulation which includes at least two kinds of drugs or active ingredients within a single dosage unit such as a tablet or capsule.

The capsule composite formulation of the present invention comprises i) an independent part of tadalafil containing tadalafil or a pharmaceutically acceptable salt thereof; and ii) an independent part of tamsulosin containing tamsulosin or a pharmaceutically acceptable salt thereof, in a separate state.

FIG. 1 is a diagram illustrating the capsule composite formulation according to an exemplary embodiment of the present invention, in which the independent part of tadalafil and the independent part of tamsulosin respectively form a separate independent layer within the hard capsule to be filled. More specifically, in an exemplary embodiment, the capsule composite formulation may comprise i) an independent tadalafil layer containing tadalafil or a pharmaceutically acceptable salt thereof; and ii) an independent tamsulosin layer containing tamsulosin or a pharmaceutically acceptable salt thereof, in a separate state.

The capsule composite formulation of the present invention has a therapeutic effect of preventing or treating erectile dysfunction and benign prostatic hyperplasia.

The independent part of tadalafil and the independent part of tamsulosin may contain water in the range of 5% or less, respectively.

The pharmaceutically acceptable salt of tamsulosin may be, for example, tamsulosin hydrochloride.

In the capsule composite formulation of the present invention, the independent part of tadalafil and the independent part of tamsulosin may respectively be in the form of a granule, a tablet, or a combination thereof.

In other words, the composite formulation of the present invention may comprise i) a tadalafil granule or a tadalafil tablet containing tadalafil or a pharmaceutically acceptable salt thereof; and ii) a tamsulosin granule or a tamsulosin tablet containing tamsulosin or a pharmaceutically acceptable salt
thereof, in a separate state.

Preferably, at least one of the independent part of tadalafil and the independent part of tamsulosin may be in the form of a tablet. For example, the capsule composite formulation may comprise a) a tadalafil tablet and a tamsulosin granule, b) a tadalafil granule and a tamsulosin tablet, or c) a tadalafil tablet and a tamsulosin tablet filled into a hard capsule. A diagram of a capsule composite formulation according to an embodiment of the present invention which comprises a tadalafil tablet and a tamsulosin granule filled into a hard capsule is shown in Fig. 1.

Tadalafil or a pharmaceutically acceptable salt thereof may be contained in the range of from 3 to 7 wt% relative to the total weight of the independent part of tadalafil. Preferably, tadalafil or a pharmaceutically acceptable salt thereof may be administered to an adult at about 5 mg daily.

Tamsulosin or a pharmaceutically acceptable salt thereof may be contained in the range of from 0.1 to 0.2 wt% relative to the total weight of the independent part of tamsulosin. Tamsulosin or a pharmaceutically acceptable salt thereof may be administered to an adult, for example, at about 0.2 mg or 0.4 mg daily.

In the capsule composite formulation of the present invention, the independent part of tadalafil and the independent part of tamsulosin may each independently contain a pharmaceutically acceptable additive, respectively, for example, a diluent, a disintegrating agent, a binder, a stabilizing agent, a lubricant, a coloring agent, or a mixture thereof.

Examples of the diluent may include microcrystalline cellulose, lactose, Ludipress, mannitol, monocalcium phosphate, starch, low-substituted hydroxypropylcellulose, and a mixture thereof. The diluent may be used in the amount of from about 1 to 95 wt% relative to the total weight of each independent part, and preferably from about 5 to 95 wt%.

Examples of the disintegrating agent may include crosspovidone, sodium starch glycolate, sodium crosscarmellose, low-substituted hydroxypropylcellulose, starch, alginic acid or a sodium salt thereof, and a mixture thereof, which can serve for stable disintegration of active ingredients. The disintegrating agent may be used in the amount of from about 0.1 to 30 wt% relative to the total weight of each
independent part, and preferably from about 2 to 15 wt%.

Examples of the binder may include hydroxypropylcellulose, hydroxypropylmethylcellulose, hypromellose, polyvinyl acetate, polyvinyl pyrrolidone, copovidone, macrogol, sodium lauryl sulfate, light anhydrous silicic acid, synthetic aluminum silicate, a silicate derivative such as calcium silicate or magnesium metasilicate aluminate, phosphate such as calcium hydrogen phosphate, carbonate such as calcium carbonate, pregelatinized starch, gums such as acacia gum, gelatin, cellulose derivatives such as ethyl cellulose, and a mixture thereof. The binder may be used in the amount of from about 0.1 to 20 wt% relative to the total weight of each independent part, and preferably from about 2 to 10 wt%.

Examples of the lubricant may include metal stearates such as stearic acid, calcium stearate, or magnesium stearate; talc; colloidal silica; sucrose fatty acid ester; hydrogenated vegetable oil; high melting point wax; glyceryl fatty acid esters; glycerol dibehenate; and a mixture thereof. The lubricant may be used in the amount of from about 0.3 to 5 wt% relative to the total weight of each independent part, and preferably from about 0.5 to 3 wt%.

In the present invention, the independent part of tadalafil and the independent part of tamsulosin may be each independently coated with a pharmaceutically acceptable coating material. The coating material to be used may include any polymer conventionally used in the related art. For example, the independent part of tadalafil may be coated by the commercial Opadry® manufactured by Colorcon Ltd. or the like as the coating material. Examples of the coating material for the independent part of tamsulosin may include, for example, methyl cellulose, ethyl cellulose, polyvinyl acetate, polyvinyl alcohol, polyvinyl pyrrolidone, povidone, mefhacrylate-ethyl acrylate copolymer, triacetin, propylene glycol, hydroxyethylcellulose, hydroxypropyl methylcellulose, etc., but are not limited thereto.

Preferably, the amount of the coating material should be maintained at the minimal level for the preparation of optimal-sized formulations and their efficient manufacture. For example, the coating material may be used in the amount of from about 0.1 to 20 wt% relative to the total weight of each independent part, and preferably from about 2 to 10 wt%.
The capsules to be used in manufacturing the capsule composite formulation of the present invention are not particularly limited, but any conventional hard capsules used in medicinal products may be used. For example, any hard capsule containing hypromellose, pullulan, gelatin, polyvinyl alcohol, or a mixture thereof may be used.

The size of the hard capsule to be used in the capsule composite formulation of the present invention is not particularly limited, but any capsule with a conventional size used in the medicinal products may be used. Each size of the capsule may have a varying amount of an internal capacity depending on the size number, for example, size No. 0 has about 0.68 mL, size No. 1 about 0.47 mL, size No. 2 about 0.37 mL, size No. 3 about 0.27 mL, size No. 4 about 0.20 mL, etc. Preferably, the capsule size should be as small as possible for the convenience of a patient to take the composite formulation of the present invention. However, due to the limitation on the amount to be filled into the capsule, capsule Nos. 0, 1, 2, 3 and 4, and preferably, capsule Nos. 0, 1, 2, and 3, may be used.

The capsule composite formulation of the present invention employs tadalafil, a PDE 5 inhibitor, as the first active ingredient, thereby having therapeutic effects of preventing and treating erectile dysfunction and benign prostatic hyperplasia, whereas it employs tamsulosin, an α1a blocker, as the second active ingredient, thereby having continuous therapeutic effects for preventing and treating dysuresia diseases, such as benign prostatic hyperplasia, chronic prostatitis, chronic abdominal pain, urolithiasis, etc.

Suitable routes for administration of the capsule composite formulation of the present invention may include oral, buccal, and sublingual routes.

In the capsule composite formulation of the present invention, a pharmaceutical composition is efficiently filled into a capsule having a limited internal capacity, and thus it is possible to fill high-dose active ingredients into a small-sized capsule. Accordingly, the capsule composite formulation of the present invention can be manufactured with high productivity, and it also provides
patients with improved convenience in taking medicines. Additionally, the two active ingredients, tadalafil and tamsulosin, are included within a hard capsule in a separate state, and thus the two ingredients can be completely separated. Therefore, the two active ingredients have little mutual impact on their dissolution rate, thus enabling an overall excellent dissolution rate.

Furthermore, the minimized reactivity between the active ingredients contributes to product stability over time thereby maximizing the therapeutic effect, and also an existing analysis method for the evaluation of stability over time of a single formulation can be used, without necessities for developing additional methods.

The capsule composite formulation of the present invention may be manufactured by a method including: a) mixing tadalafil or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable additive, and granulating or tableting the mixture; b) mixing tamsulosin or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable additive, and granulating or tableting the mixture; and c) filling the tadalafil granules or tablets prepared in step a), and the tamsulosin granules or tablets prepared in step b) into a hard capsule, in a separate state.

In step a) and step b), tablets may be manufactured by tableting the granules obtained by granulation. More specifically, tablets may be manufactured using a tableting machine according to a conventional method. Preferably, the tablets thus manufactured may have a suitable hardness, for example, an average hardness in the range of from 1 to 30 kp after tableting.

Preferably, at least one of step a) and step b) may include tableting, and thus, at least one of tadalafil and tamsulosin may be filled into a capsule in the form of a tablet. For example, the capsule composite formulation may be manufactured by performing tableting in step a), performing granulation in step b) and filling a tadalafil tablet and a tamsulosin granule, in a separate state, into a hard capsule.

Additionally, the method of manufacturing a capsule composite formulation may further include coating the granules or tablets, obtained by the granulation or
the tableting in step a) and step b), with a pharmaceutically acceptable coating material. For example, the capsule composite formulation may be manufactured by performing coating after tableting of tadalafil in step a), performing coating after granulation of tamsulosin in step b), and filling a coated tadalafil tablet and a coated tamsulosin granule, in a separate state, into a hard capsule. Examples of the coating material suitable for tadalafil and tamsulosin are the same as described above.

The present invention is further described and illustrated in examples provided below, which are, however, not intended to limit the scope of the present invention.

**Example 1: A capsule composite formulation I**

<table>
<thead>
<tr>
<th>Part of Tadalafil</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tadalafil</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>Mannitol</td>
<td>54.8 mg</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>3.3 mg</td>
</tr>
<tr>
<td>Sodium lauryl sulfate</td>
<td>0.3 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>16.1 mg</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.1 mg</td>
</tr>
<tr>
<td>Opadry® yellow</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Purified water</td>
<td>(38.0 mg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part of Tamsulosin</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamsulosin hydrochloride</td>
<td>0.2 mg</td>
</tr>
<tr>
<td>Polyvinyl acetate dispersion</td>
<td>22.84 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>123.5 mg</td>
</tr>
<tr>
<td>Hypromellose</td>
<td>5.5 mg</td>
</tr>
<tr>
<td>Povidone</td>
<td>0.36 mg</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>0.27 mg</td>
</tr>
<tr>
<td>Methacrylate-ethyl acrylate copolymer</td>
<td>2.05 mg</td>
</tr>
<tr>
<td>Triacetin</td>
<td>0.36 mg</td>
</tr>
</tbody>
</table>
The ingredients in powder form, corresponding to the independent part of tadalafil, were mixed, and the mixture was tableted by a circular punch having a diameter of 5.5 mm. The resulting tadalafil tablets were coated with a coating solution, i.e., a solution of Opadry® yellow (Colorcon Ltd.) in purified water.

Additionally, the ingredients corresponding to the independent part of tamsulosin were mixed in powder form, and the mixture was prepared into granules. The resulting tamsulosin granules were coated with an inner coating solution, i.e., a solution of povidone, propylene glycol and polyvinyl acetate in water, and then coated further with an external coating solution, i.e., a solution of methacrylate-ethyl acrylate copolymer and triacetin in water.

The tadalafil tablets and the tamsulosin granules thus coated were filled into hard capsules No. 1 having hypromellose as a capsule material, and manufactured into a capsule composite formulation containing 5 mg of tadalafil and 0.2 mg of tamsulosin hydrochloride.

Example 2: A capsule composite formulation II

A capsule composite formulation containing 5 mg of tadalafil and 0.2 mg of tamsulosin hydrochloride was manufactured in the same manner as in Example 1, except that the hard capsule used had pullulan as a capsule material.

Example 3: A capsule composite formulation III

A capsule composite formulation containing 5 mg of tadalafil and 0.2 mg of tamsulosin hydrochloride was manufactured in the same manner as in Example 1, except that the hard capsule used had gelatin as a capsule material.

Comparative Example 1: A simple mixed tablet composite formulation

tadalafil 5.0 mg
A mixture of the above ingredients was subjected to wet granulation using a binder, i.e., a solution of hydroxypropylcellulose and sodium lauryl sulfate in water, and then sieved with a 30 mesh sieve and dried.

The dried resultant was added with mannitol, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate, and then tableted by a tableting machine.

The tablet thus obtained which contains tadalafil and tamsulosin was then coated with a coating solution, i.e., a solution of Opadry® yellow in purified water. As a result, a simple mixed tablet composite formulation containing 5 mg of tadalafil and 0.2 mg of tamsulosin hydrochloride was obtained.

**Comparative Example 2: A double-layered tablet composite formulation**

- **<Tadalafil-containing layer>**
  - tadalafil 5.0 mg
  - mannitol 54.8 mg
  - hydroxypropylcellulose 3.3 mg
  - sodium lauryl sulfate 0.3 mg
  - microcrystalline cellulose 16.1 mg
  - sodium starch glycolate 4.5 mg
  - Magnesium stearate 1.lmg
  - Opadry® yellow 2.5 mg

- **<Tamsulosin-containing layer>**
  - tamsulosin hydrochloride 0.2 mg
  - mannitol 54.8 mg
  - hydroxypropylcellulose 3.3 mg
  - sodium lauryl sulfate 0.3 mg
  - microcrystalline cellulose 16.1 mg
  - sodium starch glycolate 4.5 mg
  - Magnesium stearate 1.lmg
  - Opadry® yellow 2.5 mg
purified water (38.0 mg)

<Tamsulosin containing layer>
tamsulosin hydrochloride 0.2 mg
polyvinyl acetate dispersion 22.84 mg
microcrystalline cellulose 123.5 mg
hypermellose 5.5 mg
povidone 0.36 mg
propylene glycol 0.27 mg
methacrylate-ethyl acrylate copolymer 2.05 mg
triacetin 0.36 mg
sucrose stearate 0.2 mg
purified water (100.6 mg)

First, in order to prepare a tadalafil-containing layer, tadalafil was subjected to wet granulation using a binder, i.e., a solution of hydroxypropylcellulose and sodium lauryl sulfate in water, and then sieved with a 30 mesh sieve and dried. The dried resultant was added with mannitol, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate, and then tableted by a tableting machine.

Additionally, the ingredients for the tamsulosin-containing layer were mixed and then tableted along with the tadalafil tablet prepared in advance to manufacture a double-layered tablet.

The double-layered tablet thus obtained was then coated with a coating solution, i.e., a solution of Opadry® yellow in purified water. As a result, a double-layered tablet composite formulation containing 5 mg of tadalafil and 0.2 mg of tamsulosin hydrochloride was obtained.

Test Example 1: Evaluation of dissolution

The tadalafil and tamsulosin hydrochloride composite formulations prepared in Examples 1 - 3 and Comparative Examples 1 and 2 were evaluated for their dissolution according to the conditions described below.
<Tadalafil dissolution conditions>
A dissolution test was performed according to the Paddle method of the U.S. Pharmacopeia (USP) dissolution test using 1000 mL of 0.5% sodium lauryl sulfate (SLS). Samples for the dissolution test were collected at the initial stage, and after 5 min, 10 min, 15 min, 30 min, 45 min and 60 min, respectively, and the tadalafil dissolution rate was measured via liquid chromatography under the conditions described below.

- column: a column in which a stainless steel tube having an inner diameter of about 4.6 mm and a length of about 5 cm is filled with an octadecylsilyl (ODS)-silica gel for liquid chromatography having a particle size of 3.5 \( \mu \)m (Zorbax SB-C8, Agilent Zorbax)
- detector: UV spectrophotometer (measured at 225nm of wavelength)
- flow rate: 2.0 mL/min
- input volume: 50 \( \mu \)L
- column temperature: 40°C
- mobile phase: water/methanol (50:50, v/v)
- dissolution medium: 1000 mL of 0.5% sodium lauryl sulfate (SLS)

<Tamsulosin dissolution conditions>
A dissolution test was performed according to the Paddle method of the USP dissolution test with a sinker at 100 rpm using 500 mL of the second fluid for disintegration test, i.e., pH 6.8 buffer. Samples for the dissolution test were collected in the amount of 10 mL at the initial stage, and after 15 min, 30 min, 60 min, 90 min, 120 min, 180 min, 300 min, 360 min, and 480 min, respectively. The tamsulosin dissolution rate of the samples thus collected was measured via liquid chromatography under the conditions described below.

- column: a column in which a stainless steel tube having an inner diameter of about 4.6 mm and a length of about 15 cm is filled with an octadecylsilyl (ODS)-silica gel for liquid chromatography having a particle size of 5 \( \mu \)m (Zorbax SB-C8, Agilent Zorbax)
- detector: UV spectrophotometer (measured at 225nm of wavelength)
- flow rate: adjusted to retain tamsulosin for about 6 min
- input volume: 500 \( \mu \)L
- column temperature: 40°C
- mobile phase: 8.7 mL of perchloric acid and 3.0 g of sodium hydroxide were dissolved in 1900 mL of water. The mixture was adjusted to pH 2.0 with sodium hydroxide, and then added with water to 2000 mL. 1400 mL of the resulting solution was added with 600 mL of acetonitrile to obtain a mobile phase.

- dissolution medium: 500 mL of the second fluid for disintegration test (17 g of KH₂PO₄ and 16.75 g of Na₂HPO₄ were dissolved in 10 L of purified water to prepare pH 6.8 buffer).

The result of tadalafil dissolution is shown in Table 1 and FIG. 2, and the result of tamsulosin dissolution is shown in Table 2 and FIG. 3.

<table>
<thead>
<tr>
<th>[Table 1]</th>
<th>Tadalafil dissolution rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
</tr>
<tr>
<td>Ex.1</td>
<td>0.0%</td>
</tr>
<tr>
<td>Ex.2</td>
<td>0.0%</td>
</tr>
<tr>
<td>Ex.3</td>
<td>0.0%</td>
</tr>
<tr>
<td>Comp. Ex.1</td>
<td>0.0%</td>
</tr>
<tr>
<td>Comp. Ex.2</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

As shown in Table 1 and FIG. 2, the capsule composite formulations prepared in Examples 1 to 3 and the simple mixed tablet composite formulations prepared in Comparative Example 1 revealed excellent tadalafil dissolution rates. However, in the case of the double-layered tablet composite formulation prepared in Comparative Example 2, the tadalafil dissolution rate was decreased by about 5% or more because part of tadalafil was in contact with a sustained release agent needed for tamsulosin.
<table>
<thead>
<tr>
<th></th>
<th>Tamsulosin dissolution rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
</tr>
<tr>
<td>Ex.1</td>
<td>0.0%</td>
</tr>
<tr>
<td>Ex.2</td>
<td>0.0%</td>
</tr>
<tr>
<td>Ex.3</td>
<td>0.0%</td>
</tr>
<tr>
<td>Comp. Ex.1</td>
<td>0.0%</td>
</tr>
<tr>
<td>Comp. Ex.2</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

As shown in Table 2 and FIG. 3, the capsule composite formulations prepared in Examples 1 to 3 and the double-layered composite formulation prepared in Comparative Example 2 revealed excellent tamsulosin dissolution rates. However, in the case of the simple mixed tablet composite formulation prepared in Comparative Example 1, tamsulosin was dissolved quickly due to the absence of a sustained release agent, but the formulation was not suitable for therapeutic treatment because of the short half-life of tamsulosin.

In light of the dissolution tests results above, the capsule composite formulations of the present invention can provide excellent dissolution of both tadalafil and tamsulosin for lack of interaction between them because the two active ingredients, tadalafil and tamsulosin, are filled into the capsule in a separate state.

On the contrary, in the case of the simple mixed tablet composite formulation and the double-layered composite formulation, the dissolution of tadalafil or tamsulosin was poor due to the interaction between the ingredients or the problems in the manufacture of the composite formulations.

**Test Example 2: Impurity test**

Composite formulations containing tadalafil and tamsulosin hydrochloride prepared in Examples 1 - 3 and Comparative Examples 1 and 2 were tested for their impurities according to the conditions described below.
<Accelerated conditions>
accelerated storage condition: at 40 °C with 75% of relative humidity

test timing: initial stage, after 1 month, 3 months, and 6 months

<Tadalafil impurity test conditions>
Tests were performed according to the USP impurity test. The formulation corresponding to 100 mg of tadalafil was added to a 100 mL flask, which was then filled to half with a mobile phase and shaken for 15 minutes. The resultant was dissolved by ultrasonic vibration for about 2 minutes, mixed with a mobile phase to adjust its volume, and then filtered. The resultant in the amount of 5 mL was mixed again with 20 mL of the mobile phase to prepare a sample liquid having a final concentration of 0.25 mg/mL, and tadalafil impurities were measured by liquid chromatography according to the conditions described below.

- column: a column in which a stainless steel tube having an inner diameter of about 4.6 mm and a length of about 15 cm is filled with an octadecylsilyl (ODS)-silica gel for liquid chromatography having a particle size of 3.5 µm (Zorbax SB-C8, Agilent Zorbax)
  - detector: UV spectrophotometer (measured at 285nm of wavelength)
  - flow rate: 1.0 mL/min
  - input volume: 10 µL
  - column temperature: 40°C
  - mobile phase: 0.1% trifluoroacetic acid-acetonitrile/purified water (35:65, v/v)
  - time for analysis: 30min

<Tamsulosin impurity test conditions>
Tests were performed according to the USP impurity test. The formulation corresponding to 4 mg of tamsulosin was added to a 25 mL flask, which was then diluted with a mobile phase. Exactly 10 mL of the resulting solution was taken and added into a 25 mL flask, to obtain a diluted sample. Tamsulosin impurities were measured by liquid chromatography under the conditions described below.
before main peak
- column: a column in which a stainless steel tube having an inner diameter of about 4.6 mm and a length of about 15 cm is filled with an octadecylsilyl (ODS)-silica gel for liquid chromatography having a particle size of 3.5 µm (Zorbax SB-C8, Agilent Zorbax)
- detector: UV spectrophotometer (measured at 225nm of wavelength)
- flow rate: adjusted to retain tamsulosin for about 8 min
- input volume: 100 µL
- column temperature: 40°C
- mobile phase: acetonitrile/buffer solution = 3:7 (the buffer solution was prepared by dissolving 8.7 mL of 70% perchloric acid and about 3.0 g of NaOH in 1900 mL of purified water, adjusting the pH of the mixture to pH 2.0 with IN NaOH, and then diluting it with 2000 mL of purified water)
- time for analysis: 25 min

after main peak
- column: a column in which a stainless steel tube having an inner diameter of about 4.6 mm and a length of about 15 cm is filled with an octadecylsilyl (ODS)-silica gel for liquid chromatography having a particle size of 5 µm (Zorbax SB-C8, Agilent Zorbax)
- detector: UV spectrophotometer (measured at 225nm of wavelength)
- flow rate: 1.0 mL/min
- input volume: 100 µL
- column temperature: 40°C
- mobile phase: acetonitrile/buffer solution = 1:1 (the buffer solution was prepared by dissolving 8.7 mL of 70% perchloric acid and about 3.0 g of NaOH in 1900 mL of purified water, adjusting the pH of the mixture to pH 2.0 with IN NaOH, and then diluting it with 2000 mL of purified water)
- time for analysis: 15 min

The amount of tadalafil impurities are shown in Tables 3 and 4 and FIGS. 4 and 5. The amount of tamsulosin impurities are shown in Tables 5 and 6 and FIGS. 6 and 7.
As shown in Tables 3 and 4 and FIGS. 4 and 5, the capsule composite formulations prepared in Examples 1 to 3 exhibited excellent tadalafil impurity levels and satisfied the USP standards for individual impurities and total impurities, i.e., 0.2% or below and 0.3% or below, respectively. However, in the case of the simple mixed tablet composite formulations prepared in Comparative Example 1, and the double-layered tablet composite formulations prepared in Comparative Example 2, the amount of impurities increased because part of tadalafil was in contact with tamsulosin or its excipients.
As shown in Tables 5 and 6 and FIGS. 6 and 7, the capsule composite formulations prepared in Examples 1 to 3 exhibited excellent tamsulosin impurity levels and satisfied the USP standards for individual impurities and total impurities, i.e., 0.9% or below and 1.1% or below, respectively. However, in the case of the simple mixed tablet composite formulations prepared in Comparative Example 1, and the double-layered tablet composite formulations prepared in Comparative Example 2, the amount of impurities increased because part of tamsulosin was in contact with tadalafil or its excipients.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the claims.
WHAT IS CLAIMED IS:

1. A capsule composite formulation for preventing or treating erectile dysfunction and benign prostatic hyperplasia comprising:
   i) an independent part of tadalafil containing tadalafil or a pharmaceutically acceptable salt thereof; and
   ii) an independent part of tamsulosin containing tamsulosin or a pharmaceutically acceptable salt thereof, in a separate state.

2. The capsule composite formulation of claim 1, wherein the independent part of tadalafil and the independent part of tamsulosin are respectively in the form of granules, tablets, or a combination thereof.

3. The capsule composite formulation of claim 1, wherein at least one of the independent part of tadalafil and the independent part of tamsulosin is in the form of tablets.

4. The capsule composite formulation of claim 1, wherein the independent part of tadalafil and the independent part of tamsulosin further comprise a pharmaceutically acceptable additive selected from the group consisting of a diluent, a disintegrating agent, a binder, a stabilizing agent, a lubricant, a coloring agent, and a mixture thereof.

5. The capsule composite formulation of claim 1, wherein the independent part of tadalafil and the independent part of tamsulosin respectively contain 5% or less of water content.

6. The capsule composite formulation of claim 1, wherein the independent part of tamsulosin is coated with a coating material selected from the group consisting of povidone, propylene glycol, polyvinyl acetate, methacrylate-ethyl acrylate copolymer, triacetin, and a mixture thereof.

7. The capsule composite formulation of claim 6, wherein the coating material is used in the amount of from 0.1 to 20 wt% relative to the total weight of the
independent part of tamsulosin.

8. The capsule composite formulation of claim 1, wherein the capsule composite formulation is filled into a hard capsule.

9. The capsule composite formulation of claim 8, wherein the hard capsule comprises hypromellose, pullulan, gelatin, polyvinyl alcohol or a mixture thereof as a capsule material.

10. The capsule composite formulation of claim 1, wherein the pharmaceutically acceptable salt of tamsulosin is tamsulosin hydrochloride.

11. A method of manufacturing the capsule composite formulation of claim 1, comprising:
   a) mixing tadalafil or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable additive, and granulating the mixture, or tableting the granules thus obtained into a tablet;
   b) mixing tamsulosin or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable additive, and granulating the mixture, or tableting the granules thus obtained into a tablet; and
   c) filling into a hard capsule the tadalafil granules or tablet prepared in step a), and the tamsulosin granules or tablets prepared in step b), in a separate state.

12. The method of manufacturing the capsule composite formulation of claim 11, wherein at least one of step a) and step b) includes coating of the granules or tablets obtained from the granulation or tableting process with a pharmaceutically acceptable coating material.

13. The method of manufacturing the capsule composite formulation of claim 11, wherein at least one of step a) and step b) includes a tableting step.
FIG. 1

 Independent part of tadalafil

 Independent part of tamsulosin
FIG. 2
Tadalafil dissolution

FIG. 3
Tamsulosin dissolution
FIG. 4

Individual impurities of tadalafil

![Graph showing individual impurities of tadalafil over time (month)].

- Example 1
- Example 2
- Example 3
- Comp. Ex.1
- Comp. Ex.2

FIG. 5

Total impurities of tadalafil

![Graph showing total impurities of tadalafil over time (month)].

- Example 1
- Example 2
- Example 3
- Comp. Ex.1
- Comp. Ex.2
FIG. 6

Individual impurities of tamsulosin

FIG. 7

Total impurities of tamsulosin
INTERNATIONAL SEARCH REPORT

INTERNATIONAL APPLICATION No.
PCT/KR2014/005813

A. CLASSIFICATION OF SUBJECT MATTER
A61K 9/48(2006.01)i, A61K 31/4985(2006.01)i, A61K 31/18(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 9/48; A61K 9/14; A61K 31/517; A61K 31/60; A61K 9/20; A61K 31/44; A61K 31/519; A61K 31/40; A61K 31/4985; A61K 31/18; 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: capsule, tablet, erectile dysfunction, benign prostatic hyperplasia, tadalafil, tamsulosin, coating, gelatin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>See paragraphs &lt;2&gt;, &lt;12&gt;, &lt;24&gt;, &lt;29&gt;, &lt;31&gt;, &lt;54&gt;, &lt;56&gt;; and claims 1, 8, 12.</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"R" document member of the same patent family

Date of the actual completion of the international search
10 October 2014 (10.10.2014)

Date of mailing of the international search report
10 October 2014 (10.10.2014)

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