Abstract:
The present disclosure relates to compositions for preparing an oral dispersible film comprising tadalafil or its pharmaceutically acceptable salt thereof, surfactant, plasticizer and sweetening agent; an oral dispersible film; and methods of preparing thereof. The oral dispersible film of the present disclosure can improve dissolution rate of the tadalafil without complicated processes and has superior stability compared to previous Cialis because generation of related compounds are inhibited regardless of existence of a packaging. Additionally, superior film properties comprising prevention of film breakage, securement of flexibility and prevention of oil leakage from film formulation can be maintained when comprising specific content of a polyethylene glycol 400 as the plasticizers.
Description

Title of Invention: TADALAFIL ORAL DISPERSIBLE FILM AND PREPARING METHOD THEREOF

Technical Field

[1] The present disclosure relates to a composition for preparing an oral dispersible film comprising a tadalafil or its pharmaceutically acceptable salt thereof, a surfactant, a plasticizer and a sweetening agent; an oral dispersible film; and a preparing method thereof.

Background Art

[2] There are various types of orally dispersible preparations such as tablets, chewable tablets, sublingual tablets, capsules and liquid formulations for oral administration. Within those preparations, general tablets and capsules among others are disadvantageous for patients having difficulties in taking drugs and liquid formulations are disadvantageous in light of stability and inaccurate volume amount. Therefore, necessity of a new and easily administrable preparation is arising.

[3] Recently, some formulations having different drug delivery systems are released. ODT (oral dispersible tablet) which is an oral dispersible solid preparation is one of those formulations. However, the problems are that ODT generally does not completely and consistently disintegrated in a short amount of time and frequently requires water after dose.

[4] The widely mentioned oral dispersible film is a newly proposed preparation for resolution of the above problems. This oral dispersible film preparation has some advantages that previous solid, liquid formulations and ODT do not have. The oral dispersible film preparation is useful for the elderly having a trouble with taking tablets or capsules as well as children, physically challenged person, patients on a bed and busy people because it is administrable without water, and it is assessed as the most improved type of drug disintegration compared to any preceding formulations.

[5] Especially, it is advantageous that the oral dispersible film is applicable to hepatic metabolism of drugs among drugs absorbed from alimentary canal because hepatic first pass can be evaded when drug is absorbed into oral mucosa. Therefore, various attempts are being made to produce oral dispersible film preparation for improving property of the film and drug compliance of patients.

[6] Although the oral dispersible film has the virtue, the drug has low initial dissolution and dissolution rate compared to the general tablet or the ODT, and these demerits are blocking development of generic drugs having bioequivalence and incrementally modified drugs.
Specifically, macromolecules such as hydroxypropyl methylcellulose, pullulan, polyvinyl acetate, polyethylene oxide, gelatin and alginic acid among others that are used as a film forming agent due to characteristics of the oral dispersible film are used a lot as a film formulation of the oral dispersible film in the amount of 10-90 wt% based on total solid content by exhibiting its fine capability in film formation, but these macromolecules blocks development of formulations because of its characteristics as decrement of disintegration rate and dissolution rate according to increment of contents and severer decrement of degree of dissolution rate in case when pharmaceutical active ingredients are poorly water-soluble.

In addition, preventing admixture of harmful to the human body or unnecessary substances other than main (active) ingredient in formulations is important for quality control on pharmaceuticals. The impurities expected to be admixed to pharmaceuticals are inorganic impurities, residual solvents, water and related compounds among others and the related compounds mean raw materials for synthesizing pharmaceuticals, intermediate products and resolvents produced during storage, and these are known as complicate to separate from main ingredient because of its structural similarity. Therefore, inhibiting generation of the related compounds during distribution or storage as well as preparation step of pharmaceuticals is an important factor in evaluating pharmaceutical development.

The tadalafil, an active ingredient of Cialis®, is known to have therapeutic effects of male impotence. Chemical name of the tadalafil is (6R-trans)-6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione. Chemical structure of the tadalafil (CAS# 171596-29-5) is illustrated below:

Tadalafil is a solid known as substantially water insoluble and poorly soluble to some organic solvents such as methanol, ethanol and acetone among others. U.S. Patent No. 6,841,167 teaches that it has water solubility of about 2 µg per 1 niL of water at 25°C. Therefore controlling dissolution rate of drug is very important for effective ab-
sorption of the tadalafil which has low water solubility but technical difficulties lie in application of the tadalafil to the oral dispersible film preparation because the oral dispersible film preparation has low dissolution rate.

As explained above, there is a necessity of a formulation which effectively improves dissolution rate of a drug and inhibits related compounds at the same time in light of producing a recently emerging oral dispersible film, especially an oral dispersible film including a poorly water-soluble tadalafil as an active ingredient but no such improved tadalafil oral dispersible film exists so far.

Additionally, mass production is required for commercial utilization but occasionally reduction of product value incurs due to film breakage, excessive flexibility and leakage of liquid additives for films to the surface of a film in the course of distribution. These breakage, flexibility and oil leakage among others are deemed to be the problems to be overcome for commercial use.

The above information disclosed in this Background section is only for enhancement of understanding of the background of the invention and it may therefore contain information that does not form the prior art that is already known to a person of ordinary skill in the art.

Disclosure of Invention

Technical Problem

The inventors of the present disclosure discovered that dissolution rate of the tadalafil in a film formulation could be markedly improved without complicated processes through proper adjustment of constituting ingredients and related compounds could be inhibited while researching tadalafil oral dispersible film preparation which can improve dissolution rate of a drug and minimize generation of related compounds, and accordingly completed the present disclosure. They further discovered that product value can be increased by maintaining storage stability of a film in the course of distribution, breakage prevention which is the basic property of mass production can be obtained, flexibility can be secured and oil leakage can be prevented via proper adjustment of constituting ingredients, and accordingly completed the present disclosure.

Therefore, an object of the present disclosure is to provide a composition for preparing an oral dispersible film comprising a tadalafil or its pharmaceutically acceptable salt thereof, a surfactant, a plasticizer and a sweetening agent, an oral dispersible film and a preparing method thereof.

Solution to Problem

To achieve the above object, the present disclosure provides the composition for preparing an oral dispersible film comprising a tadalafil or its pharmaceutically ac-
ceptable salt thereof, a surfactant, a plasticizer and a sweetening agent.

Furthermore, the present disclosure provides the oral dispersible film prepared by drying the above composition.

Furthermore, the present disclosure provides the method for preparing the oral dispersible film comprising (a) preparing an agitation solution by adding and agitating the tadalafil or its pharmaceutically acceptable salt thereof, the surfactant, a binding agent, the plasticizer, a disintegrant and the sweetening agent into a solvent; (b) preparing a film solution by homogenizing or comminuting the agitation solution with a homomixer, and agitating the same with an addition of the film forming agent; (c) molding the film by drying the film solution.

**Advantageous Effects of Invention**

The oral dispersible film according to the present disclosure has superior stability compared to the previous cialis tablets because it can improve the dissolution rate of the tadalafil without complicated processes and generation of the related compounds are inhibited regardless of existence of a packaging. Also, superior film properties including prevention of film breakage, securement of flexibility and prevention of oil leakage from film formulation can be maintained when comprising specific content of a polyethylene glycol 400 as the plasticizer.

**Mode for the Invention**

The present disclosure provides a composition for preparing an oral dispersible film comprising a tadalafil or its pharmaceutically acceptable salt thereof, a surfactant, a plasticizer and a sweetening agent.

The composition for preparing the oral dispersible film according to the present disclosure has superiority in production of the tadalafil oral dispersible film that dissolution rate of the tadalafil is improved and related compounds are inhibited regardless of existence of a packaging without complicated processes.

The composition for preparing the oral dispersible film according to the present disclosure has superior storage stability because it is designed to prevent tadalafil film breakage during distribution or decrease in flexibility and oil leakage.

The "tadalafil" is a phosphodiesterase (PDE) 5 inhibitor and the present disclosure includes not only the tadalafil but also solvates and hydrates thereof.

The "pharmaceutically acceptable salt" is salts prepared with an acid or base having none or less toxicity. A pharmaceutically acceptable base addition salt includes lithium, natrium, potassium, calcium, ammonium, magnesium and organic amine salt but not limited to these.

A pharmaceutically acceptable acid addition salt includes salts formed of propionic acid, isobutyl acid, oxalic acid, malic acid, malonic acid, benzoic acid, succinic acid,
suberic acid, fumaric acid, mandelic acid, phthalic acid, p-tolyl sulfonic acid, citric acid, tartaric acid, methane sulfonic acid, hydrochloric acid, bromic acid, nitric acid, carbonic acid, monohydrogen carbonic acid, phosphoric acid, monohydrogen phosphoric acid, dihydrogen phosphoric acid, sulfuric acid, monohydrogen sulfuric acid, hydrogen iodide and phosphorous acid among others but not limited to these. Also comprising amino acid salts such as alginate and analogues of organic acid such as glucuronic acid and galactunoric acid but not limited to these.

The "oral dispersible film (ODF)" also called as strip or orally dissolving film and it is a film formulation that can be taken via dissolution or minute dispersion in an oral cavity. These films usually placed on the tongue to be dissolved but also can be administered by adhere films to palate, sublingual region or buccal cavity. The film formulation according to the present disclosure is advantageous in that it is administrable without water.

The surfactant can be one or more surfactants selected from a group consisted of nonionic surfactant, cationic surfactant, anionic surfactant and amphoterion ionic surfactant, preferably can be one or more surfactants selected from a group consisted of sodium lauryl sulfate (SLS), glycerin fatty acid ester, sucrose fatty acid esters, lecithin, enzymatically modified lecithin, polysorbate, sorbitan fatty acid ester and sucrose fatty acid ester, and more preferably the surfactant can be sodium lauryl sulfate (SLS) and/or polysorbate. Polysorbate 20 (monolaurate), 40 (monopalmitate), 60 (monostearate), 65 (tristearate) and 80 (monooleate) are usable as the polysorbate without restriction but the polysorbate 20 is most preferable.

In addition, plasticizers which do not affect physical properties of the film can be used as the plasticizer without any restriction but preferably it can be one or more plasticizers selected from a group consisted of glycerin, glycerol olate, medium chain fatty acid, polyethylene glycol, propylene glycol, propylene glycol monopropionylate, propylene glycol dicaprylate, saccharide, sugar alcohols and triacetin, and more preferably the plasticizer can be glycerin or polyethylene glycol.

In addition, the sweetening agent can be one or more sweetening agents selected from a group consisted of sorbitol solution, sucralose, sodium chloride, mannitol, aspartame, acesulfame salt, saccharin salt, neotame, cyclamate salt, thaumatin, luo han guo extract, glycyrrhiza extract, and more preferably the sweetening agent can be sorbitol solution.

In addition, it is preferable that the surfactant can be sodium lauryl sulfate (SLS) and/or polysorbate 20, the plasticizer can be glycerin and/or polyethylene glycol, and the sweetening agent can be sorbitol solution for the composition for preparing the oral dispersible film.

The surfactant can be included as 1-30 wt%, preferably 1-20 wt%, and more.
preferably 1-10 wt% based on the total weight of solid contents of the film.

Also, the plasticizer can be included as 1-25 wt%, preferably 1-20 wt%, and more preferably 1-15 wt% based on total weight of solid contents of the film.

Especially when the plasticizer is polyethylene glycol 400, it is preferable to be included as 1-7 wt% based on total weight of solid contents of the film.

Additionally, the sweetening agent can be included as 1-50 wt%, preferably 1-40 wt%, and more preferably 1-30 wt% based on total weight of solid contents of the film.

The "total weight of solid contents of the film" is aggregate of weight of the solid contents comprising surfactant, tadalafil, binding agent, plasticizer, disintegrant, sweetening agent, fragrance ingredient and coloring agent among others which are compositions for preparing the tadalafil oral dispersible film wherein solvents are excluded.

Upon changing the content of the tadalafil which is an active ingredient to 10 and 20 mg, total weight of solid contents of the film changes but the weight of the surfactant, the plasticizer and the sweetening agent based on total weight of solid contents of the film can be changed while maintaining the above wt%.

The composition for preparing an oral dispersible film of the present disclosure can further selectively include various additives, binding agents, pH controllers, fragrance ingredients, coloring agents, oils, wetting agents, disintegrants and lubricants among others which are generally usable for preparing the oral dispersible film.

The additives are pharmaceutically acceptable additives and can include buffer and diluents among others, and can include a film forming agent for preparing the oral dispersible film. Various macromolecules such as pullulan, gelatin, pectin, low viscosity pectin, hydroxypropyl methylcellulose, low viscosity hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, methyl methacrylate copolymers, carboxyvinyl polymer, polyethylene glycol, alginic acid, low viscosity alginic acid, sodium alginate, starch, casein, whey protein isolate, soy protein isolate, zein, levan, elsinan, gluten, acacia gum, carrageenan, arabic gum, guar gum, locust bean gum, xanthan gum, gellan gum and agar among others are usable as the film forming agent without restriction but the pullulan is most preferable.

The pH controller can be potassium dihydrogen phosphate, sodium hydroxide, sodium hydrogen carbonate, sodium phosphate, ammonium hydroxide, sodium stannate, triethanolamine, citric acid, hydrochloric acid, sodium citrate and combinations thereof and preferably the potassium dihydrogen phosphate and/or the sodium hydroxide can be used. Sufficient pH controller may be added and adjust pH of the film to a proper value.

The fragrance ingredient can be natural fragrance ingredient, synthetic fragrance in-
gradient or its mixtures thereof without restrictions and preferably extract of leaves, flowers, and fruits of the plant and plant oil. Also, the synthetic fragrance ingredient can be synthetic fruit flavors such as lemon, orange, grape, lime and strawberry, and synthetic flavors such as vanilla, coffee, cocoa, pine needle, ginseng, red ginseng and citrus.

The coloring agent can be titanium oxide, yellow iron oxide, red iron oxide, riboflavin, betacarotene, anthocyan, carmine, indigo carmine, orange yellow, quinoline yellow, indigotin lake, brilliant blue and sunset yellow.

The oil can be safflower oil, castor oil, coconut oil, cotton seed oil, canola oil, herring oil, palm tree fruit oil, palm oil, soybean oil, rapeseed oil, flaxseed oil, rice bran oil, pine tree oil, sesame oil, sunflower oil, hydrogenated safflower oil and its mixtures thereof.

The disintegrant can be sodium croscarmellose, starch, modified starch, methyl cellulose, carboxymethylcellulose, calcium, sodium carboxymethylcellulose, hydroxypropyl cellulose, microcrystalline cellulose, colloidal silicon dioxide, gelatinized starch, mud, cellulose, cellulose powder, sodium alginic acid, alginic acid, guar gum, magnesium aluminum silicate, polacrilin potassium or its mixtures thereof.

The lubricant can be talc, stearic acid, magnesium stearate, colloidal silicon dioxide, and sodium stearyl fumarate, glycercyl behenate, and glycercyl distearate.

In addition, the present disclosure provides the oral dispersible film which is produced by drying the compositions for preparing the oral dispersible film comprising the tadalafil or its pharmaceutically acceptable salt thereof, surfactant, plasticizer and sweetening agent.

Furthermore, the present disclosure provides a method of preparing the oral dispersible film comprising (a) preparing an agitation solution by adding and agitating the tadalafil or its pharmaceutically acceptable salt thereof, the surfactant, the binding agent, the plasticizer, the disintegrant and the sweetening agent into a solvent; (b) preparing the film solution by homogenizing or comminuting the agitation solution with the homomixer, and agitating the same with addition of film forming agent; (c) molding the film by drying the film solution.

The solvent of the step (a) can be one or more solvents selected from a group consisted of purified water, alcohol, alkyl acetates, dimethyl formamide, dimethyl sulfoxide, acetone, anisole, acetic acid, butyl methyl ether, ethyl ether, ethyl formate, formic acid, pentane, heptane, methyl ethyl keton and methyl isobutylketone.

The surfactant of the step (a) can be one or more surfactants selected from a group consisted of sodium lauryl sulfate (SLS), glycerin fatty acid ester, sucrose fatty acid esters, lecithin, enzymatically modified lecithin, polysorbate, sorbitan fatty acid ester and sucrose fatty acid ester, and the plasticizer of the step (a) can be one or more plas-
ticizers selected from a group consisted of glycerin, glycerol oleate, medium chain fatty acid, polyethylene glycol, propylene glycol, propylene glycol moncaprylate, propylene glycol dicaprylate, saccharide, sugar alcohols and triacetin, and the sweetening agent of the step (a) can be one or more sweetening agents selected from a group consisted of sorbitol solution, sucralose, sodium chloride, mannitol, aspartame, acesulfame salt, saccharin salt, neotame, cyclamate salt, thaumatin, luo han guo extract, glycyrrhiza extract. Most preferably, the surfactant can be the sodium lauryl sulfate (SLS) and/or the polysorbate, the plasticizer can be the glycerin and/or the polyethylene glycol and the sweetening agent can be the sorbitol solution.

The film forming agent of the step (b) can be various macromolecules such as pullulan, gelatin, pectin, low viscosity pectin, hydroxypropyl methylcellulose, low viscosity hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, methyl methacrylate copolymers, carboxyvinyl polymer, polyethylene glycol, alginic acid, low viscosity alginic acid, sodium alginate, starch, casein, whey protein isolate, soy protein isolate, zein, levan, elsinan, gluten, acacia gum, carrageenan, arabic gum, guar gum, locust bean gum, xanthan gum, gellan gum and agar among others without restriction but the pullulan is most preferable.

Apropos of the method of preparing the oral dispersible film, dissolution rate of the tadalafil drops when viscosity of the film solution excessively increases and the film is not smoothly formed when viscosity is excessively low, thus difficulties lie in preparing the film.

Additionally, as per the method of preparing the oral dispersible film, dissolution rate of the tadalafil could drop if not using homogenizer, therefore it might be preferable to use the homogenizer for homogenizing the film solution.

In addition, the present disclosure provides the oral dispersible film produced by the method of preparing the oral dispersible film.

The oral dispersible film produced by the method of preparing the oral dispersible film has superiority in markedly increased dissolution rate in oral cavity of tadalafil and inhibition of generation of the related compounds without packaging at the same time.

The present disclosure provides a method of treating sexual dysfunction by using the oral dispersible film produced by drying the compositions for preparing the oral dispersible film comprising the tadalafil or its pharmaceutically acceptable salt thereof, the surfactant, the plasticizer and the sweetening agent.

The present disclosure provides a method of treating sexual dysfunction preferably by using the oral dispersible film produced by drying the compositions of the oral dispersible film comprising the tadalafil or its pharmaceutically acceptable salt thereof,
the sodium lauryl sulfate (SLS) and the polysorbate or its combination as the surfactant; the glycerin and the polyethylene glycol or its combination as the plasticizer; and the sorbitol solution as the sweetening agent.

[59] The sexual dysfunction is preferably impotence. The oral dispersible film can be administered to an object and effective amount for preventing or treating the sexual dysfunction can be administered when administering the oral dispersible film to the object.

[60] The present disclosure provides a use of the oral dispersible film produced by drying the compositions for preparing the oral dispersible film comprising the tadalafil or its pharmaceutically acceptable salt thereof, the surfactant, the plasticizer and the sweetening agent for treating the sexual dysfunction.

[61] Preferably, the present disclosure provides the use of the oral dispersible film produced by drying the compositions for preparing the oral dispersible film comprising the tadalafil or its pharmaceutically acceptable salt thereof, the sodium lauryl sulfate (SLS) and the polysorbate or its combination as the surfactant; the glycerin and the polyethylene glycol or its combination as the plasticizer; and the sorbitol solution as the sweetening agent.

[62] The sexual dysfunction is preferably the impotence.

[63] The numerical values set forth in this embodiment should be construed as comprising range of equivalents unless otherwise specified.

[64] The present disclosure will be described more fully hereinafter with reference to the accompanying examples and comparative examples. However, the present disclosure may be embodied in many different forms, and should not be construed as being limited to the embodiments set forth herein.

[65]

Examples

1. Preparation of Example 1

[68] Following method was conducted to produce the oral dispersible film comprising the tadalafil as an active ingredient. A stirrer (i.e. IKA® EuroStar Digital) was used for production and agitated at speed range of 300rpm through 1,000rpm.

[69] 2g of the sodium lauryl sulfate (i.e. SLS, the surfactant) was added to 200g of purified water in a preparation container 1 and completely dissolved by agitation. 20g of the tadalafil was added to the completely dissolved solution and completely dispersed by agitating again. 7g of the polysorbate 20, 7g of the polyethylene glycol 400, 7g of a concentrated glycerin (PALMERA G995) and 7g of the sorbitol solution were added to the prepared half-finished product and agitated again. 6g of the croscarmellose sodium, 12g of the microcrystalline cellulose, 4g of the sucralose and 2g of the titanium oxide were added and agitated again.

[70] Put 2g of L-menthol (i.e. the fragrance ingredient) into a beaker (i.e. preparation
container 2) and mixed with 20g of purified water which was warmed over 50°C to be dissolved and added to the preparation container 1.

24g of the pullulan was added and agitated until completely dissolved until being a homogeneous solution and used as the film solution after resting it overnight.

The film containing the tadalafil was obtained through pouring the prepared film solution on a PET film, casting the film solution with a film applicator (YASUDA SEIKI SEISAKUSHO. LTD.), drying the film solution under temperature of over 50°C and exfoliating the film solution from the PET film.

Ingredients used for preparing the film of the present disclosure, and its contents and ratio are shown in Table 1 below. The ratio was calculated as weight of the each ingredient based on total weight of solid contents wherein the purified water as a solvent was excluded, and in case of a formulation containing 10mg of the tadalafil, content was decided by maintaining the ratio of weight of the each ingredient based on total weight of the solid contents.

Table 1
Comparative Examples

Preparation of Comparative Examples 1 through 4

All the other constitutions were identical to those of Example 1 except that the glycerin was excluded in Comparative Example 1, the sorbitol solution was excluded in Comparative Example 2, the polysorbate 20 (Tween20) was excluded in Comparative Example 3 and the sodium lauryl sulfate was excluded in Comparative Example 4, and the oral dispersive film was produced by the same process set forth in Example 1.

Ingredient ratio of each remaining ingredient except the pullulan based on total weight of the solid content was maintained identically to the 20mg formulation of the tadalafil in Example 1.
The oral dispersible film produced with the identical compositions and the process was used in following Experimental Examples.

Experimental Examples

1. Dissolution Rate Analysis

Dissolution rates of the produced oral dispersible film of Example 1 and Comparative Example 1 through 4 were measured and compared to each other. A method and conditions for measuring the dissolution rate were set as followings according to the test method which is approved by the Korean Ministry of Food and Drug Safety.

- Preparation of a Test Liquid: One sheet of the film was tested with 1000mL of 0.5% sodium dodecyl sulfate (SDS) as a test solution by using a sinker at 50 rpm under temperature range of 37.0 ± 0.5°C according to the second method of dissolution test set forth in the Korean Pharmacopeia. 10ml of eluent was obtained at 10, 30 and 60 minutes after initiating the dissolution test and used as the test liquid by filtering the obtained eluent with 0.45μm membrane filter.

- Preparation of a Standard Solution: 20mg of a reference standard tadalafil was precisely measured by a 100mL volumetric flask, dissolved with a diluents (water-acetonitrile mixture (50 : 50)), filled to the gauge mark and mixed. 5ml of the solution was precisely obtained and poured into the volumetric flask with addition of a test solution by filling the volumetric flask to the mark and mixing the same, and used as the standard solution (0.02mg/mL).

- Operation: Tested with 50μL of the test liquid and the standard solution according to the liquid chromatographic method of the general tests set forth in the Korean Pharmacopeia and calculated peak area As and At of the tadalafil of the standard solution and the test liquid.

<Operational Condition>

Detector: Ultraviolet Spectrometry (wavelength range: 225nm)

Column: ZORBAX SB-C8 (4.6mm x 5cm, 3.5μm) or equivalent column

Mobile Phase: Methanol-Water Mixture (50 : 50)

Flux: 2.0mL/min

Column Temperature: 40°C

- System Suitability

- A peak symmetry factor of the tadalafil was 1.5 or less when testing with 50μL of the standard solution under the condition set forth hereinbefore.

- A relative standard deviation for peak area of the tadalafil was 2.0% or less when
conducting six times of a cyclic test with 50μL of the standard solution under the condition set forth hereinbefore.

100

- Formula

102

- Ten-minute dissolution rate for indicated amount of the tadalafil in one sheet of the film (%)

\[
\frac{A_t}{A_s} \times \frac{W_s}{20} \times P
\]

104

At: Peak Area of the tadalafil in the test liquid

105

As: Peak area of the tadalafil in the standard solution

106

Ws: Obtained amount of the reference standard tadalafil (mg)

107

20: Indicated amount of the tadalafil in one sheet of the film (mg)

108

P: Purity of the reference standard tadalafil (%)

110

- Thirty-minute dissolution rate for indicated amount of the tadalafil in one sheet of the film (%)

\[
\left( Q_{10} \times \frac{V}{V_s} \right) + \left[ \frac{A_t}{A_s} \times \frac{W_s \times 0.001}{20} \times (V_s - V) \times P \right]
\]

112

Qi_{10}: Ten-minute dissolution rate for indicated amount of the tadalafil in one sheet of the film (%)

113

v: Volume of the eluent obtained from the ten-minute dissolution test (mL)

114

V: Volume of the eluent, 1000mL

115

At: Peak Area of the tadalafil in the test liquid

116

As: Peak area of the tadalafil in the standard solution

117

Ws: Obtained amount of the reference standard tadalafil (mg)

118

0.001: dilution rate of the standard solution (5/(100×50))

119

20: Indicated amount of the tadalafil in one sheet of the film (mg)

120

P: Purity of the reference standard tadalafil (%)

122

- Sixty-minute dissolution rate for indicated amount of the tadalafil in one sheet of the film (%)

\[
\left( Q_{10} \times \frac{V_1}{V} \right) + \left( Q_{30} \times \frac{v^2}{V_1} \right) + \left[ \frac{M_t}{M_s} \times \frac{W_s \times 0.001}{20} \times (V_s - (v_1 + v_2)) \times P \right]
\]

124

Qi_{10}: Ten-minute dissolution rate for indicated amount of the tadalafil in one sheet of the film (%)

125

Q_{30}: Thirty-minute dissolution rate for indicated amount of the tadalafil in one sheet of the film (%)

126
vi: Volume of the eluent obtained from the ten-minute dissolution test (mL)

v2: Volume of the eluent obtained from the thirty-minute dissolution test (mL)

V: Volume of the eluent, 1000mL

At: Peak Area of the tadalafil in the test liquid

As: Peak area of the tadalafil in the standard solution

Ws: Obtained amount of the reference standard tadalafil (mg)

0.001: Dilution rate of the standard solution (5/(100x50))

20: Indicated amount of the tadalafil in one sheet of the film (mg)

P: Purity of the reference standard tadalafil (%)

Result of the dissolution test is shown in Table 2 below

Table 2

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Control Group</th>
<th>Example 1</th>
<th>Comparative Example 1</th>
<th>Comparative Example 2</th>
<th>Comparative Example 3</th>
<th>Comparative Example 4</th>
</tr>
</thead>
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<tr>
<td>Tadalafil</td>
<td></td>
<td>20.00</td>
<td>20.00</td>
<td>20.00</td>
<td>20.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel PH102)</td>
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<td>7.00</td>
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<td>Concentrated Glycerin (PALMERA G995)</td>
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<td>Sorbitol Solution</td>
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<tr>
<td>Polysorbate 20</td>
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<tr>
<td>Sodium Lauryl Sulfate (SLS)</td>
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</tr>
<tr>
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<th>Dissolution Rate (%)</th>
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<th>30 min.</th>
<th>60 min.</th>
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<td>70.5</td>
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<td>Comparative Example 3</td>
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<td>56.8</td>
<td>63.2</td>
</tr>
<tr>
<td>Comparative Example 4</td>
<td>56.4</td>
<td>74.7</td>
<td>80.8</td>
</tr>
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As shown in Table 2, the cialis tablet and the tadalafil oral dispersible film of the present disclosure (Example 1) exhibited remarkable dissolution rate i.e. 70% or more at 10 minute, 95% or more at 30 minute and 100% at 60 minute, but in Comparative
Example 1 through 4 wherein ingredients such as the sodium lauryl sulfate (SLS), the polysorbate 20 (T20), the glycerin, the sorbitol solution among others are excluded, dissolution rate was drastically decreased i.e. 60% or less at 10 minute, 80% or less at 30 minute and 85% or less at 60 minute. In other words, it was understood that a most desirable dissolution pattern was shown when the glycerin, the sorbitol, the polysorbate 20 and the sodium lauryl sulfate (SLS) were mixed respectively or properly.

2. Related Compounds Analysis

A related compounds analysis test was conducted to confirm stability of the oral dispersible film in Example 1. A method and conditions for analyzing the related compounds were set as followings according to the test method which is approved by the Korean Ministry of Food and Drug Safety.

- Preparation of a Test Liquid: Put twenty sheets of the film into a 200mL volumetric flask, disintegrate the films by agitating with 80mL of water for fifteen minutes, added 80 mL of acetonitrile and sonicated for five minutes, filled the volumetric flask to the mark with addition of the diluents (acetonitrile-water mixture (50 : 50)) and mixed. 10ml of the solution was precisely obtained and poured into a 100mL volumetric flask, filled the volumetric flask to the mark with addition of the diluents and used as the test liquid by filtering the mixed solution via 0.45μm membrane filter.

- Preparation of a Standard Solution: 20mg of the reference standard tadalafil was precisely measured and put into the 100mL volumetric flask, dissolved by diluents and used as the standard solution (0.2mg/mL) by filling the volumetric flask to the mark and mixing.

- Preparation of a System Suitability Solution: To transform the tadalafil to 6R and 12aS (i.e. diastereomeric), obtained 25mL of the standard solution and poured into a 100mL beaker, added 0.25mL of 5mol/L sodium hydroxide solution and agitated, and rested for thirty minutes. This solution was used as the system suitability solution via neutralization to pH 7.0 by using trifluoroacetic acid. Relative retention time was 1.0 for the tadalafil and 1.2 for the 6R, 12aS.

- Detection Solution: 50μL of the standard solution was precisely obtained and poured into the 100mL volumetric flask and used as the detection solution (0.1μg/mL) by filling the volumetric flask to the mark with diluents.

- Operation: Tested with 10μL of the test liquid, the standard solution and the system suitability solution according to the liquid chromatographic method of the general tests set forth in the Korean Pharmacopoeia and calculated peak area As and At of the tadalafil of the standard solution and the test liquid.
[148] <Operational Condition>
[149] Detector: Ultraviolet Spectrometry (wavelength range: 285nm)
[150] Column: ZORBAX SB-C8 (4.6mm x 5cm, 3.5μm) or equivalent column
[151] Mobile Phase: Acetonitrile-Water-Trifluoroacetic acid Mixture (35:65:0.1)
[152] Flux: 1.0mL/min
[153] Column Temperature: 35°C
[154] - System Suitability
[155] - Resolution of the tadalafil and the 6R,12aS (i.e. diastereomeric) was greater than 3.0 when testing with 10μL of the system suitability solution under the condition set forth hereinbefore.
[156] - A relative standard deviation for peak area of the tadalafil was 2.0% or less and symmetry factor was 2.0 or less when conducting six times of a cyclic test with 10μL of the standard solution under the condition set forth hereinbefore.
[157] - A ratio of signal to noise (S/N) of the detection solution was greater than 10.
[158] - Formula
[159] \[
\text{Individual related compound} \left( \mathcal{F}_{\text{o}} \right) = \frac{A_{\text{i}}}{A_{\text{s}}} \times 100
\]
[160] \( A_{\text{i}} \): Peak Area of the individual related compound in the test liquid
[161] \( A_{\text{s}} \): Aggregate Peak Areas of the individual related compound and the tadalafil in the test liquid
[162] * Values under 0.05% (limit of quantification, equivalent to 0.1μg/mL) were excluded.
[163] At the related compounds analysis, stability was deemed to have no problems when each individual related compound was 0.2% or less and total related compounds were 0.3% or less. To analyze the related compounds more specifically, stored the packed or unpacked oral dispersible films of Example 1 in an oven at temperature of 80°C and followed the related compounds analysis set forth hereinbefore. Cialis tablet which is a tadalafil tablet on sale was used as a control group and tested for packed or unpacked status under identical conditions. The related compounds analysis has been conducted 3 times in 15 days and the analysis result is shown in Tables 3 and 4.
[164] Table 3
As shown in Tables 3 and 4, it was confirmed that the tadalafil oral dispersible film of Example 1 was a formulation having superior stability by the result showing that the total related compounds were generated less than the threshold of 0.3% even after 15 days under both packed and unpacked status. In contrast, the cialis tablet i.e., the control group, did not meet the stability criteria because the total related compounds increased up to 0.6% after 15 days under packed status. Therefore, the tadalafil oral dispersible film of Example 1 was confirmed as an effective formulation which could be a solution to the previous cialis tablets having stability problem.

3. Property Retention Analysis

It is crucial to retain properties of the oral dispersible film which is administered by dissolving in oral cavity during distribution after production. Especially, its wide surface area and thin thickness compared to the tablets or capsules can incur breakage or problematic flexibility. Also, due to use of lots of liquid additives, thickness of the
film becomes thinner when water among others vapors and leakage of the liquid additives to the surface incurs. To resolve these problems, retention of the properties was observed through variation of amount of the polyethylene glycol 400 (i.e. PEG 400, the plasticizer).

More specifically, prepared the tadalafil oral dispersible film while varying only the content of the polyethylene glycol 400 to 1% through 9% based on total weight and observed differences of oil leakage, breakage and flexibility of the film. The prepared films are shown as Examples 1 through 5 and Comparative Example 5. 64 days of storage status was observed in a storage chamber fixed at 80°C.

Table 5

[Table 5]  
Pre and Post-properties of the film storage in the 80°C chamber.

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<th>Example 4</th>
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<td>12.00</td>
<td>12.00</td>
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<td>0.00</td>
<td>12.00</td>
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Storage (days) | Oil Observation on Storage Status of the Film |
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<td>1 Observed</td>
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</tr>
<tr>
<td>4 Observed</td>
<td>Not observed Not observed Not observed Not observed Not observed Observed</td>
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<td>8 Observed</td>
<td>Not observed Not observed Not observed Not observed Not observed Observed</td>
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<tr>
<td>15 Observed</td>
<td>Not observed Not observed Not observed Not observed Not observed Observed</td>
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<tr>
<td>36 Observed</td>
<td>Not observed Not observed Not observed Not observed Not observed Dried</td>
</tr>
<tr>
<td>54 Observed</td>
<td>Not observed Not observed Not observed Not observed Not observed Dried</td>
</tr>
</tbody>
</table>
According to the result shown in Table 5, no oil leakage from the film formulation was observed when usage of the polyethylene glycol 400 was in range of 1.0% through 7.0% based on total weight. However, when the content of the polyethylene glycol 400 was 9% (i.e. Comparative Example 5), oil leakage was observed from the initial day and dried from 36th day of observation and accordingly confirmed influences on the products caused by stains remaining on the film surface.

Additional observation on whether the above prepared tadalafil oral dispersible film has superior properties in oil leakage, flexibility and breakage was conducted and shown in Table 6 below.

Table 6

<table>
<thead>
<tr>
<th>Storage (days)</th>
<th>Breakage(B) and Flexibility(F) of the Film</th>
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<tr>
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<td>Example 2</td>
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<td>15</td>
<td>X</td>
</tr>
<tr>
<td>36</td>
<td>△</td>
</tr>
<tr>
<td>64</td>
<td>△</td>
</tr>
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</table>

X: No Breakage, △: sporadic Breakage, ○: Breakage
X: Low Flexibility, △: Normal Flexibility, ○: High Flexibility

As shown in Table 6, the tadalafil film formulations of the present disclosure all barely exhibited breakage and had satisfactory flexibility under the circumstance of long-term storage. Therefore, it was confirmed that the tadalafil oral dispersible film comprising 1-7 wt% of the polyethylene glycol 400 based on total weight of the film could maintain superior film properties in long-term comprising no breakage, satisfactory flexibility and no oil leakage.
Claims

[Claim 1] A composition for preparing an oral dispersible film comprising a tadalafil or its pharmaceutically acceptable salt thereof, a surfactant, a plasticizer and a sweetening agent.

[Claim 2] The composition for preparing the oral dispersible film according to claim 1, wherein the surfactant is one or more surfactants selected from a group consisted of a sodium lauryl sulfate (SLS), a glycerin fatty acid ester, a sucrose fatty acid esters, a lecithin, a enzymatically modified lecithin, a polysorbate, sorbitan fatty acid ester and a sucrose fatty acid ester.

[Claim 3] The composition for preparing the oral dispersible film according to claim 1, wherein the plasticizer is one or more plasticizers selected from a group consisted of a glycerin, a glycerol oleate, a medium chain fatty acid, a polyethylene glycol, a propylene glycol, a propylene glycol monocaprylate, a propylene glycol dicaprylate, a saccharide, a sugar alcohols and a triacetin.

[Claim 4] The composition for preparing the oral dispersible film according to claim 1, wherein the sweetening agent is one or more sweetening agents selected from a group consisted of a sorbitol solution, a sacralose, a sodium chloride, a mannitol, a aspartame, a acesulfame salt, a saccharin salt, a neotame, a cyclamate salt, a thaumatin, a luo han guo extract and a glycyrrhiza extract.

[Claim 5] The composition for preparing the oral dispersible film according to claim 1, wherein the surfactant is the sodium lauryl sulfate (SLS) or a polysorbate 20, the plasticizer is the glycerin or the propylene glycol and the sweetening agent is the sorbitol solution.

[Claim 6] The composition for preparing the oral dispersible film according to claim 1, comprising the sodium lauryl sulfate (SLS), the polysorbate or its combination as the surfactant; the glycerin, the polyethylene glycol or its combination as the plasticizer; and the sorbitol solution as the sweetening agent.

[Claim 7] The composition for preparing the oral dispersible film according to claim 1 wherein the surfactant is comprised 1-10 wt% based on total solid content of the film.

[Claim 8] The composition for preparing the oral dispersible film according to claim 1, wherein the plasticizer is the glycerin, a polyethylene glycol 400 or its combination.
[Claim 9] The composition for preparing the oral dispersible film according to claim 8, wherein the polyethylene glycol 400 is comprised 1-7 wt% based on total solid content of the film.

[Claim 10] The composition for preparing the oral dispersible film according to claim 1, wherein the sweetening agent is comprised 1-30 wt% based on total solid content of the film.

[Claim 11] The oral dispersible film produced by drying the composition according to any one of the claims 1-10.

[Claim 12] A method of preparing the oral dispersible film comprising (a) preparing an agitation solution by adding and agitating the tadalafil or its pharmaceutically acceptable salt thereof, the surfactant, a binding agent, the plasticizer, a disintegrant and the sweetening agent into a solvent; (b) preparing a film solution by homogenizing or comminuting the agitation solution with a homomixer, and agitating the same with addition of a film forming agent; and (c) molding the film by drying the film solution.

[Claim 13] The method of preparing the oral dispersible film according to claim 12, wherein:

the surfactant in step (a) is one or more surfactants selected from a group consisted of the sodium lauryl sulfate (SLS), the glycerin fatty acid ester, the sucrose fatty acid esters, the lecithin, the enzymatically modified lecithin, the polysorbate, the sorbitan fatty acid ester and the sucrose fatty acid ester;

the plasticizer in step (a) is one or more plasticizers selected from a group consisted of the glycerin, the glycerol oleate, the medium chain fatty acid, the polyethylene glycol, the propylene glycol, the propylene glycol monocaprylate, the propylene glycol dicaprylate, the saccharide, the sugar alcohols and the triacetin; and

the sweetening agent in step (a) is one or more sweetening agents selected from a group consisted of the sorbitol solution, the sucralose, the sodium chloride, the mannitol, the aspartame, the acesulfame salt, the saccharin salt, the neotame, the cyclamate salt, the thaumatin, the luo han guo extract and the glycyrrhiza extract.

[Claim 14] The method of preparing the oral dispersible film according to claim 12, wherein the surfactant in step (a) is the sodium lauryl sulfate (SLS), the polysorbate or its combination; the plasticizer is the glycerin, the polyethylene glycol or its combination; and the sweetening agent is the sorbitol solution.
[Claim 15] The method of preparing the oral dispersible film according to claim 14, wherein the polyethylene glycol is comprised as 1-7 wt% based on total weight of solid contents of the film.

[Claim 16] The oral dispersible film produced by the methods set forth in any one of the claims 11-15.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K 9/70(2006.01)i, A61K 47/34(2006.01)i, A61K 31/4985(2006.01)i, A61P 15/10(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 9/70; A61K 47/36; A61K 9/14; A61K 9/00; A61K 9/20; A61K 31/4985; A61K 47/34; A61P 15/10

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: tadalafl, oral dispersible film, surfactant, plasticizer, sweetening agent, stability

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>KR 10-2008-0023873 A (AMOZEN CO., LTD.) 17 March 2008 See paragraphs [0018], [0026], [0033], [0035] ; examples 1, 5 ; and claim 4.</td>
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<td>KR 10-2010-0012867 A (TEVA PHARMACEUTICAL INDUSTRIES LTD.) 08 February 2010 See the whole document.</td>
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See patent family annex.

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search
30 November 2015 (30.11.2015)

Date of mailing of the international search report
30 November 2015 (30.11.2015)

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
LEE, Jeong A
Telephone No. +82-42-481-8740

Form PCT/ISA/210 (second sheet) (January 2015)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2.☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.☒ Claims Nos. 16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

1.☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2.☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3.☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4.☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☒ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.
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