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(54) **Titre : COMPOSITION PHARMACEUTIQUE CONTENANT DU FIMASARTAN ET DE L'HYDROCHLOROTHIAZIDE**
(54) **Title: PHARMACEUTICAL COMPOSITION COMPRISING FIMASARTAN AND HYDROCHLOROTHIAZIDE**

(57) **Abrégé/Abstract:**
The present invention provides: a pharmaceutical composition having a superior physical property since fimasartan and hydrochlorothiazide, which are main components of a composite, have superior content uniformity; and a preparation method thereof.

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(54) **Title**: PHARMACEUTICAL COMPOSITION CONTAINING FIMASARTAN AND HYDROCHLOROTHIAZIDE

(54) **발명의 명칭** : 피마살탄 및 히드로클로로티아지드가 함유된 약제학적 조성물

(57) **Abstract**: The present invention provides: a pharmaceutical composition having a superior physical property since fimasartan and hydrochlorothiazide, which are main components of a composite, have superior content uniformity; and a preparation method thereof.

(57) **요약서**: 본 발명은 복합제제의 주성분인 피마살탄 및 히드로클로로티아지드가 우수한 함량균일성을 나타내어 물리적 성질이 우수한 약제학적 조성물 및 그의 제조방법을 제공한다.

【DESCRIPTION】

【Invention Title】

# PHARMACEUTICAL COMPOSITION COMPRISING FIMASARTAN AND HYDROCHLOROTHIAZIDE

【Technical Field】

The present invention relates to a pharmaceutical composition comprising fimasartan and hydrochlorothiazide and, more particularly, to a pharmaceutical composition comprising fimasartan, an angiotensin II receptor antagonist, and hydrochlorothiazide, a diuretic.

【Background Art】

Fimasartan is known as an angiotensin II receptor antagonist developed for the treatment of hypertension and other medical indications (Korean Patent No. 10-1058284). Fimasartan is chemically defined as 2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one, is a nonpeptide molecular-chemically defined, and has an empirical formula of $C_{27}H_{30}N_7OS$ and a molecular weight of 501.65. Fimasartan has been approved as a pharmaceutical product, fimasartan potassium trihydrate, for use in South Korea and commercially available.

Moreover, hydrochlorothiazide is a diuretic that is

orally administered for the treatment of edema and hypertension and has a chemical name of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide, an empirical formula of $C_7H_8ClN_3O_4S_2$, and a molecular weight of 297.74.

The combination therapy with an ARB drug including fimasartan, and hydrochlorothiazide as a diuretic, has been known to exhibit synergistic therapeutic efficacy in the treatment of hypertension, and thus many studies have been conducted to structurally combine the ARB drug and the diuretic hydrochlorothiazide, but it is difficult to uniformly combine two drugs in pharmaceutical preparations.

When a product containing high contents of main components is prepared by mixing and direct tableting, tableting problems such as capping or sticking are generally caused by the properties of the main components. Fimasartan has high scattering properties due to its relatively low bulk and tapped densities and tends to agglomerate with each other. Due to its agglomerating properties, when the fimasartan is mixed in a high share mixer, uniform mixing is very difficult to achieve. Moreover, there is a more than 10-fold difference in the mixing ratio of fimasartan and hydrochlorothiazide, and thus it is very difficult to prepare a granule in which the contents of two main components are uniform.

Therefore, there is a need to provide a pharmaceutical composition containing active ingredients of fimasartan and hydrochlorothiazide with excellent physical properties of granules for the preparation of tablets and high content uniformity of fimasartan and hydrochlorothiazide.

Prior Art Document

Patent Document:

Korean Patent No. 10-1058284

【Disclosure】

【Technical Problem】

The present invention aims at providing a pharmaceutical composition which comprises fimasartan, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof and hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof, exhibits high content uniformity of fimasartan and hydrochlorothiazide, which are the main components of a combination preparation, and has excellent physical properties, and a preparation method thereof.

【Technical Solution】

The present invention provides a pharmaceutical composition comprising: fimasartan, a pharmaceutically

acceptable salt thereof, a hydrate thereof, or a solvate thereof; hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof; and a binder exhibiting a viscosity of 20 mPa·s to 1,000 mPa·s at 25 ℃.

The pharmaceutical composition comprising a binder exhibiting a viscosity of 20 mPa·s to 1,000 mPa·s at room temperature of 25 ℃ has high content uniformity. This enables the preparation of a stable pharmaceutical composition by uniform mixing of the main components, fimasartan and hydrochlorothiazide, and exhibits an excellent effect of preventing or treating cardiovascular diseases.

The binder may be starch, gelatin, glucose syrup, polyvinylpyrrolidone, acacia, polyethylene glycol 6000, methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, etc. and may preferably comprises at least one selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone.

As used herein, the term “pharmaceutically acceptable salt” refers to a salt that is conventionally used in the pharmaceutical industry, and examples of the salt include inorganic ion salts such as those of calcium, potassium, sodium, and magnesium, etc., inorganic acid salts such as

those of hydrochloric acid, nitric acid, phosphoric acid, bromic acid, hydroiodic acid, perchloric acid, and sulfuric acid, etc., organic acid salts such as those of acetic acid, trifluoroacetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, propionic acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonic acid, vanillic acid, hydroiodic acid, mucic acid, pamoic acid, and pantothenic acid, etc., sulfonic acid salts such as those of methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, or naphthalenesulfonic acid, etc., amino acid salts such as those of glycine, arginine, lysine, etc., and amine salts such as those of trimethylamine, triethylamine, ammonia, pyridine, picoline, etc. but are not limited thereto.

The hydrate of fimasartan according to the present invention may be a monohydrate, dihydrate, trihydrate, tetrahydrate, pentahydrate, etc., preferably trihydrate.

Preferably, the pharmaceutical composition may comprise fimasartan potassium trihydrate and hydrochlorothiazide.

The pharmaceutical composition may be a solid preparation in the form of a tablet, pill, powder, granule, capsule, etc., preferably in the form of a tablet. The solid preparation may comprise at least one additive such as an

excipient, a binder, a disintegrant, a lubricant, an adsorbent, a humectant, a coating agent, or a controlled-release additive in the composition of the present invention. Specifically, examples of the additive may comprise starch, gelatin, glucose syrup, acacia, polyethylene glycol, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, avicel, carboxymethylcellulose calcium, talc, corn starch, colloidal silicon dioxide, sodium lauryl sulfate, magnesium lauryl sulfate, sodium chloride, magnesium stearate, stearic acid, glycerin, propyleneglycol, sorbitol, Eudragit, polyvinyl acetate phthalate, white beeswax, carnauba wax, paraffin, hardened vegetable oil, shellac, or zein, etc.

The tablet may be a sugar-coated tablet coated with sugar or sugar alcohol on uncoated tablet, or a film-coated tablet coated with an appropriate coating agent on uncoated tablet. Otherwise, the tablet may be a sustained-release tablet or enteric-coated tablet prepared by an appropriate method. Moreover, the tablet may be a multi-layered tablet prepared by compressing particulate matters of different compositions in multiple layers or a dry-coated tablet prepared by coating an inner core tablet with an outer layer of a different composition by an appropriate method, and the tablet may preferably comprise an uncoated tablet and a coating layer.

The present invention provides a method for preparing a

pharmaceutical composition comprising fimasartan, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof and hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof, the method comprising the steps of:

preparing a mixture comprising fimasartan, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof and hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof;

preparing granules by mixing the mixture with a binding solution in which a binder is dissolved to exhibit a viscosity of 20 mPa·s to 1,000 mPa·s at 25 ℃; and

preparing an uncoated tablet containing the granules.

The pharmaceutical composition is prepared by wet granulation method, i.e. preparing a binding solution by dissolving a binder in a solvent such as purified water or ethanol, etc, and thereafter preparing the granules by dissolving active ingredients such as fimasartan, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof and hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof in the binding solution.

The binder may be starch, gelatin, glucose syrup, polyvinylpyrrolidone, acacia, polyethylene glycol 6000,

methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, etc. and may preferably comprise at least one selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone.

The binding solution exhibiting a viscosity of 20 mPa·s to 1,000 mPa·s at 25 ℃ may comprise hydroxypropyl cellulose, hydroxypropyl methylcellulose, or polyvinylpyrrolidone, which is 3%(w/w) to 25%(w/w) at 25 ℃, and may preferably comprise: 3%(w/w) to 15%(w/w) low viscosity hydroxypropyl cellulose (Klucel-ELF/Ashland); 3%(w/w) to 10%(w/w) high viscosity hydroxypropyl cellulose (Klucel-LF/Ashland); 3%(w/w) to 15%(w/w) hydroxypropyl methylcellulose (HPMC 2910/Methocel); or 10%(w/w) to 25%(w/w) polyvinylpyrrolidone (Kollidon 30/BASF).

In the preparation method, when the binding solution exhibits a viscosity of 20 mPa·s to 1,000 mPa·s at room temperature of 25 ℃, the pharmaceutical composition has high content uniformity. This enables the preparation of a stable pharmaceutical composition by uniform mixing of fimasartan and hydrochlorothiazide, and exhibits an excellent effect of preventing or treating cardiovascular diseases.

The preparation method may further comprise the steps of:

preparing sized materials by sizing the granules;

preparing a final mixture by adding one or more additives to the sized materials; and

preparing the uncoated tablet by compressing the final mixture.

The pharmaceutical composition according to the present invention may have a relative standard deviation (RSD) 5% or less, preferably 4.0% or less, in the content uniformity test according to the content uniformity criteria described in the Uniformity of Dosage Units of Korean Pharmacopoeia 9th edition.

The pharmaceutical composition may be a solid preparation in the form of a tablet, pill, powder, granule, capsule, etc., preferably in the form of a tablet. The solid preparation may comprise at least one additive such as an excipient, a binder, a disintegrant, a lubricant, an adsorbent, a humectant, a coating agent, or a controlled-release additive in the composition of the present invention. Specifically, examples of the additive may comprise starch, gelatin, glucose syrup, acacia, polyethylene glycol, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, avicel, carboxymethylcellulose calcium, talc, corn starch, colloidal silica, sodium lauryl sulfate, magnesium lauryl sulfate, sodium chloride, magnesium stearate, stearic acid, glycerin, propyleneglycol, sorbitol, Eudragit,

polyvinyl acetate phthalate, white beeswax, carnauba wax, paraffin, hardened vegetable oil, shellac, or zein, etc.

The tablet may be a sugar-coated tablet coated with a coating agent containing sugar or sugar alcohol or a film-coated tablet coated with an appropriate coating agent. Otherwise, the tablet may be a sustained-release tablet or enteric-coated tablet prepared by an appropriate method. Moreover, the tablet may be a multi-layered tablet prepared by compressing particulate matters of different compositions in multiple layers or a dry-coated tablet prepared by coating an inner core tablet with an outer layer of a different composition by an appropriate method, and the tablet may preferably comprise an uncoated tablet and a coating layer.

The hardness of the uncoated tablet is one suitable for compression and may preferably be 7 Kp or more.

The use of the pharmaceutical composition is not particularly limited but may preferably be used for the treatment of hypertension.

The present invention provides a method for treatment of hypertension, comprising administering a pharmaceutical composition comprising: fimasartan, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof; hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof; and a binder exhibiting a viscosity of 20 mPa·s to 1,000 mPa·s at

25 ℃.

【Advantageous Effects】

The composition comprising fimasartan and hydrochlorothiazide according to the present invention exhibits an excellent effect of preventing or treating cardiovascular diseases.

Moreover, according to the present invention, when a binding solution exhibiting a viscosity of 20 mPa·s to 1,000 mPa·s is used in a combination preparation of fimasartan and hydrochlorothiazide, which tend to agglomerate and thus are not uniformly mixed, resulting in low content uniformity, it is possible to prepare a combination preparation of fimasartan and hydrochlorothiazide with high content uniformity and excellent physical properties such as hardness.

【Mode for Invention】

Hereinafter, the present invention will be described in more detail with reference to the following Examples. However, these Examples are provided only to illustrate the present invention, but the scope of the present invention is not limited thereto.

**Example 1**

A tablet comprising fimasartan potassium trihydrate and

hydrochlorothiazide was prepared using the ingredients and contents shown in the following Table 1. 132.02 mg of fimasartan potassium trihydrate, 12.50 mg of hydrochlorothiazide, 112.48 mg of lactose hydrate, 23.50 mg of microcrystalline cellulose, and 22.50 mg of croscarmellose sodium were stirred with an agitator at 100 rpm and a chopper at 200 rpm for 2 minutes (High Share Mixer SM-5C, Sejong Pharmatech) to prepare a mixture. A binding solution prepared by dissolving 2.00 mg of low viscosity hydroxypropyl cellulose (Klucel-ELF/Ashland) in 24.0 mg of ethanol and 22.0 mg of purified water was added to the mixture, and the mixture was stirred with an agitator at 200 rpm and a chopper at 2000 rpm for 2 minutes (High Share Mixer SM-5C, Sejong Pharmatech) to prepare white granules. The granules was dried at 40 ℃ for 10 hours and sized with a 30-mesh sieve to prepare sized materials. Then, 22.50 mg of croscarmellose sodium and 4.50 mg of magnesium stearate were added to the sized materials to prepare a final mixture. The final mixture was compressed at a compression pressure of 20 kN to prepare an uncoated tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide. The uncoated tablet was coated with HPMC-based Opadry to prepare a tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide.

**Example 2**

A tablet comprising fimasartan potassium trihydrate and

hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 2 of the following Table 1 were used.

**Example 3**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 3 of the following Table 1 were used.

[Table 1]

| | Example 1 | Example 2 | Example 3 |
|---|---|---|---|
| Mixing part | | | |
| Fimasartan potassium trihydrate | 132.02 mg | 132.02 mg | 132.02 mg |
| Hydrochlorothiazide | 12.50 mg | 12.50 mg | 12.50 mg |
| Lactose hydrate | 112.48 mg | 110.48 mg | 108.48 mg |
| Microcrystalline cellulose | 23.50 mg | 23.50 mg | 23.50 mg |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Binding solution part | | | |
| Low viscosity hydroxypropyl cellulose (Klucel-ELF/Ashland) | 2.00 mg | 4.00 mg | 6.00 mg |
| Ethanol | 24.0 mg | 24.0 mg | 24.0 mg |
| Purified water | 22.0 mg | 22.0 mg | 22.0 mg |
| Final mixing part | | | |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Magnesium stearate | 4.50 mg | 4.50 mg | 4.50 mg |

**Example 4**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 4 of the following Table 2 were used.

**Example 5**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 5 of the following Table 2 were used.

[Table 2]

| | Example 4 | Example 5 |
|---|---|---|
| Mixing part | | |
| Fimasartan potassium trihydrate | 132.02 mg | 132.02 mg |
| Hydrochlorothiazide | 12.50 mg | 12.50 mg |
| Lactose hydrate | 112.48 mg | 110.48 mg |
| Microcrystalline cellulose | 23.50 mg | 23.50 mg |
| Croscarmellose sodium | 22.50 mg | 22.50 mg |
| Binding solution part | | |
| High viscosity hydroxypropyl cellulose (Klucel-LF/Ashland) | 2.00 mg | 4.00 mg |
| Ethanol | 24.0 mg | 24.0 mg |
| Purified water | 22.0 mg | 22.0 mg |
| Final mixing part | | |
| Croscarmellose sodium | 22.50 mg | 22.50 mg |
| Magnesium stearate | 4.50 mg | 4.50 mg |

**Example 6**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 6 of the following Table 3 were used.

**Example 7**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 7 of the following Table 3 were used.

**Example 8**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 8 of the following Table 3 were used.

[Table 3]

| | Example 6 | Example 7 | Example 8 |
|---|---|---|---|
| Mixing part | | | |
| Fimasartan potassium trihydrate | 132.02 mg | 132.02 mg | 132.02 mg |
| Hydrochlorothiazide | 12.50 mg | 12.50 mg | 12.50 mg |
| Lactose hydrate | 112.48 mg | 110.48 mg | 108.48 mg |
| Microcrystalline cellulose | 23.50 mg | 23.50 mg | 23.50 mg |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Binding solution part | | | |

| | | | |
|---|---|---|---|
| Hydroxypropyl methylcellulose (Methocel E5/Dow Chemical) | 2.00 mg | 4.00 mg | 6.00 mg |
| Ethanol | 24.0 mg | 24.0 mg | 24.0 mg |
| Purified water | 22.0 mg | 22.0 mg | 22.0 mg |
| Final mixing part | | | |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Magnesium stearate | 4.50 mg | 4.50 mg | 4.50 mg |

**Example 9**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 9 of the following Table 4 were used.

**Example 10**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 10 of the following Table 4 were used.

**Example 11**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Example 11 of the following Table 4 were used.

[Table 4]

| | Example 9 | Example 10 | Example 11 |
|---|---|---|---|
| Mixing part | | | |
| Fimasartan potassium trihydrate | 132.02 mg | 132.02 mg | 132.02 mg |
| Hydrochlorothiazide | 12.50 mg | 12.50 mg | 12.50 mg |
| Lactose hydrate | 108.48 mg | 106.48 mg | 104.48 mg |
| Microcrystalline cellulose | 23.50 mg | 23.50 mg | 23.50 mg |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Binding solution part | | | |
| Polyvinylpyrrolidone (Kollidon 30/BASF) | 6.00 mg | 8.00 mg | 10.00 mg |
| Ethanol | 24.0 mg | 24.0 mg | 24.0 mg |
| Purified water | 22.0 mg | 22.0 mg | 22.0 mg |
| Final mixing part | | | |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Magnesium stearate | 4.50 mg | 4.50 mg | 4.50 mg |

**Comparative Example 1**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Comparative Example 1 of the following Table 5 were used.

**Comparative Example 2**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Comparative Example 2 of the following Table 5 were used.

**Comparative Example 3**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Comparative Example 3 of the following Table 5 were used.

[Table 5]

| | Comparative Example 1 | Comparative Example 2 | Comparative Example 3 |
|---|---|---|---|
| Mixing part | | | |
| Fimasartan potassium trihydrate | 132.02 mg | 132.02 mg | 132.02 mg |
| Hydrochlorothiazide | 12.50 mg | 12.50 mg | 12.50 mg |
| Lactose hydrate | 106.48 mg | 104.48 mg | 108.48 mg |
| Microcrystalline cellulose | 23.50 mg | 23.50 mg | 23.50 mg |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Binding solution part | | | |
| Low viscosity hydroxypropyl cellulose (Klucel-ELF/Ashland) | 8.00 mg | 10.00 mg | - |
| High viscosity hydroxypropyl cellulose (Klucel-LF/Ashland) | - | - | 6.00 mg |
| Ethanol | 24.0 mg | 24.0 mg | 24.0 mg |
| Purified water | 22.0 mg | 22.0 mg | 22.0 mg |
| Final mixing part | | | |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Magnesium stearate | 4.50 mg | 4.50 mg | 4.50 mg |

**Comparative Example 4**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same

method as Example 1, except that the ingredients and contents shown in Comparative Example 4 of the following Table 6 were used.

**Comparative Example 5**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Comparative Example 5 of the following Table 6 were used.

**Comparative Example 6**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Comparative Example 6 of the following Table 6 were used.

[Table 6]

| | Comparative Example 4 | Comparative Example 5 | Comparative Example 6 |
|---|---|---|---|
| Mixing part | | | |
| Fimasartan potassium trihydrate | 132.02 mg | 132.02 mg | 132.02 mg |
| Hydrochlorothiazide | 12.50 mg | 12.50 mg | 12.50 mg |
| Lactose hydrate | 106.48 mg | 112.48 mg | 110.48 mg |
| Microcrystalline cellulose | 23.50 mg | 23.50 mg | 23.50 mg |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Binding solution part | | | |
| Hydroxypropyl methylcellulose (HPMC 2910/Methocel) | 8.00 mg | - | - |
| Polyvinylpyrrolidone (Kollidon 30/BASF) | - | 2.00 mg | 4.00 mg |

| | | | |
|---|---|---|---|
| Ethanol | 24.0 mg | 24.0 mg | 24.0 mg |
| Purified water | 22.0 mg | 22.0 mg | 22.0 mg |
| Final mixing part | | | |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Magnesium stearate | 4.50 mg | 4.50 mg | 4.50 mg |

**Comparative Example 7**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Comparative Example 7 of the following Table 7 were used.

**Comparative Example 8**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Comparative Example 8 of the following Table 7 were used.

**Comparative Example 9**

A tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was prepared by substantially the same method as Example 1, except that the ingredients and contents shown in Comparative Example 9 of the following Table 7 were used.

[Table 7]

| | Comparative Example 7 | Comparative Example 8 | Comparative Example 9 |
|---|---|---|---|

| Mixing part | | | |
|---|---|---|---|
| Fimasartan potassium trihydrate | 132.02 mg | 132.02 mg | 132.02 mg |
| Hydrochlorothiazide | 12.50 mg | 12.50 mg | 12.50 mg |
| Lactose hydrate | 106.48 mg | 112.48 mg | 110.48 mg |
| Microcrystalline cellulose | 23.50 mg | 23.50 mg | 23.50 mg |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Binding solution part | | | |
| High viscosity hydroxypropyl cellulose (Klucel-LF/Ashland) | 8.00 mg | 10.00 mg | - |
| Hydroxypropyl methylcellulose (HPMC 2910/Methocel) | - | - | 10.00 mg |
| Ethanol | 24.0 mg | 24.0 mg | 24.0 mg |
| Purified water | 22.0 mg | 22.0 mg | 22.0 mg |
| Final mixing part | | | |
| Croscarmellose sodium | 22.50 mg | 22.50 mg | 22.50 mg |
| Magnesium stearate | 4.50 mg | 4.50 mg | 4.50 mg |

**Experimental Example 1: Viscosity test of binding solutions depending on type and concentration of binders**

The viscosities of the binding solutions used in Examples 1 to 11 and Comparative Example 1 to 9 were measured using a viscometer (Fungilab/Visco Basic-L) at room temperature of 25 °C. The results of the viscosity test are shown in Table 8:

[Table 8]

| | Ex.1 | Ex.2 | Ex.3 | Ex.4 | Ex.5 | Ex.6 | Ex.7 |
|---|---|---|---|---|---|---|---|
| Viscosity (mPa·s) | 20 | 140 | 480 | 80 | 640 | 30 | 230 |
| | | | | | | | |
| | Ex.8 | Ex.9 | Ex.10 | Ex.11 | Comp. Ex.1 | Comp. Ex.2 | Comp. Ex.3 |
| Viscosity | 650 | 26 | 31 | 39 | 1110 | 2210 | 1930 |

| (mPa·s) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | Comp. Ex.4 | Comp. Ex.5 | Comp. Ex.6 | Comp. Ex.7 | Comp. Ex.8 | Comp. Ex.9 | - |
| Viscosity (mPa·s) | 1640 | 7 | 12 | - | - | - | - |

In the above table 8, the preparation of the binding solution was stopped because excess load was applied to the mixer due to high viscosity when the concentration of high viscosity hydroxypropyl cellulose (Klucel-LF/Ashland) was 17.4% (Comparative Examples 7 and 8) that was higher than the concentration of the binding solution, 13.0%, and the preparation of the binding solution was also stopped by the same problem when the concentration of hydroxypropyl methylcellulose was 21.7% (Comparative Example 9). According to the test results, the binding solutions that were not prepared in Comparative Examples 7 to 9 were not used in the next experiment.

**Experimental Example 2: Content uniformity test of fimasartan potassium trihydrate and hydrochlorothiazide**

The content uniformity test of fimasartan potassium trihydrate and hydrochlorothiazide was performed on the samples collected from a total of 10 portions of the final mixtures by HPLC. The analysis conditions of HPLC are shown in Table 9, and the preparation process of the standard solution and the test solution are shown in Table 10. The results of the content uniformity test are shown in Table 11,

in which F represents fimasartan potassium trihydrate and H represents hydrochlorothiazide.

[Table 9]

| | | |
|---|---|---|
| Column | Xterra C18(5 microns, 250 * 4.6 mm) | |
| Device | Detection | 260 nm |
| Diluent | Temperature | 40 ℃ |
| Buffer | Run time | 16 min |
| Mobile phase | Injection | 20 uL |
| | Flow rate | 1.0 mL/min |
| | Sample Temp. | 25 ℃ |
| | MeOH | |
| | 0.01 M phosphate buffer (pH 2.5) | |
| | Buffer : Acetonitrile = 60 : 40 | |

[Table 10]

| Preparation of standard solution | Preparation of test solution |
|---|---|
| A. Taking an amount corresponding to 66.0 mg of fimasartan potassium trihydrate<br>↓← Diluent<br>50 mL v/f<br><br>B. Taking an amount corresponding to 12.5 mg of hydrochlorothiazide<br>↓← Diluent<br>100 mL v/f<br><br>Taking each 5 mL of A and B<br>↓← Mobile phase<br>200 mL v/f | Taking an amount corresponding to one tablet<br>↓← Purified water 10 mL<br>Sonication for 30 sec.<br>↓← Diluent 60 mL<br>Sonication for 20 min.<br>↓← Diluent<br>100 mL v/f<br><br>Taking 5 mL<br>↓← Mobile phase<br>200 mL v/f |

[Table 11]

| | Ex.1 | Ex.2 | Ex.3 | Ex.4 | Ex.5 | Ex.6 |
|---|---|---|---|---|---|---|

| | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean | 97.2 | 96.9 | 100.3 | 97.9 | 99.5 | 99.1 | 98.6 | 97.2 | 99.2 | 98.6 | 99.6 | 98.1 |
| RSD | 2.93 | 3.43 | 3.17 | 3.04 | 1.76 | 1.34 | 2.29 | 2.36 | 3.18 | 3.05 | 2.49 | 2.42 |

| | Ex.7 | | Ex.8 | | Ex.9 | | Ex.10 | | Ex.11 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) |
| Mean | 98.3 | 97.4 | 99.1 | 97.7 | 100.1 | 98.7 | 98.1 | 97.8 | 99.4 | 98.3 |
| RSD | 3.03 | 2.96 | 2.24 | 2.01 | 3.14 | 2.76 | 2.34 | 2.87 | 3.34 | 3.07 |

| | Comp. Ex.1 | | Comp. Ex.2 | | Comp. Ex.3 | | Comp. Ex.4 | | Comp. Ex.5 | | Comp. Ex.6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) | F(%) | H(%) |
| Mean | 97.1 | 95.4 | 97.4 | 96.3 | 98.3 | 97.5 | 109.4 | 98.6 | 99.9 | 98.8 | 98.9 | 98.3 |
| RSD | 9.21 | 9.47 | 10.58 | 10.55 | 15.87 | 14.95 | 12.02 | 13.53 | 3.35 | 3.25 | 3.17 | 3.38 |

As can be seen from the above Table 11, in Examples 1 to 11 and Comparative Examples 5 and 6, where binding solutions with viscosities less than 1,000 mPa·s were used, the relative standard deviations (RSDs) were 4.0% or less, indicating high content uniformity. However, in Comparative Examples 1 to 4 where binding solutions with viscosities of 1,000 mPa·s or more were used, the relative standard deviations (RSDs) were significantly increased to 9.21 to 15.87%, indicating low content uniformity. According to the test results, it could be found that the content uniformity of the final mixture of fimasartan potassium trihydrate and hydrochlorothiazide of the present invention is high when a binding solution with a viscosity in less than 1,000 mPa·s is used. Moreover, it can be seen that the binding solution

preferably contains 4.3%(w/w) to 13.0%(w/w) low viscosity hydroxypropyl cellulose (Klucel-ELF/Ashland); 4.3%(w/w) to 8.7%(w/w) high viscosity hydroxypropyl cellulose (Klucel-LF/Ashland); 4.3%(w/w) to 13.0%(w/w) hydroxypropyl methylcellulose (HPMC 2910/Methocel); or 13.0%(w/w) to 21.7%(w/w) polyvinylpyrrolidone (Kollidon 30/BASF) in a solvent at 25 ℃.

**Experimental Example 3: Hardness test of uncoated tablets comprising fimasartan potassium trihydrate and hydrochlorothiazide**

The hardness test for coating an uncoated tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide was performed by compression at a pressure of 20 kN. In order to coat the uncoated tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide, the uncoated tablet should have a minimum hardness of 7 to 8 Kp, and when the hardness is below 7 Kp, the tablet may be broken or worn during the coating process, which makes it impossible to obtain a final product of good quality. The results of the hardness test are shown in Table 12.

[Table 12]

| Sample | Ex.1 | Ex.2 | Ex.3 | Ex.4 | Ex.5 | Ex.6 |
|---|---|---|---|---|---|---|
| Average hardness (Kp) | 7.1 | 8.6 | 10.7 | 8.1 | 11.9 | 7.5 |

| Sample | Ex.7 | Ex.8 | Ex.9 | Ex.10 | Ex.11 |
|---|---|---|---|---|---|
| Average hardness (Kp) | 8.6 | 11.7 | 7.2 | 7.1 | 7.6 |

| Sample | Comp. Ex.1 | Comp. Ex.2 | Comp. Ex.3 | Comp. Ex.4 | Comp. Ex.5 | Comp. Ex.6 |
|---|---|---|---|---|---|---|
| Average hardness (Kp) | 12.3 | 13.7 | 13.5 | 13.3 | 3.4 | 4.7 |

As can be seen from the above Table 12, it was confirmed that in Comparative Examples 5 and 6 where binding solutions with viscosities in less than 20 mPa·s were used, the hardness was measured as 3.4 Kp and 4.7 Kp, respectively, indicating that the hardness is not suitable for the coating process. According to the test results, it was found that when a binding solution with a viscosity of 20 mPa·s or more was used to coat the uncoated tablet comprising fimasartan potassium trihydrate and hydrochlorothiazide, it is possible to produce a combination preparation having high hardness of 7 Kp or more.

【Industrial Applicability】

As described above, the composition comprising fimasartan and hydrochlorothiazide according to the present invention exhibits an excellent effect of preventing or treating cardiovascular diseases.

Moreover, according to the present invention, when a

binding solution exhibiting a viscosity of 20 mPa·s to 1,000 mPa·s is used in a combination preparation of fimasartan and hydrochlorothiazide, which tend to agglomerate and thus are not uniformly mixed, resulting in low content uniformity, it is possible to prepare a combination preparation of fimasartan and hydrochlorothiazide with high content uniformity and excellent physical properties such as hardness.

【CLAIMS】

【Claim 1】

A pharmaceutical composition comprising:

fimasartan, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof;

hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof; and

a binder exhibiting a viscosity of 20 mPa·s to 1,000 mPa·s at 25 ℃.

【Claim 2】

The pharmaceutical composition of claim 1, wherein the binder comprises at least one selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone.

【Claim 3】

The pharmaceutical composition of claim 1, wherein the pharmaceutical composition have a relative standard deviation (RSD) of 4.0% or less in content uniformity test.

【Claim 4】

The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of a tablet.

【Claim 5】

The pharmaceutical composition of claim 4, wherein the tablet comprises an uncoated tablet and a coating layer.

【Claim 6】

The pharmaceutical composition of claim 5, wherein the uncoated tablet has a hardness of 7 Kp or more.

【Claim 7】

The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is used for the treatment of hypertension.

【Claim 8】

A method for preparing a pharmaceutical composition comprising fimasartan, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof and hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof, the method comprising the steps of:

preparing a mixture comprising fimasartan, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof and hydrochlorothiazide, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate thereof;

preparing granules by mixing the mixture with a binding solution in which a binder is dissolved to exhibit a viscosity of 20 mPa·s to 1,000 mPa·s at 25 ℃; and

preparing an uncoated tablet containing the granules.

【Claim 9】

The method of claim 8, further comprising the steps of:

preparing sized materials by sizing the granules;

preparing a final mixture by adding one or more additives to the sized materials; and

preparing the uncoated tablet by compressing the final mixture.

【Claim 10】

The method of claim 8, wherein the binder comprises at least one selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone.

【Claim 11】

The method of claim 8, wherein the pharmaceutical composition have a relative standard deviation (RSD) of 4.0% or less in content uniformity test.

【Claim 12】

The method of claim 8, wherein the uncoated tablet has a hardness of 7 Kp or more.

【Claim 13】

The method of claim 8, wherein the pharmaceutical composition is used for the treatment of hypertension.

【Claim 14】

A tablet prepared by the method of any one of claims 8 to 13.