PHARMACEUTICAL COMBINATION PREPARATION

Technical Field

[1] The present disclosure relates to a pharmaceutical combination preparation comprising telmisartan and (S)-amlodipine with improved hygroscopic properties.

Background Art

[2] Hypertension refers to a condition where blood pressure above normal is maintained continuously. Hypertension causes various complications and may ultimately lead to death. Hypertension is classified into primary hypertension and secondary hypertension depending on the cause of the increase in blood pressure. Primary hypertension is also known as essential hypertension in which the cause of the increase in blood pressure is unknown, and secondary hypertension is a condition where the increase in blood pressure is caused by a particular disease or disorder. Secondary hypertension can be treated by removing the cause of the increase in blood pressure, but the cause of primary hypertension, which accounts for about 95% of the cases of hypertension, is not known clearly, and thus the patients with primary hypertension are treated with drug therapy based on several blood pressure-lowering mechanisms.

[3] Drugs commonly used for the treatment of hypertension are generally divided into vasodilators, diuretics, and sympatholytics depending on the mechanism of action of these drugs, and the currently widely used vasodilators are divided again into angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and calcium channel blockers.

[4] For the treatment of hypertension, it is important to prevent stroke, heart failure, coronary artery diseases such as myocardial infarction, cardiovascular complications such as renal failure, which threaten the patient's life, by maintaining blood pressure within a normal range, instead of treating the blood pressure itself, and thus it is important to regulate the blood pressure constantly and patiently. As such, it is necessary to continue to take blood pressure drugs for a long time, and thus the therapeutic agent should be carefully selected. Therefore, it is necessary to provide excellent preventive and therapeutic effects by combining drugs with different mechanisms, rather than selecting one drug, and to reduce side effects, which may be caused by long-term administration of drugs, by reducing the amount of one drug through combined administration. In the case where the effect of blood pressure regulation is not sufficiently obtained by single drug administration, it is recommended by hypertension management guidelines (JNC 7) to administer a combination of drugs

with different mechanisms.

[5] In particular, a combination therapy of an angiotensin II receptor blocker (ARB) and a calcium channel blocker (CCB), which have different mechanisms of action in the human body, is first selected in the event of a failure in blood pressure regulation through the single administration. The pharmacological actions of these two drugs for blood pressure lowering are different from each other, and thus the combined administration of these two drugs has an effective blood pressure-lowering effect and reduces the amount of drugs used, thus significantly reducing the side effects of each component.

[6] Telmisartan is one of the angiotensin II receptor blockers (ARBs) and is commercially available in two doses of 40 mg and 80 mg under the trade name of Pritor. Telmisartan is prescribed for essential hypertension and is a drug that selectively acts on an angiotensin II receptor, which acts as a potent vasoconstrictor in the renin-angiotensin-aldosterone system and, in particular, selectively acts on an AT1 receptor involved in the main physiological actions such as vasoconstriction, etc.

[7] Amlodipine is one of the calcium channel blockers (CCBs) and is commercially available in doses of 5 mg and 10 mg under the trade name of Norvasc. The isolation and administration of (S)-amlodipine, a pure optical isomer, increases the receptor binding selectivity, which shows efficacy compared to amlodipine racemate, and reduces the dose by about half, reducing the interaction between the drugs and the possibility of side effects.

[8] A complex composition comprising telmisartan and (S)-amlodipine as active ingredients, which are representative ARB and CCB drugs, has an effective blood pressure-lowering effect and reduces the amount of drugs used, which significantly reduces the side effects of each component.

[9] However, it is necessary to use a basic material to improve the solubility and solubilization of telmisartan for the formulation, and sodium hydroxide and meglumine are mainly used as the basic material. Meanwhile, when a strong basic material having deliquescence such as sodium hydroxide is used, the basic material easily absorbs water in hands during exposure to moisture or during administration due to its high hygroscopic properties, and thus the tablet is sticky or melted, which is very problematic.

Disclosure of Invention

Technical Problem

[10] An object of the present disclosure is to provide a pharmaceutical combination preparation comprising a first layer comprising telmisartan or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, and calcium silicate; and a second layer comprising (S)-amlodipine or a pharmaceutically acceptable salt thereof.

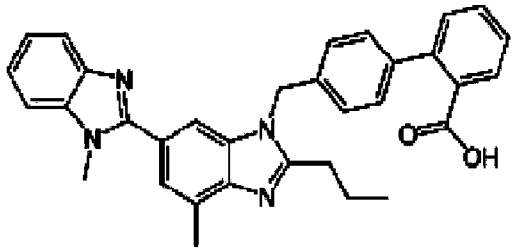
Solution to Problem

[11] In an aspect to achieve the above object, the present disclosure provides a pharmaceutical combination preparation comprising a first layer comprising telmisartan or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, and calcium silicate; and a second layer comprising (S)-amlodipine or a pharmaceutically acceptable salt thereof.

[12] The pharmaceutical combination preparation of the present disclosure comprises microcrystalline cellulose and calcium silicate in the first layer to improve the hygroscopic properties of the first layer comprising telmisartan and, at the same time, not to influence the stability of (S)-amlodipine contained in the second layer.

[13] In the present disclosure, "telmisartan" is a compound with the chemical name of 2-(4-{[4-methyl-6-(1-methyl-1H-1,3-benzothiazol-2-yl)-2-propyl-1H-1,3-benzothiazol-1-yl]methyl}phenyl)benzoic acid and is represented by the following Formula 1:

[14] [Formula 1]

[15] 

[16] In the present disclosure, telmisartan may be commercially available or synthesized by any method known in the art, but not limited thereto.

[17] Telmisartan of the present disclosure may be used in various forms such as a free acid of telmisartan or a pharmaceutically acceptable salt thereof, an isomer, a racemate, a hydrate, a solvate, etc. as long as the same pharmacological activity is maintained.

[18] The pharmaceutically acceptable salt comprises a salt derived from a pharmaceutically acceptable acid or base. As used herein, the term "pharmaceutically acceptable salt" refers to any organic or inorganic addition salt whose concentration has effective action because it is relatively non-toxic and harmless to the patients and whose side effects do not degrade the beneficial efficacy of the active ingredient.

[19] Preferably, the pharmaceutically acceptable salt of telmisartan of the present disclosure may be a sodium salt, a potassium salt, a magnesium salt, or a calcium salt of telmisartan, but not limited thereto.

[20] More preferably, the pharmaceutical combination preparation of the present disclosure comprises a free acid of telmisartan.

[21] In the present disclosure, isomer includes optical isomer, diastereomer and mixture of both.

[22] Telmisartan is prescribed for essential hypertension and is a drug that selectively acts

on an angiotensin II receptor, which acts as a potent vasoconstrictor in the renin-angiotensin-aldosterone system and, in particular, selectively acts on an AT1 receptor involved in the main physiological actions such as vasoconstriction, etc. Telmisartan has a blood pressure-lowering effect continuously for 24 hours, and thus the drug taken the day before has the effect of regulating blood pressure until the next morning when blood pressure rapidly increases. Furthermore, the renal clearance of telmisartan is less than 2%, and thus it is not necessary to adjust the dose in patients with mild to severe renal impairment. According to the recent research results, the risk of occurrence of side effects such as hyperpotassemia is very lower than other ARBs (Park Rae Woong, American Journal of Cardiovascular Drugs, (2012)), and thus it has been evaluated as the best drug among the existing ARBs.

[23] Telmisartan has very poor solubility in aqueous systems at the physiological pH range (pH 1 to 7) of the gastrointestinal tract, and thus it is preferred to use an alkalizing agent to improve the solubility and solubilization of telmisartan for the formulation.

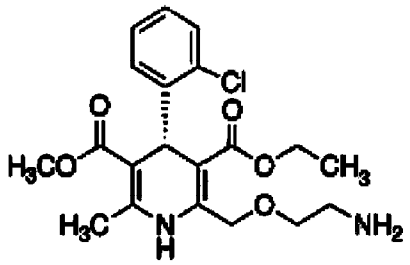
[24] Therefore, the first layer of the pharmaceutical combination preparation according to the present disclosure preferably comprises an alkalizing agent. Suitable alkalizing agents that can be used include metal hydrates, basic amino acids, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydrogen phosphate, and mixtures thereof. Examples of the metal hydrate may include sodium hydroxide, calcium hydroxide, etc.; and examples of the basic amino acid may include arginine, ricin, meglumine (N-methyl-D-glucamine), etc. Preferably, the pharmaceutical combination preparation of the present disclosure comprises dried sodium carbonate.

[25] Meanwhile, the alkalizing agent has deliquescence and hygroscopic properties, and thus when a preparation comprising an alkalizing agent is exposed to water or moisture, the preparation is sticky or melted, which is very problematic.

[26] Meanwhile, the second layer of the pharmaceutical combination preparation according to the present disclosure preferably comprises (S)-amlodipine as an active ingredient.

[27] In the present disclosure, "(S)-amlodipine" is a compound with the chemical name of 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate and is represented by the following Formula 2:

[28] [Formula 2]

[29] 

[30] In the present disclosure, (S)-amlodipine may be commercially available or synthesized by any method known in the art, but not limited thereto.

[31] (S)-amlodipine of the present disclosure may be used in various forms such as a free base of (S)-amlodipine or a pharmaceutically acceptable salt thereof, an isomer, a racemate, a hydrate, a solvate, etc. as long as the same pharmacological activity is maintained.

[32] The pharmaceutically acceptable salt comprises a salt derived from a pharmaceutically acceptable acid or base. As used herein, the term "pharmaceutically acceptable salt" refers to any organic or inorganic addition salt whose concentration has effective action because it is relatively non-toxic and harmless to the patients and whose side effects do not degrade the beneficial efficacy of the active ingredient.

[33] Preferably, the pharmaceutically acceptable salt of (S)-amlodipine of the present disclosure may be (S)-amlodipine besylate, (S)-amlodipine maleate, (S)-amlodipine orotate, (S)-amlodipine camsylate, (S)-amlodipine adipate, or (S)-amlodipine mesylate, but not limited thereto.

[34] More preferably, the pharmaceutical combination preparation of the present disclosure comprises (S)-amlodipine besylate.

[35] Amlodipine is one of the calcium channel blockers (CCBs) and is a very useful calcium channel blocker that has a half-life of 30 to 50 hours and exhibits activity continuously over a long period of time. Amlodipine blocks the influx of calcium into the vascular smooth muscle to induce peripheral arterial vasodilation, resulting in a decrease in blood pressure, and is effective in angina pectoris due to vasoconstriction. Amlodipine is a chiral compound with a chiral center, and it is known that the (S)-optical isomer of amlodipine is a potent calcium channel blocker that has higher activity than an isomeric mixture (in racemic form) (Arrowsmith et al., J. Med. Chem., 29, 1696 (1986)), and the (R)-optical isomer has activity 1,000 times lower than the (S)-optical isomer and has a kinin-mediated nitric oxide mechanism that is likely to be associated with side effects (Hintze et al., J. Cardiovasc. Pharmacol., 39(2):208-14 (2002)). Therefore, the isolation and administration of (S)-amlodipine, a pure optical isomer, increases the receptor binding selectivity, which shows efficacy compared to amlodipine racemate, and reduces the dose by about half, reducing the interaction between the drugs and the possibility of side effects.

[36] However, it is known that in view of the stability, the (S)-amlodipine is considerably more unstable than the racemate thereof, the degradation of (S)-amlodipine is experimentally faster than the racemate, and the content of related compounds also increases due to an increase in degradation products. This is because the form of thermodynamically isolated optical isomers is unstable (Hadzidedic et al., J. Pharm. Dev. Technol., 19(8): 930.941 (2014)).

[37] The (S)-amlodipine is easily hydrolyzed by the alkalizing agent used for the solubility and solubilization of telmisartan, resulting in reduced stability of amlodipine.

[38] The pharmaceutical combination preparation of the present disclosure has the advantage of improving both the hygroscopic properties of telmisartan and the reduced stability of (S)-amlodipine. Specifically, the present disclosure provides the improvement of the hygroscopic properties in the first layer of pharmaceutical combination preparation that comprises microcrystalline cellulose as an excipient and calcium silicate as an adsorbent. At the same time, it characterized in that the addition of microcrystalline cellulose and calcium silicate in the first layer does not influence the stability of the (S)-amlodipine contained in the second layer.

[39] In a specific experimental example, the degree of hygroscopic properties was tested under accelerated conditions (75% humidity, 40 °C temperature) and, as a result, after 1 day, the commercially available Micardis tablets were melted beyond recognition, while the tablets comprising microcrystalline cellulose were very little changed, resulting in significant improvement of hygroscopic properties (Experimental Example 1).

[40] Preferably, in the pharmaceutical combination preparation of the present disclosure, the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to microcrystalline cellulose is 10:25 to 10:35.

[41] Preferably, the pharmaceutical combination preparation of the present disclosure may comprise microcrystalline cellulose in an amount of 50 to 60 wt% with respect to the total weight of the first layer.

[42] In a specific experimental example, an appropriate content range of microcrystalline cellulose contained in the preparation was determined and, as a result, it was found that when the weight ratio of telmisartan to microcrystalline cellulose was 10:25 and 10:30, the friability of tablets was small, and the maximum hardness of tablets was high; in particular, when the amount of microcrystalline cellulose contained in the preparation was higher, the maximum hardness of tablets increased, and the friability of tablets decreased.

[43] Preferably, in the pharmaceutical combination preparation of the present disclosure, the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to calcium silicate is 10:1 to 10:6.

[44] More preferably, in the pharmaceutical combination preparation of the present disclosure, the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to microcrystalline cellulose is 10:25 to 10:30, and the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to calcium silicate is 10:1 to 10:5.

[45] More particularly, in the pharmaceutical combination preparation of the present disclosure, the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to calcium silicate is 10:2 to 10:3.

[46] In a specific experimental example, the improvement of hygroscopic properties and the influence on the stability of the (S)-amlodipine layer depending on the amount of calcium silicate in the preparation were tested. As a result, it was found that the addition of calcium silicate to the telmisartan layer was effective for the improvement of hygroscopic properties, but when the amount of calcium silicate added was increased, the content of (S)-amlodipine-related compounds was also increased. Therefore, it was found that an appropriate content of calcium silicate contained in the preparation, which improves the hygroscopic properties of the telmisartan layer and does not significantly degrade the stability of the (S)-amlodipine layer, that is, the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to calcium silicate was preferably 10:1 to 10:5, more preferably, 10:2 to 10:3.

[47] The pharmaceutical combination preparation of the present disclosure may further comprise at least one pharmaceutically acceptable additive. Any additives that are well known in the art may be used as long as they do not cause an interaction with telmisartan or a pharmaceutically acceptable salt thereof and (S)-amlodipine or a pharmaceutically acceptable salt thereof and does not disturb the efficacy.

[48] The pharmaceutically acceptable additive may be at least one selected from the group consisting of diluents, binders, disintegrants, lubricants, and coating agents, but not limited thereto.

[49] As used herein, the term "diluent" refers to any inert substance that is used as a filler to create desired bulk, flow properties, and compression characteristics in the preparation of solid dose formulations. Examples of the diluent may include lactose hydrate, anhydrous lactose, white sugar, corn starch, dibasic calcium phosphate, etc., but not limited thereto.

[50] As used herein, the term "excipient" refers to a substance that is added to give appropriate hardness and shape to the medicinal preparation or give certain volume and weight to the medicinal preparation to have a size that is easy to handle when the amount of the main ingredient is small. Examples of the excipient may include sugar derivatives such as mannitol, sorbitol, etc.; starches such as corn starch, potato starch, etc.; cellulose derivatives such as low substituted hydroxypropylcellulose, methylcellulose etc.; inorganic excipients such as calcium carbonate, etc., but not limited

thereto.

[51] In the present disclosure, the terms "diluent" and "excipient" can be interchangeably used.

[52] As used herein, the term "binder" refers to a substance that can impart elasticity and adhesion to increase the strength of the resulting preparation, particularly, the strength of the resulting tablets. Examples of the binder may include carboxymethylcellulose-sodium (CMC-Na), starch solutions, polyvinylpyrrolidone (PVP), gum arabic, hydroxypropylcellulose (HPC), etc., but not limited thereto.

[53] As used herein, the term "disintegrant" refers to a substance that is used to accelerate the disintegration of solid preparations such that an activator that shows efficacy in the preparation is released within a short period of time. Examples of the disintegrant may include carboxymethylcellulose-calcium (CMC-Ca), crospovidone, sodium starch glycolate, sodium croscarmellose, low substituted hydroxypropylcellulose, etc., but not limited thereto.

[54] As used herein, the term "lubricant" refers to a substance that offers improved flow characteristics. Examples of the lubricant may include colloidal silica, magnesium stearate, stearic acid, talk, sodium stearyl fumarate, etc., but not limited thereto.

[55] The pharmaceutical combination preparation of the present disclosure may be, for example, an oral solid preparation, preferably a bilayer tablet.

[56] In another aspect of the present disclosure, the present disclosure provides a method for preparing a pharmaceutical combination preparation comprising telmisartan and (S)-amlodipine. The pharmaceutical combination preparation of the present disclosure may be prepared by any method known to those skilled in the art such as wet granulation method, direct compression, dry granulation, etc.

[57] For example, the method of preparing a pharmaceutical combination preparation of the present disclosure by the wet granulation comprises the steps of preparing a binder solution; preparing a mixture by mixing a main ingredient with a diluent (or excipient); combining the binder solution with the mixture; and compressing the combination by drying, sieving, and lubrication.

[58] Moreover, for example, the method of preparing a pharmaceutical combination preparation of the present disclosure by the direct compression comprises the steps of preparing a mixture by mixing a main ingredient with an excipient; and adding a disintegrant and a lubricant to the mixture, followed by lubrication and compression.

[59] The pharmaceutical combination preparation of the present disclosure may be prepared as follows: in order to provide a telmisartan layer, for example, a solution prepared by dissolving alkaline components such as dried sodium carbonate in an appropriate solvent is sprayed onto an inert excipient and then dried to prepare an amorphous telmisartan granule composition, a granule composition of a layer

comprising (S)-amlodipine is prepared, and then the two granule compositions are compressed to prepare the pharmaceutical combination preparation of the present disclosure.

[60] Moreover, in another aspect of the present disclosure, the pharmaceutical combination preparation of the present disclosure can be effectively used for the purpose of preventing or treating a cardiovascular disease selected from the group consisting of hypertension, angina pectoris, arterial spasm, cardiac arrhythmia, cerebral infarction, heart hypertrophy, congestive heart failure, and myocardial infarction and, in particular, can be used to prevent or treat essential hypertension.

[61] Additionally, the present disclosure provides a pharmaceutical composition comprising the pharmaceutical combination preparation. The pharmaceutical composition of the present disclosure has remarkable effect in preventing and treating cardiovascular diseases.

[62] Further, the present disclosure provides a treatment method for cardiovascular diseases including administration of therapeutically effective dose of a pharmaceutical combination preparation comprising a first layer comprising telmisartan or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, and calcium silicate; and a second layer comprising (S)-amlodipine or a pharmaceutically acceptable salt thereof.

[63] The treating method for cardiovascular diseases by using the pharmaceutical combination preparation of the present disclosure includes administration of the pharmaceutical combination preparation of the present disclosure in an amount of therapeutically effective dose. The term "therapeutically effective dose" stated in the present disclosure describes an amount of the combination preparation of the present disclosure that is effective in preventing or treating cardiovascular diseases. The pharmaceutical combination preparation of the present disclosure can be applied to a treatment method by additionally combining it with one or more therapeutic agents.

[64] Also, the present disclosure provides a use of a pharmaceutical combination preparation comprising a first layer comprising telmisartan or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, and calcium silicate; and a second layer comprising (S)-amlodipine or a pharmaceutically acceptable salt thereof for preparation of medicaments for cardiovascular disease treatment. The acceptable additives *supra* can be mixed with the combination preparation of the present disclosure for preparation of medicaments.

[65] Matters stated in regard of the combination preparation, composition, treatment method and use of the present disclosure are applied identically unless these are contradictory to each other.

Advantageous Effects of Invention

[66] The pharmaceutical combination preparation comprising telmisartan and (S)-amlodipine of the present disclosure comprises microcrystalline cellulose and calcium silicate in the telmisartan layer to improve the hygroscopic properties of the telmisartan layer and, at the same time, ensure the stability of the (S)-amlodipine layer.

Brief Description of Drawings

[67] FIG. 1 is a graph showing the contents of (S)-amlodipine-related compound D measured in Examples 1 to 5 after being stored under accelerated conditions (40 °C, 75% relative humidity, and open) for 2 weeks.

[68] FIG. 2 is a graph showing the contents of individual (S)-amlodipine-related compounds measured in Examples 1 to 5 after being stored under accelerated conditions (40 °C, 75% relative humidity, and sealed) for 4 weeks.

[69] FIG. 3 is a graph showing the contents of total (S)-amlodipine-related compounds measured in Examples 1 to 5 after being stored under accelerated conditions (40 °C, 75% relative humidity, and open) for 4 weeks.

[70] FIG. 4 is a graph showing the contents of (S)-amlodipine related compound D measured in Examples 10 to 16 after being stored under accelerated conditions (40 °C, 75% relative humidity, and open) for 2 weeks.

[71] FIG. 5 is a graph showing the contents of individual (S)-amlodipine-related compounds measured in Examples 10 to 16 after being stored under accelerated conditions (40 °C, 75% relative humidity, and open) for 4 weeks.

[72] FIG. 6 is a graph showing the contents of total (S)-amlodipine-related compounds measured in Examples 10 to 16 after being stored under accelerated conditions (40 °C, 75% relative humidity, and open) for 4 weeks.

Mode for the Invention

[73] Hereinafter, the present disclosure will be described in detail with reference to Preparation Examples, Examples, and Experimental Examples for better understanding of the present disclosure. However, the following Examples and Experimental Examples are merely illustrative of the principles of the present disclosure, and the scope of the present disclosure is not limited to the following Examples and Experimental Examples. The Examples and Experimental Examples of the present disclosure are provided to more completely describe the present disclosure to those having ordinary skill in the art.

[74] **Preparation Examples: Preparation of** telmisartan and (S)-amlodipine granulation

[75] Preparation Example 1: Preparation of telmisartan granule mixture with improved hygroscopic properties.

[76] Telmisartan granule mixture was prepared using the ingredients shown in the following Table 1 by the following method:

[77] [Table 1]

Ingredients	Weight (mg/tab)
Telmisartan	80.00
D-sorbitol	242.00
Dried sodium carbonate	30.00
Povidone	20.00
Calcium silicate	20.00
Sodium stearyl fumarate	8.00
Total amount	400.00

[78] 1) Preparation of first binder solution

[79] Telmisartan, dried sodium carbonate, povidone, and calcium silicate were added to water and completely dissolved by heating and stirring.

[80] 2) Preparation and drying of granules

[81] D-sorbitol was fed into a fluid bed granulator, and the first binder solution of step 1) was sprayed thereon to prepare granules, following by drying.

[82] 3) Preparation of second binder solution

[83] Calcium silicate was added to water and completely dissolved by stirring.

[84] 4) Preparation and granulation of granules

[85] The granules of step 2) were loaded into the fluid bed, and then the second binder solution of step 3) was sprayed thereon to prepare granules. The resulting granules were dried and then sieved by a comil®.

[86] 5) Post-mixing and final mixing

[87] The sieved granule of step 4) and D-sorbitol were placed in a mixer and mixed. Then, sodium stearyl fumarate sieved through 30 mesh was added to the mixture, and the final mixing was performed to prepare the final telmisartan granule mixture.

[88] Preparation Example 2: Preparation of (S)-amlodipine granule mixture

[89] (S)-amlodipine granule mixture was prepared using the ingredients shown in the following Table 2 by the following method:

[90] [Table 2]

Ingredients	Weight (mg/tab)
(S)-amlodipine besylate ((S)-amlodipine)	3.69 (2.5)
Microcrystalline cellulose	126.55
Anhydrous dibasic calcium phosphate	64.0
Sodium starch glycolate	2.00
Blue dye No. 2	0.26
Magnesium stearate	3.5
Total amount	200.00

[91] 1) Trituration of main ingredients

[92] Anhydrous dibasic calcium phosphate was added to (S)-amlodipine besylate and triturated.

[93] 2) Mixing of granules

[94] Microcrystalline cellulose, sodium starch glycolate, and magnesium stearate were mixed with the trituration of step 1).

[95] 3) Compaction ad granulation of granules

[96] Granules were prepared by compacting and crushing the granules of step 2) using a compactor equipped with a 16 mesh sieve and sieved by a comil®.

[97] 4) Pigment trituration

[98] Microcrystalline cellulose was added to blue dye No. 2, mixed, and then milled using a sample mill.

[99] 5) Final mixing

[100] Microcrystalline cellulose, sodium starch glycolate, and anhydrous dibasic calcium phosphate were added to the sieved granule of step 3) and the pigment trituration of step 4), and then sieved magnesium stearate was added to the mixture and finally mixed to prepare the final (S)-amlodipine granule mixture.

[101] Preparation Examples 3 to 6: Preparation of telmisartan granule mixtures

[102] Telmisartan granule mixtures were prepared using the ingredients shown in the following Table 3, in which the preparation method was the same as in Preparation Example 1, except that the excipients were replaced with D-mannitol, erythritol, microcrystalline cellulose, and starch to prepare granules of Preparation Examples 3 to 6:

[103] [Table 3]

Ingredients (Unit: mg/tab)	Preparation Example 3	Preparation Example 4	Preparation Example 5	Preparation Example 6
Telmisartan	80.00	80.00	80.00	80.00
D-mannitol	262.00	-	-	-
Erythritol	-	262.00	-	-
Microcrystalline cellulose	-	-	262.00	-
Starch	-	-	-	262.00
Dried sodium carbonate	30.00	30.00	30.00	30.00
Povidone	20.00	20.00	20.00	20.00
Sodium stearyl fumarate	8.00	8.00	8.00	8.00
Total amount	400.00	400.00	400.00	400.00

[104] Preparation Examples 7 to 10: Preparation of telmisartan granule mixtures

[105] Telmisartan granule mixtures were prepared using the ingredients shown in the following Table 4, in which the preparation method was the same as in Preparation Example 1, except that the weight percent (%) of microcrystalline cellulose as an

excipient was varied to 30%, 40%, 50% and 60% to prepare granules of Preparation Examples 7 to 10:

[106] [Table 4]

Ingredients (Unit: mg/tab)	Preparation Example 7	Preparation Example 8	Preparation Example 9	Preparation Example 10
Telmisartan	80.00	80.00	80.00	80.00
D-mannitol	142.00	102.00	62.00	22.00
Microcrystalline cellulose	120.00	160.00	200.00	240.00
Dried sodium carbonate	30.00	30.00	30.00	30.00
Povidone	20.00	20.00	20.00	20.00
Sodium stearyl fumarate	8.00	8.00	8.00	8.00
Total amount	400.00	400.00	400.00	400.00

[107] Preparation Examples 11 to 17: Preparation of telmisartan granule mixtures

[108] Telmisartan granule mixtures were prepared using the ingredients shown in the following Table 5, in which the preparation method was the same as in Preparation Example 1, except that the weight ratio of telmisartan to calcium silicate was varied to 10:0, 10:1, 10:2, 10:3, 10:4, 10:5, and 10:6 to prepare granules of Preparation Examples 11 to 17:

[109] [Table 5]

Ingredients (Unit: mg/tab)	Prep. Example 11	Prep. Example 12	Prep. Example 13	Prep. Example 14	Prep. Example 15	Prep. Example 16	Prep. Example 17
Telmisartan	80.00	80.00	80.00	80.00	80.00	80.00	80.00
D-mannitol	62.00	54.00	46.00	38.00	30.00	22.00	14.00
Microcrystalline cellulose	200.00	200.00	200.00	200.00	200.00	200.00	200.00
Dried sodium carbonate	30.00	30.00	30.00	30.00	30.00	30.00	30.00
Povidone	20.00	20.00	20.00	20.00	20.00	20.00	20.00
Calcium silicate	0.00	8.00	16.00	24.00	32.00	40.00	48.00
Sodium stearyl fumarate	8.00	8.00	8.00	8.00	8.00	8.00	8.00
Total amount	400.00	400.00	400.00	400.00	400.00	400.00	400.00

[110] **Examples: Preparation of bilayer tablets comprising** telmisartan and (S)-amlodipine

[111] Example 1

[112] Bilayer tablets each having a total weight of 600 mg were prepared by compressing the telmisartan granule mixture prepared in Preparation Example 1 and the (S)-amlodipine granule mixture prepared in Preparation Example 2 using a bilayer tablet press (Sejong Pharmatech, Model: GRC-25D). The prepared bilayer tablets comprise 80 mg of telmisartan and 2.5 mg of (S)-amlodipine in each layer.

[113] Examples 2 to 5

[114] Bilayer tablets were prepared in Examples 2 to 5 by the same method in Example 1 using the telmisartan granule mixtures prepared in Preparation Examples 3 to 6 and the (S)-amlodipine granule mixtures prepared in Preparation Example 2.

[115] Examples 6 to 9

[116] Bilayer tablets were prepared in Examples 6 to 9 by the same method in Example 1 using the telmisartan granule mixtures prepared in Preparation Examples 7 to 10 and the (S)-amlodipine granule mixtures prepared in Preparation Example 2.

[117] Examples 10 to 16

[118] Bilayer tablets were prepared in Examples 10 to 16 by the same method in Example 1 using the telmisartan granule mixtures prepared in Preparation Examples 11 to 17 and the (S)-amlodipine granule mixtures prepared in Preparation Example 2.

[119] **Experimental Examples: Determination of the effect of bilayer tablets comprising** telmisartan and (S)-amlodipine on the improvement of hygroscopic properties and stability

[120] Experimental Example 1: Determination of the effect of telmisartan layers on the improvement of hygroscopic properties

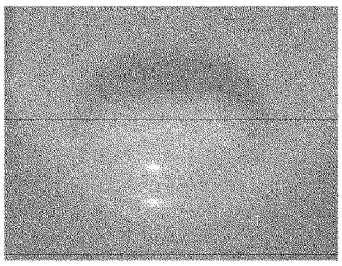
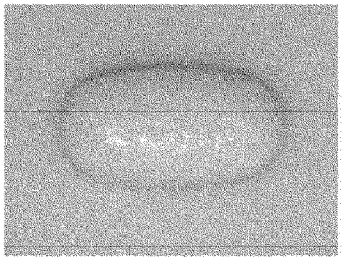
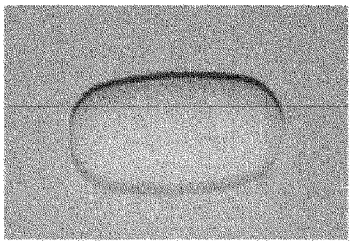
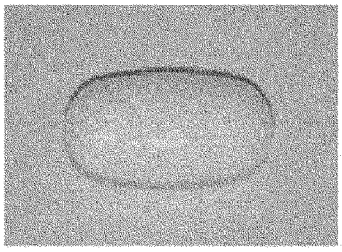
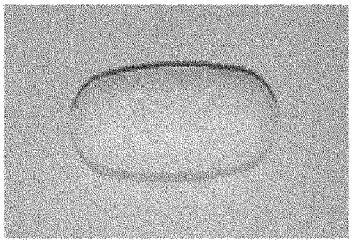
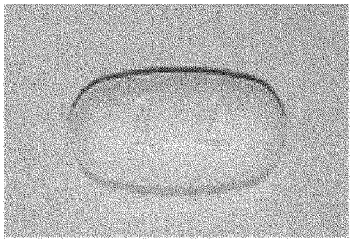
[121] 1) Experimental method

[122] The effect of the bilayer tablets prepared in Examples 1 to 5 according to the present disclosure on the improvement of hygroscopic properties was evaluated by comparison with the deliquescence of telmisartan formulations (Micardis Tab, Boehringer Ingelheim) as a control example. It was found from the FDA label that the Micardis tablet comprises telmisartan, sodium hydroxide, meglumine, sorbitol, povidone, and magnesium stearate as ingredients. In the experiment, each drug without packaging was exposed to accelerated conditions (75% humidity, 40 °C temperature), and then the degree of deliquescence after 1 day was compared by observing the appearances.

[123] 2) Experimental results

[124] As a result, Micardis tablets of the control example were melted beyond recognition as shown in the following Table 6, while the tablets of Examples 2 to 5 were very little changed with a slight reduction in gloss:

[125] [Table 6]

Micardis Tab	
Example 1	
Example 2	
Example 3	
Example 4	
Example 5	

[126] Experimental Example 2: Determination of the effect of (S)-amlodipine layers on the improvement of stability depending on the type of excipients

[127] 1) Experimental method

[128] In order to compare the effects of (S)-amlodipine on the improvement of stability, the formulations prepared in Examples 1 to 5 were stored in open HDPE bottles under accelerated conditions (75% humidity, 40 °C temperature) for 4 weeks, and then the contents of degradation products of (S)-amlodipine after the storage were measured. The specific measurement method is as follows:

[129] - Column: C18 (3.9 mm x 150 mm, 4 μm)

[130] - Detector: Ultraviolet absorptiometer (measurement wavelength: 237 nm)

[131] - Mobile phase: Mixed solution of acetonitrile, methanol, and ph 3.0 buffer (180:250:570)

[132] - Flow rate: 1.0 mL/min

[133] - Column temperature: 30 °C

[134] - Sample temperature: 5 °C

[135] 2) Experimental results

[136] The contents of related compounds of the (S)-amlodipine layer in Examples 1 to 5 in which the types of excipients were varied are shown in the following Tables 7 to 9 and Figures 1 to 3:

[137] [Table 7]

Related compound D (Unit: %)	Early stage	1 week	2 weeks
Example 1	0.04	0.38	0.59
Example 2	0.04	0.33	0.51
Example 3	0.02	0.34	0.56
Example 4	Not detected	0.23	0.56
Example 5	0.05	0.41	0.66

[138] [Table 8]

Other individual related compounds (Unit: %)	Early stage	1 week	2 weeks	3 weeks	4 weeks
Example 1	0.04	0.39	0.44	0.61	0.89
Example 2	0.05	0.24	0.43	0.62	0.77
Example 3	0.03	0.31	0.49	0.66	0.75
Example 4	Not detected	Not detected	0.37	0.42	0.48
Example 5	0.05	0.34	0.58	0.64	0.86

[139] [Table 9]

Total related compound (Unit: %)	Early stage	1 week	2 weeks	3 weeks	4 weeks
Example 1	0.05	0.51	0.88	1.29	1.46
Example 2	0.07	0.46	0.81	1.02	1.24
Example 3	0.06	0.41	0.88	1.10	1.38
Example 4	Not detected	Not detected	0.56	0.63	0.77
Example 5	0.12	0.45	0.94	1.22	1.38

[140] (Total related compounds: The sum of related compounds other than related compound D)

[141] As can be seen from Table 7, the results of the stability test of the (S)-amlodipine layer depending on the type of excipients in the telmisartan layer revealed that the contents of related compound D were all similar in the tablets of Examples 1 to 5. However, as can be seen from Tables 8 and 9, the contents of other individual related compounds and total related compounds generated under accelerated condition for 4 weeks were lowest in Example 4, compared to Examples 1 to 3 and 5, and the difference was up to about two times. Therefore, it was found that when micro-crystalline cellulose was used as an excipient in the telmisartan layer as the first layer, the (S)-amlodipine layer as the second layer was the most stable.

[142] Experimental Example 3: Effect of the amount of microcrystalline cellulose on the appearance of granules

[143] 1) Experimental method

[144] The angle of repose and specific volume of the tablets prepared by varying the amount of microcrystalline cellulose in Preparation Examples 7 to 10 were measured. Moreover, the hardness and friability of the tablets of Examples 6 to 9 were measured by the following method:

[145] [Measurement of specific volume]

[146] - Used apparatus: PT-TDI (Pharmatest Apparate, Germany)

[147] - Measurement method: Measured by tapping 1,250 times

[148] [Measurement of angle of repose]

[149] - Used apparatus: PTG-S4 + PTG-NIR (Pharmatest Apparatebau, Germany)

[150] - Measurement method: Measured using a tester in prepared samples

[151] [Measurement of hardness]

[152] - Hardness tester: TBH-225 (Pharmatest Apparatebau, GmbH, Germany)

[153] - Measurement method: Repeatedly measured 10 times and averaged

[154] [Measurement of friability]

[155] - Friability tester: SVM-102 (Pharmatest Apparatebau, GmbH, Germany)

[156] - Measurement method: 20 tablets, measured after rotated 100 times

[157] 2) Experimental results

[158] The results of the appearance evaluation of each granule and tablet as shown in the following Tables 10 and 11:

[159] [Table 10]

Item		Prep. Example 7	Prep. Example 8	Prep. Example 9	Prep. Example 10
Specific volume (ml/g)	bulk	1.80	1.78	1.9	2.0
	tapped	1.4	1.5	1.6	1.6
Angle of repose		34	35	34	33

[160] [Table 11]

Item	Example 6	Example 7	Example 8	Example 9
Maximum harness (Kp)	10	12	15	17
Friability (%)	0.27	0.20	0.15	0.07

[161] As can be seen from Table 10, the specific volume and angle of repose of granules were all similar in Preparation Examples 7 to 10. However, the maximum hardness and friability of the bilayer tablets in Examples 6 to 9 prepared by combining the granule mixtures of Preparation Examples 7 to 10 with (S)-amlodipine were different as shown in Table 11. Specifically, when the amount of microcrystalline cellulose was higher, the maximum harness increased, and the friability decreased, from which it was confirmed that the higher the weight percent of microcrystalline cellulose, the more advantageous it is for the hygroscopic properties and stability of the telmisartan and (S)-amlodipine combination preparation.

[162] Experimental Example 4: Effect of the amount of calcium silicate on hygroscopic properties

[163] 1) Experimental method

[164] The effect of the granules prepared in Preparation Examples 11 to 17 on the improvement of hygroscopic properties was evaluated. Specifically, each granule was exposed to accelerated conditions (75% humidity, 40 °C temperature), and then the degree of hygroscopic properties after 1 day was measured according to the following test method and compared by measuring the moisture (loss on drying).

[165] [Measurement of moisture (loss on drying)]

[166] - Used apparatus: HB43-S (METTLER TOLEDO, USA)

[167] - Measurement method: Heating at 105 °C for 30 minutes and measuring the weight loss

[168] 2) Experimental results

[169] As shown in the following Table 12, it was found that the amount of moisture (loss on drying) was smaller in Preparation Examples 12 to 17 comprising calcium silicate

than Preparation Example 11 comprising no calcium silicate, from which it was confirmed that the addition of calcium silicate is effective for the improvement of hygroscopic properties:

[170] [Table 12]

Item	Prep. Example 11	Prep. Example 12	Prep. Example 13	Prep. Example 14	Prep. Example 15	Prep. Example 16	Prep. Example 17
Loss on drying (%)	11.4	9.8	9.1	8.9	8.5	8.7	8.4

[171] Experimental Example 5: Determination of the effect of the improvement of stability on (S)-amlodipine layers according to the amount of calcium silicate

[172] 1) Experimental method

[173] In order to compare the effects of (S)-amlodipine on the improvement of stability, the formulations prepared in Examples 10 to 16 were stored in open HDPE bottles under accelerated conditions (75% humidity, 40 °C temperature) for 4 weeks, and then the contents of degradation products of (S)-amlodipine after the storage were measured. The measurement method is as follows:

[174] - Column: C18 (3.9 mm x 150 mm, 4 μm)

[175] - Detector: Ultraviolet absorptiometer (measurement wavelength: 237 nm)

[176] - Mobile phase: Mixed solution of acetonitrile, methanol, and ph 3.0 buffer (180:250:570)

[177] - Flow rate: 1.0 mL/min

[178] - Column temperature: 30 °C

[179] - Sample temperature: 5 °C

[180] 2) Experimental results

[181] The contents of related compounds of the (S)-amlodipine layer in Examples 10 to 16 in which the amounts of calcium silicate were varied are shown in the following Tables 13 to 15 and Figures 4 to 6:

[182] [Table 13]

Related compound D (Unit: %)	Early stage	1 week	2 weeks
Example 10	Not detected	0.21	0.55
Example 11	Not detected	0.18	0.57
Example 12	Not detected	0.20	0.57
Example 13	0.01	0.21	0.54
Example 14	0.01	0.24	0.59
Example 15	Not detected	0.21	0.52
Example 16	0.02	0.24	0.60

[183] [Table 14]

Other individual related compounds (Unit: %)	Early stage	1 week	2 weeks	3 weeks	4 weeks
Example 10	Not detected	0.13	0.32	0.42	0.47
Example 11	Not detected	0.10	0.29	0.40	0.44
Example 12	0.01	0.14	0.33	0.43	0.46
Example 13	Not detected	0.12	0.31	0.47	0.48
Example 14	0.02	0.14	0.37	0.46	0.51
Example 15	Not detected	0.17	0.37	0.50	0.54
Example 16	0.03	0.24	0.42	0.57	0.62

[184] [Table 15]

Total related compound (Unit: %)	Early stage	1 week	2 weeks	3 weeks	4 weeks
Example 10	Not detected	0.14	0.38	0.54	0.79
Example 11	Not detected	0.17	0.34	0.57	0.72
Example 12	0.01	0.15	0.39	0.60	0.81
Example 13	0.01	0.16	0.36	0.57	0.83
Example 14	0.03	0.17	0.42	0.63	0.87
Example 15	0.01	0.20	0.45	0.61	0.89
Example 16	0.05	0.28	0.54	0.72	0.98

[185] (Total related compounds: The sum of related compounds other than related compound D)

[186] As can be seen from Tables 13 to 15, the results of the stability test of the (S)-amlodipine layer depending on the weight ratio of telmisartan to calcium silicate revealed that the contents of related compound D similarly increased regardless of the amount of calcium silicate. When the contents of other individual related compounds were compared, the content of unknown related compounds detected was greatest in Example 16 in which the amount of calcium silicate was greatest. Moreover, when the amount of calcium silicate was higher, the content of unknown related compounds detected increased, and the content of total related compounds also increased. In summary, it was found from Experimental Example 4 that the addition of calcium silicate was effective for the improvement of hygroscopic properties, but when the amount of calcium silicate was higher, the content of related compounds detected also increased, and thus it is preferred that an appropriate amount of calcium silicate be contained in the formulation.

CLAIMS

1. A pharmaceutical combination preparation comprising a first layer comprising telmisartan or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, calcium silicate, and an alkalizing agent and a second layer comprising (S)-amlodipine or a pharmaceutically acceptable salt thereof,

   wherein the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to calcium silicate is 10:1 to 10:5, and the alkalizing agent comprises at least one selected from the group consisting of basic amino acids, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydrogen phosphate, and mixtures thereof.

2. The pharmaceutical combination preparation of claim 1, wherein the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to microcrystalline cellulose is 10:25 to 10:35.

3. The pharmaceutical combination preparation of claim 1, wherein the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to microcrystalline cellulose is 10:25 to 10:30 and the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to calcium silicate is 10:1 to 10:5.

4. The pharmaceutical combination preparation of claim 3, wherein the microcrystalline cellulose is contained in an amount of 50 to 60 wt% with respect to the total weight of the first layer.

5. The pharmaceutical combination preparation of claim 3, wherein the weight ratio of telmisartan or a pharmaceutically acceptable salt thereof to calcium silicate is 10:2 to 10:3.

6. The pharmaceutical combination preparation of claim 1, wherein the pharmaceutically acceptable salt of (S)-amlodipine is selected from the group consisting of (S)-

amlodipine besylate, (S)-amlodipine maleate, (S)-amlodipine orotate, (S)-amlodipine camsylate, (S)-amlodipine adipate, and (S)-amlodipine mesylate.