

【DESCRIPTION】

【Invention Title】

PHARMACEUTICAL PREPARATION

【Technical Field】

The present invention relates to a combined preparation containing fimasartan, amlodipine and rosuvastatin as an effective component. More particularly, the present invention relates to a unit dosage form, which contains fimasartan, amlodipine and rosuvastatin as an effective component, shows an excellent dissolution pattern and stability, and enhances a compliance with medication.

【Background Art】

As for hypertension, it is important to prevent coronary artery diseases and cardiovascular complications such as life-threatening stroke, cardiac insufficiency, myocardial infarction, etc., by maintaining a blood pressure within a normal range thereof rather than treating the blood pressure itself. Thus, a more focus should be put on adjusting the blood pressure below a constant pressure.

In general, patients with hypertension are often accompanied by other kinds of cardiovascular diseases including hyperlipidemia, thus showing a high rate of prescription of two concomitant drugs or more. Also, those patients are required to take drugs for a long period of time. Thus, more attention should be paid to selection of therapeutic drugs. In result, there is a need to concurrently use drugs with different mechanisms and reduce an amount of a single drug used rather than simply select one drug, thereby reducing possible side effects

resulting from a long-term use of drugs.

Fimasartan is known as an angiotensin II receptor antagonist developed to treat hypertension and other medical signs (Patent Registration No. 10-1058284).

Amlodipine is known as a calcium channel blocker developed to treat hypertension and other medical signs.

Rosuvastatin is an HMG-CoA reductase inhibitor, which prevents a reduction of HMG-CoA into mevalonate, thus showing an effect of lowering a blood lipid concentration and cholesterol, such that rosuvastatin is used for hyperlipidemia, hypercholesterolemia, atherosclerosis and the like.

For a more effective treatment of cardiovascular diseases, etc. including hypertension, it is possible to consider a combined preparation containing fimasartan, amlodipine and rosuvastatin all, having different mechanisms from each other as above. In this case, however, there may be a problem in that a mutual interference among respective components has an influence on dissolution of respective active components. In particular, Kanarb, which is released on the market as a single preparation of fimasartan, shows a low solubility at a low pH (for example, pH 1.2 to 1.4). However, if being used as a combined preparation with other pharmacologically active components, Kanarb may show a lower dissolution rate than in the single preparation.

Also, said each component has a different solubility, thus making it difficult to formulate those three components into such a preparation as to show an effective dissolution pattern, respectively. Thus, a unit dosage form has not been commercialized yet in a form of a combined preparation containing fimasartan, amlodipine and rosuvastatin all as an effective

component.

【Disclosure】

【Technical Problem】

The present invention provides a preparation, including:

a first layer containing fimasartan, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof; and

a second layer containing rosuvastatin, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof, and amlodipine, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof,

wherein said second layer contains low substituted hydroxypropyl cellulose.

【Technical Solution】

Hereinafter, the present invention will be described in more detail.

The present invention provides a preparation, including:

a first layer containing fimasartan, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof; and

a second layer containing rosuvastatin, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof, and amlodipine, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof,

wherein said second layer contains low substituted hydroxypropyl cellulose.

In the preparation of the present invention, the second layer containing low

substituted hydroxypropyl cellulose is quickly swollen in contact with water, such that the first layer and the second layer may be immediately separated from each other, and thus may disintegrate respectively while being separated from each other.

In result, said first layer and said second layer disintegrate respectively without being influenced by each other, such that active components belonging to each layer may be eluted. In other words, although disintegration patterns of the first layer and the second layer are different from each other, additives such as a pharmaceutically acceptable carrier, disintegrant, etc., or pharmacologically active components, which belong to said each layer, do not have an influence on a disintegration pattern and dissolution of the other layer. In particular, each layer may be immediately separated even in gastric fluid in an acidic state of pH 3 or less, such that each disintegration of the first layer and the second layer does not have an influence on the disintegration and dissolution of active components of the other layer and each component shows an excellent dissolution pattern. In result, three pharmacologically active components contained in the preparation of the present invention may show dissolution patterns almost the same as or similar to the single preparation containing each component.

Thus, respective components contained in the first layer and the second layer of a combined preparation of the present invention may exhibit each pharmacological activity in a sufficiently effective way without interfering with each other; may not cause any problem such as a decline in stability, etc. caused by drug interference; may remarkably enhance a compliance with medication; and may be easily put into mass production.

Also, the preparation of the present invention may show an excellent stability and thus maintain a stable state for a long period of time without having the layers separated from each other.

In the present specification, said terms such as first, second, etc., are used only to distinguish various layers, membranes, steps, etc., from each other, but not intended to indicate a sequence thereof or indicate a degree of importance thereof, and features of those layers, membranes, steps, etc. are not limited to said terms such as first, second, etc. Thus, said terms such as first, second, etc., may not be equally used all in Detailed Description of the Invention, Examples, Claims, etc. and it is sufficient only if those layers, membranes, steps, etc. may be distinguished from each other by the terms such as first, second, etc.

As used herein, the term “pharmaceutically acceptable” may mean the one that is physiologically acceptable; that does not conventionally cause an allergic reaction such as gastrointestinal disturbance and dizziness, or other similar reactions thereto, when being administered into a human; and that is conventionally used by those skilled in the art in preparing a pharmaceutical preparation.

As used herein, the term “hydrate” may mean the one, in which fimasartan, pharmaceutically acceptable salts thereof or optical isomers thereof; amlodipine, pharmaceutically acceptable salts thereof or optical isomers thereof; rosuvastatin, pharmaceutically acceptable salts thereof or optical isomers thereof; or the like are bound to water by means of a non-covalent intermolecular force, and which contains a stoichiometric or non-stoichiometric amount of water. Particularly, said hydrate may contain water at a molar ratio of about 0.25 mol to about 10 mol based on 1 mol of an active component, more particularly about 0.5 mol, about 1 mol, about 1.5 mol, about 2 mol, about 2.5 mol, about 3 mol, about 5 mol, etc. of water.

As used herein, the term “solvate” may mean the one, in which fimasartan, pharmaceutically acceptable salts thereof or optical isomers thereof; amlodipine,

pharmaceutically acceptable salts thereof or optical isomers thereof; or rosuvastatin, pharmaceutically acceptable salts thereof or optical isomers thereof are bound to a solvent, not water, by means of an intermolecular force, and which may contain a stoichiometric or non-stoichiometric amount of the solvent. Particularly, said solvate may contain a solvent molecule at a molar ratio of about 0.25 mol to about 10 mol based on 1 mol of an active component, more particularly about 0.5 mol, about 1 mol, about 1.5 mol, about 2 mol, about 2.5 mol, about 3 mol, about 5 mol, etc. of the solvent molecule.

As used herein, the term “containing fimasartan as an effective component” may mean “containing fimasartan free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof.” For example, “a layer containing fimasartan as an effective component” refers to a layer containing fimasartan free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof, and “a mixture containing fimasartan as an effective component” refers to a mixture containing fimasartan free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof.

As used herein, the term “containing amlodipine as an effective component” may mean “containing amlodipine free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof.” For example, “a layer containing amlodipine as an effective component” refers to a layer containing amlodipine free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof, and “a mixture containing amlodipine as an effective component” refers to a mixture containing amlodipine free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof.

As used herein, the term “containing rosuvastatin as an effective component” may mean “containing rosuvastatin free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof.” For example, “a layer containing rosuvastatin as an effective component” refers to a layer containing rosuvastatin free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof, and “a mixture containing rosuvastatin as an effective component” refers to a mixture containing rosuvastatin free base, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof.

In exemplary embodiments of the present invention, said preparation may be a unit dosage form containing fimasartan, rosuvastatin and amlodipine all as an effective component.

In exemplary embodiments of the present invention, said second layer may contain low substituted hydroxypropyl cellulose in an amount of 3 to 50 wt%, particularly in an amount of 5 to 40 wt% based on the weight of the second layer. If said low substituted hydroxypropyl cellulose is contained in an amount of the content above, swelling of the second layer may promptly progress, such that the first layer and the second layer may be quickly separated from each other. Thus, even if the second layer disintegrates faster than the first layer, the first layer is not influenced by the disintegration of said second layer, and each active component contained in said first layer and second layer may show an excellent dissolution pattern.

In addition to this, if said low substituted hydroxypropyl cellulose is contained in an amount of the content above, a tablet may maintain an appropriate size, thus enhancing a patient's compliance with medication and facilitating a tablet compression. Also, it is possible

to excellently maintain the content uniformity of each component contained in each tablet, and thus making it economically easy to carry out a mass production thereof.

In exemplary embodiments of the present invention, said first layer and second layer may show different dissolution rates from each other in a dissolution medium. At this time, said dissolution medium may be a hydrochloric acid aqueous solution of pH 1.2.

In exemplary embodiments of the present invention, said second layer may disintegrate earlier than the first layer in the dissolution medium, wherein said dissolution medium may be a hydrochloric acid aqueous solution of pH 1.2.

In exemplary embodiments of the present invention, said preparation may be a tablet, particularly a bilayered tablet. In exemplary embodiments of the present invention, the first layer of said bilayered tablet may contain fimasartan as an effective component, and the second layer may contain amlodipine and rosuvastatin as an effective component, such that the effective component of said first layer, i.e. fimasartan, and the effective components of the second layer, i.e. amlodipine and rosuvastatin are separated from each other, without being mixed together.

Generally, in case of the bilayered tablet, the two layers having different properties are bound to each other by means of a physical force. During disintegration, the two layers are not separated and moved apart from each other in an interface between the two layers, thus causing a problem in that a component contained in each layer degrades disintegration and dissolution of the other layer.

However, the preparation of the present invention may show an excellent dissolution pattern, in spite of containing the three components in one tablet in a form of the bilayered tablet, such that the inventive preparation may show the dissolution pattern and

bioavailability the same as or similar to the case of taking all of the preparations respectively containing fimasartan, amlodipine and rosuvastatin, thus remarkably enhancing a patient's compliance with medication.

In exemplary embodiments of the present invention, said first layer may include granules containing fimasartan as an effective component. Said granules may be dry granules or wet granules, particularly the wet granules.

In exemplary embodiments of the present invention, said second layer may have rosuvastatin, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof; and amlodipine, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof mixed together therein.

The preparation of the present invention has respective components simply mixed in said second layer, but shows an excellent stability, wherein in particular the effective component, i.e., rosuvastatin may maintain a stable state for a long period of time. Also, the effective component contained in the second layer does not need to be prepared in a form of granule, thus resulting in a simple preparation, a high production efficiency and an easy mass production.

In exemplary embodiments of the present invention, said pharmaceutically acceptable salts of fimasartan may be selected from the group consisting of inorganic ion salts, inorganic acid salts, organic acid salts, sulfonic acid salts, amino acid salts and amine salts. Particularly, such pharmaceutically acceptable salts of fimasartan may be inorganic ion salts prepared from calcium, potassium, sodium, magnesium or the like; inorganic acid salts prepared from hydrochloric acid, nitric acid, phosphoric acid, bromic acid, iodic acid, perchloric acid, sulfuric acid or the like; organic acid salts prepared from acetic acid,

trifluoroacetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, tartaric acid, fumaric acid, propionic acid, citric acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonic acid, vanillic acid, mandelic acid, mucic acid, pamoic acid, panthothenic acid, succinic acid or the like; sulfonic acid salts prepared from methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, naphthalenedisulfonic acid, naphthalenesulfonic acid or the like; amino acid salts prepared from glycine, arginine, lysine or the like; amine salts prepared from trimethylamine, meglumine, triethylamine, ammonia, pyridine, picoline, choline or the like; or the like, but types of salt meant in the present invention are not limited to those listed salts. Particularly, said pharmaceutically acceptable salts of fimasartan may be fimasartan potassium, fimasartan toluenesulfonic acid salts or fimasartan ammonia salts, more particularly the fimasartan potassium salts.

In exemplary embodiments of the present invention, hydrates of said fimasartan, pharmaceutically acceptable salts thereof or optical isomers thereof may be monohydrates or trihydrates, particularly the monohydrates or trihydrates of fimasartan potassium, and more particularly the trihydrates of fimasartan potassium.

In exemplary embodiments of the present invention, a daily dosage of fimasartan, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof may be about 0.5 mg to about 240 mg as fimasartan potassium, particularly about 10 mg to 180 mg, more particularly about 20 mg to about 120 mg, and still more particularly about 30 mg to about 60 mg, and, for example, may be about 30 mg to about 60 mg as fimasartan potassium.

In exemplary embodiments of the present invention, amlodipine of said second layer may contain a racemate of amlodipine, (S)-amlodipine or (R)-amlodipine, and particularly may contain the racemate of amlodipine or (S)-amlodipine.

In exemplary embodiments of the present invention, pharmaceutically acceptable salts of amlodipine, which may be contained in said second layer, may be selected from the group consisting of inorganic ion salts, inorganic acid salts, organic acid salts, sulfonic acid salts, amino acid salts and amine salts. Particularly, the pharmaceutically acceptable salts of amlodipine may be the ones prepared from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, citric acid, gluconic acid, besylic acid, camsylic acid or the like, and more particularly amlodipine besylate.

In exemplary embodiments of the present invention, a daily dosage of amlodipine, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof may be about 0.1 mg to about 20 mg as amlodipine, particularly about 3 mg to about 15 mg, and more particularly about 5 mg to about 10 mg, and, for example, may be about 5 mg or about 10 mg as amlodipine.

In exemplary embodiments of the present invention, pharmaceutically acceptable salts of rosuvastatin in said second layer may be selected from the group consisting of inorganic ion salts, inorganic acid salts, organic acid salts, sulfonic acid salts, amino acid salts and amine salts. Particularly, said pharmaceutically acceptable salts of rosuvastatin may be inorganic ion salts prepared from calcium, potassium, sodium, magnesium or the like, and more particularly rosuvastatin calcium salts.

In exemplary embodiments of the present invention, a daily dosage of rosuvastatin,

pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof may be about 1 mg to about 40 mg as rosuvastatin, particularly about 3 mg to about 30 mg, and more particularly about 5 mg to about 20 mg, and, for example, may be about 5 mg, about 10 mg or about 20 mg as rosuvastatin.

In exemplary embodiments of the present invention, said preparation may contain fimasartan, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof per unit dosage form in such an amount as to be about 0.5 mg to about 240 mg as fimasartan potassium, particularly about 10 mg to about 180 mg, more particularly about 20 mg to about 120 mg, and still more particularly about 30 mg to about 60 mg, and, for example, may contain in such an amount as to be about 30 mg or about 60 mg as fimasartan potassium.

In exemplary embodiments of the present invention, said preparation may contain amlodipine, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof per unit dosage form in such an amount as to be about 0.1 mg to about 20 mg as amlodipine, particularly about 3 mg to 15 mg, and more particularly about 5 mg to about 10 mg, and, for example may contain in such an amount as to be about 5 mg or about 10 mg as amlodipine.

In exemplary embodiments of the present invention, said preparation may contain rosuvastatin, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof per unit dosage form in such an amount as to be about 1 mg to about 40 mg as rosuvastatin, particularly about 3 mg to about 30 mg, and more particularly about 5 mg to about 20 mg, and, for example, may contain in such an amount as to be about 5 mg, about 10 mg or about 20 mg as said rosuvastatin.

In exemplary embodiments of the present invention, said preparation may be administered once to several times a day, particularly once to three times a day, more particularly once to twice a day, and still more particularly once a day, but not limited thereto, and may be appropriately adjusted according to a patient's state.

In exemplary embodiments of the present invention, said preparation may treat or prevent cardiovascular diseases, wherein said cardiovascular diseases may be hypertension, arteriospasm, deep vein, cardiac insufficiency, cardiomegaly, cerebral infarction, diabetes, obesity, hyperlipidemia, coronary artery disease, chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, insulin tolerance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, dyslipidemia, cognitive decline, dementia, etc., particularly hypertension, arteriospasm, deep vein, cardiomegaly, cerebral infarction, lipemia, coronary artery disease, chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, etc., and more particularly hypertension, hyperlipidemia, etc.

In exemplary embodiments of the present invention, said first layer and second layer may further contain pharmaceutically acceptable additives, respectively. The pharmaceutically acceptable additives contained in said first layer and said second layer may be the same as or different from each other.

Said pharmaceutically acceptable additives may be carriers, excipients, diluents, extenders, antioxidants, stabilizers, dissolution aids, buffer solutions, fillers, anti-coagulants, lubricants, disintegrants, humectants, flavoring agents, emulsifiers, suspending agents, surfactants, preservatives or mixtures thereof. Said additives may be formulated into a preparation so as to contain a conventional range of doses therein by selection.

In exemplary embodiments of the present invention, said second layer may contain stabilizers as pharmaceutically acceptable additives.

Particularly, said additives may be lactose, dextrose, calcium silicate, maize starch, sodium starch glycolate, sucrose, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, acacia rubber, alginate, pregelatinized starch, gelatin, calcium phosphate anhydride, calcium phosphate monobasic, calcium phosphate dibasic, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal silicon dioxide, povidone, copovidone, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, methyl hydroxybenzoate, propyl hydroxybenzoate, light anhydrous silicic acid, talcum, talc, stearic acid, magnesium stearate, calcium stearate, hydrogenated castor oil, polyethylene glycol, colloidalized silicon dioxide or mixtures thereof, but not limited thereto. For example, said additives do not react with fimasartan, rosuvastatin or amlodipine, which is contained in the preparation as an effective component, and may be substances, which do not degrade stability of the preparation.

More particularly, out of said additives, the following may be used as said stabilizers: meglumine, calcium phosphate anhydride, calcium phosphate monobasic, calcium phosphate dibasic, magnesium phosphate tribasic, aluminium phosphate tribasic, meglumine or mixtures thereof, particularly meglumine, calcium phosphate anhydride, calcium phosphate monobasic, calcium phosphate dibasic or mixtures thereof. In said additives, the following may be used as binders: hydroxypropyl cellulose, hydroxypropyl methylcellulose, starch, gelatin, glucose syrup, polyvinyl pyrrolidone, polyethylene glycol 6000, methyl cellulose, ethyl cellulose, carboxymethyl cellulose, mixtures thereof or the like. Out of said additives, the following may be used as said disintegrants: starch or modified starch such as sodium starch glycolate,

maize starch, potato starch, pre-gelatinized starch or the like; clay such as bentonite, montmorillonite, veegum or the like; celluloses such as microcrystalline cellulose, carboxymethyl cellulose or the like; alginates such as sodium alginate, alginic acid or the like; crosslinked celluloses such as croscarmellose sodium, etc.; gums such as guar gum, xanthan gum, etc.; crosslinked polymers such as crospovidone, etc.; sodium bicarbonate; citric acid; or mixtures thereof. As said glidants, the following may be used: magnesium stearate, calcium stearate, stearic acid, sodium stearate fumarate, polyethylene glycol, silicon dioxide, mixtures thereof or the like. As said diluents, the following may be used: cellulose, lactose, starch, microcrystalline cellulose, lactose hydrate, glucose, mannitol, alginate, alkaline-earth metal salt, clay, polyethylene glycol, dicalcium phosphate, mixtures thereof or the like. As said dissolution aids, the following may be used: sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid ester such as polysorbate, etc., docusate sodium, mixtures thereof or the like. As said surfactants, the following may be used: sodium lauryl sulfate, cremophor, poloxamer, docusate and pharmaceutically acceptable docusate salt or mixtures thereof, etc.

In exemplary embodiments of the present invention, said first layer may contain binders, disintegrants, lubricants, diluents, glidants or mixtures thereof as pharmaceutically acceptable additives, and said second layer may contain disintegrants, lubricants, diluents, glidants or mixtures thereof as pharmaceutically acceptable additives in addition to low substituted hydroxypropyl cellulose.

According to exemplary embodiments of the present invention, said second layer may further contain various kinds of starch, sucrose, starch 1500, calcium monohydrogen phosphate, sorbitol, calcium phosphate, calcium carbonate, mannitol, lactose, microcrystalline cellulose or mixtures thereof in addition to low substituted hydroxypropyl

cellulose. Particularly, said second layer may further contain mannitol, lactose, microcrystalline cellulose or mixtures thereof, particularly microcrystalline cellulose, in addition to low substituted hydroxypropyl cellulose.

For example, the first layer containing fimasartan as an effective component may contain croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, mannitol, lactose, lactose hydrate or mixtures thereof, and the second layer containing rosuvastatin and amlodipine as an effective component may contain crospovidone, mannitol, microcrystalline cellulose, lactose, lactose hydrate, meglumine, colloidal silicon dioxide, magnesium stearate or mixtures thereof, in addition to low substituted hydroxypropyl cellulose.

In exemplary embodiments of the present invention, said tablet may further contain an outer coating layer in addition to said first layer and second layer. A method for forming said coating layer may be appropriately selected from methods for forming a film-phase coating layer on a surface of a tablet layer by those skilled in the art, and methods such as a fluidized-bed coating method, a pan coating method, a dry coating method, etc., may be applied. Said coating layer may contain hydroxypropyl methylcellulose, ethyl cellulose, polyvinyl acetate, polyethylene glycol, titanium dioxide, iron oxide, etc., or Opadry under the proprietary name. Said coating layer may be contained, for example, in an amount of 0.5 to 10.0 wt%, particularly 1.0 to 6.0 wt%, and more particularly 2.0 to 5.0 wt% based on the total weight of the tablet.

A method for preparing a preparation according to the present invention includes:

a first step of preparing a mixture by combining fimasartan,

pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof, and pharmaceutically acceptable additives;

a second step of preparing a mixture by combining rosuvastatin, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof; amlodipine, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof; and pharmaceutically acceptable additives; and

a step of compressing the mixture prepared in said first step and the mixture prepared in said second step into a tablet.

In exemplary embodiments of the present invention, in said second step, said pharmaceutically acceptable additives include low substituted hydroxypropyl cellulose.

In exemplary embodiments of the present invention, the mixture prepared in said second step may contain low substituted hydroxypropyl cellulose in an amount of about 3 wt% to about 50 wt%, particularly in an amount of about 5 to 40 wt% based on the total weight of said mixture.

In exemplary embodiments of the present invention, said first step may include a step of preparing granules containing fimasartan, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof. Particularly, said step of preparing granules may be performed by means of a wet granulation or a dry granulation, more particularly the wet granulation.

Matters mentioned in the preparation of the present invention are also equally applied to said preparation methods, if not contradictory to each other.

The present invention provides a pharmaceutical composition for treating or preventing cardiovascular diseases, including:

a first layer containing fimasartan as an effective component; and

a second layer containing amlodipine and rosuvastatin as an effective component,

wherein said second layer contains low substituted hydroxypropyl cellulose.

The present invention provides a method for preventing or treating cardiovascular diseases, by administering a therapeutically effective amount of a pharmaceutical composition, including:

a first layer containing fimasartan as an effective component; and

a second layer containing amlodipine and rosuvastatin as an effective component,

wherein said second layer contains low substituted hydroxypropyl cellulose.

The present invention provides a use of a composition for preventing or treating cardiovascular diseases, including:

a first layer containing fimasartan as an effective component; and

a second layer containing amlodipine and rosuvastatin as an effective component,

wherein said second layer contains low substituted hydroxypropyl cellulose.

Matters mentioned in the preparation of the present invention are also equally applied to a pharmaceutical composition, a therapeutic method and a therapeutic use, if not contradictory to each other.

【Advantageous Effects】

The present invention provides a unit preparation containing fimasartan, rosuvastatin and amlodipine all as an effective component, wherein all three components show an excellent dissolution rate and stability, thus remarkably improving a compliance with medication, without an interference phenomenon, though said three components are contained in one unit dosage form.

【Description of Drawings】

Fig. 1 shows a dissolution rate of fimasartan in tablets according to Examples and tablets according to Comparative Examples.

Fig. 2 shows a dissolution rate of amlodipine in tablets according to Examples and tablets according to Comparative Examples.

Fig. 3 shows a dissolution rate of rosuvastatin in tablets according to Examples and tablets according to Comparative Examples.

In said Figs. 1 to 3, a vertical axis indicates a dissolution rate (%) and a horizontal axis does minutes.

【Mode for Invention】

Hereinafter, the present invention will be described in detail through Examples for better understanding of the present invention. However, the following Examples are provided only for the purpose of illustrating the present invention, and thus the scope of the present invention is not limited thereto. The Examples of the present invention are provided to more completely describe the present invention to those having ordinary skill in the art.

As used in said Examples and Comparative Examples, fimasartan potassium trihydrate was purchased from Boryung Pharmaceutical Co., Ltd.; amlodipine besylate from

Dr. Reddy; rosuvastatin calcium from MSN; meglumine from Merck; and crospovidone from ISP, and said low substituted hydroxypropyl cellulose used herein was NBD-021 (from ShinEtsu Co., Ltd.).

Example 1.

(1) Preparation of granules containing fimasartan as an effective component

Granules containing fimasartan as an effective component were prepared by means of a following method such that their components and contents per unit dosage form (400 mg) may comply with those described in a following table 1.

Fimasartan potassium trihydrate, microcrystalline cellulose and croscarmellose sodium were mixed together for about 10 minutes, after which said mixture was further put into a high speed mixer for about three minutes, thereby preparing a mixture containing fimasartan as an effective component.

Apart from this, hydroxypropyl cellulose was dissolved in 60 ml of purified water, thereby preparing a binder solution.

Said prepared binder solution was put into the high speed mixture, then wet-granulated with said mixture containing fimasartan as an effective component, size-regulated through a 20 mesh sieve, and then dried. After drying, croscarmellose sodium was added thereto and mixed in a double cone mixer for about five minutes, after which magnesium stearate was added thereto and further mixed for about five minutes, thereby preparing granules containing fimasartan as an effective component.

(2) Preparation of a mixture containing amlodipine and rosuvastatin as an effective component

A mixture containing amlodipine and rosuvastatin as an effective component in Example 1 was prepared such that its contents per unit dosage form may comply with those described in a following table 1.

First of all, amlodipine besylate, rosuvastatin calcium, the stabilizer, i.e., meglumine and colloidal silicon dioxide were put thereinto and mixed together for about five minutes, and sifted through a 30 mesh sieve. A resulting sifted mixture was put into the double cone mixer along with microcrystalline cellulose, low substituted hydroxypropyl cellulose and crospovidone, and mixed for about 15 minutes. As a glidant, magnesium stearate was added thereto and further mixed for about five minutes, thereby preparing a mixture containing amlodipine and rosuvastatin as an effective component.

3. Tablet compression

The granules containing fimasartan as an effective component and the mixture containing amlodipine and rosuvastatin as an effective component were respectively put into each punch die, and compressed to prepare bilayered tablets.

Bilayered tablets were prepared by means of a multi-layered tablet press (Piccola bilayered tablet press) such that a hardness of said one bilayered tablet may reach 10-15 kp. A friability of such resulting tablets was measured by means of a friability tester (100 free falls at 25 rpm). The friability was 0.1% or less, such that a hardness of the tablets was fair. The hardness was measured by means of VARIAN VK200.

Example 2.

Bilayered tablets were prepared by means of the same method as shown in Example 1 above, except that their components and contents per unit dosage form were to comply with those described in Example 2 of the table 1.

Example 3.

Bilayered tablets were prepared by means of the same method as shown in Example 1 above, except that their components and contents per unit dosage form were to comply with those described in Example 3 of the table 1.

Example 4.

Bilayered tablets were prepared by means of the same method as shown in Example 1 above, except that their components and contents per unit dosage form were to comply with those described in Example 4 of the table 1.

【Table 1】

Components and Contents of Tablet of Examples 1 to 4

mg/tablet	Example 1	Example 2	Example 3	Example 4
Granules containing fimasartan as an effective component				
Fimasartan potassium trihydrate	66.0	66.0	66.0	66.0
Microcrystalline cellulose	72.75	72.75	72.75	72.75
Croscarmellose sodium	7.5	7.5	7.5	7.5
Hydroxypropyl cellulose	1.5	1.5	1.5	1.5
Magnesium stearate	2.25	2.25	2.25	2.25
A mixing portion containing rosuvastatin and amlodipine as an effective component				
Amlodipine besylate	13.9	13.9	13.9	13.9
Rosuvastatin calcium	20.8	20.8	20.8	20.8
Microcrystalline cellulose	81.3	118.8	156.3	168.8
Low substituted hydroxypropyl cellulose	100	62.5	25	12.5
Meglumine	15.0	15.0	15.0	15.0
Crospovidone	12.5	12.5	12.5	12.5

Colloidal silicon dioxide	1.5	1.5	1.5	1.5
Magnesium stearate	5.0	5.0	5.0	5.0

Comparative Example 1

(1) Granules containing fimasartan as an effective component

Granules containing fimasartan as an effective component in Comparative Example 1 were prepared such that their components and contents per unit dosage form (400 mg) may comply with those described in a following table 2.

Fimasartan potassium trihydrate, microcrystalline cellulose and croscarmellose sodium were mixed together for about 10 minutes, after which said resulting mixture was further put into the high speed mixer for about three minutes, thereby preparing a mixture containing fimasartan as an effective component.

Apart from this, hydroxypropyl cellulose was dissolved in 60 ml of purified water, thereby preparing a binder solution.

Said prepared binder solution was put into the high speed mixture, then wet-granulated with the mixture containing fimasartan, then size-regulated through a 20 mesh sieve, and then dried. After drying, croscarmellose sodium was added thereto and mixed in the double cone mixer for about five minutes, after which magnesium stearate was added thereto and further mixed for about five minutes, thereby preparing granules containing fimasartan as an effective component.

(2) Preparation of a mixture containing amlodipine and rosuvastatin as an effective component

A mixture containing amlodipine and rosuvastatin in Comparative Example 1 was

prepared such that its components and contents per unit dosage form may comply with those described in a following table 2.

Amlodipine besylate, rosuvastatin calcium, the stabilizer, i.e., meglumine and colloidal silicon dioxide were put thereinto and mixed together for about five minutes, thereby preparing a mixture. Said mixture was put into and sifted through a 30 mesh sieve. A resulting sifted mixture was put into the double cone mixer along with mannitol and crospovidone, and mixed for about 15 minutes. As a glidant, magnesium stearate was added thereto and further mixed for about five minutes, thereby preparing a mixture containing amlodipine and rosuvastatin as an effective component.

3. Tablet compression

The granules containing fimasartan as an effective component and the mixture containing amlodipine and rosuvastatin as an effective component were respectively put into each punch die, and compressed to prepare bilayered tablets.

Bilayered tablets were prepared by means of a bilayered tablet press (Piccola bilayered tablet press) such that a hardness of said one pressed bilayered tablet may reach 10-15 kp. A friability of such resulting tablets was measured by means of a friability tester (100 free falls at 25 rpm). The friability was 0.1% or less, such that a hardness of the tablets was fair. The hardness was measured by means of VARIAN VK200.

Comparative Example 2

Bilayered tablets were prepared by means of the same method as shown in Comparative Example 1, except that lactose was used instead of mannitol, and except that the components and contents contained in a unit dosage form were to comply with those described in Comparative Example 2 of the said table 2.

Comparative Example 3

Bilayered tablets were prepared by means of the same method as shown in Comparative Example 1, except that microcrystalline cellulose was used instead of mannitol, and except that the components and contents contained in a unit dosage form were to comply with those described in Comparative Example 3 of the said table 2.

【Table 2】

Components and Contents of Bilayered Tablet of Comparative Examples 1 to 3

mg/tablet	Comparative Example 1	Comparative Example 2	Comparative Example 3
Granules containing fimasartan as an effective component			
Fimasartan potassium trihydrate	66.0	66.0	66.0
Microcrystalline cellulose	72.75	72.75	72.75
Croscarmellose sodium	7.5	7.5	7.5
Hydroxypropyl cellulose	1.5	1.5	1.5
Magnesium stearate	2.25	2.25	2.25
A mixing portion containing rosuvastatin and amlodipine as an effective component			
Amlodipine besylate	13.9	13.9	13.9
Rosuvastatin calcium	20.8	20.8	20.8
Mannitol	181.3	-	-
Lactose	-	181.3	-
Microcrystalline cellulose	-	-	181.3
Meglumine	15.0	15.0	15.0
Crospovidone	12.5	12.5	12.5
Colloidal silicon dioxide	1.5	1.5	1.5
Magnesium stearate	5.0	5.0	5.0

[Experimental Example] Dissolution rate of each component in tablets of Examples and Comparative Examples

A dissolution test was performed by means of each of Examples 1 to 4, Comparative

Examples 1 to 3, and commercial control drugs, i.e., Kanarb tab., Norvasc tab. and Crestor tab. A dissolution test method is described in a table 3. Results of the dissolution test are described in Figs. 1 to 3, indicating an average dissolution rate.

The dissolution test was performed on a combined preparation containing fimasartan, amlodipine and rosuvastatin as an effective component, which were prepared in Examples and Comparative Examples under the same conditions as described in a following table 3 according to the dissolution test method II (paddle method) of the Korean Pharmacopoeia. To compare dissolution rates with the combined preparation of the present invention, the test was performed on a single-agent product of fimasartan, i.e., “Kanarb 60 mg” of Boryung Pharmaceutical, a single-agent product of amlodipine, i.e., “Norvasc 10 mg” of Pfizer, and a single-agent product of rosuvastatin, i.e., “Crestor 20 mg” of AstraZeneca under the same conditions as in the combined preparation of the present invention.

【Table 3】

Dissolution Test Method

Item	condition
Dissolution testing device	Hanson Vision Elite 8
Dissolution test solution	pH 1.2 solution
Dissolution test solution temperature	37±0.5 °C
Amount of dissolved solution	900 mL
Rotary speed	50 rpm
Sample collection time	5, 10, 15, 30, 45, 60 minutes
Amount of sample collection	10 mL

Filter	0.45 μm syringe filter
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As identified in said Figs. 1 to 3, the dissolutions of fimasartan, amlodipine and rosuvastatin from tablets of Examples 1 to 4 were almost similar to those of single preparations of each component, i.e., Kanarb 60 mg, Norvasc and Crestor, and there was almost no difference in dissolution rates for each preparation.

Thus, it can be seen that the tablets of the present invention show the same degree of excellent dissolution as the single preparation without an interference phenomenon among respective components, though such tablets take on a form of the combined preparation.

On the other hand, the tablets according to Comparative Examples showed a remarkable decrease in dissolution rates of effective components contained therein compared to the single preparation.

From the results, it is identified for the unit dosage form of the combined preparation according to the present invention that three kinds of effective components having different mechanisms show an excellent dissolution pattern without an interference phenomenon with each other and remarkably improve a compliance with medication.

From the description above, those skilled in the art will understand that the present invention may be practiced in other specific forms without changing the technical scope or essential features thereof. In this regard, it should be understood that the Examples described above are illustrative in all aspects and are not contrived to limit the present invention. The scope of the present invention shall be interpreted to include all the modified or changed forms derived from the meaning and scope of the patent claims described below as well as equivalent concepts thereof rather than Detailed Description of the Invention.

【CLAIMS】

【Claim 1】

A preparation, comprising:

a first layer comprises granules containing fimasartan, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof; and

a second layer containing rosuvastatin, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof, and amlodipine, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof,

wherein said first layer contains croscarmellose sodium,

wherein said second layer contains at least one of calcium phosphate anhydride, calcium phosphate monobasic, calcium phosphate dibasic, magnesium phosphate tribasic, aluminium phosphate tribasic and meglumine; and low substituted hydroxypropyl cellulose,

wherein said preparation is a bilayered tablet.

【Claim 2】

The preparation according to claim 1, wherein said second layer comprises low substituted hydroxypropyl cellulose in an amount of 3 to 50 wt% based on the weight of the second layer.

【Claim 3】

The preparation according to claim 1, wherein said second layer further comprises at least one selected from the group consisting of microcrystalline cellulose, mannitol and lactose.

【Claim 4】

The preparation according to claim 1, wherein said second layer has:

rosuvastatin, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof; and

amlodipine, pharmaceutically acceptable salts thereof, optical isomers thereof, or hydrates or solvates thereof mixed together therein.