

Specification

Title

TABLET AND METHOD OF PREPARING SAME

Technical Field

The present invention relates to a tablet and a method of preparing the same.

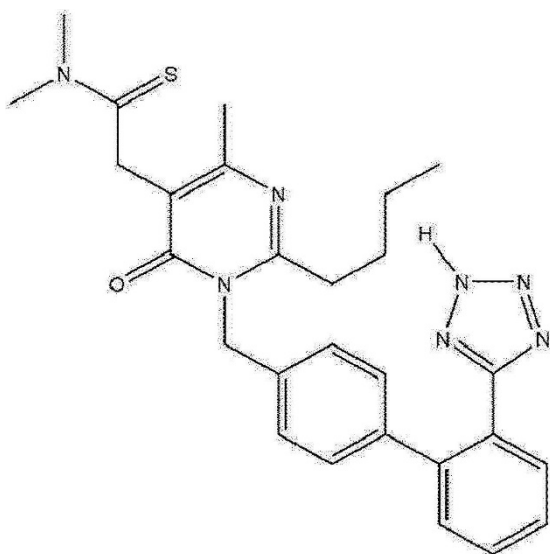
Background

As for hypertension, it is important to prevent coronary artery diseases and cardiovascular complications such as life-threatening stroke, heart failure, 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 controlling 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 combination prescription of two drugs or more. In addition, 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 reduce potential side effects resulting from a long-term use of drugs by concurrently using drugs with different mechanisms and reducing an amount of a single drug used rather than simply selecting one drug.

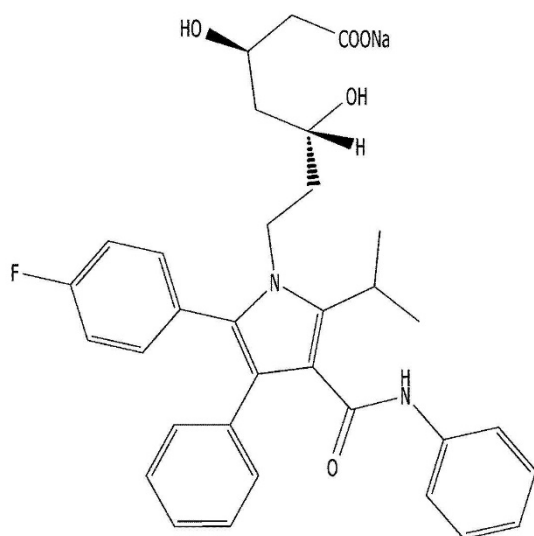
Fimasartan represented by Formula 1 below is known as an angiotensin II receptor antagonist developed to treat hypertension and other medical signs (Korean Registered Patent No. 10-1058284). The fimasartan is 2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one, which is a non-peptide described molecular-chemically. An empirical formula is $C_{27}H_{30}N_7OS$, and a molecular weight is 501.65. Fimasartan is commercially available in South Korea with a pharmaceutical approvals as fimasartan potassium trihydrate.

[Formula 1]



Meanwhile, atorvastatin represented by Formula 2 below is a selective and competitive HMG-CoA reductase inhibitor. As a representative salt of atorvastatin, atorvastatin calcium salt (chemical name: [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrol-1-heptanoic acid calcium salt (2:1)) is known as a lipid-lowering agent that lowers the concentration of low-density lipoprotein cholesterol, and is useful in the treatment of hyperlipidemia. In addition, atorvastatin calcium is known to reduce mortality caused by cardiovascular-related diseases, as well as stroke.

[Formula 2]



In order to more effectively treat cardiovascular diseases including hypertension, etc., it may be possible to consider tablet containing fimasartan and atorvastatin having different mechanisms of action as described above. However, during a tableting process as above, tableting failure such as sticking of atorvastatin occurs.

Thus, there is a need to develop a tablet containing fimasartan and atorvastatin, which can more effectively treat cardiovascular diseases including hypertension, etc., by solving the tableting failure of atorvastatin.

[Related Art Reference]

[Non-Patent Document]

(Non-Patent Document 1) Compatibility study of Atorvastatin Calcium and Telmisartan with selected excipients and formulation of a bilayer tablet using box behnken design, Bajracharya et. al., Am. J. PharmTech Res. 2015; 5(3) ISSN: 2249-3387

Detailed Description of the Invention

Technical Problem

The present invention relates to a tablet capable of remarkably improving the tableting properties in a process of tableting with fimasartan by adjusting the particle size distribution of atorvastatin granules to a certain value or more; and a method for preparing

the same.

Specifically, the present invention provides a tablet which includes: a fimasartan granule portion containing fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and an atorvastatin granule portion containing atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive, wherein the fimasartan granule portion and the atorvastatin granule portion are present while being separate from each other.

In addition, the present invention provides a tablet which includes: a first layer including granules containing fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and a second layer including granules containing atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive, wherein the granules of the second layer exhibit a particle size distribution with a D₅₀ of 80 µm or more.

In addition, the present invention provides a method of preparing a tablet, which includes: (S1) preparing a first layer including granules containing fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; (S2) preparing a second layer including granules containing atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and (S3) preparing a bilayer tablet by tableting the first and the second layers.

In addition, the present invention provides a pharmaceutical composition containing the tablet.

In addition, the present invention provides a method of preventing or treating cardiovascular diseases, which includes administering a therapeutically effective amount of

the tablet, to mammals including human.

In addition, the present invention provides a use of the tablet in the manufacture of a formulation for cardiovascular diseases.

Furthermore, the present invention provides a use of the tablet for treating cardiovascular diseases.

Technical Solution

To solve the above problems, in the present invention, a tablet containing fimasartan active ingredient and atorvastatin active ingredient was developed by solving the tableting failure of atorvastatin in the process of tableting with fimasartan with the application of a particle size control technique for atorvastatin granules, and as a weight deviation of atorvastatin is within a suitable range, the tablet can be prepared in accordance with a target weight, and thus it was confirmed that the tablet exhibits excellent content uniformity.

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

Tablet

The present invention provides a tablet which includes: a fimasartan granule portion containing fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and an atorvastatin granule portion containing atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive, wherein the fimasartan granule portion and the atorvastatin granule portion are present while being separate from each other.

The present invention provides a tablet which includes: a first layer including granules containing fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and a second layer including granules containing atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or

solvate thereof, and pharmaceutically acceptable additive, wherein the granules of the second layer exhibit a particle size distribution with a D₅₀ of 80 μm or more.

In case that a combination drug is prepared with fimasartan, atorvastatin is very difficult to be formulated. Since atorvastatin has low stability, a large amount of pulverized precipitated calcium carbonate is added as a stabilizer. It causes a tableting failure during a process of tableting fimasartan and atorvastatin into a bilayer tablet, resulting in a molding failure of some lack of the formulation. In the case of preparing on a production scale, it is also presumed that such a tableting failure may cause a machine to be stopped, thereby making a production itself difficult. In addition, even when an identification code is imprinted on the surface of the tablet, such imprinting may be missing due to a tableting failure, which becomes a major problem. Furthermore, when such a sticking on the surface of punch occurs during actual production, it is necessary to stop the production once and remove the material adheres to the surface of punch. If this trouble occurs a lot during production, it may develop into various problems such as a decrease in production efficiency and a decrease in quality due to an increase in defective tablets (decrease in yield). In some cases, lubricants such as talc are used to solve these tableting failure, but if more lubricant is added, the moldability of the formulation itself may decrease, resulting in less hardness or abrasion damage. Thus, this method does not directly solve the problem.

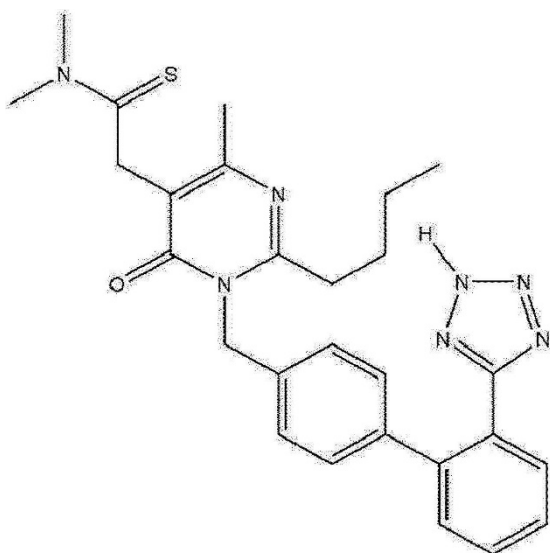
In addition, it may be possible to prevent the tableting failure by polishing the surface of the punch and die used in the tableting process. However, since the effect of polishing is not permanent, the tableting failure may occur due to abrasion, and thus this method may not directly solve the problems.

Thus, in order to solve the above problem, in the present invention, the particle size distribution of the atorvastatin granules contained in the second layer may be adjusted to a certain value or more, thereby providing an easy tableting property in a tableting process for

preparing a combination drug with fimasartan. In addition, 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 mass production thereof.

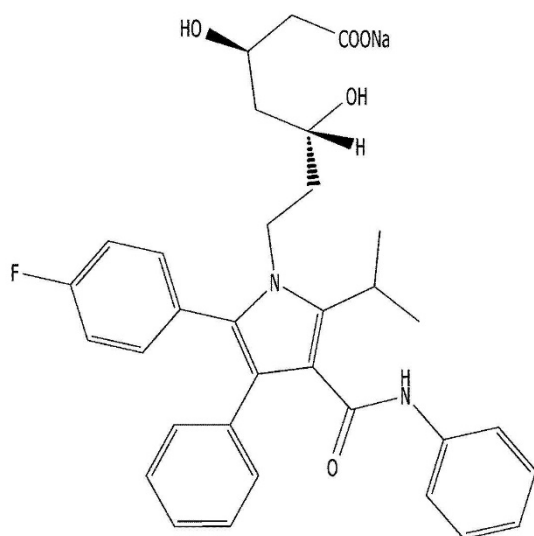
In the present invention, the term “fimasartan,” which is 2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one, represented by Formula 1 below, refers to an angiotensin II receptor antagonist developed to treat hypertension and other medical signs.

[Formula 1]



In the present invention, the term “atorvastatin,” which is a lipid-lowering agent for lowering the concentration of low-density lipoprotein cholesterol represented by Formula 2 below, is a selective and competitive HMG-CoA reductase inhibitor useful in the treatment of hyperlipidemia.

[Formula 2]



In the present invention, the term “pharmaceutically acceptable” refers to the one that is physiologically acceptable and does not conventionally cause an allergic reaction such as gastrointestinal disturbance and dizziness, or other reactions similar thereto, when being administered into humans, and the term “salt” means an acid addition salt formed by pharmaceutically acceptable free acid.

In examples of the present invention, the pharmaceutically acceptable salt of fimasartan may be selected from the group consisting of inorganic ion salt, inorganic acid salt, organic acid salt, sulfonic acid salt, amino acid salt and amine salt. Specifically, the pharmaceutically acceptable salt of fimasartan may be inorganic ion salt prepared from calcium, potassium, sodium, magnesium or the like; inorganic acid salt 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, pantoic 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. Specifically, the pharmaceutically acceptable salt of fimasartan may be fimasartan potassium, fimasartan toluenesulfonic acid salt or fimasartan ammonia salt, more specifically the fimasartan potassium salt.

In one embodiment of the present invention, the pharmaceutically acceptable salt of atorvastatin may be inorganic ion salt prepared from calcium, strontium, sodium, potassium, magnesium, ammonium, etc.; inorganic acid salt prepared from hydrochloric acid, nitric acid, phosphoric acid, bromic acid, iodic acid, perchloric acid, sulfuric acid or the like; etc., but types of salt meant in the present invention are not limited to those listed salts. Specifically, the pharmaceutically acceptable salt of atorvastatin may be atorvastatin calcium salt.

In the present invention, the term “hydrate” refers to a combination of active ingredients and water by a non-covalent intermolecular force, containing a stoichiometric or non-stoichiometric amount of water. Specifically, the hydrate may contain water at a ratio of about 0.25 to about 10 moles based on 1 mole of active ingredients, more specifically, about 0.5, about 1, about 1.5, about 2, about 3, about 5 moles, etc.

In one embodiment of the present invention, the fimasartan hydrate may be any one selected from the group consisting of fimasartan potassium trihydrate, fimasartan hydrochloride trihydrate, fimasartan calcium trihydrate, fimasartan sulfate trihydrate, fimasartan adipate trihydrate, fimasartan camsylate trihydrate and fimasartan besylate trihydrate, specifically the fimasartan hydrate may be fimasartan potassium trihydrate, but is not limited thereto.

In examples of the present invention, the hydrate of fimasartan or pharmaceutically acceptable salt thereof may be monohydrate or trihydrate, specifically the monohydrate or trihydrate of fimasartan potassium, and more specifically the trihydrate of fimasartan potassium.

In one embodiment of the present invention, the hydrate of atorvastatin or pharmaceutically acceptable salt thereof may be trihydrate, specifically the trihydrate of atorvastatin calcium, but are not limited thereto.

In the present invention, the term “solvate” refers to a combination of active ingredients and solvent by a non-covalent intermolecular force, containing a stoichiometric or non-stoichiometric amount of solvent. Preferable solvent may be volatile, non-toxic, and may be administered to humans in a very small amount thereof. For example, there may be methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-acetate, acetone, acetic acid, anisole, tetrahydrofuran, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, isobutyl acetate, n-butyl acetate, dimethyl sulfoxide, pentane, heptane, etc., but the solvate of the present invention is not limited thereto. Specifically, the hydrate may contain water at a ratio of about 0.25 to about 10 moles based on 1 mole of active ingredients, more specifically, about 0.5, about 1, about 1.5, about 2, about 3, about 5 moles, etc.

In the present invention, the term “about” refers to a 10% deviation from an indicated value (e.g., 1 mole, 2 mol%, 3 mol%, etc.) or a 10% deviation from both the lower and upper limits of a numerical range. For example, “about 1 mole” refers to the range of 0.9 to 1.1 moles.

In the present invention, the term "granule" refers to a smaller primary particle or a solid particle formed from the primary particle. The term “granule containing fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive” refers to a primary particle formed with a mixture of

fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive, or a solid particle formed from the primary particle. The term “granule containing atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive” refers to a primary particle formed with a mixture of atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive, or a solid particle formed from the primary particle.

In the present specification, “particle size” may be represented by a particle size distribution such as $D(X) = Y$ (here, X and Y are positive numbers). $D(X) = Y$ may mean that, when the particle size distribution of a drug obtained by measuring the particle diameter of the drug in a formulation is expressed by a cumulative curve, the particle sizes are accumulated in an ascending order and come to reach $X\%$ ($\%$ is calculated based on number, volume, or weight), at the point of which the particle size refers to Y . For example, $D(10)$ may refer to the diameter of a particle, at the point of which the particle size comes to reach 10%, when the particle sizes of a drug are accumulated in an ascending order. $D(50)$ may refer to the diameter of a particle, at the point of which the particle size comes to reach 50%, when the particle sizes of a drug are accumulated in an ascending order. $D(90)$ may refer to the diameter of a particle, at the point of which the particle size comes to reach 90%, when the particle sizes of a drug are accumulated in an ascending order.

In the present specification, $D(X)$ may be otherwise expressed as $D(0.X)$, and $D(X)$ and $D(0.X)$ may be used interchangeably. For example, $D(50)$ may be also expressed as $D(0.5)$, and $D(10)$ and $D(90)$ may be also expressed as $D(0.1)$ and $D(0.9)$, respectively.

Whether the particle size distribution $D(X)$ represents the percentage of the total cumulative particles based on number, volume, or weight may depend on the method used to measure the particle size distribution. Methods of measuring the particle size distribution and

the types of percentages associated therewith are known to those skilled in the art. For example, when measuring the particle size distribution by a well-known laser diffraction method, the value of X in D(X) may represent a percentage calculated by a volume average. It is known to those skilled in the art that the results of measuring the particle size distribution according to a specific method may be correlated with those obtained from other techniques based on the experience of conventional experiments. For example, the laser diffraction method may provide a volume average particle size in response to the volume of a particle, which corresponds to a weight average particle size when the density is constant.

In one embodiment of the present invention, the granules of the second layer may have a particle size distribution with a D_{50} of 80 μm or more, but is not limited thereto, and specifically, 80 to 260 μm , 90 to 240 μm , or 100 to 235 μm . When the granules of the second layer have a D_{50} within the above range, easy tableting properties may be provided during a process of tableting with fimasartan into a bilayer tablet. In addition, 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 mass production thereof.

In one embodiment of the present invention, the granules of the second layer may have D_{10} of 14 to 70 μm , but are not limited thereto, and specifically the granules of the second layer may be 14 to 50 μm . When the granules of the second layer have a D_{10} within the above range, easy tableting properties may be provided during a process of tableting with fimasartan into a bilayer tablet. 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 mass production thereof.

In one embodiment of the present invention, the granules of the second layer may have D_{90} of 290 to 600 μm , but are not limited thereto, and specifically the granules of the second layer may have D_{90} of 300 to 550 μm , or 300 to 500 μm . When the granules of the

second layer have a D_{90} within the above range, easy tableting properties may be provided during a process of tableting with fimasartan into a bilayer tablet. In addition, 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 mass production thereof.

In one embodiment of the present invention, the tablet may be in the form of a bilayer tablet including a first layer containing the fimasartan granules and a second layer containing the atorvastatin granules, but is not limited thereto.

In the present invention, the term “tablet” may refer to one including a compressed pharmaceutical dosage form of all shapes and sizes, and the term “bilayer tablet” may refer to a combination drug in which two or more different ingredients are combined in such a way that they are not mixed together, but each independently present in separate compartments. In the present invention, the first layer of the bilayer tablet may contain fimasartan granules, and the second layer may contain atorvastatin granules, in which the fimasartan granules and atorvastatin granules independently present in the first and second layers are not mixed with each other, but independently present in separate compartments, thereby more effectively treating cardiovascular diseases including hypertension.

In the present invention, the term “fimasartan granule(s)” may refer to a granule containing fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive. In the present invention, the term “atorvastatin granule(s)” may refer to a granule containing atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive.

In the present invention, the term “first and second” may be used only to distinguish various layers, membranes, steps, etc., from each other, but not intended to indicate a sequence or 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.

In one embodiment of the present invention, the fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof may be included in an amount of 0.5 to 240.0 mg per unit dosage form, specifically in an amount of 10 to 180 mg or 20 to 120 mg, but are not limited thereto.

In one embodiment of the present invention, the atorvastatin, pharmaceutically acceptable salt thereof, and hydrate or solvate thereof may be included in an amount of 1.0 to 100.0 mg per unit dosage form, specifically in an amount of 10 to 80 mg, but are not limited thereto.

In one embodiment of the present invention, the additives of the first and second layers may be any one selected from the group consisting of excipient, solubilizing agent, disintegrant, binder, lubricant and mixture thereof, but are not limited thereto.

In the present invention, the term “excipient” may refer to any substance rather than a therapeutic agent, which is used as a carrier or medium for delivering the therapeutic agent or is added to the pharmaceutical composition. Accordingly, the excipient may improve properties of handling and storage or may permit and promote formation of the composition in an amount of a unit dosage. For example, the excipient may be at least one selected from the group including precipitated calcium carbonate, lactose or hydrate thereof, microcrystalline cellulose, mannitol, and colloidal silicon dioxide, and more specifically precipitated calcium carbonate, microcrystalline cellulose, and lactose, but is not limited thereto.

In the present invention, the term “solubilizing agent” refers to a substance added for

the purpose of increasing the solubility of a poorly soluble drug to be easily dissolved in a solvent (mainly water). For example, the solubilizing agent may be isotonic solutions including physiological saline solution, glucose and other adjuvants such as D-sorbitol, D-mannose, D-mannitol and sodium chloride; alcohols such as ethanol; polyols such as propylene glycol and polyethylene glycol; and nonionic surfactants such as polysorbate 80 and HCO-50; etc., but is not limited thereto.

In the present invention, the term “disintegrant” refers to a substance added for the purpose of promoting disintegration of tablets, capsules, granules, etc., in the digestive fluid. For example, the disintegrant may be selected from the group consisting of crospovidone (crosslinked polyvinylpyrrolidone), croscarmellose sodium (crosslinked sodium carboxymethylcellulose), sodium starch glycolate, corn starch, pregelatinized starch, low-substituted hydroxypropyl cellulose and microcrystalline cellulose, but is not limited thereto.

In the present invention, the term “binder” refers to a substance added to make a drug form when making a tablet or a pill. For example, the binder may be selected from the group consisting of polyvinylpyrrolidone (povidone), a copolymer of vinylpyrrolidone and other vinyl derivatives (copovidone), hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose and pregelatinized starch, but is not limited thereto.

In the present invention, the term “lubricant” refers to an additive used to provide fluidity to granules and to make the tablets easily escape from a mold when making tablets. For example, the lubricant may be talc, magnesium stearate, sodium stearyl fumarate, or colloidal silicon dioxide, but is not limited thereto.

In one embodiment of the present invention, the granules of the second layer may include a mixture of lactose hydrate and microcrystalline cellulose, and the mixture may be included in an amount of 40 to 50 wt% based on the total weight of the granules of the second layer, but is not limited thereto. Specifically, the mixture of lactose hydrate and

microcrystalline cellulose may have an effect on the tableting properties of atorvastatin granules during a tableting process when preparing a combination drug containing atorvastatin and fimasartan as active ingredients. By including a mixture of lactose hydrate and microcrystalline cellulose in an amount of 40 to 50 wt% based on the total weight of the granules of the second layer, it may affect the particle size distribution of the atorvastatin granules of the second layer, and prevent tableting failure such as sticking in the process of tableting with fimasartan, thereby facilitating tableting. In addition, 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 mass production thereof.

In one embodiment of the present invention, the granules of the second layer may further contain precipitated calcium carbonate, but are not limited thereto. Specifically, when preparing a combination drug of atorvastatin and fimasartan, a large amount of precipitated calcium carbonate may be added to stabilize atorvastatin during the tableting process.

In one embodiment of the present invention, the mixture of lactose hydrate and microcrystalline cellulose may exhibit a particle size distribution with a D_{50} of 75 μm or more, but is not limited thereto, and specifically 75 to 200 μm , 85 to 180 μm , or 95 to 170 μm . By using the mixture of lactose hydrate and microcrystalline cellulose having a particle size distribution within the above range, the particle size of the granules of the second layer may be increased, so that easy tableting properties may be accomplished in the tableting process when preparing a combination drug with fimasartan. In addition, 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 mass production thereof.

In one embodiment of the present invention, the mixture of lactose hydrate and microcrystalline cellulose may exhibit a particle size distribution with a D_{10} of 15 to 50 μm , but is not limited thereto, and specifically 20 to 40 μm , or 23 to 35 μm . By using the mixture

of lactose hydrate and microcrystalline cellulose having a particle size distribution within the above range, the particle size of the granules of the second layer may be increased, so that easy tableting properties may be accomplished in the tableting process when preparing a combination drug with fimasartan. In addition, 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 mass production thereof.

In one embodiment of the present invention, the mixture of lactose hydrate and microcrystalline cellulose may exhibit a particle size distribution with a D_{90} of 150 to 400 μm , but is not limited thereto, and specifically 180 to 350 μm , or 200 to 300 μm . By using the mixture of lactose hydrate and microcrystalline cellulose having a particle size distribution within the above range, the particle size of the granules of the second layer may be increased, so that easy tableting properties may be accomplished in the tableting process when preparing a combination drug with fimasartan. In addition, 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 mass production thereof.

In one embodiment of the present invention, the granules of the second layer may include 1 to 10 parts by weight of atorvastatin, pharmaceutically acceptable salt thereof, hydrate or solvate thereof, 50 to 99.9 parts by weight of excipient, 0.1 to 2 parts by weight of solubilizing agent, 0.5 to 15 parts by weight of disintegrant, 0.1 to 10 parts by weight of binder, and 0.1 to 5 parts by weight of lubricant, but are not limited thereto.

In the present invention, the unit “parts by weight” may refer to a weight ratio between respective ingredients unless otherwise specified. For example, the granules of the second layer including 1 to 10 parts by weight of atorvastatin, pharmaceutically acceptable salt thereof, hydrate or solvate thereof, 50 to 99.9 parts by weight of excipients, 0.1 to 2 parts by weight of solubilizing agent, 0.5 to 15 parts by weight of disintegrant, 0.1 to 10 parts by

weight of binder, and 0.1 to 5 parts by weight of lubricant may mean that the granules of the second layer are formed by mixing atorvastatin, pharmaceutically acceptable salt thereof, hydrate or solvate thereof; excipients; solubilizing agent; disintegrant; binder; and lubricant at a weight ratio of 1~10 : 50~99.9 : 0.1~2 : 0.5~15: 0.1~10: 0.1~5. Specifically, the granules of the second layer may mean that the portion of atorvastatin granules is formed by mixing atorvastatin, pharmaceutically acceptable salt thereof, hydrate or solvate thereof; excipients; solubilizing agent; disintegrant; binder; and lubricant at a weight ratio of 3~7 : 70~85 : 0.1~0.5 : 1~10 : 0.5~2 : 0.1~0.5.

In another aspect, the granules of the second layer may mean that the granules of the second layer are formed by mixing 1 to 20 wt% of atorvastatin, pharmaceutically acceptable salt thereof, hydrate or solvate thereof, 50 to 98.2 wt% of excipient, 0.1 to 5 wt% of solubilizing agent, 0.5 to 15 wt% of disintegrant, 0.1 to 10 wt% of binder, and 0.1 to 5 wt% of lubricant. Specifically, the granules of the second layer may mean that the granules of the second layer are formed by mixing 5 to 15 wt% of atorvastatin, pharmaceutically acceptable salt thereof, hydrate or solvate thereof, 70 to 85 wt% of excipient, 0.1 to 1 wt% of solubilizing agent, 1 to 10 wt% of disintegrant, 0.5 to 5 wt% of binder, and 0.1 to 3 wt % of lubricant.

In one embodiment of the present invention, the excipient may be any one of precipitated calcium carbonate, lactose hydrate, microcrystalline cellulose, or a mixture thereof, but are not limited thereto.

In one embodiment of the present invention, the mixture of excipients may include 30 to 50 parts by weight of precipitated calcium carbonate, 20 to 40 parts by weight of lactose hydrate, and 15 to 35 parts by weight of microcrystalline cellulose, but is not limited thereto. Specifically, the mixture may mean that the mixture of excipients is formed by mixing precipitated calcium carbonate, lactose hydrate, and microcrystalline cellulose at a weight

ratio of 30~50 : 20~40 : 15~35.

In one embodiment of the present invention, said tablet may be for treating cardiovascular diseases. In the present invention, the term “cardiovascular disease” may refer to any disease that occurs in the heart and/or the vascular system (all blood vessels such as arteries, capillaries and veins).

In one embodiment of the present invention, the cardiovascular disease may be any one selected from hypertension, diabetes, obesity, hyperlipidemia, coronary artery disease, chronic stable angina, vasospastic angina, stroke, myocardial infarction, temporary ischemic attack, congestive heart failure, insulin resistance, impaired glucose tolerance, prediabetes, type 2 diabetes mellitus, diabetic nephropathy, dyslipidemia, cognitive decline, dementia, and combinations thereof, but is not limited thereto.

In one embodiment of the present invention, the tablet may be in the form of a coated tablet further including a coating layer outside, but is not limited thereto. Specifically, Opadry (Colorcon; 415 Moyer Blvd., P.O. Box 4, West Point, PA 19486-0024, U.S.A.) may be used as a coating layer.

In one embodiment of the present invention, the tablet further including a coating layer outside may further include a polishing agent outside, but is not limited thereto. In the present invention, the term “polishing agent” may refer to a substance that polishes the surface of a preparation to improve the properties of the formulation. For example, the polishing agent may be beeswax or carnauba wax, but is not limited thereto.

In one embodiment of the present invention, the granules of the first and second layers may be dry granules or wet granules, specifically the wet granules.

Method for preparing tablet

The present invention provides a method of preparing a tablet, which includes: (S1) preparing a first layer including granules containing fimasartan, pharmaceutically acceptable

salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; (S2) preparing a second layer including granules containing atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and (S3) preparing a bilayer tablet by tableting the first and second layers.

In one embodiment of the present invention, the step of tableting the first and second layers may be performed by applying a tableting pressure of 5 to 15 KN, but is not limited thereto.

Pharmaceutical composition containing tablet

The present invention provides a pharmaceutical composition containing the tablet. The pharmaceutical composition of the present invention shows a remarkable effect on the prevention and treatment of cardiovascular diseases.

The pharmaceutical composition of the present invention may be for oral administration. In the present invention, the term “oral administration” means that a substance prepared for allowing an active substance to be digested is administered into the gastrointestinal tract for absorption. A non-limiting example of the formulation for oral administration may include a tablet, troche, lozenge, water soluble suspension, oil suspension, prepared powder, granule, emulsion, hard capsule, soft capsule, syrup, elixir or the like. To formulate the pharmaceutical composition of the present invention for oral administration, the followings may be used: binders such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose, gelatin or the like; excipients such as dicalcium phosphate, etc.; disintegrants such as maize starch, sweet potato starch or the like; lubricants such as magnesium stearate, calcium stearate, sodium stearyl fumarate, polyethylene glycol wax or the like; etc., in which sweetening agents, flavoring agents, syrups, etc. may also be used. Furthermore, in case of the capsule, liquid carrier such as fatty oil, etc. may be further used in addition to the above-mentioned materials.

Method of preventing or treating cardiovascular diseases

The present invention provides a method of preventing or treating cardiovascular diseases, which includes administering a therapeutically effective amount of the tablet, to mammals including humans.

In the present invention, the term “prevention” refers to a delay of occurrence of disease, disorder or condition. If the occurrence of disease, disorder or condition is delayed for an expected period of time, the prevention may be considered as complete.

In the present invention, the term “treatment” refers to the one that partially or completely reduces, ameliorates, alleviates, inhibits or delays the occurrence of a certain disease, disorder and/or condition, reduces a severity thereof, or reduces the occurrence of at least one symptom or feature thereof.

In the present invention, the term “therapeutically effective amount” may be an amount of the tablet of the present invention, which is effective in prevention or treatment of cardiovascular diseases, in which such amount may include all the amounts of the tablet, which prevent occurrence or recurrence of cardiovascular diseases, alleviate a symptom, suppress a direct or indirect pathological outcome, prevent metastasis, reduce a progress rate, relieve or transiently alleviate a condition, or improve prognosis. In other words, the therapeutically effective amount may be interpreted to encompass all the doses in which a symptom of cardiovascular diseases takes a favorable turn or is completely cured through the tablet.

In one embodiment of the present invention, the cardiovascular diseases include hypertension, or all of hypertension, complications and the like of those who suffer from a so-called metabolic syndrome, which develops diabetes, obesity, hyperlipidemia, coronary artery disease, etc., in a complex way, and may also include chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure,

insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, diabetic nephropathy, dyslipidemia, cognitive decline, dementia and the like.

The preventing or treating method of the present invention includes not only dealing with the disease itself before expression of its symptoms, but also inhibiting or avoiding such symptoms by administering a tablet. In managing the disease, a preventive or therapeutic dose of a certain active ingredient may vary depending on a nature and severity of the disease or condition and a route of administering the active component. A dose and a frequency thereof may vary depending on an individual patient's age, weight and reactions. A suitable dose and usage may be easily selected by those skilled in the art, naturally considering such factors. In addition, the treating method of the present invention may further include administering a therapeutically effective amount of an additional active agent, which is helpful in treating the disease, along with the tablet, wherein the additional active agent may achieve a synergy effect or an additive effect together with the pharmaceutical composition.

In the present invention, the term “mammals” refers to each animal belonging to the mammalian class in terms of biotaxonomy. Specifically, mammals including a human include a mammal such as human, monkey, cow, horse, dog, cat, rabbit, rat, mouse, etc.

Use of tablet in the manufacture of a formulation for cardiovascular disease

The present invention may provide a use of the tablet in the manufacture of a formulation for cardiovascular disease.

The tablet of the present invention in the manufacture of a medicament may be prepared by mixing the above-mentioned acceptable additive, etc., for example, by including additives such as pharmaceutically acceptable stabilizer, binder, disintegrant, lubricant, diluent, coating agent, pH adjusting agent, solubilizing agent, surfactant, etc., within the range that does not undermine an effect of the present invention.

In one embodiment of the present invention, the cardiovascular diseases include

hypertension, or all of hypertension, complications and the like of those who suffer from a so-called metabolic syndrome, which develops diabetes, obesity, hyperlipidemia, coronary artery disease, etc., in a complex way, and also include chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, diabetic nephropathy, dyslipidemia, cognitive decline, dementia and the like.

Use of tablet for treatment of cardiovascular diseases

The present invention provides a use of the tablet for treating cardiovascular diseases.

In one embodiment of the present invention, the cardiovascular diseases include hypertension, or all of hypertension, complications and the like of those who suffer from a so-called metabolic syndrome, which develops diabetes, obesity, hyperlipidemia, coronary artery disease, etc., in a complex way, and also include chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, diabetic nephropathy, dyslipidemia, cognitive decline, dementia and the like.

Matters mentioned in the tablet, composition, treating method and use according to the present invention are applied the same, if not contradictory to each other.

Advantageous Effects

The present invention relates to a tablet and a method of preparing the same, which is capable of remarkably improving the tableting properties in a process of tableting with fimasartan by adjusting the particle size distribution of atorvastatin granules to a certain value or more, thereby enabling an economically easy mass-production with excellent content uniformity.

Brief Description of the Drawings

FIG. 1 is a flow chart schematically showing a method of preparing a tablet according to the present invention.

FIG. 2 is a view showing a surface of a tablet according to Comparative Example 1.

FIG. 3 is a view showing a surface of a tablet according to Example 1.

FIG. 4 is a view showing a surface of a tablet according to Example 2.

FIG. 5 is a view showing a surface of a tablet according to Example 3.

Mode for Invention

Hereinafter, the present invention will be described in more detail through exemplary embodiments. However, the scope of the present invention is not limited to these examples. The Examples of the present invention are provided to more completely describe the present invention to those having ordinary skill in the art.

Fimasartan calcium trihydrate used in the following preparation examples was purchased from Boryung Pharmaceutical Co., Ltd., atorvastatin calcium trihydrate was purchased from Dr. Reddy's, precipitated calcium carbonate was purchased from Bihoku, lactose hydrate was purchased from DFE Pharma, microcrystalline cellulose was purchased from Asahi kasei, polysorbate 80 was purchased from Croda, croscarmellose sodium was purchased from DPE Pharma, hydroxypropyl cellulose was purchased from Nippon soda, magnesium stearate was purchased from FACI, Opadry was purchased from Colorcon, and other reagents were purchased from Sigma-aldrich.

<Preparation Example 1> Preparation of fimasartan granule portion

A granule portion containing fimasartan potassium trihydrate as an effective ingredient was prepared by a following method so that ingredients and contents per unit dosage form (350 mg) comply with those described in table 1 below.

Fimasartan potassium trihydrate, microcrystalline cellulose and croscarmellose sodium were mixed together for about 10 minutes, after which the resulting mixture was put

in a high speed mixer and further mixed for about three minutes, thereby preparing a mixture containing fimasartan as an effective ingredient.

Apart from this, hydroxypropyl cellulose was dissolved in 41.7 mL of purified water, thereby preparing a binder solution.

The prepared binder solution was put into the high speed mixture, then wet-granulated with the mixture containing fimasartan as an effective ingredient, size-regulated in 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 a fimasartan granule portion.

【Table 1】

Granules containing fimasartan as an effective ingredient	
mg/per tablet	
Fimasartan potassium trihydrate	66
Microcrystalline cellulose	72.75
Croscarmellose sodium	7.5
Hydroxypropyl cellulose	1.5
Magnesium stearate	2.25

<Preparation Example 2-1> Preparation of atorvastatin granule portion 1

An atorvastatin granule portion was prepared so that the contents per unit dosage form (350 mg) comply with those described in table 2 below.

Atorvastatin calcium trihydrate (D_{50} : 3 μm), precipitated calcium carbonate (D_{50} : less than 45 μm), lactose hydrate (D_{50} : 40 μm), microcrystalline cellulose (D_{50} : 50 μm), and polysorbate 80 were mixed together for about 10 minutes, after which the resulting mixture

was put in a high speed mixer and further mixed in a high speed mixer for about three minutes, thereby preparing a mixture containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the mixture of lactose hydrate and microcrystalline cellulose, D₁₀ was 12.33 μm, D₅₀ was 53.56 μm, and D₉₀ was 128.86 μm.

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

The prepared binder solution was put into the high speed mixture, then wet-granulated with the mixture containing atorvastatin calcium trihydrate as an effective ingredient, size-regulated in a 18 mesh sieve, and then dried, thereby preparing a granule containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the granule containing atorvastatin calcium trihydrate as an effective ingredient, D₁₀ was 13.37 μm, D₅₀ was 71.66 μm, and D₉₀ was 288.58 μm.

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 an atorvastatin granule portion.

【Table 2】

Granules containing atorvastatin as an effective ingredient	
mg/per tablet	
Atorvastatin calcium trihydrate	21.7
Precipitated calcium carbonate	66
Lactose 200 (PHARMATOSE® 200M)	54.5
Microcrystalline cellulose (CEOLUS® PH101)	40
Polysorbate 80	0.8

Croscarmellose sodium	12
Hydroxypropyl cellulose	4
Magnesium stearate	1

<Preparation Example 2-2> Preparation of atorvastatin granule portion 2

An atorvastatin granule portion was prepared so that the contents per unit dosage form (350 mg) comply with those described in table 3 below.

Atorvastatin calcium trihydrate (D_{50} : 3 μm), precipitated calcium carbonate (D_{50} : less than 45 μm), lactose hydrate (D_{50} : 150 μm), microcrystalline cellulose (D_{50} : 50 μm), and polysorbate 80 were mixed together for about 10 minutes, after which the resulting mixture was put in a high speed mixer and further mixed for about three minutes, thereby preparing a mixture containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the mixture of lactose hydrate and microcrystalline cellulose, which affects the tableting of atorvastatin granules, D_{10} was 28.00 μm , D_{50} was 97.70 μm , and D_{90} was 229.38 μm .

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

The prepared binder solution was put into the high speed mixture, then wet-granulated with the mixture containing atorvastatin calcium trihydrate as an effective ingredient, size-regulated in an 18 mesh sieve, and then dried, thereby preparing a granule containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the granule containing atorvastatin calcium trihydrate as an effective ingredient, D_{10} was 15.79 μm , D_{50} was 111.06 μm , and D_{90} was 423.35 μm .

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 an atorvastatin granule portion.

【Table 3】

Granules containing atorvastatin as an effective ingredient	
mg/per tablet	
Atorvastatin calcium trihydrate	21.7
Precipitated calcium carbonate	66
Lactose 100 (PHARMATOSE [®] 100M)	54.5
Microcrystalline cellulose (CEOLUS [®] PH101)	40
Polysorbate 80	0.8
Croscarmellose sodium	12
Hydroxypropyl cellulose	4
Magnesium stearate	1

<Preparation Example 2-3> Preparation of atorvastatin granule portion 3

An atorvastatin granule portion was prepared so that the contents per unit dosage form (350 mg) comply with those described in table 4 below.

Atorvastatin calcium trihydrate (D₅₀: 3 μm), precipitated calcium carbonate (D₅₀: less than 45 μm), lactose hydrate (D₅₀: 150 μm), microcrystalline cellulose (D₅₀: 90 μm), and polysorbate 80 were mixed together for about 10 minutes, after which the resulting mixture was put in a high speed mixer and further mixed for about three minutes, thereby preparing a mixture containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the mixture of lactose hydrate and microcrystalline cellulose, which affects the tableting of atorvastatin granules, D₁₀ was 25.88 μm, D₅₀ was

115.11 μm , and D_{90} was 234.22 μm .

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

The prepared binder solution was put into the high speed mixture, then wet-granulated with the mixture containing atorvastatin calcium trihydrate as an effective ingredient, size-regulated in an 18 mesh sieve, and then dried, thereby preparing a granule containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the granule containing atorvastatin calcium trihydrate as an effective ingredient, D_{10} was 24.59 μm , D_{50} was 160.02 μm , and D_{90} was 494.80 μm .

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 an atorvastatin granule portion.

【Table 4】

Granules containing atorvastatin as an effective ingredient	
mg/per tablet	
Atorvastatin calcium trihydrate	21.7
Precipitated calcium carbonate	66
Lactose 100 (PHARMATOSE [®] 100M)	54.5
Microcrystalline cellulose (CEOLUS [®] PH102)	40
Polysorbate 80	0.8
Croscarmellose sodium	12
Hydroxypropyl cellulose	4
Magnesium stearate	1

<Preparation Example 2-4> Preparation of atorvastatin granule portion 4

An atorvastatin granule portion was prepared so that the contents per unit dosage form (350 mg) comply with those described in table 5 below.

Atorvastatin calcium trihydrate (D_{50} : 3 μm), precipitated calcium carbonate (D_{50} : less than 45 μm), lactose hydrate (D_{50} : 150 μm), microcrystalline cellulose (D_{50} : 170 μm), and polysorbate 80 were mixed together for about 10 minutes, after which the resulting mixture was put in a high speed mixer and further mixed for about three minutes, thereby preparing a mixture containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the mixture of lactose hydrate and microcrystalline cellulose, which affects the tableting of atorvastatin granules, D_{10} was 52.99 μm , D_{50} was 115.11 μm , and D_{90} was 282.48 μm .

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

The prepared binder solution was put into the high speed mixture, then wet-granulated with the mixture containing atorvastatin calcium trihydrate as an effective ingredient, size-regulated in an 18 mesh sieve, and then dried, thereby preparing a granule containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the granule containing atorvastatin calcium trihydrate as an effective ingredient, D_{10} was 47.40 μm , D_{50} was 230.84 μm , and D_{90} was 460.13 μm .

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 an atorvastatin granule portion.

【Table 5】

Granules containing atorvastatin as an effective ingredient

mg/per tablet	
Atorvastatin calcium trihydrate	21.7
Precipitated calcium carbonate	66
Lactose 100 (PHARMATOSE® 100M)	54.5
Microcrystalline cellulose (CEOLUS® PH200)	40
Polysorbate 80	0.8
Croscarmellose sodium	12
Hydroxypropyl cellulose	4
Magnesium stearate	1

<Preparation Example 2-5> Preparation of atorvastatin granule portion 5

An atorvastatin granule portion was prepared so that the contents per unit dosage form (350 mg) comply with those described in table 2.

Atorvastatin calcium trihydrate (D_{50} : 3 μm), precipitated calcium carbonate (D_{50} : less than 45 μm), lactose hydrate (D_{50} : 40 μm), microcrystalline cellulose (D_{50} : 50 μm), and polysorbate 80 were mixed together for about 10 minutes, after which the resulting mixture was put in a high speed mixer and further mixed for about three minutes, thereby preparing a mixture containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the mixture of lactose hydrate and microcrystalline cellulose, D_{10} was 12.33 μm , D_{50} was 53.56 μm , and D_{90} was 128.86 μm .

Apart from this, hydroxypropyl cellulose was dissolved in 70 mL of purified water, thereby preparing a binder solution.

The prepared binder solution was put into the high speed mixture, then wet-granulated with the mixture containing atorvastatin calcium trihydrate as an effective ingredient, size-regulated in an 18 mesh sieve, and then dried, thereby preparing a granule

containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the granule containing atorvastatin calcium trihydrate as an effective ingredient, D_{10} was 24.35 μm , D_{50} was 177.98 μm , and D_{90} was 507.06 μm .

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 an atorvastatin granule portion.

<Preparation Example 2-6> Preparation of atorvastatin granule portion 6

An atorvastatin granule portion was prepared so that the contents per unit dosage form (350 mg) may comply with those described in table 2.

Atorvastatin calcium trihydrate (D_{50} : 3 μm), precipitated calcium carbonate (D_{50} : less than 45 μm), lactose hydrate (D_{50} : 40 μm), microcrystalline cellulose (D_{50} : 50 μm), and polysorbate 80 were mixed together for about 10 minutes, after which the resulting mixture was put in a high speed mixer and further mixed for about three minutes, thereby preparing a mixture containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the mixture of lactose hydrate and microcrystalline cellulose, D_{10} was 12.33 μm , D_{50} was 53.56 μm , and D_{90} was 128.86 μm .

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

The prepared binder solution was put into the high speed mixture, then wet-granulated with the mixture containing atorvastatin calcium trihydrate as an effective ingredient, size-regulated in a 14 mesh sieve, and then dried, thereby preparing a granule containing atorvastatin calcium trihydrate as an effective ingredient. At this time, in case of the particle size distribution of the granule containing atorvastatin calcium trihydrate as an effective ingredient, D_{10} was 14.19 μm , D_{50} was 118.77 μm , and D_{90} was 303.93 μm .

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 an atorvastatin granule portion.

<Example 1> Bilayer tablet containing fimasartan and atorvastatin

Granules containing fimasartan potassium trihydrate as an effective ingredient according to <Preparation Example 1> and granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-2> were put into a punch die, respectively, and were subjected to tableting under a tableting pressure of 5 to 15 KN, so as to prepare a bilayer tablet.

The bilayer tablet was prepared by using a multilayered-tablet press (Piccola bilayer tablet press) such that a hardness of the one bilayer tablet reached 5~20 kp.

After that, coated tablet was prepared by using 10.5 mg of Opadry (Colorcon; 415 Moyer Blvd., P.O. Box 4, West Point, PA 19486-0024, USA), and the surface of coated tablet was polished by using 0.5 mg of carnauba wax, so as to prepare a bilayer tablet containing fimasartan and atorvastatin.

<Example 2> Bilayer tablet containing fimasartan and atorvastatin

Granules containing fimasartan potassium trihydrate as an effective ingredient according to <Preparation Example 1> and granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-3> were put into a punch die, respectively, and were subjected to tableting under a tableting pressure of 5 to 15 KN, so as to prepare a bilayer tablet.

The bilayer tablet was prepared by using a multilayered-tablet press (Piccola bilayer tablet press) such that a hardness of the one bilayer tablet reached 5~20 kp.

After that, coated tablet was prepared by using 10.5 mg of Opadry (Colorcon; 415 Moyer Blvd., P.O. Box 4, West Point, PA 19486-0024, USA), and the surface of coated tablet

was polished by using 0.5 mg of carnauba wax, so as to prepare a bilayer tablet containing fimasartan and atorvastatin.

<Example 3> Bilayer tablet containing fimasartan and atorvastatin

Granules containing fimasartan potassium trihydrate as an effective ingredient according to <Preparation Example 1> and granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-4> were put into a punch die, respectively, and were subjected to tableting under a tableting pressure of 5 to 15 KN, so as to prepare a bilayer tablet.

The bilayer tablet was prepared by using a multi-layered tablet press (Piccola bilayer tablet press) such that a hardness of the one bilayer tablet reached 5~20 kp.

After that, coated tablets were prepared by using 10.5 mg of Opadry (Colorcon; 415 Moyer Blvd., P.O. Box 4, West Point, PA 19486-0024, USA), and the surface of coated tablets was polished by using 0.5 mg of carnauba wax, so as to prepare a bilayer tablet containing fimasartan and atorvastatin.

<Example 4> Bilayer tablet containing fimasartan and atorvastatin

Granules containing fimasartan potassium trihydrate as an effective ingredient according to <Preparation Example 1> and granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-5> were put into a punch die, respectively, and were subjected to tableting under a tableting pressure of 5 to 15 KN, so as to prepare a bilayer tablet.

Bilayer tablet was prepared by using a multilayered-tablet press (Piccola bilayer tablet press) such that a hardness of the one bilayer tablet reached 5-20 kp.

After that, coated tablet was prepared by using 10.5 mg of Opadry (Colorcon; 415 Moyer Blvd., P.O. Box 4, West Point, PA 19486-0024, USA), and the surface of coated tablet was polished by using 0.5 mg of carnauba wax, so as to prepare a bilayer tablet containing

fimasartan and atorvastatin.

<Example 5> Bilayer tablet containing fimasartan and atorvastatin

Granules containing fimasartan potassium trihydrate as an effective ingredient according to <Preparation Example 1> and granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-6> were put into a punch die, respectively, and were subjected to tableting under a tableting pressure of 5 to 15 KN, so as to prepare a bilayer tablet.

The bilayer tablet was prepared by using a multilayered-tablet press (Piccola bilayer tablet press) such that a hardness of the one bilayer tablet may reached 5~20 kp.

After that, coated tablet was prepared by using 10.5 mg of Opadry (Colorcon; 415 Moyer Blvd., P.O. Box 4, West Point, PA 19486-0024, USA), and the surface of coated tablet was polished by using 0.5 mg of carnauba wax, so as to prepare a bilayer tablet containing fimasartan and atorvastatin.

<Comparative Example 1> Bilayer tablet containing fimasartan and atorvastatin

Granules containing fimasartan potassium trihydrate as an effective ingredient according to <Preparation Example 1> and granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-1> were put into a punch die, respectively, and were subjected to tableting under a tableting pressure of 5 to 15 KN, so as to prepare a bilayer tablet.

The bilayer tablet was prepared by using a multilayered-tablet press (Piccola bilayer tablet press) such that a hardness of the one bilayer tablet reached 5~20 kp.

After that, coated tablet was prepared by using 10.5 mg of Opadry (Colorcon; 415 Moyer Blvd., P.O. Box 4, West Point, PA 19486-0024, USA), and the surface of coated tablet was polished by using 0.5 mg of carnauba wax, so as to prepare a bilayer tablet containing

fimasartan and atorvastatin.

[Test Method]

<Method 1> Method for measuring particle size

The particle size of the obtained granule containing atorvastatin calcium trihydrate as an effective ingredient and the mixture of lactose hydrate and microcrystalline cellulose that affect the tableting of atorvastatin granule were measured by a dry method using a HELOS particle size analyzer (laser particle size analyzer) of Sumpatec Inc.

<Method 2> Method for evaluating presence of tableting failure

An imprinting on the surface of the bilayer tablet containing fimasartan and atorvastatin according to Examples 1 to 3 and Comparative Example 1 was observed with the naked eye.

<Method 3> Method for evaluating content uniformity

Granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-1> to <Preparation Example 2-4> (target weight: 200 mg) were tableted and stored at 60°C for 1 week, and thus the weight of the tablet was measured according to time, so as to calculate a weight deviation.

Hereinafter, the present invention will be described in more detail through experimental examples. However, the scope of the present invention is not limited to these experimental examples. The experimental examples of the present invention are provided to more completely describe the present invention to those having ordinary skill in the art.

Experimental Example

<Experimental Example 1> Evaluation of presence of tableting failure

It was evaluated whether the bilayer tablets containing fimasartan and atorvastatin according to Examples 1 to 3 and Comparative Example 1 show a tableting failure or not

according to above method 2.

Specifically, referring to FIG. 2, it was confirmed that the imprinting on the surface of the bilayer tablet containing fimasartan and atorvastatin according to Comparative Example 1 is torn apart to such an extent that the surface could not be identified with the naked eye.

However, referring to FIGS. 3 to 5, the imprinting on the surface of the bilayer tablets containing fimasartan and atorvastatin according to Examples 1 to 3 were clearly maintained enough to be identified with the naked eye, thus confirming that the tablet properties are good.

Accordingly, when granules containing atorvastatin calcium trihydrate as an effective ingredient are tableted (target weight: 200 mg), in the case of Comparative Example 1, a bilayer tablet may be prepared by tableting granules containing atorvastatin calcium trihydrate as an effective ingredient according to Preparation Example 2-1, wherein the granules exhibit a particle size distribution with a D_{50} of 71.66 μm . However, in Examples 1 to 3, a bilayer tablet may be prepared by tableting the granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-2> to <Preparation Example 2-4>, wherein the granules exhibit a particle size distribution with a D_{50} of 80.00 μm or more. When the particle size distribution of the granules is equal to or less than a certain level, it was confirmed that this particle size distribution causes a tableting failure phenomenon such as sticking during a tableting process, and it was also confirmed that the tablet properties (imprinting, etc.) do not meet the pharmaceutical standards.

In other words, the mixture of lactose hydrate and microcrystalline cellulose that affects the tableting in the process of tableting may be contained in an amount of 40 to 50 wt% based on the total atorvastatin granules contained in the second layer, and thus it was confirmed that the particle size distribution (D_{50}) of the granules containing atorvastatin

calcium trihydrate as an effective ingredient may reach a certain level or more by adjusting the particle size distribution (D_{50}) of the mixture of lactose hydrate and microcrystalline cellulose, so that the tableting failure may not occur when performing the tableting process in the process of tableting fimasartan and atorvastatin into a bilayer tablet.

In addition, even in case of using the mixture of lactose hydrate and microcrystalline cellulose under the same conditions, if the amount of binder solution is increased during wet granulation according to <Preparation Example 2-5>, or the regulated size of granule is increased according to <Preparation Example 2-6>, it was confirmed that the obtained particle size distribution (D_{50}) of granules may be increased more than the particle size distribution (D_{50}) of granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-1>, and as a result, the tableting failure such as sticking do not occur when the tableting process is performed during the process of tableting with fimasartan.

<Experimental Example 2> Evaluation of content uniformity

After tableting the granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-1> to <Preparation Example 2-6> according to the method 3(target weight: 200 mg), the weight deviation of the tablet was measured, and the results are shown in table 6 below.

【Table 6】

	Preparation Example 2-1		Preparation Example 2-2		Preparation Example 2-3		Preparation Example 2-4		Preparation Example 2-5		Preparation Example 2-6	
	Tablet mass	Content %	Tablet mass	Content %	Tablet mass	Content %	Tablet mass	Content %	Tablet mass	Content %	Tablet mass	Content %
Tablet weight (mg)	199.5	99.6	199.4	99.5	200.4	100.0	194.5	97.1	202.5	101.0	198.6	99.1
	191.	95.4	201.	100.	201.	100.	197.	98.7	201.	100.	199.	99.7

	6		5	5	4	5	8		5	5	7	
	175.8	87.6	200.2	99.9	199.2	99.4	195.8	97.7	200.5	100.0	199.4	99.5
	186.7	94.8	196.8	98.2	200.3	99.9	198	98.8	198.6	99.1	201.6	100.6
	203.4	101.8	197.4	98.5	198.4	99.0	200.8	100.2	201.5	100.5	200.4	100.0
	179.5	90.1	198.2	98.9	199.7	99.7	204.2	101.9	197.8	98.7	200.6	100.1
	192.3	97.6	201.5	100.5	198.4	99.0	202.8	101.2	198.0	98.8	201.8	100.7
	183.1	90.9	200.4	100.0	200.4	100.0	201.7	100.6	200.9	100.2	202.4	101.0
	195.8	96.7	198.4	99.0	201.4	100.5	200.6	100.1	199.7	99.7	197.6	98.6
	176.5	88.1	199.2	99.4	200.4	100.0	199.7	99.7	201.4	100.5	199.7	99.7
Average	188.4	94.3	199.3	99.5	200.0	99.8	199.6	99.6	200.2	99.9	200.2	99.9
Standard deviation	9.7	4.9	1.6	0.8	1.1	0.5	3.1	1.5	1.6	0.8	1.5	0.7
Relative standard deviation	5.1	5.2	0.8	0.8	0.5	0.5	1.5	1.5	0.8	0.8	0.7	0.7
Decision value (reference: within 15)		15.4		1.9		1.2		3.5		2.2		2.0

Referring to above table 6, the granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-1> had tableting failure such as sticking during the tableting process, and thus it was confirmed that, even if the equipment conditions are set in accordance with a target weight (200 mg), the weight of tablet did not reach the target weight, and the tablet was judged unsuitable for content uniformity due to a large weight deviation (decision value: 15.4, decision coefficient: 2.4, reference value: 98.5).However, it was confirmed for the granules containing atorvastatin calcium trihydrate

as an effective ingredient according to <Preparation Example 2-2> (decision value: 1.9, decision coefficient: 2.4, reference value: 99.5), the granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-3> (decision value: 1.2, decision coefficient: 2.4, reference value: 99.8), and the granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-4> (decision value: 3.5, decision coefficient: 2.4, reference value: 99.6) that a tableting failure phenomenon does not occur during the tableting process, tablet properties are good, a decision value for weight deviation is calculated to be equal to or less than a reference value (reference value: 15), and thus the tablets was judged suitable when evaluating content uniformity.

In addition, it was confirmed for the granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-5> (decision value: 2.2, decision coefficient: 2.4, reference value: 99.9), the granules containing atorvastatin calcium trihydrate as an effective ingredient according to <Preparation Example 2-6> (decision value: 2.0, decision coefficient: 2.4, reference value: 99.6) that a tableting failure phenomenon does not occur during the tableting process, tablet properties are good, a decision value for weight deviation is calculated to be equal to or less than a reference value (reference value: 15), and thus the tablets was judged suitable when evaluating content uniformity.

Specifically, when preparing granules containing atorvastatin calcium trihydrate as an effective ingredient, a large amount of precipitated calcium carbonate needs to be added as a stabilizer, which is fine powder, thereby causing a tableting failure phenomenon such as sticking during the tableting process of atorvastatin granules. However, it was confirmed that the particle size (D_{50}) of the mixture of lactose hydrate and microcrystalline cellulose may be adjusted under the same conditions, so that the particle size distribution (D_{50}) of the granules

containing atorvastatin calcium trihydrate as an effective ingredient may reach a certain value or more, thereby remarkably improving tableting properties with excellent content uniformity.

While specific portions of the present invention have been described in detail above, it is apparent to those skilled in the art that such detailed descriptions are set forth to illustrate exemplary embodiments only, but are not construed to limit the scope of the present invention. Thus, it should be understood that the substantial scope of the present invention is defined by the accompanying claims and equivalents thereto.

Claims

1. A tablet comprising:

a fimasartan granule portion comprising fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and

an atorvastatin granule portion comprising atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive,

wherein, the fimasartan granule portion and the atorvastatin granule portion are present while being separate from each other.
2. A tablet comprising:

a first layer comprising granules comprising fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and

a second layer comprising granules comprising atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive,

wherein the granules of the second layer exhibit a particle size distribution with a D_{50} of 80 μm or more.
3. The tablet of claim 2, wherein the granules of the second layer exhibit a particle size distribution with a D_{10} of 14 to 70 μm .
4. The tablet of claim 2, wherein the granules of the second layer exhibit a particle size distribution with a D_{90} of 290 to 600 μm .
5. The tablet of claim 2, wherein the tablet is a bilayer tablet.
6. The tablet of claim 2, wherein the fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof is comprised in an amount of 0.5 to 240.0 mg per unit dosage form.
7. The tablet of claim 2, wherein the atorvastatin, pharmaceutically acceptable salt

thereof, hydrate thereof or solvate thereof is comprised in an amount of 1.0 to 100.0 mg per unit dosage form.

8. The tablet of claim 2, wherein the additives of the first and second layers are any one selected from the group consisting of excipient, solubilizing agent, disintegrant, binder, lubricant and mixture thereof.

9. The tablet of claim 2, wherein the granules of the second layer comprise a mixture of lactose hydrate and microcrystalline cellulose, and wherein the mixture is comprised in an amount of 40 to 50 wt% based on the total weight of the granules of the second layer.

10. The tablet of claim 9, wherein the granules of the second layer further comprise precipitated calcium carbonate.

11. The tablet of claim 9, wherein the mixture of lactose hydrate and microcrystalline cellulose exhibits a particle size distribution with a D₅₀ of 75 µm or more.

12. The tablet of claim 2, wherein the granules of the second layer comprise 1 to 10 parts by weight of atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, 50 to 99.9 parts by weight of excipient, 0.1 to 2 parts by weight of solubilizing agent, 0.5 to 15 parts by weight of disintegrant, 0.1 to 10 parts by weight of binder, and 0.1 to 5 parts by weight of lubricant.

13. The tablet of claim 12, wherein the excipient is any one of precipitated calcium carbonate, lactose hydrate, microcrystalline cellulose, or a mixture thereof.

14. The tablet of claim 13, wherein the mixture comprises 30 to 50 parts by weight of precipitated calcium carbonate, 20 to 40 parts by weight of lactose hydrate, and 15 to 35 parts by weight of microcrystalline cellulose.

15. The tablet of claim 2, wherein the tablet further comprises a coating layer.

16. The tablet of claim 2, wherein the granules of the first and second layers are wet granules.

17. A method of preparing a tablet, the method comprising:

(S1) preparing a first layer comprising granules which comprise fimasartan, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive;

(S2) preparing a second layer comprising granules which comprise atorvastatin, pharmaceutically acceptable salt thereof, hydrate thereof or solvate thereof, and pharmaceutically acceptable additive; and

(S3) preparing a bilayer tablet by tableting the first and the second layers.

18. The method of claim 17, wherein the tableting of the fimasartan granule portion and the atorvastatin granule portion is performed by applying a tableting pressure of 5 to 15 KN.

19. The tablet of claim 2, wherein the tablet is for treating cardiovascular diseases.

20. A method of preventing or treating cardiovascular diseases, the method comprising administering a therapeutically effective amount of the tablet of claim 2, to mammals including human.

21. Use of the tablet of claim 2 in the manufacture of a formulation for preventing or treating cardiovascular diseases.

22. Use of the tablet of claim 2 for preventing or treating cardiovascular diseases.

23. The tablet of any one of claims 19 to 22, wherein the cardiovascular disease is any one selected from hypertension, diabetes, obesity, hyperlipidemia, coronary artery disease, chronic stable angina, vasospastic angina, stroke, myocardial infarction, temporary ischemic attack, congestive heart failure, insulin resistance, impaired glucose tolerance, prediabetes, type 2 diabetes mellitus, diabetic nephropathy, dyslipidemia, cognitive decline, dementia, and combinations thereof.