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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING PITAVASTATIN OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF, AND VALSARTAN OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

(57) Abstract: Disclosed is a composite composition comprising pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof and the composite pharmaceutical composition is more stable than simple formulations in combination, and is economically beneficial compared to a controlled-release formulation.

Description

Title of Invention: PHARMACEUTICAL COMPOSITION COMPRISING PITAVASTATIN OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF, AND VALSARTAN OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

Technical Field

[1] The present invention relates to a pharmaceutical composition comprising pitavastatin or a pharmaceutically acceptable salt thereof and valsartan or a pharmaceutically acceptable salt thereof as active ingredients. More particularly, the present invention relates to a pharmaceutical composition for the prevention or treatment of cardiovascular disease and dyslipidemia wherein pitavastatin or a pharmaceutically acceptable salt thereof is blended with valsartan or a pharmaceutically acceptable salt thereof.

Background Art

[2] Statins(or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by competitively inhibiting the enzyme HMG-CoA reductase(3-hydroxy-3-methyl-glutaryl coenzyme A reductase). HMG-CoA reductase is the rate-controlling enzyme of the cholesterol biosynthesis pathway, catalyzing the conversion of HMG to mevalonate. Inhibition of the reductase by statins induces the expression of LDL receptors in the liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol, resulting in a reduction in the risk of onset of atherosclerosis. Pitavastatin, serving as a subsidiary agent of diet therapy, is used to lower a total cholesterol level elevated by primary hypercholesterolemia and mixed dyslipidemia, LDL-cholesterol level, apo-B protein level, and triglyceride level, and to increase a high density lipoprotein(HDL)-cholesterol level.

[3] Valsartan is an angiotensin II receptor blocker that is known to effectively lower blood pressure without specificity depending on human race or gender. Currently, valsartan is indicated for treatment of high blood pressure, congestive heart failure, and myocardial infarction.

[4] A patient with dyslipidemia is highly apt to suffer from hypertension. Since coexistence of the two diseases further increases the risk of the onset of cardiovascular diseases, an aggressive strategy for the treatment and prevention of dyslipidemia and hypertension is needed. A combined medication exerts not only a synergistic effect on the treatment of hypertension and dyslipidemia in patients with cardiovascular

diseases, compared to either of the drugs, but also a therapeutic effect on diabetes by improving the function of endothelial cells, which form a protective layer of blood vessels, to increase sensitivity to insulin. In spite of these advantages, the drug compliance is poor for the combined medications, with the maintenance of drug uptake at a rate of 67 % for one year and 50 % for two years. One of the most important factors to determine drug compliance is the number of medicines that should be administered at a single dosage. A need for a combined medication composed of an antihypertensive agent and an anti-dyslipidemic agent has arisen because it is expected to improve in drug compliance, compared with respective single agents. Patients with both hypertension and dyslipidemia are prescribed a combination of an antihypertensive agent and an anti-dyslipidemic agent, simultaneously, but at low frequency because the combined medication has not yet sufficiently proven safe.

[5] Korean Patent Application Unexamined Publication No. 2008-0039303 discloses a controlled release complex composition comprising losartan, an angiotensin-II-receptor blocker, and simvastatin, an HMG-CoA reductase inhibitor. When administered simultaneously, losartan and simvastatin, unless released in a controlled manner, proceed to the liver where they exert competitive inhibition, thus antagonizing each other. Therefore, a combined medication cannot be expected to show optimal effects unless controlled release is designed therefor.

[6] However, when a dual formulation composed of a controlled release fraction and an immediate release fraction is applied to a combination of pitavastatin and valsartan as suggested by a dual formulation Korean Application Unexamined Publication No. 2008-0039303, the excipient such as an enteric coating base for controlled release may be negatively influential in terms of the stability of pitavastatin. Further, the formulations suggested by the patent, including a two-phase matrix tablet, a dual tablet, a cored tablet, etc. are complex so that an expensive facility is required for the production of the formulations, increasing the production cost. For a simple mixed formulation, there is high likelihood of the uneven distribution of pitavastatin because of its small amount.

[7] The present invention suggests a novel composite formulation comprising pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof that overcomes the above-mentioned problems. The composite formulation of the present invention comprises the angiotensin-II-receptor blocker valsartan and the HMG-CoA reductase inhibitor pitavastatin that are designed to be released in an immediate manner. In the formulation, pitavastatin or a pharmaceutically acceptable salt thereof is in a granular form so that it can be highly blended with valsartan or a pharmaceutically acceptable salt thereof and can be blocked from direct contact with valsartan or a pharmaceutically acceptable salt thereof. This con-

figuration guarantees the two ingredients stability to each other and improves the dissolution rates of both. Particularly, the composite formulation contains a sodium(Na)-free lubricant or stabilizer to stabilize the pitavastatin calcium ingredient that is apt to be unstable in an acidic condition.

Disclosure of Invention

Technical Problem

[8] It is therefore an object of the present invention to provide a pharmaceutical composition for the prevention and treatment of a cardiovascular disease and dyslipidemia, comprising pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof as active ingredients, wherein the pitavastatin ingredient and the valsartan ingredient are stable with a minimum physical and chemical interaction therebetween, and wherein both of them can be immediately released.

Solution to Problem

[9] In order to accomplish the above object, the present invention provides a pharmaceutical composition for prevention or treatment of a cardiovascular disease and dyslipidemia, comprising pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof as active ingredients.

[10] In another embodiment of the present invention, pitavastatin or a pharmaceutically acceptable salt thereof may be preferably separated from the valsartan or a pharmaceutically acceptable salt thereof, or pitavastatin or a pharmaceutically acceptable salt thereof may be preferably in the form of granules, and may be blended with valsartan or a pharmaceutically acceptable salt thereof.

[11] In another embodiment of the present invention, pitavastatin or a pharmaceutically acceptable salt thereof may preferably be in mixture with sodium(Na)-free lubricant or stabilizer.

[12] In another embodiment of the present invention, pitavastatin or a pharmaceutically acceptable salt thereof may be in a form of granules, and may be blended with the valsartan or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable additive.

[13] In this regard, the granules of pitavastatin or a pharmaceutically acceptable salt thereof may contain at least one selected from among low-substituted hydroxypropyl cellulose and lactose hydrate as an excipient, at least one selected from among magnesium aluminometasilicate, magnesium aluminosilicate, magnesium carbonate, aluminum hydroxide, potassium dihydrogen phosphate and aluminum chloride as a lubricant or stabilizer, and hydroxypropylmethyl cellulose as a binder.

[14] In another embodiment of the present invention, valsartan or a pharmaceutically ac-

ceptable salt thereof may contain at least one selected from among low-substituted hydroxypropyl cellulose and lactose hydrate as an excipient.

[15] In another embodiment of the present invention, the pharmaceutical composition may further comprise croscamellose sodium as a disintegrant, or magnesium stearate as a lubricant, or both.

[16] In another embodiment of the present invention, the pharmaceutical composition may include an external film coating.

[17] In another embodiment of the present invention, the external film coating may be made of a base containing at least one selected from among polyvinylalcohol, titanium oxide(TiO_2), polyethylene glycol 3350(PEG 3350) and talc, and preferably of all of them.

[18] In another embodiment of the present invention, pitavastatin or a pharmaceutically acceptable salt thereof may be contained in an amount of 0.5 mg to 8 mg.

[19] In another embodiment of the present invention, valsartan or a pharmaceutically acceptable salt thereof may be contained in an amount of 20 mg to 240 mg.

[20] In another embodiment of the present invention, the composition may contain the low-substituted hydroxypropyl cellulose in an amount of 20 mg to 200 mg, the lactose hydrate in an amount of 2 mg to 20 mg, the magnesium aluminometasilicate in an amount of 0.5 mg to 10 mg, and the hydroxypropylmethyl cellulose in an amount of 0.5 mg to 10 mg.

[21] In another embodiment of the present invention, the composition may contain the low-substituted hydroxypropyl cellulose in an amount of 20 mg to 200 mg, and the lactose hydrate in an amount of 30 mg to 300 mg.

[22] In another embodiment of the present invention, the composition may contain the croscamellose sodium ion an amount of 5 mg to 50 mg, and the magnesium stearate in an amount of 0.5 mg to 10 mg.

Advantageous Effects of Invention

[23] As described hitherto, the pharmaceutical composition of the present invention comprising pitavastatin or a pharmaceutically acceptable salt thereof and valsartan or a pharmaceutically acceptable salt thereof is designed for the simultaneous uptake of the medications, as well as for increasing the therapeutic effects with a concomitant reduction in adverse effects. Therefore, the composition allows patients to readily take the medications with improved drug compliance, and can be used as an excellent preventive and curative agent for cardiovascular diseases and dyslipidemia.

[24] In the pharmaceutical composition of the present invention, pitavastatin or a pharmaceutically acceptable salt thereof is separated from valsartan or a pharmaceutically acceptable salt thereof, and these ingredients show immediate release. Hence, this

composite pharmaceutical composition is more stable than simple formulations in combination, and is economically beneficial compared to a controlled-release formulation.

Best Mode for Carrying out the Invention

[25] The present invention addresses a pharmaceutical composition for the prevention and treatment of a cardiovascular disease and dyslipidemia in which granules of pitavastatin or a pharmaceutically acceptable salt thereof are blended with valsartan or a pharmaceutically acceptable salt thereof, and which is advantageous in terms of economy and stability over conventional formulations.

[26] Below, a detailed description will be given of the present invention

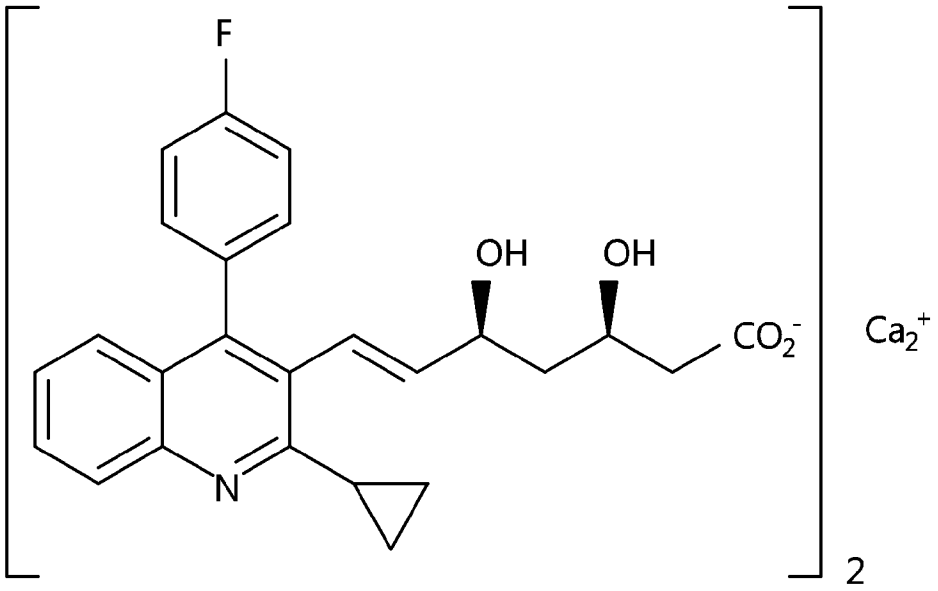
[27] The present invention provides a composition comprising pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof as active ingredients wherein the pitavastatin or a pharmaceutically acceptable salt thereof is separated from the valsartan or a pharmaceutically acceptable salt thereof.

[28] More particularly, the present invention provides a pharmaceutical composition for the prevention and treatment of a cardiovascular disease and dyslipidemia, comprising granules of pitavastatin or a pharmaceutically acceptable salt thereof in mixture with valsartan or a pharmaceutically acceptable salt thereof.

[29] So long as it is readily available to those skilled in the art, any pharmaceutically acceptable salt of pitavastatin may be used in the present invention. The pharmaceutically acceptable salt of pitavastatin may take the form of a sodium salt, a potassium salt, a hemicalcium salt, and a magnesium salt, with preference for a hemicalcium salt. Pitavastatin hemicalcium may be represented by the following Chemical Formula 1:

[30] [Chemical Formula 1]

[31]



[32] Likewise, any pharmaceutically acceptable salt of valsartan may be employed in the present invention if it is readily available to those skilled in the art. The pharmaceutically acceptable salt of valsartan may be a mono-sodium salt, a di-sodium salt, a mono-potassium salt, a di-potassium salt, a magnesium salt, a calcium salt, a bis-diethylammonium salt, a bis-dipropylammonium salt, a bis-dibutylammonium salt, a mono-L-arginine salt, a bis-L-arginine salt, a mono-L-lysine salt, a bis-L-lysine salt, or a combination thereof.

[33] As used herein, the term "pharmaceutical composition" refers to a mixture of the active ingredients of the present invention with a chemical such as a diluent or a carrier. Salts useful in the pharmaceutical composition may be prepared by reaction with an acid, such as hydrochloric acid, bromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, salicylic acid, etc.

[34] The term "separated", as used herein in connection with the relation between pitavastatin or a pharmaceutically acceptable salt thereof and valsartan or a pharmaceutically acceptable salt thereof, means that the two active ingredients, pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof, are confined within different respective fractions.

[35] When the pharmaceutical composition of the present invention is prepared into a composite formulation in which pitavastatin or a pharmaceutically acceptable salt thereof and valsartan or a pharmaceutically acceptable salt thereof are simply mixed, it may suffer from the following problems. First, pitavastatin may be less likely to be distributed over the formulation because its content is as low as 0.5 mg to 8 mg. Hence, when formed into granules, pitavastatin can be evenly distributed over the formulation. Also, pitavastatin should be stable against the other ingredient valsartan. In this regard,

the two ingredients may be "separated" from each other so that they are blocked from contacting each other. Next, at a pH of 4.0 or less, valsartan has a low solubility and is gelled so that it is very slowly dissolved. This delayed dissolution inhibits the absorption of valsartan to the small intestine. Further, the gelling of valsartan may have negative influence on the dissolution of pitavastatin, thereby interfering with the uptake of pitavastatin. In the present invention, a formulation is designed to segregate the active ingredients from each other whereby valsartan is not gelled even at a low pH.

[36] Examples of a formulation in which the two active ingredients are "separated" from each other include, but are not limited to: a coated tablet in which a tablet containing valsartan or a pharmaceutically acceptable salt thereof as an active ingredient has an outer coating containing pitavastatin or a pharmaceutically acceptable salt thereof as an active ingredient, or in which a tablet containing pitavastatin or a pharmaceutically acceptable salt thereof as an active ingredient has an outer coating containing valsartan or a pharmaceutically acceptable salt thereof as an active ingredient; a cored tablet in which a core composed of valsartan or a pharmaceutically acceptable salt thereof is covered with a sheath composed of pitavastatin or a pharmaceutically acceptable salt thereof, or in which a core composed of pitavastatin or a pharmaceutically acceptable salt thereof is covered with a sheath composed of valsartan or a pharmaceutically acceptable salt thereof; a multiple compressed tablet, such as a bilayer tablet, in which pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof are in different respective layers.

[37] As used herein, the term "dyslipidemia" refers to an abnormally elevated level of lipids including total cholesterol, LDL cholesterol, and triglycerides, or to an abnormally reduced level of HDL cholesterol in blood. For instance, hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia fall within the scope of dyslipidema. The hypercholesterolemia may be primary hypercholesterolemia(heterozygous familial and non-familial, Fredrickson type IIa), or mixed dyslipidemia(Fredrickson type IIb).

[38] The term "cardiovascular disease" refers to a class of diseases that involve the heart, the arterial vessels, or both. Examples of the cardiovascular disease may include, but are not limited to, hypertension, essential hypertension, ischemic heart diseases, coronary artery disease, angina pectoris, myocardial infarction, artherosclerosis, cerebrovascular disease, stroke, and arrhythmia.

[39] Further, the pharmaceutical composition of the present invention may be applied to the prevention and therapy of diabetes(N. Engl. J. med., 362; 16 April 22, 2010).

[40] In the pharmaceutical composition of the present invention, for example, pitavastatin or a pharmaceutically acceptable salt thereof may be contained in an amount of 0.5 mg to 8 mg, with the content of valsartan or a pharmaceutically acceptable salt thereof

ranging from 20 mg to 240 mg, but this is not limitative of the present invention.

[41] In addition to granules of pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof, the pharmaceutical composition of the present invention may comprise a pharmaceutically acceptable additive.

[42] As used herein, the term "pharmaceutically acceptable additive" is defined as a carrier or a diluent that does not degrade biological activity and physical properties of the composition.

[43] In one embodiment of the present invention, the granules of pitavastatin or a pharmaceutically acceptable salt thereof may further comprise a lubricant or stabilizer containing no sodium(Na). Sodium(Na)-containing lubricants or stabilizers have high affinity for water so they absorb water rapidly, decreasing the dissolution rate of pitavastatin calcium and valsartan tablets. Accordingly, the pitavastatin calcium that should start to be absorbed in the stomach becomes poor in bioavailability, which may be negatively influential in terms of the bioavailability of valsartan. The sodium(Na)-free lubricant or stabilizer may be selected from among magnesium aluminometasilicate, magnesium aluminosilicate, magnesium aluminate, dried aluminum hydroxide, synthetic hydrotalcite, synthetic aluminumsilicate, magnesium carbonate, precipitated calcium carbonate, magnesium oxide, aluminum hydroxide, L-arginine, potassium phosphate, dipotassium hydrogenphosphate, potassium dihydrogenphosphate, ammonium chloride, aluminum chloride, and a combination thereof.

[44] Preferably, the granules of pitavastatin or a pharmaceutically acceptable salt thereof may further comprise at least one of low-substituted hydroxypropyl cellulose and lactose hydrate as an excipient, hydroxypropylmethyl cellulose as a binder, and magnesium aluminometasilicate as a lubricant or stabilizer. More preferably, the granules may comprise low-substituted hydroxypropyl cellulose in an amount of 20 mg to 200 mg, lactose hydrate in an amount of 2 mg to 20 mg, magnesium aluminometasilicate in an amount of 0.5 mg to 10 mg, and hydroxypropylmethyl cellulose in an amount of 0.5 mg to 10 mg.

[45] In an embodiment, the fraction of valsartan or a pharmaceutically acceptable salt thereof may further comprise at least one of low-substituted hydroxypropyl cellulose and lactose hydrate as an excipient, with the contents of low-substituted hydroxypropyl cellulose and lactose hydrate on the order of 20 mg to 200 mg, and 30 mg to 300 mg, respectively.

[46] In another embodiment, the pharmaceutical composition of the present invention may further comprise croscamellose sodium as a disintegrant, or magnesium stearate as a lubricant, or both. In the composition, croscamellose sodium may be contained in an amount of 5 mg to 50 mg, and magnesium stearate is in an amount of 0.5 mg to 10 mg, but this is not limitative of the present invention.

[47] The pharmaceutical composition for the prevention or treatment of a cardiovascular disease and dyslipidemia in accordance with the present invention may comprise a typical carrier or additive in each of the granules of pitavastatin or a pharmaceutically acceptable salt thereof and the fraction of valsartan or a pharmaceutically acceptable salt thereof in addition to the above-mentioned diluents or excipients.

[48] Within the scope of the pharmaceutically acceptable carrier or additive are a diluent or excipient such as a filler, a thickener, a humectant, a lubricant, a binder, a surfactant, etc. Examples of the disintegrant include agar, starch, alginic acid or a sodium salt thereof, and anhydrous calcium monohydrogen phosphate. The lubricant may be exemplified by silica, talc, stearic acid or a magnesium salt or calcium salt thereof, polyethylene glycol, and magnesium aluminometasilicate. As a binder in the present invention, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low-substituted hydroxypropyl cellolose, or a combination thereof is useful. In addition, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycin, etc may be used as a diluent. As needed, an effervescent salts, an absorbent, a colorant, a flavorant, a sweetener, etc. may be used. The stabilizer useful in the present invention is free of sodium(Na). Examples of the sodium(Na)-free stabilizer include magnesium aluminometasilicate, magnesium aluminosilicate, magnesium aluminate, dried aluminum hydroxide, synthetic hydrotalcite, synthetic aluminumsilicate, magnesium carbonate, precipitated calcium carbonate, magnesium oxide, aluminum hydroxide, L-arginine, potassium phosphate, dipotassium hydrogenphosphate, potassium dihydrogenphosphate), ammonium chloride, aluminum chloride, and a combination thereof.

[49] The pharmaceutical composition of the present invention may have an external film coating the base of which may be composed of at least one of polyvinylalcohol, titanium oxide(TiO_2), polyethylene glycol 3350(PEG 3350) or talc, and preferably of all of them.

[50] For the external film coating, a typical coating agent may be used. Opadry™, hydroxypropylmethyl cellulose, or Eudragit series may be available as a coating base.

[51] The pharmaceutical composition of the present invention facilitates the administration of the active ingredients. There are various techniques of administering a pharmaceutical composition, including oral, intrarectal, intravaginal, intranasal, intraocular, sublingual, subcutaneous, intramuscular, intravenous, intrathecal, intradermal, and epidural administration. Preferred in the present invention is oral administration.

[52] The pharmaceutical composition of the present invention may be in the dosage form of tablets, powders, dropping pills, pulvis, bolus, tinctures, or poultices. Preferable tablets may be typical tablets, coated tablets, dispersible tablets, or effervescent tablets,

and may take the form of a multiple compressed tablet, such as a dual tablet, a core tablet, a multi-layered tablet, etc. Also, capsules, inter alia, enteric capsules are preferred.

[53] The dosage levels of pitavastatin or a pharmaceutically acceptable salt thereof and valsartan or a pharmaceutically acceptable salt thereof, contained in the pharmaceutical composition of the present invention, vary depending on various factors including patient's health state and weight, the severity of disease, the route of administration, the time of administration, etc. It will be apparent to those skilled in the art that the suitable total daily dose may be determined by an attending physician within the scope of sound medical judgment.

[54] For an adult, a total daily dose of statin and valsartan may range from 1 mg to 640 mg, and preferably from 2 mg to 350 mg so as to exert preventive or curative effects on cardiovascular disease and hyperlipidemia.

[55] In accordance with another aspect thereof, the present invention addresses a method for preparing a pharmaceutical composition for the prevention or treatment of cardiovascular disease and dyslipidemia. The method may comprise a first step of granulating pitavastatin or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or additive; and a second step of blending valsartan or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or additive with the granules of pitavastatin or a pharmaceutically acceptable salt thereof.

[56] In one embodiment of the present invention, the pharmaceutically acceptable carrier or additive of the first step preferably includes at least one of low-substituted hydroxypropyl cellulose and lactose hydrate as an excipient, magnesium aluminometasilicate as a lubricant or stabilizer, and hydroxypropylmethyl cellulose as a binder, but is not limited thereto.

[57] Preferably, the granules may comprise pitavastatin or a pharmaceutically acceptable salt thereof in an amount of 0.5 mg to 8 mg, low-substituted hydroxypropyl cellulose in an amount of 20 mg to 200 mg, lactose hydrate in an amount of 2 mg to 20 mg, magnesium aluminometasilicate in an amount of 0.5 mg to 10 mg, and hydroxypropylmethyl cellulose in an amount of 0.5 mg to 10 mg.

[58] In another embodiment of the present invention, the pharmaceutically acceptable carrier or additive of the second step may preferably include at least one of low-substituted hydroxypropyl cellulose and lactose hydrate, but is not limited thereto.

[59] In the second step, valsartan or a pharmaceutically acceptable salt thereof is preferably used in an amount of 20 mg to 240 mg, together with 20 mg to 200 mg of low-substituted hydroxypropyl cellulose and 30 mg to 300 mg of lactose hydrate.

[60] According to another embodiment of the present invention, the method may further

comprise a third step of adding at least one of croscamellose sodium as a disintegrant and magnesium stearate as a lubricant to the blend of the second step, and a fourth step of compressing the mixture of the third step into a tablet using a rotary tablet press machine, but is not limited thereto. .

[61] After the fourth step, the method may further comprise a fifth step of coating the tablet with a coating base using a coater to form an external film coating. The coating base for the external film coating may be composed of at least one selected from among polyvinylalcohol, titanium oxide(TiO_2), polyethylene glycol 3350(PEG 3350) and talc. Preferred is a coating base composed of all of them.

[62] For use in the external film coating, a typical coating agent may be suitable. For instance, Opadry™, hydroxypropylmethyl cellulose, or Eudragit series may be available.

[63] Croscamellose sodium may be used in an amount of 5 mg to 50 mg, while the amount of magnesium stearate may be on the order of 0.5 mg to 10 mg, but is not limited thereto.

Mode for the Invention

[64] A better understanding of the present invention may be obtained through the following examples that are set forth to illustrate, but are not to be construed as limiting the present invention.

[65]

[66] EXAMPLE 1: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[67] Tablets were prepared as shown for ingredient and content in Table 1, below. The contents of Table 1 were based on one tablet.

[68]

[69] <Step 1> Granulation of pitavastatin calcium

[70] Pitavastatin calcium was mixed with low-substituted hydroxypropyl cellulose(L-HPC, LH B1), lactose hydrate(Lactose 200 mesh), and magnesium aluminometasilicate in a mixe(V-mixer). Then, the mixture was agglomerated using 5% hydroxypropylmethyl cellulose as a binder in a mixer(P-Mixer), followed by screening the agglomerates through a mesh(20 mesh) to form granules. They were then dried at 50?C for 8 hrs to achieve an LOD of 3 % - 5 %. Thereafter, the dried mass was passed through a screen(Osilator, 0.4 mm screen) to afford pitavastatin calcium granules of uniform size.

[71] <Step 2> Valsartan mixture

[72] Valsartan was mixed with low-substituted hydroxypropyl cellulose(L-HPC, LH B1) and lactose hydrate(Flowlac 100) using a mixer(V-mixer).

[73] <Step 3> Preparation of pitavastatin calcium/valsartan composite formulation

[74] The pitavastatin granules of <step 1>, the valsartan mixture of <step 2>, and croscamellose sodium were blended using a mixer(V-mixer) and then mixed with magnesium stearate to give a final blend. This was compressed into tablets using a rotary press machine, and coated with the coating base Opadry™ using a coater.

[75] [Table 1]

	Function	Ingredient	Amount(mg)	Standard
Pitavastatinfraction	Active Ingredient	Pitavastatin calcium salt	4	SP*
	Excipient	Low-substituted hydroxypropyl cellulose	26	NF
	Excipient	Lactose hydrate	9.18	KP
	Binder	Hydroxypropylmethyl cellulose	2.6	KP
Valsartanfraction	Active Ingredient	Valsartan	160	USP
	Excipient	lactose hydrate	146.6	KP
	Excipient	low-substituted hydroxypropyl cellulose	72	NF
	Disintegrant	Croscarmellose sodium	22.6	NF
	Lubricant/Stabilizer	Magnesium aluminometasilicate	5.3	NF
	Lubricant	Mg stearate	3.6	KP
	Coating	Opadray™ II white	22.56	SP*

[76] *SP : separate provision

[77] EXAMPLE 2: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[78] Tablets were prepared in the same manner as in Example 1, with the exception that magnesium aluminosilicate was used instead of magnesium aluminometasilicate.

[79] EXAMPLE 3: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[80] Tablets were prepared in the same manner as in Example 1, with the exception that magnesium carbonate was used instead of magnesium aluminometasilicate.

[81] EXAMPLE 4: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[82] Tablets were prepared in the same manner as in Example 1, with the exception that aluminum hydroxide was used instead of magnesium aluminometasilicate.

[83] EXAMPLE 5: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[84] Tablets were prepared in the same manner as in Example 1, with the exception that potassium dihydrogen phosphate was used instead of magnesium aluminometasilicate.

[85] EXAMPLE 6: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[86] Tablets were prepared in the same manner as in Example 1, with the exception that aluminum chloride was used instead of magnesium aluminometasilicate.

[87] COMPARATIVE EXAMPLE 1: Preparation of Single Formulation of Pitavastatin Calcium

[88] Two Livaro® tablets(JW Pharmaceuticals), each containing 2 mg of pitavastatin calcium salt as a single formulation, were used.

[89] COMPARATIVE EXAMPLE 2: Preparation of Single Formulation of Valsartan

[90] Diovan 160® tablet(Novatis, Korea) containing 160 mg of valsartan alone was used.

[91] COMPARATIVE EXAMPLE 3: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[92] Tablets were prepared in the same manner as in Example 1, with the exception that sodium phosphate was used instead of magnesium aluminometasilicate.

[93] COMPARATIE EXAMPLE 4: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[94] Tablets were prepared in the same manner as in Example 1, with the exception that sodium benzoate was used instead of magnesium aluminometasilicate.

[95] COMPARATIE EXAMPLE 5: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[96] Tablets were prepared in the same manner as in Example 1, with the exception that sodium dihydrogen phosphate was used instead of magnesium aluminometasilicate.

[97] COMPARATIE EXAMPLE 6: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[98] Tablets were prepared in the same manner as in Example 1, with the exception that disodium hydrogen phosphate was used instead of magnesium aluminometasilicate.

[99] COMPARATIE EXAMPLE 7: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[100] Tablets were prepared in the same manner as in Example 1, with the exception that sodium succinate was used instead of magnesium aluminometasilicate.

[101] COMPARATIE EXAMPLE 8: Preparation of Composite Formulation Containing Pitavastatin Calcium and Valsartan

[102] Tablets were prepared in the same manner as in Example 1, with the exception that sodium hydrogen carbonate was used instead of magnesium aluminometasilicate.

[103] TEST EXAMPLE 1: Dissolution Assay of Pitavastatin

[104] The composite formulation of Example 1 and the single formulation of Comparative Example 1 were assayed for the dissolution of pitavastatin calcium using a dissolution tester in the following condition.

[105] <Dissolution condition>

[106] Test method: 2nd dissolution method of the Korean Pharmacopoeia(paddle method)

[107] Dissolution liquid: 900 mL

[108] Apparatus: USP paddle method, 50 rpm

[109] Results of the dissolution test are summarized in Tables 2(Example 1) and 3(Comparative Example 1).

[110] [Table 2]

Time(min)	pH 1.2	pH 4.0	pH 6.8	DW
5	88.4	75.2	96.3	82.8
10	90.8	89.5	101.8	91.5
15	92.3	92.4	102.3	93.1

[111] In Table 2, dissolution rates of pitavastatin calcium from the formulation of Example 1 are shown according to pH.

[112] [Table 3]

Time(min)	pH 1.2	pH 4.0	pH 6.8	DW
5	58.9	63.7	55.6	71.5
10	95.2	80.2	90.5	90.4
15	100.2	87.3	97.1	93.6

[113] Table 3 shows dissolution rates of pitavastatin calcium from the formulation of Comparative Example 1 by pH.

[114] TEST EXAMPLE 2: Dissolution Assay of Valsartan

[115] The composite formulation of Example 1 and the single formulation of Comparative Example 1 were assayed for the dissolution of valsartan using a dissolution tester in the same condition as in Test Example 1.

[116] Results of the dissolution test are summarized in Tables 4(Example 1) and 5(Comparative Example 2).

[117] [Table 4]

Time(min)	pH 1.2	pH 4.0	pH 6.8	DW
5	9.0	22.5	92.6	27.0
10	15.0	38.6	102.9	43.0
15	19.5	48.4	103.6	52.9
30	27.6	65.8	-	68.5
45	33.0	74.7	-	76.2
60	37.0	80.0	-	81.1
90	42.2	86.3	-	86.4
120	45.5	89.3	-	89.1
180	-	91.6	-	92.3
240	-	-	-	93.4

[118] In Table 4, dissolution rates of valsartan from the formulation of Example 1 are shown according to pH.

[119] [Table 5]

TIME(min)	pH 1.2	pH 4.0	pH 6.8	DW
5	6.0	18.8	89.9	23.5
10	10.8	31.9	101.6	34.6
15	14.7	40.5	-	41.8
30	23.0	55.2	-	54.3
45	28.5	64.1	-	61.4
60	32.5	69.9	-	65.9
90	37.8	78.0	-	72.8
120	42.2	83.9	-	76.8
180	-	90.3	-	82.8
240	-	-	-	86.6

[120] Table 5 shows dissolution rates of valsartan from the formulation of Comparative Example 2 by pH.

[121] TEST EXAMPLE 3: Bioequivalence Assay

[122] (1) Drug administration for clinical trial

[123] The composite formulation of Example 1 and the single formulations of Comparative

Examples 1 and 2 were assayed for bioequivalence on the basis of pharmacokinetic parameters. This clinical test was an open-level, single-dose, randomized, 2-treatment, 3-sequence, 3-period crossover design(see Table 6, below).

[124] [Table 6]

Sequence Group	No. of Subject	Period 1	Period 2	Period 3
A(RTR)	18	R	T	R
B(TRR)	18	T	R	R
C(RRT)	18	R	R	T

[125] The table shows the order of administration of drugs for clinical trial by period. R(Reference): single-dose of Comparative Example 1(Livaro® tablet: pitavastatin 2 mg x 2 tablets) and Comparative Example 2(Diovan 160® tablet: valsartan 160 mg) in combination. T(Test): single-dose of Example 1(pitavastatin 4 mg/ valsartan 160 mg) alone.

[126] Administration was performed for period 1 at 24:00 on day 1, for period 2 at 24:00 on day 15, and for period 3 at 24:00 on day 29. The drugs were orally administered at predetermined doses for sequence groups at 8:00 a.m., together with 240 mL of water. The subjects were fasted from 10:00 p.m. on the day of hospitalization(only water was allowed for uptake until one hour before administration). The subjects were fasted for 4 hrs after administration, but allowed to drink water only, ad lib, from 2 hrs after administration. For 4 hours after administration, they sat straight at 45 degrees or higher. The drugs for clinical trial were administered directly by the attending doctor.

[127] (2) Pharmacokinetic assay

[128] Plasma samples taken from a total of 54 subjects who were randomly selected with an age of 23.1±1.9, a height of 174.5±5.7 cm, and a weight of 68.3±6.0 kg on average were assessed for levels of pitavastatin calcium and valsartan.

[129] <Step 1> Pharmacokinetic assay

[130] In this assay, exact times at which blood samples were taken from individual subjects in practice were employed. For the cases of a detected concentration below the lower limit of quantification(LLOQ), no blood samples available, and no concentrations detected in the samples, "BQL"(below quantifiable limit), "NA"(not applicable), and "ND"(not detected) were respectively expressed in the data of drug concentrations. Blood level-time data were presented in plots on linear or log/linear axes. From the data obtained, the following pharmacokinetic parameters were estimated using a non-compartmental method with pertinent, verified pharmacokinetic software(Phoenix WinNonlin®, Version 6.3 or higher, Pharsight, CA, USA)).

[131] The area under the serum drug concentration versus time curve(AUC) from time zero to the time of the last quantifiable concentration((AUC_{0-8}, AUC_t(t=48)) was determined using linear trapezoidal summation for concentration increase period of time, and using log/linear trapezoidal summation for concentration decrease period of time.

[132] C_{max} means maximum observed plasma concentration and T_{max} means the time when the plasma concentration reach to C_{max} after drug administration. Half-life($t_{1/2\beta}$) was calculated as $\ln(2)/\lambda_z$ where λ_z is an elimination rate constant calculated by the linear regression of the log-transformed concentration of the drug in the terminal phase.

[133] For pharmacokinetic parameters, descriptive statistical analysis(mean, standard deviation, median, min, max) was performed according to administration groups and drugs. T_{max} was obtained by mean difference assay.

[134] The 90% confidence intervals(CI) for the geometric mean ratios of AUC_t and C_{max} values between the 2 treatments(test: reference drug) were calculated. The log-transformed data was analyzed using an ANOVA(analysis of variance) model with factors for sequence, subjects within sequence, period, and treatment groups. The bioequivalence test range of two treatments was set forth to be 80-125% for the 90% confidence interval of the ratio of a log-transformed exposure measure. When the coefficient of variation within the test subjects for C_{max} of Comparative Examples 1 and 2 were over 30 % as a result of three or four repetitive crossover tests, bioequivalence was determined only if the following items were satisfied(but, the extended criteria for bioequivalence according to the coefficient of variation in the individuals were not applied to pitavastatin calcium).

[135] AUC_t should be within log 0.8 to log 1.25 for the 90 % confidence interval of the log-transformed mean difference as statistically analyzed.

[136] C_{max} should fall between log 0.8 and log 1.25 for the log-transformed mean difference thereof, with the 90 % confidence interval of the log-transformed mean difference meeting the ranges according to the following formula. For a coefficient of variation greater than 50 %, the 90 % confidence interval should be within log 0.6984 to log 1.4319.

[137] [Table 7]

Coefficient of Variation (%)	90 % Confidence Interval(Ratio of Measurements)
30	0.8000~1.2500
35	0.7723-1.2948
40	0.7462-1.3402
45	0.7215-1.3859
50	0.698-1.4319

[138] In Table 7, the 90 % confidence interval of the log-transformed mean ratios of C_{max} is shown at a coefficient of variation of 30 % or higher: [upper limit, lower limit] = exp [±0.760 x(standard deviation of log-transformed C_{max} value within the subjects administered with the single formulation of Comparative Example 1 or 2)]; Coefficient of variation(%) = root value of the equation exp [(standard deviation of log-transformed C_{max} value within the subjects administered with the single formulation of Comparative Example 1 or 2)^2]-1.

[139] If the 90 % confidence of mean difference of log-transformed and statistically processed AUC_t did not fall between log 0.8 and log 1.25, criteria of scaled bioequivalence was applied to the data for reference to establish a basis for subsequent formulation studies and calculation of subjects tested.

[140] <Step 2> Statistical analysis

[141] Considering the characteristics of the tests, statistical assumption did not have to be verified for the assessment results of safety and pharmacokinetics. However, the following statistical analysis was performed with a significance of 0.05, if necessary. Continuous variables accounted for descriptive statistics(mean, standard deviation, median, minimum, maximum, etc.), while frequencies and ratios in each category were given as categorized variables. For population information, test subjects who were selected were analyzed. A safety assay was performed on the test subjects who had been administered one or more times with a medication for clinical tests while a pharmaceutical assay was performed only on the test subjects who had completed the clinical tests.

[142] With regard to age, height, and weight, the test subjects who participated in the clinical test according to sequence group were subjected to descriptive statistic analysis.

[143] For safety assessment, the behavior of adverse reactions was compared between groups administered with single formulations in combination and a composite formulation alone, using a nonparametric method. Adverse reactions in each treatment

group were analyzed for case frequency, number of test subjects who undergo the adverse reaction, severity, seriousness, and casual relation with the composite formulation of Example 1, using a descriptive statistic method. Clinical significance for individual subjects was determined, totally considering the test results obtained from vital signs, electrocardiograhy, clinical laboratory test, etc.

[144] Pharmacokinetic characteristics from the aforementioned tests are described as follows.

[145] Pharmacokinetics of Pitavastatin calcium Contained in Formulations of Comparative Example 1 and Example 1

[146] Comparison was conducted between groups administered once with the single formulations of Comparative Examples 1(pitavastatin calcium 4 mg(2 mg x 2 tablets)) and 2(valsartan 160 mg) in combination, and the composite formulation of Example 1(pitavastatin calcium 4 mg / valsartan 160 mg). In the groups administered with the single formulations of Comparative Examples 1 and 2 in combination, the blood pitavastatin level reached C_{max} at a median of 0.76 hrs(0.5 to 2.0 hrs). When expressed in the form of arithmetic mean and standard deviation, C_{max} was 97.2±40.0 ng/ml. After T_{max}, the concentration slowly decreased, and AUC_t was 279.0±86.0 hr · ng/ml as expressed as an arithmetic mean and standard deviation form.

[147] In the groups administered with the composite formulation of Example 1, the blood pitavastatin level reached C_{max} at a median of 0.5 hrs(0.25 to 1.5 hrs). When expressed in the form of arithmetic mean and standard deviation, C_{max} was 99.3±34.4 ng/ml. After T_{max}, the concentration slowly decreased, and AUC_t was 275.9±79.7 hr · ng/ml as expressed as an arithmetic mean and standard deviation form.

[148] [Table 8]

Parameter	Administration of Comparative Examples 1 and 2 in Combination	Administration of Example 1 alone	Ratio(90 % CI)
C_{max}(ng/mL)	97.2±40.0	99.3±34.4	1.052↓(0.958~1.154)
AUC_t(hr · ng/mL)	279.0±86.0	275.9±79.7	0.996↓(0.953~1.040)
T_{max}(hr)	0.76↓[0.5~2.0]	0.5↓ [0.25~1.5]	-

[149] Table 8 shows ratios of least-squares means, 90 % CI(confidence interval) for early target parameters of pitavastatin calcium after administration of Comparative Examples 1 and 2 in combination or Example 1 alone. C_{max} and AUC_t are expressed as arithmetic mean ± standard deviation, and T_{max} is represented by a median value

[minimum ~ maximum]. Herein, 90% CI was defined as a log-transformed geometric ratio of Example 1 to Comparative Example 1, accounting for the log value of difference between mean values.

[150] No statistical differences were detected in AUC_{inf}, T_{max}, and $t_{1/2}$ between treatment groups, as compared by non-parametric methods. Descriptive statistics of pharmacokinetic parameters of pitavastatin calcium in treatment groups are compared in Table 9, below.

[151] [Table 9]

Treatment	T_{max}(hr)		C_{max}(ng/mL)	AUC_t(hr · ng/mL)	AUC_8(hr · ng/mL)	$t_{1/2}$(hr)
Combination of C. Ex. 1 & 2	0.76[0.5-2.0]	Mean	97.2	279.0	303.4	13.3
		S.E.	40.0	86.0	85.9	6.1
		CV(%)	41.1	30.8	28.3	46.1
Ex. 1 alone	0.50[0.25-1.5]	Mean	99.3	275.9	302.0	13.9
		S.E.	34.4	79.7	83.8	6.0
		CV(%)	34.6	28.9	27.7	43.6

[152] Table 9 summarizes descriptive statistics of pharmacokinetic parameters of pitavastatin calcium in each treatment group. T_{max} is expressed as a median [min-max].

[153] Upon the administration of Example 1(pitavastatin 4 mg/valsartan 160 mg) alone, a point estimate value of geometrical mean ratio of C_{max} and AUC_t, and 90 % confidence interval for pitavastatin calcium were measured to be 1.052(0.958 - 1.154) and 0.996(0.953 - 1.040), respectively, in comparison with the administration of Comparative Example 1(pitavastatin 4 mg) and Comparative Example 2(valsartan 160 mg) in combination.

[154] For pitavastatin calcium, arithmetic mean values of the pharmacokinetic parameter C_{max} were calculated to be 99.3 ng/mL in the group administered with the composite formulation of Example 1(Test) and 97.2 ng/mL in the group(Reference) administered with a combination of the single formulations of Comparative Examples 1 and 2. Arithmetic mean values of AUC_t(t=48) measured 275.9 hr · ng/mL for Test group and 279.0 hr · ng/mL for Reference group. As assessed for bioequivalence in terms of the pharmacokinetic parameters(C_{max}, AUC_t(t=48)) accounting for the degree of drug exposure(WinNonlin® Pharsight, v. 6.3, CA, USA) SAS 9.1 program), ratios of geometric mean values(90% CI) between the Test group and the Reference group were within 0.958 ~ 1.154 for C_{max}(90% CI), and within 0.953 ~ 1.040 for AUC_t(t=48). Because 90 % CI for C_{max} and AUC_t fell between 0.80 ~ 1.25, the two formulations

were defined as being bioequivalent to each other.

[155] Pharmacokinetics of Pitavastatin calcium Contained in Formulations of Comparative Example 2 and Example 1

[156] Comparison between groups administered once with the single formulations of Examples 1(pitavastatin calcium 4 mg(2 mg x 2 tablets)) and 2(valsartan 160 mg) in combination, and the composite formulation of Example 1(pitavastatin calcium 4 mg / valsartan 160 mg) was carried out. In the groups administered with the single formulations of Comparative Examples 1 and 2 in combination, the blood valsartan level reached C_{max} at a median of 2.5 hrs(1.0 to 6.0 hrs). When expressed in the form of arithmetic mean and standard deviation, C_{max} was 4.4 ± 2.0 ㎍/mL. After T_{max}, the concentration slowly decreased, and AUC_t was 27.4 ± 11.4 hr · ㎍/mL as expressed as an arithmetic mean and standard deviation form.

[157] In the groups administered with the composite formulation of Example 1, the blood pitavastatin level reached C_{max} at a median of 2.5 hrs(1.0 to 4.0 hrs). When expressed in the form of arithmetic mean and standard deviation, C_{max} was 4.8 ± 1.9 ㎍/mL. After T_{max}, the concentration slowly decreased, and AUC_t was 28.4 ± 9.9 hr · ㎍/mL as expressed as an arithmetic mean and standard deviation form(Table 10).

[158] [Table 10]

Parameter	Administration of Comparative Examples 1 and 2 in Combination	Administration of Example 1 alone	Ratio(90 % CI)
C_{max}(ng/mL)	4.4±2.0	4.8±1.9	1.153(1.065~1.249)
AUC_t(hr · ng/mL)	27.4±11.4	28.4±9.9	1.062(0.987~1.143)
T_{max}(hr)	2.5[1.0~6.0]	2.5[1.0~4.0]	-

[159] Table 10 shows ratios of least-squares means, 90 % CI(confidence interval) for early target parameters of valsartan after administration of Comparative Examples 1 and 2 in combination or Example 1 alone. C_{max} and AUC_t are expressed as arithmetic mean ± standard deviation, and T_{max} is represented by a median value [minimum ~ maximum]. Herein, 90% CI was defined as a log-transformed geometric ratio of Example 1 to the combination of Comparative Example 1 and 2, accounting for the log value of difference between mean values.

[160] No statistical differences were detected in AUC_{inf}, T_{max}, and $t_{1/2}$ between treatment groups, as compared by non-parametric methods. Descriptive statistics of pharmacokinetic parameters of pitavastatin calcium in treatment groups are compared in Table 11, below.

[161] [Table 11]

Treatment	T_{max}(hr)		C_{max}(ng/mL)	AUC_t(hr · ng/mL)	AUC_8(hr · ng/mL)	$t_{1/2}$(hr)
Combination of C. Ex. 1 & 2	2.5[1.0-6.0]	Mean	4.4	27.4	29.4	6.4
		S. E.	2.0	11.4	13.0	3.8
		CV(%)	44.9	41.8	44.1	60.1
Ex. 1 alone	2.5[1.0-4.0]	Mean	4.8	28.4	30.4	6.5
		S. E.	1.9	9.9	10.5	3.4
		CV(%)	39.2	34.7	34.6	53.2

[162] Table 11 summarizes descriptive statistics of pharmacokinetic parameters of valsartan in each treatment group. T_{max} is expressed as a median [min-max].

[163] Upon the administration of the Livaro composite tablet(pitavastatin 4 mg/valsartan 160 mg) alone, a point estimate value of geometrical mean ratio of C_{max} and AUC_t, and 90 % confidence interval for valsartan were measured to be 1.153(1.065 ~ 1.249) and 1.062(0.987 ~ 1.143), respectively, in comparison with the administration of pitavastatin 4 mg(2 mg x 2 tablets) and valsartan 160 mg in combination.

[164] For valsartan, arithmetic mean values of the pharmacokinetic parameter C_{max} were calculated to be 4.8 ㎍/mL in the group administered with the composite formulation of Example 1(Test) and 4.4 ㎍/mL in the group(Reference) administered with a combination of the single formulations of Comparative Examples 1 and 2. Arithmetic mean values of $AUC_{t(}t=48)$ measured 28.4 hr · ㎍/mL for Test group and 27.3 hr · ㎍/mL for Reference group. As assessed for bioequivalence in terms of the pharmacokinetic parameters(C_{max}, $AUC_{t(}t=48)$) accounting for the degree of drug exposure(WinNonlin® Pharsight, v. 6.3, CA, USA) SAS 9.1 program), ratios of geometric mean values(90% CI) between the Test group and the Reference group were within 1.065 ~ 1.249 for C_{max}(90% CI), and within 0.987 ~ 1.143 for $AUC_{t(}t=48)$. Because 90 % CI for C_{max} and AUC_t fell between 0.80 ~ 1.25, the two formulations were defined as being bioequivalent to each other.

[165] When a combination of Comparative Examples 1(pitavastatin calcium 4 mg) and 2(valsartan 160 mg), and Example 1(pitavastatin 4 mg/valsartan 160 mg) alone were administered once, the 90 % confidence intervals of the log-transformed mean ratios of AUC_t and C_{max} for both pitavastatin calcium and valsartan were found to fall within 0.80 - 1.25. Consequently, the two formulations could be determined to meet the bioequivalence criteria.

[166] TEST EXAMPLE 4: Safety Assay

[167] A safety assay was performed on a total of 54 subjects who had been administered at least once with the medication for clinical trial. For the safety assay, 54 subjected were randomly grouped.

[168] All of the adverse drug reactions(ADR) detected were found to be light or moderate in severity, and all the subjects recovered without sequelae.

[169] When casual relations with the test drugs were assessed as "possibly related", "probably related", or "definitely related", they were all defined to be as adverse drug reactions(ADR).

[170] TEST EXAMPLE 5: Dissolution Assay According to Change in Additive

[171] A dissolution assay was performed on the composite formulations prepared in Examples 1 to 6 and Comparative Examples 3 to 8, and the single formulations prepared in Comparative Examples 1 and 2. Dissolution assay results are summarized in Table 12 for pitavastatin of the composite formulations of Examples 1 to 6 and the single formulations of Comparative Examples 1 and 2 and table 13 shows results for valsartan. Also, dissolution assay results are given in Table 14 for pitavastatin of the composite formulations prepared in Comparative Examples 3 to 8 and the single formulations prepared in Comparative Examples 1 and 2. Table 15 shows results for valsartan.

[172] <Dissolution condition>

[173] Test method: 2nd dissolution method of the Korean Pharmacopoeia(paddle method)

[174] Dissolution liquid: 900 mL

[175] Apparatus: USP paddle method, 50 rpm

[176] pH: 6.8

[177] [Table 12]

Time(min)	C. Ex. 1	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6
5	62.2	74.2	66.8	64.9	78.9	43.4	49.4
10	102.4	88.8	86.6	93.8	87.2	82.8	87.3
15	104.5	88.4	88.1	94.9	89.3	86.3	89.5

[178] In Table 12, dissolution rates of pitavastatin are shown.

[179] [Table 13]

Time(min)	C. Ex. 2	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6
5	49.7	69.9	64.2	60.3	78.4	40.6	45.6
10	93.0	92.3	87.4	94.0	90.4	86.5	89.2
15	96.2	91.9	89.4	95.7	92.5	93.7	95.2

[180] In Table 13, dissolution rates of valsartan are shown.

[181] [Table 14]

Time(min)	C. Ex. 1	C. Ex. 3	C. Ex. 4	C. Ex. 5	C. Ex. 6	C. Ex. 7	C. Ex. 8
5	62.2	17.9	14.7	21.4	23.5	25.9	30.9
10	102.4	33.3	29.7	35.3	45.8	52.3	56.1
15	104.5	46.9	44.6	46.5	63.9	75.0	75.6

[182] In Table 14, dissolution rates of pitavastatin are shown.

[183] [Table 15]

Time(min)	C. Ex. 2	C. Ex. 3	C. Ex. 4	C. Ex. 5	C. Ex. 6	C. Ex. 7	C. Ex. 8
5	49.7	17.1	12.9	22.1	26.6	25.2	29.9
10	93.0	33.7	28.0	39.3	52.2	52.6	55.7
15	96.2	48.1	43.3	52.5	74.1	76.2	75.6

[184] In Table 15, dissolution rates of pitavastatin are shown.

[185] As is understood from the data, the pitavastatin calcium salt/valsartan composite formulations, prepared in Examples 1 to 6, containing a Na-free lubricant or stabilizer, were disintegrated within about 1 min whereas the composite formulations, prepared in Comparative Examples 3 to 7, containing a stabilizer or lubricant having sodium residues were observed to disintegrate only after 5 min.

[186] Therefore, the employment of a Na-free lubricant or stabilizer guaranteed stability in an acidic condition and ensured a proper dissolution rate of pitavastatin and valsartan. That is, an improvement in the stability of pitavastatin in an acidic condition resulted in an increase in the dissolution rate of both pitavastatin and valsartan, and thus in the bioavailability thereof, as well.

[187] Although the preferred embodiments of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications,

additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

[188]

[189]

[190]

Claims

[Claim 1] A pharmaceutical composition for prevention or treatment of cardiovascular disease and dyslipidemia, comprising pitavastatin or a pharmaceutically acceptable salt thereof, and valsartan or a pharmaceutically acceptable salt thereof as active ingredients.

[Claim 2] The pharmaceutical composition of claim 1, wherein the pitavastatin or a pharmaceutically acceptable salt thereof is separated from the valsartan or a pharmaceutically acceptable salt thereof.

[Claim 3] The pharmaceutical composition of claim 2, wherein the pitavastatin or a pharmaceutically acceptable salt thereof is in mixture with a sodium(Na)-free lubricant or stabilizer.

[Claim 4] The pharmaceutical composition of claim 2, wherein the pitavastatin or a pharmaceutically acceptable salt thereof is in a granular form and is blended with the valsartan or a pharmaceutically acceptable salt thereof.

[Claim 5] The pharmaceutical composition of claim 4, wherein the pitavastatin or a pharmaceutically acceptable salt thereof is in a form of granules and is blended with the valsartan or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable additive.

[Claim 6] The pharmaceutical composition of claim 5, wherein the granules of the pitavastatin or a pharmaceutically acceptable salt thereof contain at least one selected from among low-substituted hydroxypropyl cellulose and lactose hydrate as an excipient, at least one selected from among magnesium aluminometasilicate, magnesium aluminosilicate, magnesium carbonate, aluminum hydroxide, potassium dihydrogen phosphate and aluminum chloride as a lubricant or stabilizer, and hydroxypropylmethyl cellulose as a binder.

[Claim 7] The pharmaceutical composition of claim 5, wherein the valsartan or a pharmaceutically acceptable salt thereof contains at least one selected from among low-substituted hydroxypropyl cellulose and lactose hydrate as an excipient.

[Claim 8] The pharmaceutical composition of claim 1, further comprising croscamellose sodium as a disintegrant, or magnesium stearate as a lubricant, or both.

[Claim 9] The pharmaceutical composition of claim 1, including an external film coating.

[Claim 10] The pharmaceutical composition of claim 9, wherein the external film

coating is made of a base containing at least one selected from among polyvinylalcohol, titanium oxide(TiO_2), polyethylene glycol 3350(PEG 3350) and talc.

[Claim 11] The pharmaceutical composition of claim 1, wherein the pitavastatin or a pharmaceutically acceptable salt thereof is contained in an amount of 0.5 mg to 8 mg.

[Claim 12] The pharmaceutical composition of claim 1, wherein the valsartan or a pharmaceutically acceptable salt thereof is contained in an amount of 20 mg to 240 mg.

[Claim 13] The pharmaceutical composition of claim 6, wherein the composition contains the low-substituted hydroxypropyl cellulose in an amount of 20 mg to 200 mg, the lactose hydrate in an amount of 2 mg to 20 mg, the magnesium aluminometasilicate in an amount of 0.5 mg to 10 mg, and the hydroxypropylmethyl cellulose in an amount of 0.5 mg to 10 mg.

[Claim 14] The pharmaceutical composition of claim 7, wherein the composition contains the low-substituted hydroxypropyl cellulose in an amount of 20 mg to 200 mg, and the lactose hydrate in an amount of 30 mg to 300 mg.

[Claim 15] The pharmaceutical composition of claim 8, wherein the composition contains the croscamellose sodium ion an amount of 5 mg to 50 mg, and the magnesium stearate in an amount of 0.5 mg to 10 mg.