

【DESCRIPTION】

【Invention Title】

PHARMACEUTICAL COMBINATION DRUG

5 **【Technical Field】**

The present disclosure relates to a pharmaceutical combination preparation that dissolution is improved including fimasartan and rosuvastatin.

10 **【Background Art】**

Apropos of hypertension, it is important to control blood pressure steadily below certain pressure because preventing coronary artery diseases such as stroke, cardiac failure and myocardial infarction, and cardiovascular complication such as
15 renal insufficiency which threat life by keeping blood pressure in the normal range is more important than treating blood pressure directly. Selection of a therapeutic agent should be made carefully because therapeutic agent for blood pressure is required to be administered in long-term. Therefore, side
20 effects incurred from long-term use of drug are needed to be reduced by combining drugs having different mechanisms rather than selecting only one drug and by reducing drug dosage via

the combined administration for keeping blood pressure in the normal range over long periods.

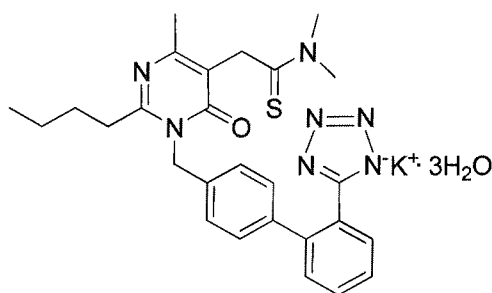
However, there are problems such as decrease of medicinal effect and incurrence of side effects due to drug combination because absorption, metabolism, distribution, expression of drug effect, and excretion-related transporter, metabolic enzyme and gene of each drug have different property and show different actions when taking two or more ingredients. For instance, drug can cause problems in absorption, metabolism and excretion in everywhere at every phase such as the first phase of passing the intestinal wall, the second phase of influx into the liver, the third phase of activation *via* metabolized in the hepatocyte and the fourth phase of leakage from the hepatocyte through the biliary tract among others. Especially, disintegration and dissolution patterns of active ingredients according to pH cause a lot of problems in drug effectiveness when performing complex treatment.

Angiotensin II receptor blocker (ARB) is a drug effective in depressing blood pressure in both myocardial systole and diastole by blocking conjugation of angiotensin II which is one of the original substances that causes vasoconstriction with

AT1 receptor among angiotensin receptors, and there are about 10 series of compound group including pharmaceutically acceptable salt. Also, these are being used for hypertension-related symptoms solely upon patients having mild through moderate symptoms or with angiotensin converting enzyme inhibitor which exhibits anti-hypertensive effect in similar mechanism [Angiotensin II Receptor Antagonist: An Overview, Am. J. Health-Syst. Pharm. 57(13): 1231-1238, 2000].

Fimasartan, one of the angiotensin II receptor blockers (ARB), is 2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[[2-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one and has a chemical formula 1, and it is approved under the title of KANARB[®] and currently available in the market (Korean Patent Registration No. 10-1058284).

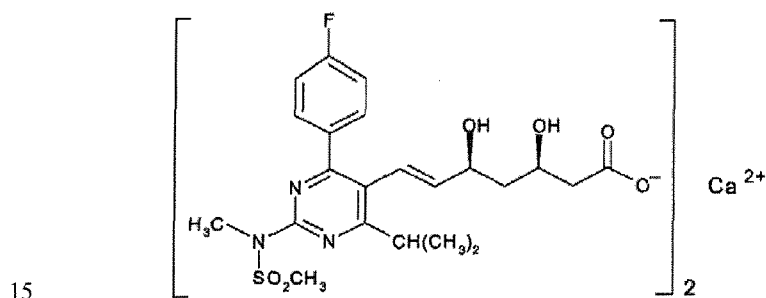
15 **【Chemical Formula 1】**



HMG-CoA reductase inhibitor has effects of decreasing blood lipid concentration and cholesterol by preventing the reduction of HMG-CoA to be mevalonate, and thus it is used for hyperlipidemia, hypercholesterolemia and atherosclerosis.

5 Rosuvastatin, one of the HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitor, is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid and has a structure of chemical
10 formula 2, and it controls synthetic pathway of cholesterol and it is approved under the title of CRESTOR® and currently available in the market (Korean Patent Registration No. 10-0105432).

【Chemical Formula 2】



Fimasartan and rosuvastatin combination preparation having different acting mechanisms can be used for

hypertension treatment but these combination preparation have a problem of affecting disintegration and dissolution of each active ingredient due to effect of interference to each other. That is, fimasartan exhibits decent solubility pattern under
5 comparatively high pH media such as purified water and pH 6.8 dissolution media, but its solubility decreases under low pH media (i.e. pH 1.0 - pH 4.0) and KANARB[®] which is a currently available fimasartan formulation in the market exhibits similar solubility pattern.

10 According to the properties of fimasartan explained above, problem of decreasing disintegration and dissolution due to interference between fimasartan and rosuvastatin is raised when preparing combination preparation with rosuvastatin. Especially, decrease of dissolution under low pH media could
15 seriously affect bioavailability at the stomach where initial disintegration and dissolution occurs at the time of oral administration.

Under these circumstances, a research on a method of keeping constant disintegration and dissolution rates of
20 fimasartan and rosuvastatin in spite of pH variation in the normal stomach is required.

【Summary of Invention】

【Technical Problem】

The present disclosure is related to a pharmaceutical combination preparation of fimasartan and rosuvastatin including meglumine. It is an object of the present disclosure to provide a superior combination preparation which increases disintegration and dissolution rate, to prevent drug interference and to ease taking of a drug with single administration.

10

【Solution to Problem】

The present disclosure provides pharmaceutical combination preparation including fimasartan, pharmaceutically acceptable salt thereof, isomer thereof, or hydrate or solvate thereof; rosuvastatin, pharmaceutically acceptable salt thereof, isomer thereof, or hydrate or solvate thereof; and meglumine.

The pharmaceutical combination preparation of the present disclosure is a superior combination preparation which greatly enhances disintegration and dissolution rates, prevents drug interference and eases taking of a drug with single

administration, and has an advantage in superior bioavailability.

The pharmaceutical combination preparation of the present disclosure includes fimasartan, pharmaceutically acceptable
5 salt thereof, isomer thereof, or hydrate or solvate thereof; rosuvastatin, pharmaceutically acceptable salt thereof, isomer thereof, or hydrate or solvate thereof as a pharmacological active ingredient. In the present disclosure, isomer includes optical isomer, diastereomer and mixture of both.

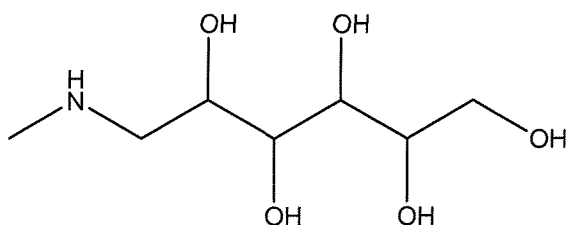
10 The fimasartan, pharmaceutically acceptable salt thereof, isomer thereof, or hydrate or solvate thereof can be included as 5.0 mg - 240.0 mg in unit dosage form, preferably 5.0 mg - 120.0 mg, and more preferably 30.0 mg - 120.0 mg, and rosuvastatin, pharmaceutically acceptable salt thereof, isomer
15 thereof, or hydrate or solvate thereof can be included as 5.0 mg - 20.0 mg in unit dosage form. It is desirable to use fimasartan potassium which is a pharmaceutically acceptable salt of the fimasartan, and more preferably fimasartan potassium trihydrate and rosuvastatin calcium which is a
20 pharmaceutically acceptable salt of the rosuvastatin as a pharmacological active ingredient.

The meglumine of the present disclosure is an amino sugar derived from sorbitol and has a structure as illustrated in the following chemical formula 3. The meglumine is an excipient of the present disclosure for inhibiting decrease of

5 disintegration and dissolution due to interference of fimasartan and rosuvastatin, and exhibits effect of inhibiting interference of active ingredients and increases disintegration and dissolution rates. This meglumine can be included in the amount of 1.0 - 30.0 wt%, preferably 2.0 - 15.0 wt%, and more

10 preferably 2.0 - 10.0 wt% based on the total weight of the combination preparation.

【Chemical Formula 3】



The pharmaceutical preparation of the present disclosure

15 is for the prevention or treatment of cardiovascular diseases, and cardiovascular diseases include hypertension or all the symptoms such as hypertension and complication of the metabolic syndrome patients who comorbidly showing diabetes, obesity, hyperlipidemia, coronary arterial diseases among others, 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, 5 cognitive impairments and dementia among others.

The combination preparation of the present disclosure can further include pharmaceutically acceptable additives *pro re nata* and can be formulated by including additives, for examples, such as stabilizer, binder, disintegrant, lubricant, 10 diluents, coating agent, pH modifier, solubilizing agent and surfactant among others which are pharmaceutically acceptable within the scope of the effects of the present disclosure.

Dibasic or tribasic calcium phosphate, tribasic magnesium phosphate and tribasic aluminium phosphate among others can be 15 used as the stabilizer. The stabilizer can be included in the amount of 1.0 - 50.0 wt%, preferably 2.0 - 30.0 wt%, and more preferably 2.0 - 10.0 wt% based on the total weight of the combination preparation.

Hydroxypropyl cellulose, hydroxypropyl methylcellulose, 20 starch, gelatin, glucose syrup, polyvinyl pyrrolidone, polyethylene glycol 6000, methylcellulose, ethylcellulose, carboxymethylcellulose, or mixture thereof among others can be

used as the binder. Preferably, the binder can include at least more than one substance selected from a group consisted of Hydroxypropyl cellulose, hydroxypropyl methylcellulose and polyvinyl pyrrolidone. Also, it is desirable to include the
5 binder in the amount of 0.2 - 5.0 wt% and preferably 0.5 - 4.0 wt% based on the total weight of the combination preparation.

Starch or modified starch such as sodium starch glycolate, corn starch, potato starch or fully gelatinized starch among others; clay such as bentonite, montmorillonite or
10 veegum among others; celluloses such as microcrystalline cellulose, hydroxypropyl cellulose or carboxymethylcellulose among others; algins such as sodium alginate or alginic acid among others; crosslinked celluloses such as croscarmellose sodium among others; gums such as guar gum, xanthan gum among
15 others; crosslinked polymers such as crospovidone among others; effervescent agents such as sodium bicarbonate and citric acid among others, or mixture thereof can be used as the disintegrant. Preferably, the disintegrant can include mixture of the croscarmellose sodium and the crospovidone. Also, it is
20 desirable to include the disintegrant in the amount of 2.0 - 30.0 wt% and preferably 5.0 - 20.0 wt% based on the total weight of the combination preparation.

Magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, polyethylene glycol or silicon dioxide can be used as the lubricant. It is desirable to include the lubricant in the amount of 0.2 - 5.0 wt% and preferably 0.5 -
5 3.0 wt% based on the total weight of the combination preparation.

Cellulose, lactose, starch, microcrystalline cellulose, lactose hydrate, glucose, mannitol, alginate, alkaline earth metal salt, clay, polyethylene glycol, dicalcium phosphate, or
10 mixture thereof can be used as the diluents. The diluents can be included in the amount of 15.0 - 90.0 wt%, preferably 30.0 - 70.0 wt% and more preferably 35.0 - 65.0 wt% based on the total weight of the combination preparation.

Hydroxypropyl methylcellulose, ethylcellulose, polyvinyl
15 acetate, polyethylene glycol, titanium dioxide, iron oxide among others or the product Opadry[®] can be included in the coating agent. The coating agent, for example, can be included in a tablet composition in the amount of 0.5 - 10.0 wt%, preferably 1.0 - 6.0 wt% and more preferably 2.0 - 5.0 wt%. It
20 is desirable to coat tablets because the coating reduces photodegradation product formation rate of the drug and

enhances storage stability of the product which can be affected by moisture and heat.

Alkalinizing agents such as precipitated calcium carbonate and aqueous ammonia can be used as the pH modifier.

5 Polyoxyethylene sorbitan fatty acid esters such as sodium lauryl sulfate and polysorbate, and docusate sodium among others can be used as the solubilizing agent.

Sodium lauryl sulfate, cremophor, poloxamer, docusate and pharmaceutically acceptable docusate salt among others can be
10 used as the surfactant.

The formulation of the present disclosure also can be prepared by using various pharmaceutically acceptable additives selected from coloring agents and flavors, and available additives are not limited to those disclosed in the present
15 disclosure. The additives can be formulated by including it within the range of conventional amount *via* selection.

The pharmaceutical combination preparation can be formulated as a formulation for oral administration in a form
20 of a tablet such as an uncoated tablet, a coated tablet, a multi-layer tablet and a cored tablet, and powder, granules or a capsule.

For instance, the pharmaceutical preparation of the present disclosure can be a form of an uncoated tablet prepared through mixing granular part of the fimasartan and mixed part of the rosuvastatin and tableting it. The granular part of the fimasartan can be prepared by dry granulation method and wet granulation method, and prepared preferably by the wet granulation method.

In addition, the pharmaceutical preparation of the present disclosure can be a form of a coated tablet which further includes additional coating layer on the exterior of the granular part of the fimasartan and mixed part of the rosuvastatin.

A method of preparing a coating layer can be selected by those skilled in the art within the methods which can form a film-type coating layer on a surface of tablet layer *pro re nata* and methods such as fluid-bed coating, pan coating, dry coating among others can be applied.

In addition, the pharmaceutical preparation of the present disclosure can be a form of a cored tablet constituted of an external layer comprising mixed part of the rosuvastatin that surrounds inner core constituted of granular part of the fimasartan and exterior of the inner core.

Human dosage of the preparation of the present disclosure is properly selected according to intracorporeal absorption rate of active ingredient, inactivation rate, and excretion rate, age and sex of patients *inter alia* but generally

5 30.0~120.0 mg of fimasartan per a day and 5.0~20.0 mg of rosuvastatin per a day can be administered for adults to act as prevention and treatment of cardiovascular diseases.

Additionally, the present disclosure provides a pharmaceutical composition including the combination

10 preparation. The pharmaceutical composition of the present disclosure has remarkable effect in preventing and treating cardiovascular diseases.

Further, the present disclosure provides a treatment method for cardiovascular diseases including administration of

15 therapeutically effective dose of the combination preparation including fimasartan, pharmaceutically acceptable salt thereof, isomer thereof, or hydrate or solvate thereof; rosuvastatin, pharmaceutically acceptable salt thereof, isomer thereof, or hydrate or solvate thereof; and meglumine.

20 The treating method for cardiovascular diseases by using the combination preparation of the present disclosure includes administration of the combination preparation of the present

disclosure in an amount of therapeutically effective dose. The term "therapeutically effective dose" stated in the present disclosure describes an amount of the combination preparation of the present disclosure that is effective in preventing or
5 treating cardiovascular diseases. Cardiovascular diseases include hypertension or all the symptoms such as hypertension and complication of the metabolic syndrome patients who comorbidly showing hypertension, or diabetes, obesity, hyperlipidemia, coronary arterial diseases among others, and
10 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 impairments and dementia among others. The
15 combination preparation of the present disclosure can be applied to a treatment method by additionally combining it with one or more therapeutic agents.

Also, the present disclosure provides a use of the combination preparation including fimasartan, pharmaceutically
20 acceptable salt thereof, isomer thereof, or hydrate or solvate thereof; rosuvastatin, pharmaceutically acceptable salt thereof, isomer thereof, or hydrate or solvate thereof; and

meglumine for preparation of medicaments for cardiovascular disease treatment. The acceptable additives *supra* can be mixed with the combination preparation of the present disclosure for preparation of medicaments and for instance, the combination
5 preparation can be prepared by including additives such as stabilizer, binder, disintegrant, lubricant, diluents, coating agent, pH modifier, solubilizing agent and surfactant among others which are pharmaceutically acceptable within the scope of the effects of the present disclosure.

10 In addition, the present disclosure provides a use for treating cardiovascular diseases by using the combination preparation including fimasartan, pharmaceutically acceptable salt thereof, isomer thereof, or hydrate or solvate thereof; rosvastatin, pharmaceutically acceptable salt thereof, isomer
15 thereof, or hydrate or solvate thereof; and meglumine.

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

20

【Advantageous Effect】

The pharmaceutical combination preparation of the present disclosure exhibits remarkable effect as a pharmaceutical combination preparation for prevention or treatment of cardiovascular diseases by resolving problems of delaying
5 disintegration and dissolution due to interference of fimasartan and rosuvastatin in low pH media by using meglumine.

【Description of Drawings】

Figure 1 illustrates analysis result of dissolution
10 pattern of the pharmaceutical combination preparation including fimasartan and rosuvastatin as active ingredient with meglumine.

【Description of the Preferred Embodiments】

15 The present disclosure will be described more fully hereinafter with reference to the accompanying preparational examples and experimental examples. However, the following preparational examples and experimental examples are intended to illustrate the present invention, and the present invention
20 is not limited by the following preparational examples and experimental examples.

【Examples】 Preparation of Combination Tablet Including

Meglumine

【Table 1】 Ingredients and Contents of the Combination Tablet

5 Including Meglumine

Unit: mg/tablet	Example 1	Example 2	Example 3
Granular Part of the Fimasartan			
Fimasartan Potassium Trihydrate	66.00	66.00	66.00
Microcrystalline Cellulose	72.75	72.75	72.75
Croscarmellose Sodium	7.50	7.50	7.50
Hydroxypropyl Cellulose	1.50	1.50	1.50
Magnesium Stearate	2.25	2.25	2.25
Mixed Part of the Rosuvastatin			
Rosuvastatin Calcium	10.40	10.40	10.40
Microcrystalline Cellulose	38.60	40.60	33.60
Meglumine	10.00	5.00	20.00
Lactose Hydrate	37.00	40.00	32.00
Crospovidone	2.00	2.00	2.00
Magnesium Stearate	2.00	2.00	2.00

Total Weight (mg/tablet)	250	250	250
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1. Example 1

(1) Preparation of the Granular Part of the Fimasartan

The granular part of the fimasartan of Example 1 was prepared to have the same weight per unit dosage form to Table 1. Fimasartan potassium trihydrate was put into the part of the microcrystalline cellulose and mixed for about two minutes, and sieved through a No. 30 mesh screen twice. Put the sieved mixture, the rest of the microcrystalline cellulose and part of the croscarmellose sodium in a high speed mixer and mixed for about three minutes. Binder solution was separately prepared by dissolving hydroxypropyl cellulose in 65 mL of purified water.

The prepared binder solution was put into the high speed mixer, sieved through No. 20 mesh screen after wet granulation with a mixed solution, and dried. Fimasartan granules were prepared through putting the rest of the croscarmellose sodium in the dried granular part of the fimasartan and mixing in a double cone mixer for five minutes and supplementally mixing with the magnesium stearate for five minutes.

(2) Preparation of the Mixed Part of the Rosuvastatin

The mixed part of the rosuvastatin of Example 1 was prepared to have the same weight per unit dosage form to Table 1. Rosuvastatin calcium was put into the meglumine and part of the lactose and mixed for about two minutes, and sieved through
5 a No. 30 mesh screen twice. Put the sieved mixture, the rest of the lactose, microcrystalline cellulose and crospovidone in a double cone mixer and mixed for about three minutes. Magnesium stearate was added as a lubricant and supplementally mixed for about five minutes.

10 (3) Tablet compression

The combination preparation was prepared by tableting with 20 kN of tableting pressure by using a rotary tablet compression machine (PICCOLA DC, RIVA) to have 249~251 mg of weight (250.0 mg of theoretical weight) and 9~10 kp of hardness per one
15 tablet. Friability of the tablets obtained through the above process was measured by using a friability tester (25 rpm, 100 free falls). The measured friability was 0.1% and below, and thus hardness of the tablets was fine.

2. Example 2

20 Altered the content of the meglumine to 5.0 mg and prepared tablets according to the contents of Table 1 via the same method explained in Example 1.

3. Example 3

Altered the content of the meglumine to 20.0 mg and prepared tablets according to the contents of Table 1 via the same method explained in Example 1.

5

【Comparative Examples】 Preparation of Combination preparation wherein Meglumine was not included

【Table 2】 Ingredients and Contents of the Combination preparation wherein Meglumine was not included

Unit: mg/tablet	Comparative Example 1	Comparative Example 2
Granular Part of the Fimasartan		
Fimasartan Potassium Trihydrate	66.00	66.00
Microcrystalline Cellulose	72.75	72.75
Croscarmellose Sodium	7.50	7.50
Hydroxypropyl Cellulose	1.50	1.50
Magnesium Stearate	2.25	2.25
Mixed Part of the Rosuvastatin		
Rosuvastatin Calcium	10.40	10.40
Microcrystalline Cellulose	43.60	41.60
Meglumine	-	-

Lactose Hydrate	42.00	41.00
Crospovidone	2.00	-
Croscarmellose Sodium	-	5.00
Magnesium Stearate	2.00	2.00
Total Weight (mg/tablet)	250	250

1. Comparative Example 1

(1) Preparation of the Granular Part of the Fimasartan

The granular part of the fimasartan of Comparative Example 1 was prepared to have the same weight per unit dosage form to Table 2. Fimasartan potassium trihydrate was put into the part of the microcrystalline cellulose and mixed for about two minutes, and sieved through a No. 30 mesh screen twice. Put the sieved mixture, the rest of the microcrystalline cellulose and part of the croscarmellose sodium in a high speed mixer and mixed for about three minutes. Binder solution was separately prepared by dissolving hydroxypropyl cellulose in purified water. The prepared binder solution was put into the high speed mixer, sieved through No. 20 mesh screen after wet granulation with a mixed solution, and dried. Fimasartan granules were prepared through putting the rest of the

croscarmellose sodium in the dried granular part of the fimasartan and mixing in a double cone mixer for five minutes and supplementally mixing with the magnesium stearate for five minutes.

5 (2) Preparation of the Mixed Part of the Rosuvastatin

The tablet of Comparative Examples was prepared to have the same weight per unit dosage form to Table 2. Rosuvastatin calcium was put into the part of the lactose and mixed for about two minutes, and sieved through No. 30 mesh screen twice.

10 Put the sieved mixture, the rest of the lactose, microcrystalline cellulose and the crospovidone (Comparative Example 1) in a double cone mixer and mixed for about three minutes. Magnesium stearate was added as a lubricant and supplementally mixed for about five minutes.

15 (3) Tablet compression

The combination preparation was prepared by tableting with 20 kN of tableting pressure by using a rotary tablet compression machine (PICCOLA DC, RIVA) to have 249~251 mg of weight (250.0 mg of theoretical weight) and 9~10 kp of hardness per one
20 tablet. Friability of the tablets obtained through the above process was measured by using a friability tester (25 rpm, 100

free falls). The measured friability was below 0.1% and thus hardness of the tablets was fine.

2. Comparative Example 2

Prepared Comparative Example 2 via the same preparation method explained in Comparative Example 1 with the compositions of Table 2 except an alteration of the disintegrant from crospovidone to croscarmellose sodium.

【Experimental Example】 Dissolution test in the combination preparation of Fimasartan and Rosuvastatin

A dissolution test for the combination preparation of fimasartan potassium trihydrate and the rosuvastatin calcium obtained through Example 1 and Comparative Examples 1-2 and the CRESTOR[®] currently available in the market were conducted under conditions stated in Table 3 below and the test result was illustrated in Figure 1.

【Table 3】 Conditions for dissolution test and HPLC analyzing

Effluent	pH 1.2 dissolution medium, 900 mL	
Method	usp paddle method, 50 rpm	
Temperature	37±0.5 °C	
Column	C ₁₈ (5 microns, 150 * 4.6 mm)	
Apparatus	Detection	260 nm, 242 nm

	Temperature	40 °C
	Run time	30 min
	Injection	20 uL
	Flow rate	1.0 mL/min
	Sample Temp.	5 °C
Mobile phase	Water: Acetonitrile : 1 vol% Trifluoroacetic acid(57 : 42 : 1, v/v/v)	

As illustrated in Figure 1, interference of fimasartan and rosuvastatin in Example 1 was remarkably low compared to the other formulations and thus it was shown that disintegration and dissolution were highly increased, and effects thereof was almost identical with the CRESTOR® on market as a single agent. However, disintegration and dissolution rates of Comparative Example wherein meglumine was not included were extremely low due to interference.

It is understood that the combination preparation of fimasartan and rosuvastatin including meglumine has superior bioavailability based on the above result.

【Industrial Applicability】

As explained hereinbefore, the combination preparation of the present disclosure can be safely and effectively used for prevention and treatment of cardiovascular diseases.

【CLAIMS】

【Claim 1】

A pharmaceutical combination preparation comprising a fimasartan, a pharmaceutically acceptable salt thereof, an
5 isomer thereof, or a hydrate or a solvate thereof; a
rosuvastatin, a pharmaceutically acceptable salt thereof, an
isomer thereof, or a hydrate or a solvate thereof; and a
meglumine.

10 **【Claim 2】**

The pharmaceutical combination preparation according to
claim 1, wherein the pharmaceutically acceptable salt of the
fimasartan is a fimasartan potassium.

15 **【Claim 3】**

The pharmaceutical combination preparation according to
claim 1, wherein the hydrate is a fimasartan potassium
trihydrate.

20 **【Claim 4】**

The pharmaceutical combination preparation according to
claim 1, wherein the fimasartan, the pharmaceutically
acceptable salt thereof, the isomer thereof, or the hydrate or
the solvate thereof are comprised 5.0 mg - 240.0 mg per unit
25 dosage form.

【Claim 5】

The pharmaceutical combination preparation according to claim 1, wherein the rosuvastatin, the pharmaceutically acceptable salt thereof, the isomer thereof, or the hydrate or the solvate thereof are a rosuvastatin calcium.

【Claim 6】

The pharmaceutical combination preparation according to claim 1, wherein ingredients of the rosuvastatin are comprised 5.0 mg - 20.0 mg per unit dosage form.

【Claim 7】

The pharmaceutical combination preparation according to claim 1, wherein the meglumine is comprised 1.0 - 30.0 wt% based on the total weight of the combination preparation.

【Claim 8】

The pharmaceutical combination preparation according to claim 1, wherein the combination preparation is for treatment of cardiovascular diseases.

【Claim 9】

The pharmaceutical combination preparation according to claim 8, wherein the cardiovascular diseases are selected from hypertension, diabetes, obesity, hyperlipidemia, coronary arterial diseases, chronic stable angina, vasospastic angina,

stroke, myocardial infarction, transient ischemic attack, congestive heart failure, insulin resistance, impaired glucose tolerance, preliminary diabetes, type 2 diabetes mellitus, diabetic nephropathy, dyslipidemia, cognitive impairments,
5 dementia and combinations thereof.

【Claim 10】

The pharmaceutical combination preparation according to any one of claims 1-9, wherein at least one of a stabilizer, a
10 binder, a disintegrant or a lubricant is further comprised.

【Claim 11】

The pharmaceutical combination preparation according to claim 10, wherein the stabilizer is comprised 1.0 - 50.0 wt%
15 based on the total weight of the combination preparation.

【Claim 12】

The pharmaceutical combination preparation according to claim 10, wherein the binder is comprised 0.2 - 5.0 wt% based
20 on the total weight of the combination preparation.

【Claim 13】

The pharmaceutical combination preparation according to claim 10, wherein the disintegrant is comprised 2.0 - 30.0 wt%
25 based on the total weight of the combination preparation.

【Claim 14】

The pharmaceutical combination preparation according to claim 10, wherein the lubricant is comprised 0.2 - 5.0 wt% based on the total weight of the combination preparation.

5 **【Claim 15】**

The pharmaceutical combination preparation according to claim 10, wherein the diluent is comprised 15.0 - 90.0 wt% based on the total weight of the combination preparation.

10 **【Claim 16】**

The pharmaceutical combination preparation according to any one of claims 1-9, wherein the combination preparation is in a form of a tablet.

15 **【Claim 17】**

The pharmaceutical combination preparation according to claim 16, wherein the combination preparation is a form of a coated tablet which additionally comprises a coating layer on the exterior.

20

【Claim 18】

A pharmaceutical composition comprising the combination preparation according to any one of the claims 1-17.

25 **【Claim 19】**

A method of treating cardiovascular diseases comprising administration of therapeutically effective dose of the

combination preparation according to any one of claims 1-17.

【Claim 20】

The method of treating cardiovascular diseases according
5 to claim 19, wherein the cardiovascular diseases are selected
from hypertension, diabetes, obesity, hyperlipidemia, coronary
arterial diseases, chronic stable angina, vasospastic angina,
stroke, myocardial infarction, transient ischemic attack,
congestive heart failure, insulin resistance, impaired glucose
10 tolerance, preliminary diabetes, type 2 diabetes mellitus,
diabetic nephropathy, dyslipidemia, cognitive impairments,
dementia and combinations thereof.

【Claim 21】

15 A use of the combination preparation for preparation of
medicaments for treatment of cardiovascular diseases according
to any one of claims 1-17.

【Claim 22】

20 A use of the combination preparation for treatment of
cardiovascular diseases according to any one of claims 1-17.