(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
01 November 2018 (01.11.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/199636 A1

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/4422* (2006.01)
A61K 9/28 (2006.01) *A61K 31/505* (2006.01)

(21) International Application Number:
PCT/KR2018/004815

(22) International Filing Date:
25 April 2018 (25.04.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2017-0053877 26 April 2017 (26.04.2017) KR

(71) Applicant: **ALVOGEN KOREA CO.,LTD.** [KR/KR]; 13 Fl., 10, Gukjegeumyung-ro, Yeongdeungpo-gu, Seoul 07326 (KR).

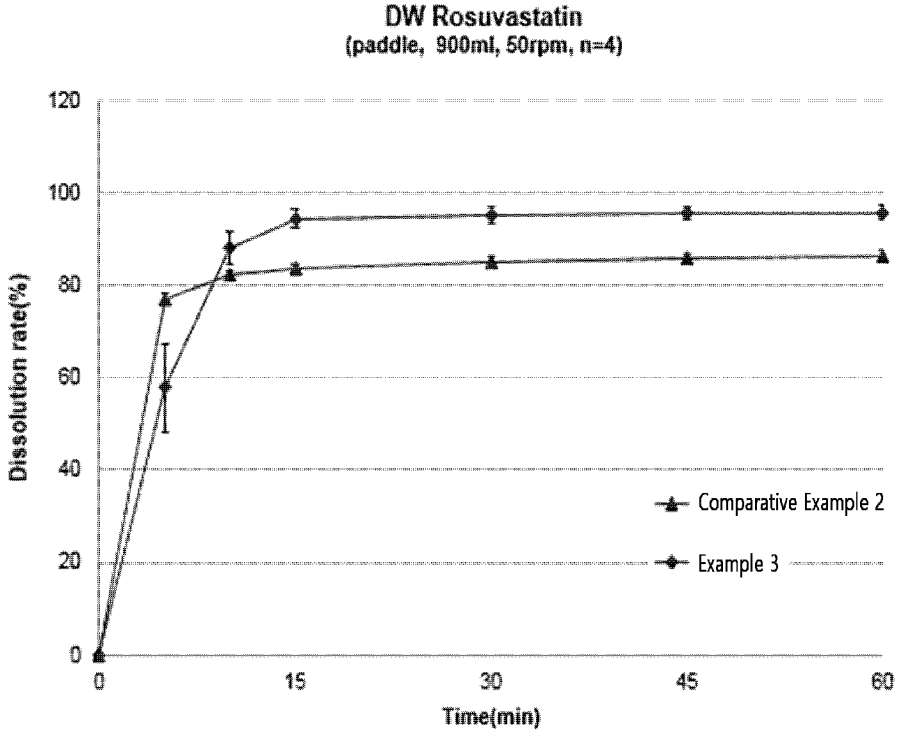
(72) Inventors: **LEE, Si Beum**; 9, Dongbaek 3-ro 60beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do 17009 (KR). **HA, Song Yi**; 114-1004, 60, Seryu-ro, Gwonseon-gu, Suwon-si, Gyeonggi-do 16459 (KR). **HONG, Hye Suk**; 411-1405, 206, Baekhyeon-ro, Bundang-gu, Seongnam-si, Gyeonggi-do 13607 (KR). **LEE, Yoon Jung**; 601-203, 53, Gwangok-ro, Giheung-gu, Yongin-si, Gyeonggi-do 16963 (KR).

(74) Agent: **SON, Min**; Hanol Intellectual Property&Law, 6th Floor, 135, Beobwon-ro, Songpa-gu, Seoul 05836 (KR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

(54) Title: A COMBINATION FORMULATION COMPRISING HMG-COA REDUCTASE INHIBITOR AND CALCIUM CHANNEL BLOCKER



(57) Abstract: The present invention relates to an oral combination formulation comprising a first composition comprising amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol; and a second composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof, and a stabilizer, and a preparation method thereof.

[Continued on next page]

WO 2018/199636 A1

MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

Description

Title of Invention: A COMBINATION FORMULATION COMPRISING HMG-COA REDUCTASE INHIBITOR AND CALCIUM CHANNEL BLOCKER

Technical Field

[1] The present invention relates to a combination formulation comprising a first composition comprising amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol; and a second composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof, and a stabilizer; and a preparation method thereof.

[2]

Background Art

[3] Hypertension is the most common cardiovascular disease, and damages blood vessels of the kidney, heart, and brain as blood pressure continually rises and elevates, thereby increasing the incidence of renal failure, coronary artery disease, heart failure, and stroke. Hypertension is divided into essential hypertension and secondary hypertension. Essential hypertension refers to high blood pressure of an unknown cause, that is, high blood pressure without a particular causative disease. Essential hypertension accounts for most (approximately 95%) of all hypertension cases, and for those in their 40s or older, most cases are related to essential hypertension. As there is no disease that causes essential hypertension, it is difficult to clearly investigate the cause thereof; however, genetic predisposition, salty eating habits, obesity, old age, stress, and excessive smoking and drinking can be problematic. Secondary hypertension refers to high blood pressure of a particular disease which secondarily increases blood pressure. Secondary hypertension accounts for 5% of all hypertension cases, and cases of hypertension in relatively young people are related to secondary hypertension. Nephritis, endocrine system abnormality, and pregnancy toxemia are primary causes, and blood pressure naturally lowers when the causative disease is treated.

[4] Antihypertensive agents, which lower blood pressure, are broadly classified into three types—diuretics, antiadrenergic agents, and vasodilators—according to major regulatory sites or mechanisms, and are divided more specifically according to the sites on which each drug acts. Diuretics are drugs which excrete water and salt from the body by increasing an amount of urine, and they lower blood pressure by reducing the amounts of water and salt in the body. The sympathetic nervous system increases the number of contractions of the heart and strengthens the contractions, and also contracts

the blood vessels, and sympathetic inhibitors are drugs that suppress the activities of the sympathetic nervous system, thereby lowering blood pressure. Sympatholytic agents include alpha blockers, which suppress the sympathetic nervous system that contracts blood vessels, beta blockers, which suppress the sympathetic nervous system that contracts the heart, and centrally acting sympatholytic agents, which act on the brain. Vasodilators are drugs which lower blood pressure by dilating blood vessels, and there are several types of vasodilators, such as ACE inhibitors, which suppress production of the vasoconstrictor angiotensin II, and angiotensin II receptor antagonists, which block angiotensin II activities. Additionally, as blood vessels contract and blood pressure elevates when intracellular calcium ion concentration increases, calcium channel blockers, which block the entry of the calcium ions and thereby lower blood pressure, are also a vasodilator.

[5] It is important to prevent life-threatening complications of coronary artery diseases such as stroke, heart failure, myocardial infarction, *etc.*; and cardiovascular complications such as renal failure, rather than treating blood pressure itself, by maintaining the blood pressure within a normal range. Accordingly, it is important to steadily and patiently control the blood pressure. As antihypertensive medications require life-long administration, a therapeutic drug should be carefully selected. For continued treatment, therefore, it is necessary to obtain more excellent prophylactic and therapeutic effects by co-administering drugs having different mechanisms and reduce risks of side effects that can be caused by the long-term administration of a single drug by reducing an amount of its intake through the co-administration of drugs, rather than selecting a single drug. Hypertension Guidelines (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC7) recommends co-administration of drugs having different mechanisms in a case where there is no sufficient controlling effect of blood pressure by a single drug administration.

[6] Meanwhile, hyperlipidemia means abnormally elevated levels of lipids in the blood, such as cholesterol, triglycerides, *etc.* In particular, hypercholesterolemia, by inducing coronary thrombosis, induces arteriosclerosis, in which an artery wall thickens as a result of accumulation of lipids, and causes ischemic heart disease, angina, and myocardial infarction by decreasing blood flow. Likewise, hyperlipidemia and arteriosclerosis are closely related, and thus, arteriosclerosis can be prevented by treating hyperlipidemia.

[7] HMG-CoA reductase inhibitors inhibit mevalonate production to thereby interrupt cholesterol biosynthesis and show an effect of lowering levels of total cholesterol and LDL-cholesterol, and thus have been used in the treatment of hyperlipidemia (see Grundi S. M., NEngl J Med, 319(1): 24-32, 25-26, 31(1998)).

[8] Hypertension is often prevalent in hyperlipidemia. Being considered as major risk factors for cardiovascular diseases, hypertension and hyperlipidemia ultimately lead to adverse cardiac symptoms. Such risk factors originate from potentially common mechanisms. Accordingly, it is advantageous for patients to receive a single prescription of a drug capable of treating all said diseases; however, when a cardiovascular disease patient co-administers an angiotensin II receptor antagonist and an HMG-CoA reductase inhibitor, not only are hypertension and hyperlipidemia treated, but also the function of endothelial cells as a blood vessel protective membrane is improved, as well as increased sensitivity to insulin, thereby also showing therapeutic effects on diabetes (see Ceriello A, Assaloni R, Da Ros R, Maier A, Piconi L, Quagliaro L, *et al.*, Circulation, 111: 2518-2524, May 2005; and Koh KK, Quon MJ, Han SH, *et al.*, Circulation, 110: 3687-3692, Dec 2004). Meanwhile, it is known that a large synergistic effect can be obtained by administering a calcium channel blocker, which is a therapeutic agent for hypertension, together with a lipid-lowering agent to treat arteriosclerosis (see Kramsch *et al.*, Journal of Human Hypertention, Suppl.1, 53-59, 1995). It is also known that the calcium channel blocker can have an advantageous effect in the treatment of early atherosclerotic lesions (see Lichtlen P.R. *et al.*, Lan et, 335, 1109-1139, 1990; and WatersD *et. al.*, Circulation, 82, 1940-1953, 1990).

[9] In particular, there is a recent study reporting that rosuvastatin, compared to atorvastatin, showed a more significant effect on atherosclerosis regression (Lee, C.W. *et al*, *Am J* Cardiol. 2012;109:1700-1704). Specifically, upon comparison of a treated group which was administered 10 mg of rosuvastatin and one which was administered 20 mg of atorvastatin for 6 months, rosuvastatin was found to show a significant reduction in atheroma.

[10] Further, at the European Society of Cardiology (ESC) Congress 2014, LISTEN (LIpid lowering with highly potent Statins in hyperlipidemia with Type 2 diabetes patiENts), a study report on the effect of statin on the lipid regulation and glycometabolism, was presented, which revealed that rosuvastatin, in comparison with atorvastatin, would have a positive influence on a blood sugar level during an early treatment.

[11] Meanwhile, a conventional oral combination formulation comprising amlodipine besylate and atorvastatin calcium is disclosed in KR 10-2006-0054495 A and KR 10-2009-0048023 A; however, there is no known combination formulation for administration comprising both amlodipine and rosuvastatin. As rosuvastatin and atorvastatin have completely different physicochemical properties, the stability of the formulation disclosed in the above-mentioned patents was confirmed to be significantly decreased when atorvastatin was substituted with rosuvastatin (Experimental Examples

6 and 7). Accordingly, there is a need for research on formulations comprising amlodipine and rosuvastatin which have high stability and a high dissolution rate.

[12] Under such circumstances, the present inventors completed the present invention to prepare a combination formulation comprising rosuvastatin and amlodipine capable of obtaining stability and an excellent dissolution rate.

[13]

Disclosure of Invention

Technical Problem

[14] Stability of the oral combination formulation of the patents mentioned in Background Art was not secured due to the physicochemical properties of rosuvastatin when atorvastatin was simply substituted with rosuvastatin (Experimental Examples 6 and 7). Under such circumstances, the present invention is to provide a combination formulation comprising amlodipine and rosuvastatin capable of possessing an excellent dissolution rate and stability and a preparation method thereof.

[15]

Solution to Problem

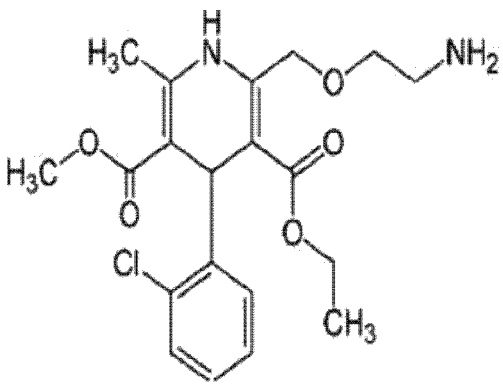
[16] In order to solve the problem, the present invention, as an aspect, provides an oral combination formulation comprising a first composition comprising amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol; and a second composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof, and a stabilizer.

[17]

[18] As used herein, the term "amlodipine" is a compound represented by Formula 1 below, and is a calcium channel blocker used mainly in the treatment of hypertension and angina. Its chemical name is 3-ethyl-5-methyl-2-(2-aminoethoxy-methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydro-3,5-pyridine dicarboxylate.

[19] [Formula 1]

[20]



[21]

[22] It would be easy for one of ordinary skill in the art to chemically synthesize the amlodipine according to a known synthesis method, or purchase a commercially manufactured product thereof.

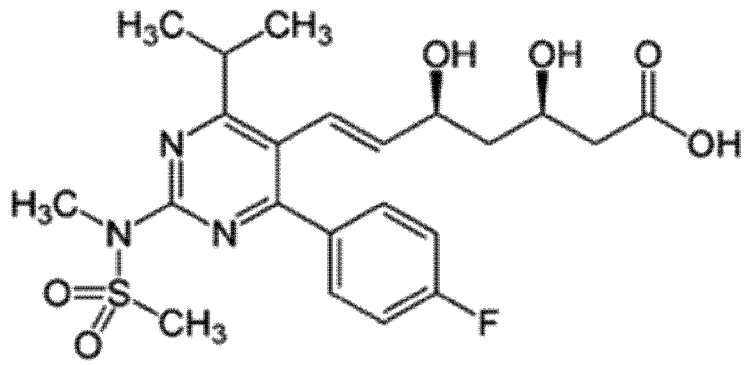
[23] The oral combination formulation of the present invention may specifically contain 3.69 mg to 14 mg of amlodipine besylate (2.5 mg to 10 mg of amlodipine); and more specifically, 13.889 mg of amlodipine besylate (10 mg of amlodipine).

[24]

[25] As used herein, the term "rosuvastatin" is a compound represented by Formula 2 below. As the type of statin which inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, rosuvastatin is used in the treatment of hypercholesteremia, hyperlipoproteinemia, atherosclerosis, *etc*. Its chemical name is (3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhepten-6-oic acid).

[26] [Formula 2]

[27]



[28] It would be easy for one of ordinary skill in the art to chemically synthesize the rosuvastatin according to a known synthesis method, or purchase a commercially manufactured product thereof.

[29] The oral combination formulation of the present invention may specifically contain 5.2 mg to 20.8 mg of rosuvastatin calcium (5 mg to 20 mg of rosuvastatin); and more specifically, 20.8 mg of rosuvastatin calcium (20 mg of rosuvastatin).

[30]

[31] As used herein, the term "pharmaceutically acceptable salt" refers to a formulation which does not damage biological activities and properties of the administered amlodipine and rosuvastatin. The pharmaceutically acceptable salts include acid addition salts formed by an acid (*e.g*., an inorganic acid such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, hydroiodic acid, *etc*.; an organic carboxylic acid such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic

acid, salicylic acid, *etc.*; a sulfonic acid such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, *etc.*; *etc.*) which forms a non-toxic acid addition salt containing a pharmaceutically acceptable anion. For example, the pharmaceutically acceptable carboxylic acid salts include metal salts or alkaline earth metal salts formed by lithium, sodium, potassium, calcium, magnesium, *etc.*; amino acid salts such as lysine, arginine, guanidine, *etc.*; organic salts such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, diethanolamine, choline, triethylamine, *etc.*; *etc.* Meanwhile, a commercially available besylic acid salt and a commercially available calcium salt are preferable for amlodipine and rosuvastatin, respectively.

[32]

[33] In the oral combination formulation of the present invention, the "first composition" comprises amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol, and "the second composition" comprises rosuvastatin or a pharmaceutically acceptable salt thereof.

[34] There is no particular meaning in the order of the first and second compositions, and the order is merely to distinguish the two compositions.

[35] The first composition may be provided in the form of a granule. The granule can be obtained according to a conventional granulation method; specifically, by mixing and sieving active ingredients and additives and dissolving the mixture in distilled water to prepare a binding solution, followed by mixing the binding solution in a high-speed mixer and drying the same.

[36] The second composition in the form of a non-granulated mixture can be added to the granulated first composition to be compressed into a tablet. A preparation process of such combination formulation is simple and a preparation cost thereof can be reduced.

[37] Due to a shortened disintegration time, the oral combination formulation releases rosuvastatin first, thereby decreasing a contact time between rosuvastatin and amlodipine. Accordingly, interactions between rosuvastatin and amlodipine can be minimized. According to an Experimental Example 1, there were interactions observed between rosuvastatin and amlodipine. Thus, it is important to minimize the contact between rosuvastatin and amlodipine.

[38] Further, as the second composition of the oral combination formulation is not granulated, the stability of rosuvastatin, which is vulnerable to moisture and heat, can be increased.

[39] The stability and uniformity of the formulation can be increased by having the second composition contain magnesium carbonate as an excipient, without being granulated.

[40] The pharmaceutical composition of the present invention can be prepared in various

types of formulations; for example, tablets such as uncoated tablets, film-coated tablets, single-layered tablets, double-layered tablets, multi-layer tablets, and core tablets; powders; and granules; capsules; *etc*. Preferably, the pharmaceutical composition of the present invention can be formulated in a single-layer tablet or double-layer tablet.

[41] According to an exemplary embodiment, due to their excellent stability and dissolution rate compared to double-layer tablets, single-layer tablets can be prepared by a simple preparation process at a low cost.

[42]

[43] As an alcohol derived from a sugar, the sugar alcohol in the first composition does not affect the stability of amlodipine and is capable of improving a dissolution profile of amlodipine. Any sugar alcohol can be used as long as it can be applied to medicine. The sugar alcohols include monosaccharide sugar alcohols such as tetritols (*e.g.*, erythritol, D-threitol, L-threitol, *etc.*), pentitols (*e.g.*, D-arabinitol, xylitol, *etc.*), hexitols (*e.g.*, D-iditol, galactitol (dulcitol), D-glusitol (sorbitol), mannitol, *etc.*), cyclitols (*e.g.*, inositol, *etc.*), *etc.*; disaccharide sugar alcohols such as maltitols, lactitols, reduced palatinoses (isomalt) *etc.*; and oligosaccharide sugar alcohols such as pentaerythritols, hydrogenated maltose starch syrup, *etc.*, but are not limited thereto.

[44] Specifically, mannitol, sorbitol, xylitol, erythritol, and inositol can be used; more specifically, mannitol can be used.

[45] In an exemplary embodiment, when mannitol was included as the sugar alcohol, amlodipine and rosuvastatin exhibited an excellent dissolution rate as well as excellent stability (Experimental Examples 3 and 4).

[46] The sugar alcohol can be included in an amount of 5 wt% to 20 wt% of the total weight of the oral combination formulation, specifically, 5 wt% to 15 wt%, more specifically, 5 wt% to 14 wt%. When the sugar alcohol is included in an amount of less than 5 wt%, the dissolution rate may not be excellent, whereas when the sugar alcohol is included in an amount of greater than 20 wt%, the stability may be remarkably decreased. It was confirmed in an exemplary embodiment that when more than 20 wt% of the sugar alcohol is included in the first composition, the amlodipine and rosuvastatin contents were remarkably reduced when stored under an extreme condition (Experimental Example 5).

[47]

[48] The disintegrants in the first composition may include sodium starch glycolate, crospovidone, sodium croscarmellose, or a mixture thereof. For example, the disintegrant may be sodium starch glycolate, and by selecting the same, excellent stability as well as an excellent dissolution rate may result.

[49]

[50] The stabilizers in the second composition are included to prevent oxidation of rosuvastatin calcium. Magnesium carbonate, magnesium oxide, magnesium hydroxide, sodium bicarbonate, calcium hydrogen phosphate, calcium hydrogen phosphate, or a mixture thereof may be used as the stabilizer. For example, the stabilizer may be magnesium carbonate, and compared to the other stabilizers, magnesium carbonate may result in excellent stability of amlodipine and rosuvastatin (Experimental Example 8).

[51] Specifically, the stabilizer is included in an amount of 1 wt% to 5 wt% of the total weight of the oral combination formulation. When the stabilizer is included in a larger amount, the stability of rosuvastatin as well as that of amlodipine may decrease, whereas when the stabilizer is included in a smaller amount, the stability of rosuvastatin may decrease.

[52]

[53] The oral combination formulation of the present invention may have a film layer on an outer surface. The film layer may be formed with a water-soluble substance selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), cellulose acetate phthalate (CAP), ethyl cellulose (EC), methyl cellulose (MC), polymethacrylate, a polyvinyl alcohol-polyethylene glycol graft copolymer, polyvinyl alcohol (PVA), and a mixture thereof.

[54]

[55] The oral combination formulation of the present invention may have a lubricant to improve mobility. Specifically, the lubricant can be selected from the group consisting of light anhydrous silicic acid, talc, stearate, iron stearate, magnesium stearate, calcium stearate, polyethylene glycol, and a mixture thereof.

[56]

[57] The first composition of the oral combination formulation of the present invention can be granulated by adding a binding agent. Specifically, the binding agent may be selected from the group consisting of polyvinyl povidone, hydroxypropyl cellulose, starch paste, gelatin, aluminum silicate, methyl cellulose, and a mixture thereof.

[58]

[59] As another aspect, the present invention provides a method for preparing an oral combination formulation, comprising:

[60] granulating a first composition comprising amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol (first step);

[61] preparing a second composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof, and a stabilizer (second step); and

[62] mixing the second composition with the granulated first composition prepared in the first step followed by compressing the mixture (third step).

[63]

[64] The terms used in the method for preparing the oral combination formulation are the same as those explained with respect to the oral combination formulation.

[65]

[66] In the first step, a mixture containing amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol is prepared and introduced to a fluidized bed granulator. By spraying a binding solution, the mixture can be granulated. The mixture can then be mixed in a high-speed mixer for 5 minutes.

[67]

[68] In the second step, the second composition can be obtained by mixing rosuvastatin or a pharmaceutically acceptable salt thereof and a stabilizer without granulating.

[69]

[70] In the third step, a lubricant can be further added into to compress the mixture.

[71]

Advantageous Effects of Invention

[72] The oral combination formulation of the present invention, which comprises a first composition comprising amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol; and a second composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof, and a stabilizer, can have an excellent dissolution rate and stability.

[73] Further, the oral combination formulation of the present invention, prepared by mixing the first composition in the form of granule with the second composition and compressing the mixture, employs a simple preparation process, and thus, a preparation cost thereof can be reduced.

[74]

Brief Description of Drawings

[75] Figs. 1a to 1c are diagrams showing phase changes of amlodipine, rosuvastatin, and a mixture thereof stored under an extreme condition.

[76] Figs. 2a and 2b are diagrams showing dissolution test results of the active ingredients of the double-layer combination formulation of Comparative Example 1 and those of the single-layer combination formulation of Example 4.

[77] Figs. 3a and 3b are diagrams showing dissolution test results of the active ingredients of the formulation of Comparative Example 2, which does not contain a sugar alcohol, and those of the formulation of Example 3, which contains a sugar alcohol.

[78]

Mode for the Invention

[79] Hereinafter, the present invention will be described in more detail with reference to the following Examples. However, these Examples are for illustrative purposes only, and the invention is not intended to be limited by these Examples.

[80]

[81] **Experimental Example 1: Interaction between calcium** rosuvastatin and amlodipine besylate

[82]

[83] In order to determine whether a combination formulation of rosuvastatin calcium and amlodipine besylate can easily be developed, stability test was carried out for each of the two active pharmaceutical ingredients and the mixture thereof.

[84]

[85] Specifically, as active pharmaceutical ingredients, rosuvastatin calcium (R), amlodipine besylate (A) , and a mixture of rosuvastatin calcium and amlodipine besylate(1:1 weight ratio) were prepared, respectively (see Table 1 below).

[86]

[87] [Table 1]

No.	Substances	Change in properties
1	Rosuvastatin Calcium (R)	●
2	Amlodipine Besylate (A)	○
3	Mixture of R and A at 1:1 weight ratio	●

[88]

[89] (○: No change, ●: Change in properties)

[90]

[91] **Experimental Example 1-1. Observation of changes in properties under extreme condition**

[92]

[93] The properties of each of the two active ingredients and the mixture thereof were observed under an extreme condition. Specifically, stored for 4 weeks, the observations were performed at 60°C at the initial stage and after 2 and 4 weeks.

[94]

[95] As shown in Figs. 1a to 1c, amlodipine besylate showed no significant change in properties, whereas rosuvastatin calcium was hardened and showed yellow discoloration. Meanwhile, the mixture of the two active ingredient, compared to rosuvastatin calcium, was further hardened and discolored.

[96]

[97] **Experimental Example 1-2. Observation of changes** in contents of active pharma-

ceutical ingredients under extreme condition

[98]

[99] Changes in the content of each active ingredient included in rosuvastatin calcium, amlodipine besylate, and a mixture thereof were observed under an extreme condition. Stored under the same condition as in Experimental Example 1-1., the changes in the content of each substance and mixture were calculated in wt% and are shown in Table 2 below.

[100]

[101] [Table 2]

No.		1	2	3
Substance		Rosuvastatin Calcium (R)	Amlodipine Besylate (A)	Mixture having R:A weight ratio of 1:1
Rosuvastatin content (%)	Initial	99.7	-	101.6
	2 weeks	97.7	-	82.1
	Δ (Initial – 2 weeks)	**2**	-	**20**
	4 weeks	97.3	-	73.4
	Δ (Initial – 4 weeks)	**2**	-	**28**
Result		○	○	●
Amlodipine content (%)	Initial	-	94.7	96.4
	2 weeks	-	94.6	80.3
	Δ (Initial – 2 weeks)	-	**0**	**16**
	4 weeks	-	95.2	79.4
	Δ (Initial – 4 weeks)	-	-	**17**
Result		○	○	●

[102] ○: content reduced to 5% or below, ●: content reduced to 5% or above)

[103] As shown above, there was no reduction in the amlodipine besylate content, whereas there was a reduction of about 2% in the rosuvastatin content at 2 weeks and 4 weeks. Meanwhile, the mixture thereof showed a reduction of 28 wt% in the rosuvastatin content at 4 weeks and a reduction of 17 wt% in the amlodipine content. This indicates that when they are in contact, rosuvastatin calcium and amlodipine have an impact on each other, thereby changing each other's properties.

[104]

[105] **Experimental Example 1-3. Observation of impurity formation under extreme condition**

[106]

[107] Each of rosuvastatin calcium, amlodipine besylate, and a mixture thereof was observed with respect to the impurity formation under an extreme condition. Stored under the same condition as in Experimental Example 1-1., the amounts of impurities were measured, and the results are summarized in Table 3 below.

[108]

[109] [Table 3]

No.		1	2	3
Substance		Rosuvastatin calcium (R)	Amlodipine besylate (A)	Mixture having R:A weight ratio of 1:1
Rosuvastatin content (%)	Initial	0.27	-	0.50
	2 weeks	0.91	-	21.20
	Δ (2 weeks - Initial)	**0.6**	-	**20.7**
	4 weeks	1.55	-	30.10
	Δ (4 weeks - Initial)	**1.3**	-	**29.6**
Result		●	-	●
Amlodipine content (%)	Initial	-	0.40	2.32
	2 weeks	-	0.46	12.46
	Δ(2 weeks - Initial)	-	**0.1**	**10.1**
	4 weeks	-	0.30	16.14
	Δ(4 weeks - Initial)	-	**0.2**	**13.8**
Result		-	○	●

[110] (○: 1% or less impurity formed, ●: 1% or more impurity formed)

[111] As described above, impurities were barely formed in amlodipine besylate, whereas about 1.3 wt% of impurities were formed in rosuvastatin at 4 weeks. Meanwhile, in the mixture thereof, 17 wt% and 28 wt% of impurities of amlodipine and rosuvastatin, respectively, were formed at 4 weeks. This indicates that when they are in contact, rosuvastatin calcium and amlodipine have an impact on each other, thereby forming excessive impurities.

[112]

[113] As described above, impurities were barely formed in amlodipine besylate, whereas about 1.3 wt% of impurities were formed in rosuvastatin at 4 weeks. Meanwhile, in the mixture thereof, 17 wt% and 28 wt% of impurities of amlodipine and rosuvastatin, respectively, were formed at 4 weeks. This indicates that when they are in contact, rosuvastatin calcium and amlodipine have an impact on each other, thereby forming excessive impurities.

[114]

[115] **Example 1**

[116] 170 mg of microcrystalline cellulose, 76.8 mg of pregelatinized starch, 20 mg of sodium starch glycolate, and 20 mg of mannitol were added into 13.889 mg of amlodipine besylate through a No. 180 mesh sieve, and mixed in a high-speed mixer for 5 minutes to prepare a mixed solution. 10 mg of polyvinyl povidone was added to 45 mg of ethanol to prepare a binding solution. The mixed solution was introduced into a mobile phase granulator, and the binding solution was sprayed thereonto to prepare a granule. The granule was then dried.

[117] Additionally, 20 mg of crospovidone, 8 mg of magnesium carbonate, and 2 mg of light anhydrous silicic acid were mixed with 20.8 mg of rosuvastatin to prepare a mixture.

[118] The thus-prepared mixture and 4 mg of magnesium stearate (*i.e.*, a lubricant) were further mixed with the amlodipine-containing granule and compressed into a tablet.

[119]

[120] **Example 2**

[121] A tablet was prepared by the same method as in Example 1, except that 190 mg of microcrystalline cellulose and 56.8 mg of pregelatinized starch were used.

[122]

[123] **Example 3**

[124] A tablet was prepared by the same method as in Example 1, except that 140 mg of microcrystalline cellulose and 50 mg of mannitol were used.

[125]

[126] **Example 4**

[127] A tablet was prepared by the same method as in Example 1, except that 140 mg of microcrystalline cellulose, 60 mg of mannitol, and 60 mg of ethanol were used when preparing the granule containing amlodipine; 16 mg of crospovidone and 4 mg of light anhydrous silicic acid were used, and 28.52 mg of microcrystalline cellulose and 20 mg of mannitol were further added to the mixture when preparing the non-granulated mixture containing rosuvastatin; and 8 mg of magnesium stearate was used as a lubricating agent.

[128] **Comparative Example 1 - A double-layer tablet of** amlodipine and rosuvastatin

[129] 111 mg of microcrystalline cellulose, 55.9 mg of pregelatinized starch, 4 mg of sodium starch glycolate, and 8.1 mg of mannitol were mixed with 13.889 mg of amlodipine besylate. The mixture was dried and then granulated.

[130] Further, 59.6 mg of microcrystalline cellulose, 89.5 mg of mannitol, 74.5 mg of Di-Tab, 21.8 mg of LH-11, and 15 mg of crospovidone were mixed with 20.8 mg of rosuvastatin calcium. The mixture was dried and then granulated.

[131] The amlodipine-containing granule as the first layer and the rosuvastatin-containing granule as the second layer were further mixed with 2.2 mg and 3.8 mg of magnesium stearate, respectively, and compressed into a double-layer tablet.

[132]

[133] The ingredients and the contents thereof in the double-layer tablet of Comparative Example 1 are shown in Table 4 below.

[134]

[135] [Table 4]

			Comparative Example 1
First granule(1st layer)	Active ingredient	Amlodipine	13.889
	Excipient	Microcrystalline cellulose	111
	Excipient	Pregelatinized starch	55.9
	Disintegrant	Sodium starch glycolate	4
	Excipient	Mannitol	8.1
	Lubricant	Calcium stearate	2.2
Second granule(2nd layer)	Active ingredient	Rosuvastatin	20.8
	Excipient	Microcrystalline cellulose	59.6
	Excipient	Mannitol	89.5
	Excipient	Di-Tab	74.5
	Excipient	LH-11	21.8
	Disintegrant	Crospovidone	15
Final mixture	Lubricant	Magnesium stearate	3.8
Total weight			480.089

[136] (Unit: mg)

[137] **Comparative Example 2 - A single-layer tablet containing no sugar alcohol**

[138] A tablet was prepared by the same method as in Example 1, except that 190 mg of microcrystalline cellulose was used and mannitol was not used.

[139]

[140] **Comparative Example 3**

[141] A tablet was prepared by the same method as in Example 1, except that 110 mg of microcrystalline cellulose and 80 mg of mannitol were used.

[142]

[143] **Comparative Examples 4 to 6**

[144] Tablets were prepared by the same method as in Example 1, except that each of sodium bicarbonate, calcium hydrogen phosphate, and precipitated calcium carbonate was used instead of magnesium carbonate.

[145]

[146] The ingredients and the contents thereof in the single-layer tablets of Examples 1 to 4, and Comparative Examples 2 to 6 are shown in Table 5 below.

[147]

[148] [Table 5]

			Comp Ex 2	Ex 1	Ex 2	Ex 3	Ex 4	Comp Ex 3	Comp Ex 4	Comp Ex 5	Comp Ex 6
1st granule	Active ingredient	Amlodipine	13.889	13.889	13.889	13.889	13.889	13.889	13.889	13.889	13.889
	Excipient	Microcrystalline cellulose	190	170	190	140	140	110	170	170	170
	Excipient	Mannitol		20	20	50	60	80	20	20	20
	Excipient	Pregelatinized starch	76.8	76.8	56.8	76.8	76.8	76.8	76.8	76.8	76.8
	Disintegrant	Sodium starch glycolate	20	20	20	20	20	20	20	20	20
Binding	Binding agent	Povidone	10	10	10	10	10	10	10	10	10
	Binding solution	Ethanol	45	45	45	45	45	45	45	45	45
Further mixture	Active ingredient	Rosuvastatin	20.8	20.8	20.8	20.8	20.8	20.8	20.8	20.8	20.8
	Excipient	Microcrystalline cellulose					28.52				
	Excipient	Mannitol					20				
	Disintegrant	Crospovidone	20	20	20	20	20	20	20	20	20
	Stabilizer	Magnesium carbonate	8	8	8	8	8	8			
		Sodium bicarbonate							8		
		Calcium hydrogen phosphate								8	
		Precipitated calcium carbonate									8
	Excipient	Light anhydrous silicic acid	2	2	2	2	4	2	2	2	2
Final mixture	Lubricant	Magnesium stearate	4	4	4	4	8	4	4	4	4
Total weight			365.489	365.489	365.489	365.489	426.009	365.489	365.489	365.489	365.489

[149] (Unit: mg)

[150]

[151] **Comparative Example 7 - A formulation analogous to** Caduet tablet

[152] A tablet was prepared by substituting atorvastatin in the formulation disclosed in a patent directed to the Caduet tablet of Pfizer (Korean Laid-open Patent Publication

No. 10-2006-0054495 A) with rosuvastatin. Contrary to Example 1, a rosuvastatin-containing granule and a a non-granulated mixture containing amlodipine were prepared, and the amlodipine mixture was then mixed with the rosuvastatin-containing granule. The specific contents thereof are shown in Table 6 below.

[153]

[154] [Table 6]

			Comparative Example 7
1st granule	Active ingredient	Rosuvastatin	20.8
	Stabilizer	Calcium carbonate	66.30
	Disintegrant	Croscarmellose Sodium	6.00
	Excipient	Microcrystalline cellulose	27.70
	Excipient	Starch, pregelatinized, 1500 con	30.00
	Excipient	Polysorbate 80	0.80
Mixture	Binding agent	Hydroxypropyl cellulose	0.40
	Binding solution	Distilled water	120.00
Further mixture	Active ingredient	Amlodipine besylate	13.889
	Excipient	Microcrystalline cellulose	20.83
	Disintegrant	Sodium croscarmellose	6.00
	Excipient	Silicon dioxide, colloid	1.30
	Lubricant	Magnesium stearate	1.50
Total weight			200

[155] (Unit: mg)

[156] **Comparative Example 8 - A formulation analogous to that of Korean Laid-open Patent Publication No. 10-2009-0048023**

[157] A tablet was prepared by substituting atorvastatin in the formulation disclosed in Example 1 of Korean Laid-open Patent Publication No. 10-2006-0054495 A with rosuvastatin. Contrary to Example 1, a rosuvastatin-containing granule and an amlodipine -containing granule were separately prepared and were then mixed. The specific contents thereof are shown in Table 7 below.

[158]

[159] [Table 7]

			Comparative Example 8
1st granule	Active ingredient	Rosuvastatin	20.8
	Stabilizer	Magnesium carbonate	40
	Excipient	Microcrystalline cellulose	20
	Excipient	Mannitol	30
	Disintegrant	Sodium croscarmellose	8
	Binding agent	Hydroxypropyl cellulose	6
	Excipient	Polysorbate 80	0.8
2nd granule	Active ingredient	Amlodipine besylate	13.889
	Excipient	Mannitol	32
	Excipient	Microcrystalline cellulose	17.54
	Disintegrant	Sodium croscarmellose	4
	Binding solution	Hydroxypropyl cellulose	2
Mixture	Disintegrant	Sodium croscarmellose	8
	Excipient	Silicon dioxide	2
Final mixture	Lubricant	Magnesium stearate	2
Total weight			200

[160] (Unit: mg)

[161] **Experimental Example 2. Comparative dissolution test for single-layer tablet and double-layer tablet**

[162] A dissolution test was performed for the active ingredients of the combination formulation of Comparative Example 1 prepared in a double-layer tablet by granulating each of amlodipine and rosuvastatin and those of the tablet of Example 4 prepared in a single-layer tablet by further mixing the non-granulated mixture containing rosuvastatin with the amlodipine-containing granule. The dissolution test was performed according to a dissolution test of the Korean Pharmacopoeia, and the details thereof are as set forth below:

[163]

[164] Test method: Dissolution Test 2 of the Korean Pharmacopoeia (paddle method)

[165] Rotation speed: 50 rpm

[166] Dissolution medium: 500 mL of a test solution having pH 6.8

[167]

[168] The amlodipine and rosuvastatin showed the dissolution rates shown in Tables 8 and

9 below, respectively (see Figs. 2a and 2b).

[169]

[170] [Table 8]

	0 min	5 min	10 min	15 min	30 min	45 min	60 min
Example 1	0	11.3	42.9	51.5	60.2	65.1	68.2
SD	0	4.3	8.6	10.1	9.7	9.2	8.7
Example 4	0	74.9	86.3	89.2	89.6	90.1	90.6
SD	0	1.0	0.7	0.6	0.5	0.7	0.4

[171] (Unit: wt%)

[172]

[173] [Table 9]

	0 min	5 min	10 min	15 min	30 min	45 min	60 min
Example 1	0	57.9	76.1	80.8	83.3	84.9	86.2
SD	0	3.6	3.5	3.3	3.6	3.7	3.4
Example 4	0	82.9	89.2	90.8	91.5	91.9	91.8
SD	0	3.3	1.3	0.8	0.6	0.3	0.6

[174] (Unit: wt%)

[175] As shown above, the combination formulation of Comparative Example 1 prepared in a double-layer tablet by granulating each of amlodipine and rosuvastatin showed a lower dissolution rated compared to the tablet of Example 4 prepared in a single-layer tablet by mixing the rosuvastatin mixed solution with the amlodipine-containing granule. This confirms that by changing the tablet from a double-layer tablet to a single-layer tablet, a more excellent dissolution rate can be obtained.

[176]

[177] **Experimental Example 3. Comparative dissolution test according to the presence of sugar alcohol**

[178] A dissolution test was performed for the active ingredients of the tablet of Comparative Example 2, which does not include a sugar alcohol in the amlodipine-containing granule, and those of the tablet of Example 3, which includes a sugar alcohol in the granule. The test was performed in the same manner as in Experimental Example 2.

[179]

[180] Amlodipine and rosuvastatin showed the dissolution rates shown in Table 10 and 11 below, respectively (see Figs. 3a and 3b).

[181]

[182] [Table 10]

	0 min	5 min	10 min	15 min	30 min	45 min	60 min
Comp Ex 2	0	54.7	69.1	72.7	72.5	74.2	74.3
SD	0	0.5	1.5	0.9	1.4	0.7	1.3
Ex 3	0	42.8	82.0	93.9	96.5	96.5	96.7
SD	0	6.9	3.9	1.9	1.3	0.9	1.5

[183] (Unit: wt%)

[184]

[185] [Table 11]

	0 min	5 min	10 min	15 min	30 min	45 min	60 min
Comp Ex 2	0	77.0	82.4	83.5	84.8	85.7	86.4
SD	0	1.1	0.7	1.0	1.2	1.0	1.2
Ex 3	0	57.8	87.9	94.3	95.1	95.5	95.7
SD	0	10.5	3.6	2.0	1.7	1.5	1.6

[186] (Unit: wt%)

[187] As shown above, the tablet of Comparative Example 2, which does not include a sugar alcohol in the amlodipine-containing granule, showed a lower dissolution rate compared to that of Example 3, which includes a sugar alcohol. This confirms that a better dissolution rate can be obtained by containing a sugar alcohol.

[188]

[189] **Experimental Example 4. Comparative stability tests according to the presence of sugar alcohol**

[190] The tablet of Comparative Example 2, which does not include a sugar alcohol in the amlodipine-containing granule, and the tablets of Examples 1 and 3, which include a sugar alcohol, were coated and were put in a vial packaged in aluminum. The vial was then stored under an extreme condition to examine chemical stability of their active ingredients; specifically, the vial was stored under the extreme conditions of 60°C and 80% relative humidity for 2 weeks, and the active ingredient contents (%) were measured via HPLC.

[191]

[192] The condition used for HPLC analysis is as follows:

[193] Detector: Ultraviolet Spectrophotometer (wavelengths: rosuvastatin - 242 nm, amlodipine - 237 nm)

[194] Column: Thermo, Hypersil Gold, C18 (4.6 X 250 mm, 5.0 μm)

[195] Mobile phase: Mobile phase A - triethylamine buffer

[196] Mobile phase B - acetonitrile

[197] Mobile phase C - methanol

[198] Flow rate: 1.0 mL/min

[199]

[200] The changes in the amlodipine and rosuvastatin contents observed for 2 weeks are shown in Table 12 below.

[201]

[202] [Table 12]

Extreme condition/Al-Al (60°C, 80%)		Amlodipine	SD	Rosuvastatin	SD
Initial	Comparative Example 2	99.5	0.1	100.6	0.7
	Example 1	99.5	0.3	99.1	0.8
	Example 3	100.7	0.3	100.3	0.2
1 week	Comparative Example 2	96.4	0.1	100.2	1
	Example 1	98.0	0.2	98.9	1.1
	Example 3	97.9	0.3	100.1	0.6
2 weeks	Comparative Example 2	95.5	0.3	97.8	0.6
	Example 1	98.2	0.2	98.7	0.4
	Example 3	96.1	0.1	100.1	0.5

[203] (Unit: wt%)

[204] In the case of the tablet of Comparative Example 2, which does not contain a sugar alcohol in the amlodipine-containing granule, the contents of the active ingredients decreased compared to those of Examples 1 and 3, which include mannitol. Based on the above result and the result of Experimental Example 1, it was confirmed that the formulation of the present invention has excellent stability as it contains a sugar alcohol in the amlodipine-containing granule and thus minimizes interactions between amlodipine and rosuvastatin.

[205] **Experimental Example 5. Comparative stability test according to sugar alcohol content**

[206] Chemical stability of the active ingredients was tested for the tablet of Comparative

Example 3, which includes 21.9 wt% of a sugar alcohol in the amlodipine-containing granule, and that of Example 1, which includes 5.5 wt% of a sugar alcohol. The stability test was performed in the same manner as in Experimental Example 3.

[207]

[208] The changes in the amlodipine and rosuvastatin contents observed for 2 weeks are shown in Table 13 below.

[209]

[210] [Table 13]

Extreme condition/ Al-Al (60°C, 80%)		Amlodipine	Reduction	SD	Rosuvastatin	Reduction	SD
Initial	Example 1	99.5	-	0.3	99.1	-	0.8
	Comparative Example 3	101.7	-	0.5	100.8	-	0.5
1 week	Example 1	98.0	1.5	0.2	98.9	0.2	1.1
	Comparative Example 3	97.0	4.7	0.4	99.4	1.4	0.3
2 weeks	Example 1	98.2	1.3	0.2	98.7	0.4	0.4
	Comparative Example 3	95.8	5.9	0.2	98.4	2.4	0.5

[211] In the case of the tablet of Comparative Example 3 which includes 21.9 wt% of a sugar alcohol in the amlodipine-containing granule, the amlodipine content was 5.9 wt% at 2 weeks, and the rosuvastatin content was 2.4 wt%, indicating a significant decrease. Meanwhile, Example 1 showed almost no change in the amlodipine and rosuvastatin contents.

[212] This result reveals an appropriate amount of sugar alcohol that would lead to the excellent stability of the present invention.

[213]

[214] **Experimental Example 6. Stability test of a formulation prepared by substituting** atorvastatin in Caduet tablet with rosuvastatin

[215]

[216] Stability was tested for the formulation of Comparative Example 7 prepared by substituting atorvastatin in the Caduet tablet, known as a combination formulation of am-

lodipine and atorvastatin, with rosuvastatin. The same test as in Experimental Example 4 was performed under the extreme condition for 1 week, and the observed changes in the amlodipine and rosuvastatin contents are shown in Table 14 below.

[217]

[218] [Table 14]

Extreme condition/Al-Al (60°C, 80%)		Amlodipine	Reduction	Rosuvastatin	Reduction
Initial	Example 1	99.5	-	99.1	-
	Comp Ex 7	100.1	-	100.5	-
1 week	Example 1	98.0	1.5	98.9	0.2
	Comp Ex 7	92.8	7.3	96.0	4.5

[219] As shown above, in Comparative Example 7, the amlodipine and the rosuvastatin showed a reduction of 7.3 wt% and 4.5 wt%, respectively, at 1 week. In Example 1, which was performed at the same time, the amlodipine and the rosuvastatin showed a reduction of 1.5 wt% and 0.2 wt%, respectively. In comparison of the two results, Comparative Example 7 showed remarkably low stability.

[220] This result shows that a combination formulation having excellent stability cannot be obtained simply by substituting atorvastatin with rosuvastatin in a conventionally known combination formulation of atorvastatin and amlodipine.

[221]

[222] **Experimental Example 7. Stability test for a formulation prepared by substituting** atorvastatin in the formulation of Korean Laid-open Patent Publication No. 10-2009-0048023 with rosuvastatin

[223]

[224] Stability was tested for the formulation of Comparative Example 3 prepared by substituting atorvastatin with rosuvastatin in the combination formulation of amlodipine and atorvastatin disclosed in Example 1 of Korean Laid-open Patent Publication No. 10-2009-0048023.

[225] The stability was measured with respect to the amount of impurities formed under an extreme condition. Specifically, the formulations of Example 1 and Comparative Example 8 were put in a vial packaged in aluminum, and each packaged vial was stored at an extreme condition (60°C, 80% relative humidity) for 2 weeks to measure the amount of the impurities that are formed.

[226]

[227] The contents of the formed impurities were measured according to the HPLC analysis method described in Experimental Example 4. The impurity contents of the

amlodipine and the rosuvastatin formed after 2 weeks are shown in Table 15 below.

[228]

[229] [Table 15]

Extreme condition/Al-Al (60°C, 80%)		Amlodipine Impurity	Difference	Rosuvastatin Impurity	Difference
Initial	Example 1	0.02	-	0.09	-
	Comp Ex 8	0.07	-	0.07	-
1 week	Example 1	0.56	0.54	0.58	0.49
	Comp Ex 8	0.75	0.68	0.45	0.38
2 weeks	Example 1	0.8	0.72	0.8	0.71
	Comp Ex 8	2.24	2.17	1.6	1.53

[230] As shown above, in Comparative Example 8, 2.17 mg and 1.53 mg of the amlodipine and rosuvastatin impurities were formed, respectively, at 2 week. In Example 1, which was performed at the same time, 0.72 mg and 0.71 mg of the amlodipine and rosuvastatin impurities were formed, respectively. In comparison of the two results, Comparative Example 8 showed remarkably low stability.

[231] This result shows that a combination formulation having excellent stability cannot be obtained simply by substituting atorvastatin with rosuvastatin in a conventionally known combination formulation of atorvastatin and amlodipine.

[232]

[233] **Experimental Example 8. Comparative stability tests according to the type of stabilizer**

[234]

[235] Stability was tested for the formulations of Example 1 and Comparative Examples 4 to 6. Stability was examined by measuring the amount of the impurities formed disclosed in Experimental Example 7.

[236]

[237] The amounts of each of the amlodipine and rosuvastatin impurities formed after 2 weeks are shown in Table 16 below.

[238]

[239] [Table 16]

Extreme conditions/Al-Al (60°C, 80%)		Amlodipine Impurity	Difference Δ	Rosuvastatin Impurity	Difference Δ
Initial	Example 1	0.02	-	0.09	-
	Comp Ex 4	0.03		0.03	
	Comp Ex 5	0.03		0.03	
	Comp Ex 6	0.03		0.03	
1 week	Example 1	0.56	0.54	0.58	0.49
	Comp Ex 4	0.50	0.47	0.50	0.41
	Comp Ex 5	1.52	1.49	1.56	1.53
	Comp Ex 6	1.06	1.03	1.03	1.00
2 weeks	Example 1	0.8	0.72	0.8	0.71
	Comp Ex 4	1.37	1.34	1.35	1.32
	Comp Ex 5	2.70	2.67	2.72	2.69
	Comp Ex 6	2.85	2.82	2.70	2.67

[240] As shown above, in Comparative Examples 4 to 6, 1.34 mg, 2.67 mg, and 2.82 mg of the amlodipine impurities were formed and 1.32 mg, 2.69 mg, and 2.67 mg of the rosuvastatin impurities were formed at 2 weeks. In comparison with 0.72 mg of the amlodipine impurities and 0.71 mg of the rosuvastatin impurities formed in Example 1, which was performed at the same time, it was confirmed that the stability measured in Comparative Examples 4 to 6 was remarkably low.

[241] From such results, it can be understood that high stability is exhibited when magnesium carbonate is used as a stabilizer.

[242]

[243] Those of ordinary skill in the art will recognize that the present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. In this regard, the described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the present invention is therefore indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within the scope of the present invention.

[244]

Claims

[Claim 1] An oral combination formulation comprising:
a first composition comprising amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol; and
a second composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof, and a stabilizer.

[Claim 2] The oral combination formulation of claim 1, wherein the sugar alcohol is comprised in an amount of 5 wt% to 15 wt% of the total weight of the combination formulation.

[Claim 3] The oral combination formulation of claim 2, wherein the sugar alcohol is selected from the group consisting of mannitol, sorbitol, xylitol, erythritol, and inositol.

[Claim 4] The oral combination formulation of any of claims 1 to 3, wherein the disintegrant is sodium starch glycolate.

[Claim 5] The oral combination formulation of any of claims 1 to 4, wherein the stabilizer is selected from the group consisting of magnesium carbonate, magnesium oxide, magnesium hydroxide, sodium hydrogen carbonate, calcium hydrogen phosphate, precipitated calcium carbonate, and a mixture thereof.

[Claim 6] The oral combination formulation of claim 5, wherein the stabilizer is magnesium carbonate.

[Claim 7] The oral combination formulation of any one of claims 1 to 6, wherein the stabilizer is comprised in an amount of 1 wt% to 5 wt% of the total weight of the formulation.

[Claim 8] The oral combination formulation of any one of claims 1 to 7, wherein the first composition is in the form of a granule, and wherein the oral combination formulation is a single-layer tablet in which a mixture of the second composition and the granule are compressed.

[Claim 9] The oral combination formulation of any of claims 1 to 8, further comprising a film layer on an outer surface of the formulation.

[Claim 10] The oral combination formulation of claim 9, wherein the film layer is formed with a water-soluble substance selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), cellulose acetate phthalate (CAP), ethyl cellulose (EC), methyl cellulose (MC), polymethacrylate, a polyvinyl alcohol-polyethylene glycol graft copolymer, polyvinyl alcohol (PVA), and a mixture thereof.

[Claim 11] A method for preparing an oral combination formulation, comprising:
granulating a first composition comprising amlodipine or a pharmaceutically acceptable salt thereof, a disintegrant, and a sugar alcohol (first step);
preparing a second composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof, and a stabilizer (second step); and
mixing the second composition with the granulated first composition prepared in the first step followed by compressing the mixture (third step).

[Claim 12] The method of claim 11, wherein the sugar alcohol is comprised in an amount of 5 wt% to 15 wt% of the total weight of the oral combination formulation.

[Claim 13] The method of claim 11 or 12, wherein the sugar alcohol is selected from the group consisting of mannitol, sorbitol, xylitol, erythritol, and inositol.

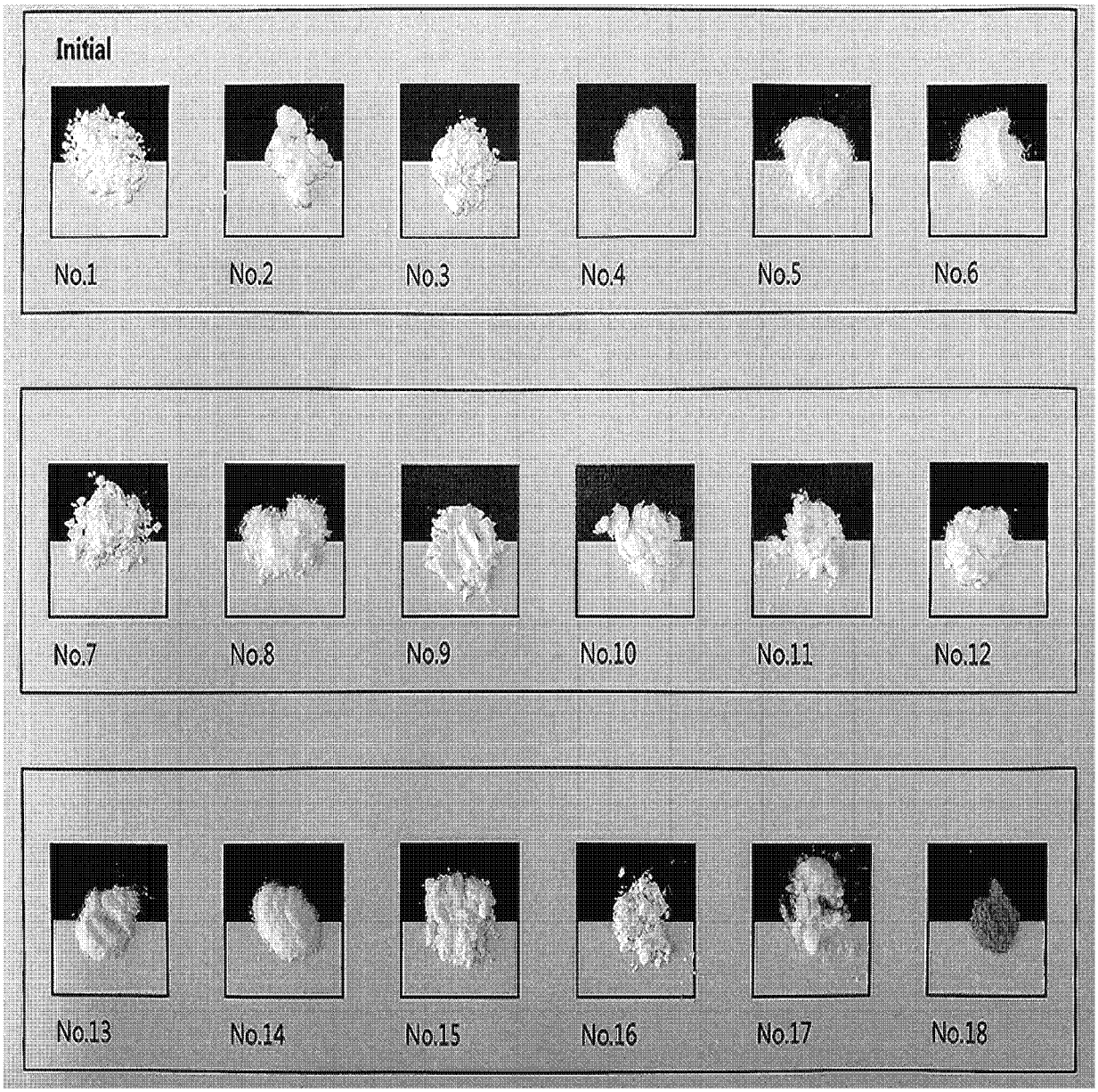
[Claim 14] The method of any of claims 11 to 13, wherein the stabilizer is selected from the group consisting of magnesium carbonate, magnesium oxide, magnesium hydroxide, sodium bicarbonate, calcium hydrogen phosphate, precipitated calcium carbonate, and a mixture thereof.

[Claim 15] The method of claim 14, wherein the stabilizer is magnesium carbonate.

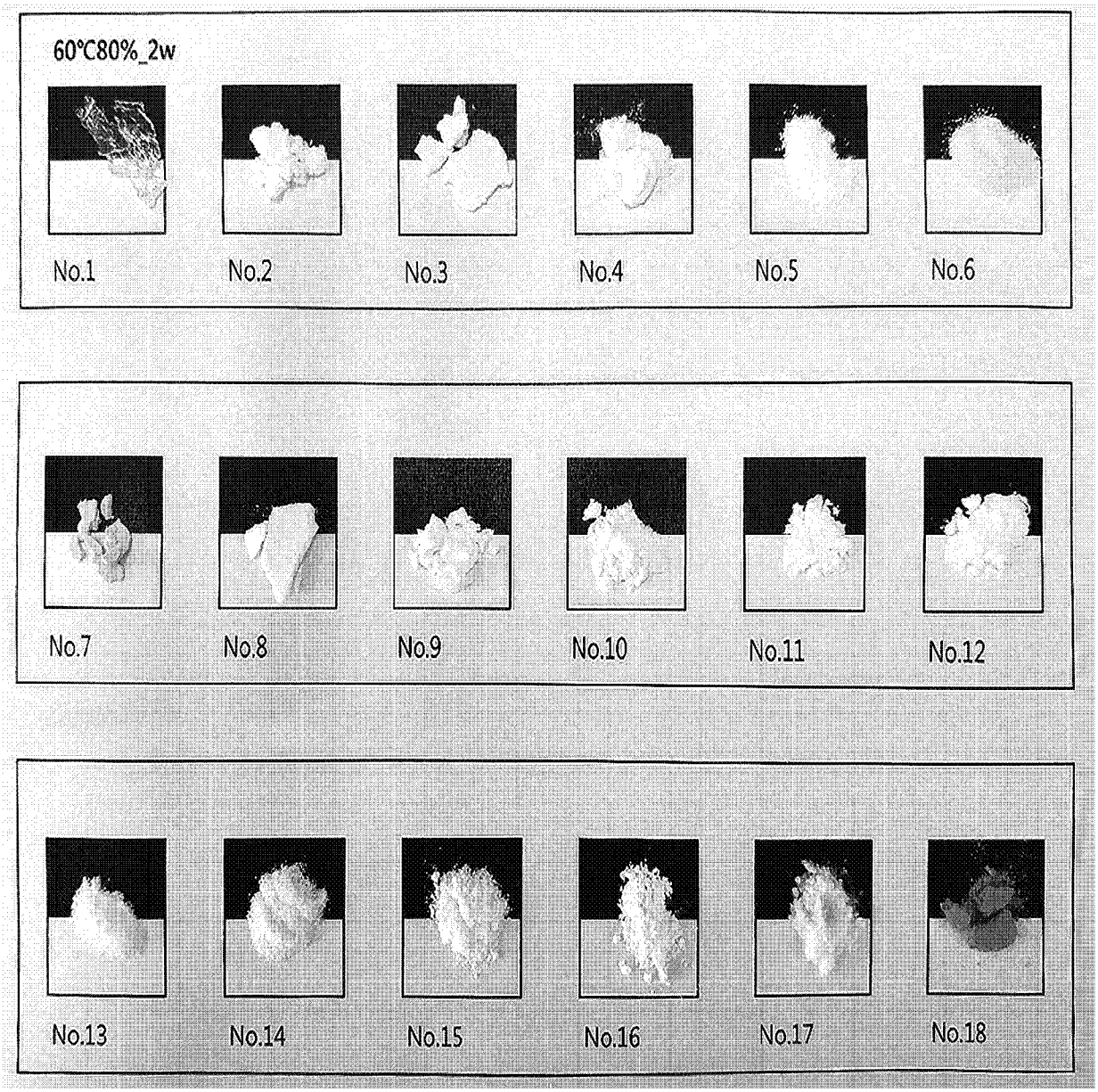
[Claim 16] The method of any of claims 11 to 15, wherein the stabilizer is comprised in an amount of 1 wt% to 5 wt% of the total weight of the formulation.

[Claim 17] The method of any of claims 11 to 16, wherein the third step comprises further adding a lubricant into the mixture before compression.

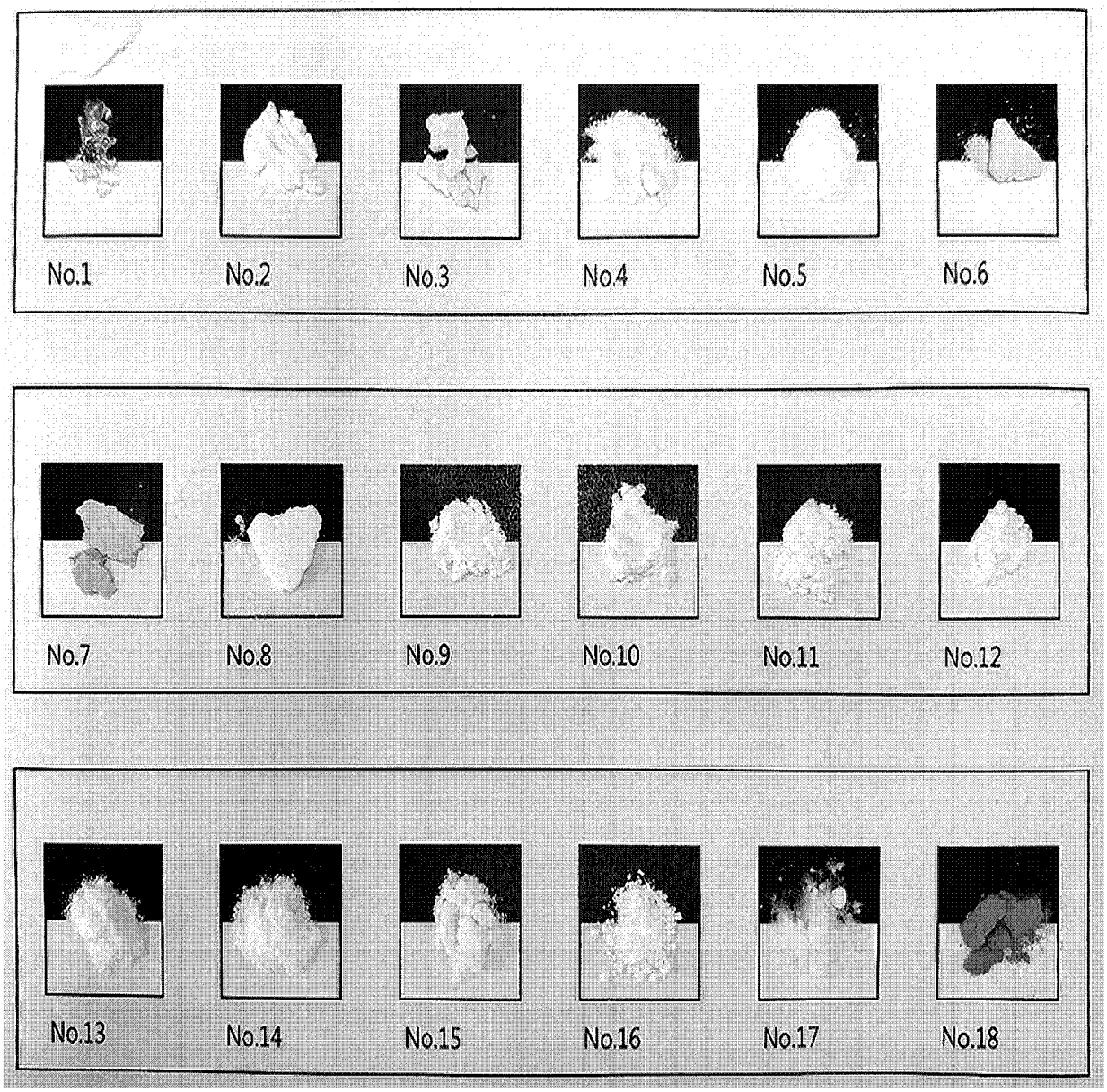
[Fig. 1a]


Initial
No.1
No.2
No.3
No.4
No.5
No.6
No.7
No.8
No.9
No.10
No.11
No.12
No.13
No.14
No.15
No.16
No.17
No.18

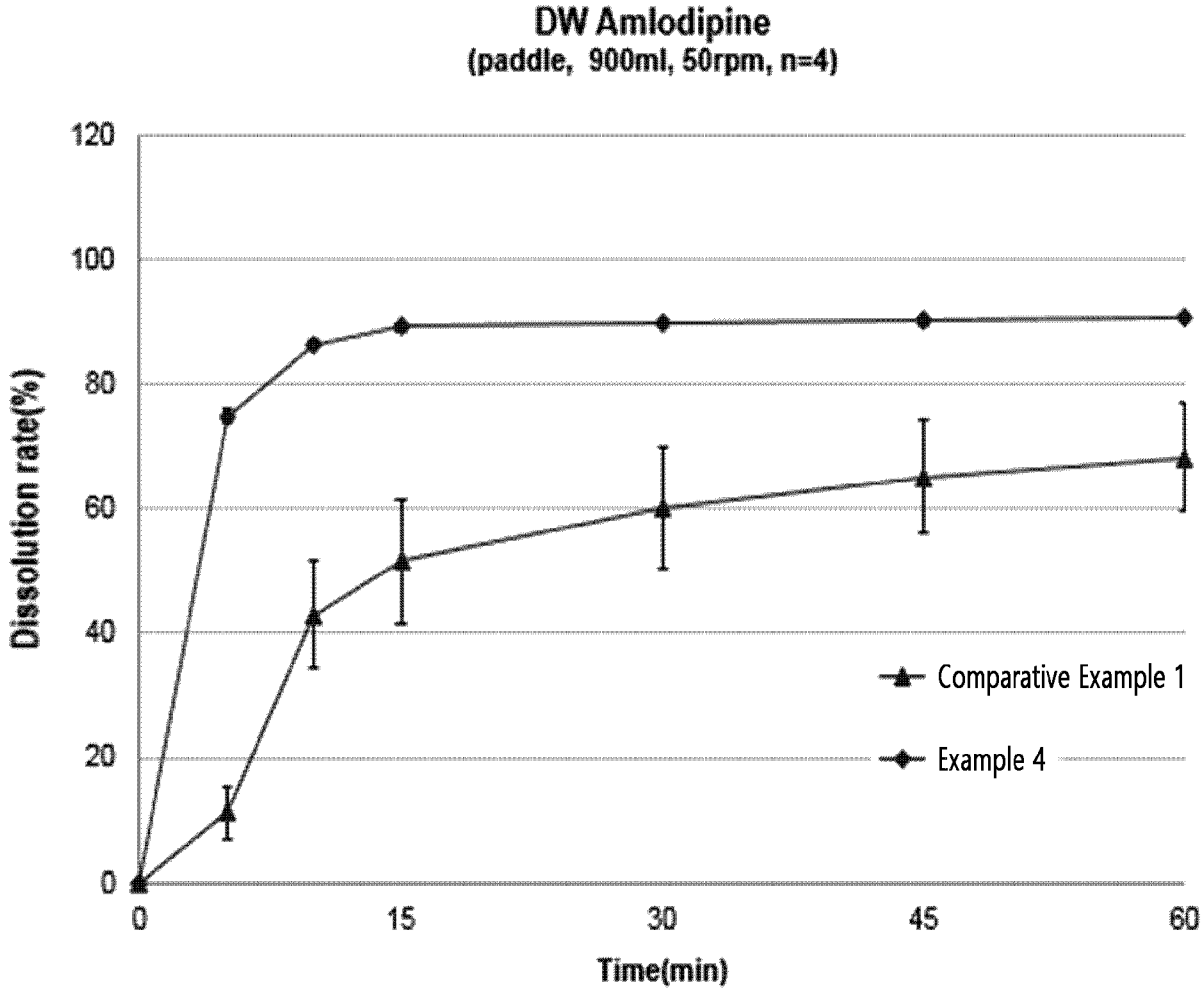
[Fig. 1b]


60℃80%_2w
No.1
No.2
No.3
No.4
No.5
No.6
No.7
No.8
No.9
No.10
No.11
No.12
No.13
No.14
No.15
No.16
No.17
No.18

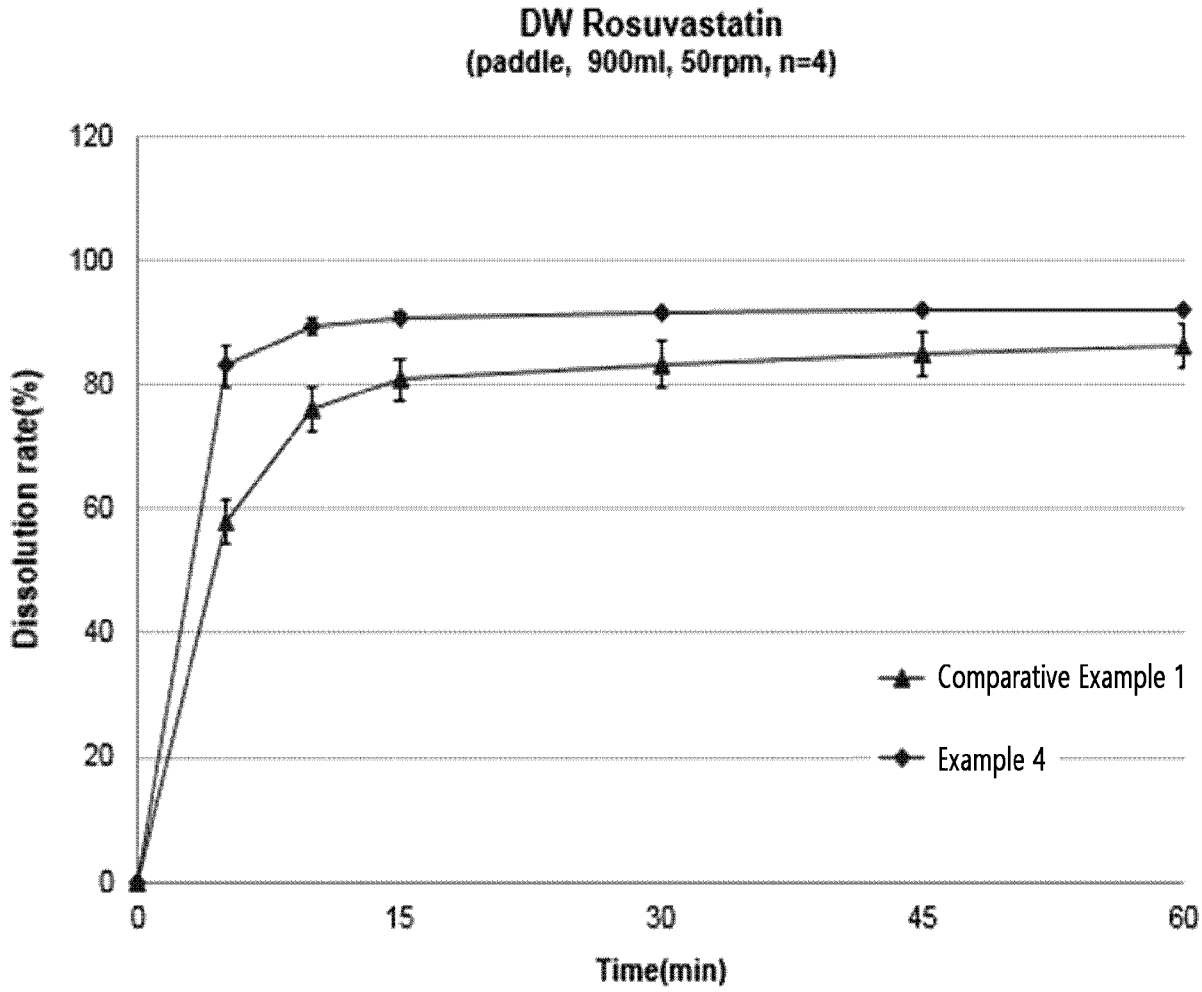
[Fig. 1c]


No.1
No.2
No.3
No.4
No.5
No.6
No.7
No.8
No.9
No.10
No.11
No.12
No.13
No.14
No.15
No.16
No.17
No.18

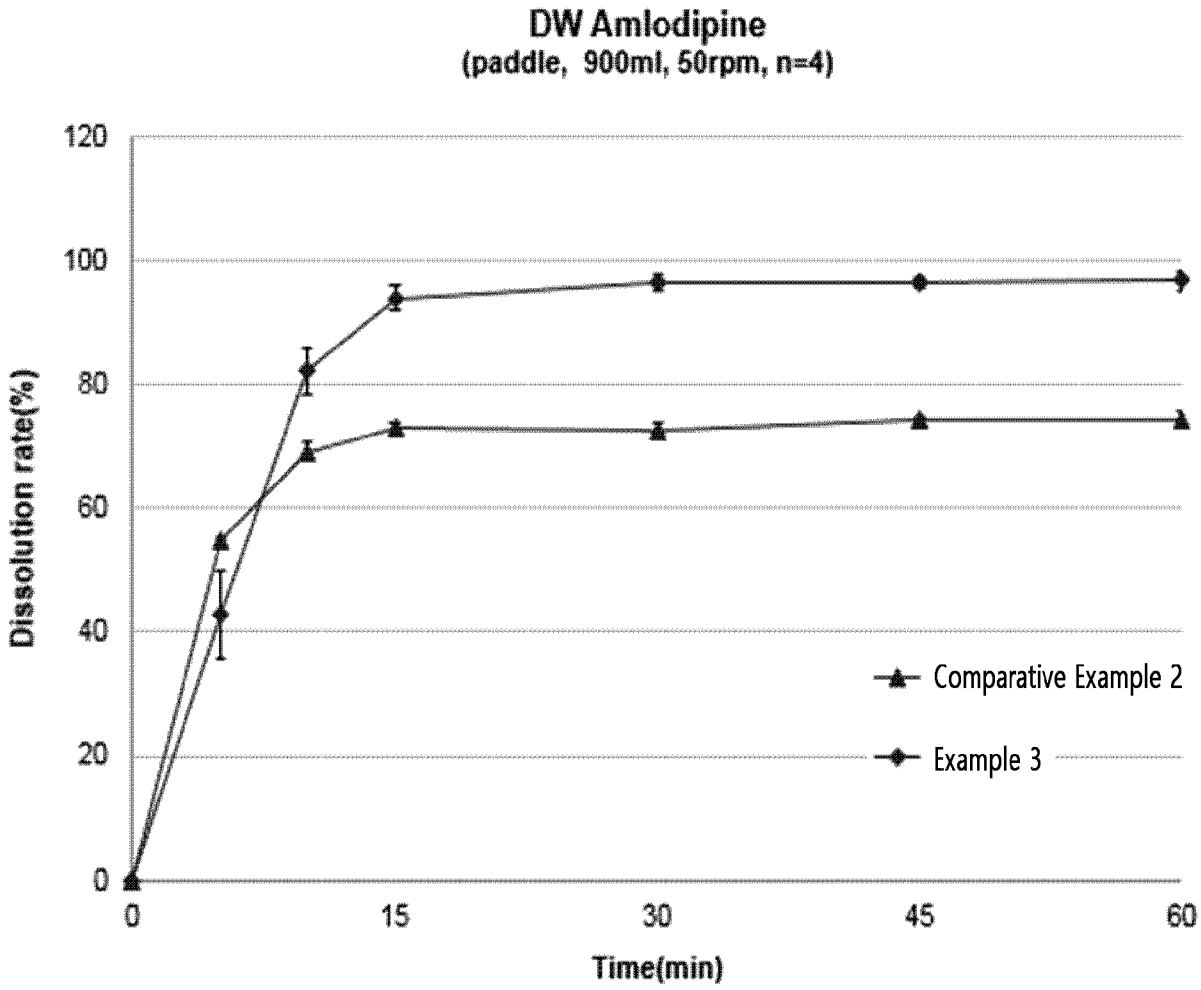
[Fig. 2a]


DW Amlodipine
(paddle, 900ml, 50rpm, n=4)
Dissolution rate(%)
120
100
80
60
40
20
0
0
15
30
45
60
Time(min)
Comparative Example 1
Example 4

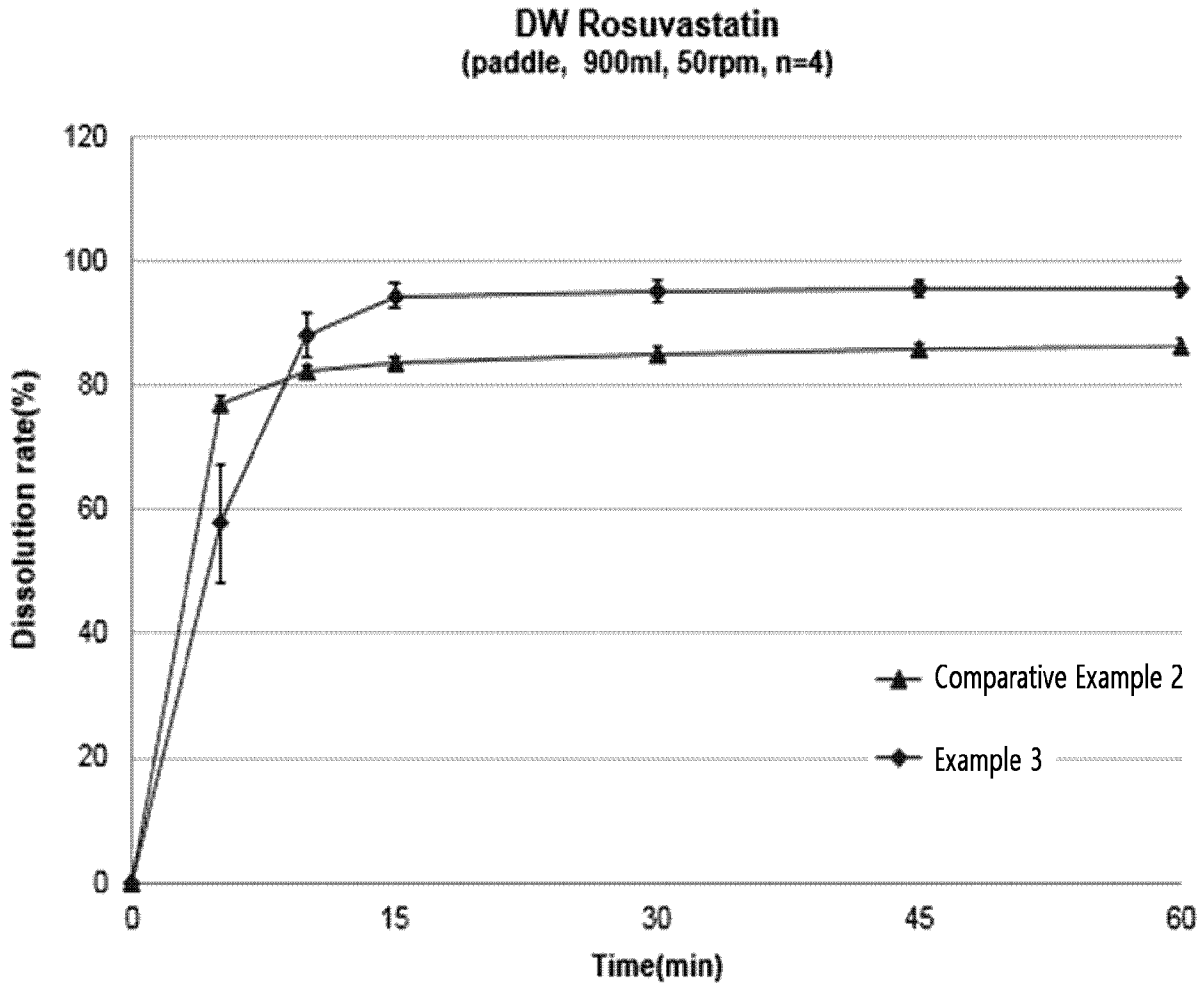
[Fig. 2b]


DW Rosuvastatin
(paddle, 900ml, 50rpm, n=4)
Dissolution rate(%)
120
100
80
60
40
20
0
0
15
30
45
60
Time(min)
Comparative Example 1
Example 4

[Fig. 3a]


DW Amlodipine
(paddle, 900ml, 50rpm, n=4)
Dissolution rate(%)
120
100
80
60
40
20
0
0
15
30
45
60
Time(min)
Comparative Example 2
Example 3

[Fig. 3b]


DW Rosuvastatin
(paddle, 900ml, 50rpm, n=4)
Dissolution rate(%)
120
100
80
60
40
20
0
0
15
30
45
60
Time(min)
Comparative Example 2
Example 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2018/004815

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/20(2006.01)i, A61K 9/28(2006.01)i, A61K 31/4422(2006.01)i, A61K 31/505(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 9/20; A61K 9/36; A61K 31/505; A61K 31/41; A61K 47/38; A61K 9/48; A61K 31/47; A61K 31/44; A61P 3/00; A61K 9/24; A61K 9/28; A61K 31/4422

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: oral combination formulation, first composition, amlodipine, disintegrant, sugar alcohol, second composition, rosuvastatin, stabilizer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 10-2017-0007695 A (CJ HEALTHCARE CORPORATION) 19 January 2017 See paragraphs [0026], [0048], [0063], [0066]; example 1; claim 1; tables 1, 13.	1-4,11-13
A	KR 10-2015-0067777 A (HANMI PHARM. CO., LTD.) 19 June 2015 See paragraph [0027]; claim 1.	1-4,11-13
A	US 2011-0130416 A1 (ZHAO, ZHIQUAN) 02 June 2011 See example 3; claim 1.	1-4,11-13
A	US 2015-0098992 A1 (HANMI PHARM. CO., LTD.) 09 April 2015 See the whole document.	1-4,11-13
A	WO 2006-070248 A1 (RANBAXY LABORATORIES LIMITED) 06 July 2006 See the whole document.	1-4,11-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 2018 (28.08.2018)	**28 August 2018 (28.08.2018)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
HEO, Joo Hyung
Telephone No. +82-42-481-8150

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2018/004815

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 6,10,15
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 6, 10 and 15 are not clear because they refer to multiple dependent claims which do not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 5,7-9,14,16,17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2018/004815

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 10-2017-0007695 A	19/01/2017	EP 3320903 A1	16/05/2018
		KR 10-1875112 B1	09/07/2018
		MX 2018000084 A	22/03/2018
		WO 2017-007287 A1	12/01/2017
KR 10-2015-0067777 A	19/06/2015	CA 2929862 A1	04/06/2015
		CL 2016001298 A1	06/01/2017
		CN 105792813 A	20/07/2016
		EP 3073998 A1	05/10/2016
		EP 3073998 A4	31/05/2017
		JP 2017-501126 A	12/01/2017
		MX 2016006415 A	19/07/2016
		PH 12016500833 A1	13/06/2016
		TW 201609198 A	16/03/2016
		US 2017-0027871 A1	02/02/2017
		US 9833413 B2	05/12/2017
		WO 2015-080433 A1	04/06/2015
US 2011-0130416 A1	02/06/2011	CN 101632672 A	27/01/2010
		CN 101632672 B	12/01/2011
		EP 2329820 A1	08/06/2011
		EP 2329820 A4	02/11/2011
		EP 2329820 B1	08/04/2015
		HK 1158057 A1	23/10/2015
		JP 2011-528670 A	24/11/2011
		JP 5504263 B2	28/05/2014
		KR 10-1303841 B1	05/09/2013
		KR 10-2011-0033940 A	01/04/2011
		US 8722697 B2	13/05/2014
		WO 2010-009619 A1	28/01/2010
US 2015-0098992 A1	09/04/2015	CN 104220050 A	17/12/2014
		EP 2836207 A1	18/02/2015
		EP 2836207 A4	19/08/2015
		HK 1204959 A1	11/12/2015
		JP 2015-517998 A	25/06/2015
		JP 6129295 B2	17/05/2017
		KR 10-1378973 B1	28/03/2014
		KR 10-2013-0115864 A	22/10/2013
		MX 2014012144 A	05/12/2014
		PE 20352014 A1	24/12/2014
		PH 12014502271 A1	10/12/2014
		RU 2014-145557 A	10/06/2016
		TW 201345568 A	16/11/2013
		TW I544936 B	11/08/2016
		WO 2013-154390 A1	17/10/2013
		ZA 201408285 B	28/09/2016
WO 2006-070248 A1	06/07/2006	EP 1833466 A1	19/09/2007

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2018/004815

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2008-0305158 A1	11/12/2008