Description

Title of Invention: COMPLEX FORMULATION COMPRISING LERCANIDIPINE HYDROCHLORIDE AND VALSARTAN AND METHOD FOR THE PREPARATION THEREOF

Technical Field

[1] The present invention relates to a pharmaceutical composition comprising lercanidipine hydrochloride and valsartan as active components and method for the preparation thereof.

[2]

Background Art

[3] Hypertension is a most common cardiovascular disease. Persistent hypertension damages blood vessels in the kidneys, heart and brain, which increases the occurrence of renal failure, coronary-artery diseases, heart failure and stroke. Hypertension is divided into two types—i.e., essential or primary hypertension and secondary hypertension. Essential hypertension, the cause of which is unknown, occurs without a specific underlying disease. Most (95%) of hypertensive patients, especially those over the age of 40, belong to this type. Even though the cause of essential hypertension cannot be found since there is no underlying disease, problematic issues may be genetics, dietary habit of eating salty food, obesity, old age, stress, heavy smoking and drinking. Secondary hypertension comes from a specific causative disease. About 5% of hypertensive patients, relatively young people, belong to this type. Secondary hypertension is caused by nephritis, endocrine disruption and toxemia during pregnancy, etc., and blood pressure goes down with treatment of the causative diseases.

[4] Antihypertensive treatment is not for the causative disease and depends on blocking the normal physiological mechanism of blood pressure regulation. Antihypertensive treatment is performed on subclinical patients, and it does not affect directly the inconvenience of the patients but prevents the symptom and death from occurring in the future by lowering blood pressure.

[5] Antihypertensive agents are generally classified according to their regulation site and mechanism of action into three categories: diuretics, sympatholytic agents and vasodilators, which are subdivided according to their active sites. Diuretics, which act to increase the amount of urine to excrete water and salts from the body, lower blood pressure by reducing water and salts in the body. A sympathetic nerve acts to increase the frequency and intensity of the heartbeat and to constrict blood vessels. Sympatholytic agents suppress the action of the sympathetic nerve to lower blood pressure. There are three types of sympatholytic agents: α-blocker suppressing the sympathetic

nerves acting to constrict blood vessels; β-blocker suppressing the sympathetic nerves acting on the heartbeat; and central sympatholytics suppressing the sympathetic nerve acting on the brain. Vasodilators lower blood pressure by dilating blood vessels. Various vasodilators are known such as ACE inhibitors which inhibit the synthesis of angiotensin II, a vasoconstrictor, and angiotensin II receptor blockers which inhibit the action of angiotensin II. A calcium channel blocker, which inhibits the inflow of calcium into cells to lower blood pressure, is also a vasodilator since high concentration of intracellular calcium results in vasoconstriction to raise blood pressure.

[6] In case a sufficient antihypertensive effect cannot be obtained due to severe hypertension, the dose of the antihypertensive agent is generally increased. However, an excessively increased dose may cause adverse effects. In this case, the combined use of medicines having different mechanisms of action, rather than the increased use of a medicine, can minimize adverse effects while obtaining sufficient effect.

[7] The advantages of a combined use of medicines are as follows:

[8] Firstly, the antihypertensive effect increases synergistically by the concurrent action of medicines having different mechanisms of action. Furthermore, a homeostasis compensatory action of a medicine is suppressed by another medicine, so that more effective antihypertensive action is obtained. For example, reflexive tachycardia and retention of salt and water, which are caused by the use of vasodilators, may be adjusted by the use of β-blockers and diuretics, respectively, so that the antihypertensive effect increases.

[9] Secondly, sufficient antihypertensive effect can be obtained by the combined use of medicines, even at low doses, so that a dose-dependent adverse effect may be reduced. In addition, adverse effects caused by the pharmacological action can be blocked and reduced.

[10] Thirdly, hypertension is nearly asymptomatic and must be regulated for life, so patient compliance with the medicine determines the outcome of the treatment. In this regard, the combined use of effective medicines having low adverse effect can improve the quality of life and increase patient compliance.

[11] Recently, complex formulations containing at least two medicines in one pill are commercially available. They are cheap and easy to take. Use of the complex formulations can increase patient compliance and prevent or delay damage of the target organ caused by hypertension.

[12]

Disclosure of Invention

Technical Problem

[13] Considering the current situation, the present inventors have conducted intensive

research to develop a new pharmaceutical composition by the combined use of at least two antihypertensive agents having different mechanisms of action for increasing the hypertensive effect synergistically, reducing adverse effects and improving patient compliance. As a result of such efforts, the present inventors have found that such purposes can be achieved by the combined use of lercanidipine hydrochloride and valsartan, especially by the specific complex formulation comprising them, and thus completed the present invention.

[14] Accordingly, the object of the present invention is to provide a pharmaceutical composition for the prevention and treatment of cardiovascular diseases which comprises as active components lercanidipine hydrochloride and valsartan having different mechanisms of action.

[15] Especially, the present invention provides a complex formulation comprising lercanidipine hydrochloride and valsartan in a separated form.

[16] Another object of the present invention is to provide a method for preparation of the complex formulation for the prevention and treatment of cardiovascular diseases which comprises as active components lercanidipine hydrochloride and valsartan.

[17]

Solution to Problem

[18] Lercanidipine hydrochloride is a dihydropyridine calcium antagonist and, like other calcium antagonists, inhibits calcium inflow into arterial smooth muscle to relax peripheral arterioles and reduce the blood pressure. Lercanidipine does not cause negative myocardial contraction but results in slight reflex tachycardia. Lercanidipine has a strong affinity to the dihydropyridine subunit of L-type calcium channel and competitively antagonizes thereto. Calcium channel antagonists are considered safe and are proven to be effective on all types of hypertension. Lercanidipine is a new kind of dihydropyridine calcium antagonist and has proven to have a strong and long-acting hypotensive effect in pre-clinical trials. Lercanidipine is favorably tolerable in a dose of 30 mg or lower and reduces blood pressure in a dose-dependent manner. Calcium antagonists are considered renal-protective due to their antihypertensive effect. This potential is proven in the renal failure and nephrotoxicity induced by chemotherapy, contrast media, cyclosporins or aminoglycoside antibiotics. In addition, calcium antagonists have a renal-protective effect on the kidneys of donors in kidney transplants. Lercanidipine is typically used in a dose of 10 to 20 mg once a day and the maximum dose is about 30 mg per day. Lercanidipine is rapidly absorbed after oral administration and reaches its maximum plasma concentration in 1.5 to 3 hours after administration, which is subjected to extensive first-pass metabolism. Absorption of lercanidipine is highly dependent on food intake and increases remarkably (3- to 4-fold)

by simultaneous intake of food. An oral tablet containing 10 or 20 mg of lercanidipine is commercially available under the trade name "Zanidip® tablet." Lercanidipine, sold by Recordati S.p.A (Milan, Italy), can be manufactured according to the method disclosed in EP 0153016 and US 4705797 of which the whole context is quoted herein. Furthermore, US-A1-2003/0180355 discloses a method of treating hypertensive patients which comprises administering a complex formulation containing lercanidipine and enalapril as active components.

[19] Valsartan ((S)-N-valeryl-N-{[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-methyl}-valine), an angiotensin II receptor antagonist, reduces blood pressure by vasodilation. Angiotensin II has a vasoconstriction and sodium retention effect. Valsartan is commercially available (Tareg® tablet) and also manufactured by a known method. For example, the preparation of valsartan is disclosed in US 5399578 of which the whole context is quoted herein. Valsartan is used for the purpose of the present invention in its isolated form or a suitable salt form. In the U.S., valsartan is used in an initial dose of 80 to 160 mg qd and the maximum dose is 320 mg qd. In Korea, valsartan is prescribed for patients with cardiac insufficiency or postmyocardial infarction syndrome in a dose of 160 mg b.i.d. However, if the blood pressure of the patient does not reach the desired value with the dose of 160 mg b.i.d, valsartan is replaced with other drugs. Valsartan is typically used in a dose of about 40 to 320 mg, preferably about 80 to 320 mg, most preferably about 80 to 160 mg in a tablet.

[20] The present inventors have conducted various experiments of lercanidipine hydrochloride and valsartan having the above-mentioned mechanisms of action and maximum daily doses to confirm that the combined use of these drugs has a synergistic effect on the prevention and treatment of cardiovascular diseases compared with that of single use, reduces the adverse effects caused by single use, and improves patient compliance. Accordingly, the pharmaceutical composition comprising lercanidipine hydrochloride and valsartan can be used effectively for the prevention and treatment of cardiovascular diseases. Examples of the cardiovascular diseases include angina pectoris, hypertension, arteriospasm, cardiac arrhythmia, cardiac hypertrophy, cerebral infarction, congestive heart failure, myocardial infarction, etc., but not limited thereto.

[21] However, a complex formulation comprising lercanidipine hydrochloride and valsartan prepared by simply mixing the two drugs may have some problems caused by the difference between their inherent physical properties.

[22] The first problem resides in the difference of their pKa value. Lercanidipine hydrochloride has a pKa value of about 6.83 and the pKa of valsartan is about 3.92. Accordingly, lercanidipine hydrochloride has an increased solubility at pH 4.0 or lower, while valsartan has an increased solubility at pH 4.0 or higher. Such a pKa difference between the two drugs affects the solubility of each drug.

[23] The second problem is gelling of valsartan. Valsartan begins to gel at pH 4.0 or lower due to its low solubility and dissolves very slowly. Such delayed dissolution causes delayed absorption of valsartan in the small intestine. In addition, gelling of valsartan can delay the dissolution of lercanidipine hydrochloride. This trouble can adversely affect the absorption of lercanidipine hydrochloride which is rapidly disintegrated and absorbed in the gastro-intestinal tract. Accordingly, gelling of valsartan at low pH in a complex formulation must be prevented.

[24] The third problem is low dissolution of the complex formulation. In the preliminary experiment in which the complex formulation was prepared by wet-granulation of the mixture of lercanidipine hydrochloride and valsartan, the complex formulation showed low dissolution due to the interaction between the two components. Such low dissolution seriously affects the absorption and bioavailability of the two components. Decreased bioavailability is also expected to decrease the efficacy of the complex formulation. Therefore, an improved manufacturing process is required to prevent the problem.

[25] The fourth problem is the difference of disintegration time between the commercially available single drug formulations, which makes it difficult to maintain the inherent dissolution pattern of each drug by using conventional formulation methods.

[26] In order to overcome the above-mentioned problems, the present inventors have contrived a complex formulation comprising lercanidipine hydrochloride and valsartan that physically separates the two components to minimize the contact area and chance of making contact. According to the present invention, the complex formulation can provide superior dissolution rates of both lercanidipine hydrochloride and valsartan.

[27]

Advantageous Effects of Invention

[28] The pharmaceutical composition comprising lercanidipine hydrochloride and valsartan according to the present invention has a superior effect on the prevention and treatment of cardiovascular diseases and their complex diseases, and reduces adverse effects of each component due to the synergistic combination of the two components having different mechanisms of action. In addition, the present invention provides a complex formulation comprising lercanidipine hydrochloride and valsartan in a separated form so that the problems caused by simple mixture of lercanidipine hydrochloride and valsartan may be overcome and the dissolution rates of both components may increase.

[29]

Brief Description of Drawings

[30] Figure 1 is a graph showing the results of a dissolution test of lercanidipine for the

complex formulations of Examples 1 to 4 compared with that of Comparative Example 1.

[31] Figure 2 is a graph showing the results of a dissolution test of lercanidipine for the complex formulations of Examples 5 to 8 compared with that of Comparative Example 1.

[32] Figure 3 is a graph showing the results of a dissolution test of lercanidipine for the complex formulations of Examples 1 to 4 compared with those of Examples 9 to 12.

[33] Figure 4 is a graph showing the results of a dissolution test of lercanidipine for the complex formulation of Example 1 compared with that of Example 13.

[34] Figure 5 is a graph showing the results of a dissolution test of lercanidipine for the complex formulation of Example 1 compared with those for the formulations of Comparative Examples 2 and 3.

[35] Figure 6 is a graph showing the change (%) of systolic blood pressure (BP) with the passage of time after the combined administration of lercanidipine hydrochloride 2 mg/kg (Z) and valsartan 16 mg/kg (V) according to Test Example 8 ($^{***}p<0.001$ (*vs.* control), $^{\#\#}p<0.01$ (*vs.* valsartan)).

[36] Figure 7 is a graph showing the change (%) of mean BP with the passage of time after the combined administration of lercanidipine hydrochloride 2 mg/kg (Z) and valsartan 16 mg/kg (V) according to Test Example 8 ($^{***}p<0.001$ (*vs.* control), $^{\#\#}p<0.01$ (*vs.* valsartan)).

[37] Figure 8 is a graph showing the change (%) of diastolic BP with the passage of time after the combined administration of lercanidipine hydrochloride 2 mg/kg (Z) and valsartan 16 mg/kg (V) according to Test Example 8 ($^{***}p<0.001$ (*vs.* control), $^{\#\#}p<0.01$ (*vs.* valsartan)).

[38] Figure 9 is a graph showing the change (%) of heart rate with the passage of time after the combined administration of lercanidipine hydrochloride 2 mg/kg (Z) and valsartan 16 mg/kg (V) according to Test Example 8 ($^{***}p<0.001$ (*vs.* control), $^{\#\#}p<0.01$ (*vs.* valsartan)).

[39]

Mode for the Invention

[40] As a preferred embodiment of the present invention, a complex formulation comprising lercanidipine hydrochloride and valsartan in a separated form is prepared by separate granulations of lercanidipine hydrochloride and valsartan.

[41] A method for the preparation of the complex formulation of the present invention comprises the steps of:

[42] (a) wet-granulating a mixture of lercanidipine hydrochloride and a pharmaceutically acceptable excipient and drying the granules;

[43] (b) wet-granulating a mixture of valsartan and a pharmaceutically acceptable excipient and drying the granules; and

[44] (c) mixing the dried granules prepared in steps (a) and (b).

[45] For example, the complex formulation of the present invention is made by preparing lercanidipine hydrochloride granules and valsartan granules separately, mixing the two granules and then pressing the mixtures into a tablet. The complex formulations of Examples 1 to 4 prepared according to the above process show improved dissolution of lercanidipine hydrochloride without affecting the dissolution of valsartan compared with the complex formulation of Comparative Example 1 which is prepared by wet-granulation of an unseparated mixture of lercanidipine hydrochloride and valsartan (see Figure 1).

[46] Another specified embodiment of the present invention provides a bilayer tablet of the complex formulation comprising lercanidipine hydrochloride and valsartan. As described in the following Examples 5 to 8, the bilayer tablet can be prepared by pressing the valsartan granules into a first tablet layer and then pressing the lercanidipine hydrochloride granules into a second tablet layer by using a bilayer tablet press. The bilayer tablet of the present invention shows superior dissolution of lercanidipine hydrochloride like the complex formulations of Examples 1 to 4 (see Figure 2).

[47] In yet another embodiment of the present invention, the bilayer tablet can comprise a separation layer between the lercanidipine hydrochloride layer and the valsartan layer so that a trilayer tablet may be obtained. The separation layer may consist of, for example, microcrystalline cellulose.

[48] A still further embodiment of the present invention provides a complex formulation comprising lercanidipine hydrochloride and valsartan in a separated form, wherein a tablet consisting of valsartan is coated with lercanidipine hydrochloride. Such a formulation can be prepared by dissolving or dispersing lercanidipine hydrochloride and an excipient in a coating solvent to make a coating composition and coating a tablet consisting of valsartan with the coating composition. Examples of the excipient include polyvinylpyrrolidone, and ethanol can be used as the coating solvent. If necessary, another separation layer may be placed between the valsartan tablet and the lercanidipine hydrochloride coating.

[49] The complex formulation of the present invention may comprise 4 to 32 parts by weight, preferably 4 to 16 parts by weight of valsartan per 1 part by weight of lercanidipine hydrochloride. If the amount of valsartan is less than 4 parts by weight per 1 part by weight of lercanidipine hydrochloride, the desired effect cannot be obtained. On the other hand, a formulation containing more than 32 parts by weight of valsartan per 1 part by weight of lercanidipine hydrochloride is not permitted.

[50] The composition of the present invention for the prevention and treatment of cardio-vascular diseases can comprise a pharmaceutically acceptable carrier or excipient in each of the lercanidipine hydrochloride granules and the valsartan granules. Examples of the pharmaceutically acceptable carrier or excipient include microcrystalline cellulose, lactose, low-substituted hydroxypropyl cellulose, disintegrating agents (e.g., croscarmellose sodium, crospovidone and sodium starch glycolate) and granulation binders (e.g., polyvinylpyrrolidone and hydroxypropyl cellulose). In addition, a lubricant such as colloidal silicon dioxide, hydrous silicon dioxide, magnesium stearate, sodium stearyl fumarate (Pruv®), glyceryl behenate (Compritol 888®), calcium stearate, stearic acid and talc may be included.

[51] In the present invention, the lercanidipine hydrochloride granules may comprise 4 to 10 parts by weight of a pharmaceutically acceptable excipient per 1 part by weight of lercanidipine hydrochloride; and the valsartan granules may comprise 1 to 2 parts by weight of a pharmaceutically acceptable excipient per 1 part by weight of valsartan. Such a ratio applies to all the formulations of the present invention including the separated granules. If the formulation has a ratio out of the above range, it may create tablets that are too small or too large, and its dissolution may be delayed or increased.

[52] Especially, the ratio of the disintegrating agent used in the present invention is noted. Conventional super-disintegrating agents, such as croscarmellose sodium, crospovidone and sodium starch glycolate, are recommended to be used in an amount of 0.5 to 8.0 wt% based on the total amount of excipients. In the present invention, however, 5 to 20 wt% overdose of the super-disintegrating agents is used to prevent gelling and show inherent dissolution behavior. Conventional formulations coated by using overdose of a super-disintegrating agent have a problem that coating is difficult due to rapid moisturizing and the coated layer cracks during storage. However, it is confirmed that the present invention does not have such troubles.

[53] Examples of coating agents available in film coating layer include conventional ones, such as hydroxypropylmethyl cellulose, Opadry® series, Eudragit® series, but not limited thereto.

[54] The present invention is explained in more detail by the following examples. However, these examples seek to illustrate the present invention only, and the scope of the present invention is not limited thereto.

[55]

[56] **Examples 1 to 4: Preparation of separated granules**

[57] Table 1

[Table 1]

Component	Example 1	Example 2	Example 3	Example 4
Lercanidipine hydrochloride granules				
Lercanidipine hydrochloride	10.0 mg	20.0 mg	10.0 mg	20 mg
Polyvinyl pyrrolidone	2.5 mg	2.5 mg	2.5 mg	2.5 mg
Microcrystalline cellulose	20.0 mg	20.0 mg	20.0 mg	20.0 mg
Lactose	26.5 mg	26.5 mg	26.5 mg	26.5 mg
Croscarmellose sodium	20.0 mg	20.0 mg	20.0 mg	20.0 mg
Magnesium stearate	1.0 mg	1.0 mg	1.0 mg	1.0 mg
Sub-total	80.0 mg	90.0 mg	80.0 mg	90.0 mg
Valsartan granules				
Valsartan	80.0 mg	80.0 mg	160.0 mg	160.0 mg
Low-substituted hydroxypropyl cellulose	25.0 mg	25.0 mg	50.0 mg	50.0 mg
Crospovidone	15.0 mg	15.0 mg	30.0 mg	30.0 mg
Microcrystalline cellulose	22.5 mg	22.5 mg	45.0 mg	45.0 mg
Croscarmellose sodium	5.0 mg	5.0 mg	10.0 mg	10.0 mg
Hydrous silicon dioxide	5.0 mg	5.0 mg	10.0 mg	10.0 mg
Hydroxypropyl cellulose	6.0 mg	6.0 mg	12.0 mg	12.0 mg
Magnesium stearate	1.5 mg	1.5 mg	3.0 mg	3.0 mg
Sub-total	160.0 mg	160.0 mg	320.0 mg	320.0 mg
Total	240.0 mg	250.0 mg	400.0 mg	410.0 mg

[58]

[59] Lercanidipine hydrochloride granules and valsartan granules having the above compositions were wet-granulated using distilled water, dried and milled to 25 mesh. The two granules were mixed and compressed into complex tablets which were then film coated. Opadry® II sold by Colorcon as PVPs was used as the film coating material, and the film coating was carried out in the same manner in all the following examples

and comparative examples. The mixture was combined for a time of 5 minutes or more so that the super-integrating agent which was added in the process of wet-granulation was sufficiently wetted. Such a sufficient combination time increases porosity of the granules, which results in the facilitation of disintegration time to prevent gelation. In the following examples, all processes of wet-granulation were carried out as above.

[60]

[61] **Examples 5 to 8: Preparation of complex bilayer tablets**

[62] Table 2

[Table 2]

Component	Example 5	Example 6	Example 7	Example 8
Lercanidipine hydrochloride granules				
Lercanidipine hydrochloride	10.0 mg	20.0 mg	10.0 mg	20 mg
Polyvinylpyrrolidone	2.5 mg	2.5 mg	2.5 mg	2.5 mg
Microcrystalline cellulose	20.0 mg	20.0 mg	20.0 mg	20.0 mg
Lactose	26.5 mg	26.5 mg	26.5 mg	26.5 mg
Croscarmellose sodium	20.0 mg	20.0 mg	20.0 mg	20.0 mg
Magnesium stearate	1.0 mg	1.0 mg	1.0 mg	1.0 mg
Sub-total	80.0 mg	90.0 mg	80.0 mg	90.0 mg
Valsartan granules				
Valsartan	80.0 mg	80.0 mg	160.0 mg	160.0 mg
Low-substituted hydroxypropyl cellulose	25.0 mg	25.0 mg	50.0 mg	50.0 mg
Crospovidone	15.0 mg	15.0 mg	30.0 mg	30.0 mg
Microcrystalline cellulose	22.5 mg	22.5 mg	45.0 mg	45.0 mg
Croscarmellose sodium	5.0 mg	5.0 mg	10.0 mg	10.0 mg
Hydrous silicon dioxide	5.0 mg	5.0 mg	10.0 mg	10.0 mg
Hydroxypropyl cellulose	6.0 mg	6.0 mg	12.0 mg	12.0 mg
Magnesium stearate	1.5 mg	1.5 mg	3.0 mg	3.0 mg
Sub-total	160.0 mg	160.0 mg	320.0 mg	320.0 mg
Total	240.0 mg	250.0 mg	400.0 mg	410.0 mg

[63]

[64] Lercanidipine hydrochloride granules and valsartan granules having the above compositions were wet-granulated using distilled water, dried and milled to 25 mesh. The two groups of granules were compressed into bilayer solid forms and thus the bilayer solid forms were film coated.

[65]

[66] **Examples 9 to 12: Preparation of complex trilayer tablets**

[67] Table 3

[Table 3]

Component	Example 9	Example 10	Example 11	Example 12
Lercanidipine hydrochloride granules				
Lercanidipine hydrochloride	10.0 mg	20.0 mg	10.0 mg	20 mg
Polyvinylpyrrolidone	2.5 mg	2.5 mg	2.5 mg	2.5 mg
Microcrystalline cellulose	20.0 mg	20.0 mg	20.0 mg	20.0 mg
Lactose	26.5 mg	26.5 mg	26.5 mg	26.5 mg
Croscarmellose sodium	20.0 mg	20.0 mg	20.0 mg	20.0 mg
Magnesium stearate	1.0 mg	1.0 mg	1.0 mg	1.0 mg
Sub-total	80.0 mg	90.0 mg	80.0 mg	90.0 mg
Separation layer				
Microcrystalline cellulose	30.0 mg	30.0 mg	60.0 mg	60.0 mg
Valsartan granules				
Valsartan	80.0 mg	80.0 mg	160.0 mg	160.0 mg
Low-substituted hydroxypropyl cellulose	25.0 mg	25.0 mg	50.0 mg	50.0 mg
Crospovidone	15.0 mg	15.0 mg	30.0 mg	30.0 mg
Microcrystalline cellulose	22.5 mg	22.5 mg	45.0 mg	45.0 mg
Croscarmellose sodium	5.0 mg	5.0 mg	10.0 mg	10.0 mg
Hydrous silicon dioxide	5.0 mg	5.0 mg	10.0 mg	10.0 mg
Hydroxypropyl cellulose	6.0 mg	6.0 mg	12.0 mg	12.0 mg
Magnesium stearate	1.5 mg	1.5 mg	3.0 mg	3.0 mg
Sub-total	160.0 mg	160.0 mg	320.0 mg	320.0 mg
Total	270.0 mg	280.0 mg	460.0 mg	470.0 mg

[68]

[69] Lercanidipine hydrochloride granules and valsartan granules having the above compositions were wet-granulated using distilled water, dried and milled to 25 mesh. The valsartan granules were added to make the first tablet part, the separation layer was added to make the second tablet part, and the lercanidipine hydrochloride granules were added to make the third tablet part. The complex trilayer tablet was obtained and film coated.

[70]

[71] **Example 13: Preparation of tablets coated with lercanidipine hydrochloride layer**

[72] Table 4

[Table 4]

Valsartan granules	
Valsartan	80.0 mg
Low-substituted hydroxypropyl cellulose	25.0 mg
Crospovidone	15.0 mg
Microcrystalline cellulose	22.5 mg
Croscarmellose sodium	5.0 mg
Hydrous silicon dioxide	5.0 mg
Hydroxypropyl cellulose	6.0 mg
Magnesium stearate	1.5 mg
Sub-total	160.0 mg
Coating layer	
Lercanidipine hydrochloride	10.0 mg
Polyvinylpyrrolidone	10.0 mg
Sub-total	20.0 mg
Total	180.0 mg

[73]

[74] The valsartan granules having the above composition were pressed into tablets which were then introduced into a coating machine. Lercanidipine hydrochloride and polyvinylpyrrolidone were dissolved and suspended in ethanol to prepare the coating

layer. The valsartan tablet was coated by spraying the coating layer thereon, and then film coated.

[75]

[76] **Comparative Example 1: Preparation of tablets from the mixture of un-separated lercanidipine hydrochloride and valsartan**

[77] Table 5

[Table 5]

Component	Amount
Lercanidipine hydrochloride	10.0 mg
Valsartan	80.0 mg
Polyvinylpyrrolidone	2.5 mg
Microcrystalline cellulose	42.5 mg
Lactose	26.5 mg
Croscarmellose sodium	25.0 mg
Low-substituted hydroxypropyl cellulose	25.0 mg
Crospovidone	15.0 mg
Hydrous silicon dioxide	5.0 mg
Hydroxypropyl cellulose	6.0 mg
Magnesium stearate	2.5 mg
Total	240.0 mg

[78]

[79] The same amounts of lercanidipine hydrochloride, valsartan and excipients as Example 1 were mixed altogether, wet-granulated and then pressed into tablets. The tablets thus obtained were film coated.

[80]

[81] **Comparative Example 2: Tablets obtained from simple mixture of commercially available granules**

[82] Table 6

[Table 6]

Lercanidipine hydrochloride granules	
Lercanidipine hydrochloride	10.0 mg
Polyvinylpyrrolidone	4.5 mg
Microcrystalline cellulose	39.0 mg
Lactose	30.0 mg
Sodium starch glycolate	15.5 mg
Magnesium stearate	1.0 mg
Sub-total	100.0 mg
Valsartan granules	
Valsartan	80.0 mg
Microcrystalline cellulose	54.0 mg
Crospovidone	15.0 mg
Colloidal anhydrous silicic acid	1.5 mg
Magnesium stearate	4.5 mg
Sub-total	155.0 mg
Total	255.0 mg

[83]

[84] Granules having the same compositions as the commercially available lercanidipine hydrochloride (Zanidip® tablet) and valsartan (Tareg® tablet) were prepared, simply mixed and pressed into tablets and then film coated.

[85]

[86] **Comparative Example 3: Commercially available preparation of lercanidipine hydrochloride**

[87] Table 7

[Table 7]

Commercially available preparation of lercanidipine hydrochloride	
Lercanidipine hydrochloride	10.0 mg
Polyvinylpyrrolidone	4.5 mg
Microcrystalline cellulose	39.0 mg
Lactose	30.0 mg
Sodium starch glycolate	15.5 mg
Magnesium stearate	1.0 mg
Opadry OY-S-6497	3.0 mg
Sub-total	103.0 mg

[88]

[89] Tablets were prepared according to the same prescription and process as the commercially available lercanidipine hydrochloride (Zanidip® tablet).

[90]

[91] **Test Example 1: Dissolution test of lercanidipine hydrochloride for preparations according to Examples 1 to 4**

[92] For the complex tablets of Examples 1 to 4 prepared from the separated granules and the complex tablets of Comparative Example 1 prepared from the unseparated mixture, a dissolution test was performed and compared under the following conditions.

[93]

[94] <Conditions for dissolution>

[95] Eluate: pH 1.2 (900 mL)

[96] Instrument: USP Paddle Method, 50 rpm

[97] Temperature: 37℃

[98]

[99] <Conditions for analysis>

[100] Column: Stainless steel column which has an inner diameter of about 4.6 mm and a length of 15 cm and which is filled with octadecylsilylated silica gel of 5 ㎛ for liquid chromatography

[101] Mobile phase: acetonitrile/pH 3.0 sodium perchlorate buffer (60/40)

[102] Flow rate: About 1.0 mL/min

[103] Detector: UV spectrophotometer (Wavelength 240 nm)

[104]

[105] <Result>

[106] As is confirmed by Figure 1, the lercanidipine hydrochloride-valsartan complex tablets of Examples 1 to 4 prepared from the separated granules showed a higher level of dissolution rate at the beginning stage, when compared with the tablets of Comparative Example 1.

[107]

[108] **Test Example 2: Dissolution test of lercanidipine hydrochloride for preparations according to Examples 5 to 8**

[109] For the complex bilayer tablets of Examples 5 to 8 prepared from the separated granules and the wet complex tablet of Comparative Example 1 prepared from the unseparated mixture, a dissolution test was performed and compared under the same conditions as Test Example 1.

[110] As is confirmed by Figure 2, the lercanidipine hydrochloride-valsartan complex tablets of Examples 5 to 8 prepared from the separated granules showed a higher level of dissolution rate, when compared with the tablets of Comparative Example 1.

[111]

[112] **Test Example 3: Dissolution test of lercanidipine hydrochloride for preparations according to Examples 9 to 12**

[113] For the complex trilayer tablets of Examples 9 to 12 prepared from the separated granules and the wet complex tablets of Examples 1 to 4 prepared from the separated granules, adissolution test was performed and compared under the same conditions as Test Example 1.

[114] As is confirmed by Figure 3, the complex trilayer tablets prepared from the separated granules and the wet complex tablets prepared from the separated granules showed similar dissolution rates.

[115]

[116] **Test Example 4: Dissolution test of lercanidipine hydrochloride for preparation according to Example 13**

[117] For the separated coating tablet of Example 13 and the wet complex tablet of Example 1, a dissolution test was performed and compared under the same conditions as Test Example 1.

[118] As is confirmed by Figure 4, the separated coating tablet and the wet complex tablet showed similar dissolution rates.

[119]

[120] **Test Example 5: Comparative dissolution test for preparations according to**

Example 1, and Comparative Examples 2 and 3

[121] For the complex tablet of Example 1 prepared from the separated granules, the tablet of Comparative Example 2 obtained from a simple mixture of commercial granules and the commercial preparation of Comparative Example 3, a dissolution test was performed and compared under the same conditions as Test Example 1.

[122] As is confirmed by Figure 5, the complex tableta according to Example 1 showed the same dissolution pattern of lercanidipine hydrochloride as the commercial preparation of lercanidipine hydrochloride according to Comparative Example 3. On the other hand, the tablet of Comparative Example 2 which was obtained by simply mixing the commercially available lercanidipine hydrochloride granules and valsartan granules and pressing them into tablets showed a very low dissolution of lercanidipine hydrochloride, which seems to be caused by the gelation of valsartan.

[123]

[124] **Test Example 6: Clinical effect by combination therapy of lercanidipine hydrochloride and valsartan**

[125] The following tests were performed to evaluate the efficacy and safety of the combination therapies of lercanidipine hydrochloride and valsartan in comparison with each component administered alone in patients with essential hypertension.

[126] The subjects were 20- to 75-year-old patients suffering from essential hypertension, who showed the blood pressure of 90 mmHg ≤ DBP (diastolic blood pressure) ≤ 109 mmHg when measured in Week 0 after the administration of placebo for 2 weeks. In order to remove the interference effect with the antihypertensive drug previously taken and to improve drug compliance, the subject patients took a placebo in a single blind during the run-in period of 2 weeks right after the drug holiday of 0 ~ 1 week. After the subjects were randomly assigned to a total of four groups consisting of one placebo group, four monotherapy groups and four combination therapy groups in the same probability, they took the drug in a double blind according to the group, measuring point and administration period in the following table. In this case, the commercially available Zanidip® tablet 10 mg was used as lercanidipine hydrochloride, and the commercially available Tareg® tablet 80 mg was used as valsartan.

[127] Table 8

[Table 8]

<table>
<tr><td>Visit 1
(Day -21)</td><td>Visit 2
(Day -14)</td><td colspan="3">Visit 3
(Day 0)</td><td>Visit 4
(Day 28)</td><td>Visit 5
(Day 56)</td></tr>
<tr><td rowspan="10">Screening Period</td><td>Run-in Period (Single-blind Placebo)</td><td colspan="5">Double-blind Treatment</td></tr>
<tr><td rowspan="9">Placebo</td><td colspan="5">Group 1: Placebo</td></tr>
<tr><td colspan="5">Group 2: Lercanidipine hydrochloride (L) 10 mg</td></tr>
<tr><td colspan="5">Group 3: Lercanidipine hydrochloride (L) 20 mg</td></tr>
<tr><td colspan="5">Group 4: Valsartan (V) 80 mg</td></tr>
<tr><td colspan="5">Group 5: Valsartan (V) 160 mg</td></tr>
<tr><td colspan="5">Group 6: Lercanidipine hydrochloride (L) 10 mg + Valsartan (V) 80 mg</td></tr>
<tr><td colspan="5">Group 7: Lercanidipine hydrochloride (L) 10 mg + Valsartan (V) 160 mg</td></tr>
<tr><td colspan="5">Group 8: Lercanidipine hydrochloride (L) 20 mg + Valsartan (V) 80 mg</td></tr>
<tr><td colspan="5">Group 9: Lercanidipine hydrochloride (L) 20 mg + Valsartan (V) 160 mg</td></tr>
</table>

[128]

[129] At each measuring point, the blood pressure of the subject patients was measured according to the blood pressure monitoring guidelines provided by the Korean Society of Hypertension to calculate the changes of DBP and SBP (systolic blood pressure) from the baselines after 8 weeks (values after 8 weeks - baseline). The effects of the combination therapies were compared with that of the monotherapy to evaluate the superiority.

[130] 130 patients satisfying the criteria of 100 mmHg ≤ DBP ≤ 109 mmHg on Visit 3 (Day 0) were tested, and the results are summarized in the following Table 9. It was

demonstrated that the patients taking the combination therapy of lercanidipine hydrochloride 20 mg + valsartan 80 mg showed a statistically significant superiority both in the changes of DBP and SBP in comparison to those taking placebo or monotherapy.

[131] In the following Table 9, "Diff." represents the differences in the blood pressure change of monotherapy in comparison to that of combination therapy (i.e., blood pressure change of monotherapy - blood pressure change of combination therapy), and Two-sided 95% CI is two-sided 95% confidence interval, which means that a significant difference can be recognized when the lower limit of the confidence interval is greater than 0. The terms are used hereinafter as having the same meaning.

[132] Table 9

[Table 9]

Monotherapy	Combination Therapy	DBP		SBP	
		Diff.	Two-sided 95% CI	Diff.	Two-sided 95% CI
Placebo	L20 + V80	10.19	4.84, 15.54	18.92	10.40, 27.43
L20	L20 + V80	6.8	1.83, 11.77	8.67	1.95, 15.39
V80	L20 + V80	5.45	0.61, 10.30	9.69	1.25, 18.13

[133]

[134] Furthermore, on Visit 3 (Day 0), 368 patients who satisfied the criteria of 90 mmHg ≤ DBP ≤ 109 mmHg and whose blood pressures were measured at trough time (22~26 hours after drug administration) on Visit 5 (Day 56) were tested. As a result, it was demonstrated that the patients taking the combination therapy of lercanidipine hydrochloride 10 mg + valsartan 160 mg or lercanidipine hydrochloride 20 mg + valsartan 160 mg showed a statistically significant superiority to those taking placebo or monotherapies both in the changes of DBP and SBP. In the case of the patients taking the combination therapy of lercanidipine hydrochloride 20 mg + valsartan 80 mg, it was demonstrated that they show superiority to those taking placebo or monotherapy of lercanidipine hydrochloride 20 mg only, both in the changes of DBP and SBP (see Tables 10 to 12).

[135] Table 10

[Table 10]

Monotherapy	Combination Therapy	DBP		SBP	
		Diff.	Two-sided 95% CI	Diff.	Two-sided 95% CI
Placebo	L10 + V160	7.72	4.82, 10.62	11.04	5.6, 16.47
L10	L10 + V160	7.08	4.11, 10.05	8.62	3.76, 13.47
V160	L10 + V160	3.45	0.7, 6.2	5.31	0.28, 10.34

[136]

[137] Table 11

[Table 11]

Monotherapy	Combination Therapy	DBP		SBP	
		Diff.	Two-sided 95% CI	Diff.	Two-sided 95% CI
Placebo	L20 + V160	8.07	4.56, 11.58	15.52	9.63, 21.4
L20	L20 + V160	6.34	3.05, 9.64	12.15	7.04, 17.26
V160	L20 + V160	3.79	0.46, 7.13	9.79	4.36, 15.23

[138]

[139] Table 12

[Table 12]

Monotherapy	Combination Therapy	DBP		SBP	
		Diff.	Two-sided 95% CI	Diff.	Two-sided 95% CI
Placebo	L20 + V80	6.4	3.06, 9.74	9.46	3.44, 15.48
L20	L20 + V80	4.67	1.54, 7.81	6.1	0.85, 11.35
V80	L20 + V80	2.09	-1.16, 5.34	2.4	-3.06, 7.86

[140]

[141] **Test Example 7: Clinical effect by combination therapy of lercanidipine hydrochloride and valsartan**

[142] The following test was performed to evaluate the efficacy and safety of the combination therapy of lercanidipine hydrochloride and valsartan in comparison with each component administered alone ton patients with essential hypertension.

[143] The subjects were 20- to 75-year-old patients suffering from essential hypertension, who showed the blood pressure of 95 mmHg ≤ DBP ≤ 114 mmHg when measured in Week 0 after the administration of placebo for 2~4 weeks. In order to remove the interference effect with the antihypertensive drug previously taken and to improve drug compliance, the subject patients took a placebo in a single blind during the run-in period of 2~4 weeks right after the drug holiday of 1 week. After the subjects were randomly assigned to a total of four groups consisting of one placebo group, two monotherapy groups and one combination therapy group in the same probability, they took the drug in a double blind according to the group, measuring point and administration period in the following table. In this case, the commercially available Zanidip ® tablet 10 mg was used as lercanidipine hydrochloride, and the commercially available Tareg® tablet 80 mg was used as valsartan.

[144] Table 13

[Table 13]

<table>
<tr><td>Visit 1 (Day -35~ -21)</td><td>Visit 2 (Day -28 ~ -14)</td><td>Visit 3 (Day 0)</td><td>Visit 4 (Day 28)</td><td>Visit 5 (Day 56)</td></tr>
<tr><td rowspan="5">Screening Period</td><td>Run-in Period (Single-blind Placebo)</td><td colspan="3">Double-blind Treatment</td></tr>
<tr><td rowspan="4">Placebo</td><td colspan="3">Group 1: Placebo</td></tr>
<tr><td colspan="3">Group 2: Lercanidipine hydrochloride (L) 10 mg</td></tr>
<tr><td colspan="3">Group 3: Valsartan (V) 80 mg</td></tr>
<tr><td colspan="3">Group 4: Lercanidipine hydrochloride (L) 10 mg + Valsartan (V) 80 mg</td></tr>
</table>

[145]

[146] At each measuring point, the blood pressure of the subject patients was measured according to the blood pressure monitoring guidelines provided by the Korean Society of Hypertension to calculate the changes of DBP and SBP from the baselines after 8 weeks (values after 8 weeks - baseline). The effect of the combination therapy was compared with that of the monotherapy to evaluate the superiority.

[147] 193 patients satisfying the criteria of 95 mmHg ≤ DBP ≤ 114 mmHg on Visit 3 (Day 0) were tested, and the results are summarized in the following Table 14. It was demonstrated that the patients taking the combination therapy of lercanidipine hydrochloride 10 mg + valsartan 80 mg showed a statistically significant superiority both in the changes of DBP and SBP to those taking the placebo. It was also demonstrated that the patients taking the combination therapy of lercanidipine hydrochloride 10 mg + valsartan 80 mg showed a statistically significant superiority in the change of SBP to those taking the monotherapy of lercanidipine hydrochloride 10 mg.

[148] Table 14

[Table 14]

Monotherapy	Combination Therapy	DBP		SBP	
		Diff.	Two-sided 95% CI	Diff.	Two-sided 95% CI
Placebo	L10 + V80	6.70	3.21, 10.20	13.24	7.66, 18.82
L10	L10 + V80	1.78	-1.44, 5.01	6.54	1.80, 11.29
V80	L10 + V80	1.61	-1.82, 5.05	3.97	-1.42, 9.36

[149]

[150] **Test Example 8: Effect from combination therapy of lercanidipine hydrochloride and valsartan in rats**

[151] Male SHRs (Spontaneous Hypertensive Rats, Orient), 13 weeks old, were acclimated and bred for 1 week while maintaining the temperature range of 22~24℃ and humidity of 50~70% in a 12-hour light-dark cycle. Feed and beverage in standard diet were provided ad libitum.

[152] One day before the drug administration, the blood pressure and heart rate of the test animals were measured using BP-2000 Blood Pressure Analysis System (Visitech). After the measurement, the animals were fasted for about 12 hours, during which beverage was provided ad libitum. The respective test drugs were orally administered to the fasted test animals in a volume of 5 ml/kg. The same volume of medium was orally administered to the negative control group. The test drugs lercanidipine hydrochloride and valsartan were used after being dissolved in 20% 2-hydroxypropyl-beta-cyclodextrin (HPCD). To increase the solubility, 0.5 ml of 1N HCl was added to lercanidipine hydrochloride and 0.5 ml of 0.05% NaOH was added to valsartan, and then thoroughly dissolved. The test groups, one of which was the combination therapy group (N=10) administered 2 mg/kg of lercanidipine hydrochloride and 16 mg/kg of valsartan and the other of which was the monotherapy group (N=10) administered 16 mg/kg of valsartan, were compared with the control group in the changes of blood pressure and heart rate, and then statistically calculated. The statistical calculation was performed in a one-way ANOVA to analyze the significant differences between the test group and the control group, and the combination therapy group and the monotherapy group.

[153] As can be seen from the results of Figures 6 to 9, the combination therapy group administered 2 mg/kg of lercanidipine hydrochloride and 16 mg/kg of valsartan showed significant blood pressure decrease and heart rate increase in comparison with both the monotherapy group administered 16 mg/kg of valsartan and the control group 1 hour after administration in SHR. On the other hand, the monotherapy group administered 16 mg/kg of valsartan showed no significant blood pressure decrease or heart rate increase in comparison with the control group.

Claims

1. A pharmaceutical composition for the prevention and treatment of a cardiovascular disease which comprises lercanidipine hydrochloride and valsartan as active components,
   wherein the lercanidipine hydrochloride and valsartan are in a separated form by mixing dried granules of the lercanidipine hydrochloride and valsartan which are prepared separately.

2. The composition according to claim 1, wherein each of the lercanidipine hydrochloride granules and valsartan granules further comprise a pharmaceutically acceptable excipient.

3. The composition according to claim 2, wherein the lercanidipine hydrochloride granules comprise 4 to 10 parts by weight of a pharmaceutically acceptable excipient per 1 part by weight of lercanidipine hydrochloride.

4. The composition according to claim 2, wherein the valsartan granules comprise 1 to 2 parts by weight of a pharmaceutically acceptable excipient per 1 part by weight of valsartan.

5. The composition according to claim 2, which comprises the combination of 10 mg of lercanidipine hydrochloride and 80 mg of valsartan, 10 mg of lercanidipine hydrochloride and 160 mg of valsartan, 20 mg of lercanidipine hydrochloride and 80 mg of valsartan, or 20 mg of lercanidipine hydrochloride and 160 mg of valsartan.

6. The composition according to claim 1, wherein each of the lercanidipine hydrochloride and valsartan is included in a separated layer.

7. The composition according to claim 6, wherein a separation layer is placed between the lercanidipine hydrochloride layer and the valsartan layer.

8. The composition according to claim 1, wherein the cardiovascular disease is at least one selected from the group consisting of angina pectoris, hypertension, arteriospasm, cardiac arrhythmia, cardiac hypertrophy, cerebral infarction, congestive heart failure and myocardial infarction.

9. A method for the preparation of the composition according to claim 1, which comprises the steps of:
   (a) wet-granulating a mixture of lercanidipine hydrochloride and a pharmaceutically acceptable excipient and drying the granules;
   (b) wet-granulating a mixture of valsartan and a pharmaceutically acceptable excipient and drying the granules; and
   (c) mixing the dried granules prepared in steps (a) and (b).