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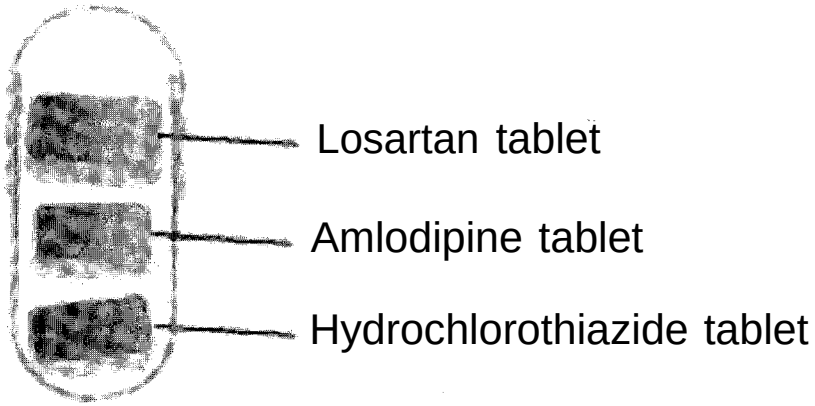
(54) **Title:** FIXED DOSE COMBINATION FORMULATION COMPRISING LOSARTAN, AMLODIPINE AND HYDROCHLOROTHIAZIDE



(57) **Abstract:** Provided is a fixed dose combination formulation for the prophylaxis or therapy of cardiovascular diseases, comprising losartan, amlodipine and hydrochlorothiazide, which is superior in dissolution rate and stability, having a higher dissolution rate compared to conventional individual single or combined dosage forms, the fixed dose combination formulation of the present invention exhibits biologically equivalent or superior behaviors to the conventional forms and guarantees higher stability over time. Therefore, the fixed dose combination formulation of the present invention can be effectively applied to the prophylaxis or therapy of cardiovascular diseases.

DESCRIPTION
FIXED DOSE COMBINATION FORMULATION COMPRISING LOSARTAN, AMLODIPINE AND HYDROCHLOROTHIAZIDE

FIELD OF THE INVENTION

The present invention relates to a fixed dose combination formulation for the prophylaxis or treatment of cardiovascular diseases, comprising losartan, amlodipine and hydrochlorothiazide, showing superior dissolution rate and stability.

BACKGROUND OF THE INVENTION

Hypertension is classified as either primary (essential) hypertension or secondary hypertension. About 90-95% of cases are categorized as primary hypertension which means high blood pressure with no obvious underlying medical cause. Secondary hypertension can be treated by removing the cause. In contrast, due to unidentifiable causes, the first line of treatment of essential hypertension is preventative lifestyle changes including rest, dietary changes, physical exercise, etc. For a greater effect on blood pressure, these non-drug therapies may be used in conjunction with medication.

Notable antihypertensive drugs include vasodilators, diuretics and sympatholytic agents. Vasodilators are most widely prescribed antihypertensive drugs, and they are divided into several groups, according to their action mechanisms, including ACE (angiotensin converting enzyme) inhibitors, angiotensin II receptor antagonists and calcium channel blockers.

In the treatment of hypertension to reduce the risks of complications such as coronary heart diseases and cardiovascular diseases, e.g., stroke, heart failure and myocardial infarction, it is more important to maintain the blood pressure within a normal range on a consistent basis than to simply lower the blood pressure level itself. Therefore, it is required to take medications for a long period of time, so care must be taken when selecting medication. For use in a steady treatment, a combination of drugs having different mechanisms has an advantage over individual drugs in terms

of preventive and therapeutic effect. In addition, a combination therapy reduces doses of individual drugs, thereby decreasing side effects which may occur due to a long-term administration of individual drugs. The treatment guidelines of high blood pressure (JNC 7) also recommends the administration of a combination of medications of different mechanisms when blood pressure is not sufficiently controlled only with a single drug.

With regard to the combination therapy, however, a prescription for the administration of two or more individual medications is apt to reduce compliance, giving rise to great inconvenience for hypertension patients who need continuous blood pressure management. Further, hypertension patients, particularly those who conduct a social life, need to carry and be administered two or more individual unit medications for a single dose of the combination therapy, and hence they experience inconvenience.

To overcome such drawbacks, various research and developments have recently been performed on fixed dose combination (FDC) drugs with specific active ingredients. The term "fixed dose combination" drug refers to a formulation of two or more medications or active ingredients combined in a single unit dosage form, and available in certain fixed doses. On the other hand, the term "free dose combination" drug, as used herein, is intended to refer to a formulation of two or more medications or active ingredients combined in two or more unit dosage forms. However, it is difficult to develop FDCs of specific active ingredients for the following reasons.

First, given the same active ingredients, it is less likely to provide the same or greater biological or pharmacokinetic effects with a fixed dose combination drug than a free dose combination drug. A fixed dose combination drug may show unexpected problems attributable to pharmacokinetic and pharmaceutical properties of the individual drugs to be formulated into a single dosage form.

For example, losartan shows an absolute oral bioavailability of about 25 to 35%. This low oral bioavailability is caused by the fact that losartan is gelled at a low pH, such as the pH of the gastrointestinal tract where the drug is predominantly absorbed (e.g., pH 1.2 to pH 2.0), and thus dissolves very slowly although it shows a very high dissolution pattern in pure water or at a relative high pH such as pH 6.8. In case of Cozaar®, a commercially available losartan preparation, the amount of

losartan released over the initial 30 minutes is less than 30% in a pH range of 1.2 to 2.0. When losartan is formulated together with amlodipine or hydrochlorothiazide into a fixed dose combination formulation, amlodipine or hydrochlorothiazide is trapped within the losartan gel and thus dissolves at a low rate.

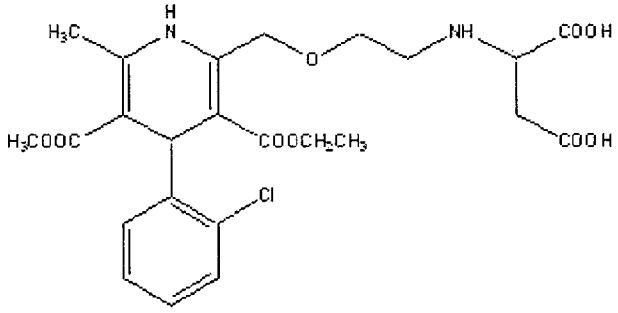
In addition, hydrochlorothiazide is low in both solubility and bioabsorption (BCS Class IV, low solubility, low permeability), and varies greatly in bioavailability even when it is administered in a single dosage form. Thus, it is difficult to develop hydrochlorothiazide into a fixed dose combination drug with other medication(s).

Another problem with the formulation of FDC is the likelihood of poor stability attributable to interaction between different active ingredients. Particularly, compounds difficult to handle make it more difficult to develop them into a fixed dose combination drug having a physicochemically stable form.

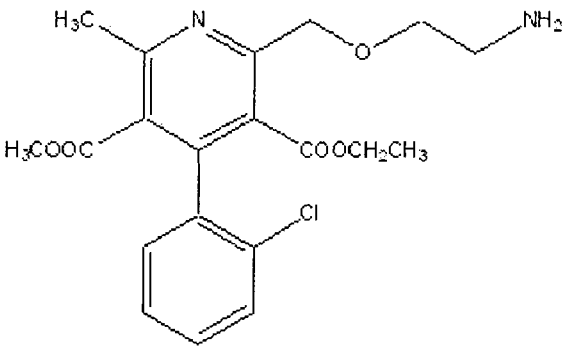
For example, an amlodipine formulation is typically prepared by combining the active ingredient amlodipine with a salt helpful in the pharmaceutical efficacy and formulation of the active ingredient. The salt is responsible for the stabilization of the active ingredient amlodipine. While amlodipine may preferably be in a free base form, it is administered as a salt form of a pharmaceutically acceptable acid because of its poor solubility in water.

When such acid addition salt of amlodipine, for example, amlodipine maleate is formulated, it may be degraded into amlodiphidine aspartate or amlo-pyridine, represented by the following Chemical Formulas 1 and 2, respectively, with the passage of time (U.S. Pat. No. 6,919,087). Thus, a pharmaceutical composition comprising amlodipine maleate has the problem of poor stability caused by degradation.

[Chemical Formula 1]



[Chemical Formula 2]



Because of the problem of poor stability, most of the currently available tablets contain amlodipine besylate disclosed in EP 244 944 (corresponding to U.S. Pat. No. 4,879,303). However, amlodipine besylate is also susceptible to decomposition into various breakdown products although to a lesser degree than amlodipine maleate. Hence, pharmaceutical compositions comprising the amlodipine besylate become poor in stability and thus in pharmaceutical efficacy over time.

The present inventors previously developed amlodipine camsylate, which is superior to amlodipine besylate in terms of physical properties such as solubility and stability, and formulated the salt into a commercially available product under the brand name of Amodipin®. Surprisingly, however, when formulated in combination with losartan, even amlodipine camsylate, which is the most stable amlodipine salt, it was found to degrade into various breakdown products, in contrast to the salt in a single dosage form. This is because amlodipine itself is unstable with regard to light and moisture. Thus, it can be very difficult to secure the stability of amlodipine when it is formulated into a fixed dose combination drug with, for example, losartan and hydrochlorothiazide. In addition, losartan potassium, known as having good stability, is degraded by heat under an acidic condition, with the concomitant production of degradation products E and F (see Z. Zhao et al., *J. Pharm. Biomed. Anal,* 20: 129-136, 1999). Also, hydrochlorothiazide is readily degraded into benzothiadiazine-related substance A.

In the course of developing a fixed dose combination drug of losartan, amlodipine and hydrochlorothiazide for the prophylaxis and treatment of cardiovascular diseases, the inventors found that a capsule filled with three respective discrete layers of the three ingredients exhibits the same bioequivalence as the individual unit formulations of the three active ingredients, with improved stability

and medication compliance.

DISCLOSURE OF THE INVENTION

It is therefore an object of the present invention to provide a fixed dose combination formulation for the prophylaxis and treatment of cardiovascular diseases, comprising losartan, amlodipine and hydrochlorothiazide, having different action mechanisms from one another, which exhibits excellent dissolution and stability properties.

The present invention provides a fixed dose combination formulation for the prophylaxis or treatment of cardiovascular diseases, comprising losartan or a pharmaceutically acceptable salt thereof; amlodipine or a pharmaceutically acceptable salt thereof; and hydrochlorothiazide as active ingredients, which is in the form of a capsule into which the active ingredients, each of which forms a discrete layer, are contained.

For a fixed dose combination formulation of the present invention, the side effects can be minimized compared to conventional individual single or combined dosage forms. Also, the formulation exhibits biologically equivalent or superior behaviors to the conventional forms owing to a higher dissolution, and shows higher stability over time. Accordingly, a fixed dose combination formulation of the present invention can be effectively used to prevent or treat cardiovascular diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic view showing a fixed dose combination formulation comprising losartan, amlodipine and hydrochlorothiazide in accordance with the present invention.

FIG. 2 is a graph showing dissolution rates of hydrochlorothiazide as measured by the method described in Test Example 1.

FIG. 3 is a graph showing dissolution rates of amlodipine as measured by the method described in Test Example 1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a fixed dose combination formulation for the prevention or treatment of cardiovascular diseases, comprising, as active ingredients, losartan or a pharmaceutically acceptable salt thereof; amlodipine or a pharmaceutically acceptable salt thereof; and hydrochlorothiazide, which is in the form of a capsule into which the active ingredients, each of which constitutes a discrete layer, are contained.

Losartan is the general name for 2-butyl-4-chloro-l-[[2'-(lH-tetrazol-5-yl)[l,l'-biphenyl]-4-yl]methyl]-lH-imidazol-5-methanol, which has been disclosed in U.S. Pat. Nos. 5,608,075, 5,138,069 and 5,153,197. Losartan potassium is commercially available under a brand name of Cozaar®. Losartan potassium is a preferred pharmaceutically acceptable salt of losartan. By blocking the interaction of angiotensin II and its receptor, losartan is mainly used for treating hypertension, heart failure, ischemic peripheral circulatory disorder, myocardial ischemia (angina pectoris), diabetic neuropathy and glaucoma, and also for preventing the progression of post-myocardial infarction heart failure. Losartan or its pharmaceutically acceptable salt may be administered at a daily dose of from 0.1 to 500 mg based on the weight of losartan, preferably at a daily dose of from 1 to 200 mg, and more preferably at a daily dose of from 25 to 200 mg.

Amlodipine is the general name for 3-ethyl-5-methyl-2-(2-aminoethoxy-methyl)-4-(2-chlorophenyl)-6-methyl-l,4-dihydro-3,5-pyridine dicarboxylate. The phannaceutically acceptable salt of amlodipine useful for the present invention may be prepared by using an acid containing a pharmaceutically acceptable anion which can form a non-toxic acid addition salt. Examples of the salt include hydrogen chloride, hydrogen bromide, sulfate, phosphate, acetate, malate, furmarate, lactate, tartrate, citrate, gluconate, besylate and camsylate, but are not limited thereto. Of them, amlodipine besylate is currently marketed as Norvasc®. Amlodipine camsylate is superior to besylate salt in solubility and stability, as disclosed in Korean Patent No. 452491. Hence, amlodipine camsylate is most preferred as the pharmaceutically acceptable salt of amlodipine for the present invention.

Amlodipine is a long-acting calcium channel blocker useful for treating cardiovascular disorders such as angina, hypertension, and congestive heart failure. Amlodipine or a pharmaceutically acceptable salt thereof may be administered at a daily dose of from 0.5 to 20 mg based on the weight of amlodipine, preferably from 1 to 10 mg, and more preferably from 2.5 to 10 mg.

Hydrochlorothiazide is the general name for 6-chloro-l,l-dioxy-3,4-dihydro-2H-l,2,4-benzothiazine-7-sulfone amide, and is commercially available under various brand names. Hydrochlorothiazide is a diuretic drug of the thiazide class that acts on kidneys to reduce sodium reabsorption in the distal convoluted tubule by inhibiting the Na/Cl co-transporter. As a result, by increasing levels of sodium and chloride in the tubular fluid, hydrochlorothiazide induces natriuresis and concomitant diuresis. Clinically, hydrochlorothiazide is used in the treatment of hypertension, heart failure, hypercalciuria and diabetes insipidus. The daily dose of hydrochlorothiazide ranges from 1 to 100 mg, preferably from 3 to 50 mg, and more preferably from 6.25 to 25 mg.

A fixed dose combination formulation of the present invention comprising losartan or a pharmaceutically acceptable salt thereof, amlodipine or a pharmaceutically acceptable salt thereof and hydrochlorothiazide may be used for the prophylaxis or therapy of cardiovascular diseases. Examples of the cardiovascular diseases include angina pectoris, hypertension, arteriospasm, cardiac arrhythmia, cardiomegaly, cerebral infarction, congestive heart failure and myocardial infarction, but are not limited thereto. A fixed dose combination formulation comprising losartan or a pharmaceutically acceptable salt thereof, amlodipine or a pharmaceutically acceptable salt thereof and hydrochlorothiazide in accordance with the present invention exhibits higher preventive and therapeutic effects on cardiovascular diseases, with decreased side effects and increased compliance, compared to conventional single formulations. However, a simple combination of losartan, amlodipine and hydrochlorothiazide for making a fixed dose combination formulation suffers from the following disadvantages due to differences in their intrinsic physical properties.

A first problem comes from the gelation of losartan. Losartan readily

dissolves in purified water and is easily released at a relatively high pH (e.g., pH 6.8), but is released very slowly at a low pH (e.g., pH 2.0 or pH 1.2) because of the gelation. This problem significantly imparts undesired effects on the dissolution rate and bioavailability of the formulation because the formulation is first exposed to the acidic gastric juice having a low pH value when orally administered. As the gelation of losartan progresses in the composition, amlodipine and hydrochlorothiazide are trapped within the losartan gel and dissolve poorly, which is demonstrated in Test Example 1 as shown in the graphs of dissolution rates of FIGS. 2 and 3. Release results of tablets prepared by simply mixing two ingredients were significantly lower than "80% dissolution at the time point of 30 minutes", the dissolution specification of the immediate release type formulation of amlodipine or hydrochlorothiazide. These results indicate that it can be impossible for a fixed dose combination formulation prepared by simply mixing losartan, amlodipine and hydrochlorothiazide to have the same bioequivalence as in the free dose combination formulations. There is, therefore, a need for the development of a fixed dose combination formulation of the three active ingredients which does not have the decreased dissolution attributed to the gelation of losartan at a low pH condition.

A second problem is associated with formulation stability. When losartan, amlodipine and hydrochlorothiazide are simply combined and tableted, impurities are increasingly produced under an accelerated condition, thus greatly decreasing the stability of the formulation. This is believed to be caused by physicochemical reactions among losartan, amlodipine and hydrochlorothiazide having negative influences on the stability of each active ingredient.

One of the considerations which may be taken as a solution to this problem is to adjust the pH of the composition with an acid or an alkalifying agent to an optimal value to stabilize the active ingredient. In this regard, however, amlodipine, which contains an intramolecular ester bond, is apt to undergo hydrolysis in an alkaline condition whereas losartan is likely to degrade in an acidic condition. In fact, as disclosed in U.S. Pat. No. 6,919,087, the amlodipine-losartan complex formulation could not be sufficiently stabilized within a pH range of from 5.5 to 7.0.

To avoid this disadvantage, separation between active ingredients may be attempted using a two- or three-layer tablet press machine. However, in addition to the requirement of a special equipment such as a two- or three-layer tablet press

machine, a reaction may be occur at the junction between the layers. Thus, it is impossible to completely separate the active ingredients from each other.

In order to guarantee the dissolution rate and stability properties of each active ingredient by preventing amlodipine and hydrochlorothiazide from decreasing in dissolution rate due to the gelation of losartan, with the resultant clinical utility thereof being maximized, the present invention provides a fixed dose combination formulation which is in the form of a capsule in which losartan or a pharmaceutically acceptable salt thereof, amlodipine or a pharmaceutically acceptable salt thereof, and hydrochlorothiazide forming respective discrete layers are charged. Because the active ingredients are physically separated from one another, the formulation of the present invention easily secures bioequivalence, and shows excellent stability. In addition, individual ingredients are produced, thereby avoiding reactions therebetween. Also, the formulation is expected to induce high medication compliance because its volume can be reduced by minimizing the amount of excipients for each layer. Moreover, the formulation of the present invention can exert higher preventive and therapeutic effects on cardiovascular diseases with the concomitant reduction of the side effects of conventional single formulations or combinations.

In one preferred embodiment, losartan, amlodipine and hydrochlorothiazide in a fixed dose combination formulation of the present invention are charged into a capsule while forming respective discrete layers in the form of tablets. In a concrete embodiment, a fixed dose combination formulation of the present invention may be a capsule comprising a tablet having losartan or a pharmaceutically acceptable salt thereof, a tablet having amlodipine or a pharmaceutically acceptable salt thereof and a tablet having hydrochlorothiazide.

Each tablet of losartan, amlodipine and hydrochlorothiazide is prepared by mixing or granulization with a pharmaceutically acceptable excipient before compression in a tablet press machine. The tablet hardness is dependent on the compression pressure of the press machine. Tablets can be given various densities under various compression pressures even though they have the same weight. Typical tablets have a density of 0.8 g/ml or greater. The tablets may be prepared so as to have a circular, rectangular or oval shape, preferably circular in shape.

In case of a circular shape, a tablet preferably ranges in diameter from 1 mm to 7 mm, and more preferably from 2 mm to 6 mm. A larger tablet results in increase of the capsule size into which the tablet is charged, thus causing inconvenience to the patient who takes the medication. On the other hand, when the tablet diameter becomes smaller, the tableting process cannot be properly conducted.

In a fixed dose combination formulation of the present invention, at least one of the tablets existing as individual discrete layers may be coated with a polymer film. Any conventional pharmaceutically acceptable polymer may be employed for the coating. Representative among them are methyl cellulose, ethyl cellulose, polyvinyl alcohol, hydroxyethyl cellulose, hydroxypropyl methyl cellulose and polyvinylpyrrolidone. The polymer is preferably used in a minimal amount in order to effectively prepare the formulation in an optimal size. Its amount preferably ranges from about 1 to about 20 wt% based on the total weight of the formulation, and preferably from about 2 to about 10 wt%.

In a fixed dose combination formulation of the present invention, the discrete layers comprising, as active ingredients, losartan or a pharmaceutically acceptable salt thereof, amlodipine or a pharmaceutically acceptable salt thereof, and hydrochlorothiazide, respectively, may further comprise a pharmaceutically acceptable excipient. The pharmaceutically acceptable excipient may include a pharmaceutically acceptable diluent, a pharmaceutically acceptable disintegrant, a pharmaceutically acceptable binder, a pharmaceutically acceptable stabilizer, a pharmaceutically acceptable lubricant, a pharmaceutically acceptable pigment, etc. In a fixed dose combination formulation of the present invention, an active ingredient may be mixed at a weight ratio of 1 : 0.25 to 1 : 20 with a pharmaceutically acceptable excipient.

Examples of the pharmaceutically acceptable diluent include microcrystalline cellulose, lactose, Ludipress, mannitol, monocalcium phosphate, starch, low-substituted hydroxypropylcellulose and a mixture thereof. The diluent may be used in an amount of from about 5 to about 95 wt% based on the total weight of the formulation, and preferably in an amount of from about 10 to about 85 wt%. Preferably, the diluent can be a soluble diluent. When the diluent is used, its ratio to the active ingredient in each discrete layer is very important. The term "soluble

diluents" refers to a diluent which is dissolved in water, like lactose, Ludipress (BASF, a mixture of lactose, crospovidone and povidone (93 : 3.5 : 3.5, w/w(%))), mannitol and sorbitol. For example, the soluble diluents, when mixed with the active ingredient losartan, allows for a maximal dissolution rate at a certain mixing ratio. This can be accounted for by the physical property that induces the gelation of losartan at a low pH value. At an optimal ratio of losartan to the soluble diluents, the losartan layer can dissolve at a high rate. Losartan is preferably mixed with an aqueous diluent at a weight ratio of 1 : 0.1 to 1 : 40, and more preferably at a weight ratio of 1 : 0.25 to 1 : 20.

As for the granules used in the tableting process for the losartan layerj it is advantageous in terms of stability to manufacture them in a simple mixing or dry method which employs neither water nor an organic solvent. Surprisingly, the stability of the losartan layer becomes rapidly worse under a high moisture condition, which might be attributed to losartan's high water solubility which causes losartan to undergo hydrolysis or a change in physical property. The losartan layer in the present invention preferably contains a moisture content of 5% or less and more preferably 3% or less.

Examples of the disintegrant useful in the fixed dose combination formulation of the present invention include crospovidone, sodium starch glycolate, croscarmellose sodium, low-substituted hydroxypropylcellulose, starch, alginic acid or sodium salt thereof, and a mixture thereof, preferably, crospovidone, sodium starch glycolate, croscarmellose sodium, low-substituted hydroxypropylcellulose, and a mixture thereof, more preferably, crospovidone and sodium starch glycolate. The disintegrant may be used in an amount of about 1 to about 30 wt% based on the total weight of the formulation, and preferably in an amount of about 2 to about 15 wt%.

Representative examples of the binder useful in the fixed dose combination formulation of the present invention include hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, copovidone, macrogol, silicate derivatives such as hard silica, synthesized aluminum silicate, calcium silicate and magnesium metasilicate aluminate, phosphates such as calcium monohydrogen phosphate, carbonates such as calcium carbonate, and a mixture thereof.

In one embodiment, the stabilizer usable in the fixed dose combination formulation of the present invention may be an anti-oxidant. The use of an anti-oxidant enhances stability of the active ingredients, particularly amlodipine, against the undesirable reaction with other pharmaceutically acceptable additives and against modification by heat or moisture with time. Representative examples of the anti-oxidant include butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbic acid, ascorbyl palmitic acid, ethylene diamine tetracetic acid (EDTA), sodium pyrosulfite, and a mixture thereof. In one embodiment, the anti-oxidant is butylated hydroxytoluene.

Concrete examples of the lubricant useful in the fixed dose combination formulation of the present invention include stearic acid, a metal stearate such as calcium stearate and magnesium stearate, talc, colloidal silica, sucrose fatty acid esters, hydrogenated vegetable oils, waxes having a high melting point, glyceryl fatty acid esters, glycerol dibehenate, and a mixture thereof.

So long as it is applicable to typical capsule medications, any hard capsule may be used for the fixed dose combination formulation of the present invention. The hard capsule may be prepared from a base material such as gelatin, hypromellose, pullulan (NP caps™, Capsugel), or polyvinylalcohol. Preferred is a gelatin capsule as an initial dissolution rate is important for the fixed dose combination formulation of the present invention.

So long as it is generally acceptable for typical capsule medications, any capsule size is possible for the hard capsule of the fixed dose combination formulation of the present invention. Depending on the capsule number, the capsule size has different internal volume. In consideration of the convenience of administration, smaller sizes are preferred. However, it is recommended to select an optimal capsule size so that the allowable lower limit of the amount may be charged into the capsule. The size of the hard capsule useful for the formulation of the present invention may be No. 0, No. 1, No. 2, No. 3, or No. 4. A schematic view showing a fixed dose combination formulation described above is given in FIG. 1.

A fixed dose combination formulation of the present invention, as shown in FIGS. 2 and 3, allow both amlodipine or a pharmaceutically acceptable salt thereof and hydrochlorothiazide to reach a dissolution rate of 80% or higher within 30

minutes after the initiation of a dissolution test.

The present invention also provides a method for manufacturing a fixed dose combination formulation for the prophylaxis or therapy of cardiovascular diseases, which comprises the steps of: a) mixing or granulizing losartan or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and tableting the mixture or the granule to obtain a losartan tablet; b) mixing or granulizing amlodipine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and tableting the mixture or the granule to obtain an amlodipine tablet; c) mixing or granulizing hydrochlorothiazide and a pharmaceutically acceptable excipient, and tableting the mixture or the granule to obtain a hydrochlorothiazide tablet; and d) filling the losartan tablet, the amlodipine tablet and the hydrochlorothiazide tablet into a capsule. The method may further comprise coating the tablet obtained from at least one of the steps a) to c) with a pharmaceutically acceptable polymer.

The fixed dose combination formulation of the present invention is equivalent or superior to currently marketed single formulations in terms of the dissolution rates of losartan, amlodipine and hydrochlorothiazide, and exhibits excellent stability with time because it undergoes a very small change of related substances as tested under a accelerated condition. Accordingly, the formulation of the present invention may be effectively used for the treatment of cardiovascular diseases including, for example, angina pectoris, hypertension, arteriospasm, cardiac arrhythmia, cardiomegaly, cerebral infarction, congestive heart failure and myocardial infarction.

The following Examples are provided to illustrate preferred embodiments of the present invention, and are not intended to limit the scope of the present invention.

Example 1: Preparation of fixed dose combination formulation I

Losartan Layer	
Losartan potassium	50.0 mg
Ludipress	15.7 mg

Copovidone	3.0 mg
Light anhydrous silicic acid	0.5 mg
Macrocrystalline cellulose	10.0 mg
Magnesium stearate	0.8 mg
Opadry Y-1-7000	2.4 mg
Distilled water	(12.0 mg)

Amlodipine Layer

Amlodipine camsylate	7.84 mg (amlodipine 5 mg)
Microcrystalline cellulose	43.76 mg
D-mannitol	14.0 mg
Sodium starch glycolate	1.7 mg
Hydroxypropyl cellulose	2.0 mg
Magnesium stearate	0.7 mg
Distilled water	(35.0 mg)
Opadry (Y-1-7000)	2.1 mg
Distilled water	(l l.O mg)

Hydrochlorothiazide Layer

Hydrochlorothiazide	12.5 mg
Microcrystalline cellulose	38.80 mg
Mannitol	13.0 mg
Sodium starch glycolate	3.0 mg
Hydroxypropyl cellulose	2.0 mg
Magnesium stearate	0.7 mg
Distilled water	(35.0 mg)
Opadry (Y-1-7000)	2.1 mg
Distilled water	(l l.O mg)

The ingredients listed above for the losartan layer were admixed. The resulting mixture was pressed into a tablet using a tablet press machine with the 5 mm diameter of the dye, followed by coating the resulting tablet with a coating solution

prepared by dissolving Opadry Y-1-7000 (Colorcon) in distilled water to prepare a losartan 50 mg tablet.

Among the above list for the amlodipine layer, 2.0 mg of hydroxypropyl cellulose was dissolved in 35 mg of distilled water, and it was used, as a binder, in wet granulation, followed by passing through a 20 mesh screen and drying to obtain the granule. The resulting mixture was pressed into a tablet using a tablet machine, and then the resulting tablet was coated with a coating solution prepared by dissolving Opadry Y-l-7000 (Colorcon) in distilled water to prepare an amlodipine 5 mg tablet.

A hydrochlorothiazide 12.5 mg tablet was prepared by tableting and coating based on the same method as the procedure of preparing amlodipine tablet.

The three tablets were charged in a No. 2 hard capsule to obtain a fixed dose combination formulation comprising losartan (50 mg), amlodipine (5 mg) and hydrochlorothiazide (12.5 mg). The total mass of the three tablets that are charged in the hard capsule is 226.6 mg, which was very small value.

Example 2: Preparation of fixed dose combination formulation II

Losartan Layer	
Losartan potassium	50.0 mg
Ludipress	15.7 mg
Copovidone	3.0 mg
Light anhydrous silicic acid	0.5 mg
Microcrystalline cellulose	10.0 mg
Magnesium stearate	0.8 mg
Hypromellose	1.6 mg
Hydroxypropyl cellulose	0.4 mg
Titanium dioxide	0.36 mg
Talc	0.04 mg
Distilled water	(28.0 mg)
Amlodipine Layer	
Amlodipine camsylate	7.84 mg (amlodipine 5 mg)
Microcrystalline cellulose	22.5 mg

D-mannitol	7.26 mg
Sodium starch glycolate	0.85 mg
Hydroxypropyl cellulose	1.15 mg
Magnesium stearate	0.4 mg
Distilled water	(20.0 mg)
Hypromellose	0.8 mg
Hydroxypropyl cellulose	0.2 mg
Titanium dioxide	0.18 mg
Yellow iron oxide	0.01 mg
Talc	0.01 mg
Distilled water	(14.0 mg)

Hydrochlorothiazide Layer

Hydrochlorothiazide	12.5 mg
Microcrystalline cellulose	18.5 mg
Mannitol	5.95 mg
Sodium starch glycolate	1.5 mg
Hydroxypropyl cellulose	1.15 mg
Magnesium stearate	0.4 mg
Distilled water	(20.0 mg)
Hypromellose	0.8 mg
Hydroxypropyl cellulose	0.2 mg
Titanium dioxide	0.18 mg
Red Iron oxide	0.01 mg
Talc	0.01 mg
Distilled water	(14.0 mg)

The procedure of Example 1 was repeated to prepare losartan, amlodipine and hydrochlorothiazide coated tablets and the three tablets were charged in a No. 2 hard capsule to obtain a fixed dose combination formulation comprising losartan (50 mg), amlodipine (5 mg) and hydrochlorothiazide (12.5 mg). The total mass of the three tablets that are charged in the hard capsule is 164.8 mg, which was very small value.

Example 3: Preparation of fixed dose combination formulation III

Losartan Layer	
Losartan potassium	50.0 mg
Ludipress	15.7 mg
Copovidone	3.0 mg
Light anhydrous silicic acid	0.5 mg
Microcrystalline cellulose	10.0 mg
Magnesium stearate	0.8 mg
Hypromellose	1.6 mg
Hydroxypropyl cellulose	0.4 mg
Titanium dioxide	0.36 mg
Talc	0.04 mg
Distilled water	(28.0 mg)
Amlodipine Layer	
Amlodipine camsylate	7.84 mg (amlodipine 5 mg)
Microcrystalline cellulose	22.5 mg
D-mannitol	7.26 mg
Sodium starch glycolate	0.85 mg
Hydroxypropyl cellulose	1.15 mg
Magnesium stearate	0.4 mg
Distilled water	(20.0 mg)
Hypromellose	0.8 mg
Hydroxypropyl cellulose	0.2 mg
Titanium dioxide	0.18 mg
Yellow Iron oxide	0.01 mg
Talc	0.01 mg
Distilled water	(14.0 mg)
Hydrochlorothiazide Layer	
Hydrochlorothiazide	25.0 mg
Microcrystalline cellulose	37.0 mg

Mannitol	11.9 mg
Sodium starch glycolate	3.0 mg
Hydroxypropyl cellulose	2.3 mg
159Magnesium stearate	0.8 mg
Distilled water	(40.0 mg)
Hypromellose	1.6 mg
Hydroxypropyl cellulose	0.4 mg
Titanium dioxide	0.36 mg
Red Iron oxide	0.02 mg
Talc	0.02 mg
Distilled water	(28.0 mg)

The procedure of Example 1 was repeated to prepare losartan, amlodipine and hydrochlorothiazide coated tablets and the three tablets were charged in a No. 2 hard capsule to obtain a fixed dose combination formulation comprising losartan (50 mg), amlodipine (5 mg) and hydrochlorothiazide (25 mg). The total mass of the three tablets that are charged in the hard capsule is 206 mg, which was very small value.

Example 4: Preparation of fixed dose combination formulation IV

Losartan Layer	
Losartan potassium	50.0 mg
Ludipress	15.7 mg
Copovidone	3.0 mg
Light anhydrous silicic acid	0.5 mg
Microcrystalline cellulose	10.0 mg
Magnesium stearate	0.8 mg
Hypromellose	1.6 mg
Hydroxypropyl cellulose	0.4 mg
Titanium dioxide	0.36 mg
Talc	0.04 mg
Distilled water	(28.0 mg)

Amlodipine Layer	
Amlodipine camsylate	15.68 mg (amlodipine 10 mg)
Microcrystalline cellulose	15.0 mg
D-mannitol	14.52 mg
Sodium Starch glycolate	1.7 mg
Hydroxypropyl cellulose	2.3 mg
Magnesium stearate	0.8 mg
Distilled water	(40.0 mg)
Hypromellose	1.6 mg
Hydroxypropyl cellulose	0.4 mg
Titanium dioxide	0.36 mg
Yellow Iron oxide	0.02 mg
Talc	0.02 mg
Distilled water	(28.0 mg)
Hydrochlorothiazide Layer	
Hydrochlorothiazide	12.5 mg
Microcrystalline cellulose	18.5 mg
Mannitol	5.95 mg
Sodium starch glycolate	1.5 mg
Hydroxypropyl cellulose	1.15 mg
Magnesium stearate	0.4 mg
Distilled water	(20.0 mg)
Hypromellose	0.8 mg
Hydroxypropyl cellulose	0.2 mg
Titanium dioxide	0.18 mg
Red Iron oxide	0.01 mg
Talc	0.01 mg
Distilled water	(14.0 mg)

The procedure of Example 1 was repeated to prepare losartan, amlodipine and hydrochlorothiazide coated tablets and the three tablets were charged in a No. 2 hard capsule to obtain a fixed dose combination formulation comprising losartan (50 mg),

amlodipine (10 mg) and hydrochlorothiazide (12.5 mg). The total mass of the three tablets that are charged in the hard capsule is 206 mg, which was very small value.

Comparative Example 1: Preparation of fixed dose combination formulation V (mixed tablet formulation)

Losartan potassium	50.0 mg
Amlodipine camsylate	7.84 mg (amlodipine 5 mg)
Hydrochlorothiazide	12.5 mg
Ludipress	15.7 mg
Copovidone	3.0 mg
Light anhydrous silicic acid	0.5 mg
Microcrystalline cellulose	92.56 mg
Mannitol	27.0 mg
Sodium starch glycolate	4.7 mg
Hydroxypropyl cellulose	4.0 mg
Magnesium stearate	2.2 mg

In accordance with the ingredients listed above, losartan, amlodipine, hydrochlorothiazide and excipients were mixed together and tabletized to obtain a fixed dose combination formulation comprising losartan (50 mg), amlodipine (5 mg) and hydrochlorothiazide (12.5 mg).

Comparative Example 2: Preparation of fixed dose combination formulation VI (mixed capsule formulation)

Losartan potassium	50.0 mg
Amlodipine camsylate	7.84 mg (amlodipine 5 mg)
Hydrochlorothiazide	12.5 mg
Ludipress	15.7 mg
Copovidone	3.0 mg
Light anhydrous silicic acid	0.5 mg
Microcrystalline cellulose	92.56 mg

Mannitol	27.0 mg
Sodium starch glycolate	4.7 mg
Hydroxypropyl cellulose	4.0 mg
Magnesium stearate	2.2 mg

In accordance with the ingredients used in Comparative Example 1, losartan, amlodipine, hydrochlorothiazide and excipients were mixed together and charged in a No. 2 hard capsule to obtain a fixed dose combination formulation comprising losartan (50 mg), amlodipine (5 mg) and hydrochlorothiazide (12.5 mg).

Experimental Example 1: Dissolution Test of Amlodipine and Hydrochlorothiazide

The fixed dose combination formulations prepared in Examples 1 and 2, the fixed dose combination formulations prepared in Comparative Examples 1 and 2, and dichlozid (Yuhan Corporation) and Norvasc tab 5 mg were each subjected to a drug dissolution test under the following conditions.

- Test Conditions -

Dissolution media: 900 raL of 0.01N HC1 (pH 2.0)
Appratus : USP paddle method, 75 rpm
Temperature: 37°C

- Analytical Conditions -

Column: stainless steel colum (inner diameter: about 4.6 mm, length : 25 cm) filled with octadecylsilylated silica gel for 5 μm liquid chromatography
Mobile phase: a mixture of 0.015 M potassium dihydrogen phosphate : acetonitrile : methanol (47 : 32 : 23, v/v)
Detector: ultraviolet spectrophotometer (absorbance at 238 nm)
Flow rate: 1.2 mL/min
Injection volume: 20 μL
Column temperature: 40°C

- Criteria of Dissolution Rate -

Dissolution rate 80% or more at 30 minutes

- Result -

As shown in FIGS. 2 and 3, the fixed dose combination formulations prepared in Examples 1 and 2, which comprises separate tablets of losartan, amlodipine and hydrochlorothiazide exhibited higher dissolution rates than Comparative Examples 1 and 2, which was prepared by direct mixing. The dissolution rate of the tablet prepared in Examples 1 and 2 met the required criteria of hydrochlorothiazide and amlodipine, whereas the formulations prepared by direct mixing of Comparative Examples 1 and 2 did not meet the criteria of hydrochlorothiazide and amlodipine.

Experimental Example 2: Stability Test under Accelerated Conditions

A stability test was performed for the fixed dose combination formulations prepared in Examples 1 and 2 and the fixed dose combination formulations prepared in Comparative Examples 1 and 2 under the following conditions to analyze the changes in production rate of related substances of losartan, amlodipine and hydrochlorothiazide under accelerated light and heat conditions. The results are shown in Table 3.

- Accelerated Test Conditions (Light Stability) -

Apparatus: Xe-3-HC (Q-Lab)

Temperature and humidity: 25°C ± 2°C / 60% ± 5% RH

Light: 0.80W/m^2/nm, 18.44 hours (1,200,000 lux, method according to ICH Guidelines)

Sample: stored on a Petri dish

Test time - initial and after the exposure (exposure to 120k lux)

- Accelerated Test Conditions (Heat Stability) -

Temperature and humidity: 50°C ± 2°C

Sample: stored in a HDPE bottle

Test time - initial and after 28 days

- Analysis Conditions (Losartan and Amlodipine Related Substances) -

Column: stainless column (internal diameter of about 4.6 mm, and length of 5 cm) packed with octadecylsilylated silica gel for 5 μm liquid chromatography (e.g., Symmetry C18, Waters)

Mobile phase A: 6 nM sodium hexanesulfonate monohydrate added with 0.05 % phosphoric acid

Mobile phase B: methanol

Table 1 Gradient System

Time (min)	Mobile phase A %	Mobile phase B %
0	56	44
5	56	44
13	20	80
13.1	56	44
15	56	44

Detector: ultraviolet spectrophotometer (absorbance at 239nm)

Flow rate: 1.5 mL/min

Injection volume: 10 μL,

Column temperature: 45°C

- Analysis Conditions (Hydrochlorothiazide Related Substances) -

Column: stainless column (internal diameter of about 4.6 mm, and length of 5 cm) packed with octadecylsilylated silica gel for 5 μm liquid chromatography (e.g., Symmetry C18, Waters)

Mobile phase A: acetonitrile : methanol = 3 : 1 (v/v)

Mobile phase B: formic acid : water = 5 : 995 (v/v)

Table 2 Gradient System

Time (min)	Mobile phase A %	Mobile phase B %
0	3	97

5	3	97
14	36	64
20	90	10
25	3	97
28	3	97

Detector: ultraviolet spectrophotometer (absorbance at 275nm)

Flow rate: 1.0 mL/min

Injection volume: 10 μL

Column temperature: 35°C

Table 3

Sample	Initial			Accel. Light, 120k lux			Accel. 50°C for 28 days		
	A (%)	B (%)	C (%)	A (%)	B (%)	C (%)	A (%)	B (%)	C (%)
Ex.1	0.01	0.01	0.04	0.02	0.10	0.09	0.05	0.09	0.11
Ex.2	0.02	0.01	0.06	0.03	0.12	0.08	0.05	0.07	0.12
Co.Ex.1	0.01	0.03	0.04	0.03	0.86	0.34	0.04	1.12	1.45
Co.Ex.2	0.04	0.05	0.11	0.09	0.78	0.43	0.55	1.36	1.98

***A: losartan related substances, B: amlodipine related substances, C: hydrochlorothiazide related substances**

As can be seen in Table 3 above, the fixed dose combination formulations comprising losartan, amlodipine and hydrochlorothiazide obtained in Examples 1 and 2 exhibited higher stability with respect to losartan, amlodipine and hydrochlorothiazide related substances. On the other hand, the fixed dose combination formulations obtained in Comparative Examples 1 and 2, which were prepared by direct-compression, produced related substances at least 10 times greater than Examples 1 and 2. This result indicates that fixed dose combination formulations prepared in accordance with the present invention have significantly improved storage stability as compared to fixed dose combination formulations prepared in a conventional manner.

What is claimed is:

1. A fixed dose combination formulation for the prophylaxis or treatment of a cardiovascular disease, comprising losartan or a pharmaceutically acceptable salt thereof; amlodipine or a pharmaceutically acceptable salt thereof; and hydrochlorothiazide as active ingredients, wherein each active ingredients, each of which forms a discrete layer, are contained.

2. The fixed dose combination formulation of claim 1, wherein the discrete layer is in the form of a tablet.

3. The fixed dose combination formulation of claim 2, wherein the tablet is coated with a pharmaceutically acceptable polymer.

4. The fixed dose combination formulation of claim 1, wherein the pharmaceutically acceptable salt of losartan is losartan potassium.

5. The fixed dose combination formulation of claim 1, wherein the pharmaceutically acceptable salt of amlodipine is amlodipine camsylate.

6. The fixed dose combination formulation of claim 1, wherein the pharmaceutically acceptable salt of amlodipine is amlodipine besylate.

7. The fixed dose combination formulation of claim 1, wherein losartan or the pharmaceutically acceptable salt thereof is contained in an amount ranging from 25 mg to 200 mg.

8. The fixed dose combination formulation of claim 1, wherein amlodipine or the pharmaceutically acceptable salt thereof is contained in an amount ranging from 2.5 mg to 10 mg.

9. The fixed dose combination formulation of claim 1, wherein hydrochlorothiazide is contained in an amount ranging from 6.25 mg to 25 mg.

10. The fixed dose combination formulation of claim 1, wherein the discrete layer comprises a pharmaceutically acceptable excipient and the active ingredient is mixed with the pharmaceutically acceptable excipient at a weight ratio of 1 : 0.25 to 1 : 20.

11. The fixed dose combination formulation of claim 10, wherein the pharmaceutically acceptable excipient comprises a disintegrant selected from the group consisting of crospovidone, sodium starch glycolate, croscarmellose sodium, low-substituted hydroxypropylcellulose, starch, alginic acid or sodium salt thereof and a mixture thereof.

12. The fixed dose combination formulation of claim 1, wherein amlodipine or the pharmaceutically acceptable salt thereof reaches a dissolution rate of 80% or higher within 30 minutes after the initiation of a dissolution test.

13. The fixed dose combination formulation of claim 1, wherein hydrochlorothiazide reaches a dissolution rate of 80% or higher within 30 minutes after the initiation of a dissolution test.

14. The fixed dose combination formulation of claim 1, wherein the cardiovascular disease is selected from the group consisting of angina pectoris, hypertension, arteriospasm, cardiac arrhythmia, cardiomegaly, cerebral infarction, congestive heart failure and myocardial infarction.

15. A method for preparing a fixed dose combination formulation for the prophylaxis or therapy of cardiovascular diseases, which comprises the steps of:

a) mixing or granulizing losartan or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and tableting the mixture or granule to obtain a losartan tablet;

b) mixing or granulizing amlodipine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and tableting the mixture or granule to obtain an amlodipine tablet;

c) mixing or granulizing hydrochlorothiazide and a pharmaceutically acceptable excipient, and tableting the mixture or granule to obtain a hydrochlorothiazide tablet; and

d) incorporating the losartan tablet, the amlodipine tablet and the hydrochlorothiazide tablet into a capsule.

16. The method of claim 15, which further comprises coating one or more tablets obtained from at least one of the steps (a), (b) and (c) with a pharmaceutically acceptable polymer.

FIG. 1

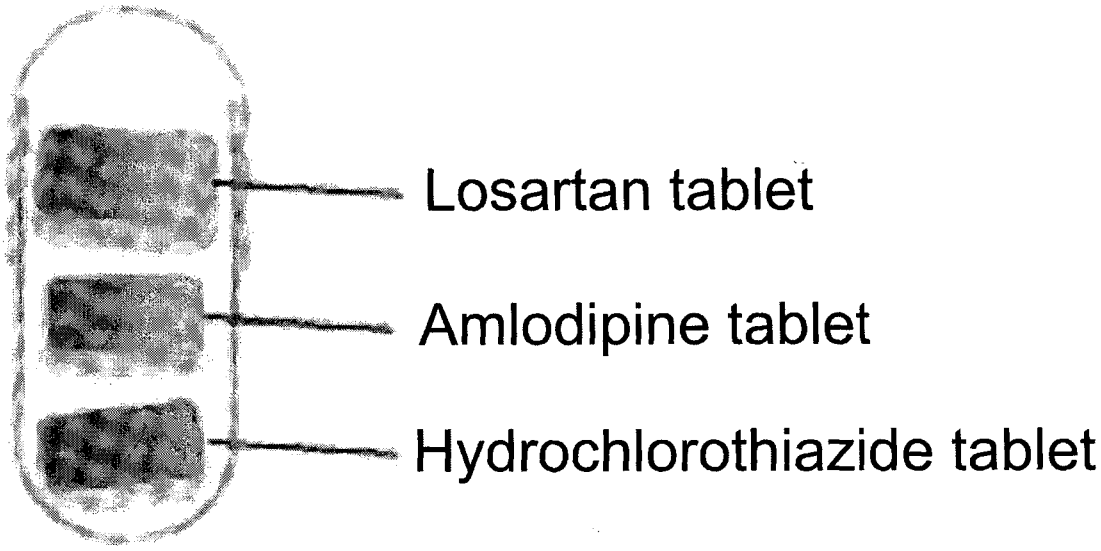

Losartan tablet
Amlodipine tablet
Hydrochlorothiazide tablet

FIG. 2

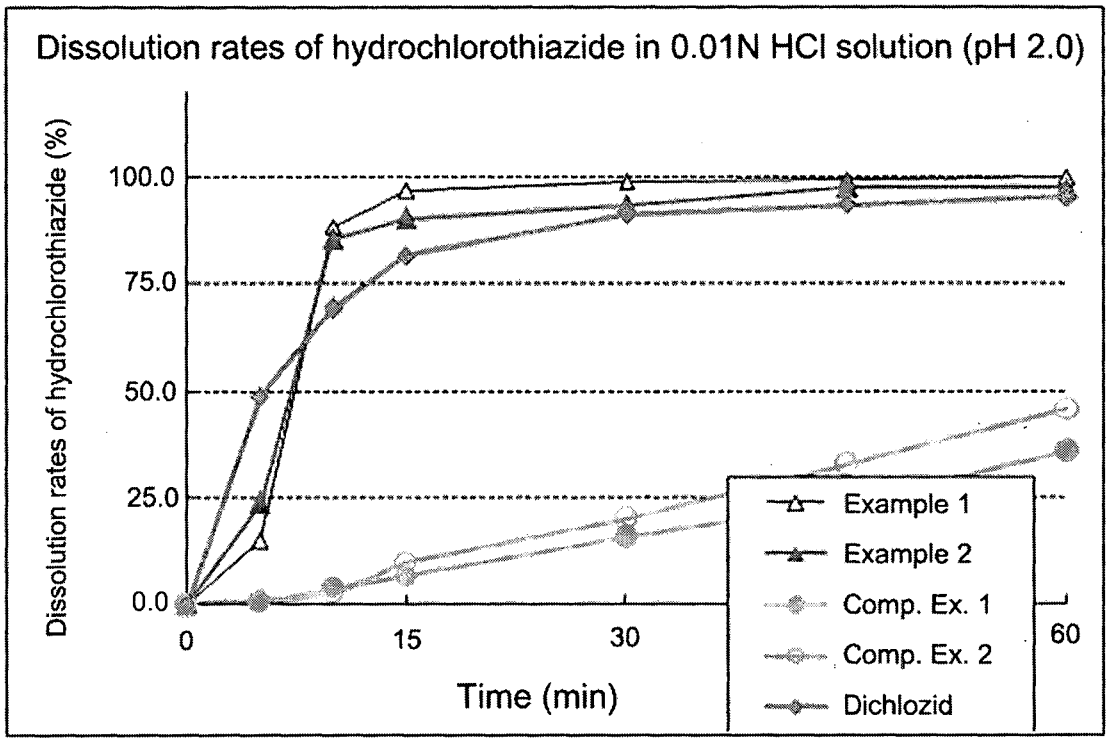
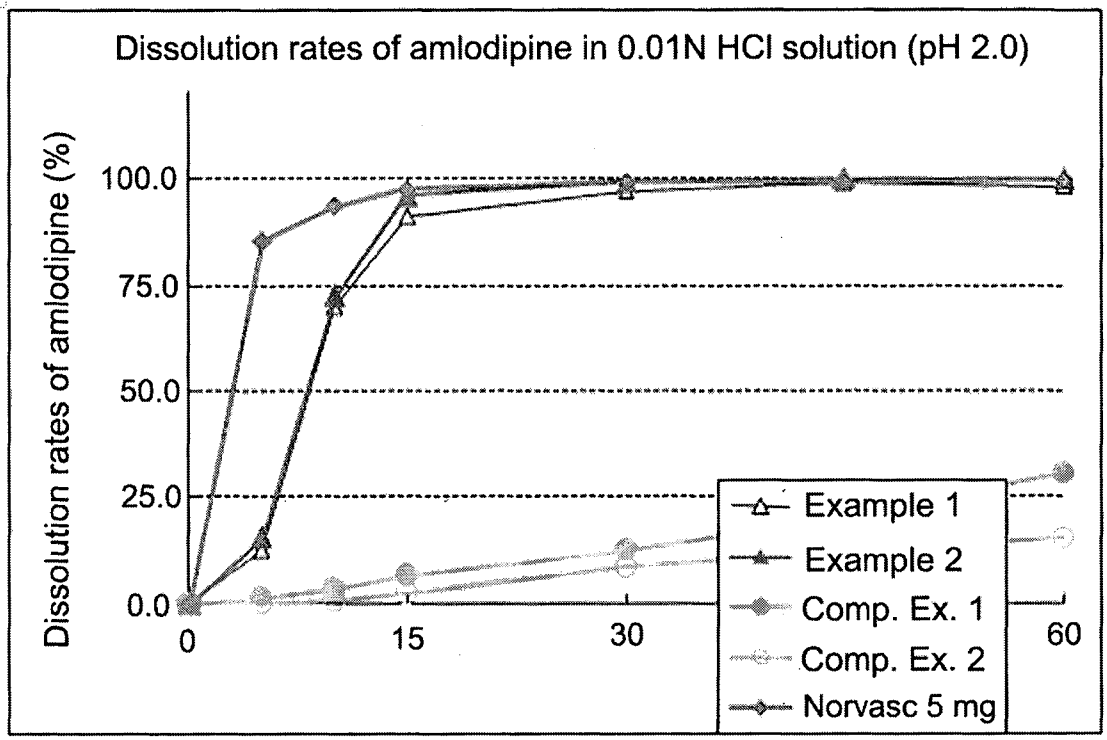

Dissolution rates of hydrochlorothiazide in 0.01N HCl solution (pH 2.0)
Dissolution rates of hydrochlorothiazide (%)
100.0
75.0
50.0
25.0
0.0
0
15
30
60
Time (min)
Example 1
Example 2
Comp. Ex. 1
Comp. Ex. 2
Dichlozid

FIG. 3


Dissolution rates of amlodipine in 0.01N HCl solution (pH 2.0)
Dissolution rates of amlodipine (%)
100.0
75.0
50.0
25.0
0.0
0
15
30
60
Example 1
Example 2
Comp. Ex. 1
Comp. Ex. 2
Norvasc 5 mg

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2012/011569

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/48(2006.01)i, A61K 31/41 7(2006.01)1, A61K 31/44(2006.01)1, A61P 9/00(2006.01)1

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 9/48; A61K 9/22; A61K 31/417; A61K 31/335; A61K 31/495; A61K 31/41; A61K 31/44; A61P 9/02; A61P 9/12

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: losartan, amlodipine, hydrochlorothiazide, discrete layer, cardiovascular, fixed dose combination.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KR 10-2008-0052852 A (HANMI PHARM. CO., LTD.) 12 June 2008 See paragraphs [0013H0016] , [0020]-[0029] , [0032]-[0034] ; examples 1, 8; test example 1; claims 1-5, 12-13.	1-16
Y	KR 10-2008-0039302 A (HANALL PHARMACEUTICAL CO. , LTD.) 07 May 2008 See paragraphs [0075]-[0082] , [0104]-[0120] ; claims 1-8; figures 1-2.	1-16
A	US 2009-0099241 Al (SHETTY, SURAJ SHIVAPPA et al.) 16 April 2009 See paragraphs [0002]-[0009] , [0011]-[0017] , [0025]-[0027] , [0031]-[0036] , [0038H0039] ; claims 1-10.	1-16
A	KR 10-2010-0086921 A (HANMI HOLDINGS CO., LTD.) 02 August 2010 See paragraphs [0014]-[0016] , [0019] ; claims 1-4, 6.	1-16
A	US 2004-0116510 Al (NICHTBERGER, STEVEN A.) 17 June 2004 See paragraphs [0019] , [0029] , [0032] , [0047] , [0062] ; claims 23, 34-35.	1-16

☐ 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

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"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
11 April 2013 (11.04.2013)	**12 April 2013 (12.04.2013)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
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Facsimile No. 82-42-472-7140

Authorized officer

KIM, Dong Seok

Telephone No. 82-42-481-8647

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2012/011569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 10-2008-0052852 A	12.06.2008	AU 2007-328630 A1	12.06.2008
		AU 2007-328630 B2	11.03.2010
		CA 2654054 A1	12.06.2008
		CA 2654054 C	08.01.2013
		CN 101472587 A	01.07.2009
		EP 2037917 A1	25.03.2009
		JP 2009-544752 A	17.12.2009
		JP 4995912 B2	18.05.2012
		MX 2008016099 A	19.01.2009
		MY 144857 A	30.11.2011
		NO 20085302 A	17.06.2009
		NZ 573223 A	27.07.2012
		RU 2008150477	27.06.2010
		US 2010-0233261 A1	16.09.2010
		WO 2008-069612 A1	12.06.2008
		ZA 200910116 A	28.07.2010
KR 10-2008-0039302 A	07.05.2008	CN 101534798 A	16.09.2009
		CN 101534798 B	15.02.2012
		EP 2079452 A1	22.07.2009
		JP 2010-508266 A	18.03.2010
		KR 10-0963389 B1	04.06.2010
		US 2010-0143470 A1	10.06.2010
		WO 2008-054121 A1	08.05.2008
US 2009-0099241 A1	16.04.2009	AR 040014 A1	09.03.2005
		AT 429223 T	15.05.2009
		AU 2003-240261 A1	02.12.2003
		AU 2003-240261 B2	28.06.2007
		BR 0310092 A	15.02.2005
		CA 2486144 A1	27.11.2003
		CA 2486144 C	07.02.2012
		CN 101890166 A	24.11.2010
		CN 1652777 A	10.08.2005
		DE 60327316 D1	04.06.2009
		DK 1507529 T3	03.08.2009
		EG 24716 A	07.06.2010
		EP 1507529 A1	23.02.2005
		EP 1507529 B1	22.04.2009
		EP 1507529 B8	24.02.2010
		ES 2325207 T3	28.08.2009
		HK 1074773 A1	11.09.2009
		IL 164925D0	18.12.2005
		JP 2005-533023 A	04.11.2005
		JP 2010-209123 A	24.09.2010
		KR 10-2011-0107877 A	04.10.2011
		MX PA04011385 A	14.02.2005
		MY 138838 A	31.07.2009
		NO 20045429 A	13.12.2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2012/011569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		NZ 536557 A	27.10.2006
		PE 04392004 A1	20.08.2004
		PL 372369 A1	25.07.2005
		PT 1507529 E	24.07.2009
		RU 2004137105 A	10.09.2005
		RU 2324482 C2	20.05.2008
		SI 1507529 T1	31.10.2009
		US 2005-222137 A1	06.10.2005
		US 2012-115854 A1	10.05.2012
		US 8101599 B2	24.01.2012
		WO 03-097045 A1	27.11.2003
		ZA 200408737 A	22.02.2006
KR 10-2010-0086921 A	02.08.2010	AR 070897 A1	12.05.2010
		AU 2009-338251 A1	29.07.2010
		AU 2009-338267 A1	29.07.2010
		AU 2009-338267 A2	29.07.2010
		AU 2009-338280 A1	29.07.2010
		CA 2749903 A1	29.07.2010
		CA 2749955 A1	29.07.2010
		CA 2749957 A1	29.07.2010
		CN 102292070 A	21.12.2011
		CN 102292084 A	21.12.2011
		CN 102292085 A	21.12.2011
		CO 6361905 A2	20.01.2012
		CO 6361914 A2	20.01.2012
		CO 6361915 A2	20.01.2012
		CR 20110448 A	10.11.2011
		CR 20110449 A	10.11.2011
		CR 20110450 A	10.11.2011
		EA 201170958 A1	30.01.2012
		EP 2391348 A1	07.12.2011
		EP 2391365 A2	07.12.2011
		EP 2413931 A1	08.02.2012
		JP 2012-515767 A	12.07.2012
		JP 2012-515768 A	12.07.2012
		JP 2012-515770 A	12.07.2012
		KR 10-1160151 B1	20.06.2012
		KR 10-1232296 B1	13.02.2013
		KR 10-2010-0086913 A	02.08.2010
		TW 201028151 A	01.08.2010
		TW 201031404 A	01.09.2010
		us 2011-0245301 A1	06.10.2011
		us 2011-0245302 A1	06.10.2011
		us 2011-0251245 A1	13.10.2011
		Wo 2010-085014 A1	29.07.2010
		wo 2010-085027 A1	29.07.2010
		wo 2010-085047 A2	29.07.2010
		wo 2010-085047 A3	04.11.2010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2012/011569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004-0116510 A1	17.06.2004	AU 2002-336267 B2	05.10.2006
		CA 2439920 A1	19.09.2002
		EP 1389114 A2	18.02.2004
		JP 2004-523569 A	05.08.2004
		WO 02-072104 A2	19.09.2002
		WO 02-072104 A3	24.07.2003