Abstract: The invention relates to a solid dosage form comprising an angiotensin II receptor antagonist and a calcium channel blocker, wherein the active ingredients are formulated such that they are not intimately mixed in said solid dosage form. The solid dosage form demonstrates improved dissolution properties.
Solid dosage form

[TECHNICALFIELD]

The present invention relates to a solid dosage form comprising an angiotensin II receptor antagonist and a calcium channel blocker.

[BACKGROUND ART]

Currently, calcium channel blockers and angiotensin II receptor antagonists are widely used clinically as medicaments for the treatment and prophylaxis of hypertension. Since calcium channel blockers exert natriuretic action in addition to vasodilatory action, they are effective against hypertension caused by fluid retention (renin-independent). On the other hand, angiotensin II receptor antagonists are particularly effective against renin-dependent hypertension, and have excellent organ protective effects. Thus, it is expected that the combined use of a calcium channel blocker and an angiotensin II receptor antagonist should allow stable and effective antihypertensive therapy regardless of the cause of the hypertension.

A number of combination drugs comprising an angiotensin II receptor antagonist and a calcium channel blocker have been proposed in the prior art, such as Patent Documents 1 to 4 below. However, there has been no disclosure in the prior art of a solid dosage form comprising an angiotensin II receptor antagonist and calcium channel blocker of the present invention in which each active ingredient is blended separately in the dosage form.

[Patent Document 3] International Publication WO 00/02543
[DISCLOSURE OF THE INVENTION]

The object of the present invention is to provide a solid dosage form comprising an angiotensin II receptor antagonist and a calcium channel blocker with improved dissolution properties.

As a result of conducting extensive research to solve the aforementioned problems, the present inventors found that the dissolution properties of a solid dosage form comprising an angiotensin II receptor antagonist and a calcium channel blocker are improved by separately blending each active ingredient to form particles and then mixing the particles comprising each active ingredient such that they are not intimately mixed in the dosage form, thereby leading to completion of the present invention.

The present invention provides a solid dosage form comprising an angiotensin II receptor antagonist and a calcium channel blocker, wherein each active ingredient is in the form of particles and the particles comprising each active ingredient are not intimately mixed in the dosage form (particularly a dosage form for the prophylaxis or treatment of hypertension), the use of an angiotensin II receptor antagonist and a calcium channel blocker to manufacture the aforementioned solid dosage form (and particularly a dosage form for the prophylaxis or treatment of hypertension), and a method for preventing or treating a disease (particularly hypertension) in which the aforementioned solid dosage form comprising pharmacologically effective amounts of angiotensin II receptor antagonist and calcium channel blocker is administered to warm-blooded animals (particularly humans).

Specifically, the present invention provides:
(1) a solid dosage form comprising an angiotensin II receptor antagonist and a calcium channel blocker, wherein the active ingredients are formulated such that they are not intimately mixed in the dosage form,
(2) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is losartan, candesartan, valsartan, telmisartan, pratosartan, olmesartan or irbesartan or a pharmacologically acceptable salt or ester thereof,
(3) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is losartan, candesartan cilexetil, valsartan, telmisartan, pratosartan, olmesartan medoxomil or irbesartan,
(4) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil,
(5) the solid dosage form according to (1) to (4) wherein the calcium channel blocker is nifedipine, nimodipine, nilvadipine, manidipine, barnidipine, nitrendipine, benidipine, nicardipine, lercanidipine, amlodipine, nisoldipine, efonidipine, cilnidipine, azelnidipine, felodipine, aranidipine or pranidipine or a pharmacologically acceptable salt thereof,
(6) the solid dosage form according to (1) to (4) wherein the calcium channel blocker is manidipine, barnidipine, benidipine, nicardipine, lercanidipine, amlodipine, efonidipine or azelnidipine or a pharmacologically acceptable salt thereof,
(7) the solid dosage form according to (1) to (4) wherein the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof,
(8) the solid dosage form according to (1) to (4) wherein the calcium channel blocker is amlodipine besylate,
(9) the solid dosage form according to (1) to (8) wherein said solid dosage form is a tablet,
(10) the solid dosage form according to (9) wherein the tablet contains particles containing an angiotensin II receptor antagonist and particles containing a calcium channel blocker,
(11) the solid dosage form according to (10) wherein an intermediate layer is present between the particles containing an angiotensin II receptor antagonist and the particles containing a calcium channel blocker,
(12) the solid dosage form according to (9) wherein the tablet is a multi-layer tablet in which each individual layer of said multi-layer tablet contains only one active ingredient selected from said angiotensin II receptor antagonist and said calcium channel blocker,
(13) the solid dosage form according to (9) wherein the tablet is a double-layer tablet, in which the angiotensin II receptor antagonist is contained in the first layer and the calcium channel blocker is contained in the second layer,
(14) the solid dosage form according to (13) wherein an intermediate layer is present between the first and second layers,
(15) the solid dosage form according to (9) wherein the tablet is a dry-coated tablet in which the angiotensin II receptor is contained in the inner core thereof and the calcium channel blocker is contained in the outer layer thereof,
(16) the solid dosage form according to (9) wherein the tablet is a dry-coated tablet in which the calcium channel blocker is contained in the inner core thereof and the angiotensin II receptor antagonist is contained in the outer layer thereof,
(17) the solid dosage form according to (15) or (16) wherein an intermediate layer is present between the inner core and outer layer,
(18) the solid dosage form according to (1) to (17) wherein said solid dosage form further comprises a hydrophilic polymer,
(19) the solid dosage form according to (10) or (11) wherein the particles containing the angiotensin II receptor antagonist further comprise a hydrophilic polymer,
(20) the solid dosage form according to (10) or (11) wherein the particles containing the calcium channel blocker further comprise a hydrophilic polymer,
(21) the solid dosage form according to (11) wherein the intermediate layer further comprises a hydrophilic polymer,
(22) the solid dosage form according to (12) to (14) wherein the layer containing the angiotensin II receptor antagonist further comprises a hydrophilic polymer,
(23) the solid dosage form according to (12) to (14) wherein the layer containing the calcium channel blocker further comprises a hydrophilic polymer,
(24) the solid dosage form according to (15) to (17) wherein the inner core further comprises a hydrophilic polymer,
(25) the solid dosage form according to (15) to (17) wherein the outer layer further comprises a hydrophilic polymer,
(26) the solid dosage form according to (18) to (25) wherein the hydrophilic polymer is at least one compound selected from cellulose derivatives and synthetic polymers,
(27) the solid dosage form according to (18) to (25) wherein the hydrophilic polymer is at least one compound selected from hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol,
(28) the solid dosage form according to (18) to (25) wherein the hydrophilic polymer is at least cellulose derivative,
(29) the solid dosage form according to (18) to (25) wherein the hydrophilic polymer is at least one compound selected from hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose,

(30) the solid dosage form according to (18) to (25) wherein the hydrophilic polymer is either or both of methyl cellulose and hydroxypropyl cellulose,

(31) the solid dosage form according to (18) to (25) wherein the hydrophilic polymer is macrogol.

In addition, a solid dosage form obtained by arbitrarily combining (1) to (31) above is also preferable, examples of which are indicated below.

(32) The solid dosage form according to (1) wherein the angiotensin II receptor antagonist is losartan, candesartan cilexetil, valsartan, telmisartan, pratosartan, olmesartan medoxomil or irbesartan and the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof,

(33) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil and the calcium channel blocker is nifedipine, nimodipine, nilvadipine, manidipine, barnidipine, nitrendipine, benidipine, nicardipine, lercanidipine, amlodipine, nisoldipine, efonidipine, cilnidipine, azelnidipine, felodipine, aranidipine or pranidipine or a pharmacologically acceptable salt thereof,

(34) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil and the calcium channel blocker is manidipine, barnidipine, benidipine, nicardipine, lercanidipine, amlodipine, efonidipine or azelnidipine or a pharmacologically acceptable salt thereof,

(35) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil and the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof,

(36) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a tablet comprising particles containing the angiotensin II receptor antagonist and particles containing the calcium channel blocker,
(37) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a double-layer tablet in which the angiotensin II receptor antagonist is contained in the first layer and the calcium channel blocker is contained in the second layer,

(38) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a dry-coated tablet in which the calcium channel blocker is contained in the inner core thereof and the angiotensin II receptor antagonist is contained in the outer layer thereof,

(39) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a tablet comprising particles containing the angiotensin II receptor antagonist and particles containing the calcium channel blocker, said particles containing the calcium channel blocker further comprising at least one hydrophilic polymer selected from hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol,

(40) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof, and the solid dosage form is a double-layer tablet in which the angiotensin II receptor antagonist is contained in the first layer and the calcium channel blocker is contained in the second layer, the layer containing the calcium channel blocker further comprising at least one hydrophilic polymer selected from hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol,

(41) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof, the solid dosage form is a dry-coated tablet in which the calcium channel blocker is contained in the inner core thereof and the
angiotensin II receptor antagonist is contained in the outer layer thereof, the inner core further comprising at least one hydrophilic polymer selected from hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol,
(42) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof, and the solid dosage form is a tablet comprising particles containing the angiotensin II receptor antagonist and particles containing the calcium channel blocker, said particles containing the calcium channel blocker further comprising a hydrophilic polymer selected from methyl cellulose and hydroxypropyl cellulose,
(43) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof, and the solid dosage form is a two-layer tablet in which the angiotensin II receptor antagonist is contained in the first layer and the calcium channel blocker is contained in the second layer, wherein the second layer containing the calcium channel blocker further comprises a hydrophilic polymer selected from methyl cellulose and hydroxypropyl cellulose,
(44) the solid dosage form according to (1) wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a dry-coated tablet in which the calcium channel blocker is contained in the inner core thereof while the angiotensin II receptor antagonist is contained in the outer layer thereof, wherein the inner core containing the calcium channel blocker further contains a hydrophilic polymer selected from methyl cellulose and hydroxypropyl cellulose, and
(45) the solid dosage form according to (32) to (44) wherein the calcium channel blocker is amlodipine besylate.

According to the present invention, a solid dosage form, that contains an angiotensin II receptor antagonist and a calcium channel blocker, with improved dissolution properties can be provided.
[BEST MODE FOR CARRYING OUT THE INVENTION]

The solid dosage form of the present invention contains an angiotensin II receptor antagonist and a calcium channel blocker as its active ingredients.

Since various medicaments have been proposed as an "angiotensin II receptor antagonist", which is one of the active ingredients in a solid dosage form of the present invention, and many are actually used clinically, a person of ordinary skill in the art can select suitable medicaments that demonstrate the desired effect as an angiotensin II receptor antagonist for use in the present invention. Suitable, non-limiting examples of angiotensin II receptor antagonists include losartan (preferably losartan potassium), candesartan cilexetil, valsartan, telmisartan, pratosartan, olmesartan medoxomil and irbesartan. Of these, olmesartan medoxomil is preferably used. Olmesartan medoxomil can be easily produced according to the methods disclosed in the art, suitable examples including the methods disclosed in Japanese Patent No. 2082519 (corresponding to US Patent No. 5,616,599).

Since various medicaments have been proposed as a "calcium channel blocker", which is one of the active ingredients in a solid dosage form of the present invention, and many are actually used clinically, a person of ordinary skill in the art can select suitable medicaments that demonstrate the desired effect as a calcium channel blocker for use in the present invention. Suitable, non-limiting examples of calcium channel blockers include nifedipine, nimodipine, nilvadipine, manidipine (preferably manidipine hydrochloride), barnidipine (preferably barnidipine hydrochloride), nitrendipine, benidipine (preferably benidipine hydrochloride), nicardipine (preferably nicardipine hydrochloride), lercanidipine (preferably lercanidipine hydrochloride), amlodipine (preferably amlodipine besylate), nisoldipine, efonidipine (preferably efonidipine hydrochloride), cilnidipine, azelnidipine, felodipine, aranidipine and pranidipine. Of these amlodipine (particularly amlodipine besylate) is preferably used. Amlodipine and its salts including amlodipine besylate can be easily produced according to the methods disclosed in the art, suitable examples including the methods disclosed in Japanese Patent No. 1401088 (corresponding to US Patent No. 4,572,909).
The pharmacologically acceptable salts of angiotensin II receptor antagonists and a calcium channel blockers described above are not specifically restricted and these salts can be selected by a person of ordinary skill in the art. Suitable pharmacologically acceptable salts include, for example, an alkaline metal salt such as a sodium salt, potassium salt or lithium salt; an alkaline earth metal salt such as a calcium salt or magnesium salt; a metal salt such as an aluminium salt, iron salt, zinc salt, copper salt, nickel salt or cobalt salt; an amine salt such as an ammonium salt, t-octylamine salt, dibenzylationamine salt, morpholine salt, glucosamine salt, phenylglycine alkyl ester salt, ethylenediamine salt, N-methylglucamine salt, guanidine salt, diethyamine salt, triethylamine salt, dicyclohexylamine salt, N,N'-dibenzylethlenediamine salt, chloroproxamine salt, procaine salt, diethanolamine salt, N-benzyl-phenethylamine salt, piperazine salt, tetramethylammonium salt or tris(hydroxymethyl)aminomethane salt; a hydrohalogenic acid salt such as a hydrofluoride, hydrochloride, hydrobromide or hydroiodide; a nitrate; a perchlorate; a sulfate; a phosphate; a C₁-C₄ alkanesulfonic acid salt, which may be optionally substituted with a halogen atom(s) such as a methanesulfonate, trifluoromethanesulfonate or ethanesulfonate; a C₆-C₁₀ arylsulfonic acid salt, which may be optionally substituted with a C₅-C₁₄ alkyl group(s), such as a benzenesulfonate or p-toluenesulfonate; a C₅-C₁₆ aliphatic acid salt such as an acetate, malate, fumarate, succinate, citrate, tartrate, oxalate or maleate; or an amino acid salt such as a glycine salt, lysine salt, arginine salt, ornithine salt, glutamic acid salt or aspartic acid salt.

The pharmacologically acceptable esters of the angiotensin II receptor antagonists described above are not particularly restricted, and can be selected by a person of ordinary skill in the art. In the case of said esters, it is preferable that such esters can be cleaved by a biological process such as hydrolysis in vivo. The group constituting the esters (the group shown as R when the esters thereof are expressed as -COOR) can be, for example, a C₁-C₄ alkoxy C₁-C₄ alkyl group such as methoxyethyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, 1-(isopropoxy)ethyl, 2-methoxyethyl, 2-ethoxyethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl or t-butoxymethyl; a C₁-C₄ alkoxylated C₁-C₄ alkoxy C₁-C₄ alkyl group such as 2-methoxyethoxymethyl; a C₆-C₁₀ aryloxy C₁-C₄ alkyl group
such as phenoxymethyl; a halogenated Ci-C₄ alkoxy Ci-C₄ alkyl group such as 2,2,2-trichloroethoxymethyl or bis(2-chloroethoxy)methyl; a Ci-C₄ alkoxycarbonyl Ci-C₄ alkyl group such as methoxycarbonylmethyl; a cyano Ci-C₄ alkyl group such as cyanoethyl or 2-cyanoethyl; a Ci-C₄ alkylthiomethyl group such as methylthiomethyl or ethylthiomethyl; a C₆-Ci₀ arylthiomethyl group such as phenylthiomethyl or naphthylthiomethyl; a Ci-C₄ alkylsulfonyl Ci-C₄ lower alkyl group, which may be optionally substituted with a halogen atom(s) such as 2-methanesulfonylethyl or 2-trifluoromethanesulfonylethyl; a C₆-Ci₀ arylsulfonyl Ci-C₄ alkyl group such as 2-benzenesulfonylethyl or 2-toluenesulfonylethyl; a Ci-C₄ aliphatic acyloxy Ci-C₄ alkyl group such as formyloxymethyl, acetoxymethyl, propiomyloxymethyl, butyryloxymethyl, pivaloyloxymethyl, valeryloxymethyl, isovaleryloxymethyl, hexanoyloxymethyl, 1-formyloxyethyl, 1-acetoxyethyl, 1-propiomyloxyethyl, 1-butyryloxymethyl, 1-pivaloyloxymethyl, 1-valeryloxymethyl, 1-isovaleryloxymethyl, 1-hexanoyloxymethyl, 2-formyloxymethyl, 2-acetoxyethyl, 2-propiomyloxyethyl, 2-butyryloxymethyl, 2-pivaloyloxymethyl, 2-valeryloxymethyl, 2-isovaleryloxymethyl, 2-hexanoyloxymethyl, 1-formyloxypropyl, 1-acetoxypropyl, 1-propiomyloxypropyl, 1-butyryloxypropyl, 1-pivaloyloxypropyl, 1-valeryloxypropyl, 1-isovaleryloxypropyl, 1-hexanoyloxypropyl, 1-acetoxybutyl, 1-propiomyloxybutyl, 1-butyryloxypentyl, 1-pivaloyloxypentyl, 1-acetoxypropyl, 1-propiomyloxypentyl, 1-butyryloxypentyl, 1-pivaloyloxypentyl or 1-pivaloyloxyhexyl; a C₅-C₆ cycloalkylcarbonyloxy Ci-C₄ alkyl group such as cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl, 1-cyclopentylcarbonyloxymethyl, 1-cyclopentylcarbonyloxypentyl, 1-cyclohexylcarbonyloxymethyl, 1-cyclohexylcarbonyloxypentyl, 1-cyclopentylcarbonyloxybutyl or 1-cyclohexylcarbonyloxybutyl; a C₆-Ci₀ arylcarbonyloxy Ci-C₄ alkyl group such as benzoyloxymethyl; a Ci-C₆ alkoxy carbonyloxy Ci-C₄ alkyl group such as methoxycarbonyloxymethyl, 1-(methoxycarbonyloxymethyl)ethyl, 1-(methoxycarbonyloxy)propyl, 1-(methoxycarbonyloxy)butyl, 1-(methoxycarbonyloxypentyl, 1-(methoxycarbonyloxy)hexyl, ethoxycarbonyloxymethyl, 1-(ethoxycarbonyloxymethyl, 1-(ethoxycarbonyloxy)ethyl, 1-(ethoxycarbonyloxy)propyl, 1-(ethoxycarbonyloxy)butyl, 1-(ethoxycarbonyloxypentyl, 1-(ethoxycarbonyloxy)hexyl, propoxycarbonyloxymethyl, 1-(propoxycarbonyloxymethyl, 1-(propoxycarbonyloxymethyl)ethyl, 1-(propoxycarbonyloxy)propyl, 1-
(propoxycarbonyloxy)butyl, isopropoxycarbonyloxymethyl, 1-
(isopropoxycarbonyloxy)ethyl, 1-(isopropoxycarbonyloxy)butyl,
butoxycarbonyloxymethyl, 1-(butoxycarbonyloxy)ethyl, 1-(butoxycarbonyloxy)propyl,
l-(butoxycarbonyloxy)butyl, isobutoxycarbonyloxymethyl, 1-
(isobutoxycarbonyloxy)ethyl, 1-(isobutoxycarbonyloxy)propyl, 1-
(isobutoxycarbonyloxy)butyl, t-butoxycarbonyloxymethyl, l-(t-
butoxycarbonyloxy)ethyl, pentyloxycarbonyloxymethyl, 1-(pentyloxycarbonyloxy)ethyl,
1-(pentyloxycarbonyloxy)propyl, hexyloxycarbonyloxymethyl, 1-(hexyloxycarbonyloxy)ethyl, 1-
(hexyloxycarbonyloxy)propyl or 1-(hexyloxycarbonyloxy)propyl; a C$_{5}$-C$_{6}$
cycloalkyloxycarbonyloxy C$_{1}$-C$_{4}$ alkyl group such as
cyclopentyloxycarbonyloxymethyl, l-(cyclopentyloxycarbonyloxy)ethyl, 1-
(cyclopentyloxycarbonyloxy)propyl, 1-(cyclopentyloxycarbonyloxy)butyl,
cyclohexyloxycarbonyloxymethyl, l-(cyclohexyloxycarbonyloxy)ethyl, 1-
(cyclohexyloxycarbonyloxy)propyl or l-(cyclohexyloxycarbonyloxy)butyl; a [5-(C$_{1}$-C$_{4}$
alkyl)-2-oxo-1,3-dioxolen-4-yl]methyl group such as (5-methyl-2-oxo-1,3-dioxolen-4-
yl)methyl, (5-ethyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxolen-4-
yl)methyl, (5-isopropyl-2-oxo-1,3-dioxolen-4-yl)methyl or (5-butyl-2-oxo-1,3-
dioxolen-4-yl)methyl; a [5-(phenyl, which may be optionally substituted with a C$_{1}$-C$_{4}$
alkyl, C$_{1}$-C$_{4}$ alkoxy or halogen atom(s))-2-oxo-1,3-dioxolen-4-yl]methyl group such as
(5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl, [5-(4-methylphenyl)-2-oxo-1,3-dioxolen-4-
yl]methyl, [5-(4-methoxyphenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, [5-(4-fluorophenyl)-
2-oxo-1,3-dioxolen-4-yl]methyl or [5-(4-chlorophenyl)-2-oxo-1,3-dioxolen-4-
yl]methyl; or a phthalidyl group, which may be optionally substituted with a C$_{1}$-C$_{4}$ alkyl
or C$_{1}$-C$_{4}$ alkoxy group(s), such as phthalidyl, dimethylphthalidyl or
dimethoxyphthalidyl.

In one preferred embodiment of the present invention, the solid dosage of the
present invention additionally contains at least one "hydrophilic polymer", i.e. a
polymer that has an affinity for water. Preferred "hydrophilic polymers" for use in the
present invention are ones which are water-soluble. Incorporation of a hydrophilic
polymer can give a solid dosage form with dissolution properties which are further
improved. Suitable, non-limiting examples of hydrophilic polymers for use in the
present invention include cellulose derivatives such as hydroxypropyl methyl cellulose, cellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose; synthetic polymers such as polyvinylpyrrolidone, aminoalkyl methacrylate copolymer, carboxyvinyl polymer, polyvinyl alcohol and macrogol (i.e. polyethylene glycol); HA Sankyo (a pre-mixed coating agent comprising a mixture of 16-26% by weight of polyvinyl acetal diethyl aminoacetate, 50-75% by weight of hydroxypropylmethyl cellulose 2910, 12-17% by weight of stearic acid and 1.5-2.3% by weight of fumaric acid), gum Arabic, agar, gelatin and sodium alginate. Of these, hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol are preferred, hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, macrogol and sodium carboxymethyl cellulose are more preferred, and methyl cellulose is most preferred. In the present invention, these hydrophilic polymers can be used alone or two or more kinds can be used in combination. Where at least one hydrophilic polymer is present in the solid dosage form of the present invention, said hydrophilic polymer (or polymers) is preferably present in an amount of from 1 to 90% by weight of the total weight of the solid dosage form, and more preferably from 5 to 85% by weight. The one or more hydrophilic polymers may be uniformly distributed throughout the entire solid dosage form, or they may be contained in only a part of said solid dosage form. If one or more film coating layers are used in the preparation of the solid dosage form, the one or more hydrophilic polymers may be contained in said film coating layers.

The solid dosage form of the present invention can where desired additionally contain at least one further additive such as a suitable pharmacologically acceptable excipient, lubricant, binder, disintegrants, emulsifier, stabilizer, corrective or diluent.

Suitable "excipients" include organic excipients including sugar derivatives such as lactose, sucrose, glucose, mannitol or sorbitol; starch derivatives such as corn starch, potato starch, a-starch or dextrin; cellulose derivatives such as microcrystalline cellulose; gum Arabic; dextran; and pullulan, and inorganic excipients including silicate derivatives such as light anhydrous silicic acid, synthetic aluminum silicate, calcium silicate or magnesium metasilicate aluminate; phosphates such as dibasic calcium
hydrogenphosphate; carbonates such as calcium carbonate; and sulfates such as calcium sulfate.

Suitable "lubricants" include stearic acid; stearic acid metal salts such as calcium stearate or magnesium stearate; talc; colloidal silica; waxes such as beeswax or spermaceti; boric acid; adipic acid; sulfates such as sodium sulfate; glycol; fumaric acid; sodium benzoate; D.H-β-eucine; lauryl sulfates such as sodium lauryl sulfate or magnesium lauryl sulfate; silicates such as silicic anhydride or silicate hydrate; and the aforementioned starch derivatives.

Suitable "binders" include hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, macrogol and compounds similar to the aforementioned excipients.

Suitable "disintegrants" include cellulose derivatives such as low-substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose or internally crosslinked sodium carboxymethyl cellulose; cross-linked polyvinylpyrrolidone; and chemically modified starches/celluloses such as carboxymethyl starch or sodium carboxymethyl starch.

Suitable "emulsifiers" include colloidal clays such as bentonite or bee gum; metal hydroxides such as magnesium hydroxide or aluminum hydroxide; anionic surfactants such as sodium lauryl sulfate or calcium stearate; cationic surfactants such as benzalkonium chloride; and nonionic surfactants such as polyoxyethylene alkyl ether, polyoxyethylene sorbitan fatty acid ester or sucrose fatty acid ester.

Suitable "stabilizers" include para-hydroxybenzoic acid esters such as methyl paraben or propyl paraben; alcohols such as chlorobutanol, benzyl alcohol or phenyl ethyl alcohol; benzalkonium chloride; phenols such as phenol or cresol; thimerosal; dehydroacetic acid; and sorbic acid.
Suitable "correctives" include sweeteners such as sodium saccharin or aspartame; sour flavourings such as citric acid, malic acid or tartaric acid; and fragrances such as menthol, lemon or orange fragrance.

Suitable "diluents" include lactose, mannitol, glucose, sucrose, calcium sulfate, calcium phosphate, hydroxypropyl cellulose, microcrystalline cellulose, water, ethanol, polyethylene glycol, propylene glycol, glycerol, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, and mixtures thereof.

The "solid dosage form" of the present invention comprises any dosage form used by the person skilled in the art to deliver one or more pharmacologically active ingredients to a patient in a solid form, but must be produced in such a manner that the calcium channel blocker and the angiotensin II receptor antagonist are not intimately mixed, i.e. each active ingredient is formed into a separate physical form such as particles which does not contain the other active ingredient and the particles are only mixed when producing the solid dosage form, or the solid dosage form is formulated in such a way that the active ingredients are kept apart in some manner (e.g. by formulating the individual active ingredients in layers). Suitable solid dosage forms will be well known to the person skilled in the art, and non-limiting examples of the solid dosage form of the present invention include tablets (including sublingual tablets and tablets that disintegrate in the mouth), capsules (including soft capsules and microcapsules), granules, pills and lozenges. Of these, tablets are most preferred.

"Particles" in the solid dosage forms of the present invention are particles having a nearly uniform shape and size obtained from raw materials, in a form such as powders, lumps, solutions or molten liquids, by granulation of said raw materials using suitable techniques such as wet granulation, dry granulation or heated granulation. Suitable examples of particles for use in the preparation of the solid dosage forms of the present invention include powders, grains or granules, and they preferably having a particle size defined in the 14th Revised Edition of the Japanese Pharmacopoeia. Granules have a size distribution such that all of said granules pass through a No. 10 (1700 µm) sieve, not more than 5% of total granules remain on a No. 12 (1400 µm) sieve and not more
than 15% of total granules pass through a No. 42 (355 µm) sieve. Powders and grains
(which are included within the definition of powders in the 14th Revised Edition of the
Japanese Pharmacopoeia) have a size distribution such that all of said powders pass
through a No. 18 (850 µm) sieve and not more than 5% of total granules remain on a No.
30 (500/µm) sieve.

Furthermore, although the shape and size of particles of the present invention
may change during the course of formulation in order to provide a solid dosage form of
the present invention, particles that do not retain their original form as a result of their
shape and size changing in this manner are still included within the scope of the
particles used in the solid dosage forms of the present invention.

In the present invention, a "multi-layer tablet" refers to a tablet in which
different active ingredients and any desired pharmacologically acceptable additives
have been laminated in separate layers in a stepwise manner and then compression
moulded to incorporate into a single dosage form.

In the present invention, a "double-layer tablet" refers to a tablet in which a first
tablet containing one active ingredient and any desired pharmacologically acceptable
additives and a second tablet containing another active ingredient and any desired
pharmacologically acceptable additives are laminated in layers. The two layers may be
in contact or an intermediate layer may be provided using an inert additive for the
purpose of avoiding direct contact between the active ingredients.

In the present invention, a "dry-coated tablet" refers to a tablet in which an inner
core containing one active ingredient and any desired pharmacologically acceptable
additives is coated with an outer layer containing another active ingredient and any
desired pharmacologically acceptable additives so as to envelop the inner core. The
inner core and outer layer may be in contact, or an intermediate layer may be provided
using an inert additive for the purpose of avoiding direct contact between the active
ingredients.
A dosage form of the present invention may be produced using any commonly used method well known to persons skilled in the art of pharmaceutical formulation technology and there are no particular limitations thereon. Examples of suitable methods include those disclosed in publications such as Powder Technology and Pharmaceutical Processes [D. Chulia et al., Elsevier Science Pub. Co. (December 1, 1993)].

Particles of the present invention can be produced by granulating in accordance with commonly used methods in the field of pharmaceutical technology. Granulation can be carried out by any conventional method, examples of which include wet granulation, dry granulation and heated granulation, and more specifically is carried out using a high-speed agitation granulator, fluidized granulation dryer, extrusion granulator or roller compactor. In addition, procedures such as drying and sizing may be carried out as necessary following granulation.

A multi-layer tablet of the present invention can be produced by a known method such as direct compression moulding of each layer containing an active ingredient, or by respectively producing each layer containing an active ingredient using an ordinary wet granulation or dry granulation (compression) technique followed by compression moulding each layer.

A double-layer tablet of the present invention can be produced by a known method such as respectively producing the first and second layers using an ordinary wet granulation or dry granulation (compression) technique followed by compressing the first and second layers, and then bonding both layers using an ordinary double-layer tablet moulding apparatus. In addition, a double-layer tablet of the present invention may also be provided with at least one layer of an outer film coating.

A dry-coated tablet of the present invention can be produced by a known method such as producing an inner core tablet to serve as the inner core, and then coating the inner core tablet with an outer layer using a dry-coated tablet press. In addition, the inner core tablet (inner core) may also be provided with a thin film coating prior to
coating with the outer layer. Furthermore, one inner core tablet or a plurality of inner core tablets may be contained in a single dosage form. A dry-coated tablet of the present invention may also be provided with at least one layer of an outer film coating.

If a film coating is desired, any film coating apparatus of a type well known in the art can be used, and as film coating bases, suitable examples include sugar coating bases, hydrophilic film coating bases, enteric film coating bases and sustained release film coating bases.

Suitable examples of sugar coating bases include saccharose, and these can be used in combination with one or more additives such as talc, precipitated calcium carbonate, calcium phosphate, calcium sulfate, gelatin, gum Arabic, polyvinylpyrrolidone and pullulan.

Suitable examples of hydrophilic film coating bases include cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose; synthetic polymers such as polyvinyl acetal diethyl aminoacetate, aminoalkyl methacrylate copolymer, polyvinylpyrrolidone and macrogol; and polysaccharides such as pullulan.

Suitable examples of enteric film coating bases include cellulose derivatives such as hydroxypropyl methyl cellulose, phthalate hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose and cellulose acetate phthalate; acrylic acid derivatives such as methacrylic acid copolymer L, methacrylic acid copolymer LD and methacrylic acid copolymer S; and natural substances such as shellac.

Suitable examples of sustained release film coating bases include cellulose derivatives such as ethyl cellulose; and acrylic acid derivatives such as aminoalkyl methacrylate copolymer RS, ethyl acrylate-methyl methacrylate copolymer emulsion.

A mixture of two or more different coating bases such as those above may also be used in a suitable ratio. In addition, the coating films may also contain suitable
pharmacologically acceptable additives such as plasticizers, excipients, lubricants, opacifying agents, colorants or antiseptics as necessary.

The doses and the dosing ratios of the angiotensin II receptor antagonist and calcium channel blocker, which are the active ingredients in the solid dosage form of the present invention, can be changed depending on various factors such as the activity of each of the active ingredients and the symptoms, age and body weight of the patient. Although the dosage varies depending on symptoms, age and the like, the dose of each class of active ingredient in the case of oral administration is typically from 0.001 mg/kg (preferably 0.01 mg/kg) per day as a lower limit to 10 mg/kg (preferably 1 mg/kg) per day as an upper limit for a human adult, and the dosage can be administered from one to six times per day depending on the symptoms of the patients.

In addition, the dosing ratio of the angiotensin II receptor antagonist and calcium channel blocker, which are the active ingredients in the solid dosage form of the present invention, can also be changed over a wide range. For example, the dosing ratio by weight of angiotensin II receptor antagonist and calcium channel blocker can typically be within a range of 1:1000 to 1000:1, preferably within a range of 1:100 to 100:1, and more preferably within a range of 1:10 to 10:1.

The solid dosage form of the present invention is effective for the prophylaxis or treatment of, for example, hypertension or diseases caused by hypertension [more specifically, hypertension, heart disease (angina pectoris, myocardial infarction, arrhythmia, cardiac insufficiency or hypercardia), kidney disease (diabetic nephropathy, glomerular nephritis or nephrosclerosis), or cerebrovascular disease (cerebral infarction or cerebral hemorrhage)] and the like.

[EXAMPLES]

The present invention will be described in more detail by way of the following examples, but the scope of the present invention is not limited thereto.

Example 1 Single-Layer Tablet Containing Two Kinds of Granules
(1) Olmesartan medoxomil, lactose, low substituted hydroxypropyl cellulose and hydroxypropyl cellulose were each weighed out in the relative amounts given in the column headed "Granules A" of Table 1 below, and they were then mixed with a high-speed agitating granulator (VG-10, Powrex). Purified water was added to the resulting powdered mixture (the amount of water added to the mixed powder was 43% by weight of the powdered mixture) and the resulting mixture was then subjected to granulation and drying with a fluidized granulation dryer (Powrex). The granules thus obtained were sized with a granule sizer (Comill, Powrex) and mixed with microcrystalline cellulose and magnesium stearate in a mixer (V-mixer, Tokuju) to give Granules A.

(2) Amlodipine besylate, lactose, low substituted hydroxypropyl cellulose and hydroxypropyl cellulose were each weighed out in the relative amounts given in the column headed "Granules B" of Table 1 below, and they were then mixed for 2 minutes in an agate mortar before kneading with purified water (the amount of water added to the mixed powder was 34% by weight of the powdered mixture). After drying the resulting mixture with a vacuum dryer, the dried mixture was passed through a 30 mesh sieve (500 µm) followed by the addition of microcrystalline cellulose and magnesium stearate to the sieved mixture and mixing for 2 minutes in an agate mortar to give Granules B.

(3) Granules A and B produced in (1) and (2) above were mixed for 2 minutes in an agate mortar to provide mixed granules. 240 mg of the resulting mixed granules were loaded into a 8.5 mm diameter mould and formed into tablets using a hydraulic single-action tablet press with a stamp having an 8.5 mm diameter surface at a tablet weight of 240 mg and pressing pressure of 10 kN. The dissolution properties of the resulting tablets (single-layer tablets containing two kinds of granules) were tested according to the procedure shown in the Test Example below and the results are shown in the following Table 2.

Example 2 Double-Layer Tablet

(1) Amlodipine besylate, lactose, low substituted hydroxypropyl cellulose and magnesium stearate were each weighed out in the relative amounts given in the column headed "Granules C" of in Table 3 below and then mixed for 2 minutes in an agate mortar to give Granules C.
(2) Next, 120 mg of Granules A obtained in Example 1 were loaded into a 7 mm diameter mould, 100 mg of Granules C were then loaded into the mould and the loaded granules were then formed into a tablet using a hydraulic single-action tablet press with a stamp having a 7 mm diameter surface at a tablet weight of 220 mg and pressing pressure of 10 kN. The dissolution properties of the resulting tablets (double-layer tablets) were tested according to the procedure shown in the Test Example below and the results are shown in the following Table 4.

Example 3 Double-Layer Tablets

(1) Amlodipine besylate, lactose, low substituted hydroxypropyl cellulose, methyl cellulose and magnesium stearate were each weighed out in the relative amounts given in the column headed "Granules D" of Table 3 below and then mixed for 2 minutes in an agate mortar to provide Granules D.

(2) Next, 120 mg of Granules A obtained in Example 1 were loaded into a 7 mm diameter mould, 100 mg of Granules D were then loaded into the mould and the loaded granules were then formed into a tablet using a hydraulic single-action tablet press with a stamp having a 7 mm diameter surface at a tablet weight of 220 mg and pressing pressure of 10 kN. The dissolution properties of the resulting tablets (double-layer tablets) were tested according to the procedure shown in the Test Example below and the results are shown in the following Table 4.

Example 4 Amlodipine Dry-Coated Tablets

(1) Amlodipine besylate, lactose, low substituted hydroxypropyl cellulose and magnesium stearate were each weighed in the relative amounts given in the column headed "Tablet E" of Table 5 below and then mixed for 2 minutes in an agate mortar. The resulting mixture was then formed into tablets using a hydraulic single-action tablet press with a stamp having a 5.5 mm diameter surface at a tablet weight of 50 mg and pressing pressure of 10 kN to give Tablet E.

(2) 60 mg of Granules A obtained in Example 1 were loaded into a 7.5 mm diameter mould followed by the loading of Tablet E into the mould. After again loading 60 mg of Granules A into the mould, tablets were formed using a hydraulic single-action tablet press at a tablet weight of 170 mg and pressing pressure of 10 kN. The dissolution
properties of the resulting tablets (dry-coated tablets) were tested according to the
procedure shown in the Test Example below and the results are shown in the following
Table 6.

Example 5 Amlodipine Dry-Coated Tablets

(1) Amlodipine besylate, lactose, low substituted hydroxypropyl cellulose, methyl
cellulose and magnesium stearate were each weighed out in the relative amounts given
in the column headed “Tablet F” of Table 5 below and then mixed for 2 minutes in an
agate mortar. The resulting mixture was then formed into tablets using a hydraulic
single-action tablet press with a stamp having a 5.5 mm diameter surface at a tablet
weight of 50 mg and pressing pressure of 10 kN to give Tablet F.

(2) 60 mg of Granules A obtained in Example 1 were loaded into a 7.5 mm diameter
mould followed by the loading of Tablet F into the mould. After again loading 60 mg
of Granules A into the mould, tablets were formed using a hydraulic single-action tablet
press at a tablet weight of 170 mg and pressing pressure of 10 kN. The dissolution
properties of the resulting tablets (dry-coated tablets) were tested according to the
procedure shown in the Test Example below and the results are shown in the following
Table 6.

(Example 6) Olmesartan Dry-Coated Tablets

(1) Olmesartan medoxomil, lactose, low substituted hydroxypropyl cellulose and
magnesium stearate were each weighed in the relative amounts given in the column
headed "Tablet G" of Table 5 below and then mixed for 2 minutes in an agate mortar.
The resulting mixture was formed into tablets using a hydraulic single-action tablet
press with a stamp having a 5.5 mm diameter surface at a tablet weight of 50 mg and
pressing pressure of 10 kN to give Tablet G.

(2) 60 mg of Granules B obtained in Example 1 were loaded into a 7.5 mm diameter
mould followed by the loading of Tablet G into the mould. After again loading 60 mg
of Granules B into the mould, tablets were formed using a hydraulic single-action tablet
press at a tablet weight of 170 mg and pressing pressure of 10 kN. The dissolution
properties of the resulting tablets (dry-coated tablets) were tested according to the
procedure shown in the Test Example below and the results are shown in the following Table 6.

Reference Example 1

Olmesartan medoxomil, amlodipine besylate, lactose, low substituted hydroxypropyl cellulose, microcrystalline cellulose and magnesium stearate were each weighed in the relative amounts given in the column headed "Reference Example 1" of Table 1 below and then mixed for 2 minutes in an agate mortar. The resulting mixture was formed into tablets using a hydraulic single-action tablet press with a stamp having a 7 mm diameter surface at a tablet weight of 140 mg and pressing pressure of 10 kN.

Test Example

Testing for the rate of dissolution of the tablets prepared in the examples above was carried out in accordance with Method 2 of the Dissolution Test (Paddle Method) described in the 14th Revised Edition of the Japanese Pharmacopoeia at 50 revolutions per minute and using 900 mL of Japanese Pharmacopoeia Solution 2 (JP-2) for the test solution. The test solution was sampled at 30 minutes and 60 minutes after the start of testing followed by measurement of the dissolution rate and dissolved amount of olmesartan medoxomil by absorption spectrometry (dissolution tester: Toyama Sangyo; spectrophotometer: Shimadzu). Testing was carried out on two tablets and their average value is indicated in each case.
### (Table 1)

<table>
<thead>
<tr>
<th>Example/Reference Example</th>
<th>Example 1</th>
<th>Reference Example 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Granules A</td>
<td>Granules B</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Amlodipine besylate</td>
<td></td>
<td>13.86</td>
</tr>
<tr>
<td>Lactose</td>
<td>76.6</td>
<td>72.74</td>
</tr>
<tr>
<td>Low substituted hydroxypropyl cellulose</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total (mg)</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Total (mg/tablet)</td>
<td>240</td>
<td>140</td>
</tr>
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</table>

### (Table 2)

<table>
<thead>
<tr>
<th>Example/Reference Example</th>
<th>Example 1</th>
<th>Reference Example 1</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Dissolution rate after 30 minutes (%)</td>
<td>80.4</td>
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<tr>
<td></td>
<td>(based on a value of 100% for Reference Example 1)</td>
<td>(159.8%)</td>
</tr>
<tr>
<td></td>
<td>Amount dissolved after 30 minutes (μg/mL)</td>
<td>8.9</td>
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<tr>
<td></td>
<td>Dissolution rate after 60 minutes (%)</td>
<td>87.5</td>
</tr>
<tr>
<td></td>
<td>(based on a value of 100% for Reference Example 1)</td>
<td>(154.9%)</td>
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<tr>
<td></td>
<td>Amount dissolved after 60 minutes (μg/mL)</td>
<td>9.7</td>
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</table>
(Table 3)

<table>
<thead>
<tr>
<th>Example</th>
<th>Example 2</th>
<th>Example 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Granules A</td>
<td>Granules C</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Amlodipine besylate</td>
<td></td>
<td>13.86</td>
</tr>
<tr>
<td>Lactose</td>
<td>76.6</td>
<td>65.14</td>
</tr>
<tr>
<td>Low substituted hydroxypropyl cellulose</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Methyl cellulose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>Total (mg)</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>Total (mg/tablet)</td>
<td>220</td>
<td></td>
</tr>
</tbody>
</table>

(Table 4)

<table>
<thead>
<tr>
<th>Example/Reference Example</th>
<th>Example 2</th>
<th>Example 3</th>
<th>Reference Example 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution rate after 30 minutes (%) (based on a value of 100% for Reference Example 1)</td>
<td>78.6 (156.3%)</td>
<td>82.9 (164.8%)</td>
<td>50.3 (100.0%)</td>
</tr>
<tr>
<td>Amount dissolved after 30 minutes (µg/mL)</td>
<td>8.7</td>
<td>9.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Dissolution rate after 60 minutes (%) (based on a value of 100% for Reference Example 1)</td>
<td>84.4 (149.4%)</td>
<td>91.5 (161.9%)</td>
<td>56.5 (100.0%)</td>
</tr>
<tr>
<td>Amount dissolved after 60 minutes (µg/mL)</td>
<td>9.4</td>
<td>10.2</td>
<td>6.3</td>
</tr>
</tbody>
</table>
As shown in Tables 2, 4 and 6 above, the solid dosage form of the present invention demonstrates superior dissolution properties for the angiotensin II receptor antagonist (olmesartan medoxomil) contained therein.
According to the present invention, a solid dosage form, comprising an angiotensin II receptor antagonist and a calcium channel blocker, with improved dissolution properties is obtained.
CLAIMS

1. A solid dosage form comprising an angiotensin II receptor antagonist and a calcium channel blocker, wherein the active ingredients are formulated such that they are not intimately mixed in said solid dosage form.

2. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is losartan, candesartan, valsartan, telmisartan, pratosartan, olmesartan or irbesartan or a pharmacologically acceptable salt or ester thereof.

3. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is losartan, candesartan cilexetil, valsartan, telmisartan, pratosartan, olmesartan medoxomil or irbesartan.

4. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil.

5. The solid dosage form according to any of claims 1 to 4 wherein the calcium channel blocker is nifedipine, nimodipine, nilvadipine, manidipine, barnidipine, nitrendipine, benidipine, nicardipine, lercanidipine, amlodipine, nisoldipine, efonidipine, cilnidipine, azelnidipine, felodipine, aranidipine or pranidipine or a pharmacologically acceptable salt thereof.

6. The solid dosage form according to any of claims 1 to 4 wherein the calcium channel blocker is manidipine, barnidipine, benidipine, nicardipine, lercanidipine, amlodipine, efonidipine or azelnidipine or a pharmacologically acceptable salt thereof.

7. The solid dosage form according to any of claims 1 to 4 wherein the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof.

8. The solid dosage form according to any of claims 1 to 4 wherein the calcium channel blocker is amlodipine besylate.
9. The solid dosage form according to any of claims 1 to 8 wherein said solid dosage form is a tablet.

10. The solid dosage form according to claim 9 wherein the tablet contains particles containing an angiotensin II receptor antagonist and particles containing a calcium channel blocker.

11. The solid dosage form according to claim 10 wherein an intermediate layer is present between the particles containing an angiotensin II receptor antagonist and the particles containing a calcium channel blocker.

12. The solid dosage form according to claim 9 wherein the tablet is a multi-layer tablet in which each individual layer of said multi-layer tablet contains only one active ingredient selected from said angiotensin II receptor antagonist and said calcium channel blocker.

13. The solid dosage form according to claim 9 wherein the tablet is a double-layer tablet in which the angiotensin II receptor antagonist is contained in the first layer and the calcium channel blocker is contained in the second layer.

14. The solid dosage form according to claim 13 wherein an intermediate layer is present between the first and second layers.

15. The solid dosage form according to claim 9 wherein the tablet is a dry-coated tablet in which the angiotensin II receptor is contained in the inner core and the calcium channel blocker is contained in the outer layer.

16. The solid dosage form according to claim 9 wherein the tablet is a dry-coated tablet in which the calcium channel blocker is contained in the inner core and the angiotensin II receptor antagonist is contained in the outer layer.
17. The solid dosage form according to claim 15 or claim 16 wherein an intermediate layer is present between the inner core and outer layer.

18. The solid dosage form according to any of claims 1 to 17 wherein said solid dosage form further comprises a hydrophilic polymer.

19. The solid dosage form according to claim 10 or claim 11 wherein the particles containing the angiotensin II receptor antagonist further comprise a hydrophilic polymer.

20. The solid dosage form according to claim 10 or claim 11 wherein the particles containing the calcium channel blocker further comprise a hydrophilic polymer.

21. The solid dosage form according to claim 11 wherein the intermediate layer further comprises a hydrophilic polymer.

22. The solid dosage form according to any one of claims 12 to 14 wherein the layer containing the angiotensin II receptor antagonist further comprises a hydrophilic polymer.

23. The solid dosage form according to any one of claims 12 to 14 wherein the layer containing the calcium channel blocker further comprises a hydrophilic polymer.

24. The solid dosage form according to any one of claims 15 to 17 wherein the inner core further comprises a hydrophilic polymer.

25. The solid dosage form according to any one of claims 15 to 17 wherein the outer layer further comprises a hydrophilic polymer.

26. The solid dosage form according to any one of claims 18 to 25 wherein the hydrophilic polymer is at least one compound selected from cellulose derivatives and synthetic polymers.
27. The solid dosage form according to any one of claims 18 to 25 wherein the hydrophilic polymer is at least one compound selected from hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol.

28. The solid dosage form according to any one of claims 18 to 25 wherein the hydrophilic polymer is at least one cellulose derivative.

29. The solid dosage form according to any one of claims 18 to 25 wherein the hydrophilic polymer is at least one compound selected from hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose.

30. The solid dosage form according to any one of claims 18 to 25 wherein the hydrophilic polymer is either or both of methyl cellulose and hydroxypropyl cellulose.

31. The solid dosage form according to any one of claims 18 to 25 wherein the hydrophilic polymer is macrogol.

32. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is losartan, candesartan cilexetil, valsartan, telmisartan, pratosartan, olmesartan medoxomil or irbesartan and the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof.

33. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil and the calcium channel blocker is nifedipine, nimodipine, nilvadipine, manidipine, barnidipine, nitrendipine, benidipine, nicardipine, lercanidipine, amlodipine, nisoldipine, efondipine, cilnidipine, azelnidipine, felodipine, aranidipine or pranidipine or a pharmacologically acceptable salt thereof.

34. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil and the calcium channel blocker is manidipine,
barnidipine, benidipine, nicardipine, lercanidipine, amlodipine, efonidipine or azelnidipine or a pharmacologically acceptable salt thereof.

35. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil and the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof.

36. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a tablet comprising particles containing the angiotensin II receptor antagonist and particles containing the calcium channel blocker.

37. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a double-layer tablet in which the angiotensin II receptor antagonist is contained in the first layer and the calcium channel blocker is contained in the second layer.

38. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a dry-coated tablet in which the calcium channel blocker is contained in the inner core thereof and the angiotensin II receptor antagonist is contained in the outer layer thereof.

39. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a tablet comprising particles containing the angiotensin II receptor antagonist and particles containing the calcium channel blocker, said particles containing the calcium channel blocker further comprising at least one hydrophilic polymer selected from hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, sodium
carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol.

40. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof, and the solid dosage form is a double-layer tablet in which the angiotensin II receptor antagonist is contained in the first layer and the calcium channel blocker is contained in the second layer, the layer containing the calcium channel blocker further comprising at least one hydrophilic polymer selected from hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol.

41. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof, the solid dosage form is a dry-coated tablet in which the calcium channel blocker is contained in the inner core thereof and the angiotensin II receptor antagonist is contained in the outer layer thereof, the inner core further comprising at least one hydrophilic polymer selected from hydroxypropyl methyl cellulose, methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, macrogol, HA Sankyo, polyvinylpyrrolidone and polyvinyl alcohol.

42. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof, and the solid dosage form is a tablet comprising particles containing the angiotensin II receptor antagonist and particles containing the calcium channel blocker, said particles containing the calcium channel blocker further comprising a hydrophilic polymer selected from methyl cellulose and hydroxypropyl cellulose.

43. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a
pharmacologically acceptable salt thereof, and the solid dosage form is a two-layer tablet in which the angiotensin II receptor antagonist is contained in the first layer and the calcium channel blocker is contained in the second layer, wherein the second layer containing the calcium channel blocker further comprises a hydrophilic polymer selected from methyl cellulose and hydroxypropyl cellulose.

44. The solid dosage form according to claim 1 wherein the angiotensin II receptor antagonist is olmesartan medoxomil, the calcium channel blocker is amlodipine or a pharmacologically acceptable salt thereof and the solid dosage form is a dry-coated tablet in which the calcium channel blocker is contained in the inner core thereof while the angiotensin II receptor antagonist is contained in the outer layer thereof, wherein the inner core containing the calcium channel blocker further contains a hydrophilic polymer selected from methyl cellulose and hydroxypropyl cellulose.

45. The solid dosage form according to any one of claims 32 to 44 wherein the calcium channel blocker is amlodipine besylate.

46. A solid dosage form according to any one of claims 1 to 45 for the prophylaxis or treatment of hypertension.

47. The use of an angiotensin II receptor antagonist and a calcium channel blocker in the manufacture of a medicament for the prophylaxis or treatment of hypertension, wherein said medicament is a solid dosage form according to any one of claims 1 to 45.

48. A method for the prophylaxis or treatment of hypertension in a patient in need thereof, said method comprising the administration to said patient of pharmacologically effective doses of an angiotensin II receptor antagonist and a calcium channel blocker in a solid dosage form according to any one of claims 1 to 45.