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(54) **Title**: MULTILAYER PHARMACEUTICAL COMPOSITION COMPRISING TELMISARTAN AND AMLODIPINE

(57) **Abstract**: The invention relates to a solid pharmaceutical composition comprising telmisartan or a pharmaceutically acceptable derivative thereof, optionally one or more basifying agents and at least one calcium channel blocker. More specifically the invention discloses a pharmaceutical composition comprising telmisartan and amlodipine that comprises at least one non- hygroscopic filler and/or at least one non-hygroscopic binder, that do not exhibit a disintegrating effect, and/or at least one hydrophilic lubricant.

MULTILAYER PHARMACEUTICAL COMPOSITION COMPRISING TELMISARTAN AND AMLODIPINE

The invention relates to a solid pharmaceutical composition comprising telmisartan or a pharmaceutically acceptable derivative thereof and at least one calcium channel blocker. More specifically, the invention discloses a pharmaceutical composition comprising a first portion comprising telmisartan and a second portion comprising amlodipine. The amlodipine portion further comprises at least one non-hygroscopic filler and/or at least one non-hygroscopic binder that do not exhibit disintegrating effect and/or at least one hydrophilic lubricant, wherein said second portion does not exhibit a disintegrating effect.

Background of the invention

Telmisartan, the chemical name of which is 2-(4-{[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]-methyl}-phenyl)-benzoic acid, is an angiotensin II receptor antagonist useful for the treatment of hypertension that was originally disclosed in EP 0 502 314 A1. Telmisartan is commercially available in particular in its free acid form, which is poorly soluble in neutral or acidic media. Thus, telmisartan is typically formulated together with a basic agent or in the form of a basic salt for improved solubility.

Calcium channel blockers, such as amlodipine, nifedipine, nimodipine, nilvadipine, manidipine, barnidipine, nitrendipine, benidipine, nicardipine, lercanidipine, nisoldipine, efonidipine, cilnidipine, azelnidipine, felodipine, aranidipine and pranidipine, exert antihypertensive action by reducing the availability of calcium ions for muscular contraction and,

therefore, resulting in decreased peripheral vascular resistance and reduced blood pressure.

Amlodipine, the chemical name of which is 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate is a long-acting calcium channel blocker (dihydropyridine class) used as an anti-hypertensive and in the treatment of angina that was originally disclosed in EP 0 089 167 A1. Amlodipine is commercially available in the form of maleate, besylate or mesylate salt. It is known that amlodipine and/or pharmaceutically acceptable salts thereof are susceptible to hydrolysis when exposed to an alkaline medium.

The findings of the study reported by Stangier et al., J Clin Pharmacol 2000, 40, 1347-1354 show that concominant telmisartan and amlodipine may be administered as there is no clinically significant variation in primary pharmacokinetic parameters of amlodipine in the presence of telmisartan and the safety is comparable to that of amlodipine alone.

Different approaches have been pursued in order to address the problem that amlodipine is susceptible to hydrolysis when exposed to basic agents that are commonly used together with the free acid form of telmisartan. One approach is to formulate each incompatible substance separately into separated forms that are then formulated together into the same dosage form. The purpose of such approach is to minimize interactions between substances and to improve the stability and release rate of the final combination product. According to one aspect, two compositions are provided in physically separated forms selected from the group consisting of powders, granules, pellets, beads, mini-tablets or tablets and similar. Another approach is to coat particles that readily disintegrates with water-soluble polymers. Yet another approach is to place each incompatible

substance into a particular layer while layers could be additonally separated by an inert intermediate layer.

WO 2006/048208 addresses the stability problem caused by the incompatibility of amlodipine with basic constituents of the telmisartan formulation by preparing a bilayer pharmaceutical tablet comprising a first layer of telmisartan in substantially amorphous form in a dissolving tablet matrix and a second layer of amlodipine in a disintegrating or eroding tablet matrix. According to this document, the term 'dissolving tablet matrix' refers to a 'pharmaceutical tablet base formulation having instant release (fast dissolution) characteristics that readily dissolves in a physiological aqueous medium' and the term 'disintegrating or eroding tablet matrix' refers to a pharmaceutical tablet base formulation having instant release characteristics that readily disintegrates or erodes in a physiological aqueous medium'. The dissolving tablet matrix is described to have neutral or basic properties, with a basic tablet matrix being preferred. It comprises a basic agent, a water soluble diluent and optionally other excipients and adjuvants. As preferred disintegrants used to prepare a disintegrating or eroding tablet matrix the following group of disintegrants is listed: croscarmellose sodium (crosslinked carboxymethylcellulose sodium), sodium starch glycolate, crospovidone (crosslinked polyvinylpyrrolidone), corn starch, pregelatinized starch, low-substituted hydroxypropylcellulose and microcrystalline cellulose. Particularly preferred are sodium starch glycolate and crospovidone.

WO 2007/001067 relates to a solid dosage form comprising an angiotensin II receptor antagonist such as inter alia telmisartan and a calcium channel blocker such as inter alia amlodipine wherein active ingredients are not intimately mixed in the dosage form. The application discloses double-layer

tablet comprising olmesartan medoxomile and amlodipine besylate both present in disintegrating matrix.

WO 2008/146178 discloses a pharmaceutical composition comprising a telmisartan blend layer having a disintegrating matrix and amlodipine tablets having a disintegrating matrix which amlodipine tablets are inlayed in an inert excipients layer representing a disintegrating matrix as well.

In the pharmaceutical compositions of the prior art, complex fixed dose formulations of telmisartan and amlodipine are necessary to address the incompatibility of the active agents and to stabilize the compositions. These complex formulations require the use of substantial amounts of expensive specialty excipients. Moreover, preparation of these formulations involves complex and costly processing steps such as wet granulation.

It is therefore an object of the present invention to provide a pharmaceutical composition comprising telmisartan or pharmaceutically acceptable salts thereof and amlodipine or pharmaceutically acceptable salts thereof in a fixed dosage form avoiding the above-discussed drawbacks and which does not only exhibit high chemical and physical stability as well as an appropriate dissolution profile and bioavailability but which can also be prepared from inexpensive excipients and can be manufactured using a simple and economical process.

This object is surprisingly achieved by the pharmaceutical composition comprising telmisartan or pharmaceutically acceptable salts thereof and amlodipine or pharmaceutically acceptable salts described herein below. In particular, the pharmaceutical composition comprises telmisartan or pharmaceutically acceptable salts thereof and amlodipine or pharmaceutically acceptable salts thereof present in different portions of the pharmaceutical composition and at least one non-

hygroscopic filler and/or at least one non-hygroscopic binder that do not exhibit disintegrating effect and/or at least one hydrophilic lubricant wherein the amlodipine portion does not exhibit a disintegrating effect. More particularly, telmisartan or pharmaceutically acceptable salts thereof and amlodipine or pharmaceutically acceptable salts thereof present in different portions of the pharmaceutical composition are separated by means of layers, coating and/or units. Even more particularly, the pharmaceutical composition according to the present invention may be formulated in the form of a tablet comprising at least two layers or in the form of telmisartan tablets coated with amlodipine or pharmaceutically acceptable salts, or in the form of a capsule comprising at least one unit comprising telmisartan or pharmaceutically acceptable salts thereof and at least one unit comprising amlodipine or pharmaceutically acceptable salts thereof. The invention also relates to a process for the preparation of said pharmaceutical composition comprising telmisartan or pharmaceutically acceptable salts thereof and amlodipine or pharmaceutically acceptable salts thereof in a fixed dosage form.

Detailed description of the invention

The invention relates to a solid pharmaceutical composition comprising

(a) at least one first portion comprising telmisartan or a pharmaceutical acceptable salt thereof; and

(b) at least one second portion comprising
amlodipine or a pharmaceutically acceptable salt thereof and
at least one non-hygroscopic excipient and/or at least one hydrophilic lubricant.

Preferably, the non-hygroscopic excipient is selected from non-hygroscopic fillers and/or non-hygroscopic binders. Moreover, the at least one non-hygroscopic excipient does preferably not exhibit any disintegrating effect, i.e. the second portion of the composition readily dissolves in a physiological aqueous medium, but does not disintegrates or erodes in such medium. In particular, the second portion comprises less than 2 wt.-%, particularly less than 1 wt.-%, more preferably less than 0.5 wt.-%, most preferably less than 0.1 wt.-% of a disintegrant as defined herein below, based on the weight of the second portion.

Therefore, in a first aspect the present invention relates to a pharmaceutical composition comprising telmisartan or pharmaceutically acceptable salts thereof present in one portion and amlodipine or pharmaceutically acceptable salts thereof and at least one non-hygroscopic filler and/or at least one non-hygroscopic binder that do not exhibit disintegrating effect and/or at least one hydrophilic lubricant present in another portion of the pharmaceutical composition wherein said amlodipine portion does not exhibit disintegrating effect.

The term "portion" according to the present invention means that both active ingredients are not in intimate contact and that they are separated from each other, for example by means of layers, coating and/or units. Thus, as used herein, the term "portion" refers to a physical part of the solid pharmaceutical composition, wherein the components of said part are not intimately mixed with the components of another portion or part of the composition. In particular, the interaction between the components of one portion and the components of another portion is reduced, for example by physically separating the first portion composition from the second portion composition, e.g. by the provision of the first portion composition and the second

portion composition in different tablet layers or units and/or by provision of a separating layer.

Contrary to the teaching of the prior art, it has now surprisingly been found that when at least one non-hygroscopic excipient, and in particular at least one non-hygroscopic filler and/or at least one non-hygroscopic binder that do not exhibit disintegrating effect, and/or at least one hydrophilic lubricant is present in the portion comprising amlodipine or pharmaceutically acceptable salts thereof, wherein said portion does not exhibit a disintegrating effect, then a similar release of amlodipine or pharmaceutically acceptable salts thereof can be achieved in comparison to known reference products comprising disintegrant(s) and/or hydrophobic lubricant(s) in the amlodipine portion. In particular, it has been found that the composition exhibits a dissolution profile that is comparable to the one typically found for tablets containing telmisartan in a dissolving portion and amlodipine in a disintegrating portion.

In addition, it has surprisingly been found that due to the specific composition of the second portion of the solid pharmaceutical composition the stability of amlodipine can be increased and the amount of degradation products of amlodipine formed via hydrolysis upon storage of the composition is reduced.

It is particularly preferred that the solid pharmaceutical composition according to the invention comprises

(a) at least one first portion comprising telmisartan or a pharmaceutical acceptable salt thereof; and

(b) at least one second portion comprising amlodipine or a pharmaceutically acceptable salt thereof and

at least one non-hygroscopic excipient.

As used herein, the term "non-hygroscopic" refers to a material that has a low ability to take up and retain water. More specifically, the term "non-hygroscopic" refers to a material that has an equilibrium moisture content of about 6% (w/w) or less as determined by dynamic vapor sorption (DVS) at a relative humidity of 60% and a temperature of 25°C. In particular, the equilibrium moisture content is determined on the basis of the sorption isotherm curve measured by DVS at a relative humidity of 60% and a temperature of 25°C.

It is also particularly preferred that in addition to the at least one non-hygroscopic excipient the second portion of the composition further comprises at least one hydrophilic lubricant.

As noted above, the non-hygroscopic excipient is preferably selected from the group consisting of non-hygroscopic fillers, non-hygroscopic binders and mixtures thereof.

Furthermore, it is preferred that the combined weight of the amlodipine or pharmaceutically acceptable salt thereof and the non-hygroscopic excipient or the combined weight of the amlodipine or pharmaceutically acceptable salt thereof, the non-hygroscopic excipient and the hydrophilic lubricant, if present, is at least 50 wt.-%, preferably at least 85 wt.-%, more preferably at least 93 wt.-%, like at least 95 wt.-% or at least 97 wt.-%, such as at least 98 wt.-%, and most preferably at least 99 wt.-% by weight of the second portion. In one embodiment, the second portion of the composition essentially consists of amlodipine or a pharmaceutically acceptable salt thereof and at least one non-hygroscopic excipient. In another embodiment, the second portion of the composition essentially consists of amlodipine or a pharmaceutically acceptable salt

thereof, at least one non-hygroscopic excipient and at least one hydrophilic lubricant.

Preferably, the second portion of the composition according to the invention comprises less than 2 wt.-%, particularly less than 1 wt.-%, more preferably less than 0.5 wt.-%, most preferably less than 0.1 wt.-% of a disintegrant, based on the weight of the second portion. According to a particularly preferred embodiment, the second portion is substantially free of disintegrant.

The term "disintegrant", as used herein, refers to any material that has wicking and/or swelling properties when it comes in contact with water. In particular, the term "disintegrant" refers to the group of compounds consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, corn starch, pregelatinized starch, low-substituted hydroxypropylcellulose and microcrystalline cellulose. Particularly, the term “disintegrant” refers to the group of compounds consisting of crospovidone, pregelatinized starch, sodium starch glycolate, hydroxypropyl starch, carboxymethylcellulose sodium and calcium, cross-linked carboxymethylcellulose sodium, polacrilin potassium, low-substituted hydroxypropylcellulose, sodium and calcium alginate, docusate sodium, methylcellulose, agar, guar gum, chitosan and alginic acid. More particularly, the term "disintegrant" refers to the group of compounds consisting of povidone, crospovidone, starch, pregelatinized starch, sodium starch glycolate, hydroxypropyl starch, microcrystalline cellulose, carboxymethylcellulose sodium and calcium, cross-linked carboxymethylcellulose sodium, polacrilin potassium, low-substituted hydroxypropylcellulose, sodium and calcium alginate, docusate sodium, methylcellulose, agar, guar gum, chitosan and alginic acid.

The bilayer tablets according to the prior art tend to be slightly hygroscopic and are therefore preferably packaged using a moisture-proof packaging material such as aluminium foil blister packs or polypropylene tubes and HDPE bottles which preferably contain a desiccant. It has been found that the disintegrants are hygroscopic or even very hygroscopic in nature. Typically, disintegrants may contain 5% w/w of water or more. At the same time, as amlodipine is susceptible to hydrolysis, it has been found beneficial to prepare a pharmaceutical formulation that substantially comprises or essentially consists of materials that contain as little water as possible. In other words, it has been found beneficial to prepare a pharmaceutial composition comprising amlodipine which composition is disintegrant-free and yet it dissolves the active-ingredient very fast. If non-hygroscopic materials are used, there is no potential that water would enter the formulation and compromise stability of amlodipine.

In one embodiment, the composition of the invention is in the form of a multilayer tablet, wherein the at least one first portion is an at least one first tablet layer and the at least one second portion is an at least one second tablet layer.

As used herein, the term "multilayer tablet" refers to a pharmaceutical tablet which is made up of at least two distinct layers, such as at least two layers, at least three layers, at least four layers, at least five layers, etc., with the individual layers being arranged one on top of another. The multilayer tablet generally has a sandwich-like appearance because the edges of each layer are exposed. Typically, adjacent layers of the tablet will be of different composition. It has to be understood that the terms "first tablet layer" and "second tablet layer" as used herein refer to tablet layers having a particular composition. However, these terms do not necessarily

reflect the order in which the layers are arranged in the tablet.

In another embodiment, the composition according to the invention is in the form of a coated tablet, wherein the at least one first portion is a tablet and the at least one second portion is at least one coating on said tablet.

The multilayer tablet or coated tablet according to the invention can further comprise at least one separating coating. In case of a multilayer tablet, such as a bilayer tablet, the separating coating is arranged between at least one first tablet layer and at least one second tablet layer. In case of a coated tablet, the separating coating is an isolating or intermediate coating arranged between the tablet representing the first portion and the coating representing the at least one second portion. The separating layer can comprise a pharmaceutically acceptable excipient such as a polymeric excipient and is particularly selected from the group consisting of Povidone and cellulose derivatives like hydroxypropyl methylcellulose.

In another embodiment, the composition according to the invention is in the form of a capsule comprising the at least one first portion in form of a first unit and the at least one second portion in form of a second unit. As used herein, the term “unit” refers to tablets, microtablets, pellets, powder forms, granules and granulates. Hence, the first and the second unit are independently selected from the group consisting of tablets, microtablets, pellets, powder forms, granules and granulates.

The multilayer tablet, coated tablet as well as capsule embodiments described above may be characterized by the same features as disclosed in connection with the general embodiment of the composition of the invention, i.e. the composition

comprising at least one first portion comprising telmisartan or a pharmaceutically salt thereof and at least one second portion comprising amlodipine or a pharmaceutically acceptable salt thereof and at least one non-hygroscopic excipient.

For example, in one aspect the present invention relates to a pharmaceutical composition in the form of a tablet comprising

a) at least one layer comprising
telmisartan or a pharmaceutically acceptable salt thereof,
b) optionally at least one separating layer comprising any pharmaceutically acceptable excipient and
c) at least one layer comprising
c1) amlodipine or a pharmaceutically acceptable salt thereof and
c2) at least one non-hygroscopic filler and/or at least one non-hygroscopic binder that do not exhibit disintegrating effect and/or at least one non-hydrophobic lubricant,
wherein said layer does not exhibit a disintegrating effect.

In another aspect, the present invention relates to a pharmaceutical composition in the form of a tablet comprising

a) at least one layer comprising
1 to 50 wt.-% telmisartan or a pharmaceutically acceptable salt thereof by weight of said layer
b) optionally at least one separating layer comprising any pharmaceutically acceptable excipient and
c) at least one layer comprising
c1) 1 to 50 wt.-% of amlodipine or a pharmaceutically acceptable salt thereof by weight of said layer and
c2) 1 to 99 wt.-% of at least one non-hygroscopic filler and/or 1 to 99 wt.-% of at least one non-hygroscopic binder that do not exhibit disintegrating effect

and/or 1 to 99 wt.-% of at least one non-hydrophobic lubricant by weight of said layer,

wherein said layer does not exhibit disintegrating effect.

In another aspect, the present invention relates to a pharmaceutical composition in the form of a coated tablet comprising

a) a telmisartan portion comprising
telmisartan or pharmaceutically acceptable salts thereof compressed into a tablet wherein said tablet is coated with

b) optionally at least one separating coating comprising any pharmaceutically acceptable excipient and

c) an amlodipine portion comprising

c1) amlodipine or pharmaceutically acceptable salts thereof and

c2) at least one non-hygroscopic filler and/or at least one non-hygroscopic binder that do not exhibit disintegrating effect and/or at least one non-hydrophobic lubricant,

wherein said amlodipine portion does not exhibit disintegrating effect.

In another aspect, the present invention relates to a pharmaceutical composition in the form of a coated tablet comprising

a) a telmisartan portion comprising
1 to 50 wt.-% of telmisartan or a pharmaceutically acceptable salts thereof by weight of said portion compressed into tablet wherein said tablet is coated with

b) optionally at least one separating coating comprising any pharmaceutically acceptable excipient and

c) an amlodipine portion comprising

c1) 1 to 90 wt.-% of amlodipine or a pharmaceutically acceptable salt thereof by weight of said portion and

c2) 1 to 99 wt.-% of at least one non-hygroscopic filler and/or 1 to 99 wt.-% of at least one non-hygroscopic binder that do not exhibit disintegrating effect and/or 1 to 99 wt.-% of at least one non-hydrophobic lubricant by weight of said portion

wherein said amlodipine layer does not exhibit a disintegrating effect.

In another aspect, the present invention relates to a pharmaceutical composition in the form of a capsule comprising

a) at least one unit comprising telmisartan or pharmaceutically acceptable salts thereof and

b) at least one unit comprising

b1) amlodipine or pharmaceutically acceptable salts thereof and

b2) at least one non-hygroscopic filler and/or at least one non-hygroscopic binder that do not exhibit disintegrating effect and/or at least one non-hydrophobic lubricant

wherein said unit does not exhibit a disintegrating effect.

In another aspect, the present invention relates to a pharmaceutical composition in the form of a capsule comprising

b) at least one unit comprising 1 to 50 wt.-% of telmisartan or pharmaceutically acceptable salts thereof by weight of said unit and

b) at least one unit comprising

b1) 1 to 90 wt.-% of amlodipine or pharmaceutically acceptable salts thereof by weight of said unit and

b2) 1 to 99 wt.-% of at least one non-hygroscopic filler and/or 1 to 99 wt.-% of at least one non-hygroscopic binder that do not exhibit disintegrating effect

and/or 1 to 99 wt.-% of at least one hydrophilic lubricant by weight of said unit

wherein said amlodipine unit does not exhibit disintegrating effect.

The term "unit" refers to tablets, microtablets, pellets, or powder form that does not include tablet comprising layers and coated tablets as defined above.

The following description of preferred embodiments of the composition according to the invention is intended to apply to the general embodiment of the composition described above which is characterized by the presence of at least one first portion and at least one second portion as well as to the multilayer tablet, coated tablet and capsule embodiments described above.

The first portion of the composition according to the invention, such as the first tablet layer, comprises telmisartan or a pharmaceutically acceptable salt thereof. Telmisartan is typically employed in its free acid form although pharmaceutically acceptable salts can also be used. The portion comprising telmisartan preferably comprises 1 to 50 wt.-%, particularly 5 to 35 wt.-%, more preferably 10 to 20 wt.-% of telmisartan or a pharmaceutically acceptable salt thereof by weight of said first portion.

According to one embodiment, the first portion of the pharmaceutical composition according to the present invention comprises telmisartan and a basic agent. The term "basic agent" as used herein refers to a substance which is characterized in that a 3 wt.-% aqueous solution thereof has a pH value of at least 8.0 Suitable basic agents include ammonia, NaOH, KOH, $Ca(OH)_2$, Na_2CO_3, K_2CO_3, $NaHCO_3$, $KHCO_3$, Na_3PO_4, K_3PO_4, Na_2HPO_4, K_2HPO_4, choline, *tert*-butylamine, ethanolamine, meglumine, piperazine, diethylamine, L-arginine and mixtures thereof.

Alkali metal hydroxides such as NaOH and KOH, amino sugars such as meglumine and mixtures thereof are preferred basic agents. It is particularly preferred that the basic agent comprises a mixture of an alkali metal hydroxide such as NaOH or KOH and an amino sugar such as meglumine in a weight ratio of 1:1 to 1:10, more particularly 1:2 to 1:5, more preferably 1:3 to 1:4, most preferably about 1:3.5. The first portion comprising telmisartan preferably comprises 0.25 to 20 wt.-%, particularly 1 to 15 wt.-%, more preferably 2 to 10 wt.-% of basic agent.

The telmisartan can be amorphous or crystalline. As used herein, the term "amorphous" includes amorphous and partly crystallized forms. Amorphous telmisartan can be obtained by methods generally known in the art such as freeze drying of aqueous solutions, coating of carrier particles in a fluidized bed, and solvent deposition on sugar pellets or other carriers.

According to another embodiment, the pharmaceutical composition according to the present invention comprises a pharmaceutically acceptable salt of telmisartan. Suitable pharmaceutically acceptable salts include alkaline salts such as the sodium salt of telmisartan. The pharmaceutically acceptable salt of telmisartan can be amorphous or crystalline.

Telmisartan or its pharmaceutically acceptable salts can be prepared by any method known from the state of the art as for example disclosed in EP 0 502 314 A1, EP 1 173 407 B1, J. Med. Chem. 1993, 36, 4051, CN 1182122, CN 1204124, WO 2004/087676, CN 1548421, WO 2005/108375, WO 2006/044648, WO 2006/044754, WO 2006/050921, WO 2006/067215, US 2006/211866, US 7692027, WO 2007/010558, US 2006/0264491, WO 2007/147889, CN 101983962, IN 2008MU02449, CN 101024631, WO 2009/004064, WO 2009/116089, WO 2009/115585, WO 2009/123483, EP 2 123 648 A, WO 2010/004385, WO 2010/018441, WO 2010/146187 or WO 2010/149565.

Moreover, telmisartan or its pharmaceutically acceptable salts can be in any known stable polymorphic forms known from the state of the art as for example disclosed in EP 1144386, EP 1442023, WO 2006/050509, US 2006/111417, IN 2005MU00164, US 2006/0276525 or WO 2009/006860.

The first portion, such as the first tablet layer, of the pharmaceutical composition according to the present invention can comprise pharmaceutically acceptable excipients. The term "pharmaceutical acceptable excipient" as used herein refers to additives useful for converting pharmacologically active compounds into pharmaceutical dosage forms which are suitable for administration to patients. Excipients suitable for use in the first portion can include fillers, binders, surfactants, crystallization retarders, lubricants, glidants and coloring agents. Other pharmaceutically acceptable excipients can also be included.

The first portion comprising telmisartan typically comprises at least one filler. Water-soluble fillers are generally preferred. Suitable fillers for use in the portion comprising telmisartan can include monosaccharides, oligosaccharides and sugar alcohols such as glucose, fructose, saccharose, lactose (anhydrous and monohydrate), raffinose, trehalose, dextrates, mannitol, erythritol, sorbitol, maltitol, xylitol and lactitol, compressible sugar, calcium hydrogen phosphate, calcium carbonate, calcium lactate and mixtures thereof. Preferred fillers are monosaccharides and oligosaccharides such as glucose, fructose, saccharose and lactose, sugar alcohols such as mannitol, erythritol, sorbitol, maltitol, xylitol and lactitol and mixtures thereof. Lactose, sorbitol and mixtures thereof are particularly preferred. It is particularly preferred that the filler comprises a monosaccharide or oligosaccharide such as lactose and a sugar alcohol such as sorbitol in a weight ratio of 1:1 to 1:10, particularly 1:2 to 1:5, most preferably

about 1:2.5. The portion comprising telmisartan preferably comprises 30 to 95 wt.-%, particularly 60 to 90 wt.-%, more preferably 70 to 80 wt.-% of filler.

Suitable binders for use in the first portion comprising telmisartan can include povidone (polyvinylpyrrolidone), copovidone (vinylpyrrolidone-vinylacetate copolymer), cellulose powder, crystalline cellulose, microcrystalline cellulose, siliconized microcrystalline cellulose, cellulose derivatives such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, maltose, starch, pregelatinized starch, polymethacrylates and mixtures thereof. Povidone is particularly preferred. The portion comprising telmisartan preferably comprises 1 to 30 wt.-%, particularly 2 to 10 wt.-%, more preferably 3 to 7 wt.-% of binder.

Suitable surfactants for use in the first portion of the pharmaceutical composition according to the present invention can include anionic, cationic, ampholytic and non-ionic surfactants such as sodium lauryl sulfate, cetrimide, N-dodecyl-N,N-dimethylbetaine, polysorbates (such as Tweens®), poloxamers and mixtures thereof. Non-ionic surfactants such as polysorbates and poloxamers are preferred. The first portion preferably comprises 1 to 30 wt.-%, particularly 2 to 10 wt.-%, more preferably 3 to 7 wt.-% of surfactant by weight of said portion. Moreover, the pharmaceutical composition preferably comprises 1 to 30 wt.-%, particularly 2 to 10 wt.-%, more preferably 3 to 7 wt.-% of surfactant by weight of said composition.

Suitable crystallization retarders for use in the first portion of the pharmaceutical composition according to the present invention can include povidone, copovidone, crospovidone, carboxymethylcellulose sodium, hydroxypropylcellulose and hydroxypropylmethylcellulose. The first portion preferably

comprises 0.1 to 20 wt.-%, particularly 0.25 to 10 wt.-%, more preferably 0.25 to 4 wt.-% of crystallization retarder by weight of said portion. Moreover, the pharmaceutical composition preferably comprises 0.1 to 20 wt.-%, particularly 0.25 to 10 wt.-%, more preferably 0.25 to 4 wt.-% of crystallization retarder by weight of said composition.

Suitable lubricants for use in the first portion comprising telmisartan can include stearic acid and stearic acid salts such as magnesium stearate, magnesium palmitate and magnesium oleate, hydrogenated vegetable oil, hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols and mixtures thereof. Stearic acid, magnesium stearate and hydrogenated vegetable oil are particularly preferred. The first portion comprising telmisartan preferably comprises 0.1 to 10 wt.-%, particularly 0.25 to 5 wt.-%, more preferably 0.5 to 2 wt.-% of lubricant.

Suitable glidants for use in the first portion of the pharmaceutical composition according to the present invention include colloidal silicon dioxide and magnesium trisilicate. The first portion comprising telmisartan preferably comprises 0.1 to 10 wt.-%, particularly 0.25 to 5 wt.-%, more preferably 0.5 to 2 wt.-% of glidant.

Suitable coloring agents for use in the first portion of the pharmaceutical composition according to the present invention include dyes and pigments such as iron oxide and titanium oxide. The first portion comprising telmisartan preferably comprises 0.001 to 1 wt.-%, particularly 0.01 to 0.5 wt.-%, more preferably 0.05 to 0.2 wt.-% of coloring agent.

According to a particular embodiment, the first portion of the composition, such as the first tablet layer, the first tablet or the first unit, comprises

(aa) 3 to 50 wt.-%, particularly 5 to 35 wt.-%, more preferably 10 to 20 wt.-% of telmisartan or a pharmaceutically acceptable salt thereof;

(bb) 0.25 to 20 wt.-%, particularly 1 to 15 wt.-%, more preferably 2 to 10 wt.-% of basic agent;

(cc) 30 to 95 wt.-%, particularly 60 to 90 wt.-%, more preferably 70 to 80 wt.-% of filler;

(dd) 1 to 30 wt.-%, particularly 2 to 10 wt.-%, more preferably 3 to 7 wt.-% of binder;

(ee) 0 to 30 wt.-%, particularly 2 to 10 wt.-%, more preferably 3 to 7 wt.-% of surfactant;

(ff) 0 to 10 wt.-%, particularly 0.25 to 5 wt.-%, more preferably 0.5 to 2 wt.-% of lubricant; and

(gg) 0 to 1 wt.-%, particularly 0.01 to 0.5 wt.-%, more preferably 0.05 to 0.2 wt.-% of coloring agent.

According to another preferred embodiment, the first portion of the composition, such as the first tablet layer, the first tablet or the first unit, comprises

(aa) 3 to 50 wt.-%, particularly 5 to 35 wt.-%, more preferably 10 to 20 wt.-% of telmisartan or a pharmaceutically acceptable salt thereof;

(bb) 0.25 to 20 wt.-%, particularly 1 to 15 wt.-%, more preferably 2 to 10 wt.-% of basic agent, wherein said basic agent is preferably selected from NaOH, KOH, $Ca(OH)_2$, Na_2CO_3, K_2CO_3, $NaHCO_3$, $KHCO_3$, Na_3PO_4, K_3PO_4, Na_2HPO_4, K_2HPO_4, choline, *tert*-butylamine, ethanolamine, meglumine, piperazine, diethylamine, L-arginine and mixtures thereof, and is more preferably selected from NaOH, meglumine and mixtures thereof;

(cc) 30 to 95 wt.-%, particularly 60 to 90 wt.-%, more preferably 70 to 80 wt.-% of filler, wherein said filler is preferably selected from monosaccharides and oligosaccharides such as glucose, fructose, saccharose and

lactose, sugar alcohols such as mannitol, erythritol, sorbitol, maltitol, xylitol and lactitol and mixtures thereof, and is more preferably selected from lactose, sorbitol and mixtures thereof;

(dd) 1 to 30 wt.-%, particularly 2 to 10 wt.-%, more preferably 3 to 7 wt.-% of binder, wherein said binder is preferably selected from povidone, copovidone cellulose powder, crystalline cellulose, microcrystalline cellulose, siliconized microcrystalline cellulose, cellulose derivatives such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, starch, pregelatinized starch, polymethacrylates and mixtures thereof, and is more preferably selected from povidone;

(ee) 0 to 10 wt.-%, particularly 0.25 to 5 wt.-%, more preferably 0.5 to 2.5 wt.-% of lubricant, wherein said lubricant is preferably selected from stearic acid and stearic acid salts such as magnesium stearate, magnesium palmitate and magnesium oleate, hydrogenated vegetable oil, hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols and mixtures thereof, and is more preferably selected from magnesium stearate, sodium stearyl fumarate and mixtures thereof; and

(ff) 0 to 1 wt.-%, particularly 0.01 to 0.5 wt.-%, more preferably 0.05 to 0.2 wt.-% of coloring agent.

The second portion of the composition according to the invention comprises a calcium channel blocker and at least one non-hygroscopic excipient. In particular, the second portion comprises amlodipine or a pharmaceutically acceptable salt thereof and at least one non-hygroscopic excipient.

Amlodipine can be in the form of pharmaceutically acceptable salts such as for example the maleate, besylate or mesylate salt

or in the form of free base. Preferably, amlodipine is in the form of besylate or maleate salt.

The non-hygroscopic excipient of the second portion is preferably selected from the group consisting of non-hygroscopic fillers, non-hygroscopic binders and mixtures thereof.

Thus, the second portion comprising amlodipine preferably comprises at least one non-hygroscopic filler that does not exhibit a disintegrating effect. Preferably, the filler of the second portion is selected from the group of fillers defined above in connection with the first portion of the composition or mixtures thereof. Hence, the filler of the second portion is preferably selected from the group consisting of monsaccharides, oligosaccharides, sugar alcohols and mixtures thereof. Preferred non-hygroscopic fillers that do not exhibit a disintegrating effect are mannitol and lactose monohydrate. Thus, the filler of the second portion is preferably selected from the group consisting of mannitol, lactose monohydrate and mixtures thereof.

The second portion comprising amlodipine can further comprises at least one binder and in particular at least one non-hygroscopic binder that does not exhibit disintegrating effect selected from the group of binders defined above in connection with the first portion of the composition. Preferred non-hygroscopic binders that do not exhibit disintegrating effect are hydroxypropylcellulose and maltose. Hence, the binder of the second portion is preferably selected from the group consisting of hydroxypropylcellulose, maltose and mixtures thereof.

The second portion comprising amlodipine preferably further comprises at least one non-hydrophobic lubricant selected from the group of lubricants defined above in connection with the first portion of the composition. Preferred non-hydrophobic

lubricants are sodium stearyl fumarate and macrogols. Thus, the second portion of the composition preferably comprises at least one hydrophilic lubricant selected from the group consisting of stearic acid, magnesium stearate, magnesium palmitate, magnesium oleate, hydrogenated vegetable oil, hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols and mixtures thereof. More preferably, the second portion of the composition preferably comprises at least one hydrophilic lubricant selected from the group consisting of sodium stearyl fumarate, macrogols and mixtures thereof.

The second portion of the composition according to the invention can generally comprise additional pharmaceutically acceptable excipients. Such additional excipients suitable for use in the second portion may include glidants, coloring agents and coating agents.

Suitable glidants for use in the second portion of the pharmaceutical composition according to the present invention include colloidal silicon dioxide and magnesium trisilicate.

Suitable coloring agents for use in the second portion of the pharmaceutical composition according to the present invention include dyes and pigments such as iron oxide and titanium oxide.

According to a preferred embodiment, the second portion of the composition, such as the second tablet layer, comprises

(aa) 1 to 50 wt.-%, particularly 2 to 20 wt.-%, more preferably 4 to 8 wt.-% like 4 to 9 wt.-% of amlodipine or a pharmaceutically acceptable salt thereof;
(bb) 50 to 99 wt.-%, particularly 80 to 98 wt.-%, more preferably 90 to 96 wt.-% of filler;
(cc) 0 to 30 wt.-%, particularly 2 to 10 wt.-%, more preferably 3 to 7 wt.-% of binder;

(dd) 0 to 10 wt.-%, particularly 0.25 to 5 wt.-%, more preferably 0.5 to 2 wt.-% of lubricant;

(ee) 0 to 10 wt.-%, particularly 0.25 to 5 wt.-%, more preferably 0.5 to 2 wt.-% of glidant; and

(ff) 0 to 1 wt.-%, particularly 0.01 to 0.5 wt.-%, more preferably 0.05 to 0.2 wt.-% of coloring agent.

According to another preferred embodiment, the second portion, such as the second tablet layer, comprises

(aa) 1 to 50 wt.-%, particularly 2 to 20 wt.-%, more preferably 4 to 8 wt.-% like 4 to 9 wt.-% of amlodipine or a pharmaceutically acceptable salt thereof;

(bb) 50 to 99 wt.-%, particularly 80 to 98 wt.-%, more preferably 88 to 94 wt.-% of filler, preferably selected from a sugar alcohol, like isomalt, xilitol or mannitol, lactose monohydrate and mixtures thereof;

(cc) 0 to 5 wt.-%, particularly 0.1 to 3 wt.-%, more preferably 0.1 to 1.5 wt.-% of binder, preferably selected from hydroxypropylcellulose, maltose and mixtures thereof, and more preferably hydroxypropylcellulose; and

(dd) 0 to 10 wt.-%, particularly 0.25 to 5 wt.-%, more preferably 0.5 to 3 wt.-% of lubricant, preferably selected from sodium stearyl fumarate, macrogols and mixtures thereof.

If the second portion of the composition is in the form of a coating comprising amlodipine coated on the first portion such as a tablet comprising telmisartane, then suitable coating agents for use in the second portion of the pharmaceutical composition of the present invention include carmellose calcium, shellac, copovidone, hydroxyethylcellulose, methylhydroxy-ethylcellulose, polymethacrylate, hydroxypropylcellulose, chitosan, hypromellose, polyvinyl alcohol, methylcellulose, polyethylene oxide, povidone, cetyl alcohol or mixtures thereof.

The second portion comprising amlodipine preferably comprises 0.01 to 20 wt.-%, more preferably 0.1 to 10 wt.-% of coating agent based on the total mass of coated pharmaceutical composition including tablet core and coating together.

According to another particular embodiment, the second portion is a tablet layer which comprises granules and an extragranular phase. Preferably, the granules comprise amlodipine, at least one non-hygroscopic filler, at least one non-hygroscopic binder and optionally further excipients like a coloring agent. Moreover, it is preferred that the extragranular phase of the second tablet layer according to this embodiment comprises at least one non-hygroscopic filler, at least one hydrophilic lubricant and optionally additional excipients such as at least one coloring agent and at least one glidant. The at least one filler of the extragranular phase can be the same as or different from the filler of the granules. Preferably, the filler of the extragranular phase is the same as the filler of the granules. Typically, preferred embodiments with regard to specific components and their amounts are described above. In particular, the filler used in the granules and in the extragranular phase is a sugar alcohol, like mannitol, and/or lactose monohydrate.

As stated above, it is preferred that in any of the above described embodiments the combined weight of the amlodipine or pharmaceutically acceptable salt thereof and the non-hygroscopic excipient, i.e. non-hygroscopic filler and non-hygroscopic binder, or the combined weight of the amlodipine or pharmaceutically acceptable salt thereof, the non-hygroscopic excipient, i.e. non-hygroscopic filler and non-hygroscopic binder, and the hydrophilic lubricant of the second portion, such as the second tablet layer, is at least 50 wt.-%, preferably at least 85 wt.-%, more preferably at least 93 wt.-%, like at least 95 wt.-% or at least 97 wt.-%, such as at least 98

wt.-%, and most preferably at least 99 wt.-% by weight of the second portion. In one embodiment, the second portion of the composition, such as the second tablet layer, essentially consists of amlodipine or a pharmaceutically acceptable salt thereof and the at least one non-hygroscopic excipient. In another embodiment, the second portion of the composition essentially consists of amlodipine or a pharmaceutically acceptable salt thereof, the at least one non-hygroscopic excipient and the at least one hydrophilic lubricant.

In an additional aspect, the present invention is directed to a process for preparing the pharmaceutical composition according to the invention. The mode of preparation can be direct compression, dry granulation or wet granulation or any other known method or combination thereof.

The process for the preparation of a solid pharmaceutical composition according to the invention typically comprises

(i) providing a first portion composition comprising telmisartan or a pharmaceutically acceptable salt thereof,

(ii) providing a second portion composition comprising amlodipine or a pharmaceutically acceptable salt thereof and at least one non-hygroscopic excipient, and

(iii) combining said portion compositions to result in the solid pharmaceutical composition having separated first and second portions.

If the composition according to the invention is in form of a multilayer pharmaceutical tablet, such tablet can be prepared in principle by any method used for manufacturing tablet formulations. Preparation of the tablet generally comprises preparing a first tablet layer composition comprising

telmisartan and a second tablet layer composition comprising amlodipine and compressing the tablet layer compositions to produce a multilayer tablet.

The first tablet layer composition comprising telmisartan can be prepared by various methods. Suitable methods include spray-drying and fluid-bed granulation. One method for preparing the first tablet layer composition comprises preparing a spray-solution by dissolving telmisartan together with at least one basic agent in an appropriate solvent (e.g. water or organic solvent). Optionally, additional excipients, such as a crystallization retarder and/or a surfactant can be included in the spray-solution. The spray solution is subsequently spray-dried to give a spray-dried granulate. The spray-dried granulate is mixed with further excipients to give a tablet layer composition ready for tableting.

Another method for preparing the first tablet layer composition comprises preparing a granulation liquid by dissolving telmisartan together with at least one basic agent in an appropriate solvent (e.g. water or organic solvent). Optionally, additional excipients, such as a crystallization retarder and/or a surfactant can be included in the spray-solution. At least one excipient selected from fillers, binders and mixtures thereof is placed into a fluid-bed granulating machine and sprayed with the granulation liquid. When granulation is completed, the granulate is dried and optionally mixed with further excipients to give a tablet layer composition ready for tableting.

The second tablet layer composition comprising amlodipine or a pharmaceutically acceptable salt thereof can also be prepared by various methods such as direct compression, compression of a granulate obtained by state of the art processes like wet, dry or thermoplastic granulation or melt extrusion. For instance, the second tablet layer composition can in a first embodiment of

the present invention be prepared using a wet granulation technique. A suitable wet granulation technique comprises preparing a granulation liquid by dissolving at least a part of a filler and/or binder in an appropriate solvent (e.g. water, organic solvent or a mixture thereof) and granulating the amlodipine or salt thereof optionally additional excipients. The obtained wet granulate is optionally dried and/or sieved and blended with at least one filler and optionally other pharmaceutical excipients such as at least one lubricant to provide a second tablet layer composition.

According to a another embodiment, the second tablet layer composition is prepared using a direct compression method where a powder premix of amlodipine or a salt thereof and at least one further excipient selected from filler, binder, lubricant, glidant and mixtures thereof is directly compressed onto the first layer containing telmisartan.

Preferred embodiments of the first tablet layer composition comprising telmisartan with regard to specific components and their amounts as well as to methods for its preparation are as described above. Also, preferred embodiments of the second tablet layer composition with regard to specific components and their amounts are as described above.

If the composition according to the invention is in form of a coated tablet, then coated tablets can be prepared by first preparing a tablet containing telmisartan or pharmaceutically acceptable salts thereof. This tablet can subsequently be coated by wet and/or dry coating procedure. Wet coating technique consists of dissolving suitable coating agent in a solvent together with optional other ingredients and sprayed onto tablet cores. Dry coating consists of spraying suitable coating agent to the tablet and/or pellet bed with simultaneous spraying of a suitable plasticizing agent. This can be achieved either with

fluidized bed, perforated coating pan or other suitable equipment.

The invention is illustrated in more detail by the following non-limiting examples.

Examples

Example 1: Bilayer tablet

Telmisartan layer	A [mg]	B [mg]
Telmisartan	80.0	80.0
Meglumine	24.0	24.0
Sodium hydroxide	6.7	6.7
Povidone	24.0	24.0
Lactose monohydrate	120.0	120.0
Sorbitol	299.7	299.7
Magnesium stearate	5.6	
Sodium stearyl fumarate		5.6
Total telmisartan layer	560.0	560.0

Telmisartan, sodium hydroxide and povidone were dissolved in water q.s. in order to prepare a granulation liquid. Lactose monohydrate and meglumine were placed in a fluid-bed granulating machine and sprayed with the granulation liquid. When granulation was completed the granulate was dried and mixed with sorbitol and magnesium stearate or sodium stearyl fumarate to form final composition ready for tabletting.

Amlodipine Layer	A [mg]	B [mg]	C [mg]	D [mg]	E [mg]	F [mg]	G [mg]	H [mg]
Amlodipine besylate	13.89		13.89		13.89		13.89	
Amlodipine maleate		12.84		12.84		12.84		12.84

Xylitol	182.11	183.16						
Lactose monohydrate			182.11	183.16				
Mannitol					182.11	183.16		
Isomalt							182.11	183.16
Magnesium stearate	4.00		4.00		4.00		4.00	
Sodium stearyl fumarate		4.00		4.00		4.00		4.00
Total amlodipine layer	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00

Amlodipine in the form of besylate or maleate was mixed with either xylitol, lactose monohydrate, mannitol or isomalt. Lubricant (magnesium stearate or sodium stearyl fumarate) was admixed subsequently to form final composition ready for tabletting by direct compression.

Bilayer tablets containing telmisartan and amlodipine were prepared by first introducing the telmisartan containing mixture ready for tabletting into the tabletting machine, followed by the amlodipine containing mixture ready for tabletting. These two layers were then compressed on a rotary tablet press in a bilayer tabletting mode.

Example 2: Bilayer tablet

Telmisartan layer was prepared by the same way as in Example 1.

Amlodipine layer	A [mg]	B [mg]	C [mg]	D [mg]	E [mg]	F [mg]
Amlodipine besylate	13.89		13.89		13.89	
Amlodipine maleate		12.84		13.89		12.84

Mannitol	50.00		50.00		50.00	
Lactose monohydrate		100.00		50.00		100.00
Hydroxypropyl Cellulose	1.50	1.50	1.50			
Maltose				3.75	3.75	3.75
Mannitol	130.61	81.66	130.61			
Lactose monohydrate				128.36	128.36	79.41
Magnesium stearate		4.00	4.00		4.00	
Sodium stearyl fumarate	4.00			4.00		4.00
Total amlodipine layer	200.00	200.00	200.00	200.00	200.00	200.00

Amlodipine in the form of besylate or maleate and either mannitol or lactose monohydrate were granulated with a water solution of either hydroxypropyl cellulose or maltose. The obtained granules were dried. The granulate was subsequently mixed with either mannitol or lactose monohydrate. Lubricant (magnesium stearate or sodium stearyl fumarate) was admixed to form final composition ready for tabletting.

Bilayer tablets containing telmisartan and amlodipine were prepared by first introducing the telmisartan containing mixture ready for tabletting into the tabletting machine, followed by the amlodipine containing mixture ready for tabletting. These two layers were then compressed on a rotary tablet press in a bilayer tabletting mode.

Example 3: Multilayer tablet

Telmisartan layer was prepared by the same way as in Example 1. Amlodipine layer was prepared by the same way as in Example 1 (Example 3a) or Example 2 (Example 3b).

Separating layer	A [mg]	B [mg]	C [mg]	D [mg]
Mannitol	48.00			
Xylitol		48.00		
Isomalt			48.00	
Maltitol				48.00
Sodium stearyl fumarate	2.00	2.00	2.00	2.00
Total separation layer	50.00	50.00	50.00	50.00

Separation layer was prepared by either mixing mannitol or xylitol or isomalt or maltitol with sodium stearyl fumarate in a tumbling mixer in order to obtain a final composition ready for tabletting.

Multilayer tablets containing telmisartan and amlodipine were prepared by first introducing the telmisartan containing mixture ready for tabletting into the tabletting machine. Then, the separation layer was introduced, followed by the amlodipine containing mixture ready for tabletting. These three layers were then compressed on a rotary tablet press in a three layer tabletting mode.

Example 4: Coated tablet

	A [mg]	B [mg]	C [mg]
Telmisartan tablet			
Telmisartan	80.0	80.0	80.0
Sodium hydroxide	6.72	6.72	6.72
Povidone	24.0	24.0	24.0
Meglumine	24.0	24.0	24.0
Lactose monohydrate	120.0	120.0	120.0
Sorbitol	98.08	215.68	294.08
Magnesium stearate	3.6	4.8	5.6
Sodium stearyl fumarate	3.6	4.8	5.6
Total telmisartan tablet	360.0	480.0	560.0

Amlodipine portion	A [mg]	B [mg]	C [mg]
Hypromellose	10.80	14.40	16.80
Amlodipine besylate	13.89		13.89
Amlodipine maleate		12.84	
Total amlodipine portion	24.69	27.24	30.69

Telmisartan, sodium hydroxide and povidone were dissolved in water in order to prepare a granulation liquid. Lactose

monohydrate and meglumine were placed in the fluid-bed granulating machine and sprayed with granulation liquid. When granulation was completed the granulate was dried and mixed with sorbitol and lubricant (magnesium stearate and sodium stearyl fumarate) to form the final composition ready for tabletting. Tablets were prepared by compression.

Then, hypromellose was dissolved in water. Amlodipine in the form of besylate or maleate was suspended in the obtained hypromellose solution. The telmisartan containing tablets were then coated with the obtained amlodipine suspension.

Example 5: Coated tablet with separating coating

	A [mg]	B [mg]	C [mg]
Telmisartan tablet			
Telmisartan	80.0	80.0	80.0
Sodium hydroxide	6.72	6.72	6.72
Povidone	24.0	24.0	24.0
Meglumine	24.0	24.0	24.0
Lactose monohydrate	120.0	120.0	120.0
Sorbitol	98.08	215.68	294.08
Magnesium stearate	3.6	4.8	5.6
Sodium stearyl fumarate	3.6	4.8	5.6
Total telmisartan tablet	360.0	480.0	560.0

Separating coating	A [mg]	B [mg]	C [mg]
Hypromellose	5.40	7.20	
Povidone			8.40
Total separating	5.40	7.20	8.40

coating			
Amlodipine portion			
Hypromellose	10.80	14.40	16.80
Amlodipine besylate	13.89		13.89
Amlodipine maleate		12.84	
Total amlodipine coating	24.69	27.24	30.69

Telmisartan, sodium hydroxide and povidone were dissolved in water in order to prepare a granulation liquid. Lactose monohydrate and meglumine were placed in the fluid-bed granulating machine and sprayed with granulation liquid. When granulation was completed the granulate was dried and mixed with sorbitol and lubricant (magnesium stearate and sodium stearyl fumarate) to form the final composition ready for tabletting. Tablets were prepared by compression.

Hypromellose or povidone was dissolved in water and telmisartan containing tablets were coated with separating coating.

Hypromellose was dissolved in water. In the obtained solution amlodipine in the form of besylate or maleate was suspended. The previously prepared coated tablets were then coated with the obtained amlodipine suspension.

Example 6: Capsule comprising two or more units

	A [mg]	B [mg]	C [mg]
Telmisartan	80.0	80.0	80.0
Sodium hydroxide	6.72	6.72	6.72
Povidone	24.0	24.0	24.0
Meglumine	24.0	24.0	24.0

Lactose monohydrate	120.0	120.0	120.0
Sorbitol	98.08	215.68	294.08
Magnesium stearate	3.6	4.8	5.6
Sodium stearyl fumarate	3.6	4.8	5.6
Total telmisartan	360.0	480.0	560.0

Telmisartan, sodium hydroxide and povidone were dissolved in water in order to prepare a granulation liquid. Lactose monohydrate and meglumine were placed in a fluid-bed granulating machine and sprayed with granulation liquid. After granulation had been completed the obtained granulate was dried and mixed with sorbitol and lubricant (magnesium stearate and sodium stearyl fumarate) to form a unit comprising telmisartan.

Then, a pharmaceutical composition comprising at least one telmisartan unit was prepared by tabletting the unit into one layer tablet. Alternatively, a composition was prepared in the form of microtablets. Alternatively, a composition was preparedin a powder or pellet form.

As amlodipine unit, an amlodipine portion as disclosed in Example 1 or in Example 2 was used.

A pharmaceutical composition comprising at least one amlodipine unit was prepared by tabletting the amlodipine unit into a one layer tablet. Alternatively, a composition was prepared in a form of microtablets. Alternatively, a composition was prepared in a powder or pellet form.

Then, any one of the above telmisartan unit (as for example tablets, microtablets, pellets or powder form) was used together with any one of the above amlodipine unit (as for example tablets, microtablets, pellets or powder form) to be filled in

any kind of hard capsules (gelatin, hypromellose or polysaccharide).

Example 7: Two separate units in a combo blister pack

Any one of the above telmisartan unit from Example 6 (as for example tablets, microtablets, pellets or powder form) was used together with or any one of above amlodipine unit (as for example tablets, microtablets, pellets or powder form) from Example 6 to prepare combo blister pack containing at least one telmisartan unit and at least one amlodipine unit.

Example 8: Preparation of cyanotelmisartan

Into a reaction vessel 360 ml of acetonitrile, 8.32 g (126 mmol) of solid 85% KOH, 36.5 g (113 mmol) of 1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-bibenzo[d]imidazole and 32.4 g (119 mmol) of 4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile were added. The reaction mixture was stirred at room temperature for 4 hours. The mixture was cooled to 0°C and filtered. The obtained product was washed with water and partially dried.

The product was suspended in 430 ml of ethyl acetate and heated to reflux temperature and stirred at this temperature for 1 hour. The suspension was cooled to a temperature below 0°C, filtered and dried.

Yield: 47.9 g (87%)
HPLC: 98.7%

Example 9: Preparation and isolation of telmisartan

Into a reaction vessel 10g (20 mmol) cyanotelmisartan and 20 ml (180mmol) H_2SO_4 (1:1) were added. The reaction mixture was heated to around 125°C and stirred at this temperature for 24 h. The reaction mixture was cooled and 200 ml of water and 10 ml of dichloromethane were added. Then pH value of mixture was adjusted to 5.3 by addition of 6M NaOH. The precipitated product was separated and washed with water and dried at 65°C under reduced pressure.

Yield: 10.5g (100%)
Area % HPLC: Telmisartan 98.2%

The product was recrystallized from DMF.

Yield: 90%
Area % HPLC: Telmisartan 99.29%

Claims

1. A solid pharmaceutical composition comprising

(a) at least one first portion comprising telmisartan or a pharmaceutical acceptable salt thereof; and

(b) at least one second portion comprising
amlodipine or a pharmaceutically acceptable salt thereof and
at least one non-hygroscopic excipient.

2. The composition according to claim 1, wherein the at least one non-hygroscopic excipient is an excipient having an equilibrium moisture content of 6% (w/w) or less as determined by dynamic vapor sorption (DVS) at a relative humidity of 60% and a temperature of 25°C.

3. The composition according to claim 1 or 2, wherein the second portion further comprises at least one hydrophilic lubricant.

4. The composition according to any one of claims 1 to 3, wherein the combined weight of the amlodipine or pharmaceutically acceptable salt thereof and the non-hygroscopic excipient or the combined weight of the amlodipine or pharmaceutically acceptable salt thereof, the non-hygroscopic excipient and the hydrophilic lubricant is at least 50 wt.-% by weight of the second portion.

5. The composition according to any one of claims 1 to 4, wherein the second portion comprises less than 2 wt.-% of disintegrant by weight of the second portion.

6. The composition according to claim 5, wherein the second portion comprises less than 2 wt.-% by weight of the second portion of one or more disintegrants selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, corn starch, pregelatinized starch, low-substituted hydroxypropylcellulose and microcrystalline cellulose.

7. The composition according to any one of claims 1 to 6, wherein the composition is in the form of a multilayer tablet, wherein the at least one first portion is an at least one first tablet layer and the at least one second portion is an at least one second tablet layer.

8. The composition according to any one of claims 1 to 6, wherein the composition is in the form of a coated tablet, wherein the at least one first portion is at least one tablet and the at least one second portion is at least one coating on said tablet.

9. The composition according to claim 7 or 8, wherein the composition comprises at least one separating coating.

10. The composition according to any one of claims 1 to 6, wherein the composition is in the form of a capsule comprising the at least one first portion in form of a first unit and the at least one second portion in form of a second unit.

11. The composition according to claim 10, wherein the first and the second unit are independently selected from the group consisting of tablets, microtablets, pellets, powder forms, granules and granulates.

12. The composition according to any one of claims 1 to 11, wherein the first portion comprises telmisartan and a basic agent.

13. The composition according to any one claims 1 to 12, wherein the non-hygroscopic excipient of the second portion is selected from the group consisting of fillers, binders and mixtures thereof.

14. The composition according to claim 13, wherein the filler of the second portion is selected from the group consisting of monosaccharides, oligosaccharides, sugar alcohols and mixtures thereof.

15. The composition according to claim 14, wherein the filler of the second portion is selected from the group consisting of glucose, fructose, saccharose, lactose (anhydrous and monohydrate), raffinose, trehalose, dextrates, mannitol, isomalt, erythritol, sorbitol, maltitol, xylitol, lactitol, compressible sugar, calcium hydrogen phosphate, calcium carbonate, calcium lactate and mixtures thereof.

16. The composition according to claim 15, wherein the filler of the second portion is selected from the group consisting of mannitol, lactose monohydrate and mixtures thereof.

17. The composition according to any one of claims 13 to 16, wherein the binder of the second portion is selected from the group consisting of hydroxypropylcellulose, maltose and mixtures thereof.

18. The composition according to any one of claims 3 to 17, wherein the hydrophilic lubricant of the second portion is selected from the group consisting of stearic acid, magnesium stearate, magnesium palmitate, magnesium oleate,

hydrogenated vegetable oil, hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols and mixtures thereof.

19. The composition according to claim 18, wherein the hydrophilic lubricant of the second portion is selected from the group consisting of sodium stearyl fumarate, macrogols and mixtures thereof.

20. Process for the preparation of a solid pharmaceutical composition according to any one of claims 1 to 19 comprising

(i) providing a first portion composition comprising telmisartan or a pharmaceutically acceptable salt thereof,

(ii) providing a second portion composition comprising amlodipine or a pharmaceutically acceptable salt thereof and at least one non-hygroscopic excipient, and

(iii) combining said portion compositions to result in the solid pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/068806

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K9/48 A61K9/50 A61K31/4184
A61K31/4422
ADD.
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

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2010/137855 A2 (DASAN MEDICHEM CO LTD [KR]; YOO HYOUNG-SUN [KR]; KWON MAN-HO [KR]; BAN) 2 December 2010 (2010-12-02) example 6	1-20
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2012	10/02/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/068806

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2007/001067 A2 (SANKYO CO [JP]; HAMAURA TAKESHI [JP]; KANNO MITSURU [JP] DAIICHI SANKY) 4 January 2007 (2007-01-04) cited in the application claim 32	1,3,4,7, 12,18,20
X	WO 2008/069612 A1 (HANMI PHARM IND CO LTD [KR]; WOO JONG SOO [KR]; YI HONG GI [KR]; CHI M) 12 June 2008 (2008-06-12) example 8	1,3,4,7, 12,18,20

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International application No
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