Title: SOLID ORAL DOSAGE FORM CONTAINING OLMESARTAN MEDOXOMIL

Abstract: The present invention provides a solid oral dosage form comprising olmesartan medoxomil and polyethylene glycol having a molecular weight of about 1,000 - 10,000.
Solid oral dosage form containing olmesartan medoxomil

The present invention relates to a pharmaceutical solid oral dosage form comprising olmesartan medoxomil. More particularly, the present invention relates to formulations, processes for preparing these formulations, and to formulations for the treatment or prevention of hypertension, heart and circulatory diseases. Specifically, the present invention relates to the use of (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl-4-(2-hydroxypropan-2-yl)-2-propyl-1-((4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl][phenyl]methyl)-1H-imidazole-5-carboxylate in the preparation of immediate release formulations.

BACKGROUND OF THE INVENTION

The compound (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl-4-(2-hydroxypropan-2-yl)-2-propyl-1-((4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl][phenyl]methyl)-1W-imidazole-5-carboxylate is known by the name of olmesartan medoxomil presented by the formula (I) below:

![Chemical structure of olmesartan medoxomil](image)

Formula (I)

EP0503785B1 discloses generically a series of 1-(biphenylmethyl)imidazole derivatives having an activity as angiotensin II receptor antagonist including olmesartan medoxomil and a process for its preparation.
Olmesartan medoxomil is a prodrug that is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan works by blocking the binding of angiotensin II to the AT₁ receptors in vascular muscle; it is therefore independent of angiotensin II synthesis pathways, unlike angiotensin converting enzyme (ACE) inhibitors. Angiotensin I is converted to angiotensin II through removal of two terminal residues by the enzyme ACE.

The renin-angiotension system provides one of the important mechanisms for maintaining the homeostasis of blood pressure in living animals. When blood pressure is reduced or the sodium ion concentration of the body fluids falls, this system is activated. As a result, the enzyme renin and ACE are activated and act on angiotensinogen, which is first decomposed by renin to produce angiotensin I (AI). This AI is then converted by ACE to angiotensin II (All). All is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium.

By blocking the binding rather than blocking the synthesis of angiotensin II, olmesartan inhibits the negative regulatory feedback on renin secretion. As a result of this blockage, olmesartan reduces vasoconstriction and the secretion of aldosterone. This lowers blood pressure by producing vasodilation, and decreasing peripheral resistance.


WO 2007/128478 A2 reports that olmesartan medoxomil is susceptible to degradation under basic conditions and also under highly acidic conditions while it is most stable at a pH in the range of 3-5. According to WO2007/128478 A2 stabilization of a pharmaceutical composition containing olmesartan medoxomil can be achieved with pharmaceutically acceptable constituents where each of the constituents being incorporated into a composition has a pH of less than 8 and wherein one of the constituents is stearic acid.
One object of the present invention is therefore to provide a solid oral dosage form containing olmesartan medoxomil which is sufficiently stable without the incorporation into a composition including pH lowering agents i.e. stearic acid as disclosed in WO 2007/128478 A2.

Surprisingly it was found that the neutral compound polyethylene glycol having a molecular weight of 1000 - 10000, without acid-base-buffer capacity has a stabilizing effect on olmesartan medoxomil.

SUMMARY OF THE INVENTION

The present invention relates to a solid oral dosage form comprising olmesartan medoxomil and polyethylene glycol having an average molecular weight of about 1000 - 10000.

Another aspect of the invention is a solid oral dosage form as described herein for the treatment and/or prevention of hypertension and disorders associated therewith.

The invention further relates to a process for the manufacture of a solid oral dosage form containing olmesartan medoxomil as a pharmaceutically active agent and polyethylene glycol having a molecular weight of about 1,000 - 10,000 as a stabilizer, comprising wet granulation.

Another aspect of this invention is a process for the manufacture of a solid oral dosage form containing olmesartan medoxomil as a pharmaceutically active agent comprising the steps of:

a) dry mixing the active agent(s) with a diluent,
b) adding an aqueous solution containing a stabilizer and a binder
c) wet granulation of the mixture to obtain granules,
d) wet sifting the granules using a comill
e) drying and additionally sifting the granules,
f) blending the granules with a lubricant and
g) optionally compressing the blend to a tablet.

A disintegrant is preferably added either to the mixture of the active agent and the diluent, i.e. step (a) or to the blend of the granules and the lubricant, i.e. step (f).
Another aspect of this invention is a solid oral dosage form obtainable by the process of the present invention.

Yet another aspect of the invention is the use of polyethylene glycol as a stabilizer of olmesartan medoxomil in a solid dosage form.

DETAILED DESCRIPTION OF THE INVENTION

The terms "dissolution profile" and "release profile" are used interchangeably in this application.

Also the terms "sifting" and "sieving" are used interchangeably herein.

The term "solid ingredient" refers to any constituent of the composition of the solid oral dosage form according to the present invention that is in the solid state under standard conditions, i.e. at 25 °C and at a pressure of 1 atm (101.325 kPa).

Generally, the phrase "Immediate release formulation" refers to any solid oral formulation that after taking, by the time olmesartan medoxomil leaves the stomach, olmesartan medoxomil is either in solution or it is in the form of a suspension of fine particles, e.g., in a form in which olmesartan can be readily absorbed. More specifically, the in vitro dissolution profiles for the immediate release formulations were generated using the paddle method USP Apparatus II at a stirring speed of 50 rpm in 0.1 HCl or phosphate buffer with a pH 6.8 at 37°C.

Generally, in the case of orally administered pharmaceuticals, bioavailability of active ingredients contained therein is quite important, and exerting a constant efficacy is also required. For that purpose, assuring uniformity, e.g. bioequivalence among formulation batches is required. In pharmacopoeias, procedures for testing disintegration or dissolution properties of solid formulations are defined for assuring a constant quality and bioequivalence of the formulations. Accordingly, pharmaceuticals are requested to meet specifications as defined based on such tests.
Active agent(s)

The solid oral dosage form of the present invention preferably contains a unit dose in the range of about 10 to 250 mg, more preferably in the range of about 10 to 40 mg, particularly of 10, 20 or 40 mg of the active agent olmesartan medoxomil.

Another object of the present invention is to provide a solid oral dosage form containing olmesartan medoxomil in combination with hydrochlorothiazide (HCTZ), amlodipine or hydrochlorothiazide and amlodipine and a process of forming the same. Amlodipine may be formulated in form of pharmaceutical acceptable salts thereof, e.g. the besylate, mesylate or maleate salt. With mentioning the term amlodipine the free base and all pharmaceutically acceptable salts are included.

Hydrochlorothiazide is a known therapeutic agent which is useful in the treatment of hypertension. It acts by inhibiting the kidneys' ability to retain water. This reduces the volume of the blood, decreasing blood return to the heart and thus cardiac output and, by other mechanisms, is believed to lower peripheral vascular resistance.

Amlodipine is known as a long-acting calcium channel blocker and used as an anti¬hypertensive and in the treatment of angina. Like other calcium channel blockers, amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle.

The present invention particularly relates to a solid oral dosage form, which contains a unit dose in the range of about 10 to 250 mg, preferably in the range of about 10 to 40 mg, particularly of 10, 20 or 40 mg of the active ingredient olmesartan medoxomil and a unit dose in the range of about 6 to 60 mg, preferably in the range of about 10 to 30 mg, particularly of 12.5 or 25 mg of the active ingredient hydrochlorothiazide.

The present invention particularly relates to a solid oral dosage form, which contains a unit dose in the range of about 10 to 250 mg, preferably in the range of about 10 to 40 mg, particularly of 10, 20 or 40 mg of the active agent olmesartan medoxomil and a unit dose in the
range of about 1 to 20 mg, particularly of 5 or 10 mg of the active agent amlodipine, calculated as amlodipine free base.

The present invention particularly relates to a solid oral dosage form, which contains a unit dose in the range of about 10 to 250 mg, preferably in the range of about 10 and 40 mg, particularly of 10, 20 or 40 mg of the active agent olmesartan medoxomil, a unit dose in the range of about 6 to 60 mg, preferably in the range of about 10 to 30 mg, particularly of 12.5 or 25 mg of the active agent hydrochlorothiazide and a unit dose in the range of about 1 to 20 mg, particularly of 5 or 10 mg of the active agent amlodipine, calculated as amlodipine free base.

The solid oral dosage forms containing olmesartan medoxomil in combination with HCTZ and/or amlodipine do also contain polyethylene glycol having a molecular weight of 1000 - 10000 and are also preferably produced by the preferred process of the present invention.

Polyethylene glycol

The pharmaceutical dosage form of the invention comprises at least one stabilizer to prevent the acid or base catalyzed decompositions of olmesartan medoxomil. The preferred stabilizer used in pharmaceutical composition is polyethylene glycol (PEG). The numbers that are often included in the names of PEGs indicate their average molecular weights. For example, PEG 400 has an average molecular weight of 400 Da.

The stabilizer present in the pharmaceutical compositions of the present invention is preferably PEG having an average molecular weight from 1,000 to 10,000, more preferably from 4,000 to 9,000, most preferably from 6,000 to 8,000.

The PEG is preferably present in an amount of 0.1 to 3 weight-%, more preferably from 0.5 to 2.5 weight-%, e.g., about 1 weight-%, based on the total weight of the composition.
Further excipients

The solid oral dosage form according to the present invention can be in the form of tablets, capsules, caplets, sachets and soft capsules. In the case of tablets or capsules, lubricants are preferably added at the steps of filling or tabletting in consideration of handling properties, precision for filling and the like. Olmesartan medoxomil has potent adhesive properties, and the use of lubricants is therefore preferred. However, the use of the lubricants causes delaying in a dissolution time.

The pharmaceutical composition according to the present invention can further comprise any additional excipients and adjuvants, which are pharmaceutically acceptable, and general coating materials, which are preferably applied as a coating to the solid form of the pharmaceutical composition of the present invention. Such further excipients and adjuvants are known to the person skilled in the art, and can be referred to the standard textbook by Fiedler ("Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete", 5th ed., 2002) or to the "Handbook of Excipients", edited by the American Pharmaceutical Association and Dr. Arthur H. Kibbe, 3rd ed., 2000.

Preferably, the pharmaceutical composition of the solid oral dosage form according to the present invention comprises one or more diluents, binders, lubricants, stabilizers and/or coating materials and optionally colourants and/or surfactants, and in particular 1 to 90 weight-% of a diluent, 0.5 to 10 weight-% of a binder, 0 to 3 weight-% of a lubricant, 0.1 to 3 weight-% of a stabilizer, 0 to 5 weight-% of a coating material, and optionally 0 to 6 weight-% of a surfactant and 0 to 3 weight-% colourants based on the total weight of the composition. The further excipients and adjuvants and optionally coating materials or colourants are present in the pharmaceutical composition of the present invention, such that the total amount of the pharmaceutical composition including the amount of the active agents results in 100 weight-%. In case of capsules, the capsule shell is excluded from the total amount of the pharmaceutical composition.

As diluent one or more components can be used, which contribute a part of the tablet to reach the necessary total mass of the tablet. Preferred diluents are inorganic phosphates, like dibasic
calcium phosphate, sugars or sugar analogues and derivatives thereof, in particular lactose, such as lactose monohydrate or water-free lactose, dextrose, sorbitol, mannitol, saccharose, maltodextrin, isomalt and Tablettose®. Celluloses like microcrystalline cellulose or powdered cellulose are further preferred diluents according to the present invention. Preferably the pharmaceutical composition according to the present invention comprises 1 to 90 weight-%, more preferably 40 to 90 weight-%, in particular 60 to 85 weight-%, e.g. about 80 weight-% of a diluent, based on the total weight of the composition.

As binders, i.e. a compound enabling granulation of the active ingredient and the further excipients and adjuvants into granules, to be used in the pharmaceutical composition of the present invention, gelatine, povidone (N-vinylpropylidone polymer), copovidone (copolymer of N-vinyl-2-pyrrolidone and vinyl acetate) and in particular hydroxypropyl cellulose or polyvinyl pyrrolidone can be exemplified, the latter being particularly preferred. The binder is preferably present in an amount of 0.5 to 10 weight-%, more preferably 0.5 to 5 weight-%, in particular 1 to 3 weight-%, based on the total weight of the composition.

As lubricants to be used in the pharmaceutical compositions of the present invention fatty acids or fatty acid derivates, such as alkali and earth alkali salts of stearic, lauric and/or palmitic acid, in particular magnesium stearate, glycerol monostearate or glycerol tristearate, glyceryl palmitate/stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, hydrogenated plant oil (Lubritab®), natriumbenzoate, or polyethylen glycol are exemplified, sodium stearyl fumarate and magnesium stearate are especially preferred. The lubricant is preferably present in an amount of 0 to 3 weight-%, more preferably 0.5 to 2.5 weight-%, such as about 1 weight-%, based on the total weight of the composition.

The pharmaceutical composition of the present invention preferably comprises at least 1 weight-%, more preferably 1-10 weight-% and even more preferably 1-5 weight-% of a disintegrant, based on the total weight of the composition. Some disintegrants are known in the art which may also be used as binders, diluents or as further excipients or adjuvants different to disintegrants. Preferably used disintegrants according to the present invention are croscarmellose sodium, low substituted hydroxypropyl cellulose, crospovidone, sodium starch glycolate and polacrilin potassium.
Stabilizers used in pharmaceutical compositions to prevent the acid or base catalyzed decompositions of olmesartan medoxomil are, e.g. polyethylene glycol (PEG), see supra. As stabilizer to be used in the pharmaceutical compositions of the present invention PEG having the molecular weight 1000-10000, preferably 4000-9000, in particular 6000-8000 are especially preferred. The stabilizer is preferably present in an amount of 0.1-3 weight-%, more preferably 0.5-2.5 weight-%, such as about 1 weight-%, based on the total weight of the composition.

In a specific embodiment, the pharmaceutical formulation of the invention does not contain stearic acid. In another embodiment, the pharmaceutical formulation of the invention does not contain stearic acid or a salt thereof.

Release profile

A particular advantage of the tablets of this invention is their advantageous dissolution profile. The tablets release a substantial portion of the active ingredient, olmesartan medoxomil, within 20 or 30 minutes, using USP Apparatus II, in 900 ml 0.05 M Phosphate Buffer, pH 6.8 at 37°C and 50 rpm. In a first embodiment, the tablets exhibit the following release of olmesartan medoxomil: at least 15% within 5 minutes, at least 50% within 10 minutes, at least 60% within 15 minutes, and at least 80% within 30 minutes, using USP Apparatus II, in 900 ml 0.05 M Phosphate Buffer, pH 6.8 at 37°C and 50 rpm.

In a second embodiment related to the dissolution profile at pH 6.8, the tablets exhibit the following release of olmesartan medoxomil: 20 to 40% within 5 minutes, 50 to 75% within 10 minutes, 60 to 90% within 15 minutes, and at least 80% within 30 minutes, determined according to USP Apparatus II, in 900 ml 0.05 M Phosphate Buffer, pH 6.8 at 37°C and 50 rpm.

The tablets release a substantial portion of the active ingredient, olmesartan medoxomil, within 10 or 15 minutes, using USP Apparatus II, in 900 ml 0.1 N HCl, pH 1.1 at 37°C and 50 rpm. In a first embodiment, the tablets exhibit the following release of olmesartan medoxomil: at least 30% within 5 minutes, at least 70% within 10 minutes, at least 80% within 15 minutes, and at
least 90% within 30 minutes, using USP Apparatus II, in 900 ml 0.1 N HCl, pH 1.1 at 37°C and 50 rpm.

In a second embodiment related to the dissolution profile at pH 1.1, the tablets exhibit the following release of olmesartan medoxomil: 40 to 70% within 5 minutes, 75 to 95% within 10 minutes and at least 85 to 100% within 15 minutes, using Apparatus II, in 900 ml 0.1 N HCl, pH 1.1 at 37°C and 50 rpm.

Use

According to another aspect of the invention, the solid oral dosage form of the present invention and all its embodiments are provided for the treatment or prevention of hypertension and diseases related thereto. Diseases related to hypertension are diseases caused by high blood pressure, like angina pectoris and diseases of the heart, the kidney and the cerebrovascular system.

Process of manufacture

Generally any known process in the art can be used for the manufacture of the solid oral dosage forms of the present invention.

Surprisingly, however, it has been found that solid oral dosage forms comprising olmesartan medoxomil and polyethylene glycol having an average molecular weight of about 1000 - 10000 formed from sized granules obtained by wet mass sifting during a wet granulation process show stable and excellently reproducible immediate release profiles with each batch. Therefore, the present invention further provides a preferred process for the manufacture of a solid oral dosage form containing olmesartan medoxomil and preferably polyethylene glycol having an average molecular weight of about 1000 - 10000. The preferred process of the invention is a wet granulation process and more preferably the wet granules obtained in the wet granulation are subjected to wet sifting subsequently by wet granulation.
In cases where formulations are prepared by a dry process, electrostatic charges are generated by physical irritations caused through processes such as pulverization, agitation, blending, granulation and the like, which in turn cause a decrease in fluidity of pulverized, blended or granulated materials, worsen handling properties, and decrease precision for content uniformity of an active ingredient.

The process for the manufacture of the solid oral dosage form according to the present invention is therefore preferably carried out in the presence of water, i.e. it is preferably a wet granulation method.

Further, and even more preferred, the wet granules are subjected to wet mass sifting, in order to obtain sized wet granules.

In a preferred embodiment of the present invention the pharmaceutical composition is in the form of a tablet which can be obtained by wet granulation followed by wet mass sifting.

The granules obtained by the preferred process of wet sifting using a comill of the present invention have a particle size of 10 to 1 mm, preferably 7 to 3 mm, in particular 4 mm after wet sifting. The preferred sieves to be used during the wet mass sifting are mesh 7L156Q03746 with a square hole size of 3.96 mm x 3.96 mm.

In another embodiment of the present invention there is provided a process for the manufacture of the solid oral dosage form according to the present invention comprising the steps of
a) dry mixing the active agent with a diluent,
b) adding an aqueous solution containing a stabilizer and a binder and granulation of the mixture to get granules
c) wet sifting using a comill, drying and additionally sifting the granules,
d) blending the granules together with a lubricant,

A disintegrant is preferably added either to the mixture of the active agent and the diluent, i.e. step (a) or to the blend of the granules and the lubricant, i.e. step (d).
All solid ingredients are preferably sieved before being employed in the process. More preferably the disintegrant and lubricant are sieved before being employed in the process.

In a preferred embodiment of the process, the blend obtained in step (iv) is compressed to tablets. The compression of the granulates to tablet cores can be carried out using a conventional tabletting machine or a rotary compression machine. The tablet cores may vary in shape and be, for example, round, oval, oblong, cylindrical or any other suitable shape, and may also vary in size depending on the concentration of the therapeutic agents. Preferably, the tablets are coated by suitable coating methods well-known in the art.

According to a further aspect of the present invention, a solid oral dosage form obtainable by the preferred processes of the present invention is provided.

Within the present invention, percentages given are referred to the weight, based on the total weight of the composition, if not indicated otherwise or obvious for the person skilled in the art. There now follows a series of examples which serve to illustrate the invention. The following examples are not to be limiting:
Examples

Example 1
Olmesartan tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Function</th>
<th>mg/Tab</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Intra Granular Material</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>Active</td>
<td>40.0</td>
<td>9.5</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>Stabilizer</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>Diluent</td>
<td>291.0</td>
<td>69.5</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Diluent</td>
<td>47.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Low substituted hydroxypropyl cellulose</td>
<td>Disintegrant</td>
<td>12.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>Binder</td>
<td>7.0</td>
<td>1.7</td>
</tr>
<tr>
<td><em>Extra Granular Material</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
<td>3.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Opadry</td>
<td>Coating material</td>
<td>14.5</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Total Weight</td>
<td>419.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Preparation process:

The tablets of example 1 were prepared using a wet granulation process:

The active agent(s), the diluent, e.g. lactose monohydrate and microcrystalline cellulose and optionally the disintegrant, e.g. low substituted hydroxypropyl cellulose were weighted out as indicated in the table. The powder blend was then mixed, followed by granulation with the binder solution, e.g. aqueous solution of a binder e.g. PVP and/or hydroxypropyl cellulose and a stabilizer e.g. PEG 6000, in a mixer/granulator and sieved 7L156Q03746 to form the "intragranular material". The wet granules were dried (in a fluid bed dryer) until a LOD (loss of drying) of typically 2.5% or less was reached, followed by passing the dried granules through a round hole screen 7L055R03732 with a diameter of 1.40 mm using a comill.
In a final step, the lubricant magnesium stearate and optionally the disintegrant, e.g. croscarmellose sodium were weighted and mixed with the granule blend described above. This final blend was then compressed into tablets using the tablet press and then optionally coated with the coating material Opadry.

**Example 2**

Olmesartan tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Function</th>
<th>mg/Tab</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra Granular Material</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>Active</td>
<td>40.0</td>
<td>9.6</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>Stabilizer</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>Diluent</td>
<td>287.5</td>
<td>69.1</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Diluent</td>
<td>49.0</td>
<td>11.8</td>
</tr>
<tr>
<td>PVP</td>
<td>Binder</td>
<td>11.0</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Extra Granular Material</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>Disintegrant</td>
<td>7.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
<td>3.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

| Opadry                                   | Coating material | 14.5 | 3.5 |

| Total Weight                             |                | 416.0 | 100.0 |

The tablets were prepared using a process similar to the process described in example 1.
Example 3
Olmesartan/Hydrochlorothiazide tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Function</th>
<th>mg/Tab</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra Granular Material</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>Active</td>
<td>20.0</td>
<td>9.1</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Active</td>
<td>25.0</td>
<td>11.3</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>Stabilizer</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>Diluent</td>
<td>131.7</td>
<td>59.5</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Diluent</td>
<td>24.0</td>
<td>10.9</td>
</tr>
<tr>
<td>PVP</td>
<td>Binder</td>
<td>5.5</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Extra Granular Material</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>Disintegrant</td>
<td>3.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
<td>1.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Opadry</td>
<td>Coating material</td>
<td>7.8</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Total Weight</strong></td>
<td></td>
<td>221.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The tablets were prepared using a process similar to the process described in example 1.

Example 4
Tablets prepared according to example 1 were further analyzed. A dissolution profile of the active ingredient was obtained by dissolving a tablet in an USP-Apparatus II in 900 ml 0.05M phosphate buffer pH 6.8 or 0.1N HCl at 37°C and stirring speed of 50 rpm. The dissolution tests were carried out using USP-Apparatus II.

The release profile is shown in Figure 1 and 2.
Claims

1. A solid oral dosage form comprising olmesartan medoxomil and polyethylene glycol having an average molecular weight of about 1,000 to about 10,000.

2. The solid oral dosage form according to claim 1, wherein the average molecular weight of the polyethylene glycol is from about 4,000 to about 9,000.

3. The solid oral dosage form according to claim 1 or 2, further comprising hydrochlorothiazide as a pharmaceutically active agent.

4. The solid oral dosage form according to any one of claims 1-3, further comprising amlodipine or a salt thereof as a pharmaceutically active agent.

5. The solid oral dosage form according to any one of claims 1-4 having a unit dose of olmesartan medoxomil of about 10 - 250 mg, preferably of about 10 - 40 mg, more preferably of 10, 20 or 40 mg.

6. The solid oral dosage form according to any one of claims 3-5 having a unit dose of hydrochlorothiazide of about 6 - 60 mg, preferably of about 10 - 30 mg, more preferably of 12.5 or 25 mg.

7. The solid oral dosage form according to any one of claims 4-6 having a unit dose of amlodipine or a salt thereof of about 1 - 20 mg, preferably of 5 or 10 mg, calculated as amlodipine free base.

8. The solid oral dosage form according to any one of claims 1-7, wherein the polyethylene glycol is present in an amount of about 0.1 - 3 wt.-%, preferably about 0.5 - 2.5 wt.-% and particularly about 1 wt.-%, based on the total weight of the composition of the solid oral dosage form.
9. The solid oral dosage form according to any one of claims 1 to 8 further comprising a diluent in an amount of about 1 - 90 wt.-%, preferably about 40 - 90 wt.-%, more preferably about 60 - 85 wt.-% and particularly about 80 wt.-%, a binder in an amount of about 0.5 - 10 wt.-%, preferably about 0.5 - 5 wt.-% and more preferably about 1 - 3 wt.-%, a lubricant in an amount of about 0 - 3 wt.-%, preferably about 0.5 - 2.5 wt.-% and particularly about 1 wt.-% and a disintegrant in an amount of about 1 - 10 wt.-% and preferably about 1 - 5 wt.-%, based on the total weight of the composition of the solid oral dosage form.

10. The solid oral dosage form according to claim 9, wherein the diluent is selected from the group consisting of inorganic phosphates, sugars, sugar analogues and derivatives thereof and celluloses, preferably dibasic calcium phosphate, lactose monohydrate, water-free lactose, dextrose, sorbitol, mannitol, saccharose, maltodextrin, isomalt, microcrystalline cellulose and powdered cellulose, the binder is selected from the group consisting of gelatine, povidone, copovidone and hydroxypropyl cellulose, the lubricant is selected from the group consisting of fatty acids and esters thereof, preferably alkali and earth alkali salts of stearic acid, lauric acid and palmitic acid, glycerol monostearate, glycerol tristearate, glycerol palmitate stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, hydrogenated plant oil, sodium benzoate and magnesium stearate and the disintegrant is selected from the group consisting of croscarmellose sodium, low substituted hydroxypropyl cellulose, crospovidone, sodium glycolate and polacrilin potassium.

11. The solid oral dosage form according to any one of claims 1-10 for the treatment or prevention of hypertension and diseases related thereto, like heart disease, kidney disease, cerebrovascular disease and angina pectoris.

12. A process for the manufacture of a solid oral dosage form containing olmesartan medoxomil as a pharmaceutically active agent and polyethylene glycol having a molecular weight of about 1,000 - 10,000 as a stabilizer, comprising wet granulation.
13. The process according to claim 12 further comprising wet sifting of the granules subsequently to the wet granulation.

14. The process according to claim 12 or 13 further comprising the steps of
   a) dry mixing the active agent(s) with a diluent,
   b) adding an aqueous solution containing the stabilizer and a binder
   c) drying and additionally sifting the granules,
   d) blending the granules with a lubricant and
   e) optionally compressing the blend to a tablet,

wherein steps a) and b) are carried out prior to the wet granulation step and steps c) to e) are carried out after the wet granulation step.

15. The process according to claim 14, wherein a disintegrant is additionally added in step a) or d).

16. The process according to any one of claims 12-15, wherein at least one of the solid ingredients is sifted before being applied into the process.

17. The process according to any one of claims 12-16, wherein said active agents include hydrochlorothiazide.

18. The process according to any one of claims 12-17, wherein said active agents include amlodipine or a pharmaceutically acceptable salt thereof.

19. The process according to any one of claims 13-17, wherein the mean particle size of the granules after wet sifting is about 1 - 10 mm, preferably about 3 - 7 mm and more preferably about 4 mm.

20. The process according to any one of claims 12-19, comprising the additional process step of coating the solid oral dosage form.
21. A solid oral dosage form obtainable by the process according to any one of claims 12-20.

22. The use of polyethylene glycol as a stabilizer of olmesartan medoxomil in a solid dosage form.
Dissolution of Olmesartan Medoxomil Release in 0.5 M phosphate buffer pH 6.8, Volume 900 ml, App USP II, 50 rpm

% Release

Time in Minutes
Dissolution of Olmesartan Medoxomil release in 0.1 N HCl pH 1.1; Volume 900 ml, App USP II, 50rpm

Figure 2