The present invention discloses a preparation of a stable formulation of alkali and alkaline earth salts of perindopril in an amorphous form, wherein perindopril in the form of a free acid, dissolved in alcohol, is neutralized with an aqueous solution of alkali or alkaline earth base, this solution is thereafter sprayed onto inert substances for the preparation of a granulate and dried in a stream of warm air at 30-50 °C or in vacuum. Substances to facilitate tablettation or additional active substances, such as diuretics, preferably indapamide, are added to this granulate to be tabletted.
Stable formulation of amorphous perindopril salts, a process for the preparation thereof on industrial scale and use thereof in the treatment of hypertension

Technical Field

The present invention belongs to the field of pharmaceutical chemistry and relates to a stable formulation of amorphous perindopril salts of formula I:

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\[ \text{formula I} \]
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wherein $B^+$ represents an alkali or alkaline earth metal cation,
a process for the preparation thereof on an industrial scale and the use thereof in treating hypertension.

Technical Problem

Best known as well as most used perindopril salt is erbumine, i.e. a salt with a tertiary butyl amine, which is a very effective vasodilator and antihypertensive agent. The low boiling point of tert-butyl amine makes this salt very thermo-sensitive and prone to decompose at elevated temperatures. Therefore, the term of durability of a medicine is considerably short, especially in the countries having average high day temperatures. Thus, there was a need for a process for the preparation of a more stable formulation of pharmaceutical preparations.
Prior Art

Known formulations comprise the active component perindopril erbumine in different polymorphic forms of formula II:

These polymorphic forms are protected by appropriate patent applications: α-form by the application WO 01/87835 Al, β-form by the application WO 01/87836 Al, and γ-form by the application WO 01/83439 Al.

To enhance the stability of the preparations with perindopril erbumine, the use of addition of weak basic components is also known, mostly sodium hydrogen carbonate in a solid form, as stated in patent applications WO 2005/094793 A and DE 102004019845 Al, wherein perindopril remains in the form of erbumine and does not react with alkaline additives.

Patent application US 6,696,481 discloses the salt of perindopril with arginine, which is more stable than erbumine. At the same time the disadvantages of erbumine are stated and it is also mentioned that sodium salt of perindopril in its pure form is unstable for the formulation, because it turns to oil and decomposes when exposed to air.
Our previous patent application WO 2007/058634 A1 discloses the preparation of a stable formulation of perindopril in the form of an amorphous sodium salt on an inert carrier, starting from perindopril erbumine or perindopril erbumine hydrate.

**Inventive Solution**

According to the present invention the stable formulations of amorphous perindopril salts are prepared directly from perindopril (acid) without the intermediate step of erbumine salt. Perindopril in the form of a free acid is \((2S,3aS,7aS)-1-[(2S)-2-[[lS]-l-ethoxycarbonyl]butyl]amino-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid of formula III:

![Chemical Structure](image)

It is formed in a synthesis as a thick oily substance which is not prone to crystallisation, but can be converted into a solid form by drying in a high vacuum.

Free acid of formula III can be used in the form of an oil, resinous substance, crystals, aqueous solution, or a solution in a water-solvent mixture.

It has been found that the perindopril salts with alkali and earth alkaline bases can be formed directly when perindopril is dissolved in alcohol and to which a solution of a suitable base in water in a molar ratio 1 : 1 is added during intense stirring. This solution is then sprayed onto a calculated amount of inert ingredients for tabletting (lactose, starch, cellulose) and dried in a stream of warm air at 30-50 °C or in vacuum.
To thus obtained dry substance (first granulate) other additives are admixed, optionally also other active substances (diuretics), by trituration in order to obtain a final mixture - second granulate, which is then tabletted. In this step also common disintegrating agents (such as croscarmellose, crospovidone, aerosil etc.), which improve disintegrating of tablets, can be added to the first granulate.

This process is better and more advanced than our previous process (WO 2007/058634 A1), since it enables higher yields of a valuable substance and is thus less expensive. The advantage of the new process is higher purity of granulate and tablets of perindopril sodium, because no traces of f-butyl amine, known for perindopril erbumine salt, are contained.

A combination of perindopril with diuretics, such as indapamide, has been known to be very favourable in the effective treatment of hypertension.

This process can also be used to prepare said composition by triturating the first granulate, obtained after the granulation phase, in an air stream with other necessary ingredients, wherein simultaneously micronized indapamide is added.

Normally, the ratio of perindopril and indapamide is 4 : 1.25.

The invention is illustrated by the following Examples, by which it is not limited.
Example 1

Perindopril (free acid) (7.9 g, 21.4 mmole) was dissolved separately in ethanol (96 %; 35 mL). The solution of sodium hydrogen carbonate (2.0 g, 23.8 mmole) in water (35 mL) was prepared separately. Both solutions were combined and stirred for 10 min, pH must be in the range from 7.0 to 7.5. This mixture was then sprayed in a stream of warm air having a temperature of 30-50 °C onto the previously prepared mixture consisting of lactose (142 g), corn starch (6 g) and microcrystalline cellulose (42.6 g). It was dried with warm air to reach the water content 0.5-1.5 % (K. Fischer method). About 200 g of the first granulate, containing 4.17 % of sodium salt of perindopril was obtained. By trituration corn starch (5.8 g), talc (4.7 g) and magnesium stearate (2.4 g) were added to this solution, which was then thoroughly homogenized. The obtained (second) granulate was used for tabletting and tablets having the weight of 90 mg were prepared, said tablets containing 3.53 mg of sodium salt of perindopril, which corresponds to the common therapeutical dose of 4.0 mg of perindopril erbumine.

Example 2

Perindopril (7.9 g, 21.4 mmole) was dissolved in ethanol (96 %; 35 mL). A solution of sodium hydroxide (0.86 g, 21.4 mmole) in water (30 mL) was prepared separately. Both solutions were combined, thoroughly stirred and pH was adjusted to 7.0-7.5. Thereafter the solution was further processed to the granulate and tablets as described in Example 1, together with the other ingredients.

Example 3

Perindopril (7.9 g, 21.4 mmole) was dissolved in ethanol (96 %; 35 mL) and the obtained solution was slowly added to the suspension of calcium hydroxide (0.95 g,
12.8 mmole) during intense stirring, and stirred for 30 min. The pH-value must be in the range from 7.0 to 7.5. The obtained slightly turbid solution was filtered to clarify. The solution was further processed to granulate and tablets as described in Example 1.

Example 4

Perindopril (7.9 g, 21.4 mmole) was dissolved in ethanol (96%; 35 mL). A solution of sodim hydrogen carbonate (2.0 g, 23.8 mmole) in water (35 mL) was prepared separately. Both solutions were combined and stirred for 10 min, pH was in the range from 7.0 to 7.5. This mixture was then sprayed in a stream of warm air having a temperature of 30-50 °C to the previously prepared mixture consisting of lactose (140.0 g), corn starch (5.9 g) and microcrystalline cellulose (41.75 g). It was dried in a stream of warm air to reach the water content of 0.5-1.5 %. 196 g of granulate was obtained, which was then homogeneously mixed with: indapamide (2.95 g), corn starch (5.9 g), talc (4.7 g) and magnesium stearate (2.4 g). This final granulate was used for the preparation of tablets having a weight of 90 mg, containing 3.53 mg of sodium salt of perindopril (corresponds to 4.0 mg of perindopril erbumine) and 1.25 mg of indapamide.

Example 5

Composition for 22000 tablets of perindopril sodium salt. Each tablet contains 3.53 mg of perindopril sodium (which corresponds to 4 mg of perindopril erbumine).

<table>
<thead>
<tr>
<th>Perindopril (acid)</th>
<th>0.079 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose monohydrate</td>
<td>1.420 kg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>0.426 kg</td>
</tr>
<tr>
<td>Corn starch</td>
<td>0.1 18 kg</td>
</tr>
</tbody>
</table>
Magnesium stearate 0.024 kg
Talc 0.047 kg
Sodium hydrogen carbonate 0.018 kg
Total 2.132 kg

Granulation:
Perindopril (acid) (0.079 kg) was dissolved in ethanol (96 %; 400 mL). Separately a solution of sodium hydrogen carbonate (0.018 kg) in water (200 mL) was prepared. Both solutions were mixed whilst stirring. In the granulation apparatus WSG type Glatt GPCG-I a dry blend of the following ingredients was prepared:

Lactose monohydrate 1.420 kg
Corn starch 0.059 kg
Microcrystalline cellulose 0.426 kg

To the dry blend of ingredients a solution of perindopril sodium (ethanol/water) was sprayed at a temperature 35—42 °C for two hours. The final humidity of the first granulate is 1-1.5 % of water.

In the next step a first granulate of perindopril sodium was blended in a homogeniser with the following ingredients:

Corn starch 0.059 kg
Talc 0.047 kg
Magnesium stearate 0.024 kg

The final granulate was used for tabletting. It was tabletted on the tabletting machine KILIAN RLA with the rate of 30000 tablets/hour.
Claims

1. Process for the preparation of a stable formulation of amorphous perindopril salts of formula I:

![Chemical Structure](image1)

wherein $B^+$ represents an alkali or alkaline earth metal cation, characterized in that perindopril in the form of a free acid of formula III:

![Chemical Structure](image2)

is dissolved in alcohol and neutralized with an aqueous solution of alkali or alkaline earth base and the obtained neutral solution of salt is sprayed onto the homogenous mixture of inert ingredients for the preparation of a granulate, dried in a vacuum or in a stream of warm air, the substances to facilitate tableting or other active substances, preferably diuretics are added, then homogenized and tableted.

2. Process according to claim 1, characterized in that a free acid of formula III in the form of an oil, resinous substance, crystals, aqueous solution, or a solution in a water-solvent mixture is used.
3. Process according to claims 1 and 2, characterized in that an alkaline earth metal is calcium or magnesium and alkali metal is sodium or potassium, preferably sodium.

4. Process according to claims 1-3, characterized in that hydroxide, oxide, carbonate or hydrogen carbonate of alkali or alkaline earth metal is used as a base.

5. Process according to claims 1-4, characterized in that drying is carried out at a temperature from 30 °C to 50 °C.

6. Process according to claims 1-5, characterized in that a substance having a diuretic activity, preferably indapamide is used as another active substance in the final phase of granulate blending.

7. Use of the formulation prepared by the process according to claims 1-6 as a medicine having an antihypertensive and a vasodilatatory activity.