Abstract:

There is disclosed a stable formulation of amorphous perindopril erbumine of the formula which is obtained in such a way that perindopril erbumine, which may also be prepared in situ from perindopril and tert-butylamine, or perindopril erbumine hydrate is dissolved in demineralized water or in a mixture of demineralized water and alcohol, to this solution a solution of sodium hydrogen carbonate is added for stabilization, inert ingredients for tabletting are wetted therewith, dried in vacuo by lyophilization or at normal pressure with a stream of warm air at not more than 40°C, hydrophobic additives to facilitate tabletting are added, it is homogenized and the granulate is tabletted. Disclosed is also a stable formulation of amorphous perindopril sodium salt obtained by modification of the drying procedure in the process of preparing the granulate. X-ray powder diffraction investigations show that perindopril erbumine is present in amorphous form and does not contain crystal α, β and γ forms.
AMENDED CLAIMS
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Claims

1. Process for the preparation, especially the industrial preparation, of a stable formulation of amorphous perindopril erbumine of the formula I

![Chemical Structure](image)

characterized in that perindopril erbumine is dissolved in water or an alcohol/water mixture in any ratio, to this solution a solution of an alcaline stabilizer is added and the whole is blended and added to a homogenous mixture of inert ingredients for the preparation of a granulate, dried in vacuo or air-dried in a stream of an air at a temperature lower than 40°C, substances to facilitate tabletting are added, it is homogenized and the granulate is formulated.

2. Process for the preparation, especially the industrial preparation, of a stable formulation of amorphous perindopril sodium salt characterized in that perindopril erbumine of the formula I is dissolved in water or an alcohol/water mixture in any ratio, to this solution an aqueous solution of sodium hydrogen carbonate is added and the whole is blended and added to a homogenous mixture of inert ingredients for the preparation of a granulate, dried in a stream of warm air with the temperature over 40°C, said temperature enabling chemical transformation of perindopril erbumine to perindopril sodium salt in amorphous form, substances to facilitate tabletting are added, it is homogenized and the granulate is formulated.

3. Process according to claims 1 and 2, characterized in that the molar rate of perindopril erbumine to NaHCO₃ is 1:1-2.
4. Process according to claims 1 to 3, characterized in that as inert ingredients for
the preparation of the granulate anhydro lactose, lactose in the form of monohydrate,
trehalose, corn starch, microcrystalline cellulose, talc and magnesium stearate are
used.

5. Process according to claim 1, characterized in that as the stabilizer there are
used substances that have a slightly alkaline action such as salts of carbon acid,
preferably sodium hydrogen carbonate.

6. Process according to claim 1, characterized in that the drying is carried out in
the temperature range from -20°C to +40°C.

7. Process according to claim 1, characterized in that perindopril erbumine is
formed in situ in a solution by dissolving perindopril in alcohol or an alcohol/water
mixture, an equimolar amount of tert-butylamine and an aqueous solution of a
stabilizer are added and subsequently, by adding to the remaining ingredients and
drying, a homogenous mixture is prepared which is later blended to a granulate.

8. Process according to claims 2 and 3, characterized in that perindopril sodium
salt is formed in situ in a solution by dissolving perindopril in alcohol or an
alcohol/water mixture, at least an equimolar amount of NaHCO₃ in water solution is
added and subsequently by adding to the remaining ingredients and drying a
homogenous mixture is prepared which is blended to a granulate.

9. Stable formulation of perindopril erbumine stabilized with trehalose.

10. Stable formulation of amorphous perindopril erbumine granulate in the mixture
with anhydro lactose, starch, microcrystalline cellulose, talc and magnesium stearate
or any other additive usually used in pharmaceutical formulations.
11. Stable formulation of amorphous perindopril sodium salt granulate in the mixture with anhydro lactose, starch, macrocrystalline cellulose, talc and magnesium stearate or any other additive usually used in pharmaceutical formulations.

12. Stable formulations according to claims 1 to 11, characterized in that in said formulations also a diuretic is included as further active substance.

13. Formulation according to claims 1 to 12, characterized in that it is in the form of a granulate, a tablet or a capsule.

14. Use of the formulation according to claims 1 to 13 for the preparation of a medicine having an antihypertensive and a vasodilatatory action.

15. Amorphous form of perindopril erbumine granulate obtained according to claim 1.

16. Amorphous form of perindopril sodium salt granulate obtained according to claims 2 and 3.