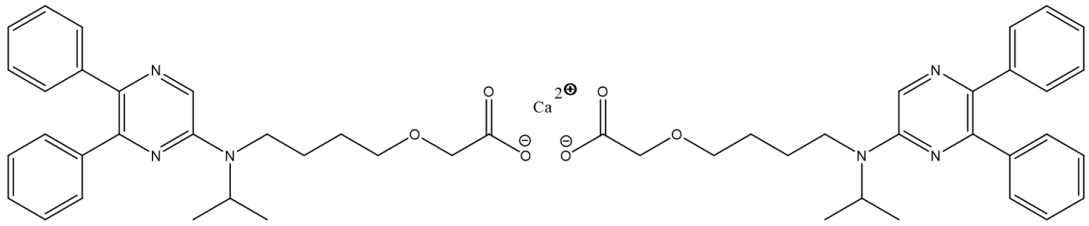
Claims

1. A process for the manufacturing of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I), or a pharmaceutically acceptable hydrate or solvate thereof:



Formula (I);

comprising the steps of:

mixing {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid and a first calcium source with a solvent (a) to obtain a mixture;

heating or maintaining the mixture at a temperature in the range of 20°C to 85°C;

isolating the obtained solid product; and

optionally re-slurrying the isolated solid product in a solution of a second calcium source in solvent (b) at a temperature in the range of 20°C to 85°C.

2. The process of claim 1, wherein the mixing step comprises:

mixing {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid and solvent (a) to obtain a mixture; and

heating or maintaining the mixture at a temperature in the range of 20°C to 85°C prior to the addition of the first calcium source.

3. The process of claim 1, wherein the first calcium source is dissolved in solvent (b) to obtain solution (b) prior to the addition of solution (b) to the mixture of {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid and solvent (a).

4. The process of claim 1, wherein the steps comprise:

(1) dissolving {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid in a solvent (a) to obtain solution (a);

(2) heating solution (a) to a temperature in the range of 20°C to 85°C;

(3) dissolving a first calcium source in solvent (b) to obtain solution (b);

(4) dosing solution (b) to solution (a);

(5) isolating the obtained solid product; and

(6) optionally re-slurrying the product of step (5) in a solution of a second calcium source in solvent (b) at a temperature in the range of 20°C to 85°C.

5. The process according to claim 1, wherein the first calcium source is added in an amount of 0.4 mol to 1 mol per mol {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid, or from 0.4 to 0.8 mol per mol {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid, or from 0.4 to 0.6 mol per mol {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid, or from 0.45 to 0.6 mol per mol {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid, or from 0.45 to 0.55 mol per mol {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid or from 0.5 to 0.6 mol per mol {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid, or from 0.5 to 0.55 mol per mol {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid.

6. The process according to any one of claims 1 to 5, wherein the first calcium source is added in two or more dosages.

7. The process according to any one of claims 1 to 6, wherein solvent (a) is an organic solvent or an organic solvent mixed with water.

8. The process according to claim 7, wherein the organic solvent in solvent (a) is selected from the group consisting of acetone, tetrahydrofuran (THF), acetonitrile, MEK (methyl ethyl ketone), DMSO, DMF, 1,4-dioxane, pyridine, dimethylacetamide (DMA), methyl acetate (MeOAc), methanol, ethanol, propanol (1-propanol, or 2-propanol), and butanol (1-butanol, 2-butanol, 2-methylpropan-1-ol, or 2-methylpropanol).

9. The process according to claim 4, wherein solution (a) is subjected to a filtering step.

10. The process according to any one of claims 1 to 9, wherein solvent (b) is selected from water or a mixture of water and an organic solvent, preferably water.

11. The process according to any one of claims 1 to 10, wherein seed crystals of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I) are added to solution (a) or the mixure in an amount of up to 25% w/w in respect of amount of {4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetic acid used as starting material.

12. The process according to claim 11, wherein the seed crystals of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I) have an X-ray powder diffraction pattern with at least five peaks, or at least seven peaks, or at least nine peaks having angle of refraction 2θ (2theta) values selected from: 5.1°, 5.4°, 8.8°, 9.9°, 11.4°, 13.4°, 13.8°, 16.3°, 19.7°, 20.9°, 21.4°, 22.9°, 25.1°, wherein the Xray powder diffraction diagram is obtained by using Cu Kα radiation, wherein the accuracy of the 2θ (2theta) values is in the range of 2θ +/- 0.2° (2theta +/- 0.2°).

13. The process according to any one of claims 1 to 12, wherein the first, second, or both calcium sources are selected from $Ca(OAc)_2$, calcium propionate, calcium formate, and calcium pantothenate.

14. The process according to claim 13, wherein the first calcium source and the optional second calcium source is $Ca(OAc)_2$.

15. The product obtained by the process of any one of claims 1 to 14.

16. Calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I) with a Ca^{2+} content of 7.0 ± 0.1 %w/w or less, preferably 7.0 ± 0.1 %w/w to 4.0 ± 0.1 %w/w.

17. A crystal Form 2 of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I) showing an X-ray powder diffraction pattern with at least five peaks having angle of refraction 2θ (2theta) values selected from 3.2°, 6.3°, 7.7°, 9.3°, 10.4°, 11.6°, 24.0°2theta; preferably at least five peaks, or at least seven peaks, or at least nine peaks selected from 3.2°, 6.3°, 7.7°, 9.3°, 10.0°, 10.4°, 11.6°, 12.7°, 19.2°, 22.9°, 24.0°2theta; wherein said X-ray powder diffraction diagram is obtained by using Cu Kα radiation; and the accuracy of the 2θ (2theta) values is in the range of 2θ +/- 0.2° (2theta +/- 0.2°).

18. A crystal Form 3 of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I) showing an X-ray powder diffraction pattern with peaks having angle of refraction 2θ (2theta) values selected from 4.5°, 7.9°, or 11.9°2theta; preferably at least five peaks, or at least seven peaks, or at least nine peaks selected from 4.5°, 4.8°, 5.0°, 7.9°, 10.0°, 11.9°, 14.9°, 15.6°, 17.1°, 18.7°, 22.1° and 22.7°2theta; wherein said X-ray powder diffraction diagram is obtained by using Cu Kα radiation; and the accuracy of the 2θ (2theta) values is in the range of 2θ +/- 0.2° (2theta +/- 0.2°).

19. A crystal Form 5 of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I) showing an X-ray powder diffraction pattern with at least five peaks, or at least seven peaks, or at least nine peaks having angle of refraction 2θ (2theta) values selected from 4.9°, 8.8°, 9.8°, 11.0°, 12.8°, 13.1°, 16.9°, 19.5°, 21.1°, 21.5° and 22.6°2theta; wherein said X-ray powder diffraction diagram is obtained by using Cu Kα1 radiation; and the accuracy of the 2θ (2theta) values is in the range of 2θ +/- 0.2° (2theta +/- 0.2°).

20. A pharmaceutical composition comprising the product of any one of claims 17 to 19.

21. The pharmaceutical composition of claim 20, in the form of an intramuscular or subcutaneous injectable.

22. Use of the crystal form of any one of claims 17 to 19 in the manufacture of a medicament for the treatment or prevention of ulcer, digital ulcer, diabetic gangrene, diabetic foot ulcer, pulmonary hypertension, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, Fontan disease and pulmonary hypertension associated with Fontan disease, sarcoidosis and pulmonary hypertension associated with sarcoidosis, peripheral circulatory disturbance, connective tissue disease, chronic kidney diseases including glomerulonephritis and diabetic nephropathy at any stage, diseases in which fibrosis of organs or tissues is involved, or respiratory diseases, preferably pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH).

23. Use of a pharmaceutical composition according to claim 20 or 21 in the manufacture of a medicament for preventing and/or treating ulcer, digital ulcer, diabetic gangrene, diabetic foot ulcer, pulmonary hypertension, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, Fontan disease and pulmonary hypertension associated with Fontan disease, sarcoidosis and pulmonary hypertension associated with sarcoidosis, peripheral circulatory disturbance, connective tissue disease, chronic kidney diseases including glomerulonephritis and diabetic nephropathy at any stage, diseases in which fibrosis of organs or tissues is involved, or respiratory diseases, in a human subject in need thereof.