calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate, or a pharmaceutically acceptable hydrate or solvate thereof, in a high purity.

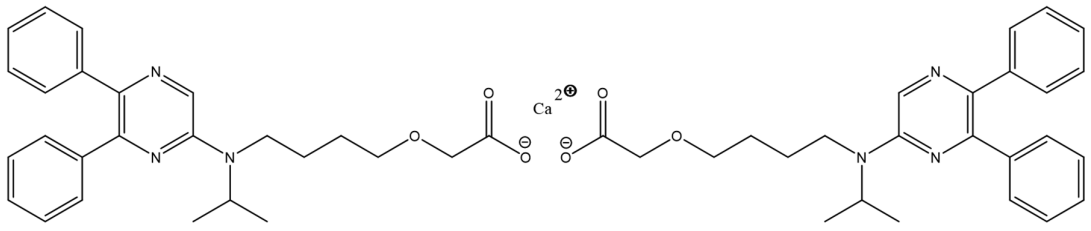
Summary of the Invention

It is an object of the present invention to provide an improved process for the manufacture of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate, or a pharmaceutically acceptable hydrate or solvate thereof. Moreover, it is an object of the present invention to provide new crystal forms of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate.

It has now been found that calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate can be efficiently produced by the present process in high purity, i.e. avoiding excess of residual Ca^{2+}, i.e. calcium salt from the starting material, in particular $Ca(OH)_2$ in the final product. In addition, the new process ensures improved conversion of the starting material selexipag metabolite, i.e. a lower proportion of excess selexipag metabolite in the product. Moreover, new crystal forms and hydrates/solvates have been produced. The new process may use various calcium salts to provide high yield, high conversion to the calcium salt, and high purity of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate.

Due to the low solubility in water of the calcium salt of selexipag metabolite obtained by the present process, this product and various crystalline forms are suitable for the manufacturing of long-acting formulations, such as for instance long-acting injectables. The improved process of the present invention allows for the production of particularly pure products, which is important in the manufacturing of drug compounds.

In one aspect, there is provided 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.

In another aspect, there is a product obtained by the process described herein.

In yet another aspect, there is provided 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.

In another aspect, there is provided 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°).

In yet another aspect, there is provided 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°).

In a further aspect, there is provided 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°).

In another aspect, there is provided a pharmaceutical composition comprising the product as described herein.

In yet another aspect, there is provided a use of the crystal form as described herein 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).

In a further aspect, there is provided a use of a pharmaceutical composition as described herein 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

Description of the Figures

Fig. 1 shows the X-ray powder diffraction diagram of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate in crystalline Form 1. The X-ray diffraction shows the following peaks: 5.1° (85%), 5.4° (20%), 8.8° (63%), 9.9° (100%), 11.4° (38%), 13.4° (21%), 13.8° (21%), 16.3° (65%), 18.1° (19%), 18.7° (27%), 19.7° (52%), 20.9° (51%), 21.4° (31%), 22.9° (51%), 23.6° (36%), 25.1° (37%).

The above-listed peaks describe the experimental results of the X-ray powder diffraction diagram shown in Figure 1. It is understood that not all of these peaks are required to fully and unambiguously characterise Form 1.