suspension comprising microparticles of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate or hydrate or solvate thereof.

The long-acting profile of the formulation allows to avoid plasma peak levels and achieves minimal toxic concentration and longer therapeutic duration.

In one aspect, there is provided a pharmaceutical composition in the form of an aqueous suspension comprising (a) calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I), or a pharmaceutically acceptable hydrate or solvate thereof, having a particle size distribution Dv50 of 1 to 50 µm (micrometer); (b) a surfactant and/or wetting agent; and (c) a pharmaceutically acceptable aqueous carrier at a pH in the range of 6 to 8.5.

In another aspect, the present disclosure provides a container containing the pharmaceutical composition as described herein, wherein the container is a syringe or a vial.

In yet another aspect, there is provided a process for preparing a pharmaceutical composition as described herein, said process comprising the steps of (a) adding a crystalline form of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate, or a pharmaceutically acceptable hydrate or solvate thereof, to a liquid medium comprising a surfactant and/or wetting agent, optionally a resuspending agent; and a pharmaceutically acceptable aqueous carrier at a pH in the range of 6 to 8.5, to form a premix/predispersion; and (b) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the average effective particle size.

In a further aspect, there is provided a process for preparing a lyophilized pharmaceutical composition, said process comprising the steps of freezing the pharmaceutical composition as described herein, followed by a drying step comprising applying a vacuum.

In another aspect, the present disclosure provides a lyophilized pharmaceutical composition obtainable by the process as described herein.

In yet another aspect, there is provided a reconstituted pharmaceutical composition prepared from the lyophilized pharmaceutical composition as described herein, by adding at least one diluent.

In another aspect, there is provided a process for preparing a sterile pharmaceutical composition as described herein, wherein the pharmaceutical composition is sterilized with

autoclavation (steam sterilisation), or with gamma-irradiation; or wherein calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate is sterilised with gamma-irradiation and is used for preparing the pharmaceutical composition.

In yet another aspect, there is provided a use of the pharmaceutical composition as described herein in the preparation of a medicament for the treatment and/or prevention of a disease and/or disorder selected from the group consisting of ulcer, digital ulcer, diabetic gangrene, diabetic foot ulcer, pulmonary hypertension, Fontan disease, 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, and respiratory diseases.

In a further aspect, the present disclosure provides a use of a pharmaceutical composition in the preparation of a long acting injectable in the treatment of and/or prevention of pulmonary hypertension, wherein the pharmaceutical composition is in the form of an aqueous suspension comprising calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I), or a pharmaceutically acceptable hydrate or solvate thereof.

In another aspect, the present disclosure provides microparticles 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 said microparticles having a particle size distribution Dv50 of 1 to 50 µm (micrometer), preferably 2 to 30 µm or 2 to 20 µm or 5 to 15 µm.

In yet another aspect, the present disclosure provides a use of the microparticles as described herein in the preparation of a medicament for the treatment of pulmonary hypertension.

Description of the Figures

Fig. 1 shows the plasma concentrations of the different studied formulations containing selexipag, selexipag metabolite (2-(4-((5,6-diphenylpyrazin-2-yl)(isopropyl)amino)-butoxy)acetic acid; ACT333679), and the calcium salt of selexipag metabolite (calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate; Ca-salt of ACT333679) in function of time

Fig. 2 and Fig.3 show pK rat profiles with different particles (2, 5, 8 µm (micrometer)) of calcium salt of selexipag metabolite and different surfactants/wetting agents (Polysorbate 20 and Poloxamer 338)

Fig. 4 shows resulting particle size distributions of the differently formulated drug (calcium salt of selexipag metabolite) with different particle size

Fig. 5 shows resulting particle size distributions of the differently formulated drug (calcium salt of selexipag metabolite) with different surfactants/wetting agents

Fig. 6 shows resulting particle size distribution with calcium salt of selexipag metabolite at a concentration of 200 mg/mL

Fig. 7 shows resulting particle size distributions of the differently formulated drug (calcium salt of selexipag metabolite) with different amounts of resuspending agent

Fig. 8 shows the results of zeta potential as function of pH of suspension

Detailed Description of the Invention

The present invention is concerned with a pharmaceutical composition in the form of an aqueous suspension comprising calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I), or a pharmaceutically acceptable hydrate or solvate thereof: