IMPROVED FORMULATION FOR RADIOPHARMACEUTICAL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to a formulation for the PentixaFor precursor and derivatives thereof, which can be used in preparing a radiopharmaceutical composition or compound. More specifically, the present invention concerns a solid composition, a method for the preparation of the solid composition, a kit of parts comprising the solid composition, a method for the manufacture of a radiopharmaceutical comprising a chelate and a method of collecting data for the diagnosis of a tumor in a patient. As used herein the term "PentixaFor precursor" refers to the PentixaFor which is not radiolabeled.

BACKGROUND OF THE INVENTION

The CXC motif chemokine receptor type 4 (CXCR4) is a seven transmembrane G-protein coupled receptor expressed on different cells of the haematopoietic system and involved in several physiological processes including embryonic development, haematopoiesis and angiogenesis. The activation of the receptor by its endogenous ligand CXCL12 (SDF-1, stromal cell derived factor 1) leads to the proliferation of cells and directed migration towards the source of the ligand. Hence, the CXCR4/CXCL12 axis is important for the homing and retention of stem cells and the trafficking of lymphocytes towards the sites of tissue damage or inflammation. Overexpression of this receptor has been reported in more than 30 different types of cancer playing an essential role in the process of tumour metastasis. Thus, the CXCR4 has been described as a useful biomarker in diagnostic and therapeutical oncology.

Accordingly, several radiotracers have been developed for PET and SPECT imaging of the CXCR4, among which the peptide [^{68}Ga]Ga-PentixaFor (INN: Gallium (^{68}Ga) boclatixafortide) has shown not only optimal pharmacological properties but also improved diagnostics in several clinical settings. For early clinical development, [^{68}Ga]Ga-PentixaFor was obtained by automated radiosynthesis (SCINTOMICS® module) in HEPES buffer using 20 to 40 µg of the PentixaFor precursor acetate from 250 µg provided aliquots, a commercially available reagent set for chelator-conjugated peptides and a [^{68}Ga]$GaCl_3$ solution for radiolabelling (NPL 1). After the ^{68}Ga-radiolabelling, the product was purified via solid-phase extraction, reformulated in ethanol and PBS and sterile filtrated to give the final radiopharmaceutical solution. More recently, [^{68}Ga]Ga-PentixaFor has been established in additional automated

platforms with slight modifications regarding the amount of drug substance and buffer used (NPLs 2 and 3).

The manufacturing facilities of [^{68}Ga]Ga-PentixaFor can be further increased and the process itself can be simplified by performing the radiolabelling without the assistance of an automated module and without the need of extensive analytical equipment. Consequently, a cold kit for radiolabelling has been established to obtain and release the radiopharmaceutical in a manual, rapid and streamlined fashion. A cold kit for radiolabelling is already thoroughly used for the manufacture of ^{99m}Tc- radiopharmaceuticals (NPL 4) and several gallium-68 based kits have advanced to commercial stage (NPL 5). Basically, these gallium-68 kits contain a lyophilised powder of the active pharmaceutical ingredient (API) plus excipients and a buffering substance.

Non-Patent References

NPL 1: Martin, R., Jüttler, S., Müller, M., & Wester, H.-J. (2014). Cationic eluate pretreatment for automated synthesis of [^{68}Ga]CPCR4.2. *Nuclear Medicine and Biology*, *41*(1), 84–89. https://doi.org/10.1016/j.nucmedbio.2013.09.002

NPL 2: Kaufmann, J., Berroteran-Infante, N., Castillo, J., & Hartmann, T. (2021). SP-048—Design space approach to optimise the [68Ga]Ga-Pentixafor radiolabelling process. *Nuclear Medicine and Biology*, *96–97*, S60. https://doi.org/10.1016/S0969-8051(21)00365-6

NPL 3: Spreckelmeyer, S., Schulze, O., & Brenner, W. (2020). Fully-automated production of [68Ga]Ga-PentixaFor on the module Modular Lab-PharmTracer. *EJNMMI Radiopharmacy and Chemistry*, *5*. https://doi.org/10.1186/s41181-020-0091-2

NPL 4: *Technetium-99m Radiopharmaceuticals: Manufacture of Kits*. (2008). INTERNATIONAL ATOMIC ENERGY AGENCY. https://www.iaea.org/publications/7867/technetium-99m-radiopharmaceuticals-manufacture-of-kits

NPL 5: Satpati, D. (2021). Recent Breakthrough in ^{68}Ga-Radiopharmaceuticals Cold Kits for Convenient PET Radiopharmacy. *Bioconjugate Chemistry*, *32*(3), 430–447. https://doi.org/10.1021/acs.bioconjchem.1c00010

SUMMARY OF THE INVENTION

The selection of pharmaceutical excipients, and ultimately the final formulation, represents a challenge in the development of these kits. The composition must be chosen considering the following aspects:

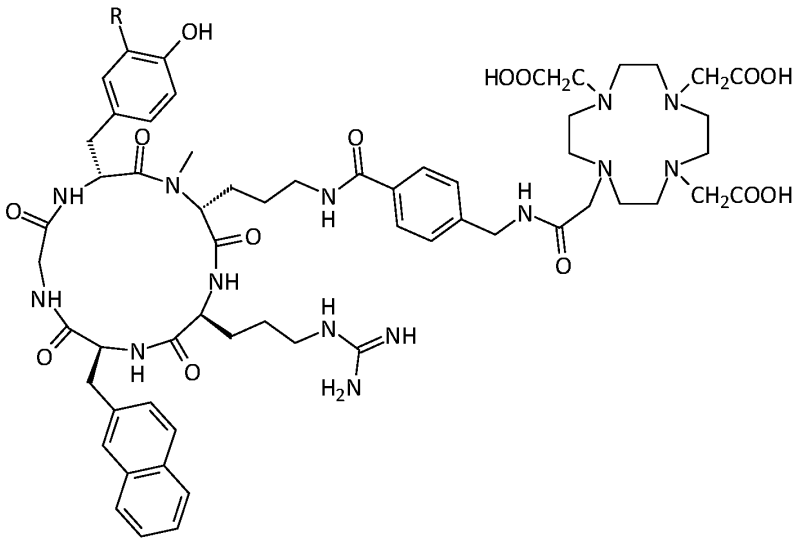
- Achievement of a suitable stability of the lyophilizate and thus an appropriate shelf-life
- Offering an efficient lyophilization process
- Yielding of satisfactory results after radiolabelling, i.e. high chemical and radiochemical purity, etc.

The compositions previously known did not achieve a satisfactory performance regarding the three properties set out above.

The present inventors therefore set out to provide a composition which achieves stability of the lyophilizate, extended shelf-life, enables an efficient lyophilization process, and yields high chemical and radiochemical purity, etc. for the obtained radiolabelled product.

In a first aspect, the present invention relates to a solid composition comprising

(i) 1 part by weight of a compound of formula (I) or a salt thereof:



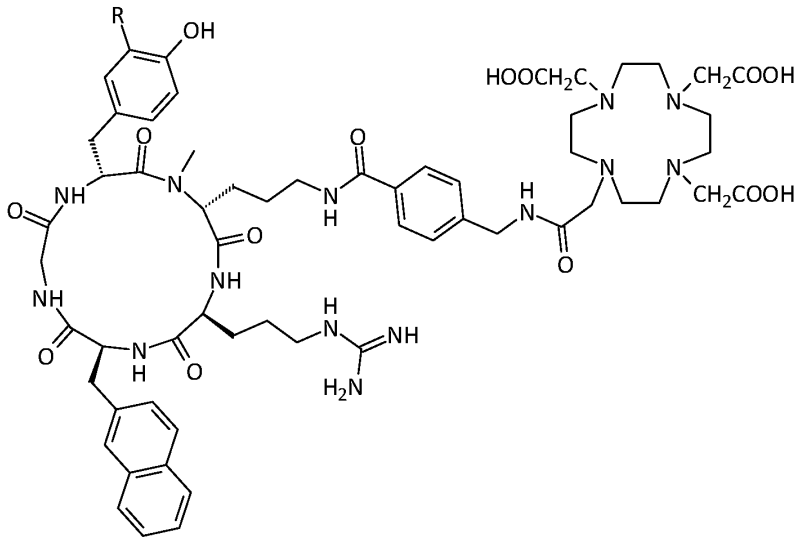
wherein R is selected from hydrogen, C_{1-6} alkyl, fluorine, chlorine, bromine and iodine,

(ii) 40 to 400 parts by weight of ascorbic acid or a salt thereof, calculated as mass of ascorbic acid per mass of the compound of formula (I),

(iii) one or more mono-, di- or oligo-saccharides or salts thereof, and

(iv) one or more surfactants.

In a second aspect, the present invention relates to a method for the preparation of a solid composition comprising (i) a compound of formula (I) or a salt thereof:



wherein R is selected from hydrogen, C_{1-6} alkyl, fluorine, chlorine, bromine and iodine; and ascorbic acid or a salt thereof,

said method comprising the steps of

(a) providing an aqueous solution which comprises

a compound of formula (I) or a salt thereof,

ascorbic acid or a salt thereof,

one or more mono-, di- or oligo-saccharides or salts thereof, and

one or more surfactants

(b) subjecting the solution to lyophilisation to obtain a solid composition.

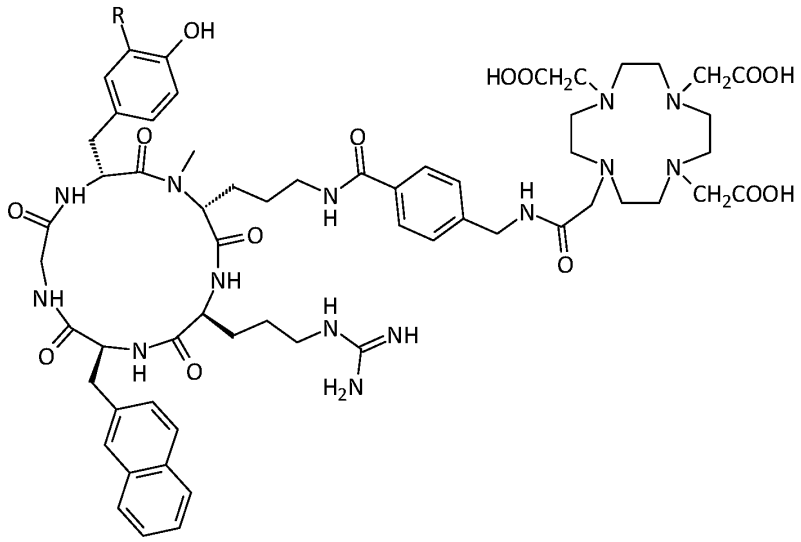
In a third aspect, the present invention relates to a kit of parts comprising

(a) a solid composition according to the first aspect; and

(b) a buffer solution.

In a fourth aspect, the present invention relates to a method for the manufacture of a radiopharmaceutical comprising a chelate formed by

(a) a compound of formula (I)



wherein R is selected from hydrogen, fluorine, chlorine, bromine and iodine; and

(b) a radionuclide;

wherein the method comprises step (i) of dissolving or dispersing the solid composition according to the first aspect in a buffer solution and step (ii) of combining it with a radionuclide.

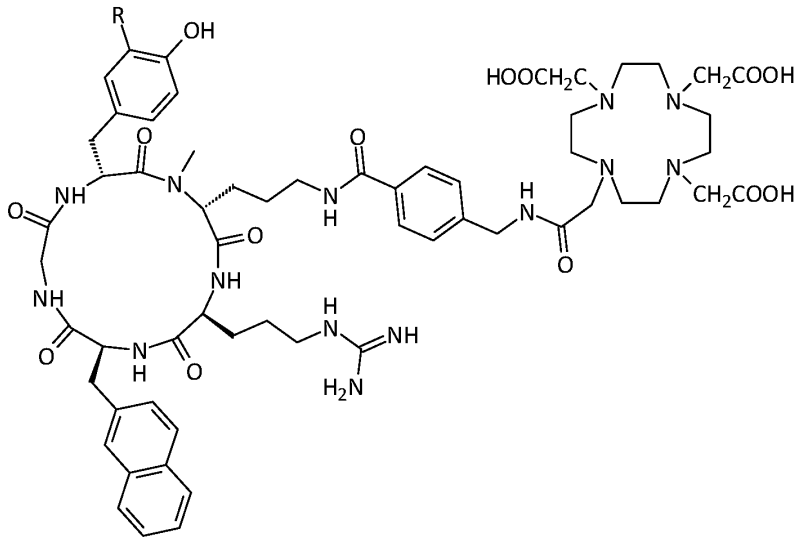
Other objects, features, advantages and aspects of the present invention will become apparent to those skilled in the art from the following description and appended claims. It should be understood, however, that the following description, appended claims, and specific examples, which indicate preferred embodiments of the application, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following.

DETAILED DESCRIPTION OF THE INVENTION

Solid compositions

The present invention particularly relates to a solid composition (herein also referred to as the "first aspect" of the present invention) comprising

(i) 1 part by weight of a compound of formula (I) or a salt thereof:



wherein R is selected from hydrogen, C_{1-6} alkyl, fluorine, chlorine, bromine and iodine

(ii) 40 to 400 parts by weight (pbw) of ascorbic acid or a salt thereof, calculated as mass of ascorbic acid per mass of the compound of formula (I),

(iii) one or more mono-, di- or oligo-saccharides or salts thereof, and

(iv) one or more surfactants.

In the compound of formula (I), R is preferably H or I. In certain embodiments, R is H.

The ascorbic acid or salt thereof is contained in the solid composition preferably in an amount of 80 to 350 parts by weight, more preferably 120 to 320 parts by weight, even more preferably 150 to 300 parts by weight, still more preferably 180 to 280 parts by weight, still even more preferably 220 to 260 parts by weight, or even more preferably 230 to 250 parts by weight, most preferably about 240 parts by weight, calculated as mass of ascorbic acid per mass of the compound of formula (I).

The "ascorbic acid or a salt thereof" in (ii) is preferably ascorbic acid or a mixture of ascorbic acid and one or more salts thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof.

The pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

Preferred salts of ascorbic acid include ammonium ascorbate, sodium ascorbate, potassium ascorbate, magnesium ascorbate and calcium ascorbate.

The solid composition contains a mono-, di- or oligo-saccharide or salt thereof. The mono-, di- or oligo-saccharide or salt thereof is preferably contained in the solid composition in an amount of 600 to 1600 parts by weight, more preferably 700 to 1400 parts by weight, more preferably 800 to 1200 parts by weight, more preferably 900 to 1100 parts by weight, more preferably 950 to 1050 parts by weight, most preferably about 1000 parts by weight, calculated as a total mass of mono-, di- or oligo-saccharide per mass of the compound of formula (I).

The term "mono-, di- or oligo-saccharides or salts thereof" as used herein refers to any monosaccharide, disaccharide, trisaccharide, tetrasaccharide, pentasaccharide, hexasaccharide, heptasaccharide, octasaccharide, any salt of a monosaccharide, salt of a disaccharide, salt of a trisaccharide, salt of a tetrasaccharide, salt of a pentasaccharide, salt of a hexasaccharide, salt of a heptasaccharide, salt of a octasaccharide, or any mixture of any of these. It is preferred that the "mono-, di- or oligo-saccharides or salts thereof" are selected from mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, and octa- saccharides, such as di-, tri-, tetra-, penta-, or hexa-saccharides, or any mixtures of any of these. The "mono-, di- or oligo-saccharides or salts thereof" are preferably non-reducing. Accordingly, the "mono-, di- or oligo-saccharides or salts thereof" are preferably "non-reducing di- or oligo-saccharides or salts thereof". Examples of preferred "mono-, di- or oligo-saccharides" include sucrose, trehalose, raffinose, stachyose, and verbascose. More preferably, the "mono-, di- or oligo-saccharides or salts thereof" is a non-reducing disaccharide. The non-reducing disaccharide is typically selected from sucrose and trehalose, more preferably trehalose.

The mono-, di- or oligo-saccharide may be present in the solid composition in its anhydrous form or as hydrate. In embodiments where the mono-, di- or oligo-saccharide is trehalose, it is preferably present as trehalose dihydrate. The amount of trehalose in the solid composition in these embodiments is based on the molecular weight of trehalose dihydrate.

The solid composition furthermore contains one or more surfactants. The one or more surfactants are typically non-ionic surfactants, and are preferably selected from polyvinylpyrrolidone (PVP), and ethoxylated sorbitan fatty acid esters. The ethoxylated sorbitan fatty acid esters are preferred and are preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having from 4 to 40 oxyethylene units; more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units; even more preferably polyoxyethylene (20) sorbitan monooleate. More preferred are one or more surfactants

selected from polyvinylpyrrolidone (PVP), polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate and polyoxyethylene (20) sorbitan monooleate. Even more preferred are one or more surfactants are selected from polyoxyethylene (20) sorbitan monolaurate or polyoxyethylene (20) sorbitan monooleate. Polyoxyethylene (20) sorbitan monooleate is particularly preferred as a surfactant. It is to be understood that combinations of one or more of these surfactants may be contained in the solid composition.

The one or more surfactants is/are preferably contained in an amount of 0.05 to 10 parts by weight, more preferably 0.1 to 8 parts by weight, more preferably 0.1 to 5 parts by weight, more preferably 0.1 to 2 parts by weight, more preferably 0.1 to 0.5 parts by weight, most preferably about 0.2 parts by weight, calculated as mass of surfactant(s) per mass of the compound of formula (I).

In certain embodiments, in the compound of formula (I) R is H, the ascorbic acid or salt thereof is ascorbic acid, the one or more mono-, di- or oligo-saccharides or salts thereof is trehalose dihydrate, and the one or more surfactants is polyoxyethylene (20) sorbitan monooleate.

It will be understood that the solid composition in accordance with the first aspect of the invention is generally a composition which is not radiolabeled.

It is preferred that the total amount of the compound of formula (I) or a salt thereof, ascorbic acid or a salt thereof, one or more mono-, di- or oligo-saccharides or salts thereof and one or more surfactants is 50 wt.-% or more, more preferably 70 wt.-% or more, even more preferably 80 wt.-% or more, or even 90 wt.-% or more, relative to the weight of the solid composition. The composition may also consist of the compound of formula (I) or a salt thereof, the ascorbic acid or a salt thereof, one or more mono-, di- or oligo-saccharides or salts thereof and one or more surfactants.

The solid composition is preferably obtainable by lyophilization. Lyophilisation is herein also referred to as freeze-drying and typically refers to freezing a mixture containing water and a desired compound or compounds and removing water by sublimation, e.g., at a pressure below 0.5 bar, preferably below 0.2 bar, more preferably 0.1 bar or less. Typically, at least 95%, preferably at least 97% or even at least 98%, such as at least 99%, of the water initially contained in the mixture is removed.

In view of the above, it will be understood that a preferred solid composition contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 600 to 1600 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,

- 80 to 350 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.05 to 10 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 700 to 1400 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 120 to 320 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 8 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition even more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 800 to 1200 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected

from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,

- 150 to 300 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 5 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition still more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 900 to 1100 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 180 to 280 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 2 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition still even more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,

- 950 to 1050 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 220 to 260 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 1 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition particularly preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 950 to 1050 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 230 to 250 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 0.5 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition most preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- about 1000 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- about 240 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- about 0.2 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition may contain:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 950 to 1050 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 220 to 260 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.2 to 1 part by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition may contain:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 950 to 1050 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 230 to 250 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- about 1 part by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The solid composition may contain:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 1000 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- about 240 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 1 part by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

Thus, in one example, the solid composition preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 900 to 1100 parts by weight of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose, especially in the form of trehalose dihydrate,
- 180 to 280 parts by weight of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 2 parts by weight of one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, preferably polyoxyethylene (20) sorbitan monooleate, more preferably polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2.4 to 2.8 and preferably 2.5 to 2.7.

Thus, in one example, the solid composition more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 950 to 1050 parts by weight of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose, especially in the form of trehalose dihydrate,
- 220 to 260 parts by weight of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 1 parts by weight of one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, preferably polyoxyethylene (20) sorbitan monooleate, more preferably polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2.4 to 2.8 and preferably 2.5 to 2.7.

In one more preferred example, the solid composition contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 950 to 1050 parts by weight of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose, especially in the form of trehalose dihydrate,
- 220 to 260 parts by weight of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and

- 0.1 to 0.5 parts by weight of polyoxyethylene (20) sorbitan monooleate, preferably polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2.4 to 2.8 and preferably 2.5 to 2.7.

In one more preferred example, the solid composition contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- about 1000 parts by weight of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose, especially in the form of trehalose dihydrate,
- about 240 parts by weight of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- about 0.2 parts by weight of polyoxyethylene (20) sorbitan monooleate, preferably polyoxyethylene (20) sorbitan monooleate PS-80,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2.4 to 2.8 and preferably 2.5 to 2.7.

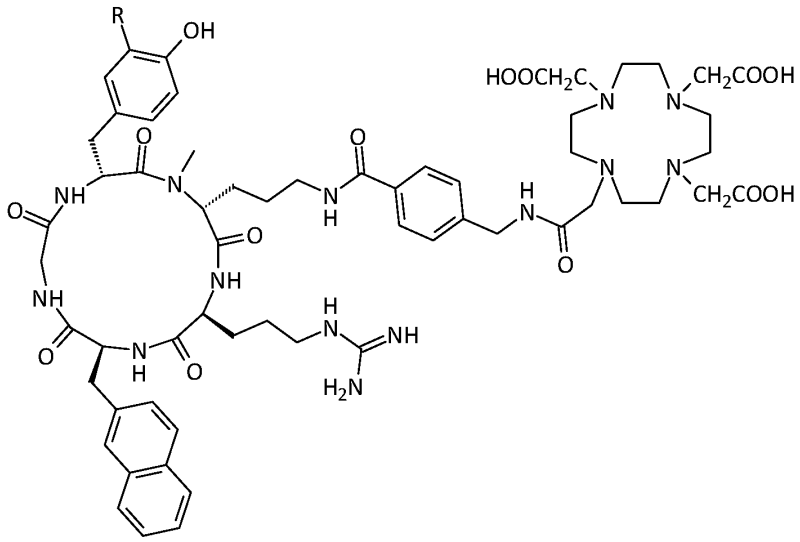
In an especially preferred example, the solid composition contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- about 1000 parts by weight of trehalose dihydrate,
- about 240 parts by weight of ascorbic acid, and
- about 0.2 parts by weight of polyoxyethylene (20) sorbitan monooleate,

wherein optionally the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2.4 to 2.8 and preferably 2.5 to 2.7.

Methods for preparation of the solid compositions

The present invention also relates to a method for the preparation of a solid composition comprising (i) a compound of formula (I) or a salt thereof:



wherein R is selected from hydrogen, C_{1-6} alkyl, fluorine, chlorine, bromine and iodine; and ascorbic acid or a salt thereof,

said method comprising the steps of

(a) providing an aqueous solution which comprises

a compound of formula (I) or a salt thereof,

ascorbic acid or a salt thereof,

one or more mono-, di- or oligo-saccharides or salts thereof, and

one or more surfactants,

(b) subjecting the solution to lyophilization to obtain a solid composition.

It is to be understood that the "solid composition" prepared by the above method is typically the solid composition of the first aspect of the present invention and may be characterized by any of the features and preferred features which are set out herein for the solid composition of the first aspect.

The "ascorbic acid or a salt thereof" used in step (a) is preferably ascorbic acid or a mixture of ascorbic acid and one or more salts thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof.

The aqueous solution used in step (a) further contains one or more mono-, di- or oligo-saccharides or salts thereof and one or more surfactants as described for the solid

composition of the first aspect of the present invention. Water may be the only solvent used in the aqueous solution used in step (a), but the aqueous solution may also contain, in addition to the water, a co-solvent such as ethanol.

It is preferred that the aqueous solution used in step (a) contains 5 to 350 mg, preferably 10 to 200 mg, more preferably 20 to 100 mg solids per 1 ml of the aqueous solution. Typically, the aqueous solution used in step (a) contains 5 to 350 mg, preferably 10 to 200 mg, more preferably 20 to 100 mg in total of the compound of formula (I) or the salt thereof, the ascorbic acid or the salt thereof, the one or more mono-, di- or oligo-saccharides or salts thereof and the one or more surfactants per 1 ml of the aqueous solution. The aqueous solution used in step (a) typically contains 650 to 995 mg, preferably 800 to 990 mg, more preferably 900 to 980 mg water per 1 ml of the aqueous solution.

It is particularly preferred that the aqueous solution used in step (a) contains 10 to 200 µg (more preferably 30 to 70 µg, even more preferably 40 to 60 µg, or 45 to 55 µg) in total of the compound of formula (I) or the salt thereof, 2 to 50 mg (more preferably 5 to 20 mg, even more preferably 8 to 15, or 10 to 14 mg) in total of the ascorbic acid or the salt thereof, 10 to 200 mg (more preferably 30 to 70 mg, even more preferably 40 to 60, or 45 to 55 mg) in total of the one or more mono-, di- or oligo-saccharides or salts thereof and 1 to 50 µg (more preferably 2 to 40 µg, even more preferably 6 to 20 µg, or 8 to 10 µg) in total of the one or more surfactants per 1 ml of the aqueous solution.

The aqueous solution used in step (a) preferably has a pH in the range of from 1 to 5, more preferably in the range of from 2 to 3.5, even more preferably in the range of from 2.3 to 3.0, still more preferably in the range of from 2.5 to 2.8.

The aqueous solution used in step (a) preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 600 to 1600 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 80 to 350 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.05 to 10 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein the pH of aqueous solution is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The aqueous solution used in step (a) more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 700 to 1400 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 120 to 320 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 8 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein the pH of aqueous solution is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The aqueous solution used in step (a) even more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 800 to 1200 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 150 to 300 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 5 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein the pH of aqueous solution is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The aqueous solution used in step (a) still more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 900 to 1100 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 180 to 280 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 2 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein the pH of aqueous solution is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The aqueous solution used in step (a) still even more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 950 to 1050 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 220 to 260 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 1 part by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein the pH of aqueous solution is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The aqueous solution used in step (a) particularly preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 950 to 1050 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- 230 to 250 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 0.5 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein the pH of aqueous solution is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

The aqueous solution used in step (a) most preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- about 1000 parts by weight of mono-, di- or oligo-saccharides or salts thereof, preferably non-reducing di- or oligo-saccharides or salts thereof, preferably one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, most preferably trehalose, especially in the form of trehalose dihydrate,
- about 240 parts by weight of ascorbic acid or salt thereof, preferably containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- about 0.2 parts by weight of one or more surfactants, preferably non-ionic surfactants, even more preferably ethoxylated sorbitan fatty acid esters, still even more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, most preferably polyoxyethylene (20) sorbitan monooleate, such as polyoxyethylene (20) sorbitan monooleate PS-80,

wherein the pH of aqueous solution is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

Thus, in one example, the aqueous solution used in step (a) preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 900 to 1100 parts by weight of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose, especially in the form of trehalose dihydrate,
- 180 to 280 parts by weight of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 2 parts by weight of one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, preferably polyoxyethylene (20) sorbitan monooleate, more preferably polyoxyethylene (20) sorbitan monooleate PS-80,

wherein it is preferred that the pH of the aqueous solution used in step (a) is about 2.4 to 2.8 and preferably 2.5 to 2.7.

Thus, in one example, the aqueous solution used in step (a) more preferably contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- 950 to 1050 parts by weight of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose, especially in the form of trehalose dihydrate,
- 220 to 260 parts by weight of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 1 parts by weight of one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units, preferably polyoxyethylene (20) sorbitan monooleate, more preferably polyoxyethylene (20) sorbitan monooleate PS-80,

wherein it is preferred that the pH of the aqueous solution used in step (a) is about 2.4 to 2.8 and preferably 2.5 to 2.7.

In one more preferred example, the aqueous solution used in step (a) contains:

- 1 part by weight of the compound of formula (I) or salt thereof,

- 950 to 1050 parts by weight of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose, especially in the form of trehalose dihydrate,
- 220 to 260 parts by weight of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 0.1 to 0.5 parts by weight of polyoxyethylene (20) sorbitan monooleate, preferably polyoxyethylene (20) sorbitan monooleate PS-80,

wherein it is preferred that the pH of the aqueous solution used in step (a) is about 2.4 to 2.8 and preferably 2.5 to 2.7.

In one more preferred example, the aqueous solution used in step (a) contains:

- 1 part by weight of the compound of formula (I) or salt thereof,
- about 1000 parts by weight of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose, especially in the form of trehalose dihydrate, especially in the form of trehalose dihydrate,
- about 240 parts by weight of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- about 0.2 parts by weight of polyoxyethylene (20) sorbitan monooleate, preferably polyoxyethylene (20) sorbitan monooleate PS-80,

wherein it is preferred that the pH of the aqueous solution used in step (a) is about 2.4 to 2.8 and preferably 2.5 to 2.7.

Kits of parts

A further aspect of the present invention is a kit of parts comprising the solid composition according to the invention as described above and a buffer solution. The buffer solution preferably has a composition which allows the kit to have a final pH in the range of from 3.0 to 4.0, preferably from 3.1 to 3.6. In other words, the buffer solution preferably has a composition which provides a final pH in the range of from 3.0 to 4.0, preferably from 3.1 to 3.6, when the solid composition and the buffer solution of the kit are combined. The solid composition and the buffer solution are typically contained in separate containers. It is to be understood that the "solid composition" comprised in the kit is typically the solid composition of the first aspect of the present invention and may be characterized by any of the features and preferred features which are set out herein for the solid composition of the first aspect.

The solid composition and the buffer solution preferably result, when combined, in a composition which contains, per 1 mL:

- 10 to 100 µg of the compound of formula (I) or salt thereof,
- 10 to 100 mg of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose,
- 1 to 20 mg of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 1 to 1000 µg of polyoxyethylene (20) sorbitan monooleate, preferably polyoxyethylene (20) sorbitan monooleate PS-80.

The solid composition and the buffer solution more preferably result, when combined, in a composition which contains, per 1 mL:

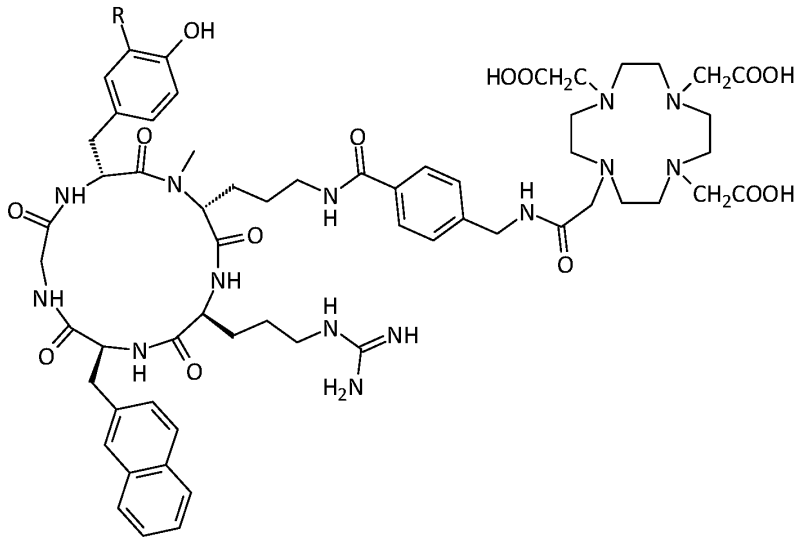
- 30 to 60 µg of the compound of formula (I) or salt thereof,
- 20 to 60 mg of one or more selected from sucrose, trehalose, raffinose, stachyose, and verbascose, preferably trehalose,
- 1 to 15 mg of ascorbic acid or salt thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof, and
- 1 to 100 µg of polyoxyethylene (20) sorbitan monooleate, preferably polyoxyethylene (20) sorbitan monooleate PS-80.

The kit of parts preferably further comprises instructions for performing a radiolabelling procedure, such that when the solid composition is combined with the buffer solution and exposed to a radionuclide or a salt thereof, a radiolabelled compound of formula (I) or a salt is formed which can preferably be administered to a patient without further purification.

Methods for manufacture of a radiopharmaceutical

Another aspect of the present invention is a method for the manufacture of a radiopharmaceutical comprising a chelate formed by

(a) a compound of formula (I)



wherein R is selected from hydrogen, fluorine, chlorine, bromine and iodine; and

(b) a radionuclide;

wherein the method comprises step (i) of dissolving or dispersing the solid composition described herein in a buffer solution and step (ii) of combining it with a radionuclide.

It is to be understood that the "solid composition" used in the above method is typically the solid composition of the first aspect of the present invention and may be characterized by any of the features and preferred features which are set out herein for the solid composition of the first aspect.

Step (ii) is preferably conducted at a temperature of 50°C to 120°C, preferably 80°C to 110°C, more preferably 90 to 100°C, even more preferably 93 to 97°C. The duration of step (ii) is preferably 5 to 25 minutes, more preferably 5 to 10 minutes, even more preferably 7 to 9 minutes.

The radionuclide used for the kit of parts and the method of manufacturing of the present invention is preferably one or more selected from ^{43}Sc, ^{44}Sc, ^{47}Sc, ^{51}Cr, ^{52}Fe, ^{52m}Mn, ^{62}Cu, ^{64}Cu, ^{66}Ga, ^{67}Ga, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{69}Yb, ^{72}As, ^{82}Rb, ^{86}Y, ^{88}Y, ^{89}Zr, ^{90}Y, ^{94m}Tc, ^{97}Ru, ^{99m}Tc, ^{103}Ru, ^{105}Rh, ^{109}Pd, ^{111}In, ^{117m}Sn, ^{121}Sn, ^{133m}In, ^{140}La, ^{141}Ce, ^{142}Pr, ^{143}Pr, ^{149}Pm, ^{151}Pm, ^{153}Sm, ^{157}Gd, ^{161}Tb, ^{165}Dy, ^{166}Ho, ^{166}Dy, ^{166}Ho, ^{167}Tm, ^{168}Yb, ^{169}Er, ^{172}Tm, ^{175}Yb, ^{177}Lu, ^{186}Re, ^{188}Re, ^{198}Au , ^{199}Au, ^{203}Pb, ^{211}Bi, ^{211}At, ^{212}Bi, ^{212}Pb, ^{213}Bi, ^{214}Bi, and ^{225}Ac, preferably ^{99m}Tc, ^{111}In, ^{90}Y, ^{177}Lu, ^{225}Ac, ^{68}Ga, ^{61}Cu and ^{64}Cu, more preferably ^{99m}Tc, ^{111}In, ^{68}Ga, ^{61}Cu and ^{64}Cu, and is even more preferably ^{68}Ga.

It is to be understood that the radionuclide is preferably present in the compounds, compositions and kits of the present invention in in an oxidation state of +1, +2, +3, +4, +5,

+6, or +7, more preferably +1, +2, +3 or +4, even more preferably +2 or +3, most preferably +3.

More preferably, the radionuclide used for the kit of parts and the method of manufacturing of the present invention is $^{68}Ga^{3+}$.

In the compound of formula (I), R is preferably H or I. In certain embodiments, R is H.

Use in medicine

The solid composition or the kit of parts of the present invention are preferably for use in medicine. It is preferred that the solid composition or kit of parts are to be used in diagnostics or therapy. Such diagnostics or therapy may include the imaging or treatment of a tumor, cardiovascular disorders, or inflammatory diseases. It is to be understood that the imaging preferably relates to the imaging of a target (such as a tissue) indicative of the disease. The disease to be imaged or treated is preferably a disease associated with CXCR4-expression (typically CXCR4-overexpression), such as a tumor, cardiovascular disorders, or inflammatory diseases related to CXCR4-expression. The tumor to be imaged or treated is preferably associated with primary aldosteronism or any one selected from hematological and solid cancers, including multiple myeloma, chronic lymphocytic leukemia, acute relapsed myeloid leukemia, non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, breast cancer, gastric/gastro-esophageal/pancreatic adenocarcinoma, colorectal cancer, colorectal cancer with hepatic metastasis, lung cancer, renal cell carcinomas, adrenal cancer, adrenal adenomas and glioblastoma. The tumor to be imaged or treated is more preferably associated with a cancer selected from hematological and solid cancers, including multiple myeloma, chronic lymphocytic leukemia, acute relapsed myeloid leukemia, non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, breast cancer, gastric/gastro-esophageal/pancreatic adenocarcinoma, colorectal cancer, colorectal cancer with hepatic metastasis, lung cancer, renal cell carcinomas, adrenal cancer, adrenal adenomas and glioblastoma.

For example:

(i) the tumor to be imaged or treated is preferably associated with a malignant tumor leading to cancerous diseased among hematological and solid cancers, including multiple myeloma, chronic lymphocytic leukemia, acute relapsed myeloid leukemia, non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, breast cancer, gastric/gastro-esophageal/pancreatic adenocarcinoma, colorectal cancer, colorectal cancer with hepatic metastasis, lung cancer, renal cell carcinomas, adrenal cancer and glioblastoma, and

(ii) the tumor to be imaged or treated is preferably associated with a benign tumor leading to among others adrenal adenomas, preferably those leading to primary aldosteronism.

In the kit of parts, the composition obtained from the kit is preferably to be administered by intravenous bolus or infusion injection. Administration may include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The present invention also relates to a method of collecting data for the diagnosis or treatment of a disease in a patient comprising:

(a) bringing a specific body part or body area suspected to contain target indicative of the disease into contact with a composition obtained from the kit according to the invention which contains the compound of formula (I) and the radionuclide;

(b) allowing the compound of formula (I) with the radionuclide to bind to the target indicative of the disease;

(c) in case of diagnosis detecting the compound of formula (I) with the radionuclide bound to the target indicative of the disease; and

(d) optionally correlating the presence or absence of compound of formula (I) binding with the specific body part or body area with the presence or absence of a target indicative of the disease in the specific body part or body area.

The target indicative of the disease is preferably a tumor. In the case of cardiovascular disorders and inflammatory diseases, the target is preferably any structure indicative of inflammation. It is preferred that the method be an in vitro method. Thus, the "specific body part or body area" is preferably a "specific body part" which has typically been removed from a living organism. The method is preferably not practiced on the human or animal body. It is to be understood that the combination of the compound of formula (I) with the radionuclide is used in the methods of collecting data for the diagnosis or treatment of a disease in a patient. It is believed that the compound of formula (I) binds to the target indicative of the disease via its cyclic peptide part and that the radionuclide is bound by chelation by at the DOTA-type part of the compound of formula (I). The method of collecting data for the diagnosis or treatment of a disease in a patient is preferably a method of collecting data for the diagnosis of a disease in a patient.

For example, the present invention furthermore relates to a method of collecting data for the diagnosis or treatment of a disease in a patient comprising:

(a) bringing a specific body part or body area suspected to contain target indicative of the disease into contact with a composition obtained from the kit according to the invention which contains the compound of formula (I) and the radionuclide;

(b) allowing the compound of formula (I) with the radionuclide to bind to the target indicative of the disease;

(c) in case of diagnosis detecting the compound of formula (I) with the radionuclide bound to the target indicative of the disease; and

(d) optionally correlating the presence or absence of compound of formula (I) binding with the specific body part or body area with the presence or absence of a disease in the specific body part or body area.

The method is more preferably a method of collecting data for the diagnosis of the disease in a patient. The body part is preferably a body part that has been removed from the body and is preferably not returned to the body after the imaging or treatment.

A preferred type of disease are diseases associated with CXCR4-expression (typically CXCR4-overexpression). The disease is preferably selected from tumor, cardiovascular disorders, or inflammatory diseases, in particular those tumors, cardiovascular disorders, and inflammatory diseases associated with CXCR4-expression (typically CXCR4-overexpression). The disease is more preferably a tumor, cardiovascular disorder, and/or inflammatory disease, more preferably a tumor.

Thus, for example, the method is a method of collecting data for the diagnosis of a tumor in a patient comprising:

(a) bringing a specific body part or body area suspected to contain a tumor into contact with a composition obtained from the kit according to the invention which contains the compound of formula (I) and the radionuclide;

(b) allowing the compound of formula (I) with the radionuclide to bind to the tumor;

(c) detecting the compound of formula (I) with the radionuclide bound to the tumor; and

(d) optionally correlating the presence or absence of compound of formula (I) binding with the specific body part or body area with the presence or absence of a tumor disease in the specific body part or body area.

The compositions (in particular the composition obtained from the kit) may further comprise components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavoring agents, salts for varying the osmotic pressure, buffers, masking agents, antioxidants, and further active agents. They can also comprise still other therapeutically valuable substances.

Suitable excipients are well known to those skilled in the art and are described in detail in, e.g. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (2004) Lippincott, Williams & Wilkins, Philadelphia; Remington: The Science and Practice of Pharmacy (2000) Lippincott, Williams & Wilkins, Philadelphia; and Handbook of Pharmaceutical Excipients (2005) Pharmaceutical Press, Chicago. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives.

The compound can also be administered parenterally in the form of solution or suspension. In such formulations, diluents or pharmaceutically acceptable carriers such as sterile water and physiological saline buffer can be used. Other conventional solvents, pH buffers, stabilizers, anti-bacteria agents, surfactants, and antioxidants can all be included. For example, useful components include sodium chloride, acetates, citrates or phosphates buffers, glycerin, dextrose, fixed oils, methyl parabens, polyethylene glycol, propylene glycol, sodium bisulfate, benzyl alcohol, and the like. The parenteral formulations can be stored in any conventional containers such as vials and ampoules.

In therapeutic applications, pharmaceutical compositions are to be administered in a manner appropriate to the disease to be treated, as determined by a person skilled in the medical arts. An appropriate dose and suitable duration and frequency of administration can vary within wide limits and will be determined by such factors as the condition of the patient, the type and severity of the disease, the particular form of the active ingredient(s), the method of administration, among others. In general, an appropriate dose and administration regimen provides the pharmaceutical composition in an amount sufficient to provide therapeutic benefit, for example an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or lessening of symptoms severity, or any other objectively identifiable improvement as noted by the clinician. Effective doses may generally be assessed or extrapolated using experimental models like dose-response curves derived from in vitro or animal model test systems, or from clinical trials.

DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

The following definitions apply throughout the present specification and claims, unless specifically indicated otherwise.

As used herein, the term "alkyl" refers to a monovalent saturated acyclic (i.e., non-cyclic) hydrocarbon group which may be linear or branched. Accordingly, an "alkyl" group does not comprise any carbon-to-carbon double bond or any carbon-to-carbon triple bond. As used herein, the "alkyl" typically refers to a "C_{1-6} alkyl". A "C_{1-6} alkyl" denotes an alkyl group having 1 to 6 carbon atoms. Preferred exemplary alkyl groups are methyl, ethyl, propyl (e.g., n-propyl or isopropyl), or butyl (e.g., n-butyl, isobutyl, sec-butyl, or tert-butyl). Unless defined otherwise, the term "alkyl" more preferably refers to C_{1-4} alkyl, even more preferably to methyl or ethyl, and still more preferably to methyl.

A "patient" or "subject" for the purposes of the present invention includes both humans and other animals, particularly mammals. Thus, the methods and uses of the invention are applicable to both human therapy and veterinary applications. In a preferred aspect the subject or patient is a mammal, and in the most preferred aspect the subject or patient is a human (e.g. a male or female human).

The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing a disease (herein, cancer) or symptom thereof and/or may be therapeutic in terms of partially or completely curing or ameliorating a disease (i.e. cancer) and/or a symptom or adverse effect attributed to the disease or partially or completely halting the progression of a disease and/or a symptom or adverse effect attributed to the disease. The term "treatment" as used herein covers any treatment of a disease (i.e. cancer) in a patient and includes, without limitation, any one or more of the following: (a) preventing cancer in a patient which may be predisposed/at risk of developing cancer; (b) delaying the onset of cancer; (c) inhibiting cancer, i.e. arresting, delaying or slowing down its development/progression; or (d) relieving the cancer, i.e. causing (complete or partial) regression, correction or alleviation of cancer. The present invention specifically and distinctly relates to each one of these forms of treatment.

As used herein, the term "diagnosis" preferably refers to the process of identifying a disease, condition, or injury, as well as preferably identifying the progression of said disease, condition, or injury, typically based on its signs and symptoms.

As used herein, the term "therapeutically effective amount" refers to the amount sufficient to produce a desired biological effect (e.g., a therapeutic effect) in a subject. Accordingly, a therapeutically effective amount of a compound may be an amount which is sufficient to treat a disease (i.e. cancer), and/or delay the onset or progression of the disease, and/or alleviate one or more symptoms of the disease, when administered to a subject suffering from or susceptible to that disease.

As used herein, the term "radionuclide" may refer to any isotope having a $t_{1/2}$ of less than 2 x 10^{19} years, preferably less than 10 years, more preferably less than 1 year, more preferably

less than 1 month, even more preferably less than 2 weeks, still more preferably 10 days or less.

As used herein, a "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and/or bases of the specified compound and that is not biologically or otherwise undesirable. A compound may possess sufficiently acidic, sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of a compound according to the invention, with a mineral or organic acid, such as hydrochlorides, hydrobromides, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrophosphates, dihydrophosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, nitrates, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, ethane-sulfonates, propanesulfonates, benzenesulfonates, toluenesulfonates, trifluoromethansulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, mandelates, pyruvates, stearates, ascorbates, or salicylates. When a compound carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands such as ammonia, alkylamines, hydroxyalkylamines, lysine, arginine, N-methylglucamine, procaine and the like. Pharmaceutically acceptable salts are well known in the art.

As used herein, a "pharmaceutically acceptable solvate" refers to a complex of variable stoichiometry formed by a solute and a pharmaceutically acceptable solvent such as water, ethanol and the like. A complex with water is known as a hydrate.

As used herein, a "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" refers to non-API (API refers to Active Pharmaceutical Ingredient) substances such as disintegrators, binders, fillers, and lubricants used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration and/or the European Medicines Agency. Pharmaceutically acceptable carriers or excipients are well known to those skilled in the art.

The term "aqueous solution" refers to a solution wherein only water is present as a solvent, or wherein the water represents the main solvent and is typically present in an amount of more than 50 wt.-%, preferably at least 80 wt.-%, more preferably at least 90 wt.-%, even

more preferably at least 95 wt.-%, based on the total amount of solvents (e.g. of all components which are in a liquid state at 25°C and 1 atm) contained in the aqueous solution. The term "solution" does not require that all components in the solution are dissolved. Thus, the term "solution" may also refer to a composition in which some components are fully dissolved, while other components are only partially dissolved or undissolved. Preferably, all components in a solution a dissolved.

As used herein, unless explicitly indicated otherwise or contradicted by context, the terms "a", "an" and "the" are used interchangeably with "one or more" and "at least one".

The expression "comprise", as used herein, besides its literal meaning also includes and specifically refers to the expressions "consist essentially of" and "consist of". Thus, the expression "comprise" refers to embodiments wherein the subject-matter which "comprises" specifically listed elements does not comprise further elements as well as embodiments wherein the subject-matter which "comprises" specifically listed elements may and/or indeed does encompass further elements. Likewise, the expression "have" is to be understood as the expression "comprise", also including and specifically referring to the expressions "consist essentially of" and "consist of". The term "consist essentially of", where possible, in particular refers to embodiments wherein the subject-matter comprises 20% or less, in particular 15% or less, 10% or less or especially 5% or less further elements in addition to the specifically listed elements of which the subject-matter consists essentially of.

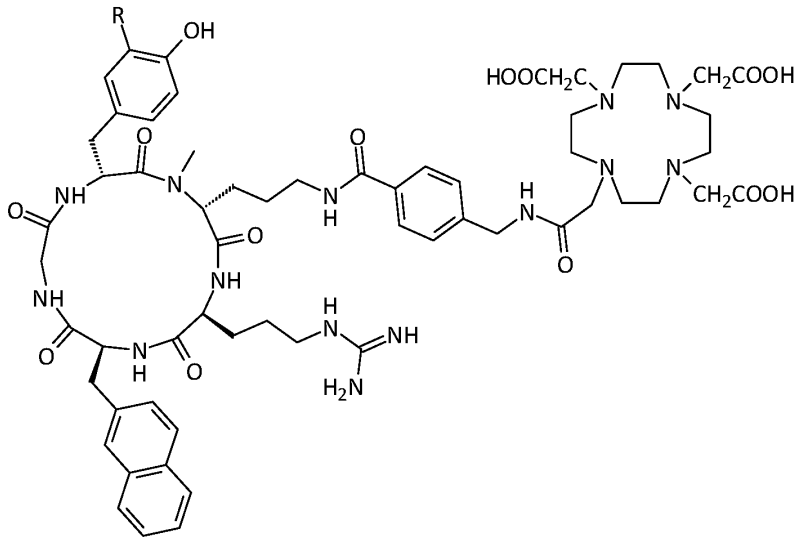
The term “about”, as used herein, in particular refers to the indicated value +/- 10% of said value, especially +/- 5% of said value and in particular +/- 2% of said value. In certain embodiments, the term “about” also specifically refers to the exact value.

EMBODIMENTS OF THE INVENTION

The present invention may be summarized by the following items:

1. A solid composition comprising

   (i) 1 part by weight of a compound of formula (I) or a salt thereof:



wherein R is selected from hydrogen, C_{1-6} alkyl, fluorine, chlorine, bromine and iodine,

(ii) 40 to 400 parts by weight of ascorbic acid or a salt thereof, calculated as mass of ascorbic acid per mass of the compound of formula (I),

(iii) one or more mono-, di- or oligo-saccharides or salts thereof, and

(iv) one or more surfactants.

2. The solid composition according to item 1, wherein the solid composition contains the ascorbic acid or salt thereof in an amount of 80 to 350 parts by weight, preferably 120 to 320 parts by weight, more preferably 150 to 300 parts by weight, even more preferably 180 to 280 parts by weight, still more preferably 220 to 260 parts by weight, still even more preferably 230 to 250 parts by weight, calculated as mass of ascorbic acid per mass of the compound of formula (I).

3. The solid composition according to item 1 or 2, wherein the solid composition contains the ascorbic acid or salt thereof in an amount of 230 to 250 parts by weight, calculated as mass of ascorbic acid per mass of the compound of formula (I).

4. The solid composition according to any one of items 1 to 3, wherein the ascorbic acid or a salt thereof in (ii) is ascorbic acid or a mixture of ascorbic acid and one or more salts thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof.

5. The solid composition according to any one of items 1 to 4, wherein the ascorbic acid or a salt thereof in (ii) is ascorbic acid.

6. The solid composition according to any one of items 1 to 5, wherein the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is preferably about 2 to 3.5, more preferably 2.2 to 3.3, even more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

7. The solid composition according to any one of items 1 to 6, wherein the pH of a composition obtained by dissolving 100 mg of the solid composition in 1000 mg water is about 2.5 to 2.7.

8. The solid composition according to any one of items 1 to 7, wherein the solid composition contains the one or more mono-, di- or oligo-saccharides or salts thereof in an amount of 600 to 1600 parts by weight, preferably 700 to 1400 parts by weight, more preferably 800 to 1200 parts by weight, more preferably 900 to 1100 parts by weight, more preferably 950 to 1050 parts by weight, calculated as mass of the mono-, di- or oligo-saccharides per mass of the compound of formula (I).

9. The solid composition according to any one of items 1 to 8, wherein the solid composition contains the one or more mono-, di- or oligo-saccharides or salts thereof in an amount of 950 to 1050 parts by weight, calculated as mass of the mono-, di- or oligo-saccharides per mass of the compound of formula (I).

10. The solid composition according to any one of items 1 to 9, wherein the one or more surfactants are selected from polyvinylpyrrolidone (PVP), and ethoxylated sorbitan fatty acid esters;

wherein the ethoxylated sorbitan fatty acid esters are preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having from 4 to 40 oxyethylene units; more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units; even more preferably polyoxyethylene (20) sorbitan monooleate,

more preferably selected from polyvinylpyrrolidone (PVP), polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate and polyoxyethylene (20) sorbitan monooleate,

even more preferably selected from polyoxyethylene (20) sorbitan monolaurate or polyoxyethylene (20) sorbitan monooleate, and

still more preferably from polyoxyethylene (20) sorbitan monooleate.

11. The solid composition according to any one of items 1 to 10, wherein the one or more surfactants are polyoxyethylene (20) sorbitan monooleate.

12. The solid composition according to item 10, wherein the one or more surfactants is/are contained in an amount of 0.05 to 10 parts by weight, more preferably 0.1 to 8 parts by weight, more preferably 0.1 to 5 parts by weight, more preferably 0.1 to 2 parts by weight, more preferably 0.1 to 0.5 parts by weight, calculated as mass of surfactant(s) per mass of the compound of formula (I).

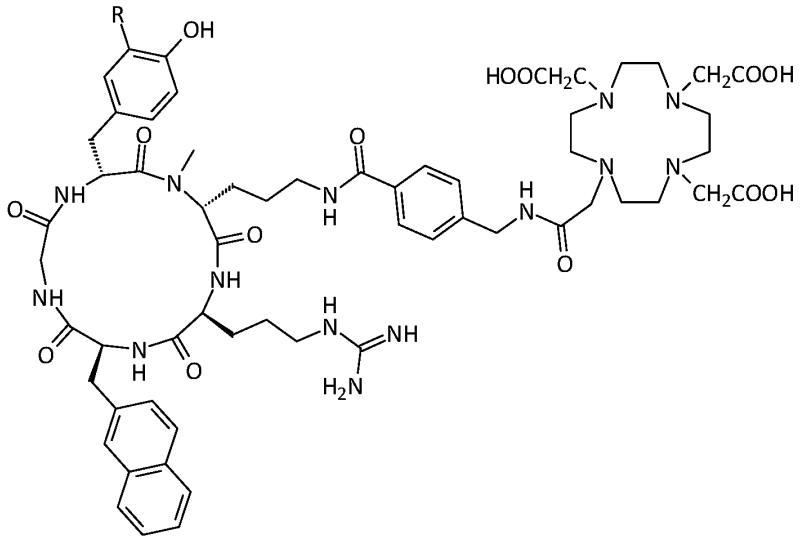
13. The solid composition according to item 10 or 12, wherein the one or more surfactants is/are contained in an amount of 0.1 to 0.5 parts by weight, calculated as mass of surfactant(s) per mass of the compound of formula (I).

14. The solid composition according to any one of items 1 to 13, wherein the one or more mono-, di- or oligo-saccharides are selected from non-reducing disaccharides, wherein the non-reducing disaccharides are preferably selected from sucrose and trehalose, more preferably trehalose, especially in the form of trehalose dihydrate.

15. The solid composition according to any one of items 1 to 14, wherein the one or more mono-, di- or oligo-saccharides are trehalose, especially in the form of trehalose dihydrate.

16. The solid composition according to any one of items 1 to 15, wherein the solid composition is obtainable by lyophilization.

17. A method for the preparation of a solid composition (which is preferably the solid composition of any of items 1 to 16) comprising (i) a compound of formula (I) or a salt thereof:



wherein R is selected from hydrogen, C_{1-6} alkyl, fluorine, chlorine, bromine and iodine; and ascorbic acid or a salt thereof,

said method comprising the steps of

(a) providing an aqueous solution which comprises

a compound of formula (I) or a salt thereof,

ascorbic acid or a salt thereof,

one or more mono-, di- or oligo-saccharides or salts thereof, and

one or more surfactants

(b) subjecting the solution to lyophilisation to obtain a solid composition.

18. The method according to item 17, wherein the ascorbic acid or a salt thereof is contained in the aqueous solution in step (a) at 40 to 400 parts by weight, calculated as mass of ascorbic acid per mass of the compound of formula (I).

19. The method according to item 17 or 18, wherein the aqueous solution in step (a) contains the ascorbic acid or salt thereof in an amount of 80 to 350 parts by weight, preferably 120 to 320 parts by weight, more preferably 150 to 300 parts by weight, even more preferably 180 to 280 parts by weight, still more preferably 220 to 260 parts by weight, still even more preferably 230 to 250 parts by weight, calculated as mass of ascorbic acid per mass of the compound of formula (I).

20. The method according to any one of items 17 to 19, wherein the aqueous solution in step (a) contains the ascorbic acid or salt thereof in an amount of 230 to 250 parts by weight, calculated as mass of ascorbic acid per mass of the compound of formula (I).

21. The method according to any one of items 17 to 20, wherein the ascorbic acid or a salt thereof in step (a) is ascorbic acid or a mixture of ascorbic acid and one or more salts thereof, containing at least 80 wt.-%, preferably at least 90 wt.-% ascorbic acid, relative to the total weight of the mixture of ascorbic acid and one or more salts thereof.

22. The method according to any one of items 17 to 21, wherein the ascorbic acid or a salt thereof in step (a) is ascorbic acid.

23. The method according to any one of items 17 to 22, wherein the pH of the aqueous solution in step (a) is about 2 to 3.5, preferably 2.2 to 3.3, more preferably 2.4 to 2.8 and most preferably 2.5 to 2.7.

24. The method according to any one of items 17 to 23, wherein the pH of the aqueous solution in step (a) is about 2.5 to 2.7.

25. The method according to any one of items 17 to 24, wherein the aqueous solution in step (a) contains the one or more mono-, di- or oligo-saccharides or salts thereof in an amount of 600 to 1600 parts by weight, preferably 700 to 1400 parts by weight, more preferably 800 to 1200 parts by weight, more preferably 900 to 1100 parts by weight, more preferably 950 to 1050 parts by weight, calculated as mass of the mono-, di- or oligo-saccharides per mass of the compound of formula (I).

26. The method according to any one of items 17 to 25, wherein the aqueous solution in step (a) contains the one or more mono-, di- or oligo-saccharides or salts thereof in an amount of 950 to 1050 parts by weight, calculated as mass of the mono-, di- or oligo-saccharides per mass of the compound of formula (I).

27. The method according to any one of items 17 to 26, wherein the one or more surfactants are selected from polyvinylpyrrolidone (PVP), and ethoxylated sorbitan fatty acid esters; wherein the ethoxylated sorbitan fatty acid esters are preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having from 4 to 40 oxyethylene units; more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units; even more preferably polyoxyethylene (20) sorbitan monooleate, more preferably selected from polyvinylpyrrolidone (PVP), polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate and polyoxyethylene (20) sorbitan monooleate, even more preferably selected from polyoxyethylene (20) sorbitan monolaurate or polyoxyethylene (20) sorbitan monooleate, and still more preferably from polyoxyethylene (20) sorbitan monooleate.

28. The method according to any one of items 17 to 27, wherein the one or more surfactants are polyoxyethylene (20) sorbitan monooleate.

29. The method according to any one of items 17 to 28, wherein the one or more surfactants is/are contained in an amount of 0.05 to 10 parts by weight, more preferably 0.1 to 8 parts by weight, more preferably 0.1 to 5 parts by weight, more preferably 0.1 to 2 parts by weight, more preferably 0.1 to 0.5 parts by weight, calculated as mass of surfactant(s) per mass of the compound of formula (I).

30. The method according to any one of items 17 to 29, wherein the one or more surfactants is/are contained in an amount of 0.1 to 0.5 parts by weight, calculated as mass of surfactant(s) per mass of the compound of formula (I).

31. The method according to any one of items 17 to 30, wherein the one or more mono-, di- or oligo-saccharides are selected from non-reducing disaccharides, wherein the non-reducing disaccharides are preferably selected from sucrose and trehalose, more preferably trehalose, especially in the form of trehalose dihydrate.

32. The method according to any one of items 17 to 31, wherein one or more mono-, di- or oligo-saccharides are trehalose, especially in the form of trehalose dihydrate.

33. A kit of parts comprising

(a) a solid composition according to any one of items 1 to 16; and

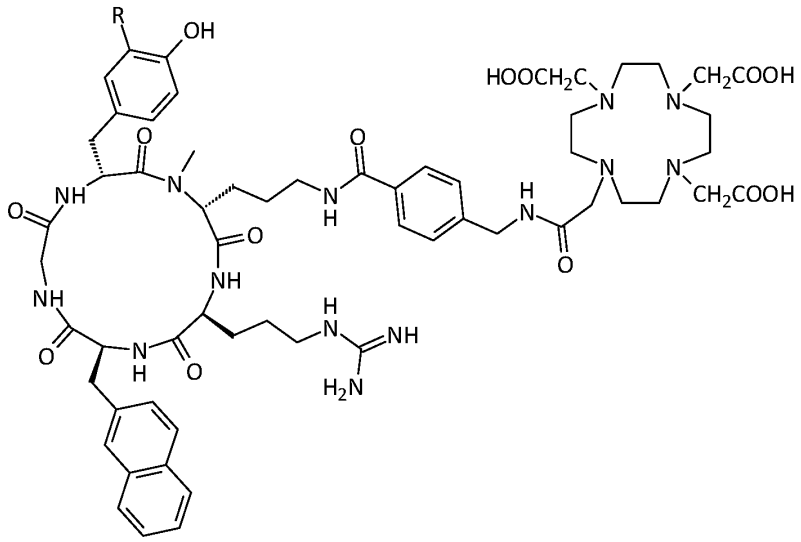
(b) a buffer solution.

34. The kit of parts according to item 33, further comprising

(c) instructions for performing a radiolabelling procedure, such that when the solid composition is combined with the buffer solution and exposed to a radionuclide or a salt thereof, a radiolabelled compound of formula (I) or a salt is formed which can preferably be administered to a patient without further purification.

35. A method for the manufacture of a radiopharmaceutical comprising a chelate formed by

(a) a compound of formula (I)



wherein R is selected from hydrogen, fluorine, chlorine, bromine and iodine; and

(b) a radionuclide;

wherein the method comprises step (i) of dissolving or dispersing the solid composition according to any one of items 1 to 16 in a buffer solution and step (ii) of combining it with a radionuclide.

36. The method for the manufacture of a radiopharmaceutical according to item 35, wherein step (ii) is conducted at a temperature of 50°C to 120°C, preferably 80°C to 110°C, more preferably 90 to 100°C, even more preferably 93 to 97°C, for a duration of 5 to 25 minutes, preferably 5 to 15 minutes, more preferably 5 to 10 minutes, even more preferably 7 to 9 minutes.

37. The method for the manufacture of a radiopharmaceutical according to item 35 or 36, wherein step (ii) is conducted at a temperature of 93 to 97°C, for a duration 7 to 9 minutes.

38. The kit of parts according to item 33 or 34 or the method according to any one of items 35 to 37, wherein the radionuclide is one or more selected from ^{43}Sc, ^{44}Sc, ^{47}Sc, ^{51}Cr, ^{52}Fe, ^{52m}Mn, ^{62}Cu, ^{64}Cu, ^{66}Ga, ^{67}Ga, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{69}Yb, ^{72}As, ^{82}Rb, ^{86}Y, ^{88}Y, ^{89}Zr, ^{90}Y, ^{94m}Tc, ^{97}Ru, ^{99m}Tc, ^{103}Ru, ^{105}Rh, ^{109}Pd, ^{111}In, ^{117m}Sn, ^{121}Sn, ^{133m}In, ^{140}La, ^{141}Ce, ^{142}Pr, ^{143}Pr, ^{149}Pm, ^{151}Pm, ^{153}Sm, ^{157}Gd, ^{161}Tb, ^{165}Dy, ^{166}Ho, ^{166}Dy, ^{166}Ho, ^{167}Tm, ^{168}Yb, ^{169}Er, ^{172}Tm, ^{175}Yb, ^{177}Lu, ^{186}Re, ^{188}Re, ^{198}Au , ^{199}Au, ^{203}Pb, ^{211}Bi, ^{211}At, ^{212}Bi, ^{212}Pb, ^{213}Bi, ^{214}Bi, and ^{225}Ac, preferably ^{99m}Tc, ^{111}In, ^{90}Y, ^{177}Lu, ^{225}Ac, ^{68}Ga, ^{61}Cu and ^{64}Cu, more preferably ^{99m}Tc, ^{111}In, ^{68}Ga, ^{61}Cu and ^{64}Cu, and is even more preferably ^{68}Ga.

39. The kit of parts according to item 33 or 34 or the method according to any one of items 35 to 38, wherein the radionuclide is ^{68}Ga.

40. The solid composition according to any one of items 1 to 16, the method according to any of items 17 to 32, or the kit of parts according to any of item 33 or 34 or item 38 or 39, wherein R is H or I.

41. The solid composition according to any one of items 1 to 16 and 40 or the kit of parts according to any one of items 33, 34, and 38 to 40, for use in medicine.

42. The solid composition for use or kit of parts for use according to item 41, wherein the solid composition or kit of parts is for use in diagnostics or therapy.

43. The solid composition for use or kit of parts for use according to item 41 or 42, wherein the solid composition or kit of parts is for use in the imaging or treatment of a disease associated with CXCR4-expression, preferably selected from a tumor, cardiovascular disorder, and/or inflammatory disease.

44. The solid composition for use or kit of parts for use according to item 43, wherein the tumor to be imaged or treated is associated with primary aldosteronism or any one selected from hematological and solid cancers, including multiple myeloma, chronic lymphocytic leukemia, acute relapsed myeloid leukemia, non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, breast cancer, gastric/gastro-esophageal/pancreatic adenocarcinoma, colorectal cancer, colorectal cancer with hepatic metastasis, lung cancer, renal cell carcinomas, adrenal cancer, adrenal adenomas and glioblastoma, wherein the tumor to be imaged or treated is preferably associated with any one selected from hematological and solid cancers, including multiple myeloma, chronic lymphocytic leukemia, acute relapsed myeloid leukemia, non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, breast cancer, gastric/gastro-esophageal/pancreatic adenocarcinoma, colorectal cancer, colorectal cancer with hepatic metastasis, lung cancer, renal cell carcinomas, adrenal cancer, adrenal adenomas and glioblastoma.

45. The kit of parts for use according to any of items 40 to 43, wherein the composition obtained from the kit according to any one of items 33, 34, and 38 to 40 is to be administered by intravenous bolus or infusion injection.

46. A method of collecting data for the diagnosis of a disease comprising:

(a) bringing a specific body part or body area suspected to contain target indicative of the disease into contact with a composition obtained from the kit according to any one of items 33, 34 and 38 to 40 which contains the compound of formula (I) and the radionuclide;

(b) allowing the compound of formula (I) with the radionuclide to bind to the target indicative of the disease;

(c) detecting the compound of formula (I) with the radionuclide bound to the target indicative of the disease; and

(d) optionally correlating the presence or absence of compound of formula (I) binding with the specific body part or body area with the presence or absence of a target indicative of the disease in the specific body part or body area.

47. A method of collecting data for the treatment of a disease comprising:

(a) bringing a specific body part or body area suspected to contain target indicative of the disease into contact with a composition obtained from the kit according to any one of items 33, 34, and 38 to 40 which contains the compound of formula (I) and the radionuclide;

(b) allowing the compound of formula (I) with the radionuclide to bind to the target indicative of the disease; and

(d) optionally correlating the presence or absence of compound of formula (II) binding with the specific body part or body area with the presence or absence of a target indicative of the disease in the specific body part or body area.

FIGURES

Figure 1 shows radiochemical purity of different [^{68}Ga]Ga-PentixaFor formulations as a function of the amount of ascorbic acid in the formulation.

Figure 2 shows radiochemical purity of different [^{68}Ga]Ga-PentixaFor formulations as a function of the amount of polysorbate 20 in the formulation.

EXAMPLES

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

1. General information

1.1 Materials used

Chemicals	Provider	Product Number
PentixaFor precursor (Bulk)	ABX	9914.0500
PentixaFor precursor (GMP)	ABX	9916.0000.250/001;
PentixaFor precursor (reference standard)	ABX	9916S
PentixaFor precursor (GMP)	ABX	9916
Trehalose	Pfanstiehl	T-104-4
L-Ascorbic acid	Sigma-Aldrich	33034
(+)-Sodium L ascorbate	Sigma Aldrich	11140
Polysorbate 80 (PS-80)	Merck	8.17061.1000
Hydrochloric acid	VWR Chemicals	85447.320
Sodium hydroxide	Merck	1.09137.1000
Ammonium acetate	Merck	1.01116.0500
Methanol	J.T. Baker	8402
Water HPLC grade	Fisher	W/0106/17
WFI (water for injection)	B.Braun	8609338; (medpex)
Sodium acetate anhydrous	Sigma Aldrich	32319
Sodium acetate trihydrate	Merck	1.06265.5000
Acetic acid glacial	Merck	1.00056.5000
TLC stripes	Agilent	SGI0001

1.2 Equipment used

Equipment	Manufacturer	Product number
^{68}Ge/^{68}Ga-Generator GalliaPharm®	Eckert & Ziegler AG	BNGE21 GNGK01
TLC Scanner	Eckert & Ziegler AG	TLC-SCAN 61-2-0
20 µL pipette	Eppendorf	N15315D
200 µL pipette		N20081I
1000 µL pipette		G32123J
5000 µL pipette		R41163I
Volumetric flask (PP)	B. Braun	612-4078 (VWR)
HPLC system	Agilent	1260 Infinity II
Spatula	Bürkle	231-0606 (VWR)
Injection vial 10 R	Thüringer Pharmaglas GmbH	05 0010 131 20 (PharMediPack)

GT-stopper	West Pharmaceutical services Deutschland GmbH	01 1319 349 01 (PharMediPack)
FOS cap	West Pharmaceutical services Deutschland GmbH	03 5199 030 01 (PharMediPack)

2. Analytics

2.1 HPLC analytics of the samples obtained after lyophilization

HPLC column	Gemini® 3 µm NX-C18, 110 Å, (150 x 4.6 mm)
Column temperature	25 °C
Sampler temperature	20 °C
Mobile Phase A	Water with 0.1 % TFA (HPLC grade, Fisher)
Mobile Phase B	ACN with 0.1 % TFA (HPLC grade, Promochem)
Flow rate	1.0 mL/min
Detection parameter	
UV	220 nm (width 4)
Slit width	Wide
Response time	1 s
Data collection rate	5 Hz
UV range	190 – 350 nm
Sample concentration	0.04 mg/mL, 0.05 mg/mL, 0.06 mg/mL
solvent	WFI
Injection volume	20 µL
Data collection time	25 min

Gradient:

Time [min]	**Mobile phase A [%]**	**Mobile phase B [%]**
0	80	20
19	50	50
20	50	50
21	80	20
25	80	20

2.2 HPLC analytics of gallium-68 labelled samples

HPLC column	Gemini® 3 µm NX-C18, 110 Å, (150 x 4.6 mm)
Column temperature	25 °C
Sampler temperature	20 °C
Mobile Phase A	Water with 0.1 % TFA (HPLC grade, Fisher)

Mobile Phase B	ACN with 0.1 % TFA (HPLC grade, Promochem)
Flow rate	1.0 mL/min
Detection parameter	
UV	220 nm (width 4)
Slit width	Wide
Response time	1 s
Data collection rate	5 Hz
UV range	190 – 350 nm
Sample concentration	6.66 µg/mL, 8.33 µg/mL, 10.0 µg/mL
Injection volume	20 µL
Data collection time	11 min

Gradient:

Time [min]	**Mobile phase A [%]**	**Mobile phase B [%]**
0	80	20
9	50	50
10	50	50
11	80	20

Preparation of sample solution:

- The samples containing [^{68}Ga]Ga-PentixaFor were used without further dilution.

2.3 TLC analytics

The TLC plates were developed in a glass chamber shielded with lead blocks. The glass chamber contained a 50/50 (v/v) 1.0 M ammonium acetate/methanol mixture as mobile phase.

Preparation of 1.0 M ammonium acetate solution:

- 7.7 g ammonium acetate were weighed directly into a 100 mL volumetric flask (PP) and dissolved with water HPLC grade to 100 mL.

Preparation of sample solution:

- The sampled IMP solution was used without dilution.

3. Preparation of samples

3.1 Preparation of lyophilizates

For each example, the materials indicated in the following table were mixed with water for injection (WFI) ad 1 mL and lyophilized.

3.2 Storage conditions

The lyophilized samples were stored at 40 °C. At defined time points (0, 1 week, 2 weeks, 4 weeks, 8 weeks and 12 weeks), the samples were retrieved and analysed.

3.3 Chemical stability testing

The lyophilization samples were dissolved in water for injection (WFI) and used without further dilution.

3.4 Radiolabelling

The lyophilization samples were dissolved in 1 mL buffer solution. For the radiolabelling, the reactor of the Pharmtracer (Device EC-0243) module was used, unless otherwise indicated. For this, the template for the labelling of PentixaFor precursor via Pharmtracer was loaded and switched to manual mode. The reactor was turned on and the temperature was set to 102 °C (to ensure 95 °C inside the reaction vial). The reactor was preheated for 10 min. Afterwards, the dissolved lyophilization sample was placed in the reactor and pre heated for 5 min. Then, the generator was eluted with approximately 5 mL of HCl directly into the sample vial. The reaction ran for 8 min. Afterwards, the activity was measured and quality control was performed.

4. Results

4.1 Chemical stability and content of PentixaFor of samples after storage (40 °C /75% RH)

36 different formulations of PentixaFor were prepared and analyzed, containing the following components:

Material	Amount
PentixaFor	40 / 50 / 60 µg
Trehalose dihydrate	0 / 30 / 50 / 80 mg
Ascorbic acid	0 / 2 / 5 / 8 / 10 / 12 / 15 mg

Polysorbate 80 (polyoxyethylene-(20)-sorbitan-monooleate)	0 / 0.001 / 0.01 / 0.05%
Water for injection	Ad 1 mL
Alternative ingredients	
Dextran	10 / 40 mg
Sorbitol	20 mg
Inositol	10 / 30 mg
Sodium ascorbate	5 mg
Polyvinylpyrrolidone	30 mg
Polysorbate 20 (polyoxyethylene-(20)-sorbitan-monolaurate)	0.01%

Exemplary formulations samples:

Material	**Formulation sample 1**		**Formulation sample 35**	
	Amount	**Rel. amount**	**Amount**	**Rel. amount**
PentixaFor	50 µg	1	50 µg	1
Trehalose dihydrate	50 mg	1000	50 mg	1000
Ascorbic acid	5 mg	100	12 mg	240
Polysorbate 80	0.01%	2	0.001%	0.2
Water for injection	ad 1 mL		ad 1 mL	

The following tables show the stability of selected samples as a function of time (HPLC analysis)

Formulation #	**FS 1**	**FS 35**
t [weeks]	**relative area [%]**	**relative area [%]**
0	98.93	98.78
1	99.39	99.37
2	98.33	99.24
4	98.98	98.75
8	99.94	98.58
12	98.91	98.67

The compositions of formulation samples 1 and 35 are thus highly stable under the chosen storage conditions (40 °C).

4.2 Radiochemical purity of the samples

Experiment Description

Control formulation

- Buffer preparation:
  - 1293.8 mg anhydrous sodium acetate are weighed into a 10 mL volumetric flask (Propylene) and dissolved in approximately 5 mL WFI. 1435 µL glacial acetic acid were added and the mixture filled with WFI to the 10 mL mark.
- Peptide preparation:
  - 2.6 mg PentixaFor (Bulk) were weighed in a 2 mL Eppendorf tube and dissolved with 2 mL WFI. With a net peptide content of 83.6% the concentration of the PentixaFor stock solution is 1.09 mg/mL.
- Labeling reaction:
  - The reaction temperature was set to 102 °C (in order to guarantee 95°C inside the reaction vial) and the reactor heated for 10 min. 50 µL of the stock solution were transferred into a 10 mL vial and 1 mL of the buffer solution was added afterwards and placed in the reactor. After 5 min preheating, the generator was eluted with approximately 5 mL of HCl 0.1 M directly into the reaction vial. The reaction was allowed to run for 8 min.

Formulation samples

- Buffer preparation:
  - 1046.9 mg sodium acetate trihydrate were weighed into a 10 mL volumetric flask (PP) and dissolved in approximately 5 mL WFI. 1435 µL glacial acetic acid were added and the mixture filled with WFI to the 10 mL mark.
- Peptide preparation:
  - The formulation sample was prepared in a 10 mL injection vial.
- Labeling reaction:
  - The reaction temperature was set to 102 °C (in order to guarantee 95°C inside the reaction vial) and the reactor heated for 10 min. The formulation sample, t = 0, was placed in the reactor and preheated for 5 min. After preheating, the generator was eluted with approximately 5 mL HCl 0.1 M, directly into the reaction vial. The reaction was allowed to run for 8 min.

Final execution

The heater/ incubator is switched on, the temperature was set to 102°C in order to guarantee 95°C inside the reaction vial, and pre-heated for 10 min.

Vial A and B are brought to room temperature.

The sterile filters and micro pins are unpacked. The sterile filter is attached to one of the two micro pins and the micro pin is inserted with the attached filter into vial A. The second micro pin is inserted into vial B.

The 1 mL syringe is connected to vial B via micro pin on vial B and 1 mL of buffer solution are drawn while being aware of vacuum occurrence.

The syringe with micro pin is disconnected and the syringe with micro pin is connected to vial A. The buffer solution is transferred into vial A while making sure all solid is dissolved.

The syringe is disconnected without micro pin, 1 mL of air is drawn, and the syringe is rinsed with air through the before used micro pin. The syringe without micro pin is discarded.

Vial A with micro pin and micro pin plus filter is placed into the heater/ incubator and pre-heated the reaction mixture for 5 minutes.

The $^{68}Ge/^{68}Ga$-generator is connected to the micro pin without filter.

After 5 minutes preheating, the $^{68}Ge/^{68}Ga$-generator is eluted into vial A according to manufacturer instructions using 5 mL of 0.1 m HCl.

The $^{68}Ge/^{68}Ga$-generator tubing and the micro pins are disconnected in separate steps from vial A while the reaction is allowed to run for 8 minutes.

After 8 minutes reaction time, vial A is removed from the heater/ incubator and place it into a lead container. The vial is cooled down at room temperature for approximately 10 min.

The final activity of the product is measured and reported together with the measurement time and the product is submitted to quality control.

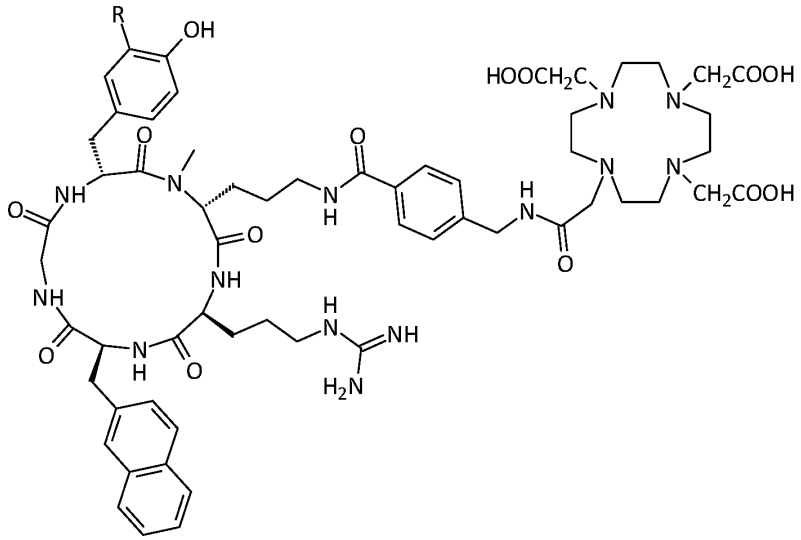
Results

The results demonstrate that radiochemical purity depends on the formulation of PentixaFor. In particular, it was shown that the amount of ascorbic acid as well as the amount of polysorbate 80 have an influence on the radiochemical purity (see Figures 1 and 2). The best results were obtained with 12 mg ascorbic acid and 0.01% polysorbate 80. Therefore, formulation sample 35 provided the optimal PentixaFor composition.

CLAIMS

1. A solid composition comprising

(i) 1 part by weight of a compound of formula (I) or a salt thereof:



wherein R is selected from hydrogen, C_{1-6} alkyl, fluorine, chlorine, bromine and iodine,

(ii) 40 to 400 parts by weight of ascorbic acid or a salt thereof, calculated as mass of ascorbic acid per mass of the compound of formula (I),

(iii) one or more mono-, di- or oligo-saccharides or salts thereof, and

(iv) one or more surfactants.

2. The solid composition according to claim 1, wherein the solid composition contains the ascorbic acid or salt thereof in an amount of 80 to 350 parts by weight, preferably 120 to 320 parts by weight, more preferably 150 to 300 parts by weight, even more preferably 180 to 280 parts by weight, still more preferably 220 to 260 parts by weight, still even more preferably 230 to 250 parts by weight, calculated as mass of ascorbic acid per mass of the compound of formula (I).

3. The solid composition according to claim 1 to 2, wherein the solid composition contains the one or more mono-, di- or oligo-saccharides or salts thereof in an amount of 600 to 1600 parts by weight, preferably 700 to 1400 parts by weight, more preferably 800 to 1200 parts by weight, more preferably 900 to 1100 parts by weight, more preferably

950 to 1050 parts by weight, calculated as mass of the mono-, di- or oligo-saccharides per mass of the compound of formula (I).

4. The solid composition according to any one of claims 1 to 3, wherein the one or more surfactants are selected from polyvinylpyrrolidone (PVP), and ethoxylated sorbitan fatty acid esters;

wherein the ethoxylated sorbitan fatty acid esters are preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having from 4 to 40 oxyethylene units; more preferably one or more selected from ethoxylated polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, each preferably having 15 to 25 oxyethylene units; even more preferably polyoxyethylene (20) sorbitan monooleate,

more preferably selected from polyvinylpyrrolidone (PVP), polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate and polyoxyethylene (20) sorbitan monooleate,

even more preferably selected from polyoxyethylene (20) sorbitan monolaurate or polyoxyethylene (20) sorbitan monooleate, and

still more preferably from polyoxyethylene (20) sorbitan monooleate.

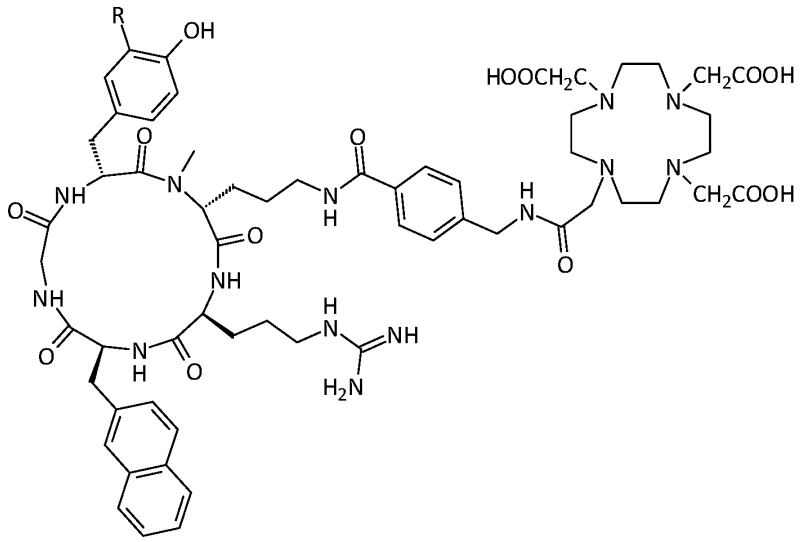
5. The solid composition according to claim 4, wherein the one or more surfactants is/are contained in an amount of 0.05 to 10 parts by weight, more preferably 0.1 to 8 parts by weight, more preferably 0.1 to 5 parts by weight, more preferably 0.1 to 2 parts by weight, more preferably 0.1 to 0.5 parts by weight, calculated as mass of surfactant(s) per mass of the compound of formula (I).

6. The solid composition according to any one of claims 1 to 5, wherein the one or more mono-, di- or oligo-saccharides are selected from non-reducing disaccharides, wherein the non-reducing disaccharides are preferably selected from sucrose and trehalose, more preferably trehalose, especially in the form of trehalose dihydrate.

7. The solid composition according to any one of claims 1 to 6, wherein R is H or I.

8. The solid composition according to any one of claims 1 to 6, comprising

(i) 1 part by weight of a compound of formula (I) or a salt thereof:



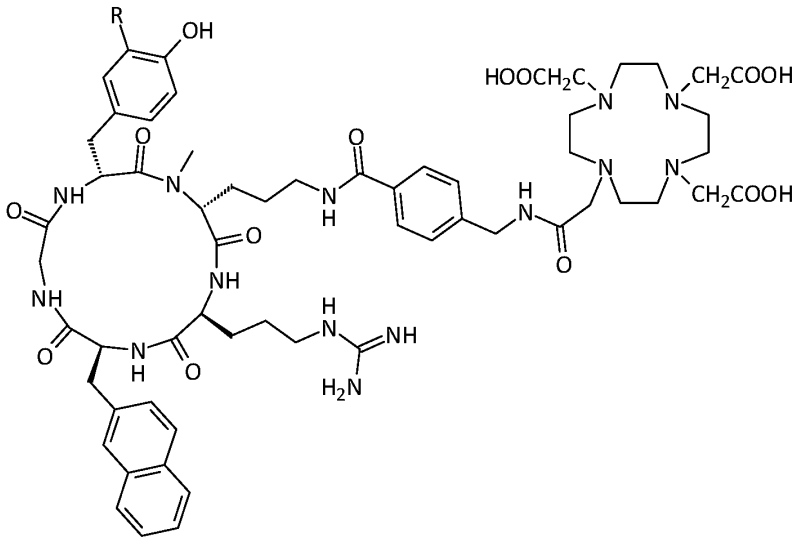
wherein R is selected from hydrogen and iodine,

(ii) about 240 parts by weight of ascorbic acid, calculated as mass of ascorbic acid per mass of the compound of formula (I),

(iii) about 1000 parts by weight of trehalose dihydrate, calculated as mass of trehalose dihydrate per mass of the compound of formula (I), and

(iv) about 0.2 parts by weight of polyoxyethylene (20) sorbitan monooleate, calculated as mass of polyoxyethylene (20) sorbitan monooleate per mass of the compound of formula (I).

9. A method for the preparation of a solid composition comprising (i) a compound of formula (I) or a salt thereof:



wherein R is selected from hydrogen, C_{1-6} alkyl, fluorine, chlorine, bromine and iodine; and ascorbic acid or a salt thereof,

said method comprising the steps of

(a) providing an aqueous solution which comprises

a compound of formula (I) or a salt thereof,

ascorbic acid or a salt thereof,

one or more mono-, di- or oligo-saccharides or salts thereof, and

one or more surfactants

(b) subjecting the solution to lyophilisation to obtain a solid composition.

10. The method according to claim 9 for the preparation of the solid composition according to any one of claims 1 to 8.

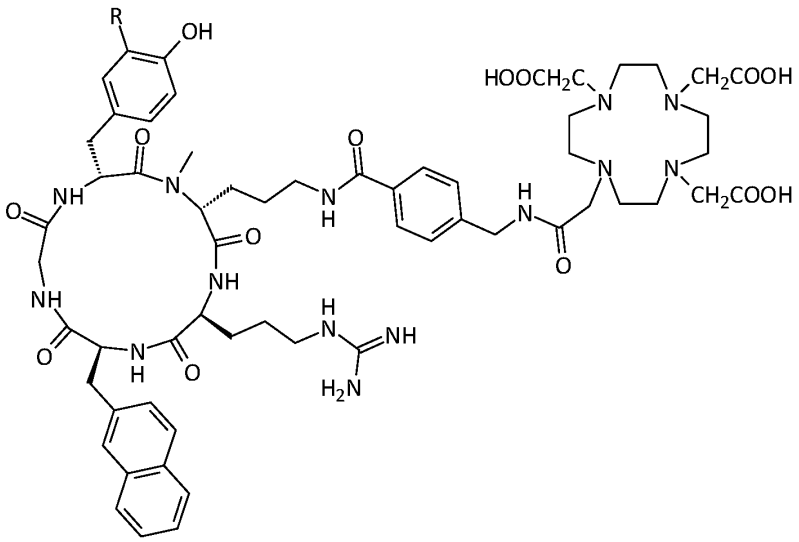
11. A kit of parts comprising

(a) a solid composition according to any one of claims 1 to 8; and

(b) a buffer solution.

12. A method for the manufacture of a radiopharmaceutical comprising a chelate formed by

(a) a compound of formula (I)



wherein R is selected from hydrogen, fluorine, chlorine, bromine and iodine; and

(b) a radionuclide;

wherein the method comprises step (i) of dissolving or dispersing the solid composition according to any one of claims 1 to 8 in a buffer solution and step (ii) of combining it with a radionuclide.

13. The method for the manufacture of a radiopharmaceutical according to claim 12, wherein step (ii) is conducted at a temperature of 50°C to 120°C, preferably 80°C to 110°C, more preferably 90 to 100°C, even more preferably 93 to 97°C, for a duration of 5 to 25 minutes, preferably 5 to 15 minutes, more preferably 5 to 10 minutes, even more preferably 7 to 9 minutes.

14. The method according to claim 12 or 13, wherein the radionuclide is one or more selected from ^{43}Sc, ^{44}Sc, ^{47}Sc, ^{51}Cr, ^{52}Fe, ^{52m}Mn, ^{62}Cu, ^{64}Cu, ^{66}Ga, ^{67}Ga, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{69}Yb, ^{72}As, ^{82}Rb, ^{86}Y, ^{88}Y, ^{89}Zr, ^{90}Y, ^{94m}Tc, ^{97}Ru, ^{99m}Tc, ^{103}Ru, ^{105}Rh, ^{109}Pd, ^{111}In, ^{117m}Sn, ^{121}Sn, ^{133m}In, ^{140}La, ^{141}Ce, ^{142}Pr, ^{143}Pr, ^{149}Pm, ^{151}Pm, ^{153}Sm, ^{157}Gd, ^{161}Tb, ^{165}Dy, ^{166}Ho, ^{166}Dy, ^{166}Ho, ^{167}Tm, ^{168}Yb, ^{169}Er, ^{172}Tm, ^{175}Yb, ^{177}Lu, ^{186}Re, ^{188}Re, ^{198}Au , ^{199}Au, ^{203}Pb, ^{211}Bi, ^{211}At, ^{212}Bi, ^{212}Pb, ^{213}Bi, ^{214}Bi, and ^{225}Ac, preferably ^{99m}Tc, ^{111}In, ^{90}Y, ^{177}Lu, ^{225}Ac, ^{68}Ga, ^{61}Cu and ^{64}Cu, more preferably ^{99m}Tc, ^{111}In, ^{68}Ga, ^{61}Cu and ^{64}Cu, and is even more preferably ^{68}Ga.

15. The solid composition according to any one of claims 1 to 8 or the kit of parts according to claim 11 for use in medicine, preferably for use in diagnostics or therapy.

16. The solid composition for use or kit of parts for use according to claim 15, wherein the solid composition or kit of parts is for use in the imaging or treatment of a disease associated with CXCR4-expression, preferably selected from a tumor, cardiovascular disorder, and/or inflammatory disease, wherein the tumor to be imaged or treated is preferably associated with primary aldosteronism or any one selected from hematological and solid cancers, including multiple myeloma, chronic lymphocytic leukemia, acute relapsed myeloid leukemia, non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, breast cancer, gastric/gastro-esophageal/pancreatic adenocarcinoma, colorectal cancer, colorectal cancer with hepatic metastasis, lung cancer, renal cell carcinomas, adrenal cancer, adrenal adenomas and glioblastoma, wherein the tumor to be imaged or treated is more preferably associated with any one selected from hematological and solid cancers, including multiple myeloma, chronic lymphocytic leukemia, acute relapsed myeloid leukemia, non-Hodgkin lymphoma, indolent non-Hodgkin lymphoma, breast cancer, gastric/gastro-esophageal/pancreatic adenocarcinoma, colorectal cancer, colorectal cancer with hepatic metastasis, lung cancer, renal cell carcinomas, adrenal cancer, adrenal adenomas and glioblastoma.