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(54) **STABLE, CONCENTRATED RADIONUCLIDE COMPLEX SOLUTIONS**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to radionuclide complex solutions of high concentration and of high chemical stability, that allows their use as drug product for diagnostic and/or therapeutic purposes. The stability of the drug product is achieved by at least one stabilizer against radiolytic degradation. The use of two stabilizers introduced during the manufacturing process at different stages was found to be of particular advantage.

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STABLE, CONCENTRATED RADIONUCLIDE COMPLEX SOLUTIONS

RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 16/140,962 filed Sep. 25, 2018, which is a continuation-in-part of U.S. application Ser. No. 16/045,484 filed Jul. 25, 2018 and claims priority to, and the benefit of International Application No. PCT/IB2018/055575 filed Jul. 25, 2018, the contents of each of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to radionuclide complex solutions of high concentration and of high chemical and radiochemical stability, that allows their use as commercial drug product for diagnostic and/or therapeutic purposes.

BACKGROUND OF THE INVENTION

The concept of targeted drug delivery is based on cell receptors which are overexpressed in the target cell in contrast to the not-to-be-targeted cells. If a drug has a binding site to those overexpressed cell receptors it allows the delivery of the drug after its systemic administration in high concentration to those target cells while leaving other cells, which are not of interested, unaffected. For example, if tumor cells are characterized by an overexpression of a specific cell receptor, a drug with binding affinity to said receptor will after intravenous infusion accumulate in high concentration in the tumor tissue while leaving the normal tissue unaffected.

This targeted drug delivery concept has also been used in radiomedicine to deliver radionuclides selectively to the target cells for diagnostic or therapeutic purposes.

For this radiomedicinal application the target cell receptor binding moiety is typically linked to a chelating agent which is able to form a strong complex with the metal ions of a radionuclide. This radiopharmaceutical drug is then delivered to the target cell and the decay of the radionuclide is then releasing high energy electrons, positrons or alpha particles as well as gamma rays at the target site.

One technical problem with those radiopharmaceutical drug products is that the decay of the radionuclide occurs constantly, e.g. also during the manufacturing and during storage of the drug product, and the released high energy emissions induce the cleavage of the chemical bonds of the molecules which form part of the drug product. This is often referred to as radiolysis or radiolytic degradation. The radiolytic degradation of the receptor binding moiety of the drug may lead to a decrease in its efficacy to act as a diagnostic and/or therapeutic.

The poor stability of those radiopharmaceutical drug products and their lack of any significant shelf-life required that those drugs have so far to be manufactured as an individual patient's dose unit in the laboratories at the hospital and administered immediately to the patient who had to be present at that hospital already awaiting the radiological treatment. To facilitate such drug preparation in the hospital laboratories, "cold" (i.e. non-radioactive) freeze-dried kits have been developed which comprise the cell receptor binding moiety linked to a chelating agent without the radionuclide. The freeze-dried content of those kit vials is then to be reconstituted with an solution of the

Radioanal Nucl Chem 2014, 299, 1389-1398; Das et al. *Current Radiopharmaceuticals* 2014, 7, 12-19; Luna-Gutierrez et al. *J Radioanal Nucl Chem* 2017, 314, 2181-2188). However, those kits are not "ready-to-use" as they require the reconstitution step and in addition further processing steps (e.g. applying heat for the complexation reaction) as well as purification and sterilization steps before the drug can be finally administered.

To reduce radiolysis of radiopharmaceutical drug products and thus improve stability, various strategies have been explored with more or less success: The drug product may be stored at low temperatures, or produced in high dilution, or stabilizers may be added.

Adding stabilizers however may be problematic as those chemicals may have a negative impact on the complexation of the radionuclide into the chelating agent or may have a limited solubility and precipitate from the solution. Ethanol has been reported as stabilizer against radiolysis (WO 2008/009444). While ethanol might not have a negative impact on the complexation or a solubility issue, higher amounts of ethanol in an infusion solution may be physiologically problematic and may have a negative impact on the tolerability of the drug product.

Producing the drug product in high dilution has the disadvantage that large volumes of infusion solutions need to be administered to patients. For the convenience of patients and for drug tolerability reasons it would be highly desirable to provide the radiopharmaceutical drug product in a high concentration. Those highly concentrated solutions however are in particular prone to radiolysis. Therefore, there are contradictory positions between, on the one hand, avoiding radiolysis by dilution of the drug product but, on the other hand, avoiding patient discomfort during treatment by providing a concentrated drug solution. In Mathur et al. *Cancer Biotherapy and Radiopharmaceuticals*, 2017, 32(7), 266-273 a product of high concentration has be reported and claimed being ready-to-use. However, that composition may be problematic with respect to tolerability as it contains high amounts of ethanol.

It remains therefore a challenge to design a ready-to-use radiopharmaceutical drug product which can be produced at commercial scale and delivered as a sufficiently stable and sterile solution in a high concentration which leads to a for patient convenient small infusion volume and which has a composition of high physiological tolerability (e.g. a composition which does not contain ethanol).

SUMMARY OF THE INVENTION

The present inventors have now found a way to design and produce a highly concentrated radionuclide complex solution which is chemically and radiochemically very stable even if stored at ambient or short term elevated temperatures so that it can be produced on commercial scale and supplied as ready-to-use radiopharmaceutical product.

The present invention is provided in various aspects as outlined in the following:

A pharmaceutical aqueous solution comprising

(a) a complex formed by

(ai) a radionuclide, and

(aii) a cell receptor binding organic moiety linked to a chelating agent; and

(b) at least one stabilizer against radiolytic degradation;

wherein

said radionuclide is present in a concentration that it provides a volumetric radioactivity of at least 100 MBq/mL

Said stabilizer(s), component (b), is (are) present in a total concentration of at least 0.2 mg/mL, preferably at least 0.5 mg/mL, more preferably at least 1.0 mg/mL, even more preferably at least 2.7 mg/mL.

A pharmaceutical aqueous solution, comprising

(a) a complex formed by

(ai) the radionuclide ^{177}Lutetium (Lu-177), present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) the chelating agent linked somatostatin receptor binding organic moiety DOTA-TATE (oxodotreotide) or DOTA-TOC (edotreotide);

(bi) gentisic acid or a salt thereof as the first stabilizer against radiolytic degradation present in a concentration of from 0.5 to 1 mg/mL;

(bii) ascorbic acid or a salt thereof as the second stabilizer against radiolytic degradation present in a concentration of from 2.0 to 5.0 mg/mL.

A process for manufacturing said pharmaceutical aqueous solution as defined above, comprising the process steps:

(1) Forming a complex of the radionuclide and the chelating agent linked cell receptor binding organic moiety by

(1.1) preparing an aqueous solution comprising the radionuclide;

(1.2) preparing an aqueous solution comprising the chelating agent linked cell receptor binding organic moiety, a first stabilizer, optionally a second stabilizer; and

(1.3) mixing the solutions obtained in steps (1.1) and (1.2) and heating the resulting mixture;

(2) Diluting the complex solution obtained by step (1) by

(2.1) preparing an aqueous dilution solution optionally comprising a second stabilizer; and

(2.2.) mixing the complex solution obtained by step (1) with the dilution solution obtained by the step (2.1).

The present invention provide the following advantages:

The high concentration allows administering a high dose within a short time frame. E.g. in the case of ^{177}Lu-DOTA-TATE, the high dose of 7.4 GBq can be provided in a small volume of 20.5 to 25.0 mL which allows the IV infusion administration to be completed within about 20 to 30 minutes.

The use of suitable stabilizer(s), according to the present invention as described, herein ensures high stability, at least 95%, 96%, 97%, 98%, 99% or 100% chemical stability with respect to the chemical purity for the cell receptor-binding molecule after 72 hours at 25° C., even if this molecule is a sensitive peptide molecule. E.g. for DOTA-TATE 100% chemical purity were found after 72 hours at 25° C. and even after 48 hours at 32° C. were found. Even under short term elevated temperature conditions (32° C. for 12 h and 25° for 60 h) such high stability was found with respect to chemical purity.

Further, the use of suitable stabilizer(s), according to the present invention as described, herein ensures high stability, at least 95% radiochemical stability with respect to the radiochemical purity radionuclide complex. E.g. for ^{177}Lu-DOTA-TATE at least 95% radiochemical purity were found after 72 hours at 25° C. Even under short term elevated temperature conditions (32° C. for 12 h and 25° for 60 h) such high stability was found with respect to radiochemical purity.

While sufficient stability may be achieved already with one single stabilizer, the use of two stabilizers has been found to be of particular suitability in stabilizing sensitive one stabilizer during complex formation and another stabilizer added after the complex formation is of advantage as it ensures that already during the complexation reaction, the cell receptor-binding molecule is protected against radiolysis and the other stabilizer enhances the protecting effect for the shelf-life period. Further, by this sequential application of the two stabilizers it is ensured, that during complexation only a relatively small amount of stabilizer is present (which minimizes the potential interference of that stabilizer with the complexation reaction) and after complexation a large amount of a stabilizer combination is present (which strengthens the protective power of the stabilizers for the following drug product storage time period).

This sequential application of two stabilizers also reduces the overall thermal stress of those stabilizers as one of them is not present when the complexation reaction, which involves high temperatures, takes place.

Further, particularly the use of two different stabilizers is advantageous as this combination is more efficacious in reacting to the various different radicals possibly formed by the radiolysis of the cell receptor binding molecule than only one single stabilizer can do.

The composition of the radiopharmaceutical solution does not require the presence of ethanol. The solution is sufficiently stable without ethanol. The absence of ethanol is of advantage with respect to the physiological tolerability of the solution.

A shelf-life of at least 3 days is required to allow a radiopharmaceutical drug product to be manufactured from a centralized pharmaceutical production site and to commercialize it as a ready-to-use drug product.

Therefore, due to the high stability (72 h at 25° C.) the present invention allows centralized pharmaceutical production at highest quality standards (e.g. cGMP) and at industrial scale, e.g. at 74 GBq or 148 GBq batch size which provides the drug product in numerous dose units, e.g. enough dose units for the treatment of 10 to 20 patients at the same time.

Further, due to the high stability, there is sufficient time for the present invention to be shipped from a centralized pharmaceutical production site to remote clinical centers.

Even further, due to the high stability, the present invention can be provided as a ready-to-use infusion solution which can be immediately administered to the patient without a need for the clinical staff to perform any preparatory work before administration.

The present invention of particular suitability for the somatotatin receptor binding peptides, here in particular for the very sensitive somatostatin analogues octreotide and octreotate which are in particular prone to degradation reactions. Further, the present invention of particular suitability for the radionuclide Lutetium-177 with its specific radioactivity characteristics.

DETAILED DESCRIPTION OF THE INVENTION

Herein after, the present invention is described in further detail and is exemplified.

In general, the present invention is concerned about a pharmaceutical aqueous solution, in particular a radiopharmaceutical aqueous solution. The solution is for intravenous (IV) use/application/administration. The solution is stable, concentrated, and ready-to-use.

The stability of the solution ascertained by the use of

In general, the stabilizers used in accordance with the present inventions may be selected from gentisic acid (2,5-dihydroxybenzoic acid) or salts thereof, ascorbic acid (L-ascorbic acid, vitamin C) or salts thereof (e.g. sodium ascorbate), methionine, histidine, melatonine, ethanol, and Se-methionine. Preferred stabilizers are selected from gentisic acid or salts thereof and ascorbic acid or salts thereof.

Ethanol is considered as less preferred stabilizer due to tolerability issues associated with it if present in higher concentrations. Ethanol should be ideally avoided in the solutions of the present invention (in other words: free of ethanol), at least the amount of ethanol in the solutions of the present invention should be limited, e.g. less than 5%, preferably less than 2%, more preferably less than 1% in the final solution which is foreseen to be injected/infused. Even more preferably, the solution is free of ethanol.

In accordance with the present invention the following embodiments are provided:

1. A pharmaceutical aqueous solution comprising
   (a) a complex formed by
      (ai) a radionuclide, and
      (aii) a cell receptor binding organic moiety linked to a chelating agent; and
   (b) at least one stabilizer against radiolytic degradation;
   wherein
   said radionuclide is present in a concentration that it provides a volumetric radioactivity of at least 100 MBq/mL, preferably of at least 250 MBq/mL.
2. The pharmaceutical aqueous solution according to embodiment 1 ,
   wherein said stabilizer(s), component (b), is (are) present in a total concentration of at least 0.2 mg/mL, preferably at least 0.5 mg/mL, more preferably at least 1.0 mg/mL, even more preferably at least 2.7 mg/mL.
3. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein said radionuclide is present in a concentration that it provides a volumetric radioactivity of from 100 to 1000 MBq/mL, preferably from 250 to 500 MBq/m L.
4. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein said stabilizer(s) is (are) present in a total concentration of from 0.2 to 20.0 mg/mL, preferably from 0.5 to 10.0 mg/mL, more preferably from 1.0 to 5.0 mg/mL, even more preferably from 2.7 to 4.1 mg/mL.
5. The pharmaceutical aqueous solution according to any one of the preceding embodiments,
   wherein the component (b) is only one stabilizers against radiolytic degradation, i.e. only a first stabilizer.
6. The pharmaceutical aqueous solution according to any one of the preceding embodiments,
   wherein the component (b) are at least two stabilizers against radiolytic degradation, i.e. at least a first and a second stabilizer, preferably only two stabilizers, i.e. only a first and a second stabilizer.
7. The pharmaceutical aqueous solution according to any one of the embodiments 5 to 6, wherein the first stabilizer is present in a concentration of from 0.2 to 5 mg/mL, preferably from 0.5 to 5 mg/mL, more preferably from 0.5 to 2 mg/mL, even more preferably from 0.5 to 1 mg/mL, even more preferably from 0.5 to 0.7 mg/mL.
8. The pharmaceutical aqueous solution according to embodiment 6 or 7, wherein the second stabilizer is present in a concentration of from 0.5 to 10 mg/mL, more preferably from 1.0 to 8.0 mg/mL, even more preferably from 2.0 to 5.0 mg/mL, even more preferably from 2.2 to
9. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the stabilizer(s) is (are) selected from gentisic acid (2,5-dihydroxybenzoic acid) or salts thereof, ascorbic acid (L-ascorbic acid, vitamin C) or salts thereof (e.g. sodium ascoorbate), methionine, histidine, melatonine, ethanol, and Se-methionine, preferably selected from gentisic acid or salts thereof and ascorbic acid or salts thereof.
10. The pharmaceutical aqueous solution according to any one of the embodiments 5 to 9, wherein the first stabilizer is selected from gentisic acid and ascorbic acid, preferably the first stabilizer is gentisic acid.
11. The pharmaceutical aqueous solution according to any one of the embodiments 6 to 10, wherein the second stabilizer is selected from gentisic acid and ascorbic acid, preferably the second stabilizer is ascorbic acid.
12. The pharmaceutical aqueous solution according to any one of the embodiments 6 to 8, wherein the first stabilizer is gentisic acid or a salt thereof and the second stabilizer is ascorbic acid or a salt thereof, and the ratio of the concentration (in mg/mL) of the first stabilizer to the concentration (in mg/mL) of the second stabilizer is from 1:3 to 1:7, preferably from 1:4 to 1:5.
13. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the radionuclide is selected from ^{177}Lu, ^{68}Ga, ^{18}F, ^{99m}Tc, ^{211}At, ^{82}Rb, ^{166}Ho, ^{225}Ac, ^{111}In, ^{123}I, ^{131}I, ^{89}Zr, ^{90}Y, preferably selected from ^{177}Lu and ^{68}Ga, more preferably is ^{177}Lu.
14. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the cell receptor binding moiety is a somatostatin receptor binding peptide, preferably said somatostatin receptor binding peptide is selected from octreotide, octreotate, lanreotide, vapreotide and pasireotide, preferably selected from octreotide and octreotate.
15. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the chelating agent is selected from DOTA, DTPA, NTA, EDTA, DO3A, NOC and NOTA, preferably is DOTA.
16. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the cell receptor binding moiety and the chelating agent form together molecules selected from DOTA-OC, DOTA-TOC (edotreotide), DOTA-NOC, DOTA-TATE (oxodotreotide), DOTA-LAN, and DOTA-VAP, preferably selected from DOTA-TOC and DOTA-TATE, more preferably is DOTA-TATE.
17. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the radionuclide, the cell receptor binding moiety and the chelating agent form together the complex ^{177}Lu-DOTA-TOC (^{177}Lu-edotreotide) or ^{177}Lu-DOTA-TATE (^{177}Lu-oxodotreotide), preferably ^{177}Lu-DOTA-TATE.
18. The pharmaceutical aqueous solution according to any one of the preceding embodiments, further comprising a buffer, preferably said buffer is an acetate buffer, preferably in an amount to result in a concentration of from 0.3 to 0.7 mg/mL (preferably about 0.48 mg/mL) acetic acid and from 0.4 to 0.9 mg/mL (preferably about 0.66 mg/mL) sodium acetate.
19. The pharmaceutical aqueous solution according to any one of the preceding embodiments, further comprising a sequestering agent, preferably said sequestering agent is diethylentriaminepentaacetic acid (DTPA) or a salt thereof, preferably in an amount to result in a concentration of from 0.01 to 0.10 mg/mL (preferably about 0.05

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