METHOD FOR PREPARING AN [18F] RADIOLABELLED COMPOUND WITH LOW WATER CONTENT DURING LABELLING STEP

Field of the Invention

The present invention generally relates to a method of preparing a radio-labelled compound. It has been found that water content and origin of the water within the reaction process have a significant effect on both the yield and the purity of the product of the radio-labelling process.

Background

Radiopharmaceuticals are compounds labelled with a radioactive element, suitable for *in vivo* mammalian administration, for use in the field of medical imaging, diagnosis or therapy. Radiopharmaceutical compositions comprise a radio-labelled compound or a pharmaceutically acceptable salt thereof, solvent, and one or more stabilizers.

Fluorine-^{18} ([^{18}F]) is a radioactive fluorine isotope commonly used in radiopharmaceuticals suitable for use in diagnosis. Fluorine-^{18} decay occurs by positron emission (97%) and electron capture (3%). As the radioisotope [^{18}F] decays, the positrons emitted are utilised in positron emission tomography (PET) imaging. This *in vivo* imaging method is used, *inter alia*, in cardiac imaging, tumour imaging and brain imaging.

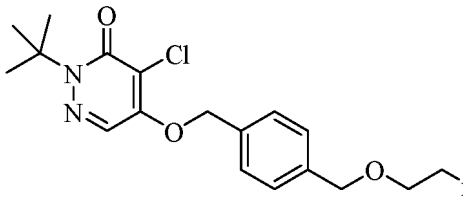
Automated synthesis systems are important for the production of radiopharmaceuticals. Synthesis modules of the prior art are described in WO 2007/042781 and WO 2011/097649. Synthesis modules, such as the FASTlab® (GE Healthcare) provide for production of doses of radiopharmaceuticals for clinical applications. The FASTlab synthesis module accepts and operates a method through a device for producing a radiopharmaceutical.

In processes preparing radiolabelled compounds, radiochemical impurities and unreacted [^{18}F]fluoride are undesirable by-products. It would be advantageous to minimise these by-products.

Summary

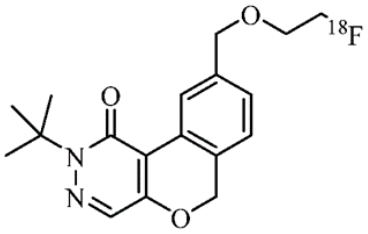
In one aspect, the present disclosure refers to a composition comprising:

(i) [^{18}F]Flurpiridaz, or a pharmaceutically acceptable salt thereof



; and

(ii) a compound (B) having a structure of:



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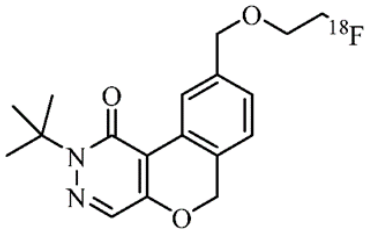
In another aspect, the present disclosure refers to a method of preparing an [^{18}F]radiolabelled compound, wherein the method comprises

(a) an initial drying step comprising evaporating water and acetonitrile from a solution comprising [^{18}F]fluoride;

(b) a further drying step (fluoride activation step) comprising azeotropic distillation of water from said solution comprising [^{18}F]fluoride with acetonitrile; and

(c) labelling a precursor compound with [^{18}F]fluoride from the solution comprising [^{18}F]fluoride yielded from step (b) to obtain a composition comprising an [^{18}F]radiolabelled compound and a compound (B) having a structure of:



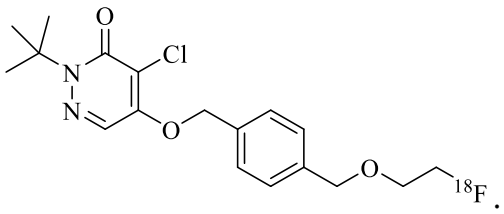
;

wherein the water content during labelling step (c) that originates from the solution comprising [^{18}F]fluoride after drying step (b) is less than 500 ppm; and

wherein the water content during labelling step (c) that originates from the precursor compound is no more than 2000 ppm; and

wherein the [^{18}F]radiolabelled compound is a [^{18}F]fluorine-labelled radiopharmaceutical, or a pharmaceutically acceptable salt thereof; and

wherein the [^{18}F]fluorine-labelled radiopharmaceutical is [^{18}F]flurpiridaz, or a pharmaceutically acceptable salt thereof



The present disclosure relates to an improved method for preparing an [^{18}F]fluoride radiolabelled compound.

An example of the disclosure relates to a method of preparing an [^{18}F]radiolabelled compound, wherein the method comprises

(a) an initial drying step comprising evaporating water and acetonitrile from a solution comprising [^{18}F]fluoride;

(b) a further drying step (fluoride activation drying step), comprising azeotropic distillation of water from said solution comprising [^{18}F]fluoride with acetonitrile; and

(c) labelling a precursor compound with [^{18}F]fluoride from the solution comprising [^{18}F]fluoride yielded from step (b) to obtain an [^{18}F]radiolabelled compound;

wherein the water content during labelling step (c) that originates from the solution comprising [^{18}F] after drying step (b) is less than 500 ppm; and

wherein the water content during labelling step (c) that originates from the precursor compound is no more than 2000 ppm.

Preferably at least two cycles of the azeotropic distillation with acetonitrile are carried out. More preferably, three cycles of azeotropic distillation with acetonitrile are carried out.

In an example of the disclosure, the water content during the labelling step that originates from the solution comprising [^{18}F] after drying step (b) is less than 400 ppm. Preferably, the water content during the labelling step that originates from the solution comprising [^{18}F] after drying step (b) is less than 350 ppm. In an example of the disclosure, the water content during the labelling step that originates from the precursor compound is no more than 1500 ppm. Preferably, the water content during the labelling step that originates from the precursor compound is between 500 ppm and 1000 ppm. In an example of the disclosure, the total water content during the labelling step is less than 2500 ppm, for example, less than 1000 ppm.

In another example of the disclosure, the radioactivity of [^{18}F] prior to step (a) (at the start of synthesis) is up to around 500 GBq, for example up to around 450 GBq, up to around 400 GBq, up to around 350 GBq, up to around 300 GBq, or for example between 50 GBq and 250 GBq. By using the process of the disclosure, a high yield of the fluorinated product and a low amount of radiochemical impurity are obtained, even when the radioactivity of [^{18}F]fluoride at the start of synthesis in the process of the disclosure (the starting activity) is greater than 100 GBq. The ability to use a higher starting activity and

still achieve a high yield and low amount of radiochemical impurity enables a greater number of product doses to be prepared in a single batch.

In another example of the disclosure, the radiolabelled compound is a [^{18}F]fluoride-labelled radiopharmaceutical, or a pharmaceutically acceptable salt thereof.

Figures

Figure 1 is a flow chart of the current process steps for preparing a radiolabelled product.

Figure 2 is a flow chart of the process of the invention for preparing a radiolabelled product.

Detailed Description of the Invention

The term 'radiopharmaceutical' has its conventional meaning and refers to a radioactive compound suitable for *in vivo* mammalian administration for use in diagnosis or therapy. A radiopharmaceutical as referenced herein may be a Positron Emission Tomography (PET) tracer.

Before a radiopharmaceutical composition, or 'drug product' can be administered to a patient, it must undergo a thorough quality control (QC) process, to ensure that it complies with requirements, such as purity.

Radiochemical purity (RCP) is determined using radio TLC or HPLC and can be defined as the ratio of the (radio-labelled) drug substance peak to the total (radio-labelled) peaks in the chromatogram. If one manufactures a radiopharmaceutical with high radioactive concentration (RAC), the drop in RCP during storage is likely to be higher than at lower RAC due to increased radiolysis. High radioactive concentration results in the drug substance destroying itself (i.e. radiolysis).

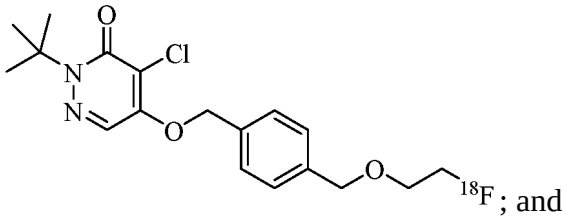
The term 'comprising' has its conventional meaning throughout this application and implies that the method, system, product or the like must have the components listed, but that other, unspecified components may be present in addition.

A radio-labelled compound may comprise various radio-isotopes. For example, the radio-labelled compound may be a ^{18}F-labelled radiopharmaceutical, or a pharmaceutically acceptable salt thereof. The radio-labelled compound may be: an ^{18}F-labelled radiopharmaceutical, or a pharmaceutically acceptable salt thereof.

CLAIMS

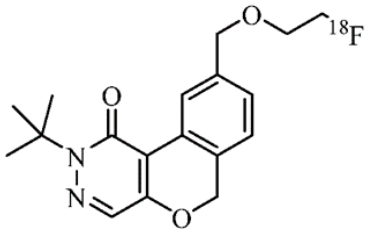
1. A composition comprising:

(i) [^{18}F]Flurpiridaz, or a pharmaceutically acceptable salt thereof



; and

(ii) a compound (B) having a structure of:



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2. The composition of claim 1, wherein the composition comprises less than about 3.5% of the compound (B).

3. The composition of claim 1 or claim 2, wherein the composition comprises:

(i) at least about 97% of [^{18}F]Flurpiridaz, or a pharmaceutically acceptable salt thereof, and

(ii) at least about 0.7% of the compound (B).

4. The composition of any preceding claim, wherein the composition comprises between about 96% and about 99% of [^{18}F]Flurpiridaz, or a pharmaceutically acceptable salt thereof.

5. The composition of any preceding claim, wherein the composition comprises:

(i) less than about 3% of the compound (B); or

(ii) less than about 2.5% of the compound (B); or

(iii) less than about 2% of the compound (B); or

(iv) less than about 1.5% of the compound (B).

6. The composition of any of claims 1 to 4, wherein the composition comprises:

(i) from about 1.5% to about 3.5% of the compound (B); and/or

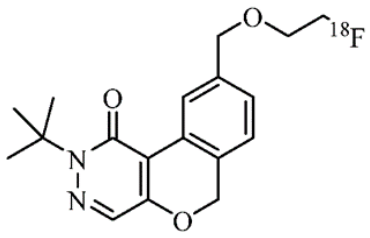
(ii) at least about 97% of [^{18}F]Flurpiridaz, or a pharmaceutically acceptable salt thereof and less than about 2% of the compound (B).

7. A method of preparing an [^{18}F]radiolabelled compound, wherein the method comprises

(a) an initial drying step comprising evaporating water and acetonitrile from a solution comprising [^{18}F]fluoride;

(b) a further drying step (fluoride activation step) comprising azeotropic distillation of water from said solution comprising [^{18}F]fluoride with acetonitrile; and

(c) labelling a precursor compound with [^{18}F]fluoride from the solution comprising [^{18}F]fluoride yielded from step (b) to obtain a composition comprising an [^{18}F]radiolabelled compound and a compound (B) having a structure of:



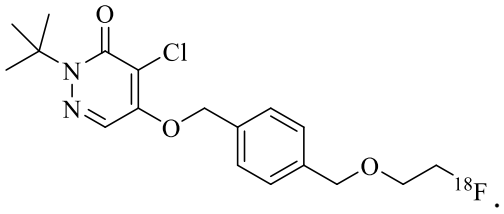
;

wherein the water content during labelling step (c) that originates from the solution comprising [^{18}F]fluoride after drying step (b) is less than 500 ppm; and

wherein the water content during labelling step (c) that originates from the precursor compound is no more than 2000 ppm; and

wherein the [^{18}F]radiolabelled compound is a [^{18}F]fluorine-labelled radiopharmaceutical, or a pharmaceutically acceptable salt thereof; and

wherein the [^{18}F]fluorine-labelled radiopharmaceutical is [^{18}F]flurpiridaz, or a pharmaceutically acceptable salt thereof



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8. The method according to claim 7, wherein at least two cycles of the azeotropic distillation with acetonitrile are carried out.

9. The method according to claim 7 or claim 8, wherein three cycles of azeotropic distillation with acetonitrile are carried out.

10. The method according to any one of claims 7 to 9, wherein the water content during the labelling step that originates from the solution comprising [^{18}F] after drying step (b) (the fluoride activation step) is less than 400 ppm.

11. The method according to any one of claims 7 to 10, wherein the water content during the labelling step that originates from the solution comprising [^{18}F] after drying step (b) (the fluoride activation step) is less than 350 ppm.

12. The method according to any one of claims 7 to 11, wherein the water content during the labelling step that originates from the precursor compound is no more than 1500 ppm.

13. The method according to any one of claims 7 to 12, wherein the water content during the labelling step that originates from the precursor compound is between 500 ppm and 1000 ppm.

14. The method according to any one of claims 7 to 13, wherein the total water content during the labelling step is less than 2500 ppm.

15. The method according to any one of claims 7 to 14, wherein the total water content during the labelling step is less than 1000 ppm.

16. The method according to any one of claims 7 to 15, wherein the solution comprising [^{18}F]fluoride is the eluent from an ion exchange resin, for example, an anion solid phase extraction cartridge.

17. The method according to any one of claims 7 to 16, wherein the [^{18}F]radiolabelled compound obtained in step (c) subsequently undergoes purification steps.

18. The method according to any one of claims 7 to 17, wherein the starting activity is:
(i) greater than 100 GBq; or

(ii) 200 to 350 GBq; or

(iii) greater than 300 GBq.

19. The method according to any one of claims 7 to 18, wherein the amount of the compound (B) is less than 3.5%.

20. The method according to any one of claims 6 to 19, wherein the method is carried out carried out on an automated synthesis system.