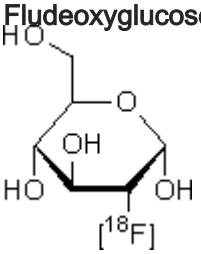
Fludeoxyglucose (^{18}F) injection (Fludeoxyglucosi (^{18}F) injectio)



$C_6H_{11}{}^{18}FO_5$

Chemical names. 2-deoxy-2-[^{18}F]fluoro-α-D-glucopyranose; 2-deoxy-2[^{18}F]fluoro-D-glucose.

Other name. ^{18}F-FDG injection.

Description. Fludeoxyglucose (^{18}F) injection is a colourless or slightly yellow solution.

Fluorine-18 has a half-life of 109.8 minutes.

Category. Diagnostic.

Additional information. Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in millilitres.

Labelling. State the synthesis pathway (nucleophilic or electrophilic) to prepare 2-[^{18}F]fluoro-2-deoxy-D-glucose.

Requirements

Complies with the monograph for "Parenteral Preparations" and with that for "Radiopharmaceuticals".

Definition. Fludeoxyglucose (^{18}F) injection is a sterile solution of fluorine-18 in the form of 2-deoxy-2-[^{18}F]fluoro-α-D-glucopyranose, suitable for intravenous administration and that contains sufficient sodium chloride to make the solution isotonic with blood. It contains not less than 90% and not more than 110% of the content of fluorine-18 stated on the label at the reference date and time stated on the label. Not less than 99% of the total radioactivity is due to fluorine-18. Not less than 95% of the total fluorine-18 radioactivity is present as 2-deoxy-2[^{18}F]fluoro-D-glucose and 2-deoxy-2[^{18}F]fluoro-D-mannose with the latter not exceeding 10% of the total. The content of 2-deoxy-2-fluoro-D-glucose is not more than 10 mg per V.

Manufacture

Radionuclide production. Fluorine-18 may be prepared by proton irradiation of oxygen-18, deuteron irradiation of neon-20 or alpha irradiation of oxygen-16 and processed in a manner that fluorine-18 obtained is carrier free.

Radiochemical synthesis. 2-deoxy-2[^{18}F]fluoro-D-glucose may be synthesized by a nucleophilic or electrophilic pathway, which lead to different products in terms of specific radioactivity, by-products and possible impurities.

STARTING MATERIAL

Precursors for organic synthesis

- *1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose*. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the *reference spectrum* of 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose.
Melting range. 119-122°C.

- *3,4,6-Tri-O-acetyl-D-glucal*. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the *reference spectrum* of 3,4,6-tri-*O*-acetyl-D-glucal.
Melting range. 53-55°C.

A. Nucleophilic pathway

This is the most widely used method by a phase transfer catalysed nucleophilic substitution of 1,3,4,6-tetra-*O*-trifluoromethanesulfonyl-β-D-mannopyranose with [^{18}F]fluoride. Generally [^{18}F]fluoride is absorbed on an anion-exchange resin and eluted with a solution of potassium carbonate which is then evaporated to dryness. Addition of a phase transfer catalyst such as an aminopolyether in dry acetonitrile may be used to enhance the nucleophilicity of the [^{18}F]fluoride. Hydrolysis using hydrochloric acid may lead to the formation of 2-chloro-2-deoxy-D-glucose. Hydrolysis under alkaline conditions may lead to the formation of 2-deoxy-2[^{18}F]fluoro-D-mannose as a by-product. Variations of the method substitute the aminopolyether by a tetra-alkyl ammonium salt, or use solid phase catalysed nucleophilic substitution on derivatized anion-exchange resin, e.g. derivatized with 4-(4-methylpiperidin-1-yl)pyridine.

B. Electrophilic pathway

This method for production of 2-deoxy-2[^{18}F]fluoro-D-glucose proceed by the reaction of molecular fluorine-18 or [^{18}F]acetylhypofluorite with 3,4,6-tri-*O*-acetyl-D-glucal. [^{18}F]Acetylhypofluorite is obtained by conversion of molecular fluorine-18 on a solid complex of acetic acid and potassium acetate. The production of molecular fluorine-18 requires the addition of small amounts of fluorine to the neon target gas, usually from 0.1 per cent to 1 per cent, resulting in the reduction of the specific radioactivity of the end-product. Hydrolysis of the *O*-acetyl protected [^{18}F]fluorinated sugar yields 2-deoxy-2[^{18}F]fluoro-D-glucose and usually small amounts of 2-deoxy-2[^{18}F]fluoro-D-mannose.

The preparation can be purified by serial chromatography on combinations of ion-retardation resin, ion-exchange resin, alumina and octadecyl derivatised silica gel. Removal of the phase transfer catalyst can be achieved by different methods, all using combinations of separation cartridges.

Aminopolyether. This test is performed only on the bulk solution before addition of sodium chloride by the producer and it is not intended for the final preparation to be injected. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel for chromatography R as the coating substance and a mixture of 1 volume of ammonia R and 9 volumes of methanol R as the mobile phase.

Apply separately to the plate 2 µl of the following 2 solutions. For solution (A) use the injection to be examined. For solution (B) dissolve 0.110 g of aminopolyether R in water R and dilute to 10.0 mL with the same solvent. Dilute 0.2 mL of this solution to V with the same solvent. Develop the plate for a distance of about 8 cm. After removing the plate from the chromatographic chamber, allow it to dry in air for 15 minutes. Expose the plate to iodine vapour for at least 10 minutes. Examine the chromatogram in daylight.

Any spot due to aminopolyether in the chromatogram obtained with solution A is not more intense than the corresponding spot obtained with solution B (2.2 mg per V).

Tetra-alkyl ammonium salts. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (12.5 cm x 4.0 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). As the mobile phase, use a mixture of 25 volumes of a 0.95 g/l solution of toluenesulfonic acid R and 75 volumes of acetonitrile R.

For solution (A) usethe injection to be examined. For solution (B) dilute 2.1 mL of tetrabutylammonium hydroxide (0.1 mol/l) VS to 20 mL with water R. Dilute 1 mL of this solution to V with the same solvent. Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm. Inject separately 10 µl each of solutions A and B.

In the chromatogram obtained with solution A, the area of the peak corresponding to tetrabutylammonium ions is not greater than that of the corresponding peak obtained with solution B (2.75 mg per V).

Solid phase derivatisation agent 4-(4-methylpiperidin-1-yl)pyridine. Measure the absorbance of the following solutions at the maximum of 263 nm. For solution (A), use the preparation to be examined. For solution (B) dissolve 20 mg of 4-(4-methylpiperidin-1-yl)pyridine R in water R and dilute to 100.0 mL with the same solvent. Dilute 0.1 mL of this solution to V with the same solvent.

The absorbance obtained from solution A is not greater than the absorbance obtained from solution B (0.02 mg per V).

Production of radiopharmaceutical preparation. Fludeoxyglucose (^{18}F) injection may contain antimicrobial preservatives and/or stabilizing agents. The injection may be sterilized by "Heating in an autoclave" (see 5.8 Methods of sterilization).

Identity tests

• Either tests A and C or tests B and C may be applied.

A. Record the gamma-ray spectrum using a suitable instrument with a sample of fluorine-18, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of fluorine-18 in that it exhibits a major peak of 511 keV, maximum of 633 keV. A sum peak of 1020 keV may also be seen depending on geometry and detector efficiency.
Standardized fluorine-18 solutions are available from laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 105 and 115 minutes.

C. Examine the radiochromatogram obtained in the test for radiochemical purity. The distribution of the radioactivity contributes to the identification of the preparation.

pH value. Carry out the test as described in the monograph for “Radiopharmaceuticals”. pH of the injection, 4.5 to 8.5.

Sterility. The injection complies with the test described under 3.2 Test for sterility, modified as described in the monograph for "Radiopharmaceuticals". Test for sterility will be initiated on the day of manufacture. The injection may be released for use before completion of the test.

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins, modified as described in the monograph for "Radiopharmaceuticals". The injection contains not more than 175/V I.U. of endotoxins per millilitre. The injection may be released for use before completion of the test.

Radionuclidic purity. Record the gamma-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of fluorine-18 and radionuclidic impurities that may be present. Not less than 99% of the total radioactivity is due to fluorine-18.

Radiochemical purity. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel for chromatography R as the coating substance and a mixture of 95 volumes of acetonitrile R and 5 volumes of water R as the mobile phase. Apply to the plate about 5 µl of the injection, suitably diluted with water R to give an optimum count rate. Allow the plate to dry in air and determine the radioactivity distribution by a suitable method. In this system, fludeoxyglucose has an Rf value of about 0.4. Not less than 90% of the total radioactivity is in the spot corresponding to fludeoxyglucose.

Chemical purity

Toxic substances or by products including aminopolyether, tetra-alkyl ammonium salts and 2-chloro-3-deoxy-D-glucose are to be controlled at appropriate limits.

2-deoxy-2-fluoro-D-glucose and 2-chloro-2-deoxy-D-glucose. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25 cm x 4.0 mm) packed with strongly basic anion-exchange resin for chromatography R (10 µm). As the mobile phase, use carbonate-free sodium hydroxide (0.1 mol/l) VS.

Operate with a flow rate of 1 mL per minute. As a detector, use suitable detectors for radioactivity and for carbohydrates in the required concentration range.

A. If the product is prepared by nucleophilic pathway, prepare the following solutions.

For solutions (1), (2) and (3) use the solutions described under A for electrophilic pathway. For solution (4) dissolve 1.0 mg of 2-chloro-2-deoxy-D-glucose R in water R and dilute to 2 mL with the same solvent then dilute 1 mL of this solution to V with the same solvent. For solution (5) dissolve 1.0 mg of 2-deoxy-2-fluoro-D-mannose R in water R and dilute to 2 mL with the same solvent. Mix 0.5 mL of this solution with 0.5 mL of solution (3).

Inject alternately 10 µl of solutions (1), (2), (3), (4) and (5).

In the chromatogram obtained with the detector for carbohydrates and solution (1) the principal peak corresponds to the principal peak in the chromatogram obtained with solution (2) (D-glucose). The peaks, if present, are eluted at the following retention times with reference to 2-deoxy-2-fluoro-D-glucose (retention time 12 minutes): 2-deoxy-2-fluoro-D-mannose about 0.9; 2-chloro-2-deoxy-D-glucose about 1.1.

In the chromatogram obtained with the detector for carbohydrates and solution (5), the test is not valid unless the resolution between the peaks due to 2-deoxy-2-fluoro-D-mannose and 2-deoxy-2-fluoro-D-glucose is at least 1.5 and the peak due to 2-deoxy-2-fluoro-D-glucose is detected with a signal-to-noise ratio of at least 10.

In the chromatogram obtained with solution (1):
- the area of the peak corresponding to 2-deoxy-2-fluoro-D-glucose is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (10 mg per V);
- the area of any peak corresponding to 2-chloro-2-deoxy-D-glucose is not greater than the area of the corresponding peak in the chromatogram obtained with solution (4) (0.5 mg per V).

B. If the product is prepared by electrophilic pathway, prepare the following solutions.

For solution (1) use the injection to be examined. For solution (2) dissolve 10 mg of glucose R in water R and dilute to 100 mL with the same solvent. For solution (3) dissolve 10 mg of 2-deoxy-2-fluoro-D-glucose R in water R and dilute to V with the same solvent.

Inject alternately 10 µl of solutions (1), (2) and (3).

In the chromatogram obtained with the detector for carbohydrates and solution (1) the principal peak corresponds to the principal peak in the chromatogram obtained with solution (3) (2-deoxy-2-

fluoro-D-glucose).

In the chromatogram obtained with solution (1), the area of the peak corresponding to 2-deoxy-2-fluoro-D-glucose is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (10 mg per V).

Radioactivity. Measure the radioactivity as described under R.1.1 Detection and measurement of radioactivity in a suitable calibrated counting equipment by comparison with a standardized fluorine-18 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized fluorine-18 solutions are available from laboratories recognized by the relevant national or regional authority.