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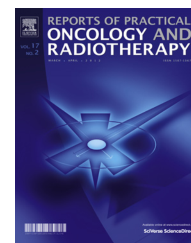

Original research article

Synthesis, quality control and determination of metallic impurities in ^{18}F-fludeoxyglucose production process

Krzysztof Kilian[b,*], *Bartłomiej Chabecki*[a], *Justyna Kiec*[a], *Agnieszka Kunka*[a], *Barbara Panas*[a], *Maciej Wójcik*[a], *Anna Pękal*[b]

[a] *University of Warsaw, Department of Physics, Hoża 69, 00-681 Warsaw, Poland*
[b] *University of Warsaw, Heavy Ion Laboratory, Pasteur 5a, 02-093 Warsaw, Poland*

ARTICLE INFO

Article history:
Received 16 September 2013
Received in revised form
15 February 2014
Accepted 11 March 2014

Keywords:
^{18}FDG
Radionuclidic impurities
Radiopharmaceuticals
Gamma-spectrometry

ABSTRACT

Aim: The aim of this study was to synthesize ^{18}FDG in some consecutive runs and check the quality of manufactured radiopharmaceuticals and to determine the distribution of metallic impurities in the synthesis process.
Background: For radiopharmaceuticals the general requirements are listed in European Pharmacopeia and these parameters have to be checked before application for human use.
Materials and methods: Standard methods for the determination of basic characteristics of radiopharmaceuticals were used. Additionally, high resolution γ spectrometry was used for the assessment of nuclidic purity and inductively coupled plasma with mass spectrometry to evaluate metallic content.
Results: Results showed sources and distribution of metallic and radiometallic impurities in the production process. Main part is trapped in the initial separation column of the synthesis unit and is not distributed to the final product in significant amounts.
Conclusions: Produced ^{18}FDG filled requirements of Ph.Eur. and the content of radionuclidic and metallic impurities was in the acceptable range.
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1. Background

Positron emission tomography (PET) is a dynamically developing imaging method of nuclear medicine, which allows to diagnose metabolic changes in human body. PET diagnostic techniques use β+ emitting isotopes for labeling biologically active compounds and track their distribution in a living organism. Due to its relatively long half-life (110 min), ^{18}F is the most commonly used radioisotope in PET and is produced in medical cyclotrons (mostly proton-deuteron 10–20 MeV machines). Nowadays, the most widely used radiopharmaceutical for diagnostic procedures using PET is ^{18}FDG, the glucose derivative labeled with ^{18}F, which applications are regularly reviewed[1–7] and standardized.[8]

* *Corresponding author at*: Heavy Ion Laboratory, University of Warsaw, Pasteur 5a, 02093 Warsaw, Poland. Tel.: +48 22 55 46 214.
E-mail address: kilian@slcj.uw.edu.pl (K. Kilian).
http://dx.doi.org/10.1016/j.rpor.2014.03.001
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2. Aim

One of the most important aspects of working with ^{18}FDG is a short time (about 30 min) that can be spent on quality control and release procedures, thus the speed, simplicity and reliability of developed analytical methods are critical factors. For radiopharmaceuticals, the general requirements are listed in European Pharmacopoeia[9] and these parameters have to be checked before application for human use. Short-lived radiopharmaceutical preparations may be released before completion of some tests, specified in individual monographs. The aim of this study was to synthesize ^{18}F-FDG in some consecutive runs and check the quality of manufactured radiopharmaceuticals. Several tests were performed to determine chemical and radiochemical impurities, chemical identity and other adequate parameters for parenteral formulation. During production process, trace amounts of metallic radioisotopes are produced due to radio activation on the metal target housing. In addition, the distribution of metallic impurities on synthesis and dispensing module was measured by gamma spectroscopy and level of non-radioactive metals was determined with inductively coupled plasma with mass spectrometry (ICP-MS).

3. Materials and methods

3.1. ^{18}FDG manufacturing

^{18}FDG was synthesized in six independent runs with standard method from mannose triflate with alkaline hydrolysis as initially proposed in Ref. 10. Cyclotron GE PETtrace840 with high yield niobium target (General Electric, Uppsala, Sweden) was the source of anionic fluorine. Standard produced activity in ^{18}O(p,n)^{18}F reaction with 16.5 MeV proton beam at 40–45 μA, was 4.0 ± 0.2 Ci (140.6–155.4 GBq) after 120 min of irradiation and was transferred to the GE MX_{FDG} unit (General Electric, Liege, Belgium), where the synthesis and purification were performed. In the synthesis path, the ^{18}F-fluoride solution was passed through an ion exchange column, which trapped anions. Cations, including some metal contaminants, were collected with the recovered enriched water. [^{18}F]fluoride was then eluted to the reaction vessel with a mixture of potassium carbonate and Kryptofix 2.2.2, then water was removed by azeotropic distillation with acetonitrile and ^{18}F reacted with mannose triflate. After alkaline hydrolysis, the solution was purified with sequence of C18-RP and alumina columns and eluted with water. The final product was formulated with saline, passed through a 0.22 μm filter and dispensed in automatic module DDS-Vials (Tema-Synergie, Italy). Starting materials were, ready-to-use, Ph.Eur. compliant kits, obtained from ABX (Radeberg, Germany).

3.2. Identification

Identification tests were performed as described in Ref. 9. For γ-spectrometry, high resolution germanium detector GMX-20190-P with digital signal processor (DSPEC, Ortec) and GammaVison software was used. 2 μL sample was applied on silica plate, fixed in a holder and inserted into a 5 cm Pb shielded, low-background housing. Spectra was recorded for 5 min.

Half-life was measured with Atomlab300 (Biodex, USA) dose calibrator: 300 μL (1.2–1.5 GBq) sample was crimped in penicillin vial, fixed in a standard vial holder and measured in triplicate at 20 min intervals.

Identity of manufactured ^{18}FDG was confirmed by comparison of retention time to the certified reference standard (CRS) of main compound (ABX, Radeberg, Germany).

3.3. Radionuclidic purity

Radionuclidic purity and radionuclidic impurities were determined using gamma spectroscopy with a high resolution germanium detector GMX-20190-P with a digital signal processor (DSPEC, Ortec) with GammaVison software. Efficiency and energy calibration was performed with ^{241}Am (255.162 kBq at the day of measurements), ^{137}Cs (203.425 kBq at the day of measurements) and ^{152}Eu (260.733 kBq at the day of measurements) sources at 13.9, 17.8, 26.47, 59.67, 121.9, 244.8, 344.37, 661.7, 788.98, 964.13, 1085.92, 1112.17 and 1408.14 keV, respectively. For sources and samples, a universal holder, fixed in 14 cm from a detector window was constructed and located in a fully shielded (5 cm Pb) low-background housing.

The spectra were recorded in 10,800 s each for final product and purification cartridges used during the synthesis of 2-[^{18}F]FDG: ion exchange columns Accel Plus QMA Sep-Pak^{TM}, used for preconcentration and separation of ^{18}F from target, reverse phase separation columns Sep-Pak^{TM} C-18 RP used in a basic hydrolysis and purification process of FDG, alumina columns Sep-PakTM N Plus for ionic contaminants removal. Isotopes were identified on the basis of the characteristic γ-emissions. Only for final determination of impurities in ^{18}FDG, the time was extended to 21,600 s. Each peak was analyzed by marking the region of interest and recording the energy, count rate and background corrected area.

The γ-ray spectra for radionuclidic purity test A was recorded immediately after synthesis and test B was performed 24 h after irradiation. Recorded activities were calibrated at the end of synthesis (EOS).

The γ-ray spectra of the residual radionuclides were collected 72 h (36 times the ^{18}F half-life) after irradiation, because by that time the ^{18}F activity decreased to a level comparable to longer-lived compounds and did not hamper the spectra recording.

3.4. Radiochemical purity

Radiochemical purity (test A) was performed with an ion chromatography system ICS-5000+ (Thermo Scientific, former Dionex) with a pulsed amperometric detector and radiometric detector (GabiStar, Raytest, Germany). 20 μL sample was injected via a manual multiport valve. The separation was done on Thermo Scientific Carbopac PA-10 column (250 mm × 4.0 mm i.d., 10 μm), with 0.1 M NaOH (CO_2-free) as a mobile phase and 1 mL/min flow rate. Data acquisition and processing was preformed with Chromeleon software.

Radiochemical purity determination (test B) was conducted with a thin layer chromatography system Bioscan

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