Macedonian pharmaceutical bulletin, 68 (Suppl 1) 225 - 226 (2022)
Online ISSN 1857 - 8969
*DOI:*10.33320/maced.pharm.bull.2022.68.03.107
Short communication

Production of 2-[^{18}F]Fluoro-2-deoxy-D-glucose radiopharmaceutical at the University Institute of Positron Emission Tomography, Skopje

Maja Velichkovska*, Katerina Kolevska, Marija Atanasova Lazareva, Maja Chochevska, Filip Jolevski, Ana Ugrinska

University Institute of Positron Emission Tomography, 1000 Skopje, North Macedonia

Introduction

Fludeoxyglucose (^{18}F) injection is a sterile solution of fluorine-18 in the form of 2-deoxy-2-[^{18}F]fluoro-α-D-glucopyranose, intended for intravenous administration. [^{18}F]FDG is the most widely used radiopharmaceutical for molecular imaging by positron emission tomography (PET). University Institute of Positron Emission Tomography in Skopje is a GMP facility for production of radiopharmaceuticals, equipped with a cyclotron for production of radioisotopes and specially designed radiochemical laboratories for production and quality control. [^{18}F]FDG production laboratory is equipped with a double hot cell for synthesis where two fully automated modules for [^{18}F]FDG synthesis - Synthera V2 are placed, and a hot cell for dispensing with automatic dispensing system for radiopharmaceuticals – volumetric dispenser Clio. The production process starts by F-18 radioisotope production in the cyclotron and continues with a synthesis of [^{18}F]FDG radiopharmaceutical in the synthesis module. The synthesis is based on nucleophilic substitution of radioisotope with mannose triflate as precursor, followed by basic hydrolysis. The last step of the synthesis is a purification of [^{18}F]FDG. When the synthesis of the radiopharmaceutical is finished, next phase is quality control of the final product and dispensing of the doses for patients.

Materials and methods

F-18 radioisotope production

F-18 radioisotope is produced by cyclotron GE PETTrace 800 via nuclear reaction ^{18}O(p,n)^{18}F of irradiation of the enriched water O-18 with protons with energy 16.5MeV in the niobium target.

Synthesis of [^{18}F]FDG radiopharmaceutical

The production of [^{18}F]FDG radiopharmaceutical is performed in automated synthesis module following six steps. First step is a purification of the produced radioisotope F-18 on quaternary ammonium anion exchange cartridge (QMA). Retained on the resin, [^{18}F] fluoride ion is then eluted with aqueous acetonitrile solution containing potassium carbonate and equimolar amount of KryptofixTM 222. Next step is evaporation of the water/acetonitrile mixture. After the protonic residues are removed, the production of the [^{18}F] fluorinated intermediate takes place with nucleophilic [^{18}F] fluorination on organic precursor 1,3,4,6- tetra-O-acetyl-2-O-trifluoromethanesulfonyl-b-D mannopyranose (mannose triflate). Subsequent step is base-catalyzed hydrolysis of the acetyl protecting groups. The last step is purification of the [^{18}F]FDG by passing the mixture through purification cartridges: strong cation exchange cartridge (SCX) to retain positively charged complex K+/KryptofixTM 222, basic aluminum oxide cartridge (Alumina B) to retain unreacted [^{18}F] fluoride ion and C18 bonded silica cartridge to retain partially hydrolyzed F-18 intermediate.

*mvelickovska@yahoo.com

Dispensing of the [^{18}F]FDG *final product*

The dispensing is performed in class A chamber, by an automatic dispensing system for radiopharmaceuticals - Clio. This volumetric dispenser uses single use kit for dispensing, with a 0.22 μm filter for sterilisation. 0.9% NaCl solution is used for dilution. Every dose, after the filing, is measured in dose calibrator and afterwards it is delivered in special lead container, previously correctly labelled. At the end of the dispensing, a filter integrity test is performed.

Quality control of [^{18}F]FDG radiopharmaceutical

The quality specification is in accordance with European Pharmacopoeia general monograph Radiopharmaceutical preparations and with quality requirements and acceptance criteria of the European Pharmacopoeia monograph for Fludeoxyglucose (^{18}F) injection. Quality control of [^{18}F]FDG includes release and post-release tests. The parameters necessary to evaluate before administration to patients are: appearance, identification, pH, radiochemical and chemical purity. Post-release tests comprise evaluation of bacterial endotoxins, sterility, radionuclidic purity and residual solvents.

Results and discussion

University Institute of Positron Emission Tomography Skopje officially has started the routine [^{18}F]FDG production on June 1, 2017. In 2017, 59 [^{18}F]FDG productions were realized with 61.82 % average yield decay corrected (d.c.). In 2018, 107 [^{18}F]FDG productions were performed (average yield d.c. 56 %); in 2019, 152 [^{18}F]FDG productions (average yield d.c. 52%); in 2020, 138 [^{18}F]FDG productions (average yield d.c. 57.16%) and 139 [^{18}F]FDG productions in 2021 (average yield d.c. 60.51%). The radiochemical yield was in an acceptable range. The average yield of produced [^{18}F]FDG was 56.48% d.c. Maximum produced activity of [^{18}F]FDG was 73.26 GBq. The concentration of the final product was 1000 MBq/ml ± 200 MBq/ml.

The radioactivity of all dispensed doses was in acceptance criteria ± 10 %. The radiochemical purity was more than 99 % in each of the batches, while the radionuclidic purity was more than 99.9 %. The results of filter integrity test, as part of the tests necessary to evaluate before administration to patients, met the acceptance criteria for all the batches. For every produced batch, the quality control tests results were in acceptance criteria defined in the [^{18}F]FDG specification.

Conclusion

[^{18}F]FDG radiopharmaceutical production is established and routinely performed at the University Institute of Positron Emission Tomography, Skopje, continuously ensuring safe final product which fulfil the quality requirements.

References

European Pharmacopoeia 10.0, 2020, Monograph no. 1325, "Fludeoxyglucose (^{18}F) injection" (01/2014:1325 corr. 8.2)

European Pharmacopoeia 10.0, 2020. General monographs, Radiopharmaceutical Preparations (07/2016:0125)

Richards, M.L., Scott, P.J.H., 2012. Synthesis of [^{18}F]-Fluorodeoxyglucose ([^{18}F]FDG), in: Scott, P.J.H., Hockley, B.G. (Eds.), Radiopharmaceuticals for positron emission tomography (Radiochemical syntheses Volume 1), John Wiley & Sons, Inc., Hoboken, New Jersey, pp. 3-13.