RPE | Radiation Physics & Engineering
An International Peer-Reviewed Journal
Published by K.N. Toosi University of Technology
http://rpe.kntu.ac.ir
Research Article

Radiation Physics and Engineering 2020; 1(1):7–11
https://doi.org/10.22034/RPE.2020.57883

Introducing a novel FDG synthesis method in Iran based on alkaline hydrolysis

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HIGHLIGHTS

- 18F-FDG PET/CT is introduced in Iran based on news synthesis according GMP.
- It is used for diagnostic tumors, treatment monitoring and radiation therapy planning.
- The synthesis and quality control are described in details.
- It could be used as reference method for other PET centers.

ABSTRACT

18F-FDG PET/CT is commonly used for evaluation and diagnostic of many types of cancer, such as; tumor diagnosis, treatment monitoring, and radiation therapy planning. Accurate diagnostic is needed in meticulous patient preparation, including restrictions of diet and activity and management of blood glucose levels in diabetic patients, as well as an awareness of the effect of medications and environmental conditions. All of these conditions play important roles toward obtaining good-quality images, which are essential for accurate interpretation. This article introduces the new synthesis and quality control method for obtaining the best quality FDG which is used as radiopharmaceutical. All the reactions are carried out and completed in one reaction vessel without any replacement. The paper is including details of synthesis, quality control and transportation step. It is the first time that the alkaline FDG synthesis is introducing by details in Iran.

KEYWORDS

Alkaline Hydrolysis
Synthesis
FDG=[^{18}F]Fluorodeoxyglucose

HISTORY

Received: 9 October 2017
Revised: 25 December 2017
Accepted: 7 January 2018
Published: January 2020

1 Introduction

In clinical practice, ^{18}F-FDG PET/CT is commonly used for evaluation and management of many types of cancer, including tumor diagnosis, staging, restaging, treatment monitoring, oncology and radiation therapy planning. The FDG ([^{18}F]Fluorodeoxyglucose) synthesis protocol is important for quantity of FDG uptake which is a useful tool in qualitative interpretation of images, as the percentage change in tumor standardized uptake value (SUV) is more reproducible than the percentage change in CT tumor size (Surasi et al., 2014; Jacene et al., 2009).

Modern development of tracers for PET and SPET is based on biochemical concepts. For this purpose, natural substrates and biomolecules, as well as drugs, are labeled with short-lived positron or single photon emitters. [^{18}F] with the half-life of 110 min is an ideal analogue tracer, which is used often to label a biomolecule without producing radical changes in its biological behavior. In some cases, the metabolism of a biomolecule is even simplified when a hydroxyl group is replaced by fluorine, as in the case of FDG.

Considerable progress has been achieved in [^{18}F] labeling chemistry during the last two decades. This is particularly true for no-carrier-added labeling via nucleophilic substitution reactions. Nucleophilic fluoride [^{18}F] can be obtained in extremely large activity levels via the ^{18}O(p,n)^{18}F process using an enriched $H_2\,^{18}O$ target (IAEA, 2012).

Also, FDG has gained additional importance in conjunction with its application in a non-PET mode using a gamma camera with a high energy collimator, or simple gamma-gamma coincidence imaging devices. [^{18}F] is interesting radionuclide for developing countries with cyclotrons, since it can be used to develop labeled biomolecules for diagnostic nuclear medicine studies. [^{18}F] radiopharmaceuticals have half-lives suitable for a limited transportation within the so-called satellite concept. The satellite concept is already practiced in many countries, such as Iran, whereby hospitals with a PET scanner but

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no cyclotron can be served if they can be reached within reasonable travel time (IAEA-TECDOC-1310, 2002).

To minimize dietary glucose-related competitive inhibition of FDG uptake and reduce serum insulin to near basal levels, complete fasting for a minimum of 6.0 h before the scan, including cessation of tube feeding, dextrose-containing intravenous fluids, and parenteral hyperalimentation is recommended. Good hydration, typically oral, before the study for radiation safety reasons and to ensure a low FDG concentration in urine is needed. It is recommend a high-protein, low-carbohydrate diet for 24 h before scanning to minimize dietary glucose-related competitive inhibition of FDG uptake. The exercises such as jogging, cycling, weightlifting, strenuous housework, yardwork, and sexual activity is avoided for a minimum of 24 h (ideally 48 h) before the scan to minimize uptake of radiotracer in skeletal muscles.

The PET center personnel need to recognize that several commonly prescribed medications can elevate serum glucose levels, including glucocorticoids, phenothiazines, lithium, tricyclic antidepressants, phenytoin, thiazide diuretics, isoniazid, rifampin, and ephedrine then all prescription medications should be considered for the patients. The benzodiazepine derivatives injection 30∼60 min before FDG injection is highly recommended for better results (Delbeke et al., 2006; Boellaard et al., 2010; Shankar et al., 2006; ACR-SPR, 2014; Graham et al., 2011; Beyer et al., 2011).

In general, this paper is focused on the optimization of syntheses and quality control of FDG based on USP. Selective labeling procedure which is using prosthetic groups is applied to [^{18}F]. The details include introduction and investigation of alkaline synthesis of FDG in Iran which is leading in Karaj Cyclotron Center.

Because ^{18}F-FDG injection is the most commonly used PET radiopharmaceutical in home, the discussion is focused on the synthesis and quality assurance procedures of it. The introduced synthesis and quality control method is the newest synthesis method based on alkaline hydration. The method is based on United State Pharmaceutical (USP). The author hopes for the promotion of the familiarity and using of the FDG and other PET radiopharmaceutical.

2 Methods

The procedure is begin with [^{18}O]water, which is enriched with the stable isotope O-18 up to 98%. Upon bombardment with suitable energy protons using a cyclotron, this stable isotope is transformed into F-18, which is in the chemical form of [^{18}F] fluoride ion. Some radiochemical and chemical impurity from target body and windows is entered during the bombardment of [^{18}O]-enriched water which contains [^{18}F] fluoride ion. The first step of chemical procedure is the separation and purification of [^{18}F] fluoride from the bombardment water result. The QMA column is able to complete this step successfully. The trapped [^{18}F] fluoride ion is washed from the column using dry acetonitrile containing suitable amounts of Kryptofix (K.2.2.2) and potassium ions. The solution is transferred to the reaction vessel and heat up to 110 °C to dry and eliminate all the residual water and other liquids impurities.

In the next step, solution of mannose triflate dissolved in dry acetonitrile is added to the reaction vessel. Then the substitution reaction (radiolabeling) is directed to substitute the [^{18}F] fluoride ion instead of triflate leaving group on mannose molecule. The reaction is SN2 substitution and the conformation of the C2 is changed. After completing of the reaction, all the solvent and liquid is removed again from reaction vessel by heating up the vessel to 110 °C.

The last step of the synthesis is hydrolysis of the acetates protecting group to hydroxyl using alkaline hydrolysis. The reaction is completed using 1.0 M NaOH solution. After completing the hydrolysis, all residual solvents again are evaporated and dried up to 112°C. Then the FDG radiopharmaceutical is transferred from reaction vessel to FDG bulk vessel using 10.0 mL (2 × 5.0 mL) sterile and injectable water. During the transferring the filtration of the FDG also is completed. The filtration includes three steps of filtering in situ. The first filter is a SCX column for removing residual cations and cationic impurities, the next is an alumina column for removing the residual and unreacted F-18, and the last one is C-18 column for removing the organic residual of all synthesis procedure. During the synthesis using thermal, pressure and radioactive sensors the temperature, pressure and radioactive levels change at the all steps the procedure are controlled and recorded on the control graph. The FDG is collected in a single vial and after completing the quality control and quality assurance, could be released to patients use.

3 Results and discussion

The precursor molecule for the radiochemical synthesis of FDG is 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-b-D-mannopyranose (molecule 1 in Fig. 1), which is commonly called mannose triflate. The precursor is an acetylated mannose molecule, with four protecting groups (tetra-acetyl) which contains a triflate as a suitable leaving group (trifluoromethanesulfonyl), for a facile nucleophilic reaction. In order to accomplish radiolabeling of glucose the leaving group (triflate) is displaced by radioactive [^{18}F]fluoride through nucleophilic SN2 substitution. The nucleophile ([^{18}F]fluoride) approaches the reaction center (C2) from the opposite side of the leaving group and displaces the triflate.

In the subsequent step, the protective acetyl ester groups are removed by alkaline hydrolysis and converting the groups to hydroxyl (OH). This leads to formation of the final product FDG (molecule 3 in Fig. 1). Non-radioactive D-glucose (DG) (molecule 4 in Fig. 1) is a major by product resulting from the unreacted mannose triflate and will be present in all FDG preparations. The synthesis and hydrolysis steps are shown in Fig. 1.

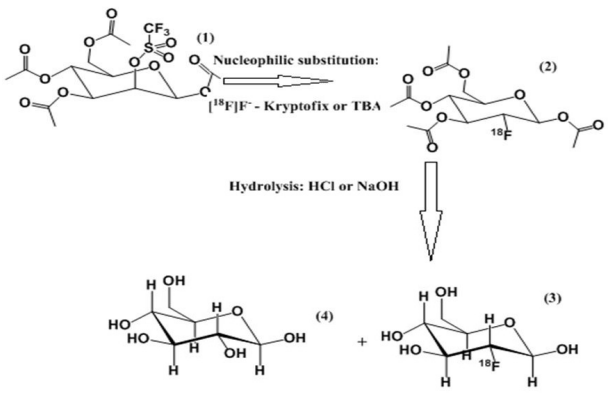

Figure 1: Synthesis and hydrolysis steps for FDG.

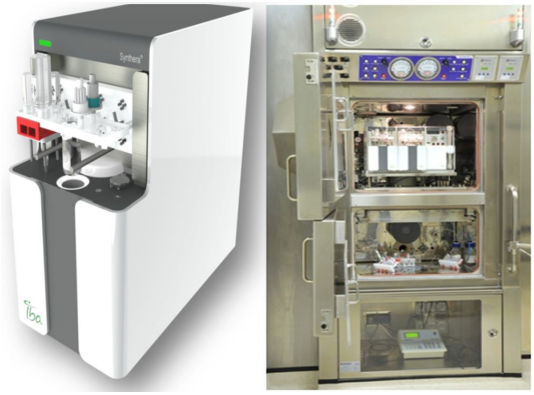

Figure 2: The synthesis module and Hot-cell for FDG.

In each synthesis batch, the FDG activity is up to 3.0 Curie (Ci). Because of radioactive hazards, the synthesis is carried out using automated synthesis module in sealed hot-cells. The used modules are Synthra model 2.0 from IBA Company. They are used for synthesis of FDG and other 18-F fragments and radio-pharmaceuticals. An IBA module with suitable Hotcell for FDG synthesis is shown at Fig. 2.

As it mentioned at previous sections, the temperature, pressure and radioactivity levels are controlled and recorded as graphical print for easy visual control of synthesis steps. A graphical sample for this control is shown in Fig. 3. The red, blue and green lines are used for displacement of the temperature, pressure and activity respectively.

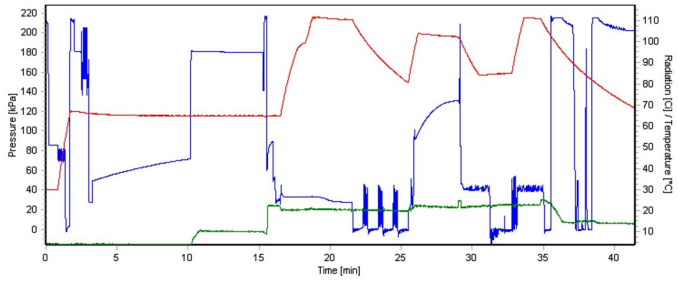

Figure 3: Typical graph for the controlling of temperature, pressure and radioactivity which is respectively showed by red, blue and green lines.

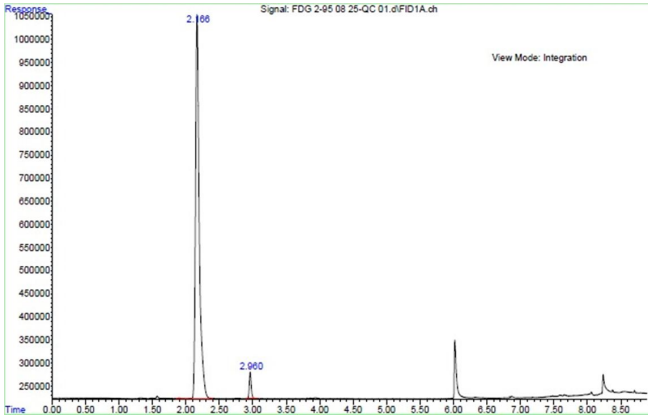

Figure 4: A typical result of GC for determination of ethanol and acetonitrile of the FDG.

After completing the synthesis, the quality of the FDG is needed to be controlled before injection use for patients. Most important factors such as, pH, chemical and radiochemical purity (FDM, F-18, alcohol, acetonitrile and half-life), sterility and endotoxin test most be completed before release. The pH is determined accurately using a digital pH meter, the exact value of pH most be between 5.5∼7.5. Other values cause to reject of FDG radiopharmaceutical.

The alcohol (ethanol) and acetonitrile concentrations are determined by GC instrument simultaneous. A typical result of GC is shown in Fig. 4. The concentration of ethanol and acetonitrile must be less than 5000 and 400 ppm, respectively. The concentrations higher than these amounts cause to reject of FDG radiopharmaceutical.

For determination of FDM/FDG ratio and F-18 amounts it is usual to use HPLC chromatography. Also, it is completed using RTLC (Radioactive TLC) chromatography. The peak area and compare of the FDG, FDM and F-18 is completed by the instruments software. The acceptable ratio of FDG to FDM+F-18 is more than 90%. Lower amounts would cause to reject.

The HPLC and RTLC sample chromatogram is illustrated in Fig. 5. Hence the purity of the FDG directly depended to the temperature and pressure of the reaction vessel, the control of the temperature and pressure has great importance. This control is done by sensors and recorded as graph (Fig. 3).

The radionuclide purity and half-life of the FDG is determined by gamma spectroscopy using high pure germanium detector. A typical spectrum is illustrated on Fig. 6. The half-life between 100∼120 minutes is acceptable. The half-life of the F-18 is almost 110 minutes.

The sterility and pyrogenic of the FDG is tested by LAL test which is replaced instead of Charles-River test. The replaced test is standardized and validated for the 4 levels by comparing. Because of the clear fluid and easily flow of the results correspond to levels 1 and 2, they are accepted. The results of level 3 are accepted or rejected by experienced person. The level 4 results are rejected because it changes to chelate and has no flow.

As mentioned before, [^{18}F]fluoride radiopharmaceuticals have half-lives suitable for a limited transportation

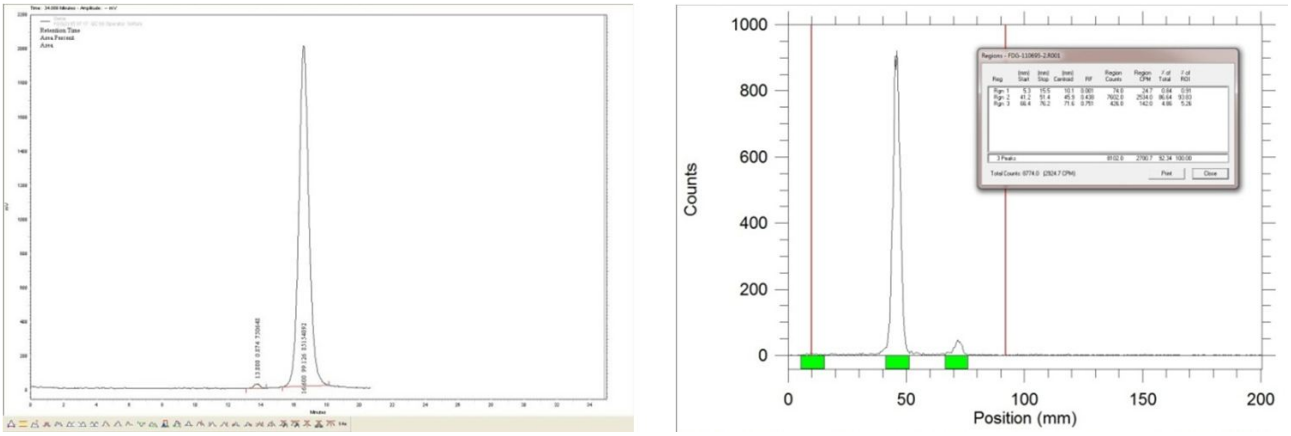

Figure 5: The HPLC (left) and RTLC (right) chromatograms of the FDG for determination of FDM and F-18 ratio.

within the so-called satellite concept. The satellite concept is already used in our country (Iran), whereby hospitals with PET scanner camera placed in Tehran and the cyclotron and PET production center is placed in Karaj, 50 km far from it. The distance is reasonable and the FDG is reached on time, because it needs at least 75 minutes to complete quality control test.

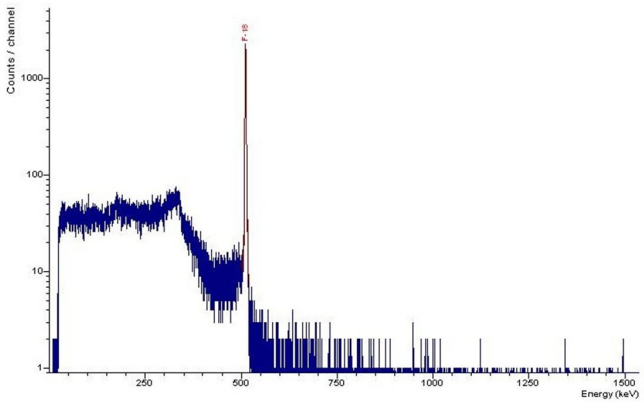

Figure 6: Gamma Spectrum of FDG.

4 Conclusion

The introduced synthesis process, according alkaline hydrolysis, is a new and simple method. All the reactions are carried out and completed in one reaction vessel without any replacement. The synthesis process of the FDG radio-pharmaceutical is highly sensitive to the presence of impurities, moisture content, temperature and pressure. The precursors may be able to revise the recommended acceptance criteria, testing procedure and testing schedule to meet production capability and constraint. The smallest amount of chemical impurity and humidity cause the sharp decreases at synthesis efficiency.

During the synthesis, if the temperature and pressure are not controlled accurately, the FDM/FDG ration increases. Therefore, ensuring the dryness of solvents is the first and most important step of the synthesis. The yield of synthesis is, at best, 55-50% relative to the [^{18}F]fluoride initial activity. The standard, recommended QA tests, which stated in the official sources (*e.g.*, USP), is carried out accurately before FDG release. The introduced method is the latest method of synthesis and QC in Iran.

Acknowledgment

The author thanks Pars Isotope Co. and Karaj Radiomedicine production facility.

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