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^{18}F-Fluorodeoxy Glucose [^{18}F]-FDG: Automated Production Methodology and its Quality Control as Clinical usable Radiotracer

Chemistry

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ABSTRACT

The clinical applications of positron emission tomography (PET) have increased dramatically due to the production and widespread distribution of one major molecule i.e. 2-deoxy-2-[18F] Fluoro-D-glucose ([18F] FDG). Currently it is one of the most widely successful and usable PET radiopharmaceutical. It is used for the measurement of glucose metabolism using PET in the diagnosis, staging, and restaging of several clinical conditions such as lung cancer, colorectal cancer, lymphoma, melanoma, head and brain cancer, neck and breast cancer. The increasing demand of [18F] FDG, for clinical pet investigation requires this compound to be producible in large amounts, with a high purity and with reliable results. This article focuses on a concise detail of 18F-Fluorodeoxy Glucose Production via automated synthesis module and their Quality Control with standard for clinical usable

KEYWORDS

Positron emission tomography, 2-deoxy-2-[18F] Fluoro-D-glucose, radiopharmaceutical, Production, Quality Control.

INTRODUCTION

2-[^{18}F]-Fluoro-2-deoxy-D-glucose (2-[^{18}F]FDG) is one of the most important radiopharmaceutical used for the measurement of glucose metabolism using positron emission tomography (PET). [^{18}F]-FDG is a fluorinated analog of D-glucose labeled with positron emitting ^{18}F ($T_{1/2}$ = 110 min; $I_{\beta+}$ = 97%; $E_{\beta+}$ = 0.63 MeV). The chemical structure of [^{18}F]-FDG is similar as glucose except that the hydroxyl group on the 2-carbon position of a glucose molecule is replaced by a fluoride atom.[1]

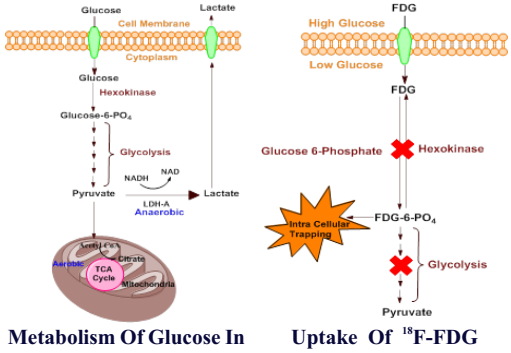
When [^{18}F]-FDG is injected to a cancerous patient it gets phosphoryl ated similarly as glucose in the body but in contrast to glucose, it does not take part in subsequent metabolic stages and is accumulated in cancerous cells.[2] [^{18}F]-FDG whole body PET imaging measures glucose metabolism in all organ systems with a single examination. Since cancer is a systemic disease, it allows the early detection and quantification of metastasis.

Therefore, it have been used in the diagnosis, staging, and restaging of several clinical conditions such as lung cancer, colorectal cancer, lymphoma, melanoma, head and brain cancer, neck and breast cancer.[3]

Why [^{18}F]FDG As A PET Diagnostic Agent

[^{18}F]-FDG is a glucose analogue in which the hydroxyl group present on the 2-carbon position of glucose is replaced by a fluoride atom. Just like glucose molecule, [^{18}F]FDG is transported into the cell mediated by a group of structurally related glucose transport proteins (GLUT).[6] [^{18}F]FDG is taken up into living cells by facilitated transport and then phosphorylated by hexokinase. Normally, when the glucose is once phosphorylated it continues along the glycolytic pathway for energy production. However[^{18}F]FDG cannot enter glycolysis and get trapped as FDG-6-Phosphate. Cells causing tumor usually show an increased number of glucose transporters, specially GLUT-1 and GLUT-3, as well as higher levels of hexokinase, isoforms type I and II.

Tumor cells are highly metabolically active (high mitotic rates), and favor the more inefficient anaerobic pathway adding to the already increased glucose demands. These combined mechanisms allow for tumor cells to uptake and retain higher levels of [^{18}F]FDG when compared to normal tissues.[7]



Metabolism Of Glucose In Cancer Cell **Uptake Of ^{18}F-FDG In Cancer Cell**

Figure 2. Metabolism of glucose and uptake of [^{18}F]FDG in cancer cell.

When the labeled [^{18}F]FDG is administered to the patient the radiation emitted by the ^{18}F can be detected by a (PET scan) system which allows the distribution in the body to be traced and represented as an image in form of scan. Since [^{18}F]FDG is not cancer specific it will not be completely metabolized as normal glucose would, it will accumulate or be 'trapped' in cells with high glucose uptake and can be expected in sites of muscular, nervous (hyperactivity); infection, sarcoid, arthritis, etc.; tissue repair, etc. (active inflammation), providing a high positive image contrast.[8]

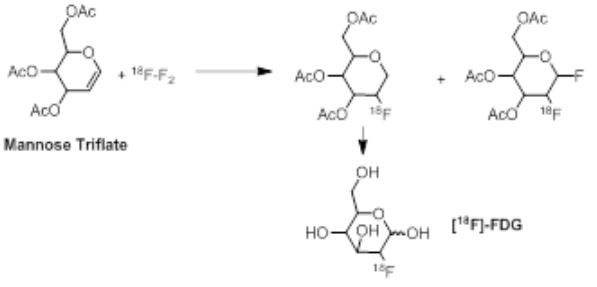
Since the first synthesis of [^{18}F]-FDG in 1978 (Ido *et al*., 1978) different synthesis methods have been developed using both electrophilic and nucleophilic fluorination. Although the nucleophilic substitution reaction is more widely used nowadays, the electrophilic fluorination reaction has an important place in the synthesis of ^{18}F-FDG.[4]

With the increasing demand for [^{18}F]-FDG requires an increase in production without a decrease in quality. Because of 110 min half-life

of ^{18}F, it is possible to deliver [^{18}F]-FDG to PET imaging centers distant from cyclotron and production facilities. Some of the most commonly used automated synthesizers for [^{18}F]FDG production are shown below (Figure 1).The synthesis of [^{18}F]FDG begins with the production of [^{18}F]-fluoride in a cyclotron, typically in a target chamber containing [^{18}O]-H_2O, followed by a nucleophilic reaction with 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-*β*-D-mannopyranose (mannose triflate), and subsequent de-blocking of the protecting groups (acetyl), resulting in ^{18}F-FDG formation. [5]

Synthesis Of [^{18}F]FDG

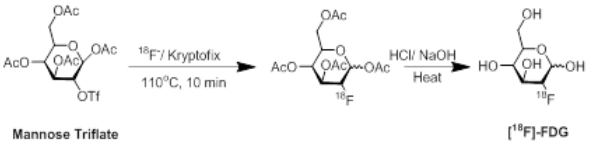
There are two different types of method for the synthesis of [^{18}F]FDG i.e. electrophilic and nucleophilic fluorination. [^{18}F]FDG first synthesis was carried out by electrophilic substitution method by Wolf et al. in 1976. The term electrophilic fluorination means fluorine atoms addition across a double bond, producing a difluoro derivative of the parent compound. Electrophilic fluorination is the process by which fluorine atoms are delivered across a double bond, producing the parent compound of difluoro derivative. Wolf et al. electrophilic fluorination synthesis involved the usage of 3, 4, 6-tri-O-acetyl-D-glucal as a precursor.[9] Here the ^{18}F-F_2 was treated with glucal to produce a mixture 3:1 of ^{18}F labeled difluoro-glucose and difluoro-mannose derivatives. The derivative of difluoro-glucose (Scheme 1) was separated and hydrolyzed with hydrochloric acid to form 2-fluoro-2-deoxyglucose with the total synthesis time of 2 hours and the overall yield of 8%. In the process of electrophilic fluorination described above a lot of changes have been made thereafter. One of the major modifications was the use of acetylhypofluorite ^{18}F-CH_3CO_2F as it can be produced in situ from ^{18}F-F_2 with high yield. One of the major limitations of this process was that only 50% of the radioactive fluorine atoms were incorporated into the precursors.[10]



Scheme 1. Radiosynthesis of [^{18}F] Fluoro-deoxy-Glucose by electrophilic substitution.

By Nucleophilic Fluorination

Nucleophilic substitution is a reaction which involves the addition of a nucleophilic molecule (highly negatively charged molecule) into a leaving group molecule (electron drawing group attached to the parent molecule through an unstable chemical bond). The nucleophilic molecule has a high affinity towards the electron deficient center in the parent molecule created by the electron pulling leaving group. As a result, the nucleophilic molecule forms a covalent bond with the parent molecule and displaces the leaving group. The parent molecule stereo-chemistry was also changed. To develop a nucleophilic substitution method for the synthesis of [^{18}F]FDG a lot of attempts have been made such as the use of ^{18}F-CsF, ^{18}F-Et_4NF, and ^{18}F-KHF.[11] But Hamacher et al. in the year 1986 reported the use of a catalyst named as Kryptofix222 which proved to be a major breakthrough in the synthesis of FDG as the reaction time was shortened to 50 min and the overall reaction had a consistent yield of 50%. In [^{18}F]FDG synthesis ^{18}F ion is the nucleophile. Here mannose triflate is the precursor in which the 1,3,4,6 position carbons of a mannose molecule are protected with an acetyl group and triflate is the leaving group at the 2-carbon. Together in Kryptofix222 and acetonitrile presence ^{18}F ion approaches the mannose triflate at the 2-carbon, while the triflate group leaves the protected mannose molecule to form [^{18}F]-FDG. [9,12]



Scheme 2. Radiosynthesis of [^{18}F] Fluoro-deoxy-Glucose by nucleophilic substitution.

MATERIAL AND METHODOLOGY

Reagents, Solvents And Disposables: - The precursor, Mannose Triflate ultra-pure, authentic nonradioactive standard [^{18}F] FDG and ^{18}O Water were obtained from ABX, Germany. Solvents and reagents were purchased from Sigma (Milwaukee, WI, USA) and Fisher Scientific (Mumbai, India). Sterile vial, USP-grade 0.9% NaCl, and sterile water for injection were purchased from B. Braun Melsungen AG, Melsungen, Germany. The Sep-Pak QMA light cartridge, Sep-Pak Alumina plus cartridge and Sep-Pak PS-2 cartridge was purchased from Waters Corporation. The Maxi-Clean IC-H cartridges were purchased from Grace Davison Discovery Science.

Radiosynthesis

Production Of Fluorine-18 (^{18}F):- Fluorine-18 (^{18}F) is a fluorine radioisotope which is an important source of positrons. This radiopharmaceutical is prepared by using fluorine-18 obtained by irradiating oxygen-18 with proton. Due to its simplicity of managing the process, we currently use ^{18}O-H_2O as their target material an SN2 nucleophilic substitution reaction. Since ^{18}F- is produced by an ^{18}O (p, n) ^{18}F- reaction.

Scheme 3: Production of Flourine-18

Scheme 4: Decay pattern of Fluorine -18

In this study we have generated fluorine-18 on a Sumitomo HM-18 cyclotron equipped with Niobium targets, and then manufactured [^{18}F] FDG using two different synthesis modules i.e. F300E-FDG synthesizer and MPS100 synthesizer.

Quality Control Methods

The quality requirements of [^{18}F] FDG are set out in various pharmacopoeia including the USP [20], BP [21], EP [22], etc.Quality Control of [^{18}F] FDG prepared at our laboratory for clinical use is carried out according to the USP recommendations detailed below. After successfully meeting all release criteria, doses are released to physicians for clinical use.

Particulates: - The [^{18}F] FDG product solution is examined visually. Evaluating the chemical purity by visual inspection is straightforward. The final drug product in the vial should be clear and colorless without any visible particulates as per USP ⟨823⟩ and USP ⟨631⟩ Color and Achromaticity.

Filter Integrity Test: - Because the USP sterility test requires 14 days to complete, the [^{18}F]-FDG product solution sterility cannot be assured prior to injection. The [^{18}F]-FDG product is passed through a 0.22 m sterilizing filter into the final product vial. After the [^{18}F]-FDG product is collected, the sterilizing filter is tested for filter integrity to give an indication of likelihood of the product sterility. Filter integrity is tested in a bubble point procedure, whereby the sterilizing filter is placed on a gas line with a pressure gauge and the outlet of the filter is placed under water. The gas pressure on the inlet to the filter is increased slowly until a steady stream of bubbles is observed at the filter outlet. The pressure at which the bubble stream begins is recorded and compared with the manufacturer's pressure rating (typically 50 psi) for the filter (from the certificate of quality). If the initial integrity test fails filter will be rewetted with 30mL of water and retested.

Kryptofix [2.2.2] Test:-. The qualified K2.2.2 test is based on the method by Mock et al. [14], which uses a color spot test for the detection of residual K2.2.2 in the final drug product. The FDA has proposed a maximum permissible level of 50 g/mL of K2.2.2 in 2-[^{18}F]-fluoro-deoxy-glucose; therefore this maximum permissible level is appropriate for the [^{18}F]-FDG final product.

Radiochemical Purity: - Radiochemical purity is determined by monitoring the radioactivity signal from the detector coupled in series with HPLC or by measuring the radioactivity distribution with

radioactivity scanners or imagers after TLC separation. High Performance Liquid Chromatography (HPLC) was carried out on a Agilent HPLC system equipped with a refractive index detector preset to 280 nm and a radioactive detector (Carroll and Ramsey Associates, CA, USA).the samples were injected on to an analytical C18 column (Agilent, Eclipse Plus C18, 4.6 × 250nm, 110A, 5µm), which was eluted with a mobile phase of 100% water. The column flow rate was 0.5 ml/min and was kept at temperature 35ºC.

***Radionuclidic Identity*: -** Radionuclidic identity is confirmed by measuring the half-life of radiopharmaceutical doses and comparing it to the known half-life of fluorine-18 (109.77min). For the test, an aliquot of the [^{18}F]-FDG product was counted in an ion chamber or gamma counter at least five times. The half-life of the radioactivity was determined for each activity measurement using the following equation (1):

$T_{1/2}$ = −ln2 (time difference/ (ln (ending activity/starting activity))

***Bacterial Endotoxin*: -** Levels of bacterial endotoxin were tested and qualified using one of two procedural methods. Both are based on USP recommendations but use control standard endotoxin referenced to the USP. Either a gel-clot method or the portable test system (PTS) from Charles River Laboratories was used. All of the bacterial endotoxin levels were <175 EU per batch for the initial qualification syntheses.

***pH*:-** Because the product volume is small, as well as radioactive, pH was measured using an appropriate variation of USP ⟨791⟩ pH. The pH test strips were checked by pipetting pH 5 and pH 7 calibrated commercial pH standards onto individual strips. The color on the strips must match the pH5 and pH 7 on the color key supplied with the test strips. Then the [^{18}F] FDG was pipetted onto another test strip, the color checked against the color key, and the result recorded. The measured pH 7 for the [^{18}F] FDG product to be released.

***Sterility*: -** Sterility was tested using the direct inoculation method as is required by USP. It is not a releasing test.

***Stability And Expiration Dating*: -** The final drug product was left at room temperature for up to 12h. During this time, the product was measured periodically for radiochemical purity using analytical HPLC and TLC. In addition, the [^{18}F]-FDG product was examined for changes in UV absorbance of the product peak with time. There was no UV detectable breakdown of the product over that time period. The expiration time (typically 8–10 hrs) was set based on stability data.

RESULTS

***Residual Organic Solvents Content*: -** Gas chromatography was performed on 7890B Agilent system, equipped with a J&W HP-5 column (30 m × 0.32 mm × 0.25 µm). GC system was supplied with an H_2 (30 mL/min) from CFH200 generator (Peak Scientific, UK), ensuring 99.9995% of hydrogen purity, zero-air (400 mL/min) from a Jun-Air 0F301-4B generator (Jun-Air, UK) and He (6.0, Air Products, flow rate25 mL/min). Gas chromatographic system was operated at the following conditions: oven temperature 40°C for 1 min, inlet temperature 150°C, detector temperature 180°C.The samples were injected via auto sampler. For a comfortable sample application, 5-microliter single-use capillaries (Drummond Scientific, USA) were used for transfer the radioactive sample to 10 mL vials with aluminum caps and PTFE/Si septa (Agilent). Head-space injector was set to 80°C for 2 min, and then sample was equilibrated for 0.2 min and transferred to the GC system. The loop and transfer line were heated to 105°C and 110°C, respectively. Chemstation software was used for operation of chromatograph, acquisition and processing of data.

Bacterial Endotoxins (LAL Test):- The bacterial endotoxins level is commonly tested using the gel-clot technique. The technique uses a lysate of amoebocytes from horseshoe crab, Limulus Polyphemus. The addition of bacterial endotoxins to a lysate solution produces turbidity, precipitation or gelation of the mixture.

Method 1(F300E-FDG Synthesizer)

[^{18}F]-FDG synthesis was performed in F300E module which is a dedicated synthesizer only for FDG. The system is configured with a locked synthesis software template, our first priority to established the synthesis of [^{18}F]-FDG and access its quality for prior clinical application. The synthesis starts with pre-checking of the system internal parameters as such as temperature of the reactor, pressure, flow of the dry Nitrogen and air, on-off of respective each and every valve for flow and leak detection. As system QC passed it is ready for the [^{18}F]-FDG synthesis. System received the required no carrier-added [^{18}F]-fluoride in [^{18}O]H_2O from an ^{18}O(p, n)^{18}F reaction via in-house cyclotron (Sumitomo's HM-18) connected through internal delivery line. [^{18}F]fluoride delivered from a cyclotron was trapped on a preconditioned QMA cartridge and was eluted with K_2CO_3: Kryptofix 2.2.2 solution(0.2 ml in H_2O : 0.7 ml in dry acetonitrile, phase transfer catalyst), marked as yellow neck vial K_2CO_3/ K222.

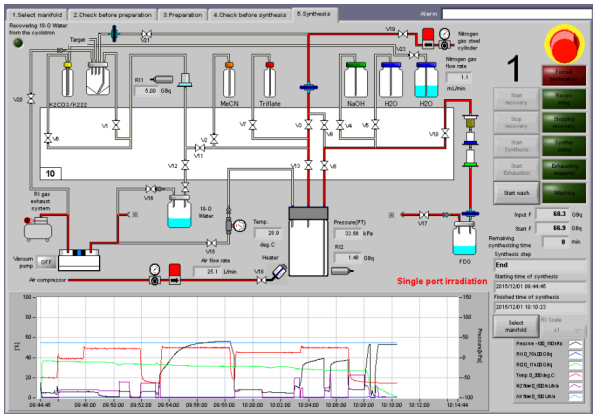


Figure 5:- Schematic diagram of the automated synthesis of [^{18}F]-FDG of F300E synthesizer

The solution was azeotropically dried by stream of dry Nitrogen and negative pressure to form dried KF^{18} at 100^{0}C for 8 minutes by adding dry acetonitrile (0.2ml), the fluorination was done by adding Mannose triflate (20mg in 1.8ml of dry acetonitrile) to this dried reaction mixture. The nucleophilic substitution reaction was performed for 6 minutes at 100^{0}C by replacing triflate ions by fluoride ion to produced acetylated fluorinated glucose (2-fluoro-1,3,4,6- tetra-O-acetyl-D-glucose). The system performed the one more drying cycle at 90^{0}C for 5 minutes, in order to removed he volatile impurities especially acetonitrile. The base mediated hydrolysis was performed at 100^{0}C for 5 minutes using 0.3M solution of NaOH. The reaction mixture was cooled down and loaded on purifying cartridges assembly. The preconditioned cartridges are used to remove the impurities such as to trap Kryptofix 2.2.2., $^{18}F^-$ Fluorinated TATM, TATM and the activity was transferred to the product vial. Finally the product was eluted with 5ml of the sterile water which passes through the reaction vial to refining columns, in order to wash out any activity left to reaction vial, into the sterile product vial having a 0.22 µM sterile membrane filter. The Total synthesis takes about 26 min and yield is about 65%. The [^{18}F]-FDG solution is clear, colorless, neutral and isotonic. It is subjected to pass the quality tests before being use for clinical studies. After successfully performing ten hot runs and comparing their QC data we moved for support the clinical studies.

Method 2 (MPS-100 Synthesizer)

After successful optimization of production of [^{18}F]-FDG via F300 module, we move forward to work with multipurpose synthesis module. This module has capabilities to perform the ^{11}C, ^{13}N, ^{15}O and ^{18}F chemistries as desired by user. The module has open software operation with programming capabilities to modify it as per chemistry. For doing ^{18}F-chemistry it has individually operated five vial valves and one closed reactor. These valves and reactor can be programed as per need and operated with designed software template. After completion of reaction the crude can be either loaded to appropriate solid Sep-Pak cartridge system for purification or loaded into integrated semi-preparative HPLC system for purification, the purified product will be transfer to housed rotatory vacuum evaporator to reduce the HPLC solvent. The final purified product will then diluted to physiological solution to finally transfer through sterile filter for clinical studies after performing the quality assurance tests.

In brief, the bombarded [^{18}O]-H_2O was transfer to the collection vial cyclotron line and then Valve V66, V10, V11, and V75 open to trap the ^{18}F ions to precondition QMA cartridge and remnant [^{18}O]-H_2O was collected to Vial marked as ^{18}O-water. The trapped activity was eluted with mixture of K_2CO_3 and $K_{2.2.2}$ (0.2 ml/0.7 ml) and transferred to reaction vessel via opening of valve V11, V12, V13, and V14. The azeotropically drying of reaction mixture was performed at 100^{0}C for 8

minutes followed by second cycle of drying via addition of acetonitrile (0.2 ml) via opening of valve V74 for 5 minutes at 90^{0}C. After cooling down the reactor the precursor mannose triflate was added via opening of valve V73. The fluorination was performed at 100^{0}C for 10 minutes followed by drying of excess of acetonitrile.

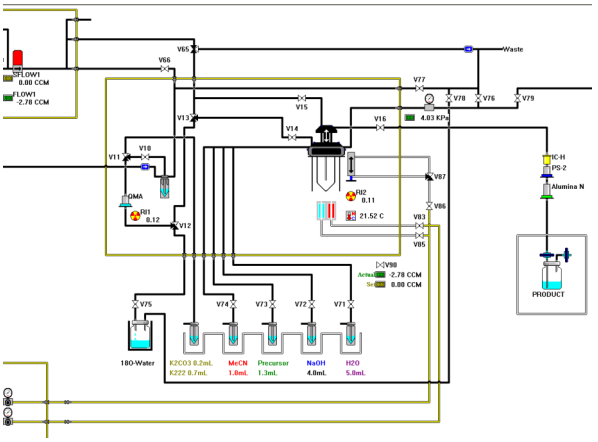


Figure 7:- Schematic diagram of the automated synthesis of [^{18}F]-FDG of MPS-100 module

The hydrolysis accomplished at 100^{0}C for 3 minutes, by addition of 0.3M NaOH to reaction vessel. The reactor was cooled down and crude was loaded to set of purification cartridges. To accomplish the complete transfer of crude mixture the reaction vessel was washed with 5ml of water of injection and this water is passed through the purification cartridge to elute out the purified [^{18}F]-FDG where as all the impurities were trapped within these cartridges. The finally [^{18}F]-FDG was collected in sterile product vial through sterile filter and is ready for quality control and clinical studies. The total synthesis time was about 58 minutes and yield is approx 50 %. Table 3 summarises the overall reaction time of [^{18}F]-FDG during particular steps between F300E and MPS100 synthesizer whereas table 4 and 5 shows the percentage yield of both the synthesizers.

Table 3: Comparison of overall reaction time during particular steps between F300E and MPS100 synthesizer.

Synthesis Parameter	F300E	MPS100
	Time (Sec)	Time (Sec)
Recovery (V-Vial)	180	181
QMA Trap	360	46
Drying	360	1633
Fluorination	300	810
Hydrolysis	360	823
Total time duration during synthesis	1560 sec / 26.00 min	3492.6 sec/ 58.21 min

Table 4: [^{18}F] FDG synthesis with F300E synthesizer

18F-FDG synthesis with F300E synthesizer						
No. of Runs	18F at Recovery (V-Vial) (GBq)	18F at QMA Trap (GBq)	18F at Fluorination (Gbq)	18F at Hydrolysis (GBq)	Final activity (GBq)	Yield %
1.	78	60	55	42	40.815	70
2.	78	59	52	40	38.854	67.79
3.	78	60	54	41	42.845	68.33
4.	76	59	53	41	41.276	69.49
5.	72	55	49	38	38.417	69.09
6.	70	53	48	38	36.382	71.69

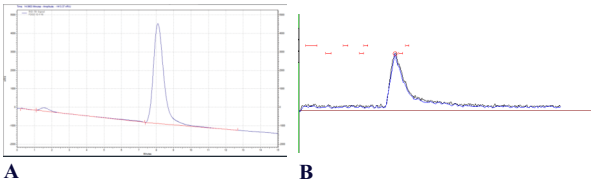
Table 5: [^{18}F] FDG synthesis with MPS100 synthesizer.

18F-FDG synthesis with MPS100 synthesizer						
No. of Runs	18F at Recovery (V-Vial) (GBq)	18F at QMA Trap (GBq)	18F at Fluorination (GBq)	18F at Hydrolysis (GBq)	Final activity (GBq)	Yield %
1.	72	53	29.5	20	17.72	37.73
2.	78	56	33.5	25	15.206	44.64
3.	72	53	30	22	16.5	41.50
4.	70	53	32	24	18.4	45.28
5.	68	51	28	20	22.75	39.21
6.	76	56	33.4	29	26.229	51.78

DISCUSSION

Practical Considerations

Initially, we have generated fluorine-18 on a Sumitomo HM-18 cyclotron equipped with Nb fluorine-18 targets, and manufactured FDG using the F300E-FDG synthesis module. A typical production of FDG began by generating [^{18}F] fluoride with the Sumitomo HM-18 cyclotron via the ^{18}O (p, n) ^{18}F reaction. Bombarding an Nb target containing $H_2{}^{18}O$ (~ 1.6 mL) with a 40 µA proton beam for 30-40 min depending upon the port side (dual port i.e. port A and port B) produced 1073±87.5 mCi of [^{18}F] fluoride per day and 6618±113mCi per week. FDG was prepared by standard fluorination of mannose triflate, followed by base hydrolysis (NaOH). This amount of FDG was adequate when scanning up to ~ 16 or 17 patients per day at Sanjay Gandhi post graduate institute of medical sciences (S.G.P.G.I.M.S., Lucknow, India). However, as discussed above, there has been steadily increasing demand for FDG within our PET Center. Concurrent with this growth, F300E-FDG synthesis module (Cassettes based system) motivated us to reproduced ^{18}F-FDG in another system i.e. MPS100 module (^{18}F-Tray based) which is an automated system designed for multiple tracer production. From a practical perspective, the transition from F300E-FDG module to MPS100 ^{18}F-FDG module was seamless. Though the preparation method for both the process is same but synthesis time and % yield of ^{18}F-FDG are the most important factor in terms of production and maintenance. Practically the F300E-FDG synthesis module (Cassettes based system) is a simple, robust and reproducible method with compact designing. While MPS100 (^{18}F-Tray based) based on programmable designing. F300E synthesizer is a fully dedicated system for ^{18}F-FDG while in MPS100 it is not. Short timing of operation i.e. 26 mins while it is time taking operation in MPS100 58. 21 mins. Single tubing system, makes the reaction fast while the other system have multiple tubing system and the reaction takes much longer time to complete. F300E synthesizer is user friendly while the other is based on the programming of the user. We reasoned that having both sumitomo synthesizer in the same mini-hotcell would not allow us to run one while conducting maintenance on the other. Therefore we have two separate mini-hotcells. Our workflow is simplified in F300E system with the yield of about 60% to 70% while it is 30% to 50% in MPS100. Manufacturing this amount of FDG at 8:00 am allows us to run clinical PET-CT scanners for 8h per day, and scan up to 15 patients a day with ^{18}F-FDG. The particulate test shows clear and colorless solution, pH was 7, RTLC (R_f) was 0.6 and Kryptofix 222 was <50 µg/ml. The radiochemical yield was 98.6 while the radiochemical purity was 97.8% and endotoxin was <2 (EU/mL) is shown in table 6. Trend of activity of HPLC via Refractive Index Detector shows the retention peak at 8.3 min of the [^{18}F]-FDG product is depicted in figure 8.



A B

Figure 8: Trend of activity of HPLC and Radiation , A) Refractive Index Detector signal, B) Radiation peak of the [^{18}F]-FDG product.

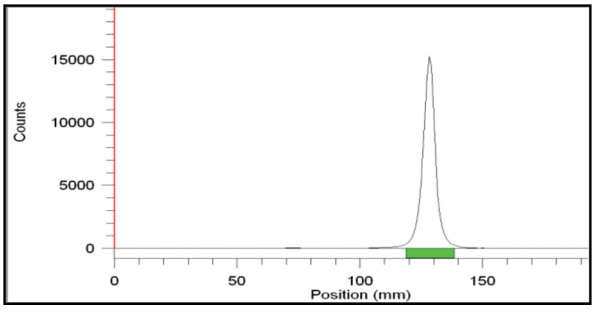


Figure 9: Radio TLC scan chromatogramTable 6: Quality Control Tests for the [^{18}F]-FDG qualification run

Table 6: Quality Control Tests for the [^{18}F]-FDG qualification run

Batch Number	MBR-FDG-05-02-2019-001	MBR-FDG-06-03-2019-001	MBR-FDG-06-05-2019-001
Test Performed			
Particulate Test	clear and colorless	clear and colorless	clear and colorless
pH	7	7	7
Filter Integrity (psig)	55	60	60
Kryptofix [2.2.2] µg/mL	<50	<50	<50
RTLC (Rf)	0.6	0.6	0.6
Radio Chemical yield	98.6	97.65	98.2
Radio Chemical purity (%)	97.8	99.7	98.3
Half-life (min)	110	110	110
Measured Endotoxin (EU/mL)	<2	<2	<2

CONCLUSION: We developed two different protocols over these machines in order to serve the patients who are coming to our PET centre for their studies. The development of the ^{18}F-FDG synthesis software template over MPS-100 synthesizer facilitates our centre to serve the patients when our fully dedicated synthesizer failed the production. The failure of dedicated synthesizer may account either to some technical issues or Quality control test failure. The protocol developed with MPS-100 synthesizer yield ^{18}F-FDG approximate about 45% (EOB) with synthesis time of around 35 minutes. Finally our centres have two automated synthesis modules which have the capability to produced ^{18}F-FDG to do the patient studies in good yield and purity. Our protocol is simple, reproducible and robust to work over it.

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