Production of Radioactive [18F] FDG by using Explora FDG4 Radiochemistry Module at Neurospinal & Cancer Care Institute

Hatim Ali Najmuddin, Rizwan Farooq

Abstract— Today, PET/CT is one of the promising diagnostic tool for investigation of oncology indication with 18F FDG that are installed worldwide over 5000 facilities. Pakistan has only six PET/CT centers in the whole region. Out of these, one of the Non-profit organization the **NCCI - Neurospinal & Cancer Care Institute** serves the nation. Production of 2-[18F]fluoro-2-deoxy-D-glucose [18F] FDG at NCCI by using **SIEMENS CYCLOTRON – ECLIPSE RD**, bombardment for 1 hour at 35 mA and synthesis by **SIEMENS EXPLORA FDG4** Radiochemistry Module based on nucleophilic displacement reaction. The yield of [18F] Fluoride around 2000 ± 100 mCi (2013), 1800 ± 300 mCi (2014), 1500 ± 100 mCi (2015), 1500 ± 200 mCi (2016), 1300 ± 300 mCi (2017), 1400 ± 200 mCi (2018) and 1100 ± 200 mCi (2019) out of this Explora producing 65% to 70% yield of [18F] FDG on every run.

Index Terms— Siemens, Eclipse Cyclotron, Explora FDG4, [18F] FDG, Radioisotope Production.

1 Introduction

David Townsend was the first who came up with the concept of PET/CT (Positron emission tomography) in 1988[1], [2] and after a successful result of its prototype, PET/CT becomes the ideal choice for the variety of clinical indications for oncology. Today, PET/CT is one of the promising diagnostic tool for investigation of oncology indication with 18F FDG being the radiopharmaceutical tracer of choice in most of these indications, that are installed worldwide over 5000 facilities [3]. Pakistan lacks in a number of PET scan machines according to population and increasing cancer patients. Pakistan only has six PET/CT centers in the whole region. Denser the population caters to the healthcare needs of its residents. Well, in this case, Karachi the largest city of the country only has 4 PET/CT systems. In which one of the nonprofit organizations that serve the nation in advancing the quality of patient care through innovation, technology, and research. The **NCCI - Neurospinal & Cancer Care Institute** serves the nation since 1995 under the umbrella of M. Hashim Memorial Trust [4]. NCCI organization equipment with the latest state of art technologies of Radiation therapy, oncology investigation, and other diagnostic tools which counts organization providing the best facilities to their peoples. The spirit that led NCCI to offer a great deal in advancing its organization with the latest and advanced technologies for therapeutics and diagnostics to provide best facilities to all categories of people. One of the latest, state of art PET/CT along with CYCLCTRON for radiopharmaceutical production [4] that caters to the need for other PET/CT machines becomes functional in early 2013. The only institute in Karachi which has the Siemens first **PET mCT 64 slices scanner** with **Cyclotron Eclipse RDS** and synthesis module **SIEMENS EXPLORA FDG4** with automated hot lab and inclusive QC solutions. Besides, this system will not only fulfill the need of its own institute but also can supply isotopes to the other PET scanning facilities in Karachi. The molecular formula of 18 F-2-fluoro-2-deoxyglucose (2-FDG) is C_8 H_{11} $18FO_5$ and 181.3 Daltons in molecular weight. The half-life of this radioactive substance is 110 mins.

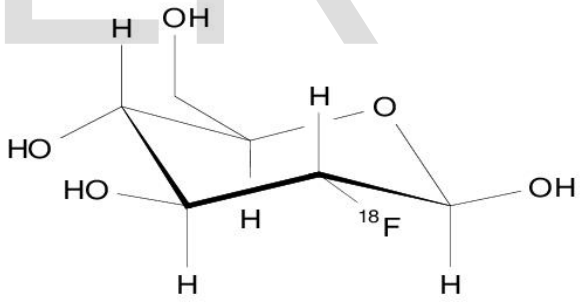

Fig1: Structure of FDG molecule

18F-FDG is a glucose analog in which the hydroxyl group on the 2-carbon of a glucose molecule is replaced by a fluorine atom. Like glucose, 18F-FDG is taken up into living cells by facilitated transport and then phosphorylated by hexokinase. Unlike glucose, 18F-FDG cannot undergo further metabolism because the hydroxyl group at the 2-carbon is a requirement for the process [5], [6]. Nevertheless, 18F-FDG is a good indicator of glucose uptake and cell viability. So, there are two possible ways to produce 18F-FDG, the one with 18F-fluorine gas by electrophilic substitution the vintage way to produce, and the second with 18F-fluorine ions by electrophilic displacement reaction, this is the most useful choice of method for 18F-FDG synthesis because of its radiochemical yield is more than of the conventional way of producing FDG by substitution reaction method. The whole synthesis is automated [7].

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[18F]FDG is produced per under Good Manufacturing Practice (GMP). The synthesis procedure of [18F] FDG has been validated, but certain quality measures should be taken for every batch to maintain the quality and the purity of the final product. [18F]FDG is delivered to on-site patients and other hospitals after a successful quality control test.

2 Material & Method

All reagents of the [18F] FDG synthesis were of the highest available purity. The majority of the reagents are purchased from **Abx Advance Biochemical Compound** and used without further purification. [18O]Water is purchased from **Huayi Isotopes Co.** For trapping of [18F] Fluoride ions Pre-Conditioned Sep-Pak QMA cartridge is used, and Solid-phase purification of [18F]FDG was performed with Sep-Pak column including dry reaction vessel, 30 ml vial for final [18F]FDG and 0.22mm filter.

3 Production of [18F] Fluoride Using Siemens Eclipse Cyclotron 11MeV:

The cyclotron employed for production is Siemens Eclipse 11MeV cyclotron located at the NCCI – Neurospinal & Cancer Care Hospital in Karachi, Pakistan.

Siemens manufacturing two models of Eclipse cyclotron under the RDS label, HP and RD. Our Crump cyclotron is Siemens RDS 111 (Radiochemistry Delivery System) Eclipse RD is built around 11 MeV negative Hydrogen ion cyclotron. The RD model flexibly designs with 8 position target carousel ability to run 40mA. The Eclipse cyclotron is self-shielded movable consist of an interlocking block of polyethylene and boron carbide cement [8].

Production of [18F] Fluoride begins with the nuclear reaction using over 95% [18O]Water, which is similar to ordinary water except it is enriched with the stable isotope O-18. Upon bombardment with an Eclipse cyclotron 11MeV photons. The volume of a target is 1.4ml and the normal irradiation time is 1 hour with 35mA beam current, this stable isotope is transformed into F-18, which is in the chemical form of [18F] fluoride ion. The cyclotron is producing 18F since it was installed in 2013 till now.

The yield of [18F] Fluoride throughout these years is varied due to different condition and maintenance issues as it can be seen in the following table:

TABLE 1
YIELD OF [18F] FLUORIDE FROM 2013 TO 2019.

S.No	Year	[^{18}F] Fluoride (mCi)
1	2013	2000 ± 100 mCi
2	2014	1800 ± 300 mCi
3	2015	1500 ± 100 mCi
4	2016	1500 ± 200 mCi
5	2017	1300 ± 300 mCi
6	2018	1400 ± 200 mCi
7	2019	1100 ± 200 mCi

4 Synthesis of [18F]FDG Using Siemens Explora FDG4 Module:

Along with Siemens cyclotron for producing [18F] Fluoride, Siemens Explora FDG4 Module is required for synthesizing of 18F-FDG.

Explora FDG4 Specification:

- 45-minute synthesis
- 75% decay corrected yield
- Multiple runs without interference (maximum 4 runs)
- Customizes your own recipes
- Remote diagnostic capability
- Auto-cleaning on one click
- Rich user feedback (radiation, temperature, pressure sensors)
- Comparatively less operational cost
- > 99% uptime
- 40% more likely than other commercial systems to provide yields over 75%

4.1 Trap And Released of [18F] Fluoride Ions:

The most proper way to execute this step is to use of [18F] Fluoride Ion exchange resin Sep-Pak light QMA (Quaternary ammonium anion exchange) column that is treated with 10ml of Potassium Carbonate K2CO3. When [18F] Fluoride/ [18O]Water passes through the QMA column 18F- retained in the QMA while 18O water collected in a separate vial. The 18F ion is then transferred into the reaction vessel by addition of the solution called Kryptofix K 2.2.2 and its volume is adjusted according to the recipe (i.e. 0.98ml x 2). K2.2.2 binds with the potassium ions to prevent any formation of 18F- with free K+ ion but also bind loosely with K+ ion. Kryptofix facilitates the transfer of 18F ions to the reaction vessel.

4.2 Evaporation of Residual Water:

The Explora FDG4 performs the drying of 18F ion solution into multiple evaporations. The subsequent azeotropic distillation occurs after the addition of Anhydrous Acetonitrile and volume can be adjusted according to the recipe (i.e. 1.4ml). This evaporation removes the remaining water from the solution.

The temperature of the top and bottom air heater is typically set at 1400 C to facilitate evaporation. Nitrogen gas is bubbled into the solution to aid the drying process.

When the reaction vessel is completely dry, the temperature rapidly rises. At this point, the evaporation of the solution inside the reaction vessel is complete [9].

4.3 Production of [18F] fluorinated Intermediate:

After complete evaporation, the next step is the process of synthesizing 18F-FDG. This step involves the addition of Mannose triflate and the amount according to the recipe i.e. 2.2ml.

During this step, the mannose triflate react with [18F] fluoride ion to produce the [18F] fluorinated Intermediate (2-deoxy-2-[18F]fluoro-1,3,4,6-tetra-O-acetyl-D-glucopyranose)[11] via the SN2 mechanism. The temperature of the bottom air heater during the reaction is 900C. The acetonitrile associate in the preparation of mannose triflate is evaporating during this re-

action. The temperatures of the top and bottom air heater are typically set to 1400C to facilitate evaporation.

4.4 Acid-Catalyzed Hydrolysis:

The fourth step of producing [18F]FDG is the acid hydrolysis of the intermediate compound of [18F]FDG. Hydrochloric acid (HCl) is used to perform this reaction. 2 ml of HCL then added with the intermediate in the reaction vessel and starts heating. The acetyl group during hydrolysis turns to acetic acid due to the heating effect and the hydroxyl free group of FDG is generated.

The temperature of the bottom air during the acid hydrolysis is 1650C, while the top air heater is 900C. The concentration of HCl is 1 normal. It takes approximately 8 minutes for completion using one normal HCl[12].

4.5 Purification and collection of Final [18F]FDG product:

The fifth and final step is the purification and neutralization process of the final FDG product. A series of column cartridge is placed in the last step to acquire the final product used to purify the FDG by passing through the column. The order of series is not necessary but includes:

- Removal of kryptofix by **Cation exchange**.
- Some unhydrolyzed and partially hydrolyzed intermediate of FDG will trap in the **C-18** column.
- During synthesis, some fluoride remains unreacted which are then trapped by the **Alumina column**.
- The final product should be in neutralized form with the help **Ion retardation**, also adjusting the pH.

Following the purification, water is added according to the recipe or to your adjustment into the reaction vessel and passes through the column to collect as much of the activity retained in the column as possible.

Finally the collection of [18F]FDG after releasing from the purification column into the sterile evacuated vial with additional purification by passing through 0.22mm sterile filter membrane for bacteria free product.

Step 1:

$$[^{18}F]F^{-}(\text{aqueous}) + K_2CO_3/K2.2.2 \xrightarrow{CH_3CN} (K/K2.2.2.)^{+}/[^{18}F]F^{-}\ (\text{aqueous})$$

Step 2:

$$(K/K2.2.2.)^{+}/[^{18}F]F^{-}(\text{aqueous}) \xrightarrow{\text{Distillation}} (K/K2.2.2.)^{+}/[^{18}F]F^{-}\ (\text{anhydrous})$$

Step 3:

$$(K/K2.2.2.)^{+}/[^{18}F]F^{-}\ (\text{anhydrous}) + \text{MannoseTriflate} \xrightarrow{\text{Distillation}} \text{Tetra-Acety}\,[^{18}F]\text{FDG}$$

Step 4:

$$\text{Tetra-Acety}\,([^{18}F]\text{FDG} \xrightarrow{\text{HCl Hydrolysis}} \text{Crude}\,[^{18}F]\text{FDG}$$

Step 5:

$$\text{Crude}\,[^{18}F]\text{FDG} \xrightarrow{\text{Purification and Neutralization}} [^{18}F]\text{FDG}$$

The reaction scheme for the production of [18F]FDG[10]

4.6 Quality Control and Dispensing:

After the final product received in a separate vial, the product has to go under standard quality control tests. The quality control of every batch of [18F] FDG includes:

- Visual checking
- pH measurement by pH strips
- Chemical purity by K-TLC
- Residual solvent by using Gas Chromatography
- Radionuclidic identity by measuring its Half-life and purity by obtaining gamma spectrum using Multi-Channel Analyzer (MCA)
- Radiochemical purity by TLC method,
- Bacterial Endotoxin by LAL test
- Sterility check through a culture medium of fluid Thioglycollate
- Last, Filter membrane integrity test by passing air pressure through a filter.

After successful performing of quality control test, the product will then released for dispensing to provide doses to patients and for packaging and shipping to other centers.

5 Discussion:

Siemens Eclipse RD Cyclotron and Explora FDG4 Module have been helpful in the synthesis of 18F FDG since it's installation but it has more capacity to cater to the needs of other PET/CT machines in the city which are not fully utilized by other institutes or because of lack of proper marketing. Normally one cyclotron is enough to cover the need of almost 10 PET/CT machines but due to competence trend or non-compliance of regulation of IAEA, other cyclotrons were installed for just one PET/CT machine which is totally waste of money and will eventually increase cyclotron radioactive waste.

6 Result:

Neurospinal And Cancer Care Institute Hospital - NCCI is serving the nation with great cause especially in the diagnosis and treatment of cancer patients using state of the art modern technologies, one which includes the production of FDG radiopharmaceutical for the diagnosis. We generate fluoride-18 ions by using SIEMENS ECLIPSE RDS 11 MeV Cyclotron equipped with Radiochemical synthesis module SIEMENS EXPLORA FDG4 to synthesize FDG using fluoride ions. Oxygen O18 water used to bombard for 1 hour ± 15mins at 35 mA current to produce on average about 1500 ± 200 mCi of fluoride-18 ions as shown in Table 1. Production of FDG passes through various steps mainly by fluorination of mannose triflate which is then followed by hydrolysis of intermediate

compound of FDG using HCL. Activity yield of FDG using EXPLORA FDG4 synthesizer on average of about 1000 ± 130 mCi, corresponding to 65% of yield. Quality for the final product is measured by standard guidelines of US pharmacopeia recommended quality test to perform.

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[12] Siemens Explora FDG4 Operating Instruction Manual, Page 25