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Optimization of ^{18}F Radioisotope Production with Cyclone 18/9 MeV IBA Cyclotron Installed at NINMAS

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Abstract

A cyclotron is a particle accelerator, which employs electromagnetic fields to accelerate charged particles to extremely high speeds and energy. It is used to create radioisotopes for radiopharmaceuticals, which are used to diagnose and treat cancer. Because cyclotron-produced radiopharmaceuticals are exceptionally effective in identifying various cancers. Cyclotrons are fast evolving and will play an increasingly important role in the healthcare industry, particularly in advanced medical imaging techniques like positron emission tomography-computed tomography (PET-CT) and single photon emission computed tomography (SPECT). An 18/9 MeV cyclotron (18 MeV for proton and 9 MeV for deuteron, Model: Cyclone 18/9, IBA) was installed at the National Institute of Nuclear Medicine and Allied Science (NINMAS), Bangladesh Atomic Energy Commission (BAEC). Radioisotopes such as ^{18}F, ^{11}C, ^{13}N, and ^{15}O can be produced with this cyclotron. Solid target option is also available here which can be used for producing ^{67}Ga, ^{68}Ga, ^{124}I, ^{123}I, ^{111}In, ^{99m}Tc, ^{64}Cu, and ^{89}Zr radioisotopes. ^{18}F is the radioisotope of choice for many radiopharmaceuticals due to its glucose analogous and half-life of 110 min. We are producing FDG on a regular basis. For a 60-minute bombardment time, a 40 to 50 micro amp beam current is employed to produce ^{18}F with a mass of 2500 to 3500 mCi. Because of the variable production parameters used, the production of ^{18}F varies. Parameters used in the production of ^{18}F radioisotope are limited to physical factors such as target material, target volume, collimator, stripper foil, and ion source. As a result, we consider ^{18}F yield to be the most important aspect in providing sufficient activity since we want to find the best operating point that minimizes both production time and cost. In order to produce an optimal ^{18}F radioisotope production, all parameters such as dee voltage, vacuum label, beam current, irradiation time, amount of enriched ^{18}O water, target pressure, and others are taken into account.

Keywords: Cyclotron, Optimization, FDG, enriched ^{18}O water, mCi, Yield

I. Introduction

There have been efforts to enhance the quantity of ^{18}F radioisotope generated by cyclotron in a single run due to the rising demand for [^{18}F] FDG for clinical PET-CT. The amount of ^{18}F is determined by the nuclear reaction's saturation yield, irradiation time, magnetic field, dee voltage, radiofrequency, beam energy, and the beam current hitting the target[1]. The beam energy (which for PET cyclotrons is normally fixed), the enrichment of the ^{18}O water (which is typical > 97%), and the effectiveness of the target design all affect the saturation yield. Engineering compromises between several requirements are necessary to maximize yield for commercial cyclotrons. Optimization process during the commissioning phase and the regular preventative maintenance is essential to ensure maximum performance. Optimal production of ^{18}F -FDG can be achieved by optimizing the different parameters. The main source of the shorter-lived, proton-rich radioisotopes currently employed in a variety of medicinal uses is the cyclotron[2]. This system used for ^{18}F - production through ^{18}O (p,n) ^{18}F nuclear reaction faces several conflicting requirements that include: reliability/uptime, the number of consumables, safety, cost, and yield. With the commercialization of PET tracer distribution, a higher yield has become one of the most important requirements. In a cyclotron, particles are accelerated to energies sufficient for bringing about the required nuclear reactions. The electric field makes the particles accelerated when they are in between the plates and the magnetic field produces a force on them (because they are moving) towards the center of the circle. By using the same electrode over and over again, the path of the beam of particles is bent into a circle[3]. The central region is one of the most critical issues in cyclotron design since even tiny variations of the magnetic field have a large influence on the beam. To minimize beam losses, the extracted current and the stability of the beams have to be optimized during commissioning and maintenance by fine-tuning the magnetic field[4]. A vacuum level of more than 10^{-5} mbar is needed during irradiations. This is achieved using oil diffusion pumps (ODP), always kept in operation. A fixed frequency of radio frequency system is chosen mostly to limit the costs. This implies careful tuning during the commissioning phase aimed at minimizing the reflected power maintaining stable dee voltage. In the case of the IBA 18/9 MeV cyclotron, the frequency of 42 MHz is used to achieve the best beam profile[5].

The most preferable method of nuclear reaction for ^{18}F radioisotope production for clinical use with a particle accelerator is ^{18}O (p,n) ^{18}F[6]. This nuclear reaction occurs within a conical target chamber made of niobium metal. Radioisotope production formulae is given below:

$$\frac{dn}{dt} = R = nI\left(1-e^{-\lambda t}\right)\int_{E_s}^{E_0} \frac{\sigma(E)}{\frac{dE}{dx}} dE$$

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This is the theoretical formula for producing radioisotopes during a nuclear reaction[7]. However, the optimal radioisotope production depends on the other physical parameters. The amount of [^{18}F] fluoride that can be produced in a cyclotron dependents on beam energy, beam current, irradiation time, ^{18}O water (97-99%), target body construction, target design (thickness of the target)[8]. Volume of enriched ^{18}O water, target current, the energy of the beam, helium pressure on the target, irradiation time, target status (new or old target or the total number of previous bombardments on the same target) are considered in optimal production of the ^{18}F radioisotope.

II. Objective

^{18}F production could not be merely increased by increasing beam current. Production of ^{18}F radioisotope is limited to the target pressure, temperature, target body design, ion source, etc. Changing all these parameters is related to ion current hence beam current. The aim of the study is to find the optimal production with the best production parameters.

III. Materials and Methods

Cyclone 18/9 MeV (18 MeV for proton and 9 MeV for deuteron), IBA cyclotron was installed at the National Institute of Nuclear Medicine and Allied Science (NINMAS) in 2021 and has been used for routine production for ^{18}F radioisotopes. To optimize the production of ^{18}F radioisotope for different beam currents, the yield of ^{18}F has been observed and analyzed. We have done more than 100 production batches to produce ^{18}F radioisotopes by irradiating ^{18}O enriched water. The magnetic field of 1.9 T at the hill and 0.35 T at the valley of this cyclotron were in use. Penning Ion Gauge (PIG) cold cathode ion sources were used. Dee voltage of 32 kV and radiofrequency (RF) of 42 MHz were applied for all production. The vacuum level was maintained at a 3.5×10^{-6} mbar during irradiation. Accelerated protons (negative hydrogen ion $^{-}$H) of 18 MeV bombarded on ^{18}O enriched water being used as the target in the cyclotron, producing ^{18}F isotope via ^{18}O (p, n) ^{18}F. Some 2.5 ml of ^{18}O enriched water were used for loading into the target chamber for all production. We have operated a niobium-bodied water target for the production of ^{18}F -fluoride for approximately 2 years. The water cooling system was used to cool the target, magnet, pop up probe, and ion source of the cyclotron. Because ions in the water may get radioactive, deionized water was used for cooling the cyclotron. We used helium gas and water for cooling the target. The vacuum level always was 3.5×10^{-6} mbar that was maintained by four oil diffusion pumps (ODP). To find the optimal yield for the optimization beam current, we used beam currents of 40 microamps, 45 microamps, and 50 microamps respectively for different irradiation times where others parameters were fixed. The vacuum level always was 3.5×10-6 mbar that was maintained by four oil diffusion pumps (ODP). To find the optimal yield for the optimization beam current, we used beam currents of 40 microamps, 45 microamps, and 50 microamps respectively for different irradiation times where others parameters were fixed; likely; target volume 2.5 ml, Dee voltage 32 kV and vacuum 4.5×10-6 mbar. (last para in materials and methods)

IV. Results

For the optimization of ^{18}F radioisotope production using the IBA 18/9 MeV cyclotron, more than 100 production batches were done. For various beam currents and irradiation times, the yield data were recorded at the end of the bombardment. All production batches data did not include in the table due to the same yield for the same irradiation time. The volume of ^{18}O enriched water, vacuum level and dee voltage were fixed.

Table 1. Yield of F-18 at the end of bombardment for beam current 40 µA.

Number of observation during production	Irradiation time, min	Activity at EOB,mCi
1	30	1400
2	35	1460
3	42	2037
4	49	2300
5	50	2370
6	53	2441
7	56	2484
8	65	3102
9	75	3520

Table 2. Yield of F-18 at the end of bombardment for beam current 45 µA.

Number of observation during production	Irradiation time, min	Activity at EOB,mCi
1	30	1608
2	37	1860
3	43	2300
4	50	2619
5	55	2760
6	60	3160
7	65	3242
8	72	3700
9	75	3740

Table 3. Yield of F-18 at the end of bombardment for beam current 50 µA.

Number of observation during production	Irradiation time, min	Activity at EOB,mCi
1	30	1845
2	37	2140
3	44	2606
4	48	2800
5	50	2827
6	55	2876
7	59	3260
8	67	3700
9	75	3976

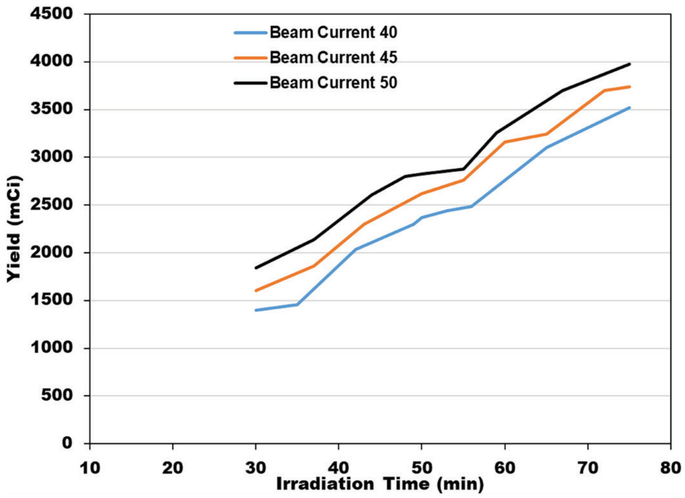

Fig. 1. Yield of F-18 radioisotope from the $^{18}O(p,n)^{18}F$ nuclear reaction was measured at the end of bombardment for beam current 40 µA, 45 µA and 50 µA.

V. Discussion

All parameters regarding the production of ^{18}F should be chosen in such a way that new settings of all parameters should give the maximum yield. In our experiment, some parameters like load volume of enriched ^{18}O water, vacuum level, radio frequency, and dee voltage were fixed due to the out of scope of use for the cyclotron. It was found that, with the increase of beam current, the ^{18}F yield increased (shown in Fig 1). To find the maximum yield we applied a beam current of more than 50 microamps. The amount of enriched ^{18}O water to be loaded into the target depends on the cavity volume of the target and the irradiation beam current since the target pressure developed in the target during the irradiation of the ^{18}O water depends on the target volume. The target volume of the niobium target of this cyclotron is 3.2 ml. So the average load volume of enriched ^{18}O water is 2.5 ml. Increasing beam current produces more power resulting in more heat and temperature[9]. Target foil rupture occurred as a result of the foil's inability to withstand the rapid pressure rise in the target chamber and the resulting rapid increase in heat deposited on the foil and target chamber because of the increasing beam current. When the ^{18}O water temperature rises to 200-240°C (during the irradiation), the water density decreases by 10-15% thus the adjusted water thickness becomes 3.6-3.7 mm. thereby increasing the target pressure to 35 bar (shown in Table 4)[10]. When the beam current is increased to its maximum permissible pressure, the defect is caused by a pinhole that is just on the edge of the foil in the insert, generally on the water cooling side of the target. For the daily production, we used a beam current of 45-50 µA corresponding to a target pressure of 30 bars. When the target beam current is limited to 50 µA, the mean lifetime of the havar foil insert is about 10000 µAh. Practically the operating pressure inside the target should not exceed 30 to 35 bars. In any case, going over this limit doesn't help increase production. In a liquid target, the pressure increases exponentially towards a vertical asymptote and it is observed, for large volumes, that a slight current increase of more than 50µA causes the pressure to rise very rapidly (shown in Figure 2). Therefore, there must be enough liquid inside the target to stop the beam but equally important not to overfill the target either. It is consequently possible to determine whether or not the target is correctly filled by comparing a current value to the pressure present in the target. Theoretically, only the region within the depth of the beam stopping power (3.5mm) reacts with the protons, with the remaining free target volume acting as a compressible volume as the target's pressure rises and as a means of increasing the heat exchange surface during the operation in the vapor phase. Therefore, it is impractical to load enriched ^{18}O water of more than 2.5 ml for this target chamber design of this cyclotron. Because, in practice, the water stopping power is determined by the entire target depth, as the beam first encounters a mixed liquid/vapor phase (due to the higher temperature), followed by a liquid phase (condensation). The water volume must be sufficient to ensure that the majority of the beam strikes the target below the liquid surface, thereby stopping the beam and allowing for the vapor phase, which also stops the upper part of the beam[11]. Furthermore, irradiation time should not be much longer because electricity costs would increase. Though the system had the design limitation of the target chamber (small volume), temperature and pressure issue and other parameters like Dee voltage, radio frequency, Magnetic field which are one kind of inbuilt parameters with the cyclotron, the optimal production yield of ^{18}F has been shown satisfactory for the beam current of 50µA.

Table 4. Pressure vs Temperature in a liquid target for 18F production (These data table and graph were taken from the IBA Nitra target training manual MID 35946 - ver.01)

Number of	Irradiated Water Temperature, 0C	Pressure, bar
1	100	1
2	120	2
3	140	4
4	160	6
5	180	10
6	200	16
7	220	23
8	240	33
9	260	47
10	280	64

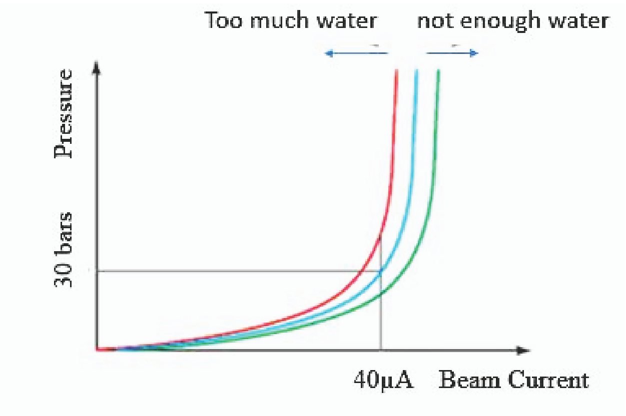

Fig. 2. Evolution of pressure in a liquid target

VI. Conclusion

Optimization of the yield of ^{18}F radioisotope producing from the cyclotron is important for the smooth operation of cancer services. In consideration of the trade-off of the consumable items of the cyclotron, the half-life of the product, dispensing time, longer services, and other costs related to the operation of the cyclotron, it would be helpful to find the optimal production for the parameters needed. Though some parameters could not be chosen due to the beyond scope of uses for this cyclotron, yield was satisfactory. So finding the best yield for the best parameters can help the better services for the cyclotron operation.

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