Installation of First Medium Energy Medical Cyclotron in Bangladesh at National Institute of Nuclear Medicine and Allied Sciences (NINMAS) for PET radiopharmaceuticals Production


ABSTRACT
PET-CT (positron emission tomography and computed tomography) is a gold-standard cancer imaging tool for diagnosis and management, as well as prognostic information based on treatment. Positron-emitting radionuclide $^{18}$F (Fluorine) is generated by accelerating particles to energies high enough to cause a certain nuclear reaction $^{18}$O(p,n)$^{18}$F within the particle accelerator, the cyclotron. Mannose triflate is converted to 2-[$^{18}$F] Fluoro-2-deox-D-glycose ([$^{18}$F]FDG) via nucleophilic reaction. Under the ownership of Bangladesh Atomic Energy Commission installed a medium energy (18/9 MeV, IBA) Cyclotron at National Institute of Nuclear Medicine and Allied Sciences (NINMAS). The facility was established in the oncology Building (Block F) of Bangabandhu Sheikh Mujib Medical University (BSMMU). Cyclotron vault and the Control room are located in the underground i.e. basement floor. Each wall of the cyclotron vault and ceiling is made of concrete with a density of 2.35 g/cm$^3$ and a thickness sufficient to shield gamma and neutron radiation. On the ground floor, there are Synthesis room, Quality control laboratory, and the Decontamination room. PET-CT rooms are located on the first floor. Identification, Radionuclide purity (Gamma spectrum detection and half-life measurement), Radiochemical Purity, Chemical purity, Residual solvent measurement, pH measurement, Sterility, and bacterial endotoxins (LAL test) are performed to maintain the quality of the product. The current uses of the Cyclotron are mostly for the synthesis of $^{18}$F-FDG.

Key words: Cyclotron, $^{18}$F-FDG, PET-CT.

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INTRODUCTION
Noncommunicable diseases (NCDs) have become a severe health issue in Bangladesh. Among all NCDs, Cancer is the sixth leading cause of death, accounting for 10% of all fatalities (1) and expected to rise to 13% by 2030 (2). Positron Emission Tomography and Computed Tomography (PET-CT) is considered a gold standard cancer imaging modality for diagnosis and management, as well as prognostic information provider depending on treatment (2,3). The prominent radioisotopes used to diagnose malignant cells in PET-CT are $^{11}$C (Carbon), $^{13}$N (Nitrogen), $^{15}$O (Oxygen), and $^{18}$F (Fluorine). $^{18}$F (Fluorine) is most commonly used because of its half-life of around 110 minutes, which is greater than $^{11}$C (twenty minutes), $^{13}$N (ten minutes), and $^{15}$O (two minutes). It decays by generating positrons with the minimum energy 511keV, leading to high image acquisition. By bombardment with high-energy protons, $^{18}$F (Fluorine) is produced from water enriched with $^{18}$O (Oxygen), and the efficient nuclear reaction is viz. $^{18}$O (p,n) $^{18}$F. Positron-emitting radionuclides are generated by accelerating charged particles (protons) to energies high enough to cause the certain nuclear processes within the particle accelerator, the cyclotron. Then $^{18}$F FDG has been synthesized using auto synthesizer Synthera®, IBA, which is given to patients. According to the IAEA's database, the world has 1500 (fifteen hundred) cyclotron facilities, with 1300 (thirteen hundred) of them coming from only 95 countries (4). Previously, in Bangladesh, there was only one small energy (9.6 MeV) cyclotron at United hospital, a private-owned sector. Bangladesh Atomic Energy Commission (BAEC) initiated the process of constructing cyclotron facility to meet the needs for radiotracers, particularly $^{18}$FFDG and then the first medium energy (18/9 MeV, IBA, Belgium) medical cyclotron was installed at NINMAS, BAEC, BSMMU, Dhaka.
CYCLOTRON FACILITY

The Cyclotron (Model: Cyclone® 18/9 from IBAS. A., Belgium) with radiochemistry facility has been installed in the F-block (Oncology building) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka with the ability to accelerate both proton at an energy of 18 MeV and deuteron at 9 MeV (Figure 1). The bunker room and control room are located in the basement level-2 of the oncology building, Block-F. The cyclotron has eight target ports. Among them three target ports have been chosen for the $^{18}$F, one for $^{11}$C, one for $^{13}$N, one for $^{15}$O, one for dummy and one for solid target. Synthesis room, reagent preparation room and the quality control laboratories are on the basement level -1. There is a hot cell with four chambers. Two Synthera® auto synthesizers have been installed in one chamber for the production of $[^{18}\text{F}]$FDG and $[^{18}\text{F}]$NaF. One equipped with HPLC has been installed in a chamber for the production of $[^{18}\text{F}]$FLT and $[^{18}\text{F}]$FMISO, one chamber has been designed for the production of $[^{11}\text{C}]$ Methionine, $[^{11}\text{C}]$ Acetate, $[^{11}\text{C}]$ Choline and $[^{13}\text{N}]$NH3 and another one for the radiotracer dispensing unit.

Each wall of the cyclotron vault and ceiling is made of concrete with a density of 2.35 g/cm$^3$ and a thickness sufficient to shield gamma and neutron radiation while adhering to atomic energy regulations. The vault door is composed of gamma and neutron protected material, and it’s engineered in such a way that beam creation is impossible when it's open. On the raised floor, three power supply units have been kept. The fresh air supply arrives at 300 m$^3$/h through the supply duct of AHU-1 under the elevated floor (behind the RF amplifier PS2). The return duct collects the exhaust air from the power supply room from the top. The power supply room's heat dissipation is less than 12 kW. To keep the cyclotron equipment cold, there is an IBA water conditioner system with a twin pump closed water circuit and water tank (max 100L).

Figure 1: a) Recent view of 18/9 MeV Cyclotron, IBA S. A., Belgium b) Hot cells for synthesis and dispensing c) Quality control room d) Philips Ingenuity TF PET/CT
SYNTHESIS ROOM

[\textsuperscript{18}F]FDG has been synthesized by Synthera\textsuperscript{\textregistered} auto-synthesizer (Figure 2) installed inside the hot cell in the synthesis room. Mannose triflate is converted to [\textsuperscript{18}F]FDG via a conventional technique including alkaline hydrolysis. To trap the ions, the aqueous \textsuperscript{18}F-Fluoride ion is passed via an ion-exchange column, then eluted to the reaction vessel with a mixture of potassium carbonate and Kryptofix 2.2.2, then water is removed by azeotropic drying with acetonitrile, and [\textsuperscript{18}F]-fluoride combined with mannose triflate. The solution is purified with a succession of \textsuperscript{18}C and alumina B-cartridges and eluted with distilled water after alkaline hydrolysis.

QUALITY CONTROL (QC) LABORATORY

In this laboratory, Identification, Radionuclide purity (Gamma spectrum detection and half-life measurement), Radiochemical Purity, Chemical purity, Residual solvent measurement, pH measurement, Sterility, and bacterial endotoxins (LAL test) are performed. The physical appearance is examined first. The gamma spectrum is detected immediately after synthesis using a Multi-Channel Analyzer (Elysa Raytest-Mucha, Germany). The ISOMED 2010 Dose Calibrator (Dresden, Germany) is used to calculate the half-life using the standard formula \(t_{1/2} = \frac{0.693}{t} \ln \left(\frac{A_0}{A_t}\right)\), where \(t_{1/2}\) (half-life), \(t\) (time interval in minutes), \(A_0\) (starting activity), and \(A_t\) (activity measured after 10 min). The radiochemical purity of [\textsuperscript{18}F] FDG is measured by scanning Radio-TLC strips using a Radio TLC Scanner (Elysa Raytest miniGita-Beta Positron Detector) utilizing silica gel thin-layer chromatography (Radio-TLC). A gas chromatograph (Shimadzu GC-2010 Plus) is used to determine the amount of residual solvent (Ethanol and Acetonitrile). The confirmation of the microbiological purity of the final [\textsuperscript{18}F] FDG product is assessed using bacterial endotoxin (BET) and sterility tests (Figure 3).

PRESENT ACTIVITIES

The current uses are mostly for the synthesis of radiotracers ([\textsuperscript{18}F]FDG) for seven government and private PET-CT centers in Dhaka. The Cyclotron facility has been operational since October 2020, with more than 100 batch of [\textsuperscript{18}F]FDG production completed successfully.

FUTURE PLAN

This cyclotron will also be used to synthesize radioisotopes \(\textsuperscript{11}C, \textsuperscript{13}N, \textsuperscript{15}O\), in addition to \(\textsuperscript{18}F, \textsuperscript{68}Ga, \textsuperscript{124}I, \textsuperscript{99m}Tc, \textsuperscript{64}Cu, \textsuperscript{86}Y \) and \(\textsuperscript{89}Zr\) radioisotopes will be manufactured by using the solid target in the future.

ACKNOWLEDGMENTS

We appreciate the cooperation of BAEC and the authorities of BSMMU in the installation of the Cyclotron. Special thanks to Ministry of Science and Technology (MOST) of People's Republic of Bangladesh for funding the establishment project of the “PET-CT & Cyclotron Facility” through ADP of Bangladesh Government.

REFERENCES