Operational Challenges and Achievements in ^{18}F-Fluorodeoxyglucose Production during the Pre-automation Phase of Cyclotron at NINMAS

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ABSTRACT

An important step forward for nuclear medicine in Bangladesh was the establishment of the 18/9 MeV Cyclotron (Model: Cyclone 18/9, IBA) at the National Institute of Nuclear Medicine and Allied Sciences (NINMAS) under the Bangladesh Atomic Energy Commission (BAEC). This cyclotron, capable of operating at 18 MeV for protons and 9 MeV for deuterons, has been pivotal in producing 18F, a crucial radioisotope for PET imaging. During the pre-automation phase, the cyclotron supported limited ^{18}F production, addressing the initial demand for ^{18}F-FDG and significantly reducing patient waiting times for PET scans in Dhaka. Initially, ^{18}F production was performed with a low beam current of 10–12 μA, yielding a modest amount of radioisotope transferred for synthesis. Despite the limitations of manual operations, nearly 10 batches of ^{18}F-FDG were successfully produced during this phase. The transition to automation allowed the cyclotron to operate at its full capacity, with beam currents increased to 40–50 μA. This enhancement enabled the production of ^{18}F within a 60-120 minute bombardment period, meeting the growing demand for PET imaging. This paper highlights the operational challenges encountered during the pre-automation period, including low production efficiency and manual handling constraints. Key factors influencing ^{18}F production, such as beam current, irradiation time, enriched ^{18}O water quantity, Dee voltage, vacuum levels, and other parameters, were carefully studied to optimize yield. The pre-automation phase provided valuable insights into cyclotron operation, laying the groundwork for current automated processes that have greatly enhanced production efficiency and reduced operational costs. This study is a testament to the innovative efforts that bridged the gap between manual and automated 18F production, ensuring the availability of radiopharmaceuticals in Bangladesh.

Keywords: Cyclotron, ^{18}F-Fluorodeoxyglucose, Positron Emission Tomography, Half-life.

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INTRODUCTION

The radioisotope ^{18}Fluorine- has emerged as a cornerstone in positron emission tomography (PET) imaging, a transformative diagnostic tool widely used in oncology, neurology, and cardiology (1). PET radionuclides such as ^{18}F, ^{11}C, ^{15}O, and ^{13}N are commonly produced using medical cyclotrons (2). Due to their relatively short half-lives, the installation of cyclotrons near PET scanners is necessary for radionuclides like ^{11}C (half-life of 20 min) and ^{13}N (half-life of 10 min), or within a reasonable transport distance for 18F, which has a half-life of 110 min (3).

Authors explored the foundational efforts in ^{18}F production using an 18/9 MeV medical cyclotron during its pre-automation phase at NINMAS. Focusing on this period illuminates the operational challenges and achievements that laid the groundwork for advancements in automation, providing valuable insights into the transition towards optimized production processes (4,14).

The installation of the 18/9 MeV cyclotron at NINMAS marked a critical milestone in enhancing nuclear medicine capabilities in Bangladesh. The cyclotron's dual-energy operation (18 MeV for protons and 9 MeV for deuterons) enables the efficient production of ^{18}F, alongside other medically relevant isotopes, significantly improving PET imaging availability in the region (5). The pre-automation phase, characterized by manual operation and intervention, presented unique challenges in target irradiation, chemical processing, and overall production management. However, this phase also provided a fertile ground for innovation, skill development, and operational optimization (6,7,13).

The exploration of ^{18}F production's technical intricacies, highlighting the importance of human expertise and adaptability in overcoming manual system limitations and

driving automation evolutions are highlighted in this context (8,9). The experiences from the pre-automation era at NINMAS not only contribute to the global understanding of cyclotron-based ^{18}F production but also highlight the significance of technological progression in enhancing the safety, efficiency, and accessibility of PET imaging technologies.

The objective was to explore the operational challenges and achievements during the pre-automation phase of ^{18}F production using the 18/9 MeV Cyclotron at NINMAS. Specifically, it examines the production runs conducted to evaluate the yield of ^{18}F and the quality of ^{18}F-FDG synthesized for patient administration. This study aims to provide insights into the effectiveness of manual operations, the optimization of production parameters, and the lessons learned in transitioning towards automated systems for enhanced efficiency and reliability in ^{18}F-FDG production.

MATERIALS AND METHODS

This study focuses on the operational challenges and achievements during the pre-automation phase of ^{18}F radioisotope production using the 18/9 MeV Cyclotron (Cyclone 18/9, IBA) at NINMAS. The cyclotron, installed within the basement of the PET facility at NINMAS, serves as a critical infrastructure for generating positron-emitting radionuclides, including ^{18}F, 15O, ^{13}N, and ^{11}C. During the pre-automation period, the cyclotron was primarily utilized for the production of ^{18}F for ^{18}F-FDG synthesis. The cyclotron operates on well-established physical principles and equations, which govern the acceleration of charged particles and the nuclear reaction for ^{18}F production. Cyclotrons accelerate charged particles using a perpendicular magnetic field and an alternating radiofrequency (RF) electric field. The fundamental equations governing the operation are as follows:

Cyclotron Frequency, $f = qB / (2\pi m)$, where: q is the charge of the particle (e.g., 1.602 × 10-19 C for protons), B is the magnetic field strength in Tesla (T), m is the mass of the particle (e.g., 1.67 × 10-27 kg for protons) [2,11]. For Cyclone 18/9, the RF system operates at a frequency of 42 MHz, ensuring resonance between the particle motion and the RF field (10). The radius of Particle Orbit, $r = mv / (qB)$, Where v is the particle's velocity. The magnetic field ensures the confinement of the particles within the cyclotron (2,10).

Energy of Accelerated Particles, $E = (1/2)\ mv^2 = (q^2B^2r^2) / (2m)$

For F-18 production, protons are accelerated to 18 MeV, reaching the target with sufficient energy to induce the nuclear reaction (10,11). The ^{18}F isotope is produced via the ^{18}O (p, n) ^{18}F reaction, where accelerated protons bombard O-18 enriched water. The cross-section and reaction yield depend on the proton energy and target properties (2).

Cyclotron Operation for ^{18}F Production

During the pre-automation phase, the cyclotron was operated with specific parameters to ensure optimal performance. The magnetic field strength was maintained at 1.9 T in the hill regions and 0.35 T in the valley regions, while the dee voltage was set at 28 kV. The beam current, ranging from 9 to 12 μA, was manually regulated by adjusting the magnetic current and hydrogen gas flow. Additionally, the vacuum level was sustained at $5–8 \times 10^{-6}$ mbar to provide optimal conditions for particle acceleration (10,11). Enriched ^{18}O water (2.5 ml) was manually injected into the target chamber. The nuclear reaction yielded ^{18}F, which was subsequently transported to the Synthera® synthesis module for ^{18}F-FDG production. Helium gas pressure facilitated the transfer of activity through a Teflon pipeline (2,10).

Production and Synthesis

After bombardment, ^{18}F was transferred to the Synthera® module for the synthesis of ^{18}F-FDG. The synthesis involved chemical reactions that were optimized for radiochemical yield and purity. The process was completed within 30–40 minutes, followed by quality control checks (2).

Quality Control (QC)

The QC lab utilized thin-layer chromatography (TLC), gas chromatography (GC), and high-performance liquid chromatography (HPLC) to evaluate radiochemical purity, sterility, and other critical parameters, ensuring the suitability of ^{18}F-FDG for patient administration (2,12). This manual and physics-based approach during the pre-automation phase provided a foundation for understanding operational parameters and optimizing ^{18}F production for clinical applications.

The pre-automation setup involved a combination of manual interventions and reliance on existing infrastructure, highlighting both the challenges of limited automation and the achievements in producing reliable radiopharmaceuticals for clinical use.

RESULTS

Manual Test Runs and Operational Parameters

During the pre-automation phase of the cyclotron operation, multiple test runs were conducted to assess the operational parameters and production efficiency of ^{18}F and ^{18}F-FDG. The manual operation phase involved non-computer-controlled units, with connections and processes managed entirely by human intervention. Throughout these runs, critical parameters for 18F production, including beam current, Dee voltage, radiofrequency (RF), and vacuum levels, were carefully monitored and documented.

Table 01 summarizes the operational parameters recorded during a single 38-minute production run under varying beam currents, constant Dee voltage, and RF frequency. Vacuum conditions exhibited slight variations.

Table 1: Operational parameters for 38-minute production with varying beam currents, constant Dee voltage, and RF frequency.

Time	Beam Current (µA)	Dee Voltage (KV)	RF (MHz)	Vacuum During ON (mbar)
8.52 am	10.6	28	42	6.80E-06
8.54 am	11.2	28	42	7.40E-06
8.58 am	12.2	28	42	7.50E-06
9.00 am	12.2	28	42	5.60E-06
9.01 am	12	28	42	7.80E-06
9.02 am	12.1	28	42	7.70E-06
9.04 am	11.6	28	42	6.80E-06
9.05 am	12	28	42	7.80E-06
9.06 am	11.8	28	42	7.20E-06
9.07 am	12	28	42	7.10E-06
9.08 am	12.3	28	42	7.20E-06
9.09 am	12.4	28	42	7.80E-06
9.10 am	12.28	28	42	5.40E-06
9.12 am	13.3	28	42	7.50E-06
9.14 am	13	28	42	7.30E-06
9.20 am	12.24	28	42	7.20E-06
9.23 am	12.47	28	42	7.80E-06
9.25 am	13.26	28	42	6.10E-06
9.26 am	13.2	28	42	7.10E-06
9.27 am	13.18	28	42	7.20E-06
9.30 am	12.18	28	42	6.80E-06
9.31 am	12.4	28	42	6.50E-06
9.33 am	12.54	28	42	7.80E-06

The beam current showed fluctuations within the range of 9 to 12 µA during this production cycle.

FDG Activity Post-Synthesis

After irradiation and synthesis, the activity was measured using a dose calibrator. The measured activities showed variation correlated with beam current and irradiation time. The activity post-synthesis represents the average yield across different beam current settings.

Table 2: FDG production yield after synthesis for eight production batches with varying irradiation times.

Date	Irradiation Time(min)	Activity after Synthesis (mCi)
26/11/2020	25	148.4
30/11/2020	27	154.4
03/12/2020	29	142.4
07/12/2020	38	172.4
10/12/2020	23	180.2
14/12/2020	29	179.7
17/12/2020	27	161.3
21/12/2020	38	178.1

The production yield exhibited a consistent correlation with irradiation time, indicating improved performance athigher durations.

Correlation between Yield and Beam Current

Figure 01 illustrates the relationship between the measured [18]F-FDG yield post-synthesis (represented by dots) and the theoretical yield (straight line) based on an assumption of 50% efficiency. The observed data points align closely with the theoretical model, validating the production parameters used during the pre-automation phase.

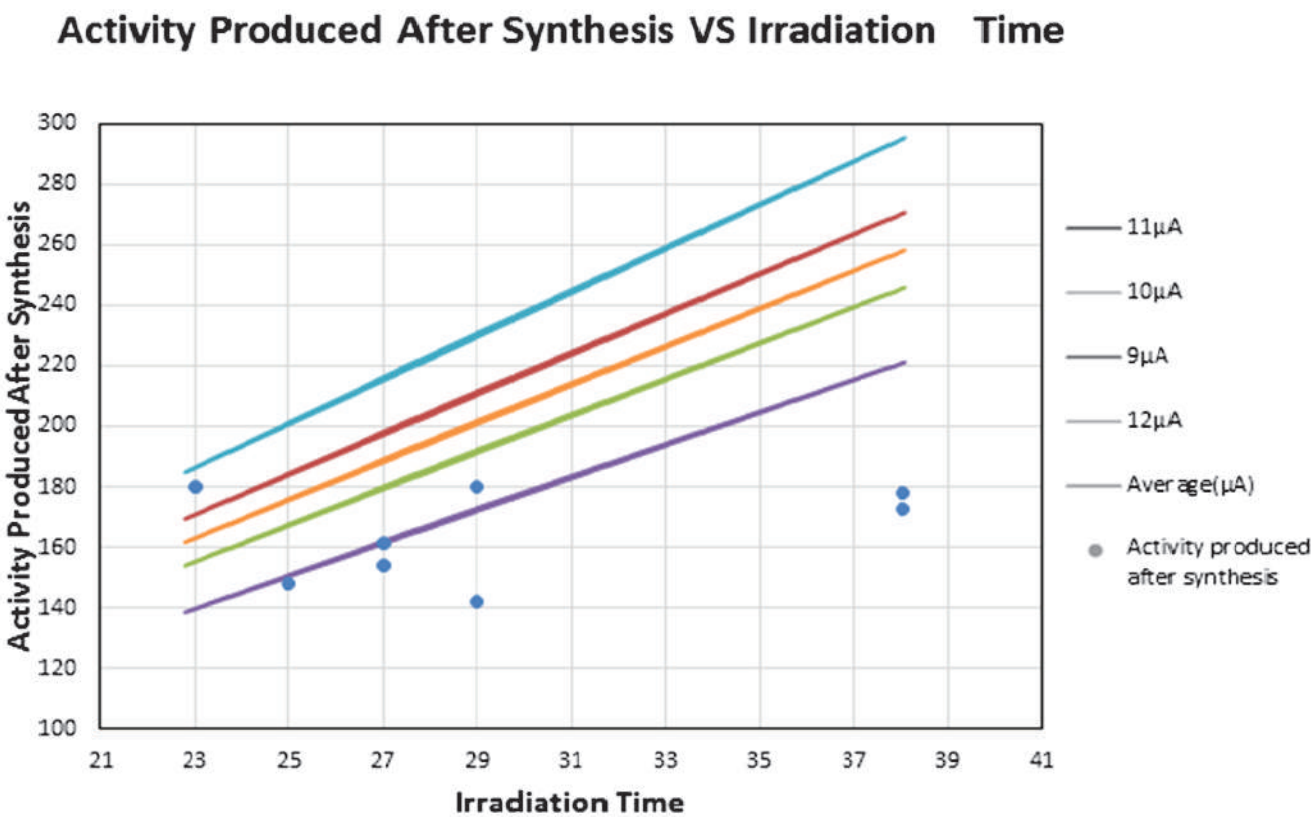

Figure 01: Correlation between [18]F-FDG production yield post-synthesis (dots) and theoretical yield (straight line) at varying beam currents.

The results demonstrate that the pre-automation operational framework, although labor-intensive, successfully produced ^{18}F and synthesized FDG with acceptable yields and quality. These findings paved the way for optimization and subsequent automation efforts to enhance production efficiency.

DISCUSSION

The Cyclone 18/9 MeV medical cyclotron, with its dual-energy capability (18 MeV for protons and 9 MeV for deuterons), has been pivotal in producing radionuclides such as fluorine-18, widely used in positron emission tomography (PET) imaging for oncology, neurology, and cardiology. This discussion focuses on the operational challenges and achievements during the pre-automation phase at the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), highlighting the implications for production efficiency and healthcare delivery.

During the pre-automation phase, F-18 production faced significant operational challenges due to manual interventions in cyclotron operation and radiopharmaceutical synthesis. Parameters such as beam current, dee voltage, irradiation time, and vacuum levels required meticulous monitoring and manual adjustments. These constraints limited the production capacity and introduced variability in yields, as evidenced by the fluctuations in beam current (9-12 μA) during production runs (Table 1). The manual introduction of enriched ^{18}O water into the target chamber and the subsequent transfer of ^{18}F to the synthesis module further underscored the labor-intensive nature of the process. Studies have shown that manual handling increases the potential for errors and inconsistencies in yield (4,13). Despite these limitations, the pre-automation phase at NINMAS demonstrated the feasibility of F-18 production, achieving yields sufficient to meet local clinical demands.

The production of ^{18}F-FDG during this phase exhibited a clear correlation between irradiation time and activity post-synthesis (Table 2). Longer irradiation times generally resulted in higher yields, consistent with theoretical models of cyclotron operation (1). However, deviations from expected yields, potentially due to equipment limitations such as nitrogen pressure imbalances or loose connections in the Synthera® synthesis module, highlighted areas for improvement. Optimization of operational parameters was crucial for maximizing production efficiency. For example, maintaining a stable vacuum level (5-8 × 10-6 mbar) and ensuring precise control over beam current were instrumental in achieving consistent yields.

Local production of ^{18}F-FDG significantly reduced patient waiting times for PET scans, enhancing diagnostic capabilities in Dhaka. This advancement underscores the critical role of medical cyclotrons in improving access to nuclear medicine. The transition to automation marked a transformative step, enabling higher beam currents (40-50 μA) and significantly increasing production capacity to 2500-5500 mCi within a 60-120 minutes bombardment period. Automation also minimized human errors and operational inefficiencies, aligning with global trends in cyclotron technology (7).

The experiences from the pre-automation phase provide valuable insights for optimizing ^{18}F production. Future efforts should focus on addressing equipment limitations and further automating critical processes. Advances in cyclotron design, such as compact systems tailored for local hospitals, could enhance accessibility and reduce operational costs (12). Additionally, integrating real-time monitoring and control systems would further improve yield consistency and safety.

CONCLUSION

The pre-automation phase of ^{18}F production at NINMAS using the Cyclone 18/9 MeV Cyclotron demonstrated significant achievements despite manual limitations. This phase addressed initial clinical demands, reduced patient waiting times, and laid a foundation for automation. Automation has since increased production capacity, improved efficiency, and enhanced radiopharmaceutical availability. Future advancements, such as compact cyclotron designs and real-time monitoring, promise further improvements in production and safety. NINMAS' journey from manual to automate[d] ^{18}F-FDG production

exemplifies progress in nuclear medicine and serves as a model for similar efforts worldwide.

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