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Original Article

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Assessment of Radioactivity Yield and Quality Controls of [^{18}F]FDG Production in Mongolia's First Cyclotron Facility: A Two-Year Experience (2022-2023)

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ABSTRACT

Purpose: The objective of this study was to evaluate the estimated radiochemical yield (RCY) and quality of routine [^{18}F]FDG production over two years (2022 and 2023) at Mongolia's first cyclotron facility, utilizing the MINItrace Qilin cyclotron (GE Healthcare, 9.6 MeV) and FASTLab 2 radiosynthesizer (GE Healthcare).

Methods: [^{18}F]Fluoride was generated using a MINItrace Qilin cyclotron, producing up to 2 Ci of radioactivity per run, 2-3 runs per week. The [^{18}F]FDG production was carried out using the FASTLab 2 radiosynthesizer utilizing FDG Duo and Single Citrate cassettes through nucleophilic radiofluorination of mannose triflate followed by basic hydrolysis. Quality Controls, including radiochemical purity, radionuclidic purity and identity, chemical purity, residual solvents, assay for radioactivity, bacterial endotoxins, and sterility, were performed in accordance with United States Pharmacopeia (USP) standards using bSCAN TLC Scanner, Captus-3000 MCA, Scion-456 GC, and Endosafe nexgen-PTS. Facility design and operation were managed in accordance with International Atomic Energy Agency guidelines to ensure GMP compliance.

Results: All quality control tests met the USP requirements, ensuring safe injections for patients. The RCY were within acceptable ranges. The RCY of the FASTLab 2 Duo cassette was consistently higher than that of the Single Citrate cassette throughout the study period. The RCY for both cassettes were gradually decreased over time, with no significant correlation between cyclotron maintenance and subsequent RCY.

Conclusions: Further investigation is needed to identify factors contributing to the decreasing radiochemical yield.

Key Words: Cyclotron facility, Radiochemical yield, FDG, Automated synthesis, Quality control

Introduction

Fluorodeoxyglucose ([^{18}F]FDG) is the most successful radiotracer in the expanding medical imaging technology of Positron Emission Tomography (PET) which is used for the diagnosis, staging, and restaging of several clinical conditions such as lung cancer, col-

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orectal cancer, lymphoma, melanoma, head and neck cancer, brain and breast cancer. FDG-PET also has been used in neurology, cardiology and inflammation/infection (1). Therefore, this radiopharmaceutical is typically the primary choice for countries initiating cyclotron-based radiopharmaceutical production.

Second State Central Hospital of Mongolia (SSCH, Ulaanbaatar city) is the first hospital introduced PET/CT technology in Mongolia along with the in-house cyclotron based production of [^{18}F]FDG from August, 2021. Despite the COVID-19 pandemic, with the assistance of the Mongolian government, KOFIH (Korea Foundation for International Healthcare) and KIRAMS (Korea Institute of Radiological and Medical Sciences), the hospital successfully arranged the installation and operation of the necessary equipment and laboratories, as well as trainings of the professionals. The facility design and operation management were organized in accordance with the International Atomic Energy Agency guidelines in order to achieve GMP requirements compliance (2). From 2022 to 2023, the routine production of [^{18}F] FDG and quality control tests were conducted, followed by its clinical application. Additionally, the several test productions of [^{18}F]NaF was performed in order to initiate the process of radiopharmaceutical approval certificate from Medicine and Medical Devices Regulatory Agency of Mongolia.

Methods

1. General Remarks

All reagents were purchased from commercial sources and used as received unless mentioned otherwise.

2. Production of [^{18}F]

For the production of [^{18}F]fluoride radioisotope, based on the ^{18}O(p,n)^{18}F nuclear reaction, the 9.6 MeV medical cyclotron (GE MINITrace Qilin, 2020) was used (3). The cyclotron is equipped with two currently installed Nb targets and a total of six target ports, with the potential to extend to target systems for ^{11}C, ^{13}N, and ^{15}O, along with one dummy target for testing. The enriched water $H_2{}^{18}O$ was purchased from Huayi Isotopes Co., China. The [^{18}F]fluoride was produced by bombardment of the target with extracted proton beam (~35-45 μA, 7-8 MeV) for 60-110 minutes from medical cyclotron.

3. Synthesis of ^{18}F−FDG

Radioactive [^{18}F]fluoride is transferred as liquid 2.5ml to the FASTLab2 synthesizer (GE Healthcare co.), where two types of cassettes (GE Healthcare co.) were used: citrate cassette for single production and duo citrate cassette for two production runs. First step of the synthesis was trapping the activity in QMA cartridge, then the [^{18}F]fluoride was eluted from the QMA into the reactor with an eluent mixture (0.5 mL of a solution, containing 3.75-5.75 mg of K_2CO_3 and 23-30 mg of kryptofix-2.2.2 (K2.2.2) in a 1:4 mixture of water and acetonitrile) and azeotropically dried. A solution of mannose triflate (33 ± 3 mg in 1.7 mL acetonitrile) was added and the radiofluorination was conducted at 125°C for 2 min to give [^{18}F]fluoro-1,3,4,6-tetra-O-acetyl-D-glucose ([^{18}F]FTAG). The reaction mixture containing [^{18}F]FTAG was diluted with water (11 mL) and passed through a C-18 Sep-Pak cartridge. [^{18}F]FTAG was trapped on the C-18 Sep-Pak cartridge, washed with additional water (13 mL), and base hydrolysis occurred on the cartridge at room temperature using 2 N NaOH (1 mL) for 3 min to give [^{18}F]FDG. [^{18}F]FDG was then eluted from the cartridge with citrate buffer (1.7 mL), passed through a second C-18 Sep-Pak (to remove any partially-protected [^{18}F]FDG) followed by an alumina-N cartridge (to remove any unreacted [^{18}F]fluoride ion) and diluted with water before being dispensed into a sterile intermediate vial (4, 5). The resulting solution (~

22 mL) was then passed through a 0.22 μm sterile filter, and dispensed into patient (~ 20 mL), quality control (~ 0.5 mL) and sterility (~ 1.5 mL) vials using an Comecer Timotheo LT semi-automated dispensing system. The bulk activity was measured by Comecer VIK 203 dose calibrator before dispensing aforementioned samples.

Synthesizer, Timotheo LT dispensing system and Comecer VIK 203 Ionization chamber were installed within the fully shielded Comecer hotcells: BBS2 and BBST, in order to comply with the radiation safety requirements and to maintain environmental conditions for radiopharmaceutical production. Compressed zero air and nitrogen gas with a purity of 99.9999% were used for the operation of pneumatic components and for transferring fluids and evaporation of solvents, respectively. The FASTLab 2 should ideally be operated at temperatures between 5°C and 35°C, with a relative humidity below 80%. It shoul be meantioned, that high temperatures (> 35°C) may impact performances of the chemical processes. The average temperature of the production cleanroom was 24.0 ± 1.7°C (max = 27.4°C) with a relative humidity of 35.4 ± 3.9% (max = 49%). The storage conditions for raw materials were 22.0 ± 1.4°C (max = 25.1°C) for temperature and 37.0 ± 5.0% (max = 51%) for humidity. The average activity at the start of synthesis was 1247 ± 218 mCi in 2022 and 1489 ± 343 mCi in 2023.

The yields mentioned in this study represent the decay non-corrected estimated yields at the end of synthesis (EOS), obtained from the FASTLab2 synthesis report.

4. Quality Control tests

Quality tests were performed following the USP standard criteria (6). And consisted of visual inspection (doses must be clear, colorless and free of particulates), pH (pH paper, must be 4.5-7.5), residual K2.2.2 (spot test, must be ≤ 50 μg/mL), radiochemical purity (bSCAN TLC Scanner, must be > 90%), radiochemical identity (bSCAN TLC Scanner, RF of radiotracer and reference standard match), radionuclidic identity (CRC-55t dose calibrator, half-life must be 105-115 min), residual solvent analysis (Scion-456 GC, < 400 ppm MeCN; < 5000 ppm EtOH), bacterial endotoxin analysis (Endosafe nexgen-PTS, ≤ 175 endotoxin units/dose), and sterility per USP Chapter 71 (fluid thioglycolate media and soybean casein digest agar media tubes, no evidence of microbial growth found). Additional periodic QC testing included radionuclidic purity (Captus-3000 MCA, Energy peak 0.511 MeV). All doses of FDG discussed in this article met or exceeded all of these quality control release criteria and were stable for 12 h after end-of-synthesis (EOS) (7).

Results

1. Evaluation of estimated RCY from 2 years production

A total of 224 batches of [^{18}F]FDG were produced by SSCH, with 154 of them utilizing duo citrate cassettes and the remaining batches using single citrate cassettes. The average RCY for single citrate cassette was 62.4 ± 1.8% (n = 70), as for the duo citrate cassette 71.2 ± 3.5% (n = 154) which shows that the RCY for the duo cassettes was much higher than the single cassette (8). Figure 1 shows that the RCY for both single and duo citrate cassettes were gradually decreasing. For the duo cassettes: average RCY of 2022 was 73.0 ± 3.2% (n = 68), while at 2023 it equated 69.7 ± 3.2% (n = 86). For single citrate cassettes the RCY dropped from 63.1 ± 1.5% (n = 41) to 61.4 ± 1.6% (n = 29). Despite the slight difference in average values, the graphic above indicates that there is indeed a decrease occurring. This lowering of yield could be associated with the lack of proper maintenance performed on either the cyclotron or synthesizer equipment, capillary transfer line condition etc (9). However, additional investigation is required.

The second observation was that the second run's

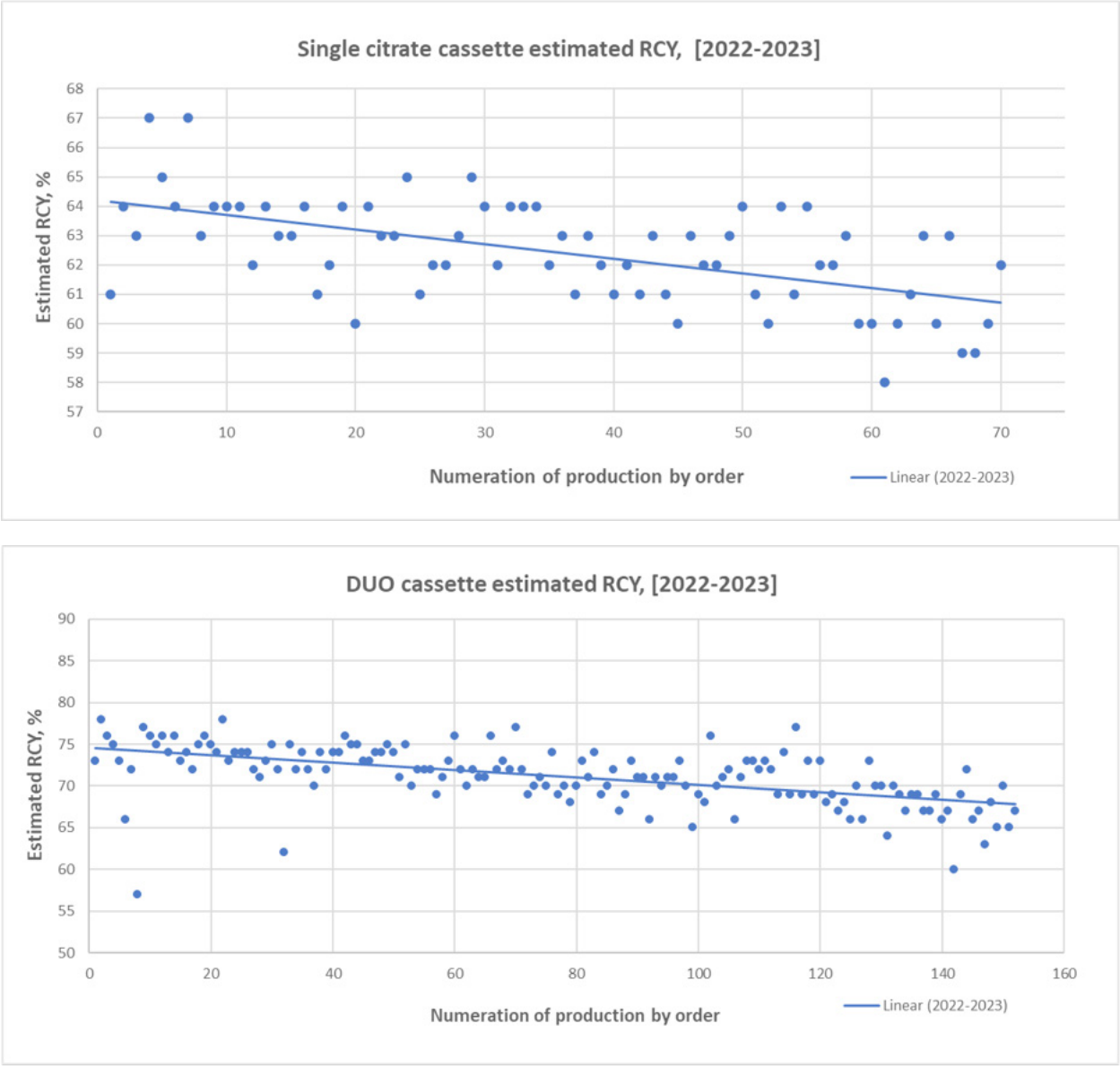

Figure 1. Estimated RCY of production using both single and duo citrate cassettes, 2022-2023 years.

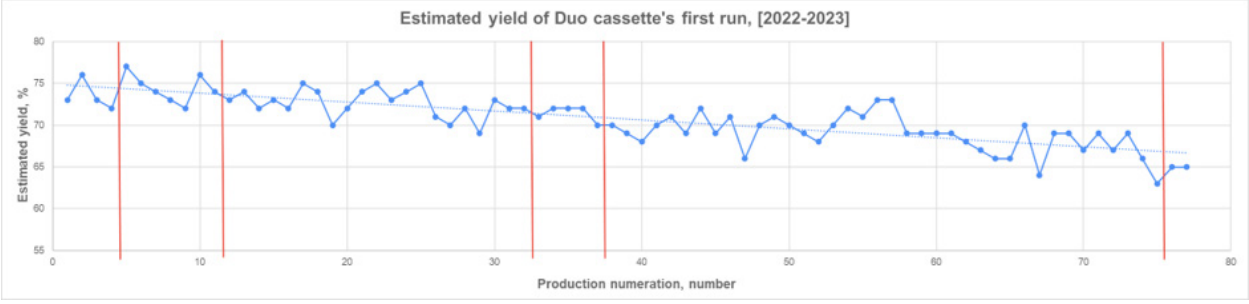

Figure 2. Estimated RCY of production without time data, 2022-2023 years.

Table 1. Quality control test results of [^{18}F]FDG, 2022-2023.

Quality parameter	Specification	Result
Appearance	Colorless/Clear/No particle	Colorless/Clear/No particle
Kryptofix 2.2.2 test	< 50 μg/mL	< 50 μg/mL
Bacterial Endotoxin Test	< 17.5 EU/mL	< 5.00 EU/mL (DF=100)
pH	4.5 - 7.5	6.5 ± 0.5
Radiochemical Purity	> 90%	99.9 ± 0.35% (max = 100)
Half life	105 - 115 min	110.4 ± 2.3 min (max = 115)
Gamma-ray Energy	511/1022 KeV	511 KeV
Residual ACN	< 400 ppm	51.2.5 ± 67.2 ppm (max = 375)
Residual ethanol	< 5000 ppm	2602.5 ± 986.2 ppm (max = 4732)
Sterility test (FTM & TSB)	No growth	No growth

Source: data of 2022-2023 at SSCH, NMC

RCY (71.6 ± 3.9%, n = 77) from duo cassette was mainly greater than the first run (70.7 ± 2.9%, n = 77). A two-tailed p-value of 4% (or 0.04) from a paired t-test suggests that there is a statistically significant difference between the two sequences of first and second runs of duo cassettes. It could be related to the relatively few numbers of productions per week (2-3 times per week), where the downtime of the cyclotron would be 4-5 days. Considering this, the relationship to the cyclotron maintenance was further examined by comparing the RCY of the duo cassette's first runs.

2. RCY in relation to the cyclotron maintenance

The RCY of the first run of the duo cassette was selected for comparison to determine whether cyclotron maintenance is affecting the radiochemical yield. In Figure 2, the cyclotron maintenance period is indicated with a red line, showing the point before which the maintenance was performed. From the graphic, there wasn't a significant relationship between cyclotron maintenance and the RCY of subsequent productions. However, increasing the production frequency in the future (to 4-5 days per week) would allow for more consistent operation to observe the impact of cyclotron maintenance to the RCY.

3. Quality control results

During the two years, there were no returned batches of [^{18}F]FDG, indicating that all batches met the USP criteria. Table 1. shows the average values of quality control tests from 2022 to 2023 years. The radiochemical purity was more than 90%, the average half-life of [^{18}F] fluoride was 110.4 ± 2.3 minutes, the average pH was 6.5 ± 0.5 and the residual solvents were within the expected range. Radionuclidic identity test was conducted with the MCA Captus 3000, verifying the 511 keV energy peak. Calibration was performed before each test using ^{137}Cs and ^{152}Eu standard sources. The quality of final product fulfilled all the requirements set by the USP. No immediate or delayed side effects have been reported after injecting to the patients.

Conclusion

Unlike other countries, Mongolia's initial production of [^{18}F]FDG currently does not have a backup system,

requiring more rigorous maintenance technology. The present study represents a two-year analysis of [^{18}F] FDG production data to keep the best FDG's production condition, focusing on RCY and quality control test results. All quality control tests met the USP requirements and radiochemical yield were in an acceptable range, ensuring safe injections for patients. The RCY of the FASTLab2 duo cassette was consistently higher than that of the single run citrate cassette across all periods. The RCY for both single and duo citrate cassettes were gradually decreasing. There was no significant correlation between the maintenance of foil exchange in cyclotron's target and the RCY of subsequent productions. However, to ascertain the different factors contributing to the decreasing overall RCY, additional investigations must be conducted.

Acknowledgements

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