Routine Production of $^{18}F^-$ with a Beam Current of 200 μA on a GE PETtrace Cyclotron: Experience over > 18 Months

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Introduction

The increasing demand for [^{18}F]FDG for clinical PET-CT and the efficiencies associated with large production runs have encouraged endeavors to increase the amount of $^{18}F^-$ produced by cyclotrons in a single run, thus providing a saving in starting materials, consumable and staff costs. The amount of $^{18}F^-$ is determined by the saturation yield of the nuclear reaction, the irradiation time and the beam current striking the target. The saturation yield is a function of beam energy (typically fixed for PET cyclotrons), the enrichment of the $H_2{}^{18}O$ (typically >97%) and the efficiency of the target design. Target design has already been optimized on current systems. Diminishing gains in activity are achieved by extending the irradiation time much beyond 3 hrs, so the main focus has been to increase the target beam current. Increasing the beam current requires: i) a cyclotron capable of producing the increased beam current; ii) targets that tolerate the beam current without appreciable loss in saturation yield; iii) sufficient shielding of the cyclotron and hot cells to accommodate the proportionally larger radiation dose rates during higher current irradiation and from the larger activities delivered to the hot cells.

We reported [1] that the self-shielded targets fitted to our cyclotron can accommodate 100 μA currents without appreciable loss in saturation yield. We also identified the potential of routine production at 200 μA (100 μA per target in dual target irradiation mode), but had not established its long-term viability in routine use. We present our experience in using 200 μA for routine production of $^{18}F^-$ from September 2012 to July 2014 and demonstrate that with close monitoring of critical components and parameters, good reliability of the cyclotron could be achieved.

Material and Methods

Component Upgrades

Our PETtrace cyclotron was installed in 2002 with initial total proton target beam current specification of 75 μA and has been used for routine production of various ^{18}F and ^{11}C tracers since January 2003. It has been upgraded incrementally so that it is now equivalent to a current generation PETtrace 880 cyclotron, which is specified at a total proton target beam current of 130 μA. The main upgrades which facilitate increased beam currents include:

- RF intermediate amplifier and RF control unit – accommodate the higher RF power requirements of high beam currents.
- Collimators changed from tantalum to graphite and extraction foil holder from aluminum to graphite – improved tolerance to higher temperatures generated in these components with higher beam currents.
- New ion source anode design – increased ion source output to facilitate higher beam currents.
- Silver $^{18}F^-$ targets replaced (fill volume 1.6 mL) with larger volume niobium targets (fill volume 2.5 mL) – higher target current capacity.

The only components on our cyclotron currently not part of the standard PETtrace 880 cyclotron configuration are the self-shielded targets and a license which allows a total proton target beam current of 200 μA.

Self-shielded $^{18}F^-$ Targets

The self-shielded targets utilize a W/Cu alloy for the main body of the target surrounding the Havar foil to reduce dose rate from the Havar foil by a factor of about 10 and dose rate from any remnant $^{18}F^-$ activity in the targets by a factor of about 100 [1]. The niobium target chamber is the same size as used in the standard GE Nb25 Niobium targets. The targets are filled with approximately 2.5 mL of water which leaves a small gas bubble at the top of the target chamber. As with the standard Nb25 target, an over pressure of about 30 bar is applied to the targets. The self-shielded target dispenses with the He cooling and the vacuum foil. Only the water foil is used, which is directly exposed to the vacuum in the chamber. Foil cooling is by the water in the target chamber. The elimination of the 25 micron vacuum Havar foil reduces the total thickness of foils the beam has to traverse from 75 micron to 50 micron. The performance and service interval of this target was investigat-

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ed at 100 μA per target (200 μA total for dual irradiation) beam currents.

Operating Parameter Optimisation

Effective high current operation requires optimization of operating parameters. DEE voltages were selected to provide a good compromise between load on RF system, beam shape and ion source current. While increased ion source gas flow can increase ion source output, it also results in increased beam stripping and hence reduced transmission of beam from ion source to target. Beam stripping at high currents is particularly important, as the amount of beam stripped which impacts on the components in the cyclotron is proportional to beam current. At high currents, this can result in a runaway condition, where the effects of the stripped beam hitting components inside the vacuum tank deteriorate vacuum. The deteriorated vacuum then causes more beam to be stripped, leading to further deterioration of vacuum. The increased beam stripping and deteriorated vacuum are compensated by increasing the ion source current, until maximum ion source current is reached, causing the beam to shut down. The vacuum and hence beam stripping are affected by the efficiency of the vacuum system and the ion source gas flow. Hence optimum ion source gas flow was investigated. The effect of diffusion pump maintenance on vacuum system performance was also investigated.

We have found previously that running the ion source gas at a low flow rate (2 sccm) when cyclotron is not used greatly reduces deterioration of ion source performance over time and with use [1]. This gas flow also appears to have a beneficial effect on the vacuum. Ion source gas flow when cyclotron is off has been employed throughout the evaluation period.

[^{18}F]FDG Yield and Stability

[^{18}F]FDG was produced with TRACERlab MX_{FDG} modules or FASTlab modules using both Phosphate and Citrate cassettes. Stability studies of [^{18}F]FDG were performed to ensure it met specifications over the specified expiry time for the higher activities produced with the higher beam currents.

[^{18}F]FDG yields were calculated using input activity estimates from saturation yield (8400 MBq/μA) determined at acceptance and from subsequent measurements and beam time and current and the non-decay corrected [^{18}F]FDG activity measured at the end of synthesis. Thus yield calculations include target yield variations and losses in the transfer lines and not just synthesis yield.

Results and Conclusions

$^{18}F^-$ Targets

The saturation yields remained consistent with increasing beam currents up to a target current of 100 μA (Figure 1). The saturation yields for 90 and 100 μA target currents were measured with the self-shielded target only, while the lower current results included measurements from Nb25 targets.

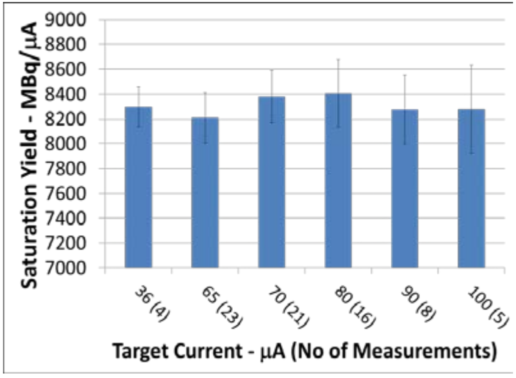

Figure 1. Saturation yields for target currents ranging from 36 to 100 μA.

The data shown in Figure 1 indicate consistent yields up to 100 μA. However, very narrow beams appear to result in a slight decrease in yield for 100 μA target currents.

The service interval for the self-shielded targets was gradually increased to over 20,000 μAh. At close to 20,000 μAh, slight reductions in FDG yield (about 5%) were being observed and the 20,000 μAh service interval has been chosen to limit reduction in FDG yield.

The only issue we found with the self-shielded targets during re-build was galvanic corrosion of the W/Cu in the cooling water cavities of the targets, thought to be due to the two dissimilar metals (W and Cu) being in contact with the cooling water. It is understood that this issue in our prototype has been addressed in the current version of the self-shielded target.

Operating Parameter Optimisation

Figure 2 demonstrates the increase in ion source output, based on flip-in probe current, with increasing ion source gas flow reaching a maximum at about 6 sccm. The percentage beam transmission from probe to extraction foils is shown in Table 1 and Figure 3 as a function of ion source gas flow. As expected, transmission decreases with increasing gas flow due to increase in beam stripping. Based on these data, an optimal gas flow of between 5 and

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5.5 sccm has been found and typically a gas flow of 5.5 sccm is used.

The improvement achieved in probe to foil transmission by diffusion pump maintenance is highlighted in Table 1 and Figure 3. The period between the previous diffusion maintenance and this maintenance was the recommended 5 years. Based on these results, diffusion pump maintenance interval has now been changed to 2 years.

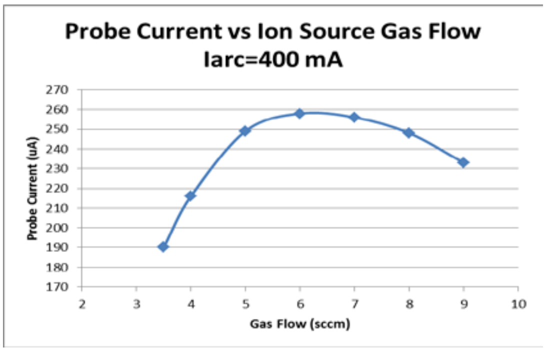

Figure 2. Flip-in probe current as a function of ion source gas flow for an ion source current (Iarc) of 400 mA.

Ion Source Gas Flow (sccm)	Probe to Foil Transmission before DP Service (%)	Probe to Foil Transmission after DP Service (%)
3.5	76.7%	78.8%
4.0	74.3%	76.2%
5.0	69.9%	73.0%
6.0	63.7%	68.0%
7.0	59.4%	64.6%
7.5	57.4%	62.0%
8.0	56.0%	60.6%

TABLE 1. Flip-in probe to extraction foil transmission as a function of ion source gas flow before and after diffusion pump (DP) maintenance.

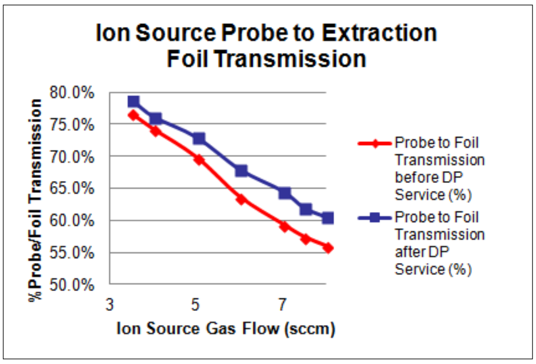

Figure 3. Flip-in probe to extraction foil transmission as a function of ion source gas flow before and after diffusion pump (DP) maintenance.

Using the optimized DEE voltage of 38.5 kV and Delta DEE of 3.5 kV and an ion source gas flow of 5.5 sccm, the following operating parameters are typically obtained for a beam with total target current of 200 μA (dual 100 μA per target beam).

- Anode current of approximately 3 A (maximum recommended 3.2 A)
- Tube amplifier drive voltage of approximately 120 V (maximum recommended 180 V)
- Ion source current <600 mA over 2 hr run (maximum recommended 700 mA)
- Collimator currents <5% with new extraction foils, change extraction foils when collimator currents exceed 7 to 8%.

Thus even at 200 μA target currents, all parameters are within the maximum recommended values. However, the head room and safety margin is substantially reduced compared to lower beam current operation. It should be noted that the optimized parameters are cyclotron specific and other PETtrace cyclotrons are likely to have different optimal operating parameters.

[^{18}F]FDG Yield and Stability

Over the period from 1st September 2012 to end of July 2014, a total of 419 [^{18}F]FDG productions were performed at total target beam currents ranging from 160 μA to 200 μA, with 335 production runs being performed at 200 μA. Beam times were typically 90 to 120 min, with some productions up to 180 min. The FASTlab phosphate cassette yields have been plotted in Figure 4. The [^{18}F]FDG yields are summarized in Table 2. The yields for the FASTlab phosphate and citrate cassettes have been listed separately in Table 2 as they are known to be different [2,3]. The [^{18}F]FDG yields obtained with the TRACERlab MX$_{FDG}$ are also shown in Table 2 and plotted separately in Figure 5.

Parameter	< 200 μA Beam (n)	200 μA Beam (n)
FLP Yield	73.4±11.2% (54)	73.3±4.3% (145)
FLC Yield	63.7±8.2% (27)	65.0±4.3% (33)
MX Yield	54.4±5.8% (111)	50.7±5.7% (157)

TABLE 2. [^{18}F]FDG Yield for FASTlab Phosphate (FLP), FASTlab Citrate (FLC) and TRACERlab MX$_{FDG}$ (MX) syntheses for beam currents <200 μA and at 200μA. The number (n) of runs are given in brackets.

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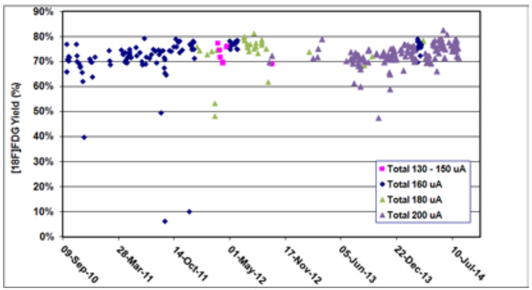

Figure 4. Plot of [^{18}F]FDG activity yield data between 10 September 2010 to 31 July 2014 at beam currents from 130 to 200 µA for FASTlab module using phosphate cassettes

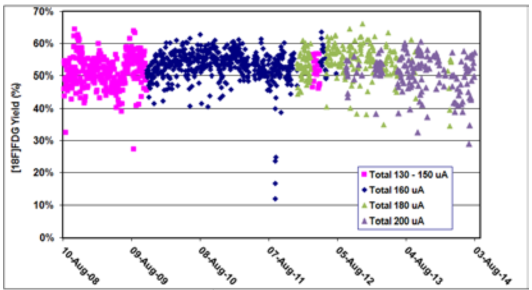

Figure 5. Plot of [^{18}F]FDG activity yield data between 01 August 2008 to 31 July 2014 at beam currents from 130 to 200 µA for TRACERlab MX$_{FDG}$ module.

As shown in Table 2, yields at beam currents < 200 µA and at 200 µA for the FASTlab phosphate and citrate cassettes are within 2% and no drop in yield is observed with 200 µA. For the TRACERlab MX$_{FDG}$ cassettes the < 4% difference can be attributed to a lower yielding cassette batch towards the latter part of 2014 when 200 µA beam currents were predominantly used. The coefficient of variations in Table 2 demonstrate that consistency of yield is not adversely impacted by the 200 µA total target current.

We aseptically add 0.2 mL of 25% sodium thiosulphate to the product vial as stabilizer to limit radiolysis [4]. In addition, for the FASTlab phosphate cassettes, which do not use ethanol as part of the synthesis, we add 0.5 mL of ethanol to the 100 mL water bag. With this regime, [^{18}F]FDG stability was maintained over a 24 hour period even at the activities of approximately 650 GBq (17.6 Ci) [^{18}F]FDG at EOS capable of being produced by a 130 min, 200 µA target current run with the FASTlab phosphate cassettes. Thus clinical productions with the FASTlab phosphate cassettes are currently limited to 130 min until validation has been performed for longer beam times with the phosphate cassettes. The FASTlab citrate cassettes and TracerLab MX cassettes have been validated up to a beam time of 180 min. A 180 min, 200 µA test production using the FASTlab phosphate cassette produced 763 GBq (20.6 Ci) at EOS, demonstrating the potential amounts of FDG which can be produced in a single run.

Maintenance Schedule Impact

The tolerance to a reduction in performance of the critical components to achieve high current operation (RF, ion source output and vacuum system) is reduced at high beam currents. This may result in a lower safety margin of critical components during beam irradiation, hence close monitoring of critical parameters is essential to minimize cyclotron outage. The requirements for routine maintenance of ion source, targets and extraction system, however, have not increased with the increase in beam current from 160 µA to 200 µA. Extraction foil life and ion source maintenance intervals have remained at about 2000 µAh and >120 Ah (>50,000 µAh on targets), respectively. As more experience has been gained with the self-shielded targets, service interval has actually been extended from about 10,000 µAh to 20,000 µAh, despite the higher beam currents.

Diffusion pump maintenance is currently recommended every 5 years by the manufacturer, but a 2 year maintenance interval has been implemented for 200 µA, given the observed deterioration over a 5 year period and the improvement in performance post service (Table 1). The more frequent service is associated with the additional costs of diffusion pump oil and an extra day of scheduled down-time.

Typically, vacuum is sufficiently well established 12 h after opening of the vacuum tank to run 200 µA beams with the vacuum and beam conditioning that we employ. The conditioning after tank closure which we employ is as follows: i) RF and ion source gas flow is started as soon as vacuum allows (typically 20-25 min after tank closure); ii) a conditioning beam starting typically at dual 20 µA and gradually increasing target current to dual 90-100 µA. If necessary, degraded vacuum from higher beam currents is allowed to recover by reducing beam current to dual 5 µA for about 15-20 min before increasing beam current again. The conditioning beam typically takes 2-3 h depending on the number of components changed in the tank.

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Problems Experienced with Higher Beam Currents

The targets generally have tolerated the 100 µA per target current (200 µA total beam current for dual target irradiation) well over this 18 month period. However, currents of 80 µA to 100 µA per target in dual target irradiation mode reduce the tolerance to sudden increases in one of the target currents. There were four occasions (two test beams and two production beams) when there were sudden increases of target current from 90 µA and 100 µA to about 150 µA. The rapid increase in heat deposited on the foil and target chamber and the resultant rapid pressure rise in the target chamber could not be withstood by the foil and target foil rupture ensued. This compared to one target foil issue over a similar period of time (18 months) at lower beam currents on the standard Nb25 target.

Three separate causes were identified for these overshoots in target current: 1) behavior of control system when beam is allowed to continue past the set time; 2) large manual change of set current of one of the two targets irradiated during a dual irradiation conditioning beam and 3) an issue with DEE voltage regulation caused by the mechanical flap controls. Issues 1 and 2 have been addressed by procedural changes. For issue 1, the beam time is set longer than the required beam time and beam is stopped and target contents delivery is commenced before the set time is reached. For issue 2, if changes to target currents are required while dual beam is running (eg for conditioning beam after vacuum tank closure), changes are limited to 10 µA increments at a time to avoid overshoot of one of the target currents when a large change in beam current is called for on the other target. Issue 3 was resolved by replacing the original worn mechanical flap controls with an available upgrade of the mechanical flap control mechanism which provides more precise control of the flap positions. The two target foil ruptures during production did not cause cancellation or delays to patient scanning, as the demand could be met by additional production runs after restoration of vacuum from target rupture and deliveries from the unaffected target. No unscheduled down-days occurred during the evaluation period.

The current PETtrace 880 cyclotron is specified at 130 µA total target beam current. This conservative specification allows for differences in performance between cyclotrons and provides considerable headroom to tolerate less than optimum set up and performance of the cyclotron subsystems potentially seen across PETtrace sites. We have been able to achieve routine operation at 200 µA beam current through careful optimization of the operating parameters and the central region in close collaboration with GEMS PET Systems AB, Uppsala, Sweden. Even with careful optimization as performed here, 200 µA beam currents may not necessarily be achievable on all other PETtrace 880 cyclotrons due to potential variations between cyclotrons.

High performance is maintained through our maintenance regime that we have detailed previously [1]. This maintenance scheme for routine 200 µA operation has largely remained the same as for our previous lower current operation. We also run the ion source gas at 2 sccm while the cyclotron is not in use. We believe this has been instrumental in minimizing wear on the ion source, and consequential loss of output, and thus maximizing the time between ion source rebuilds. At the high beam currents, the safety margin and tolerance is small, so careful monitoring of the system is required to ensure that issues in one of the subsystems do not cause major events such as target foil ruptures.

The prototype self-shielded targets have performed well over this period and have the advantage of not requiring target removal for the majority of minor maintenance tasks due to the shielding of the Havar foils and remnant activity. This greatly facilitates the proactive maintenance required for 200 µA operation. Issues, such as galvanic corrosion have been addressed in the current version of the targets but highlight the importance of performing long term tests on prototypes to ensure potential long term issues are identified and addressed before release of product.

Our [^{18}F]FDG yields and stability have been maintained at the higher current and 200 µA allows large quantities of [^{18}F]FDG to be produced routinely with relatively short beam times. The large FDG activities capable of being produced minimizes the number of productions required to fulfill customer demands and readily accommodates decay associated with long transport times for some of our customers.

The routine operation at 200 µA for almost 2 years is providing valuable information on the ability of the various cyclotron components to withstand these higher currents and the ability of the critical substance to maintain the required performance. This allows improvements to be made to marginal systems. There are no plans to

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go beyond 200 μA total target current as effort required to increase current is likely to considerably outweigh the gain in extra current and activity. In addition, increased activity can be more readily achieved through longer beam times, providing FDG stability can be maintained at even higher activity levels.

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