

Dose on Demand

Dual Dose [^{18}F]FDG Syringe using the ABT BG75 system.

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SUMMARY:

Proof of concept for the production of a dual dose syringe (2 doses, > 10 [mCi]) is presented. In a mini-batch process, a dose of sufficient activity so as to allow for the injection of two patients is produced using a single disposable dose synthesis cards (DSC). Upgrades and improvements in both the ABT radio isotope generator (RIG) and chemistry production module (CPM) are necessary to produce a system capable of producing a dual dose syringe. Hardware improvements and process optimization resulting from this project will form the basis for our next generation Biomarker Generator.

I. BACKGROUND:

The current BG75 system has been deployed at several locations worldwide in both research and clinical environments¹⁻³. The BG75 system comprises three automated and self-shielded modules: A) a small 7.5 MeV particle accelerator; B) Nucleophilic substitution-based synthetic module equipped with measuring/transferring pumps and C) HPLC-based quality control system (figure 1). The use of a low energy cyclotron ensures by design a high radionuclidic purity compared to high energy cyclotrons, as previously demonstrated.⁴ The capability of running the system on-demand producing a single-dose to be injected locally i.e. within 30 minutes, has the potential to reduce the chances for radiolysis and radiochemical impurities deriving from a large activity concentration typical in commercial formulations.

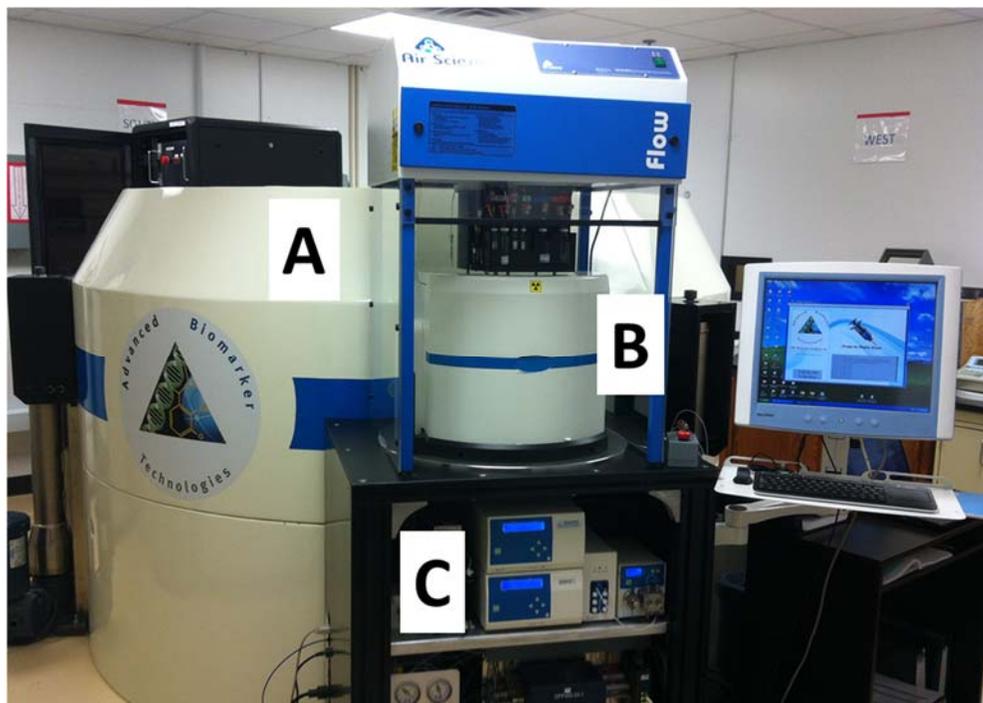


Figure 1: BG75 system showing its three automated and self-shielded modules.

Dual Dose [¹⁸F]FDG Syringe using the ABT BG75 system.

Our continuing efforts to improve reliability, ease of use, and responsiveness to customer needs led to the exploration of a system capable of producing mini-batches of on-demand [¹⁸F]FDG. Adding the flexibility to produce dual dose syringe along with our traditional single-dose syringe will increase the flexibility of the BG75 system to respond to customers ever changing patient loads and allow for greater adaptability to scanner availability.

Every [¹⁸F]FDG dose is manufactured inside an irradiated and double-bagged DSC. The card is considered a closed system that can potentially overcome the burden of having strict environmentally controlled rooms for radiotracer manufacture, in fact results on more than 30 manufactures performed in worst-case scenarios i.e. no environmental control, no aseptic techniques, have been negative for sterility tested according to USP <71> entire hardware was controlled by a National Instruments DAQ using LabView software.

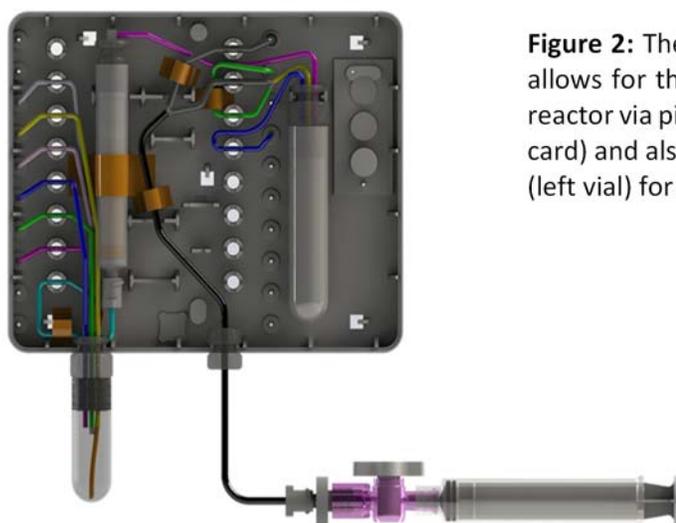


Figure 2: The new vacuum enabled DSC allows for the complete isolation of the reactor via pinch valves (tubes on right of card) and also supports a larger collector (left vial) for more flexible dosing.

II. METHOD:

By integrating a number of tested and proposed hardware changes into a development system, produce a dual dose syringe of sufficient volume and activity. The goal set is to allow for the injection of two patients with approximately 10 [mCi] of activity 15 minutes after end of synthesis. This time allows for the completion of the auto-QC record and any manual QC as well as dispensing time needed to qualify the doses.

Chemistry optimization was carried out by splitting the overall synthesis plan into three stages, 1) ¹⁸O evaporation, 2) production of ¹⁸F labeled FTAG, and 3) hydrolysis to produce [¹⁸F]FDG. Since previous work on the DSC has established a robust purification protocol, this last step was not a focus of optimization. The primary hardware change was the addition of a vacuum pump in line with the gas trap and the realignment of the DSC internals to support more precise isolation of the reactor. Furthermore a larger collection vial was fitted into the DSC to allow for more flexibility in the volume of liquid delivered to the final dual dose syringe.

III. RESULTS:

The conditions established for the vacuum based system are milder than normal single-dose method while achieving equal or faster evaporation times and a near elimination of losses to the trap during H₂¹⁸O evaporation.

Table 1: Comparison of yields.

Decay Corrected Yield	Vacuum	Current
[¹⁸ F]FTAG	59 ± 7 [%]	51 ± 4 [%]
[¹⁸ F]FDG	47 ± 14 [%]	35 ± 6 [%]

Optimization of the labeling chemistry was more challenging than initially expected. While the vacuum system would deliver a drier ¹⁸F-PTC complex at the end of evaporation, a significant fraction of the activity is still lost during the labeling process. Initial experiments showed that using the active cooling capabilities introduced with the 30-minute cycle system allowed for precise temperature control was necessary to maximize yield. Addition of the precursor mannose triflate at lower temperature improved yield. From that point on the primary variables modified were the labeling time and temperature. Essentially no statistically significant improvements in yield were achieved at any combination of temperatures between 70 [°C] and 90 [°C] and times between 90 seconds and 5 minutes. Despite not being able to eliminate losses during labeling we were able to achieve typical FTAG DCY of ~60 [%] with >85 [%] RCP. The majority of the contaminant is unreacted ¹⁸F.

Figure 2 below illustrates the dual dose syringe performance synthesis cycle and yields. After synthesis, 33.3 [mCi] of [¹⁸F]FDG was achieved. After purification and sterile filtration, > 26 [mCi] was present in the syringe.

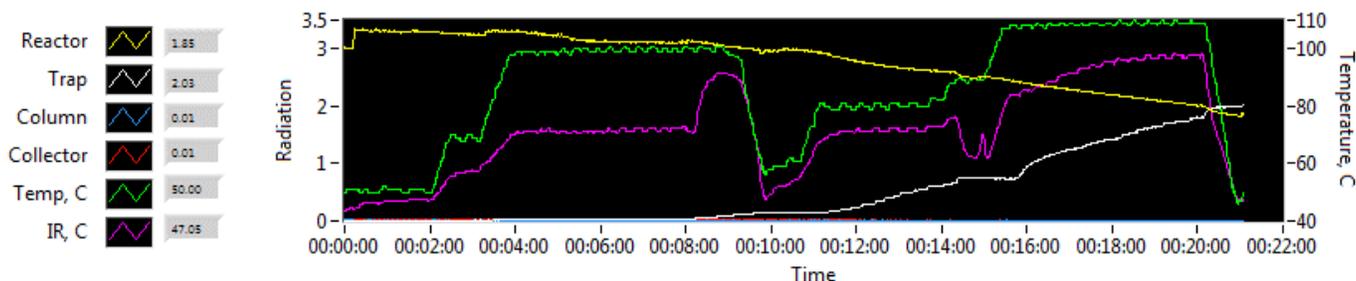


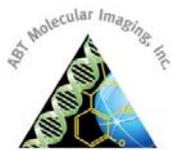
Figure 2. Dual Dose Syringe synthesis on the BG system. The final yield before purification was 33.3 [mCi] from an initial starting activity of 71.1 [mCi] (95.23 [%] RCP, 56.6 [%] DCY).

The decay corrected yield (DCY) was shown to be consistent across a range of initial activities as shown in the table below.

Table 2: Decay corrected yield (DCY) as a function of initial activity for the new Vacuum dose synthesis card.

Starting Activity [mCi]	Activity after Synthesis [mCi]	DCY [%]
36.7	16.9	59.41
35	14.4	55.36
58.8	20.9	50.86
71.1	33.3	56.60

Further work is ongoing to optimize the system and script package for maximum yield of purified [¹⁸F]FDG in a minimal amount of time. The primary focus is now on addressing the hydrolysis losses and maximizing the amount of radio tracer that is delivered to the syringe. The ultimate goal will be integration of this workflow into the software so that the user can choose from standard single dose syringe, 30-minute cycle time, or dual dose syringe, Na¹⁸F.



IV. CONCLUSIONS:

The BG system is capable of producing a dual dose syringe (> 26 [mCi]) which can be used to inject two patients with > 10 [mCi], one at 15 [min] after production and the second 15-45 [min] after production. This will allow sites with two PET scanners to be serviced by one BG system. Further hydrolysis and synthesis time optimization will occur before release of Dual Dose Syringe in Q4 2014.

V. REFERENCES:

- 1) Awasthi, V.; Watson, J.; Gali, H.; Matlock, G.; McFarland, A.; Bailey, J.; Anzellotti A., "A Dose on Demand Biomarker Generator for Automated Production of [^{18}F]F⁻ and [^{18}F]FDG", *Appl. Radiat Isot.* (2014), 89, 167 – 175.
- 2) Awasthi, V.; Gali, H.; McFarland, A.; Anzellotti A., "Automated production of [^{18}F]F⁻ and [^{18}F]FDG at the University of Oklahoma Health Sciences Center (OUHSC)", *J Nucl Med.* (2013), 54, 1166.
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