30 Minute [^{18}F]FDG Cycle Time Development on the BG75 system.

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SUMMARY:

The purpose of this project was to implement features to lower dose-to-dose cycle time to below 30 minutes while keeping [^{18}F]FDG yield >=10mCi. Improvements in target yield, reducing target unload time, reducing the synthesis time, and a faster QC injection have reduced the average cycle time of producing a purified and qualified dose from < 45 [min] to < 30 [min].

I. BACKGROUND:

The University of North Carolina at Chapel Hill owns a BG75 system that is currently pursuing an aNDA application for [^{18}F]FDG manufacture. The BG75 system is self-shielded and comprises a small, 7.5 MeV positive ion cyclotron, and automated synthesis (Card Chemistry System, CCS) and quality control modules (Fig. 1). The central idea on the BG75 system is the use of a single-use and sterile card (DSC) to make a dose of radiotracer, at any time is required (dose-on-demand). Reagents are loaded in a metering sub-assembly located at the top of the CCS and then measured/transferred into the inside of a sterile DSC where manufacture occurs in a close system, the dose is then purified using a solid phase column and transferred to a sterile syringe via a non-vented 0.2 µm filter.

The current cycle time is < 45 [min] to produce a dose of [^{18}F]FDG. It is desirable to reduce the cycle time down to < 30 [min] to permit the scanning of more patients in a day.

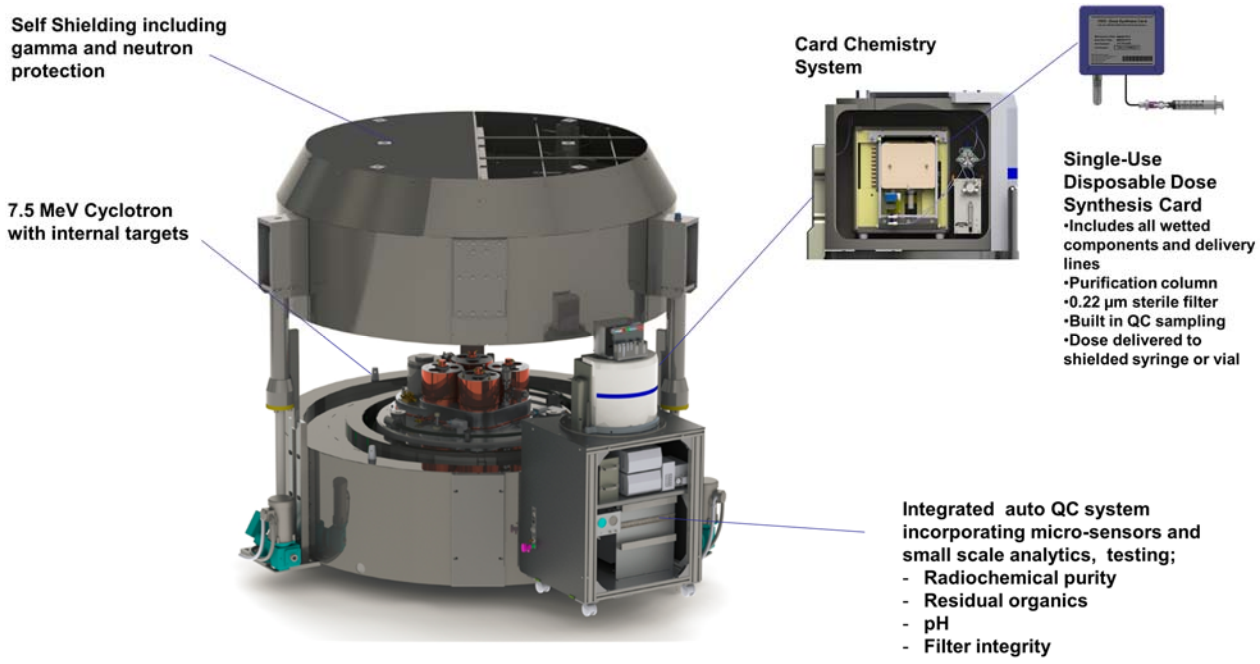

Figure 1: Scheme of [^{18}F]FMISO radiosynthesis.

II. METHOD:

The following processes were optimized in the production of [^{18}F]FDG synthesis:

A. Target Yield
B. Active Cooling
C. Synthesis Improvements
    a. Labeling {temperature, time}
    b. Hydrolysis {time}
D. Target Load
E. Larger Syringe
F. Faster QC Injection

The sections below describe the changes the above components and processes.

Target Yield

In order to achieve a 30 minute cycle time, the target yield of the current target (> 1.0 [mCi/min]) needs to be increased to > 1.3 [mCi/min] in order to produce 32 [mCi] in 25 [min]. A new target design, referred to as the Tantalum target, has been developed. The target replaces the stainless steel base of the target with Tantalum for improved cooling as shown in Figure 2. In addition, cooling tube has been increased in diameter from 0.040 [in] to 0.0625 [in] in the target. This reduces the temperature of the target from < 250 [°C] to < 205 [°C]. The yield of the Tantalum target meets the 30 minute requirement of 32 [mCi] in 25 [min].

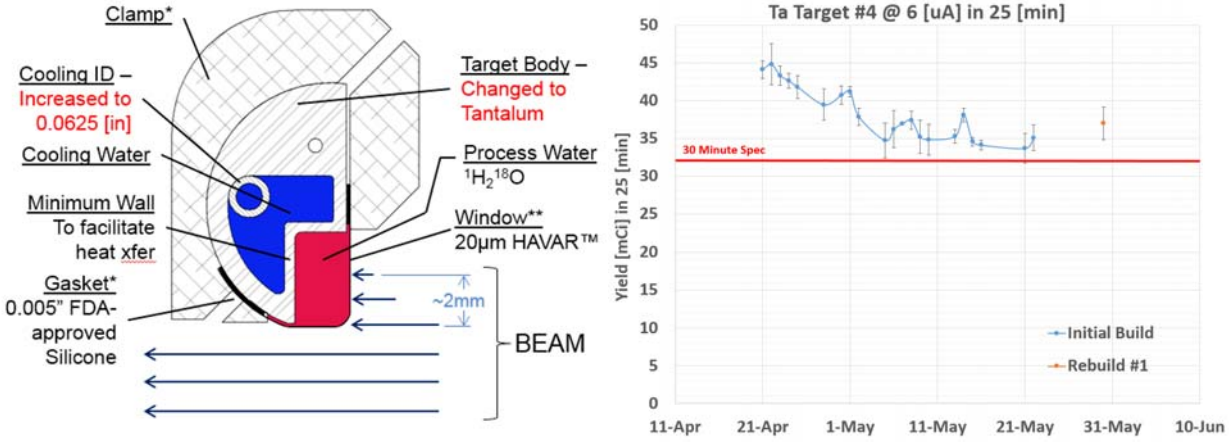

Figure 2. (Left) Schematic top view of Tantalum Target. The increased diameter cooling inlet line and Tantalum target body are shown identified. (Right) Tantalum Target #4 Yield.

Active CO_2 Cooling

The process of cooling the reaction vessel after evaporation is currently not controlled. Production cooling times are on the order of 5 minutes through conduction and convection through the atmosphere. Active CO_2 cooled air was implemented to reduce the cooling time from 5 minutes to < 1 minute (see Table 1). Figure 3 shows the active cooling block which has be optimized for air flow and thermal mass. Figure 4 and

Figure 5 (Left) describe the updates to the chemistry card system (CCS) and the gas manifold to account for the active cooling.

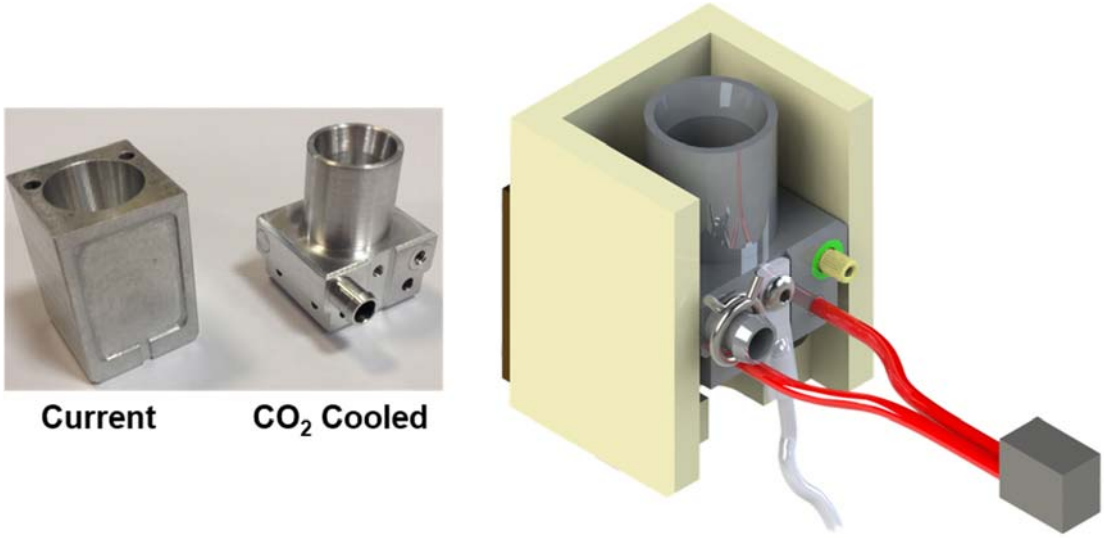

Figure 3. Active cooling block used to cool the temperature of the reaction chamber. It has a lower mass, an internal chamber for CO_2 cooling and results in improved heater mounting.

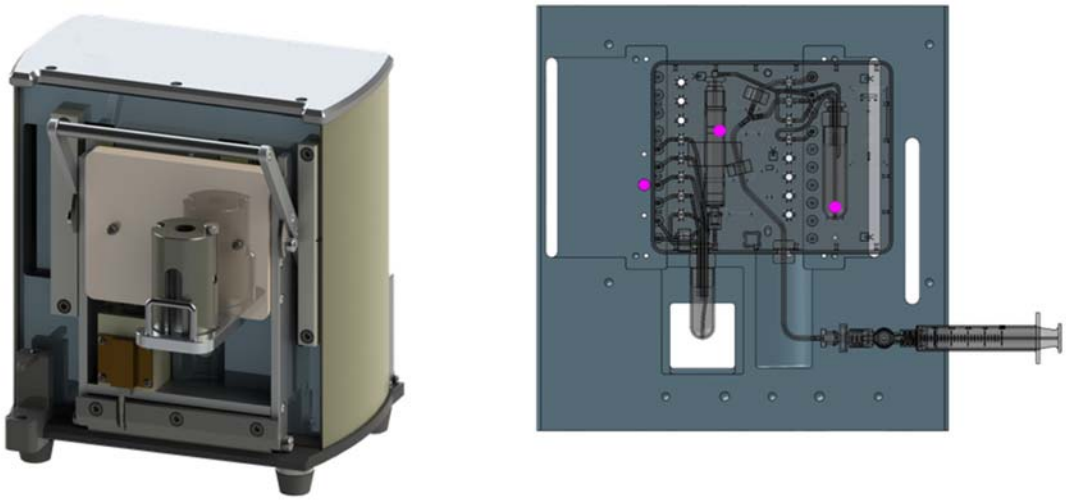

Figure 4. The Chemistry Card System (CCS) faceplate requires update to accommodate the active cooling and bulkhead fittings for CO_2 cooling.

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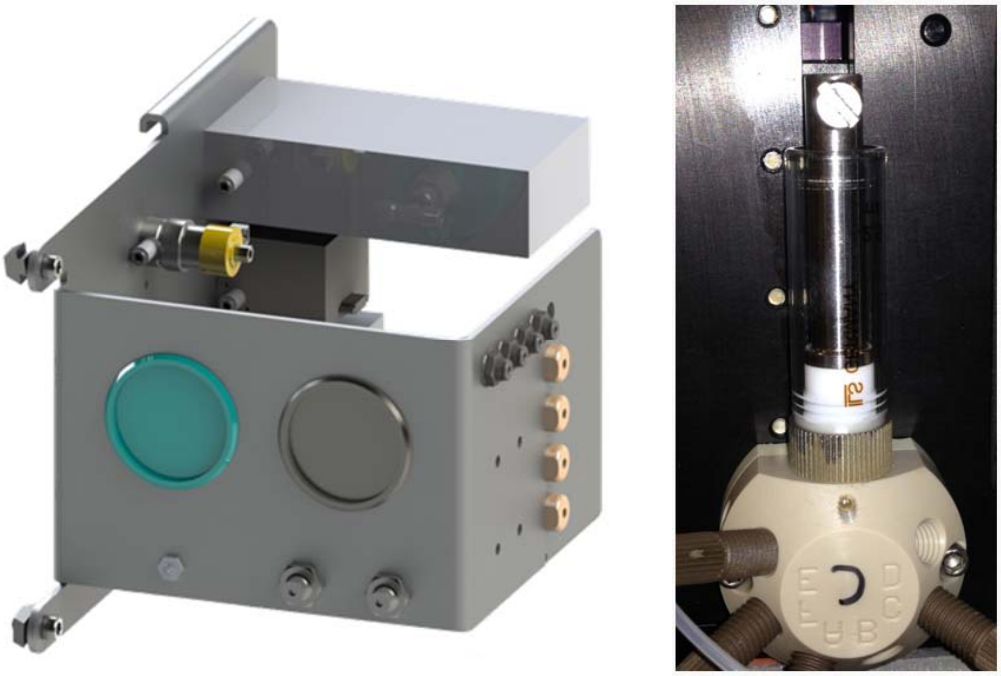

Figure 5. (Left) The gas manifold was updated with active cooling components. (Right) Syringe size was increased from 250µL & 500µL syringes to 1.0mL & 2.5mL. This reduces the number of strokes and therefore reduces the time for each injection. All syringes now larger than there highest respective process requirement. Air chase can be metered with reagent to reduce inject strokes.

Synthesis Optimization

The production evaporation of the O-18 water, labeling of the F-18 to manostriflate, and hydrolysis steps required to produce [^{18}F]FDG have not been optimized (e.g. temperature, time). A design of experiments was constructed to optimize the evaporation temperature and time, labeling temperature and time, and hydrolysis time. The table below shows the results of the optimization.

Table 1. Design of experiments around synthesis to optimize evaporation, labeling, and hydrolysis time.

Process	Current Cycle Time	Optimized
Evaporation Temperature	110 [°C]	130 [°C]
Evaporation Time	6 [min]	~3.5min
Labeling Temperature	80C	80C
Labeling Time	120 [sec] + MeCN Evap	60 [sec] + MeCN Evap
Hydrolysis Time	300 [sec]	240 [sec]
Cool Down Time	5 [min]	< 30 [sec]

Other Improvements

Larger syringes were employed to reduce the reagent addition time as showing Figure 4 (Right). Improvements to the target load from the cycle time were also optimized. Finally, the QC injection was improved resulting in faster delivery of the QC sample to the QCM for analysis.

III. RESULTS:

The results from the new target are shown in Table 2. The new Tantalum target can consistently achieve yields > 1.7 [mCi/min].

Table 2. F-18 Yield data from 3 days of running the Tantalum Target Serial #3. Data shows a mean activity of 1.786 ± 0.057 [mCi/min] with no data points < 1.3 [mCi/min].

Date	Run	SOB	EOB	Run Time	Set Current	Activity	Activity/min
[DD/MM/YYYY]	[#]	[hh:mm]	[hh:mm]	[min]	[µA]	[mCi]	[mCi/min]
4/21/2014	1	13:43	14:14	25	6	43.3	1.732
4/21/2014	2	14:16	14:46	25	6	43.1	1.724
4/21/2014	3	14:48	15:18	25	6	44.5	1.780
4/21/2014	4	15:20	15:51	25	6	45.6	1.824
4/22/2014	1	13:33	14:05	25	6.5	45.5	1.820
4/22/2014	2	14:07	14:37	25	6.5	44.3	1.772
4/22/2014	3	14:39	15:10	25	6.5	48.5	1.940
4/22/2014	4	15:12	15:42	25	6.5	45.1	1.804
4/23/2014	1	10:24	10:53	25	6	43.2	1.728
4/23/2014	2	10:55	11:24	25	6	45	1.800
4/23/2014	3	12:56	13:26	25	6	44.3	1.772
4/23/2014	4	13:28	13:59	25	6	44.5	1.780
4/23/2014	5	14:01	14:29	25	6	43.7	1.748
						Mean	**1.786 +/- 0.057**

Figure 6 shows the times savings of the design changes relative to the current method. Figure 7 illustrates the heater and infrared profiles for the current and 30 minute cycle times.

Feature	HW LoE	SW LoE	Script LoE	Time Savings	Estimated Overall
Current Release				0	41
Large Syringe	Low	None	Med	2	39
Faster QC Injection	Low	None	Med	1	38
Active Cooling - Air	High	Low	Low	4	34
Evap Optimization - Time, Temp	None	None	High	2	32
Labeling Optimization - Time, Temp	None	None	High	1	31
Hydrolysis Optimization	None	None	Med	1	30
Target Unload via Rad Trace	None	None	Med	1	29
Faster Validate	None	None	Med	0.5	28.5

Figure 6. Time savings of the design changes for the 30 minute project resulting in an overall reduction of typical cycle times of 41 [min] to 28.5 [min].

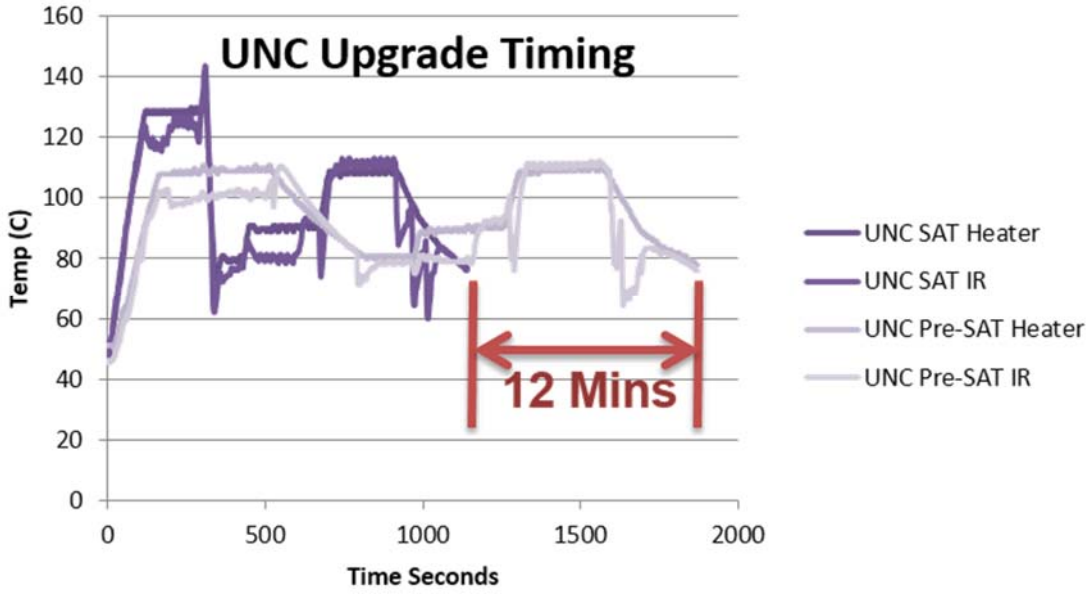

Figure 7. Plot comparing the 30 minute heater and infrared (IR) profiles between the current (light purple) and 30 minute cycle time (dark purple).

The implementation of all time saving features in the Methods section in addition to the new target resulted in a reduction of the [18F]FDG cycle time from < 45 [min] (typical 41 [min]) to < 30 [min] (typical 28.5 [min]). All samples passed all QC tests.

IV. CONCLUSIONS:

Cycle time optimization of the production of [18F]FDG was achieved by improving target yield, reducing target unload time, reducing the synthesis time, and QC injection. This resulted in an average cycle time for a purified and qualified dose in < 30 [min]. The 30 minute cycle time will be released in Q3 of 2014 for commercial use.