PRODUCTION OF F-18 FLUORODEOXYGLUCOSE WITH A COMPUTER-CONTROLLED SYNTHESIS UNIT

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ABSTRACT

Between January 20, 1988 and June 1, 1989, 253 batches of 2-[F-18]-fluoro-2-deoxy-D-glucose (FDG) were made in a computer-controlled synthesis unit using F-18 ion from proton bombardment of 0-18 water, by a modification of the stereo-specific method of Hamacher et al.[1] Irradiated water was delivered by nitrogen pressure through 67 feet of polyethylene tubing. Average activity at end of synthesis was 85 mCi; maximum, 184 Mci. Beam current was limited to 10 μA by our beam-line configuration, not by the target itself. Bombardments ranged up to 15 μA-hr; most common were 7.5 and 10 μA-hr. All preparations had pH 5.7 - 5.9, and were 99+% FDG by HPLC. Average FDG yields, low at first, improved to 59% (corrected to EOB) in May, 1988. Thereafter, FDG yields over 55% occurred frequently, but average yields declined steadily and reached 42% in Nov. 1988. Finally, December 12, poor yield <15%, and failure of delivery of irradiated 0-18 water halted production. The nickel-plated copper target body was replaced, and new 0-18 water restored FDG production, poorly at first, but later increasing to averages of 50% - 60% (June, 1989). New delivery lines, longer (90 feet) but less elevated, solved water delivery problems. With our production limitations, 2 runs per clinical day are frequently required, increasing radiation dose to operating personnel. Our experience suggests that nickel-plated targets produce fluoride ion with diminished fluorination capability in this synthesis of FDG; we will try a silver target and reconfigure the target setup to remove beam current limitations.

INTRODUCTION

In Aug. 1987, a [F-18]-FDG production system[2] consisting of a target assembly for proton irradiation of 0-18 water (adapted for a CS-30 cyclotron), a chemical process unit for FDG synthesis and a computer for process control, was installed in our PET facility.

Trial production provided proof of the system's ability to furnish a sterile, non-pyrogenic and radiochemically acceptable product. Quality control procedures were made routine. By January 20, 1988, the FDG yields were acceptable and the product was determined suitable for patient studies.

Average FDG yields reached 56% (corrected to EOB) during March-May. Yields were inconsistent, however, with a large spread between maximum and minimum yields (e.g. 74% corrected yield in a 2-week period bounded by 22% and 27% yields). Maximum production was 184 Mci on June 28, 1988.

Average yields declined slowly, but production was adequate for the clinical demand. However, increasing need collided with diminishing yield, and September 9 saw a second FDG run (in one day) following an initial "fair" run (130 Mci, 42% yield). Thereafter, second same-day runs became common as yields declined and became unacceptable on December 12, when low yield and severe water-delivery difficulties (including "milky" irradiated water) caused cessation of production.

INVESTIGATION OF THE PROBLEM, AND RECOVERY OF PRODUCTION

Approximately 0.32 mL water containing 95+% 0-18 is bombarded with 10 MeV protons in a nickel-plated copper target, producing F-18 ion ($^{18}O(p,n)^{18}F$). Saturation yield was about 135 mCi per μA (10 min at 10 μA produces 85 mCi). Irradiated water was delivered to the "hot lab" through 67 feet of polyethylene tubing (0.035" ID) with low-pressure nitrogen gas.

FDG synthesis is carried out in a chemical process module[3] which provides two heated oil baths, two movable reaction vessels, reagent supply vials and appropriate transfer tubing, an air column heater

and exhaust fan, a valved pressure manifold, purification columns and which is computer-controlled with proprietary software. The synthesis generally follows the procedure recommended by Coenen, et al,[4] using the aminopolyether, "Kryptofix 222" to promote nucleophilic fluorination of the sugar substrate, a tetraacetlyated triflate mannopyranose, "Triflate", which is then hydrolyzed to remove the acetyl groups. The final product is taken up in sterile water for injection, column-purified and made isotonic by addition of sterile saline.

Production records include assay of the F-18 activity in the system components at disassembly. These records were reviewed to determine the presence of trends in the following areas: FDG yields by month, noting maxima, minima and averages (as percent at EOB), calculation of mCi/μA-hr, F-18 activity theoretically available for fluorination, but which failed of incorporation, integrity of target water delivery and efficiency of hydrolysis. Samples of unirradiated 0-18 water from two lots, one from Mound Labs. and one from Isotec were analyzed by Inductively Coupled Plasma Mass Spectrometry (ICPMS) and graphite furnace atomic absorption (GFAA). The first had produced the milky irradiated water, and the latter was the one with which production was later resumed.

Before production was resumed, a new target was purchased and mounted.

New polyethylene (PE) delivery lines, presumably the same as the original, were mounted along a path essentially the same.

Many target loadings, trial irradiations, target unloadings and water deliveries were performed to ensure correct loading and recovery. When recovery difficulties persisted even with new lines, a clean original line was made available, to little avail. Following the discovery that the new lines were a small, but critical, amount smaller in diameter than the original, a completely new bundle, 90 feet instead of 67 feet, but not higher than 7 feet above the floor was installed. This set contains one each, 0.035", 0.038" and 0.045" ID PE and TFE tubing; only the smaller two PE have been used.

However, before the last set of lines was installed, and while the investigation was still in progress, production was resumed with the new target and with Isotec 0-18 water.

In review of production records, the F-18 activity remaining in the fluorination vessel and its output silica purification cartridge, and the inlet tube was taken as a measure of the "unavailability" of fluoride ion. Activity in the alumina and C-18 cartridges was taken as an inverse indication of hydrolysis effectiveness.

The review indicated:

1. Average FDG yields peaked in May, 1988 and declined approximately linearly through November. Maximum yields were always much greater than average and minimum (non-zero) yields were much less than average for most months. "Unavailable" fluoride increased as yield decreased. See Figures 1 and 2.
2. Average FDG yields declined with increasing μA-hr of irradiation, while "unavailable" fluoride ion increases. While fluoride "unavailability" could have been a function of total charge, it appeared to increase with bombardment time alone. See Figure 3.
3. Poor hydrolysis occurred occasionally, but was not major problem.
4. Activity blown out of the delivery line after water bolus delivery indicated the degree of bolus breakup.
5. Just when potentially most useful, during September, October and November measurement of system component activity was discontinued owing to high radiation absorbed dose to operators disassembling the synthesis unit; this concealed evidence of increasing delivery problems. Some yields estimated to be poor, were in fact not as bad as estimated because not all of the expected activity was recovered. In other cases, it was determined that forcible recovery with higher pressures sputtered irradiated water on the sides of the receiving vessel, where the F-18 stuck, increasing "unavailability".

The "milky" irradiated water appeared colloid-like, but on standing, the white substance settled in a manner indicating a particulate suspension. GFAA analysis of the "milk" showed much higher concentrations if Ni, Si, Ca and Zn than in the unirradiated water. This L of water was not used again

and was consumed in testing, except for 10 mL that was returned to Mound Laboratories.

The results of the ICPMS and GFAA analyses are shown below:

Selected elements found in 2 lots of 0-18 (95+%) water, in ng/mL (ppb).

ELEMENT	MOUND HH 6-88-007		ISOTEC NS0065	
	ICPMS	GFAA	ICPMS	GFAA
boron	841	---	110	---
magnesium	49	---	25	26
aluminum	<1.6	---	<1.6	0.64
silicon	1640	---	424	10
calcium	677	---	172	120
iron	<1.5	0.81	<1.5	3.8
nickel	1040	770	15.8	15
zinc	252	---	99	---

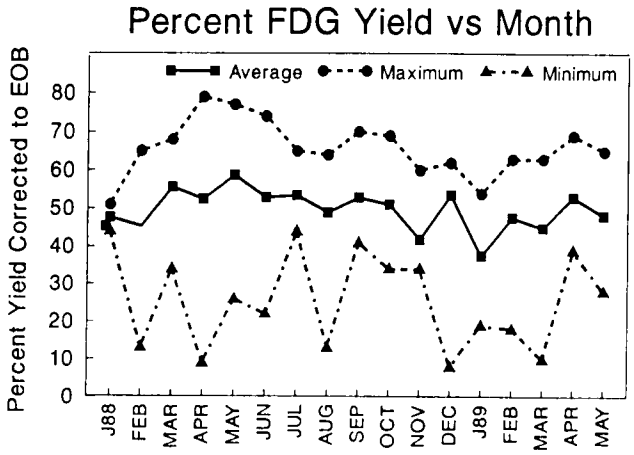

Figure 1

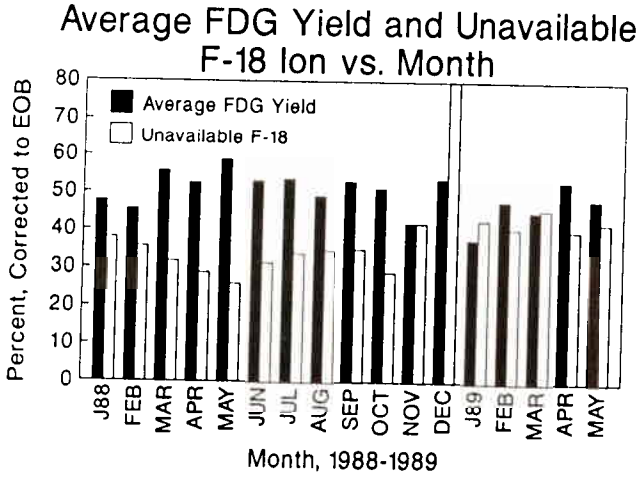

Figure 2

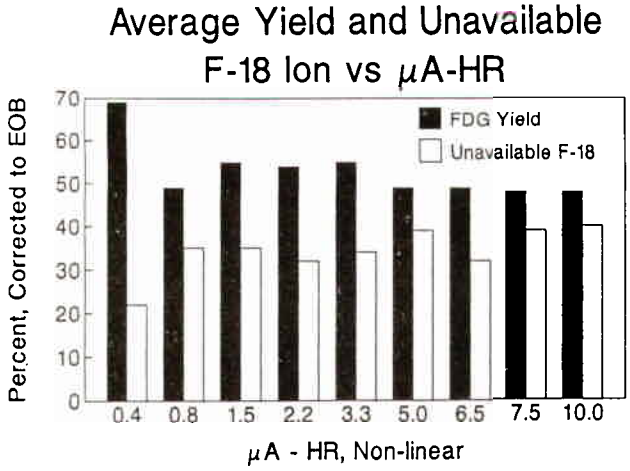

Figure 3

Target water is now routinely filtered through a small (100 - 200 mg) Chelex-100 resin column to remove divalent and trivalent metal ions.

A grayish substance was removed from the irradiation chamber of the target body and from the target side of the Havar entrance foil, neither of which had been cleaned since first use. The substance exhibited activities in the 0.1 to 1 uCi range, and had two easily identified components: Co-57 and Mn-52, from nickel and chromium in the Havar foil. The large amount of deposit, and the fact that it carried removable activity were startling.

It was discovered that the new PE delivery tubing, was actually 0.031" ID, compared with the original's 0.035 inch ID. The slight difference meant the difference between success and failure at delivery, which began with a 7 foot vertical lift. Later, repeated bolus breakup occurred with clean, original 0.035" ID PE tubing; we installed a new bundle which ramps gently up from the target for 2 feet, then is level until it enters the hot lab. The one 0.038" ID PE tubing in this bundle is providing reliable delivery; however, a 0.035" ID PE tubing gave erratic delivery after a few weeks of service for reasons unknown. It is unknown why an original line, with 7 feet vertical lift, worked well until 10/88, and why an unused identical line failed in 1/89.

It was learned that prolonged soaking of glass vessels in isopropyl alcohol/KOH solution etches the glass and causes sticking of fluoride ion.

DISCUSSION

By the time production was interrupted, a large number of mishaps in synthesis module operation had been identified. Most are operator-caused, but were not responsible for the long-term decline in yields.

When the investigation began, there were so many problems that one could not be observed without interference from another. The entire target support unit was re-plumbed, and has since been replaced. Water loading was discovered to depend on the piston position in a remotely driven polypropylene syringe, due to variable bulging of the barrel. This was corrected by use of a glass syringe with teflon-faced piston. Only then was target loading reliable enough to allow correct loading for proper target internal cooling and water delivery. Correction of this class of problems required over 3 weeks.

The failure of the Mound water was traceable to high levels of Ni, Zn, Ca and Si. This was a spectacular distraction, but was not responsible for the steady decline in FDG yield as it was not placed in use until November.

While metal ions found in some batches of O-18 water are of concern, di- and trivalent ions can be removed by filtering through a Chelex-100 column before irradiation. We have little hope of combatting introduction into target water of Ni, Co, Cr, Fe or Mn from the effects of bombardment on the target and/or target foil.[4,5]

The history of our efforts seem to parallel strongly those of Tewson[5] who has agreed with our conclusion that "the target is doing something to the fluoride ion during bombardment, and the longer the bombardment, the worse it gets".[6] It is likely that our failure to clean the target properly over so long a time aggravated our problem, but Tewson cleaned his target and still experienced the same decline in yield.

Overlooked until late was the fact that each target was once irradiated empty of water. However, the good performance of the first target came after its mishap, and the second was cleaned immediately after its empty run. It is clear from the large amount of removable Co-57 and Mn-52 from cleaning that neither target benefitted from the abuse of irradiation while empty.

Throughout, the quality of the FDG product by HPLC (Aminex HPX-87C column) has been consistently high, 99+% FDG, with minimally detectable levels of Kryptofix; quality has been maintained despite reduced production.

To accomplish our normal mix of 2 myocardial evaluations and 4 neurological studies in a single day requires the morning production of at least 180 mCi. If the first FDG run produces less, (or if the myocardial studies involve dipyridamole stress) another run is necessary. When a second FDG synthesis unit is not available, the one unit must be disassembled while still quite radioactive. This greatly increases the operators' radiation exposures, which currently are unacceptably large.

With existing limitations on beam current (10 μA), and with the impaired fluorination we encounter in our FDG synthesis unit, we still expect to make at least 100 mCi with 30 min. bombardment time. Bombardments longer than 35-40 minutes produce greater FDG activity, but at lowered efficiency. This also causes high activity levels in a unit disassembled for a second run.

CONCLUSIONS

1. Remote, automated synthesis of FDG using F-18 fluoride ion produced by the $^{18}O(p,n)^{18}F$ reaction provides FDG that is satisfactorily radiochemically pure, sterile and non-pyrogenic. However, low yields can require two FDG production runs on many days.
2. Two FDG runs per day in one unit causes excessive radiation exposures.
3. Poor or mediocre yields occur occasionally, for reasons that may escape identification. We have made some changes in O-18 water, synthesis step timing and in reagents, with consistent results only recently (May '89).
4. For good yields, cleanliness is required in target, delivery lines, reaction vessels and other synthesis system components. We now expect to replace delivery lines and reaction vessels after a few weeks of service.
5. Beam current limitations are due to our setup, not the target itself. To increase current on target, we are improving the beam profile by modifying the beam line configuration and by installing a new energy degrader (27 MeV --> 11 MeV), with better geometry and improved water-cooling.
6. Longer bombardment times result in greater fluoride ion "unavailability". We believe this to be a property of a nickel-plated copper target, and our observations are consistent with the experiences of Tewson et al.[5] To circumvent this problem we are obtaining a pure silver target.

ACKNOWLEDGEMENT

We gratefully acknowledge the assistance and suggestions of Michael Zalutsky, Duke University Medical Center. We are pleased to acknowledge the extraordinary endeavors of our technical support staff, Sharon Hamblen, Mark Estrada, Vernon Dew, Michael Dailey and David Coates. We acknowledge with gratitude the continuing support of Henry Padgett, Bruce Wieland, and Paul Kretz of CTI Cyclotron

Systems, Inc., of Berkeley, CA. Joanna Fowler, Dave Schlyer and Dave Alexoff of Al Wolf's group at Brookhaven National Laboratory continue to interact beneficially with our efforts, and for this we are most grateful. We thank Keith Smith of Isotec for referring us to Elemental Resources, Inc., who performed the ICPMS analyses of our water samples with rapid results. Tim Tewson has encouraged our efforts to find an effective solution, and we thank him for his support.

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