

Direct Simultaneous Production of [¹⁵O]Water and [¹³N]Ammonia or [¹⁸F]Fluoride Ion by 26 MeV Proton Irradiation of a Double Chamber Water Target

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A simple double liquid chamber target was developed to provide the option for simultaneous production of [¹⁵O]H₂O and either ¹³N or ¹⁸F using a single proton beam. Irradiation of natural water in a thin aluminium front chamber produced [¹⁵O]H₂O by the ¹⁶O(p, pn)¹⁵O reaction directly. Large (0.5–1.0 Ci) doses of sterile [¹⁵O]H₂O (>99.95% radionuclide purity) were routinely prepared in 1 min from end of 20 μA bombardments using this target and an in-line mixed bed ion exchange column purification. Water in the thin front chamber degraded proton energies on exit to 20–18 MeV. The rear silver liquid chamber was threefold thick to 17 MeV protons in water and it efficiently produced either ¹³N by the ¹⁶O(p, α)¹³N reaction or [¹⁸F]fluoride ion by the ¹⁸O(p, n)¹⁸F reaction. Both target chambers were overpressurized with at least 6 atm of gas to minimize boiling/cavitation of water at high beam currents. Using hydrogen as the overpressure gas on the back chamber and an in-line anion exchange column radionuclidic cleanup process, high yields of sterile, aqueous [¹³N]NH₃ (40–200 mCi; 20 μA) were produced directly from the back chamber at the same time that [¹⁵O]H₂O was being produced from the front chamber. The combination of this target system with a cyclotron capable of generating 26–30 MeV protons provides great flexibility and simplicity for rapid, high volume production of the three best validated and most widely used radiopharmaceuticals at the present time in clinical positron emission tomography: [¹⁵O]H₂O, [¹³N]NH₃ and [¹⁸F]FDG.

Introduction

The clinical usefulness of positron emission tomography (PET) studies using [¹⁵O]water for regional blood flow measurement and [¹³N]ammonia for assessment of cardiac perfusion is well established. Along with 2-[¹⁸F]fluoro-2-deoxy-D-glucose ([¹⁸F]FDG), these agents are the best validated and most widely used PET tracers in humans and they will remain the core against in clinical PET programs for the foreseeable future. As the demand for PET studies increases, cyclotron-PET facilities must find ways to economically provide large volumes of these routine tracers for clinical use while at the same time making other ¹⁸F and ¹¹C tracers available for research studies. At larger centers with several cameras operating simul-

taneously, each unit must be supplied with tracers on schedule. Matters are further complicated by study protocols that call for sequential use of two agents in a patient in the same sitting. For instance, [¹⁵O]H₂O/[¹⁸F]FDG combinations are often used in brain studies as are [¹³N]NH₃/[¹⁸F]FDG combinations for heart studies. Under these circumstances it is important both for isotope production schedules to be flexible and agent syntheses to be simple, reliable and fast.

The technical and logistical challenges of producing multiple daily batches of shortlived isotopes ¹⁵O, ¹³N, ¹¹C and ¹⁸F to meet busy clinical schedules are formidable, and they are being approached in several ways. Some facilities use two accelerators, with one deuteron accelerator machine used predominantly for ¹⁵O production by the ¹⁴N(d,n)¹⁵O reaction, and the other isotopes being produced on a proton accelerator. Another option currently being promoted by medical cyclotron manufacturers is the use of low

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energy (10–16 MeV) proton-only machines (with minimal space and shielding requirements) to make all four isotopes. While the production capacities for ^{18}F and ^{11}C with these systems appears to be more than sufficient for clinical needs, the low proton energies require the use of expensive-to-operate ^{15}N gas targets for ^{15}O production by the $^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$ reaction (Sajjad *et al.*, 1984) and ^{13}C slurry targets for ^{13}N production by the $^{13}\text{C}(\text{p},\text{n})^{13}\text{N}$ reaction. Questions remain to be settled concerning the costs and ensured availability of the enriched target isotopes required as well as the robustness of these low energy proton ^{15}O and ^{13}N isotope production systems in a busy clinical setting.

A third approach, which is the situation at this facility, is the use of a single medium energy, multi-particle accelerator which switches back and forth between deuterons (primarily for ^{15}O water production) and protons (^{18}F , ^{11}C , ^{13}N). The switch time varies depending on the type of machine. Our CS-30 cyclotron (26.6 MeV protons, 15 MeV deuterons) requires 15–30 min for particle switch over. In a busy clinical schedule calling for all four isotopes throughout the day, this long switching time hinders efficient use of the machine for isotope production, complicates scanning logistics and reduces patient throughput. Therefore we have sought approaches for making ^{15}O from protons to avoid the wasteful switch time as much as possible.

In addition to the $^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$ reaction mentioned above, another proton reaction is available for making ^{15}O ; this is the $^{16}\text{O}(\text{p},\text{pn})^{15}\text{O}$ reaction (Sajjad *et al.*, 1985). An advantage of the $^{16}\text{O}(\text{p},\text{pn})$ reaction is that it uses cheap natural ^{16}O as the target material (the enriched ^{15}N gas required for the $^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$ route, costs \$U.S. 200–300/L STP, by comparison). While the p,pn reaction has a high threshold energy of about 17 MeV, its excitation function rises very steeply. At 26 MeV the reported saturation yield in a gas target is quite large [100 mCi/ μA (Sajjad *et al.*, 1985)]. The feasibility of making medically useful quantities of ^{15}O -agents by the $^{16}\text{O}(\text{p},\text{pn})$ reaction with a CS-30 cyclotron has been demonstrated previously using gas targets (Beaver *et al.*, 1976; Fernandez-Rubio *et al.*, 1981). Using somewhat higher proton energies (29 MeV) in a gas target Ruth (1985) has also produced large amounts of ^{15}O (^{15}O) $_2$ (30 mCi/ μA at saturation) by this reaction. An elegant extension of this idea was development of a gas-liquid tandem target (Koh *et al.*, 1983) in which the front $^{16}\text{O}_2$ filled gas chamber both produced ^{15}O (which could be combusted to ^{15}O) H_2O and served as the degrader for the rear ^{16}O water chamber where ^{13}N $\text{NO}_3^-/\text{NO}_2^-$ was produced by the $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ reaction (Whitehead and Foster, 1958); this was subsequently reduced to ^{13}N NH_3 by Devarda's alloy.

The tandem target concept is appealing for its simplicity and versatility. In principle it permits simultaneous production of ^{15}O and any one of several

other proton derived isotopes with nuclear reaction cross sections below 20–17 MeV, including ^{18}F and ^{11}C in addition to ^{13}N . Therefore we decided to investigate this approach as a possible remedy to our long particle switchover delays. However, instead of a gas-liquid dual target, we explored a liquid-liquid dual chamber target patterned after a pressurized liquid target design previously developed for ^{18}F fluoride ion and direct ^{13}N NH_3 production (Mulholland *et al.*, 1989a, c). We envisioned a system in which both ^{15}O H_2O and ^{13}N NH_3 could be formed directly in-target and purified from radio-nuclidic as well as radiochemical impurities by simple on-line ion exchange column methods. An added bonus would be the ability to make ^{18}F fluoride ion in the rear chamber. Here we report the development of such a dual chamber system and its successful use for deliveries of large clinical doses of either ^{15}O H_2O plus ^{13}N NH_3 or ^{15}O H_2O plus ^{18}F fluoride ion (when the rear chamber is filled with ^{18}O H_2O).

Methods

General

A TCC CS-30 positive ion cyclotron with a rated proton beam energy of 26.6 MeV was used in this work. The proton beam passes down a 7 m beamline, through a beamline terminus window (0.127 mm aluminum) and a 3 cm forced air gap (1.5 atm) for foil cooling before impinging on the front target window. The calculated mean proton beam energy at the point of foil contact was calculated to be no greater than 26.1 MeV. Helium sparged deionized (Milli-Q[®]) water or ^{18}O enriched water (Isotec) were used as target liquids. The front target body was fabricated from aluminum 6061 stock. Silver foils (99.9%) were purchased from Aldrich Chemical Co. Aluminum foils and silver billet for fabrication of the rear target body were purchased from A. D. Mackay Inc., Red Hook, N.Y. All gases were obtained from Air Products and were of "Ultra Pure Carrier" or "Research" grade. All ion exchange resins used were Biorad "Biotechnology" grade.

Target construction and operation

The double target assembly is shown in Fig. 1. It consists of a stack of 76 mm diameter metal disks, some with central cavities machined into them. Foils sandwiched between the discs form and separate the front and rear chambers. Six bolts running longitudinally through holes spaced at 60° angles around the perimeters of the disks bind the assembly together with the beamline mounting flange. Each chamber has top (vent) and bottom (fill/dump) ports drilled through the rims of the disks. The ports terminate with standard Swagelok or 1/4 × 28 threaded fittings. Silver foil (0.25 mm thick) "donut" crush seals are compressed between the target disk faces and foils to seal the target chambers. The front chamber is a 19.05 mm diameter cylindrical hole drilled through

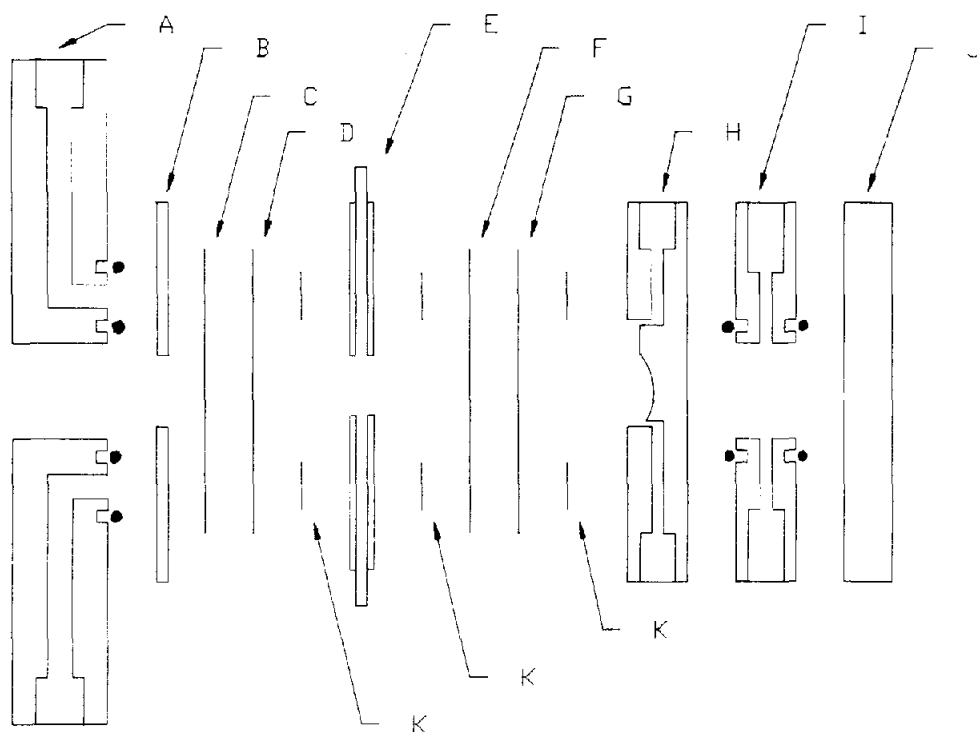


Fig. 1. Exploded side view of double chamber target. A, Aluminum beamline mounting flange with water channels, O-rings and air jets (not shown) for foil cooling. B, Aluminum front target sealing plate. C, Havar foil 0.025 mm. D, Aluminum foil 0.05 mm. E, Aluminum front target body with SS fill and vent tubes shown. F, Aluminum foil 0.25 mm, or Havar 0.025 mm. G, Silver foil 0.025 mm. H, Silver back target body fill and vent ports. I, Aluminum disk for circulating cooled water showing inlet and outlets. J, Aluminum back plate. K, Silver crush seals (0.25 mm).

the center of a 5.1 mm thick aluminium disk. It holds approx. 1.5 mL of water. The front chamber is cooled by passive conduction through other components of the target assembly. The aluminum front target disk is faced from the beam side with a 0.025 mm Havar foil directly apposed to a 0.05 mm aluminum foil. The beam exists the front chamber through a septal foil combination (0.25 mm aluminum/0.025 mm silver was used for most of these studies but we have since switched to 0.025 mm Havar/0.025 mm silver because of the greater durability of this combination) and enters a silver rear hemispherical chamber (maximum depth 6.35 mm) with a volume of approx. 1.2 cm³. The rear silver target body disk (approximate mass 500 g) is cooled by 10–15°C water circulated over its back face. The front and back chambers are loaded through the bottom ports with solenoid or syringe pumps. Both target chambers are overfilled in normal operation, with the overflow being held in reservoirs connected directly to the top (vent) ports. The volume of the overflow reservoir on the front chamber is 7.5 cm³ and it is overfilled by 4–6 mL. For ¹³N production, the back target is overfilled by 1–1.5 mL. In the case of ¹⁸F production, only about 0.1 mL overfill of expensive [¹⁸O]H₂O is permitted in the back target.

Irradiations were conducted with the target water in the static (noncirculating) mode. Beam currents

varied between 10 and 30 μA, with most irradiations conducted at 20 μA. No beam “wobbling” devices were used over the course of this work and the target experienced the full stress of any beam irregularities which may have occurred during irradiations. Normally the front target chamber was pressurized with 6–7 atm of helium dynamically (open to the gas tank regulator) through the top part during irradiations. The rear chamber was pressurized similarly with either hydrogen or helium (7–10 atm). Three to five cm³ of total gas head space in the form of Teflon tubing existed above each target chamber. Following irradiation, target water was transferred by gas pressure to the radiochemistry laboratory through 20 m of 1 mm i.d. Teflon or polyethylene tubing. Transfers were usually complete within 25–50 s.

Radioactivity measurements were made in ionization chambers (Capintec Model CRC745). At least two countings of each sample were taken in order to determine the amounts of ¹⁵O and ¹³N present; one at ≤5 min EOB (¹⁵O + ¹³N) and one at >20 min (¹³N alone). Fluorine-18 samples were counted at least 60 min after irradiation to insure that any coproduced ¹³N present had the chance to decay. Measurements were decay corrected to end-of-bombardment. Irradiated target water was analyzed by radio-HPLC using a strong cation exchange (SCX) column (Tilbury and Dahl, 1979). It was also checked for

long half-life γ emitting radionuclidic species over the energy range of 90 keV–1.8 MeV using a Ge(Li) detector. The mixed bed ion exchange resin columns used for removal of potential radionuclidic contaminants from [^{15}O]H $_2\text{O}$ were prepared by slurry packing 3:1:1 wt ratios of AG1(Cl $^-$):AG50(H $^+$):Chelex 100(Na $^+$) (all 2% crosslinked, 200–400 mesh) into 7 mm i.d. \times 50–70 mm columns with luer fittings. The [^{13}N]NH $_3$ purification columns (7 mm i.d. \times 40 mm) consisted solely of AG1(Cl $^-$) resin.

Results

Preliminary experiments employed a single chamber (8.9 mm maximum depth, \sim 1.7 cm 3 volume) silver target with a 0.127 mm aluminium foil to determine the feasibility of ^{15}O production with our cyclotron configuration. In Table 1 the ^{15}O and ^{13}N production results obtained using this target are summarized. Yields are decay corrected to end of bombardment. In Table 2 are shown the ^{15}O and ^{13}N isotope production for the front and rear chambers during 17 irradiations of the double chamber target having 0.025 mm Havar/0.05 mm Al front foils and 0.127 mm Al/0.025 mm Ag rear (septal) foils. The front chamber was pressurized to 6–6.7 atm (helium) and the rear chamber to 6.5–10 atm (He or H $_2$) during these runs. Under these conditions 91% \pm 1.8 of the total (front plus rear) ^{15}O production was segregated to the front chamber and 82% \pm 4.7 of the total ^{13}N was formed in the rear chamber. The target was irradiated more than 50 times on one set of foils before failure of the septal foils occurred. In Table 3, are shown the typical end-of-synthesis yields of [^{15}O] water at 1 min post-irradiation and [^{13}N] ammonia at 5 min post-irradiation. These figures represent the amount of final formulated product ready for use following ion exchange purification. The production of active [^{18}F] fluoride ion from the rear target (filled with [^{18}O] water) was essentially the same as that reported previously for the single chamber modification (Mulholland *et al.*, 1989a).

Discussion

The $^{16}\text{O}(p,pn)^{15}\text{O}$ excitation function measured from gas targets (Sajjad *et al.*, 1985) is negligible below 17 MeV and rises sharply to a broad peak over the energy range of 29–40 MeV. The reported satu-

ration yield of ^{15}O at 26 MeV is 100 mCi/ μA . Examination of the reaction cross section below 26 MeV shows that almost 95% of the ^{15}O production occurs between 26 and 20 MeV and 50% occurs between 26 and 24 MeV. Thus an important design factor to permit maximal ^{15}O production with the 26–25 MeV (incident on target) proton beam available from our CS-30 cyclotron was to make the front target foil window very thin to minimize beam degradation. At the same time the front foil needed to be strong enough to withstand the substantial gas overpressures which were applied to the front target to hinder boiling and voiding of target liquid during high current irradiations. Target pressurization was also important for maintaining the proper direction of foil flexure and chamber thicknesses.

Initial ^{15}O production experiments employed a 0.127 mm aluminium foil on a 8.9 mm deep, single chamber target. This target was calculated to be approx. 2.5-fold thick for 25 MeV protons when filled with water, and thus both ^{15}O and ^{13}N [by the $^{16}\text{O}(p,\alpha)^{13}\text{N}$ reaction, Whitehead and Foster (1958)] were produced in the same chamber. Irradiations of this target at 20 μA showed excellent ^{15}O production, approaching the saturation yields reported for 26 MeV protons in gas targets, with this water target geometry and foil. However, less than expected ^{13}N formation was observed at 2 atm overpressure of helium. As an overpressure was increased to 5 atm, ^{13}N yields rose and ^{15}O yields remained high (Table 1). The interpretation of these results was that boiling was occurring in the target during 20 $\mu\text{A}/2$ atm irradiations, which effectively made the target "thin" to \sim 25 MeV protons. The higher overpressure made the target "thick" once again by suppressing cavitation, resulting in the lower MeV range protons being completely expended in the water to produce ^{13}N by the $^{16}\text{O}(p,\alpha)$ reaction. Suppression of in-target boiling by gas overpressurization during irradiation has recently been verified visually (Heselius *et al.*, 1989).

After this preliminary demonstration of the feasibility of producing large quantities of ^{15}O , we next proceeded to a double chamber configuration to attempt to segregate ^{15}O production from ^{13}N production. The goal was to make the water filled front chamber thick enough to degrade the proton beam energy from 26–25 MeV down to \sim 20–18 MeV at exit. The front chamber thickness was thus the critical dimension and it optimized for a given set of operating conditions through an iterative process in which the yields of ^{15}O and ^{13}N were measured from both front and rear [^{16}O] water-filled chambers following irradiations. The nominal depth of the rear target chamber (not taking into account any septal foil bending) was calculated to be threefold thick to 17 MeV protons. If large amounts of ^{13}N were observed to form in the front chamber in addition to the ^{15}O , then a thinner front chamber was installed. Conversely, if much ^{15}O formed in the rear chamber,

Table 1. Single chamber "thick" target yields of ^{15}O and ^{13}N by irradiation of natural water with 26 MeV protons. Except for the 30 μA entry, each value represents the mean and standard deviation of 3–5 runs.

Beam (μA)	Irrad. (min)	Helium (atm)	^{15}O Yield (mCi)	^{13}N Yield (mCi)
20	3	2	1190 \pm 52	66 \pm 14
20	3	5–10	1250 \pm 50	94 \pm 12
20	5	5–10	1516 \pm 50	181 \pm 18
20	10	5–10	1971 \pm 67	268 \pm 35
30	3	6.5	1765	163

the front chamber was made thicker. Although calculations had indicated that a front chamber water thickness of 2.54 mm should be sufficient to achieve a 26–20 MeV energy degradation, a front chamber of twice that nominal depth (5.1 mm) was eventually found by this procedure to give the best separation of ¹⁵O and ¹³N production between the front and rear targets. Possible reasons for the discrepancy between calculated and empirically derived optimal thicknesses include cavitation-induced reduction in the average water density within the front chamber under beam or unequal deformation of front and back foils under pressure. Because the foils flex, the front chamber thickness varies depending on the beam intensity and profile and the level of target pressurization. The direction of septal foil bending can be controlled by maintaining an overpressure differential between chambers. If the front chamber is held at lower pressure than the rear, the thin septal foils flex beamward and cause the front chamber to become thinner. Conversely the front chamber can be made thicker by keeping the pressure there higher than that in the rear chamber.

The double chamber design employed initially a 0.127 mm aluminum front foil. Unfortunately, this foil was found to lack sufficient tensile strength to resiliently withstand the 6–7 atm of helium overpressure applied in the front chamber during irradiations. It deformed plastically (“ballooned”) outward over a series of runs, gradually expanding the longitudinal dimension of the front chamber to the beam. Consequentially the energy drop within the front water chamber rose and the ¹³N production there increased with time at the expense of ¹³N formation in the rear chamber. Use of the stronger front combination foil of 0.025 mm Havar and 0.05 mm aluminum corrected this problem. The calculated proton energy drop for this combination foil was about the same as for 0.127 mm aluminum (0.51 vs 0.55 MeV) but it easily resisted 30 μA irradiations at front chamber overpressures of 6.5 atm without ballooning. With this

foil modification in place, the amount of ¹³N in the rear chamber was generally at least 80% of the total (front plus rear) ¹³N yield and this ratio remained roughly constant over a period of many runs (Table 2). This average percentage is probably an underestimate because it includes some runs where substantial levels of volatile gaseous ¹³N species (probably N₂) formed but could not be quantified due to their loss when the rear target contents were collected for measurement. If these runs are omitted, the average separation of ¹³N production into the rear chamber rises to 90%.

Oxygen-15 production under these conditions was 91% segregated to the front chamber, on average (Table 2). For the subset of 10–20 μA irradiations, the percentage was 93.5%. In the few 30 μA runs conducted so far, front target ¹⁵O separation was reduced to 82%. This increased spillover of ¹⁵O formation into the rear chamber can again be explained by greater boiling and cavitation at the highest beam intensities which reduce the average water density within the front chamber so that a beam with higher net energy enters the rear chamber. Further studies on the effects of higher beam currents and target pressurizations on relative percentages of front and rear chamber ¹⁵O formation are underway.

The double chamber target design was made from fairly cheap, easily machined metals. The high thermal conductivities of both aluminum and silver made liquid cooling channels in the target bodies unnecessary. Pressure-tight sealing to at least 10 atm was achieved without need of elastomeric O-rings. The front chamber is always kept filled with water, and it serves as a “water cooled” degrader for the silver-lined rear chamber when only ¹³N or ¹⁸F is required. This system has been disassembled and examined five times since this work has begun. No obvious thermal effects (blackening) have been noted on either front or septal foils from beam currents as high as 30 μA. Rather surprisingly, the foils survived several unintentional target irradiations with an empty front

Table 2. Total ¹⁵O and ¹³N measured from double chamber target

Beam (μA)	Irrad. (min)	Front chamber		Back chamber		Irrad. order
		¹⁵ O (mCi) ¹³	N (mCi)	¹⁵ O (mCi)	¹³ N (mCi)	
10	10	898	34	30	190	7
20	3	1094	11	108	10*	11
20	3	1160	15	117	95	12
20†	5	1243	47	43	47*	3
20†	5	1278	41	63	162	4
20	5	1404	20	120	203	8
20	5	1419	17.5	282	170	9
20	5	1320	22	ND	240	13
20	5	1270	100	Not emptied		14
20	5	Not filled		1227	313	1
20	6	1563	48	Not emptied		17
20	10	2010	62	Not filled		2
20	10	1643	21	108	295	5
20	10	1720	25	75	329	6
20	50	Not filled		1060	632	10
30	5	1803	45	490	196*	15
30	10	2103	34	408	510	16

*Additional gaseous radioactivity observed but not quantified.

†Beam current instability during runs.

chamber without obvious ill effect. Foil ruptures that occurred during this work appear to have resulted mainly from fatigue caused by foil movement under changing pressures in the target system. This problem has been remedied through the use of tougher Havar foils in place of aluminum, by adjusting downward the static pressure within the beamline foil air cooling gap and changing the order in which the target chambers are pressurized and dumped to minimize abrupt flexing.

Clinical [^{15}O]water production

In normal operation the front target contents plus the top port overfill (6–7.5 mL of total water) are forced from the target by helium pressure through a mixed bed AG1/AG50/Chelex 100 resin column and sterile filtered in line into a multi-dose vial to which was previously added enough concentrated saline to make the final product isotonic. Mixing between the front target contents and the overfill reservoir during irradiation is limited and the water in the reservoir serves to quickly flush residual activity left in target, lines and column into the vial after irradiation. While the front target is emptied, the rear target remains closed and pressurized to minimize flexing of the septal foils. The entire procedure requires between 25 and 50 s to complete and routinely yields between 500 and 1000 mCi of [^{15}O]water at end of synthesis following 3–6 min/20 μA irradiations. The mixed bed column is very effective in removing radionuclidic impurities ([^{13}N]NO $_3^-$, NO $_2^-$, NH $_3$, [^{18}F]F $^-$) from the [^{15}O]H $_2\text{O}$. Radionuclidic purity of the final product, as measured by decay rate, was routinely above 99.95%. The Chelex resin was added as an extra precaution to ensure that any potential target-derived activated metal ions did not reach the final product solution, even though examination with a Ge(Li) detector of target water samples passed through AG1(Cl $^-$) did not show any long-lived isotopes above background levels to be present. Both the mixed bed [^{15}O]H $_2\text{O}$ columns and the AG1 (Cl $^-$) columns for [^{13}N]NH $_3$ purification were reused numerous times without requiring regeneration between runs, and multiple [^{15}O]H $_2\text{O}$ runs (4 in a 60 min period) have been conducted using the same column without loss of efficiency in removing radionuclidic impurities. The amount of residual [^{15}O]H $_2\text{O}$ left on the column after completion of target dumping varies (10–35% of total activity), depending on the particular column and the amount of overfill water used. Additional rinse water completely removes residual [^{15}O] activity from the column at the expense of time and further dilution of final product. The main precautions taken with these columns were: (1) to start with a good quality of ion exchange resin, (2) to make sure the beds were uniform and equilibrated with water before runs to avoid compaction or channelling and (3) to store them under sterile conditions (35% ETOH) at 3°C when not in use.

[^{13}N]ammonia production

Direct [^{13}N]NH $_3$ production in the rear chamber when it was maintained under a reducing overpressure of H $_2$ (7–10 atm) was essentially the same as with the single chamber silver target modification recently reported (Mulholland *et al.*, 1989c). A more detailed examination of direct [^{13}N]NH $_3$ production in a water target is the subject of another communication (Mulholland *et al.*, in preparation). Reproducible [^{13}N]NH $_3$ production in the double chamber modification required flushing the rear target and lines with hydrogen before irradiation and the use of clean, helium sparged target water. Significant amounts of volatile ^{13}N activity, presumably N $_2$ formed as a result of the presence of carrier nitrogen, was observed if these steps were not followed. When the rear target was operated at a H $_2$ pressurization of 10 atm the relative yield of [^{13}N] NH $_3$, as a percentage of the total aqueous ^{13}N activity, did not vary significantly with irradiation times up to 20 min beam currents up to 20 μA . However, beam intensities greater than 25 μA resulted in a lowered yield of [^{13}N]NH $_3$. At 30 μA , almost all aqueous ^{13}N activity collected from the rear target was in the chemical forms of NO $_3^-$ /NO $_2^-$ (Table 3). The dependence of in-target [^{13}N]NH formation on beam intensity has been previously reported (Tilbury and Dahl, 1979).

Platinum wire was originally placed in the rear target vent port on the supposition that it would help catalyze the reduction of ^{13}N species to [^{13}N]NH $_3$. Control experiments conducted later without the Pt wire found it to be unnecessary for in-target [^{13}N] NH $_3$ production. With regard to the influence of other metals, water in the rear target normally contacted only silver. However, on several occasions it was exposed to aluminum during irradiation, when the septal foil was breached. Under these conditions no significant inhibition of in-target [^{13}N]NH $_3$ production was observed.

The AG1 column was effective in removing [^{13}N]NO $_3^-$ /NO $_2^-$ and [^{18}F]F $^-$ from the [^{13}N]NH $_3$. The target dumping procedure was the same as for [^{15}O]H $_2\text{O}$ with the exception that the system was generally rinsed with two fresh targetfuls of water to elute all [^{13}N]NH $_3$ from the ion exchange column. A drawback of this ion exchange approach is the possibility that some [^{15}O]H $_2\text{O}$ may be present in the final [^{13}N]NH $_3$. However, this is generally not a problem as small amounts of ^{15}O usually have time to decay

Table 3. Typical "end of synthesis" yields of [^{15}O]water and [^{13}N]ammonia final formulated products

Beam	Irrad. (min)	mCi [^{15}O]H $_2\text{O}$ (1 min EOB)	mCi [^{13}N]NH $_3$ (5 min)*
20	3	300–500	40–100
20	5	400–700	80–150
20	6	650–800	ND
20	10	800–1000	100–200
30	3	500–800	traces

*Final products were counted at >20 min EOB and decay corrected to 5 min.

before the [¹³N]NH₃ is used. In cases where removal of all ¹⁵O is a critical issue, it can be achieved quickly using an AG50 cation exchange column which selectively retains [¹³N]NH₄⁺ ion.

[¹⁸F]fluoride production

The yields and chemical behavior of [¹⁸F]fluoride produced in the double chamber target modification with [¹⁸O]H₂O in the rear chamber were similar to that seen in the single chamber silver target previously reported (Mulholland *et al.*, 1989a). For example, 350–450 mCi of [¹⁸F]fluoride were routinely recovered from 20 min/20 μA irradiations. The [¹⁸F]fluoride produced from the rear chamber could be trapped efficiently and activated on the aminopyridinium resins we use for heterogeneous nucleophilic radiolabeling reactions (Mulholland *et al.*, 1989b; Toorongian *et al.*, 1990) except on rare occasions when the septal foils lost integrity and the rear chamber contents came in contact with aluminum surfaces of the front chamber [the detrimental effect of aluminum on fluoride reactivity has been noted—see Tewson *et al.* (1988)].

It is worth re-emphasizing that at anytime during irradiation of this target for [¹⁸F]fluoride production [¹⁸O]H₂O can be drawn off from the front chamber and be immediately available for use. This capability provides much flexibility in clinical situations such as short notice [¹⁸O]H₂O blood flow studies, repeat administration protocols, or where two or more PET cameras are operating at the same time. With the present system, the beam is removed from the target briefly during emptying and refilling of the front chamber to avoid striking it without target water; however it would be a fairly simple matter to modify the plumbing so that the front target contents are displaced by circulated water instead of gas pressure, and thus permit continuous access to [¹⁸O]H₂O without interrupting beam and isotope production in the back chamber at all.

Conclusions

A simple double chamber liquid target and in-line ion exchange resin purification method allows the preparation of large clinical doses of both [¹⁵O]H₂O and [¹³N]NH₃ at short notice. Multiple doses of these agents can be produced over a narrow time frame without changing setups or increasing the exposure risks to the operator. Provided that the capacity for accelerating 26 MeV or higher energy protons exists, this system can make [¹⁵O]H₂O available on a continuous basis without interrupting production of ¹³N, ¹⁸F and, in principle, other isotopes such as ¹¹C formed in low energy (<17 MeV) proton nuclear reactions. The flexibility that double chamber targets can provide to PET radiotracer production should be taken into consideration when deciding on the size of medical cyclotron to purchase for a clinical PET facility.

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