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CYRIC annual report

volume

1986

page range

171-177

year

1986

URL

http://hdl.handle.net/10097/49356
III. 4 [\textsuperscript{18}F]Fluoride Production with a Circulating [\textsuperscript{18}O]Water Target

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Introduction

Since nucleophilic substitution reactions with no-carrier-added [\textsuperscript{18}F]fluoride have recently been developed\textsuperscript{1-4}, the [\textsuperscript{18}O(p, n)[\textsuperscript{18}F] reaction with [\textsuperscript{18}F]fluoride production with a small cyclotron. Large quantities of [\textsuperscript{18}F]fluoride, depending on the degree of [\textsuperscript{18}O]-enrichment in target water, may be produced by the high current proton beams with accelerated energies of less than 20 MeV. The marked difference between the [\textsuperscript{16}O(\alpha, d)[\textsuperscript{18}F] and [\textsuperscript{20}Ne(d, α)[\textsuperscript{18}F] reactions and the [\textsuperscript{18}O(p, n)[\textsuperscript{18}F] reaction is that the latter nuclear reaction requires the smallest possible volume of [\textsuperscript{18}O] water simply because it is expensive. From this viewpoint a number of target systems for this reaction has been constructed\textsuperscript{5-11}). Although many of these use a static target with the minimum volume, our preliminary experience with such a production system led us to the adoption of a circulating water target\textsuperscript{10,12}). Circulation of the target water was expected to prevent the bubbles, consisting of vapor produced by the local deposition of heat and/or gases formed by proton radiolysis of the target, from reducing the effective target thickness which is considered to be a major reason for reduction of the yield. Thus, parameters affecting [\textsuperscript{18}F]fluoride production yield such as beam current, window material and flow rate of a circulating target have been systematically investigated and optimized with this system.

Materials and Methods

A target vessel was assembled with an aluminum flange, a titanium target cavity insert, and an aluminum cooling block. The titanium inserts shown in Fig. 1 have differently shaped target cavities. The model A was designed for a static target with the additional rectangular space above the 2.0 cm diameter circular target cavity to prevent the bubbles from removing a part of the target from the vessel\textsuperscript{11}). The model B was used for a circulating target having an additional triangular space above the 2.0 cm diameter circular cavity to allow any bubbles produced to flow swiftly away from the target cavity.

Target thickness was varied by changing the distance between the front and back windows which were placed on either side of the target vessel. A 200 µm thick Al foil laminated by a 25 µm thick Ti foil or 20 µm thick Ag foil from a target side was used as a front window. The back window was a 1.0 mm thick plate of either Ti or Ag which was the same material as the
front inside window. In Fig. 2 is shown the $^{18}\text{F}$ fluoride production system. The target was cooled through the back window with a rapid flow of water-ethylene glycol supplied by a recirculating cooling bath maintained at 0°C. This coolant flow also passed through the gas separator where vapor, if any, was condensed into the target and gases produced radiolytically were separated from the circulating target. The gases consisted of $\text{H}_2$ and $\text{O}_2$. They were catalytically recombined into $\text{H}_2\text{O}$ on $\text{Pd/Al}_2\text{O}_3$ heated at about 150°C. Reproduced $^{18}\text{O}$ water was returned to the target with a peristaltic pump (MasterFlex pump; Cole Parmer Instr. Co. U.S.A.), which also circulated the target water with a flow rate ranging from 30 to 80 mL/min. Target loading and recovery were remotely operated through polyethylene tubing (1 mm i.d. and about 20 m length) by using two small electric solenoid valves. $^{18}\text{O}$ water enriched in 20 atom% (Amersham, U. K.) was injected into the loading line with a syringe and then transferred to the target vessel under He pressure (0.5 kg/cm$^2$). During target transit the He flow rate was monitored with a thermal flow meter. A sudden increase in the monitored He flow rate from about 10 mL/min to 20 mL/min indicated that the transfer of target water had been completed.

After the 18 MeV proton beam passed through the front window, the incident energy was calculated as 16 MeV, corresponding to a 2.8 mm proton range in water. Prior to irradiations, the beam profile was always monitored through a TV camera. Irradiations were carried out by varying the current in the range from 5 to 20 μA and also the irradiation time ranging from 30 min to 2 hours. During irradiations the gases evolved from the target were collected in a 3 liter balloon at the hot laboratory. After the irradiation the target was transferred and collected in a glass vial. As the target contained natural oxygen in 80 atom%, $^{13}\text{N}$ was concomitantly produced by the $^{16}\text{O}(p, \alpha)^{13}\text{N}$ reaction. Therefore, the $^{18}\text{F}$ yields were determined by decay curve analysis. A theoretical saturation yield of $^{18}\text{F}$ for the present target was calculated as 39 mCi/μA by using the literature value$^{13}$. The $^{18}\text{F}$ fluoride thus obtained was assayed for its specific activity with an ion selective electrode. The effect of metal ions contained in the recovered target on subsequent syntheses was checked by synthesizing $^{18}\text{F}$ FDG according to the literature$^2$.

Results and Discussion

A static target is considered to have the advantage that it allows reduction of the volume of the expensive target to less than 1 mL if a target thickness of 3 mm corresponding to a 16 MeV proton range in water is chosen. From the correlation between the $^{18}\text{F}$ fluoride yield and the current obtained with a static target in Fig. 3, however, it can be clearly seen that a static target does not provide a high production yield at beam currents of more than 10 μA. Especially around 10 μA the yield was not predictable, varying between 30 and 90%. This lack of reproducibility in the yield with a static
target has been also reported by Huszar. Kilbourn and Berridge observed that about half of the target water was forced out of the vessel by the gas radiolytically produced within the first few minutes of the irradiation. The extra space above the target cavity was expected to improve the yield by allowing the target water reflux inside the vessel, however this expectation was not realized. It seems reasonable to assume from these results that local voiding caused by the vapor and gas produced in the beam path reduces the effective thickness of the target and that this reduction is very detrimental to a very intensive irradiation on a small volume of liquid target. A beam uniformly defocussed over the whole area of the target is required to reduce this effect for efficient production of $^{18}\text{F}$fluoride with a static target at more than 10 $\mu\text{A}$ irradiation. However, it seems very difficult to get a constantly uniform beam profile by defocussing and wobbling since variation of the beam profile during different irradiations appears to be reflected by the un reproducible yields at about 10 $\mu\text{A}$ shown in Fig. 3.

Knust developed it to cool the target water outside the irradiation vessel and remove radiolytic gases from the system for production of $^{18}\text{F}$fluoride via the $^{16}\text{O}(^3\text{He}, d)^{18}\text{F}$ reaction. He circulated 30 mL of natural water as a target. Recently, Keinonen also adopted this method, but applied only 6 $\mu\text{A}$ to 0.6 mL of circulating $^{18}\text{O}$water. In the present work, effects of circulating water target on the production yield were investigated with beam currents of more than 10 $\mu\text{A}$. The correlations of yield with the current, obtained with a fixed circulation rate of 35 mL/min and 60 min irradiation, are given in Fig. 4. The correlations show that a circulating target remarkably improved the yield in comparison with a static target, but it should be noted that the yields were nevertheless decreased with increasing the beam current. The correlation between yield and current is different for Ag and Ti windows, probably due to difference in thermal conductivity between the two materials. Silver has about 20 times larger thermal conductivity than titanium. Since the amount of radiolytic gases produced in the target using a Ag window is not different from that using a Ti window, it may be suggested that the higher yields using a Ag window are due to the smaller amount of vapor produced in the beam path compared to that produced using a Ti window.

There seems to be no significant difference among the yields obtained with the different target thicknesses although rather large deviations were observed in the yield correlation curves. These deviations are also probably due to variations in the beam profile. The extremely low yields at beam currents of about 20 $\mu\text{A}$ shown in Fig. 4 were obtained without wobbling the beam. These irradiations caused severe damage to the back titanium window, indicating that circulation of the target alone did not effectively reduce voiding made by a focused beam. The effects of circulation rates of the target water on the yield were also investigated. It was expected that a faster flow rate would give a higher yield by clearing bubbles more rapidly.
from the beam striking area. Fig. 5 shows the correlation between the yield and the circulation rate. At a flow rate of 80 mL/min, the yield was not increased so much as expected probably because the flow rate was too high for the bubbles to be completely separated from the circulating target in the gas separator resulting in some of them being returned to the vessel. The following assumption may be drawn from the results obtained. The majority of gases, radiolytically produced and dissolved in the target, are reconverted to water by the radiolytic reactions while some part forms bubbles which remain in the target. A more focused beam produces more bubbles mainly by heating and vaporizing the target where the radiolytic gases are dissolved. Consequently, it seems that a uniformly distributed beam on the target is much preferable to a focused and wobbled beam for efficient production of $^{18}$F fluoride with either a static or circulating target. The specific activity of the $^{18}$F fluoride was at first not so high because of contamination by some stable fluorides mainly derived from the circulation pump. This was improved by replacing it with a peristaltic pump. It should be pointed out that any part constituting the production system should be carefully selected as to its materials. Thus, an average specific activity of the $^{18}$F fluoride was increased from about 200 Ci/mmol to more than 4000 Ci/mmol which is high enough for subsequent synthetic use although it can be increased to more than 50000 Ci/mmol by using 99% enriched $^{18}$O water. The synthesis of $^{18}$F FDG from the $^{18}$F fluoride was carried out to check its reactivity. Radiochemical yields from 50 to 60% were obtained, showing that the $^{18}$F fluorides were as reactive as those obtained as $^{18}$F HF by the $^{20}$Ne(d, α)$^{18}$F reaction$^2$.

References


Fig. 1. Front view of the titanium target inserts.
Fig. 2. Schematic diagram of the target system for production of $^{18}$F F-with a circulating target.

Fig. 3. Correlation between the $^{18}$F F-production yield and the current with a static target.

○: 4 mm thick target, Ti window  □: 5 mm thick target, Ti window  ■: 5 mm thick target, Ag window
Fig. 4. Correlations between the $^{18}\text{F}$ production yield and the current with a circulating target.
- O: 4 mm thick target, Ti window
- □: 5 mm thick target, Ti window
- ◆: 3 mm thick target, Ag window
- ■: 5 mm thick target, Ag window
Irradiation time: 60 min
Circulation flow rate: 35 mL/min

Fig. 5. Effects of a circulation flow rate on the $^{18}\text{F}$ production yield.
Irradiation: 20 µA, 60 min
Target: 5 mm thick
Window: Ag