PRODUCTION OF ^{18}F USING STATIC AND CIRCULATING [^{18}O]-WATER TARGETS

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ABSTRACT

A static and a circulation water target for ^{18}F production are described in terms of cooling capacity, recovery of isotopically enriched water as well as ^{18}F yield, purity and labelling suitability. With the circulation target and water enriched to 98.3% ^{18}O at least 30 GBq of ^{18}F EOB can be produced by irradiation with a 20 μA beam of 16 MeV protons in 1 hour.

INTRODUCTION

During the past years the use of the $^{18}O(p,n)^{18}F$ reaction and [^{18}O]-water targets have gained increased interest and application for preparation of ^{18}F containing radiopharmaceuticals. The (p,n) reaction on water targets enriched in ^{18}O, resulting in ^{18}F as fluoride anion, is yet the most effective reaction for ^{18}F production with low-energy bombarding particles from compact cyclotrons. Moreover, due to newly developed methods stereospecific and regiospecific labelling of substrates has become possible with almost carrier-free amounts of ^{18}F and high labelling yields. In respect to both ^{18}F yields and ^{18}F labelling characteristics, the $^{18}O(p,n)^{18}F$ reaction and the resulting ^{18}F product are superior to the $^{20}Ne\ (d,\alpha)^{18}F$ reaction and its resulting product [^{18}F]-F_2 used earlier for production of radiopharmaceuticals.

This paper describes a static and a circulation water target, used by the Cyclotron Group of the Department of Physics at the Eindhoven University of Technology. The aim is to produce 30 GBq of ^{18}F EOB using a 16 MeV proton beam from the Eindhoven AVF cyclotron in 1h irradiation time. The particular aspects dealt with are:
(i) appropriate cooling of the water target, (ii) reduction of losses of enriched water due to radiolysis, (iii) high yield recovery of ^{18}F from the target, (iv) appropriate physico-chemical form of ^{18}F for adequate labelling to radiopharmaceuticals, and (v) high yield recovery of enriched water after irradiation.

MATERIALS AND METHODS

Static target

The first design as a feasibility study was a static target, without any circulation of the water to be irradiated (see Figure 1). The target chamber was made of brass and silver-plated. Cavity dimensions were 13 mm diameter and 2.6 mm depth, resulting in a 0.35 ml water content and 0.6 ml including inlet and outlet.

The protons enter via a 15 μm Duratherm foil. In the water layer of 2.6 mm the proton energy decreases from 16 MeV to 4 MeV. Cooling of the target chamber is performed with a 2 l. min^{-1} flow of cooling water of 20 ^{o}C. During the irradiation the pressure was monitored and the water temperature measured with a thermocouple.

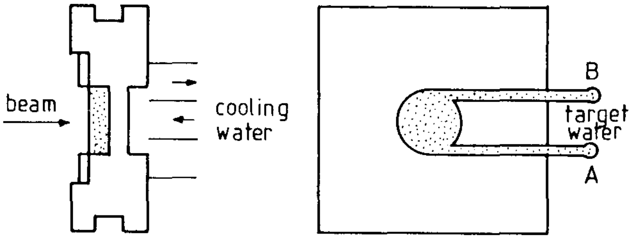

Fig. 1

Target for ^{18}O enriched water
a) static target: A closed, B to manometer,
b) circulation target: A = inlet, B = outlet.

All experiments were performed with water with the natural isotopic composition. The results were transformed into values related to water enriched to 98.3% ^{18}O and an 1 h irradiation period.

Circulation target

The second design was a circulation target.

The target chamber was again made of brass and silver-plated. Two versions were used, with cavity dimensions of 13 mm diameter each and 2.6 mm and 5.0 mm depth respectively. In the latter target the backside was lined with a 2 mm thick sheet of silver.

In the first version the protons are slowed down in the water layer to 4 MeV, and in the second version they are completely stopped in the water. The protons enter the chamber via a 15 µm Duratherm foil. The target water is circulated via a cooled gas/water separator (see Figure 2). Pumping is performed with a peristaltic pump allowing two flow rates, viz. 100 ml. min^{-1} and 300 ml.min^{-1}. The amount of water in the circuit is 4.5 ml. Cooling of the target chamber and the gas/water separator is performed with a 2 l.min^{-1} flow of cooling water with a temperature of 14°C. Thermocouples monitored the inlet and outlet temperatures of the target water. The experiments were performed with either water of the natural isotopic composition or with low ^{18}O enrichment. The results are transformed into values related to water enriched to 98.3% ^{18}O and an 1 h irradiation period.

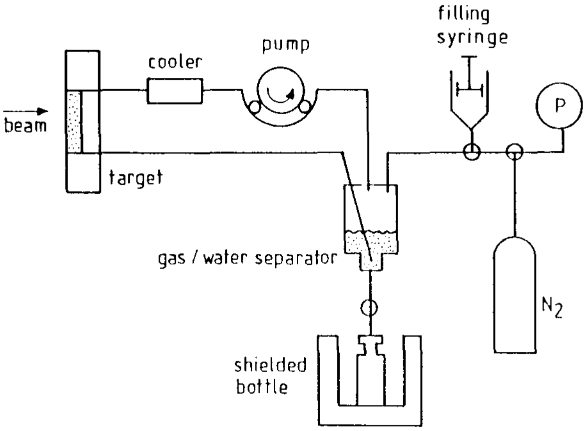

Fig. 2

Target water circulation circuit.
Cooling water supplies to target chamber, cooler and gas/water separator are not shown.

Labelling

The suitability of the ^{18}F produced was tested by using the radionuclide for preparation of ^{18}F-FDG (fluoro-deoxy-glucose), using a modification of the method of Hamacher et al.$^{1)}$.

The modification consisted of (i) use of borosilicate glass vessels instead of pyrolytic carbon, (ii) evaporation of most of the water before adding reagents and (iii) replacement of the SEP-PAK C-18 purification step by a triple evaporation/water-washing step.

RESULTS

^{18}F yields and cooling

The yield for the static target does not increase proportionally with beam current above 5 µA. This is due to formation of substantial amounts of gas (water vapour), thus reducing the effective water thickness for the protons. The maximum EOB yield amounts to 10 - 12 GBq of ^{18}F and is reached for beam currents between 5 and 15 µA (see Figure 3).

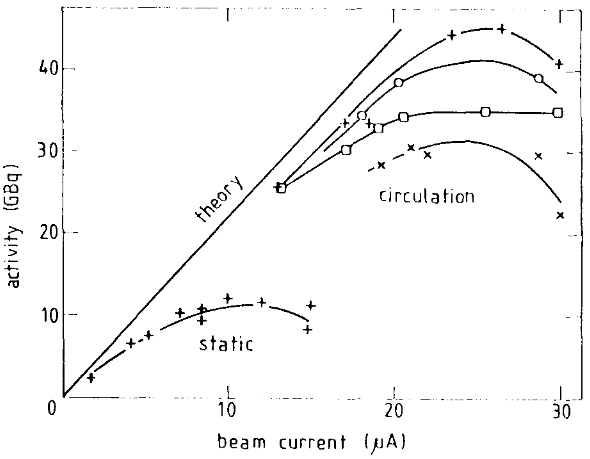

Fig. 3:
Production rate for static target and for circulation target with 2.6 mm deep cavity. Extrapolation to ^{18}O enrichment of 98.3% and 1 hour irradation.

The results for the circulation target with 2.6 mm deep cavity and a water flow rate of 100 ml.min^{-1} are given in Figure 3. The curve now starts to level off at 20 µA, and a maximum EOB yield of 30 - 40 GBq of ^{18}F is obtained. This yield is a substantial improvement compared to the maximum yield obtained for the static target. The data for the circulation target, however, scatter widely. This is due to corrosion of the silver-plated backside of the cavity (also indicated by the emergence of activated corrosion products), gradually reducing the yield and requiring frequent cleaning of the cavity with ethanol and water.

For this reason the 5 mm deep cavity chamber has been made, provided with a 2 mm thick backplate of pure silver. The results obtained with this chamber using a water flow of 100 ml.min^{-1} are given in Figure 4. The results now show less scatter. The maximum yield EOB ranges between 30 and 35 GBq, being obtained at a beam current of 20 µA.

Increase of the flow rate of the target water from 100 to 300 ml.min^{-1} resulted in lower inlet and outlet temperatures of the target water, and thus in principle to a larger cooling capacity. However, there was no shift of the maximum to higher yields and beam currents, due to gas entrainment from the gas/water separator at the 300 ml.min^{-1} flow rate. Application of an additional cooler (see Figure 2) in the target water circuit resulted in only a marginal yield improvement.

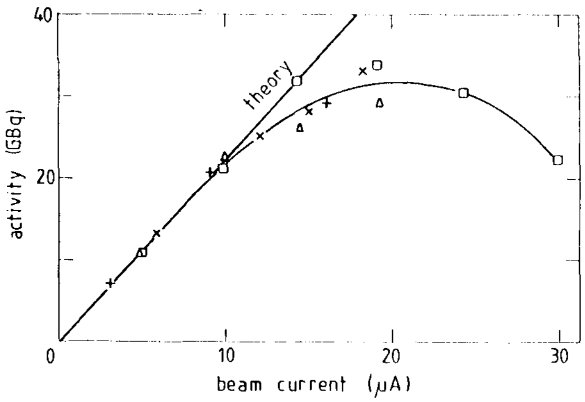

Fig. 4
Production rate for circulation target with 5 mm deep cavity. Extrapolation to ^{18}O enrichment of 98.3% and 1 hour irradiation.

Water loss due to radiolysis and water recovery

The loss of water due to radiolysis was investigated with four types of water using the static target. The results are given in Table I.

Table I. Radiolysis of the target water

Type of water	gas production ml.min^{-1}.µA^{-1}	^{18}F yield %
sterile/pyrogene-free	0.018	95
deionized	0.030	85
boiled tap water	0.055	79
tap water	0.077	63

The radiolytic yield is negatively related with the ^{18}F yield. The lowest gas production is obtained for the purest water, indicating that trace contaminants may enhance the net gas production, which in turn lowers the ^{18}F yield due to reduction of the effective water layer for protons. Therefore, always the purest water has been used for irradiation.

After irradiation usually 90% of the water is recovered from the target chamber. The rest is not not lost, but can be used in a next irradiation run.

In the labelling, the first step is evaporation of the water. This enables a recovery of at least 80% of the 4 ml of water without any loss of ^{18}F. In principle this water can be used for a next irradiation.

Recovery, purity and labelling suitability of ^{18}F

The recovery of ^{18}F from the target is about 90%. Except for ^{13}N (half-life 10 min), no radionuclidic impurities could be detected using the 5 mm deep chamber, while the 2.6 mm deep chamber showed activated corrosion products originating from the backside (e.g. ^{63}Zn and ^{65}Zn).

The overall preparation yield for [^{18}F]-FDG was about 50%, with an incorporation yield of 75% for the labelling step itself. Due to decay during the 2.5 h preparation period, the overall yield is finally 20%. Since these data compare well with the data of Hamacher et al.$^{1)}$, it may be concluded that no substantial amounts of interfering impurities are present in the ^{18}F containing irradiated water.

DISCUSSION AND CONCLUSIONS

With the circulation water target containing 4.5 ml water enriched to 98.3% ^{18}O amounts of ^{18}F between 30 and 35 GBq EOB can be prepared by irradiation with a 20 μA beam of 16 MeV protons during 1 hour. This is sufficient activity to produce [^{18}F]-FDG to be administered as 500 MBq doses to two patients, to one of them 4 hours after ending of the [^{18}F]-FDG preparation, and to the other patient 2 hours later.
The silver-plated cavity and the 2 mm thick silver lining at the backside of the cavity enable a high recovery of ^{18}F. This agrees with the results obtained recently by Tewson et al.$^{3)}$. The ^{18}F produced is free of longlived radionuclidic impurities and has shown good labelling properties.

The results obtained for the loss of water due to radiolysis are much lower than the value of 1.2 ml.min^{-1}.μA^{-1} calculated on theoretical grounds. This effect has also been observed by other authors, e.g. Iwata et al.$^{2)}$. Possibly, the high ionized-particle density favours recombination of radiolysis components to water. In our experiments radiolysis doesnot lead to problems.

The recovery of the enriched water in the labelling step is ca 80% of 4 ml, and thus 0.8 ml is yet not recovered. Since water enriched to about 95% ^{18}O costs $60 - $90 per gram, a further increase of the recovery of the enriched target water is desirable.

Increase of the ^{18}F production rate will require a more advanced cooling, for instance by using a larger cooling surface. However, this should not be accompanied by a larger water volume, since that will lead to a longer time for evaporation of the water, and thus to a greater reduction in activity due to a longer decay.

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