

## Performance assessment of O-18 water purifier

Haruhiro KITANO,\* Yasuhiro MAGATA,\*\* Akira TANAKA,\*\*\* Takahiro MUKAI,\* Yuji KUGE,\*\*\*\*  
Kotaro NAGATSU,\*\*\* Junji KONISHI\* and Hideo SAJI\*\*

\*Department of Nuclear Medicine and Diagnostic Imaging, Graduate School of Medicine, Kyoto University

\*\*Department of Patho-Functional Bioanalysis, Graduate School of Pharmaceutical Sciences, Kyoto University

\*\*\*Quantum Equipment Business Center, Sumitomo Heavy Industries, Ltd.

\*\*\*\*Department of Tracer Kinetics, Graduate School of Medicine, Hokkaido University

In the synthesis of  $^{18}\text{F}$ -FDG by the nucleophilic substitution method,  $^{18}\text{O}$ - $\text{H}_2\text{O}$  is usually used as target water. The target water should be recovered after synthesis and reused, because it is expensive, but recovered water contains impurities such as organic substances, and it must be purified before reuse. For this reason Sumitomo Heavy Industries, Ltd. developed an O-18 water purifier for elimination of organic substances in recovered water. This instrument consists of a UV irradiation unit and low-temperature distillation unit. Our institution had an opportunity to test use this instrument and evaluated its performance. The concentrations of organic substances after UV irradiation was greatly reduced, and recovery efficiency after distillation by the low-temperature distillation unit was very satisfactory at  $99.3 \pm 0.5\%$ . Furthermore, the yield of  $^{18}\text{F}$ -FDG from  $^{18}\text{O}$ - $\text{H}_2\text{O}$  purified with this instrument was sufficient for the clinical use.

**Key words:** O-18 water purifier,  $^{18}\text{O}$ - $\text{H}_2\text{O}$ ,  $^{18}\text{F}$ -FDG

### INTRODUCTION

F-18-labeled fluorodeoxyglucose ( $^{18}\text{F}$ -FDG), which is used for PET at many facilities, is generally synthesized by the nucleophilic substitution method, which rapidly produces  $^{18}\text{F}$ -FDG at a high yield.<sup>1–3</sup> By the nucleophilic substitution method,  $^{18}\text{O}$ - $\text{H}_2\text{O}$  is irradiated by protons accelerated with a cyclotron, and  $^{18}\text{F}$ -fluoride produced by means of nuclear reaction of  $^{18}\text{O}(p,n)^{18}\text{F}$  are used for synthesis of  $^{18}\text{F}$ -FDG.  $^{18}\text{O}$ - $\text{H}_2\text{O}$  is still expensive although its market price fluctuates, and its procurement may be difficult due to the high demand for it. Therefore,  $^{18}\text{O}$ - $\text{H}_2\text{O}$  used for the synthesis of  $^{18}\text{F}$ -FDG must be recovered and reused. But recovered  $^{18}\text{O}$ - $\text{H}_2\text{O}$  has passed the piping of the synthetic apparatus and ion-exchange resin so that it is contaminated to various degrees by organic substances

(ethanol, methanol, acetonitrile, etc.) and inorganic ions ( $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Cl}^-$ , etc.).<sup>4,5</sup> If recovered water containing many of these impurities is reused as target water, problems such as abnormal increases in target pressure during irradiation and a reduction in the target chamber life-span may occur.<sup>6,7</sup> It may also result in a reduction in the production yield of  $^{18}\text{F}$ -fluoride, so that the yield of  $^{18}\text{F}$ -FDG is reduced. Therefore, organic substances and various ions contained in recovered  $^{18}\text{O}$ - $\text{H}_2\text{O}$  must be eliminated as much as possible for its reuse. Moreover, the loss of  $^{18}\text{O}$ - $\text{H}_2\text{O}$  by purification must be minimized. This instrument is designed to optically decompose organic substances present in recovered  $^{18}\text{O}$ - $\text{H}_2\text{O}$  by means of an ultraviolet (UV) irradiation unit and further purify it in a low-temperature distillation unit with a halogen lamp. Our institution tested this water purifier and evaluated its performance. We first compared the concentrations of organic substances contained in  $^{18}\text{O}$ - $\text{H}_2\text{O}$  before and after UV irradiation and examined the recovery efficiency of  $\text{H}_2\text{O}$  after distillation. Next, we synthesized  $^{18}\text{F}$ -FDG for clinical use from  $^{18}\text{O}$ - $\text{H}_2\text{O}$  purified with this instrument (purified water) and from  $^{18}\text{O}$ - $\text{H}_2\text{O}$  with an isotopic enrichment of 95% immediately after purchase (virgin water) and compared the yield of  $^{18}\text{F}$ -FDG.

Received May 15, 2000, revision accepted September 14, 2000.

For reprint contact: Yasuhiro Magata, Ph.D., Department of Patho-Functional Bioanalysis, Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida Shimoadachi-cho, Sakyo-ku, Kyoto 606–8501, JAPAN.

E-mail: magata@pharm.kyoto-u.ac.jp

## OUTLINE OF $^{18}\text{O}\text{-H}_2\text{O}$ PURIFIER

### Structure

This instrument consists of a UV irradiation unit (left) and a low-temperature distillation unit (right) as shown in Figure 1. The UV irradiation unit consists of a metal cylinder, the inside of which is given a mirror finish, and a UV lamp in the center of the cylinder. Glass sample tubes to contain recovered water can be arranged around the UV lamp. Each sample tube contains 2 ml of recovered water, and about 12 ml of water can be irradiated at a time. The low-temperature distillation unit consists of a glass distiller, halogen lamp for heating, aspiration pump to create a negative pressure inside the distiller, and a dewar bottle to contain liquid nitrogen for cooling and condensing the vapor. The glass distiller, which consists of a dome-shaped glass upper part and an inverted conical condenser made of quartz (lower part), is sealed with packing and a special fastening device. A Glassy Carbon reservoir with a capacity of 30 ml, which holds UV irradiated  $^{18}\text{O}\text{-H}_2\text{O}$  before distillation, is placed in the glass evaporator. About 30 ml of water can be distilled at a time. The distillation rate is 2–3.5 ml/hour. Both units are equipped with a timer so that the time of UV irradiation or low-temperature distillation can be readily prolonged or shortened.

### Operation method

After filling the sample tubes with recovered target water and sealing them, the water is irradiated with UV in the UV irradiation unit for 4 hours. The UV irradiated water is transferred manually to the reservoir in the glass distiller of the low-temperature distillation unit, and a negative pressure is produced inside the distiller with an aspiration pump to promote evaporation of  $^{18}\text{O}\text{-H}_2\text{O}$ . The  $^{18}\text{O}\text{-H}_2\text{O}$  is gradually distilled at low temperature by directing the halogen lamp into the water from above the distiller. Distilled  $^{18}\text{O}\text{-H}_2\text{O}$  is cooled in the condenser part with liquid nitrogen and frozen. It is thawed at room temperature and used as purified water.

## MATERIALS AND METHODS

$^{18}\text{O}\text{-H}_2\text{O}$ , with a purity of 95%, was obtained from ROTEM INDUSTRIES, Israel.  $^{16}\text{O}\text{-H}_2\text{O}$ , as an injectable distillation water, was purchased from Otsuka Pharmaceutical Co. Ltd., Tokyo. All other reagents were purchased from Aldrich Chemical Company, Milwaukee, WI.  $^{18}\text{F}\text{-FDG}$  was synthesized by the nucleophilic substitution method with a  $^{18}\text{F}\text{-FDG}$ -synthesizing instrument, F-100 (Sumitomo Heavy Industries, Co. Ltd., Tokyo) and a cyclotron, CYPRIS-325R (Sumitomo Heavy Industries, Co. Ltd., Tokyo).

### Comparison of concentrations of organic substances

The effect of UV irradiation for the elimination of organic substances was evaluated. Methanol is a contaminant in

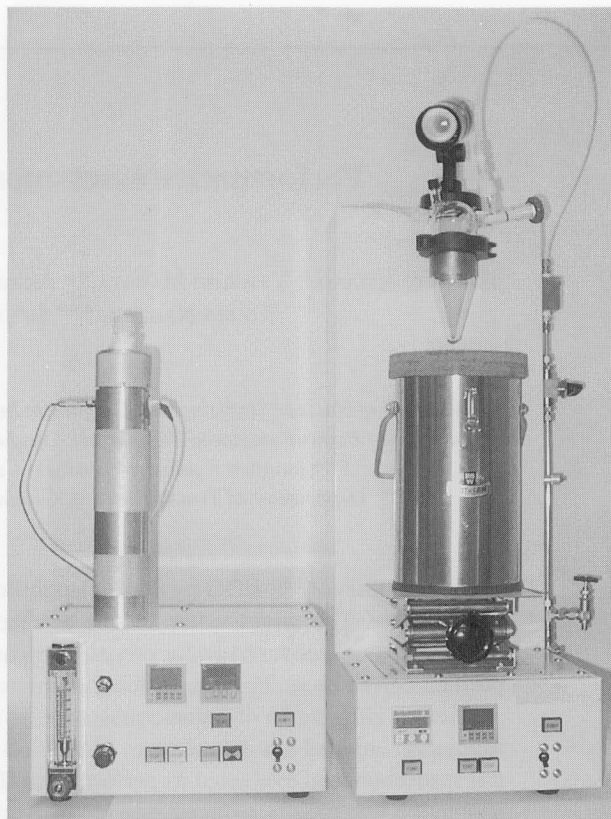
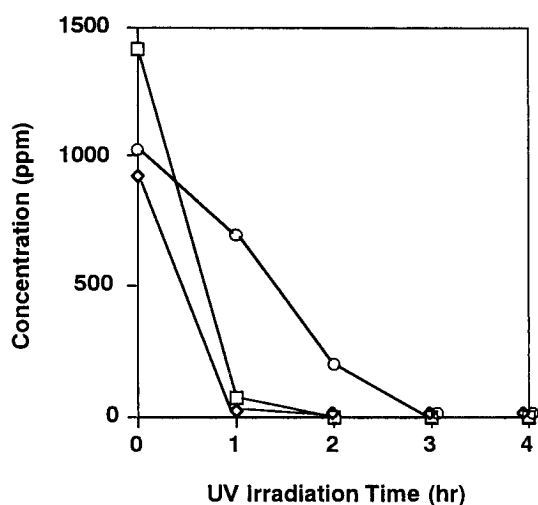


Fig. 1 Appearance of the instrument. UV irradiation unit (left) and low-temperature distillation unit (right).

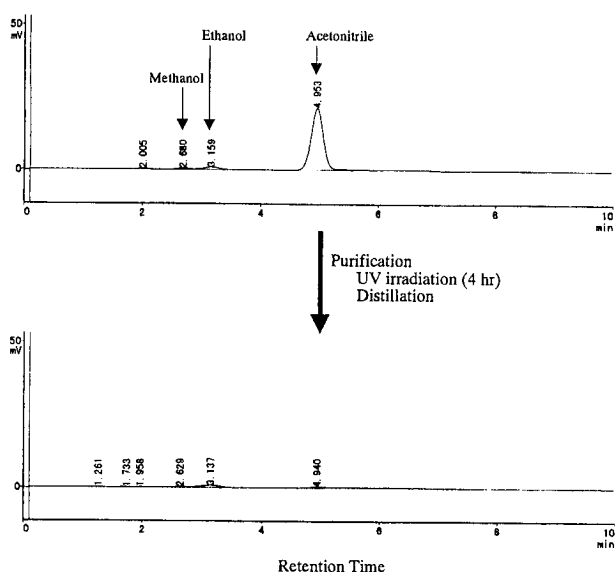
the recovered  $^{18}\text{O}\text{-H}_2\text{O}$  if  $^{18}\text{F}\text{-FDG}$  is synthesized with FDG MicroLab (GE Medical Systems, Milwaukee, WI). Ethanol could be a contaminant in the recovered water because 70% ethanol is used for sterilization of the FDG synthesizer. Moreover, because acetonitrile is used for the solvent to synthesis of  $^{18}\text{F}\text{-FDG}$ , organic substances that may be contained in the recovered water include methanol, ethanol and acetonitrile. These 3 organic solvents were therefore added to  $^{16}\text{O}\text{-H}_2\text{O}$  simultaneously, the water was UV irradiated with the UV irradiation unit. The concentrations of organic substances in the sample before and after UV irradiation were analyzed by gas chromatography with a Shimadzu GC-14B gas chromatograph and a Shimadzu TSG-1 15% SHINCARBON A 60/80 glass column (3.1 m  $\times$  3.2 mm I.D.) at a column temperature of 90°C, an injector temperature of 180°C, FID temperature of 180°C, and flow rates of 50 kPa for  $\text{H}_2$ , 50 kPa for air, and 70 kPa for He. The retention times for methanol, ethanol and acetonitrile were 2.6–2.7, 3.1–3.2 and 4.9–5.0 min, respectively.

### Evaluation of the recovery efficiency for water after distillation

The recovery efficiency for water after distillation was evaluated.  $^{16}\text{O}\text{-H}_2\text{O}$  which varied from about 10 to 25 ml was weighed with a chemical balance (AT250, Methler)



**Fig. 2** Decomposition of organic substances by UV irradiation. □; methanol, ◇; ethanol, ○; acetonitrile. Each point presents mean and s.d. of 3 experiments.

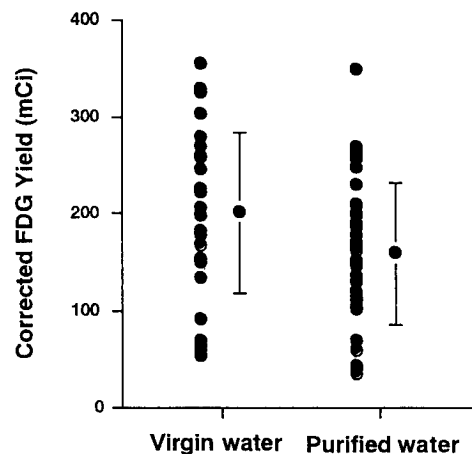


**Fig. 3** Effect of purification of  $^{18}\text{O}\text{-H}_2\text{O}$  on the amount of organic substances. Pre-purification of  $^{18}\text{O}\text{-H}_2\text{O}$  (upper) and post-purification of  $^{18}\text{O}\text{-H}_2\text{O}$  (lower).

and distilled with the low-temperature distillation unit. After distillation, the water obtained was weighed again and the recovery efficiency was calculated.

#### Comparison of the yield of synthesized $^{18}\text{F}\text{-FDG}$

$^{18}\text{F}\text{-FDG}$  was synthesized by using virgin water and with purified water as target water, and the yields were compared. The isotopic enrichment of virgin water was 95%. Purified water had been used 3–5 times at our institution with purification by means of this instrument, and the percent content of  $^{18}\text{O}\text{-H}_2\text{O}$  in this experiment was not



**Fig. 4** Comparison of the yield of  $^{18}\text{F}\text{-FDG}$  synthesis. Each point presents the yield of  $^{18}\text{F}\text{-FDG}$  determined by correcting the synthetic condition for an irradiation time of 60 min and a beam current of  $15\ \mu\text{A}$ .

known.  $^{18}\text{F}\text{-FDG}$  was synthesized 29 times with virgin water and 39 times with purified water. Since the irradiation time and the beam current are not always fixed at certain levels, they were corrected as follows. The radioactivity produced is in proportion to the beam current on the target and  $1 - e^{-\lambda t}$  at the irradiation time  $t$  ( $\lambda$ : the decomposition constant of F-18). Therefore, the yield of  $^{18}\text{F}\text{-FDG}$  was determined by correcting the synthetic conditions for an irradiation time of 60 min and a beam current of  $15\ \mu\text{A}$ .

## RESULTS

#### Comparison of the concentrations of organic substances before and after UV irradiation

As shown in Figure 2, organic substances contained at 1,000 ppm or above could be decomposed nearly completely in 1 hour for methanol and ethanol and in 3 hours for acetonitrile.

#### Evaluation of the recovery efficiency for water after distillation

As shown in Table 1, the recovery efficiency was extremely high at 98% or higher on all runs, and the mean value was  $99.3 \pm 0.5\%$ .

#### Example of purification of $^{18}\text{O}\text{-H}_2\text{O}$

Figure 3 shows one example of pre-purified  $^{18}\text{O}\text{-H}_2\text{O}$  and post-purified  $^{18}\text{O}\text{-H}_2\text{O}$  with this instrument. Purification was carried by UV irradiation for 4 hrs followed by low-temperature distillation. A sample of  $^{18}\text{O}\text{-H}_2\text{O}$  used for  $^{18}\text{F}\text{-FDG}$  synthesis with  $^{18}\text{F}\text{-FDG}$ -synthesizing instrument (Sumitomo Heavy Industries, Co. Ltd.) was analyzed. 128 ppm of acetonitrile was detected as a major peak in pre-purified water (upper). After purification of

**Table 1** Recovery efficiency of the water after distillation procedure

Run No.	Pre-distillation (g)	Post-distillation (g)	Recovery yield (%)
1	9.83	9.69	98.6
2	10.05	10.05	100.0
3	9.96	9.89	99.3
4	24.13	24.00	99.5
5	21.65	21.59	99.7
6	19.55	19.26	98.5
7	14.80	14.66	99.1

this sample, almost all organic substances were eliminated from the water (lower).

#### Comparison of the yields of $^{18}\text{F}$ -FDG

Figure 4 shows the yields of  $^{18}\text{F}$ -FDG. Each point presents the yield of  $^{18}\text{F}$ -FDG determined by correcting the synthetic condition for an irradiation time of 60 min and a beam current of  $15\ \mu\text{A}$ . The yield of  $^{18}\text{F}$ -FDG synthesized from virgin water was  $202 \pm 82\ \text{mCi}$ , and that from purified water was  $159 \pm 73\ \text{mCi}$ . The time needed for  $^{18}\text{F}$ -FDG synthesis was about 60 minutes in both cases.

#### DISCUSSION

In this study the recovery efficiency for water after distillation was 98% or higher (Table 1). Each part of the unit is dried before it is used to distill recovered water, so that the isotopic enrichment of  $^{18}\text{O}$ - $\text{H}_2\text{O}$  does not decrease during distillation, and there is no loss of  $^{18}\text{O}$ - $\text{H}_2\text{O}$  during UV irradiation, so that  $^{18}\text{O}$ - $\text{H}_2\text{O}$  was purified with this instrument with minimum loss of  $^{18}\text{O}$ - $\text{H}_2\text{O}$ .

Organic substances (methanol, ethanol, and acetonitrile) contained in recovered water were almost completely decomposed by 4-hour UV irradiation, as expected.<sup>8</sup> The purified water is therefore considered to be free from these organic contaminants after 4-hour UV irradiation and low-temperature distillation with this instrument, and inorganic ions and metal ions considered to be derived from the target box are not considered to enter the purified water, because it is distilled at low temperature, although the amounts were not measured in this study.

$^{18}\text{F}$ -FDG is considered to be synthesized from purified  $^{18}\text{O}$ - $\text{H}_2\text{O}$  by means of this instrument with a satisfactory yield for clinical use, although the yield of  $^{18}\text{F}$ -FDG synthesized from purified water was reduced in comparison with that from virgin water. During synthesis of  $^{18}\text{F}$ -FDG, the recovered water is diluted as it passes through the lines and anion exchange resin for  $^{18}\text{F}$ -fluoride extrac-

tion from the bombarded target water, and the purified water used for  $^{18}\text{F}$ -FDG synthesis in this study had been used 3–5 times at our institution, so that the isotopic enrichment of  $^{18}\text{O}$ - $\text{H}_2\text{O}$  was not known. On the other hand, the yield of  $^{18}\text{F}$ -FDG varied both when virgin water was used and when purified water was used for  $^{18}\text{F}$ -FDG synthesis, probably because of variation in  $^{18}\text{F}$ -FDG production efficiency and the beam pattern. From these observations, this instrument appears to be useful for clinical  $^{18}\text{F}$ -FDG synthesis by efficiently eliminating impurities from recovered  $^{18}\text{O}$ - $\text{H}_2\text{O}$  without the loss of volume.

#### ACKNOWLEDGMENT

This module is commercialized by Sumitomo Heavy Industries, Ltd. Japan under the licensing agreement with Forschungszentrum Juelich.

#### REFERENCES

1. Hamacher K, Coenen HH, Stocklin G. Efficient stereospecific synthesis of no-carrier-added 2- $^{18}\text{F}$ -fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med* 1986; 27: 235–238.
2. Chaly T, Dahl JR. Thin layer chromatographic detection of kryptofix 2.2.2 in the routine synthesis of  $^{18}\text{F}$ -2-fluoro-2-deoxy-D-glucose. *Int J Rad Appl Instrum B* 1989; 16: 385–387.
3. Moerlein SM, Brodack JW, Siegel BA, Welch MJ. Elimination of contaminant Kryptofix 2.2.2 in the routine production of 2- $^{18}\text{F}$ -fluoro-2-deoxy-D-glucose. *Int J Rad Appl Instrum [A]* 1989; 40: 741–743.
4. Schlyer DJ, Firouzbakht ML, Wolf AP. Impurities in the  $^{18}\text{O}$ -water target and their effect on the yield of an aromatic displacement reaction with  $^{18}\text{F}$ -fluoride. *Appl Radiat Isot* 1993; 44: 1459–1465.
5. Schwarz SW, McCarthy TJ, King N, Lechner KR, Margenau WH, Ficke, DC, Courtney B, Welch M.  $^{18}\text{F}$ -FDG PETtrace MicroLab: average  $^{18}\text{F}$ -FDG E.O.S. activity compared to the source of the  $^{18}\text{O}$ -water used. Proceedings of the 7th Workshop on Targetary and Target Chemistry, Heidelberg; Germany, 1997: 246–247.
6. Mangner TJ, Mulholland GK, Toorongian SA, Jewett DM, Kilbourn MR. Purification of used O-18 target water by photochemical combustion. *J Nucl Med* 1992; 33: 982–983.
7. Toorongian SA, Mulholland GK, Jewett DM, Bachelor MA, Kilbourn MR. Routine production of 2-deoxy-2- $^{18}\text{F}$ -fluoro-D-glucose by direct nucleophilic exchange on a quaternary 4-aminopyridinium resin. *Int J Rad Appl Instrum B* 1990; 17: 273–279.
8. Armstrong FAJ, Wolliams PM, Strickland JDH. Photo-oxidation of organic matter in sea water by ultra-violet radiation, analytical and other applications. *Nature* 1966; 211: 481–484.