Development of a New Automated Synthesis System of [F-18]FDG

III. 6 Development of a New Automated Synthesis System of [F-18]FDG

Nakanishi H.*, Monma M., Ishiwata K., Iwata R. and Ido T.
Cyclotron and Radioisotope Center, Tohoku University
Shimadzu Corporation, Kyoto*

2-Deoxy-2-[F-18]fluoro-D-glucose(^{18}FDG) is one of the most important radiopharmaceuticals for PET studies and is used for measurement of glucose metabolism in the brain[1,2] and heart[3] and tumor detection.[4] An automated synthesis system of ^{18}FDG using electrophilic fluorinations with $^{18}F_2$ has already reported.[5] However, several synthesis methods of ^{18}FDG has been reported[6,7] and the synthesis by the reaction of 3,4,6-tri-o-acetyl-D-glucal (TAG) with AcO^{18}F has been indicated to be most suitable. The procedure of the reaction is simple and ^{18}FDG can be rapidly produced with high yield and high purity by the reaction. In addition, the contamination of 2-deoxy-2-[F-18]fluoro-D-mannose(^{18}FDM) in the ^{18}FDG preparations is least in several synthetic methods.[8,9] In this way, the reaction is well suited for automated synthesis. Therefore, we have developed a new automated synthesis system of ^{18}FDG basis on the reaction of AcO^{18}F.

Materials and Methods

AcOK was prepared by the method of R. E. Ehrenkaufer et al.[10] and packed in a glass tube (O.D. of 8 mm, I.D. of 6 mm and length of 7 cm). The AcOK column was preserved on P_2O_5 in a desiccator under vacuum.

The reaction sequence is shown in Fig. 1. The synthetic procedure consists of 3 processes as follows: (1)reaction with AcO^{18}F with TAG (25 mg) in CCl_3F (15 ml) at room temperature (2)hydrolysis in 1N HCl (3 ml), (3)purification of ^{18}FDG by passing the hydrolysate through an ion exchange resin (Bio-RAD, AG11A8) column and an active charcoal and alumina column.

Fig. 2 shows the schematic diagram of the synthesis system. Temperature sensors (TS1,TS2), radioactivity detectors (RS1, RS2) and optical liquid level sensors (LS1-LS7) are used to control the system automatically. TS1 is used to control the outside temperature of the reaction vessel and TS2 measures the inside temperature to detect the end of vacuum evaporation of solvent and to control hydrolysis exactly. RS1 monitors the recovered ^{18}F radioactivity and RS2 monitors collecting ^{18}FDG eluted from the column of active charcoal and alumina. LS1-LS7 are set in glasswares and plastic bottles and detect an existance of liquid materials from outside. The sterile and pyrogen-free 3-way cocks and extension tubes which are commercially available are used and controlled with 3-way cock actuators. The fluorination and hydrolysis are carried out by the one pot synthesis in the reaction vessel. The reactants

can be heated, cooled and mixed in the wobbling evaporator. The system is supplied with a pressurized He gas for transferring liquid materials, vacuum for evaporating a solvent from the reaction vessel and transferring liquid materials, and liquid CO_2 for rapidly cooling the hydrolysate.

Fig. 3 shows the photographic view of the system. It is designed to be compact size (H. of 40 cm, W. of 50 cm and D. of 35 cm) and convenience for routine production and automatically controlled with the microcomputer. After the computer is switched on, the system starts checking set up conditions as follows: (1)target pressure, (2)movement of 3-way cock actuators, (3)heater, (4)He, vacuum and liquid CO_2 connections, (5)leak test, (6)existance of liquid materials. After the check, the system starts to wash AG11A8 with sterilized distilled water and washing is completed during irradiation. And just after the end of irradiation, TAG solution of CCl_3F is transferred to the reaction vessel. Thus, the production of ^{18}FDG is carried out by detecting a completion of each step procedure through the sensors.

The radiochemical purity of ^{18}FDG was determined by radio-HPLC[9] on μBondapak C-18 Carbohydrate (Waters) with CH_3CN/water(85:15) and Aminex HPX-87C (Bio-RAD) with water.

Results and Discussion

The typical results of step procedure are shown in Fig. 4. $^{18}F_2$ was converted to AcO^{18}F through AcOK column. The conversion yield of AcO^{18}F was about 40 % on the average of 10 runs. The one pot synthesis of the reaction of TAG with AcO^{18}F in CCl_3F at room temperature and hydrolysis (step 1-step 6) was carried out without problem using the original reaction vessel which was placed in the wobbling evaporator. Fig. 5 shows the internal temperature curve of the reaction vessel from step 3 to step 6. During evaporation of CCl_3F, the internal temperature of the vessel decreased under -10 °C in spite of heating from outside at 70 °C. When CCl_3F was completely evacuated, the temperature increased. Thus, the computer could know whether vacuum evaporation was completed or not. In addition, hydrolysis and cooling hydrolysate were exactly controlled by measurement of the internal temperature and it was resulted in the shortening synthesis time. The purification of hydrolysate were carried out by passing through AG11A8 column and active charcoal and alumina column. To prevent the thermal decomposition of AG11A8 the hydrolysate was cooled under 50 °C.

The automated synthesis of ^{18}FDG was carried out within 50 min after the end of irradiation. A neutral, sterile and pyrogen-free ^{18}FDG solution reproducibly provided with the radiochemical yield of 20-25 % and the radiochemical purity of over 97 % at the end of synthesis. When the 120 min irradiations were carried out with an incident energy of 15.7 MeV and a current of about 12 μA, about 60 mCi of ^{18}FDG was produced with the system. In addition, the system can be used to produce other sugars including the

fluorinations with $AcO^{18}F$ such as 2-deoxy-2-[^{18}F]fluoro-D-galactose, which is a tracer for assessment of sugar metabolism in the liver, and 2-deoxy-2-[^{18}F]fluoro-L-fucose.

This system has been confirmed to be suitable for routine production. The automated synthesis of ^{18}FDG by using the method of $AcO^{18}F$ was improved in a radiochemical yield and a synthesis time in comparison with the method of $^{18}F_2$.

References

1) Reivich M., Kuhl D., Walf A. et al., Circ. Res. 44 (1979) 127.
2) Phelps M., Huang S-C., Hoffman E. et al., Ann. Neurol. 6 (1979) 371.
3) Marshall R., Tillish J., Phlpes M. et al., Circulation 67 (1983) 766.
4) Fukuda H., Matsuzawa T., Abe Y. et al., Eur. J. Nucl. Med. 7 (1982) 294.
5) Iwata R., Ido T., Takahashi T. et al., Int. J. Appl. Radiat. Isot. 35 (1984) 445.
6) Shiue C-Y., Salvadori P., Wolf A. et al., J. Nucl. Med. 23 (1982) 899.
7) Bida G., Satyamurthy N. and Barrio J., J. Nucl. Med. 25 (1984) 1327.
8) Shiue C-Y., Fowler J., Wolf A. et al., Personal Communication)
9) Ishiwata K., Ido T., Nakanishi H. and Iwata R., CYRIC Annual Report (in this issue)
10) Ehrenkaufer R., Rotocki J. and Jewett D., J. Nucl. Med. 25 (1984) 333.

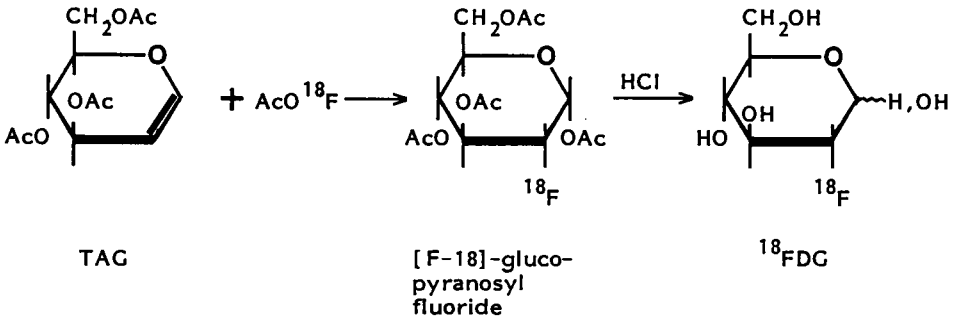

Fig. 1. Synthetic sequence of ^{18}FDG

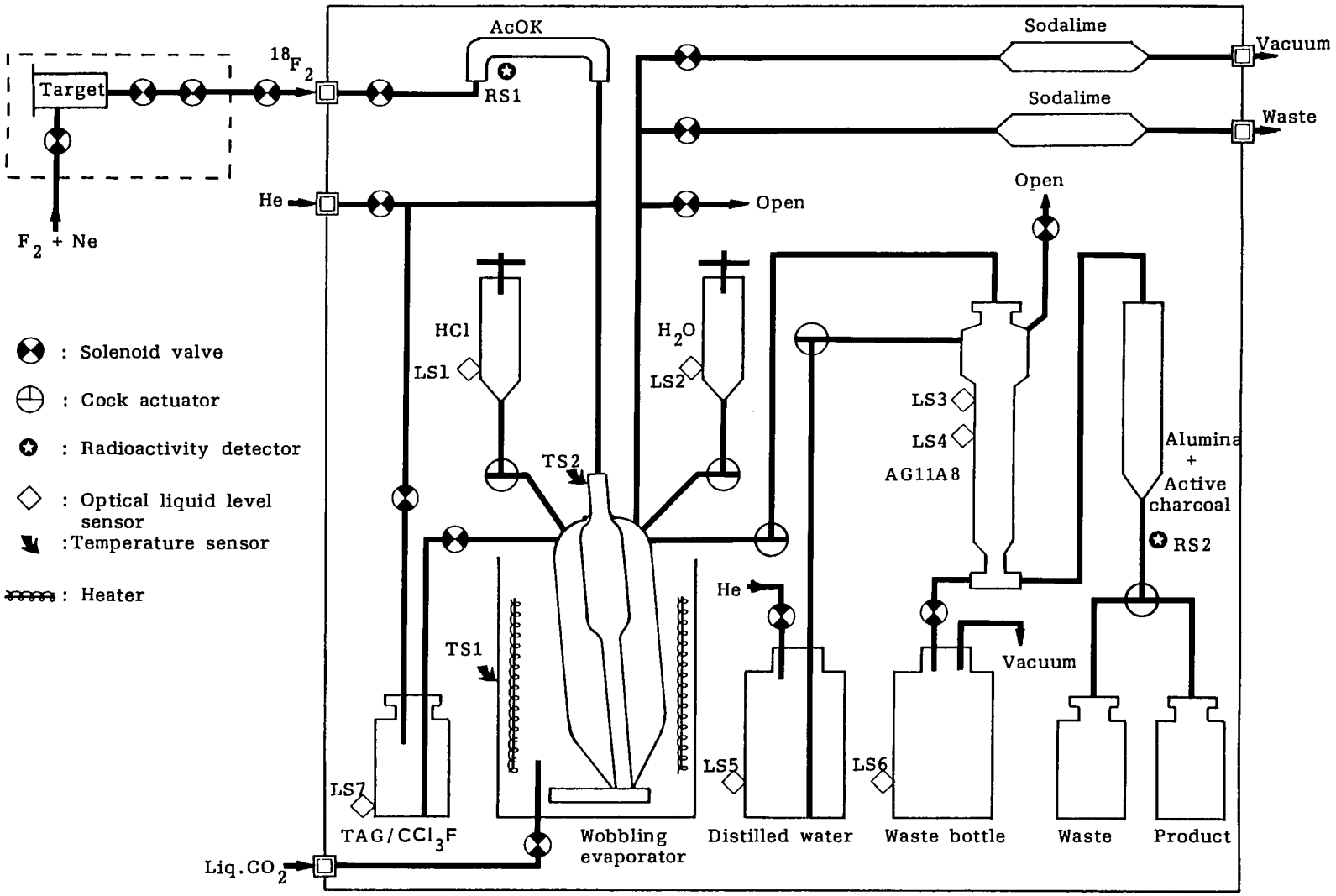

Fig. 2. Schematic diagram of the system

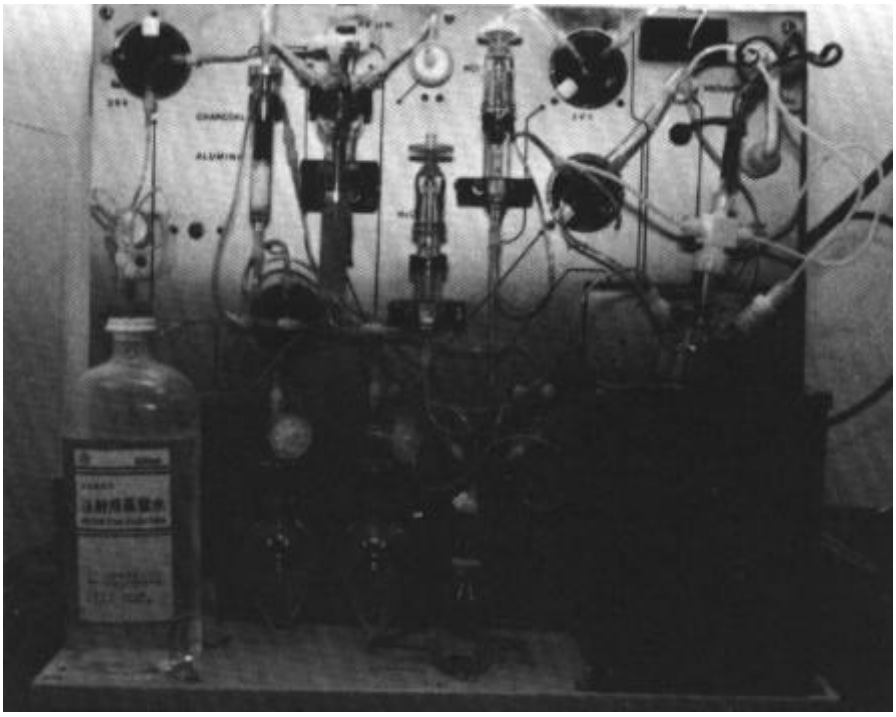

Fig. 3. Photographic view of the system

Synthesis

* Total synthesis time : 05:11:46 - 06:00:02 (48.3 min)

No.	Step procedure	Step elapsed time	Stepped by
(1)	$AcO^{18}F$ INTRODUCTION	05:11:46 - 05:24:12 (12.5 min)	Auto
(2)	He SWEEP	05:24:12 - 05:24:45 (0.5 min)	Auto
(3)	Cl_3CF EVAPORATION	05:24:45 - 05:29:12 (4.5 min)	Auto
(4)	HCl INJECTION	05:29:12 - 05:29:43 (0.5 min)	Auto
(5)	HYDROLYSIS	05:29:43 - 05:41:43 (12.0 min)	Auto
(6)	COOLING	05:41:43 - 05:44:27 (2.7 min)	Auto
(7)	TRANSFER	05:44:27 - 05:47:22 (2.9 min)	Auto
(8)	CHROMATO	05:47:22 - 05:47:42 (0.4 min)	Auto
(9)	WATER INJECTION	05:47:42 - 05:48:25 (0.7 min)	Auto
(10)	TRANSFER	05:48:25 - 05:48:37 (0.2 min)	Auto
(11)	CHROMATO	05:48:37 - 06:00:02 (11.4 min)	Auto

Fig. 4. Results of the step procedures

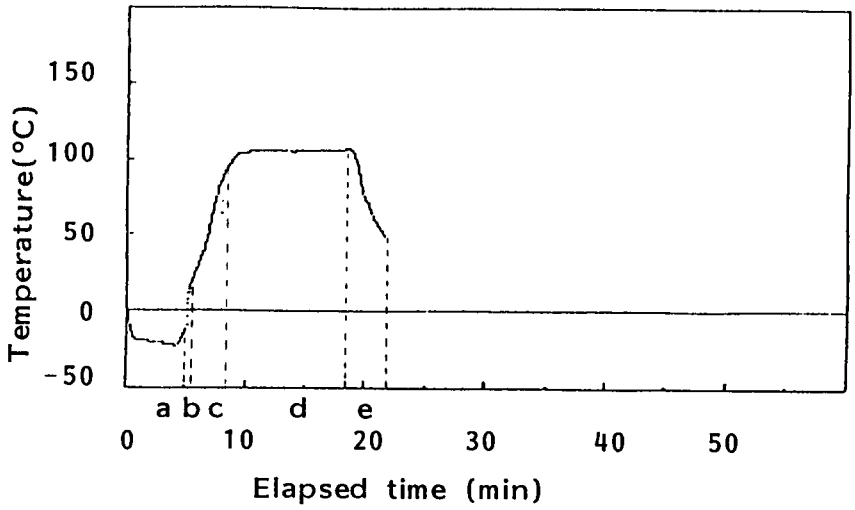

Fig. 5. Internal temperature curve of the reaction vessel
a. Evaporating of CCl_3F
b. Injection of HCl
c. Heating up over 90°C
d. Hydrolysis
e. Cooling of hydrolysate