Automated Synthesis of [18F]-Methyl Fluoride

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Positron-emitting fluorine-18 labeled methyl fluoride ($CH_3{}^{18}F$) was reported to be a favorable tracer for the measurement of regional cerebral blood flow due to its high solubility in blood, high diffusibility from blood to cerebral tissue and physiologically inert characteristics.[1,2] Synthesis of $CH_3{}^{18}F$ for clinical use has been reported by Gatley et al.[3] This method, however, was not suitable for automated synthesis.

So, we report a simple method that is suitable for automated synthesis of $CH_3{}^{18}F$ using an in-house medical cyclotron.

Methods

Cold experiment

The reaction mixtures of various KF concentrations (5, 10 and 20 μmole), methyl methanesulfonate or methyl p-toluesulfonate (5.9 m mol), 18-Crown-6-ether (100 μmole) and 20 mg of Ag_2O were sealed and then heated at various temperatures (60°, 100° and 140°C).

Hot experiment

^{18}F-F_2 was produced by the deutron irradiation of neon gas with carrier F_2. $^{18}F^-$ was produced by the proton irradiation of ^{18}O-enriched water (20 %).

After the irradiation, the target was recovered into a TFE reaction vessel containing five micromole of KOH or KF and the water was distilled away in a microwave oven. 18-Crown-6-ether (100 μmole) dissolved in methyl methanesulfonate (5.9 m mole) and 20 mg of Ag_2O were introduced quickly into the reaction vessel. The vessel was sealed and heated at 100°C for 30 min, and then $CH_3{}^{18}F$ produced was collected in a balloon from the reaction vessel with a He flow of 50 ml/min.

Analysis

The gaseous products were analysed by gas chromatography on Porapake N (2 m × 1.8 mm) at 30°C and a He flow rate of 25 ml/min,

Resuts and discussion

Effects of reaction temperature, reaction time and Ag_2O on the production yield of CH_3F were examined at different KF amounts. The production yield of CH_3F reached the plateau at 30 min in any case. It was increased with the higher reaction temperature in the case of large KF amounts, but was not affected in the case of 5 μmole KF. The presence of Ag_2O increased the yield of CH_3F in every case and this effect was more significant in the case of the smaller KF amount (Table 1). In our experiment we observed that Ag_2O increased the yield

of CH_3F only when it was added at the beginning of the reaction. The significant difference in the reactivity of F^- with methyl methanesulfonate and methyl p-toluenesulfonate was not observed.

We developed the system for the automated synthesis of CH_3F (Fig. 1). The radiochemical yield of $CH_3{}^{18}F$ at various conditions obtained by using this system are shown in Table 2. About 30 min was required for preparation of anhydrous $K^{18}F$ after the irradiation, and the final product of $CH_3{}^{18}F$ was obtained with a radiochemical purity of 100 % with additional 30 min for the synthesis. From the results we determined the following optimal synthetic conditions: methyl methanesulfonate; 5.9 m mole, 18-Crown-6-ether; 100 μmole, Ag_2O; 20 mg, KF; 5 μmol, reaction time; 30 min, reaction temperature; 100°C. Using the automated synthesis system, we obtained $CH_3{}^{18}F$ with higher radiochemical yield than the case of manual synthesis (Table 2). An elimination of moisture by the replacement of air with He, an uniformity of heating and an increment of the ^{18}F-gas recovery rate might result in the increase in radiochemical yield.

This simple synthetic procedure is suitable for an automated production of $CH_3{}^{18}F$.

References

1) Phelps M. D., Mazziota J. C. and Huang S. C., J. Cereb. Blood Flow Metabol., 2 (1982) 113.
2) Holden J. E., Gatley S. J., Hichwa R. D., Ip W. R., Shaughnessy W. J., Nickles R. J. and Plocyn R. E., J. Nucl. Med., 22 (1981)
3) Gatley S. J., Hichwa R. D., Shaughnessy W. J. and Nikles R. J., Int. J. Appl. Radiat. Isot., 32 (1981) 32.
4) Gatley S. J., Int. J. Appl. Radiat. Isot., 33 (1982) 255.

Table 1. Effects of KF and Ag_2O on the yield of CH_3F.

Reaction conditions: 5.9 μmoles methyl methanesulfonate/100 μmoles 18-Crown-6-ether/100°C/30 min

KF(μmoles)	5	10	20	30
Ag_2O(20 mg)/none	12.5	6.8	3.0	2.2

Table 2. Radiochemical yield of $CH_3{}^{18}F$.

	Manual synthesis			automated synthesis		
Target	^{18}O	^{18}O	^{20}Ne	^{18}O	^{18}O	^{18}O
Foil	Ti	Ti	Al-Ni	Ti	Havar	Havar
Carrier (μmole)	—	5	5	—	—	5
$CH_3{}^{18}F$ yield (%)	3.7	17.0	65.0	19.2 10.8	18.5 14.3	24.8

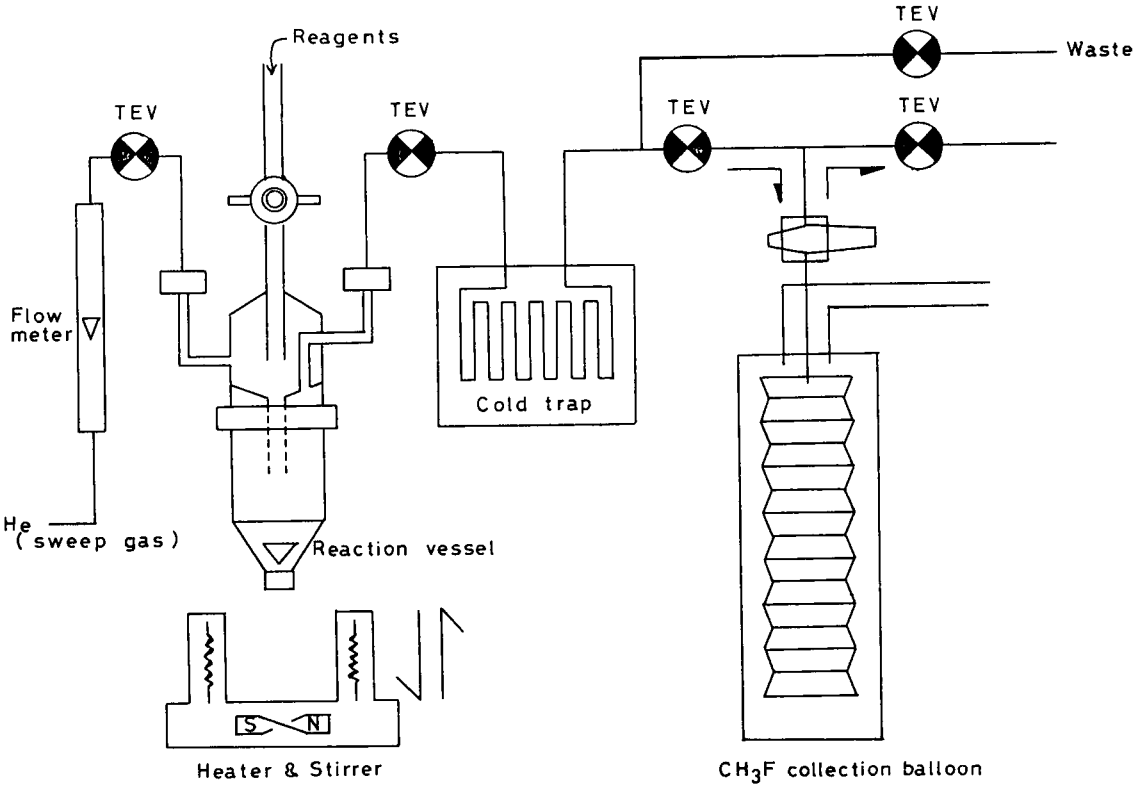

Fig. 1. Flow chart of the semi-automated synthesis system for ^{18}F-methyl fluoride. Sequence program is as follows: vessel setting and reagent injections (manual), pressure leak test and air removal by He gas, heating and ^{18}F-gas collection by He flow. He flow rate, temperature and time program can be set at any desired levels within the limit.

Fig. 2. Semi-automated synthesis system for ^{18}F-methyl fluoride.