Concentration of [11C]Methyl Triflate for Microreactor Radiosynthesis of 11C-Probes

VI. 1. Concentration of [11C]Methyl Triflate for Microreactor Radiosynthesis of 11C-Probes

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A microreactor has been expected to be a powerful platform for rapid and efficient radiosynthesis of positron-emitting radiopharmaceuticals because their specific activities are generally very high; in other words, carrier amounts involved in radiosyntheses are very low, while their starting labeled precursors such as [11C]methyl iodide ([11C]MeI) and [18F]fluoride are often produced in a large volume of gases or water. Rapid and efficient concentration of these labeled precursors is thus needed to introduce them into a microreactor. Since [18F]fluoride is rather easily concentrated by a combined use of ion exchange and evaporation or more conveniently, electrochemical adsorption and release[1], many applications have been so far reported for 18F-labeled probes, whereas a very few for 11C-probes[2] for lack of a practical method for concentrating [11C]MeI in a solvent in microliter volume.

[11C]Methyl triflate ([11C]MT), converted on-line from [11C]MeI, is widely used as a more reactive 11C-methylation agent than [11C]MeI. It can be efficiently trapped even by water due to its higher boiling point (100-102°C). This excellent property led us to develop an automated module for trapping flowing [11C]MT in a small cold trap, recovering it in a small volume of a reaction solvent and introducing it into a microreactor.

[11C]MeI was produced by the gas-phase reaction of [11C]methane and I_2 with a MicroLab MeI module (GE) and supplied to an automated concentration module with a He current (10~50 mL/min). The automated module consists of a AgOTf column heated at 200°C, two syringe pumps (PSD4, Hamilton), and a spiral tube cooled with a thermoelectric cooler as shown in Fig. 1. The thermoelectric cooler was made of a Peltier device (19.5 W) coupled with a small free-piston Stirling cooler (FPSC module UD08, Twinbird). Its

construction is illustrated in Fig. 2. One side of the Peltier device contacted with a metal spiral tube of stainless steel (SS) or Cu (0.3~0.75 mm i.d. x 200~400 mm long) for trapping [11C]MT below -40°C and the other side with the FRSC to remove heat from the Peltier. The module was controlled with a LabVIEW software.

[11C]Methyl triflate carried with He was converted on-line from [11C]MeI on the AgOTf column and continuously flowed through the spiral metal tube. The tube was then warmed up to room temperature and the [11C]MT trapped was eluted with acetone (25 µL/min). The trapping efficiency was obtained by varying the He flow rate and the temperature (see Table 1). The radioactivity of [11C]MT was monitored with two radiation sensors located at the tube (RIS-01) and the mixing line (RIS-02), respectively. The reactivity of a recovered [11C]MT was preliminarily evaluated by preparation of [11C]raclopride. A solution of desmethylraclopride triflate in acetone (1 mg/400 µL) and NaOH (0.5 M, 15 µL) and the [11C]MT in acetone were flowed at a rate of 25 µL/min each and mixed at an inlet of a Y-shaped micromixer (YMC KC-M-Y-SUS, 18.4 µL) at room temperature. The reaction mixture (34 µL) was added to H_3PO_4 (10 mM, 0.8 mL) and then injected into a semi-preparative HPLC column (YMC ODS-A324, 10 x 250 mm). An elution profile was compared with that obtained by the loop method[3].

The results shown in Table 1 clearly indicate that temperature was more critical than the other parameters of material and dimension of the spiral tube and He flow rate. The temperatures below -70°C gave the efficiencies of over 90%, suggesting that the melting point (-64°C) of MT was a critical temperature rather than the boiling point (100-102°C). No difference was found between SS and Cu, and no distinct effect could be drawn from the limited results for the size of tube and the He flow rate. However, it should be mentioned that the decrease in flow rate results in increasing processing time, i.e., more decay of radioactivity although it may be favorable for efficient trapping. The dimension of the tube is apparently an important parameter directly related with the volume of the recovery solvent.

Figure 3 demonstrates a typical trapping and elution profile of [11C]MT (Entry 9 in Table 1). It took nearly 4 min to transfer [11C]MeI from the MicroLab MeI module and flow [11C]MT through the trapping tube at a He flow rate of 15 mL/min since a total volume of He needed for recovering the all from the module was ca. 60 mL. Additional flowing for a few min confirmed that the trapped [11C]MT was not released into He again. Then, the [11C]MT was eluted successfully in 14±6 µL acetone with a recovery of >93%. Microfluidic

radiosynthesis of [11C]raclopride was carried out. Although the reaction was not optimized, it was suggested by comparison of the HPLC separation profiles that the reaction of the concentrated [11C]MT was the same with that used in routine production of [11C]raclopride by the loop method[3]. Further study on microreactor radiosynthesis of 11C-labeld probes is in progress.

References

1) Saiki H, Iwata R, Nakanishi H, et al., *Appl Radiat Isot* **68** (2010) 1703.
2) Kawashima H, et al., *Chem Pharm Bull* **63** (2015) 737.
3) Iwata R, et al., *Appl Radiat Isot* **55** (2001) 17.

Table 1. Trapping efficiency of [11C]MT vs. temperature and He flow rate with various metal tube.

| Entry	Spiral tube		Temperature	He flow rate	Trapping efficiency
	Material	Inner diameter x length (volume)			
5	SS*	0.75 x 300 mm (132 μL)	-44°C	50 mL/min	<1%
2	SS*	0.75 x 300 mm (132 μL)	-61°C	50 mL/min	2%
3	SS*	0.5 x 200 mm (39 μL)	-79°C	30 mL/min	96%
4	Cu	0.5 x 300 mm (59 μL)	-61°C	15 mL/min	<1%
5	Cu	0.5 x 300 mm (59 μL)	-72°C	15 mL/min	98%
6	Cu	0.5 x 300 mm (59 μL)	-74°C	15 mL/min	95%
7	Cu	0.3 x 400 mm (28 μL)	-74°C	10 mL/min	99%
8	Cu	0.3 x 200 mm (14 μL)	-74°C	10 mL/min	98%
9	Cu	0.3 x 200 mm (14 μL)	-85°C	15 mL/min	98%

*Stainless steel
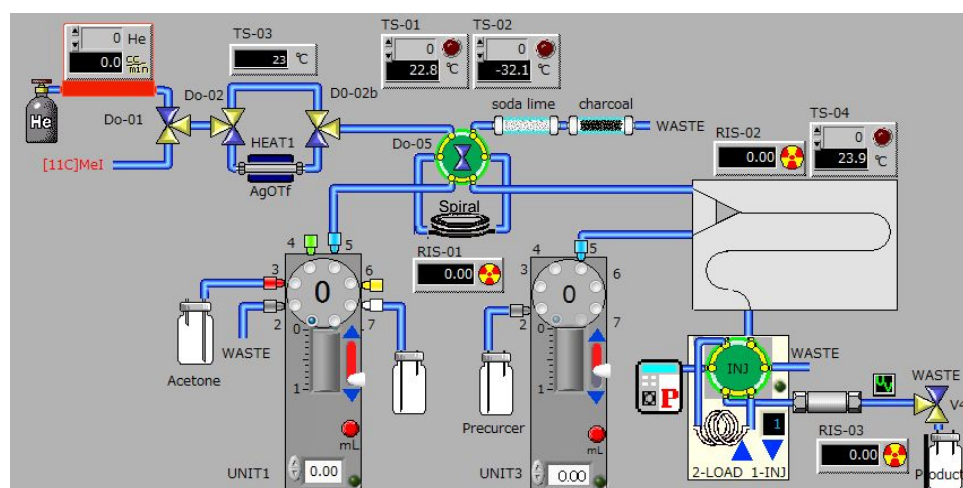
Figure 1. A PC control view of the automated concentration module and reaction/HPLC separation modules.
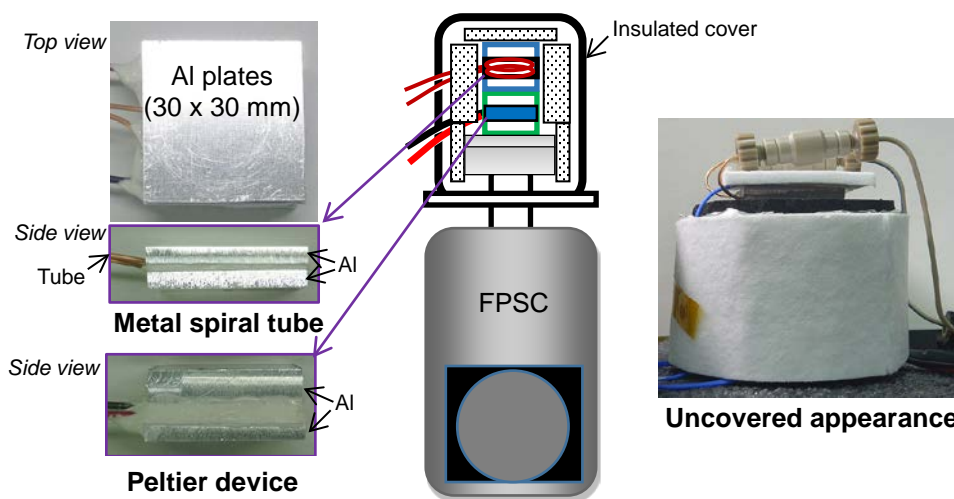
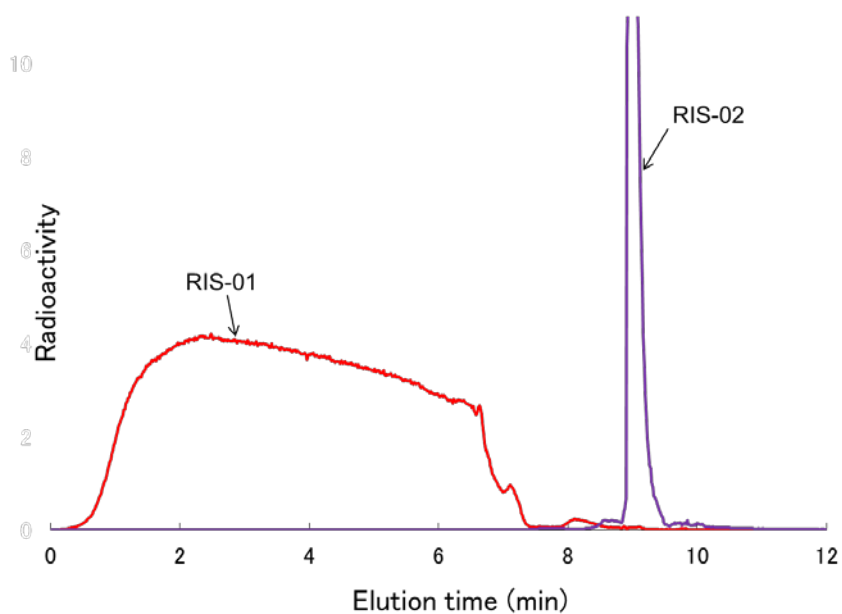Figure 2. Construction of a trap of flowing [^{11}C]MT with metal tube cooled with a thermoelectric cooler.

Figure 3. A typical trapping and eluting profile of [^{11}C]MT.