Automated Preparation of [18F]FRP-170 as a Hypoxic Cell Marker for Clinical PET Studies

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VII. 1. Automated Preparation of [^{18}F]FRP-170 as a Hypoxic Cell Marker for Clinical PET Studies

Ishikawa Y., Morita M.[*], *Furumoto S.*[**], *Takai Y.*[***], *and Iwata R.*

Cyclotron and Radioisotope center, Tohoku University
Graduate School of Engineering, Tohoku University[*]
Institute of Development, Aging and Cancer, Tohoku University[**]
University Hospital, Tohoku University[***]

2-Nitoroimidazoles have high reduction potential and radiosensitizing activity. Since reduction of the nitro group in the molecule leads to selective binding and retention in hypoxic cells, F-18 labeled 2-nitroimiodazole analogs such as [^{18}F]FMISO[1,2], [^{18}F]fluoroetanidazole[3], [^{18}F]EF1[4] and [^{18}F]EF5[5] are expected to be a good candidate for imaging tumor hypoxia by positron emission tomography (PET). Fluorine-18 labeled FRP-170 ([^{18}F]FRP-170) was developed by modification of RP-170[6], a radiosensitizer of POLA Chem.[7], and evaluated as a new imaging agent for hypoxia at Tohoku University[8]. For applying this potential radiopharmaceutical to routine clinical diagnosis by PET an automated system was developed in this study.

The synthetic procedure (see Fig. 1) consisted of (1) separation of [^{18}F]fluoride from the target water, (2) drying the aqueous mixture of Kryptofix 222 and [^{18}F]KF by evaporation, (3) reaction with the precursor in DMF, (4) purification of the intermediate product by solid-phase extraction, (5) deprotection of the purified product by base hydrolysis and (6) final purification by high performance liquid chromatography (HPLC). They were modified or simplified to adapt to automation as follows:

Frequently used procedures of addition of liquid reagents, transfer of reaction solutions and evaporation of solvents were automated by sensing the change in He flow[9]. As seen in Fig. 2 the He flow was markedly changed according to the vapor pressure in the reaction vessel during evaporation or the presence of liquid in the tube and thus completion of each process could be detected without requiring a manual interruption.

An original glass reaction vessel was substituted for a small round bottom flask with thin walls (10 mL, Wheaton) to reduce the time for azeotopic distillation of

water-acetonitrile. This was also useful for preventing the contamination of carrier fluoride derived from the plastic cap and sealing O-ring used for the original vessel.

On-column hydrolysis using a Sep-Pak C18 cartridge was introduced to simplify the procedure. The protected intermediate product retained by the cartridge was hydrolyzed on-column by filling with the NaOH solution and thus second vessel for this reaction could be omitted. It can be seen from Fig. 3 that the on-column method requires a much higher concentration of NaOH whereas it is efficiently hydrolyzed even with 0.1 M NaOH by the conventional vessel method. A 0.5 M concentration of NaOH was adopted. After hydrolysis the cartridge was first washed with water and then the deprotected product was eluted with an appropriate solvent.

Elution of [^{18}F]FRP-170 from the C18 cartridge was optimized. In order to simplify the procedure the solvent used for the elution was directed to an HPLC column. In general, a product retained by the C18 cartridge is more efficiently eluted with a lower polar solvent. However, this lower solvent, if injected onto an HPLC column for subsequent separation, may spoil the separation by leading compounds together. This is clearly demonstrated in Fig. 4. Only the solvent of <15% MeCN contents provides a satisfactory separation between [^{18}F]FRP-170 and an undesired non-radioactive by-product. Using a 2 mL portion of this solvent system, the [^{18}F]FRP-170 was eluted only in 30% efficiencies from the Sep-Pak. The elution efficiency was twice improved with a 1 ml portion of the solvent system of water-MeCN (70:30) followed by a 1 mL portion of water.

A commercial automated synthesis system, F121 (Sumitomo Heavy Industries), was adapted to the automated preparation of [^{18}F]FRP-170 (see Figs. 5 and 6). Using the automated system [^{18}F]FRP-170 was prepared in decay-corrected radiochemical yields of 15-20% within 50 min. The method developed in the present study was also demonstrated to be simple and reliable enough to carry out the reproducible production of [^{18}F]FRP-170 for routine use.

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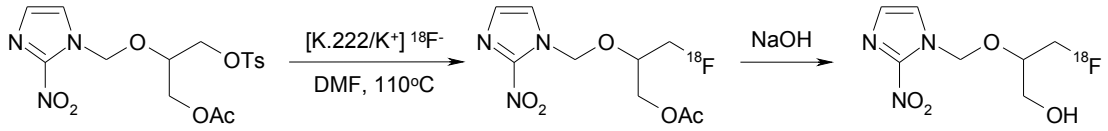

Fig. 1. A synthetic scheme of [^{18}F]FRP-170 from [^{18}F]fluoride.

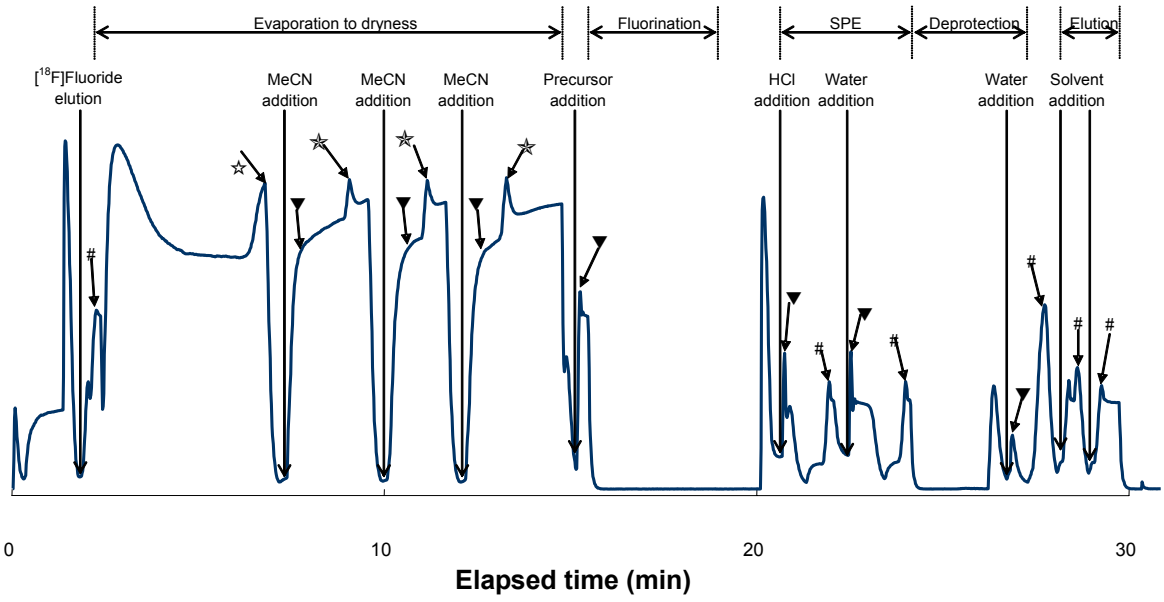

Fig. 2. A typical He flow change during the automated preparation.

☆: completion of evaporation
▼: completion of addition
#: completion of passage

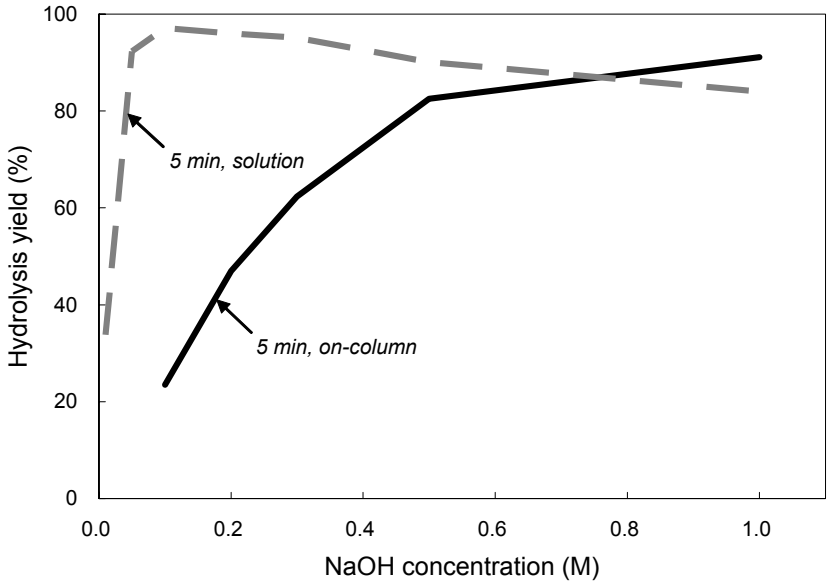

Fig. 3. Dependence of base hydrolysis on NaOH concentration.

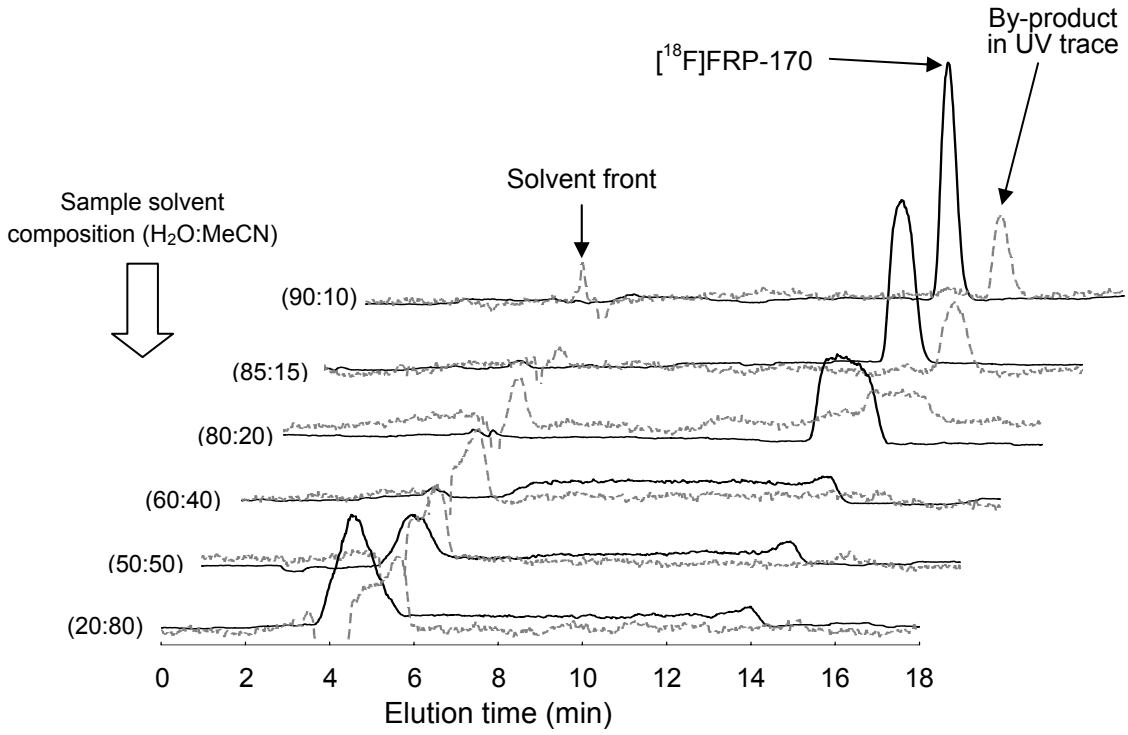

Fig. 4. Effects of polarity of sample solvent on separation profiles of [^{18}F]FRP-170 from the by-product.

- Column: YMC ODS-A-324
- Solvent: MeCN-H2O (12:88), 4.0 mL/min
- UV: 280 nm

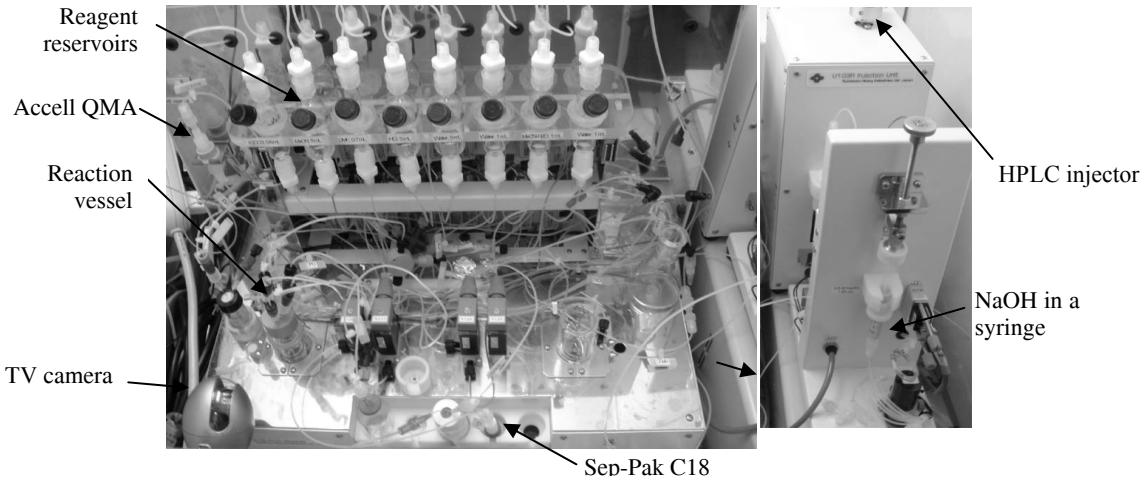

Fig. 5. An automated system (F121).

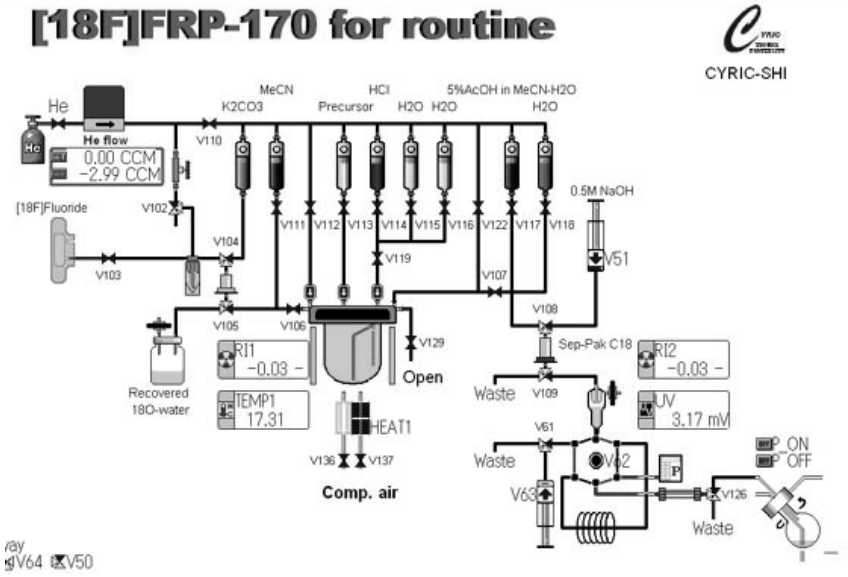

Fig. 6. A flow diagram of an automated system for [^{18}F]FRP-170