Automated Synthesis of 18F-5-Fluoro-2'-Deoxyuridine

III. 6 Automated Synthesis of ^{18}F-5-Fluoro-2'-Deoxyuridine

Ishiwata K., Monma M., Iwata R. and Ido T.
Cyclotron and Radioisotope Center, Tohoku University

As 5-fluorouracil(FUra) and its derivatives used in tumor chemotherapy are related in nucleic acid metabolism, the tumor uptakes of ^{18}F-labeled compounds have been investigated[1-3], and ^{18}F-FUra was applied to human study.[4] We have also studied the tumor uptakes of ^{18}F-FUra, ^{18}F-5-fluoro-2'-deoxyuridine(^{18}F-FdUrd) and ^{18}F-5-fluorouridine(^{18}F-FUrd) and confirmed that these would be useful for the tumor detection in human, especially tumors in the brain and lung, by positron emission tomography and that the ^{18}F-FdUrd would be more suitable among three pyrimidines.[5,6] For routine production of the ^{18}F-FdUrd we have developed the automated synthesis system.

^{18}F-FdUrd was synthesized by the method of Shiue et al.[7] with some modifications(Fig. 1). The system developed for the computer controlled automated synthesis of ^{18}F-2-deoxy-2-fluoroglucose[8] is applied to the production of ^{18}F-FdUrd and consists of the synthesis unit, the ^{18}F-F_2 production unit, the leak test unit and the controller unit. The system for the production is shown schematically in Fig. 2.

The controller unit consists of a microcomputer, a graphic printer, a color CRT, interfaces and a radioactivity monitor.

The synthesis unit is compact(a size of 30×40×30 cm)(Fig. 3) and is installed in a shielded box. Synthetic process consists of three steps:(1) addition of ^{18}F-F_2 to 3', 5'-di-O-acetyl-2'-deoxyuridine(diAcdUrd), (2) hydrolysis of the ^{18}F-adduct and (3) chromatographic purification. ^{18}F-F_2 is produced by deutron irradiation(an incident energy of 15.7 MeV) of a Ne target containing 0.1% F_2 at 25 kg/cm with the ^{20}Ne(d,α) ^{18}F reaction. After the irradiation, the ^{18}F-F_2 is bubbled into 4 ml gracial acetic acid containing 15-20 mg diAcdUrd in a vessel A with a flow rate of 500 ml/min at room temperature. The reaction mixture is transferred into the vessel B. Acetic acid is then injected into the vessel A for washing and transferred into the vessel B. In the second part of the unit the apparatus that rotates the bottom of the vessel B horizontally is designed to evaporate solvents rapidly but not vigorously at 75°-80°C under reduced pressure or to dissolve residue completely. The solvent of ^{18}F-adduct is evaporated. The residue is dissolved in 4 ml C_2H_5OH containing 0.05 g C_2H_5ONa and hydrolyzed at 75°-80°C for 5 min to give ^{18}F-FdUrd. After the evaporation, the residue is dissolved in 2 ml water and transferred to the serial combined of AG 50W × 8(H^+ form, 1.6×5cm) and neutral alumina(1.6×11cm). The solution is then passed through the columns. The vessel B and the columns are washed with 2 ml water followed by elution with water. On AG 50W the solution is neutralized and on alumina the ^{18}F-FdUrd is purified. Finally the fraction of 25-45 ml is collected as the ^{18}F-FdUrd(Fig. 4). The transfer of all

fluids is controlled by applying He pressure with solenoid and pinch values. Each synthetic procedure described above is controlled by a computer with a timer, optical liquid lecel sensors or a radioactivity monitor.

The radiochemical purity was determined by radio-high performance liquid chromatography on μBondapak C18(Waters) with a solvent system of CH_3OH and water(10:90) with a flow rate of 2 ml/min. The apyrogenicity was confirmed by Limulus Amebocyte Lysate Test (Mallinckrodt).

The synthesis of ^{18}F-FdUrd was carried out within 60 min after the 60 min-deutron irradiation with 12 μA. At the end of synthesis 20-35 mCi of ^{18}F-FdUrd was obtained as a sterile and apyrogenic solution(eluate in the (b) region in Fig. 4) with radiochemical purity of over 99% and with radiochemical yield of 15-25%. ^{18}F-FdUrd was purified on an alumina column with water instead of a silica gel column with organic solvent. The use of the combined columns for neutralization and purification makes the automated procedures easier.

Analysis of the eluates in (a) and (b) regions in Fig. 4 shows that most radioactive impurities are eluted earlier than the ^{18}F-FdUrd. ^{18}F-FdUrd was separated from 2'-deoxyuridine and the eluate in the (b) resion gave higher radio-chemical purity(over 99%) than in our previous result.[9] This system was applied to the production of ^{18}F-FUra by using the same program and could give uracil-free ^{18}F-FUra with radiochemical yield of 43% and with radiochemical purity of over 99%.

In conclution this automated synthesis system is suitable for the production of the ^{18}F-FdUrd in routine clinical study and will be applied to other ^{18}F-FUra derivatives.

References

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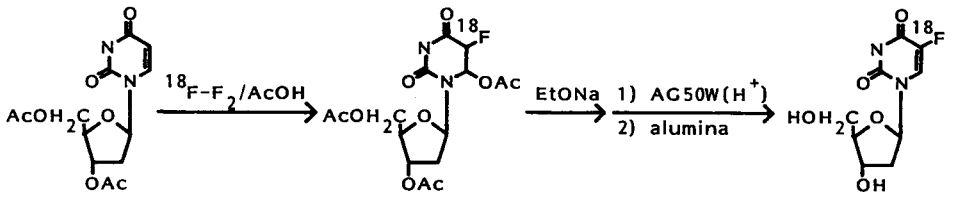

Fig. 1 Synthesis of ^{18}F-5-fluoro-2'-deoxyuridine.

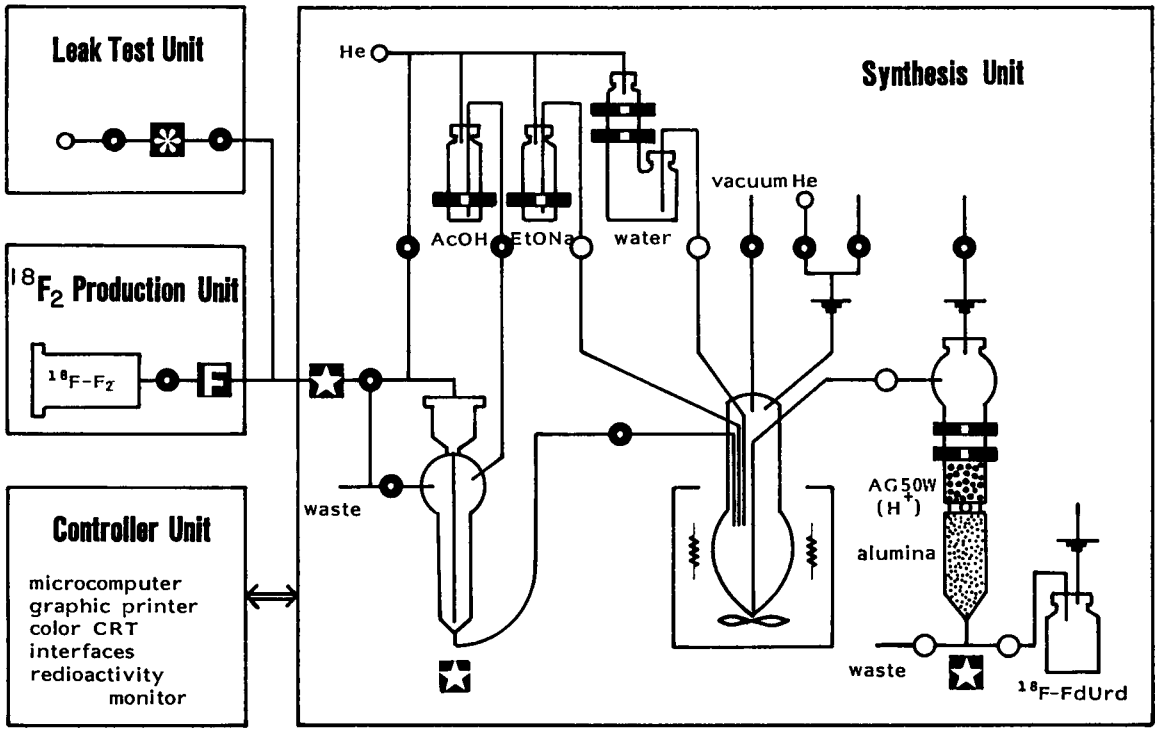

Fig. 2 Flow chart of ^{18}F-5-fluoro-2'-deoxyuridine production system.

● :Solenoid valve, ○ :Pinch valves,
▬ :Optical liquid level sensor, ▸ :Membrane filter,
☆ :Radioactivity detector, F :Flow controller,
◘ :Pressure sensor,

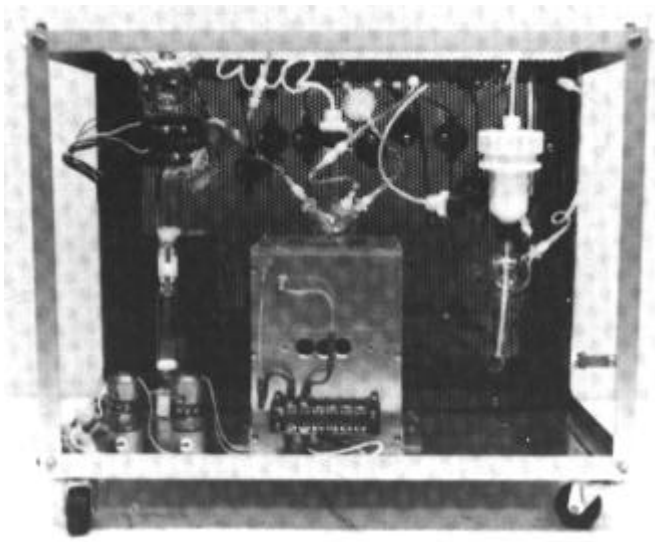

Fig. 3 Synthesis unit of the production system of ^{18}F-5-fluoro-2'-deoxyuridine.

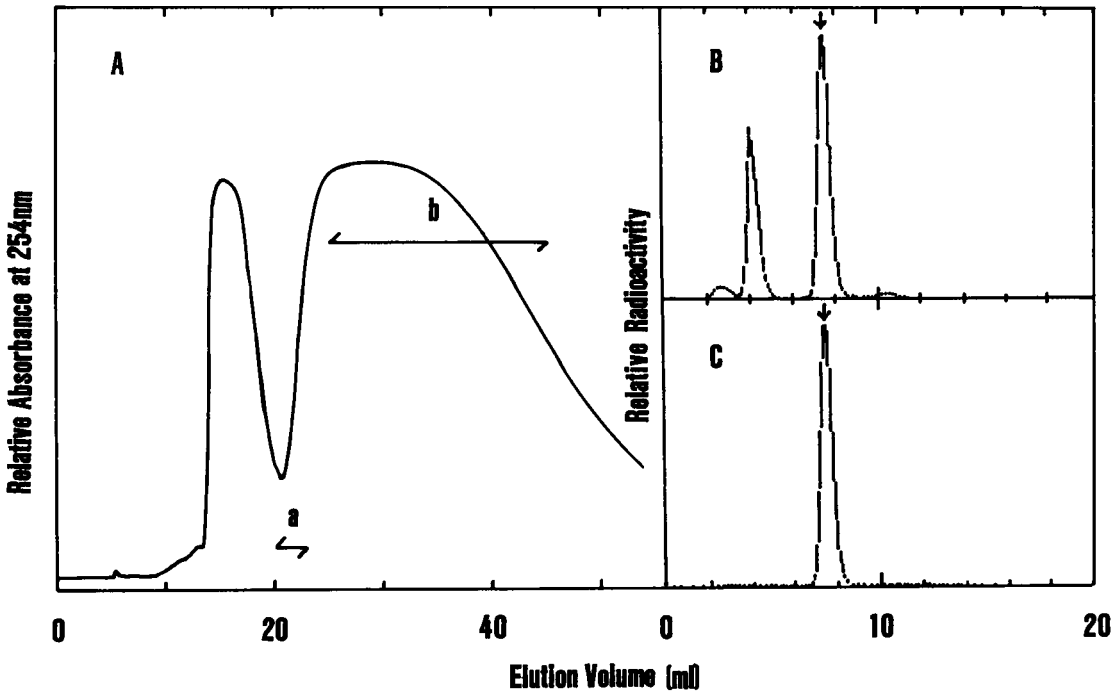

Fig. 4 Purification of ^{18}F-5-fluoro-2'-deoxyuridine on AG50W(H^+) and neutral alumina columns. (A) shows the chromatogram. The eluates in (a) and (b) in (A) analyzed by radio-HPLC (μBondapak C18, 10% MeOH, 2 ml/min) are shown in (B) and (C), respectively. Arrow shows the elution volumn of authentic 5-fluoro-2'-deoxyuridine.