III. 4 Syntheses of $^{18}$F-2-Fluoro-2-deoxyglucose and $^{18}$F-2-Fluoro-2-deoxymannose

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$^{18}$F is an ideal positron-emitter for positron tomography since its energy is the lowest in a series of positron-emitters ($^{11}$C, $^{13}$N, $^{15}$O etc.). Its relatively long half-life (109.8 min.) is also favorable for the syntheses of various $^{18}$F-radiopharmaceuticals. In the syntheses of $^{18}$F-radiopharmaceuticals, $^{18}$F-$P_2$ is one of the useful reagents because of its high reactivity.$^{1}$ In particular, its additional reaction to various double bonds is simple and widely used. This method is expected to be used for the development of various $^{18}$F-radiopharmaceuticals. We tried the syntheses of $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$F-FDG) and $^{18}$F-2-fluoro-2-deoxymannose ($^{18}$F-FDM) by the use of above labeling method. $^{18}$F-FDG has been used as a tracer for the exchange of glucose between plasma and brain and its phosphorylation by hexokinase in the tissue$^{2}$ and moreover used as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo.\(^3\) $^{18}$F-FDG is a more useful radiopharmaceutical in positron nuclear medicines and $^{18}$F-FDM, which is an isomer of $^{18}$F-FDG, has been also expected to be used for the same purpose as $^{18}$F-FDG. We synthesized $^{18}$F-FDG and $^{18}$F-FDM by the reaction of 3,4,6-tri-O-acetylglucal with $^{18}$F-$P_2$. In this present paper, we report the routine syntheses of $^{18}$F-FDG and $^{18}$F-FDM in high radiochemical purity by making a few modifications for better in the conventional method.$^{4}$

MATERIALS AND METHODS

The synthetic steps of $^{18}$F-FDG and $^{18}$F-FDM are roughly divided into the following four main procedures: (i) production of $^{18}$F-$P_2$ (ii) reaction of 3,4,6-tri-O-acetylglucal with $^{18}$F-$P_2$ (iii) column chromatography and isolation of $^{18}$F-glucopyranosyl difluoride and $^{18}$F-mannopyranosyl difluoride (iv) hydrolysis of $^{18}$F-glucopyranosyl difluoride and $^{18}$F-mannopyranosyl difluoride and purification of $^{18}$F-FDG and $^{18}$F-FDM. The synthetic route and the synthetic method of $^{18}$F-FDG and $^{18}$F-FDM are respectively shown in chart 1 and fig. 2.

(i) Production of $^{18}$F-$P_2$; $^{18}$F-$P_2$ was produced from the deuteron bombardment of neon-fluorine gas mixture by the $^{20}$Ne(d,$\alpha$)$^{18}$F nuclear reaction. The external deuteron beam of our cyclotron was used to bombard neon gas containing 0.05 % fluorine at a pressure of 25 atm in a nickel target chamber for 2 hr at a current of 10 uA.

(ii) Reaction of 3,4,6-tri-O-acetylglucal with $^{18}$F-$P_2$; Before end of bombardment (EOB), a solution of 67 mg (250 umol) of 3,4,6-tri-O-acetylglucal in 10 ml of freon-11 (CFC$_3$) was introduced into the reaction vessel, which was immersed in a dry ice/methanol bath. After EOB, $^{18}$F-$P_2$ in neon was released from the target chamber at a controlled flow rate and bubbled through the glucal solution at
approximately 200 ml/min. After 30 min, neon was added to the target chamber at a pressure of 3 atm as a purge and bubbling was continued for 5 min.

(iii) Column chromatography and isolation of $^{18}$F-glucopyranosyl difluoride and $^{18}$F-mannopyranosyl difluoride; The cooled solution of reaction products, which consisted of 3,4,6-tri-O-acetyl-2-fluoro-2-deoxy-α-D-glucopyranosyl fluoride and 3,4,6-tri-O-acetyl-2-fluoro-2-deoxy-β-D-mannopyranosyl fluoride, was transferred to a glass collection vessel. The reaction vessel was rinsed with 5 ml of n-hexane and 5 ml of fresh CFCl$_3$, which were also transferred to the collection vessel, and the combined solution was transferred to the top of a silica gel column, 0.9 cm i.d. x 10 cm, previously equilibrated with n-hexane. After eluting the silica gel column with 50 ml of n-hexane, the solvent was exchanged for diethyl ether : n-hexane (1:1). $^{18}$F-Glucopyranosyl difluoride was eluted with 20-30 ml of diethyl ether : n-hexane (1:1) (fr.10-fr.15, each fraction : ca. 2 ml) and $^{18}$F-mannopyranosyl difluoride with 70-90 ml (fr.35-fr.45). The solvent of each collected fraction was evaporated in vacuo.

(iv) Hydrolysis of $^{18}$F-glucopyranosyl difluoride and $^{18}$F-mannopyranosyl difluoride and purification of $^{18}$F-FDG and $^{18}$F-FDM; The solvent-free residue containing the $^{18}$F-glucopyranosyl difluoride was suspended in 5 ml of 1N-HCl and refluxed for 15 min (oil-bath temperature : 135°C). The products of hydrolysis were transferred to the top of a series of columns, which had been packed with 0.9 cm i.d. x 1 cm of activated charcoal, 0.9 cm i.d. x 10 cm of AG11A8 resin and 0.9 cm i.d. x 5 cm of neutral alumina, previously equilibrated with water. $^{18}$F-FDG was eluted with 5-20 ml of water (fr.2-fr.4, each fraction : ca. 5 ml). From the collected fractions, water was evaporated in vacuo. 15-20 mCi of $^{18}$F-FDG was obtained. $^{18}$F-FDM was synthesized in the same method as $^{18}$F-FDG. The solvent-free residue containing the $^{18}$F-mannopyranosyl difluoride was suspended in 5 ml of 5N-HCl and refluxed for 15 min (135°C). The products of hydrolysis were transferred to the top of a series of columns, 0.9 cm i.d. x 1 cm of activated charcoal, 0.9 cm i.d. x 20 cm of AG11A8 resin and 0.9 cm i.d. x 5 cm of neutral alumina. $^{18}$F-FDM was eluted with 10-25 ml of water (fr.3-fr.5). Water was evaporated in vacuo. 5-7 mCi of $^{18}$F-FDM was obtained.

Radiochemical analysis of $^{18}$F-FDG and $^{18}$F-FDM; The radiochemical purity of $^{18}$F-FDG and $^{18}$F-FDM was determined by HPLC (column : μ-Bondapak C-18 (carbohydrate); eluent : CH$_3$CN/H$_2$O (85/15); flow rate : 2ml/min). HPLC radiochromatogram of $^{18}$F-FDG is shown in fig. 2. The radiochemical purity of $^{18}$F-FDG was found to be >98 % and that of $^{18}$F-FDM 99 % (Table 1).

RESULTS AND DISCUSSION

Compared with the conventional method, we improved the syntheses as follows:

(1) a large excess of the starting material was used to prevent the overoxidation of products by F$_2$. (2) $^{18}$F-glucopyranosyl difluoride and $^{18}$F-mannopyranosyl difluoride were purely separated in silica gel column before their hydrolysis.
(3) before eluting a silica gel column with diethyl ether : n-hexane (1:1), 50 ml of n-hexane was eluted to remove the unreactive starting material. By these modifications, we succeeded in obtaining $^{18}$F-FDG and $^{18}$F-FDM in high radiochemical purity ($^{18}$F-FDG : >98 %, $^{18}$F-FDM : 99 %). By administering $^{18}$F-FDG and $^{18}$F-FDM to rats bearing AH109A tumor, they have been demonstrated to be mainly accumulated in brain, heart and tumor. Now, the need for frequent production of $^{18}$F-FDG made necessary the development of automated synthesis system for its processing. We have already developed the automated synthesis system of (i)-(iii) steps.

References


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3,4,6-tri-O-Acetylglucal in CFCl₃

$^{18}$F-F₂ was bubbled (dry ice - methanol)

reaction mixture

silica gel column
(n-hexane:ether=1:1)

effluent (first)

solvent was evaporated in vacuo

residue

hydrolysis (1N-HCl)

reaction mixture

active charcoal column

ion exchange column (AG11A8)

$^{18}$F-PDG

Fig. 1. Synthetic Method of $^{18}$F-2-Fluoro-2-deoxyglucose and $^{18}$F-2-Fluoro-2-deoxymannose.

$^{18}$F-PDM

effluent (secondly)

solvent was evaporated in vacuo

residue

hydrolysis (5N-HCl)

reaction mixture

active charcoal column

ion exchange column (AG11A8)

alumina column

Fig. 2. Radiochemical Analysis of $^{18}$F-2-Fluoro-2-deoxyglucose.
Chart 1 Syntheses of $^{18}$F-2-Fluoro-2-deoxyglucose and $^{18}$F-2-Fluoro-2-deoxymannose.