Production System for $^{18}$F-2-Deoxy-2-fluoro-D-glucose
—A trial for automatic production—

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We have developed a production system for $^{18}$F-2-deoxy-2-fluoro-D-glucose ($^{18}$F-2FDG), which assures reliable production with easy handling and reduces radiation exposures to the operator. Chemical procedures in this system are the same as manual method developed in NIRS. This system has 2 operation modes; one is remote controlled manual operation mode and the other is microcomputer controlled automatic operation mode. In remote controlled mode, we tested this system 5 times and $^{18}$F-2FDG synthesized was supplied for clinical use once. The mean radiochemical yield of $^{18}$F-2FDG from the target gas recovery with decay time correction was 8%, that is the same as in the manual synthesis. It took about 2 hours from end of bombardment (EOB) to end of synthesis (EOS). Since this time is shorter than in manual synthesis, the available activity at EOS is increased.

Key Words: 18-fluorine-2-deoxy-2-fluoro-D-glucose, automatic production system, radiopharmaceuticals, liquid sensor, radiation sensor

1. Introduction

Positron imaging of regional brain glucose metabolism with $^{18}$F-2-deoxy-2-fluoro-D-glucose ($^{18}$F-2FDG) has come to be one of the most feasible technique in current nuclear medicine. The principle of $^{18}$F-2FDG preparation was established by Ido, et al. In National Institute of Radiological Sciences (NIRS), $^{18}$F-2FDG has been manually synthesized for clinical use from 1980. Up to the present, efforts have been made to develop remote controlled $^{18}$F-2FDG production systems. We have developed a fully automated $^{18}$F-2FDG production system, which assures reliable production with easy handling as well as reduces radiation exposure to the operator. Chemical procedures of the system are the same as in the manual method which had been developed in NIRS and been published by Irie, et al.

2. System and Procedure

Schematic diagram of the system is shown in Fig. 1. All parts in this system (4) were assembled in standard cases for cabinet racks (total size is about 40 cm width, 45 cm depth and 50 cm height) and installed in a hot cell. A target chamber (6) is set on the beam line in the irradiation room. An automatic target gas supply system (5) is also shown in Fig. 1.

This system has 2 operation modes. One is a remote controlled manual operation mode, the other is microcomputer controlled automatic operation mode. A manual controller is prepared for manual operation mode, and a microcomputer system having a colour display, a printer, 2 digital cassette MT and interface boards is connected with the manual controller. Selection of these 2 modes is done by a push switch on the front panel of the manual controller. Most of programs for the microcomputer are written by BASIC.

We developed 2 types of sensors for this system. One is a liquid sensor and the other is a radiation sensor. The liquid sensor is mounted on a glass or teflon tube, and used to know...

whether a point of interest on the tube is filled with liquid or air, or is occupied with liquid surface. The sensor consists of a light-emitting diode (LED) and a photo-transistor, each of which is arranged at opposite side of the tube. Liquid in the tube acts as a lens so that the output current from photo-transistor is increased; on the other hand, liquid surface acts as a scatter so that the output current is decreased. In this way we can distinguish each liquid conditions in the tube with a simple circuit. Eighteen liquid sensors are assembled in the system for monitoring of liquid transfer.

The radiation sensor is composed of a 1.27 cm diameter and 1.27 cm length NaI scintillator and a photo-diode operated without high voltage. Lower limit of detection is about 1.85 MBq (50 μCi) for positron emitters, and is good enough for our purpose. Four radiation sensors were assembled in the system for monitoring of activity transfer. Signals from all the sensors are taken by the microcomputer to be processed for system control, and signals from the liquid sensors are also taken by the manual controller to be displayed on its front panel.

A nickel target chamber whose size is 2.7 cm internal diameter and 14.5 cm length is used. A 22.5 MeV deuteron beam accelerated by NIRS cyclotron (CGR-MeV 930) is degraded to 16 MeV through a 0.03 mm thick titanium, 0.02 mm thick nickel and 0.6 mm thick aluminium foils. About 24 kg/cm² neon gas containing 0.1~0.2% of fluorine gas is bombarded about 2 hours by 10~15 μA deuteron beam. After bombardment, $^{18}$F-2FDG synthesis is accomplished by the following steps.

Step 1. 3,4,6-tri-O-acetylglucal (TAG) injection to reaction vessel—TAG solution in Freon 11 is injected from the vial (8) to the first reaction vessel (7) with pressurized helium gas (10).
About 40 mg of TAG in several ml Freon 11 is used. The reaction vessel is cooled to −78°C in a dry-ice acetone bath.

Step 2. Recovery of ¹⁸⁹F-F₂ to the first reaction vessel—Produced ¹⁸⁹F-F₂ gas is recovered in the first reaction vessel from the target chamber through solenoid valves, a mass flow meter/controller and a nickel tube line about 10 m long. It takes about 30 minutes for the recovery.

Step 3. Transfer of reaction solution to silica gel column—After recovery, Freon 11 solution is transferred to silica gel column (11) (1.5 cm internal diameter and 10 cm length) with pressurized helium gas.

Step 4. Rinse of the first reaction vessel—Several ml of n-hexane (9) is injected to the reaction vessel and is transferred to silica gel column.

Step 5. Silica gel column chromatography—Absorbed ¹⁸⁹F-adducts are eluted with n-hexane/ether (3:4) solution (14) to separate ¹⁸⁹F-labelled 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-D-glucopyranosyl fluoride. At the exist of the column, the eluted activity is monitored by a radiation sensor. Measured activity is recorded on a recorder or taken by microcomputer and displayed on a colour display. It takes about 15 minutes to elute glucopyranosyl fluoride. Separated eluate is directly sent to the second reaction vessel (15).

Step 6. Evaporation—Separated elute is evaporated from the second reaction vessel. It takes about 20 minutes for the evaporation.

Step 7. HCl injection and hydrolysis—After evaporation, 3 ml of 1 N HCl (16) is injected to the second reaction vessel with pressurized helium gas. Hydrolysis is done about 30 minutes at 130°C in an oil bath.

Step 8. Purification—The hydrolyzate is purified by a resin column (21) and an alumina column (22). The resin column (0.8 cm inner diameter, 8 cm length) is used to remove HCl, and the alumina column (0.6 cm inner diameter, 6 cm length) is used to remove ¹⁸⁹F⁻ ion. Activated charcoal is also added in the alumina column to remove coloured by-products. The hydrolyzate is transferred to the resin column with pressurized helium gas at first. Then the resin column and the alumina column are eluted with water (24) sent by a pump (23). Finally, 3 fractional portion of ¹⁸⁹F-2FDG solution are obtained in collection vials (25) (26) (27).

After these steps, ¹⁸⁹F-2FDG solution is sterilized by millipore filter and then suitable amounts of NaCl are added. The radiochemical purity is checked by high performance liquid chromatography (HPLC) with Bodapak C18 Carbohydrate column and CH₃CN/H₂O (85:15). The pyrogen test is accomplished by Pyrogent.

Before the run, all glass reaction vessels, columns, alumina and charcoal were sterilized by heating to 250°C for 3 hours. Teflon joints were also sterilized by steam at 120°C for 20 minutes. Resin column was washed with 500 ml sterilized water before it was assembled in the system. After every run, glass reaction vessels and columns were renewed. The downstream teflon tubes and teflon solenoid valves from the second reaction vessel were washed and filled with ethyl alcohol to keep their insides in sterilized. Before the run, the alcohol was purged by helium gas and inside of the vessels were washed with sterilized water.

3. Results and Discussion

We tested this system 5 times in the remote control mode, and ¹⁸⁹F-2FDG synthesized was supplied for clinical use once. The development of software for fully automated production is continued.

The typical parameters for target irradiation are 12 μA beam current and 2 hours bombardment time. The theoretical yield of ¹⁸⁹F is about 23.67 GBq (639.7 mCi) at the end of bombardment (EOB), if we assume the saturation yield of ¹⁸⁹F for 16 MeV deuteron beam to be 3.719 GBq/μA (100.5 mCi/μA). Percent recovery of ¹⁸⁹F from the target chamber and the distribution of the recovered activities are described in Table 1, with the average ± S.D. in 5 runs. Percent recovery was calculated by dividing the total amounts of recovered ¹⁸⁹F activities by theoretical yield. The recovery of 57.5% is slightly lower than previous data. It would be caused by poor conditions of the target chamber and recovery line, and not be caused by the target pressure nor carrier concentration, as judged from the previous experience. The dis-
Table 1 Target recovery and yield data

<table>
<thead>
<tr>
<th>Percent recovery of $^{18}$F from target chamber</th>
<th>57.5±10.4(%)</th>
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<tbody>
<tr>
<td>Distribution of $^{18}$F</td>
<td></td>
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<tr>
<td>Reaction solution</td>
<td>70.6± 8.1</td>
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<tr>
<td>Reaction vessel residual</td>
<td>16.9± 6.3</td>
</tr>
<tr>
<td>Soda lime trap</td>
<td>4.5± 0.6</td>
</tr>
<tr>
<td>Gas trap</td>
<td>7.9± 5.4</td>
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<tr>
<td>Radiochemical yield</td>
<td></td>
</tr>
<tr>
<td>Silica gel chromatography</td>
<td>32.4± 2.0</td>
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<tr>
<td>Purification</td>
<td>8.0± 2.7</td>
</tr>
</tbody>
</table>

The dispersion of the distribution data between each run is comparatively large. It may be due to the same reason.

The typical pattern of eluted activities from the silica gel column is shown in Fig. 2. Three peaks were observed. The first small peak corresponded to an impurity, and the second peak was glucopyranosyl fluoride. According to the previous study, the other impurities were also involved in the front and back tailing in the second main peak. The oblique lines in Fig. 2 shows the fractionated part. The third broad peak corresponded to mannopyranosyl fluoride. The radiochemical yield data are also described in Table 1. The yield was calculated as a percentage of the recovered $^{18}$F activities from the target chamber. Mean radiochemical yield of 32.4% for silica gel chromatography is larger than previous data. The radiochemical yield of 8.0% after purification is almost the same as previous data, but the dispersion for each run is large because the precise synthesis method for this production system has not been established enough.

The radiochemical purity of final products is slightly lower than previous data. The best value in 5 runs was 95%, as measured by HPLC with Bodapak C18 Carbohydrate column.

It took about 2 hours to prepare $^{18}$F-2FDG from EOB to end of synthesis (EOS). It takes about 3 hours in manual synthesis, so that the available activity of $^{18}$F-2FDG at EOS is increased about 1.4 times though the radiochemical yields are the same.

Liquid sensors and radiation sensors were working well. The cost of such sensors are so low that it is possible to assemble many sensors in the system and monitor liquid and activity transfer. Such monitoring is essential to make a fully automated production system such as $^{18}$F-2FDG production system, because it is necessary to know whether every process has been completely or successfully accomplished or not, and succeed to next step. So the software for a fully automated production system should have an ability of judgement for every status in the system. In general to make such software is not easy. BASIC may not be suitable language to make such software, but is very feasible to improve a program easily. We thus are trying to develop a software for $^{18}$F-2FDG automatic production system with BASIC language.

Sterilization is one of the most important subjects to prepare injections. We sterilized the system and materials as described before. Unfortunately, we didn’t pay special attention to mount or dismount the reaction vessels and columns in easy and reliable way when we designed the system, so such works before and after every run are comparatively complicated. We are developing reaction vessels and columns to be easily exchangeable. Furthermore, we have to consider again about the sterilization method of automatic production system for injection.

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References