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Changes in the radiochemical purity of [^{18}F]FDG radiopharmaceutical according to the amount of ethanol added

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► ***Technical note***

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ABSTRACT

Background: we aimed to find the optimal level of ethanol that can be added such that the radiochemical purity of [^{18}F]FDG is increased and the MFDS and USP stipulated guidelines are met. ***Materials and Methods:*** Changes in the radiochemical purity of [^{18}F]FDG were analyzed according to changes in the concentrations of ethanol added. The study used 1 L of 99.9% pure ethanol. The ethanol concentrations used were 0.0% (0 µL) for the control group and 0.1% (1 µL), 0.2% (2 µL), and 0.3% (3 µL) for the experimental groups. Since the radiochemical purity of [^{18}F]FDG may differ according to the radioactive concentrations used, four different radioactive concentrations were prepared: 1580 mCi/16 mL, 3320 mCi/16 mL, 4840 mCi/16 mL, and 6470 mCi/16 mL. ***Results:*** The radiochemical purity of [^{18}F]FDG increased significantly when ethanol was added to it at different radioactive concentrations in comparison to when ethanol was not added. When ethanol concentrations of 0.1%, 0.2%, and 0.3% were added, the radiochemical purity increased at all radioactive concentrations (100 mCi/mL, 200 mCi/mL, 300 mCi/mL, and 400 mCi/mL) while meeting the KP and USP standards even after 10 hours following the EOS. ***Conclusion:*** It was determined in our study that adding ethanol at the concentration of 0.1% to [^{18}F]FDG is most suitable as it generates the least residual ethanol while maintaining the radiochemical purity of [^{18}F]FDG at stable levels that meet the KP and USP standards.

Keywords: *[^{18}F]FDG, ethanol, radiochemical purity, radiopharmaceutical, US pharmacopeia, Korean pharmacopeia*

INTRODUCTION

2-Deoxy-2-[^{18}F]fluoroglucose (^{18}F-FDG) is a radiolabeled radiopharmaceutical compound of D-glucose and ^{18}F radioisotope. It is injectable and is used on patients, in nuclear medicine, during positron emission tomography (PET). It is also one of the most widely used radiopharmaceuticals in the world [1,2]. In Korea, since June 2006, its cost has been covered by health insurance[1]. Radiopharmaceuticals must meet the standards for radiochemical purity stipulated by the Korean Pharmacopeia (KP) and the United States Pharmacopeia (USP), and those that do not meet such standards should not be used on human patients [3-7]. The radiochemical purity of [^{18}F]FDG decreases due to the cleavage of the ^{18}F radioisotopes from [^{18}F]FDG by radiolysis. Large amounts of the ^{18}F radioisotope are taken up into the bones causing bone images to appear along with the desired PET image. Consequently, the image resolution and the reliability of the standard uptake value (SUV) are degraded, leading to a compromise in the diagnostic accuracy of the PET scan [8-9]. The addition of ethanol is one of many methods utilized to increase the radiochemical purity of radiopharmaceuticals. When ethanol is added to [^{18}F]FDG, it acts as a free radical trapping agent and reduces the radiolysis caused by free

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radicals, thereby increasing the radiochemical purity of [18F]FDG [10-12].

The Residual Solvent Guidelines of the Korea Ministry of Food and Drug Safety (MFDS) and the USP 30 chapter on residual solvents (Chemical Test/<467> Residual Solvents) contain regulations on using Class 3 substances, including ethanol, with caution since they have a low toxicity and are hazardous to human health. According to these guidelines, the residual ethanol in the [18F]FDG injection may not exceed a daily dose of 50 mg (5000 ppm or 0.5%) [13-15]. The exposure of the human body to organic solvents above this standardized level may cause complications like carcinogenesis, deformation, and neurotoxicity; and a significant level of exposure may be fatal. Therefore, the use of these organic solvents should be limited to diagnostic and therapeutic pharmaceuticals, making sure that the residual concentration remaining in the body is within the limits provided by relevant guidelines. In the present study, we aimed to find the optimal level of ethanol that can be added such that the radiochemical purity of [18F]FDG is increased and the MFDS and USP stipulated guidelines are met.

MATERIALS AND METHODS

Changes in the radiochemical purity of [18F]FDG were analyzed according to changes in the concentrations of ethanol added. 18F was prepared using a cyclotron (Manufacturer: GE Healthcare, Model: PET trace) with a proton acceleration energy of 16.5 MeV. [18F]FDG was synthesized from 18F using a synthesis module (Siemens Healthcare USA, Model: Explora FDG4) as seen in figure 1. Radioactive concentrations were measured using a radioisotope calibrator (dose calibrator) (Manufacturer: CAPINTEC, Model: CRC-ULTRA). The study also used 1 L of 99.9% pure ethanol (Manufacturer: OCI). The ethanol concentrations used were 0.0% (0 μL) for the control group and 0.1% (1 μL), 0.2% (2 μL), and 0.3% (3 μL) for the experimental groups. Since the radiochemical purity of [18F]FDG may differ according to the radioactive concentrations used, four different radioactive concentrations were prepared: 1580 mCi/16 mL, 3320 mCi/16 mL, 4840 mCi/16 mL, and 6470 mCi/16 mL. The concentrations of the radiopharmaceutical were set to four levels: 100 mCi/mL (actual radioactive concentration, 99 mCi/mL; relative error, 1%), 200 mCi/mL (actual radioactive concentration, 208 mCi/mL; relative error, 4%), 300 mCi/mL (actual radioactive concentration, 303 mCi/mL; relative error, 1%), and 400 mCi/mL (actual radioactive concentration, 404 mCi/mL; relative error, 1%). A radio TLC scanner was used to measure the radiochemical purity of [18F]FDG in 2-hour intervals for 10 hours from the end of synthesis (EOS). Gas chromatography was used to analyze the amount of residual ethanol generated when ethanol concentrations of 0.0%, 0.1%, 0.2%, and 0.3% were added to [18F]FDG at radioactive concentrations of 100, 200, 300, and 400 mCi/mL.

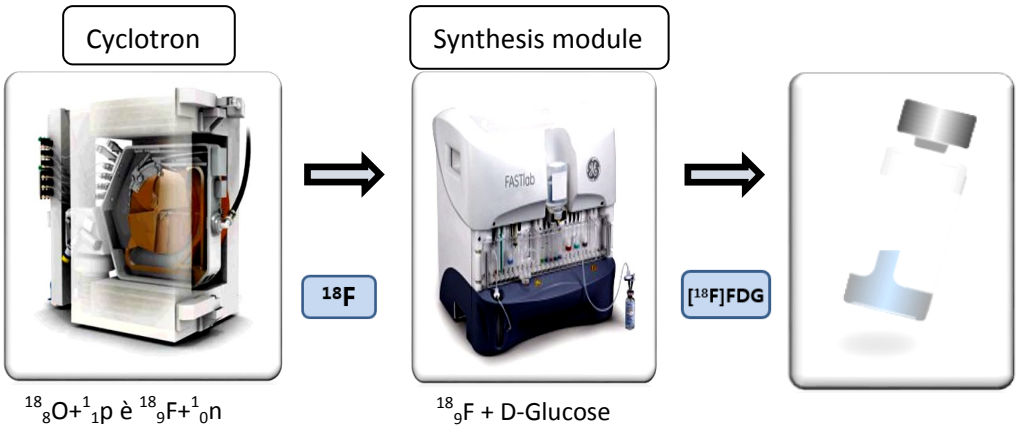

Figure 1. [18F]FDG Manufacturing process.

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RESULTS

Radiochemical Purity of [18F]FDG at various Radioactive Concentrations

The radiochemical purity of [18F]FDG increased significantly when ethanol was added at to it at different radioactive concentrations in comparison to when ethanol was not added. However, the differences in the radiochemical purity across the different ethanol concentrations tested were not significant. With no ethanol added, the KP and USP standards for radiochemical purity were met at radioactive concentrations of 100 mCi/mL and 200 mCi/mL but not at concentrations of 300 mCi/mL and 400 mCi/mL. KP (The Korean Pharmacopeia) and USP (United States Pharmacopeia) maintain well-defined standards of radiochemical purity. When ethanol concentrations of 0.1%, 0.2%, and 0.3% were added, the radiochemical purity increased at all radioactive concentrations (100 mCi/mL, 200 mCi/mL, 300 mCi/mL, and 400 mCi/mL) while meeting the KP and USP standards even after 10 hours following the EOS. We also found that the addition of ethanol increased the radiochemical purity of [18F]FDG less at lower radioactive concentrations and more at higher radioactive concentrations, suggesting that the effects of ethanol on the radiochemical purity varied according to the radioactive concentration as seen in table 1 and figure 2. The present study used gas chromatography to analyze the amount of residual ethanol generated when ethanol concentrations of 0.0%, 0.1%, 0.2%, and 0.3% were added at radioactive concentrations of 100, 200, 300, and 400mCi/㎖. The results showed that the mean residual ethanol generated was 32ppm when no ethanol was added. This is because a small amount of ethanol remained as a residual solvent in [18F]FDG radiopharmaceutical after being used as the preservative in the purification column and solvent of precursors for synthesis of acetonitrile during the preparation of [18F]FDG. When ethanol with concentrations of 0.1%, 0.2%, and 0.3% were added, the level reached up to 2,305ppm in proportion to the ethanol concentrations.

Table 1. Changes in radiochemical purity according to the amount of ethanol added to different radioactive concentrations of ^{18}F-FDG

Radioactive concentration	Ethanol concentration	0 h	2 h	4 h	6 h	8 h	10 h	t½
100 mCi/mL	0.0%	98.4%	96.4%	95.8%	95.3%	95.4%	94.4%	198 h
	0.1%	98.2%	96.9%	96.5%	96.8%	96.4%	96.4%	462 h
	0.2%	98.3%	97.1%	96.9%	96.7%	96.7%	96.4%	433 h
	0.3%	98.0%	96.9%	96.8%	96.3%	96.2%	96.5%	462 h
200 mCi/mL	0.0%	98.2%	94.8%	94.4%	93.4%	92.4%	92.3%	121 h
	0.1%	98.1%	96.8%	96.6%	95.8%	95.7%	95.6%	277 h
	0.2%	98.2%	96.7%	96.6%	96.3%	95.8%	95.8%	315 h
	0.3%	96.9%	96.8%	96.7%	96.2%	96.1%	96.2%	770 h
300 mCi/mL	0.0%	96.1%	93.4%	92.1%	91.5%	89.7%	90.5%	113 h
	0.1%	96.1%	95.3%	94.4%	94.6%	93.6%	94.7%	385 h
	0.2%	96.6%	95.8%	95.4%	95.3%	93.3%	94.8%	277 h
	0.3%	96.0%	95.7%	95.4%	94.8%	94.7%	95.4%	630 h
400 mCi/mL	0.0%	96.2%	91.1%	88.4%	86.7%	85.3%	85.7%	57 h
	0.1%	98.5%	94.8%	94.4%	94.2%	93.8%	93.8%	173 h
	0.2%	96.6%	94.9%	94.4%	94.7%	94.3%	93.9%	301 h
	0.3%	96.5%	95.5%	94.3%	94.6%	94.4%	94.0%	301 h

* t½ represents a half-life in half of the radiochemical purity of [18F] FDG radiopharmaceutical.

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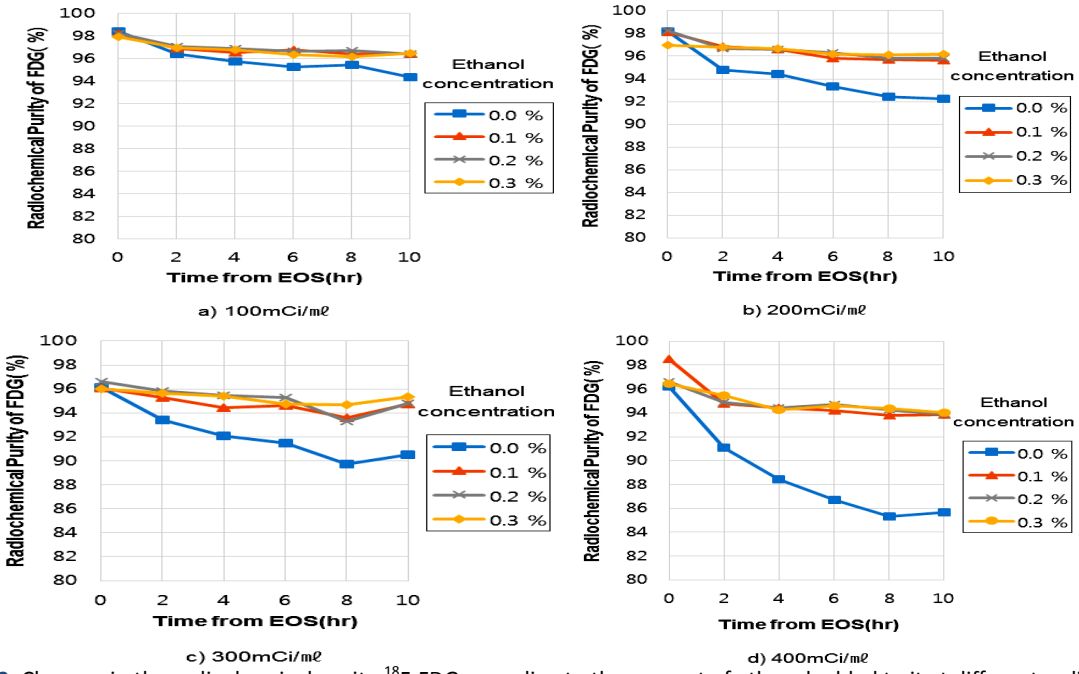

Figure 2. Changes in the radiochemical purity ^{18}F-FDG according to the amount of ethanol added to it at different radioactive concentrations.

Changes in the amount of residual ethanol generated

Using gas chromatography, the mean residual ethanol generated was found to be 32 ppm when no ethanol was added. This was because ethanol was used as the preservative in the purification column and as the solvent of the precursors for the synthesis of acetonitrile during the preparation of [^{18}F]FDG, and small amounts of ethanol probably remained as a residual solvent. When ethanol at concentrations of 0.1%, 0.2%, and 0.3% were added, the residual ethanol level reached up to 2,305 ppm in proportion to the ethanol concentrations. These levels were all below the cut-off of 5,000 ppm for ethanol (Class 3 low toxicity solvent) given in the Guidelines of the MFDS and the USP 30. To minimize the residual ethanol generated, during [^{18}F]FDG preparation, ethanol should not be added when its radioactive concentration is below 200 mCi/mL, whereas an ethanol concentration of 0.1% should be added when the radioactive concentration is above 200 mCi/mL. However, additional studies may be needed for the production of radiopharmaceuticals at radioactive concentrations that exceed 400 mCi/mL, as seen in table 2.

Table 2. Residual ethanol levels according to the amount of ethanol added at different radioactive concentrations of ^{18}F-FDG. [unit: ppm]

Radioactive concentration	Ethanol concentration	0 h	2 h	4 h	6 h	8 h	10 h
100 mCi/mL	0.0%	20	19	14	21	35	50
	0.1%	838	778	826	877	678	858
	0.2%	1373	1617	1216	1416	1535	1750
	0.3%	1856	2101	1927	2055	2101	2155
200 mCi/mL	0.0%	24	17	11	24	47	50
	0.1%	797	678	569	568	519	882
	0.2%	1384	1136	1362	994	1370	1276
	0.3%	1756	1946	2201	2180	2275	2305
300 mCi/mL	0.0%	39	41	27	25	58	34
	0.1%	537	558	604	604	449	651
	0.2%	931	1214	1132	1344	1218	1337
	0.3%	2204	2577	1656	1921	1839	2053
400 mCi/mL	0.0%	51	30	29	43	28	27
	0.1%	892	959	986	828	770	884
	0.2%	1235	1259	1351	1128	1087	1163
	0.3%	1650	1533	1535	1308	1556	1457

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DISCUSSION

The MFDS and USP 30 divide residual solvents into three classes. Class 1 residual solvents show strong toxicity or contaminate the environment and are not included as radiopharmaceuticals. Class 2 residual solvents show genotoxicity, and their use in pharmaceuticals is limited. However, class 3 residual solvents are relatively less toxic, causing less hazard to human health than Class 1 and 2 solvents; however their use is recommended with caution. Ethanol is a low toxicity solvent belonging to Class 3. A daily residual level of up to 50 mg (5000 ppm or 0.5%) of ethanol is allowed. In the present study, when no ethanol was added, the radiochemical purity standards of the KP and USP were met at radioactive concentrations of 100 mCi/mL and 200 mCi/mL, but not at 300 mCi/mL and 400 mCi/mL. Therefore, the addition of ethanol at radioactive concentrations that exceed 200 mCi/mL, during the preparation and storage of [^{18}F]FDG was unavoidable to maintain stable levels of radiochemical purity that meet the KP and USP standards. It was determined in our study that adding ethanol at the concentration of 0.1% to [^{18}F]FDG is most suitable as it generates the least residual ethanol while maintaining the radiochemical purity of [^{18}F]FDG at stable levels that meet the KP and USP standards. It was determined in our study that adding ethanol at the concentration of 0.1% to [^{18}F]FDG is most suitable as it generates the least residual ethanol while maintaining the radiochemical purity of [^{18}F]FDG at stable levels that meet the KP and USP standards. These findings were similar to the results from a study reporting that the radiochemical purity increases less when ethanol is added to lower radioactive concentrations compared to when it is added to higher radioactive concentrations because little radiolysis takes place at lower radioactive concentrations compared with those at higher radioactive concentrations [11]. The addition of ethanol increases the radiochemical purity of [^{18}F]FDG by reducing its radiolysis [3,7,13-14]. Additional studies for the production of radiopharmaceuticals at radioactive concentrations that exceed 400 mCi/mL are necessary. It is necessary to consider other aspects as well in further studies. Radioactive concentration had the greatest effect on the radiochemical purity of [18F]FDG, followed by EtOH addition and storage volume.

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***Conflicts of interest*:** *Declared none.*

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