

# Unsuspected reduced radiochemical purity of the $^{18}\text{F}$ -FDG may decrease image resolution, SUV reliability and diagnostic accuracy

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## Abstract

**Objective:** Our aim was to identify the conditions required to stably maintain the radiochemical purity of fluorine-18-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) above the Korean Pharmacology (KP) and United States Pharmacology (USP) standards for expiration time (time from the end of synthesis (EOS), 8h even at a high radioactive concentration exceeding 7.4GBq/mL. **Materials and Methods:** The changes in the radiochemical purity of  $^{18}\text{F}$ -FDG were assessed according to the changes in radioactive concentration, ethanol (EtOH) concentration, amount of water for dilution storage temperature, and storage volume. **Results:** Controlling the radioactive concentration as much as possible during the production of  $^{18}\text{F}$ -FDG is necessary to improve the radiochemical purity of  $^{18}\text{F}$ -FDG. In the production of  $^{18}\text{F}$ -FDG, a radioactive concentration <7.4GBq/mL was sufficient to maintain the radiochemical purity above the KP and USP standards for 10h after the EOS. If the radioactive concentration exceeded 7.4GBq/mL during synthesis, the addition of EtOH to  $^{18}\text{F}$ -FDG is essential to maintain the radiochemical purity above the KP and USP standards. To minimize residual solvent EtOH production, the addition of 0.1% EtOH to the  $^{18}\text{F}$ -FDG is the ideal combination. **Conclusion:** Increasing the radiochemical purity of the  $^{18}\text{F}$ -FDG increases the quality of images, the reliability of the SUV during PET scanning and consequently increases the accuracy of diagnosis. Furthermore,  $^{18}\text{F}$ -FDG can be synthesized at a high radioactive concentration in large volume, and its effective date could also be prolonged.

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## Introduction

Fluorine-18-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) radiopharmaceutical is a radioactive tracer compound of D-glucose and  $^{18}\text{F}$  radioisotope, mainly used as an injectable tracer material for positron emission tomography (PET) scanning in nuclear medicine. Its glucose metabolism has been used for the diagnosis of cancers or cerebral and myocardial diseases, and its health insurance coverage in Korea commenced in June 2006. Fluorine-18-FDG is one of the most frequently used nuclear medicinal agents worldwide [1-3].

However, massive and high radioactive concentrations of  $^{18}\text{F}$ -FDG need to be synthesized when numerous patients require PET scanning, the  $^{18}\text{F}$ -FDG manufacturing facility and the hospital are usually far apart, or if the  $^{18}\text{F}$ -FDG needs to be used for different studies. In this case, the radiochemical purity of  $^{18}\text{F}$ -FDG decreases and is sometimes even below the standards of the Korean Pharmacopeia (KP) and US Pharmacopeia (USP), which renders the agent unusable for patients [4-10]. The reduced radiochemical purity of  $^{18}\text{F}$  is due to the loss of bonds between  $^{18}\text{F}$ -FDG and  $^{18}\text{F}$  radioisotope from radiolysis. When the product has reduced purity, one may see in PET scans false bone uptake and free  $^{18}\text{F}$ . Consequently, the image resolution decreases, the reliability of SUV decreases, and the accuracy of diagnosis may be negatively affected [11, 12].

In this study, we aimed to identify the conditions required to stably maintain the radiochemical purity of  $^{18}\text{F}$ -FDG above the KP and USP standards for expiration time (time from the end of synthesis (EOS), 8h) even at a high radioactive concentration exceeding 7.4GBq/mL.

## Materials and Methods

The changes in the radiochemical purity of  $^{18}\text{F}$ -FDG were assessed according to the chan-

ges in radioactive concentration, ethanol (EtOH) concentration, amount of water for dilution, storage temperature, and storage volume. The following are the measurement standards: a) Radioactive concentration: 3.7, 7.4, 11.1, 14.8GBq/mL, b) EtOH concentration: 0.0% (0μL), 0.1% (1μL), 0.2% (2μL), and 0.3%(3μL), c) Amount of water for dilution: water for injection 0, 1, 3 and 7mL, d) Storage temperatures: 3, 20, and 40°C (cool, actual storage, and relatively high temperatures, respectively), e) Storage volume: 1, 2, and 4mL.

Fluorine-18 was produced using a cyclotron with proton acceleration energy of 16.5MeV (GE Healthcare, Model; PETtrace). Fluorine-18-FDG was synthesized from  $^{18}\text{F}$  using a synthesis module equipment (Siemens Healthcare USA; Model name, Explora FDG4). Radioactive concentrations of 58.5, 122.8, 179.1 and 239.4GBq/16mL were used for the production because  $^{18}\text{F}$ -FDG exhibits differences in radioactive concentration based on the EtOH concentration, amount of water for dilution, storage temperature, and storage volume. There were four different radioactive concentrations for the radiopharmaceutical; 3.7GBq/mL (actual radioactive concentration of 3.7GBq/mL, relative error of 0%), 7.4GBq/mL (actual radioactive concentration of 7.7GBq/mL, relative error of 4%), 11.1GBq/mL (actual radioactive concentration of 11.2GBq/mL, relative error of 1%), and 14.8 GBq/mL (actual radioactive concentration of 14.9GBq/mL, relative error of 1%). Radioactive concentrations were measured using a radioisotope calibrator (dose calibrator; Model, CRC-ULTRA, CAPINTEC). Ethanol volume was 1L (99.9% purity, OCI). Water used was water for injection, stored in a refrigerator (Model, SRL358US, JISICO). The refrigerator temperature was measured using a digital thermostat (Model, 174H; Testo). A dry oven (Model name, CF18T, COMECER) was also used, and its temperature was measured using another thermostat (Model name, 176T4, Testo). Vials used in the experiments (sterile vacuum vial 10 and 25mL; Huayi Isotopes) were manufactured under a Good Manufacturing Practices (GMP) environment. The pH level was measured using pH paper (Model name, Universal Indicator Strips, pH 0-14; JTP), and the residual solvent ethanol was measured using gas chromatography (Model name, YL-6100GC; YL Instruments). The above information is represented in Table 1.

## Results

A decrease in radioactive concentration significantly increased the radiochemical purity. Based on the KP and USP standards, 3.7 and 7.4 but not 11.1 and 14.8GBq/mL concentrations were unsuitable. The effect of radioactive concentration on radiochemical purity exhibited clear changes in Figure 1.

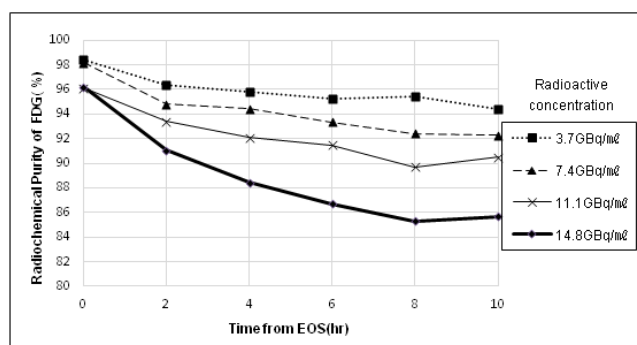
When EtOH was added, radiochemical purity was significantly increased. Changes in the added EtOH concentrations (0.1%, 0.2%, and 0.3%) had no significant effect on the radiochemical purity. In the absence of EtOH, 3.7 and 7.4 but not 11.1 and 14.8GBq/mL were suitable concentrations based on KP and USP standards. However, with EtOH at diffe-

rent concentrations (0.1%, 0.2%, and 0.3%), the radiochemical purity was improved, and all radioactive concentrations (3.7, 7.4, 11.1 and 14.8GBq/mL) were suitable based on the KP and USP standards in Figure 2.

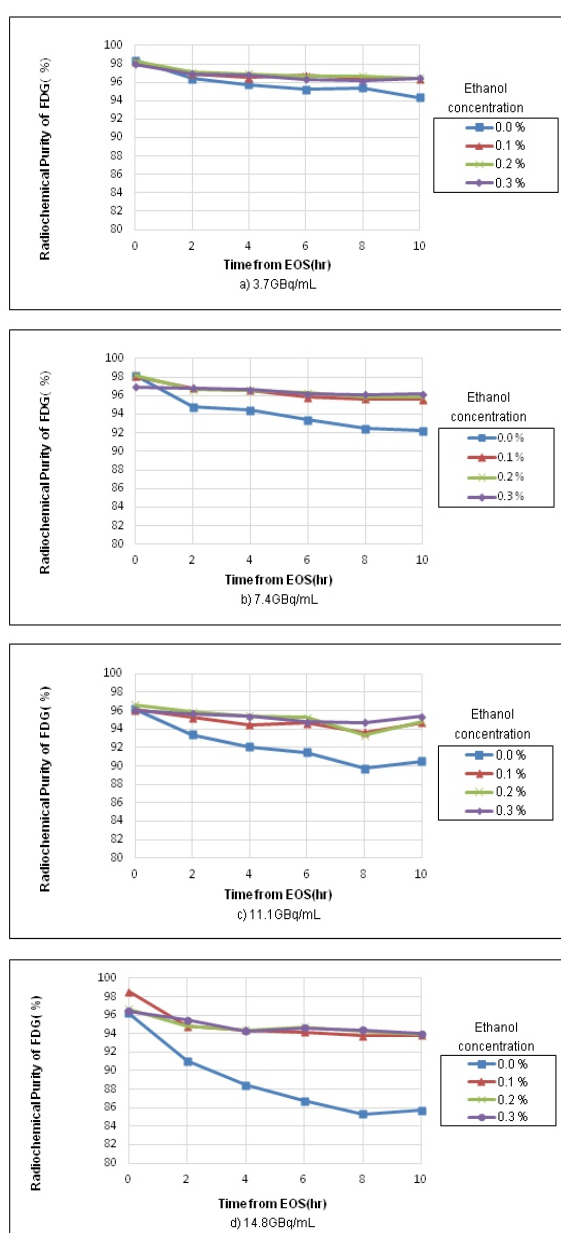
**Table 1.** Experimental methods for different experimental purposes.

Purpose	Method
<b>Effects of radioactive concentration on radiochemical purity</b>	Assessment of radiochemical purity at different radioactive concentrations of , 3.7, 7.4, 11.1 and 14.8GBq/mL Control group: radioactive concentration of 14.8GBq/mL Experimental group: radioactive concentrations of 3.7, 7.4, and 11.1GBq/mL
<b>Effects of EtOH concentration on radiochemical purity</b>	Assessment of radiochemical purity based on changes in EtOH concentrations of 0.0% (0μL), 0.1% (1μL), 0.2% (2μL), or 0.3% (3μL) at radioactive concentrations of 3.7, 7.4, 11.1 and 14.8GBq/mL Control group: EtOH concentration of 0.0% Experimental group: EtOH concentrations of 0.1, 0.2, and 0.3%
<b>Effects of diluent (water) amount on radiochemical purity</b>	Assessment of radiochemical purity based on changes in diluent (water for injection) amount of 0, 1, 3, or 7mL at radioactive concentrations of 3.7, 7.4, 11.1 and 14.8GBq/mL Control group: Diluent amount was 0mL Experimental group: Diluent amounts were 1, 3, and 7mL
<b>Effects of storage temperature on radiochemical purity</b>	Assessment of radiochemical purity based on changes in storage temperatures of 3, 20, or 40°C at radioactive concentrations of 3.7, 7.4, 11.1 and 14.8GBq/mL Control group: Storage temperature of 20°C (actual storage temperature) Experimental group: Storage temperatures of 3°C (cool) and 40°C (high)
<b>Effects of storage volume on radiochemical purity</b>	Assessment of radiochemical purity based on changes in storage volumes of 1, 2, or 4 mL at radioactive concentrations of 3.7, 7.4, 11.1 and 14.8GBq/mL Control group: Storage volume of 1mL Experimental group: Storage volume of 2 and 4mL

*Common experimental method:*  $^{18}\text{F}$ -FDG was synthesized using a radio TLC scanner. After the end of synthesis (EOS), radiochemical purity was measured at the interval of 2h for 10h

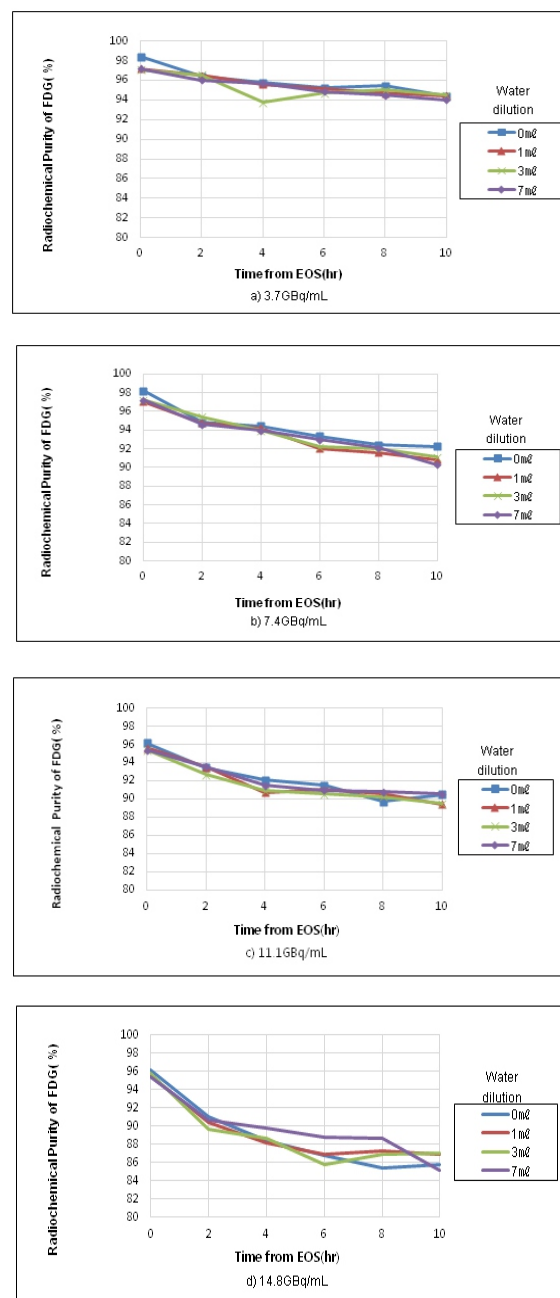


**Figure 1.** Radiochemical purity-time profiles at different radioactive concentrations. \*Immediately after the end of synthesis (EOS, 0h), radiochemical purity was high at all concentrations: 98.4, 98.2, 96.1, and 96.2% at 3.7, 7.4, 11.1 and 14.8GBq/mL, respectively. However, the radiolysis steadily increased with time and, consequently, radiochemical purity steadily decreased. Then, 10h after the EOS, radiochemical purity was much lower at all concentrations: 94.4, 92.3, 90.5, and 85.7% at 3.7, 7.4, 11.1 and 14.8GBq/mL, respectively.



**Figure 2.** Radiochemical purity-time profiles at different ethanol (EtOH) concentrations.

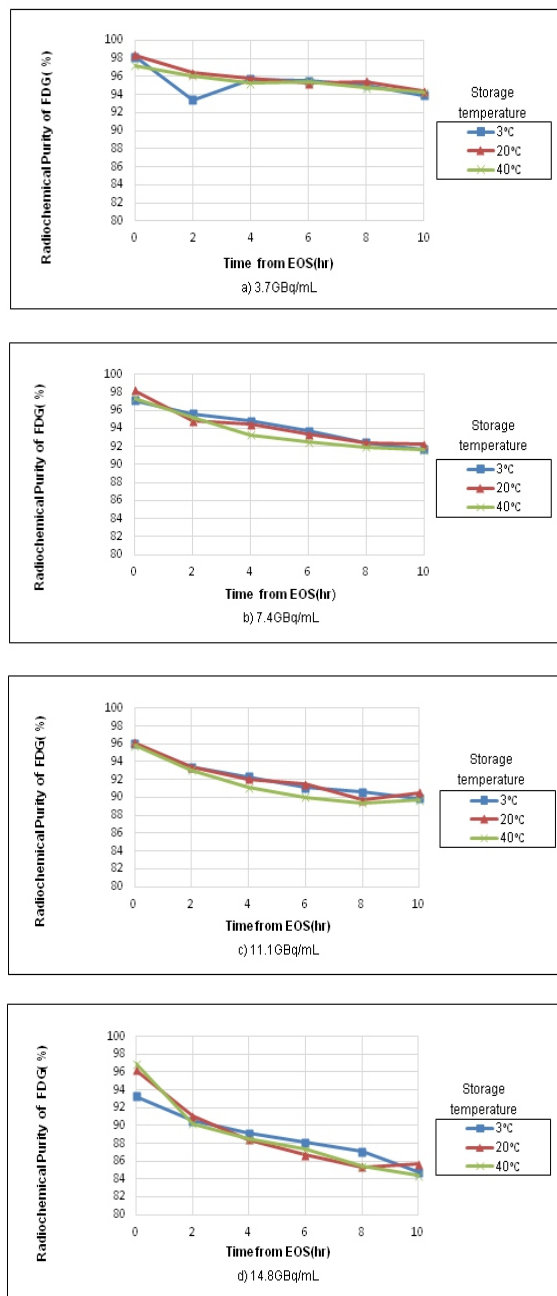
Water as a diluent did not have significant effects on the radiochemical purity, and changes in the amount of water diluent (0, 1, 3, or 7mL) also had no significant effect. In the absence of added water, 3.7 and 7.4 but not 11.1 and 14.8 GBq/mL were suitable based on the KP and USP standards. There was no significant improvement in radiochemical purity at all water diluent volumes (1, 3, or 7mL), and 3.7 and 7.4 but not 11.1 and 14.8GBq/mL were suitable based on the KP and USP standards in Figure 3.



**Figure 3.** Radiochemical purity-time profiles with different volume of water for dilution.

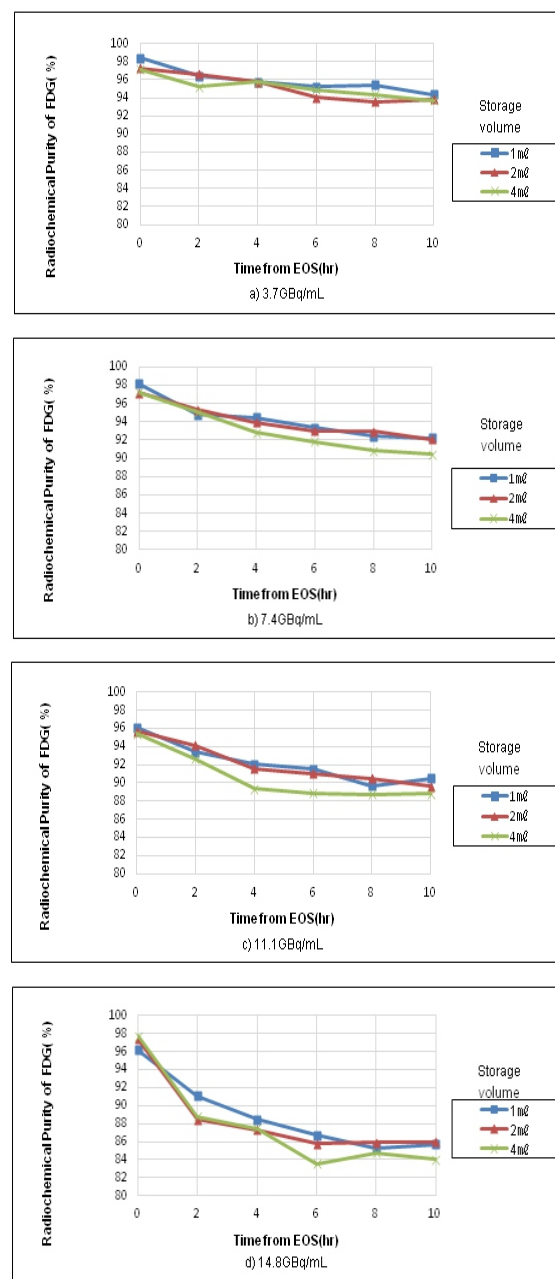
Storage temperature did not have significant effect on radiochemical purity, and changes in the storage temperature (3, 20, or 40°C) also had no significant effect. When stored at 20°C (the actual storage temperature of  $^{18}\text{F}$ -FDG), 3.7 and

7.4GBq/mL were suitable, whereas 11.1 and 14.8GBq/mL were unsuitable based on the standards of KP and USP. At storage temperatures of 3°C or 40°C, there was no significant improvement in radiochemical purity. Furthermore, 3.7 and 7.4 but not 11.1 and 14.8GBq/mL are based on the KP and USP standard in Figure 4.



**Figure 4.** Radiochemical purity-time profiles at different storage temperatures.

For storage volume of 1mL, 3.7 and 7.4 but not 11.1 and 14.8GBq/mL were unsuitable based on the KP and USP standards and a similar trend was observed at storage volumes of 2 and 4mL. However, increasing the storage volume from 1 to 2 and, subsequently 4mL, steadily decreased the radiochemical purity. We found that storage volume had a significant effect on the radiochemical purity in Figure 5.



**Figure 5.** Radiochemical purity-time profiles at different storage volumes.

## Discussion

Radioactive concentration had the greatest effect on the radiochemical purity of  $^{18}\text{F}$ -FDG, followed by EtOH addition and storage volume. On the other hand, the water diluent amount and storage temperature had no significant effect on the radiochemical purity. The results of this study show that controlling the radioactive concentration as much as possible during the production of  $^{18}\text{F}$ -FDG is necessary to improve the radiochemical purity of  $^{18}\text{F}$ -FDG. In the production of  $^{18}\text{F}$ -FDG, a radioactive concentration <7.4GBq/mL was sufficient to maintain the radiochemical purity above the KP and USP standards for 10h after the EOS. If the radioactive concentration exceeded 7.4GBq/mL during the syn-

thesis, the addition of EtOH to  $^{18}\text{F}$ -FDG radiopharmaceutical is essential to maintain the radiochemical purity above the KP and USP standards. The addition of EtOH at different concentrations (0.1%, 0.2%, or 0.3%) was sufficient to stably maintain the radiochemical purity above the KP and USP standards even at high radioactive concentrations exceeding 7.4GBq/mL for 10h from the EOS. To minimize residual solvent EtOH production, the addition of 0.1% EtOH to the  $^{18}\text{F}$ -FDG radiopharmaceutical is the ideal combination.

*In conclusion*, implementing the findings of this study during the synthesis or storage of  $^{18}\text{F}$ -FDG, could improve the radiochemical purity and ensure its maintenance above the KP and USP standards for 10h after the EOS even at high radioactive concentrations exceeding 7.4GBq/mL. Increasing the radiochemical purity of the  $^{18}\text{F}$ -FDG increases the quality of images and reliability of the SUV during PET scanning, consequently increasing the accuracy of diagnosis. Furthermore,  $^{18}\text{F}$ -FDG can be synthesized at a high radioactive concentration in large volume, and its effective date could also be prolonged.

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