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Preparation and stability of ethanol-free solution of [^{18}F]florbetapir ([^{18}F]AV-45) for positron emission tomography amyloid imaging

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We have developed an ethanol-free formulation method of [^{18}F]florbetapir ([^{18}F]AV-45) using a commercially available automated JFE multi-purpose synthesizer. We have also evaluated the radiochemical stability in an ethanol-free solution of [^{18}F]AV-45 under visible light irradiation and dark conditions by comparison with a conventional 10% ethanol solution of [^{18}F]AV-45. [^{18}F]AV-45 was obtained with a radiochemical yield of 55.1 ± 2.2% (decay-corrected to end of bombardment), specific activity of 591.6 ± 90.3 GBq/μmol and radiochemical purity of >99% within a total synthesis time of about 73 min. The radiochemical purity of [^{18}F]AV-45 formulated by dissolving the ethanol-free solution was found to decrease as a function of the period of exposure to visible light. In contrast, the visible light photolysis could be suppressed by adding 10% ethanol to the formulation or by avoiding exposure to visible light. In the radiosynthesis of [^{18}F]AV-45 formulated by dissolving the ethanol-free solution, [^{18}F]AV-45 could be obtained with high radiochemical purity and high stability by avoiding exposure to visible light. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: [^{18}F]AV-45; β-amyloid; Alzheimer's disease; automated synthesis; disposable components

Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disorder with a relentless progression. The β-amyloid protein (Aβ) is believed to be the key mediator of AD pathology.[1–3] *In vivo* positron emission tomography (PET) imaging of Aβ may improve both early detection of AD and efficacy assessment of new treatments for AD.

Recently, various Aβ imaging tracers, such as [^{11}C]PIB (2-[4-[(^{11}C)methylamino]phenyl]benzothiazole-6-ol),[4,5] [^{11}C]BF-227 (2-[2-[2-[[(^{11}C)methyl]methylamino]-5-thiazolyl]ethenyl]-6-(2-fluoroethoxy)benzoxazole),[6,7] [^{11}C]AZD2184 (2-[6-[(^{11}C)methylamino]-3-pyridyl]benzothiazol-6-ol),[8,9] [^{11}C]SB13 (4′-[(^{11}C)methylamino]stilbene-4-ol),[10,11] [^{18}F]FDDNP (2-[1-[6-[[2-(^{18}F)fluoroethyl]methylamino]-2-naphthyl]ethylidene]malononitrile),[12,13] [^{18}F]flumetamol ([^{18}F]GE-067; 2-[3-(^{18}F)fluoro-4-methylaminophenyl]benzothiazole-6-ol),[14,15] [^{18}F]FACT (6-[2-(^{18}F)fluoroethoxy]-2-[2-[2-[dimethylamino]-5-thiazolyl]ethenyl]benzoxazole),[16] [^{18}F]florbetaben ([^{18}F]BAY 94-9172; 4-[4-[2-[2-[2-(^{18}F)fluoroethoxy]ethoxy]ethoxy]styryl]-*N*-methylaniline),[17,18] and [^{18}F]florbetapir ([^{18}F]AV-45; (*E*)-2-[2-[2-[2-(^{18}F)fluoroethoxy]ethoxy]ethoxy]-5-[4-methylaminostyryl]pyridine),[19–24] have been developed (Figure 1).

Among them, ^{11}C-labeled Pittsburg compound B ([^{11}C]PIB), a derivative of thioflavin T, is the most widely used PET tracer for assessing Aβ in the brain.[4,5] However, the short physical half-life of ^{11}C (20.4 min) limits the use of [^{11}C]PIB to PET centers equipped with an on-site cyclotron. This limitation may be overcome by radiolabeling with ^{18}F, which has a longer half-life (109.8 min) and thus may provide an Aβ PET tracer that is useful for widespread clinical applications.

[^{18}F]AV-45 is a new ^{18}F-labeled tracer capable of selectively binding to Aβ plaques. It displays high binding affinity and specificity to Aβ plaques (K_d = 3.72 ± 0.30 nM).[22,23] Camus *et al*. reported

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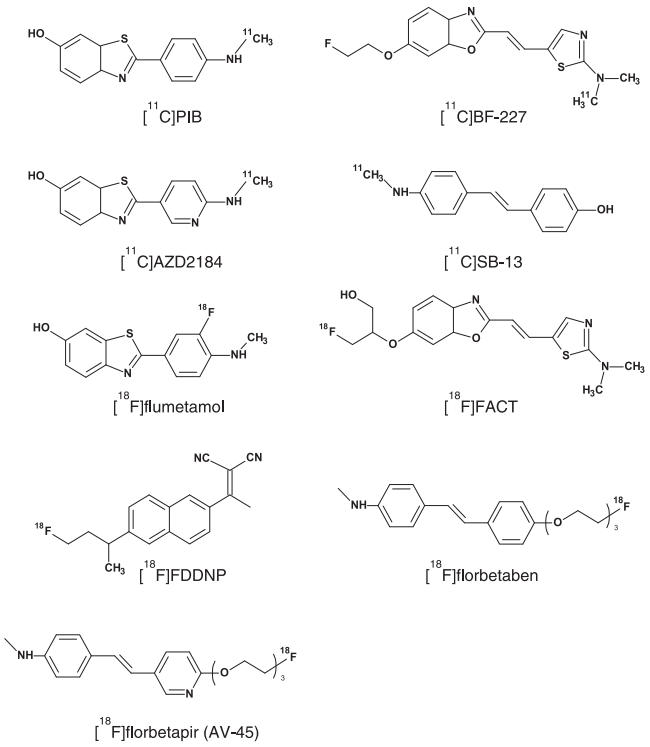

Figure 1. Structures of reported Aβ PET tracers in clinical trials.

that [^{18}F]AV-45 PET is a safe and suitable biomarker for AD capable of being used routinely in a clinical environment.[24]

In the formulation of [^{18}F]AV-45, the final injectable solution is generally provided as a 5–10% ethanol–saline solution.[19–24] ^{18}F-labeled tracers formulated by dissolving a 10% ethanol–saline solution were used at some overseas PET centers.[25–27] However, because many Japanese are genetically light drinkers and we are concerned about possible side effects of ethanol, it is difficult for us to use ^{18}F-labeled tracers formulated by dissolving 10% ethanol–saline solution in clinical studies. Approximately, half of the Japanese have an inherited deficiency of aldehyde dehydrogenase 2 (ALDH2) activity.[28] People with the mutated ALDH2 allele can become very ill (disulfiram-like reaction) after exposure to small amounts of ethanol.[29] For example, [^{18}F]FLT was purified by preparative HPLC using the 10% ethanol–saline solution as the mobile phase and the HPLC fraction containing [^{18}F]FLT was collected directly to give the final product.[30] Instead, in our laboratory, the HPLC fraction containing [^{18}F]FLT was evaporated in vacuo with a rotary evaporator and then the residue was dissolved in saline to give the final product.

Morais *et al.* reported that the *E-Z* isomerization of fluorinated styryl benzazoles as Aβ tracers was induced by exposure to visible light.[31] For example, because *Z*-isomer of [^{11}C]BF-227 was generated by exposure to visible light, the formulation and quality control of [^{11}C]BF-227 were performed under dark conditions.

In this study, we established an ethanol-free formulation method of [^{18}F]AV45 and also evaluated the radiochemical stability in an ethanol-free solution of [^{18}F]AV-45 by comparison with the conventional 10% ethanol solution of [^{18}F]AV-45.

Results and discussion

Automated synthesis of [^{18}F]AV-45

The automated synthesis of [^{18}F]AV-45 was performed as described in Figure 2.

As shown in Table 1, we examined the effect of the reaction solvent on the radiochemical yield of [^{18}F]AV-45. At the fluorination temperature of 120 °C, the use of MeCN as the reaction solvent gave higher radiochemical yields than the use of dimethylsulfoxide (DMSO). The preparative HPLC chromatograms of the crude product are shown in Figure 3. Using MeCN, many chemical impurities were generated and some co-eluted with [^{18}F]AV-45. Therefore, we decided to use DMSO as the reaction solvent in this study.

Then, we examined the effect of the reaction temperature on the radiochemical yield of [^{18}F]AV-45. The [^{18}F]fluorination reactions were performed with 1 mg of the precursor, (*E*)-2-[2-[2-[5-[4-[*tert*-butoxycarbonyl[methyl]amino]styryl]pyridine-2-yloxy] ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (AV-105), in DMSO (1.0 mL) at 120, 140, 160, 180 or 200 °C for 10 min. The results are shown in Table 1. The radiochemical yield of [^{18}F]AV-45 depended on the reaction temperature. At the reaction temperature of 180 °C, we could achieve the best radiochemical yield of 55.1 ± 2.2% (decay-corrected to end of bombardment). [^{18}F]AV-45 has been successfully synthesized using a JFE multipurpose synthesizer (Figure 4(A)). In a preliminary study, we measured the reaction mixture by submerging a thermocouple probe in the reaction solution. The internal reaction temperature was 30 °C lower than the temperature (180 °C) that was set and indicated by the synthesis module. Therefore, the best reaction temperature may be lower than 180 °C.

Quality control of [^{18}F]AV-45

The retention time of [^{18}F]AV-45 was 3.4 min.

After proton bombardment (12 MeV, 35 μA) of [^{18}O]H_2O for 20 min, the radioactivity and the specific activity of [^{18}F]AV-45 were 6.2 ± 0.6 GBq/vial and 591.6 ± 90.3 GBq/μmol, respectively. The radiochemical purity determined with HPLC was >99%. The pH of [^{18}F]AV-45 ranged from 6.1 to 6.3. Residual solvents such as DMSO and MeCN were below the quantitation limit (<0.05 ppm). Additionally, in formulation method A (ethanol-free solution), the EtOH concentration was 0.005–0.014%.

Stability of [^{18}F]AV-45

As shown in Figure 5(A), in formulation method A (ethanol-free solution), the radiochemical purity of [^{18}F]AV-45 formulated by dissolving the ethanol-free solution decreased to 25.1 ± 1.3% when the solution was stored in a clear glass vial but remained at 97.7 ± 0.7% when the solution was stored in the amber glass vial during 6 h after the end of synthesis (EOS). The radiochemical purity of [^{18}F]AV-45 was found to decrease mainly because of

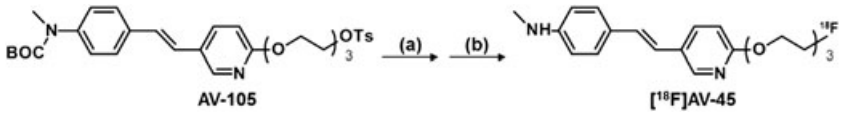

Figure 2. Reaction scheme for the synthesis of [^{18}F]AV-45. (a) [K^+/K.222]$^{18}F^-$, DMSO, 180 °C, 10 min; (b) 1 M HCl, 120 °C, 5 min.

Table 1. Effect of the reaction temperature on the radiochemical yield of [^{18}F]AV-

	Radiochemical yield (%) *($n = 3$)				
	Temperature (°C)				
Reaction solvent	120	140	160	180	200
MeCN	53.7 ± 2.4				
DMSO	42.0 ± 2.8	47.4 ± 2.1	53.1 ± 2.0	55.1 ± 2.2	48.8 ± 3.1

*Ethanol-free [^{18}F]AV-45 injection yield decay-corrected.

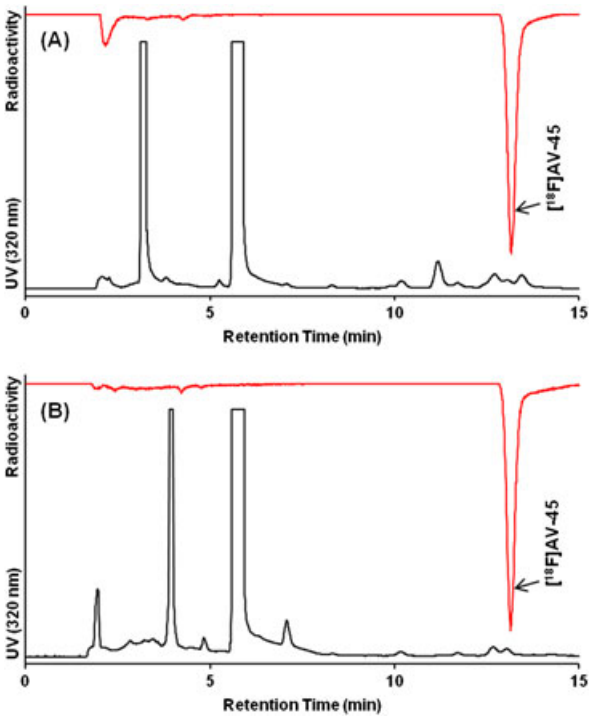

Figure 3. Preparative HPLC purification of [^{18}F]AV-45 (column: COSMOSIL Cholester, mobile phase: MeCN/50 mM $AcONH_4$-AcOH buffer (pH 4.6)/25% ascorbic acid injection = 260/238/2, flow rate: 6.0 mL/min, wavelength: 320 nm). (A) The use of MeCN as the reaction solvent; (B) the use of DMSO as the reaction solvent.

the increase in the radiochemical impurity with the retention time of 2.9 min. The generation of the radiochemical impurity increased rapidly with the exposure time of visible light (Figure 5(B)). After 5 and 10-min exposure, the radiochemical impurities were 7.7% and 28.6%, respectively. From these results, it was suggested as well as [^{11}C]BF-227 that *E*-isomer of [^{18}F]AV-45 might be isomerized to *Z*-isomer by exposure to visible light. However, because we did not have a reference standard of (*Z*)-AV-45, we could not identify whether the peak at the retention time of 2.9 min was (*Z*)-[^{18}F]AV-45. Therefore, the formulation and quality control of [^{18}F]AV-45 were performed under dark conditions. In addition, if necessary, features such as solvent evaporation were confirmed using handheld LED light (590 nm). Using this handheld LED light for only a short time, the photolysis of [^{18}F]AV-45 could be prevented.

As shown in Figure 5(A), in formulation method B (10% ethanol solution), the radiochemical purities of [^{18}F]AV-45 formulated by dissolving the 10% ethanol solution remained 92.5 ± 2.4% in the clear glass vial and 97.8 ± 1.2% in the amber glass vial at 6 h after EOS. As a result, the photolysis of [^{18}F]AV-45 could be suppressed by adding 10% ethanol. Then, the effect of ethanol concentrations on the radiochemical stability of [^{18}F]AV-45 was evaluated. At ethanol concentrations of 5% and 7.5%, the radiochemical purity of [^{18}F]AV-45 remained 90.7 ± 1.3% and 92.8 ± 2.1% in the clear glass vial at 6 h after EOS, respectively. Therefore, under exposure to visible light, the radiochemical purity of [^{18}F]AV-45 formulated by dissolving the 5–10% ethanol solution was more than 90% over a period of at least 6 h after EOS.

Furthermore, in the presence of sodium ascorbate, the radiolysis of [^{18}F]AV-45 could be prevented in all samples over a period of at least 6 h after EOS.

Materials and methods

The precursor, (*E*)-2-[2-[2-[5-[4-[*tert*-butoxycarbonyl[methyl]amino] styryl]pyridine-2-yloxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (AV-105), and the reference standard, (*E*)-2-[2-[2-[2-fluoroethoxy] ethoxy]ethoxy]-5-[4-methylaminostyryl]pyridine (AV-45), were provided by Avid Radiopharmaceuticals, Inc. (Philadelphia, USA). Kryptofix 222 (K.222) and potassium carbonate (K_2CO_3) were purchased from Merck (Darmstadt, Germany). Anhydrous acetonitrile (MeCN), anhydrous methanol (MeOH) and anhydrous DMSO were purchased from Wako Pure Chemical Industries (Osaka, Japan). Pharmaceutical grades of 25% ascorbic acid injection, polysorbate 80 (Tween 80), anhydrous ethanol (EtOH), saline, ethanol for disinfection, and sterile water for injection were used. All chemicals were obtained from commercial sources and used without further purification. Sep-pak Light Accell Plus QMA Carbonate cartridge (QMA cartridge) and Sep-pak Plus tC18 cartridge (tC18 cartridge) were purchased from Waters (Milford, USA). The QMA and tC18 cartridges were washed with 5 mL of ethanol for disinfection and washed with 10 mL of sterile water for injection prior to use.

Production of [^{18}F]fluoride

No-carrier-added [^{18}F]fluoride ([^{18}F]F^-) was obtained through the nuclear reaction of ^{18}O(p,n)^{18}F by irradiation of ^{18}O-enriched water ([^{18}O]H_2O) target (>98% isotopic enrichment; Taiyo Nippon Sanso, Tokyo, Japan) with a 12 MeV proton beam in a CYPRIS HM-12S self-shielded cyclotron ([^{18}O]H_2O volume: 2.0 mL; Sumitomo Heavy Industry, Tokyo, Japan) at the RIKEN Center for Molecular Imaging Science.

Synthesis module

The fully automated synthesis of [^{18}F]AV-45 was carried out using a JFE multi-purpose synthesizer (JFE Technos, Yokohama, Japan), which was connected through an injection unit to an HPLC purification unit and a formulation unit. The HPLC purification unit

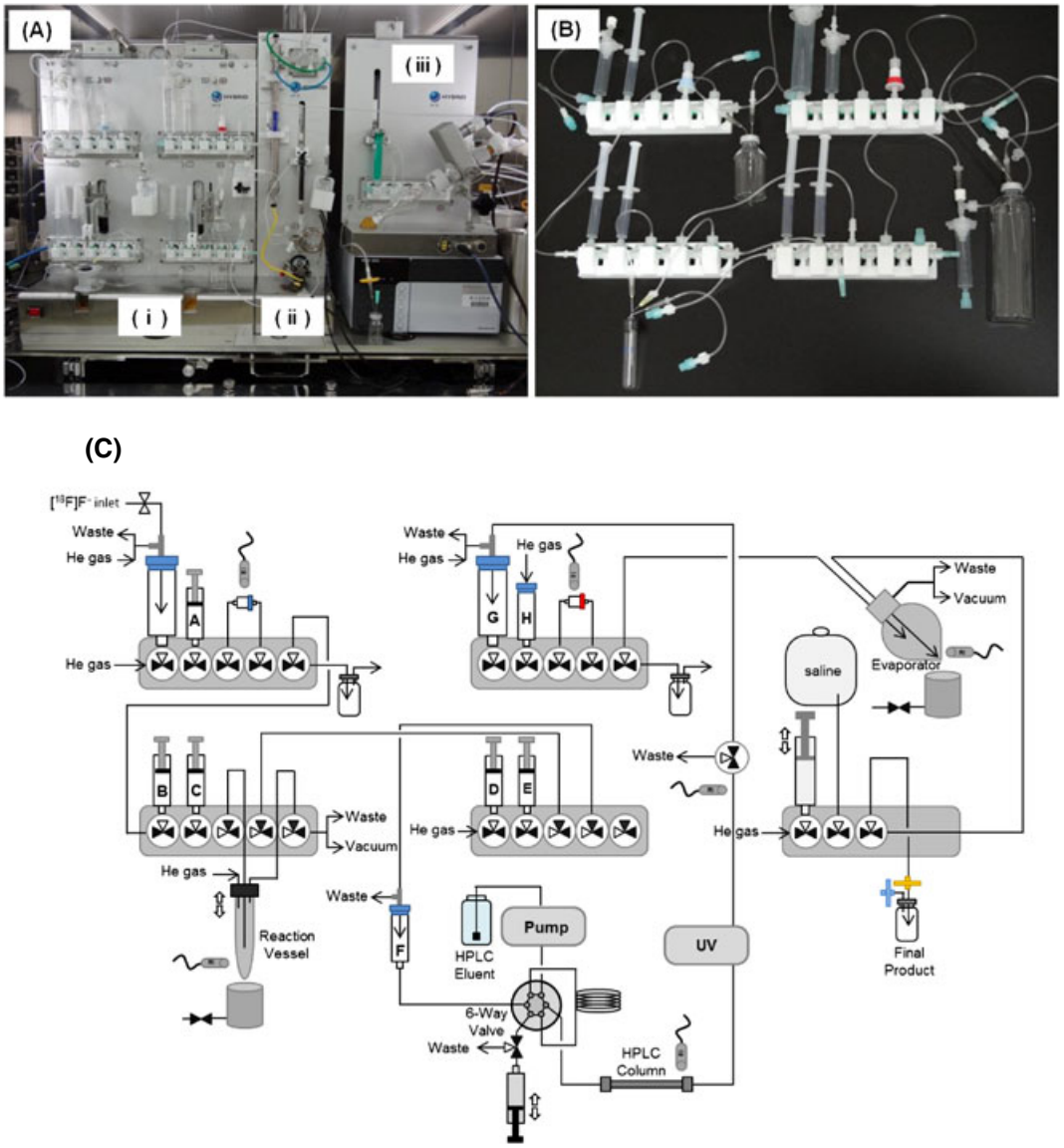

Figure 4. (A) JFE multi-purpose synthesizer. (i) Main synthesis unit; (ii) HPLC injector unit; and (iii) formulation unit. (B) Fluorination kit combining commercially available disposable components. (C) Schematic diagram of the synthesis of [^{18}F]AV-45 by the ethanol-free formulation method. (a) K.222 and K_2CO_3 in MeOH/H_2O (96/4 v/v); (b) anhydrous MeCN; (c) AV-105 in anhydrous DMSO; (d) 1 M HCl; (e) 3 M AcONa; (f) 25% ascorbic acid injection; (g) 25% ascorbic acid injection in sterile water for injection; and (h) anhydrous EtOH.

consisted of a pump (LC-20AB; Shimadzu, Kyoto, Japan), a UV detector (SPD-20A; Shimadzu), a column (COSMOSIL Cholester, 10 mm inner diameter (id) × 250 mm, 5 μm; Nacalai Tesque, Kyoto, Japan), and a NaI(Tl) radioactivity detector (Oyokoken, Tokyo, Japan) (Figure 4(A)). The sequence program of the whole system, including main synthesis unit, HPLC injection unit, HPLC purification unit and formulation unit, was modified to reflect reaction conditions optimized by automated experiments.

Preparation of [^{18}F]fluorination kit

Polybutadiene tube (1.1 mm id × 2.1 mm outer diameter (od); top, Tokyo, Japan), polypropylene 3-way stop-cock (top), syringe needles (Termo, Tokyo, Japan), and luer cap for infusion (termo) were used as medical disposable products. Polypropylene syringes sterilized using ethylene oxide gas (Henke Sass Wolf, Tuttlingen, Germany) were used as research disposable products. Butyl rubber septum (Maruemu, Osaka, Japan), screw-top cap (Nichiden-rika Glass, Hyogo, Japan), and polypropylene fittings (Value Plastics, Fort Collins, USA) were sterilized using a steam autoclave. The reaction vessel (13 mm od × 65 mm length, 4 mL; Systech, Tokyo, Japan) was sterilized using dry heat. As shown in Figure 4(B), these products were combined, and [^{18}F]fluorination kit was prepared.

Automated synthesis of [^{18}F]AV-45

Before starting synthesis, K.222 (3.8 mg) and K_2CO_3 (0.7 mg) in MeOH-H_2O (96/4 v/v; 1.0 mL), anhydrous MeCN (1.5 mL), AV-105 (1 mg) in anhydrous DMSO (1.0 mL), 1 M hydrochloric acid (HCl) (1.0 mL), 3 M sodium acetate (AcONa) (1.0 mL), 25% ascorbic acid injection (0.1 mL), 25% ascorbic acid injection (0.4 mL) in sterile water for injection (20 mL), and anhydrous EtOH (1.0 mL) were contained in reservoirs (a–h) in the synthesis module, respectively. Additionally, 25% ascorbic acid injection (0.1 mL) and Tween 80-EtOH (1/4 v/v; 375 μL) were injected into a rotary evaporator flask (Figure 4(C)) in the synthesis module. The automated

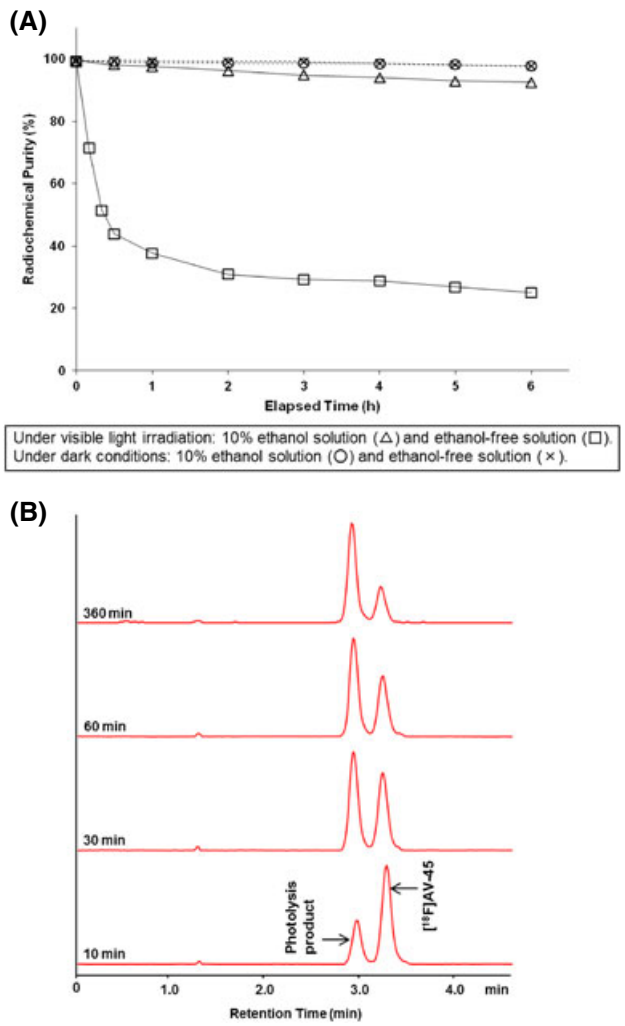

Figure 5. (A) Effect of the formulation solvent on the radiochemical stability of [^{18}F]AV-45 under visible light irradiation and dark conditions. (B) Radioactivity chromatogram of [^{18}F]AV-45 in the ethanol-free solution after the different exposure times to visible light (10, 30, 60, and 360 min).

synthesis of [^{18}F]AV-45 was performed according to the synthesis scheme (Figure 2).

No-carrier-added [^{18}F]F^- (17–20 GBq) from the cyclotron was isolated from [^{18}O]H_2O by trapping on a QMA cartridge and eluted with a mixture of K.222 (3.8 mg) and K_2CO_3 (0.7 mg) in MeOH-H_2O (96/4 v/v; 1.0 mL) into a reaction vessel. The [^{18}F]F^- solution was evaporated under a vacuum and N_2 gas flow at 130 °C. The residue was dried by azeotropic evaporation with anhydrous MeCN (2 × 0.5 mL) to ensure anhydrous reaction conditions for fluorine labeling. The precursor, AV-105 (1 mg), dissolved in anhydrous DMSO (1.0 mL), was added to the reaction vessel and heated at 180 °C for 10 min. After [^{18}F]fluorination, the reaction mixture was cooled to 50 °C and 1 M HCl (1.0 mL) was added to the reaction vessel and heated at 120 °C for 5 min owing to the hydrolysis of protecting groups. For neutralization of the reaction mixture, the reaction mixture was cooled to room temperature and 3 M AcONa (1.0 mL) was added to the reaction vessel. The reaction mixture was transferred to an HPLC reservoir containing 25% ascorbic acid injection (0.1 mL). Then, the reaction mixture in the HPLC reservoir was introduced into a 5-mL sample loop of a 6-way HPLC injector valve (C2-1006E; VICI AG International, Schenkon, Switzerland) with a syringe pump. The injector valve was turned on and the reaction mixture was injected onto the HPLC column (COSMOSIL Cholester, 10 mm id × 250 mm length, 5 μm; Nacalai Tesque, mobile phase: MeCN/50 mM $AcONH_4$-AcOH buffer (pH 4.6)/25% ascorbic acid injection = 260/238/2, flow rate: 6.0 mL/min, wavelength: 320 nm). The HPLC fraction containing the purified [^{18}F]AV-45 (retention time = 13.2 min) was collected into a dilution reservoir containing sterile water for injection (20 mL) and 25% ascorbic acid injection (0.4 mL). The mixture solution was passed through a tC18 cartridge. Henceforth, the formulation of [^{18}F]AV-45 was performed under dark conditions.

Formulation of [^{18}F]AV-45

Formulation method A (ethanol-free solution)

After the tC18 cartridge was dried under N_2 gas flow, the trapped [^{18}F]AV-45 on tC18 cartridge was eluted with anhydrous EtOH (2.0 mL) into a rotary evaporator flask containing 25% ascorbic acid injection (0.1 mL) and Tween 80-EtOH (1/4 v/v; 375 μL). The solution was evaporated under a vacuum at 150 °C and the residue was dissolved in saline (10 mL). The solution was passed through a 0.22 μm sterile filter (Medical Millex-GV; Millipore) into a sterile dose vial.

Formulation method B (10% ethanol solution)

After the tC18 cartridge was washed with sterile water for injection (10 mL) containing 25% ascorbic acid injection (0.2 mL), the trapped [^{18}F]AV-45 on tC18 cartridge was eluted with anhydrous EtOH (1.0 mL), followed by saline (4.0 mL), into a collection reservoir containing saline (5.0 mL) and 25% ascorbic acid injection (0.1 mL). The solution was passed through a 0.22 μm sterile filter (Medical Millex-GV; Millipore, Billerica, MA, USA) into a sterile dose vial.

Quality control of [^{18}F]AV-45

The radioactivity of the final product was measured with a dose calibrator (Dose calibrator CRC-25R; Capintec, Ramsey, USA).

The chemical impurities, radiochemical purity, and specific radioactivity were measured with a Shimadzu prominence comprehensive HPLC system that consisted of a system controller (CBM-20A), a pump (LC-20AB), a degasser (DGU-20A_3), a photodiode array detector (SPD-M20A), a column oven (CTO-20 AC), a sample injector valve (7725i; Rheodyne, Rohnert Park, USA) with a 5 μL loop, and a NaI(Tl) radioactivity detector (US-3000; Universal Giken, Kanagawa, Japan). [^{18}F]AV-45 was analyzed using an analytical reversed phase column (XBridge RP_{18}, 3.0 mm id × 50 mm length, 2.5 μm; Waters) with MeCN-H_2O (95/5 v/v)/100 mM ammonium phosphate buffer (pH 2.1) = 25/75 (v/v) at a flow rate of 1.0 mL/min. The effluent from the column was monitored by UV absorption (320 nm) and radioactivity.

The residual organic solvent levels in the final product were analyzed using a GC system equipped with an FID detector (GC-2014; Shimadzu) and a capillary column (DB-WAX, 0.32 mm id × 30 m length, 0.25 μm; J&W Scientific/Agilent Technologies, Santa Clara, USA).

The pH of the final product was measured using a pH meter (HM-30R, DKK-Toa, Tokyo, Japan) coupled with a micro-pH electrode (ELP-036, DKK-Toa).

Stability of [^{18}F]AV-45

The radiochemical stability was measured by the aforementioned analytical HPLC method at appropriate time intervals up to 6 h. Approximately1 mL of the final product (540–740 MBq/mL) was dispensed into a clear or amber glass vial. The samples in the clear glass vial were kept at room temperature under visible light irradiation, and the samples in the amber glass vial were kept at room temperature under the dark conditions.

Conclusion

We developed an ethanol-free formulation method of [^{18}F]AV-45 using the JFE multi-purpose synthesizer. [^{18}F]AV-45 was synthesized with a radiochemical yield of 55.1 ± 2.2% (decay-corrected, $n = 3$), specific activity of 591.6 ± 90.3 GBq/μmol at EOS, radiochemical purity of >99%, and total synthesis time of 72.6 ± 2.4 min. In the amber glass vial, the radiochemical purity of [^{18}F]AV-45 in the ethanol-free solution remained 97.7 ± 0.7% at 6 h after EOS. However, in the clear glass vial, the radiochemical purity of [^{18}F]AV-45 in the ethanol-free solution was decreased mainly because of the increase in radiochemical impurity under exposure to visible light. In contrast, the visible light photolysis of [^{18}F]AV-45 could be prevented by adding 10% ethanol. In the radiosynthesis of [^{18}F]AV-45 formulated by dissolving the ethanol-free solution, [^{18}F]AV-45 could be obtained with high radiochemical purity and high stability by avoiding exposure to visible light.

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Conflict of Interest

The authors did not report any conflict of interest.

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