Applied Radiation and Isotopes 71 (2013) 41–46

Contents lists available at SciVerse ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Automated synthesis of [^{18}F]Florbetaben as Alzheimer's disease imaging agent based on a synthesis module system

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HIGHLIGHTS

- We radiosynthesized [^{18}F]Florbetaben from a new precursor using a one-step procedure.
- The radiosynthesis of [^{18}F]Florbetaben was performed on a commercial module within 50 min.
- The automated radiosynthesis strategy ensured a high radiochemical yield in a shorter time.

ARTICLE INFO

Article history:
Received 25 December 2011
Received in revised form
10 August 2012
Accepted 17 September 2012
Available online 28 September 2012

Keywords:
^{18}F-labeling
Automated synthesis
[^{18}F]Florbetaben

ABSTRACT

An automated synthesis procedure of [^{18}F]Florbetaben ([^{18}F]BAY94-9172), a radiolabeled imaging agent in phase III study for *in vivo* mapping of fibrillar amyloid β (Aβ) with PET, was developed using the commercial PET-MF-2V-IT-1 synthesizer. The automated radiosynthesis was carried out via a one-step nucleophilic fluorination of methanesulfonic acid 2-[2-(2-{4-[2-(4-methylamino-phenyl)-vinyl]-phenoxy}-ethoxy)-ethoxy]-ethyl ester, as a new precursor, and separation with semi-preparative high performance liquid chromatography (HPLC). The total synthesis time amounted to 50 min with 20–25% yield (uncorrected for decay) and radiochemical purities of more than 95% in all runs. The described automated radiosynthesis allows the production of [^{18}F]Florbetaben using a commercial radiosynthesis module and enables clinical trials of this compound.

1. Introduction

Alzheimer's disease (AD) is a progressive and fatal neurodegenerative brain disorder with loss of progressive episodic memory and decrease of cognitive functions. Amyloid β (Aβ) plaques composed of aggregated Aβ peptide fibrils and neurofibrillary tangles (NFTs) consisted of filaments of hyperphosphorylated tau proteins are two primarily pathologic hallmarks of AD (Förstl and Kurz, 1999; Heininger, 2000; Hardy and Selkoe, 2002). Radioactive probes for *in vivo* imaging of Aβ plaques with non-invasive imaging techniques, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), would greatly improve diagnosis and therapy monitoring of AD (Johnson et al., 1998; Lopez et al., 2001). Various positron-radiolabeled probes, such as [^{11}C]PIB (Klunk et al., 2004), [^{11}C]SB-13 (Verhoeff et al., 2004), [^{18}F]AH110690 (Koole et al., 2009), [^{18}F]FDDNP (Shoghi-Jadid et al., 2002), [^{18}F]Florbetaben (Rowe et al., 2008) and [^{18}F]AV-45 (Choi et al., 2009), were tested and demonstrated potential value in clinical use. Bayer's Florbetaben ([^{18}F]BAY94-9172) was one of the most promising ^{18}F-radiolabeled imaging agents and was used to diagnose AD patients (O'Keefe et al., 2009; Barthel and Sabri, 2011).

To facilitate its routine clinic application, it is very important to establish a reliable automated synthesis for [^{18}F]Florbetaben. The automated synthesis of [^{18}F]Florbetaben has been reported to feature a two-step reaction sequence, consisting of the nucleophilic displacement of the methanesulfonic acid leaving group in the precursor, methanesulfonic acid 2-{2-[2-(4-{2-[4-(tertbutoxycarbonyl-methyl-amino)-phenyl]-vinyl}-phenoxy)-ethoxy]-ethoxy}-ethyl ester (Boc-Stilbene-PEG-OMs) with activated [^{18}F]$^-$ fluoride, followed by acidic hydrolysis to remove the protecting group (Zhang et al., 2005). We already reported the one-step preparation of [^{18}F]Florbetaben starting from a new precursor, Stilbene-PEG-OMs (Scheme 1) (Wang et al., 2011). This method is very easy to translate into automated module synthesis. In the present study, we report the automated synthesis of [^{18}F]Florbetaben by a one-step nucleophilic ^{18}F-fluorination of the new precursor (Stilbene-PEG-OMs).

2. Results and discussion

An automated synthesis of [^{18}F]Florbetaben has been reported using HPLC purification by a two-step reaction sequence consisting

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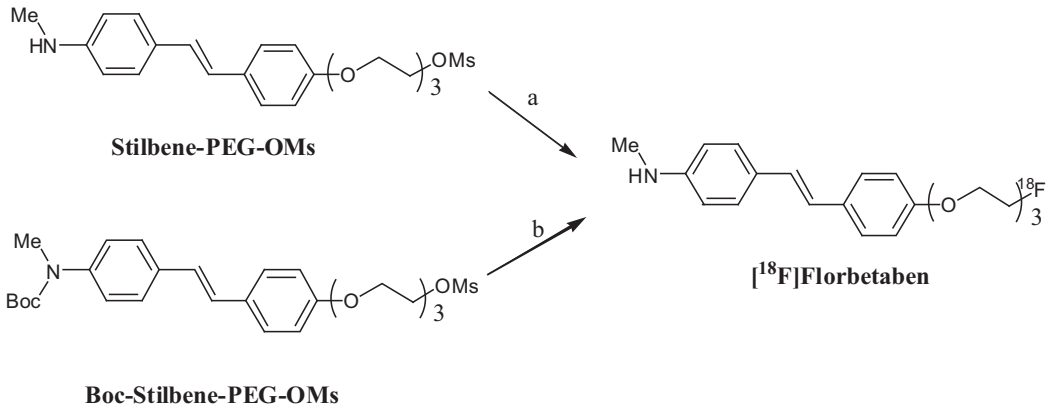
http://dx.doi.org/10.1016/j.apradiso.2012.09.014



Scheme 1. The radiosynthesis routes of [^{18}F] Florbetaben with two different precursors. a: $^{18}F^-/K_{2.2.2.}/K_2CO_3$, DMSO, 120 °C; b: (i) $^{18}F^-/K_{2.2.2.}/K_2CO_3$, DMSO, 120 °C; (ii) 10% HCl aq, 100 °C.

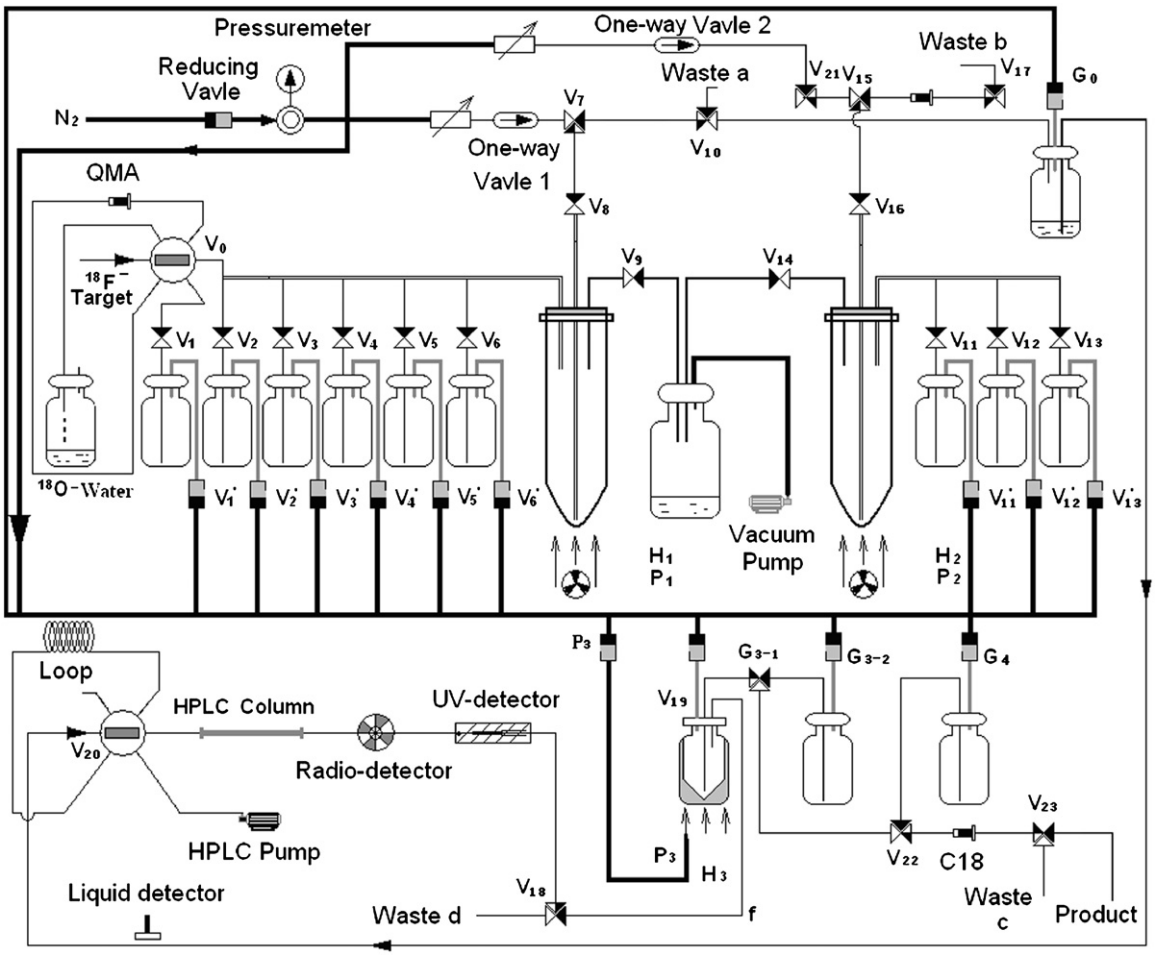


Fig. 1. Graphical display of the monitor of the PET-MF-2V-IT-1 synthesis module.

of [^{18}F]fluorination of an *N*-BOC-protected mesylate compound (Boc-Stilbene-PEG-OMs) and deprotection of the *tert*-butoxycarbonyl group by hydrolysis (Zhang et al., 2005), as shown in Scheme 1. In this study, the automated synthesis of [^{18}F]Florbetaben was performed on the PET-MF-2V-IT-1 synthesis module. The module is specifically designed for the routine, large amount of production of [^{18}F]FDG with two reaction vessels. The module automatically runs under the control of a computer-programmed synthesis recipe with a high level of automation and convenience. It is also a highly reliable system for the development of new ^{18}F labeled tracers and it can perform new automated radiosyntheses protocols after minimal modifications.

In this work, the [^{18}F]Florbetaben was obtained by a one-step [^{18}F]fluorination of Stilbene-PEG-OMs as the new precursor (Scheme 1). The automated synthesis of [^{18}F]Florbetaben was developed based on this module through connecting the reaction portion with in-built semi-preparative HPLC and solid phase extraction units (SPE units). Steps for the preparation of [^{18}F]Florbetaben were listed in Table 1. The first seven steps (A–G) were carried out in the [^{18}F]Florbetaben synthesis unit, then the next two steps (H–I)

were performed within the HPLC purification unit and the last four steps (J–M) were performed within the solid phase extraction unit. The reagents were loaded into the Vials 1–4 and the formulation solutions were loaded into the Vials G3-2 and G4 of the synthesizer according to the graphical display shown in Fig. 1.

The corresponding schematic diagram is depicted in Fig. 1. The reaction was performed in DMSO in the presence of K_2CO_3 and Kryptofix $K_{2.2.2}$. Initially, we attempted to purify the crude product with Sep-Pak cartridges instead of semi-preparative HPLC according to the following procedure: After [^{18}F]fluorination, the reaction mixture was diluted with a large amount of water and passed through a Sep-Pak plus C18 cartridge into waste. [^{18}F]Florbetaben was retained on the C18 cartridge, and then eluted with ethanol. The preparation of [^{18}F]Florbetaben only took about 30 min with 23–25% radiochemical yield (uncorrected for decay), and the radiochemical purity was above 95% (Wang et al., 2011). The main chemical impurities in the [^{18}F]Florbetaben solution were the hydrolysis byproduct of the precursor and trace amounts of DMSO (Fig. 2). However, the byproduct also showed excellent affinity with Aβ plaques (Zhang et al., 2005), which would be adverse for [^{18}F]Florbetaben as receptor imaging probe for *in vivo* PET imaging. Although there was no significant effect for the uptakes of [^{18}F]Florbetaben purified with Sep-Pak cartridges in the brains of the AD mice models from our preliminary animal experiments, the high purified [^{18}F]Florbetaben would be available for the further clinical use. Thus we adopted the purification procedure with semi-preparative HPLC instead of Sep-Pak cartridges.

Table 1
Summary of operation steps to get injectable doses of [^{18}F]Florbetaben.

Fluorination of the precursor
A. $^{18}F^-$ trapped by QMA cartridge
B. Addition of eluent to elute $^{18}F^-$ from QMA cartridge
C. Drying of $^{18}F^-$with MeCN
D. Addition of precursor solution to reaction vessel
E. [^{18}F]fluorination at 120 °C for 6 min
F. Addition of HPLC eluent to reaction vessel
G. Transfer of the solution to HPLC loop

HPLC purification
H. Elution using MeCN/ammonium formate aqueous (0.1 M)=6/4; flow rate, 3 mL/min; detection, UV 254 nm
I. Collection of the radioactive peak of [^{18}F]Florbetaben (retention time, 19–22 min)

Solid phase extraction with cartridge
J. Dilute the fraction with water
K. Transfer of the solution through a C18 Sep-Pak cartridge and the product trapped on C18 Sep-Pak cartridge
L. Elute the final product with absolute ethanol
M. Sterile filtration

After the radiofluorination, the reaction mixture was diluted and transferred into the intermediate Vial G0 as crude product and then loaded into semi-preparative HPLC for purification. Finally [^{18}F]Florbetaben with high radiochemical and chemical purities was obtained with 20–25% radiochemical yields (uncorrected for decay) in 50 min (Table 2). In addition, we also prepared [^{18}F]Florbetaben from the reported precursor (Boc-Stilbene-PEG-OMs) according to the reported procedure with little modification. The 10% aqueous HCl solution was used for hydrolysis so as to deprotect the *tert*-butoxycarbonyl group completely, and the radiosynthesis time and radiochemical yield were 60 min and 15–17% (decay uncorrected from $^{18}F^-$), respectively (Table 2). Therefore, the one-step automated synthesis of [^{18}F]Florbetaben with Stilbene-PEG-OMs as the precursor had advantages over the two-step method with regard to radiosynthesis time and radiochemical yield.

The quality of the final [^{18}F]Florbetaben solution was evaluated by analytical HPLC, radio-TLC, and other physical and chemical characteristics. The specifications of [^{18}F]Florbetaben from one-step synthesis and purification with semi-preparative HPLC were shown in Table 3. The radiochemical purity was greater than 98% obtained from analytical HPLC and radio-TLC (Fig. 3) and the corresponding Rt and Rf were 6.73 min and 0.57, respectively. The specific activity was more than 40 GBq/mmol.

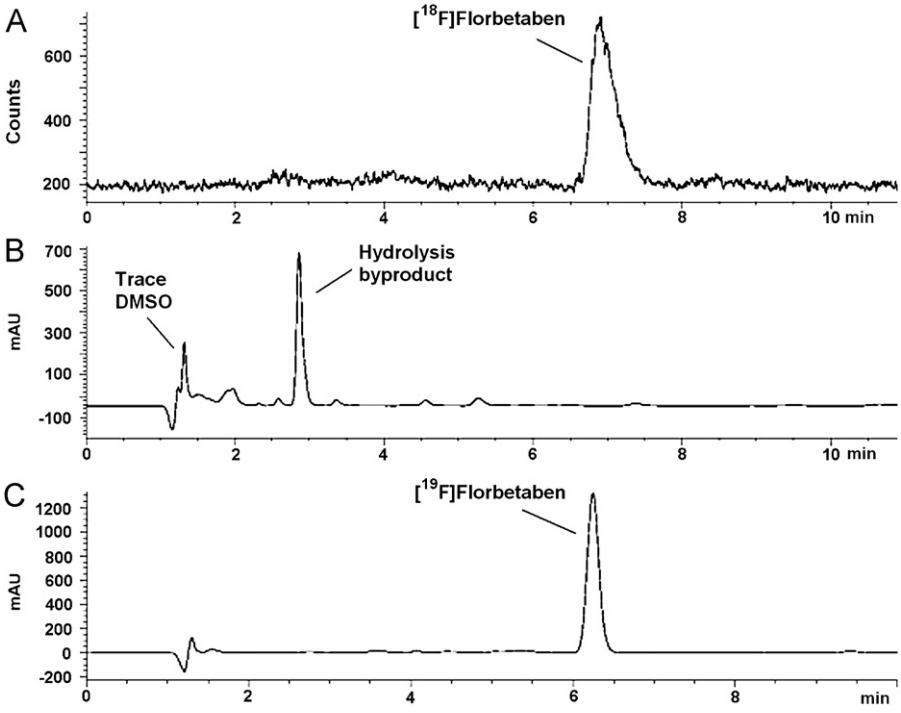


Fig. 2. Analytical HPLC chromatograms of [^{18}F]Florbetaben (Stilbene-PEG-OMs as the precursor) purified with Sep-Pak cartridges. (A) The radioactive chromatogram for [^{18}F]Florbetaben. (B) The UV chromatogram. (C) The UV chromatogram for [^{19}F]Florbetaben.

Table 2
Radiosynthesis of [^{18}F]Florbetaben with different methods.

Precursors	Reactions	Purification	Radiosynthesis time (min)	Radiosynthesis Yield (%)[a], (*n*)
Stilbene-PEG-OMs	Fluorination	Sep-Pak cartridges	30	23–25(5)[c]
Stilbene-PEG-OMs	Fluorination	PR-HPLC[b]	50	20–25(7)
BOC-Stilbene-PEG-OMs	Fluorination hydrolysis	Sep-Pak cartridges	45	18–20(5)[c]
BOC-Stilbene-PEG-OMs	Fluorination hydrolysis	PR-HPLC[b]	60	15–17(3)

[a] Decay uncorrected radiochemical yield calculated from the starting radioactivity of $^{18}F^-$; *n*, number of runs.
[b] PR-HPLC: semi-preparative HPLC.
[c] Wang et al., 2011.

Table 3
Specifications of [^{18}F]Florbetaben from one-step synthesis and purification with semi-preparative HPLC (mean $\pm$ SD from seven productions).

Parameter	Value	Parameter	Value
Synthesis time	50 min	Radiochemical purity	$>98\%$
Radiochemical yield	$23 \pm 2\%$[a]	Residual $K_{2.2.2}$	Undetected
Physical characteristics	Clear, colorless liquid; no suspended particles	Content of Ethanol	10% (v/v)
pH value[b]	7–8	Sterility	Compile with specifications
Specific activity[c]	>40 GBq/mmol	Endotoxins	<1.5 EU/mL

[a] Uncorrected for decay.
[b] Test with indicator paper (pH 5.5–9.0).
[c] Using 3.7 GBq of [^{18}F]F^- as a starting activity.

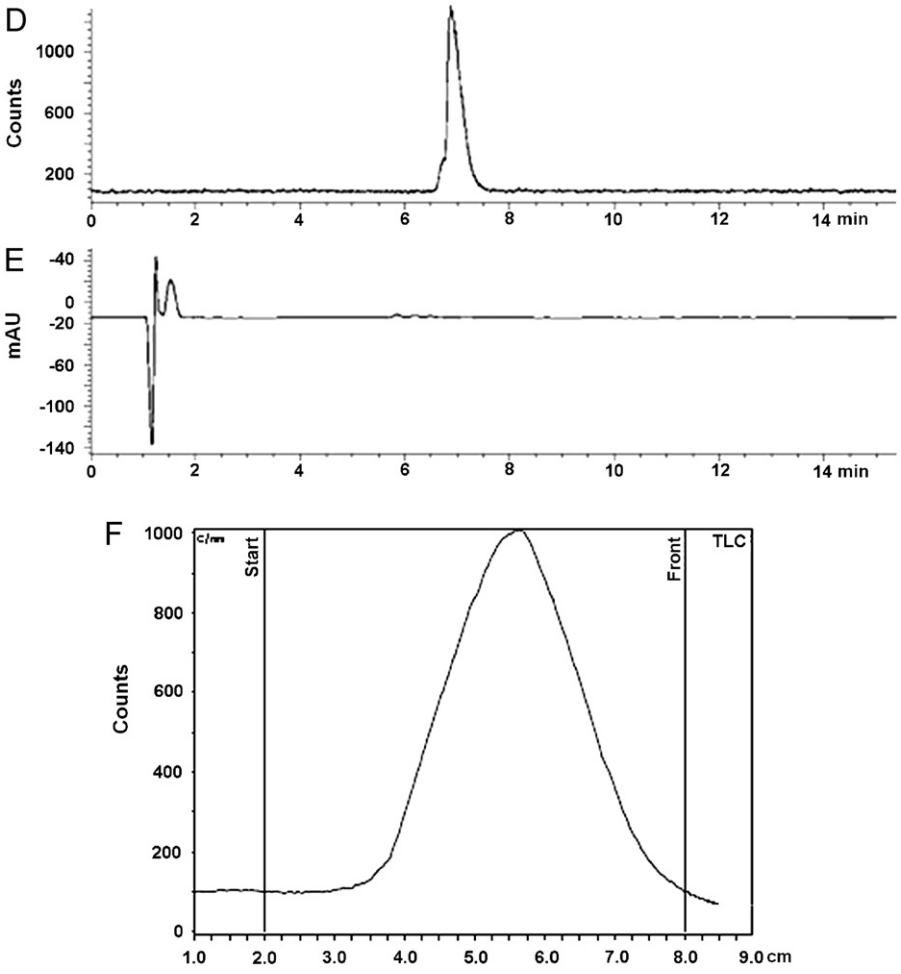


Fig. 3. Analytical HPLC and radio-TLC chromatograms of [^{18}F]Florbetaben (Stilbene-PEG-OMs as the precursor) purified with semi-preparative HPLC. (D) The radioactive chromatogram for [^{18}F]Florbetaben injection. (E) The UV chromatogram for [^{18}F]Florbetaben injection. (F) The radio-TLC for [^{18}F]Florbetaben injection.

The pH was about 7.0–8.0 tested by indicator paper (pH 5.5–9.0). The appearance of [^{18}F]Florbetaben solution was clear, colorless as checked by visual observation. The stability in isotonic saline was evaluated by analytical HPLC and the radiochemical purity was greater than 95% within 6 h. The detection of $K_{2.2.2.}$ was checked by color spot test via TLC and it did not show any traces of $K_{2.2.2.}$. Finally bacterial endotoxins and sterility were also tested and the results were in compliance with the requirements of China pharmacopoeia.

3. Conclusion

We developed a one-step automated synthesis of [^{18}F]Florbetaben with methanesulfonic acid 2-[2-(2-{4-[2-(4-methylamino-phenyl)-vinyl]-phenoxy}-ethoxy)-ethoxy]-ethyl ester as a new precursor using a commercial PET-MF-2V-IT-1 synthesizer. This rapid, efficient preparation route of [^{18}F]Florbetaben could be completed with a synthesis time of 50 min, the uncorrected for decay radiochemical yields was about 20–25% and the radiochemical purity was more than 95%. This implementation will make this amyloid PET tracer more accessible for routine production in clinical research.

4. Experimental

4.1. Materials

The compounds [^{19}F]Florbetaben, methanesulfonic acid 2-{2-[2-(4-{2-[4- (tertbutoxycarbonyl-methyl-amino)-phenyl]-vinyl}-phenoxy)-ethoxy]-ethoxy}-ethyl ester (Boc-Stilbene-PEG-OMs) and methanesulfonic acid 2-[2-(2-{4- [2-(4-methylamino-phenyl)-vinyl]-phenoxy}-ethoxy)-ethoxy]-ethyl ester (Stilbene-PEG-OMs) were synthesized as previously described (Wang et al., 2011). 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8,8,8]hexacosane ($K_{2.2.2.}$), acetonitrile (MeCN) and dimethylsulfoxide (DMSO) were obtained from Sigma-Aldrich. All other chemicals obtained commercially were analytical grade and used without further purification. Sep-Pak light QMA and plus C18 cartridges were purchased from Waters (Milford, MA). Millex®-GS 0.22 μm micropore membrane filters were purchased from Milipore and enriched [^{18}O]H_2O from Huayi (Changzhou, China). GF_{254} silica gel plate based on plastic was obtained from Macherey-Nagel (Germany). No-carrier-added [^{18}F]fluoride in [^{18}O]H_2O was obtained through nuclear reaction $^{18}O(p, n)^{18}F$ by irradiation of 10-MeV proton on [^{18}O]water using a Cyclone 10/5 cyclotron (IBA Technologies, Belgium). Analytical high performance liquid chromatography (HPLC) (1200 series, Agilent, USA) and radioactive thin layer chromatography scanner (radio-TLC) (MiniGita Star, Raytest, Germany) were applied to monitor the reaction extent and analysis of the product purity. Analytical HPLC analysis was carried out on HPLC system with a reverse-phase analytical XDB-C18 column (4.6 × 150 mm, 5 μm) consisting of two pumps and equipped with a variable wavelength UV detector (Agilent interface 35900E) and a B-FC-3200 high energy PMT Detector (Bioscan Inc, Washington DC, USA). The preparation of [^{18}F]Florbetaben was performed on the commercial PET-MF-2V-IT-1 synthesis module (PET Co. Ltd., China) and purification with in-built HPLC system equipped with a semi-preparative reverse-phase C18 column (10 × 250 mm, 10 μm), a UV detector (Alltech 201, USA) and a radioactivity detector (PET Co. Ltd., China). Radioactivity was determined using a calibrated ion chamber (Capintec CRC-15R).

4.2. General one-step procedure ^{18}F-labeling synthesis

The radiochemical synthesis of [^{18}F]Florbetaben was achieved by using one-step nucleophilic fluorination of the precursor Stilbene-PEG-OMs and purification with semi-preparative HPLC and/or with solid phase cartridge. The Sep-Pak QMA cartridge was treated with $NaHCO_3$ (1M, 10 mL) aqueous solution and then with distilled water (10 mL). Then the Sep-Pak plus C18 cartridge was treated with ethanol (10 mL), followed by distilled water (10 mL). Before delivery of [^{18}F]fluoride to the synthesis module, the Sep-Pak QMA and plus C18 cartridges were placed into the right position and correctly connected with the inlet and outlet tubes according to Fig. 1. The solution of K_2CO_3 (4.1 mg, 0.14 mL water) and $K_{2.2.2}$ (17.7 mg, 1.36 mL MeCN), MeCN (2 mL) and the precursor (8.0 mg, 0.6 mL anhydrous DMSO) were loaded into Vial 1, 2 and 3, respectively. Vial 4 was filled with a mixture of 0.1 M ammonium formate and MeCN (v/v=6:4, 3 mL); Vial G3-2 was filled with water (20 mL) and Vial G4 was filled with absolute ethanol (1.5 mL).

The [^{18}O]H_2O containing $^{18}F^-$ was passed through a pre-treated Sep-Pak light QMA cartridge where the $^{18}F^-$ was trapped. The $^{18}F^-$ was released from the QMA cartridge by passing the $K_{2.2.2.}$/ K_2CO_3 solution from Vial 1 and allowed to enter into the reaction vessel. The solvent was evaporated to dryness by heating at 116 °C under a stream of nitrogen. Then azeotropic drying was repeated once with MeCN (2 mL) from Vial 2 at 116 °C to generate the anhydrous $[K/K_{2.2.2.}]^+{}^{18}F^-$ complex. The precursor solution from Vial 3 was added to the dried $[K/K_{2.2.2.}]^+{}^{18}F^-$ complex and the reaction vial was sealed and heated at 120 °C for 8 min. After fluorination, the reaction system was cooled down to room temperature and the solution from Vial 4 (3 mL) was added to dilute the reaction mixture. Finally, the mixture was transferred into Vial G0 as crude product and purified by the in-built semi-preparative HPLC system with MeCN/0.1 M ammonium formate (v/v=6/4) as mobile eluents at a flow rate of 3 mL/min. The appropriate fraction of [^{18}F]Florbetaben (Rt=25 min) was collected in Vial 19, diluted with water (25 mL) from Vial G3-2, and passed through a Sep-Pak C18 cartridge between V22 and V23 into the waste. The purified [^{18}F]Florbetaben was trapped on Sep-Pak C18 cartridge, eluted with absolute ethanol (2 mL) from Vial G4 and collected in a final product vial containing saline through the syringe filter Millex®-GS.

4.3. General two-step procedure ^{18}F-labeling synthesis

The two-step procedure for the radiosynthesis of [^{18}F]Florbetaben was performed as described before (Wang et al., 2011) with only slight modifications. Fluorination was achieved after drying of the fluoride in one step. After fluorination of the precursor (Boc-Stilbene-PEG-OMs), 10% HCl (2 mL) was added from Vial 4 and the mixture was heated to 100 °C for 10 min. The NaOH aqueous solution (6 M, 0.5 mL, Vial 5) was added to the mixture, which was then diluted with a mixture of 0.1 M ammonium formate and MeCN (v/v=6:4, 2 mL, Vial 6). Then [^{18}F]Florbetaben was purified with semi-preparative HPLC, using the same procedure as described above.

4.4. Quality control

The aforementioned analytical HPLC and radio-TLC systems were used to check for the presence of radiochemical purities and to evaluate the radiochemical stability of [^{18}F]Florbetaben in isotonic saline. Analytical HPLC was performed using MeCN/0.1 M ammonium formate (v/v=6/4) as the mobile phase at a flow rate of 1 mL/min. Radio-TLC was developed on silica gel plate using MeCN/H_2O (v/v=9/1) as the eluent. $K_{2.2.2}$ detection tests were performed

on the silica gel 60 coated plate, developed with methanol/ammonium hydroxide ($v/v=9/1$) as the solvent system and using iodine vapor for staining of the spots (Tang et al., 2008). The bacterial endotoxins and sterility were tested by the well described procedures (Runkle et al., 2011).

Acknowledgments

This work was supported by Tianjin University, the National Natural Science Foundation (No.30970856), the National High Technology Research and Development Program of China (863 Program, No. 2008AA02Z430), the Science Technology Foundation of Guangdong Province (No. 2010B031600054), and Sun Yat-Sen University (No. 80000-3126132).

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