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ScienceDirect
Nuclear Medicine and Biology 34 (2007) 345–351
NUCLEAR MEDICINE — AND — BIOLOGY
www.elsevier.com/locate/nucmedbio

One-step high-radiochemical-yield synthesis of [^{18}F]FP-CIT using a protic solvent system

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Received 8 November 2006; received in revised form 22 January 2007; accepted 16 February 2007

Abstract

Although [^{18}F] fluoropropylcarbomethoxyiodophenylnortropane (FP-CIT) is a promising radiopharmaceutical for dopamine transporter imaging, it has not been used for clinical studies because of low radiochemical yield. The purpose of our study was to develop a new radiochemistry method using a protic solvent system to obtain a high radiochemical yield of [^{18}F]FP-CIT in single-step manual and automatic preparation procedures. [^{18}F]F^- was trapped on a QMA Sep-Pak cartridge or PS-HCO_3 cartridge and eluted with Cs_2CO_3/K_{222} buffer or $TBAHCO_3$, respectively, or 8 μl of TBAOH was added directly to [^{18}F]$F^-/H_2^{18}O$ solution in a reactor without using a cartridge. After drying, [^{18}F] fluorination was performed with 2–6 mg of mesylate precursor, 100 μl of CH_3CN and 500 μl of *t*-BuOH at 50–120°C for 5–30 min, followed by high-performance liquid chromatography (HPLC) purification to obtain the final product. For comparison, the same procedure was performed with a tosylate precursor. Manual synthesis gave a decay-corrected radiochemical yield of 52.2±4.5%, and optimal synthesis conditions were as follows: TBAOH addition, 4 mg of precursor, 100°C and 20 min of [^{18}F] fluorination (n=3). We obtained low radiochemical yields of [^{18}F]FP-CIT with carbonate elution systems such as Cs_2CO_3 or $TBAHCO_3$. We also developed an automatic synthesis method based on manual synthesis results. In automatic production, we obtained a decay-corrected radiochemical yield of 35.8±5.2% after HPLC purification, and we did not have any synthesis failures (n=14). Here, we describe our new method for the synthesis of [^{18}F]FP-CIT using a protic solvent system. This method gave a high radiochemical yield with high reproducibility and might enable [^{18}F]FP-CIT to be used clinically and commercially.

Keywords: [^{18}F]FP-CIT; Protic solvent; Nucleophilic substitution; Parkinson's disease; Dopamine transporter

1. Introduction

The pathological process of Parkinson's disease is accompanied by a loss of dopamine transporters (DAT) localized in presynaptic nigrostriatal nerve terminals. Therefore, in vivo imaging of DAT using radiopharmaceuticals has been very useful for the diagnosis and monitoring of Parkinson's disease. Cocaine analogs (e.g., β-CIT [1] and its derivatives such as CFT [2], PE2I [3], FE-CNT [4], IPT [5]) and fluoropropylcarbomethoxyiodophenylnortropane (FP-CIT) [6–12] have been shown to bind to DAT and have been studied as radiochemical ligands for DAT imaging in the human brain.

Among these, FP-CIT has high affinity to DAT, specific binding to DAT and fast kinetics, and has been labeled with [^{11}C] carbon, [^{123}I] iodine and [^{18}F] fluoride [6–12]. However, due to the short half-life of [^{11}C] carbon ($t_{1/2}$= 20 min), *O*-methyl-[^{11}C]FP-CIT is not an ideal radiopharmaceutical for DAT positron emission tomography (PET) imaging since peak equilibrium in the striatum is attained over 70–90 min after the injection of FP-CIT. Recently, [^{123}I]FP-CIT has been widely used for DAT imaging because it has been commercialized in Europe. However, it also has several limitations, including serotonin transporter uptake of radioactive metabolite and low resolution of single-photon emission computed tomography compared to PET.

[^{18}F]FP-CIT has several advantages for DAT imaging, including fast kinetics, relatively long half-life of [^{18}F] fluoride, a hydrophilic metabolite and high-resolution

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doi:10.1016/j.nucmedbio.2007.02.007

images with PET. Dosimetry results for humans showed low radiation exposure after injection of [^{18}F]FP-CIT [13]. However, it has not been widely used for DAT imaging because of a very low radiochemical synthetic yield [9,10].

There are two methods for the synthesis of [^{18}F]FP-CIT. The first involves one-step synthesis from a mesylate nortropane precursor [9]. This reaction has the advantage of simple preparation but has shown a very low radiochemical yield (<5%) in previous reports. The second method is a two-step reaction in which [^{18}F] fluorination of 1,3-propanediolditosylate is followed by alkylation with nor-β-CIT [10,11]. This method also showed low radiochemical yield (~5%) and required a long alkylation time at high temperature, which may cause epimerization to a less active α-isomer [14,15].

Aliphatic nucleophilic substitution is generally performed in a polar aprotic solvent system such as CH_3CN, and the use of a polar protic system such as alcohol has not previously been reported [16]. Recently, our group has developed a new chemistry for aliphatic nucleophilic substitution of tertiary alcohols. Using this polar protic solvent chemistry, we obtained a very dramatic increase in radiochemical yield for nucleophilic [^{18}F] fluorination [17].

In this study, we developed a new method using a protic solvent system for the radiosynthesis of [^{18}F]FP-CIT. We optimized this method with respect to phase-transfer catalyst, precursor amount and [^{18}F] fluorination conditions in manual and fully automatic preparations to obtain high radiochemical yields of [^{18}F]FP-CIT.

2. Materials and methods

2.1. Chemicals and precursor

N-[3′-(mesyloxy)propyl]-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (mesylate precursor), *N*-[3′-(tosyloxy)-propyl]-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (tosylate precursor) → *N*-[3′-(mesyloxy)propyl]-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (mesylate precursor; **1**), *N*-[3′-(tosyloxy)propyl]-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (tosylate precursor; **2**) and cold FP-CIT were supplied by FutureChem (Seoul, Korea). Other solvents and reagents, including *t*-BuOH with ACS reagent grade, were purchased from Sigma-Aldrich (USA) and used as supplied.

2.2. [^{18}F] fluorination

We evaluated three experimental conditions for the single-step synthesis of [^{18}F]FP-CIT. In the first experiment, 185 MBq/0.5 ml of [^{18}F]F^-/$H_2{}^{18}O$ was trapped on a QMA Sep-Pak cartridge (Waters, USA), and [^{18}F]F^- was eluted with a solution of 7 mg of Cs_2CO_3, 22 mg K_{222}/300 μl of CH_3CN and 300 μl of H_2O. In the second experiment, 185 MBq/0.5 ml of [^{18}F]F^-/$H_2{}^{18}O$ was trapped on a PS-HCO_3 (Machery-Nagel, Germany) cartridge, and [^{18}F]F^- was eluted with a solution of 10 μl of TBAHCO_3/300 μl of H_2O and 300 μl of CH_3CN. Lastly, we tested TBAOH as a phase-transfer catalyst without using any cartridges by direct addition of 8 μl of TBAOH to a reactor containing 100 μl of 185 MBq of [^{18}F]F^-.

After complete drying, we added 2–6 mg of the mesyl precursor, 100 μl of CH_3CN and 500 μl of *t*-BuOH. To determine optimal conditions, the reaction mixture was incubated at 50–120°C for 5–30 min. After [^{18}F] fluorination, 2 ml of MeOH was added to rinse the reactor, and the mixture was injected into the high-performance liquid chromatography (HPLC) system for purification.

The same procedure was performed with the tosylate precursor. The synthesis scheme is shown in Fig. 1. For each condition, we carried out three independent experiments.

2.3. Purification, quality control and stability

Crude HPLC conditions were MeOH:H_2O:NEt_3 (750:250:2), 4 ml/min and 220 nm of UV detection with an Alltech Econosil C_{18} column (10×250 mm; 10 μm). We used a Thermo Separation Product HPLC system with a UV 4000 detector system. Analytical HPLC was performed using the same HPLC conditions with an Alltech Econosil analytical C_{18} column (4.6×250 mm; 5 μm). [^{18}F] fluorination yield was determined by radio thin-layer chromatography (radioTLC) using hexane:diethyl ether:NEt_3 (7:3:1) as a developing solvent. Residual organic solvents such as *t*-BuOH and MeOH in the final product were analyzed using gas chromatography (Acme-2000; YoungLin Instrument, Korea). Supelcowax-10 (Sigma-Aldrich) and a fused silica capillary column (60 m×0.25 mm×0.25 μm film thickness) were used for analysis. The oven temperature was 75°C, while that of the injector and detector was 250°C. A flame ionization detector system with a flow rate of 105 ml/min was used. Gas chromatography analysis was performed with an Autochro-2000 (Younglin Instrument).

2.4. Automation

For automatic preparation of [^{18}F]FP-CIT, we used a TracerLab FX_{FN} module (GE Healthcare) and created the sequence program according to manual synthesis results [17]. The scheme of TracerLab FX_{FN} module is presented in Fig. 2, and this module has nine reagent supply vials at the upper part of Vials 1–9 (V1–V9), from left to right in Fig. 2. We added a mixture of 8 μl of TBAOH, 100 μl of H_2O and 1 ml of CH_3CN to V1; 1 ml of CH_3CN to V2; a mixture of

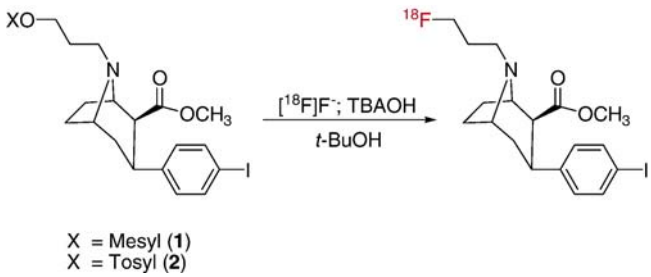

Fig. 1. Radiosynthesis of [^{18}F]FP-CIT from its mesylate precursor (**1**) or tosylate precursor (**2**) by one-step preparation.