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Automated radiosynthesis of [^{18}F]ciprofloxacin

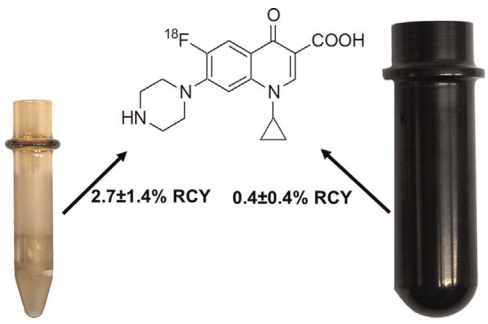
Johann Stanek [a,b], Severin Mairinger [a], Thomas Wanek [a], Claudia Kuntner [a], Markus Müller [b], Oliver Langer [a,b,*]

[a] Health and Environment Department, AIT Austrian Institute of Technology GmbH, A-2444 Seibersdorf, Austria
[b] Department of Clinical Pharmacology, Medical University of Vienna, Währiger-Gürtel 18-20, A-1090 Vienna, Austria

HIGHLIGHTS

- Automated synthesis of [^{18}F]ciprofloxacin in a TRACERlab^{TM} FX$_{FDG}$ (GE Healthcare) synthesis module was developed.
- Dependence of radiochemical yield on reactor type was observed.
- 3-mL V-shaped borosilicate glass reactor gave higher radiochemical yield as compared with standard 15-mL glassy carbon reactor.
- V-shaped borosilicate glass reactor might also give higher radiochemical yield for other [^{18}F]radiotracers than [^{18}F]ciprofloxacin.

GRAPHICAL ABSTRACT



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ABSTRACT

We transferred the previously published manual synthesis of [^{18}F]ciprofloxacin (decay-corrected RCY: 5.5 ± 1.0%) to an automated synthesis module (TRACERlab^{TM} FX$_{FDG}$, GE Healthcare) and observed a strong decrease in RCY (0.4 ± 0.4%). When replacing the standard 15-mL glassy carbon reactor of the synthesis module with a 3-mL V-shaped borosilicate glass reactor a considerable improvement in RCY was observed. [^{18}F]Ciprofloxacin was obtained in a RCY of 2.7 ± 1.4% (n=23) with a specific activity at EOS of 1.4 ± 0.5 GBq/μmol in a synthesis time of 160 min.

1. Introduction

Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinolone-3-carboxylic acid) is a still widely prescribed fluoroquinolone antibiotic which displays a broad spectrum of activity against Gram-negative and Gram-positive bacteria. Ciprofloxacin has been described as a substrate of several different active membrane transporter proteins belonging to the solute carrier (SLC) or adenosine triphosphate-binding cassette (ABC) families, such as organic anion transporter 3 (OAT3), breast cancer resistance protein (BCRP), multidrug resistance protein 4 (MRP4) and multidrug and toxin extrusion protein 1 (MATE1) (Mulgaonkar et al., 2012). These transporters mediate hepatobiliary and renal excretion of their substrates and drug–drug interactions involving inhibition of one or several of these transporters could lead to altered tissue distribution of ciprofloxacin, which may have an impact

* Corresponding author at: Health and Environment Department, AIT Austrian Institute of Technology GmbH, A-2444 Seibersdorf, Austria. Fax: +43 50550 2136.
E-mail address: oliver.langer@ait.ac.at (O. Langer).

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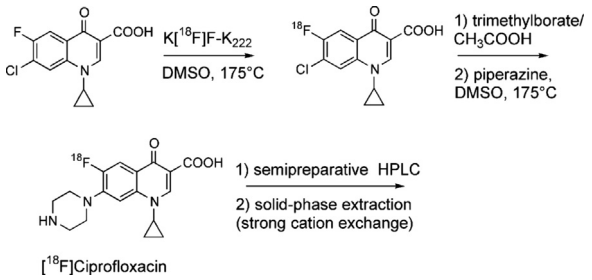

Fig. 1. Reaction scheme for the synthesis of [^{18}F]ciprofloxacin.

on its efficacy and safety (Giacomini et al., 2010). Ciprofloxacin contains fluorine in its structure which can be replaced with the positron-emitting radionuclide fluorine-18 (^{18}F, half-life 109.8 min) (Langer et al., 2003a,b). We have previously shown that positron emission tomography (PET) imaging with [^{18}F]ciprofloxacin can be used to non-invasively study the tissue distribution of ciprofloxacin in humans (Langer et al., 2005). Studying the tissue distribution of [^{18}F]ciprofloxacin in genetically modified mice, which lack one or several membrane transporter proteins, may help to identify the relevant transporters, which are likely to affect ciprofloxacin tissue distribution in humans.

In previous studies, ciprofloxacin has been prepared by a manual two-step one-pot synthesis method comprising a nucleophilic ^{18}F/^{19}F exchange reaction of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid followed by reaction of the ^{18}F-labeled carboxylic acid derivative with piperazine (Fig. 1) (Langer et al., 2003a,b). Aim of this work was to develop an automated synthesis of [^{18}F]ciprofloxacin in a commercially available automated synthesis module (TRACERlab^{TM} FX_{FDG}, General Electric Healthcare, Uppsala, Sweden) in order to reduce the radiation exposure associated with manual radiosynthesis.

2. Materials and methods

2.1. General

All chemicals were purchased from Sigma-Aldrich Handels GmbH (Vienna, Austria) and used without further purification. Aqueous (aq.) [^{18}F]fluoride was produced using a PETtrace cyclotron (GE Healthcare) *via* the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of a 2.6 mL water target containing 95.9% enriched [^{18}O]water (ABX-advanced biochemical compounds, Radeberg, Germany) with a 16.5 MeV proton beam.

Radiochemical purity and specific activity of [^{18}F]ciprofloxacin were determined with analytical high-performance liquid chromatography (HPLC) using an Agilent 1200 system (Agilent Technologies Österreich GmbH, Vienna, Austria) consisting of a quaternary pump, an auto-sampler and a column oven. Ultraviolet (UV) absorption was detected with an Agilent 1200 diode array detector at a wavelength of 280 nm in series with a Raytest "Gabi Star" detector (raytest Isotopenmessgeräte GmbH, Straubenhardt, Germany) for radioactivity detection. A PRP-1 column (4.1×250 mm^2, 5 μm, Hamilton Bonaduz AG, Bonaduz, Switzerland), heated to 40 °C, was isocratically eluted with a 85/15 (v/v) mixture of aq. 0.01 M phosphoric acid (H_3PO_4) and ethanol at a flow rate of 1 mL/min. Osmolality (mosmol/kg) of formulated [^{18}F]ciprofloxacin solution was measured using a Wescor Vapro 5520 Pressure Osmometer (Wescor Inc., Logan, USA). The pH value was determined with a pH-Meter Inolab pH720 (WTW Wissenschaftlich-Technische Werkstätten GmbH, Weilheim, Germany).

2.2. Automated synthesis of [^{18}F]ciprofloxacin

Radiosynthesis of [^{18}F]ciprofloxacin was performed as a two-step one-pot reaction (Fig. 1) in a custom-modified dual-reactor TRACERlab^{TM} FX_{FDG} synthesis module (GE Healthcare). This synthesis module originally contained two independent synthesis units in a single housing and was originally designed to operate two consecutive [^{18}F]FDG syntheses without reloading and opening the hot cell. Our synthesis module was custom-modified by the manufacturer to enable two-pot [^{18}F]radiosyntheses (Fig. 2). We used the synthesis module either in standard configuration with two large-volume glassy carbon reactors (15 mL) (configuration A) or in a modified configuration in which one large-volume glassy carbon reactor (reactor 1) had been replaced with a small-volume V-shaped borosilicate glass reactor (3 mL) (configuration B, Fig. 3). In configuration B also the heating block of the reactor was replaced so that the bore size fitted to the smaller diameter of the reactor (Fig. 3, left picture). In order to facilitate reflux of the reaction solution in configuration B the 3-mL V-shaped borosilicate glass reactor was mounted in a way that 1.5 cm remained outside the heating block. In both configurations the two reaction steps of the [^{18}F]ciprofloxacin synthesis were performed in reactor 1 (Figs. 2 and 3). All reagent solutions were prepared prior to start of synthesis and placed in the synthesis module storage vessels. Amounts of reagents and solvent volumes were different for configurations A and B as indicated below.

After delivery of the irradiated [^{18}O]water to the synthesis module, [^{18}F]fluoride was trapped on an anion exchange cartridge (PS-HCO3, 45 mg, Macherey-Nagel, Düren, Germany), which had been pre-activated with ethanol (3 mL) and water (5 mL). [^{18}F]Fluoride was eluted into the synthesis reactor by rinsing the cartridge with a mixture of kryptofix 2.2.2 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8] hexacosane, configuration A: 16 mg, 42.5 μmol; configuration B: 12 mg, 31.9 μmol) in acetonitrile (0.9 mL) and potassium carbonate (3.5 mg, 25.3 μmol) in water (0.1 mL) (added *via* valve 1, V1, see Fig. 2). After adding acetonitrile (0.5 mL) to the synthesis reactor (*via* V2), the solvent was evaporated azeotropically under vacuum, first for 3 min at 60 °C and then for further 5 min at 120 °C to remove the remaining water. To the dried K[^{18}F]F-K_{222} complex, radiolabelling precursor 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (configuration A: 12.0 mg, 42.6 μmol; configuration B: 6.0 mg, 21.3 μmol) dissolved in dimethyl sulfoxide (DMSO, configuration A: 0.8 mL; configuration B: 0.3 mL) was added (V6) and the reaction mixture was heated at 175 °C for 40 min. The reaction mixture was then cooled to 40 °C and a mixture of trimethylborate (configuration A: 100 μL, 897 μmol; configuration B: 20 μL, 179 μmol) and glacial acetic acid (configuration A: 100 μL, 1747 μmol; configuration B: 20 μL, 349 μmol) in DMSO (configuration A: 0.3 mL; configuration B: 0.1 mL) was added (V5) and the reaction mixture was stirred at 40 °C for 2 min. Then a solution of piperazine (configuration A: 57 mg, 661.7 μmol; configuration B: 20 mg, 232.2 μmol) in DMSO (configuration A: 0.7 mL; configuration B: 0.35 mL) was added (V4) and the mixture was reacted at 175 °C for 40 min. After cooling to 40 °C, a mixture of aq. 0.01 M H_3PO_4 and ethanol (85/15, v/v, configuration A: 2.5 mL; configuration B: 1 mL) was added (V3) and the crude reaction mixture was injected into the built-in semipreparative HPLC system. A Hamilton PRP-1 column (10×250 mm^2, 10 μm) equipped with a PRP-1 guard column (10×40 mm^2) was eluted at a flow rate of 3 mL/min for the first 12 min with a mixture of aq. 0.01 M H_3PO_4 and ethanol (97/3, v/v) followed by an increase of the ethanol percentage to 15%. The HPLC eluate was monitored in series for radioactivity and UV absorption at a wavelength of 280 nm. [^{18}F]Ciprofloxacin, which eluted with a retention time of 25–30 min in a volume of 15–20 mL (Fig. 4), was directly passed over a strong cation exchange