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A rapid and efficient preparation of [^{123}I]radiopharmaceuticals using a small HPLC (Rocket®) column

Andrew Katsifis*, Vahan Papazian, Timothy Jackson, Christian Loc'h

Radiopharmaceuticals Division R&D, Australian Nuclear Science & Technology, Organisation, Menai, NSW 2234, Sydney, Australia

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Abstract

A simplified method for the rapid and efficient preparation of [^{123}I]radiopharmaceuticals is described. Three radiopharmaceuticals, [^{123}I]β-CIT, [^{123}I]MIBG and [^{123}I]clioquinol, were synthesised and purified as model compounds. The radiotracers were labelled with iodine-123 using electrophilic oxidative conditions and purified by a compact semi-preparative reverse phase column (C-18, 3 μm, 7 × 53 mm, Alltima Rocket®, Alltech) using aqueous-ethanol as HPLC solvents that were directly used for radiopharmaceutical formulation. The radiochemical purity of the radioiodinated tracers as assessed by analytical HPLC was higher than 99% with specific activity higher than 3 GBq/nmol. The total preparation time of a radiotracer ranged from 40 to 60 min and, starting from 3.7 GBq of iodine-123, more than 2.5 GBq of formulated radiopharmaceuticals were available for clinical investigations.

Keywords: Radioiodination; RP-HPLC; Rapid purification; MIBG; β-CIT; Clioquinol

1. Introduction

In radiopharmaceutical preparation, the purification step provides the most critical challenge. To fulfil pharmaceutical criteria such as chemical and radiochemical purity, radiotracers are purified by chromatography techniques (Meyer et al., 1993). For this purpose, high-performance liquid chromatography (HPLC) has been widely used. HPLC allows easy recovery of the radiotracer with all the prerequisites of purity, but the nature and volume of the organic eluent that has to be evaporated hampers radiopharmaceutical preparation. Solid phase extraction (SPE) has been used to eliminate the HPLC solvent prior to radiopharmaceutical formulation (Lever et al., 1996; Lemaire et al., 1999). In addition, SPE has also been used to directly purify the reaction mixture using normal and/or reverse phase media (Zea-Ponce et al., 1995, Krasikova et al., 2000; Berthommier et al., 2002). However, the chemical and radiochemical purity of radiopharmaceuticals from SPE is generally lower than those purified by HPLC (Zea-Ponce et al., 1995; Mitterhauser et al., 2003) and can be a drawback for receptor studies when very high purity is mandatory and where reproducibility and regulatory issues are paramount.

To shorten the preparation and to simplify the formulation step, we propose the use of HPLC as the purification medium but with a new, small, compact column and aqueous-ethanol solutions which act as eluent for purification of crude labelling mixtures as well

*Corresponding author. Tel.: +61 2 9717 9094; fax: +61 2 9717 9262.
E-mail address: akx@ansto.gov.au (A. Katsifis).

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as the formulation medium of the product. We report here the results obtained from the preparation of [^{123}I]β-CIT, [^{123}I]MIBG and [^{123}I]clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) using optimized labelling and purification conditions.

2. Experimental

2.1. General

3-β-(4′-Trimethylstannylphenyl)-tropane-2-β-carboxylic acid methyl ester (Trimethyltin β-CIT) was obtained from Guilford Pharmaceuticals. Cloxyquin (5-chloro-8-hydroxyquinoline), peracetic acid and chloramine-T were purchased from Sigma-Aldrich. The 3-trimethylsilylbenzylguanidine was prepared according to literature methods (Vaidyanathan and Zalusky, 1993). Other chemicals were used as purchased without further purification. Solvents for chromatography were of HPLC grade. Iodine-123 was produced by the National Medical Cyclotron, Sydney, Australia, using the ^{124}Xe(p, 2n) reaction and delivered as Na[^{123}I] in 0.1 M NaOH solution at a concentration of 37 GBq/mL. The radioactivity was measured with a radioactive dose calibrator (Capintec).

2.2. HPLC purification

After radioiodination, the crude reaction mixtures were purified by HPLC on a Waters, 510 pump on a small semi-preparative reverse phase column (C-18, 3 μm, 7 × 53 mm, Alltima Rocket®, Alltech) and ethanol solutions according to the conditions described in Table 1. A UV variable detector (Linear, model 200), with wavelength fixed at 225 nm for β-CIT and at 254 nm for MIBG and clioquinol, and a NaI radioactivity detector were used to monitor the eluent. The radioactive peak eluting at the retention time of the authentic tracers was collected and the activity measured. The radiolabelling yield was obtained by comparing the activity of the collected fraction with the starting activity.

2.3. Radiolabelling

Radiolabelling was performed-according to classical radioiodination methods using peracetic acid or chloramine–T as oxidants and organometallic precursors for [^{123}I]β-CIT (Carroll et al., 1991; Neumeyer et al., 1991; Coenen et al., 1995; Zea–Ponce et al., 1995) and [^{123}I]MIBG (Vaidyanathan and Zalutsky, 1993, 1995) or by direct regiospecific ortho-iodination of cloxyquin for [^{123}I]clioquinol (Papazian et al., submitted). A summary of the radiolabelling conditions is briefly described.

Preparation of [^{123}I]β-CIT

To a solution of 3-β-(4′-trimethylstannylphenyl)-tropane-2-β-carboxylic acid methyl ester (50 μg, 0.15 μmol in 200 μL of ethanol) were successively added 100 μL 6 M HCl, nca Na[^{123}I] (3.7 GBq) and peracetic acid (2% in 100 μL of acetic acid) solution. The reaction was allowed to proceed for 2 min at room temperature and quenched by the addition of 1 mg $Na_2S_2O_5$ in 100 μL water. The crude mixture was then purified by HPLC.

Preparation of [^{123}I]MIBG

To a vial containing 1 mg of chloramine-T, were successively added 0.5 mg of trimethylsilyl-*m*-benzylguanidine dissolved in 200μL of trifluoroacetic acid and nca Na[^{123}I] (3.7 GBq). The reaction was allowed to proceed for 15 min at room temperature and then quenched by the addition of 400 μL of 10 M

Table 1
HPLC conditions for purification and quality control analysis of the iodinated radiotracers

	[^{123}I]β-CIT	[^{123}I]MIBG	[^{123}I]clioquinol
Semi- preparative HPLC			
Column	C-18, 3 μm, 7 × 53 mm, Alltima Rocket®		
Eluent	Ethanol–0.1 M H_3PO_4 30–70 1.6 mL/min	Ethanol–water 30–70 1.6 mL/min	ethanol–0.1 M H_3PO_4 60–40 1.6 mL/min
UV	225 nm	254 nm	254 nm
Collection time	5.3–6.5 min	4.3–5.3 min	6.5–7.7 min
Quality control			
Column	5 μm, 4.6 × 150 mm Luna Phenomenex	5 μm, 4 × 250 mm Spherisorb S5 W Waters	5 μm, 4.6 × 150 mm Altima-C18 Alltech
Eluent	AcN–0.05 M KH_2PO_4 25–75 1 mL/min	MeOH–10 M NH_4OH–1 M NH_4NO_3 90–6.6–3.4 1 mL/min	THF–0.1 M H_3PO_4 50–50 0.6 mL/min
UV	233 nm	254 nm	254 nm
Retention time	14.1 min	8.8 min	12.9 min