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Short communication

1-Minute quality control tests for positron emission tomography radiopharmaceuticals

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ABSTRACT

An ultra-fast, sensitive and versatile radio-liquid chromatographic (LC) procedure was developed and validated for quality control (QC) tests of PET radiopharmaceuticals. For a wide variety of radio-probes, the usual LC conditions were used: (1) column: Waters XBridge RP_{18} (50 mm × 3.0 mm ID, 2.5 μm), (2) mobile phase: a mixture of three modifiers (90% CH_3CN, ammonium phosphate at pH 2.1 and pH 9.3), and (3) detection: UV absorption and NaI(Tl) scintillation. The introduction of a short column packed with small particles of 2.5 μm allowed excellent separation of target analytes within a very short run time of 1 min; only a 3% decline of radioactivity was observed during QC analysis of ^{11}C-labelled pharmaceuticals. Combining ammonium-phosphate buffer as the mobile-phase component and low-wavelength UV detection led to an improvement in the applicability and sensitivity. All 34 pharmaceuticals investigated could be successfully applied to determine the specific radioactivity, radiochemical and chemical purity with 10-times better sensitivity than traditional LC. We could analyze different pharmaceuticals in a short period since this system utilized a common column and mobile phase. The proposed procedure fulfils the requirements for routine QC tests in terms of rapidity, sensitivity, simplicity and applicability.
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1. Introduction

The quality control (QC) of positron emission tomography (PET) radiopharmaceuticals has gained increased attention due to the widespread use of various probes in clinical studies. These radio-probes, because of their short half-lives (e.g. ^{11}C; $t_{1/2}$ = 20.4 min), must be produced as needed and subjected to several QC testings at most production facilities before clinical application. Specific radioactivity is one of the most important issues for successful visualization of *in vivo* PET imaging as well as quality assurance of radiopharmaceutical preparations. Chemical/radiochemical impurities, such as precursors, intermediates and analogues that might be contained in the final preparation, may interfere with PET measurements, and may cause adverse reactions in human application. In the United States Pharmacopeia (USP) and European Pharmacopeia (EP), several PET pharmaceuticals, such as [^{11}C]flumazenil, [^{11}C]*N*-methylspiperone, [^{11}C]raclopride, [^{18}F]FDG, have been listed with the acceptance criteria of their specific radioactivity and impurities [1,2]. The most widely used method to analyze PET radiopharmaceuticals is liquid chromatography coupled with radiometric detection (radio-LC). Radio-LC provides good resolution; however, it has limited rapidity or sensitivity for the analysis of pharmaceutical samples under traditional conditions, e.g. recommended by the USP and EP [1,2]. Several QC tests need to be conducted prior to human administration and synthetic products often have extremely low concentrations (ng–μg/mL) due to the high specific radioactivity. Thus, the development of a QC method rapid and sensitive enough to measure a trace amount of PET molecules is of great importance.

Recently, chromatographic performance was improved by introducing fast LC and ultra performance LC technology [3–6]. These LC utilize a short column packed with small particles at high pressure, allowing ultra-fast analysis with excellent resolution and sensitivity. These techniques increased the widespread use for numerous purposes, such as clinical analysis, new drug development, validation of manufacturing process, proteomics and metabonomics studies where a high sample analysis rate and/or superior peak capacity is required.

Further, we found that ammonium-phosphate buffer is a preferable mobile-phase component for sensitive UV detection. Ammonium and phosphate have wide range of pK_a at 2.1, 7.2, 9.3 and 12.3 with low background absorption below 210 nm, where most compounds could be detected significantly under the desired

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pH condition, which would lead to improved applicability and sensitivity for QC analysis of PET probes.

The aim of this work was to develop a general methodology for QC analysis in which a wide array of PET radiopharmaceuticals (Fig. 1) can be applied and by which quantification is possible at a lower level in an ultra-fast and easily operated manner. The LC system was established and their conditions optimized by taking the following factors into consideration: (i) 1-minute separation of target analytes, (ii) sensitive determination of PET molecule concentration, and employing (iii) a common LC procedure, including a column and mobile phase for numerous PET radiopharmaceuticals. The usefulness of this method was demonstrated using a wide range of ^{11}C, ^{18}F-labelled pharmaceutical preparations.

2. Experimental

2.1. Materials

Authentic samples of the compounds and precursors of PET radiopharmaceuticals (Fig. 1) were obtained commercially or as gifts, and used without further purification unless otherwise specified. All other chemicals were of reagent or LC grade unless otherwise stated.

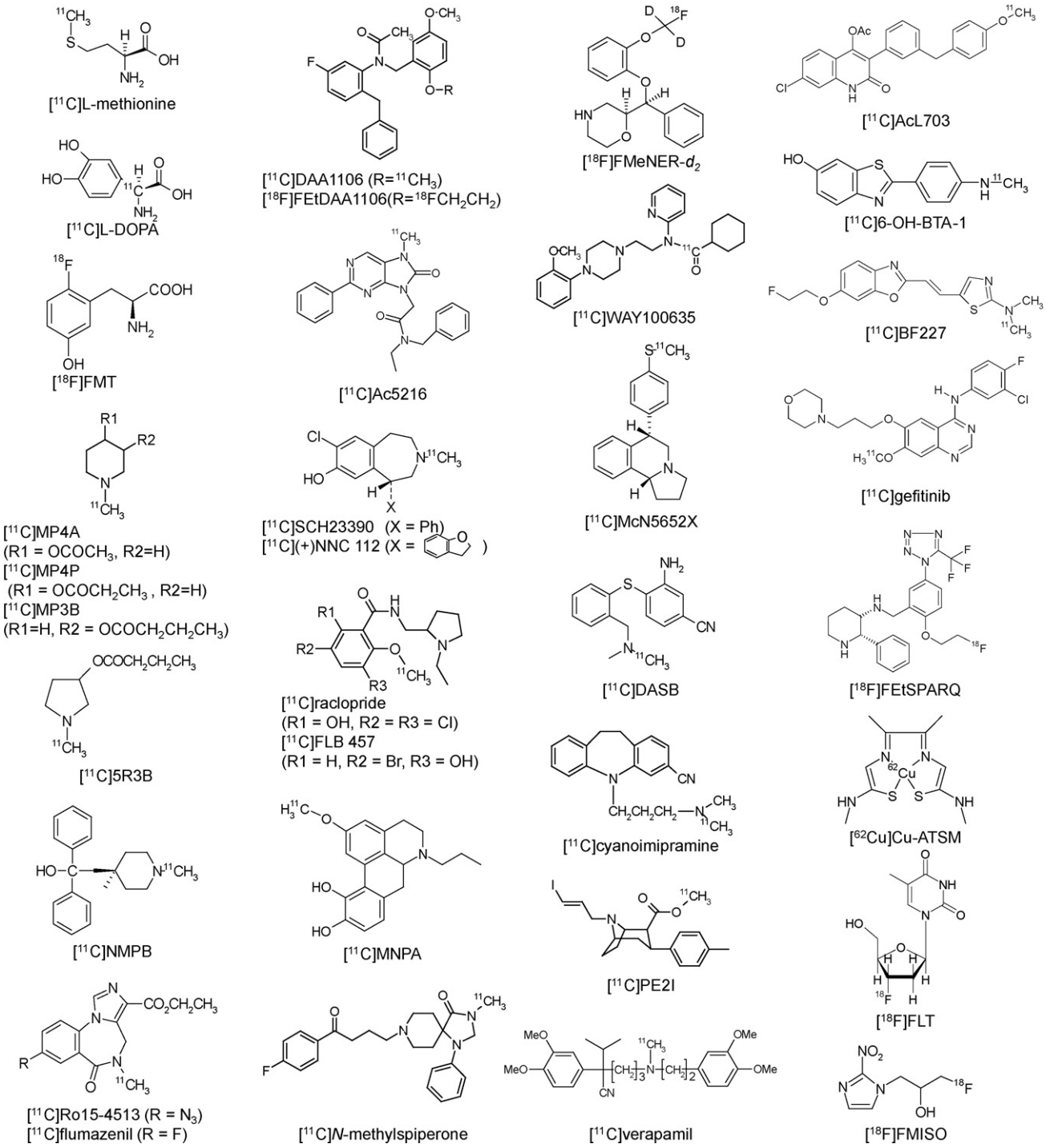

Fig. 1. PET radiopharmaceuticals examined in this study.

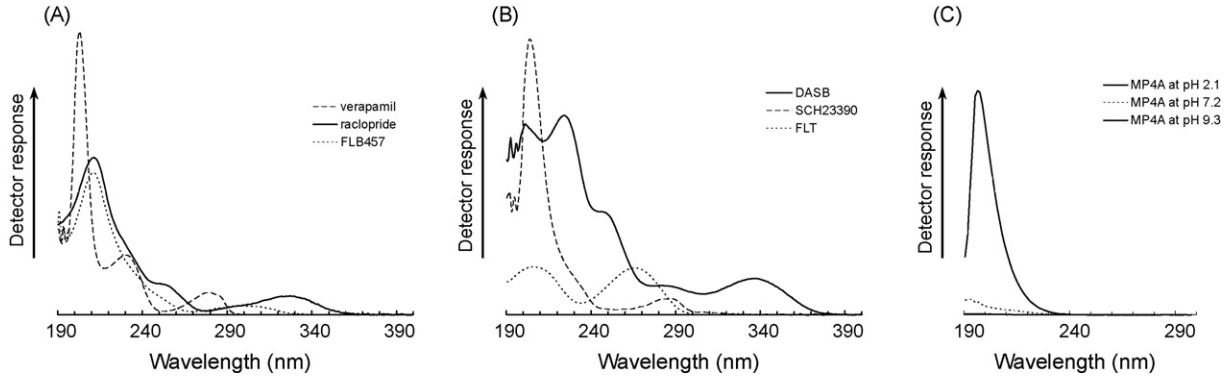

Fig. 2. UV absorption spectrum of (A and B) a wide range of PET molecules and (C) effect of pH value on UV absorption intensity of MP4A. Samples: (A and B) verapamil, raclopride, FLB457, DASB, SCH23390 and FLT dissolved in 100 mM ammonium phosphate at pH 7.2 (each 1 μg/mL). (C) MP4A dissolved in 100 mM ammonium phosphate at pH 2.1, 7.2 and 9.3 (25 μg/mL).

[^{11}C]Raclopride, [^{11}C]MP4A, [^{11}C]FLB457 and [^{18}F]FLT preparations were produced by versatile synthesis equipment for multiple production of PET radiopharmaceuticals developed in our facility [7].

2.2. LC apparatus and conditions for QC analysis of a range of PET radiopharmaceuticals

LC was carried out using three LC pumps (515; Waters, New England, USA) and a syringe-loading sample injector valve (Model 7125; Rheodyne, Cotati, USA) with a 5-μL loop. Chromatographic separation was performed on a reversed-phase column, an XBridge RP_{18} (Waters, 50 mm × 3.0 mm ID, 2.5 μm), and a mixture of (i) 90% CH_3CN, (ii) 100 mM ammonium-phosphate at pH 2.1 containing 5 mM sodium octansulfonate, and (iii) 50 mM ammonium phosphate at pH 9.3 as the mobile phase delivered by each LC pump at a total flow rate of 1.0–1.2 mL/min. Effluent from the column was monitored by a UV absorption detector (2487; Waters) and a NaI(Tl) detector (VD12-E2; EG&G, Princeton, USA). Data collection (10 points/s) and control of the LC system were performed using an acquisition server (Waters; LAC/E^{32}). All connections were made with minimum length of 0.25 mm ID tubing to minimize extra-column volume.

3. Results and discussion

3.1. Optimization of LC conditions for ultra-fast QC analysis of a range of PET radiopharmaceuticals

Fig. 2 shows the UV absorption spectrum of typical PET molecules. Almost all compounds examined had an absorbance maximum at lower than 230 nm. The traditional QC procedure selected for 254 nm or characteristic absorption at a longer wavelength [1,2], but intensities at a lower wavelength were—50-fold higher than such wavelengths, for example, the absorption of raclopride at 210 nm increased by factors of 5.3 and 8.4 from 254 nm and 326 nm, respectively. In particular, MP4A, which is believed to have no available chromophore for detection at radiopharmaceutical levels (–μg/mL; ppm) [8], was also detectable photometrically under weak alkaline conditions; the detector response of MP4A at pH 9.3 was enhanced 14-fold and 250-fold from in neutral and acidic medium (Fig. 2C). Of the 34 pharmaceuticals examined, all compounds could be detected at 1 μg/mL by optimizing the pH value of the dissolved buffer solution.

Initially, we studied the possibility of establishing a generally applicable LC system using sodium-phosphate buffer at pH 2.1 and pH 7.2 as the ionic modifier of LC mobile phase; however, several pharmaceuticals could not be separated from their precursors and/or could not be detected at ppm levels. Improved applicability and sensitivity were attained by using ammonium-phosphate buffer. They have a wide range of pK_a at 2.1, 7.2, 9.3 and 12.3 with low background absorption below 210 nm, enabling sensitive low-wavelength detection with a wide applicability of target analytes. Other salts, such as acetate, formate, trifluoroacetate, carbonate and triethylamine, frequently used for reversed phase LC, were not suitable due to the relatively higher background at 210 nm (Fig. 3) and narrow pH coverage. Ammonium salt offers advantages over sodium salt in the lifetime of the column and solubility in organic solvents. As an organic modifier, acetonitrile was found to be preferable since it does not absorb light at higher than 195 nm and relatively minimal column back pressure. From these findings, (i) 90% CH_3CN, (ii) 100 mM ammonium phosphate at pH 2.1, and

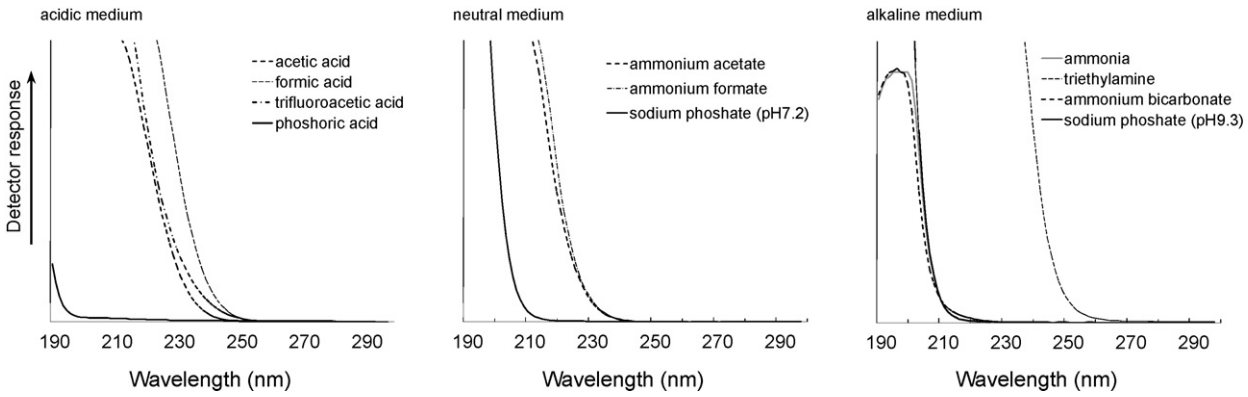

Fig. 3. UV absorption spectrum of a range of components used for mobile phase. Samples: each 100 mM (aqueous solution).

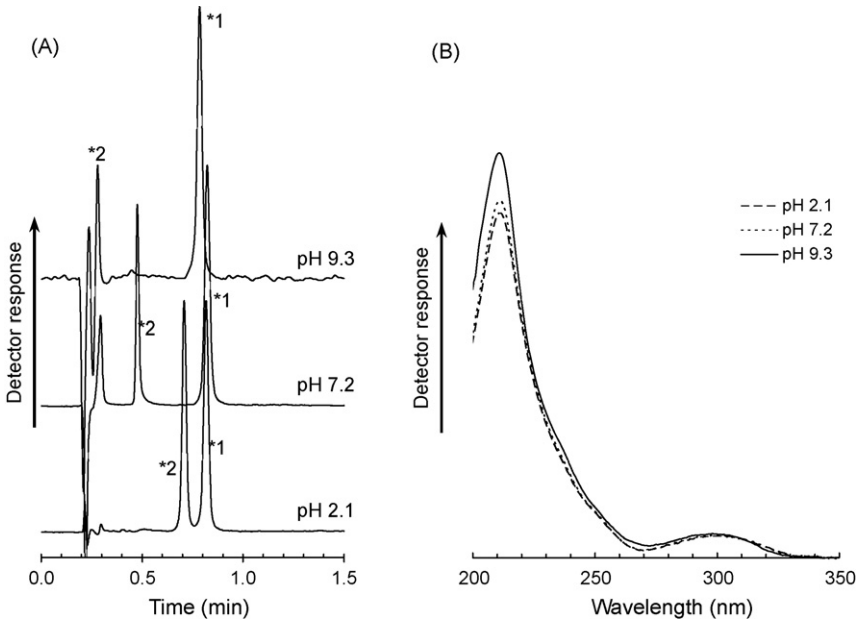

Fig. 4. Optimization of the LC condition for QC analysis of [^{11}C]FLB457. Effects of eluent pH on (A) separation of FLB457 [*1] and its desmethyl precursor [*2] and (B) detector response of FLB457. LC conditions: column, XBridge RP_{18} (50 mm × 3.0 mm ID, 2.5 μm); mobile phase, 90% CH_3CN/100 mM ammonium phosphate at pH 2.1 containing 5 mM sodium 1-octansulfonate/50 mM ammonium phosphate at pH 9.3 = 0.34/0.66/0 mL/min (pH 2.1), 0.34/0.33/0.33 mL/min (pH 7.2), 0.55/0/0.45 mL/min (pH 9.3). Samples: FLB457 and desmethyl-FLB457 (each 1 μg/mL).

Table 1
Optimized LC conditions for the ultra-fast analysis of PET radiopharmaceuticals.

PET radiopharmaceutical	Mobile phase (mL/min)			Wavelength (nm)	Retention time (min)	
	90% CH_3CN	Buffer at pH 2.1[a]	Buffer at pH 9.3[b]		Precursor	Product
[^{11}C]L-methionine	0.13	0.87	–	205	–	0.84
[^{11}C]L-DOPA	0.15	0.85	–	210	0.85	0.55
[^{18}F]FMT	–	0.50	0.50	210	–	0.82
[^{11}C]MP4A	0.14	–	0.86	210	0.35	0.86
[^{11}C]MP4P	0.23	–	0.77	210	0.36	0.84
[^{11}C]MP3B	0.36	–	0.64	210	0.43	0.84
[^{11}C]5R3B	0.27	–	0.73	210	0.41	0.87
[^{11}C]NMPB	0.49	–	0.51	210	0.43	0.81
[^{11}C]Ro15-4513	0.33	0.67	–	269	0.59	0.82
[^{11}C]flumazenil	0.28	0.72	–	245	0.58	0.82
[^{11}C]DAA1106	0.73	0.47	–	210	0.75	0.89
[^{18}F]FEtDAA1106	0.73	0.47	–	210	0.76	0.86
[^{11}C]Ac5216	0.58	0.42	–	290	0.62	0.78
[^{11}C]SCH23390	0.59	–	0.41	210	0.47	0.82
[^{11}C](+)NNC112	0.61	–	0.39	210	0.51	0.87
[^{11}C]FLB457	0.34	0.33	0.33	210	0.48	0.82
[^{11}C]raclopride	0.40	0.60	–	210	0.64	0.88
[^{11}C]MNPA	0.35	0.65	–	215	0.40	0.86
[^{11}C]*N*-methylspiperone	0.42	0.58	–	247	0.66	0.84
[^{18}F]FMeNER-d_2	0.45	–	0.55	210	0.67	0.89
[^{11}C]WAY100635	0.52	–	0.28	268	0.40	0.86
[^{11}C]McN5652X	0.43	0.57		260	–	0.86
[^{11}C]DASB	0.68	–	0.32	225	0.44	0.83
[^{11}C]cyanoimipramine	0.62	–	0.38	235	0.45	0.87
[^{11}C]PE2I	0.45	0.55	–	220	0.49	0.86
[^{11}C]verapamil	0.48	0.26	0.26	230	0.51	0.87
[^{11}C]AcL703	0.70	0.30	–	225	0.74	0.88
[^{11}C]6-OH-BTA-1	0.56	0.44	–	354	0.86	0.76
[^{11}C]BF227	0.52	0.48	–	380	0.50	0.81
[^{11}C]gefitinib	0.50	–	0.50	330	0.37	0.84
[^{18}F]FEtSPARQ	0.39	0.61	–	210	0.45	0.83
[^{62}Cu]Cu-ATSM	0.42	0.58	–	307	0.63	0.83
[^{18}F]FLT	0.09	–	0.91	210	–	0.80
[^{18}F]FMISO	0.09	–	0.91	215	–	0.77

[a] Buffer at pH 2.1 = 100 mM ammonium-phosphate at pH 2.1 containing 5 mM sodium 1-octansulfonate.
[b] Buffer at pH 9.3 = 50 mM ammonium-phosphate at pH 9.3.

Table 2
Reproducibility, linearity, detection limit and accuracy for the analysis of PET radiopharmaceuticals afforded by the ultra-fast LC procedure.

Analytes	Reproducibility (R.S.D.%)[a]				Linear range (μg/mL)[b] [r^2][c]	Detection limit (ng/mL)[d]	Accuracy recovery (%)	
	Retention time		Peak area				0.1 μg/mL added	1.0 μg/mL added
	Intra-day	Inter-day	Intra-day	Inter-day				
L-Methionine	0.1	1.0	1.1	0.8	0.01–100 [1.0000]	10	101.4 ± 1.8	95.5 ± 0.3
MP4A	2.2	2.6	2.5	2.2	0.1–100 [0.9986]	50	–	–
Flumazenil	0.4	1.1	0.9	1.0	0.01–100 [0.9999]	1	–	–
DAA1106	0.1	1.6	0.6	1.5	0.01–100 [0.9999]	2	–	–
FEtDAA1106	0.1	1.6	1.6	2.5	0.01–100 [1.0000]	2	100.3 ± 2.0	99.6 ± 1.6
Ac5216	0.3	1.8	0.7	1.9	0.01–100 [0.9999]	2	99.4 ± 0.3	100.8 ± 0.4
SCH23390	0.6	1.6	2.8	2.4	0.01–100 [0.9999]	2	–	–
FLB457	0.1	2.2	0.6	1.3	0.01–100 [0.9999]	3	–	–
Raclopride	0.1	1.3	0.3	1.1	0.01–100 [0.9999]	2	99.3 ± 0.6	98.9 ± 2.7
MNPA	0.9	2.5	1.8	1.7	0.01–100 [0.9999]	3	98.0 ± 1.7	100.0 ± 1.2
N-Methylspiperone	0.3	2.7	1.2	1.6	0.01–100 [0.9988]	2	–	–
WAY100635	0.5	1.6	1.5	2.0	0.01–100 [0.9999]	8	–	–
DASB	0.2	2.0	1.9	1.3	0.01–100 [0.9992]	2	101.1 ± 2.8	98.6 ± 2.6
PE2I	0.1	2.2	1.6	0.9	0.01–100 [0.9999]	6	–	–
Verapamil	0.6	0.2	2.3	1.7	0.01–100 [0.9999]	3	–	–
6-OH-BTA-1	0.2	1.7	0.5	2.1	0.01–100 [0.9999]	1	97.6 ± 2.3	102.6 ± 0.9
FEtSPARQ	0.1	1.7	1.6	2.7	0.01–100 [0.9999]	6	98.0 ± 3.8	95.5 ± 0.9
Cu-ATSM	0.1	1.9	0.5	2.3	0.01–100 [0.9999]	1	95.9 ± 2.1	98.3 ± 1.9
FLT	0.1	1.7	1.7	1.3	0.01–100 [0.9980]	8	99.9 ± 2.4	95.5 ± 1.4

[a] R.S.D. (%) = relative standard deviations obtained from repetitive seven injections of standard solution (1 μg/mL).
[b] 5-μL injection volume.
[c] r^2 = correlation coefficient.
[d] Defined as the concentration in the injection volume (20 μL) giving a signal-to-noise ratio of 3.

(iii) 50 mM ammonium phosphate at pH 9.3 were adopted as the mobile phase and their composition was selected for each pharmaceutical. In order to be applied for the analysis of [^{11}C]L-methionine, the most polar compound examined in this study, 5 mM sodium 1-octanesulfonate was added to buffer at pH 2.1 as the ion-pair reagent to increase the affinity to a reverse phase column. In this LC system, a neutral mobile phase (ca. pH 7.2) can be prepared by the combination flow of pH 2.1 and pH 9.3 buffers.

In the design of an LC system offering quick analysis, the chromatographic separation time should be as short as possible. Recently, LC employing a short column (ca. 50 mm) packed with small particles (<3 μm) resulted in a very flat Van Deemter plot and a linear velocity faster than usual with 5–10 μm particles, which consequently improved the resolution, speed and sensitivity of LC analysis [3–6]. Good separation and peak shapes were obtained using a reversed-phase column, an XBridge Shield RP_{18} (50 mm × 3.0 mm ID, 2.5 μm). The analyte peak heights obtained by 2.5 μm particle were ca. 50% higher than that at 3.5 μm (data not shown). This column utilizes hybrid particles containing a bridged ethylsiloxane/silica structure allowing a wide pH operating range (pH 2–12) [9]. Although use of a column filled with sub-2 μm particles is more attractive for chromatographic performance, due to

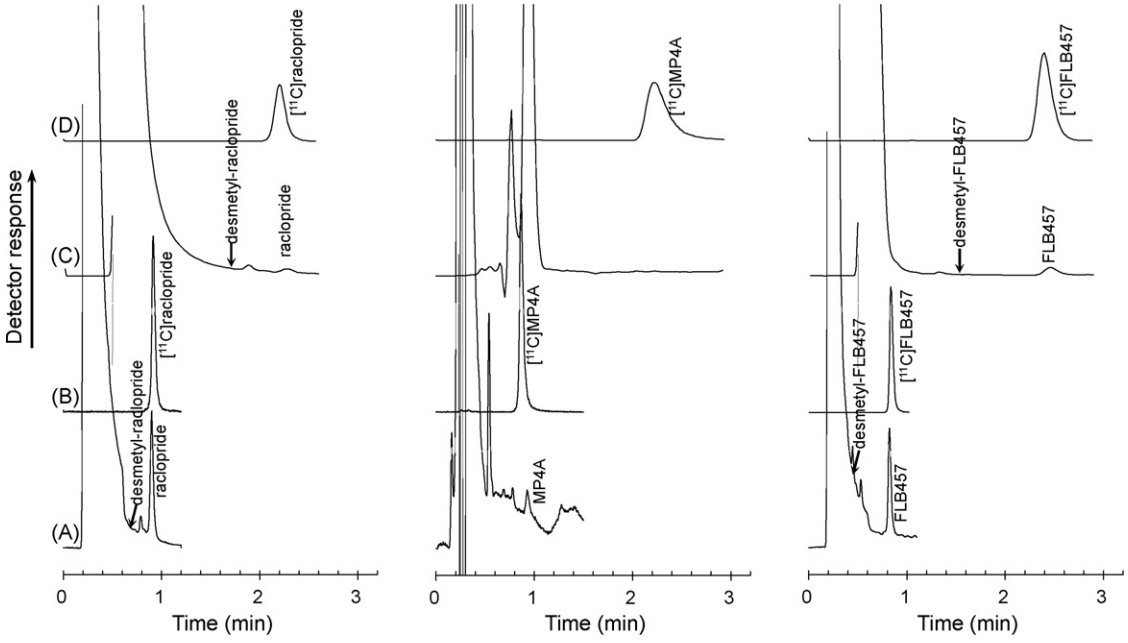

Fig. 5. Chromatograms of [^{11}C]raclopride, [^{11}C]MP4A and [^{11}C]FLB457 preparations obtained by (A and B) ultra-fast LC procedure and (C and D) conventional method. Detection: (A and C) UV (210 nm); (B and D) NaI(Tl) scintillation. Ultra-fast LC conditions were as described in Table 1. Traditional LC conditions: column, μBondapak C_{18} (150 mm × 3.9 mm ID, 10 μm); mobile phase, CH_3CN/100 mM sodium phosphate at pH 2.1 = 0.95/2.05 mL/min ([^{11}C]raclopride), CH_3CN/20 mM sodium phosphate at pH 7.2 = 0.6/1.4 mL/min ([^{11}C]MP4A), CH_3CN/100 mM sodium phosphate at pH 2.1 = 0.75/2.25 mL/min ([^{11}C]FLB457).

high backpressure at typical LC flow rates, such a column cannot be operated by a common LC pump (maximum pressure ca. 30–40 MPa). The aim of this study is to develop a widely acceptable procedure for any PET facility, so 2.5 μm packed column was selected.

Using the methodology established above, the analysis conditions were optimized for each radiopharmaceutical. For example, the dependence of mobile phase pH on the separation and detection behavior of [^{11}C]FLB457 is shown in Fig. 4. When a mixture of 90% CH_3CN and pH 2.1 buffer was used for the mobile phase, FLB457 and its desmethyl substrate did not separated completely. The precursor was not retained under pH 9.3 buffer with a high background level. Sufficient separation was attained by pH 7.2 buffer giving a high signal-to-noise (S/N) ratio. FLB457 had an absorption maximum at 210 nm with 16-fold higher intensity than 300 nm and this absorption spectrum was not influenced by pH (Fig. 3B); thus, 90% CH_3CN/buffer at pH 2.1/buffer at pH 9.3 = 34/33/33 (mobile phase) and 210 nm (detection) was adopted as optimum for QC analysis of [^{11}C]FLB457 preparation. Under this condition, FLB457 and desmethyl-FLB457 were eluted at 0.82 min and 0.48 min, respectively, at a flow rate of 1.0 mL/min; maximum resolution was attained at 0.5–1.2 mL/min in this LC procedure. The optimized LC conditions for all 34 radiopharmaceuticals are listed in Table 1. These conditions were selected so that not only was analysis completed within 1 min with highly sensitive detection, but also the selective determination of target analytes while formulation components of radiopharmaceutical preparation, such as sodium ascorbate and Tween80, often hamper analysis. Back pressure was 20–28 MPa under optimized LC conditions to be acceptable for conventional LC apparatus.

3.2. Method validation

The method validation data (reproducibility, analytical dynamic range, detection limit and accuracy) for the 19 compounds are summarized in Table 2. Intra-day reproducibility was obtained from repetitive injections of a standard of 1 μg/mL, and inter-day reproducibility was established by making determinations on consecutive days. Relative standard deviations of the retention time and peak area were within 3% (n = 7), below the USP mandated limit of 3.2–10% for ^{11}C-labelled radiopharmaceuticals [1]. The detector exhibited a linear response in the range of at least 0.1–100 μg/mL at 5-μL injection volume with correlation coefficients (r^2) of more than 0.998. Detection limits at 5-μL injection volume (S/N = 3) were ppb levels. These sensitivities were sufficiently low as to be valuable for determining the quantity of PET molecules in ^{11}C-labelled pharmaceutical fluid. The accuracy of this method was determined by the analysis of samples spiked with a standard. The recovery was found to be 95.5–102.6%, indicating that the proposed method

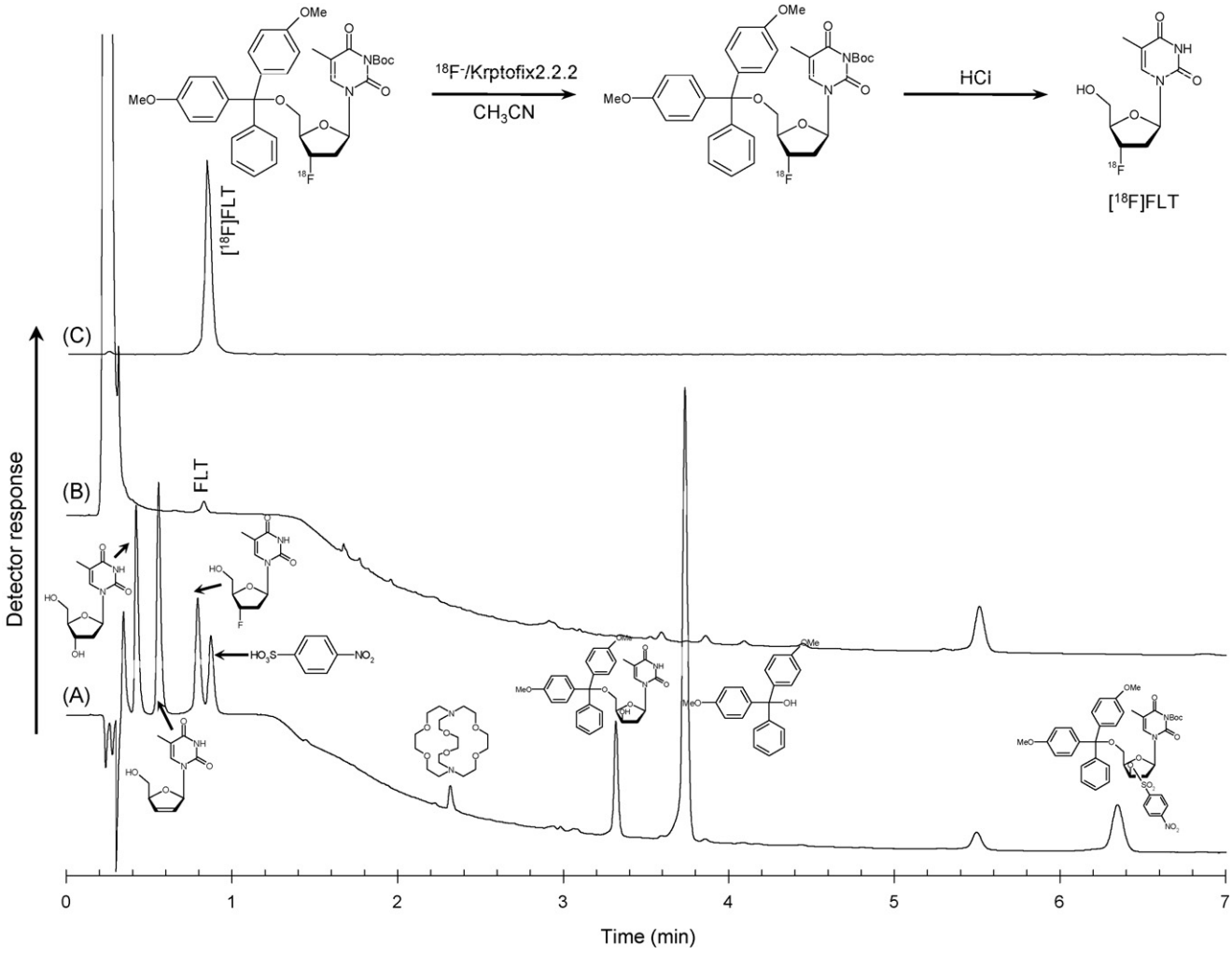

Fig. 6. The production scheme of [^{18}F]FLT and chromatograms obtained with (A) a standard mixture (each 10 μg/mL) and (B and C) [^{18}F]FLT preparation. Detection: (A and B) UV (210 nm); (C) NaI(Tl) scintillation. Mobile phase, 90% CH_3CN/50 mM ammonium phosphate at pH 9.3 = 0.09/0.91 mL/min (0–0.6 min) → 0.7/0.3 mL/min (0.6–7.0 min). Other conditions were as described in Table 1.

would be acceptable for the QC analysis of PET radiopharmaceutical formulations.

3.3. Ultra-fast analysis of ^{11}C-labelled radiopharmaceuticals

The established LC procedure was applied to the QC analysis of ^{11}C-labelled pharmaceutical products. Fig. 5 displays typical chromatograms of the [^{11}C]raclopride, [^{11}C]MP4A and [^{11}C]FLB457 preparations, obtained with the simultaneous detection by UV absorption and NaI(Tl) scintillation. As a comparison, analyses were performed on a conventional LC column (L1 described in the USP [10]) with 10 μm particles. In the present method, the narrow peak shape of the analytes resulted in increased sensitivity (19-fold and 14-fold higher in peak heights of raclopride and FLB457) and 70% shorter analysis time than the traditional method. We could perform QC analysis of [^{11}C]MP4A with sufficient sensitivity to determine the actual concentration of MP4A in PET pharmaceutical fluid; the observed concentration was 0.66 μg/mL. The QC tests, including specific radioactivity, radiochemical and chemical purities, were completed within 1 min. The observed QC results of [^{11}C]raclopride (specific radioactivity: 220 GBq/μmol, desmethyl-raclopride: <0.002 μg/mL, radiochemical purity: 99.9%) and [^{11}C]FLB457 (specific radioactivity: 290 GBq/μmol, desmethyl-FLB457: <0.003 μg/mL, radiochemical purity: 99.8%) preparations were similar to those obtained by traditional LC procedure.

A special feature of QC for short-lived PET radiopharmaceuticals is that they have to be performed within a strict time limit between their production and human application, and the synthetic products to be tested are present in extremely small amounts. Difficulties associated with the current QC procedure often need to be overcome to facilitate the use of a large sample volume and/or to release the product prior to completion of the tests. In this study, in an attempt to resolve current problems we established an ultra-fast, sensitive and simple LC system for a wide array of PET radiopharmaceuticals. Combining a 50 mm long column packed with 2.5 μm particles, ammonium-phosphate buffer as the mobile phase and low-wavelength UV detection led to excellent separation of target analytes within a very short run of 1 min with a significant improvement in the applicability and sensitivity. This sensitivity increase resulted not only from the improved sensitivity provided by low-wavelength detection but also from a benefit provided by fast LC; high efficacy due to limited diffusion, so that only a 5 μL sample is required for QC tests of specific radioactivity and radiochemical/chemical purities. Consequently, QC data can be obtained and evaluated prior to human administration without extensive loss of radioactivity, and with increased safety when compared to tests performed after release of the product. The common column and mobile phase could be employed for a wide variety of ^{11}C, ^{18}F, ^{62}Cu-labelled pharmaceuticals using conventional LC apparatus. This characteristic offer many advantages: (1) ability to analyze different pharmaceuticals in a short period; only 7 min was required to equilibrate the analysis condition for [^{11}C]DASB after the QC test of [^{11}C]L-methionine, (2) effective minimization of human error and radiation exposure to the operators, and (3) easy to incorporate into the routine and automated QC program of any PET facility.

On the other hand, [^{18}F]FLT has recently been described as a promising PET probe for visualizing cellular proliferation [11,12]. The most widely accepted radio-synthesis method for [^{18}F]FLT employs a nosylate precursor with *N*-BOC and *O*-4,4′-dimethoxytrityl (DMTr) protecting groups by 2-step reaction (fluorination in the presence of Krptofix 2.2.2 and acid hydrolysis) (Fig. 6) [13]; however, several non-radioactive products, such as DMTr methanol, p-nitrobenzene sulfonic acid, 2′,3′-didehydro-3′-deoxy-thymidine and thymidine are produced and might be contaminated in the final preparation of [^{18}F]FLT. Using the present system, QC tests for not only specific radioactivity and radiochemical purity of [^{18}F]FLT but also chemical impurities, including Krptofix 2.2.2, precursor and their by-products could be performed utilizing a gradient elution profile. All seven of these analytes were separated and detected within 7 min with sufficient sensitivity (Fig. 6). Although this system was not applicable to [^{18}F]FDG preparation without prior chemical modification due to high polarity, chemical impurity tests, including cold FDG, ClDG and Krptofix 2.2.2, could be achieved by this system using a pre-column derivatization technique, as reported previously [14].

4. Conclusion

A novel LC system for QC tests of specific radioactivity, radiochemical and chemical purities has been presented as a tool for clinical use of a wide array of short-lived PET radiopharmaceuticals. Radiopharmaceutical analysis was completed within a very short run time with a significant improvement in applicability and sensitivity. The proposed procedure could be incorporated into the routine QC program of a PET facility and, furthermore, might be applied for QC tests of other PET radiopharmaceuticals.

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