Venkatachalam T. K. (Orcid ID: 0000-0001-9747-1105)

Bhalla R. (Orcid ID: 0000-0003-1421-3667)

Investigation on the impact of three different QMA cartridges on the radiosynthetic yields of [^{18}F]fluoromethyl tosylate

D.H.R. Stimson, Z. Qiao, D. Reutens, T.K. Venkatachalam and *R. Bhalla.

Centre for Advanced Imaging, Building 57, University of Queensland, St. Lucia, QLD, Australia 4072.

*Corresponding author: r.bhalla@uq.edu.au

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jlcr.3781

Abstract

Our recent investigations for the radiosynthesis of [^{18}F]fluoromethyl tosylate have highlighted that choice of quaternary methyl ammonium (QMA) cartridge used during the radiosynthesis can significantly impact the radiochemical yields. Often the details of the QMA cartridge used in fluourine-18 syntheses are not fully described. However, our studies demonstrate that the type, the size and nature (method by which it has been conditioned) of the QMA cartridge used during the radiosynthesis can make a significant impact in the labelling efficiency. This paper investigates the use of three QMA cartridges and demonstrates that radiochemical yield (decay corrected) of [^{18}F]fluoromethyl tosylate can increase from 46 to 60% by simply changing the QMA cartridge (and leaving all other reagents and labelling conditions exactly the same). These learnings may be applied to improve the radiochemical yields of a number of [^{18}F]-fluorinated tracers (and synthons) where the labelling step is base-sensitive to increase the radiochemical yield, thereby significantly benefiting the radiochemistry and nuclear medicine community. This paper also highlights the necessity of the radiochemistry community to ensure the details of QMA cartridges used in fluorine-18 chemistry are fully and accurately described, since this will improve the translation of radiochemical methods from one laboratory to another.

Keywords

PET, synthon, [^{18}F]Fluoromethyl tosylate, [^{18}F]Fluoromethylation, QMA

1. Introduction

[^{18}F]Fluoromethyl tosylate is a versatile prosthetic group for the fluoromethylation of various compounds to produce imaging probes for positron emission tomography (PET). Consequently, a robust radiosynthesis of this fluorine-18 synthon is an important requirement for the production of many PET tracers. Other methods to introduce fluoromethyl groups use synthons such as [^{18}F]fluoromethyl bromide and [^{18}F]fluoromethyl iodide [1] are less easy to handle (volatile) and the yield of the final labelled product is lower. Since the initial description of the preparation of [^{18}F]fluoromethyl tosylate, it has been used to in the synthesis of a wide range of tracers including [^{18}F]fluoromethyl choline [1a, 2], [^{18}F]fluoromethyl D_4-choline[3] and fluorobenzothiazole analogues [4]

In 2005, Neal et al reported an elegant improvement in the method of synthesis of [^{18}F]fluoromethyl tosylate (Scheme 1) which highlighted the importance of the inclusion of a small quantity of water in the labelling step.[5] Their studies demonstrated that the by-product [^{18}F]tosyl fluoride formed during the fluorination of methylene-ditosylate was reduced by addition of water. However, Smith et al.[2b] reported that despite using the exact same labelling methods their radiochemical yields of [^{18}F]fluoromethyl tosylate were significantly lower than that of Neal et al.[5] In order to get comparable yields to Neal, Smith et al needed to modify their radiochemistry – switching from Kryptofix® as the phase transfer catalyst to 18-crown-6 ether.

The [^{18}F]fluoride used in nucleophilic reactions is generally separated from the cyclotron target ^{18}O-water using a QMA cartridge allowing the enriched water to be recovered. Typically the first step of the process involves [^{18}F]fluoride being trapped onto a QMA cartridge, and this is followed by elution of the [^{18}F]fluoride typically using a basic aqueous mixture with a phase transfer agent such as [K(Kryptofix®)]$_2$[CO_3]. Although the amount of the basic solution

[K(Kryptofix®)]$_2$[CO_3] used for the elution is accurately measured, this paper demonstrates that the amount of base that is eluted into the reaction will also be dependent on the QMA cartridge used in the process. This is important since the presence of excess base in a fluorination reaction may cause unwanted side reactions such as hydroxylation or elimination [6]. Attempts to finely control the amount of base by using different cartridge elution methods have been reported [7], involving the use of inert potassium salts such as potassium methanesulfonate and potassium trifluoromethanesulfonate. Alternatively, radiolabelling using [^{18}F]fluoride in enriched water directly from the cyclotron target may be achieved with accurate addition of base to enhance the radiochemical yield, however target generated impurities including various radionuclides and metals [8] are not removed in this process.

This paper reports a systematic investigation of the use of three QMA cartridges, demonstrating that the radiochemical yields of [^{18}F]fluoromethyl tosylate are "dependent" on the choice of cartridge. Synthesis has been up-scaled using the most favourable QMA with an automated synthesiser and HPLC purification and re-formulation of the [^{18}F]fluoromethyl tosylate. We hypothesise that some of the variation observed in radiochemical yields between different research groups for the synthesis of [^{18}F]fluoromethyl tosylate is due to the QMA cartridge that they use during their radiosynthesis.

2. Results and Discussion

Our initial attempts in establishing the radiosynthesis of [^{18}F]fluoromethyl tosylate based on literature protocols seemed to result in a lower end of synthesis yield than anticipated. In a typical labelling process, the [^{18}F]fluoride was trapped onto a pre-conditioned 130mg Waters QMA Carbonate Plus Light cartridge, followed by elution with using Kryptofix® and potassium carbonate into the reaction vessel. Following the drying step, bis(tosyloxy) methane (dissolved in 97% acetonitrile / 3% water) was labelled at 105°C for 10 minutes (Figure 1a,

Table 1). This resulted in a radiochemical conversion determined by radio-HPLC (system 1) of 46%. In order to probe the impact of this pre-conditioned 130 mg QMA, we investigated the radiolabelling step (using identical conditions, including the exact quantities of potassium carbonate and Kryptofix®) without the use of a QMA cartridge using a manual radiolabelling rig (see Supporting Information for details of the manual setup). The decay corrected radiochemical yields increased from 46 to 58%, which indicates that the 130 mg pre-conditioned cartridge has a negative impact on the yield. Since a QMA cartridge is essential to remove radionuclidic impurities, we investigated other QMA cartridges. A summary of the results are presented in Table 1 and representative HPLCs of these reactions can be found in both Figure 1 and in the Supplementary Information.

Switching from a pre-conditioned carbonate QMA (initial experiment) to a QMA chloride cartridge 130 mg (which was manually conditioned with 0.1 M potassium carbonate and water) resulted in an increase of radiochemical yield from 45 to 60% - the 60% yield is comparable to the radiochemical yield without the use of a QMA. Finally we investigated a smaller 46 mg pre-conditioned carbonate QMA – this also resulted in higher radiochemical yields of 58%.

The amount of base introduced to the radiolabelling step as a result of [^{18}F]fluoride elution from the QMA cartridge has been investigated previously and the fine control of base has been highlighted as an important factor during fluorinations [7].The use of a lower quantity of base to improve radiosynthesis has also been described previously [9]. However the effect of particular QMA cartridges and/or their pre-conditioning has not been well explored previously. Our radiolabelling studies highlight that there is an impact on the radiochemical yield of [^{18}F]fluoromethyl tosylate which can be fine-tuned by switching the type of ion exchange cartridge used in the initial trap and release of [^{18}F]fluoride]. We suspect that this difference

may be caused by additional quantities of base which may elute from the original pre-conditioned 130 mg Water QMA Carbonate Plus Light cartridge we used in our study, which subsequently has a negative impact on radiochemical yield.

Since the pre-conditioned conditioned 46 mg QMA cartridge gave results comparable to the manually conditioned 130 mg cartridge, we have fully automated the radiosynthesis of [^{18}F]fluoromethyl tosylate using the 46 mg pre-conditioned QMA cartridges . Non-corrected end of synthesis yields 30 ± 2% (n = 3) have be obtained when using the 46 mg pre-conditioned QMA cartridge. The molar (radio)activity of [^{18}F]fluoromethyl tosylate was determined to be 487 ± 105 GBq/μmol (n = 3). Figure 2 shows a typical profile of the radio-HPLC trace of purification of the radiosynthesis and Figure 3 shows the HPLC trace of the purified product.

3 Experimental Procedure

3.1 Material and methods

All chemicals were purchased from Sigma-Aldrich Chemical Company and used as received. Bis(tosyloxy) methane was synthesised using modified literature methods [10] Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker 700 MHz instruments and chemical shifts are reported in parts per million relative to tetramethylsilane, which was the internal standard. 13C NMR spectra were recorded in CDCl3, on the same instruments. The chemical shifts reported for 13C NMR spectra are referenced to chloroform at 77.0ppm.

[^{18}F]Fluoride was manufactured via the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of isotopically enriched water (>98% ^{18}O, *Huayi, China*) with 18 MeV protons using the "Cyclone 18 Twin" (*IBA, Belgium*) fixed energy cyclotron. A small volume liquid target (fill volume of approximately 0.7 mL) was used for [^{18}F]F^{-} production, connected to delivery points within hot-cells via 1.6 mm external diameter polypropylene homopolymer tubing drawn through

conduit encased in the concrete of the building's structure. The saturation yield for this target is around 40 GBq within 60 minutes at 14 μA beam current.

Manual (non-automated) syntheses were conducted without purification using a rig comprising an adjustable nitrogen gas supply and a temperature controlled heating block located within a lead-brick castle housed inside a shielded fumehood (see Supporting Information).

Automated radiosyntheses were conducted using the Synthra RN-Plus (*Synthra*, *GmbH*) automated module, which allows radiolabelling, semi-preparative High Performance Liquid Chromatography (HPLC) purification and subsequent reformulation.

The Synthra RN-Plus is equipped with two reaction vessels, however only one is required for the synthesis of [^{18}F]fluoromethyl tosylate. To allow the transfer of the crude reaction mixture from the reaction vessel to the HPLC injection loop, the output valve from the reaction vessel (V15) is short-cut to valve position 3 of the syringe driver (see Supporting Information for simplified Synthra Graphical Users Interface). A dose calibrator has been installed within the larger RES hot-cell which enables accurate measurement of the quantity of [^{18}F]F^- delivered from the cyclotron target before transfer to the synthesis module.

3.2 Chemical Procedures

All chemical reagents were purchased from *Sigma-Aldrich Pty Ltd* unless otherwise stated. Bis(tosyloxy) methane was made according to literature methods.[10b]

3.2.1 Synthesis of [^{19}F]fluoromethyl tosylate

In a flask was placed 1.4 g of bis(tosyloxy) methane (3.93 mmol) and 30 mL of anhydrous tetrahydrofuran was added and the contents stirred to form a homogenous solution. To this solution was added a solution of 2.2 mL of tetrabutyl ammonium fluoride (1 M) in anhydrous THF (2.2 mmol) when a dark brown solution was obtained. The contents were allowed to

reflux over an oil bath for 3 hours when a clear solution was obtained. The mixture was cooled to room temperature and the solvent evaporated under vacuum and to the residue was added 50 mL of ethyl acetate and 20 mL of water. The organic layer was separated and further washed with water (30 mL) followed by brine. The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated to give a viscous liquid. This was subjected to column chromatography over silica gel using a mixture of 5:2 hexane/ethyl acetate to furnish the desired compound as an oil (0.096 g, 0.47 mmol, 12%).

The calibration curve of [^{19}F]fluoromethyl tosylate used for determining the molar activity of the [^{18}F]fluoromethyl tosylate is included in the Supporting Information.

^{1}H NMR (700 MHz, CDCl3) δ ppm 7.82 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.72 (d, 2H), 2.44 (s, 3H); ^{13}C NMR (175 MHz, CDCl3) δ ppm 145.6, 133.8, 129.9, 127.9, 98.1 (d, J = 229.5 Hz), 21.7.

3.3 Radiochemical Procedures

3.3.1 Manual [^{18}F]fluorination procedure (without QMA): A solution of Kryptofix® (4 mg, 10.6 mmol) and potassium carbonate (0.69 g, 5 mmol) in a 50:50 solution of water :acetonitrile (1 mL) was added to a vial containing [^{18}F]fluoride (186 MBq) in $H_2{}^{18}O$ (50µL) and the vial was sealed with a rubber septa and crimped with an aluminium seal and placed transferred to a heater. Two needles were inserted into the seal, one connected to a nitrogen line and the other connected to a vent line with in-line solvent trap. The reaction vessel was heated to 100°C under nitrogen flow at 0.1 L/min for approximately for 10 minutes, followed by 0.2 L/min for 10 mins and finally 0.3 L/min effectively drying the contents of the vessel. The needles were carefully removed and the reaction vessel was then cooled to approximately 30°C before the addition of bis(tosyloxy) methane (5mg, 14 mmol) in 1mL solvent (97:3 of

MeCN: water). The radiolabelling reaction was conducted at 105°C for 10 minutes. The reaction vessel was then allowed to cool to room temperature and 1mL of water was added and the solution mixed in the vial to ensure any unreacted fluoride was dissolved in solution. A sample of this solution was then analysed by radio-HPLC

Note: addition of 1 mL water is critical to ensure all the unreacted [^{18}F]fluoride dissolves in solution. To demonstrate that all radioactivity was in solution we took representative reaction and transferred them to a clean glass vial. In all cases this resulted in confirmation that greater than 95% of the radioactivity was transferred to the clean glass vial. Failure to add the 1mL of water has a risk of not dissolving all the unreacted [^{18}F]fluoride, and therefore underestimating the percentage of unreacted [^{18}F]fluoride in the radio-HPLC.

3.3.2 Manual [^{18}F]fluorination procedure (with QMA):

Three QMA cartridges were used

i) Sep-Pak® Accell Plus QMA Carbonate Plus Light, 130 mg sorbent, (186004051, Waters)

ii) Sep-Pak® Accell Plus QMA Plus Light Cartridge, 130 mg sorbent, (WAT023525, Waters)

iii) Sep-Pak® Accell Plus QMA Carbonate Plus Light, 46mg sorbent, (186004540, Waters)

Both the 130 mg and 46 mg Sep-Pak® Accell Plus QMA Carbonate Plus Light cartridges were used without further conditioning.

The Sep-Pak® Accell Plus QMA Plus Light Cartridge, 130mg sorbent, (WAT023525) was conditioned as follows before use in the radiolabeling studies:

i) 10 mL of 0.1 M K_2CO_3

ii) 10 mL water

iii) 2 × 10 mL of air (using syringe)

To ensure direct consistency all manual reactions were carried out as follows.

The labelling procedure can be broken down to four steps (a) trap of [^{18}F]fluoride on QMA , (b) release of [^{18}F]fluoride from QMA, (c) evaporation of solvents to dry [^{18}F]fluoride and (d) radiolabeling reaction with bis(tosyloxy) methane.

3.3.2(a) Trap

[^{18}F]fluoride (300 to 500 MBq, in approx 50 to 100 µL of $H_2{}^{18}O$) was trapped on to a QMA cartridge using a 1mL syringe. Water (1mL) was then passed through the QMA (this was to replicate a volume of water that is typical of target volumes from a cyclotron). The QMA was then dried with 2 × 1 mL air (using a 1 mL syringe). The radioactivity of the QMA (and the time of measurement) were recorded. In all cases greater than 99.9% of the radioactivity trapped onto the QMA.

3.3.2(b) Elute

A solution of Kryptofix® (4 mg, 10.6 µmol) and potassium carbonate (0.69 mg, 5 µmol) in a 50:50 solution of water:acetonitrile (1 mL) was used to elute the trapped [^{18}F]fluoride from the QMA into a 10 mL glass vial. This was followed by passing through 2 × 1 mL air through the QMA cartridge to ensure maximum transfer all the radioactivity / solution from the QMA into the glass vial. The glass vial was sealed with a rubber septa and crimped with an aluminium seal. The radioactivity on the QMA and in the glass vial were then subsequently measured.

In all three cases less than 3% residual activity remained trapped on the QMA post elution, with 97 to 98% of the [^{18}F]fluoride eluting into the glass vial.

3.3.2(c) Dry

The vial was placed transferred to a heater and two needles were inserted into the seal, one connected to a nitrogen line and the other connected to a vent line with in-line solvent trap. The reaction vessel was heated to 100°C under nitrogen flow at 0.1 L/min for approximately for 10 minutes, followed by 0.2 L/min for 10 mins and finally 0.3 L/min effectively drying the contents of the vessel. The needles were carefully removed and the reaction vessel was then cooled to approximately room temperature. No losses of radioactivity were observed during the drying procedure.

3.3.2(d) Radiolabel

Bis(tosyloxy) methane (5 mg, 14 μmol) in 1mL solvent (97:3 of MeCN: water) was added to the glass vial containing the dried [^{18}F]fluoride. The radiolabelling reaction was conducted at 105°C for 10 minutes. The reaction vessel was then allowed to cool to room temperature and 1 mL of water was added and the solution mixed in the vial to ensure any unreacted fluoride was dissolved in solution. A sample of this solution was then analysed by radio-HPLC.

3.3.3 Automated (^{18}F)fluorination of bis(tosyloxy) methane (see supplementary for scheme of automated synthesis) : [^{18}F]Fluoride in enriched water was delivered under helium pressure to the hot-cell where it was measured in a dose calibrator and then transferred into the "V-vial" of the Synthra RN-Plus module. The aqueous [^{18}F]F^- was transferred under vacuum via valve V1 to the QMA cartridge (note that 3 types were assessed, as described above), with the enriched water directed to a $H_2{}^{18}O$ recovery vial via V13. The [^{18}F]F^- was eluted from the cartridge via V13, V2, and V14 and collected in the glassy carbon reaction vessel using an eluent solution (from vial A1) of 4 mg Kryptofix® (10.6 μmol) in 0.5mL MeCN and K_2CO_3 (0.69 mg, 5 μmol) in 0.5mL water. Drying of the fluoride was performed under helium flow (V18) with vacuum applied (V19, V22) at a temperature of 68°C for 5 minutes, then at 95°C

for a further 10 minutes. Helium flow ceases and the reaction vessel was cooled to 30°C before the vacuum was stopped. The temperature of 30°C was employed to ensure that there was no loss of the solvent added in the subsequent step. Bis(tosyloxy) methane (5 mg, 14 μmol) dissolved in 1mL MeCN/water (97:3) was transferred from vial A3 into the reaction vessel and radiolabelling was conducted at 105°C for 10 minutes whilst stirring. The reaction vessel was then cooled to 30°C to ensure that the solvent re-condenses and 1mL water is added from vial A4. The diluted crude reaction mixture is be drawn-up into the syringe unit using position 3 of the syringe valve. The syringe unit can then then load the 5mL volume HPLC loop, pre-loaded with HPLC solvent, with the diluted crude reaction mixture via position 2 of the syringe valve and the HPLC injected using V26. Semi-prep HPLC purification was achieved under isocratic conditions using a Nucleodur® C18 Pyramid, 250 x 10 mm, 7μm (p/n 762290.100, *Macherey-Nagel, GmbH*) with a mobile phase of water/MeCN (50:50) at 3 mL/min.

The purified product, identified using the radiochromatogram, was cut to a collection vial containing 30 mL of water via V27 and stirred. Helium pressure was applied to the vial to transfer the contents through a manually preconditioned (10 mL EtOH, 10 mL water then 20 mL air) C18 cartridge (Sep-Pak® C18 Plus Short Cartridge, *Waters*, p/n WAT020515) to waste via V35 and V36. The loaded cartridge was then washed with 10mL of water from vial C3 directed to waste, and then dried using helium flow via vial C1. The [^{18}F]fluoromethyl tosylate was eluted from the C-18 cartridge with 2 mL DMF from C2 to the vented product collection vial. The total synthesis time (which has not been optimised) from ^{18}F delivery to reformulated product collection was under 70 minutes. This may be reduced if drying of the C18 cartridge before elution is not required.

Quality Control

Two different HPLC systems were used in this work. The analytical method was the same for HPLC systems – however there is slight difference in retention time between the two systems. Full production of [^{18}F]fluoromethyl tosylate (which included purification) were all analysed on System 2 The calibration curve for [^{19}F]fluoromethyl tosylate was also obtained on System 2.

System 1: Analyses of the crude product were performed using a quaternary pump (model 1260 Infinity, *Agilent*) equipped with a 20 µL injection loop, dual wavelength UV detector and a radio-detector (Bioscan *Flow Count* with a pin-diode detector) in conjunction with *OpenLab CDS ChemStation* software. A Zorbax Eclipse Plus C18 (*Agilent*), 4.6 X 150mm, 5µm analytical column was used with an eluent of water/MeCN delivered at 1 mL/min using the following method: 0-1 min 30% MeCN, 1-25 min 30 – 95% MeCN, 25-30 min 95% MeCN, 30-31 min 95 to 30% MeCN, 31-33 min 30% MeCN. The retention time of fluoromethyl tosylate was established as 11.5 minutes at 254nm.

System 2: HPLC analysis of the purified [^{18}F]fluoromethyl tosylate was performed using a quaternary pump (model LC-20AD, *Shimadzu*) with diode array detector, thermostatic column compartment, and a radio-detector (Bioscan *Flow Count* with a pin-diode detector) in conjunction with *LCsolutions* software. The analytical column and elution conditions were those described above. The temperature of the column was maintained at 40°C during analyses. Using a 20 µL sample injection, the retention time of fluoromethyl tosylate was established as 10.5 minutes at 239 nm.

4. Conclusion

Our studies have demonstrated that radiochemical yields of [^{18}F]fluoromethyl tosylate are strongly influenced by the choice of the QMA cartridge used during the radiochemical synthesis. These results highlight that there is a greater need for radiochemists to be clearer (and more detailed) about the types of ion exchange cartridge that have used during the radiosynthesis since this may have a significant impact on the final radiochemical yield.

References

[1] a) T. R. DeGrado, S. W. Baldwin, S. Wang, M. D. Orr, R. P. Liao, H. S. Friedman, R. Reiman, D. T. Price, R. E. Coleman, *J Nucl Med* **2001**, *42*, 1805-1814; b) T. R. DeGrado, R. E. Coleman, S. Y. Wang, S. W. Baldwin, M. D. Orr, C. N. Robertson, T. J. Polascik, D. T. Price, *Cancer Research* **2001**, *61*, 110-117; c) J. Bergman, O. Eskola, P. Lehikoinen, O. Solin, *Applied Radiation and Isotopes* **2001**, *54*, 927-933; d) J. Zessin, O. Eskola, P. Brust, J. Bergman, J. Steinbach, P. Lehikoinen, O. Solin, B. Johannsen, *Nuclear Medicine and Biology* **2001**, *28*, 857-863; e) L. Zheng, M. S. Berridge, *Applied Radiation and Isotopes* **2000**, *52*, 55-61; f) M. R. Zhang, J. Maeda, K. Furutsuka, Y. Yoshida, M. Ogawa, T. Suhara, K. Suzuki, *Bioorganic & Medicinal Chemistry Letters* **2003**, *13*, 201-204.

[2] a)M. E. Rodnick, A. F. Brooks, B. G. Hockley, B. D. Henderson, P. J. H. Scott, *Applied Radiation and Isotopes* **2013**, *78*, 26-32; b) G. Smith, Y. Zhao, J. Leyton, B. Shan, Q.-d. Nguyen, M. Perumal, D. Turton, E. Årstad, S. K. Luthra, E. G. Robins, E. O. Aboagye, *Nuclear Medicine and Biology* **2011**, *38*, 39-51.

[3] T. H. Witney, I. S. Alam, D. R. Turton, G. Smith, L. Carroll, D. Brickute, F. J. Twyman, Q.-D. Nguyen, G. Tomasi, R. O. Awais, E. O. Aboagye, *Clinical Cancer Research* **2012**, *18*, 1063-1072.

[4] U. Berndt, C. Stanetty, T. Wanek, C. Kuntner, J. Stanek, M. Berger, M. Bauer, G. Henriksen, H.-J. Wester, H. Kvaternik, P. Angelberger, C. Noe, *Journal of Labelled Compounds and Radiopharmaceuticals* **2008**, *51*, 137-145.

[5] T. R. Neal, S. Apana, M. S. Berridge, *Journal of Labelled Compounds and Radiopharmaceuticals* **2005**, *48*, 557-568.

[6] B. S. Lee, J. W. Seo, S. J. Lee, S. J. Oh, D. Y. Chi, *Bulletin of the Korean Chemical Society* **2011**, *Volume 32*, 71 - 76.

[7] S. J. Lee, S. J. Oh, D. Y. Chi, D. H. Moon, J. S. Ryu, *Bulletin of the Korean Chemical Society* **2012**, *33*, 2177-2180.

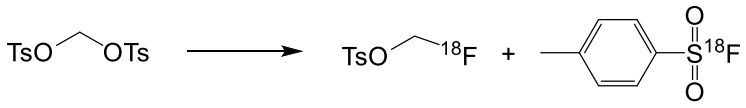
[8] a) D. J. Henderson, R. K. Barnes, R. M. Fawdry, D. H. Stimson, *ANZ Nuclear Medicine* **1997**, *28*; b) J. M. Gillies, N. Najim, J. Zweit, *Applied Radiation and Isotopes* **2006**, *64*, 431-434; c) M. A. Avila-Rodriguez, J. S. Wilson, S. A. McQuarrie, *Applied Radiation and Isotopes* **2008**, *66*, 1775-1780; d) D. Ferguson, P. Orr, J. Gillanders, G. Corrigan, C. Marshall, *Applied Radiation and Isotopes* **2011**, *69*, 1479-1485.

[9] a) M. Suehiro, S. Vallabhajosula, S. J. Goldsmith, D. J. Ballon, *Applied Radiation and Isotopes* **2007**, *65*, 1350-1358; b) P. Marchand, A. Ouadi, M. Pellicioli, J. Schuler, P. Laquerriere, F. Boisson, D. Brasse, *Nuclear Medicine and Biology* **2016**, *43*, 520-527.

[10] a) D. Block, H. H. Coenen, G. Stöcklin, *Journal of Labelled Compounds and Radiopharmaceuticals* **1987**, *24*, 1029-1042; b) W. D. Emmons, A. F. Ferris, *Journal of the American Chemical Society* **1953**, *75*, 2257-2257.

Table 1. Comparison of the radiochemical yields of [^{18}F]fluoromethyl tosylate using different QMA cartridges.

QMA cartridge	**Conditioning protocol**	**Elution efficiency**	**HPLC yield of [^{18}F]Fluoromethyl tosylate**	**Decay corrected yield = (Elution efficiency × HPLC yield)/100**	
None	N/A	N/A	57%	57%	58 ± 1% (n = 3)
			59%	59%	
			59%	59%	
Sep-Pak® Accell Plus QMA Carbonate Plus Light, 130 mg p/n 186004051, Waters	Pre-conditioned	97%	45%	44%	46 ± 1.5% (n=3)
		97%	47	46%	
		97%	49	47%	
Sep-Pak® Accell Plus QMA Plus Light Cartridge, 130 mg p/n WAT023525, Waters	10 mL 0.1M K_2CO_3 and 10mL water (then 2 × 10 mL air via syringe)	98%	63%	62%	60 ± 1.5% (n = 3)
		98	60	59%	
		97	62	60	
Sep-Pak® Accell Plus QMA Carbonate Plus Light, 46 mg p/n 186004540, Waters	Pre-conditioned	98%	61%	60%	58 ± 1.5% (n = 3)
		98	59	58	
		98	58	57	



Scheme 1: Radiosynthesis of [^{18}F]Fluoromethyl tosylate

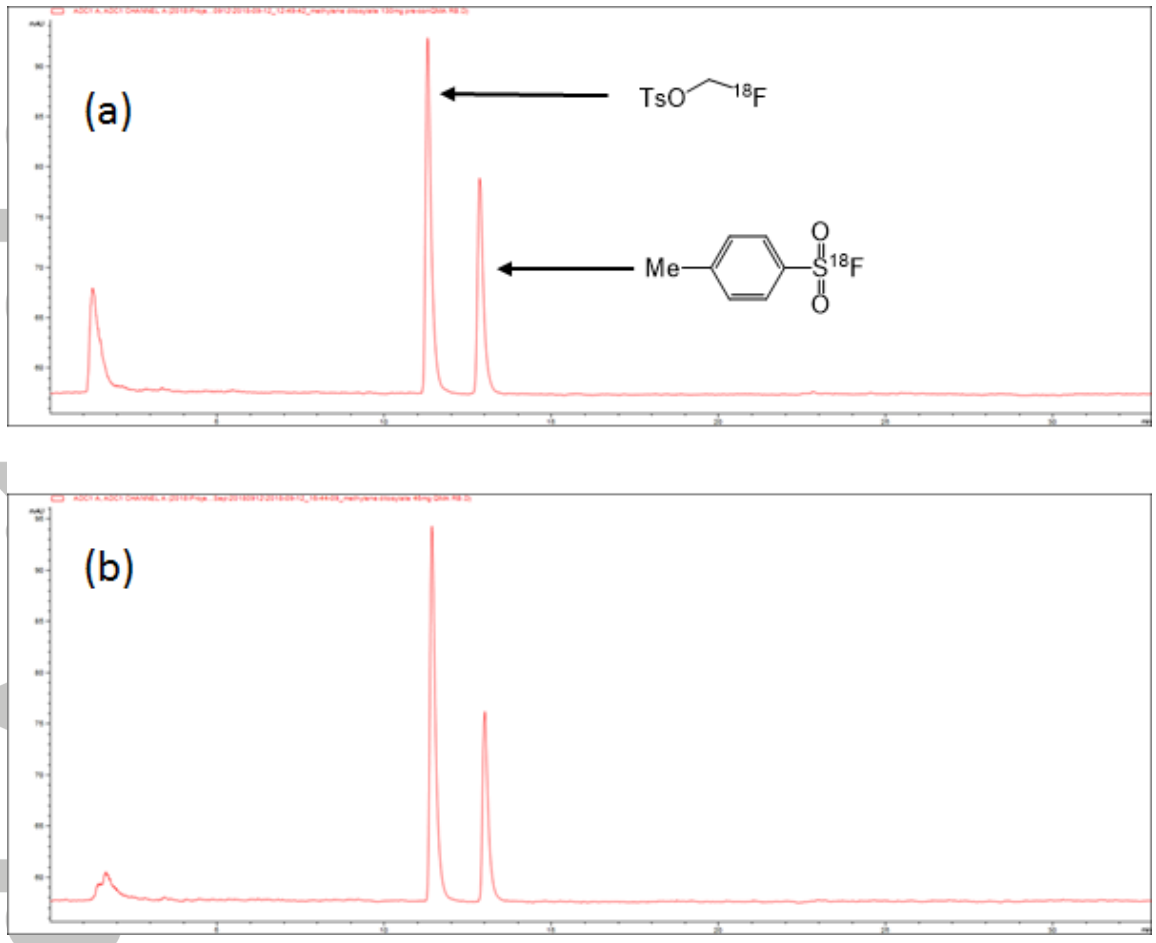


Figure 1. Comparison of radio-HPLC of labelling reaction (a) using a 130 mg and (b) 46 mg pre-conditioned QMA cartridge using HPLC *System 1*.

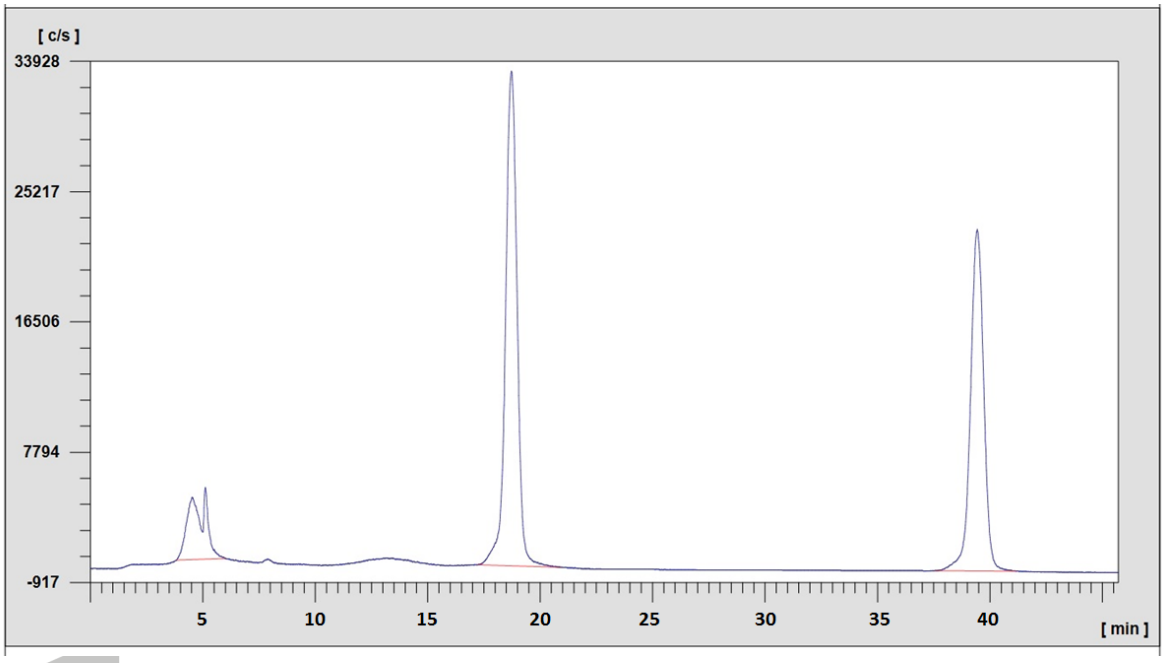


Figure 2. Typical semi-preparative radio-chromatogram of [^{18}F]fluoromethyl tosylate. Peak at approx. 18 min corresponds to [^{18}F]fluoromethyl tosylate and peak at 39 minutes corresponds to [^{18}F]tosyl fluoride. HPLC conditions: Nucleodur® C18 Pyramid, 250 x 10mm, 7µm with a mobile phase of water / MeCN (50:50) at 3 mL / min.

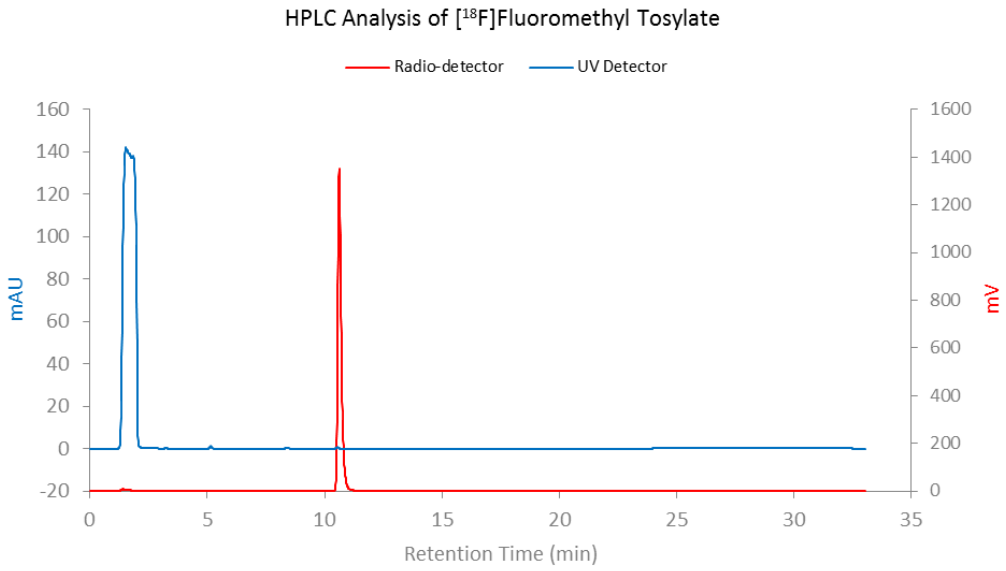


Figure 3. Analytical chromatograms of semi-preparative HPLC purified and reformulated [^{18}F]fluoromethyl tosylate in DMF using HPLC *System 2*. The large peak at around 2 minutes in the UV trace is due to the solvent DMF.