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Teflon radiolysis as the major source of carrier in fluorine-18

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The practical upper limit of fluorine-18 specific activity has remained constant for many years among cyclotron facilities internationally. Although there have been isolated reports of very high specific activity and hints concerning the sources of carrier, experiments designed to identify carrier sources have been inconclusive and largely ineffective. This report describes experiments to test the hypothesis that radiolysis of fluorinated components is a source of carrier fluoride. Controlled experiments were performed in which contributions of irradiated fluorinated components to the mass of synthesized [^{18}F]fluorobenzaldehyde (FBA) were measured. There was clear correlation between irradiation of Teflon and carrier mass. There was an additive effect of carrier due to different fluoropolymer components. It was concluded that in typical target and radiosynthesis systems it is radiolysis of fluorinated material and not the material itself that generates a large majority of the carrier typically reported. All Teflon and other fluorinated materials in contact with the [^{18}F]fluoride solution were removed. With no further efforts to reduce carrier fluoride, FBA produced from a modest irradiation attained a reduction in mass from over 500 nmol to 30 nmol, and an increase in specific activity from 0.1 TBq (3 Ci) to 1.9 TBq (51 Ci) per micromole.

Keywords: fluorine-18; carrier; specific activity; Teflon

Introduction

F-18 specific activity has historically been 18-111 GBq (0.5–3 Ci) per μmol.[1–10] However, the theoretical specific activity of F-18 is 63 TBq (1.7 MCi) per μmol. The typical dilution of F-18 with F-19 is more than 500-fold. With very few exceptions this has applied to F-18 labeled products internationally regardless of the details of cyclotron, target, or synthetic apparatus. O-18 enriched target water, synthetic apparatus, and reagents have been commonly considered to be similar potential sources of carrier,[11] with O-18 water most often being cited anecdotally. However, target water[12–15] rarely contains the carrier fluoride observed in labeled products. Furthermore, in many laboratories it is common practice to recycle used O-18 water for subsequent irradiations, thereby removing any carrier. Contributions from target materials such as target seals or impurities in the target body have also been suspected. Finally, synthetic reagents and apparatus have been considered. No source has been proven.

Previous unreported work ancillary to the synthesis of [^{18}F]fluorocarazolol[12] included a systematic exploration of possible carrier fluoride sources. That work used an apparatus containing Teflon tubing and valves. The synthesis was performed many ways to isolate the source of carrier. Finally, enriched ^{18}O-water was passed through the target and delivery system but not irradiated, and ^{16}O-water was irradiated in the target. All experiments produced negligible mass compared to a normal radiolabeling experiment with irradiated ^{18}O-water. At that time it was concluded that the investigation had failed, because it was not acceptable to conclude that a micromole of ^{19}F was produced by 17 MeV proton irradiation of ^{18}O-water. Based upon further consideration of that work, on the results of Fuchtner *et al.*[16] and Horti,[11] and on other anecdotal reports, we hypothesized that carrier fluoride is produced by radiolysis of fluorinated polymers by ^{18}F.

In this work the carbonate and Kryptofix-assisted synthesis of [^{18}F]fluorobenzaldehyde (FBA, Scheme 1) from [^{18}F]-fluoride was used as a model reaction to evaluate the source of carrier fluoride. FBA was chosen because it provides a convenient synthesis that includes all aspects typical of radiofluorinations and because the intensity of its UV absorption allows accurate HPLC determination of carrier mass up to two orders of magnitude lower than normally achieved. The synthesized product mass in relation to the amount of radioactivity used and the configuration of fluorinated components in the system was investigated. Controlled experiments using irradiated Teflon were performed to measure radiolytic generation of carrier fluoride.

Results

The HPLC UV response was calibrated using standard FBA samples in the range of 0.1–1000 nmol in the 15 μl injected sample. The calibration value (200.2 mAU s/nmol) was reproducible and linear. There were no interfering peaks at the retention time of the product; however, one peak immediately preceded

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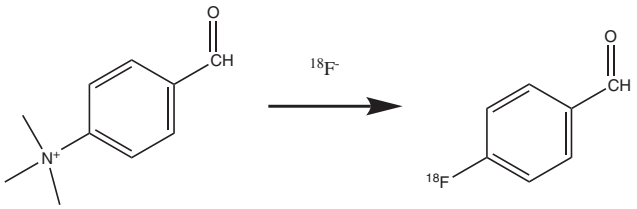

Scheme 1. Synthesis of [^{18}F]*p*-FBA.

the product with near-baseline separation at the quantities seen during the work. The detection limit, calculated from area of a peak of height twice the detector noise level, was 0.003 nmol HPLC-injected mass. The observed minimum HPLC-injected mass from experiments was 0.02 nmol, or nearly ten times the detection threshold. This corresponded to a total mass of carrier fluoride of 8 nmol. Measured values of carrier ranged from 8 to 1000 nmol. Figure 1 shows a chromatogram from an experiment with carrier mass at the low end of the detected range, with 0.03 nmol injected on the HPLC.

The configuration of the synthesis apparatus was adjusted for this work. Previously, Teflon tubing was used to transport irradiated target water, to contain the ion exchange resin, and to direct gas flow into the solution in the reaction vessel. Teflon slider valves were in the flow path of the ^{18}F-fluoride solutions. Labeled products typically had specific activity of 30–150 GBq (1–5 Ci)/μmol, with total mass of 400–800 nmol. For this work, all fluorinated tubing, fittings, and valves exposed to ^{18}F-fluoride were replaced with nonfluorinated materials, leaving only PEEK, glass, and polypropylene wetted surfaces. The Teflon-containing materials were then placed in the fluid flow path between the ion exchange resin and reaction vessel. This resulted in a more reproducible exposure of all components to labeled fluoride, but reduced the exposure of some of the components.

Control experiments explored non-Teflon sources of carrier. Carrier fluorobenzaldehyde in reaction solvents and reagents was below the 1 nmol detection limit. Carrier was detected in all experiments that allowed the precursor an opportunity to react. Control reaction on the benchtop with reagents only was repeated in triplicate, then repeated with addition of carbonate in 1 ml of high-purity water to mimic a fluoride elution, and again by passing the carbonate solution over prepared ion exchange resin. An average 25 nmol of carrier fluoride (Table 1) was produced, with a range of 10–50 nmol under all these conditions indistinguishably.

Baseline radiolabeling reactions were performed with no Teflon in the system. Reactions using any amount of ^{18}F from zero (no target irradiation) to 95 MBq (2.5 Ci) produced no discernable difference in product mass from the control experiments. Carrier fluoride introduced by the target, irradiation, and delivery was therefore negligible compared with that introduced by the reagents. These syntheses produced the lowest carrier mass and highest specific activities we have measured to date. Because of the radiation exposure concerns during the handling-intensive measurements, only four syntheses were performed using sufficient target irradiation to produce high specific activities. These experiments were performed only to determine whether additional mass was produced by extended irradiation in the target, and they did not produce more than half the potential radioactivity yield of the target. The chromatogram from one of these experiments is shown as Figure 1 and was among the lowest masses observed. The four higher-activity experiments produced masses of 8, 31, 69, and 10 nmol, and specific activities of 1.2, 1.9, 0.98, and 0.88 TBq (32, 51, 26, and 24 Ci)/μmol, respectively.

With Teflon components added to the flow path but without target irradiation no additional carrier was observed. With ^{18}F use in the Teflon-containing system, however, carrier was produced. Experiments were performed using 40 μA, 10 min irradiations (10 GBq, 300 mCi, fluoride EOB). With all Teflon components in place 357 nmol (average) carrier were produced, giving a specific activity of 22 GBq (600 mCi)/μmol, consistent with previous experience. Components of the system were then removed in turn. Experiments were done in triplicate. The results are shown in Table 1. Carrier produced by each component was expressed as the difference in measured carrier with and without that component in place. The sum of individual components by this method was equal to the carrier produced when all components were in use. Production of carrier increased with the wetted Teflon surface area and with the time of exposure of the Teflon to the radioactivity. Thus, the transfer tubing with its large surface area and the small tube used for evaporation of solvents, which experienced extended exposure time in the radioactive solution, both provided large carrier mass, while the slider valves, which had small surface area and short exposures, provided relatively little. No quantitative relationship between exposure time or surface area and carrier mass was evident from the data although it was clear that both contributed. However, estimation of these variables was only approximate.

Target water was clearly not a source of carrier. Target water is recycled routinely, such that no water was available in the laboratory that had not previously been used. Carrier fluoride intentionally added to the water (100 nmol) was measured as estimated carrier (115 nmol) in the first synthesis. Subsequent uses of the same water sample produced only control amounts of carrier. However, reagents accounted for the control quantities of carrier. Increasing the carbonate solution tenfold produced an additional 90 nmol. A similar increase in Kryptofix produced over 300 nmol. Alteration of precursor quantity did not produce a measurable effect. We conclude that carbonate normally provides roughly 10 nmol of fluoride, while Kryptofix seems to contribute the majority of the observed carrier in our control experiments. Passage of Kryptofix solution through ion exchange resin reduced observed carrier, though sufficient statistics were not gathered to quantify it accurately.

Teflon disks were incubated in aqueous ^{18}F to explore radiolytic carrier production. Figure 2 shows the mass generated from 20 min incubations vs activity. There is an apparent S-shaped curve. A rise may be present below 15 GBq (400 mCi), but mass in this region is consistent with controls. However, a sharp rise is seen between 15 and 20 GBq, followed by a possibly gradual increase as radioactivity is increased further. This surprising result is consistent with the observation that the Teflon-containing apparatus previously produced 200–500 nmol of carrier with no clear relationship to the radioactivity quantity when greater than 10 GBq was present, while production of 4 GBq produced less than 100 nmol of carrier. When duration of exposure was examined carrier rose to 100–200 nmol within 2 min of exposure, but then did not reach 300 nmol even after 30 min. Results with the Teflon-containing apparatus suggest that the numerical value of the threshold and possibly of the plateau observed in Figure 2 may also depend upon the usage history, and accumulated radiation damage, of the Teflon.

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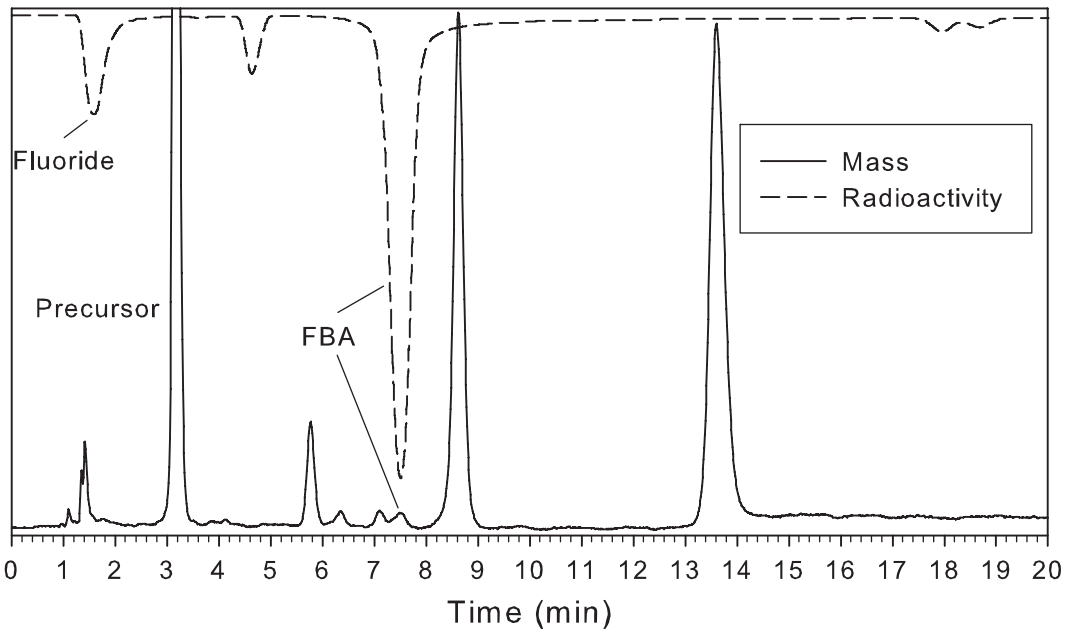

Figure 1. Chromatogram representative of analytical results, from a synthesis in a non-Teflon apparatus: target irradiation 40 μA, 10 min, 13.6 GBq (367 mCi) [^{18}F]fluoride EOB, 0.03 nmole injected on HPLC, 7.8 nmole total carrier in sample, specific activity 1.185 TBq (32,027 mCi)/μmole at 60 min EOB.

Table 1. Carrier mass from 11.1 GBq (300 mCi) exposure to system components

Teflon item	Surface (cm^2)	Time (min)	Mass (nmol)
1.5 mm Teflon tubing (790 cm)	252	1.25	72
Teflon resin holder	3.8	3	47
Teflon tube in reaction vessel	1.7	20	170
Rheodyne slider valve	2.3	1.25	6.3
Control-reagents only	0	0	25
Control-mock target water	0	0	23
All components	267	N/A	357

For each component, the estimated wetted Teflon surface area, the estimated exposure time to [^{18}F]fluoride solution during processing, and the attributed carrier mass is shown. Mass was calculated as the average difference of mass produced in a system containing, and not containing, the component. The 'All components' entry, however, shows the full mass produced in the experiment with all components present, including baseline amounts.

Discussion

Radiolysis of Teflon was established as the primary source of carrier in the former system. Without Teflon radiolysis, only 5–10% of typical radiopharmaceutical carrier was observed. Therefore, the major source of carrier was clearly radiolysis of Teflon. The radiation dose dependency of fluoride production from fresh pieces of Teflon was not simple. There were apparent production thresholds for both exposure duration and radiation dose rate. Less than two minutes of exposure sufficed to generate a full measure of carrier with fresh Teflon. Radiation dose rates below those typically generated during radiopharmaceutical production generated little carrier, but at the threshold a large increase occurred, which did not increase further with additional radiation dose. However, the Teflon-containing system provided evidence of a greater dependence on exposure time, which may have been due to cumulative radiation damage from repeated exposure of the Teflon components. This hypothesis is supported by the fact that, in pilot work, after a change in irradiation parameters three irradiations were necessary to achieve reproducible carrier production in a Teflon-containing system. Data from the various components indicated that exposed Teflon surface area and exposure time are important. The data suggest that the mechanism of fluoride release causes a steady state with successive use. This data is consistent with a previous report[16] of a correlation of carrier with neutron radiation dose to Teflon tubing near the target. The mechanism of radiolytic fluoride production appears complex and unclear. One report[17] has explored the subject and shown that fluoride is among a large number of other fluorinated fragments produced from fluorocarbons by radiolysis. That report demonstrates the complexity of the chemistry, but does not explain the radiation dose-dependency of this data. However, if fluorinated materials are eliminated the issue becomes moot.

Contrary to popular belief,[11] there was no detectable carrier contributed by target water, the target body, or non-Teflon apparatus. These items are of no concern. Recycled water, especially, was proven to be completely carrier-free. As a corollary of this work, in a laboratory which does not recycle target water and suspects it of containing unwanted carrier, it will suffice to pass the water over an ^{18}F recovery ion exchange cartridge before use, in imitation of the water recovery process. It was presumed that all detected mass represented fluoride carrier. However, the possibility of the formation of a non-FBA product with an identical retention time to give the appearance of carrier was not rigorously excluded. Although that is unlikely, if it occurred the actual carrier would be lower than estimated here. Among reagents, Kryptofix seemed to contain the majority of the non-Teflon related carrier, with less in the carbonate. Very little, if any, came from the labeling precursor, demonstrating

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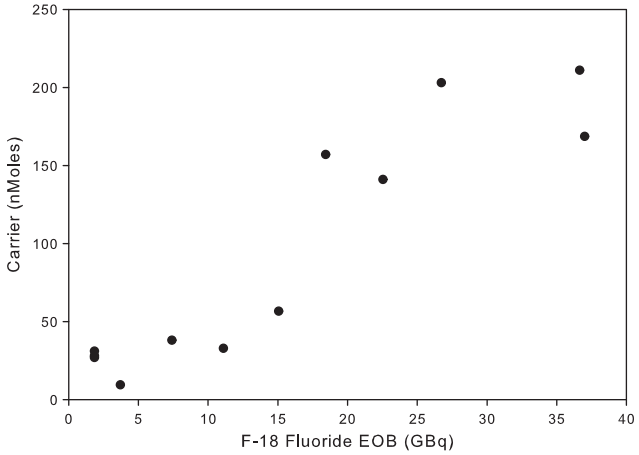

Figure 2. The effect of ^{18}F quantity on carrier mass. Selected quantities of [^{18}F]fluoride were incubated with a Teflon disk for 20 min before use in synthesis and measurement of carrier mass.

not only that the precursor contained little fluoride ion but also that there was little or no fluoride production via radiolysis of the triflate salt, as is sometimes feared.[11] Following this ten-fold reduction in carrier by elimination of Teflon, further improvement in specific activity will rely upon treatment of reagents and glassware and reduction of reagent quantities. It is reasonable to expect that reduction of reagents commensurate with the reduced level of carrier might be made without adverse effects.

It was not our goal here to demonstrate high specific activity. Most experiments were performed with modest radioactivity. No experiments were performed with more than half the possible ^{18}F production, and most were performed with less than one-tenth of the maximum radioactivity. To calculate the specific activity expected in more typical radiopharmaceutical production work, we may assume a 40 GBq (ca. 1 Ci) final radioactivity and use the mass measured from each non-Teflon experiment to calculate an 'effective specific activity'. This is a valid estimate in light of our observation that the amount of radioactivity produced in the non-Teflon apparatus does not affect the carrier mass. By this estimate, 15 of our experiments exceeded 1.8 TBq (50 Ci)/μmol, giving a maximum of 4.7 TBq (128 Ci)/μmol. This, without further effort at carrier reduction, approaches one tenth of the theoretical value for ^{18}F (63.37 TBq/μmol). It may also be noted that one may readily produce three to ten times this amount of radioactivity.

These results explain much of the confusing information from previous work. Prior irradiation of natural abundance water, which produced N-13, did not produce significant amounts of carrier, while irradiation of oxygen-18 enriched water produced the typical carrier in excess of 100 nmol. This was true though radiolytic damage by N-13 should be similar to F-18 (within 5%) because of the counterbalancing relationship between positron energy and range, according to Varskin software calculations, seeming to indicate that carrier generation involves irradiation of O-18 enriched water. However, in those experiments, the N-13 radioactivity (3–6 GBq, 80–160 mCi) was less than the F-18 radioactivity (ca. 40 GBq, 1 Ci), which was not considered significant at the time because a threshold effect of radioactivity was not expected. The threshold relationship observed in Figure 2 now explains the confusing result. Prior observations showed that one could remove 10 m of Teflon delivery tubing (target to hot cell) from a system, leaving only a few centimeters path length in Teflon valves and reaction vessel tubing, and still note substantial generation of carrier, seeming to indicate that Teflon was not the main source. This observation is explained by the contributions of mass of the different components shown in Table 1. Finally, we have previously argued that Teflon radiolysis should not be a significant source of carrier because an increase in radioactivity under normal production conditions increases specific activity rather than holding it constant. This observation, too, is explained by Figure 2 through the plateau noted above the threshold level.

Conclusion

Teflon radiolysis has been proven to be the major source of mass in F-18 syntheses. Elimination of Teflon lowered carrier mass to about 20 nmol in a full batch. Specific activity of 1900 GBq (51 000 mCi)/μmol (32 nmol) at 60 min EOB was obtained from 90 GBq fluoride EOB (17- to 30-fold improvement). The remaining carrier (still 20-fold over theoretical) is contained in synthetic reagents, but not target water or system components. Purification of reagents and materials was previously insignificant, but is straightforward and may produce additional improvement. Use of production quantities of ^{18}F will also increase specific activity. These results explain previous data that implied that Teflon was not a major source of carrier fluoride. Therefore, if one uses a system without fluorinated materials, performs target irradiations near the capacity of the cyclotron, and uses care in preparation and handling of reagents, it may be anticipated that products with specific activity within a factor of two of the theoretical value will be produced at one hour EOB.

Experimental

Solvents and reagents were purchased from Fisher Scientific and Sigma-Aldrich and used without further purification. Water was prepared using a Barnstead water purification system with deionization and organics cartridges to produce final water of resistance 18 MΩ/cm. Potassium carbonate was ACS grade, > 99.0%.

F-18 was produced on a Siemens Eclipse 11 MeV cyclotron using the $^{18}O(p,n)^{18}F$ reaction on 95% O-18 water in a 2.5 ml tantalum target. Water was removed from the target through PEEK tubing (8 m, 0.7 mm ID × 1.5 mm OD (0.03 × 1/16 in.)) with PEEK connectors and through a Rheodyne 9010 valve with a PEEK rotor seal (Rheodyne, Rohnert Park, CA). Target water passed over ion exchange resin (Bio-Rad AG-1X8, converted to carbonate form by washing with potassium carbonate per manufacturer's instructions) contained in polypropylene (7.6 cm × 1.5 mm (1/16") ID × 3 mm (1/8") OD), and was collected for recycling. Fluoride eluted from the resin by 150 μl water containing 24 μmol potassium carbonate. Various target irradiations were used.

HPLC was performed with a Hewlett-Packard 1090 system with autoinjector, diode array UV detector (254 nM), and reverse phase Hewlett-Packard ODS Hypersil 5 μm 200 × 4.6 mm column eluted with 7 mM ammonium acetate in 35% aqueous methanol, 1.6 ml/min. Solvents were filtered and degassed but not otherwise purified. A calibration curve using volumetric dilutions of aqueous FBA standard (0.1–1000 nmol injected in 15 μl) was produced. The calibration was re-verified during the work. Retention times (min): fluoride 1.7, *p*-trimethylammoniumbenzaldehyde triflate (precursor) 3.2, *p*-FBA 7.54, unidentified radiolabeled products: 4.8, 18.1, and 18.9. Mass peaks were

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observed at 4.1, 5.8, 6.3, 7.15, 8.6, 9.8, and 13.7 min. These were minor impurities from the precursor or products of precursor degradation or reaction with ambient nucleophiles (hydroxide, chloride, etc.) and were not identified. Chromatograms were displayed with correction for the 0.15 min time delay of sample passage through the two detectors. There is therefore no time offset between the mass and radiation measurements on the accompanying figure.

F-18 FBA

[^{18}F]-Fluoride was eluted into a 10 ml conical reaction vessel at 100°C, and evaporated under vacuum with a flow of 25 ml/min argon. Kryptofix 2.2.2 (10 mg, 26 μmol) in 0.3 ml acetonitrile was added and evaporated to near-dryness. Acetonitrile (2 × 0.3 ml) was added and evaporated, gas flow stopped, and precursor, *p*-trimethylammoniumbenzaldehyde triflate[18] (6–8 mg in 700 μl of DMSO) was added and heated 10 min at 100°C. The solution was cooled to 50°C, 7 ml water added, passed over a C18 cartridge (Waters Sep-pak, WAT051910), and collected as waste. Radiolabeled FBA was retained on the C18 cartridge while a large majority of the precursor and unreacted fluoride was not. Methanol (2.0 ml) was used to rinse the reaction vessel and elute the product mixture from the C18 cartridge. Radioactivity in the methanol solution, waste, and residual radioactivity on the C18 cartridge and reaction vessel were measured in a dose calibrator for yield calculation. A 50.0 μl sample was removed using a volumetric syringe, placed in an HPLC autoinjector vial, measured in the dose calibrator, and carrier mass analyzed by HPLC. Pilot experiments with Teflon apparatus showed a change in generated carrier in response to a change in irradiation parameters that required to the third successive irradiation to become reproducible. Irradiation parameters were therefore kept constant as much as possible, and after any change, two syntheses would be performed and the batches discarded without performing the analysis.

Mass and specific activity analysis

A 15 μl sample was injected onto the HPLC from the autoinjector vial. All radioactivity measurements were decay-corrected to 60 min EOB. Mass of FBA in the 15 μl sample was directly measured by HPLC using the calibration factor determined previously. Total FBA mass in the entire 2 ml collected product was calculated ([2000 μl total volume]/[15 μl HPLC injected volume] · [HPLC-measured mass]). The accuracy of the volume ratio and solution uniformity was checked using the measured radioactivity ratios of the collected sample (2 ml) and the autoinjector sample (50 μl). A correction for the FBA reaction yield based on fluoride was also performed to give total carrier mass in the reaction. The chemical yield of the reaction was calculated as

$$\text{Yield} = \text{FBA}/\text{Total} \cdot P/W$$

where Yield is the fractional yield of FBA in the 2 ml collected product relative to starting fluoride radioactivity, FBA is the radiochromatogram peak area of FBA, Total is the sum of all radiochromatogram peak areas, *P* is the radioactivity in the 2.0 ml collected product fraction, and *W* is the sum of the radioactivity in the collected product fraction, collected waste fraction and residual radioactivity on the C18 cartridge and reaction vial. The total carrier mass in the reaction was then calculated as the total FBA mass in the 2 ml collected product divided by this calculated FBA yield. Specific activity was calculated by dividing the total measured radioactivity at EOB, decay corrected to 60 min EOB, by the calculated total fluoride mass.

Control experiments were performed exactly as above with the exception that the reaction was performed in its reaction vessel on the benchtop without using any part of the synthesis system. These experiments included no target or other water, no irradiation, no added fluoride. Additional control experiments introduced carbonate solution normally used for resin elution, which was added and evaporated without passage over ion exchange resin. Finally, 2 ml purified water in place of irradiated target water was passed over resin, which was then eluted in normal fashion with carbonate.

Teflon apparatus taken from the previous system were added in the elution path from the ion exchange resin to explore their carrier contributions. Components used were as follows: transport tubing (Teflon, Alltech, 8 m × 1.5 mm × 0.75 mm), resin cartridge (Teflon, Alltech, 7.62 cm × 3 mm × 1.5 mm), 1.5 mm × 0.75 mm Teflon tubing that extended to the bottom of the reaction vial to allow reagent addition and gas bubbling (2 cm wetted length during reaction), and one Rheodyne model 5300 slider valve (Rheodyne) (ca. 4.5 cm wetted length, estimated diameter 0.7 mm). The Rheodyne valve is constructed using Teflon and Tefzel, according to the manufacturer's literature. Tefzel is a modified ethylene–tetrafluoroethylene polymer expected to behave similarly to Teflon for this purpose. Components were added and removed in selected combinations.

Controlled Teflon experiments were performed with a fresh Teflon disk, 8 mm dia. × 0.1 mm, folded in fourths and placed in the conical vial. Fluoride was eluted into the reaction vessel and made up to 1.0 ml with water to cover the Teflon disk. After a selected incubation time, the disk was removed using PEEK tipped tweezers. The vessel was then placed in the synthesis apparatus, water evaporated, and the reaction continued as above. To investigate the effect of radioactivity concentration, the disk was incubated with 1.85–37 GBq (50–1000 mCi) per ml for 20 min. To investigate the effect of exposure time, it was incubated with 22 GBq (600 mCi) for 1–30 min.

Reagents' contribution to carrier was investigated by varying the amounts of reagents used in the reaction. Kryptofix was used with half and ten times the nominal quantity, carbonate at ten times the nominal amount, and precursor at half the nominal amount. Further, solutions of Kryptofix (without carbonate) and precursor were passed over ion exchange resin in carbonate form before use in an attempt to remove potential fluoride ion contamination.

O-18 water contributions

Behavior of fluoride in target water was assessed by addition of fluoride (100 nmol/ml) to purified water, of which 1.0 ml was then used in place of target water. The water was recovered normally and reused in a second and third synthesis to detect carrier that remained in recovered water.

References

[1] W. J. McBride, R. M. Sharkey, H. Karacay, C. A. D'Souza, E. A. Rossi, P. Laverman, C. H. Chang, O. C. Boerman, D. M. Goldenberg, *J. Nucl. Med.* **2009**, *50*, 991–998.

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[2] B. Shen, W. Ehrlichmann, M. Uebele, H. J. Machulla, G. Reischl, *Appl. Radiat. Isot.* **2009**, *67*, 1650–1653.
[3] Y. Y. Huang, W. S. Huang, T. C. Chu, C. Y. Shiue, *Appl. Radiat. Isot.* **2009**, *67*, 1063–1067.
[4] E. M. van Oosten, A. A. Wilson, K. A. Stephenson, D. C. Mamo, B. G. Pollock, B. H. Mulsant, A. K. Yudin, S. Houle, N. Vasdev, *Appl. Radiat. Isot.* **2009**, *67*, 611–616.
[5] J. M. Beauregard, E. Croteau, N. Ahmed, J. E. van Lier, F. Benard, *J. Nucl. Med.* **2009**, *50*, 100–107.
[6] J. Yoo, C. S. Dence, T. L. Sharp, J. A. Katzenellenbogen, M. J. Welch, *J. Med. Chem.* **2005**, *48*, 6366–6378.
[7] Y. S. Ding, J. S. Fowler, S. L. Dewey, J. Logan, D. J. Schlyer, S. J. Gatley, N. D. Volkow, P. T. King, A. P. Wolf, *J. Nucl. Med.* **1993**, *34*, 619–629.
[8] Y. S. Ding, J. S. Fowler, S. J. Gatley, S. L. Dewey, A. P. Wolf, *J. Med. Chem.* **1991**, *34*, 767–771.
[9] J. W. Brodack, M. R. Kilbourn, M. J. Welch, J. A. Katzenellenbogen, *Int. J. Rad. Appl. Instrum. A* **1986**, *37*, 217–221.
[10] C. Y. Shiue, J. S. Fowler, A. P. Wolf, M. Watanabe, C. D. Arnett, *J. Nucl. Med.* **1985**, *26*, 181–186.
[11] A. G. Horti, V. L. Villemagne, *Curr. Pharm. Des.* **2006**, *12*, 3877–3900.
[12] L. Zheng, M. S. Berridge, P. Ernsberger, *J. Med. Chem.* **1994**, *37*, 3219–3230.
[13] D. M. Jewett, S. A. Toorongian, M. A. Bachelor, M. R. Kilbourn, *Int. J. Rad. Appl. Instrum. A.* **1990**, *41*, 583–586.
[14] D. M. Jewett, *Int. J. Rad. Appl. Instrum. A.* **1991**, *42*, 410–411.
[15] H. Kitano, Y. Magata, A. Tanaka, T. Mukai, Y. Kuge, K. Nagatsu, J. Konishi, H. Saji, *Ann. Nucl. Med.* **2001**, *15*, 75–78.
[16] F. Fuchtner, S. Preusche, P. Mading, J. Zessin, J. Steinbach, *Nuklearmedizin.* **2008**, *47*, 116–119.
[17] S. R. Allayarov, D. A. Gordon, I. P. Kim, *J. Fluorine Chem.* **1999**, *96*, 61–64.
[18] M. S. Haka, M. R. Kilbourn, G. L. Watkins, S. A. Toorongian, *J. Lab. Cmpds. Radiopharm.* **1988**, *27*, 823–833.

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