

# Extraction of [ $^{18}\text{F}$ ]Fluoride from [ $^{18}\text{O}$ ]Water by a Fast Fibrous Anion Exchange Resin

DOUGLAS M. JEWETT, STEVEN A. TOORONGIAN,  
MICHAEL A. BACHELOR and MICHAEL R. KILBOURN

Division of Nuclear Medicine, Department of Internal Medicine, University of Michigan Medical School,  
Ann Arbor, MI 48109-0552, U.S.A.

(Received 27 September 1989)

[ $^{18}\text{F}$ ]Fluoride for nucleophilic radiofluorination was recovered from target water by trapping on a fibrous anion exchange resin in the hydroxide form and subsequent displacement into wet methanolic  $\text{K}_2\text{CO}_3$ . Extraction into methanol facilitated rapid evaporation and resolubilization of the [ $^{18}\text{F}$ ]fluoride as an ion pair. The resin was first dried *in situ* and rehydrated with [ $^{18}\text{O}$ ] $\text{H}_2\text{O}$  to avoid isotopic dilution of the target water.

## Introduction

The extraction of [ $^{18}\text{F}$ ]fluoride from water by an anion exchange resin greatly simplifies the handling and recovery of oxygen-18 enriched target water. In the original method of Schlyer *et al.* (1987; 1990) the [ $^{18}\text{F}$ ]fluoride was eluted by aqueous  $\text{K}_2\text{CO}_3$  requiring the subsequent evaporation of the water in the presence of a quaternary ammonium salt or cryptand to obtain a reactive ion pair. A multiphase extraction method was subsequently reported which permitted the extraction of [ $^{18}\text{F}$ ]fluoride into an organic solvent (Jewett *et al.*, 1988) facilitating evaporation and resolubilization. The recent availability of a fibrous anion exchanger with very fast exchange kinetics (Yoshioka and Shimamura, 1983) has now permitted the development of an even simpler extraction procedure. The fibrous exchange resin is readily packed from a slurry into small, disposable columns. The resin is then dried and rehydrated with a small amount of [ $^{18}\text{O}$ ]water before use. In this way, isotopic dilution of the target water is avoided. The [ $^{18}\text{F}$ ]fluoride can be recovered from the resin in high yield by wet methanolic  $\text{K}_2\text{CO}_3$  or similar organic eluant. Thus the evaporation of large amounts of water is avoided. The fibrous structure and relative hydrophobicity of the resin permits drying and changes between aqueous and organic solvents *in situ* without loss of site accessibility or impairment of flow through the resin bed. If necessary, the effluent from the anion exchange column can be passed through an equivalent column of a fibrous proton exchange resin to neutralize the solution before further reaction.

## Materials and Methods

### Preparation of columns

Disposable columns were prepared by forcing 1.65 mm o.d. Teflon tubing into the ends of short lengths of polyolefin tubing (Bev-A-Line, Cole-Parmer; 4.8 mm o.d.  $\times$  1.59 mm i.d.  $\times$  32 mm). Small plugs of polypropylene wool (Aldrich) were placed in the ends of the columns to retain the resin. A fibrous ion exchange resin with quaternary ammonium functionality (Toray TIN-200; C. I. Specialty Chemicals, Inc., New York, NY 10118) was obtained wet in the chloride form. The wet resin (1.5 g; 0.62 g dry weight) was suspended in 100 mL 30% aqueous ethanol in a polypropylene vessel. Aliquots (1 mL) were dispensed into polypropylene test tubes with a disposable polypropylene pipette. This method of handling avoided aggregation or sticking of the resin. An aliquot of the resin was resuspended by briefly swirling the tube and drawn into a column. While still attached to the vacuum the column was washed with 2 mL of 1 N NaOH, 2 mL deionized  $\text{H}_2\text{O}$ , and 2 mL MeOH. These steps were accomplished very quickly because of the fast exchange kinetics and high bed permeability of the resin. The methanol was removed by passing nitrogen through the column for 3 min. The columns were sealed and stored at  $-20^\circ\text{C}$ . Just before use, 20  $\mu\text{L}$  of [ $^{18}\text{O}$ ]water was injected directly onto the resin bed. Proton exchange columns of approximately equivalent exchange capacity were prepared from the analogous fibrous cation exchange resin (Toray TIN-100,  $\text{H}^+$ ).

### Measurement of elution profiles

Solutions were prepared containing 1.0 mg  $K_2CO_3$  (or other salt) in 1.0 mL methanol or other solvent containing varying amounts of water. In some cases 10 mg/mL of Kryptofix 2.2.2 (4,7,13,16,21,24-hexa-oxa-1,10-diazabicyclo[8.8.8]-hexacosane; Aldrich) was used to solubilize the  $K_2CO_3$ . Trace amounts of [ $^{18}F$ ]fluoride were trapped on fibrous anion exchange columns prepared as described above. The various solutions were passed through the columns, and 50  $\mu$ L aliquots of the effluent were collected in individual tubes. These were counted in an ionization chamber.

### Clinical scale syntheses of [ $^{18}F$ ]FDG

In this case 84% aqueous MeCN containing 1 mg/mL  $K_2CO_3$  and 10 mg/mL Kryptofix 2.2.2 was used as the eluant, since this solution was considered to be directly usable as the reaction medium (after azeotropic removal of water) for the subsequent nucleophilic incorporation step. After evaporation of the aqueous MeCN from the eluted [ $^{18}F$ ]fluoride solution two 100  $\mu$ L aliquots of dry MeCN were introduced and evaporated at 100°C to remove water. Then 10 mg 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl- $\beta$ -D-mannopyranose (Aldrich) was introduced in 1 mL dry MeCN, and the reaction tube was heated 10 min at 100°C. Subsequent hydrolysis and purification were by published methods (Jewett *et al.*, 1988; Padgett *et al.*, 1989).

### Model reactions to demonstrate reactivity of recovered [ $^{18}F$ ]fluoride

Oxygen-18 enriched target water containing 137 mCi of [ $^{18}F$ ]fluoride from a silver target was passed through a fibrous anion exchange column, prepared as described previously at the rate of 1 mL/min. Greater than 99.9% of the radioactivity was collected on the column. The column was then eluted with 1.0 mL 90% aqueous methanol containing 1 mg  $K_2CO_3$ . This step eluted 93.6% of the radioactivity (128.3 mCi). This eluant was passed through a column containing 12 mg (wet weight) of the analogous proton exchange resin (TIN-100) to

neutralize the  $K_2CO_3$ . This latter column retained 1.2% of the radioactivity (1.54 mCi). The neutralized eluant was divided between four tubes each containing 10 mg Kryptofix 2.2.2 and 1 mg  $K_2CO_3$ . The aqueous methanol was evaporated at about 100°C. Then two 200  $\mu$ L aliquots of absolute ethanol were added and evaporated to remove traces of water.

To two of the tubes were added 10 mg of mannose triflate in 1 mL dry MeCN. These were heated 10 min at 100°C then allowed to stand several half-lives to permit safer handling. The contents of each tube was taken up in 20 mL  $H_2O$ , and the resulting solutions were passed through  $C_{18}$  Sep-Paks (Waters) followed by water rinse. The product fraction was eluted from the Sep-Paks by acetone (91.4 and 91.6% recovery of radioactivity). By radio TLC this product was >95% tetraacetyl [ $^{18}F$ ]FDG.

To the other two tubes were added 3 mg 4-nitrobenzotrile in 100  $\mu$ L DMSO. These were heated 5 min at 150°C. These samples were diluted with water, extracted on  $C_{18}$  Sep-Paks and recovered with acetone as above. Recoveries of radioactivity were 89.5 and 83.5%. Radio TLC indicated approx. 90% 4-fluoro-benzotrile in the product.

In a series of experiments to study the effects of extraction variables on the incorporation of [ $^{18}F$ ]fluoride into FDG (Table 1) tracer amounts of [ $^{18}F$ ]fluoride were used under similar reaction conditions (10 mg Kryptofix 2.2.2; 1.2 mg  $K_2CO_3$ ; 20 mg mannose triflate). Aqueous methanol and acetonitrile were compared as the extracting solvents, and ethanol and acetonitrile were compared as the azeotropic drying agents. In addition, pairs of experiments were done with and without a proton exchange column downstream from the anion exchange column during the elution step. The anion exchange resin was converted to the carbonate form by aqueous  $K_2CO_3$  before use. These anion exchange columns extracted 96% of tracer amounts of fluoride from pure water. The eluting solvents contained 1.2 mg  $K_2CO_3$  in 1 mL. In experiments where this  $K_2CO_3$  was subsequently removed by a proton exchange column (**2a,b**; **4a,b**) 1.2 mg  $K_2CO_3$  was added directly to the reaction tubes to compensate. When equivalent proton exchange columns were used

Table 1. Comparison of different conditions for [ $^{18}F$ ]fluoride extraction on the incorporation of [ $^{18}F$ ]fluoride into [ $^{18}F$ ]FDG

Expt No.	Eluant	H <sup>+</sup> resin column used?	Azeotrope agent	Efficiency of elution; % radioactivity eluted or retained on columns			Efficiency of incorporation; % of eluted radioactivity in product or other fractions			Overall % incorporation based on initial radioactivity
				Anion exchange column	Cation exchange column	Eluted	Aqueous phase	Reaction tube wall	Mannose triflate	
1a	90% aq.	No	EtOH	0.3	—	99.7	34.9	7.1	58.0	57.8
1b	MeOH	No	EtOH	0.3	—	99.7	38.0	3.3	58.7	58.5
2a	90% aq.	Yes	EtOH	0.2	1.7	98.1	23.8	6.2	70.0	68.7
2b	MeOH	Yes	EtOH	0.3	1.6	98.1	36.6	3.0	60.4	59.3
3a	80% aq.	No	MeCN	2.7	—	97.3	26.0	8.2	65.8	64.0
3b	MeCN	No	MeCN	4.6	—	95.4	26.4	6.9	66.7	63.6
4a	80% aq.	Yes	MeCN	2.3	5.0	92.7	13.3	4.5	82.2	76.2
4b	MeCN	Yes	MeCN	3.7	3.5	92.8	14.4	5.0	80.6	74.8

downstream of the anion exchange columns the pH of the solutions after elution and dilution with equal parts water was 6–7.

### Results and Discussion

Qualitatively the performance of the fibrous resin was the same as that reported by Schlyer *et al.* (1987, 1990) for Dowex 1 × 8. Trace amounts of [<sup>18</sup>F]fluoride were 96–99.9% extracted from pure water. Extraction of [<sup>18</sup>F]fluoride from target water under production conditions was frequently somewhat lower. However, this could usually be attributed to problems with transfer of water from the target, resulting in too fast or nonuniform flow through the resin. Slow passage of the recovered target water through a second column of the resin in such cases removed essentially all of the [<sup>18</sup>F]fluoride.

A number of different anionic substitutions of the resin were evaluated for ability to extract [<sup>18</sup>F]fluoride from water (OH<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, CO<sub>3</sub><sup>2-</sup>, OAc<sup>-</sup>, trifluoroacetate). For all of these, trapping of trace amounts of [<sup>18</sup>F]fluoride was >90%. However, only the hydroxide form trapped essentially 100% of the radioactivity. A number of different salts were used for displacement in a variety of wet polar solvents in addition to pure water. While almost all inorganic salts appeared capable of displacing the [<sup>18</sup>F]fluoride, K<sub>2</sub>CO<sub>3</sub> was most compatible with subsequent nucleophilic reactions. Even fairly concentrated NH<sub>4</sub>OH did not displace [<sup>18</sup>F]fluoride from the resin. The following solvents (1 mL, containing 1.0 mg K<sub>2</sub>CO<sub>3</sub>) extracted >99% of the trapped [<sup>18</sup>F]fluoride from the columns: water, 80% v/v aqueous MeCN, 75% v/v aqueous EtOH and anhydrous MeOH. In all cases, as shown in Fig. 1 for methanol, increasing the amount of water caused the radioactivity to elute from the column in a narrower fraction closer to the solvent front.

Eleven clinical doses of [<sup>18</sup>F]FDG were prepared using the TIN-200 resin in the hydroxide form to extract [<sup>18</sup>F]fluoride. While trapping and recovery of

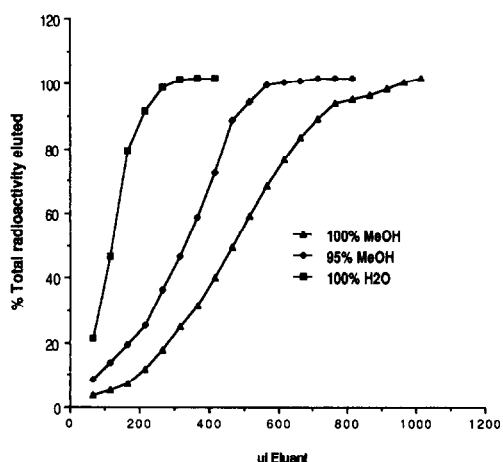


Fig. 1. Elution of [<sup>18</sup>F]fluoride from TIN-200 resin as a function of water content of the eluant.

[<sup>18</sup>F]fluoride were good, overall radiochemical yields of [<sup>18</sup>F]FDG were low, ranging from 7 to 25% uncorrected. While the reasons for these low yields cannot be determined with certainty, some observations have been made which may pertain to the use of resin-based extractions of [<sup>18</sup>F]fluoride in general: When 1 mL of water or wet solvent containing 1 mg K<sub>2</sub>CO<sub>3</sub> was passed through an anion exchange column (12 mg wet weight TIN-200) in the hydroxide form, the pH of the solution increased from 10.58 to 11.65, i.e. a greater than 10-fold increase in the concentration of free hydroxide. Because triflates and other substrates for nucleophilic radiofluorination tend to be labile under basic conditions, this additional hydroxide may affect reaction conditions and yields. Secondly, it was observed that when acetonitrile was heated in the presence of small amounts of a strong base (tetrabutylammonium hydroxide or Kryptofix/KOH) under conditions encountered in nucleophilic radiofluorination, a substance formed which reacted instantaneously with 4-nitro-benzonitrile in DMSO to form an unstable deep blue chromophore. In control experiments where MeCN was replaced by EtOH or MeOH no such species was formed. The established practice of using dry MeCN to remove water azeotropically may be the cause of some of the variability encountered in nucleophilic radiofluorinations. Thirdly, it is possible that trace amounts of metallic cations from the target or nucleophilic amines from the decomposition of the anion exchange resin may cause lower incorporation yields, since yields were higher when a proton exchange resin was included downstream of the anion exchange column during the elution step (Table 1; Expt 2 vs Expt 1; Expt 4 vs Expt 3).

In view of the low and inconsistent yields obtained in the preparative synthesis of [<sup>18</sup>F]FDG described above, it was desirable to demonstrate that the low yields were not an inherent consequence of the use of the resin-based extraction. Thus both [<sup>18</sup>F]tetraacetyl-FDG and [<sup>18</sup>F]4-fluoro-benzonitrile were made on a preparative scale from a single lot of resin-extracted [<sup>18</sup>F]fluoride. Anhydrous EtOH rather than MeCN was used for the azeotropic removal of water. A proton exchange column was used to eliminate excess base from the reaction systems. The satisfactory incorporations in both of the model nucleophilic exchange systems (90% for [<sup>18</sup>F]FDG; 77% for 4-[<sup>18</sup>F]fluoro-benzonitrile) demonstrate that the innovations introduced in these experiments, i.e. the use of a proton column for neutralization as well as the use of a wet organic solvent as an eluant, can be useful extensions of the resin-based extraction method introduced by Schlyer *et al.* (1987, 1990)

Fibrous ion exchange resins offer a valuable addition to the basic set of tools available for fast radiosynthetic procedures. Their faster exchange kinetics are compatible with the need for accomplishing reactions quickly in the smallest possible volumes. The very high bed permeabilities avoid instrumental

problems from excessive pressure drop. Their fibrous nature allows them to be rapidly and reproducibly packed from slurries, and subjected to repeated cycles of ion exchange, solvent exchange, drying and rehydration without the changes in bed permeability or loss of site-accessibility often encountered with conventional resins.

*Acknowledgements*—This work was supported by Grant DE-FG02-87ER60561 from the Department of Energy and by Grant PO1 NS 15655 from NINCDS. We are indebted to T. Yoshioka and to C.I. Specialty Chemicals, Inc. for samples of the Toray resins.

### References

- Jewett D. M., Toorongian S. A., Mulholland G. K., Watkins G. L. and Kilbourn M. R. (1988) Multiphase

extraction: rapid phase-transfer of [ $^{18}\text{F}$ ]fluoride ion for nucleophilic radiolabeling reactions. *Appl. Radiat. Isot.* **39**, 1109.

Padgett H. C., Schmidt D. G., Luxen A., Bida G. T., Satyamurthy N. and Barrio J. R. (1989) Computer-controlled radiochemical synthesis: a chemistry process control unit for the automated production of radiochemicals. *Appl. Radiat. Isot.* **40**, 433.

Schlyer D. J., Bastos M. and Wolf A. P. (1987) A rapid quantitative separation of fluorine-18 fluoride from oxygen-18 water. *J. Nucl. Med.* **28**, 764.

Schlyer D. J., Bastos M., Alexoff D. and Wolf A. P. (1990) Separation of [ $^{18}\text{F}$ ]fluoride from [ $^{18}\text{O}$ ]water using anion exchange resin. *Appl. Radiat. Isot.* **41**, 531.

Yoshioka T. and Shimamura M. (1983) The preparation and fundamental characteristics of polystyrene-based ion exchange fiber. *Bull. Chem. Soc. Jpn.* **56**, 3726.