technical note

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Aqueous Carbonic Acid: a Readily Removable Electrolyte for the Recovery of [^{18}F]Fluoride from Anion Exchange Resins

DOUGLAS M. JEWETT

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

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[^{18}F]Fluoride was recovered from [^{18}O]target water in high yield by trapping it on a microcolumn of an anion exchange resin (20 mg Dowex 1 × 8, 400 mesh) and subsequent elution of the column (in the reverse direction) by aqueous carbonic acid at 52 atm. The carbonic acid was removed from the [^{18}F]fluoride solution by brief heating at 85°C, 1 atm. Thus no extraneous electrolyte was introduced by the extraction process. The resulting bicarbonate form of the resin was immediately capable of trapping further [^{18}F]fluoride, permitting a repetitive remote system for recovery of [^{18}O]water. Chloride was substantially retained on the column permitting separation of [^{18}F]fluoride from the former.

Introduction

Because of the high cost of the [^{18}O]water used in targets for the production of [^{18}F]fluoride simple methods employing anion exchange resins have been developed to separate the [^{18}F]fluoride ion (Schlyer *et al.*, 1987, 1990; Jewett *et al.*, 1990). After recovery of the [^{18}O]water the [^{18}F]fluoride is eluted from the resin by dilute K_2CO_3 or other electrolyte. A problem with these methods is that the [^{18}F]fluoride is contaminated with cations from the electrolyte and by their counterions. Because these ions are often present in concentrations greater than that of the [^{18}F]fluoride they may affect subsequent reactions. It will be shown below that, at a pressure of approximately 52 atm, carbon dioxide dissolves in water to produce carbonic acid of sufficient ionic strength to readily displace [^{18}F]fluoride from anion exchange resins. Residual carbonic acid can be removed from the resulting aqueous [^{18}F]fluoride by brief warming at atmospheric pressure. An apparatus for handling carbonic acid at 52 atm will be described. After the extraction the resin is in the bicarbonate form and thus capable of trapping more [^{18}F]-fluoride without further conditioning. Depending on the purity of the [^{18}O]water several trapping and elution cycles are usually possible before the resin accumulates sufficient amounts of nonextractable anions to affect the trapping of [^{18}F]fluoride. This makes possible a remote extraction system situated close to the target. Of additional interest is the observation that chloride ion is not readily extracted from the anion exchange resin by carbonic acid. Because chloride is a nucleophile, there are cases where its presence can result in a lower effective specific activity for the product radiopharmaceutical. Most of the chloride contaminant can readily be separated from [^{18}F]fluoride by carbonic acid extraction. In the experiments described operations were performed by connecting the various components manually. However, all standard HPLC components and fittings were used, and the construction of a remote system based on an automatic HPLC injection valve will be apparent.

Materials and Methods

Aqueous carbonic acid

A 300 ml stainless steel cylinder was equipped with a stainless steel bellows valve and an adapter to allow it to be connected to 0.0625 in. o.d. tubing. The bellows valve was disconnected temporarily while 100 mL pure water was added to the cylinder. The valve was replaced, and the cylinder was connected to a tank of CO_2 (siphon configuration) and completely filled with liquid CO_2. The cylinder was inverted several times to mix the liquid phases. It was allowed to stand at least 1 h before use to permit equilibration and was used in the inverted position to dispense aqueous carbonic acid.

Flow restrictor

This was provided to allow the anion exchange column to be maintained at 52 atm with an elution rate of 1 mL/min. A polymeric packing was used to avoid adsorption of fluoride, and the narrow diameter was chosen to allow a high pressure drop while introducing minimal dead volume. A 0.0625 in. o.d. × 0.055 in. i.d. × 22 in length of PEEK tubing was connected at its outlet to a low dead volume in-line filter fitted with a 10 μ UHMW frit and was slurry packed with a polymeric HPLC phase (PRP1, 10 μ, Hamilton Co.). In use, the flow restrictor was connected directly downstream of the anion exchange column by a Tefzel "fingertight" 10–32 nut. The column, filter, frits and fittings were all obtained from Upchurch.

Anion exchange column

The anion exchange resin (Dowex 1 × 8, 400 mesh, 20 mg, chloride form) was slurry packed in a stainless steel HPLC guard column (2 × 20 mm i.d., Upchurch). Instead of the usual frits, 4 mm plugs of polypropylene wool (Aldrich) were placed at each end of the resin bed, and the column was sealed at the ends by Teflon rings (0.1 in thick) cut from 0.25 in. o.d. × 0.0625 in. i.d. tubing. The frits usually used with such columns rapidly became plugged with particulate matter from the target water, while the polypropylene wool plugs did not. The resin was converted to the carbonate form by elution with 2 mL 10% aqueous K_2CO_3 followed by 2 mL pure water. After connection of the outlet of the anion exchange column to the flow restrictor the former was eluted with about 5 mL of aqueous carbonic acid at 52 atm. Columns of other anion exchangers (TIN 200 fibrous polystyrene quaternary ammonium resin, 20 mg; and basic carbon, 40 mg; Jewett *et al.*, 1990; Jewett, 1990) were prepared in the same way.

Recovery of [^{18}F]fluoride

[^{18}O]Water, 1 mL, containing [^{18}F]fluoride produced by proton irradiation in a silver target was passed through the anion exchange column at about 1 mL/min. In some experiments a proton exchange column (TIN 100 H^+, 20 mg; Jewett, 1990) was connected upstream of the anion exchange column to increase the trapping efficiency. After the [^{18}F]-fluoride was trapped the column was reversed and connected downstream to the flow restrictor and upstream to the cylinder of aqueous carbonic acid, such that the liquid flow through the column was reversed relative to that during trapping. The flow restrictor was passed through a concentric ionization detector (Sipilä *et al.*, 1985) so that the eluted

Table 1. Recovery of [^{18}F]fluoride from different ion exchangers under different conditions. The elution curves identified are shown in Fig. 1

Solid phase	H^+ resin precolumn?	%Fluoride trapped	Eluant ($+H_2CO_3$)	Eluant direction	Temperature (°C)	%Fluoride eluted	Elution vol. mL	Elution curve
Dowex 1 × 8	No	98	Water	Forward	23	69	4.2	a
Dowex 1 × 8	Yes	100	Water	Reverse	23	99	2.4	b
Dowex 1 × 8	No	99	Water	Reverse	104	97	1.5	c
TIN-200	No	92	Water	Forward	23	99	4.0	d
TIN-200	No	100	Water	Reverse	23	98	4.0	e
TIN-200	Yes	99	Water	Reverse	85	99	1.5	f
TIN-200	Yes	100	80% MeOH	Reverse	23	96	3.0	g
Basic carbon	Yes	100	Water	Forward	23	90	2.5	h
Basic carbon	Yes	99	Water	Reverse	23	92	1.4	i
Basic carbon	Yes	90	Water	Reverse	100	86	2.5	j

radioactivity could be monitored. The bellows valve was opened to start the flow of aqueous carbonic acid, and the effluent was collected in a polyethylene vessel. When necessary, at the end of elution this vessel was warmed at 85°C for 1 min under a gentle N_2 purge to remove traces of carbonic acid.

Measurement of chloride retention by anion exchange columns

Aqueous [^{36}Cl] NaCl (1 mL, 1.5 μEquiv, 4.4×10^5 dpm) was trapped on a column of 20 mg Dowex 1 × 8 as described above for fluoride. The column was then eluted in the reverse direction with aqueous carbonic acid at 52 atm, and the effluent was collected in 1 mL fractions. The eluted radioactivity was determined by liquid scintillation counting. After elution with 7 mL of carbonic acid the residual chloride was eluted from the column by 3 1-mL aliquots of 3% NaCl, and this residual radioactivity was determined by liquid scintillation counting.

Results of Discussion

The results of the recovery of [^{18}F]fluoride with three different anion exchangers are summarized in Table 1. All of the trapping took place with anion exchangers that had been previously eluted with carbonic acid at 52 atm to simulate conditions that would occur in a repetitive remote system. In most cases the same column of a given anion exchanger was used for all of the experiments reported, demonstrating the possibility of recycling in a remote system. Carbonic acid in water at equilibrium with CO_2 at 52 atm is a weak electrolyte so that elution in the reverse direction from trapping is required for efficient removal of the [^{18}F]fluoride from the anion exchanger.

The eluted [^{18}F]fluoride appeared to be substantially free of contaminating electrolytes after brief heating to 85°C, in that it could be trapped completely on an aminopyridinium functionalized Merrifield resin of the type used for direct nucleophilic radiofluorination. If the eluted [^{18}F]fluoride was not heated first trapping was sometimes incomplete indicating interference by residual carbonic acid.

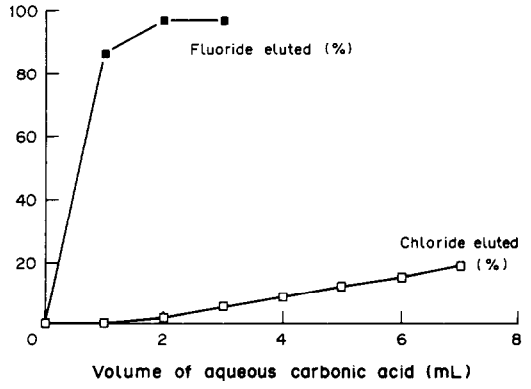

Fig. 1. Comparison of the elution of [^{36}Cl]chloride and [^{18}F]fluoride from a 20 mg column of Dowex 1 × 8 resin by aqueous carbonic acid at 23°C. Elution was in the reverse direction from trapping.

Chloride contamination in [^{18}F]fluoride may be a problem for receptor agents where a very high specific activity is desirable. Figure 1 compares the elution (flow reversed with respect to trapping) of [^{18}F]fluoride and [^{36}Cl]chloride from Dowex 1 × 8 by aqueous carbonic acid. Almost all of the chloride was removed by the extraction process. The separation could be expected to be even greater if the elution were carried out in the same direction as the trapping step, however, the recovery of the [^{18}F]fluoride is less efficient under such conditions.

The above results suggest that it will be possible to construct a practical remote system capable of extracting [^{18}F]fluoride from [^{18}O]water repeatedly with a single column of an anion exchange resin. The [^{18}F]fluoride may then be transported and handled without regard to recovery or isotopic contamination of [^{18}O]water, allowing a simplification of systems for radiofluorination. Important problems remain. First, it was not found to be possible to remove all residual water from the resins by a flow of dry nitrogen alone (Jewett, 1990). Thus some contamination of the [^{18}O]water by [^{16}O]-water occurred at each cycle. While water could be completely removed from the anion exchangers by dry MeOH, use of the latter would appear to compromise the simplicity of the method and also introduce the risk of isotopic contamination of the [^{18}O]water. Secondly, depending on the target materials and purity of the target water, contaminating anions which cannot be eluted by carbonic acid eventually accumulate on the anion exchange resin resulting in a finite lifetime for the column.

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