Tetrahedron Letters 51 (2010) 64–66

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Fast production of highly concentrated reactive [^{18}F] fluoride for aliphatic and aromatic nucleophilic radiolabelling

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ARTICLE INFO

Article history:
Received 21 August 2009
Revised 13 October 2009
Accepted 16 October 2009
Available online 22 October 2009

Keywords:
Radiofluorination
Radiopharmaceuticals
Fluoride
F-18
Nucleophilic substitution
Positron emission tomography
SPE

ABSTRACT

The use of a polymeric solid support loaded with a long alkyl chain quaternary ammonium allows the rapid and efficient recovery of cyclotron produced [^{18}F]F$^-$ from [^{18}O]water to a low water content organic solution compatible with fast nucleophilic labelling of most precursors for PET radiopharmaceuticals in high yield.

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Among the techniques used for molecular imaging, positron emission tomography (PET) is one of the most sensitive modalities that can be used for in vivo applications. Fluorine-18 has the most favourable physical properties in the group of commonly used positron-emitting radionuclides (lowest positron energy and a convenient half-life of about 110 min).[1,2] Fluorine-18 is mostly produced by irradiation of oxygen-18 enriched water (H_2[^{18}O]O) with cyclotron accelerated protons, through the nuclear reaction ^{18}O (p,n) ^{18}F. The radionuclide is obtained in water in the form of fluoride, [^{18}F]F$^-$, with a specific activity higher than 40 GBq/μmol. The incorporation of the fluorine-18 into an organic structure, in order to obtain a radiolabelled pharmaceutical with specific biological properties suitable for PET imaging, proceeds by nucleophilic substitution of a precursor with a convenient leaving group. To achieve a high yield incorporation of the radionuclide, it is first necessary to dry [^{18}F]F$^-$ to enhance its nucleophilicity which is strongly reduced by interaction with water. Classically, this water elimination is performed in a two-step procedure: first, the irradiated water is passed through an anion exchange support in order to trap [^{18}F]F$^-$ and to separate it from the enriched water. The radioactivity is then eluted from the support with a small volume of a solution of an alkali carbonate (cesium, rubidium and potassium) in water, a solution of tetra-alkyl ammonium hydroxide in water or a solution of potassium carbonate and K222 cryptate in water/acetonitrile (ACN) 50/50 V/V. In a second step, the eluted mixture is dried by azeotropic evaporation of water with ACN and finally recovered in a solvent suitable for nucleophilic radiolabelling, for example ACN.[3–5] At present, most PET tracers are produced in reactors with a high internal volume (1–5 ml). However, it may be advantageous to consider the use of microfluidic devices to improve the yield of [^{18}F]F$^-$ incorporation, the rapidity of synthesis and the purity of the final radiotracer.[6] The usefulness of this concept has been proven for 2-[^{18}F]fluoro-2-deoxy-D-glucose.[7]

Since the advent of nucleophilic fluorine-18 radiochemistry,[8] research has focused predominantly on improvements of the labelling step (i.e., microwaves,[9] ionic liquids,[10] tertiary alcohols[11] and fluorous chemistry[12]). Even very recently, a new catalytic fluorination method was proposed for radiofluorination of aromatic compounds.[13] Now, in the case of microfluidics, an important problem arises prior to labelling. This problem is the incompatibility of the closed small volume devices with solvent evaporation.[7] It is thus imperative to find alternative methods of concentration and drying for [^{18}F]fluoride.

Different techniques have nevertheless been described in the literature to avoid thermal evaporation before the labelling step: direct labelling on the anion exchanger used to trap [^{18}F]fluoride,[14] electrochemical recovery[15] and use of a gas-permeable poly(dimethylsiloxane) matrix to obtain a solvent exchange.[7] C_{18}-derived supports (polystyrene resin or silica) associated with a

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doi:10.1016/j.tetlet.2009.10.085

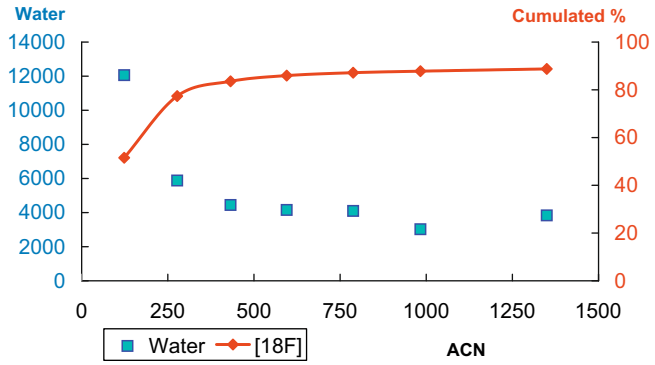

Figure 1. Fractionated [^{18}F]F$^-$ elution in ACN from 100 mg of support loaded with *n*-tetradecyl-trimethylammonium bicarbonate.

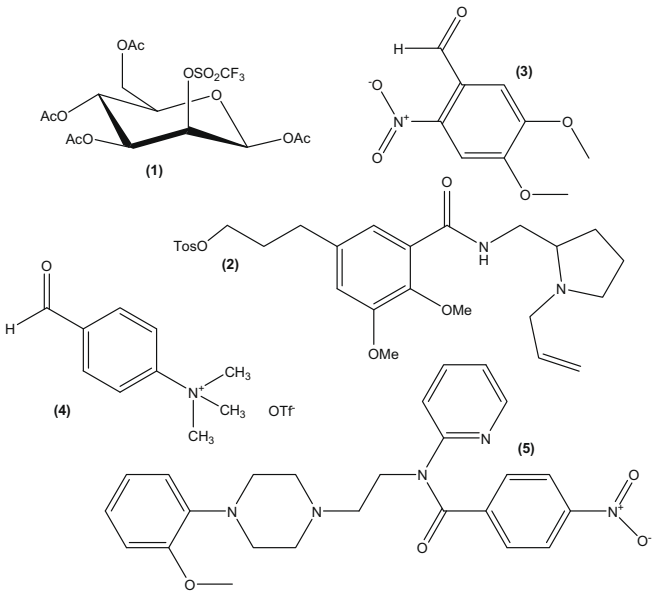

Figure 2. Structures of the precursors.

quaternary ammonium have been used to concentrate [^{18}F]F$^-$ in acetonitrile before evaporation.[16]

Here we describe the use of water-wettable macroporous copolymers loaded with a long alkyl chain quaternary ammonium carbonate to directly recover [^{18}F]fluoride from H_2[^{18}O]O to provide a low water content organic solution compatible with the nucleophilic labelling, without the use of an evaporation step. The modified commercial support was easily prepared using of solution of *n*-tetradecyl-trimethylammonium bicarbonate or another quaternary ammonium salt.[17] Once introduced into a solid phase extraction (SPE) cartridge,[18] the modified support allowed the quantitative trapping of [^{18}F]F$^-$ from a large volume of water (typically 2 ml for 50 mg of support, higher than 5 ml for 100 mg). After trapping, the cartridge was purged with nitrogen and the elution performed using 1 ml of dried ACN (lower than 100 ppm water).[19] More than 90% of the trapped activity was recovered in the eluted solution in the form of *n*-tetradecyl-trimethylammonium [^{18}F]fluoride together with *n*-tetradecyl-trimethylammonium carbonate. Figure 1 shows a typical elution profile, obtained by fractionating the solution dropping from the cartridge in order to measure the radioactivity and to estimate the water content in each separated fraction. The reported values are the cumulated eluted activity (right *y*-axis) and the Karl-Fischer estimated water content in each fraction (left *y*-axis) as a function of the volume passed through the cartridge.

When considering the total recovered volume after elution, the resulting concentration of residual water is higher (4850 ppm for the example in Fig. 1) than that obtained after classical recovery by azeotropic evaporation of a potassium carbonate/K222 solution (lower than 1000 ppm).[20] Nevertheless, this concentration is compatible with most nucleophilic labelling procedures.

In addition to ACN, other non protic solvents can be employed to recover [^{18}F]F$^-$, such as dimethylsulfoxide (DMSO) or dimethylformamide (DMF). Typical percentages of elution are higher than 85% with 1 ml of solvent.

After elution, [^{18}F]fluoride is present as an ion pair with the long chain quaternary ammonium in the non protic solvent. Such a solution has been used successfully for radiofluorination with different tetra-alkyl ammoniums as counter ion,[5,16] even if these cations are known to be instable in the presence of basic species, especially when heating and when the water content is very low.[21] Such an elimination reaction could modify [^{18}F]F$^-$ into less nucleophilic species. However, the labelling yields obtained with tetra-alkyl ammoniums[5] and our incorporation results (see below) demonstrate that in the drying and labelling conditions used (temperature, water concentration and duration), fluorine-18 remains in a reactive form.

Several precursors (Fig. 2) used in our laboratory have been labelled[22] with high radiochemical yield in capped reactors These experimental conditions are therefore similar to those in a microfluidic device, in which no water evaporation can occur during labelling. Examples of labelling results are presented in Table 1. The [^{18}F]F$^-$ solutions eluted from modified supports show a good nucleophilic reactivity towards several precursors, either aliphatic or aromatic. An additional basic component is sometimes necessary to permit the nucleophilic substitution (entries #4, 6 and 7) or helpful to enhance it (comparison of entries 1a and 1b). For entry 2, starting from 11,200 MBq of [^{18}F]F$^-$ eluted from the support, the specific activity (SA) was measured by HPLC after purification

Table 1
Labelling conditions and yields for different precursors

Entry	Support	Precursor		Solvent		Labelling		Yields (%)	
			mg		ml	°C	min	This work	Litter
#1a	C_{10}Br	(1)	40	ACN	1	95	10	49	
#1b	C_{10}Br	(1)	40	ACN	1	95	10	89[a]	
#2	$C_{14}HCO_3$	(1)	40	ACN	1	95	5	71	80–90[4]
#3	C_{14}Br	(1)	40	ACN	1.4	25	20	66	
#4	C_{10}Br	(2)	15	ACN	0.8	95	10	55[a]	25[23]
#5	C_{10}Br	(3)	15	DMSO	1	190	20	68	50[24]
#6	C_{14}Br	(4)	30	DMSO	1	110	10	84[b]	90[25]
#7	C_{10}Br	(5)	15	DMSO	1	170	20	57[a]	16[26]

Additive (in reactor): [a] K_2CO_3, 7 mg and Kryptofix K222, 22 mg. [b] Tetraethtylammonium bicarbonate, 50 mg.

of the labelled product. SA was 40.33 GBq/μmol, 90 min after the end of labelling. The labelling yields reached are comparable with published values, or even better, for aliphatic[4,23] and aromatic[24–26] precursors.

Moreover, this method of $[^{18}F]F^-$ recovery presents several advantages in comparison with the classical evaporation:

1. The recovery is compatible with a closed system, proceeding without evaporation of a liquid phase.
2. $[^{18}F]F^-$ is recovered without heating and is reactive for the labelling at room temperature (entry 3, 25 °C). The method is thus very interesting for thermally unstable precursors.
3. The radioactivity is recovered directly in solution reducing the loss of large amounts of $[^{18}F]F^-$ on the reactor surfaces (<10% in comparison with 15–25% lost in classical $[^{18}F]$ chemistry).

The classical azeotropic evaporation of water is a time consuming step in radiofluorination processes. Once included in an automated synthesis, the proposed method to concentrate $[^{18}F]$fluoride without evaporation will allow an appreciable gain of time for the synthesis of a short-lived $[^{18}F]$ radiotracer. We believe that the method described here is a promising tool for the development of reliable radiosynthesis of $[^{18}F]$ labelled tracers. These modified supports open a pathway to the use of less stable precursors and to the automation of high activity level PET radiochemistry at a microfluidic scale.

Acknowledgments

This research was supported by a grant from the EU's FP6 STRP 516984 MI-Lab-On-Chip. A. Plenevaux is a research associate from FRS-F.N.R.S. Belgium.

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17. *Preparation of modified support*: 25 mg of *n*-tetradecyl-trimethylammonium bicarbonate ($C_{14}HCO_3$) or *n*-tetradecyl-trimethylammonium bromide ($C_{14}Br$) or *n*-decyltrimethyl-ammonium ($C_{10}Br$) was dissolved in 1 ml of ACN. The solution was added to 100 mg of *N*-vinyl lactame/divinylbenzene copolymer sorbent, a typical example is Waters Oasis™ HLB. The suspension was triturated until complete evaporation of the solvent.
18. Preparation of extraction cartridges: 50 mg or 100 mg of modified support were introduced into an SPE reservoir (Isolute® empty reservoir 1 ml, internal diameter 5–6 mm) between two frits (Isolute® frits 20 μm 1 ml). When using a bromide salt, the solid was conditioned with 200 μl/50 mg of a solution of 50% P/P K_2CO_3 in water and rinsed with 3 ml of water. When using a bicarbonate salt, the functionalised sorbent was used without conditioning.
19. Typical $[^{18}F]F^-$ recovery procedure: The water solution containing $[^{18}F]F^-$ was passed through the extraction cartridge (at 1 ml/min). The cartridge was dried for 4 min with a nitrogen flow (10 l/min, upstream pressure 3.25 bar). The radioactivity was eluted with 1 ml ACN (dried on molecular sieves, <100 ppm water).
20. A Waters Sep-pak® QMA cartridge was eluted with a mixture of equal volumes of potassium carbonate in water (35 mg/1.5 ml) and Kryptofix K222 in ACN (110 mg/1.5 ml). A 500 μL aliquot was submitted to an azeotropic drying (95 °C, nitrogen flow, 5 min). The residue was dissolved in 1 ml of dry ACN (water <100 ppm) and the mixture was heated at 100 °C in capped reactor to simulate a labelling step. After cooling, the residual water concentration was estimated by Karl Fisher titration (541 ± 118 ppm, $n = 3$).
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