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A simple method to generate [^{18}F]triflyl fluoride for ^{18}F radiosynthesis

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ABSTRACT

A simple, continuous-flow solid-phase radiosynthesis method has been developed for the generation of [^{18}F]triflyl fluoride as a source of [^{18}F]fluoride for the preparation of ^{18}F labeled radiopharmaceuticals without the need for an azeotropic drying step. After [^{18}F]fluoride was trapped and dried on an anion-exchange resin cartridge, gaseous [^{18}F]triflyl fluoride was generated directly by eluting the cartridge with a solution of PhN(OTf)$_2$, followed by isolation from the eluted reaction mixture *via* an empty cartridge and conversion to [^{18}F]fluoride in a basic solution for radiofluorination. A peristaltic pump was used to maintain flow through the above stages, eventually providing reaction-ready [^{18}F]fluoride in over 90% radiochemical yield in less than 10 min. Up to 0.057 μg non-radioactive fluoride was introduced from the reagents and components used during the above processes. Several radiolabeling reactions were carried out using the [^{18}F]fluoride generated in this manner, affording the labeled products in good to high radiochemical yields. This method should have great potential for the safe and convenient preparation of ^{18}F labeled radiopharmaceuticals.

Introduction

Fluorine-18 labeled radiopharmaceuticals play an important role in the field of nuclear imaging using positron emission tomography (PET), and they are often prepared from [^{18}F]fluoride produced by an ^{18}O (p, n)^{18}F reaction by proton irradiation of ^{18}O enriched water (95%) using a medical cyclotron. The hydrated [^{18}F]fluoride in the ^{18}O water needs to be converted to more reactive forms in an anhydrous solvent suitable for radiolabeling, except for reactions that can be carried out in water [1]. Azeotropic drying with acetonitrile is the most commonly used method for this purpose but has many drawbacks [2]. Therefore, significant efforts have been undertaken to develop methods for labeling without this azeotropic drying step, but applications of these methods have been limited [3].

Fluorine-18 labeled sulfonyl fluorides have shown promise as a source of [^{18}F]fluoride for the preparation of ^{18}F labeled radiopharmaceuticals [2,4–7]. This strategy takes advantage of the high affinity of sulfonyl groups for fluoride, and the quantitative conversion of sulfonyl fluorides to the fluoride ion under basic conditions, thereby enabling the conversion of [^{18}F]fluoride from an aqueous solution in the ^{18}O water to an anhydrous organic solvent that is suitable for radiolabeling [8]. A rapid and reliable method for generating [^{18}F]triflyl fluoride ([^{18}F]TfF) as a gaseous source of [^{18}F]fluoride has been reported [2]. This method includes trapping [^{18}F]fluoride on an anion-exchange resin cartridge, eluting [^{18}F]fluoride with an aqueous potassium salt solution, converting it to volatile [^{18}F]triflyl fluoride using a bistriflate precursor PhN(OTf)$_2$, distilling and drying this gas through a column of P_2O_5, and trapping the activity with base in a solvent suitable for radiolabeling. The suitability of using [^{18}F]TfF for radiolabeling has been demonstrated by model reactions and the preparation of ^{18}F labeled radiopharmaceuticals [2].

In this report, we present a simple method (continuous-flow solid-phase radiosynthesis) for the generation of gaseous [^{18}F]TfF for radiolabeling, using a peristaltic pump for loading, drying, eluting, and distilling/converting the radioactivity in a safe and controlled manner. [^{18}F]TfF was generated directly on the anion-exchange resin cartridge (generally termed solid-phase extraction (SPE) cartridge) and separated from other components *via* an empty cartridge. Some commonly used radiolabeling reactions using [^{18}F]TfF generated in this manner are reported, and the factors important for the preparation of ^{18}F labeled radiopharmaceuticals are also discussed.

Results and discussion

[^{18}F]Fluoride in ^{18}O water from the cyclotron target was first trapped in an anion-exchange resin cartridge to allow recovery of

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the expensive isotopically enriched water, a procedure that is routinely used for the azeotropic drying protocol. We used an in-house made anion-exchange resin cartridge (AG MP-1M−HCO_3), which is equivalent to a 30-PS-HCO_3 cartridge. Next, the [^{18}F]fluoride and the cartridge were dried by rinsing with acetonitrile. A manual elution with PhN(OTf)$_2$ (5 mg) in acetonitrile resulted in release of over 95% radioactivity from the cartridge within a few seconds, with [^{18}F]TfF as the only radioactive product (see Fig. S1). However, while PhN(OTf)$_2$ was still present in the eluted solution, a test labeling directly with the eluted solution resulted in no radiofluorination, presumably due to the interference with the large amount of PhN(OTf)$_2$. This initial result led us to further explore the elution of radioactivity in a more controlled manner and to develop a method to separate [^{18}F]TfF from PhN(OTf)$_2$ in the eluted solution.

Peristaltic pumps are typically used in medical devices to pump clean/sterile fluids and in industry for containing highly reactive chemicals during their transfer; for both of these purposes there is a critical need that the flowing components be isolated from the environment. As illustrated in Figs. 1 and 2, a peristaltic pump can accomplish all of the tasks needed for the generation of gaseous [^{18}F]TfF and can do so in a safe and controlled fashion. Different solvents were first tested for the elution of [^{18}F]TfF. Acetonitrile provided the highest elution efficiency (96%) (Table 1), and it is compatible with the pump material; therefore, it was selected as the solvent for elution.

In the previous report, an inert gas was used to distill [^{18}F]TfF from the reaction mixture/vessel [2]. In our investigation, several designs, an empty cartridge, a vial with needles, and cartridges containing inert materials (illustrated in Table 2 and Fig. S2) were tested in order to separate [^{18}F]TfF from the eluted solution, with the peristaltic pump providing the gas flow for distillation. Both the empty cartridge and the vial methods worked equivalently well, with less than 1% of radioactivity left in them. However, the empty cartridge is a much simpler design. The inert material design gave variable results, with an alumina N cartridge completely trapping the radioactivity. We took advantage of this by using an alumina N cartridge as a vent at the end of the apparatus to trap any escaped radioactivity. It is worthwhile mentioning that as little as 15 mL air was needed for the efficient distillation of [^{18}F]TfF from the eluted solution. This low volume is ideal for the trapping/converting step that follows.

The trapping of [^{18}F]TfF with potassium bicarbonate/Kryptofix 222 ($KHCO_3$/K_{222}) was studied extensively in the previous report [2]. In our investigation, the commonly used potassium carbonate/Kryptofix 222 (K_2CO_3/K_{222}) was studied. As shown in Table 3, the trapping efficiency is dependent on the amount and type of base, the type of solvent, the amount of fluoride, and the flow rate. Contrary to the previous report, we found K_2CO_3/K_{222} to be better at trapping than $KHCO_3$/K_{222}. At the flow rate of 10 mL/min, [^{18}F]TfF was trapped by 1 mg (1.1 μmol) K_2CO_3/K_{222} in 84.8% vs 32.3% by 1.4 mg (2.9 μmol) $KHCO_3$/K_{222}. When amyl alcohol, a unique solvent for radiofluorination, was used [9], the trapping efficiency dropped significantly, from 97.8% in acetonitrile to 31.9% in amyl alcohol. In some cases, non-radioactive fluoride was added to [^{18}F]fluoride to simulate the use of large amounts of radioactivity (0.1 μmol and 1 μmol fluoride from 37 GBq (1000 mCi) with molar activity of 370 GBq /μmol or 37 GBq /μmol, respectively). At least a 50-fold excess amount of K_2CO_3/K_{222} over TfF is needed for efficient conversion. When a 1:1 ratio is used, only 15.7% was trapped, indicating that the conversion of TfF to fluoride is not "instant". Increasing the trapping temperature, however, did not help the conversion.

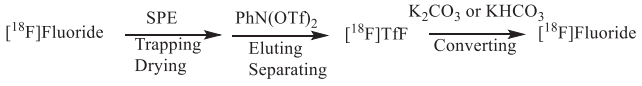

Fig. 1. Chemical transformation of [^{18}F]fluoride from aqueous solution to organic solution for labeling.

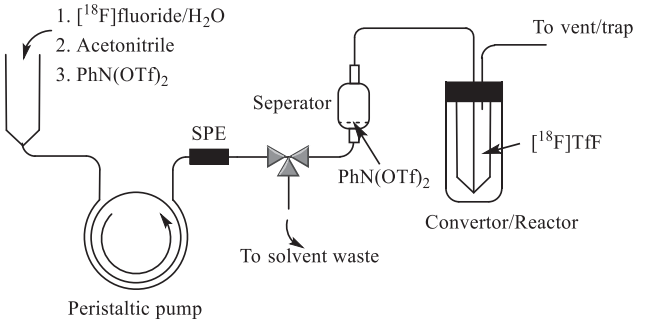

Fig. 2. Continuous-flow solid-phase apparatus for the synthesis of [^{18}F] triflyl fluoride for radiolabeling.

Table 1
Effect of eluting solvents on efficiency.

Entry	Solvent (mL)[a]	EE (%)[b]
1	MeCN (0.5 mL)	96
3	DMSO (0.5 mL)	68
4	Amyl alcohol (0.5 mL)	94
5	THF (0.5 mL)	95

Note: a. Eluted with Tf_2NPh (5 mg) at 3 mL/min and distilled at 10 mL/min; b. Eluting efficiency (EE) (%) = 1-radioactivity left in SPE/total radioactivity.

Table 2
Summary of separators.

Entry	Type	Radioactivity left
1	Empty cartridge	<1%
2	Vial/Needle	<1%
3	Na_2SO_4	3.9 ± 1.2% (n = 3)
4	Silica gel	27%
5	Alumina N	100%

The amount of non-radioactive fluoride released from the components used in overall process was determined by derivatizing fluoride as tosyl fluoride, which was then measured by HPLC [10]. Excluding the fluoride from ^{18}O water, it was found that a total of 0.057 μg fluoride (including up to 0.008 μg from the MP-1M−HCO_3 resin) was introduced from the overall process using 10 mg PhN(OTf)$_2$.

The reactivity of [^{18}F]fluoride generated in this manner was tested using several precursors, including those used to produce FDG, ^{18}F glutamine (FGln) [11] and [^{18}F]FluorThanatrace (FTT) [12], and the results are shown in Figure 3 and Table S1. The radiochemical conversions are comparable to those previously reported, suggesting that [^{18}F]fluoride generated by our method has high reactivity. The radiosynthesis of [^{18}F]FGln used only 2 mg precursor and 1.5 mg K_2CO_3/K_{222} and afforded 59% radiochemical conversion of the intermediate. Starting from 43 mCi of [^{18}F]fluoride in ^{18}O water, conversion *via* [^{18}F]TfF to reactive [^{18}F]fluoride in acetonitrile was achieved in 89% radiochemical yield (RCY). [^{18}F]FTT was then synthesized from this converted [^{18}F]fluoride in 57% RCY (decay corrected), with molar activity of 43.7 GBq/μmol (1182 mCi/μmol), and used for an animal study (conducted at Washington University in St Louis (WUSTL) under WUSTL Animal Studies Committee IACUC-approved protocols). This RCY is comparable to those obtained using conventional methods [13], and the molar activity of the starting [^{18}F]fluoride, measured as [^{18}F] tosyl

Table 3
Summary of the trapping efficiency of [^{18}F]TfF.

Entry	Base[a]	(mg)	FR (mL/min)[b]	TE (%)[c]	Note
1	K_2CO_3/K_{222}	5	3	96.4 ± 2.6 (n = 5)	–
3	K_2CO_3/K_{222}	5	10	96.5 ± 2.1 (n = 6)	–
4	K_2CO_3/K_{222}	5	10	98.3 ± 0.1 (n = 2)	0.1 μmol fluoride (KF) added
5	K_2CO_3/K_{222}	5	3	91.4	Solvent: 1:4 MeCN/amyl alcohol
6	K_2CO_3/K_{222}	2.5	3	97.8 ± 1.2 (n = 3)	–
7	K_2CO_3/K_{222}	2.5	3	31.9	Solvent: amyl alcohol (300 μL)
8	K_2CO_3/K_{222}	1	3	92	–
9	K_2CO_3/K_{222}	1	10	84.8	–
10	K_2CO_3/K_{222}	1	10	76.3	Trapping at 105 °C
11	K_2CO_3/K_{222}	1	3	15.7	1 μmol fluoride (KF) added
12	$KHCO_3/K_{222}$	4.76	3	98.2 ± 0.5 (n = 2)	–
13	$KHCO_3/K_{222}$	1.4	10	32.3	–

Note a. K_2CO_3/K_{222} 1:2 (MW 891.19, 5 mg/5.6 μmol), $KHCO_3/K_{222}$ 1:1 (MW 476.61, 4.76 mg/10 μmol) in acetonitrile (0.5 mL) except for as noted; b. FR: Flow rate of distillation; c. TE: Trapping efficiency of [^{18}F]TfF (%) = trapped radioactivity in the reactor/trapped radioactivity in the reactor and in the alumina N trap.

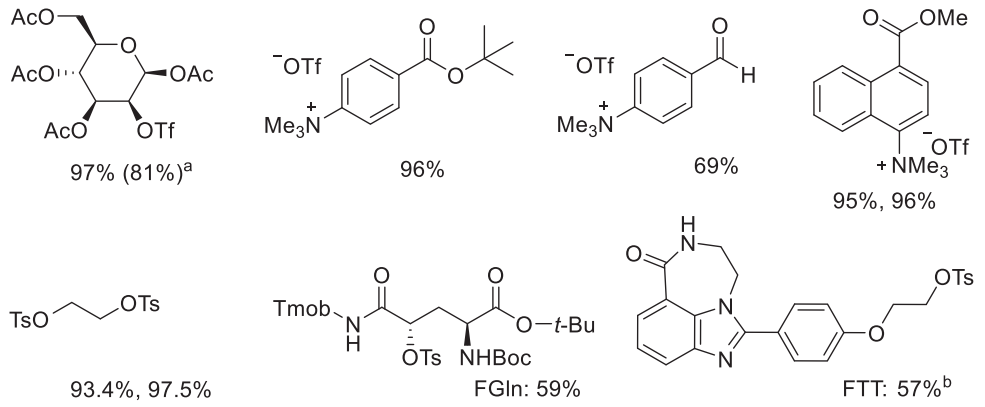

Fig. 3. Labeling precursors and their radiochemical conversions using [^{18}F]TfF as the source of [^{18}F]fluoride. Radiochemical conversion was determined by radio-TLC and confirmed by radio-HPLC. Note: a. 0.1 μmol KF was added as carrier to simulate a large amount of radioactivity; b. HPLC isolated radiochemical yield (decay corrected).

fluoride, was 118.4 GBq/ μmol (3200 mCi/μmol) at the same time point. This [^{18}F] tosyl fluoride method [10] can be used to determine the molar activity of fluoride at any stage of the conversion process.

The use of ^{18}F labeled sulfonyl fluorides is a promising strategy for the preparation of ^{18}F labeled radiopharmaceuticals without the need for an azeotropic drying step. [^{18}F]TfF was generated directly on the anion-exchange resin using the high affinity of the sulfonyl group for fluoride, and was isolated from the reaction mixture in gaseous form. While the high volatility of [^{18}F]TfF makes it extremely dangerous with respect to radiation safety, the use of a peristaltic pump provides an ideal solution for effecting the elution and distillation in a well-controlled manner that isolates this radioactive gas from the environment. As shown in Figure 2, fewer components are needed for the generation of [^{18}F]TfF by our method than by the previously reported one, which should result in more reliable production of [^{18}F]TfF. The use of an empty cartridge greatly simplifies the procedure for the distillation of [^{18}F]TfF. The small amount of non-radioactive [^{19}F]fluoride, which is found after the processing step (0.057 μg), is presumed to originate from the resin (up to 0.008 μg from the MP-1M−HCO_3; for comparison, 0.011 μg would come from 30-PS-HCO_3) and PhN$(OTf)_2$ (10 mg). Consequently, lower amounts of PhN$(OTf)_2$ are preferred to ensure that the final products are obtained in high molar activity. This is a particular concern when a small amount of radioactivity is to be used (e.g., 10 mCi), because even small amounts of non-radioactive fluorine could lower the molar activity of the labeled radiopharmaceuticals to levels that would be insufficient for imaging molecular targets of low concentration. The water-free conversion of dry [^{18}F]TfF to [^{18}F]fluoride, especially with $KHCO_3/K_{222}$ prepared by dissolving the complex in anhydrous acetonitrile, is expected to generate dry and highly reactive [^{18}F] fluoride. However, very dry [^{18}F]fluoride is not always preferred for radiolabeling because it may be absorbed non-specifically onto the surface of reaction vessels and might result in more side reactions (see Table S1). In this regard, we found that 20–30% of converted [^{18}F]fluoride in the acetonitrile/trapping container could become insoluble if not used right away. This may have contributed to the irreproducible results in the production of [^{18}F] FES and [^{18}F]FET noted in the previous report [2]. Furthermore, it has also been reported that long term storage of K_2CO_3/K_{222} in stock solutions (water/acetonitrile) resulted in lower labeling yields [14] and it is well known that overheating [^{18}F]fluoride/ K_2CO_3/K_{222} during azeotropic drying can also reduce the yield of labeling reactions. Hence, we believe that dry, water-free [^{18}F]fluoride obtained by the conversion of ^{18}F in the ^{18}O water *via* [^{18}F]TfF under these mild and controlled protocols should be well suited for ^{18}F fluorination in general, similar to that of other reagents ([^{18}F] AcF [15] and [^{18}F]Me_3SiF [16]) that have been used as the source of [^{18}F]fluoride for labeling. The trapping of [^{18}F]TfF in the base solution is critical for the application of this method in radiolabeling. Compared with the conventional method which requires about 1 mg K_2CO_3 to efficiently elute radioactivity from a cartridge, much less K_2CO_3 (0.15 mg) in K_2CO_3/K_{222} (1 mg) is needed to trap over 90% radioactivity transferred *via* [^{18}F]TfF, but this depends to some degree on the amount of radioactivity and its molar activity. The small amount of base allows for the use of small amounts of a base-liable precursor for labeling (e.g., [^{18}F]FGln) and should facilitate the purification step. We have used this method to radiosynthesize [^{18}F]FTT with trapping and the reaction conducted

in one pot. The molar activity of [^{18}F]FTT is somewhat less than that of [^{18}F]fluoride itself in the ^{18}O water measured as [^{18}F]TsF, but the non-radioactive fluoride from the processing only contributes 23.8 % (0.057 μg out of 0.24 μg) of total fluoride obtained when 10 mg of PhN(OTf)$_2$ is used for elution. Finally, it is notable that by using the [^{18}F] tosyl fluoride method [10] it is possible to determine the molar activity of fluoride at any stage of the conversion and radiolabeling processes, and thereby identify steps that might be compromising the utility of the final tracer material due to reduced molar activity and implement changes to minimize this dilution.

Conclusion

We have developed a simple method for the generation of [^{18}F] triflyl fluoride as the source of [^{18}F]fluoride for radiolabeling. This method is an example of continuous-flow solid-phase radiosynthesis, capable of generating labeling-ready [^{18}F]fluoride in high radiochemical yield and high molar activity within a short time. This method has advantages for radiolabeling over the conventional azeotropic drying method, although with some limitations, as discussed above. Nevertheless, it should have great potential for expediting the preparation of ^{18}F labeled radiopharmaceuticals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153273.

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