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Magnetic Droplet Microfluidics as a Platform for the Concentration of [^{18}F]Fluoride and Radiosynthesis of Sulfonyl [^{18}F]Fluoride

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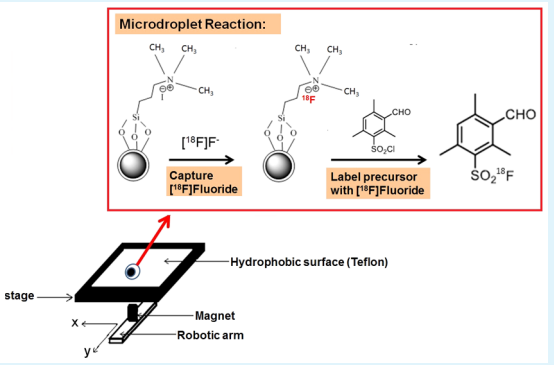
ABSTRACT: The radioisotope ^{18}F is often considered the best choice for positron emission tomography (PET) owing to its desirable chemical and radiochemical properties. However, nucleophilic ^{18}F-fluorination of large, water-soluble biomolecules, based on C−F bond formation, has traditionally been difficult. Thus, several aqueous fluorination approaches that offer significant versatility in radiopharmaceutical synthesis with sensitive targeting vectors have been developed. Furthermore, because ^{18}F decays rapidly, production of these ^{18}F-labeled compounds requires an automated process to reduce production time, reduce radiation exposure, and minimize losses due to the transfer of reagents during tracer synthesis. Herein, we report the use of magnetic droplet microfluidics (MDM) as a means to concentrate [^{18}F]fluoride from the cyclotron target solution, followed by the synthesis of an ^{18}F-labeled compound on a microfluidic platform. Using this method, we have demonstrated ^{18}F preconcentration in a small-volume droplet through the use of anion exchanging magnetic particles. By using MDM, the preconcentration step took approximately 5 min, and the [^{18}F]fluoride solution was preconcentrated by 15-fold. After the preconcentration step, an ^{18}F-labeling reaction was performed on the MDM platform using the S−F bond formation in aqueous conditions to produce an arylsulfonyl [^{18}F]fluoride compound which can be used as a prosthetic group to label PET targeting ligands. The high radiochemical purity of 95 ± 1% was comparable to the 96% previously reported using a conventional method. In addition, when MDM was used, the total synthesis time was improved to 15 min with lower reagent volumes (50−60 μL) used.



KEYWORDS: *magnetic particles, droplet microfluidics, positron emission tomography (PET), ^{18}F, radiotracer, arylsulfonyl fluoride*

INTRODUCTION

In the diagnosis and treatment of diseases such as cancer, one needs a technique to image and understand the functions of both normal and aberrant tissues at the molecular level. With this understanding, it is possible to detect disease while treatable, to monitor disease progression, and to evaluate an individual patient's response to therapy.

Over the years, positron emission tomography (PET) has emerged as the premier choice for functional imaging due to its high sensitivity and spatial resolution.[1] This procedure requires positron-emitting biomolecules that selectively bind to the biological area of interest (i.e., cellular targets or receptors). The radioisotope ^{18}F is often considered to be the best positron-emitter, owing to its appropriate decay half-life (109.7 min), which balances patient dose with pharmacokinetic clearance of the tracer itself. The half-life is also long enough to allow time for synthesis of radiotracers without much decay loss, and hence, ^{18}F can be manufactured commercially at offsite locations then shipped to PET centers. Furthermore, ^{18}F has desirable decay properties such as high spatial resolution, large positron abundance (~97% β^+-emission), good availability of target material, such as $H_2{}^{18}O$, and high ^{18}F isotopic purity.[2] However, direct ^{18}F-fluorination of large biomolecules (such as proteins and peptides) via C−F bond formation is undesirable since the reaction requires virtually anhydrous conditions. Elevated reaction temperatures (80−150 °C) are also often required and can result in decomposition of the precursor, the product, or both.[3] Recently, aqueous [^{18}F]-fluoride chemistries have been developed whereby small molecule prosthetic groups, which can be prepared in aqueous conditions, are synthesized and then attached to a biomolecule in a second reaction. A few aqueous ^{18}F reaction strategies have been reported, namely, (1) reaction with aryl boronic esters to form aryltri[^{18}F]fluoroborates,[4] (2) reaction with silicon fluorides to form triorgano [^{18}F]fluorosilanes,[5] (3) reaction with aluminum trichloride to produce aluminum-^{18}F chelates,[6] and (4) reaction with arylsulfonyl chlorides to form arylsulfonyl [^{18}F]fluorides.[7] The development of these aqueous approaches has offered significant progress in radiopharmaceutical synthesis of ^{18}F radiotracers.

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These aqueous ^{18}F-labeling strategies reported have so far all been performed using conventional methods, where reagents and precursors were manually added and transferred from one vial to another. Generally, the synthesis involves several procedural steps. The first step is the generation of the radioisotope [^{18}F]fluoride, which is produced by the proton bombardment of the target material (heavy oxygen water or $H_2{}^{18}O$)), and the radionuclide is released from the cyclotron in the form of [^{18}F]fluoride/$H_2{}^{18}O$ solution. The second step is preconcentration, which involves selectively isolating [^{18}F]-fluoride from $H_2{}^{18}O$ to recover this expensive target material and to concentrate the [^{18}F]fluoride solution to increase the nucleophilicity of fluoride ions.[8] Currently, [^{18}F]fluoride/$H_2{}^{18}O$ solution is concentrated by first passing it through a short column of anion-exchange resin and then by eluting the [^{18}F]fluoride with an aqueous metal carbonate solution (e.g., K_2CO_3) and in the presence of a phase transfer catalyst such as a cryptand (e.g. Kryptofix 2.2.2 or K2.2.2), or a large organic counterion, e.g. tetrabutyl ammonium bicarbonate.[9] The third step is the fluorination reaction, which involves attaching [^{18}F]fluoride to a prosthetic group for subsequent incorporations onto a peptide or other biomolecule. After the synthesis of the labeled compound, the fourth step, purification, should be conducted to remove unreacted ^{18}F ions and other impurities from it. Purification can be performed by solid phase extraction (SPE) or high-performance liquid chromatography (HPLC). Sterilization is also performed so that the product will be suitable for patient injection.

The conventional method available to execute the steps described above is difficult to achieve in a short time scale (within one half-life of the radioisotope, i.e. 109.7 min). Furthermore, because the mass of fluoride generated is small, significant losses of activity can occur during transfer from one vial to another. These two issues can result in lower radiochemical yields.[8]

It is also important to note that handling radioactive species requires these key steps to be performed with the lowest possible exposure to the operator. Thus, ^{18}F radiopharmaceutical production requires an automated process to reduce production time, reduce radiation exposure, and minimize the transfer of reagents during radiotracer synthesis in order to reduce sample transfer loss.

Microfluidics has been explored as a platform that can bring multiple advantages for radiopharmaceutical development.[10] These advantages include (1) the ability to handle small volumes, (2) the potential of thorough mixing of reagents due to high surface-to-volume ratio, (3) good control over reaction conditions, (4) automated and fast synthesis, and (5) high recovery of radioactive product. The manipulation of liquid droplets for sampling and reaction has been carried out by droplet microfluidics based on electrowetting.[11] Another method is to use a magnetic field to move magnetic particles and the liquid droplet associated with the particles.[12] To the best of our knowledge, application of magnetic manipulation of liquid droplets for carrying out radiochemical reactions has not been reported.

Herein, we report a study to explore the use of a microfluidic platform to conduct [^{18}F]fluoride preconcentration and synthesis of ^{18}F-labeled compounds through manipulating liquid droplets of microliter scale with the help of magnetic particles. The platform is called magnetic droplet microfluidics (MDM). A magnet is moved to manipulate the magnetic particles which hold a small liquid droplet by surface tension. The particles also have an ion-exchange property that is capable of capturing and releasing fluoride ions. These particles are used to preconcentrate the [^{18}F]fluoride ion in the $H_2{}^{18}O$ liquid droplet. [^{18}F]fluoride ions are then released, and are used to synthesize a prosthetic compound which can subsequently be used to label a biomolecule (e.g., peptide) for PET.

As an application of the MDM platform, we demonstrated the synthesis of 3-formyl-2,4,6-trimethylbenzene-sulfonyl [^{18}F]-fluoride (2) (Figure 1), which has been previously demonstrated as a prosthetic group in peptide radiolabeling.[7]

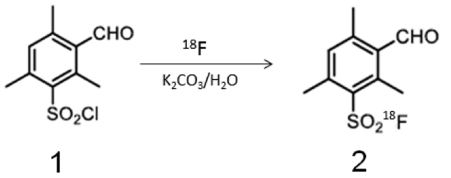

Figure 1. Conversion of 3-formyl-2,4,6-trimethylbenzene-sulfonyl chloride (1) to 3-formyl-2,4,6-trimethylbenzene-sulfonyl [^{18}F]F$^-$ (2).

EXPERIMENTAL SECTION

Materials. All chemicals were of analytical grade and used without further purification. Tetraethylorthosilicate (TEOS), iodomethane and K_2CO_3 were purchased from Caledon Laboratories. (3-aminopropyl)-triethoxysilane (APTES) was purchased from MP Biomedicals. All other chemicals used were purchased from Sigma−Aldrich. The disc-shaped carrier magnet (5 mm diameter × 1 mm thickness) which was used to hold the magnetic particles was purchased from Indigo Instruments, Inc., and the Teflon sheet from Johnston Industrial Plastics, Ltd.

Deionized water (18 MΩ/cm) was used in all experiments. The precursor, 3-formyl-2,4,6-trimethylbenzenesulfonyl chloride (1) and the standard, 3-formyl-2,4,6-trimethylbenzenesulfonyl fluoride were synthesized as previously reported.[7]

MDM Platform. The MDM platform consists of a robotic arm which was modified from an X−Y plotter (Figure 2). The movement

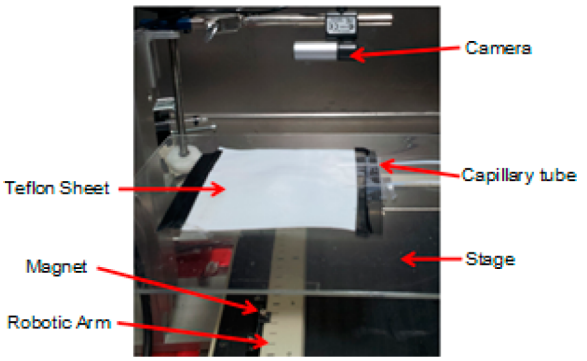

Figure 2. Image of the MDM platform. The Teflon sheet was placed on the stage, and the robotic arm underneath the Teflon sheet was used to control movement of magnetic particles above it.

of the arm that carried a magnet was controlled by a computer using the software Labview 8.2 (National Instruments). A stage which held a Teflon sheet was placed above the robotic arm. On this Teflon surface, the magnetic particles and the liquid droplets were placed.

A camera was mounted above the MDM platform to record the droplet movement. A capillary tube, which was used to collect the $H_2{}^{18}O$ target material, was mounted on the surface and connected to a syringe pump.

Preparation of Fe_3O_4 Magnetic Particles. A $FeCl_2$ solution (22.5 mL, 0.24 M) was placed in a round-bottomed flask. The solution

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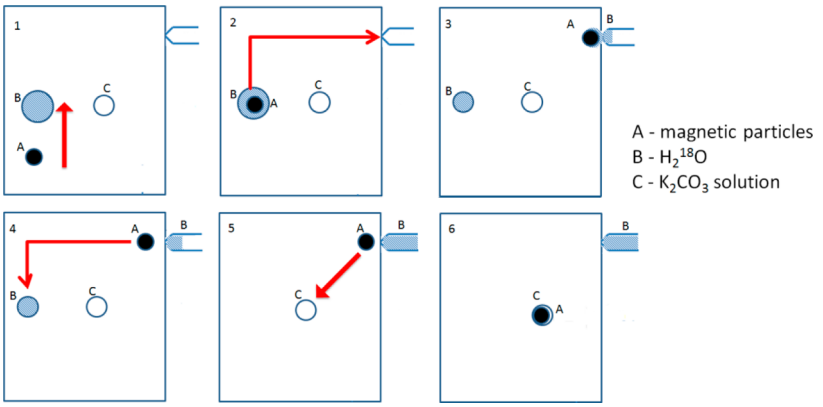

Figure 3. Steps for [^{18}F]fluoride preconcentration on the MDM platform. (1, A) The magnetic particles were moved toward the (B) $H_2{}^{18}O$ solution containing [^{18}F]F$^-$. The particles were looped in a circular motion within the solution to induce stirring motion. (2) The particles, carrying a droplet of $H_2{}^{18}O$, were moved toward the capillary tube. (3) The $H_2{}^{18}O$ droplet was collected by the capillary tube under suction. (4) The particles were moved back to the $H_2{}^{18}O$ solution to carry another droplet. Steps 2–4 was repeated continuously until $H_2{}^{18}O$ was completely consumed. (5) The particles moved toward K_2CO_3 solution (C) to release [^{18}F]F$^-$ ions. The particles containing the [^{18}F]F$^-$ ions again looped in a circular motion within the solution to induce stirring motion. (6) The preconcentrated [^{18}F]fluoride was then pipetted out from the platform and placed in a vial for analysis.

was mixed with poly(vinyl alcohol) (PVA, 1.50 g), which had been previously dissolved in 30 mL water by heating at 95 °C. The resulting greenish-brown solution was sonicated at 50 °C for 10 min under a nitrogen gas flow. A solution of H_2O_2 (30 mL, 0.24 M) was then added dropwise to the mixture which was stirred mechanically. NaOH (30 mL, 3M) was then added and the color of the solution immediately turned black. The solution was stirred for 2 h at room temperature under nitrogen gas. The solution was then transferred from the flask to a centrifuge tube (50 mL) and was spun (using Centrifuge 5804, Eppendorf) at 1100 reactive centrifugal force (rcf) for 20 min. The black particles were then collected with the aid of a magnet placed outside the tube. The particles were washed with ethanol (~30 mL) three times while the big particle chunks were broken apart into smaller ones using a glass rod.

Silica Coating of Fe_3O_4 Particles. The resulting black magnetic particles were stirred with 150 mL of ethanol, mixed with 12 mL of ammonium hydroxide solution (28–30% NH_3) under N_2 flow. Then, 400 μL TEOS was added dropwise to the liquid mixture to produce silica (SiO_2) and coat on the particle surface. The particles were then separated from the liquid using a magnet and they were washed with ethanol three times. The above steps were conducted twice to ensure that the particle surfaces were sufficiently coated with silica. The silica-coated particles were washed with ethanol (~30 mL) and then removed from the solution with the aid of a magnet. The particles were stored dry until the next step.

Attachment of Amine Group in Silica-Coated Fe_3O_4. This procedure is adapted from a previous report.[13] Silica-coated Fe_3O_4 was stirred with HCl (20 mL, 5% v/v) for 20 min to activate surface silanol groups. Then, the particles were washed with ethanol until the solution pH dropped between 4 and 5. Then, 20 mL of anhydrous ethanol was added to the magnetic particles followed by the addition of 4 mL of APTES to introduce the amine functional group on the particles. The solution was then refluxed for 3 h at 60 °C. After heating, the particles remained black and they were washed with 50 mL chloroform to remove unreacted APTES.

Conversion of Primary Amine to Quaternary Methylammonium (QMA) Iodide. To introduce the ion-exchange functional groups on the magnetic particles, we converted the primary amine on the particles to quaternary methylammonium iodide. First, the amine-functionalized particles were added to 50 mL of acetonitrile in a flask that contained 5.0 g of K_2CO_3 and 1.50 mL of CH_3I. The mixture was refluxed at 70–75 °C for 20 h. The flask was covered with aluminum foil to prevent photo-oxidation of iodide ion to iodine. The black particles were then separated from the solution with the aid of a magnet, and they were washed with dichloromethane.

Preconcentration of [^{18}F]Fluoride on the MDM Platform. High-energy protons (13 MeV) were produced on a TR13 cyclotron at TRIUMF, Canada. [^{18}F]Fluoride was produced by proton bombardment (10 mA, 5 min) on 1 mL of [^{18}O]H_2O. Typical production of [^{18}F]fluoride was 40.5–70.2 mCi (1.5–2.6 GBq) at the end of bombardment. The activity of the [^{18}F]fluoride solution produced was measured. For safety reasons, an aliquot with a lower activity of approximately 2 mCi was taken. This aliquot was diluted to a volume of 1 mL for the fluoride preconcentration experiment.

The MDM platform was set up as shown in Figure 2. The step-by-step operation procedures are depicted in Figure 3. In step 1, the magnetic particles (A), approximately 25 mg, were placed on the Teflon sheet. These particles were adhered to a disc-shaped carrier magnet so that they were moved as a group on the Teflon sheet. In step 2, the magnetic particles were pulled toward the [^{18}F]fluoride/$H_2{}^{18}O$ droplet, controlled via the magnet on the robotic arm. The magnetic particles were looped around the droplet to induce a stirring effect. This continuous looping was also computer-controlled, and the operation could be stopped at a desired time. Once the desired operation time (e.g., 2 min) was reached, the particles were moved toward the capillary tube for removal of the $H_2{}^{18}O$ (B) target material (in steps 2–4). Steps 2–4 were performed repeatedly until $H_2{}^{18}O$ (B) was completely removed. [^{18}F]fluoride ions captured by the quaternary ammonium groups on the particles were released using 50 μL of K_2CO_3 (C) solution [0.0774 and 0.145 M] (step 5).

The activity of the $H_2{}^{18}O$ solution collected in the capillary tube was measured using a gamma detector (Capintec, CRC-127R Dose Calibrator). The activity left on the particles as well as the activity released into the solution was also measured.

Synthesis of 3-Formyl-2,4,6-trimethylbenzene-sulfonyl [^{18}F]-Fluoride (2) on the MDM Platform. The preconcentration step and the synthesis reaction (Figure 1) were consecutively conducted on the MDM platform. The same steps outlined in Figure 3 were performed here except that droplet (C) now contains both the K_2CO_3 solution and the precursor (1). First, 50 μL of preconcentrated [^{18}F]fluoride (~2 mCi) in aqueous K_2CO_3 (0.0145 M) was allowed to react with 50 μL of precursor (1) (3 μmol, 0.060 M), in *t*-BuOH. Total reaction volume was 100 μL and the final concentration of precursor (1) became 0.030 mM. The reactants were allowed to react for ~5 min. For the purposes of this study, the product mixture was collected from the MDM platform using a 1 mL syringe. The reaction mixture was diluted with 10 mL water and manually transferred to a SPE column (Waters tC18 "light") to remove excess fluoride and *t*-BuOH. Before use, the column was activated with EtOH (2 mL) and water (6 mL), washed with water (5 mL), and dried with air for 5 min. The product was eluted from the column with 1 mL acetonitrile. After SPE

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purification of [^{18}F]2 an aliquot (40 μL) of known activity was directly assayed by HPLC using both the UV absorbance detector and the radioactive detector to calculate the specific activity. The amount of the reference standard, [^{19}F]2 and the total activity of the sample was used to calculate the specific activity of [^{18}F]2.

RESULTS

The surface coating of the magnetic particles was modified to contain an F^- anionic exchange functional group. Because these particles were magnetic, they can be manipulated by the use of a magnet to facilitate the movement of the particles on the MDM platform. The preparation of Fe_3O_4 particles was conducted under an inert gas atmosphere. PVA acts as a protective agent to stabilize the colloidal dispersion of Fe_3O_4 and also coats the particles to prevent the reaction of the particles with oxygen in the surrounding atmosphere during storage and downstream radiochemistry experiments.[14] In addition, the silica coating is used to provide protection for Fe_3O_4 from being oxidized to Fe_2O_3, which is brown in color and has no magnetic property. After the particles were coated with silica, it was occasionally found that the particles could still be oxidized to Fe_2O_3. This problem may be caused by the porous nature of the silica coating.[15] In our previous experience, either black or brown particles were obtained when only one silica deposition was performed. Therefore, we decided to perform two deposition cycles, and it was found to consistently produce black Fe_3O_4 magnetic particles. We found that these doubly coated particles remained black even after 3 months or longer. These particles were stored in a tightly sealed glass container.

The structure of the quaternary amine modified magnetic particle is shown in Figure 4. The quaternary amine served as the ion-exchanging group and it can be utilized to capture the [^{18}F]fluoride ion in exchange for the resident iodide ion.

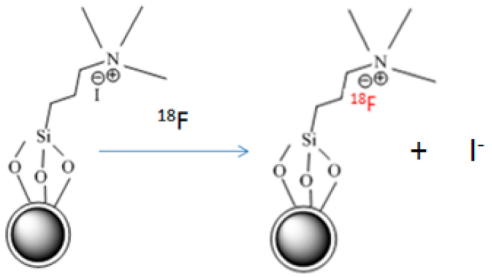

Figure 4. F^- ion-exchanging Fe_3O_4 particles which can capture [^{18}F]fluoride.

An elemental analysis was performed on the particles by the energy-dispersive X-ray (EDX) scan (conducted on a scanning electron microscope) to characterize the elements present in the sample. Figure 5A shows that iodine, which was expected to be present on the surface of the quaternary ammonium iodide tagged particle, was initially present on EDX scans. To test the ion exchange efficiency of these particles, we exposed the beads to a NaF solution (0.01 mM, 10 mL), followed by release experiments by incubating with a $NaClO_4$ solution (0.0817 M, 0.2 mL). After performing the ion-exchange reaction, a second scan (Figure 3, 2B) was conducted on the particles and clearly showed that the iodine peak is no longer present, having been replaced by a prominent chlorine peak, which suggests the presence of ClO_4^-.

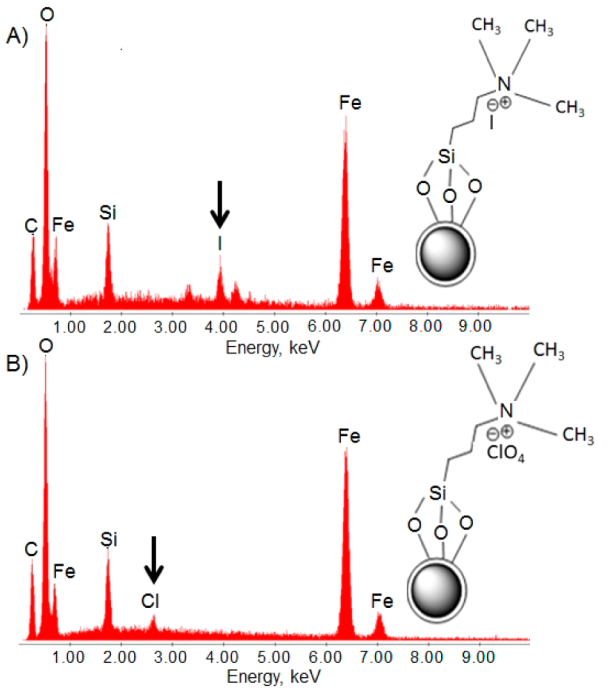

Figure 5. EDX spectra for quaternary methylammonium iodide-functionalized particle: (A) before fluoride capture (the black arrow points at the signal of I) and (B) after fluoride capture and subsequent exchange by ClO_4^- to release fluoride (the black arrow points at the signal of Cl).

The particles obtained in the initial trials were bigger, and their sizes ranged between 200 and 250 μm. When the particles aggregates were manually ground using a glass rod, 50−100 μm particles were obtained. To avoid oxidation of the magnetic particles, the grinding process was performed inside a glovebag under argon. The procedure took less than 1 h to complete.

During the capture and release steps, the magnetic particles were allowed to loop in a circular motion within the liquid droplet to induce stirring. This procedure was conducted at different operation times (1−8 min) using 50−100 μm particles. There was an increase of both capture and release efficiencies when the operation time was increased to from 1 to 2 min. The increase in the capture efficiency was 1.3-fold (from 60 to 79 ± 3%, n = 3), and that for release efficiency was also 1.3-fold (from 70 to 93 ± 3%, n = 3). When the operation time was increased further to 4 and 8 min, no improvement was observed. Thus, the optimal operation time was selected to be 2 min for both the capture and release steps.

The capture efficiency, which was 79 ± 3% suggests that the accessible ion-exchange sites were at or close to saturation. Therefore, the [^{18}F]F^- ion-exchange capacity of 25 mg of particles was investigated by varying the initial activity of [^{18}F]fluoride/$H_2{}^{18}O$ thereby varying the initial amount of [^{18}F]F^- ions in the solution. From Table 1, it was found that when the initial ^{18}F activity was decreased (thereby decreasing the mass of fluoride), the capture efficiency increased. This trend can be explained by the fact that the ion-exchange sites on the particles are more likely to be occupied and became saturated as the amount of fluoride increased.

We believe that the ion-exchange capacity of the particles may increase as the particle size is reduced. This is because the surface area available for the formation of $NR_4^+I^-$ should be greater in smaller sized particles. Therefore, we compared the

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Table 1. Effect of the Activity of [^{18}F]Fluoride Solution and Particle Size on the Capture Efficiency of 25 mg Quaternary Methylammonium Tagged Magnetic Particles

particle size (μm)	initial ^{18}F activity (mCi) in 1 mL droplet[a]	estimated mass of F^- (μg)[a]	capture efficiency (%)[a]
200−250	1.86 ± 0.05	0.018 ± 0.001	86 ± 3
	2.56 ± 0.05	0.024 ± 0.001	70 ± 3
	6.91 ± 0.05	0.066 ± 0.001	63 ± 2
50−100	1.96 ± 0.05	0.019 ± 0.001	93 ± 3
	3.50 ± 0.05	0.033 ± 0.001	79 ± 3
	6.97 ± 0.05	0.066 ± 0.001	59 ± 3

[a]The errors are SD (n = 3). All activities were decay-corrected to EOB.

capture efficiency of the two batches of particles (200−250 and 50−100 μm). It must be noted that the breaking of the particles to smaller sizes was performed before silica coating and functionalization of the particle surface. The mass of fluoride was estimated assuming that the specific activity of ^{18}F produced from the TR-13 cyclotron is approximately 2 Ci/μmol.[4,16] From Table 1, the particles with a 50−100 μm size were observed to generally produce higher capture efficiency than those with a larger size. This increase in efficiency is clearly observed when the amount of fluoride is less.

The capture efficiency using a higher mass of magnetic particles is also determined. When an initial activity of 32 ± 2 mCi of [^{18}F]/$H_2{}^{18}O$ was used, the capture efficiency using 25 mg of magnetic particles (50−100 μm) was 35 ± 3% (n = 3). This value is smaller than 59 ± 3% when 6.97 mCi of initial activity was used (Table 1). When the mass of the magnetic particles was increased from 25 to 40 mg, the capture efficiency increased 1.5 times from 35 ± 3 to 51 ± 3%. These results support the observation in Table 1 that the capture efficiency is dependent on the number of ion-exchange sites on the surface of the particle. The capture efficiency of 51% is lower than the previous values because the initial activities used in these new studies are higher (i.e., 32 ± 2 mCi).

On the basis of our results, we have found that the amount of activity captured is dependent more on the number of ion-exchange sites rather than the total mass of the particles used. In the future, our group intends to study a variety of particles with a higher number of ion-exchange sites and the effect this has on the overall capture efficiency, as well as capture and release rates when using higher Curie quantities of activity that are typically produced in cyclotron facilities on a daily basis.

To study the release efficiency, we tested two different concentrations of K_2CO_3 (50 μL of 0.0774 or 0.145 M) to determine their effect on [^{18}F]fluoride release efficiency. From the experimental results tabulated in Table 2, the [^{18}F]fluoride release efficiency observed was 82 ± 2% for 0.0774 M, and a higher value was found for 0.145 M of K_2CO_3. This result can be explained by considering the effect of additional CO_3^{2-} available to exchange with F^-, generating higher release efficiency. Based on these observations, we chose to use 0.145 M of K_2CO_3 in subsequent studies on the MDM platform.

Table 2. Release Efficiency of [^{18}F]Fluoride Ions Trapped on Quaternary Methylammonium Tagged Particles Using K_2CO_3 in the Release Solution

$[CO_3^{2-}]$ (M)	initial activity captured on particles (mCi)[a]	release efficiency (%)
0.0774	3.17 ± 0.05	82 ± 2 (n = 3)
0.145	3.50 ± 0.05	93 ± 4 (n = 5)

[a]Small-sized particles (50−100 μm, 25 mg) were used. All activity values are decay-corrected to EOB. Errors are SD.

As previously reported, ^{18}F-labeling of sulfonyl chlorides tolerate the presence of water in the reaction mixture, and good yields were still achieved.[7] However, preconcentration of fluoride is still beneficial to increase the rate of radiochemical reactions, which typically employ small amounts of precursor in nano- or micro-mole quantities and in microliter volumes.[8]

To determine the preconcentration factor, we employed an operation time of 2 min for both the capture and release steps. Because low initial activities (~2 mCi) were used, only 25 mg of magnetic particles were sufficient for capturing fluoride. For the release step, 50 μL of K_2CO_3 (0.145 M) was used. With a capture efficiency of 78.5−79.3% and a release efficiency of 90.9−94.5%, the average preconcentration factor calculated was 14.7 ± 0.3.

After [^{18}F]fluoride preconcentration was completed, the synthesis of [^{18}F]2 was conducted on the same platform. Following the same procedure as previously reported,[7] a 1:1 volume ratio of the precursor (1) and [^{18}F]fluoride solution was used. However, we wanted to reduce the volume to 50 μL for both reactants. Using a lesser volume, we also aimed at reducing the reaction time to 5 min. Then, the product mixture was collected, and its activity was measured. Thereafter, a 40 μL aliquot was taken for HPLC analysis.

Figure 6 shows the HPLC chromatogram of the product mixture using both the UV-absorbance and radioactive

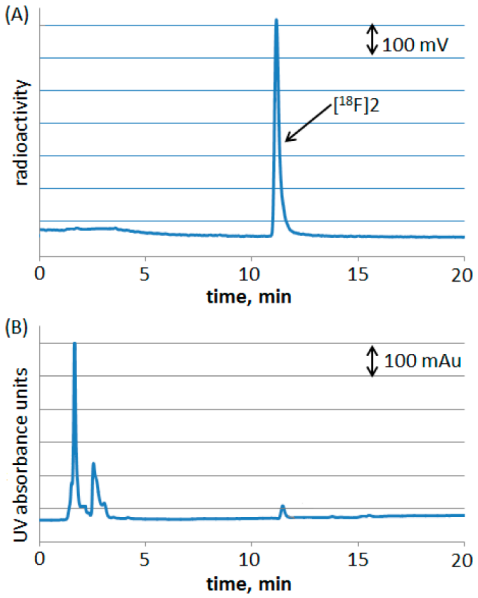

Figure 6. HPLC result of the product mixture of [$^{18/19}$F]2 after SPE purification. (A) Radioactive detection showing the presence of [^{18}F]2 (B) UV detection (254 nm). HPLC conditions: Isocratic flow =1.00 mL/min, 30:70 MeCN:H_2O.

detectors. The retention time for [^{18}F]2 was found to be at 10.9 min. The apparent specific activity of [^{18}F]2 prepared in this fashion was estimated to be 48 ± 3 GBq/μmol (1.3 ± 0.1 Ci/μmol, n = 3) based on the UV-HPLC signal and the radioactive signal. For comparison, a value of 18.5 GBq/mmol

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ACS Appl. Mater. Interfaces 2015, 7, 12923−12929

(0.5 Ci/ μmol) is generally considered as the minimum activity required for PET imaging applications[17] and a value of 37−74 GBq/mmol (1−2 Ci/ μmol), is described as high.[8] Nevertheless, our measured apparent activity was found to be lower compared to 105 GBq/μmol (2.8 Ci/μmol) that was previously reported.[7] This difference may be attributed to the fact that we did not selectively degrade the sulfonyl chloride precursor in this case with pyridine base.

The results for the synthesis of [^{18}F]2 are tabulated in Table 3. A radiochemical purity of 90−95% was obtained from the HPLC peak area percentage. The radiochemical yield is calculated based on the activity of the isolated product against initial radioactivity and the values calculated are 62−72%.

Table 3. Results for the Synthesis of [^{18}F]2

volume of 0.06 M precursor (1) used (μL)	radiochemical purity (%)[a]	radiochemical yield (RCY) (%)[a]
50	90 ± 1	62 ± 5
60	95 ± 1	72 ± 1

[a]Activities are decay-corrected to EOB and errors are SD (n = 3).

It was found that an increase in the amount of precursor (1) used increases the amount of the product formed. This increase leads to an improvement of the radiochemical purity from 90 to 95%, thereby increasing the radiochemical yield (RCY) value to 72%. It was observed that although the release percentage was quite high, the low capture percentage has resulted in a low overall RCY. We believe that this low capture percentage is caused by the saturation of the quaternary ammonium binding sites in the magnetic particle surface. This issue could be resolved by using more magnetic particles and in smaller sizes.

We compared our results with those obtained from the conventional method[7] and from a previous report using the Advion System,[18] (Table 4). The radiochemical purity of 96% and RCYs of 72% obtained from our MDM method are comparable with those values obtained from the other two methods. Moreover, the automated process performed on the MDM platform is an attractive feature because of reduced operator radiation exposure and less contribution of human error, resulting in better results. Similar to most microfluidic systems, our MDM platform offers the advantage of dealing with small volumes of reagents and precursors.

In the work published by Matestic et al.,[18] only the mixing of [^{18}F]fluoride and precursor took place in the microreactor. But the preconcentration step was still conducted on a conventional quaternary methylammonium (QMA) anion-exchange column. In our case, we demonstrated that both preconcentration and synthesis could be conducted on the same platform. The drying method after [^{18}F]fluoride preconcentration was eliminated, and the total synthesis time was reduced to ∼15 min.

With our preconcentration method, [^{18}F]fluoride was released and our radiochemistry performed in a smaller volume (50 μL) when compared to conventional methods (using the QMA ion-exchange column). Even when the procedure was performed in low volumes, we were able to produce the [^{18}F]2 at high radiochemical purity (95%). Our MDM method offers a simple and safe approach leading to an easier module development for the preparation of ^{18}F-labeled radiotracers.

CONCLUSIONS

This study introduces the use of a novel microfluidic design as a potential method for the routine production of ^{18}F radiotracers.

Herein, we showed that the synthesized QMA-tagged magnetic particles can be used to capture [^{18}F]fluoride ions in a solution, and the captured [^{18}F]fluoride ions are released by ion-exchanging with a K_2CO_3 solution. The capture efficiency was investigated with different masses of magnetic particles and with varying amounts of activity. With these investigations, we found that the amount of activity which can be captured on the particles is dependent on the number of ion-exchange sites on the surface of the particles.

When the MDM platform is used to carry out a radiochemical reaction, the method was successful in integrating the preconcentration and synthesis steps on the same platform resulting in a reduced overall reaction time while using microliter volumes of reagents.

This automated process offers minimal operator exposure and facile operation outside the hotcell, giving a safe and simple alternative method to carry out radiochemical reactions.

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Notes

The authors declare no competing financial interest.

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Table 4. Method Comparison for the Synthesis of [^{18}F]2

	[^{18}F]fluoride solution	precursor (1)	reaction time	total synthesis time (min)	radiochem purity, (%)	RCY (%)
conventional (Inkster et al.)[7]	5−10 mCi 100−200 μL	0.060 M 100 μL	15 min	20−25	96 ± 1	73 ± 7
Advion system (Matestic et al.)[18]	0.27−0.40 mCi 10 μL per batch	0.0081 M 10 μL	2 min per batch	15−20	97	75
magnetic droplet microfluidics (MDM)	2−6 mCi 50 μL	0.060 M 50−60 μL	5 min	10−15	95 ± 1 (n = 3)	72 ± 1 (n = 3)

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ACS Appl. Mater. Interfaces 2015, 7, 12923−12929

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