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On-chip pre-concentration and complexation of [^{18}F]fluoride ions *via* regenerable anion exchange particles for radiochemical synthesis of Positron Emission Tomography tracers

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ABSTRACT

Microfluidic approaches have demonstrated a relevant impact on radiochemical reactions involving Positron Emission Tomography (PET) nuclides, due to shorter reaction times and smaller precursor quantities. However, little attention has been given to the integration of the initial pre-concentration and drying of radioactive [^{18}F]fluoride ions, required for the labeling of radiotracer compounds. In this work we report the design, fabrication and implementation of a glass microfluidic device filled with recyclable anion exchange particles for the repeated recovery of [^{18}F] and [^{19}F]fluoride ions. The device was first tested with non radioactive [^{19}F]fluoride ions and it was shown to repeatedly trap and elute >95% fluoride over 40 successive experimental runs with no decrease in efficiency. The same device was then tested for the trapping and release of [^{18}F]fluoride ions over 20 experiments with no measurable decrease in performance. Finally, the [^{18}F]fluoride ions were eluted as a K^{18}F/K2.2.2 complex, dried by repeated dissolution in acetonitrile and evaporation of residual water, and reacted with ethyl ditosylate (EtDT) leading to the desired product ([^{18}F]fluoroethyltosylate) with 96 ± 3% yield (RCY). The overall time needed for conditioning, trapping, elution and regeneration was less than 6 min. This approach will be of great benefit towards an integrated platform able to perform faster and safer radiochemical synthesis on the micro-scale.

1. Introduction

Positron Emission Tomography (PET) is a molecular imaging modality able to detect the distribution of positron-emitting probes or radiotracers in living subjects with high resolution and very high sensitivity. [^{18}F]-labeled compounds are the most predominantly used radiopharmaceuticals and are widely employed in the fields of disease diagnosis and staging in oncology, cardiology and neurosciences. 2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) is nowadays the most used molecule worldwide in PET but several other fluorine-based radiotracers are also available [1,2]. Fluorine labeling of biologically active substrates is preferentially achieved *via* nucleophilic reaction of fluorides on aliphatic and aromatic compounds, in polar aprotic solvents such as acetonitrile, DMF or DMSO and in the presence of a phase transfer catalyst such as a cryptand, *e.g.* Kryptofix 2.2.2 (K2.2.2), or large organic counterions, *e.g.* tetrabutyl ammonium bicarbonate [3].

The overall fluorinated radiotracer production requires several procedural steps that are generally represented by (a) [^{18}F]fluoride ions production by accelerated particle bombardment of ^{18}O-enriched water targets in a cyclotron, (b) [^{18}F]fluoride recovery from aqueous solution and its subsequent drying, (c) fluorination reaction, (d) purification and (e) formulation for administration. All of these steps must be conducted in a consecutive manner with high speed and efficiency, due to the short half-life of ^{18}F (109.7 min). For this reason, specialized automated equipment located in heavily shielded hot cells and remotely operated by trained personnel is generally employed in production sites. In addition, the manufacturing of compounds for human use, often referred to as radiopharmaceuticals, must fulfill strict regulatory guidelines, in order to provide solutions suitable for injection into humans. Therefore, optimization of all the process steps, in terms of the reduction of processing times and the increase of yields and reproducibility, is required in this specific area of radiopharmaceutical synthesis.

In recent years lab-on-a-chip devices have been explored as a promising alternative to traditional vessel-based radiotracer synthesis due to their superior control over reaction conditions, reduced reagent consumption and radioactive waste production, as well as their potential for automation with minimized shield-

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ing requirements [4,5]. The benefits of microfluidic techniques have been evident for the procedural step of the radiofluorination reaction [6–15], but few examples have been reported on the implementation of [^{18}F]fluoride ions pre-concentration and purification in such devices. One microfluidic chip device including a pre-concentration step based on an anion exchange process has been published [16], but this method suffered from being too slow to handle the typical volumes (1–5 mL) of the fluoride starting solution within a reasonable time. A stand-alone microfluidic device based on an electrochemical process has been reported [17,18], but so far has only achieved a low recovery yield. Small columns of ion exchange packing have been reported and are currently used <100 mg [19] but the regeneration and reusability of the ion exchange material over repeated synthesis steps has not been presented.

The only integrated device reported so far, consisting of a module for pre-concentration fluorination and solvent exchange [16], has still to be further developed, in terms of material optimization, integration of a purification step, and availability of sufficient doses, in order to compare with the normal daily PET center needs. Therefore, the challenge for the development of a simpler, faster, reliable, versatile and fully integrated module for radiosynthesis remains high.

We are working towards a modular microfluidic approach for the complete process of [^{18}F]FDG synthesis, including fluoride pre-concentration modules, solvent exchange modules and synthesis modules (http://www.roc-project.eu). In this paper, the design, fabrication and implementation of a microfluidic module for [^{18}F]fluoride ion pre-concentration is presented. Pre-concentration and subsequent drying of [^{18}F]fluoride ions is the first step of the multi-stage radiotracer production process, and is conventionally performed *via* trapping of radioactive fluoride from an aqueous solution onto milliliter scale anion exchange cartridges. The fluoride is subsequently recovered by elution from the cartridge with high ionic strength salt solutions. The effectiveness of this process will affect all subsequent steps in terms of purity and yield. In this work we will focus on a new approach for performing this important first stage with improved repeatability by using microfluidics. A microflow cell, filled with anion exchange particles, was studied for its fluoride trapping/releasing capacity and for the suitability of downstream synthesis. We were particularly interested in investigating particle regeneration for multiple pre-concentration cycles, which would be beneficial for safety and automation, increasing process throughput and speed, and reducing waste generation. The procedure was first optimized with non-radioactive [^{19}F] and then applied to the radioactive isotope [^{18}F].

2. Materials and methods

2.1. Microfluidic device set-up

The microfluidic device (Fig. 1) was fabricated from glass by conventional photolithography and wet-etching techniques [20]. The design featured a chamber of 300 μm depth with a 1.5 mm diameter hole for loading of the anion exchange particles, and a shallow triangular section of 50 μm depth with a 400 μm outlet hole. Polytetrafluoroethylene (PTFE) tubing (0.3 mm i.d., 1.58 mm o.d., Supelco, UK) was glued into the inlet hole using Araldite Rapid epoxy resin (RS Components, Northamptonshire, UK) and interfaced to a syringe pump (PHD 2000, Harvard Apparatus, USA). Polyether ether ketone (PEEK) tubing (150 μm i.d., 360 μm o.d., Idex, USA) was glued in a similar way to the outlet. The chamber was filled with commercially available anion exchange particles, namely Chromabond PS-HCO_3 (100 μm diameter, ABX, Germany) or Sep-Pak Light Plus QMA (60 μm diameter, Waters, USA). The particles were introduced as dry powder from the larger hole by using a micro spatula and constantly tapping the device in a vertical position to obtain a homogenous packing, as shown in Fig. 1b. 20–30 mg of ion exchange particles could be trapped in the chamber.

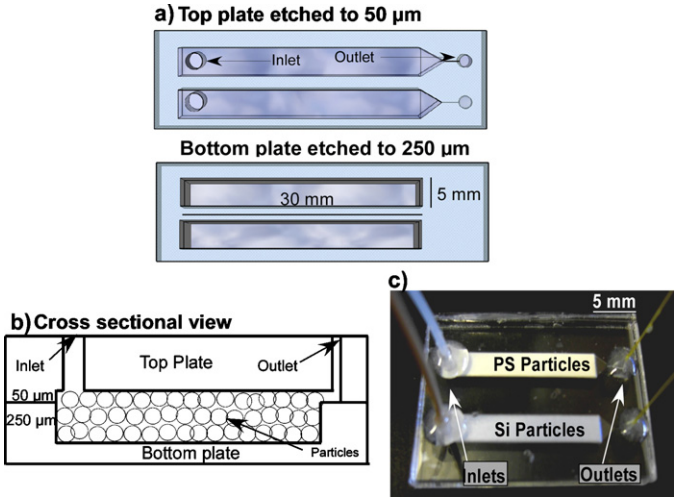

Fig. 1. (a) Schematic representation of the chip design. The bottom plate featured two chambers (3 cm long, 5 mm wide, 250 μm deep). The top plate, etched to a depth of 50 μm, also featured two chambers (3 cm long, 5 mm wide). This top plate also featured a triangular section (2.5 mm long), leading to a channel of 100 μm width that formed a shallow section for bead trapping when the top and bottom plates were thermally bonded. On the left hand side, 1.5 mm diameter holes were drilled into the top plates for the inlets, while on the right, 400 μm diameter holes were drilled for the outlets. (b) Cross sectional view of the chip showing the two plates bonded together to form a chamber for the trapping of particles. (c) Photograph of the glass device. The upper chamber was filled with polystyrene (Chromabond PS-HCO_3) particles and the lower chamber filled with silica (Sep-Pak Light Plus QMA) particles.

2.2. Non radioactive [^{19}F]fluoride trapping and release

2.2.1. Chemicals and solutions

All chemicals were of analytical grade and used without further purification. Ultrapure water (18 MΩ cm^{-1}) was employed unless otherwise stated. A solution of [^{19}F] (1 μg mL^{-1}) prepared from sodium fluoride (Sigma–Aldrich, UK) was used as a reference standard. The eluting solution consisted of 10 mg of Kryptofix 2.2.2 (K2.2.2) (Sigma–Aldrich, UK) dissolved in 900 μL anhydrous acetonitrile (MeCN) (Sigma–Aldrich, UK) and 100 μL of 0.01 M aqueous potassium carbonate (K_2CO_3) (Sigma–Aldrich, UK).

2.2.2. Required amount of fluoride

The amount of [^{19}F]fluoride ions used for experiments and the amount of ion exchange packing used in the device were chosen according to the amount of [^{18}F]fluoride ions routinely used for FDG tracer synthesis. The radioactivity of 1–2 mL "hot water" used for FDG production can be as high as 150 GBq. Considering a specific activity between 300 GBq μmol^{-1} and 43,000 GBq μmol^{-1} (maximum theoretical activity = 63,000 GBq μmol^{-1}), it was calculated that the maximum amount of [^{18}F]fluoride ions present in cyclotron irradiated water should not exceed 9.5 μg, with a typical average of 0.5 μg [21–23]. The experiments with the radioactive fluoride isotope were carried out with hot water as would routinely be used for FDG synthesis. Experiments involving standard solutions of fluoride were carried out with 1 μg of fluoride ions.

2.2.3. On-chip procedure

The on-chip particle bed was activated prior to trapping by flushing with 2 mL ethanol and 2 mL purified water at a flow rate of 1000 μL min^{-1}. For trapping, 1 mL of fluoride standard solu-

tion was pumped through the particle packing at a flow rate of 500–1800 μL min^{-1}. This was followed by flushing with 1 mL water. The trapped fluoride was subsequently eluted with the K2.2.2/acetonitrile/K_2CO_3 solution at a flow rate of 500 μL min^{-1}. The particle bed was then regenerated by flushing the chip with 2 mL of 1.0 M potassium bicarbonate ($KHCO_3$) (Sigma–Aldrich, UK) followed by 3 mL of purified water at 1000 μL min^{-1}.

2.2.4. Fluoride detection

Eluted solutions were collected after both the trapping and elution steps for the quantification of fluoride. 25 μL of each collected solution was injected into an ion chromatography system (ICS-2000, Dionex, USA) equipped with an AS-11HC analytical anion exchange column and a conductivity detector. The flow rate was 0.25 mL min^{-1}, and 15 mM potassium hydroxide was used as the eluent.

2.3. Radioactive [^{18}F]fluoride trapping and release

2.3.1. Chemicals and solutions

High-purity grade solvents were stored on molecular sieves and vented through a sodalime molecular sieve trap during radiochemical experiments. [^{18}F]fluoride ion was produced at a cyclotron (PETtrace, GE, USA) by proton bombardment (E_p = 16.7 MeV, 5–10 min at 20–25 μA) of 1.3 mL ^{18}O-water (enrichment > 98%) using a 1.5 mL silver target-holder. The produced target water with a starting activity of 5–7 GBq was diluted with pure water to a volume of 4 mL. Ethyl ditosylate (EtDT) was synthesized as published [24,25].

2.3.2. Fluorination mixture analysis

HPLC with radioactivity detection was performed using a Delta 600 pump (Waters, USA) equipped with a Synergi Fusion-RP C-18 column (Phenomenex, UK) (4 μm, 3 mm × 150 mm) and a Gabi Star gamma detector (Raytest, Germany) connected in series to a 996 Photo Diode Array UV detector (Waters, USA).

2.3.3. Microfluidic chip set-up for fluoride trapping test

The microfluidic chips were connected to an Advion Nanotek radiotracer synthesis system (Advion, USA) by modifying the standard connections (Fig. 2). The inlet of the chip was interfaced to a port of an 8-way bridged valve bearing a 0.5 mL syringe on the common port and was operated under negative or positive pressure as required. The remaining ports were connected to vials containing (i) a solution of aqueous 1.0 M sodium bicarbonate ($NaHCO_3$) or H_2O, (ii) K2.2.2 solution which was prepared by adding a solution of 10 mg K2.2.2 in 1 mL acetonitrile to 80 μL aqueous K_2CO_3 (5%, w/v), (iii) air for drying the particle bed and (iv) irradiated target water. The remaining ports on the valve were blocked off. The chip outlet was connected to a software controlled solenoid valve (SV) to direct the fluids towards either a waste or a collection vial.

2.3.4. Procedure for trapping and releasing of fluoride

A flow rate of 500 μL min^{-1} was employed for all steps. 0.5 mL of target irradiated water (activity ranging from 620 to 875 MBq) was delivered into the microfluidic chip packed with Chromabond PS-HCO_3 particles followed by 1 mL of air to dry the particles. The solenoid valve was then turned off/on to direct liquid to the collection vial. 0.5 mL of K2.2.2 solution was pumped through the chip followed by 1 mL of air to ensure recovery of the [^{18}F]fluoride complexed solution. The solenoid valve was turned back to direct liquid to the waste vial and, finally, 0.5 mL of pure H_2O was delivered to waste. The entire procedure took 6 min.

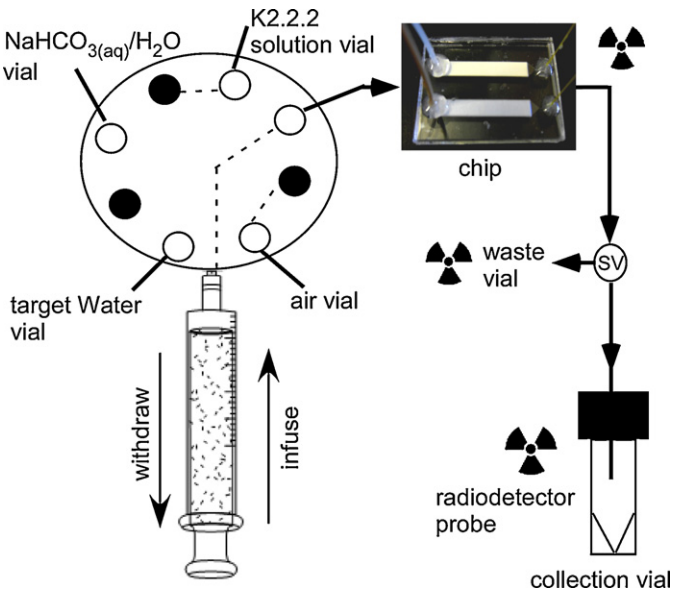

Fig. 2. Schematic representation of the microfluidic chip integrated with the Advion synthesis system, showing the 8 way valve connected to a driving syringe, vials with target water (containing aqueous radioactive [^{18}F]fluoride ions), aqueous carbonate solution or water, K2.2.2/acetonitrile elution solution, air, and finally the microfluidic anion-exchange chip. The chip outlet was connected to a solenoid valve (SV) which could direct liquid either to a waste vial or a collection vial. Radioactivity detectors were placed on the anion-exchange chip, next to the waste vial and next to the collection vial.

2.3.5. Procedure for regeneration of the ion-exchange particles

The packed chip was rinsed with 2 mL of $NaHCO_3$ and subsequently with 2 mL of H_2O, both at a flow rate of 500 μL min^{-1}. The reconditioning procedure lasted 4 min.

Three radiation probes were employed for continuous on-line count rate monitoring at different locations of the hardware: one was placed on top of the microfluidic chamber to measure the radiation in the particle bed, the second for measuring radioactivity in the waste vessel, and the third for measuring radioactivity in the collection vessel. The hardware operations for the trapping and releasing of [^{18}F]fluoride ions, as well as regeneration of the particle bed, were programmed using Nanotek's provided software (version 1.4) in order to minimize direct intervention of the operator. At the end of each trap, release and reconditioning cycle, the waste vials and collection vials were counted and replaced with empty ones. The cycles were repeated for as long as target water was available; a maximum of eight consecutive runs was possible from the same batch of [^{18}F]fluoride ion solution.

2.4. [^{18}F]fluoride labeling reaction

When the fluoride solution was used for labeling reactions, the whole volume of target water (1.5 mL), containing [^{18}F]fluoride ion was trapped in the chip and the elution step was performed at a slower flow rate, thus allowing the delivery of 100 μL drops directly into separate 3 mL V-vials preheated at 110 °C, while applying nitrogen flow (1.2 bar) and a vacuum for speeding up evaporation. Azeotropic evaporation of the excess water was achieved by dropwise addition of 0.5 mL acetonitrile under the same nitrogen flow, leading to a bubble-free evaporation. This last step was achieved by alternating the recovery of a 100 μL drop in the collecting vial to 20 s pause allowing evaporation; this confined the entire radioactivity to the bottom of the V-shaped vial. The dry residue was then reconstituted with 0.5 mL of acetonitrile and the labeling medium was charged into a 403 μL storage loop. A solution of EtDT (25 mg mL^{-1} in acetonitrile) was pumped into a second 429 μL storage loop.

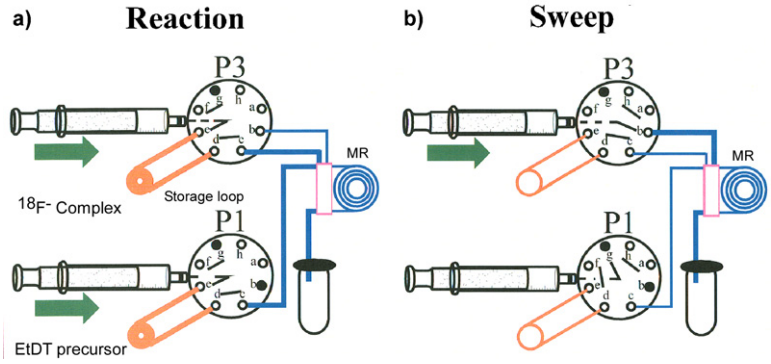

Fig. 3. Schematic representation of the EtDT labeling reaction process within the Advion automated system after drying of excess of water has been performed. The precursor solution was pumped into the loop of pump 1 (P1) while the labeling solution was introduced into the sample loop of pump 3 (P3). (a) In the reaction step, fluoride complex and precursor solution aliquots were delivered into the capillary microreactor (MR) preheated at a temperature 150 °C from the storage loops by pushing with pure solvent (acetonitrile); in this phase the fluids moved through the lines indicated in bold. (b) In the sweep step, the microreactor system was rinsed with pure solvent through the lines indicated in bold and prepared for a further reaction with other aliquots of reagents.

Finally, several labeling reactions were conducted by employing 10 μL aliquots of both reactants dispensed at 20 μL min^{-1}, each into a 15.7 μL fused silica reactor preheated to 150 °C. The plumbing scheme for this procedure is shown in Fig. 3.

3. Results and discussion

3.1. On-chip [^{19}F]fluoride ion trapping, elution and regeneration

3.1.1. Optimization of fluoride detection

The first step involved the calibration of the ion chromatography instrument for fluoride detection in the lowest ppm region. A calibration curve of [^{19}F]fluoride ion concentration was plotted in the range 0.5–50 ppm with R^2 = 0.992 and a calculated LOD (3σ) for fluoride was found to be 50 ppb (0.05 μg ml^{-1}), which was sufficient for the amount of fluoride to be detected. It was found that carbonate, which was the eluent used for releasing the fluoride from the on-chip solid phase packing at a concentration of 0.36 M, interfered with the fluoride peak. The maximum tolerable carbonate concentration for fluoride detection was found to be 0.01 M. The fluoride trapping and release protocol was therefore adjusted as detailed in Section 2.

After the first trapping, another peak overlapping with the fluoride was observed and was found to be acetate which has a retention time close to that of fluoride, as shown in Fig. 4 (top and middle). This species was probably formed *via* a reaction between $KHCO_3$ and acetic acid (present in the polymeric particle packing) during the regeneration step. For this reason, the height of the peak was used to determine the amount of fluoride trapped, rather than the area under the peak. The ion chromatography system was found to be suitable for [^{19}F]fluoride ion detection due to its high sensitivity, the small volume required (25 μL) and reproducibility.

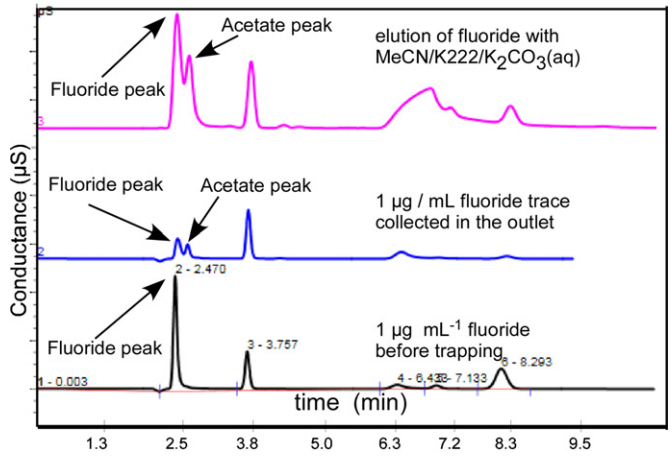

Fig. 4. Chromatograms for the trapping and elution of non-radioactive [^{19}F]fluoride ions, showing 1 μg mL^{-1} fluoride before trapping (bottom), the diminished fluoride peak of waste solution collected during trapping (middle), and the full fluoride peak following elution (top).

3.1.2. Initial tests on anion-exchange particle beds

Both the silica (Sep-Pak Light Plus QMA) and the polystyrene (Chromabond PS-HCO_3) particles were tested initially to compare their performance for the trapping and releasing of fluoride. In each case a microfluidic chamber was filled with particles as described in Section 2.1, and the fluoride standard (1 μg mL^{-1}) was trapped and subsequently eluted, with no difference in performance between the two types of anion-exchange particles. However during the regeneration steps a significant chloride peak was detected in the eluate from the silica-based ion exchange material. This material was originally in the chloride form but was rinsed extensively with 2 mL of 1 M $KHCO_3$ solution prior to its use in our experiment. The presence of chloride can interfere with the following radiofluorination reaction by forming undesired chlorinated byproducts, as it has already been reported for the synthesis of FDG [26]. Moreover, the silica particles were found to be difficult to remove from the device while the polystyrene particles (PS) could be easily removed by treating the chip in a furnace at 500 °C for several hours. For these reasons, the Chromabond PS-HCO_3 particles in the carbonate form were chosen over silica in the chloride form for subsequent investigation.

3.1.3. Trapping and elution efficiency

The PS particle chip was then tested for the trapping and elution of fluoride. 1 μg mL^{-1} fluoride standard was pumped through the chip containing the PS particles in the bicarbonate form at a maximum flow of 1500 μL min^{-1}. Each collected solution was analyzed for the presence of fluoride. The peak height of fluoride was normalized against the peak height of fluoride present in purified water and then converted to the percentage to give the amount of trapped fluoride. The fluoride was eluted with a 1 mL solution containing 10 mg K2.2.2 in 900 μL acetonitrile and 100 μL K_2CO_3 (0.01 M) pumped at 250 μL min^{-1} through the chip. The eluted solution was dried and reconstituted with 1 mL water, as acetonitrile is not a suitable solvent for ion chromatography, before being analyzed for the presence of fluoride. This experiment was repeated up to 40 times and it was found that the [^{19}F]fluoride could be trapped and released always with more than 90% efficiency.

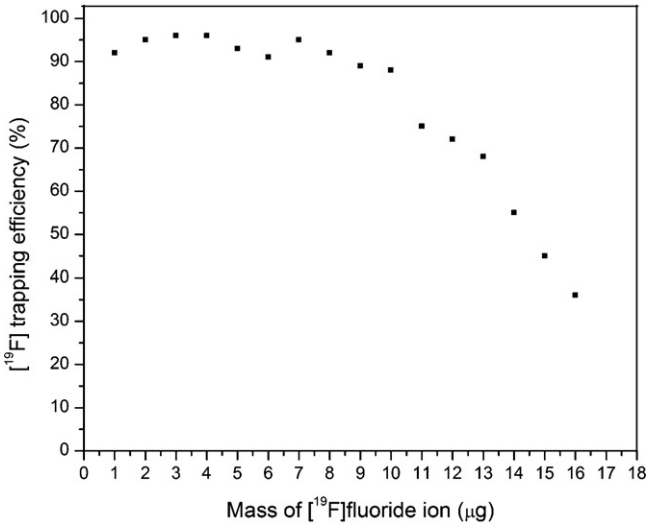

Fig. 5. Breakthrough plot of the anion-exchange chip showing the trapping efficiency versus the amount of [^{19}F]fluoride ions continuously introduced into the chip. As the mass of fluoride was increased, the trapping efficiency decayed linearly as the number of trapping sites on the particles decreased. The maximum capacity of the anion exchange particles (Chromabond PS-HCO_3) before loss of efficiency was determined to be 0.55 μg mg^{-1}.

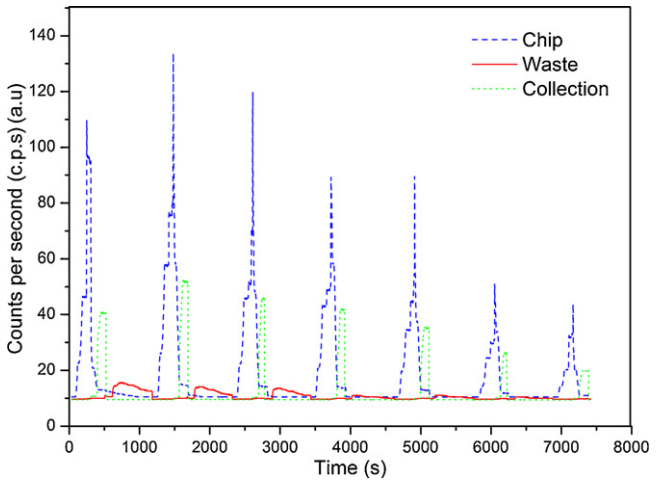

Fig. 6. Seven consecutive runs of the trapping and elution of radioactive [^{18}F]fluoride ions. Counts per second (c.p.s.) were measured by three independent radioactivity detectors: on the chip (blue/dashed line), in the collection vessel after elution (green/dotted line), and in the waste vessel (red/solid line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

The full capacity of the particle packing with respect to the [^{19}F]fluoride ion was investigated by the determination of the breakthrough capacity. 1 mL aliquots of fluoride solutions (1 μg mL^{-1}) were consecutively introduced into the chip, at a flow rate of 500 μL min^{-1}, until fluoride was detected at the outlet; the percentage of fluoride trapped versus the mass of fluoride introduced is shown in Fig. 5. The amount of fluoride trapped was about 90% over the first ten injections, before gradually decreasing down to 40%, as expected due to the reduced number of binding sites present in the particle bed. The trapping capacity determined by breakthrough analysis specific for [^{19}F]fluoride ion was found to be 11 ± 4 μg per 20 ± 5 mg of dry particles which is equal to 0.55 μg mg^{-1} of particles (0.028 meq g^{-1}). This was found to be 28 times less than the maximum loading capacity provided by the manufacturer (0.80 meq g^{-1}) [27].

3.2. On-chip [^{18}F]fluoride ion trapping, elution, synthesis and regeneration

3.2.1. Conditioning and regeneration of the integrated anion-exchange chip

After optimization of the trapping procedure with non-radioactive fluoride, the method was tested for radioactive [^{18}F]fluoride ion as outlined in Section 2. The possibility of trapping and releasing several aliquots of aqueous [^{18}F]fluoride ion was investigated. The first aspect to be considered was the set up of a suitable procedure for preconditioning of the anion-exchange particle bed. Since the chosen polymer was polystyrene based, at the beginning of each experimental day 2 mL of 96% ethanol (EtOH) solution was flushed through the chip in order to fully wet the particle bed. However, before reconditioning the counter anion with $NaHCO_3$, an additional rinse of the chip with 2 mL of pure water was required, since it was found that passing bicarbonate solution immediately after EtOH caused copious salt precipitation in the hardware. After this first EtOH/H_2O preconditioning step, the system was then ready for bicarbonate reconditioning. This was performed by flushing the chip with 2 mL $NaHCO_3$ (1 M), followed by 2 mL H_2O, and no further EtOH preconditioning cycles were required during the same experimental day. The trapping of [^{18}F]fluoride ions was conducted using 0.5 mL portions withdrawn from a batch of irradiated water, with total starting radioactivity ranging from 5 to 7 GBq, and whose volume was adjusted to 4 mL with pure water. This process was chosen for conducting as many experiments as possible with one batch of irradiated water.

3.2.2. [^{18}F]fluoride ion trapping in the integrated chip

Radioactivity, as indicated earlier, was monitored in three key positions of the hardware; the microfluidic chamber, waste vial and collection vial. As shown in Fig. 6, complete trapping of the radioactivity was always observed in the chip, and during the delivery of [^{18}F]fluoride ion into the chip there was no radioactivity detected in the waste vial (Fig. 6, red line/solid line). Experiments were also conducted by trapping the whole 4 mL of target water in order to determine whether volume or fluoride mass was detrimental for trapping, whereupon it was found that the performance of the chip remained excellent and there was no escape of radioactivity. In this trapping step, as well as in the elution step, it was important to dry the system void volumes by using 1 mL of air. We also tested flow rates from 50 to 500 μL min^{-1} to investigate any flow related effects and found that the total radioactivity was always trapped on the particles, independent of the applied flow rate.

3.2.3. [^{18}F]fluoride ion elution in the integrated chip

0.5 mL of K2.2.2 in acetonitrile solution containing 5% K_2CO_3 (0.36 M) was used for elution of the fluoride complex from the anion-exchange particle bed. This volume was sufficient for eluting more than 95% of the radioactive fluoride trapped on the particles. As a matter of fact, by monitoring the signal from the radioactivity monitor placed on the chip, we noticed that the first 200–250 μL of eluent already removed all of the radioactivity from the particle bed; the rest of the volume and the air served for emptying the tubing up to the collecting vial and drying the system. Also in this case, we tested various flow rates from 50 to 500 μL min^{-1} and found no decrease in the performance of the elution step. Hence, we adopted the maximum flow rate as the optimal working condition, in order to achieve the fastest possible processing times.

After elution, 0.5 mL of H_2O was used to rinse the system and prepare it for the reconditioning cycle, and also to avoid the previously described precipitation problems encountered when using concentrated bicarbonate solution. During this stage, a small decrease in radioactivity counts was observed in the chip; this fact

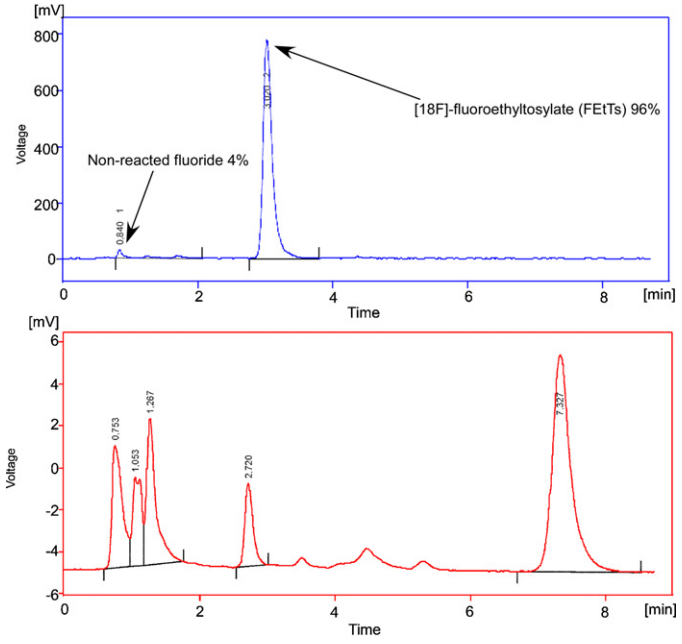

Fig. 7. Typical Radio-HPLC profile for the labeling of ethyl ditosylate (EtDT) to yield [^{18}F]fluoroethyltosylate. The top trace represents the radioactivity and it shows the percentage of unreacted fluoride against the percentage of product formed, while the bottom trace represents the UV absorbance at 254 nm showing the unreacted EtDT peak (R_t = 7.3 min).

was justified by the elution of fluoride residuals from the anion-exchange particles. This remaining radioactivity was completely recovered in the waste vial during the $NaHCO_3/H_2O$ reconditioning phase, as illustrated in Fig. 6. The waste vial counting revealed that the amount of [^{18}F]fluoride ion that could not be recovered as elution complex with this procedure, was <5% of the total radioactivity. No radioactivity was detected in the particle bed at the end of the whole cycle, since the on-chip detector always returned to background values.

The same chip was used for performing a total of 20 trap and release cycles over three experimental days, and the performance of the system was always consistent in recovering >95% of the total radioactivity in the acetonitrile/K2.2.2 elution phase.

3.2.4. Labeling reaction

To demonstrate the reactivity of the [^{18}F]fluoride ion solution produced *via* this process, its efficiency for labeling was tested in a model aliphatic substitution reaction frequently used in our laboratory, namely the fluorine substitution of the tosylate group of ethyl ditosylate (EtDT). The concentrated [^{18}F]fluoride solution eluted from the chip was collected and excess water was removed by azeotropic distillation as described in Section 2.4. The dried, activated labeling solution was used to perform sequential on-capillary reactions with EtDT precursor solution using a commercial Advion microfluidic module. Briefly, the reactants were charged into small-bore PEEK loops of adequate volume and delivered, by pushing pure solvent on the opposite head of the loops into the 2 m long micro capillary (100 μm i.d.) housed in a heater (Fig. 3a). After each run, the system was cleaned with pure solvent (the sweep step, Fig. 3b), and a further run performed in a similar manner. A sample from each consecutive run was analyzed by Radio-HPLC and an average incorporation yield of 96 ± 3% (Fig. 7) demonstrated very good chemical reactivity and high process stability over repeated runs.

4. Conclusions

Both radioactive [^{18}F] and non-radioactive [^{19}F]fluoride ions could be repeatedly recovered by employing a chip containing a smaller amount of anion exchange particles than conventional cartridges. The entire process required less than 6 min and had a trapping efficiency >90%, while the particles could be repeatedly regenerated and reused up to 40 times *via* a multicycle approach, without loss of performance. The radioactive solution resulting from this innovative process was highly reactive and could be employed in the radiofluorination of EtDT. On this basis, the chip could easily be integrated into automated systems to provide highly reactive fluoride complexes for the production of fluorinated PET radiotracers in high yields. The ability to regenerate the anion-exchange chip would also allow many batches of radiopharmaceuticals to be synthesized without requiring continuous manual interaction of personnel within the shielded synthesizer.

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