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Short Research Article

Separation of (^{18}F)fluoride ion from proton-irradiated (^{18}O)water within an EOF-driven micro-reactor powered by the Capilix Capella™ platform[†]

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Introduction

PET radiosyntheses in micro-reactors or microfluidic devices[1–5] has become of interest because these devices have the potential to deliver many advantages, such as: more efficient use of hot-cell space for production of multiple radiotracers; use of less non-radioactive precursor for saving precious material and a reduced separation challenge; highly controlled, reproducible and reliable radiotracer production; and the use of cheap, interchangeable, disposable and quality-assured radiochemistry processors.

For the preparation of fluorine-18 labeled radiopharmaceuticals, nucleophilic substitution reactions using cyclotron-produced [^{18}F]fluoride ion are most widely used.[6] [^{18}F]Fluoride ion is commonly produced as an aqueous solution in a [^{18}O]water target and must be dried to become adequately nucleophilic. The removal of water is normally carried out through azeotropic distillation with a solvent such as acetonitrile. Although reliable and simple, the procedure is cumbersome to be adopted in micro-reactors.

As described here we are exploring the electrokinetic properties of [^{18}F]fluoride ion and aim to develop a process for the preparation of reactive [^{18}F]fluoride ion in glass electroosmotic flow (EOF)-driven micro-reactors.

Results and discussion

Microfluidic capillary electrophoresis platform

The CapiliX Capella™ capillary electrophoresis (CE) platform[7] (Figure 1) comprises a PSU-4 high-voltage power supply for EOF, a cartridge docking station linked to PSU-4 via high-voltage cables and a microfluidic chip cartridge in which the fluidic connections to the glass chip are sealed using Kalrez™ rubber O-rings.

Glass micro-reactor

Micro-reactor design R1 (Figure 2) has two flow restrictions between port 1 to junction and port 2 to junction, so that hydrodynamic flow can be minimized. There are no restrictions at the outlet to prevent any entrapment of air bubbles. At 500 V and 10 mm height difference between ports 1 and 4, the EOF-driven flow is 10 × hydrodynamic flow.

Typical experimental set up

The channels of the micro-reactor were primed with 0.09% saline. Air bubbles inside the channel and rubber O-rings were carefully removed. Ports 1 and 2 were filled with additional saline (25 μl each). [^{18}F]Fluoride ion in $H_2{}^{18}O$ (~100 mCi, 5–10 μl) was placed in port 4. Low radioactivity was used for safety

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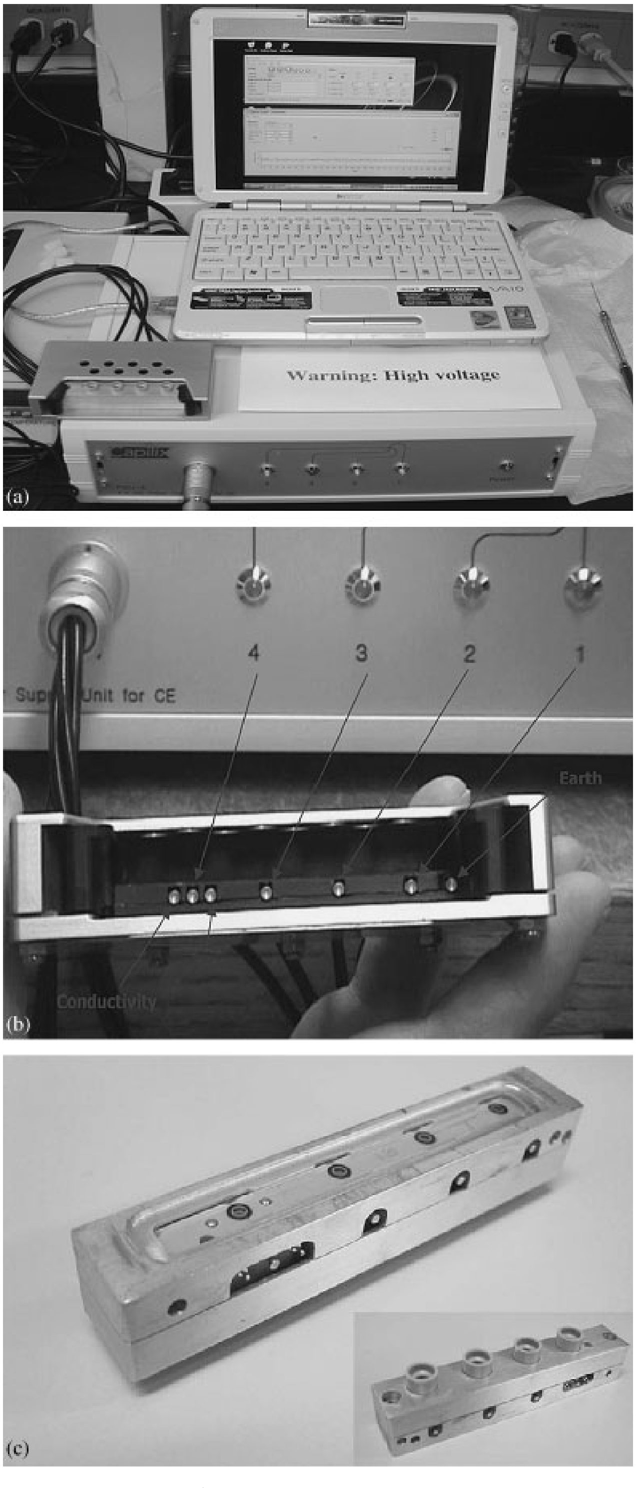

Figure 1 From left: (a) bench top experimental station; (b) cartridge docking station connection via high-voltage cable and corresponding indicators; (c) picture of the microfluidic chip cartridge (MCC, inset); and details of glass chip/O-ring seal arrangement.

considerations; higher radioactivity should be equally applicable. The voltages (at times with step increases) were applied using a Labview-based Capella software. At the end of the experiment, liquid from ports 1 and 2 was pipetted out and its radioactivity was measured. Baseline experiment was carried out with zero voltage. To check the effect of hydrodynamic flow on radioactivity migration, the experiment was also carried out with radioactivity placed in reversed order.

Saline (0.09%) was selected as a running buffer (background electrolyte). No apparent electrolysis was observed. The preliminary results are summarized in Table 1.

When ports 1 and 2 are positively charged and port 4 is loaded with $^{18}F^-$ in water, radioactivity is collected from ports 1 and 2 which indicates that [^{18}F]fluoride ions are retained around the positively charged side of the micro-reactor. The migration of the radioactivity due to diffusion or hydrodynamic flow can be discounted. In the experimental set-up, ports 1 and 2 have higher volumes of liquid. Had hydrodynamic flow occurred, the flow direction would be from ports 1 and 2 to port 4. The blank experiment (entry 1) also supports that the flow restriction design effectively eliminated hydrodynamic flow within the micro-reactor. When radioactivity is placed in port 2, $^{18}F^-$ remains in port 2 and nearby channel when positive voltage is applied (entry 6).

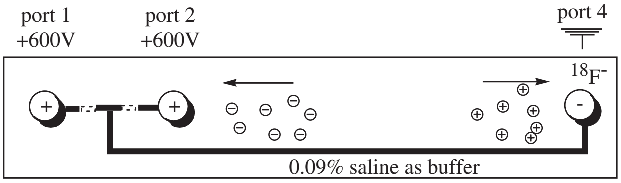

Figure 2 Schematic representation of the R1 micro-reactor. Channel cross section = 250 × 50 mm^2. denotes flow restriction (cross section = 150 × 5 mm^2, length 2 mm). The voltage and the charge migration directions are as illustrated.

Table 1 Summary of $^{18}F^-$ ion electrophoresis in R1 micro-reactor

Entry	Power (V)	Time (min)	Radioactivity in port 4 before CE (μCi)	Radioactivity in port 4 after CE (μCi)	Radioactivity in ports 1/2 after CE (μCi)	%Radio-activity migrated
1	0	65	140	140[a]	0	0
2	600	60	93	84.4[a]	7.8	8.4
3	600	30	107	105[a]	2.7	2.5
4	800[b]	70	87.4	83.6[a]	3.8	4.3
5	0	60	0	0	406[a]	0
6	600	60	0	0	45.3[a]	0

[a] The total remaining radioactivity in port and channel.
[b] Voltage increase in steps.

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Since organic solvents, such as acetonitrile and DMF, are widely used for radiofluorination, how water molecules and organic molecules behave under such condition needs to be investigated. An organic running buffer that is based on an organic solvent, in which the labeling fluorination is carried out, would be extremely useful. The ultimate goal is to retain the activity whilst stripping the water off so that the resulting 'naked' [^{18}F]fluoride ion can be used for subsequent labeling reactions also in a micro-reactor.

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