

# SEPARATION OF [<sup>18</sup>F]FLUORIDE ION FROM PROTON-IRRADIATED [<sup>18</sup>O]WATER WITHIN AN EOF-DRIVEN MICRO-REACTOR POWERED BY THE CAPELLA CE PLATFORM

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## INTRODUCTION

Miniaturization of PET radiosynthesis devices has 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 cheap, interchangeable, disposable and quality-assured radiochemistry processors.

For the preparation of fluorine-18 labeled radio-pharmaceuticals, nucleophilic substitution reactions using cyclotron-produced [<sup>18</sup>F]fluoride ion are the most widely used labeling methods. [<sup>18</sup>F]Fluoride ion is commonly produced as an aqueous solution in a [<sup>18</sup>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.

We are exploring the electrokinetic properties of [<sup>18</sup>F]fluoride ion and aim to develop a process for the preparation of reactive [<sup>18</sup>F]fluoride ion in glass electroosmotic flow (EOF)-driven micro-reactors.

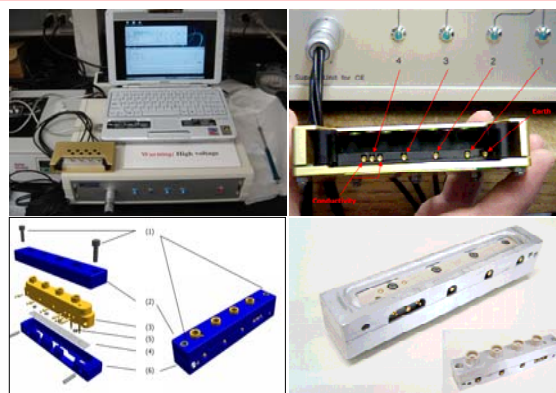
## EXPERIMENTAL

### Microfluidic capillary electrophoresis platform

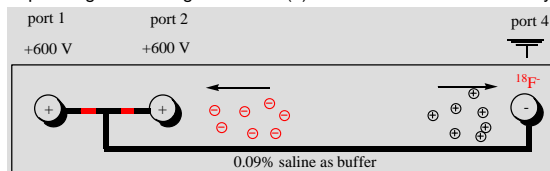
The Capella capillary electrophoresis (CE) platform (Figure 1) comprises a PSU-4 High voltage power supply for electroosmotic flow (EOF), a cartridge docking station linked to PSU-4 via high voltage cables and a microfluidic chip cartridge in which the fluidic connections to the glass chip are sealed using 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 restriction at the outlet to prevent trapping of air bubble. At 500 V and 10 mm height difference between ports 1 and 4, the EOF driven flow is 10x hydrodynamic flow.



**Figure 1** Clockwise from top-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 and (d) Details of the MCC assembly.



**Figure 2** Schematic representation of the R1 micro-reactor. Channel cross section = 250 x 50 μm<sup>2</sup>. ■ denotes flow restriction (cross section = 150 x 5 μm<sup>2</sup>, length 2 mm). The voltage and the charge migrate directions are as illustrated.

### 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 inspected and removed. Ports 1 and 2 were filled with additional saline (25 μl each). [<sup>18</sup>F]fluoride ion in H<sub>2</sub><sup>18</sup>O (~100 μCi, 5-10 μl) is placed in port 4. Low radioactivity was used for safety 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 were pipetted out and its radioactivity measured. Baseline experiment was carried out with 0 voltage. For checking the effect of hydrodynamic flow on radioactivity migration, the experiment was carried out with radioactivity placed in reversed order.

**Table 1** Summary of <sup>18</sup>F- ion electrophoresis in R1 micro-reactor

N	Power (V)	Time (min)	Radioactivity in port 4 before CE (μCi)	Radioactivity in port 4 after CE (μCi)	Radioactivity in ports 1 / 2 (μCi)	% radioactivity migrated
1	0	65	140.0	140.0*	0	0
2	600	60	93.0	84.4*	7.8	8.4
3	600	30	107.0	105.0*	2.7	2.5
4	800 in steps	70	87.4	83.6*	3.8	4.3
5	0	60	0	0	406	0
6	600	60	0	0	45.3	0

\* The total radioactivity remaining in port and channel

## RESULTS AND DISCUSSION

0.09% saline 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 <sup>18</sup>F- in water, radioactivity is collected from ports 1 and 2 which indicates that [<sup>18</sup>F]fluoride ions are retained around the positively charged side of the micro-reactor. Migration of the radioactivity due to diffusion of hydrodynamic flow can be discounted. In the experimental set up, ports 1 and 2 have higher volumes of liquid, had hydrodynamic flow to occur, the flow direction would be from ports 1 and 2 to port 4. 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, <sup>18</sup>F- remains in port 2 and nearby channel when positive voltage is applied (entry 6).

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