PDMS EVAPORATION CHIP TO CONCENTRATE [^{18}F]FLUORIDE FOR SYNTHESIS OF PET TRACERS IN MICROFLUIDICS

W.-Y. Tseng[1], J. Cho[2], X. Ma[1], K. Mahal[3], A. Chatziioannou[1,2] and R. M. van Dam[1,2*]

[1]Crump Institute for Molecular Imaging and Department of Molecular & Medical Pharmacology, University of California, Los Angeles, USA, [2]Biomedical Physics Interdepartmental Program, University of California, Los Angeles, USA and [3]Electrical Engineering Department, University of California, Los Angeles, USA

ABSTRACT

To synthesize Positron Emission Tomography (PET) tracers in batch microfluidic systems, concentration of [^{18}F]fluoride is needed to ensure a sufficient amount of the radioisotope is loaded. We demonstrate a PDMS microfluidic device based on solvent evaporation through a gas-permeable membrane to perform this task. A "directional" pattern of solvent evaporation occurs in this device, but is terminated before complete solvent removal to achieve concentration while avoiding clogging of microchannels observed in previous studies of [^{18}F]fluoride drying in PDMS chips. Preliminary results including concentration to 2X and 10X, and elution of the solutions with nitrogen, are described.

KEYWORDS: Positron Emission Tomography (PET), Microfluidics, Cerenkov radiation, Radiochemical synthesis, Fluorine-18, [^{18}F]fluoride concentration

INTRODUCTION

PET provides specific and quantitative measurements of *in vivo* biological processes for diagnosis and treatment monitoring in cancer patients, as well as the study of cancer biology and the development of new diagnostics and therapeutics. A large number of radiotracers have been developed to monitor various processes, but in nearly all cases production of the tracer is prohibitively expensive. Microfluidic radiosynthesis platforms that have been recently reported [1][2] promise to reduce these costs, potentially by integration of the entire synthesis process into a single compact chip [3]. Before delivering [^{18}F]fluoride from the cyclotron to the synthesis chip, it must be concentrated due to the volume disparity of cyclotron target volume and microfluidic chip. Concentration has been reported using macroscopic (off-chip) ion-exchange cartridges [4] and on-chip cartridges [3], though reliability of cartridge preparation and efficiency in the latter case were significant issues.

Here we report an alternative integrated (on-chip) concentration technique based on evaporation of solvent through a gas-permeable membrane. It could be used as a last-stage concentration device to provide [^{18}F]fluoride in sub-microliter volumes for radiosynthesis of PET tracers in batch microfluidic chips [5]. Other applications requiring on-chip concentration of samples may also benefit from this approach.

The device stems from our previous work to systematically study radiosynthesis of [^{18}F]FDG in PDMS chips [6]. A Cerenkov imaging system [7] was developed to enable characterization and optimization of the [^{18}F]fluoride drying process. Though the "directional" pattern of evaporation frequently led to device failure due to channel clogging, we observed that the radioactivity remains in solution as solvent is removed and concentration increases, and also that there is very low loss of radioactivity. In this paper, we perform partial directional evaporations to leverage these desirable behaviors while avoiding the clogging problem.

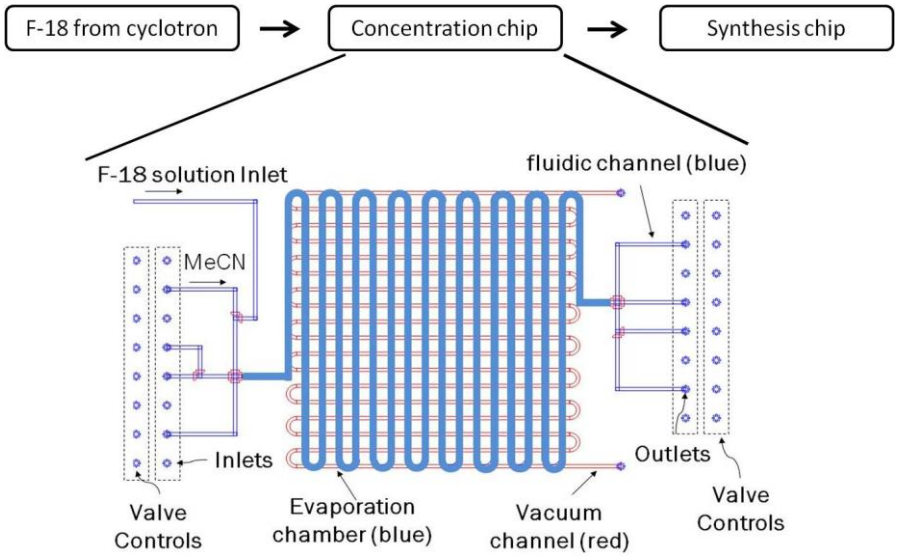

Figure 1. (Top) Concentration chip bridges the volume gap between cyclotron target and synthesis chip. (Bottom) Design of PDMS evaporative concentration chip.

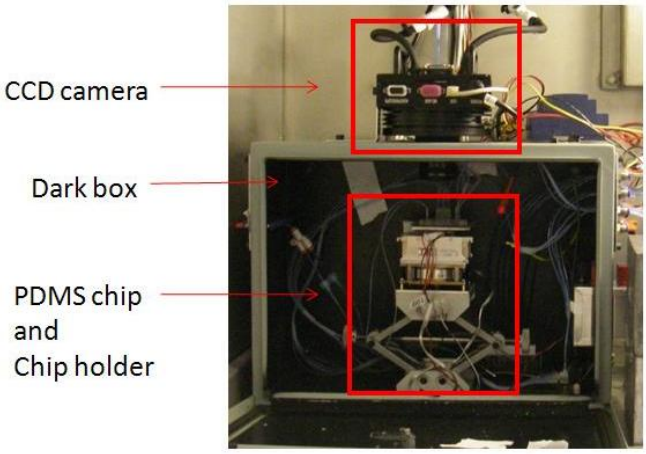

Figure 2. Cerenkov imaging system.

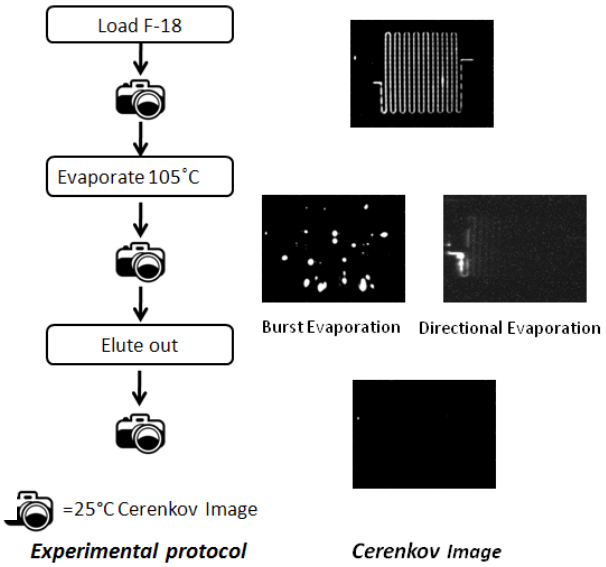

Figure3. (Left) Experimental protocol for evaporation and elution studies. (Right) Example Cerenkov images after each process step. Evaporation is characterized by two qualitatively different patterns that we call "burst" and "directional".

EXPERIMENTAL

Concentration of [^{18}F]fluoride was performed in a multi-layer PDMS chip (Figure 1). In the top layer is an evaporation channel with relatively large volume (3.3 µL in this design, but scalable to much larger volumes) and in the bottom layer are valve control channels and a vacuum channel. Solvent is removed from the solution loaded into the evaporation channel through a gas-permeable PDMS membrane by applying heat and vacuum. The solvent volume can be reduced in a short time (<10-12 min), then the concentrated solution eluted to a small-volume reaction chip (possibly integrated with the concentration chip in future designs).

The microfluidic chip was operated inside a light-tight box and observed with a sensitive lens-coupled CCD camera as shown in Figure 2. The flow of the fluid is controlled by nitrogen pressure and pneumatically-controlled valves in the microfluidic chip, and the temperature of the chip is controlled using a Peltier system. Cerenkov radiation is emitted when energetic positrons from decay of F-18 travel through the surrounding medium (solvent, PDMS, glass) with a velocity greater than that of light in that material. This faint blue light is detected by the CCD camera, with intensity proportional to the radioactivity from a given location. Distribution and relative quantity of radioactive solution within the chip were monitored at each stage by Cerenkov imaging.

In previous studies to perform drying, [^{18}F]fluoride was loaded into the chip, the solvent was removed by evaporation, and the dried residue was then eluted out of the chip by anhydrous solvent (Figure 3). Here we deliberate choose the "directional" pattern of evaporation, but heat is removed before complete solvent removal to prevent channel clogging and to avoid loss of radioactivity through two correlated mechanisms that occur under prolonged heating (Figure 4). The resulting concentrated [^{18}F]fluoride solution was then pushed out of the chip with nitrogen and amount of residue measured.

RESULTS AND DISCUSSION

Because [^{18}F]fluoride residue distributed evenly in the evaporation chamber after burst evaporation, we initially attempted to concentrate by "mopping up" the completely-dried [^{18}F]fluoride residue into small slugs of MeCN eluent. However, the small MeCN slugs evaporate when moving in the channel and fail to be transported to the synthesis chip.

More reliable operation was achieved by using partial directional evaporation. During directional evaporation, the solvent is evaporated along the length of the evaporation chamber. Previous study shows the microchannels are clogged by salts under these conditions when all of the solvent is removed. However, we found partial evaporations can be achieved during directional evaporation and there is sufficient time resolution to control the amount of solvent removed. When [^{18}F]fluoride remains in the dissolved state, it will not block the channel and it can be transported out of the channel to the downstream synthesis chip. Based on the

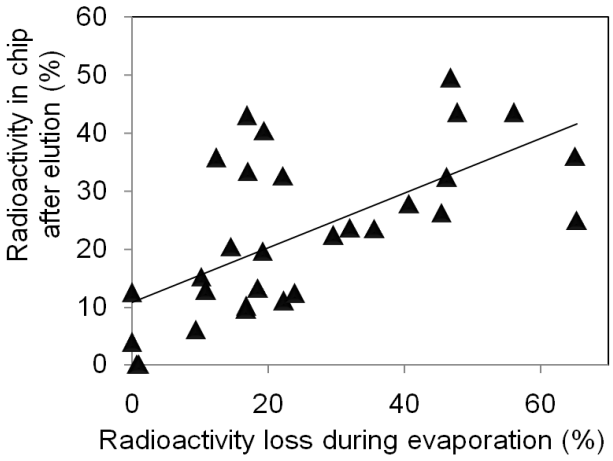

Figure 4. Correlation between radioactivity lost during evaporation and radioactivity that remains permanently stuck in the chip after elution.

saturation point of solutions used here, up to ~40X concentration is possible in principle.

Figure 5 shows examples of 2X and 10X concentrations with low loss of radioactivity (4-7%), and subsequent elution out of the chip by air. Ongoing studies are aimed at increasing the efficiency of transferring the concentrated solution to the attached (or integrated) synthesis chip.

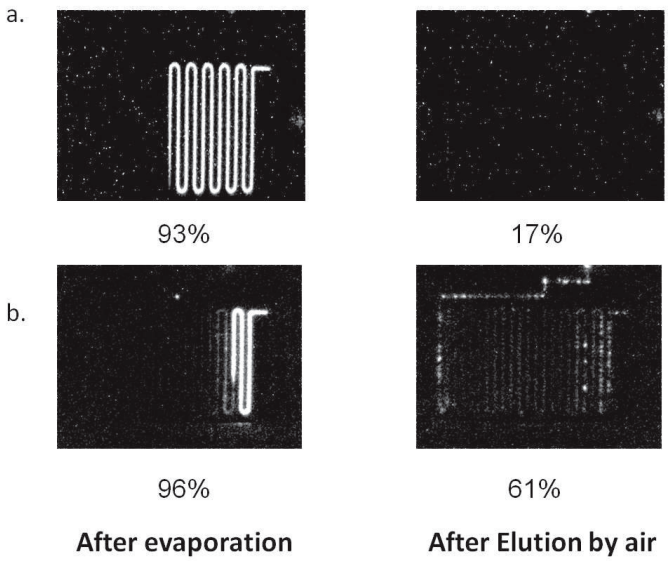

Figure 5. (a) Evaporation to ~50% of original solvent volume (2X concentration). 93% of radioactivity remained in the chip (i.e. only 7% was lost). Most of the concentrated [^{18}F]fluoride could be eluted from the chip with air; only 17% remained in the chip after elution. (b) Evaporation to ~10% of original solvent volume. Only 4% of radioactivity was lost. Elution with air was less effective in this case, leaving 61% behind. Ongoing studies are focused on improving transfers.

CONCLUSION

This concentration chip will enable radiosynthesis in batch microfluidic chips (e.g. PDMS[3] and EWOD[5]), that have reaction volumes on the scale of several hundred nanoliters, with quantities of radioactivity sufficient for preclinical and possibly clinical PET.

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CONTACT

* R.M. van Dam, mvandam@mednet.ucla.edu