

INTERDIGITATED EVAPORATION CHIP FOR EFFICIENT SOLVENT EXCHANGE IN MICROCHANNELS

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ABSTRACT

Evaporative solvent exchange, a critical process in multi-step batch synthesis of positron emission tomography (PET) tracers, can readily be accomplished in poly(dimethylsiloxane) (PDMS) chips due to its high vapor permeability. Early proof-of-concept chips, however, suffered reliability issues, such as clogged channels and stuck valves. We demonstrated in previous work that by controlling the evaporation in such a way as to fragment the partially-evaporated liquid leads to random distribution of solutes throughout the channel and avoids clogging. The chip presented here results in improved uniformity of solute residue by using a valve structure to subdivide the liquid sample before evaporation.

KEYWORDS: Positron Emission Tomography (PET), Microfluidics, Cerenkov radiation, Radiochemical synthesis, Fluorine-18

INTRODUCTION

Microfluidic devices are promising platforms for synthesis of short-lived positron emission tomography (PET) tracers because they often enable faster and higher yielding reactions, and their small size minimizes the amount of radiation shielding needed and thus lowers the cost of producing PET tracers [1-2]. The synthesis of [^{18}F]FDG (including multiple solvent exchange steps and reaction steps) has been demonstrated in microfluidic devices made of poly(dimethylsiloxane) (PDMS) but frequent device failures (such as leaking valves, stuck valves, clogged channels and high loss of radioactivity) during solvent exchange steps seem to have prevented more widespread use of this approach [3-4].

In previous research [5], we have studied the source of these failures using Cerenkov imaging, a technique that enables *in situ* quantitative analysis of the spatial distribution of the radioactivity within the chip [6]. We determined that the problem of high loss of radioactivity can be overcome by avoiding prolonged heating of the dry residue during the evaporation of solvent from the [^{18}F]fluoride solution. Another finding was that the problem of clogging can be avoided by controlling the evaporation process. Evaporation of solvent was found to follow one of two distinct patterns: (1) If an air bubble is present prior to evaporation, vapor is removed from the liquid air interface and the interface gradually recedes while the solution becomes progressively more concentrated and eventually results in precipitation and clogging of the channel. (2) If all air initial bubbles are eliminated, evaporation occurs predominantly due to pervaporation of solvent all along the channel until the collapsing channels suddenly exhibit elastic restoration to their original size. This fragments the liquid, and the ensuing evaporation of small amounts of liquid leads to random distribution of residue throughout the channel that prevents clogging. Unfortunately, at certain concentrations, we found that this preferred second pattern still caused channel clogging due to non-uniform deposition of the dry residue.

Here, we demonstrate a new microfluidic chip design that provides better control over the evaporation process and ensures a more uniform distribution of residue that avoids clogging even at higher concentrations.

DESIGN OF INTERDIGITATED EVAPORATION CHIP

The new chip (Figure 1) to facilitate solvent exchange of more concentrated solutions is composed of three layers: top PDMS fluidic layer (blue), middle PDMS control layer (pink, red and green) and bottom glass substrate layer. The critical difference from previous designs is in the control layer: a large valve structure (green) was added, interdigitated between the vacuum channels (red) of the original design. This interdigitated “separate valve” subdivides the total liquid volume into a large number of small isolated subchambers. The operation of the interdigitated solvent exchange chip (Figure 2) includes four steps: (a) loading of initial solution, (b) subdivision of fluid, (c) parallel evaporation in subchambers

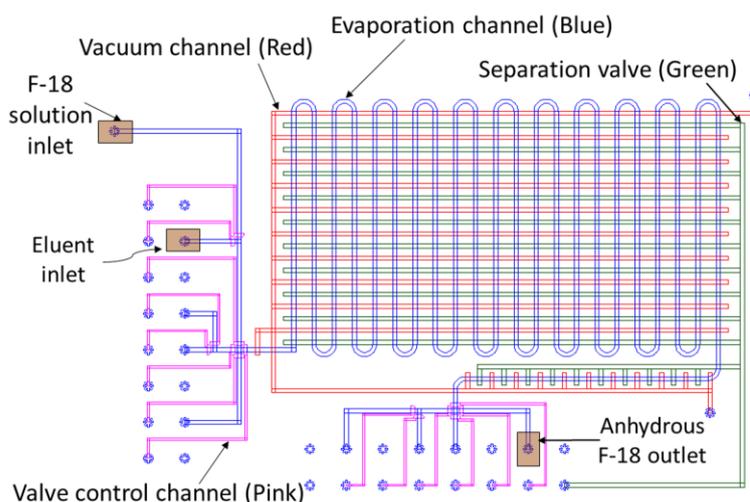


Figure 1. Design of evaporation chip. An interdigitated separation valve structure enhances solvent exchange.

and (d) elution of dried residue in the new solvent. The separation valve separates the liquid into small isolated volumes before the evaporation step. Chambers remain isolated during heating, ensuring only the amount of solute originally within each subvolume is deposited in the subchamber after solvent evaporation.

EXPERIMENT

The microfluidic chip was operated inside a light-tight box with a sensitive lens-coupled CCD camera [5]. The fluid was driven by nitrogen pressure along the flow channel and controlled by pneumatically-actuated microvalves in the chip. A Peltier system was used to control the temperature of the chip.

During experiments, the distribution and relative quantity of radioactive solution within the chip were monitored by Cerenkov imaging. For each experimental run, Cerenkov images were taken after sample loading, after subdivision of the fluid, after evaporation and after elution. The images were then processed by dark current correction, flat field correction and decay correction and the amount of radioactivity lost or remaining after each step was quantified.

RESULTS AND DISCUSSION

Figure 3 shows optical micrographs of the solvent exchange process (using a solution of green food dye). In each small isolated chamber, the solution of food dye shrinks during heating and becomes more and more concentrated and darker during the process. After the solvent is completely dried out, small dark green spots of concentrated residue can be observed (Figure 3d). We also tested two different concentrations of solutions of salt (K_2CO_3) and phase transfer agent (Kryptofix K_{222}) in 80:20(v/v) MeCN:water. This solution is used in the synthesis of many PET tracers during the $[^{18}F]$ fluoride drying process to remove residue water from bombardment in the cyclotron target. In both cases (2.6mM K_2CO_3 / 5.2mM K_{222} ; and 26mM K_2CO_3 / 52mM K_{222}), dry residues had uniform distribution in the microfluidic chip after the drying process, and no clogging was observed.

Next we repeated these experiments with $[^{18}F]$ fluoride added to the above solutions. In Figure 4, we show Cerenkov images from drying of a $[^{18}F]$ fluoride solution containing 26mM K_2CO_3 and 52mM K_{222} and $50\mu Ci/\mu L$ of $[^{18}F]$ fluoride. Figure 5 compares the $[^{18}F]$ fluoride distribution after the “burst” evaporation pattern observed in our previous work [5] and in the new chip with interdigitated separation valve. It can be clearly seen that the $[^{18}F]$ fluoride residue is distributed more evenly after evaporation in the interdigitated chip. Performance of four consecutive solvent evaporation processes in the same chip is summarized in Figure 6 by analyzing the quantitation of radioactivities in Cerenkov images. During these four experiments, the loss after drying is less than 15% and less than 5% of the radioactivity remains stuck in the chip after elution with 0.5mL MeCN. Consecutive solvent exchange processes could not reliably be performed at this concentration in the previous chip design where we relied on burst evaporation to randomly distribute the residue.

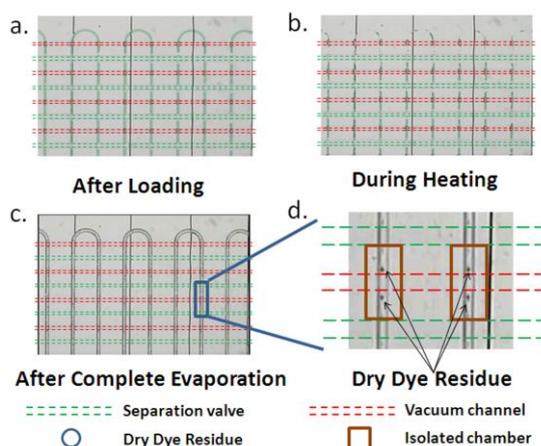


Figure 3. Micrographs of green dye-filled chip during solvent evaporation.

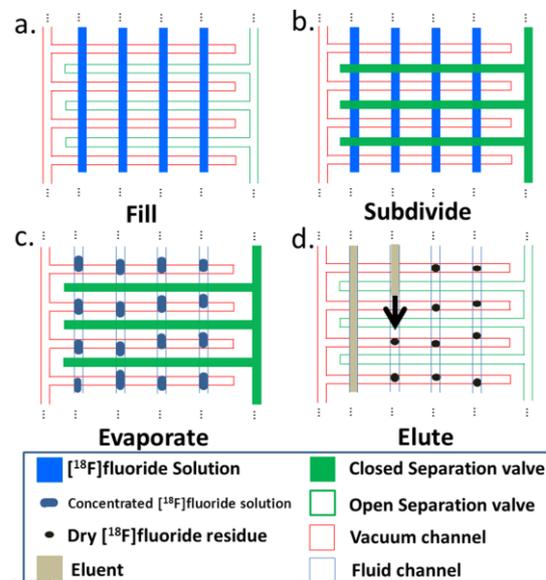


Figure 2. Schematic of solvent exchange process.

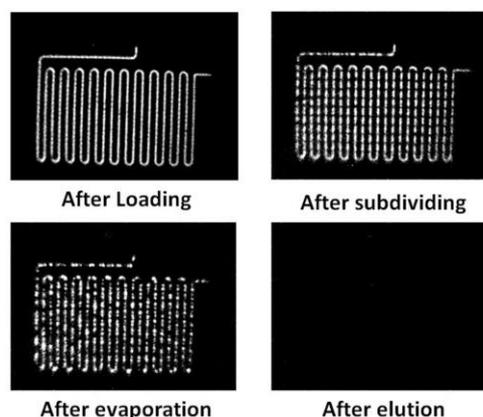


Figure 4. Cerenkov images after different stages of solvent exchange: (a) after loading, (b) after subdividing, (c) after evaporation, (d) after elution.

CONCLUSION

We developed a new microfluidic chip with an interdigitated valve structure that can achieve uniform distribution of solute residue after evaporation (e.g. drying of [^{18}F]KF/K₂₂₂ complex in the synthesis of PET tracers). This chip enhances the solvent exchange step and enables solutions with higher salt concentrations to be dried without clogging channels. The microfluidic chip solves a critical problem observed in previous work in PET tracer synthesis in PDMS chips.

ACKNOWLEDGMENTS

We thank Prof. David Stout and the staff of the Crump Preclinical Imaging Technology Center for providing [^{18}F]fluoride and for use of analytical equipment. This work was funded in part by the Department of Energy Office of Biological and Environmental Research (DE-SC0001249).

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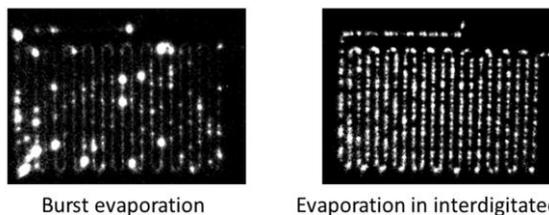


Figure 5. The distribution of [^{18}F]fluoride after drying in (left) the previous chip after burst evaporation, and (right) the current chip with interdigitated separation valve.

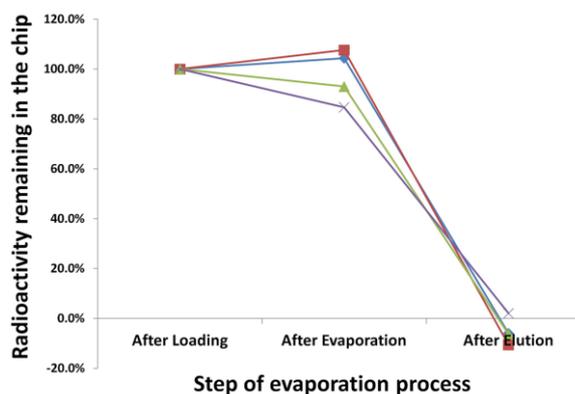


Figure 6. Radioactivity remaining at each step of four consecutive drying experiments (different color lines and markers) in the same chip.