ON-CHIP DETECTION OF RADIOACTIVITY VIA SILICON-BASED SENSORS FOR THE QUALITY CONTROL TESTING OF RADIOPHARMACEUTICALS

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ABSTRACT

We present the use of highly sensitive, small footprint, low cost silicon photomultipliers (SiPM) for radioactivity detection in microfluidic channels, with a view to their integration into miniaturised quality control (QC) platforms for the testing of positron emission tomography (PET) radiopharmaceuticals. While SiPMs are light sensors, it was determined that they are also sensitive to other sources, e.g. direct interaction with positrons and gamma rays, making them suitable for radiation detection with standard chip materials, including those that are opaque, as well as for detection of gamma emitting radiotracers.

KEYWORDS: Positron emission tomography (PET), Quality control (QC), Radiation detection, Radiopharmaceuticals, Silicon photomultiplier (SiPM)

INTRODUCTION

PET is a powerful medical imaging technique that relies on the injection into a patient of a radiotracer: a targeting molecule that has been labelled with a positron-emitting isotope (e.g. ^{18}F, ^{11}C, ^{68}Ga). However, these radiotracers, particularly the most common tracer, 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), are synthesised in multi-dose batches and transported to hospitals for scanning. While cost-effective, this yields a "one-size-fits-all" approach to treatment. Dose-on-demand production may revolutionise PET by offering stratified treatment of patients, with single doses of appropriate tracer generated "as-and-when" required for a specific patient.

Key to dose-on-demand is microfluidic technology, which is essential for handling the low volumes of radioisotope solution available. While on-chip radiosynthesis has been demonstrated [1], other production aspects have largely been ignored, particularly QC testing which requires a dedicated lab setup and ~40 min. We are developing an integrated microfluidic QC platform that will enable dose-on-demand production by reducing sample volumes, analysis times, and instrumentation. Several QC criteria require radioactivity detection (radioisotope and radiochemical identity/purity) [2,3], but conventional detectors are not amenable to microfluidics due to their bulk, cost, and shielding requirements. Only a handful of detectors have been developed for microfluidic devices, e.g. CCD-based Cerenkov imaging [4], solid-state beta cameras [5], phosphor imaging [6], and photodiode detectors [7], but these have varying limitations including cost, complex fabrication, and insufficient sensitivity and/or speed. Recently, the size, price, performance and availability of commercial silicon photomultiplier (SiPM) light sensors have vastly improved, making them ideal for microfluidic integration. Here, we perform initial studies to determine their ability to detect radioactivity within microfluidic channels.

EXPERIMENTAL

Microfluidic devices were fabricated by milling a serpentine channel into substrates (30 x 30 mm^2) of different materials and thicknesses. The milled plates were then bonded via double-sided tape to a polycarbonate top plate featuring two access holes (Fig. 1a). Several chip materials were tested using 4 mm thick milled substrates: polycarbonate, B-270 glass, soda-lime glass, and Borofloat glass. The effect of material thickness was tested by milling channels into polycarbonate substrates having thicknesses of

2-12 mm. Completed devices were filled with a solution (40 µL) of positron-emitting [^{18}F]fluoride and sealed with tape, before measuring the level of radioactivity in a dose calibrator. The chip was then transferred to a 3D-printed chip holder and positioned on a 4 x 4 array of SensL C-Series SiPMs (Fig. 1b). Detection signals were recorded for 5 min at different radioactivity levels. Further tests included the use of opaque chip substrates, including PTFE and painted polycarbonate, and the detection of the PET radiotracers, [^{18}F]FDG and [^{68}Ga]gallium-citrate. A solution of technetium-99m, a gamma emitter used in single-photon emission computed tomography (SPECT) imaging, was also tested in the chip.

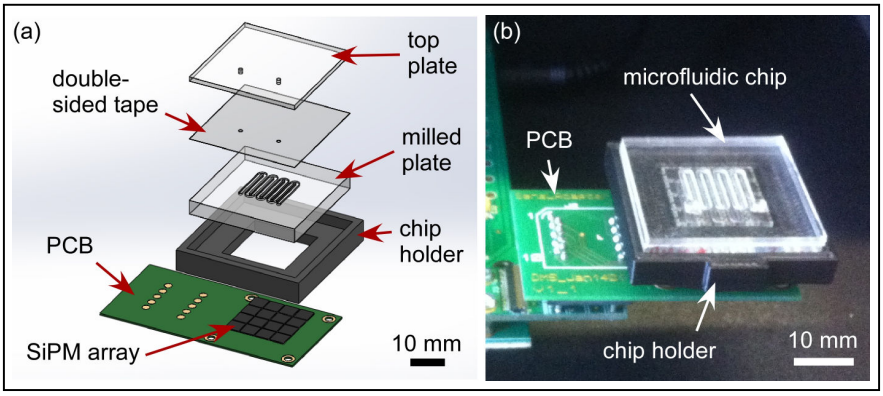

Figure 1: (a) Exploded schematic of the chip setup, consisting of a serpentine channel milled into a substrate, then bonded to a top plate. The chip was placed in a holder for positioning over an array of SiPM sensors. (b) Photograph of the final setup.

RESULTS AND DISCUSSION

The SiPM detector showed a linear response to activity levels in the microfluidic devices. Chip material had an almost negligible effect on the signal detected (Fig. 2a), although polycarbonate yielded slightly higher signals compared to the more dense glasses. Tests of material thickness demonstrated an increase in signal as the substrate became thinner (Fig. 2b). This method of radioactivity detection was validated by introducing a solution of [^{18}F]FDG into a polycarbonate chip (4 mm thick) and determining the amount of radioactivity based on the earlier [^{18}F]fluoride calibration signals; the results showed an excellent comparison to the radioactivity levels determined via the dose calibrator. To ensure that other types of positron-emitters could be analysed using the SiPM setup, a series of experiments were performed with different substrate materials and thicknesses using [^{68}Ga]gallium-citrate (Fig. 3a), with results showing similar trends to [^{18}F]fluoride.

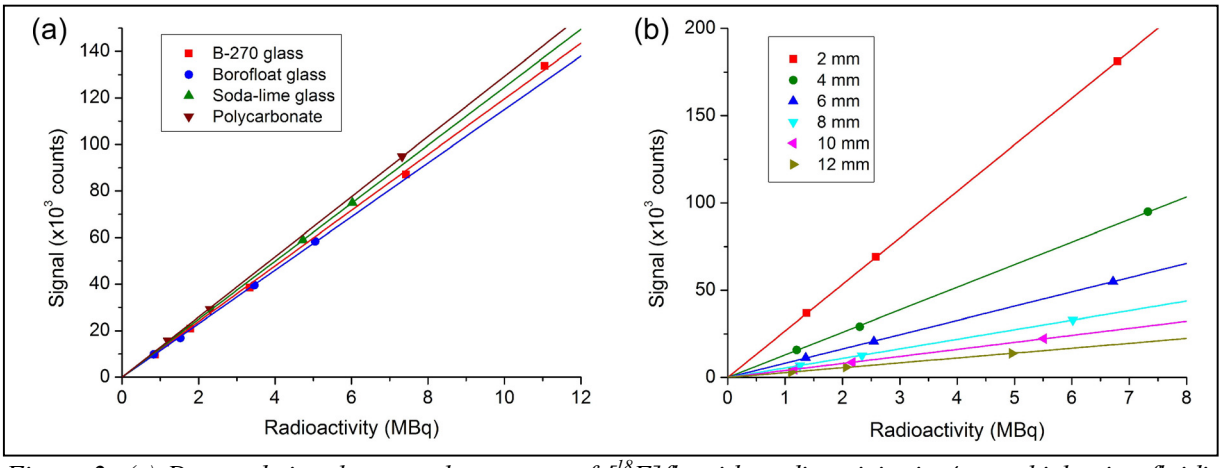

Figure 2: (a) Detected signal versus the amount of [^{18}F]fluoride radioactivity in 4 mm thick microfluidic devices fabricated from different substrates. (b) Detection of [^{18}F]fluoride radioactivity in polycarbonate chips manufactured with varying thicknesses (2-12 mm).

Originally, the source of the SiPM signal was thought to be Cerenkov radiation: light generated as positrons move through a material. However, when experiments were performed with opaque chip materials, i.e. polycarbonate chips coated with paint and PTFE chips, the resultant detection signal was actually similar to those of the transparent substrates (Fig. 3b), suggesting that the SiPMs were sensitive to other sources (e.g. direct positron or gamma ray interaction). This was further confirmed by testing with the gamma emitting radioisotope, ^{99m}Tc, which also yielded a strong SiPM signal despite the absence of positrons. Regardless of the detection mechanism, in all cases the detection signal was linear with radioactivity, showing promise for the use of SiPM sensors in the QC testing of radiopharmaceuticals.

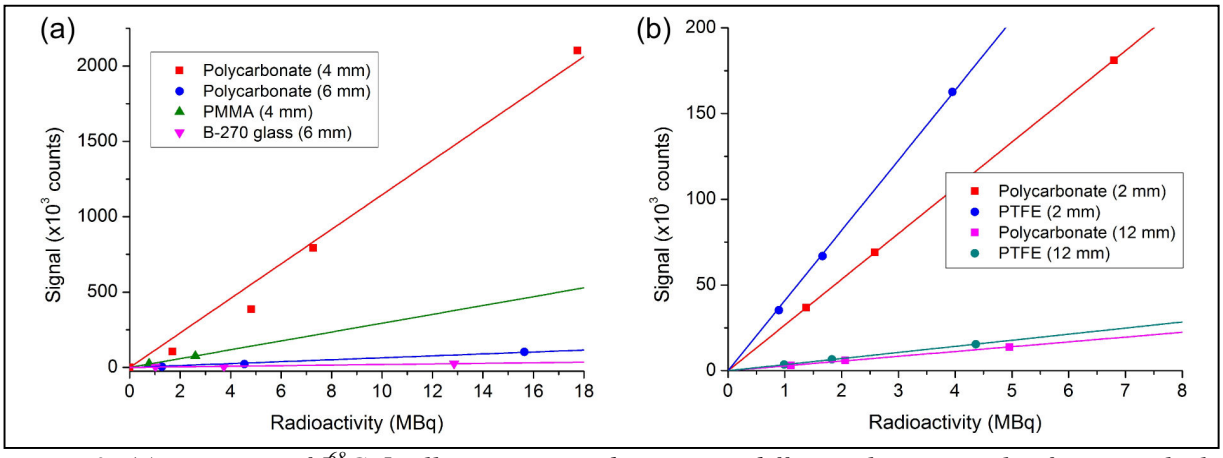

Figure 3: (a) Detection of [^{68}Ga]gallium-citrate radiotracer in different chip materials of varying thicknesses. (b) Comparison of detected activity in opaque PTFE chips and transparent polycarbonate chips.

CONCLUSION

We have demonstrated the use of on-chip radioactivity detection using low-cost, miniaturised SiPM detectors. The sensors were sensitive to direct positron and/or gamma ray interactions, enabling detection of radiopharmaceuticals used in both PET and SPECT imaging. SiPMs are ideal for microfluidic QC testing, which will help to realise dose-on-demand radiotracer production for the stratified treatment of patients. Future work will see the use of SiPMs for radioisotope (e.g. half-life, radionuclidic identity) and radiochromatographic (i.e. radiochemical purity) analysis in an integrated QC system.

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