ON-CHIP ABSORBANCE SPECTROSCOPY FOR THE DETERMINATION OF OPTICAL CLARITY AND PH FOR THE QUALITY CONTROL TESTING OF [^{18}F]FDG RADIOTRACER

Mark D. Tarn, Anri Isu, Stephen J. Archibald and Nicole Pamme*

Department of Chemistry and Positron Emission Tomography Research Centre, University of Hull, HU6 7RX, UK

ABSTRACT

We present on-chip absorbance-based determination of pH and optical clarity for quality control (QC) testing of 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), a positron emission tomography (PET) radiotracer. The platform allows fast analysis times, reduces radioactive exposure to personnel, and requires only minimal sample volumes, making it suitable for dose-on-demand radiotracer synthesis.

KEYWORDS: Absorbance spectroscopy, [^{18}F]FDG, Optical clarity, pH determination, Positron emission tomography (PET), Quality control

INTRODUCTION

Traditionally, [^{18}F]FDG is synthesised in batch (~20 doses) and transported to hospitals. Recently, dose-on-demand production, whereby a single dose is generated when required via an on-site mini-cyclotron and miniaturised synthesis-unit, is becoming an important strategy for stratified medicine. With miniaturised synthesis [1] comes the need for miniaturised QC: for conventional QC an entire dose is needed; not a viable option for dose-on-demand. An ideal QC platform would require a small fraction of the dose, would perform rapid testing due to the time concerns related to radioisotope decay, and would avoid the need for manual handling of radioactive material. Here, we present a simple on-chip absorbance-based system for performing two of the required QC tests [2,3] in a fast manner (few min) with small volumes (<2 μL). In the first test, the optical clarity of the [^{18}F]FDG doses was monitored to determine whether they met the requirement of being "clear and colourless". This is normally performed by visual inspection, a subjective test that exposes the analyst to radiation. The second test concerned the determination of the pH of the dose, which must be between pH 4.5 and 8.5 to pass QC and is conventionally performed with a pH electrode or pH paper, again exposing the operator to radiation.

EXPERIMENTAL

A three-layer glass chip was fabricated to enable colourimetric reactions in the top layer, absorbance detection in the middle layer, and removal of solutions via the bottom layer (Fig. 1a). The channel features were 150 μm wide and 50 μm deep, while the pathlength channel was 3.1 mm long and 368 μm in diameter. The chip was inserted into an aluminium holder and aligned with optical fibres via an x-y translational stage (Fig. 1b). One fibre directed light from a halogen lamp (HL-2000, Ocean Optics) into the pathlength channel, while a second fibre collected light that had passed through the pathlength channel and directed it into a miniaturized spectrometer (USB2000, Ocean Optics).

Optical clarity: Appearance testing was performed simply by pumping [^{18}F]FDG doses directly into the chip and monitoring the resulting spectra. The spectra were compared to a blank of pure water.

pH determination: A solution of universal indicator was pumped into one of the inlets of the microfluidic device, while pH standards (pH 1-13) were pumped into the second inlet. The solutions were allowed to mix in the serpentine channel before being monitored by absorbance spectroscopy in the pathlength channel. Following this, real [^{18}F]FDG samples were pumped through the chip and reacted with universal indicator in the same manner in order to determine their pH values.

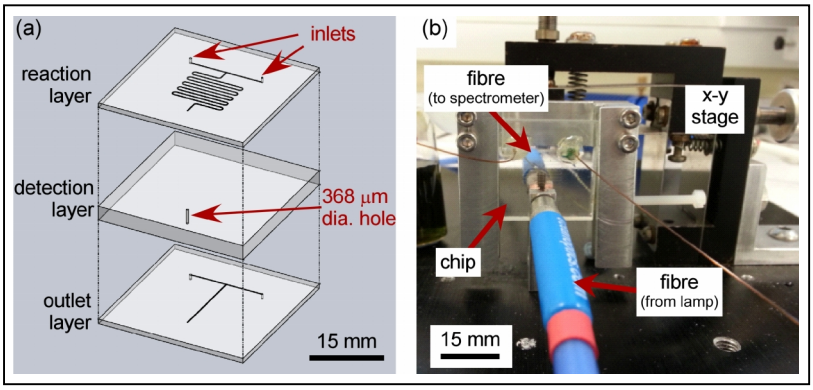

Figure 1: (a) Schematic of the three-layered device featuring a 3.1 mm long pathlength in the middle layer for absorbance spectroscopy, and two inlets in the top layer for colourimetric assays. (b) Photograph of a glass chip held in a translation stage for alignment of the pathlength channel with optical fibres for illumination and light collection.

RESULTS AND DISCUSSION

Optical clarity: Multiple doses of [^{18}F]FDG were pumped into the chip and compared to a blank of water. Most doses showed only noise around the baseline (Fig. 2a), with visual inspection confirming that they were clear and colourless. A failed dose (#5387) that was yellow to the eye featured a prominent peak at 380 nm, and this was traced back to a contaminant formed by the reaction of a metal syringe needle with an acidic solution. This demonstrated the potential of the system for automated absorbance-based clarity testing to determine the pass or fail of injectable doses, which would help to eliminate the subjective nature of the conventional test while minimising exposure to personnel.

pH determination: pH standards (pH 1 - 13) were pumped into the microfluidic chip and reacted with universal indicator in flow before passing through the detection channel, allowing the resultant spectra to be recorded (Fig. 2b). Multiple [^{18}F]FDG doses also underwent the same procedure and their spectra were recorded. Two data analysis methods were developed for determining pass/fail criteria.

In one method, a V-shaped plot was constructed from absorbance values at 551 nm, which allowed a line to be drawn across the points for pH 4.5 and pH 8.5 (0.14 a.u.) (Fig. 2c). [^{18}F]FDG doses with absorbance values below this line would thus fall within the acceptable pH range (4.5 - 8.5), while those above the line would fail the QC test. For example, [^{18}F]FDG dose #5369 yielded an absorbance value of 0.08 a.u. and so passed the QC, with a value of pH 7 confirmed by pH electrode. The unpurified dose #5395, however, exhibited an absorbance value of 1.47 a.u., thus failing the requirements (confirmed to be pH 1 by pH electrode).

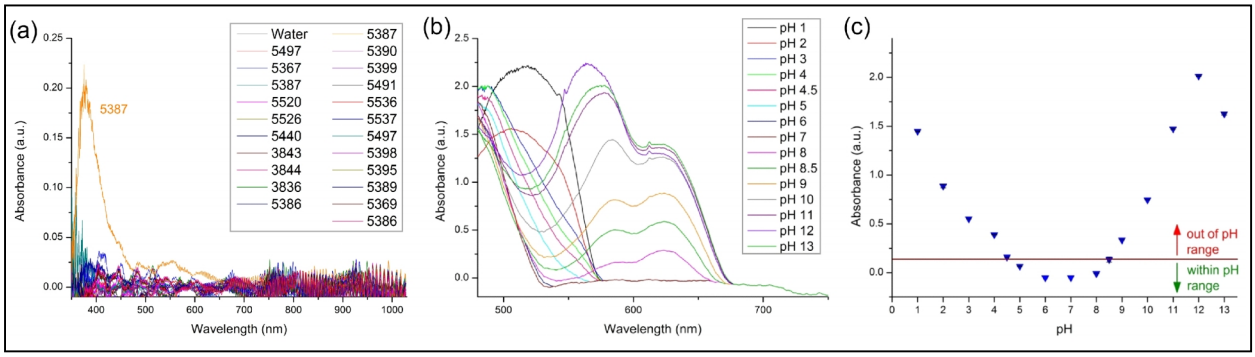

Figure 2: (a) Optical clarity spectra for multiple [^{18}F]FDG doses. A large peak at 380 nm can be seen for the failed dose, #5387, which exhibited a slight yellow colour. (b) Absorbance spectra of pH standards (pH 1 - 13) after being reacted on-chip with universal indicator solution. (c) V-plot prepared from the pH standard spectra at a wavelength of 551 nm. A horizontal line is drawn across the pH 4.5 and pH 8.5 values. Absorbance values of [^{18}F]FDG doses reacted with universal indicator that were below this line were within the acceptable pH range, while those above the line would fail the QC test.

In the second analysis method, star plots of absorbance values for each pH standard over a wavelength range of 520 - 640 nm (Fig. 3) were generated, and the determination of the pH of [^{18}F]FDG doses was based on shape recognition. For example, the shape of the plot for [^{18}F]FDG dose #5395 matched that of the pH 1 standard, indicating that this was the pH value, and so again failed the criteria. However, the shape of DOSE #5369 most closely matched that of the pH 7 standard, thereby passing the QC criteria. All pH measurements were confirmed separately via pH electrode measurements. Thus, the described method was shown to be a viable option for flow-based analysis by flow-based colourimetric reactions and absorbance detection, showing promise for automation of the process.

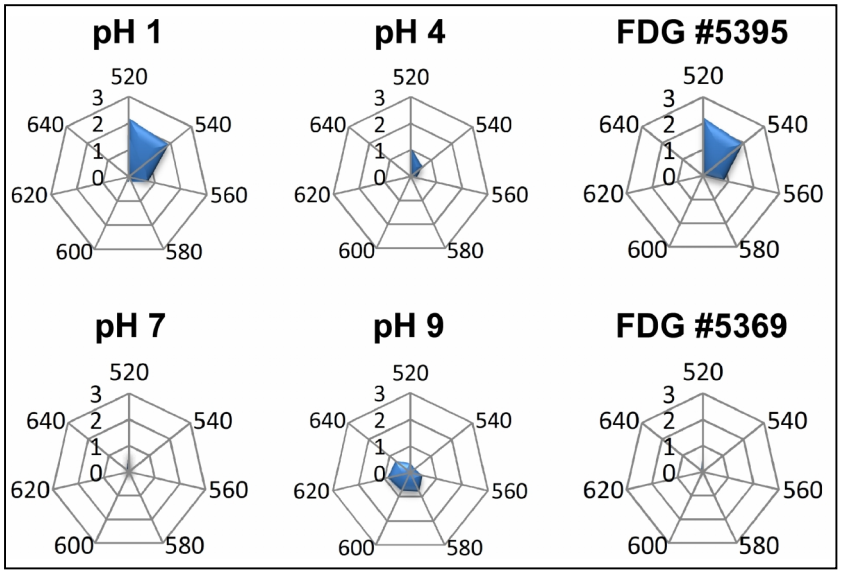

Figure 3: A selection of star plots taken from pH standards reacted with universal indicator over a wavelength range of 520 - 640 nm. The shape of [^{18}F]FDG dose #5395 had the same shape as the pH 1 standard and would fail the QC test. However, the shape of dose #5369 most closely matched that of the pH 7 standard, and so would pass the QC test. All results were confirmed by pH electrode.

CONCLUSION

We have developed a simple absorbance-based microfluidic system for the rapid determination (a few min) of pH and optical clarity of [^{18}F]FDG using low sample volumes (<2 μL). The platform eliminates the subjectivity of some of the standard tests, and could be incorporated into an automated dose-on-demand QC platform. This would minimise the exposure of personnel to radiation while reducing the amount of injectable dose that would need to be sacrificed for QC.

ACKNOWLEDGEMENTS

The authors thank the Daisy Appeal (grant no. DAhul0211) for financial support.

REFERENCES

[1] C. Rensch, A. Jackson, S. Lindner, R. Salvamoser, V. Samper, S. Riese, P. Bartenstein, C. Wängler, "Microfluidics: A groundbreaking technique for PET tracer production?", *Molecules*, 2013, **18**, 7930-7956.

[2] S. Yu, "Review of ^{18}F-FDG synthesis and quality control", *Biomed. Imaging. Interv. J.*, 2006, **2**, e57.

[3] J. C. Hung, "Comparison of various requirements of the quality assurance procedures for ^{18}F-FDG injection", *J. Nucl. Med.*, 2002, **43**, 1495-1506.

CONTACT

* N. Pamme; phone: +44 1482 465027; n.pamme@hull.ac.uk