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Retraction for *RSC Advances*:

Broadband cavity enhanced absorption spectroscopy (BBCEAS) as a detection technique for a microfluidic flow cell made of Zeonor®

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We, the named authors, hereby wholly retract this *RSC Advances* article due to problems with the reliability and reproducibility of some of the data quoted in the article. This article was submitted for publication without the knowledge and approval of any of the Oxford-based authors, therefore Claire Vallance, Cathy Rushworth and Yathukulan Yogarajah disassociate themselves from the content of the article.

Signed: Ruchi Gupta, N J Goddard, Stephan Mohr, Cathy M. Rushworth, Claire Vallance and Yathukulan Yogarajah, September 2013

Retraction endorsed by Sarah Ruthven, Managing Editor, *RSC Advances*

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Broadband cavity enhanced absorption spectroscopy (BBCEAS) as a detection technique for a microfluidic flow cell made of Zeonor®

Abstract

Broadband cavity enhanced absorption spectroscopy (BBCEAS) has so far been used for increasing the effective optical path length and hence detection sensitivity of flow cells made of high-optical quality glass. Glass, however, is fragile, expensive and difficult to process. In this work, the feasibility of BBCEAS for high sensitivity detection in a microfluidic flow cell made of a cyclic olefin copolymer, Zeonor® has been demonstrated for the first time. The Zeonor® device is disposable and is suitable for applications in areas such as clinical diagnostics, where glass devices would be unsuitable. The effective number of passes of light through the Zeonor® device was increased by two orders of magnitude on placing it between two 99±0.3% reflectivity broadband (400-800 nm) mirrors. At 572 nm, the minimum detectable absorption coefficient (i.e. absorbance per unit length) achieved using the Zeonor® device was 2.9×10^{-3} cm^{-1}, which corresponds to a limit of detection of 1.1 μM potassium permanganate solution. This is two orders of magnitude better than the typical LOD achieved by performing single pass absorbance measurements in microfluidic devices.

Keywords: absorption spectroscopy, Zeonor®, cavity enhanced, microfluidics, sensitivity.

1. Introduction

Microfluidic devices offer a number of useful properties, such as high throughput, low-cost, portability, and the potential for automation and use in remote sensing or field studies [1]. Such devices present an ideal platform for point-of-care testing, clinical and forensic analysis, medical diagnostics, environmental monitoring and food analysis [2-3]. In addition, microfluidic devices are particularly beneficial for applications in which the liquid volume used must be minimised, either due to high reagent costs or limited sample availability.

On one hand the small fluid volumes involved in microfluidic devices are advantageous, but on the other hand they pose a significant challenge to high sensitivity detection in microchannels [4]. Laser induced fluorescence (LIF) is commonly used to perform high sensitivity detection in microfluidic devices [4]. However, as most compounds do not show native fluorescence, LIF detection requires extra labelling chemistries. These labelling protocols are usually lengthy and often have to be carried out off-chip. In addition, tagging of

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analytes with fluorophores can result in incomplete derivatisation (and hence errors in quantitative results) or formation of multiple peaks due to multi-derivatisation, or both [5]. In comparison to LIF, absorption spectroscopy does not require extra labelling chemistries, since all species absorb over some wavelength range within the electromagnetic spectrum. In addition, broadband absorption spectroscopy is advantageous because the full spectral profile of a species can be obtained in a single measurement which can permit its identification. The detection sensitivity of single pass absorption spectroscopy for microfluidic devices is, however, poor because the optical path length through the sample is small. Thus, a number of approaches have been developed to increase the optical path length through the sample and hence to achieve high sensitivity absorption spectroscopy in microfluidic devices.

The distance travelled by light through the sample has, for example, been increased using liquid core waveguides (LCW) which rely on total internal reflection to confine light in liquid samples. This implies that LCWs require using either high refractive index liquids (e.g. aromatics, carbon disulphide and halogenated compounds) [6-8] or using tubes made of low refractive index polymers such as Teflon [9] or coating the walls of flow cells with Teflon [10]. The use of high refractive index liquids, however, limits the type of chemistry that may be used. The integration of Teflon tubing with microfluidic systems is cumbersome and polymer-coated flow cells have limited long-term performance as a result of degradation of the coating. Alternatively, anti-resonant reflecting optical waveguides (ARROW) have been used to perform high sensitivity detection in microfluidic flow cells. In ARROW, light is confined into a liquid sample by coating the walls of flow cells with dielectric mirrors [11-12]. ARROWs, however, are difficult to fabricate and place constraints on the dimensions of microfluidic flow cells.

The optical path length has also been increased by placing waveguides parallel to the long axis of flow cells [13] and allowing the evanescent field of light travelling in the waveguide to interact with the sample. The effectiveness of this scheme, however, requires maximising the fraction of optical mode power propagating in the evanescent region. Thus, tapered and U-bend waveguides have been used to "push" the evanescent field deeper into the sample layer [14-15]. The coupling of light into waveguides has been cumbersome because it requires alignment of the light beam with the sub-micron thickness of the waveguide [16]. The distance over which the evanescent light wave interacts with the sample has also been enhanced using whispering gallery mode (WGM) microresonators [17-18]. Some limitations

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of WGM microresonators are as follows: Firstly, such structures can in general only be used to record absorbance over a relatively narrow range of wavelengths which is governed by the availability of tuneable lasers. Secondly, microresonators are point detectors and hence need to be fabricated at desired locations to monitor absorbance at different points in microfluidic flow cells. Finally, the fabrication methods (e.g. high power lasers and oxy-hydrogen flames) currently used to make WGM microspheres require a degree of skill and are not suitable for mass production. In contrast, broadband cavity enhanced absorption spectroscopy (BBCEAS) offers a relatively simple approach to increasing the optical path length by several orders of magnitude by placing a microfluidic device within an optical cavity comprising two high reflectivity mirrors.

To our knowledge, BBCEAS has so far only been used as a detection technique for flow cells made of glass [19-20]. This is because glass has high optical transmission in the visible region of the electromagnetic spectrum, and can be manufactured with high surface quality. This in turn minimises scattering and absorption losses introduced by a glass flow cell placed in an optical cavity made of high reflectivity mirrors. As a result, the total number of effective passes of light (and hence the optical path length) through the sample is increased. Glass is, however, expensive and fragile relative to other materials in widespread use in microfluidics. In addition, the fabrication of glass-based devices often requires the use of harmful chemicals such as hydrofluoric acid, and sealing the devices by thermal bonding is a slow process which can have a high failure rate [21-22]. It is also difficult to drill fluidic connection ports in devices made of glass. In contrast to glass, Zeonor®-based flow cells can be made using a number of fabrication techniques (e.g. injection moulding) that are suitable for mass production of devices [23-24]. In addition, Zeonor® costs at least 10 times less than glass. As a result, the use of cyclic olefin copolymers such as Zeonor® is gaining popularity for constructing low cost disposable microfluidic devices [25]. This work, for the first time, investigates the feasibility of BBCEAS as a detection technique for a microfluidic device made of Zeonor® fabricated using pressure sensitive adhesive bonding. Limit of detection (LOD) and the effective number of passes of light for the device has been estimated using dilute samples of potassium permanganate.

2. Experimental

2.1 Chemicals

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Potassium permanganate used in this work was purchased from Sigma-Aldrich (≥99%, Sigma-Aldrich, Gillingham, UK). All solutions were made up using 18.2 MΩ water (Elix®, Millipore, UK).

2.2 Microfabrication

A commercial flow cell from Starna, Essex, UK (catalogue number: 45/Q/0.1) of path length 100 µm was used as a high-optical quality standard for comparison with the measurements employing the microfluidic device made of Zeonor® (shown in Figure S1). In order to construct the Zeonor® device, a 5 mm wide and 2.8 cm long window was cut into 80 µm thick pressure sensitive adhesive (3M8153LE, Viking Industrial Products Ltd, Keighley, UK) using a scalpel. In addition, access holes of 1 mm diameter were drilled through 188 µm thick Zeonor® film (ZF14-188, Zeon Corporation, Tokyo). The channel was formed by placing the pressure sensitive adhesive in between the Zeonor® film with access holes and another piece of the Zeonor® film. In order to impart mechanical rigidity to the Zeonor® device, it was clamped onto a plastic frame manufactured in-house by CNC machining. Finally, the fluidic connections for the Zeonor® device were made using in-house manufactured connectors.

2.3 Instrumentation

A schematic of the experimental set-up is shown in Figure 1.

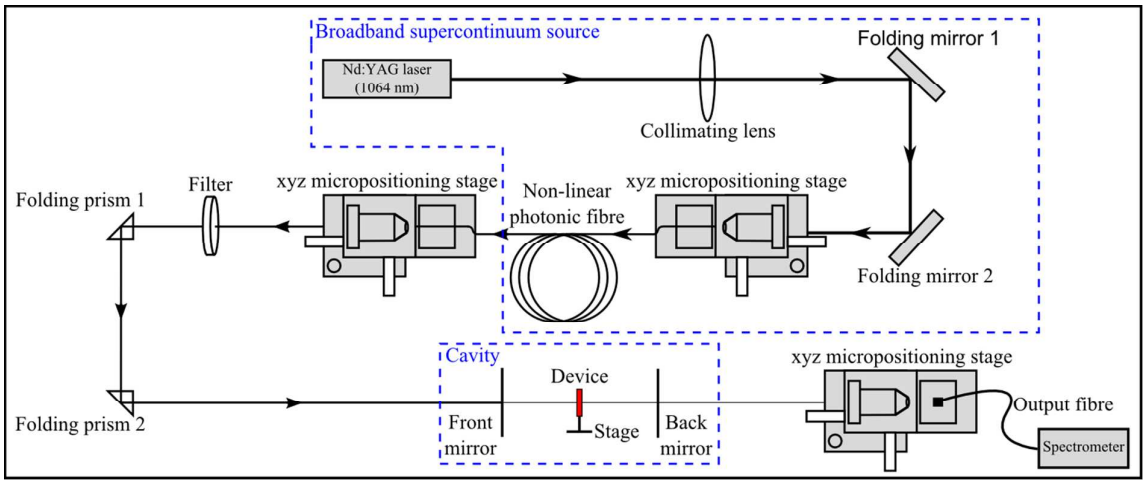

Figure 1: A schematic of the experimental set-up

Broadband supercontinuum light was generated by pumping a non-linear photonic crystal (microstructured) fibre (SC-5.0-1040, NKT Photonics, Germany) with the focussed 1064 nm

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output of a Nd:YAG laser (NP-10620-100, Teem Photonics, Edinburgh, UK). The output from the fibre passed through an objective (06 OD 03, Comar Instruments Ltd, Cambridge, UK) and a bandpass filter (FGS900, Thorlabs, Cambridge, UK), yielding a collimated beam with a bandwidth of 480-710 nm. The light beam was steered using two right angle prisms (16 RX 01, Comar, Cambridge) into the optical cavity. The cavity was formed from two high reflectivity concave mirrors ($R_{400\text{-}800\ nm}$= 99±0.3% and radius of curvature = 1 m, Layertec, Germany) placed 13 cm apart. The light exiting the cavity was focussed using an objective (25 OD 09, Comar, Cambridge, UK) and coupled to a spectrometer (HR4000, 10 μm slit, Ocean Optics, Germany) using a multimode optical fibre (M15L02, Thorlabs, Cambridge, UK) with a core diameter of 105 μm. The spectrometer was USB interfaced to a computer and data was acquired via a LabVIEW (National Instruments, Texas, USA) program.

The flow cell was mounted onto an assembly of optical stages (M-423, M-443-4, Newport, Oxfordshire, UK and 70 XT 65, Comar, Cambridge, UK) to permit its linear movement in the directions perpendicular to the propagation axis of light and rotational movement in the horizontal and vertical planes. The device was placed at the centre of the optical cavity at normal incidence to the propagation axis of light. While reflection losses associated with the chip can in some cases be reduced by placing the device at Brewster's angle within the cavity, for high quality devices with all surfaces parallel, inserting the device at right angles to the beam path allows light reflected from the surfaces to be recycled into the cavity [26]. The latter configuration was chosen both for the ease of cavity alignment and because it provides a well-defined (single pass) optical path length. The optical power incident on the device is estimated to be 300 mW because the supercontinuum source generated pulses of duration of 1 ns with an energy of 3 μJ, of which $R_{400\text{-}800nm}^{2}$ was coupled inside the cavity.

2.4 Experimental procedure

In BBCEAS, light is injected continuously into an optical cavity, and the time-integrated light intensity emerging from the cavity is dispersed into its constituent wavelengths prior to detection. The wavelength-dependent absorbance, A, is defined as [22]:

$$A = \varepsilon c l = \frac{(I_0 / I) - 1}{\mathrm{CEF}} \qquad (1)$$

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where ε is the wavelength-dependent molar extinction coefficient, c is the sample concentration, l is the single pass optical path length through the sample, I_0 and I are the measured intensity of light in the absence and the presence of the sample respectively. The absorption coefficient (is absorbance per unit length) can be calculated as a product of concentration and molar extinction coefficient. CEF is the cavity enhancement factor, which is a measure of the effective number of passes of light through the sample for a given experimental set-up. The total optical loss associated with the set-up was estimated by taking the inverse of the CEF [27].

The optical cavity was initially aligned such that all back reflections from the mirrors and surfaces within the microfluidic device were merged with the path of the incident beam. The alignment of the mirrors and microfluidic device was then fine tuned to optimise the intensity of the output signal of the cavity. Unless stated otherwise, a spectrometer integration time of 10 ms was used for all the experiments.

A dilution series of potassium permanganate solutions in the concentration range from $2.5\text{x}10^{-5}$ M to $1\text{x}10^{-3}$ M was prepared. Solutions were introduced into the device using a syringe pump (Fusion 400, Chemyx, Stafford, UK) fitted with a 10 ml plastic syringe (BD, Oxford, UK). For each absorption measurement, the microfluidic device was initially flushed with 1.5 ml of deionised water at a flow rate of 0.5 ml/min, and the output spectrum of the cavity over the wavelength range from 480-710 nm was recorded, averaged over 50 traces. This spectrum constituted the baseline absorption measurement (I_0 in Equation (1)). The device was then flushed with the appropriate potassium permanganate solution and the spectrum recorded to obtain the 'signal' absorption measurement (I in Equation (1)). These steps were repeated 3 times for each concentration of potassium permanganate solution.

The molar extinction coefficient, ε, of potassium permanganate was determined in the wavelength range between 400 nm and 800 nm (as shown in Figure S2) using a commercial UV-vis spectrometer (Cary 100 Bio UV-Vis, Varian, Sussex, UK). The single pass optical path length, l, in Equation (1) is governed by the physical dimension of the flow cell along the path of the light beam. The data was substituted into Equation (1) to calculate the CEF for each device. The LOD was determined using a plot of measured wavelength-dependent absorbance against the concentration of potassium permanganate solutions. The LOD is given

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by the y-axis intercept plus three times the standard deviation, s_B, associated with that value. The standard deviation, s_B, was calculated as follows [28]:

$$s_B = \sqrt{\frac{\sum (y_i - \hat{y}_i)^2}{n-1} \frac{\sum x_i^2}{n \sum (x_i - \bar{x})^2}} \qquad (2)$$

where y_i is the observed absorbance, $\hat{y}_i$ is the calculated absorbance, n is the number of data points, x_i is the concentration of potassium permanganate solutions used and $\bar{x}$ is the mean of the concentration of potassium permanganate solutions.

3. Results and discussion

3.1 Initial study

Light injected into the cavity had a bandwidth of 480-710 nm and potassium permanganate absorbs between 450 nm and 600 nm. The mirrors used have a reflectivity of 99±0.3% in the wavelength range from 400 nm to 800 nm. The shortest wavelength of light with 92% transmission through (Spectrosil® quartz) glass and (ZF14-188) Zeonor® is approximately 190 nm and 300 nm [29] respectively. Thus, the feasibility of BBCEAS as a detection technique was studied in the wavelength range between 480 nm and 600 nm, where the lower and upper limits were determined by the supercontinuum light source and the absorbance spectrum of potassium permanganate respectively. Despite the limited wavelength range studied in this work, the detection scheme used is universal provided that appropriate light sources, mirrors and absorbing species are chosen.

A commercial flow cell made of high-optical quality glass was placed inside the cavity to determine the CEF as a function of wavelength for the reference system (see Figure 2 (a)). CEF is inversely related to the total optical loss, which is determined by the reflectivity of the mirrors comprising the optical cavity as well as by scattering and absorption characteristics of the flow cell placed inside the cavity. Based on the data provided by the manufacturer, the scattering and absorption characteristics of the glass flow cell were independent of the wavelength in the range between 480 nm and 600 nm. The reflectivity of large bandwidth mirrors used in this work, however, was variable in the wavelength range studied because they were constructed by depositing multiple dielectric layers. The variations in the reflectivity of mirrors with wavelength can be observed by considering a typical output

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spectrum of the cavity, which is shown in Figure 2 (b). The intensity of light exiting the cavity is high at wavelengths where the reflectivity of mirrors comprising the cavity is high (and hence losses are low). This implies that the dependence of CEF on the wavelength of the excitation light is due to variations in the mirror reflectivity with wavelength. As a result, the total optical loss and hence the CEF were a function of the wavelength of the excitation light. As shown in Figure 2 (a), the maximum CEF for the glass flow cell was 178 and was obtained approximately at the wavelength where the intensity of light exiting the cavity was the highest. This corresponds to the wavelength at which the total optical loss was lowest.

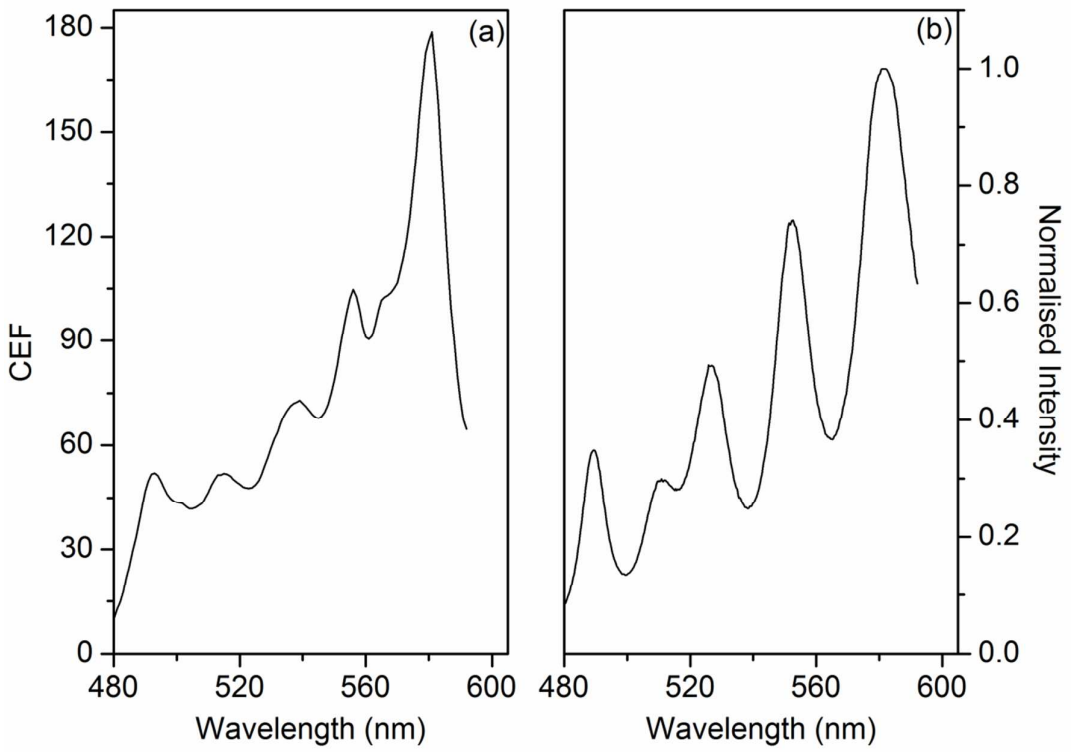

Figure 2: Plot of (a) CEF vs. wavelength for the commercial flow cell made of high-optical quality glass (spectrometer integration time is 10 ms) and (b) cavity output spectrum without a flow cell (spectrometer integration time is 3 ms and was chosen to avoid signal saturation)

3.2 Investigation with the microfluidic flow cell made of Zeonor®

A comparison of the cavity output spectra of the microfluidic device made of Zeonor® and glass flow cells is shown in Figure 3. The intensity of light exiting the cavity with the Zeonor® device was similar to the glass flow cell, thereby suggesting that the optical losses associated with the two were comparable. A plot of the CEF of the Zeonor® device as a

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function of the wavelength of the excitation light is shown in Figure 4. A comparison of Figure 2 (a) and Figure 4 shows that the CEF of the Zeonor® device was comparable to the glass flow cell. Subsequently, the CEF of the Zeonor® device was measured at three different spatial locations, which are shown in the inset in Figure 4, by moving the selected regions of the device in the path of the light beam. As shown in Figure 4, the CEF at the "L" and "R" locations of the Zeonor® device is ~80 at 572 nm, which is ~31% lower than the CEF at "C". This could be due to variations in the thickness of the pressure sensitive adhesive and imperfections (e.g. scratches) on the surface of the polymer.

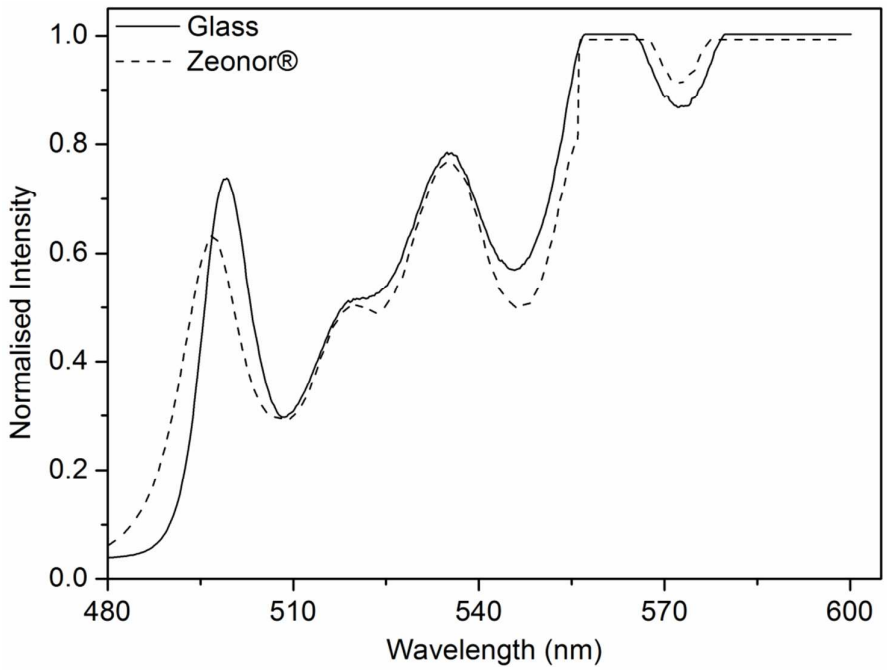

Figure 3: A comparison of the cavity output spectra for the glass and the Zeonor® flow cells (where spectrometer integration time is 10 ms and a common normalisation constant of 16383 was used for both glass and Zeonor®)

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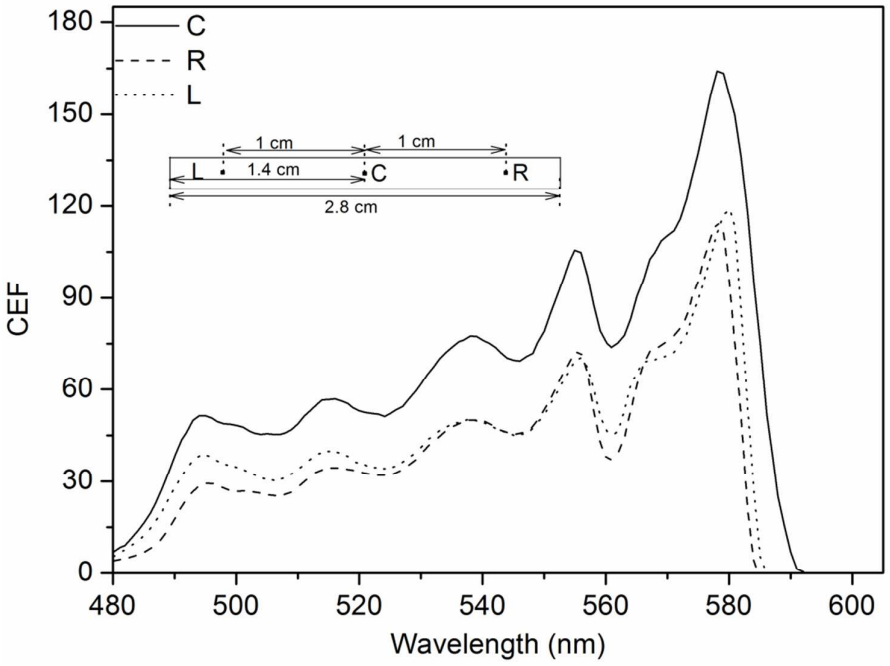

Figure 4: CEF of the flow cell made of Zeonor® vs. wavelength (where the inset depicts the location of "C", "R" and "L" on the device and spectrometer integration time is 10 ms)

A summary of other parameters of interest such as the relationship between absorbance and concentration of potassium permanganate, CEF, LOD and minimum detectable absorption coefficient of the glass and the Zeonor® flow cells at 572 nm is provided in Table 1.

Material	**Fabrication method**	**Relation between absorbance and concentration**	**R^2**	**CEF**	**LOD (µM)**	**Minimum detectable absorption coefficient (cm^{-1})**
Glass	Commercially available	0.0099+3140.5c	0.999	115.3	1.0	2.6×10^{-3}
Zeonor®	Pressure sensitive adhesive	0.001+2458.5c	0.999	115.8	1.1	2.9×10^{-3}

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Table 1: Summary of the various parameters of interest for the flow cells at 572 nm (where ε = 2653 $M^{-1}cm^{-1}$, c is the concentration of potassium permanganate in M and spectrometer integration time is 10 ms)

Linear absorbance response was observed in the range from $2.5x10^{-5}$ M to $1x10^{-3}$ M potassium permanganate for the Zeonor® device. The relationship between the absorbance and the concentration of potassium permanganate in the linear range for the device is given by A= 0.001+2458.5c with r^2=0.999. The CEF of the Zeonor® device at 572 nm is ~116. It is thought that the maximum achievable CEF is limited by the reflectivity of the mirrors used to perform the work. The effective optical path length is the product of the CEF and the physical dimension of a flow cell along the path of the light beam. Thus, the optical path length of the Zeonor® device can be increased from 80 μm to 9.3 mm at the chosen conditions. The LOD of potassium permanganate was 1.1 μM at 572 nm, which corresponds to a minimum detectable absorption coefficient of 2.9×10^{-3} cm^{-1}. This is two orders of magnitude better than the typical LOD obtained via single pass absorbance spectroscopy in microfluidic flow cells [30]. Thus, BBCEAS is well suited to perform high sensitivity detection in the microfluidic flow cell made of Zeonor®.

A possible application of the Zeonor® device interfaced with BBCEAS is in multi-wavelength spectrometric measurements for simultaneous detection of, for example, Haemoglobin derivatives [31]. Another possible application could be in the sensitive detection of (bio) chemical species (e.g. proteins, iron, calcium and so on) in microfluidic flow cells via colorimetric assays.

4. Conclusions

Absorbance is a widely applicable detection technique, but the sensitivity of absorbance spectroscopy in microfluidic devices is normally restricted by the short optical path length of the microchannels. One way of increasing the effective optical path length is by using broadband cavity enhanced absorption spectroscopy (BBCEAS) in which the device is placed inside a cavity comprising high reflectivity mirrors to achieve multiple passes through the sample. The suitability of BBCEAS as a detection technique has so far only been demonstrated for devices made of glass. This paper for the first time investigates the feasibility of BBCEAS as a detection technique for a microfluidic flow cell made of Zeonor®, which is important because the device is particularly well suited for single-use applications

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such as clinical diagnostics. Zeonor® is cheaper, simpler to process and easier to dispose of than glass. In addition, Zeonor® devices can be mass produced using techniques such as injection moulding.

In this work, an optical cavity was formed from two mirrors, with reflectivity of 99±0.3% in the wavelength range between 400 nm and 800 nm, placed 13 cm apart. Simultaneous measurements were made at all wavelengths in the absorption region, ranging from 480 nm to 600 nm, of potassium permanganate. The wavelength range studied was determined by the supercontinuum light source and the absorber (rather than the transmission characteristics of the polymer material) used. The CEF of the Zeonor® device constructed using the pressure sensitive adhesive bonding method was enhanced by two orders of magnitude. For example, the CEF of the Zeonor® device was 116 at 572 nm, which corresponds to a detection sensitivity of 2.9×10^{-3} cm^{-1} or 1.1 μM potassium permanganate. In conclusion, BBCEAS is well suited as a detection technique for the microfluidic device made of Zeonor®.

Although this study was performed in the wavelength range between 480 nm and 600 nm, the set-up is universal provided that suitable light sources, mirrors and absorbing species are used. In case single-wavelength measurement is desirable, the instrumentation can be simplified by replacing, for example, the supercontinuum light source and the spectrometer by a laser and a charge coupled device respectively. The suitability of interfacing BBCEAS with microfluidic devices made of other polymers will be investigated in future. Future work will also concentrate on interfacing injection moulded Zeonor® devices with BBCEAS to determine bio(chemical) species.

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