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Citation: Whittaker, N. S., Nguyen, T. H., Fabian, M., Sun, T., Grattan, K. T. V., Khan, K., Parker, A. & Holt, A. (2025). Detection of codeine using a molecularly imprinted polymer-coated optical fibre sensor. *Optics Communications*, 578, 131427. doi: 10.1016/j.optcom.2024.131427

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Detection of Codeine using a Molecularly Imprinted Polymer-coated Optical Fibre Sensor

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Abstract

The ease of access to codeine and the related concerns of dependence, misuse and fatality are increasing in importance because codeine is an analgesic – it is chemically similar to morphine, although not as potent. The focus in the literature is on detection of higher Schedule drugs such as morphine and cocaine, rather than codeine.

This work builds on the state-of-the-art previous work from some of the authors: a low-cost molecularly imprinted polymer-optical fibre sensor using a fluorophore, with a 30-minute response time, that is selective to codeine amongst drugs such as cocaine and ketamine that it is normally paired with for recreational use. Applicable to both laboratory and in-the-field applications, it takes full advantage of the robustness of the optical fibre, being resistant to electromagnetic, chemical, and biological interference, marrying the two technologies to create a selective, durable and potentially inexpensive, yet sensitive technology. The sensor is also sensitive, presenting a 25 µM limit of detection.

This investigation also reports the limitations of using fluorescence-based molecularly imprinted polymer-optical fibre sensors, in terms of their lifetime, which has not been documented in previous similar analyses. A non-imprinted polymer was also produced as a control template, showing no response to codeine, nor any of the drugs trialled as part of cross-sensitivity analysis.

Keywords

Chemical sensor, optical fibre sensor, molecularly imprinted polymer, codeine, codeine detection

1. Introduction

Codeine is, depending on its concentration, a Schedule II and III drug under *the Single Convention on Narcotic Drugs* and in major developed countries, including the United States, codeine is regulated under various narcotic control laws. It is available in pharmacies across the world and provided over the counter in forms such as co-codamol, providing mild to moderate pain relief to patients [1,2], and is often considered the less potent cousin of morphine. Its ease of access often lends itself to the thought that codeine is relatively harmless, however, at high doses, codeine use can lead to respiratory failure, coma, and eventually death – from 2020-21, there was in 25% increase in codeine-related deaths in England and Wales [3], with increases in the number of deaths continuing [4]. Its risk is also heightened when combined with Central Nervous System (CNS) depressants such as alcohol or other opioids. Codeine's accessibility has drawn increasing concerns as it is garnering more attention as a recreational drug and therefore, its misuse and the prospect of addiction deserves more attention. Unfortunately, addiction to painkillers and the abuse of codeine is a serious issue in society; without a prescription, codeine can be obtained in co-codamol in 8 mg doses with 500 mg paracetamol, however, in some countries, it is available at higher, up to 20 or 30 mg, when sold with 500 mg paracetamol.

Given its wide use, the accurate detection of codeine is important and many commercial opiate screening tests, directed at morphine, cross-react appreciably with codeine and its metabolites. When codeine is used whether recreationally or not, it often results in morphine as an excretion product. For example, familiar chromatographic techniques can easily distinguish codeine from other opiates and opioids, but these techniques are not field based. Non-laboratory-based tests are important given the wide use of codeine and thus there is a major market for low cost, easy to use tests which do not require a high level of expertise to administer. Opioid detection is

usually directed to substances like morphine or heroin due to their standing as highly addictive, whereas detection for codeine is vastly underrepresented.

Detection techniques for codeine vary through traditional methods such as liquid chromatography-based (LC) techniques [5–8] gas chromatography-mass spectrometry (GC-MS) [5,9–11], gas chromatography-flame ionization detector (GC-FID) [12], differential scanning calorimetry (DSC) [13] and ion mobility spectroscopy (IMS) [14], to newer ones such as those that use electrochemical-based analysis [15–19]. These technologies are extremely sensitive, but are costly, require trained staff for maintenance and/or require sample preparation and therefore are time-consuming. Several new technologies have emerged in the past few years which challenge the need for such expensive tests requiring, as they do, experienced (and usually hard to resource) staff time – these are sensors, which include biosensors as well as electrochemical [20–22] and fluorescence-based mechanisms [23]. Stand-alone sensor techniques have also been applied to other opioids, such as cocaine [23–34], fentanyl [35–41] and ketamine [34,42–45]. Such sensors challenge the current analytical landscape, showing the advantages of being portable, low cost and selective, and are well documented in the literature for applications to many industries. In the defence industry, for example, there is an on-going need for a variety chemical sensor, and the approach to their design using the so-called ‘molecularly imprinted polymers’ is highly topical. This, which when combined with fluorescent polymers as indicator materials, is able to challenge the use of mass spectroscopy [46] for convenience and above all cost. A chemical sensor of this type – using the molecularly imprinted polymer approach, works using a polymer matrix to create complementary recognition sites for a target molecule, deemed the ‘template’ through polymerization. The sites are complementary to the structure of the template, post-polymerization, and are selective to the template and allow its rebinding *in-situ* [23]. Such sensors can be inexpensive to produce in volume and are disposable, avoiding cross-contamination issues.

The detection of codeine by this method shows real potential for wider use and this work builds on the successful approach taken in this laboratory [23]. In that work, this method was originally designed with cocaine as the template molecule, but the approach has been adapted to sense a similar, and more widely used molecule, codeine. The successful detection method from the previous work, the use of a changing fluorophore response, can therefore be applied to codeine monitoring and thus used to assess its concentration in solution. Given its successful use in the previous work the same fluorophore, acrylamidofluorescein (AAF) has been used, as this binds to amine groups that are the basis of many drugs, including codeine, as well as a cross-linker to further stabilize the complex.

2. Method

The method in this study involves coating an optical fibre, first with an adhesion layer and followed by the deposition of an MIP, that responds to the presence of codeine in solution, in order to create a codeine sensor. Integrated in the MIP complex is a fluorophore, that when excited with light of a certain wavelength re-emits it at a different wavelength when codeine binds to the MIP. The sensor is then tested in different concentrations of codeine, other drugs, and repeatability tests to assess the sensor’s lifetime, for its suitability as a disposable or reusable sensor.

2.1. Materials

All chemicals used were of analytical grade and purchased from Sigma-Aldrich. They were used without any further purification, except for ethylene glycol dimethacrylate (EGDMA) which was previously prepared and distilled. The fluorophore used, acrylamidofluorescein (AAF) was prepared using fluoresceinamine, documented previously in the literature [23,47]. Concentrated sulphuric acid and hydrogen peroxide were purchased from Sigma Aldrich Ltd, azobisisobutyronitrile (AIBN) was purchased from Glentham Life Sciences - all other solvents were of HPLC grade from Fischer Scientific.

The optical fibre that forms the basis of the sensor is a 1000 µm multimode silica core (0.37 numerical aperture, high OH) was purchased from ThorLabs.

2.2. Preparation of Optical Fibres

A similar approach to the preparation of the compounds used and the fabrication of the sensor probes was taken [23] using a molecularly imprinted polymer approach: a fluorescence-based optical fibre was made using cocaine as the template molecule, in which the MIP was selective to cocaine. Similarly, illustrated schematically in Figure 1 is the approach for this study: an optical fibre is coated with an MIP, that is imprinted with codeine, and then is washed to remove the codeine, and reveal gaps within the polymer for codeine to rebind.

One end of the 8 cm 1000 μm optical fibre were polished with films with decreased grit – 30 μm , 9 μm , 3 μm and 1 μm . During this step, the condition of the face of the optical fibre is checked under a light microscope. The end was cleaned using isopropanol (IPA). The end was connectorized using an SMA connector in order to connect the sensor to the light source.

One end of the approximately 80 mm long fibre is initially stripped, removing roughly 20 mm of the jacket and the cladding, before being immersed in Piranha solution (30/70 v/v 30% Hydrogen peroxide, concentrated sulphuric acid) for 60 minutes to remove any residual cladding material from the fibre surface.

It is then rinsed with distilled water to remove any remaining Piranha solution on the fibre, before drying it in an oven at 100°C for 30 minutes.

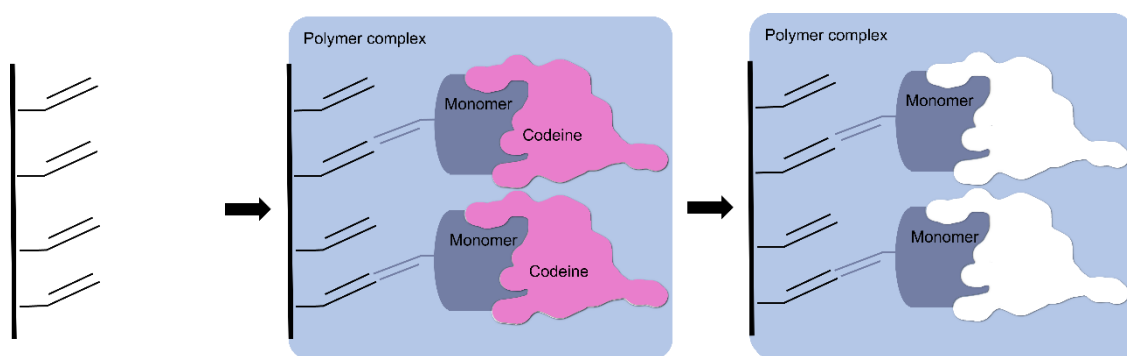


Figure 1 Simplified schematic of the molecularly imprinted polymer approach used.

2.3. Coating Process

The components used to make an MIP each have different roles: the template (in this case, codeine), to imprint the polymer complex; the monomer, to form the complexes with the template, which is what forms the gaps when codeine is washed out to then later rebind to; the cross-linker, to further stabilise the complexes; and a solvent, to dissolve the components during the process [48]. Moreover, the ratio of the components that make up the pre-polymerisation solution is a key factor to its success.

Prior to creating the MIP pre-polymerisation solution, the stripped section of the optical fibre underwent silanisation, for the polymer to adhere to the fibre surface. The stripped optical fibre section is immersed in the following solution: 10% 3-trimethoxysilylpropyl methacrylate (TMSPMA, silanisation agent) in dry ethanol, and then washed in ethanol. The fibre is then dried in the oven at 70 °C for 2 hours, in order to polymerise the acrylate groups.

Using the method illustrated in Figure 1, the pre-polymerisation mixture was prepared by sequentially combining the solutions – adding acrylamide (monomer) to acetonitrile (solvent), codeine (template), EGDMA (cross-linker), AAF (fluorophore) and finally, adding the mixture to AIBN (initiator) to create the final solution. The molar ratio of the pre-polymeric mixture components is 80:2:14:1 (acrylamide/codeine/EGDMA/AAF) respectively.

AIBN was added last as it initiates at room temperature, so the polymerization reaction started quickly after its addition. The solution was purged with argon gas for 10 minutes and then added to a capillary tube (~20 mm) that was sealed on one side using a syringe and needle. The prepared fibre is then inserted in the capillary tube slowly, ensuring the stripped fibre section was covered with the solution, and any air bubbles are removed by

tapping the tube. This was then sealed with PTFE tape before being placed in the oven for ~16 hours at 70 °C [23]. Despite the entire exposed surface of the fibre being polymerized, it is only the MIP on the distal end of the fibre that plays a role, not the MIP on the sides of the fibre – however, it improves the intensity of the overall response. Verification of polymerization having occurred was confirmed by sight of the colour deposit on the exposed fibre, a distinct yellow colour.

After polymerization, the capillary tube is carefully removed, and the fibre was removed from the oven and washed repeatedly using methanol-acetic acid (8:2 v/v), followed by washing with methanol only. The purpose of the washing process was to remove the template and create cavities for codeine to rebind *in-situ*, as well as any unreacted/unbound material. When not being used the sensor is stored in a cool dark place to maintain the integrity of the fluorophore.

In addition, for test purposes, a control device, designed to be a non-imprinted polymer (NIP)-based ‘dummy’ sensor was also created using the same method as above, without the addition of codeine. The aim of creating such a device was to ensure that the sensor actually responded to the presence of the codeine signal (and not due to some other artifact e.g. a temperature or pH change), as is discussed in the experimental work described below.



Figure 2 Photograph of the ‘dummy sensor’ (NIP) – a optical fibre coated with a material which is not imprinted and thus has no interaction with the codeine (indicated by the absence of the yellow colour), and the molecularly imprinted sensor (MIP) – giving the yellow colour.

Figure 2 shows both, an image of the ‘dummy sensor’ (NIP) and the sensor once it has been imprinted with the MIP – the yellow deposit at the distal end of the fibre shows where the coating has been added, this being indicative of the presence of the fluorophore. When codeine binds to the polymer complex, it binds to the fluorophore, AAF, producing the yellow colour. Conversely, despite AAF being present in the polymer complex used to produce the NIP, as it is not codeine-imprinted, codeine does not bind to AAF, and does not produce the yellow colour.

Despite the active region of the sensor being the distal end, due to the manual imprinting process, the stripped (sensor with the blue jacket and cladding removed) areas also have some MIP coating on them. This is not evenly applied across the surface – this is possibly due to the method itself, which was performed manually rather than mechanically (which may create a more even exposure to the MIP during the process). However, this excess of the coating material does not interfere with the operation of the sensor, in which the interaction occurs on the coating at the distal end.

2.4. Experimental Setup

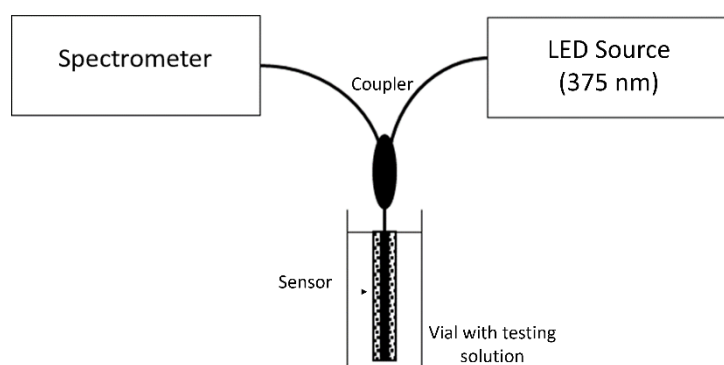


Figure 3 Experimental set-up comprising of a light source (LED), the sensor, and a detector (spectrometer).

Figure 3 depicts the experimental setup. Light from an LED source (375nm) is coupled through a 2 x 1 fibre coupler (QBIF600-UV-VIS, Ocean Optics) to the sensor probe; the other end of the coupler is connected to a spectrometer (Ocean Optics USB2000). The output, showing the response of the sensor, is shown on a monitor screen which is connected to the spectrometer. Fluorescence measurements of aqueous solutions were carried out using OOIBase 32 as the analysis software.

Using this set up, a number of sensor probes, which have been fabricated as described above, were used in a series of tests on the operation of the sensor, as discussed below. Those tests included exposing the sensors to known concentrations of the codeine solutions as well as their response to the other possible contaminant substances.

3. Results and Discussion

A number of tests on the sensor system developed and fabricated were planned and carried out to evaluate the performance of the device in terms of response time of the sensor probe, response to different concentrations of codeine, sensor selectivity towards other likely contaminant substances and reproducibility and durability of the sensor under normal use and after multiple cycles of washing. The results of those tests are reported in detail below. The thickness of the MIP and its effects on performance was not investigated in this work; the capillary tubes used during the deposition process in Section 2.2 are the same diameter, and therefore, somewhat regulated the thickness that adhered to the fibre surface, across the analyses.

3.1. Response Time of the Sensor

All the probes evaluated showed a typical response time of ~30 minutes to peak response for each concentration of codeine solution used, in the range 0 μM (control) to 1000 μM . This showed that the fabrication process was consistent and enabled achieving an approximately similar response time.

Furthermore, a comparison of the results carried out shows that this is typical of MIP-based systems for the response time to be in this region, and in this case, given the nature of the coating and, in comparison to other MIP analysis, this is a relatively short response time [23].

3.2. Sensor Response to Codeine

In order to determine the response of the probe to the different concentrations of codeine, and thus to create a calibration of its performance, a series of measurements was made by immersing the sensor in codeine solutions of concentrations over the range from 0 μM to 1000 μM . In the course of this experiment the sensor was kept in the same position (and thus with the same exposure to the solution) to achieve consistency of the results.

The experiments undertaken were carried out by preparing a series of codeine stock solutions of different concentrations, these being 0, 25, 50, 100, 250, 500 and 1000 μM , which were then added to the probe in the test environment, illustrated in Figure 3. These were measured into a vial of a 9:1 (v/v) solution of distilled water and acetonitrile. The principle of the probe is that as the concentration of codeine trapped by the MIP complex increases, the intensity of the fluorescent response increases, as more codeine is being bound to more AAF in the binding sites. The response of the probe to these different concentrations is shown in Figure 4. The control solution was made up using the same solution as the different concentrations, but without the addition of codeine – so effectively is 0 μM codeine. The response seen in Figure 4 reflects the response of AAF to the solution, giving the 'baseline response' – although AAF is not being bound to, there is a minimal level of fluorescence that is apparent due to the presence of AAF. The results show a consistent performance with a strong peak, as expected, at a wavelength of ~517 nm (the fluorescent wavelength of AAF when excited at 375 nm), and this seen to be increasing with concentration.

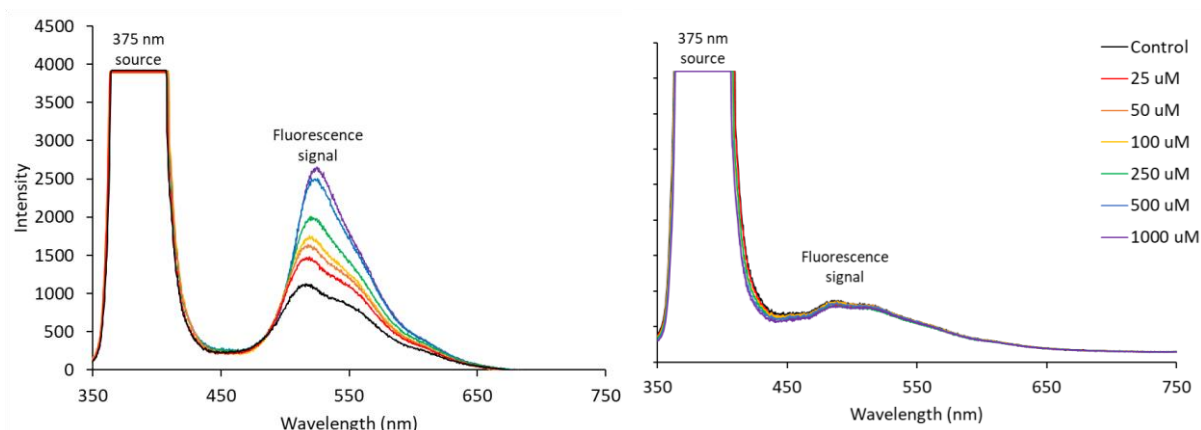


Figure 4 Response of MIP (left) and NIP (right) sensor to different concentrations of codeine.

After each set of measurements was completed, the sensor was washed with 8:2 (v/v) methanol and acetic acid. In order to validate that the sensor was truly responding to codeine (and not some other property of the solution), the response of the NIP-based 'dummy' probe was also evaluated in the same way as the actual probe to the change in the codeine concentration over the same range from the control (0 μM codeine) to 1000 μM . The results of this experiment are also shown in Figure 4. It is clear from Figure 4, that this 'dummy' probe did not give any response to codeine, indicating that the NIP was not interacting with the solution. This is a positive message for the success of the actual probe design – the result is what would be expected from an NIP response, as the matrix does not contain the template and therefore, is not specific to its structure. It is also expected to give the same negative response to other similar structures which have been identified as potentially interfering due to their similarity to codeine, as the NIP has not been created to be complementary to their structure either, discussed in Section 3.4.

3.3. Sensor Calibration

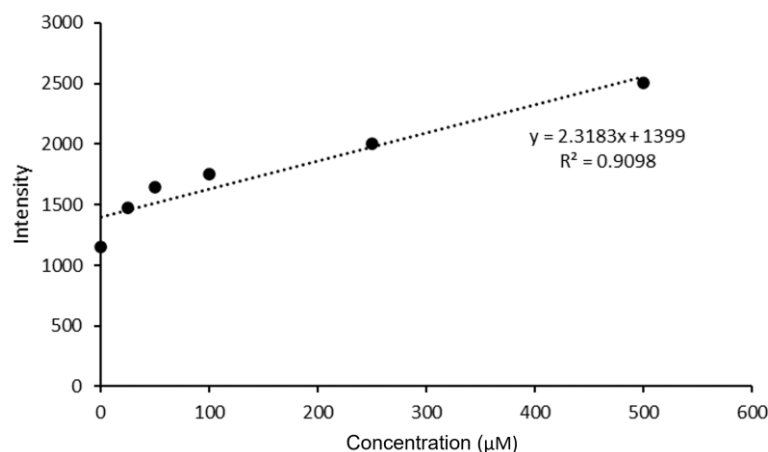


Figure 5 Calibration curve of sensor response (fluorescence intensity vs concentration of codeine)

The calibration curve in Figure 5 depicts the sensor response, i.e. the fluorescence intensity against the concentration of codeine, which can be approximated to a linear relationship for concentrations up to 500 μM . Beyond that the sensor response begins to saturate (section 3.5).

The sensitivity achieved is 2.3 counts per micromole (for an integration time of 50 ms of the spectrometer). The base level of fluorescence at zero concentration originates in the fluorophore being excited by the incident light without codeine being bound to it (Section 3.2).

Future investigations will focus on the limit of detection (concentrations below 25 μM). Lower concentrations were not tested here because the focus was on establishing a general relationship between the fluorescence intensity and codeine.

3.4. Cross-Sensitivity and Selectivity towards other substances

As noted above, codeine is a member of the opioid family, and therefore there are other substances that are frequently encountered when codeine is used in a range of situations that have similar shapes or functional groups that could bind to the MIP, in the place of codeine. This is particularly important as in medicinal applications, codeine is usually used in addition to other drugs, in order to amplify their effects. Thus, given the likelihood of codeine being found with other illicit substances, the probe was evaluated in its response to a range of common substances often found with codeine – these being amphetamine sulphate, ecgonine methyl ester, ketamine and buprenorphine hydrochlorate. The responses to these substances were evaluated in a standard way [23], using a 500 μM concentration of the substance under consideration in a water and acetonitrile (9:1, v/v) solution.

As can be seen from Figure 6, the response of the probe was as it was designed to be – it was highly selective to codeine but given the nature of the molecules used and their similarity to the codeine molecule, it also has a small, and varying, response to the other molecules. Figure 6 shows this in a diagrammatic form, with a copy of the molecular structure of the interfering molecule and the response with respect to a normalized figure of 100 for codeine.

This highly satisfactory result which demonstrates the successful selectivity of the sensor to codeine. The response from cocaine is not surprising, given the chemical similarity, but significantly lower. The response to all these other compounds can be explained by the non-selective binding of the other compounds – each is very similar in structure or due to similar functional groups and thus will give rise to some degree of binding.

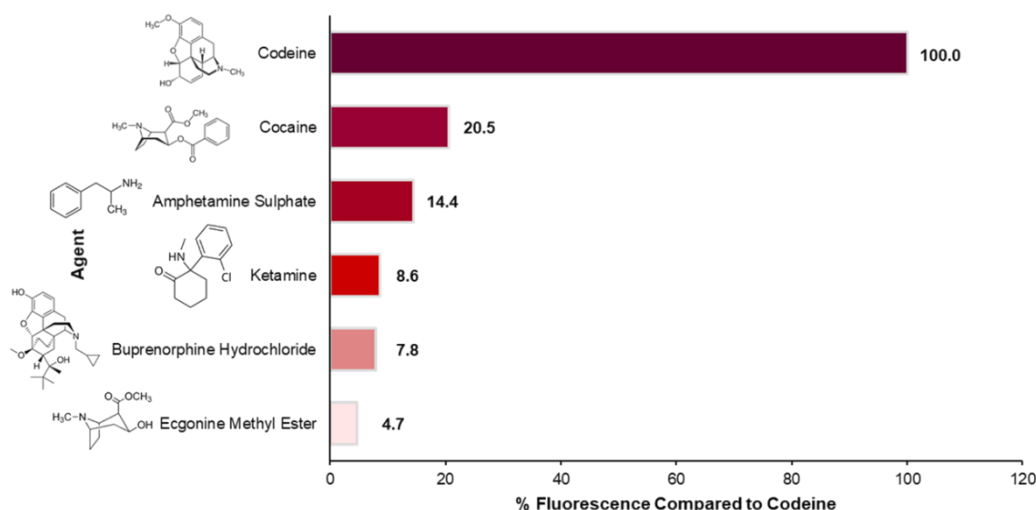


Figure 6 Comparison of the fluorescence response of the probe for a range of other substances, when analysing 500 μM of each compound relative to codeine, taken after 1 wash (relative to Codeine = 100%)

The response of the 'dummy probe' (Figure 7) to the contaminant species was also evaluated and as expected, essentially a 'zero response' was seen, in the region around the peak wavelength of ~ 500 nm, indicating that the probe was not active. This is the expected response as the NIP is non-imprinted with codeine or any of the contaminant species, so should not respond to their presence.

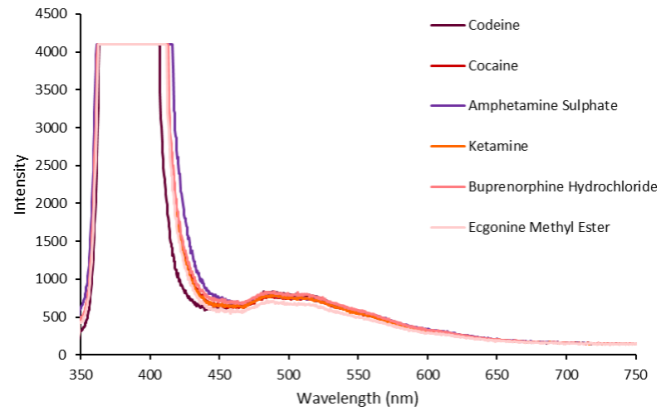


Figure 7 Response of NIP-based sensor with different contaminants.

3.5. Repeatability of the sensor response

In order to assess the lifetime of the developed sensor, it was repeatedly tested and washed (Section 2.3) until no measurable response was observed. Figure 8 shows the effect of repeated washing with Figure 8(a) showing the actual sensor response to codeine after an increasing number of washes and Figure 8(b) highlighting the decay rate of the sensor response.

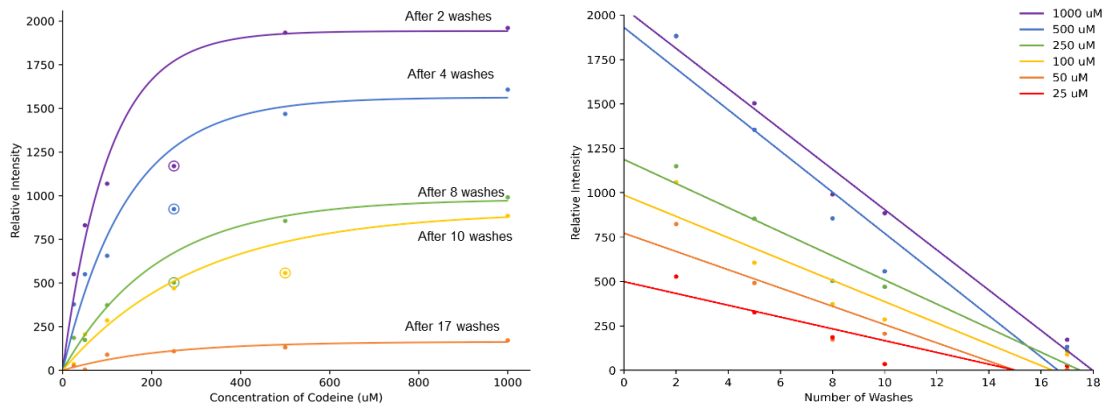


Figure 8 Sensor performance versus number of washes. (a) Relative fluorescence intensity versus codeine concentration for different washing cycles. (b) Relative fluorescence intensity versus number of washes for different codeine concentrations.

It is clear from Figure 8(a) that as the number of washes was increased, the sensor response to codeine decreased. Figure 8(b) suggests that with each wash the sensor response drops linearly until, after 10 to 17 washes, the response is minimal (depending on the codeine concentration).

When analysing the relative intensity of the sensor response compared to the concentration of codeine in Figure 8(a), it is evident that it follows an exponential relationship regardless of the number of washes, which satisfies the definition of fluorescence intensity in equation 1 [51]:

$$I_f = kI_o\phi[1 - (10^{-\epsilon bc})]$$

Eq. 1

where I_f is the fluorescence intensity, k the proportionality constant given to instrument, I_o the incident light intensity, ϕ the fluorescence quantum yield, ϵ the molar absorptivity of the analyte, b the path length, and c the concentration of the analyte, in this case codeine.

When substituting the constant terms in equation 1, i.e. " $k \cdot I_o \cdot \Phi$ " and " $\epsilon \cdot b$ " for " α " and " β " respectively, then the curve fitting model used in Figure 8(a) can be expressed as [52]:

$$I_f = \alpha \left(1 - \left(10^{\left(\frac{c}{\beta} \right)} \right) \right) \quad \text{Eq. 2}$$

As part of the imprinting process, the polymer is imprinted with a number of cavities as a result of the concentration of codeine (0.06 mM) in the pre-polymerisation solution – this means that there is a concentration at which all the cavities will be filled. This results in a plateau for each trace in Figure 8(a).

With respect to the overall decrease in fluorescence intensity with the number of washes, one potential reason could be the use of an incompatible washing method, that damaged or disrupted the fluorophore in the matrix, leading to it leeching out after each wash. This, however, is unlikely as a similar method to that used here was reported in literature [23,49] but excluded an investigation of the number of washes. Other washing methods reported have seen the use of a water, ethanol and a phosphate buffer solution [35,50]. However, the molecules used in these studies have different structures to codeine. The result here is comparable to previously reported degradation studies - one where the effective probe lifetime was approximately 20 washes [49]. It is worth noting that the former method does not use a fluorophore, which may be the reason for the difference in sensor lifetime. As expected, the best response is the initial response from the sensor shown in Figure 4, after 2 washes. As the number of washes increases, the fluorescence decreases, and it becomes more challenging to observe a positive response from the spectrometer.

There are other factors that could influence the decreasing intensity with washes such as time and the solubility of the fluorescein in water. However, it has been confirmed in the literature that good stability over time remains - one study conducted tested the response from a sensor after 24 hours and after one month [23], and there was no significant difference observed over that period. As this study repeated this method, it was not necessary to conduct this test again.

As noted above, sensor degradation due to repeated washing can be overcome if the sensor is used as a disposable device. The fibre optic approach lends itself well to this (as optical fibres are inexpensive) and fibres can be coated in a volume production of the sensors in the same way. The probes can then be used with the same type of spectrometer-based interrogation system and replaced as needed. However, if needed, a probe clearly can be recalibrated for use more than once.

3.6. Impact of the MIP imprinting ratio on the sensor response

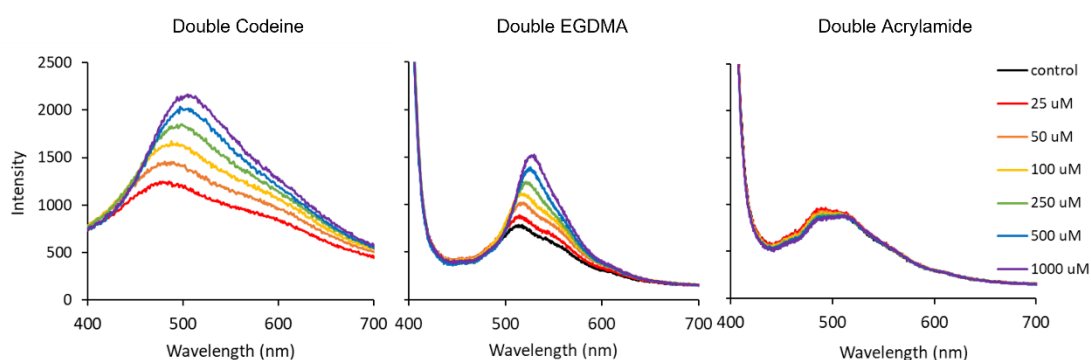


Figure 9 Impact of the MIP imprinting ratio on the sensor response: doubling the concentration of codeine, EGDMA and acrylamide (left to right) respectively.

Figure 9 shows the situation where the probe is imprinted with double the concentration of different components at the imprinting stage. When comparing Figure 9 to Figure 4, doubling the concentration of acrylamide does not present the same response with increasing concentrations – there is no change in the response. This is because an excess of monomer will increase non-specific binding between molecules and causes a self-aggregation of monomers [48], lowering the overall selectivity of the MIP and the availability of the binding sites within it, and thus leads to a low response. In fact, the response produced when doubling the concentration of acrylamide is more similar to that of the NIP (Figures 4 and 7), which is a negative response.

The same would be applicable with a deficit of monomer – there are not enough binding sites created, leading to an NIP, as the MIP is not selective to codeine/template.

Figure 9 also shows the response when doubling the initial imprinting concentration of EGDMA – this is the cross-linker which helps maintain the structural integrity of the polymer itself. In comparison with Figure 4, increasing the concentration of EGDMA lowers the MIP response (~2500 max intensity in Figure 4 and ~1500 max in Figure 9) – it is likely that as a cross-linker, this had similar effects to an excess of monomer. However, it is also likely it's structurally stronger, which would possibly affect the retention of the template in washing stages and improve selectivity.

Finally, increasing the concentration of codeine in the pre-polymerisation solution broadens the peak – in Figure 4, the peak expands from ~500 - ~600nm, compared to ~400nm – ~700nm in Figure 10. By doubling the imprinting concentration, there are more sites for codeine to bind, but Figure 9 only tests up to 1000 μ M codeine; it could be non-specific binding due to the increased number of sites that are responding to the presence of codeine causing the fluorescence peak to widen.

The results shown reinforce the importance of MIP technology and that an optimal ratio needs to be achieved to get the maximum response from it – some work reported in the literature has achieved this using computational calculations to predict this [22,53] and thus lower the need for initial experimentation. However, these computational predictions were not used in this paper as the results shown are preliminary results.

4. Conclusions

In this study, the imprinting of codeine into a polymer matrix on an optical fibre has been used to develop a stable, relatively rapid response sensor probe which has been proven to be very selective to codeine. The design of the probe around a simple coating on an optical fibre makes it both easy and inexpensive to produce and to use in both laboratory and conveniently, in-the-field applications (as the spectral read-out can be battery powered, is light weight and easily connected to a PC).

The research considered the use of the probe, either as a disposable or reusable (i.e. washed) probe. If the probe is to be re-used, then this is possible through the recording of the characteristic change of the performance of the probe with repeated washings to give the longest useable lifetime of the probe. However, if the probe is produced in volume, it should be sufficiently inexpensive to be disposable, and thus these issues do not arise.

This work does, however, show the value of the use of molecularly imprinted polymer (MIP) technology with optical fibres, to create inexpensive, easy-to-reproduce probes which work well in terms of their selectivity and sensitivity and therefore have wide applicability for a number of applications – reinforcing previous investigations in the literature. Given the success of the above, further work is planned on the optimization of the imprinting ratio, which has not yet been extensively investigated. Creating such an optimized ratio could yield a more stable structure of the polymer complex which would provide the most favourable conditions for trapping the template, as well as possibly maintaining the integrity of the gaps, post-washing and providing a probe which has a longer, yet durable lifetime. Work in this direction is continuing, such as assessments of interferents such as paracetamol and other white powders. One avenue of interest to build on this investigation, would include investigating the thickness of the MIP and its effect on the performance, cross-referencing this against the thickness of the NIP, and establishing a limit of detection, amongst other avenues.

Acknowledgements

This work was funded via the Industrial PhD Partnership scheme part of the Future Aviation Security Solutions (FASS) programme - a joint Department for Transport and Home Office initiative - with support from Smiths Detection-Watford Limited. The authors would like to thank the Worshipful Company of Scientific Instrument Makers and the Worshipful Company of Tin Plate Workers alias Wire Workers for their support of this project.

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