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Development of a novel flexible polymer-based biosensor platform for the thermal detection of noradrenaline in aqueous solutions

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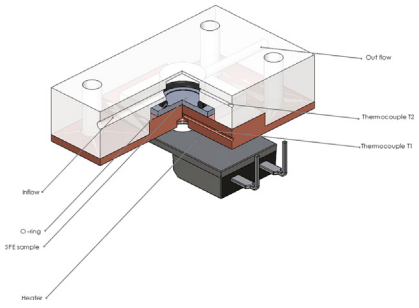
HIGHLIGHTS

- Preparation and optimization of MIPs for detection of noradrenaline.
- Screen-printing MIPs onto different support surfaces (polyester, PVC and paper).
- Thermal detection noradrenaline with HTM and TWTA.
- Development paper-based MIP sensing platform, which is sustainable and flexible.

GRAPHICAL ABSTRACT



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ABSTRACT

Molecularly Imprinted Polymers (MIPs) are synthesized for the neurotransmitter noradrenaline with the optimal composition and binding conditions being determined *via* optical batch rebinding experiments. Next, the obtained MIP polymer particles are mixed within screen-printed inks to produce mass-producible bulk modified MIPs screen-printed electrodes (MIP-SPEs). In this contribution, the supporting surface which the MIP-SPEs are screen-printed upon are explored to deviate from conventional polyester, to polyvinylchloride, tracing paper and household-printing paper. The performance of the MIP-SPEs are measured using the Heat-Transfer Method (HTM), a straightforward and low-cost detection technique based on thermal resistance. At first, the noise on the signal is minimized by adjusting the settings of the temperature feedback loop. Second, the response of the MIP-SPEs to noradrenaline is measured and compared for the different substrate materials. Sensors printed onto paper are considered in further experiments as their response to noradrenaline is the highest and advantageous material properties, including sustainability and flexibility of the material. Subsequently, dose-response curves are determined by simultaneously measuring HTM and Thermal Wave Transport Analysis (TWTA). The latter is a new thermal detection method that relies on the use of thermal waves and has the advantage of a short measurement time (2 min). With these thermal methods, it is possible to specifically detect noradrenaline in aqueous solutions and quantify it at relevant concentrations. In summary, by combining synthetic receptors with thermal measurement techniques it is possible to develop a portable sensor platform that is capable of low-cost and straightforward detection of biomolecules. Through exploring

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novel SPE substrates, a system is designed that is flexible and holds potential for the use in commercial biomedical devices and complex sensor architectures.

1. Introduction

Noradrenaline is a catechol neurotransmitter that has a crucial role in the function of the renal, hormonal, cardiovascular and central nervous system [1,2]. It is associated with the fight-or-flight response, as the release of noradrenaline is significantly increased in stressful and dangerous situations, which mobilizes the brain and body for action [3,4]. Low levels of the neurotransmitter are associated with depression and postural hypotension [5], while high levels indicate stress, thyroid hormone deficiency [6] and congestive heart failure [7]. Noradrenaline is an active component of a variety of drugs, ranging from treatment of hypertension to organic heart disease, diabetes [8], and anxiety [9]. In recent years, noradrenaline has attracted attention as a tumour biomarker [10]. Urine and plasma tests are used to diagnose pheochromocytoma, an endocrine tumour of the adrenal glands that secretes high amount of catechol amines [11,12]. If undetected, these tumours present a high risk of mortality [13] since fluctuating levels of noradrenaline can result in organ damage from dangerously high blood pressure, which leads to heart attacks and kidney failure [14]. Recent reports suggest that stress hormones such as noradrenaline are involved in the initiation and progression of tumours, which occurs through the overexpression of enzymes [15,16]. Work by Choi et al. [17] have demonstrated that by stimulating cells with noradrenaline, metastasis of ovarian cancer cells was enhanced. Due to its relevance as a biomarker, various analytical techniques have been employed to determine noradrenaline concentrations in biological samples. The most common methods include chromatographic [18,19] and electrochemical biosensor techniques [20–22]. Electrochemical methods are inexpensive and fast compared to chromatographic measurements, but applications are limited due to poor selectivity and interference of other metabolites present in biological samples. To enhance the selectivity, Molecularly Imprinted Polymers (MIPs) have been used [23]. MIPs, referred to as plastic antibodies, possess high affinity for their template molecules but have superior stability and are inexpensive compared to natural antibodies [24–26]. The imprinting process takes place by co-polymerizing functional and cross-linking monomers in the presence of a molecular template [27,28]. After removal of the template, cavities are formed that are complementary in shape, size and functional groups to the template molecule and are able to rebind it with high affinity and selectivity [29,30]. In certain areas commercial applications are available, and recently, MIPs were used for the first time as an active ingredient in a cosmetic product [31]. Examples of MIPs in literature designed for catecholamines, the class of molecules noradrenaline belongs to, are sparse and focus around chromatographic applications [32,33]. Huang et al. [34] developed a monolithic MIP for the chiral separation of (−)-noradrenaline from buffer solutions. To extract catecholamines from a biological matrix, respectively human plasma samples, magnetic-carbon nanotubes MIPs were prepared which were combined with ultra-fast liquid chromatography-tandem quadrupole mass spectrometry (UFLC-MS/MS) [35]. Electropolymerization has the advantages over preparation of monoliths that instead of particles an imprinted film is formed on the electrode, but the main drawback is that a conductive monomer is required [36]. Rosy et al. [23] synthesized an imprinted polymer film with o-aminophenol and evaluated noradrenaline binding by determining the increase in peak current. By implementing the MIP into the sensor platform, the selectivity was enhanced compared to traditional noradrenaline electrochemical sensors.

Electrochemical techniques offer fast and low-cost measurements, but are not compatible with every target molecule and there are limitations to the selectivity. The Heat-Transfer Method (HTM), is a promising and straightforward alternative that relies on thermal detection [37]. It was first discovered for the process of DNA melting; with the transition from well-defined double-stranded DNA to single-stranded DNA where the strands are random coils without a regular structure. As a result, the surface coverages increases by 150% and this leads to a significant increase in the electrical resistance due to the formation of an additional insulating layer on the surface [38]. The electrical resistance is linked to the thermal resistance and this additional insulating layer blocks the heat-flow in a certain direction, which corresponds to a measurable increase in the thermal resistance. This effect has been well-studied for various applications, such as detection of proteins with aptamers [39], screening of cancer cells [40] and studying of DNA mutations [38]. For sensors with MIPs as recognition element, binding of the templates to specific cavities in the porous polymer layer, leads to increase in the thermal and electrical resistance that is described by the "pore-blocking" model [41]. Advantages of this thermal method include that a low-cost home-made set up is used, which requires the use of only two thermometers and an adjustable heat source. In recent work, screen-printed electrodes (SPEs) were used to prepare a biosensing platform by the direct mixing of the MIP particles into the screen-printing ink, which results in mass producible MIP-SPEs [42]. As a first proof-of-concept, the binding of the neurotransmitter dopamine was studied by using HTM and Thermal Wave Transport Analysis (TWTA). The latter is a novel thermal method that relies on applying thermal waves rather than keeping the thermal resistance of samples fixed [43]. It is demonstrated that this improves the detection of dopamine by lowering the noise ratio on the signal and it has the additional benefit of shorter measurement time [42].

In this contribution, a MIP with a high specificity for noradrenaline is developed by evaluating the composition of various charged monomers. Next, MIP particles are mixed with screen-printing ink and screen-printed onto a variety of substrates; polyester, which was used in previous work [42], and an array of substrates that have not been used before in combination with MIPs namely, polyvinylchloride (PVC), tracing paper, and household printing-paper. The effect of the SPE substrate on thermal detection is studied by exposing the prepared MIP-SPEs to an aqueous solution with a 1 mM noradrenaline concentration. In consideration of all the substrates, the paper-based SPEs ensure a high stability and exhibit the highest analytical response (measured as a phase shift in the thermal signal) towards noradrenaline. Therefore, these MIP-SPEs are evaluated in further thermal measurements (HTM and TWTA) and dose-response curves are constructed to quantify the noradrenaline concentration in aqueous solutions.

The developed polymer-based platform is sustainable due to the use of paper and has potential for the use in pharmaceutical applications because of it its simplicity, low-cost, and portability of the set up [37]. The ability to adapt the MIP layer offers a great