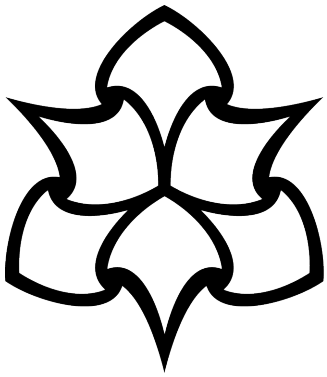

Reviewing the use of chitosan and polydopamine for electrochemical sensing

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Abstract

Biopolymers possess highly favourable properties for electro-chemical biosensing such as their inherent biocompatibility, inexpensive nature, and strong interfacial adhesion. In this mini-review, we will focus on chitosan and polydopamine, two of the most commonly used biopolymers, for electrochemical sensing applications. Chitosan is a polysaccharide that exhibits high chemical resistance, offers straightforward modification and cross-linking, and possesses antibacterial properties and mucoadhesion. Polydopamine has the benefit of universal adhesion, in addition to the ability to form self-assembled structures. We will demonstrate how the unique structural and electrochemical features of these biopolymers can be used in a range of electrochemical biosensing platforms.

Keywords

Biopolymer, Chitosan, Polydopamine, Biosensors, Electrochemistry, Electrochemical sensing.

Introduction

International Union of Pure and Applied Chemistry (IUPAC) defines biopolymers as macromolecules, including proteins, nucleic acids, and polysaccharides, that are formed by living organisms [1]. Generally, bio-polymers can be divided into three classes depending on their monomer units: polynucleotides; polypeptides; and polysaccharides [2]. Considering the exponential surge in plastic waste, it is expected that biopolymers, especially those available from waste material, will play an important role in future-proofing advanced materials including advanced electrochemical sensors [3]. The focus of this mini-review will be on chitosan and poly-dopamine (PDA), two of the most commonly used biopolymers, which promote sustainability as they are nontoxic and can be produced via 'green chemical' synthesis routes. The focus of this minireview will be on chitosan and PDA, two of the most commonly used biopolymers, which promote sustainability as they are non-toxic and can be produced via "green chemical" synthesis routes. However, there are significant barriers to implementation of these materials including costs, conductivity, and reproducibility, which is why they are not routinely used in electrochemical sensors. The review outlines challenges in the field as a result of the growing use of electrochemical sensors for in vitro and in vivo detection and highlights the foreseen next generation of hybrid biopolymer materials which have potential to overcome current shortcomings.

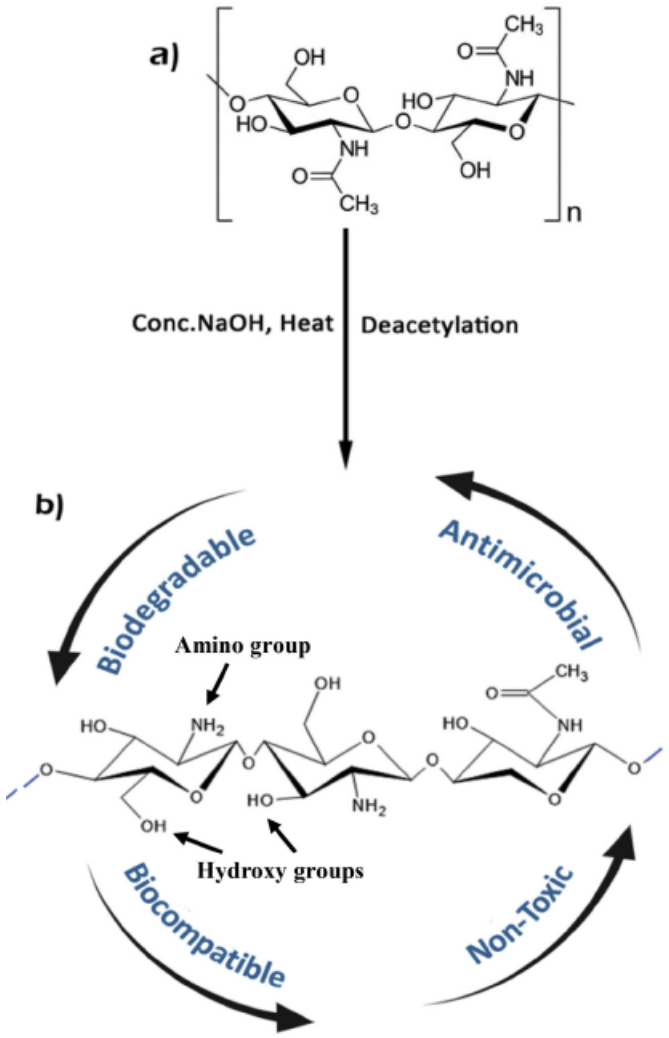
Chitosan

Chitosan is commercially produced from the biopolymer chitin because it is only naturally found in small quantities in some fungi. It is a partially, or to a significant extent, deacetylated derivative of chitin (Figure 1), which is the second most abundant polysaccharide in nature after cellulose and is found in cell walls of green algae, insect cuticles, and crustacean exoskeletons [4].

The number of monosaccharides in chitosan can vary quite significantly, leading to large variations in the degree of deacetylation, molecular weight, and pKa values of even commercial batches, which complicates reproducibility of the material. Chitosan has two reactive groups, a primary amine and hydroxy on the glycosidic residue, which can be used for side group attachment 5]. These groups are strongly pH-dependent, and therefore have excellent applications in drug delivery but can lead to complications with electrostatic repulsion under specific conditions [6]. Generally, chitosan is cross-linked to improve susceptibility to mechanical and physiochemical damage; these cross-linked materials may exhibit new properties, such as fluorescence while retaining their own critical characteristics [7].

Figure 1

Formation of chitosan: (partial) deacetylation of chitin (a) into chitosan (b) where the dashed lines represent continuation of the structure

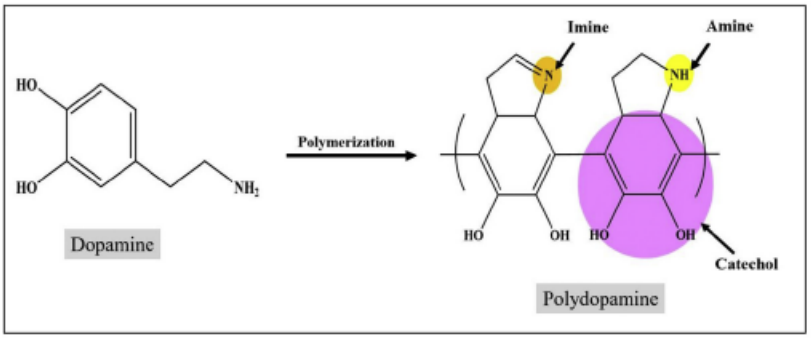


Polydopamine

PDA is a dark brown biopolymer produced by autoxidation of dopamine, which is also a synthetic analogue of naturally occurring melanin (a pigment) [8]. PDA's chemical structure is rich in functional groups such as catechol, amine, and imines [Figure 2]. The favourable adhesive properties of the compound are attributed to different chemical reactions and interaction mechanisms with the catechol group such as Michael type addition, Schiff base reactions, and hydrogen bonding [9]. Although the catechol group plays a key role in adhesive properties, the other functional groups make PDA a versatile material with applications in different areas such as sensing [10].

Figure 2

Polymerization reaction of dopamine. The arrows indicate functional groups on the polymer, such as the imine, amine, and catechol.



Sensing applications Chitosan-based sensors

Chitosan can be produced as three-dimensional structures, brushes, or thin films using various approaches including electrodeposition and drop-casting [11-13]. The material can have various functions in sensors such as serving as a matrix material, improving dispersion because of its hydrophilic nature, and guaranteeing selectivity by forming noncovalent bonds [14]. As a three-dimensional network, chitosan has a very large surface area, in addition to good structural and chemical stability, which makes it highly suitable for the impregnation of recognition elements. For example, a chitosan/polyaniline-gold nanocomposite was deposited onto tin oxide-coated glass plates for the detection of cholesterol using cholesterol oxidase enzymes [15]. This voltammetric sensor exhibited a linear range from 50 to 500 mg/dL, with a shelf-life of three weeks. An example of a chitosan/graphene-based sensor is shown in Figure 3, where detection of chromium VI was possible in a wide linear range (10^{-5} x 10^{-9} mol/L) using differential pulse voltammetry, which generally is the electrochemical sensing strategy with the highest specificity [16*]. There is also considerable interest in incorporating antibodies into chitosan because traditional matrices composed of inorganic nanomaterials are hydrophobic which can lead to low/heterogenous surface coverage.

Recently, research has focused on comixture nanomaterials by using chitosan's ability to interlink with other materials [17]. However, the use of biological elements such as antibodies and enzymes has the disadvantage of limited stability in extreme environments (e.g. high temperatures), and immobilization of recognition elements is not always straightforward. Molecularly imprinted polymers (MIPs), porous materials containing high-affinity binding sites to a specific target, present an interesting alternative. A comprehensive review of MIPs based on chitosan is provided in the study reported by Zouaoui et al. [18**]. The most promising approach to achieve a controlled structure of porous chitosan in MIP-based sensors is by electrodeposition. In short, electrodeposition can be achieved by immersing a working electrode into a chitosan solution (deposition solution) followed by application of the desired voltage (typically 1.5V) for a fixed amount of time [11]. At this potential, the amine group of chitosan becomes a cationic polyelectrolyte, and the positively charged molecule of the polymer is attracted toward the negatively charged cathode. Because the electrochemical performance of these films is hampered by chitosan's poor electrical conductivity, it is vital to include nanomaterials to improve electron transfer. These can be inorganic materials or conductive polymers because chitosan can form hybrids through conjugated p-bonds with polypyrrole and polyaniline [19]. Chitosan can also be applied as brushes, and layer-bylayer grafting techniques have been used to deposit chitosan onto metal alloys to make them suitable as implant materials [20]. PDA surface modification can be used in this process because it is used as a strong adhesive in various environments and improves the overall stability of the system [21].

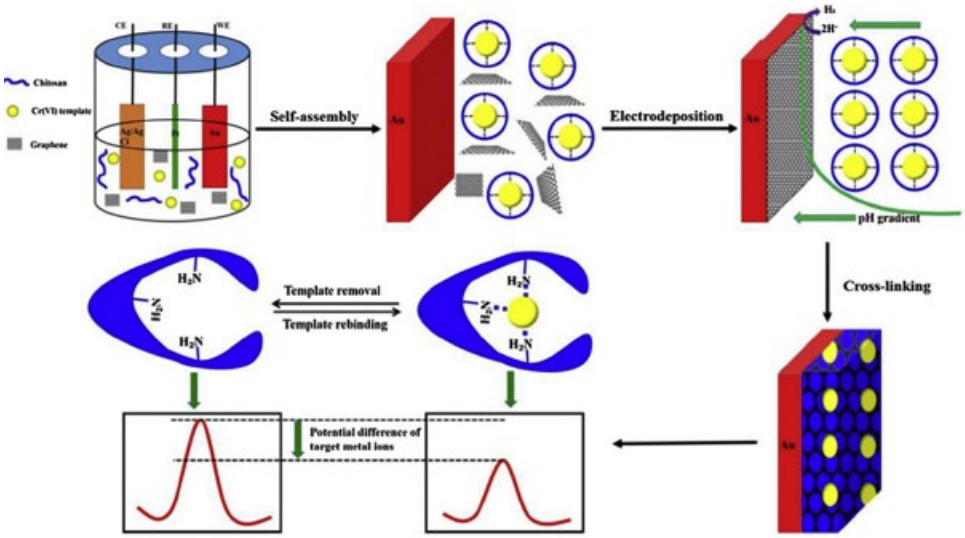


Figure 3
Electrodeposition of graphene/chitosan constructs onto electrodes in the presence of a Cr (VI) template. After washing the surface, binding sites are formed, and rebinding of the template leads to a distinct change in the DPV signal [16*]. Reprinted with permission from Elsevier. DPV, differential pulse voltammetry.

Wang et al. [12], developed a high-performance electrochemical sensor for hydroquinone and catechol by using the advantageous properties of multiwalled carbon nanotubes (surface area), PDA (conductivity), and chitosan (selective detection). These brushes can also be combined with biomimetic recognition elements such as aptamers. A rapid electrochemical sensor for Listeria monocytogenes was developed using chitosan-aptamer nanobrushes that could detect the microorganism of interest without preconcentration, even in the presence of other Gram-positive cells [22]. The high selectivity of brush borders in natural systems was the inspiration for this article; compared with traditional stimulus materials such as poly (N-isopropyl acrylamide) and ionic polymer-metal composites, chitosan is the most attractive for analysis of food samples owing to its low cost and biocompatibility [23]. However, challenges with this approach mainly stem from the fact that chitosan exhibits pH-dependent behavior, which impedes detection in real samples.

PDA-based sensors

PDAs' popularity for electrochemical sensing applications stems from their structure and functional groups, which lead to the formation of strong affinities with a plethora of solid surfaces, intrinsic chemical reactivity with nucleophiles, ability to chelate metal ions, and redox activity [24]. The thickness of PDA films deposited using alkaline oxygenated solutions can be controlled by varying the concentration of dopamine monomer, which can also affect the surface morphology of the film [25]. These systems must be carefully designed as many features of PDA formation and structure remain unknown, and the intrinsic chemical reactivity of the PDA toward nucleophiles is spontaneous [26**]. In addition, a well adhered, full coverage of PDA on an electrode surface is undesirable in many electrochemical applications owing to fouling of the electrode. The full mechanism of PDA formation remains unclear, with it expected to be a 2-electro 2 proton transfer process. However, there are a plethora of after oxidation reactions that can occur depending on the electrode surface that can lead to the formation of compounds that inhibit electron transfer. PDA nanospheres present an alternative to surface modification and can be formed through stirring in alkaline media [27]. This offers the ability to control PDA nanosphere size, use functional groups to form linkages or anchors to other structures through covalent bonding, and even form self-assembled monolayers on surfaces for sensing applications [28,29].

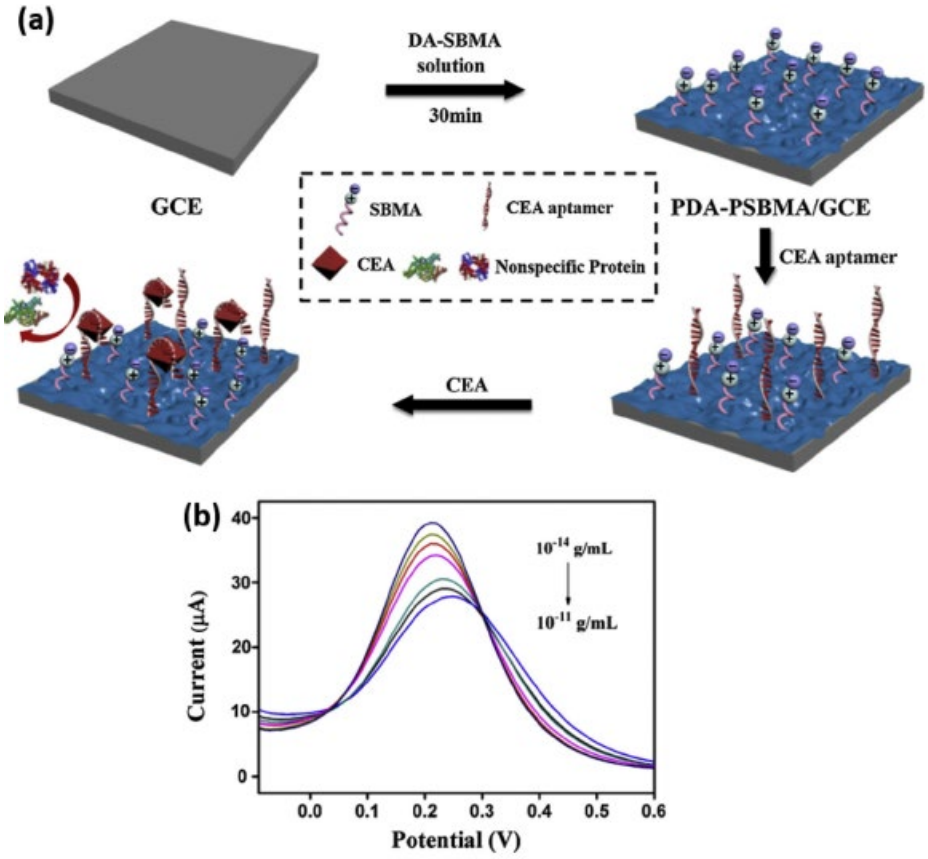


Figure 3
PDA-PSMBA sensor fabrication. (a) Illustration of the PDA-PSBMA-based sensor's fabrication. (b) DPV response to increasing concentrations of CEA. Modified with permission from Elsevier, see the study reported by Xu et al. [42*]. CEA, carcinoembryonic antigen; DPV, differential pulse voltammetry; PDA, polydopamine; PSBMA, poly(sulfobetaine methacrylate).

The ability to form a multifunctional surface can be used in conjunction with nanomaterials to enhance the electrochemical biosensing capabilities of different platforms [30]. Liu et al. [31] demonstrated this through the use of PDA-coated reduced graphene oxide as a base for the formation of an o-phenylenediamine MIP film for the detection of 2,4-dichlorophenol using differential pulse voltammetry. PDA can also be used as the MIP itself, the presence of catechol and amine functional groups and their ability to form strong noncovalent interactions with target molecules and proteins have given rise to the popularity of using dopamine as the functional monomer. Through spontaneous alkaline aqueous oxidation, these MIPs can be incorporated into biosensing platforms in various forms such as hollow MIPs and magnetic MIPs [32,33]. Alternatively, PDA MIPs can be formed through electropolymerization of the dopamine monomer [34,35].

One of the first examples by Liu et al. [36] used cyclic voltammetry in a deoxygenated solution of dopamine in the presence of their target nicotine, creating a compact, insulating film. Tretjakov et al. [37] used a surface linker to immobilize their target before polymerization. They designed PDA films of specific thicknesses via electrodeposition and compared their performance for the detection of immunoglobulin G, achieving the best imprinting effect with a film thickness of 17 nm. The formation of MIPs for large targets can be hindered by the formation of PDA as it is kinetically driven and has a saturation limit of less than 50 nm owing to dopamine depletion, although we note PDA layers can be deposited onto preexisting layers [26**]. Kanyong et al. [38] electropolymerized dopamine hydrochloride onto a screen-printed carbon electrode (SPCE) through cyclic voltammetry to form the PDA-SPCE. This modified electrode produced well-defined redox peaks when scanned in Britton Robinson buffer. Proof-of-concept application for the detection of biomolecules was achieved using guanine in which a 5-fold increase in anodic peak current was observed when using the PDA-SPCE.

Finally, PDA can also be incorporated with other polymers on electrode surfaces to produce electrochemical sensing platforms [39]. Salgado et al. [40] used electrochemical techniques to prepare poly (3,4-ethylenedioxythiophene) nanowires onto Pt surfaces modified with PDA. Research into the copolymerization of PDA for electrochemical sensor platforms has also been reported recently with polypyrrole to increase film conductivity [41]. This work used the functional groups of PDA to facilitate adhesion between a zwitterionic polymer with antifouling properties to aptamer recognition elements for selective detection. Another recent study by Xu et al. developed an electrochemical biosensor for the tumor biomarker carcinoembryonic antigen using copolymerized PDA and the zwitterionic polymer poly (sulfobetaine methacrylate). The polymers were deposited onto a glass carbon electrode and were able to detect the relevant target well within physiologically relevant range as illustrated in Figure 4.

Future work and outlook

The use of chitosan and PDA for biomedical applications is relatively new; chitosan was approved for medical use in the United States in 2003, and the first works on PDA for multifunctional coatings and its polymerization mechanism were published in 2007 [43*]. This means commercial products are limited, with no applications in electrochemical sensing to date. It is expected that a trend will emerge of increased use of these materials especially in hybrid form because they can bring unique properties (e.g. adhesion and biocompatibility) to sensors. Both materials will have challenges in terms of costs, and large-scale production is limited; therefore, incentives should be considered to promote the use of 'green' production of biopolymers to prevent further increase of plastic waste. However, the use of these materials in the future is prone to different challenges.

For chitosan, the main challenges are improving batch-to- batch variation to have access to medium to largescale industrial batches with reproducible properties and incorporation of materials to increase conductivity. As conductivity will remain an inherent problem, this biopolymer might find more applications in platforms using nonelectrochemical read-out techniques(thermal, optical, gravimetric detection, and so on). Alternatively, chitosan can be used as matrix material to improve the surface area or added to improve overall biocompatibility, although it has to be noted that not all structures of chitosan are biocompatible. Chitosan-based electrochemical sensors can also be explored for the detection of specific cells and combined with targeted drug delivery. PDA is generally conductive; however, when coated onto electrodes, the conductivity of the electrode decreases, especially on microelectrodes that are typically required for in-vivo detection [44]. Care must be taken when developing electrochemical sensors using PDA owing to its inherent spontaneous chemical reactivity toward nucleophiles and possible interference from redox peaks depending on the layer thickness and morphology [45]. However, this reactivity is also its main benefit because it facilitates adhesion between different structures. The biocompatibility of both materials in microstructures can be questioned. However, PDA and chitosan coatings on different nanoparticles generally ensure good physicochemical properties and biocompatibility, thus facilitating in-vivo biosensing, cell imaging, and detection of various diseases. In light of the abovementioned advantages of chitosan and PDA, there is great potential for their further use in portable electrochemical devices if costs are reduced, and large-scale commercial production is achieved in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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