Received: 16 August 2021 Revised: 13 December 2021 Accepted article published: 18 December 2021 Published online in Wiley Online Library: 6 January 2022

(wileyonlinelibrary.com) DOI 10.1002/pi.6358

Polydopamine: a bioinspired adhesive and surface modification platform

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Abstract

Polydopamine is a biopolymer that is gaining widespread interest as a surface modifying agent due to its simplicity of preparation, versatility and biocompatibility. The material was first described during electrochemical studies of dopamine, but recognition of its structural similarity to key components of mussel adhesive proteins, which are able to adhere to a diverse range of surfaces in water, has led to its incorporation into a host of composite materials. This review will examine some of the emerging investigations into the complex mechanism of polydopamine formation, proposed structures and potential applications, with an emphasis on its use in biomedicine.

Keywords: polydopamine; surface coatings; biomaterials; medical applications

INTRODUCTION

Polydopamine (PDA) has recently been described as one of the most powerful tools available for modification of surfaces due to its simplicity, versatility and biocompatibility.[1] PDA can act as an adhesive that is capable of coating a wide variety of substrates. The monomer can be easily derivatized, and the surface modification of PDA materials after polymerization is also facile.[1,2] The polymer was first observed during electrochemical studies of catecholamines, where electrodes became fouled during oxidation.[3] Later, studies of mussel adhesive proteins, which were found to be rich in the amino acids 3,4-dihydroxy-L-phenylalanine (DOPA) and hydroxyproline.[4] This insight led to the development of the chemical oxidation of dopamine in solution to create precipitates and films of PDA.[2]

Mussels are able to adhere to virtually any surface, ranging from metals to fluoropolymers, and in both dry and aqueous environments.[2] These adhesive properties come from the mytilus foot proteins Mfp-3 and Mfp-5.[5] The amino acid compositions of the proteins have been identified as the components that make these proteins so 'sticky'. There are two key features of the proteins that are connected to the interfacial adhesive properties (Fig. 1). One is the high catechol content due to the presence of DOPA residues, which binds tightly to ions and inorganic surfaces. The second is the high amine content which comes from the presence of lysine and histidine residues.[2] The combination and intimate association of these two chemical features are the origin of the adhesivity of this material. These features are also found in dopamine, which led to the proposal that its polymer was a 'simple' structural mimic of Mfp-3 and Mfp-5.[2,5]

PDA FORMATION AND STRUCTURE

PDA is a complex, heterogeneous polymer that is formed through oxidation of the dopamine monomer.[1,6] While the basic polymerization process is straightforward, the actual mechanism behind it is probably quite complex because of the variety of simultaneous reactions occurring. Multiple pathways for PDA formation have been proposed, including the aggregation of monomers through crosslinking by non-covalent forces,[7] the formation of PDA through a combination of non-covalent and covalent forces[8] and competing pathways of formation that are dependent on reaction conditions, such as concentration and type of buffer.[9]

It is widely accepted that the initial driving force for the polymerization of dopamine to PDA is the oxidation due to dissolved oxygen at alkaline pH (Fig. 2).[6] This may produce radicals that self-couple, but also a dopamine-quinone, which is then believed to undergo a nucleophilic intramolecular cyclization reaction leading to the formation of 5,6-dihydroxyindole (DHI).[10] Proposed pathways after DHI are both abundant and speculative, but it is likely that a variety of oligomeric species is formed that contain pyrrole rings as well as open-chain dopamines. Support for this comes from the hydrogen-peroxide-induced degradation of PDA.[11] It is also likely that the many available recipes for PDA formation favor certain pathways and structural components over others. Even the presence of a deposition substrate, as opposed to suspension polymerization, may result in materials of somewhat different composition.[12]

Copolymerization of DHI and polycatechols leads to a material with a variety of functional groups that are able to react with nearly any material through hydrogen bonding, π–π interactions, π–cation interactions, radical coupling, metal coordination and others. In addition to strong adhesive properties, a defining feature of PDA is the ability to modify substrate surface behavior through chemical derivatization of deposited thin films. There are a few approaches to this functional versatility. One route is through post-modification, where additional functional groups

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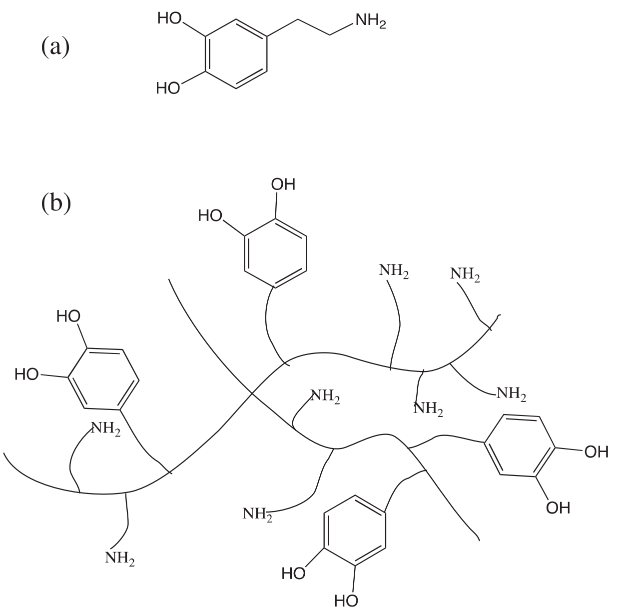

Figure 1. (A) Dopamine structure, which includes a catechol and amine group. (B) Simplified molecular representation of the catechol and amine groups of mussel mytilus foot proteins that contribute to adhesion.

(i.e. alkyl, carboxyl, amino, alkylthiol) are added to a deposited PDA coating or nanoparticle. Another route is through copolymerization of dopamine and other monomer units.[12,13] There can also be a combination of these two, where copolymerized surfaces are post-modified.[14] There are a wide variety of molecules that can be immobilized onto PDA particles or coatings, including thiol- and amine-terminated polymers, biomolecules such as collagen, trypsin, Arg-Gly-Asp (RGD) peptides, antifreeze proteins and others.[2] The use of PDA as interface components in composite materials is a particularly exciting area of current interest, including for biomedical applications.[15]

SYNTHESIS OF PDA MATERIALS

There are several methods for PDA thin film and nanomaterial preparation and, through specific deposition processes, the film thickness and homogeneity can be controlled.[12,16] PDA can be formed through a solution oxidation method, enzymatic oxidation processes or by electropolymerization. The solution oxidation method is the most common approach. When dopamine (usually dopamine hydrochloride) is added to an alkaline solution (pH 7.5) it will self-polymerize upon oxidation by O_2.[17] Autooxidation has some drawbacks when coating biological, alkali-sensitive or other surfaces that are not compatible with the reaction conditions. In addition, the reaction typically produces large quantities of insoluble precipitate, leading to rough surfaces and difficulty in controlling film thickness.[18] Enzymatic oxidation will also produce PDA, and Kim *et al*. have demonstrated well-controlled and material-efficient thin film formation from multiple catecholamines.[19] Tan *et al*. utilized a laccase-catalyzed polymerization in order to develop PDA bio-nanocomposite cast thin films for biosensing and biofuel cell applications.[20]

The electropolymerization of PDA allows for the polymer to be directly deposited onto the surface of a conducting substrate. This is typically done utilizing cyclic voltammetry with a specific potential range and potential sweep rate.[17,21] For example, Kim *et al*. fabricated polypyrrole (PPy) and PDA films using cyclic voltammetry with a range from −0.7 to 0.8 V at a scan rate of 0.02 V s^{-1}.[21]

With these different methods there are a variety of reaction parameters that can be manipulated. These include the polymerization method, solvent, pH, reactant concentration, dopamine concentration, UV irradiation and reaction time.[1] For example, Jiang *et al*. investigated the surface characteristics of PDA deposited onto a hydrophobic polymer. They examined the effects of deposition temperature on surface energy and found that higher reaction temperatures lowered the surface energy.[22] In another study, Farnard *et al*. looked at PDA nanoparticles as a tool for removing copper ions from an aqueous solution. The reaction pH was varied to determine effects on copper absorption. They found that the absorption of copper increased from pH 2 to pH 5 but then quickly fell when the pH was higher than 5.[23]

Perhaps the most active area of PDA research currently is the use of PDA in composite materials, where its adhesive properties can improve the physical stability of the composite. For example, the electrically conducting polymer PPy can be electrochemically grown on electrode surfaces and has found broad use for improved performance in a variety of applications. A limitation to this material is its poor adhesion to common electrode materials. Kim *et al*. showed that simultaneous oxidative polymerization of pyrrole and dopamine led to a conductive surface with much improved adhesion to an indium tin oxide (ITO) electrode as well as decreased impedance compared to the unmodified electrode (Fig. 3).[21] Similarly, we have investigated electrochemically grown PDA/PPy composites on titanium as a platform for supporting cellular growth.[24] Improvements in PPy adhesion, as evidenced by simple tape tests, were observed.

APPLICATIONS

PDA-based materials have found their way into many applications. In a comprehensive 2014 review, Liu, Ai and Lu discussed the use of PDA in the synthesis of hybrid materials, energy devices, biomedical sciences, water treatment and sensing.[25] Since that time, thousands of publications in which PDA has played a central role have been produced. More recent reviews have highlighted the role of PDA in rechargeable batteries,[26] catalysis[27] and especially in biomedicine.[28,29] These include a focus on nanostructures and interfaces,[15,30] as well as the development of PDA antibacterial surfaces.[31]

PDA in batteries can be used to enhance the thermal stability of existing materials and can be used as the actual electrode material.[17] Recently it was shown that dopamine derivatized with pendent sulfonates polymerize to give smooth, well-adhered films, unlike those from PDA which are rougher due to island growth. In combination with multiwalled carbon nanotubes, highly efficient and stable cathodes for both lithium and potassium ion batteries could be prepared with the sulfonated monomer.[32] PDA itself has been used in supercapacitors as a surface coating to avoid disadvantages seen with many commonly used materials. It has also served as a carbon source for enhancing conductivity.[33–35]

PDA, in the form of nanoparticles, has found use as structural colors.[36] In addition to pure PDA nanoparticles, non-iridescent colorants made from PDA with silica shells have been prepared. The shells may be used to tune the hue and brightness of the colors.[37] Conversely, stable colorants have been prepared by coating polystyrene nanoparticles with PDA.[38] The particles were found to strongly adhere to flexible cotton textiles.

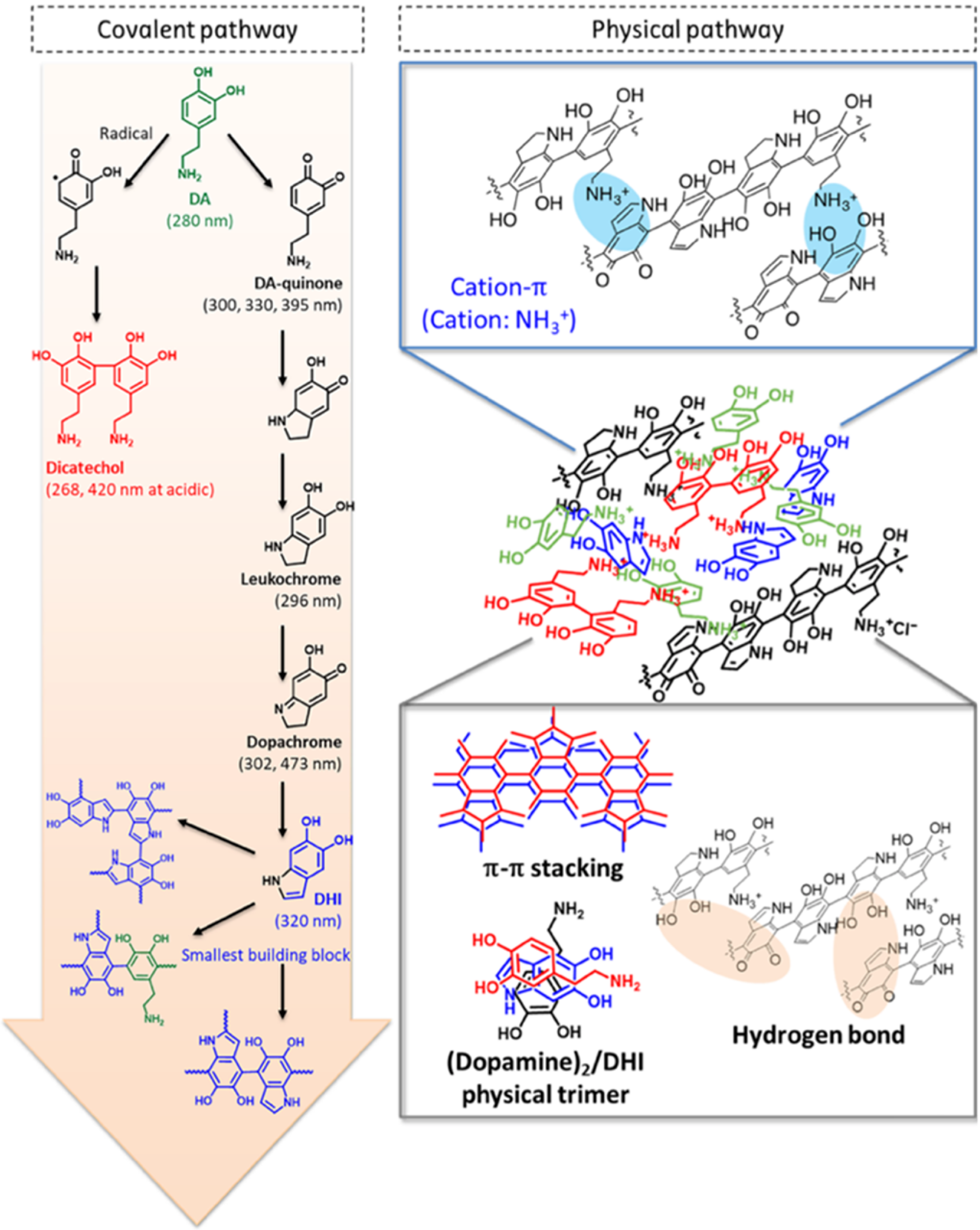

Figure 2. Proposed pathway for PDA coating formation through chemical oxidation and physical self-assembly. Reproduced with permission from reference 10. Copyright 2018, American Association for the Advancement of Science (AAAS).

Environmental applications taking advantage of PDA properties are common. For example, PDA has been used to reduce marine biofouling in order to combat greenhouse gas emissions,[39] to assist in the removal of heavy metals, organic dyes and other toxic pollutants from water, for seawater desalination, and for water/oil separation.[40] Mishra *et al*. used PDA to grow and immobilize gold nanoparticles onto cellulose fibers.[41] The fibers were then incorporated into a flow-through reactor to degrade model pollutants, including *p*-nitrophenol and dyes in various concentrations. The reactor was operated for more than 24 h without significant loss of activity. The slight decrease in performance that was observed could be restored with a simple water rinse.

The use of PDA in biomedical research has become very widespread (Fig. 4). For sensing applications, the abundance of functional groups on PDA allows for species such as biotin, fluorescent labels, DNA and proteins to be linked to particle or film surfaces.[15] Some of the earlier examples in this field include PDA coatings for biosensing and in biofuel cells.[20] Building on earlier reports, Yang *et al*. have recently developed a 'turn-on' glucose sensor by preparing fluorescent nanodots of PDA and treating them with $AgNO_3$.[42] The nanodots reduced the Ag^+, creating Ag nanoparticles that decorated the dots and quenched the fluorescence emission. Glucose oxidase was then bound to the surface of the particles. In the presence of glucose, the enzyme

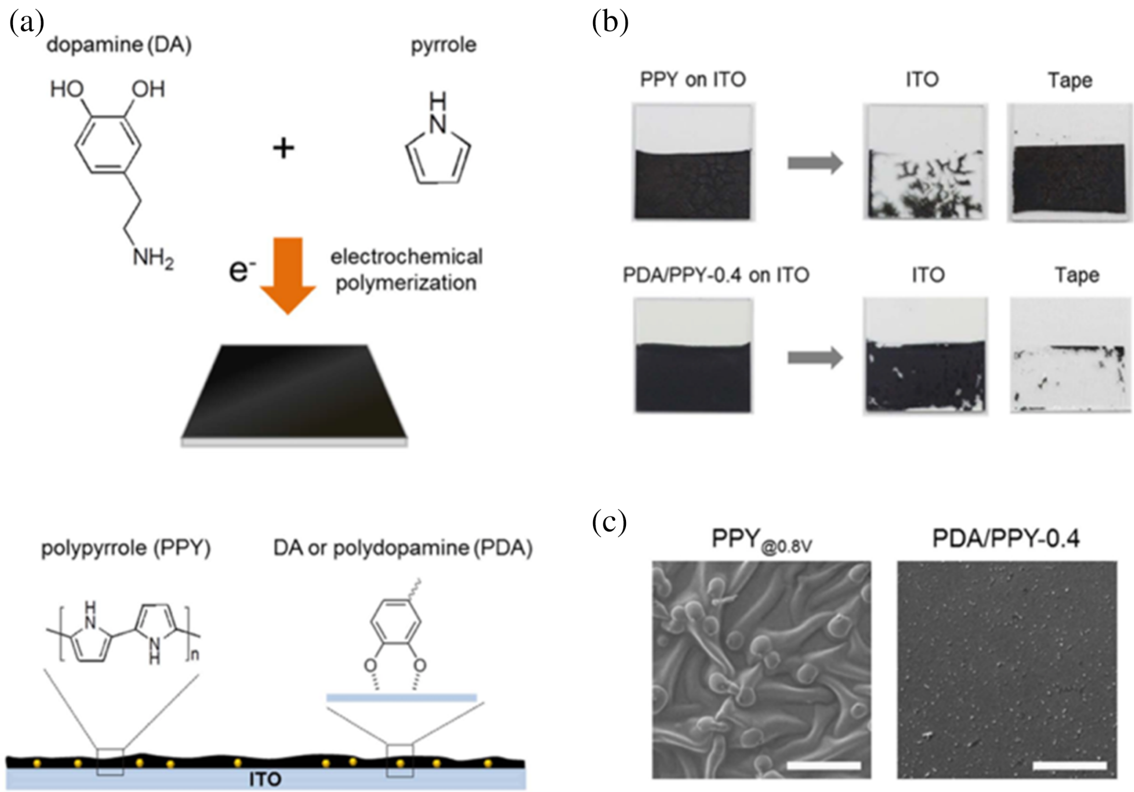

Figure 3. (a) Simultaneous oxidative electrochemical polymerization of PPy and dopamine on ITO. (b) Photographs of tape tests showing improved adhesion in the presence of PDA. (c) SEM micrographs of PPy and PDA/PPy. Reproduced with permission from reference.[21] Copyright 2016, Springer Nature.

generated H_2O_2 and gluconic acid. The peroxide degraded the PDA matrix and oxidized the Ag nanoparticles to Ag^+, which then leached from the PDA nanodots, restoring the fluorescence. Yang *et al*. took a different approach when developing sensors for microRNA.[43] They oxidatively polymerized pyrrole onto PDA nanosheets forming a 'nanoquencher'. Adjustment of the PPy–PDA ratios enabled tuning of the nanosheet bandgap. Using a single stranded DNA probe labeled with a fluorescent dye, they were able to reliably detect microRNA down to 23.1 pmol L^{-1}.

PDA hydrogels and coatings have also been used for tissue engineering purposes. Suneetha *et al*. incorporated PDA with sodium alginate and polyacrylamide to form hydrogels for creating skin tissue scaffolds.[14] Zhu *et al*. looked at the biocompatibility of titanium and soft tissue with PDA and PDA-incorporated surface modifications. A titanium alloy was coated with PDA to

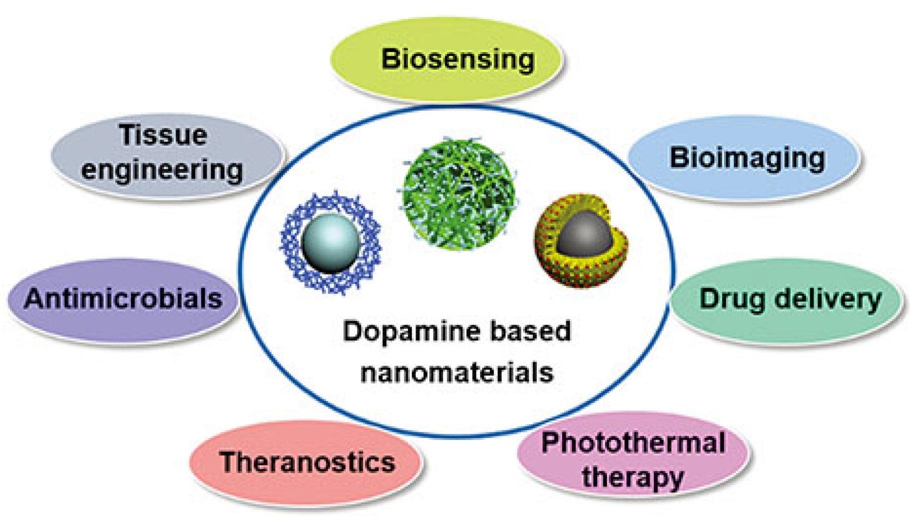

Figure 4. Uses of polydopamine in biomedicine. Reproduced with permission from reference.[46] Copyright 2018, Progress in Chemistry, Chinese Academy of Sciences.

improve stability and then collagen was conjugated onto the surface with the hope of facilitating soft tissue adhesion.[44] Liu and coworkers have used PDA nanosheets to fabricate multifunctional injectable hydrogel wound dressing.[15] The nanosheets were prepared by the autooxidation of dopamine in the presence of DNA. The nanosheets assembled as the PDA was forming through the self-complementarity of the components. The sheets were doped with *N*,*N*′-di-sec-butyl-*N*,*N*′-dinitroso-1,4-phenylenediamine (BNN6), which acted as a source of NO on near infrared irradiation. The hydrogel was then crosslinked to add stability. The resulting composite showed good cytocompatibility and antibacterial properties. It was also effective at accelerating the healing of wounds through photothermal therapy. Other examples of PDA-containing hydrogels in wound healing have recently been reviewed.[45]

SUMMARY AND PERSPECTIVE

PDA and related polycatecholamines are highly versatile materials that can be used in a host of fields and applications. They are deceptively easy to prepare and structurally modify, but optimal performance for a given application will require further investigation into synthetic methodologies and a better understanding of the structural makeup of the resulting products. Computational studies of the PDA structure using quantum mechanical methods have recently been reported,[47] as have density functional theory and molecular dynamics studies of PDA adhesion and interfaces.[48] These approaches promise new insights but, given the rapid increase in the number of publications in the field, database and machine learning approaches should also be explored. In the area of biomedicine, concerns have been raised about the potential for negative health effects from PDA degradation products.[25,50] This warrants increased attention to help guide those developing new PDA healthcare technologies.

ACKNOWLEDGEMENTS

This work was supported by the National Science Foundation EPSCoR Program under NSF Award OIA-1655740. Any opinions, findings and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect those of the National Science Foundation. HF is grateful for the invitation by the ACS Division of Polymer Chemistry to participate in the 2021 ACS Excellence in Graduate Polymer Research Symposium.

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