Chapter 6

Oxidative Polymerization of Dopamine: A High-Definition Multifunctional Coatings for Electrospun Nanofibers - An Overview

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Additional information is available at the end of the chapter

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Abstract

The invention that catecholamines undergo oxidative polymerization under alkaline conditions and form adhesive nanocoatings on wide variety of substrates has ushered their potential utility in engineering and biomedical applications. The oxidative polymerization of catecholamines can be triggered by light, chemical and physical methods, thus representing one of the widely explored surface coating methods. The overall objectives of this chapter are to compile the various methods of accomplishing surface coatings and compare the structural diversity of catecholamines. The progress achieved so far on polydopamine (pDA) coatings on electrospun polymers will be discussed. Finally, we will summarize the research efforts on catecholamine coatings for biomedical applications as well as their potential as a high definition coating method.

Keywords: surface coatings, polydopamine, electrospinning, functional coatings, tissue engineering

1. Introduction

There has been a great demand on modification of material surfaces with functional coatings that will present superior translation of desirable features in both biomedical and industrial settings. In particular, the coating methods with wide substrate applicability, ease of processing and subsequent modification and optimum durability are highly desired. One of the key aims of coatings is transform surface functions instead of altering the bulk composition
of the substrate materials. Among the various surface coating methods, the water-resistant wet adhesive bonding by marine mussels has become a leading model for biomimetic modification of surfaces. Ever since the first report that oxidative polymerization of dopamine under alkaline conditions generates material-independent nanocoatings on wide variety of substrates, the topic has become one of the most widely explored area in material science [1]. In their pioneering work by Lee et al., the substrates were immersed in 2 g/L dopamine solution in 10 mM Tris-buffer (pH 8.5) overnight with constant stirring to generate 45 ± 5 nm thick polydopamine (pDA) coating. Organic substrates coated by the above method were more stable to combined acid and ultrasonication than the coated inorganic substrates. The versatility of pDA coating is attributed to the wide variety of chemical interactions conferred by the catecholamine chemistry [2].

The mechanism involves slow oxidation of dopamine (DA) to dopamine quinone (DQ) via dopamine semiquinone (DSQ), which rapidly undergoes Michael-type intramolecular cycloaddition reaction forming leucodopaminechrome (DAL). Oxidation of DAL and subsequent rearrangement results in the formation of heteroaromatic 5,6-dihydroxyindole (DHI) and its oxidized product 5,6-indolequinone (Figure 1). The latter two

\[
\begin{align*}
\text{DA} & \rightarrow \text{DSQ} \\
\text{DAL} & \rightarrow \text{DAC} \\
\text{DHI} & \rightarrow \text{DQ}
\end{align*}
\]

Figure 1. Initial steps in the autoxidation of dopamine to form polydopamine nanocoating in alkaline pH.
molecules undergo branching reactions at positions 2, 3, 4 and 7 leading to variety of isomeric dimers or higher order oligomers, which self-assemble to form thin film coating of substrates [3].

Thus, pDA coating generates supramolecular assembly of diverse structures which are resistant to common organic solvents but can be detached under high basic conditions (pH > 10.5). The key step in the formation of polydopamine coating is the oxidation of dopamine to dopamine quinone. Several factors can trigger the conversion of dopamine to dopamine quinone, thus pDA coating can be accomplished by a number of experimental conditions. We will detail these methods in the following section.

2. Factors controlling pDA nanocoatings and its stability

2.1. Dissolved oxygen, dopamine concentration, pH, buffers and temperature

The pDA coating process by Tris-HCl route is slow (1.2–2.1 nm/h) and the thickness of the coating leveled off (45 ± 5 nm) in 24 h. When the coating was carried out at the air-water interface, the thickness increased linearly over entire period and coating speed increased to 3.2 nm/h [4]. These results together with the observations that no detectable coating was observed when the coating process was carried out in nitrogen confirm that the presence of dissolved oxygen was critical for the pDA nanocoatings by Tris-HCl route [5]. When compared to aerial oxidation, exogenous addition of oxygen in solution accelerates the rate of pDA nanocoatings (8 nm/h). It has been shown that the dopamine consumption rate constant was doubled when the coating was carried out in pure oxygen compared to aerial oxidation [5]. The pDA coating in an oxygen atmosphere displayed homogenous thickness distribution compared with coating performed in air.

The aerial deposition of pDA films in Tris-HCl follows a two-step model in which a rapid increase in thickness during the early stages (stage I, <2 h) is accompanied by a slower deposition with increasing time (stage II, 2–10 h), indicating depletion of dopamine concentration with increasing time which resulted in lower rate of deposition [6]. Thus, the coating speed can be accelerated by increasing the concentration of dopamine. Indeed, increasing the concentration of dopamine resulted in an increase in coating speed of 4 nm/h with a maximum thickness of ~80 nm could be achieved with no further increase observed above 8 g/L [7, 8]. Alternatively, the thickness of the coating can be improved by multiple immersion of the substrates in freshly prepared dopamine solution for 15 minutes [9]. A maximum coating speed of 4 nm/h could be achieved by the multiple immersion process while decreasing the immersion cycle to 5 minutes increased the coating speed to 7 nm/h.

The presence of surfactants such as sodium dodecyl sulfate or hexadecyltrimethylammonium bromide and polyvinylpyrrolidone or boric acid, which interact strongly with dopamine, completely prevented or decreased the formation of pDA coating on quartz [10–12]. These results further suggest that the presence of free unoxidized dopamine in solution is essential for the formation of pDA nanocoating as well as to increase the coating thickness.
The buffer pH plays an important role in achieving optimum coating thickness by Tris-HCl method. At a given dopamine concentration, the coating speed increased in a step-wise manner between pH 7 and 10.2 and maximum speed could be achieved between pH 9 and 10.2 [8]. The coating speed approached 10.8 nm/h at pH 8.5 and increased 15.6 nm/h between pH 9.0 and 10.2. The choice of buffers (i.e., phosphate, carbonate or Tris) also determines the thickness of the coating [13]. Dynamic light scattering and small angle neutron scattering studies showed that the aggregates formed in inorganic buffers (phosphate or bicarbonate) contained slow diffusing particles (hence higher molecular weight) than aggregates present in Tris buffers. Higher film deposition rates achieved in inorganic buffers than in Tris was attributed to the covalent interaction of Tris with dopamine oligomers, thus modulating the nanocoating thickness [14]. Zangmeister et al. reported a pDA coating thickness of 8–10 nm in 1 h by using carbonate/bicarbonate buffer (pH = 8.5, Ref. 15). These authors further showed that an immersion time of at least 10 minutes was required to form continuous pDA nanocoatings.

For a given substrate, the rate of pDA coating could also be accelerated by increasing the temperature of coating. Increasing the temperature of coating from 25 to 35°C increased the coating speed from 1.8 to 2.2 nm/h [6]. However, more than 10-fold increase in film thickness was achieved within 8 h by increasing the temperature to 60°C than pDA coating carried out under ambient conditions for 24 h. The high temperature deposited coatings displayed increased surface roughness and greater relative friction coefficient with heterogeneous distribution of pDA nanoparticles [16].

2.2. Accelerating the coating speed of pDA coatings

In the absence of any external additives, the formation of pDA coating takes place slowly but can be accelerated by metal ions, enzymes or organic amines. A number of redox active metal ions and salts have been shown to catalyze the oxidative polymerization of dopamine under neutral or weakly acidic conditions, thus expanding the repertoire pH of pDA deposition. Bernsmann et al. have shown that the presence of stoichiometric excess of Cu$^{2+}$ ions in Tris buffer at pH 4.5 resulted in an increase in coating thickness of >70 nm which was difficult to achieve by conventional Tris-HCl route wherein the thickness did not increase beyond 45 ± 5 nm [17]. When compared to copper ions, the presence of other transition metal ions such as Fe$^{3+}$ and Ce$^{4+}$ has also been shown to accelerate the pDA coating under weakly acidic conditions [18]. Park et al. reported the pDA coating under neutral pH by adding fourfold stoichiometric excess of vanadyl (VO$^{2+}$) ions to the dopamine solution. Addition of vanadium accelerated the pDA coating speed by about 7 times when compared to conventional pDA coating [19].

Alternatively, the combined use of metal ion and hydrogen peroxide has been shown to greatly accelerate the pDA coating speed on variety of substrates under alkaline pH [20]. The reactive oxygen species produced by Cu$^{2+}$/H$_2$O$_2$ increased the coating speed to 43 nm/h and produced defect-free pDA coating with inherent antioxidant and antimicrobial properties. The pDA nanocoatings prepared by this method displayed remarkable resistance to solvents and acid/alkali treatment in comparison to the pDA coating prepared by Tris-HCl.
method. Similarly, Zhu et al. reported solvent-resistant and rapid pDA deposition on ultrafiltration membrane by using Fe$^{3+}$/H$_2$O$_2$ under acidic (pH = 3.5) conditions [21].

In addition to metal ions, oxidizing agents such as ammonium persulfate and sodium periodate catalyze the pDA formation. The presence of ammonium persulfate (pH 7.0) could accelerate the pDA formation with coating speed as high as 35 nm/h [22]. In a systematic study, Ponzio et al. showed that pDA coating with superhydrophilic/superoleophobic properties could be accomplished by the addition of stoichiometric excess of sodium periodate under weakly acidic conditions in acetate buffer [23]. The coating speed can be controlled by appropriate oxidant-dopamine ratio. These authors further showed that increasing the temperature of sodium periodate containing dopamine solution to 70°C accelerated the coating speed to 90 ± 5 nm/h. These results suggest that the combined effect of oxidant and temperature could enhance the coating speed of pDA nanocoatings. Interestingly, Hong et al. demonstrated that more than 200-fold increase in coating speed when compared to Tris-HCL route could be achieved by controlling the molar ratio of dopamine concentration, sodium periodate:dopamine ratio and pH [8]. These authors further demonstrated the utility of such approach in preparing ultrafast coating of substrates by spraying the dopamine solution containing the oxidant. The use of oxidant-induced pDA formation is advantageous since the process can be carried out under deoxygenated conditions at acidic pH values, thus useful for substrates that are sensitive to alkali pH. However, the presence of stoichiometric excess of oxidants (dopamine:oxidant = 2–4) or metal ions is necessary to achieve a higher coating speed. The process may leave impurities in the resultant films and modify the surface properties. In addition to the metal ions or oxidants, multicopper oxidase enzyme, laccase, could catalyze the pDA coating, and the coating speed was doubled in the presence of enzyme (2.7 nm/h) compared to Tris-HCL route [24]. The enzymatic process can also be accomplished in neutral pH [25, 26]. A smooth coating of pDA could also be achieved by the enzyme, tyrosinase, which catalyzes the oxidation of dopamine with a coating speed of ~2.3 nm/h [27].

Organic bases such as hexamethylenediamine (HD), polyethylenimine (PEI), aminopropyl triethoxysilane (APTES) and dihydroxy indazole have been shown to catalyze the pDA coating. In a systematic study, Yang et al. reported the biocompatible coating of stainless steel by HD along with dopamine hydrochloride (4:1 molar ratio) in Tris-HCL buffer (pH 8.5) [28]. The methodology produced fourfold higher coating thickness (140 nm) that was difficult to achieve by traditional Tris-HCl route with a coating speed of 6 nm/h. In another approach, a free-standing pDA-PEI composite film can be prepared at the air-water interface in Tris-HCL buffer (pH = 8.5) [29]. Using this method, a coating speed of 50 nm/h can be achieved at dopamine:PEI ratio of 4:1. A coating thickness of ~1 μm was possible to achieve by this method by varying dopamine:PEI ratio and reaction time. Similarly, Knorr et al. reported the use of APTES as organic base for the preparation of pDA-silicate composite films in both neutral and basic pH conditions [30]. In both pH, the coating thickness and coating speed depend on APTES:dopamine ratio. A maximum coating speed of 19.6 nm/h in both pH and a thickness of 140 nm can be achieved at APTES:dopamine ratios 3.5 and 5. Interestingly, the composite films facilitated the subsequent functionalization such as metallization, mineralization and covalent immobilization of hyaluronic acid [28, 29]. Similarly,
Fan et al. used a DHI:dopamine molar ratio of 1:3 to obtain a coating speed of 7 nm/h and threefold higher coating thickness than pDA coating prepared by Tris-HCl route [31].

The presence of oxidizing agents, enzymes or organic bases may interfere with the intrinsic properties of pDA; however, a number of physical approaches have been reported that can generate pDA coatings without any chemical interfering agents with higher coating speed. For example, Wang et al. showed that pH-independent (in the range pH 4–8) pDA coating with a coating speed as high as 53 nm/h could be achieved by the use of argon microplasma [32]. Since the pDA coating occurred at the plasma-liquid interface, the method can be extended for the preparation of direct pDA patterning of substrates. Chen et al. used plasma-activated water for pDA coating under acidic conditions (pH 2.5–5.4, Ref. [33]). The pDA particles formed under these conditions remained stable for 3 months, whereas those prepared by conventional method precipitated in 24 h. The use of microwave-assisted radical initiation also accelerates the pDA coating speed. Lee et al. reported a coating thickness of 72 nm/h in Tris buffer (pH ~ 8.5) by using high-power microwave radiation [34]. Recently, Coskun et al. reported pDA coating on glass substrates by chemical vapor deposition of dopamine in the presence of sulfuric acid/sodium sulfate as the oxidizing agents at 300°C in a nitrogen atmosphere [35]. The methodology produced homogenous and highly conductive coating with a coating speed of 339 nm/h, the highest pDA deposition speed achieved so far. The changes in electrical properties are attributed to the homogenous structure of the pDA films that was different from pDA formed by alkaline route.

pDA coating of electrically conductive substrates can also be accomplished by electrochemical methods. pDA coating of metallic implants or gold-coated non-metallic substrates can be accomplished by cyclic voltammetry methods under neutral pH [35, 36]. Unlike solution-based routes, the electrochemical deposition relies on the conductivity of the substrate and the coating is confined to the substrate surface. As a result, the method produced a higher coating speed (6–8 nm/h) and smoother coating than coating prepared by Tris-HCl method. The method has the advantage of direct pDA coating of cardiovascular stents or metallic implants and simultaneous/subsequent functionalization with biomolecules or metal ions [36–38].

pDA nanocoatings can also be triggered photochemically which has the advantage of controlling the onset and the termination of the process [39]. The reactive oxygen species triggered by UV irradiation encouraged the pDA nanocoatings in acidic, neutral and basic pH values. Though fourfold increase in the coating speed was observed by UV irradiation, the method has the advantage of making 2D surface patterns using photomasks or surface grafting of polymers [40]. Figures 2 and 3 summarize the working pH range for various pDA coating methods and coating speed reported so far.

2.3. pDA nanocoatings in organic solvents

All the above methods utilize the aqueous buffers/conditions for the generation of pDA nanocoatings. To broaden the scope of the coating, You et al. reported the use of organic solvents with relative polarity ≥0.386 and organic bases such as piperidine, trimethylamine and 2-methoxyethyl amine (dopamine:organic ratio 1:2) for the controlled coating of pDA [41].
The presence of an organic base is important for the deprotonation of dopamine and subsequent oxidative polymerization. Among the three organic bases, piperidine showed rapid pDA coating within 12 h whereas in the presence of 2-methoxy ethylamine as high as 60 h.

Figure 2. pH map of the various pDA coating methods reported in the literature so far. PAW is plasma-assisted water.

Figure 3. Coating speed achieved with various pDA coating methods reported in the literature. APTES – 3-aminopropyl triethoxy silane; LPEI – linear polyethylenimines; CVD – chemical vapor deposition.

The presence of an organic base is important for the deprotonation of dopamine and subsequent oxidative polymerization. Among the three organic bases, piperidine showed rapid pDA coating within 12 h whereas in the presence of 2-methoxy ethylamine as high as 60 h.
was required. The coating speed and coating thickness can be controlled by the polarity of the solvent. At dopamine:piperidine ratio 1:2, a coating speed of 27 nm/h could be achieved in methanol which was decreased to 11 nm/h in ethanol. The authors demonstrated the utility of this approach in establishing pDA coating of water-labile electrospun nanofibers, controlled release of hydrophobic drug, paclitaxel and immobilization of organothiols. Liu et al. reported the pDA coating in ethanol and in the presence of large excess of tetramethylethylenediamine (TEMED) [42]. Despite the large excess of (TEMED: dopamine = 26), a maximum coating thickness of 28 nm was achieved in 48 h. When compared to other organic bases, piperidine showed higher coating thickness and coating speed and attributed to the strong basic properties (low pKb) and higher nucleophilicity of piperidine.

Thus, pDA coating of various thicknesses and surface smoothness can be accomplished by altering the variables such as concentration, temperature and oxidizing agents. The combined effects of oxidizing agents and temperature could maximize the coating thickness in short time. The non-chemical approach broadens the scope of the coating, thus achieving high coating speed in extreme pH conditions.

2.4. Stability of pDA nanocoating

The versatile material-independent pDA nanocoating has the potential in repertoire of applications including industrial and biomedical applications. However, the stability of nanocoatings to harsh conditions realized in the end-use industrial and biomedical applications would impact the lifespan and performance characteristics of the pDA-modified materials. Here, we detail the stability of pDA-coated substrates reported so far in the literature. Ou et al. reported that pDA coating of ATPS-modified silicon was resistant to electrochemical oxidation, thus conferring corrosion-resistant properties [6]. In an another study, Chen et al. showed that the corrosion resistance of dodecanethiol functionalized pDA nanocoating of copper can be improved by 1000-fold in comparison to pristine copper films [43]. The alkane thiol-modified film remained intact even after immersion in simulated sea water for 20 days. In a systematic study, Singer et al. investigated the effect of pH, dipping angle, immersion time and dopamine concentration on the stability of pDA-coated magnesium [44]. The results suggested that pDA-coated magnesium prepared by using 1 mg/mL of dopamine in 50 mM Tris buffer for 2 h (pH 10 and a dipping angle 0°) produced corrosion-resistant coating. The stability of pDA coating is dependent on the pH of the solution and substrates as well. Wei et al. compared the pH stability of pDA coatings on three different polymer films. Among them, pDA coating of polypropylene was the lowest, whereas maximum for nylon films [45]. These authors further showed that the presence of unreacted dopamine was responsible for the poor alkali stability of pDA coating and could be improved by the addition of oxidants. Zhang et al. compared the chemical and pH stability of the pDA coating obtained by two different methods [20]. Their results suggest that the oxidant (CuSO$_4$/H$_2$O$_2$) catalyzed pDA coating displayed remarkable chemical resistant to organic solvents etching and superior acid/alkali stability than air oxidized films. Kang et al. investigated the stability of pDA coating on gold substrates in phosphate buffered saline (pH 7.4, 5% CO$_2$ at 37°C). Only a marginal decrease in coating thickness (4–15.8%) was observed for the pDA coatings after 26 days, confirming excellent
aqueous durability of the coatings under physiological conditions [46]. Similarly, Yang et al. showed that pDA-coated 316 stainless steel immersed in PBS displayed increased swelling of the nanocoatings after 30 days, corroborating the above results [28]. An elegant demonstration on the stability of pDA nanocoatings to pH, chemical and ultrasonication was reported using surface plasmon resonance recently by Yang et al. [47]. The method has the advantage of monitoring the formation and detachment of the coatings directly and in real times. The results suggested that the pDA coating on gold chips was poor in extreme pH values, that is, pH 1–3 and 11–14, as well as in polar organic solvents such as dimethyl sulfoxide and dimethylformamide. The coating was also stable to ultrasonication in water for 1 h and the stability could be enhanced by increasing the ionic strength of the buffer. Alternatively, the alkali pH stability could also be enhanced by the addition of metal ions [48, 49]. In our work on pDA coating, we have shown that pDA-coated titanium implant covalently linked with an antimicrobial peptide prevented the *Staphylococcus aureus* colonization in rabbit cornea and was superior to prophylactic antibiotic treatment, thus confirming the stability of the coating in a biological milieu [50]. In addition to chemical and biostability, the pDA coatings were stable to UV radiation and protect UV-sensitive compounds from rapid degradation [51].

2.5. Structure: activity relationship on pDA coating

Few reports discussed the structure-activity relationship of modified dopamine derivatives. The presence of catechol group and aminoethyl group is essential for the oxidative polymerization of dopamine and the concomitant material-independent adhesive properties. The aromatic ring of dopamine has been modified to generate structures in order to control the formation of pDA nanocoatings. Cui et al. reported the effects of electron withdrawing groups in the aromatic ring on the coating thickness [52]. Substitution of Cl- or –NO2 groups at the 6th position in the aromatic ring retarded the pDA formation. Chlorodopamine formed 7-nm thick pDA-like coating after 48 h, a threefold decrease in coating thickness observed for dopamine under the same conditions. No pDA-like structure was observed for the nitrodopamine even after incubation in alkaline pH for 48 h. The presence of 2 mM sodium periodate, however, catalyzed the oxidative process, and a film thickness of 2.8 nm was achieved after 48 h. Taken together, these results suggest that the presence of an electron with drawing group in the aromatic ring conferred greater oxidative stability, decreased the pDA nanocoating formation and increased metal ion chelation and interfacial adhesion [53, 54]. When compared to dopamine, the presence of electron donating group has been shown to accelerate the pDA formation. Zhang et al. have shown that the presence of 5-methoxy group in the aromatic ring of dopamine accelerated the pDA formation with concomitant twofold increase in coating thickness in comparison to dopamine [55]. However, the methoxy derivative weakens the thermal stability of nanocoating.

Substituents at the 2-amino ethyl group of dopamine have also been shown to affect the polymerization kinetics and surface characteristics of the coating. Norepinephrine, the natural analogue of dopamine with hydroxyl group at the benzylic position of DA displayed similar coating potential as dopamine by alkaline pH or in the presence of laccase [56–58]. When compared to pDA coating, polynorepinephrine (pNE) coating appeared smoother and the
benzylic –OH group facilitated the ring opening polymerization of ε-caprolactone, whereas the secondary amine readily formed diazonium diolates with nitric oxide, thus providing a source for the controlled release of NO \[56, 57\].

In our work, we compared the changes in mechanical properties of polyvinyl alcohol (PVA) films reinforced with various catecholamines. Among them, pDA-reinforced films displayed the highest mechanical strength and toughness in comparison to other catecholamines; an indication that any functionalization in the amino ethane weakened the interfacial adhesion \[26\]. Interestingly, the polyepinephrine-reinforced PVA films inhibited the growth of various Gram-positive strains \[26\]. The results highlight the material-independent coating with inherent antimicrobial properties of a naturally occurring dopamine derivative.

In a seminal work, Hu et al. investigated the effect of increasing the chain length of 2-aminoethyl group on properties of various catecholamines \[58\]. Their results suggest that dopamine and 3-aminopropyl catechol readily formed material-independent coating with similar mechanism. However, catecholamines containing 4, 5 and 12 methylene groups do not form heteroaromatic products. The adhesion strength of the polycatecholamine coating was not affected by increasing the chain length from 2 (dopamine) to 5, whereas substantial decrease was observed for catecholamine containing 12 methylene groups.

In summary, the polydopamine nanocoating offers a convenient way of transforming an inert surface into one with multifunctional features. The ease of achieving appropriate coating thickness, availability of methods with higher coating speed and the structural diversity of dopamine or catecholamine present ample opportunities to develop surfaces with specific surface features. Subsequent derivatizations of pDA layers expand the robustness of the approach.

3. Applications of pDA coating for electrospun polymers

Besides the premise that nanoscale structures of the extracellular matrix play an important role in tissue regeneration, numerous methods have been introduced for producing ultrathin nanofibers. Electrospinning, the oldest among them, has become a very attractive technique due to its versatility in spinning wide range of polymeric fibers \[59\]. The method is capable of producing polymer fibers with diameters ranging from 10 nm to 10 μm using both synthetic and biosynthetic polymers by controlling the intrinsic and extrinsic parameters \[60\]. The inherent hydrophobicity of synthetic polymers such as polycaprolactone (PCL), poly(lactide-coglycolide) and poly(lactide-co-caprolactone) and the absence of cell recognition sites render them unsuitable for biomedical applications. Conventional surface modification methods of electrospun polymers, however, require tedious preparation steps, rigorous reaction conditions and limited choice of substrate materials \[61, 62\]. Taking into consideration the simplicity, hydrophilicity, aqueous durability under physiological conditions, biocompatibility and ease of functionalization with cell recognition molecules, pDA nanocoatings have been reported on electrospun polymers for various tissue engineering.

Ku and Park were the first to demonstrate the utility of pDA coating for possible vascular tissue engineering applications \[63\]. These authors compared the growth of human umbilical
vein endothelial cells on pDA- or gelatin-coated PCL nanofiber mats. The results showed that pDA-coated PCL mats displayed threefold to sevenfold higher cell viability, cell attachment and spreading with well-stretched cytoskeletal components than gelatin-coated PCL nanofibers. In addition, the cells grown on pDA-coated mats displayed increased expression of endothelial cell markers highlighting the healthy status of the cells. Similar to the above work, pDA coating of poly(L-lactic acid) (PLLA) conferred higher human mesenchymal stem cell adhesion, penetration, proliferation and osteogenic differentiation than pristine fibers [64]. These authors showed that 1 h immersion of the as-electrospun nanofibers in dopamine in Tris-HCl (pH = 8.5) was enough to achieve optimum biological properties. Similarly, pDA nanocoating of PCL/gelatin nanofibrous membrane was shown to enhance the mouse adipose-derived stem cell (mASC) adhesion, penetration and spreading compared to PCL/gelatin nanofiber mats. The layer-by-layer assembly of pDA-coated PCL/gelatin showed higher expression of key osteogenic marker proteins and calcium deposition than PCL/gelatin [65]. In an interesting approach, Roy et al. reported the utility of pDA coating for macroporous 3D electrospun PVA for hard tissue engineering [66]. These authors performed pDA coating on glutaraldehyde crosslinked electrospun polymers. The pDA-coated PVA was shown to have excellent shape recovery properties and higher cell adhesion, spreading, penetration and PVA scaffolds.

In a systematic study, Sun et al. reported the utility of pDA coating of poly(lactide-co-glactic acid) (PLGA) nanofibers and subsequent covalent functionalization of basic fibroblast growth factor (bFGF) on pDA-coated PLGA nanofibers [67]. The pDA coating and subsequent bFGF functionalization enhanced primary human dermal fibroblast adhesion and proliferation. In a rabbit model of wound healing, pDA coating followed by bFGF functionalization increased the wound closure and higher re-epithelialization than pristine and pDA-coated PLGA. Wounds treated with pDA-coated PLGA also showed higher wound closure and re-epithelialization than pristine PLGA, highlighting biocompatibility of pDA coating. In a subsequent work, these authors further showed the feasibility of pDA coating followed by bFGF immobilization in drug-loaded PLGA fiber mats [68]. The pDA nanocoating by Tris-HCl route of a drug-loaded PLGA could be achieved with minimum drug efflux, by optimizing dopamine concentration and pH.

Shin et al. reported the utility of pDA coating of electrospun nanofibers poly-L-lactide-co-ε-caprolactone (PLCL) followed by functionalization with gelatin for cardiac tissue engineering [69]. These authors compared the biological properties of gelatin immobilization on PLCL scaffolds by two different methods. The results suggested that pDA nanocoating followed by subsequent immobilization of gelatin resulted in higher rat myoblast adhesion and spreading, superior cytoskeletal organization and cell proliferation than gelatin immobilized by 1-ethyl-3-(3-dimethylaminopropyl)-1-carbodiimide hydrochloride/N-hydroxysuccinimide (EDC/NHS) coupling. Interestingly, the pDA-coated PLCL (without gelatin immobilization) showed superior biological properties than gelatin immobilized with EDC/NHS method, possibly due to immobilization of serum protein on pDA-coated nanofibers. In an extension, these authors investigated the ability of RGD peptide immobilized onto pDA coating with PLCL [70]. In serum-free conditions, the peptide-immobilized pDA-coated PLCL scaffolds displayed higher mouse myoblast adhesion and spreading while enhancing the cell proliferation synergistically with serum proteins. These observations suggest possible inherent cell supportive nature of pDA coatings. Extending the approach further, Ku and Park have demonstrated that pDA-coated uniaxially oriented (aligned) electrospun nanofibers enhanced mouse myoblast adhesion, increased expression of myosin
heavy chain and maturation than mats without pDA coating [71]. To enhance the preferential migration of cells, Shin et al. reported the use of pDA-coated radially aligned PCL nanofibers [72]. The surface modification and radial alignment of the fibers enhanced the human mesenchymal stem cell adhesion, proliferation and spreading. In addition, cells displayed an elongated morphology along the fiber axis. These results highlight the importance of surface chemistry and topographical cues for possible skeletal tissue engineering. It has been suggested that serum proteins such as fibronectin and vitronectin react readily to the pDA surfaces and the presence of integrin-binding sites in the immobilized proteins promotes focal adhesion and spreading. Davoudi et al. reported the dual functionalization of pDA-coated electrospun polyurethane nanofibers with heparin and vascular endothelial growth factor (VEGF) [73]. The biomolecules immobilized nanofiber mats displayed higher endothelial cell adhesion and spreading and poor platelet adhesion, demonstrating the potential utility of pDA nanocoatings for cardiovascular tissue engineering. Recently, pDA coating of PCL nanofibers followed by immobilization of basement membrane fragments (laminin-111 fragments) was demonstrated by Horejs et al. [74]. In vitro assays demonstrated that the laminin-111 fragment immobilized nanofiber mats prevented the TGFβ1-induced epithelial mesenchymal transition of mouse mammary gland epithelial cells and downregulated the expression of matrix metalloprotease 2 (MMP2). In a mice model of TGFβ1-induced peritoneal fibrosis, the laminin or laminin fragment immobilized nanofiber mats decreased the MMP2 expression and controlled the tissue fibrosis without causing any inflammatory response at the site of implant. The immobilization strategy is advantageous owing to the restricted access of the ligand to the target receptors and to overcome any off-target effects.

All the above approaches report pDA coating under alkaline conditions for biodegradable and water-insoluble polymers. The aqueous alkaline condition used for the polymers is not suitable for hydrogel polymers such as gelatin. To overcome this, we electrospun dopamine and gelatin and expose the resultant as-electrospun nanofibers to ammonium carbonate. The methodology takes advantage of the sublimation of (NH₄)₂CO₃ (referred hereafter as ammonium carbonate diffusion method, ADM) to generate ammonia and carbon dioxide. The ammoniacal conditions raised the pH ≥ 9.5 and triggered the oxidative polymerization of catecholamines in situ [75]. As a result, the pDA-coated electrospun gelatin displayed better aqueous durability and mechanical properties than pristine gelatin nanofibers. We further demonstrated that alkaline exposure did not alter the antimicrobial properties of cationic polymers, antibacterials or antifungal compounds [76, 77]. Interestingly, the combined effect of pDA coating and antibacterials/antifungals which interact with the gelatin nanofibers resulted in long-term antimicrobial activity and excellent durability of gelatin nanofibers. In a porcine model of partial thickness burn injury, gelatin nanofibers coated with pDA did not interfere with the wound closure, whereas the antibiotics-loaded mats display higher wound healing than untreated wounds. Taken together, these results highlight that pDA coating of gelatin did not interfere with the wound healing while the addition of vancomycin accelerated the process when compared to untreated burns.

In another work, we showed that electrospinning of a collagen dope solution containing dopamine and Ca²⁺ permits the partial oxidation of dopamine [78]. Subsequent ammonium carbonate exposure of the Ca²⁺-pDA mats would result in the complete formation of pDA and mineralized nanofibers. The mineralized nanofibers displayed superior mechanical properties than collagen or collagen mats crosslinked with pDA. The mechanically robust scaffold displayed superior cell adhesion and spreading than electrospun collagen scaffold.
The ammonium carbonate diffusion method has numerous advantages over conventional Tris-HCl route. Electrospun water labile polymers such as PVA and gelatin could not be pDA coated under aqueous alkaline methods, owing to their poor stability in aqueous media. However, such polymers can be readily coated by ADM. The pDA coating by ADM produced homogenous products, contrary to heterogeneous mixture of products formed by Tris-HCl. No ammonia or amine group is incorporated into the product, whereas Tris-base is covalently linked to oxidative products of dopamine, adding further complexity to the final products. As a result, Tris-HCl route produced aggregates of pDA nanoparticles on fiber surface, whereas the vapor phase alkaline exposure triggered smooth pDA coating both along the surface and at the nanofiber contact points, forming “soldered” junctions. Avoiding the use of aqueous or organic solvents could minimize any morphological defects caused by the interference from solvents. The method did not interfere with the biological properties of additives. Simultaneous in situ mineralization and crosslinking of electrospun nanofibers produced mats with excellent mechanical properties and aqueous durability.

4. Conclusion

pDA nanocoating of organic/inorganic substrates is an effective way to modify surface properties of the materials. The availability of myriads of protocol to achieve the nanocoatings in both neutral and extreme pH conditions would expand the application landscape of the method. The development of high speed coating methods together with the diversity of catecholamines will have wide impact on the design and fabrication of polycatecholamine interfaces. The development of high speed spray coating method may overcome the difficulties posed by solution-based methods for industrial applications. One step co-deposition of biologically relevant macromolecules with high speed coating will be useful for the preparation of biointerfaces. The ammonium carbonate diffusion method would allow facile formation of smooth pDA coating on water labile electrospun polymers in solid state, thus potentially avoiding the use of hazardous solvents/organic bases. The protocol would overcome the difficulties in using water-soluble substrates as well as hydrophobic compounds for the preparation of functionalized surfaces.

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Conflict of interest
N/A.

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