Chapter 19
Polydopamine-Based Simple and Versatile Surface Modification of Polymeric Nano Drug Carriers

Malay K. Das, Anupam Sarma, and Trinayan Deka

Abstract The surface modification of polymeric nanoparticle (NP) with bioactive ligands and/or secondary polymeric layers is a common strategy to govern the interaction of NPs with cells, proteins, and other biomolecules. But such surface engineering is not always so simple when the surface is chemically nonreactive. Because of this, NP surface modification processes generally employ reactive connector or coupling agents or prefunctionalization of the polymer, which are very tricky and ineffective. However, prefunctionalization of polymers can reduce the ability of drug encapsulation efficiency if the inserted ligands hamper the chemical properties of the polymer. To solve this issue, scientists have discovered a method of dopamine polymerization as a way of NP surfaces functionalization. In brief, this method involves the incubation of raw NPs in a weak alkaline solution of dopamine and subsequent incubation with ligands. This reaction furnishes a universal coating of polydopamine for metals, polymers, and ceramics, irrespective of their physicochemical characteristics. Polydopamine-based surface modified nanomaterials emerge as novel nanocomposite and get the interests in the area of drug delivery and therapy because of their unique physicochemical features, such as multifaceted adhesive property, great chemical reactivity, exceptional biocompatibility and biodegradability, and strong photothermal conversion capacity. This chapter highlights the recent development of polydopamine-based surface modified polymeric nanoparticles for smart drug delivery and therapy.

Keywords Polymeric nanoparticle · Surface coating · Polydopamine · Drug targeting · Tumour targeting

M. K. Das (✉) · A. Sarma · T. Deka
Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, India
e-mail: mkdps@dibru.ac.in

Y. V Pathak (ed.), *Surface Modification of Nanoparticles for Targeted Drug Delivery*, https://doi.org/10.1007/978-3-030-06115-9_19

1 Introduction

Over the past few decades, polymeric nanoparticles (NPs) have gained attention in relation to targeted drug delivery, which improves the drug distribution in the desired site and also reduces the toxic effects on other organs. To maximize drug delivery to the desired site, NPs should possess a long circulatory half-life until they reach the target site (stealth effect) and should bind and enter the target cells (internalization). The stealth behavior of NPs can be reached by trimming the NP surface with hydrophilic, electrically neutral polymers like polyethylene glycol (PEG) [1, 2]. The interaction of NPs with the target can be accelerated by coupling cell-specific ligands on the NPs surface, which enhance cell attachment and uptake of NPs. Hence, to achieve targeted and controlled drug delivery, NPs should be modified with various functional moieties, such as surface modifiers and targeting ligands [3, 4], and should possess triggered release property toward cellular stimuli, such as pH, redox reactions, and enzymes [5–7]. Moreover, surface functionalization of polymeric NPs is quite difficult if the surface is chemically nonreactive. In this case, it is necessary to activate the NPs surface with the help of reactive linkers [8, 9] or coupling agents [10, 11]. In another approach, NPs can be prepared using prefunctionalized polymers by conjugating functional ligands with polymers [12–14]. But, the process for the synthesis of the polymer–ligand conjugate is a bit lengthy and inefficient and different for each ligand. However, the ligand can change the chemical properties of the conjugate, hindering the drug encapsulation ability of the polymer. To overcome these issues, scientists have employed a dopamine polymerization-based simple and versatile surface functionalization strategy. Dopamine (3,4-dihydroxyphenylethylamine) is a catecholamine that acts as an important neurotransmitter in the nervous system [15]. On oxidation, dopamine undergoes self-polymerization and forms polydopamine (PDA), which is analogous to naturally occurring melanin (eumelanin) [16]. PDA shows identical physicochemical properties as melanins in optics, electricity, and paramagnetism, and also biocompatibility and biodegradation. Another important characteristic of PDA is that it is rich in reactive groups like catechol, amine, and imine. Owing to these versatile functional moieties, PDA employed as a versatile adhesive podium to bind desired materials, realizing a diversity of composites such as metals, oxides, ceramics, polymers and even Teflon with tunable structures and functions [17–19]. The PDA on NP surfaces binds with ligands via Michael addition and/or Schiff base reactions to link them over the surface [20, 21]. The only requirement is the availability of nucleophilic functional groups such as amine and thiol on the ligand molecules. As of its simplicity and versatility, this principle has widely been utilized for surface modification of different types of polymeric NPs [20]. The preparation process of PDA is simple, less laborious, and the physicochemical properties can be tailored by further chemical modification. Furthermore, PDA shows low cytotoxicity and excellent biocompatibility, which make it a versatile podium for drug delivery application. The aim of this chapter is to figure out the progress of PDA-based surface modified polymeric nanococarriers for drug delivery application.

2 Features of Polydopamine

A better knowledge of basic characteristic of PDA in details would help to gain more ideas from different sectors to promote the potential applications in future. PDA possesses the amino and catechol groups from the starting material dopamine. The basic chemical reactions involved that lead to the formation of PDA aggregates are oxidation, cyclization, reorganization, coupling, and oxidative degradation [22, 23]. The chemical heterogeneity of PDA is confirmed by the broad optical absorption of PDA from deep ultraviolet to near infrared [24, 25]. PDA also contains phenolic, amino, and pyrrole–carboxylic acid groups that have a charge at mild pH values. PDA does have an ampholytic character that can be utilized to control the transport of ions [26]. PDA particles formed from Tris buffer are 3D fractal objects [27]. The high-resolution transmission electron microscopy (TEM) has revealed that PDA is comprised of stacked aromatic structures. The interlayer spacing of these stacked structures is 0.35 nm [28]. PDA absorbs UV radiation exponentially toward the ultraviolet spectrum. Because of its strong absorbance in the ultraviolet wavelengths, PDA shows photoprotection effect. The radical scavenging ability of PDA has also been evaluated in vitro based on 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. At a dose level of 120 μg, PDA nanoparticles could scavenge 85% of DPPH organic free radicals. More interestingly, the radical scavenging activity of PDA nanoparticles had a trend of increasing as the nanoparticle size decreased, being comparable to the value of ascorbic acid, a universal free radical scavenging material [29]. One of the most important properties of PDA that particularly intrigues physicists and chemists is its robust and strong adhesion to virtually all types of surfaces, regardless of the surface chemistry [30–34].

3 Modification of Polydopamine Surfaces

There are two major features of PDA those make it suitable for surface functionalization. First, it has the ability to form a nanoscale, conformal, and durable coating to any type of surface. Second, PDA coated surfaces are capable of further modification as per the requirement.

3.1 Chemical Modification of Dopamine Monomer

The catechol and amine functional group make PDA-coated surfaces reactive to a range of chemicals. However, in some cases, dopamine has been remodeled prior to polymerization for further surface modification. For example, dopamine modified with bromoisobutyryl bromide when applied with unmodified dopamine at a molar ratio of 1:1, creates a PDA macro initiator coating which is suitable for further

surface initiation of radical polymerization [35, 36]. When dopamine is modified with 1,3-propane sultone, a sulfonate variant has been formed which creates a negatively charged coating surface to allow better dispersion of coated particles [37].

3.2 Chemical Modification of Polydopamine Surfaces

PDA can be used as an intermediary surface material to allow attachment of other materials or chemical species without requiring prefunctionalization. The reactivity of PDA surfaces toward nucleophiles is dependent on the catechol–quinone equilibrium and consequently, alkaline pH accelerates conjugation reactions [21, 38]. In this instance, the pK_a of the nucleophile is also relevant as it is deprotonated nucleophiles that react and so for neutral pH imidazole (p$K_a \approx 6$) reacts better than a primary amine (p$K_a \approx 10$), but this is reversed at higher pH [21, 39, 40]. The coupling between nucleophiles and PDA surfaces have been used for the attachment of small molecules, synthetic polymers, biomolecules, and the construction of metal-organic frameworks [21, 40–45]. Due to the importance of the quinone group to PDA reactivity, thermal oxidation [46] has been used to increase the concentration of quinone in PDA coatings, doubling the attachment of nucleophiles to the surface [47]. The presence of hydroxyl and amine groups at the surface of PDA coatings also allows for more functionalization methods based on the reactivity of these groups. For example, a random copolymer containing glycidyl groups was attached to PDA coatings through reaction to amines and hydroxyl groups [48]. Also, the free amine groups of PDA have been used as a surface initiator for the ring opening polymerization of lactide, generating a polylactic acid coating [49].

3.3 Physical Modification of Polydopamine

PDA coatings can also be physically modified by changing to the coating method. For example, multiple depositions have been used to increase surface coating thickness which is limited for most surfaces with single coatings. Also, coatings can be smoothed by sonication in Tris buffer after coating and roughened by rapid agitation (200–300 rpm) during coating [50–52]. Another physical method of inducing surface roughness in PDA coatings was made by applying the coating to a uniaxial prestrained polydimethylsiloxane substrate. Upon release of the substrate strain, a striped wrinkled pattern emerges in the PDA film [53]. At lower temperatures (<150 °C) the annealing process caused reorientation within the film structure, allowing unreacted amines to take part in cyclization and cross-linking reactions, stabilizing the film [54].

4 Method and Mechanism of Polydopamine-Based Surface Modification

The simple surface coat of PDA can be achieved by incubating raw NPs in 0.5 mg/mL solution of dopamine hydrochloride dissolved in 10 mM Tris buffer (pH 8.5) at room temperature for 3 h with stirring [55–60]. Alternatively, dopamine solution can also be added to the NPs suspension [61–66]. Due to the chemical reaction, the dopamine is polymerized and deposited over the NPs and forms a layer over the NPs. The coated particles are then collected by centrifugation (12,000 rpm for 20 min) at 4 °C [67–71]. In some cases, the undeposited PDA and PDA coated NPs are separated by dialysis method in deionized water [72].

The versatile surface modification of polymeric NPs involves the second component during the deposition of dopamine over nanoparticles, including polymers, bio-macromolecules, small organic molecules, nanomaterials, and inorganic precursors. For surface functionalization, PDA coated NPs are resuspended in Tris buffer (10 mM, pH 8.5), which contained different ligands, incubated at room temperature for 30 min with rotation. The ligands are conjugated with the dopamine precoat by different physicochemical interaction. The functionalized particles are then washed with deionized water after collection by centrifugation [55, 57, 59, 69].

Lee et al. had proposed at first about the mussel-inspired chemistry for surface functionalization. In that study, they reported that a well-known neurotransmitter, dopamine, can form PDA coating on various materials after self-polymerization in the weak alkaline solution under the open air [20]. The mechanism of PDA coating involves two major ways: oxypolymerization and surface adhesion.

On oxidation, Dopamine is transformed to dopaminequinone and subsequently, it converted to 5,6 dihydroxyindole (DHI) through the intermolecular cyclization and then to polydopamine (Fig. 19.1) [19]. Scientists showed three different views on the polymerization mechanism of dopamine. PDA can form by dopamine molecules through noncovalent bonds including hydrogen bonding and π–π stacking [73], PDA may also form by the formation of dimers and trimmers via oxidation, coupling and then congregated to the PDA [74] and Liebscher et al. reported that some oligomers are produced in the solution of dopamine [75]. PDA is widely considered as a supramolecular aggregate rather than a covalent polymer with high molecular weight and the noncovalent bonds play a crucial role during the dopamine coating.

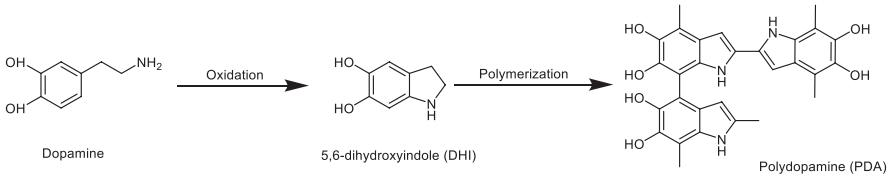

Fig. 19.1 Schematic illustration of Polydopamine (PDA) formation

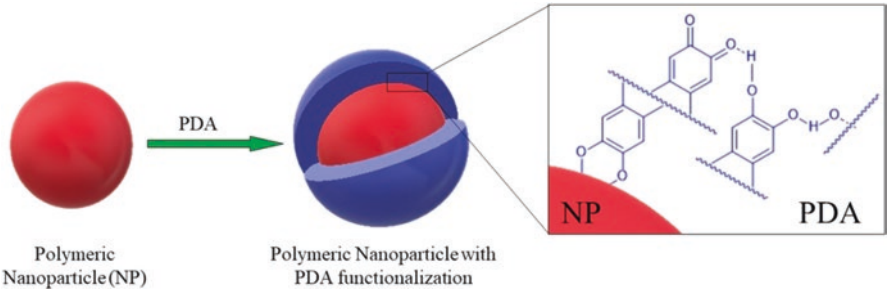

Fig. 19.2 Schematic illustration of PDA functionalization over polymeric nanoparticle

Another critical factor is the adhesion mechanism of PDA over nanoparticles (Fig. 19.2). The amino and catechol groups of PDA could interact with the surface of nanoparticles [76]. The aromatic structure present on PDA could interact with hydrophobic surfaces of nanoparticles through hydrophobic interaction and π–π stacking [77]. Whereas both amino and catechol functional groups of PDA are hydrogen donor, so it can able to form hydrogen bonds with the hydrogen acceptor group possessing polymers like PVP [78]. The electrostatic interactions are also observed in the case of charged surfaces because the amino groups are positively charged while the catechol groups are negatively charged [79]. In summary, the mechanism of PDA deposition combines the formation of PDA assemblies through single or multiple covalent/noncovalent interactions. The cross-linked structure in PDA also contributes to the adhesion.

The dopamine-assisted versatile surface modification of NPs is very vital as the interactions between the cocomponent and the PDA determines the deposition behavior and the final functionalization properties. There are various groups present in the dopamine molecule and PDA aggregate, like amino, phenolic hydroxyl, and an aromatic ring. Therefore, dopamine/PDA can interact with cocomponents via noncovalent interactions including hydrogen bond, hydrophobic force, and electrostatic attraction. For example, Zhang et al. investigated the interactions of several nonionic polymers like poly(ethylene glycol) (PEG), poly(*N*-vinyl pyrrolidone) (PVP), and poly(vinyl alcohol) (PVA) as cocomponents with PDA in the coating assembly, where the hydrogen bonds play a significant role [78]. But it was observed that the deposition amount of PDA/cocomponent decreases as compared to that of the neat PDA, especially in the case of PDA/PVP. The scientist postulated that PVP could hinder the formation of PDA aggregates by interrupting the noncovalent interactions of hydrogen bonding between PVP and DHI.

PDA is also able to interact with cocomponents via the electrostatic interactions. The amine group of codeposits can react with dopamine via Michael addition and Schiff-base reactions, whereas the quaternary amine can interact with PDA via the electrostatic interactions because PDA is always negatively charged in the deposition condition (generally in a pH range of 7–9). By contrast, polyanions can inhibit not only PDA aggregation but also PDA deposition. It has been found that PDA can be codeposited with poly(sulfobetaine methacrylate) (PSBMA), a typical

zwitterionic polymer, onto polypropylene membrane and steel mesh surfaces [80, 81]. The main mechanism of interaction is postulated as the local electrostatic attractions between the deprotonated phenol group and the quaternary ammonium rather than the hydrogen bonding [82]. But the hydrogen bonds may also form between PDA and zwitterionic polymer. For example, Chang et al. coated Si wafers by PDA with poly(methacryloyloxyethyl phosphorylcholine) (PMPC) through hydrogen bonding and the cation–π interaction [83].

As compared to the noncovalent versatile surface modification, the covalent versatile surface modification provides a stable coating. For example, PDA and low-molecular-weight polyethyleneimine (PEI) can be codeposited onto the surfaces of microporous polypropylene membrane [84, 85]. Due to the interaction between PDA and PEI accelerates the deposition process. Although PDA may react with PEI via different routes, Zhao et al. found that PEI molecules coupled with PDA mainly via the Michael addition reaction [86]. Individually PDA generally creates rough coating due to the stacking of large PDA aggregated particles. While the codeposited coating becomes uniform because the incorporation of PEI prevents the noncovalent interactions in PDA and reduces the particle size. Last but most important, the stability of the codeposited coating is greatly improved, especially in acidic and alkaline environments due to the formation of covalent bonds. Quan et al. reported the versatile surface modification by dopamine and poly(ethylene glycol) diglycidyl ether through reactions between the epoxy group and the hydroxyl or amino groups in dopamine [87].

5 Factors Affecting the Polymerization of Dopamine

The coating of NPs by PDA is generally held at room temperature in Tris–HCl buffer of pH 8.5. Numerous studies have been performed to find out the crucial parameters that can affect dopamine polymerization (i.e., duration of coating, dopamine coating solution concentration, pH of Tris–HCl, and temperature). Since dopamine is polymerized by oxidation hence some oxidizing agents are generally involved in the reaction. Normally, the dissolved oxygen that already in the coating solution is sufficient to progress the polymerization process [88]. But to maintain uniform oxygen concentration in the mixture, it must be kept on agitating during the reaction time. Otherwise, the fine PDA coat is formed at the air-water interface that increases in thickness as compared to submerged surfaces with reaction time over 24 h [89]. Usually for surface coating by PDA involves dopamine at a concentration of 2 mg/mL in 10 mM Tris buffer of pH 8.5 and applied to the surface with agitation under ambient temperature and pressure [20]. Under these circumstances, the thickness of the PDA coating depends upon coating time, remarkably 10 nm in 3 h and achieved approximately 40–50 nm thickness within 24 h [20, 21, 50]. Dopamine concentration also has an influence on PDA coating rate and thickness. It has been seen that coating rate increases with dopamine concentration up to 7.6 mg/mL [90]. Likewise, increasing the dopamine concentration within 0.5–10 mg/mL has been found to

Table 19.1 Factors affecting the polydopamine coating

Factors	Effects on the polydopamine coating
Rate of oxidation	Coating efficiency increases with increase in oxidation rate
Concentration of dopamine	Coating efficiency increases with increase in dopamine concentration
Coating duration	Coating efficiency increases with increase in coating time
Buffer pH	At pH $\leq$ 4.5 poor coating happens At pH 7 relatively improved coating happens At pH 8.5 highest coating efficiency observed At pH $\geq$ 11 an unstable coating forms
Temperature	Coating efficiency increases with rise in temperature

increase maximum film thickness, but with an unwanted increase in surface roughness [51, 91, 92]. Generally, temperature has shown proportionately minimal effects on coating kinetics compared to other universally accepted factors (i.e., 2 mg/mL, pH 8.5) [93]. A report suggested that higher temperature with agitation could increase coating kinetics, and the resultant PDA coat exhibit the same type of reactivity that had been modified at standard conditions [94]. Under UV light dopamine undergoes quick polymerization and form PDA coat more rapidly, resulting in 80 nm thick coating after 10 h as compared to 20 nm for coating conducted in the dark environment. The UV irradiation accelerates the intramolecular cyclization of oxidized quinone, generating a larger quantity of reactive monomers, which speeds up the polymerization [95]. Also, UV irradiation stabilizes catechol or nitrogen centered radicals for continuing polymerization and has been used in surface initiated free radical polymerization for modification of PDA surfaces. The Table 19.1 describes the different factors that affect the PDA coating.

6 Stability of Polydopamine Coating

Defining stability for PDA coatings can be difficult, particularly in the mild base in which monomers and poorly bound oligomers can be released without necessarily completely destroying the structure of the coating [39]. This release can occur because the stability in the mild base is in part mediated by the charge of the dopamine monomers. Under acidic and neutral conditions, the amine in dopamine is protonated and the charge is positive, while the overall charge of the aggregate is negative leading to opportunities for electrostatic interactions [96]. However, as the pH increases, deprotonation of the first hydroxyl ($pK_a \approx 9$) followed by the ammonium ($pK_a \approx 10.5$) and the second hydroxyl group ($pK_a \approx 12$) [76] changes the charge on the unreacted dopamine to negative [97]. This breaks the electrostatic interactions between dopamine monomers and the aggregate, releasing the dopamine into the solution. Similarly, relatively nonpolar DHI monomers will gain negative charge with deprotonation and become more soluble in polar solution [25]. As the dopamine and DHI monomers are part of the overall PDA supramolecular

structure, their release, along with the changing charge profile of the aggregate, can lead to changes to both the coating structure as well as to the supramolecular associations of the coating with the surface [98].

7 The Recent Development of Polydopamine-Based Surface-Modified Polymeric Nanoparticles for Drug Delivery

In many clinical situations, the most of the therapeutic agents are nonspecific and unable to reach the desired site in the body in adequate quantity due to various reasons which lead to systemic side effects and improper treatment. To reduce these inadequacies, the development of functional nanoparticles as drug delivery systems came across, which enable selective delivery of therapeutic agents at desired target sites of the body in the appropriate way. Polydopamine has been recently proposed as a good material for drug delivery, not only because of their excellent chemical versatility, high water solubility, excellent biocompatibility and biodegradation but also because of their cavities as well as their surfaces that allow for high payloads of drug molecules.

Now a day functionalization of the surface of a polymeric nanoparticle (NP) with cell targeting ligands or secondary polymeric layers is a trend to control the interaction between NPs and cells/proteins. However, this is not so easy when the surface is chemically nonreactive. To overcome this problem, generally, prefunctionalization of the polymer with reactive linkers or coupling agents is employed. Moreover, in this process, the polymers may lose the ability to encapsulate a drug. To solve this issue, Park et al. prepared a poly(lactic-co-glycolic acid) (PLGA) NPs, surface-modified with dopamine by incubating the preformed NPs in a weak alkaline dopamine solution. The PDA-derived NPs were then incubated with three different surface modifiers folate, Arg-Gly-Asp peptide, and polymer [poly(carboxybetaine methacrylate)] which act as a ligand and form the particle of size 100 nm. The cell uptake study on KB cells and HUVEC cells illustrates the effective internalization of the functionalized NPs as shown by confocal microscopy and flow cytometer [59]. Gastric cancer retains the third place in cancer-related mortality worldwide. Although gradually its occurrence is decreased, but still it poses a major challenge due to poor prognosis and limited treatments. Barbaloin (BBL) is the major bioactive composition of aloe vera possessing antioxidant, anti-inflammatory, and antitumor activities. The surface modification of polymeric NPs by Polydopamine (pD) is easy with the ability to conjugate ligands and additional polymeric layers. Wang et al. developed BBL-loaded pD-functionalized NPs, which were prepared by polylactide-TPGS (PLA-TPGS) (pD-PLA-TPGS/NPs). And galactosamine (Gal) was conjugated as a ligand on the NPs (Gal-pD-PLA-TPGS/NPs) for targeting the gastric cancer cells. The particle size of the prepared NPs was found 204.8 nm with a zeta potential of −13.8 mV. The cellular uptake study revealed that BBL-loaded Gal-pD-PLA-TPGS/NPs were efficiently taken up by gastric cancer cells

(SGC-7901) and significantly reduced the gastric cancer cell viability. In vivo study on mice showed that Gal-pD-PLA-TPGS/NPs were specifically targeted to tumor site as confirmed by the low tumor volume and tumor weight. And there was no significant difference was observed in body and liver weight, as well as the histological changes in major organs isolated from each group of mice which indicated the nontoxic behaviour of the formulation [55]. It is universally accepted that bone comprises of collagen and nanohydroxyapatite (nano-HA) in needle-like shapes. Because of its excellent bone-binding capacity and biological stability, HA material has great application in the clinic as artificial bone. However, it was also mentioned that nano-HA can hinder the growth of osteoblasts depending upon concentration. So to use HA as implantation candidate in bone graft substitutes, nano-HA need to be further modified. Mussel-inspired polydopamine (pD) coatings have several unique characteristics such as durability, versatility, and robustness. Sun et al. successfully prepared a novel bone forming peptide BMP-7 decorated, mussels inspired adhesive proteins dopamine coated nano-HA. Here nano-HA was prepared and coated by pH favoured dopamine polymerization, subsequently, the BMP-7 peptide was affixed onto polydopamine (pDA)-coated nano-HA (HA-pDA). The cell line study demonstrated that the BMP-7 conjugated nano-HA crystals could prompt the adhesion and proliferation of MG-63 cells. Moreover, the surface engineered nano-HA showed high alkaline phosphatase activity which signifies that the grafted peptide could maintain its bioactivity after conjugation with HA-pDA. These functionalized nano-HA crystals have the immense potential as biologically active materials in bone repairing and bone regeneration coating applications [72]. Sunoqrot et al. have designed and developed pD-coated methoxypolyethylene glycol-b-poly(ε-caprolactone) NPs (mPEG-PCL@pD) for gastro-retentive drug delivery (GRDD) with particle size 55.4 ± 3.7 nm and zeta potential −0.1 ± 0.6 mV. The mucoadhesive property of pD-coated NPs was studied in vitro using mucin under simulated condition mimicking the stomach lumen environment. The Mucin and NPs interactions at ratios of 1:1, 1:2, and 1:4 w/w were observed by dynamic light scattering, and an altered particle size was noticed. The increased turbidity of mucin/NPs was observed, which implies the development of bulky mucin-NP conjugation. They also concluded that there were no electrostatic interactions between mucin-pD-coated NPs as confirmed by zeta potential. The ex vivo wash-off experiment showed 78% attachment of pD-coated NPs on sheep stomach mucosa after incubation of 8 h, as compared to 33% of uncoated NPs. And a similar in vitro controlled release profile of rifampicin was observed between pD-coated and uncoated NPs [61]. Incorporating imaging and targeted moieties in multifunctional nanomaterials of biocompatible constituents provides great possibilities in cancer theranostic applications. Ao et al. showed a combination approach for surface modification of PDA based nanocomposites with magnetic and stimuli-controlled drug release property for clinical cancer theranostics. Here the iron oxide nanolayer was sandwiched in between PDA nanoparticles and surface coating PDA layer of the nanocomposite with increased near-infrared (NIR) photothermal conversion as well as great superparamagnetic property. Moreover, due to the high reactive property of PDA, it allowed facile linkage with doxorubicin and polyethylene

glycol chains for in vivo chemotherapy of cancer. The particle size of the nanocomposite was found 267 nm and a partially neutralized zeta potential of −15.6 mV. With the application of magnetic resonance imaging/photoacoustic imaging, the dual-modal tumor imaging and active magnetic tumor targeting of the nanocomposite for the successful tumor abolition were attained as confirmed by confocal imaging of 4 T1 cells [62]. Stability of nanoformulation in vitro as well as in vivo plays a vital role in nanotherapeutics. Amoozgar et al. prepared a protein-based doxorubicin loaded PLGA nanotherapeutic formulations to enhance the stability and therapeutic efficiency. In the study, proteins were embedded in the surface of PDA functionalized nanoparticles (NPs) to enhance protein stability and enzymatic activity. The NPs formed showed the particle size of <180 nm and surface charges −10 mV. The surface-coated protein provided a barrier, preventing the burst release of encapsulated doxorubicin. So the sustained delivery of doxorubicin reduced drug resistance in a breast tumor cell line, 4 T1 [63]. Nowadays, demand for chemically active polymeric layers of functionalized nanoparticles has arrived, which is a very complicated task as it may lead to the loss of ability to encapsulate the drug in sufficient amount. Bi et al. developed a pH-sensitive platform for functionalizing the surface of PLGA nanoparticles with PDA. Doxorubicin was successfully conjugated (DOX)-PDA-(PLGA) NPs with two targeting moieties folate (FA) and a peptide (Arg-Gly-Asp, RGD). The particle size came out 162.9 nm with negative zeta potential. The particles were quite stable in different physiological solutions and showed pH-dependent drug release property. In comparison to DOX-NPs, the targeting nanoparticles have tremendous targeting capability in HeLa cells. Moreover, the in vivo study explains 70% tumor inhibition by targeting nanoparticles with decreased DOX related side effects and improve drug accumulation in tumor site [67]. Metronomic chemotherapy hinders the development of drug resistance. But to achieve sustained tumor-specific chemotherapy remains difficult. Amoozgar et al. prepared paclitaxel-loaded PLGA nanoparticles functionalized with PDA and a successive layer of poly(ethylene glycol) (PEG). The particle size of the NPs was found 161.53 ± 1.42 nm and zeta potential −4.50 ± 8.92 mV. These particles attained a 3.8-fold higher loading compared to PLGA−PEG copolymer based nanoparticle. In vitro drug release kinetics and in vivo drug distribution profiles exhibited sustained release of paclitaxel. Moreover, administration of prepared nanoparticles intraperitoneally to drug-resistant ovarian tumor-bearing mice showed significant survival benefits without any systemic toxic effect [65]. Nie et al. developed a novel drug delivery system for the treatment of breast cancer using a PDA-based surface modification of NPs. The docetaxel (DTX)-loaded star-shaped copolymer cholic acid-PLGA nanoparticles (CA-PLGA@PDA/NPs) were coated with PDA and were conjugated with amino-poly(ethylene glycol)-folic acid (NH_2-PEG-FA) and bortezomib (BTZ) to form the targeting nanocomposite. The particle size of the nanocomposite was found 168.7 ± 4.2 nm and zeta potential −11.20 ± 3.6 mV. The in vitro cell uptake study on MCF-7, a breast cancer cell line, showed active targeting of the NPs. Moreover, BTZ release from the NPs was pH dependent on the tumor acidic environment for synergistic action with DTX [66]. Han et al. developed a nanoparticulate drug carrier system that interacts with tumor cells of the

mildly acidic microenvironment. The prepared polymeric nanoparticles were coated with PDA and modified with amidated TAT peptide. The treatment of cis-aconitic anhydride (CA) and succinic anhydride (SA) with the TAT-conjugated nanocomposite, transformed the amine groups of lysine in TAT peptide into β-carboxylic amides, by inserting carboxylic groups that go through pH-dependent protonation and deprotonation. The nanoparticles conjugated with amide derived TAT peptide (NLpT-CA and NPpT-CA) withstand the interactions with colon cancer cell line LS174T and macrophages cell line J774A.1 at pH 7.4, but showed the interaction with LS174T cell line at pH 6.5, and delivered paclitaxel effectively to the cells in a short contact time. In a mice model, NPpT-CA exhibited less localization in the lung compared to NPpT, indicating the shielding effect of amidation with minimal tumor accumulation of NPpT and NPpT-CA [68]. The main limitations of cancer chemotherapy include the ineffective strategy for targeted chemotherapeutic drug delivery and the difficulty to obtain significant efficacy from a single treatment. Kong et al. reported a synergistic strategy of chemophotothermal therapy for cancer. They have prepared docetaxel-loaded CA-(PCL-ran-PLA) based nanoparticles functionalized with polydopamine (pD) and conjugated with aptamer (Apt) for effective targeting and enhanced therapeutic effect. The particle size of the final NPs was 124.6 ± 5.1 nm and zeta potential −19.2 ± 5.2 mV with entrapment efficiency of 94.18 ± 2.76%. The cell uptake study on MCF-7 cells showed excellent internalization and increased drug concentration in tumor sites in vivo [57]. Xiong et al. synthesized block copolymer methoxy poly(ethylene glycol)-b-poly(ε-caprolactone) by ring-opening polymerization method and developed paclitaxel (PTX)-loaded MPEG-b-PCL nanoparticles, surfaces coated with polydopamine (PTX-loaded MPEG-b-PCL NPs@PDA) for malignant melanoma therapy. The modified nanoprecipitation technique was utilized for NPs preparation. The particle size was found as 141.8 ± 5.8 nm and zeta potential of 10.9 ± 1.5 mV. The cell uptake study showed effective internalization of coumarin-6-loaded NPs@PDA in A875 cells lines. The PTX-loaded NPs@PDA significantly suppress tumor growth as compared to Taxol® and pristine PTX-loaded NPs in nude mice model [99]. Zhu et al. synthesized DTX-loaded NPs using D-a-tocopherol polyethylene glycol 1000 succinate-poly(lactide) (pD-TPGS-PLA/NPs) and surface modified with polydopamine. Galactosamine was linked over prepared NPs (Gal-pD-TPGS-PLA/NPs) to increase the targeting efficiency in hepatocarcinoma cells, via ligand-driven endocytosis. The size of Gal-pD-TPGS-PLA/NPs was found 209.4 ± 5.1 nm and zeta potential of −13.7 ± 2.1 mV. The coumarin 6-loaded Gal-pD-TPGS-PLA/NPs exhibited effective cellular uptake in HepG2 cell line, as confirmed by confocal microscopy and flow cytometry. DTX-loaded Gal-pD-TPGS-PLA/NPs suppress the development of HepG2 cells in a greater extent than a clinically available DTX formulation (Taxotere). The in vivo anticancer efficacy study showed the decreased tumor size on hepatocarcinoma-bearing nude mice model [58]. In an another study Tao et al. prepared a DTX-loaded CA-PLGA-b-TPGS NPs (DTX/NPs) with polydopamine (pD)-based surface modification subsequently conjugated with aptamer (Apt-pD-DTX/NPs) for enhanced therapeutic effects of breast cancer. The size of the particles was found 112.1 ± 5.3 nm and zeta potential of −14.3 ± 3.9 mV. The aptamer conjugated NPs

showed great in vitro internalization in MCF-7 cells and MDA-MB-231 cells barely changed the characters of NPs. The in vivo animal studies in the rat model explains that the Apt-pD-DTX/NPs have the significant targeting ability and increased therapeutic response as compared to clinical Taxotere [69]. The Nanoparticle-based drug delivery to cancer is hampered by the heterogeneity of the enhanced permeability and retention (EPR) effect in cancer cells and release of drug during circulation before reaching the tumor site. To overcome this challenge Park et al. prepared a magnetophoretic strategy to NP delivery to cancer cells. They prepared polymer–iron oxide nanocomposites (PINCs) from PLGA and colloidal Fe_3O_4 and coated with PDA. The *Z*-average of PINCs was found 218 nm with a zeta potential of −12 mV. The PINCs were stable in serum-containing medium and gives a quick response to magnetic field gradients over 1 kG/cm. Under the field gradients, PINCs were rapidly get entered into SKOV3 cells as confirmed by cell uptake study. The In vivo study showed accumulation of PINCs in poorly vascularized subcutaneous SKOV3 xenografts without EPR effect [70]. Low molecular weight chitosan (LMWC) is a potential polymer for surface engineering of nanoparticles (NPs), which can perform stealth effect and electrostatic interaction with tumors at mild acidic pH. Abouelmagd et al. prepared paclitaxel loaded PLGA NPs coated with PDA and conjugated with LMWC (PLGA-pD-LMWC NPs). The size of the particles were found 209 nm and zeta potential measurement showed positive value when dispersed in MES buffer pH 6.2 and a negative value when dispersed in phosphate buffer pH 7.4. So, PLGA-pD-LMWC NPs had a pH-dependent surface charge and acid-specific NP-cell interaction and increased drug delivery to weakly acidic cell environment as showed by cell uptake study on SKOV-3 cells. PLGA-pD-LMWC NPs also showed less uptake by phagocyte as described by J774A.1 macrophages uptake study [71]. Gullotti et al. prepared PTX loaded PLGA NPs coated with PDA and further modified with TAT peptide (PLGA-pDA-TAT NPs) or dual modified with TAT peptide and hybrid of PEG and MMP-substrate peptide (peritumorally activatable NPs, PANPs). The particle size of the formulation was found 291.8 nm with a zeta potential of +0.3 mV. PLGA-pDA-TAT NPs and MMP-2-pretreated PANPs exhibited better cellular uptake in SKOV-3 cells [60]. Some of the important polydopamine based surface modified nano drug carriers are listed below (Table 19.2).

8 Conclusion and Future Prospects

In this chapter, an overview of the recent progress in research on dopamine-based surface modified polymeric nanoparticles in drug therapy is presented. Since the discovery of self-polymerization of dopamine by oxidation for fabrication of PDA derived materials, the focus has been on the preparation and applications of PDA-based nanocomposites. As time passed researchers starts to give attention to the interaction and cofabrication of dopamine with other materials to form a functional component. Dopamine derived materials possess many interesting physicochemical

Table 19.2 Polydopamine-based surface modified polymeric nanoparticle and its application

Polymer	Drug	Ligand	Cell line	Application	Ref.
PLGA	–	Folate, Arg-Gly-Asp, and poly(carboxybetaine methacrylate)	KB cells or HUVEC	Cancer	[59]
Polylactide-TPGS	Barbaloin	Galactosamine	SGC-7901	Gastric cancer	[55]
Hydroxyapatite	BMP-7	–	MG-63	Bone regeneration	[72]
Methoxypolyethylene glycol-b-poly(ε-caprolactone)	Rifampicin	–	–	GRDD	[61]
Polydopamine	Doxorubicin	–	4 T1	Brest cancer	[62]
PLGA	Doxorubicin	Lysozyme, DNase, collagenase I, or E-selectin antibody	4 T1	Brest cancer	[63]
PLGA	Doxorubicin	Folate and RGD	HeLa	Cervical cancer	[67]
PLGA	Paclitaxel	–	BR5FVB1-Akt	Ovarian cancer	[65]
Cholic acid-poly(lactide-co-glycolide)	Docetaxel, Bortezomib	Amino-poly(ethylene glycol)-folic acid	MCF-7	Breast cancer	[66]
PLGA	Paclitaxel	TAT peptide	LS174T or J774A	Colon cancer	[68]
CA-(PCL-ran-PLA) copolymer	Docetaxel	AS1411 Aptamer	MCF-7	Breast cancer	[57]
Methoxy poly(ethylene glycol)-b-poly(ε-caprolactone)	Paclitaxel	–	A875	Malignant melanoma	[99]
D-a-tocopherol polyethylene glycol 1000 succinate-poly(lactide)	Docetaxel	Galactosamine	HepG2	Liver cancer	[58]
CA-PLGA-b-TPGS	Docetaxel	AS1411 aptamer	MCF-7 or LNCaP	Breast cancer	[69]
PLGA	–	–	SKOV3	Ovarian cancer	[70]
PLGA	Paclitaxel	–	SKOV-3	Ovarian cancer	[71]
PLGA	Paclitaxel	TAT peptide	SKOV-3	Ovarian cancer	[60]

properties, including versatility in adhesion to the surface of any type and shape, great chemical reactivity with thiol and amino terminated materials and metal ions, and superb biocompatibility and biodegradability. These exciting features make dopamine-based nanomaterials very enticing for fabrication of functional

nanomedicine, which has been widely utilized in the treatment of various diseases, from diagnosis of a tumor, bio imaging, targeted or site-specific, controlled drug delivery, photo thermal therapy to combination therapy and imaging-guided therapies.

Although dopamine-based materials possess impressive advances in the preparation, functionalization, and drug delivery applications, there are still many challenges that should be sorted out in the near future to transform these materials from research into clinical applications. One of these is the lack of proper understanding of the mechanism of polymerization and the detailed structures of PDA. For a better understanding of the adhesive properties of the materials, such knowledge is essential. As dopamine itself is a drug, it is an immediate requirement for the toxicity evaluation of dopamine-based materials. Furthermore, more efforts must be directed to dopamine-based nanoplatform in targeted drug delivery and controlled release, which is a development direction for biomedicine in future.

In summary, due to its unique features and the simplicity of derivatization dopamine-based materials have been greatly utilized only in anticancer research till date. But equally, it has the potential for site-specific drug delivery including to brain as well. Although various obstacles exist in their clinical applications, it can be expected that dopamine-based materials will be available in the near future, creating a new solution in drug therapy.

Declaration All figures and tables are original and self-made.

References

1. Hong, R., Huang, C., & Tseng, Y. (1999, November). Direct comparison of liposomal doxorubicin with or without polyethylene glycol coating in C-26 tumor-bearing mice: Is surface coating with polyethylene glycol beneficial? Direct comparison of liposomal doxorubicin with or without polyethylene glycol coa. *Clinical Cancer Research, 5*, 3645–3652.
2. Hatakeyama, H., Akita, H., & Harashima, H. (2011). A multifunctional envelope type nano device (MEND) for gene delivery to tumours based on the EPR effect: A strategy for overcoming the PEG dilemma. *Advanced Drug Delivery Reviews, 63*(3), 152–160.
3. Kim, D., Kim, E., Kim, J., Park, K. M., Baek, K., Jung, M., Ko, Y. H., Sung, W., Kim, H. S., Suh, J. H., Park, C. G., Na, O. S., Lee, D. K., Lee, K. E., Han, S. S., & Kim, K. (2007). Direct synthesis of polymer nanocapsules with a noncovalently tailorable surface. *Angewandte Chemie, International Edition, 46*(19), 3471–3474.
4. Kim, E., Kim, D., Jung, H., Lee, J., Paul, S., Selvapalam, N., Yang, Y., Lim, N., Park, C. G., & Kim, K. (2010). Facile, template-free synthesis of stimuli-responsive polymer nanocapsules for targeted drug delivery. *Angewandte Chemie, International Edition, 49*(26), 4405–4408.
5. Liang, K., Such, G. K., Zhu, Z., Yan, Y., Lomas, H., & Caruso, F. (2011). Charge-shifting click capsules with dual-responsive cargo release mechanisms. *Advanced Materials, 23*(36), 273–277.
6. Yan, Y., Wang, Y., Heath, J. K., Nice, E. C., & Caruso, F. (2011). Cellular association and cargo release of redox-responsive polymer capsules mediated by exofacial thiols. *Advanced Materials, 23*(34), 3916–3921.

7. Ochs, C. J., Such, G. K., Yan, Y., Van Koeverden, M. P., & Caruso, F. (2010). Biodegradable click capsules with engineered drug-loaded multilayers. *ACS Nano, 4*(3), 1653–1663.
8. Sahoo, S. K., & Labhasetwar, V. (2005). Enhanced antiproliferative activity of transferrin-conjugated paclitaxel-loaded nanoparticles is mediated via sustained intracellular drug retention. *Molecular Pharmaceutics, 2*(5), 373–383.
9. Rao, K. S., Reddy, M. K., Horning, J. L., & Labhasetwar, V. (2008). TAT-conjugated nanoparticles for the CNS delivery of anti-HIV drugs. *Biomaterials, 29*(33), 4429–4438.
10. Narayanan, S., Binulal, N. S., Mony, U., Manzoor, K., Nair, S., & Menon, D. (2010). Folate targeted polymeric 'green' nanotherapy for cancer. *Nanotechnology, 21*(28), 1–13.
11. Mo, Y., & Lim, L. Y. (2005). Paclitaxel-loaded PLGA nanoparticles: Potentiation of anticancer activity by surface conjugation with wheat germ agglutinin. *Journal of Controlled Release, 108*(2–3), 244–262.
12. Gu, F., Zhang, L., Teply, B. A., Mann, N., Wang, A., Radovic-Moreno, A. F., Langer, R., & Farokhzad, O. C. (2008). Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers. *Proceedings of the National Academy of Sciences, 105*(7), 2586–2591.
13. Hrkach, J., Von Hoff, D., Ali, M. M., Andrianova, E., Auer, J., Campbell, T., De Witt, D., Figa, M., Figueiredo, M., Horhota, A., Low, S., McDonnell, K., Peeke, E., Retnarajan, B., Sabnis, A., Schnipper, E., Song, J. J., Song, Y. H., Summa, J., Tompsett, D., Troiano, G., Hoven, T. V. G., Wright, J., LoRusso, P., Kantoff, P. W., Bander, N. H., Sweeney, C., Farokhzad, O. C., Langer, R., & Zale, S. (2012). Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. *Science Translational Medicine, 4*(128), 1–11.
14. Tosi, G., Costantino, L., Rivasi, F., Ruozi, B., Leo, E., Vergoni, A. V., Tacchi, R., Bertolini, A., Vandelli, M. A., & Forni, F. (2007). Targeting the central nervous system: In vivo experiments with peptide-derivatized nanoparticles loaded with Loperamide and Rhodamine-123. *Journal of Controlled Release, 122*(1), 1–9.
15. Bibb, J. A., Snyder, G. L., Nishi, A., Yan, Z., Meijer, L., Flenberg, A. A., Tsai, L. H., Kwon, Y. T., Girault, J. A., Czernik, A. J., Huganir, R. L., Hemmings, H. C., Nairn, A. C., & Greengard, P. (1999). Phosphorylation of DARPP-32 by Cdk5 modulates dopamine signalling in neurons. *Nature, 402*(6762), 669–671.
16. d'Ischia, M., Napolitano, A., Ball, V., Chen, C.-T., & Buehler, M. J. (2014). Polydopamine and eumelanin: From structure-property relationships to a unified tailoring strategy. *Accounts of Chemical Research, 47*(12), 3541–3550.
17. Cui, X., Yin, Y., Ma, Z., Yin, Y., Guan, Y., Rong, S., Gao, J., Niu, Y., & Li, M. (2015). Polydopamine used as hollow capsule and core–shell structures for multiple applications. *Nano, 10*(05), 1530003-1–1530003-23.
18. Lynge, M. E., Van Der Westen, R., Postma, A., & Städler, B. (2011). Polydopamine – A nature-inspired polymer coating for biomedical science. *Nanoscale, 3*(12), 4916–4928.
19. Liu, Y., Ai, K., & Lu, L. (2014). Polydopamine and its derivative materials: Synthesis and promising applications in energy, environmental, and biomedical fields. *Chemical Reviews, 114*(9), 5057–5115.
20. Lee, H., Dellatore, S. M., Miller, W. M., & Messersmith, P. B. (2007). Mussel-inspired surface chemistry for multifunctional coatings haeshin. *Science, 318*(5849), 426–430.
21. Lee, H., Rho, J., & Messersmith, P. B. (2009). Facile conjugation of biomolecules onto surfaces via mussel adhesive protein inspired coatings. *Advanced Materials, 21*(4), 431–434.
22. Dreyer, D. R., Miller, D. J., Freeman, B. D., Paul, D. R., & Bielawski, C. W. (2013). Perspectives on poly(dopamine). *Chemical Science, 4*(10), 3796–3802.
23. D'Ischia, M., Napolitano, A., Ball, V., Chen, C. T., & Buehler, M. J. (2014). Polydopamine and eumelanin: From structure-property relationships to a unified tailoring strategy. *Accounts of Chemical Research, 47*(12), 3541–3550.
24. Wu, T. F., & Hong, J. D. (2016). Synthesis of water-soluble dopamine-melanin for ultrasensitive and ultrafast humidity sensor. *Sensors Actuators, B Chemical, 224*, 178–184.

25. Watt, A. A. R., Bothma, J. P., & Meredith, P. (2009). The supramolecular structure of melanin. *Soft Matter, 5*(19), 3754–3760.
26. Yu, B., Liu, J., Liu, S., & Zhou, F. (2010). Pdop layer exhibiting zwitterionicity: A simple electrochemical interface for governing ion permeability. *Chemical Communications, 46*(32), 5900–5902.
27. Fyodor, N., Vecchia, D., Luchini, A., Napolitano, A., Errico, G. D., Vitiello, G., Szekely, N., Ischia, M., Paduano, L., Ii, F., & Tecchio, P. V. (2014). Tris buffer modulates polydopamine growth, aggregation, and paramagnetic properties. *Langmuir, 30*(32), 9811–9818.
28. Zheng, W., Fan, H., Wang, L., & Jin, Z. (2015). Oxidative self-polymerization of dopamine in an acidic environment. *Langmuir, 31*(42), 11671–11677.
29. Barreto, W. J., Ponzoni, S., & Sassi, P. (1998). A Raman and UV-Vis study of catecholamines oxidized with Mn(III). *Spectrochimica Acta, Part A, 55*(1), 65–72.
30. Tsai, W. B., Chien, C. Y., Thissen, H., & Lai, J. Y. (2011). Dopamine-assisted immobilization of poly(ethylene imine) based polymers for control of cell-surface interactions. *Acta Biomaterialia, 7*(6), 2518–2525.
31. Coyne, K. J., Qin, X. X., & Waite, J. H. (1997). Extensible collagen in mussel byssus: A natural block copolymer. *Science, 277*(5333), 1830–1832.
32. Akemi Ooka, A., & Garrell, R. L. (2000). Surface-enhanced Raman spectroscopy of DOPA-containing peptides related to adhesive protein of marine mussel, *Mytilus edulis*. *Biopolymers, 57*(2), 92–102.
33. Lee, B. P., Dalsin, J. L., & Messersmith, P. B. (2002). Synthesis and gelation of DOPA-modified poly(ethylene glycol) hydrogels. *Biomacromolecules, 3*(5), 1038–1047.
34. Lee, B. P., Chao, C. Y., Nunalee, F. N., Motan, E., Shull, K. R., & Messersmith, P. B. (2006). Rapid gel formation and adhesion in photocurable and biodegradable block copolymers with high DOPA content. *Macromolecules, 39*(5), 1740–1748.
35. Zhu, B., & Edmondson, S. (2011). Polydopamine-melanin initiators for surface-initiated ATRP. *Polymer, 52*(10), 2141–2149.
36. Ye, G., Lee, J., Perreault, F., & Elimelech, M. (2015). Controlled architecture of dual-functional block copolymer brushes on thin-film composite membranes for integrated 'defending' and 'attacking' strategies against biofouling. *ACS Applied Materials & Interfaces, 7*(41), 23069–23079.
37. Chung, Y. C., & Huang, J. Y. (2014). Water-borne composite coatings using nanoparticles modified with dopamine derivatives. *Thin Solid Films, 570*(Part B), 376–382.
38. Mostert, A. B., Powell, B. J., Pratt, F. L., Hanson, G. R., Sarna, T., Gentle, I. R., & Meredith, P. (2012). Role of semiconductivity and ion transport in the electrical conduction of melanin. *Proceedings of the National Academy of Sciences, 109*(23), 8943–8947.
39. Ball, V. (2014). Physicochemical perspective on 'polydopamine' and 'poly(catecholamine)' films for their applications in biomaterial coatings. *Biointerphases, 9*(3), 030801-1–030801-10.
40. Yeroslavsky, G., Girshevitz, O., Foster-Frey, J., Donovan, D. M., & Rahimipour, S. (2015). Antibacterial and antibiofilm surfaces through polydopamine-assisted immobilization of lysostaphin as an antibacterial enzyme. *Langmuir, 31*(3), 1064–1073.
41. Cai, T., Li, X., Wan, C., & Chung, T. S. (2016, September). Zwitterionic polymers grafted poly(ether sulfone) hollow fiber membranes and their antifouling behaviors for osmotic power generation. *Journal of Membrane Science, 497*, 142–152.
42. Schaubroeck, D., Mader, L., Dubruel, P., & Vanfleteren, J. (2015). Surface modification of an epoxy resin with polyamines and polydopamine: Adhesion toward electroless deposited copper. *Applied Surface Science, 353*, 238–244.
43. Wang, N., Liu, Y., Qiao, Z., Diestel, L., Zhou, J., Huang, A., & Caro, J. (2015). Polydopamine-based synthesis of a zeolite imidazolate framework ZIF-100 membrane with high H_2/CO_2 selectivity. *Journal of Materials Chemistry A, 3*(8), 4722–4728.
44. Fu, L., Shi, Y., Wang, K., Zhou, P., Liu, M., Wan, Q., Tao, L., Zhang, X., & Wei, Y. (2015). Biomimic modification of graphene oxide. *New Journal of Chemistry, 39*(10), 8172–8178.

45. Vaish, A., Vanderah, D. J., Richter, L. J., Dimitriou, M., Steffens, K. L., & Walker, M. L. (2015). Dithiol-based modification of poly(dopamine): Enabling protein resistance via short-chain ethylene oxide oligomers. *Chemical Communications, 51*(30), 6591–6594.
46. Luo, R., Tang, L., Wang, J., Zhao, Y., Tu, Q., Weng, Y., Shen, R., & Huang, N. (2013, June). Improved immobilization of biomolecules to quinone-rich polydopamine for efficient surface functionalization. *Colloids Surfaces B Biointerfaces, 106*, 66–73.
47. Martín, M., Orive, A. G., Lorenzo-Luis, P., Creus, A. H., González-Mora, J. L., & Salazar, P. (2014). Quinone-rich poly(dopamine) magnetic nanoparticles for biosensor applications. *Chemphyschem, 15*(17), 3742–3752.
48. Yang, W. J., Neoh, K.-G., Kang, E.-T., Lay-Ming Teo, S., & Rittschof, D. (2013). Stainless steel surfaces with thiol-terminated hyperbranched polymers for functionalization via thiol-based chemistry. *Polymer Chemistry, 4*(10), 3105–3115.
49. Mrówczyński, R., Nan, A., Turcu, R., Leistner, J., & Liebscher, J. (2015). Polydopamine – A versatile coating for surface-initiated ring-opening polymerization of lactide to polylactide. *Macromolecular Chemistry and Physics, 216*(2), 211–217.
50. Bernsmann, F., Ponche, A., Ringwald, C., Hemmerlé, J., Raya, J., Bechinger, B., Voegel, J., Schaaf, P., & Ball, V. (2009). Characterization of dopamine−melanin growth on silicon oxide. *Journal of Physical Chemistry C, 113*(19), 8234–8242.
51. Cho, J. H., Katsumata, R., Zhou, S. X., Bin Kim, C., Dulaney, A. R., Janes, D. W., & Ellison, C. J. (2016). Ultrasmooth polydopamine modified surfaces for block copolymer nanopatterning on flexible substrates. *ACS Applied Materials & Interfaces, 8*(11), 7456–7463.
52. Su, L., Yu, Y., Zhao, Y., Liang, F., & Zhang, X. (2016). Strong antibacterial polydopamine coatings prepared by a shaking-assisted method. *Scientific Reports, 6*(24420), 1–8.
53. Meng, J., Xie, J., Han, X., & Lu, C. (2016, May). Surface wrinkling on polydopamine film. *Applied Surface Science, 371*, 96–101.
54. Proks, V., Brus, J., Pop-Georgievski, O., Večerníková, E., Wisniewski, W., Kotek, J., Urbanová, M., & Rypáček, F. (2013). Thermal-induced transformation of polydopamine structures: An efficient route for the stabilization of the polydopamine surfaces. *Macromolecular Chemistry and Physics, 214*(4), 499–507.
55. Wang, Y. R., Yang, S. Y., Chen, G. X., & Wei, P. (2018). Barbaloin loaded polydopamine-polylactide-TPGS (PLA-TPGS) nanoparticles against gastric cancer as a targeted drug delivery system: Studies in vitro and in vivo. *Biochemical and Biophysical Research Communications, 499*(1), 8–16.
56. Wang, H., Zhu, W., Huang, Y., Li, Z., Jiang, Y., & Xie, Q. (2017, October). Facile encapsulation of hydroxycamptothecin nanocrystals into zein-based nanocomplexes for active targeting in drug delivery and cell imaging. *Acta Biomaterialia, 61*, 88–100.
57. Kong, N., Deng, M., Sun, X. N., Chen, Y. D., & Sui, X. B. (2018). Polydopamine-functionalized CA-(PCL-ran-PLA) nanoparticles for target delivery of docetaxel and chemo-photothermal therapy of breast cancer. *Frontiers in Pharmacology, 9*(125), 1–14.
58. Zhu, D., Tao, W., Zhang, H., Liu, G., Wang, T., Zhang, L., Zeng, X., & Mei, L. (2016, January). Docetaxel (DTX)-loaded polydopamine-modified TPGS-PLA nanoparticles as a targeted drug delivery system for the treatment of liver cancer. *Acta Biomaterialia, 30*, 144–154.
59. Park, J., Brust, T. F., Lee, H. J., Lee, S. C., Watts, V. J., & Yeo, Y. (2014). Polydopamine-based simple and versatile surface modification of polymeric nano drug carriers. *ACS Nano, 8*(4), 3347–3356.
60. Gullotti, E., Park, J., & Yeo, Y. (2013). Polydopamine-based surface modification for the development of peritumorally activatable nanoparticles. *Pharmaceutical Research, 30*(8), 1956–1967.
61. Sunoqrot, S., Hasan, L., Alsadi, A., Hamed, R., & Tarawneh, O. (2017, August). Interactions of mussel-inspired polymeric nanoparticles with gastric mucin: Implications for gastro-retentive drug delivery. *Colloids Surfaces B Biointerfaces, 156*, 1–8.

62. Ao, L., Wu, C., Liu, K., Wang, W., Fang, L., Huang, L., & Su, W. (2018). Polydopamine-derivated hierarchical nanoplatforms for efficient dual-modal imaging-guided combination in vivo cancer therapy. *ACS Applied Materials & Interfaces, 10*(15), 12544–12552.
63. Amoozgar, Z., & Goldberg, M. S. (2017). Surface modulation of polymeric nanocarriers enhances the stability and delivery of proteins and small molecules. *Nanomedicine, 12*(7), 729–743.
64. Cui, J., Yan, Y., Such, G. K., Liang, K., Ochs, C. J., Postma, A., & Caruso, F. (2012). Immobilization and intracellular delivery of an anticancer drug using mussel-inspired polydopamine capsules. *Biomacromolecules, 13*(8), 2225–2228.
65. Amoozgar, Z., Wang, L., Brandstoetter, T., Wallis, S. S., Wilson, E. M., & Goldberg, M. S. (2014). Dual-layer surface coating of PLGA-based nanoparticles provides slow-release drug delivery to achieve metronomic therapy in a paclitaxel-resistant murine ovarian cancer model. *Biomacromolecules, 15*(11), 4187–4194.
66. Nie, J., Cheng, W., Peng, Y., Liu, G., Chen, Y., Wang, X., Liang, C., Tao, W., Wei, Y., Zeng, X., & Mei, L. (2017). Co-delivery of docetaxel and bortezomib based on a targeting nanoplatform for enhancing cancer chemotherapy effects. *Drug Delivery, 24*(1), 1124–1138.
67. Bi, D., Zhao, L., Yu, R., Li, H., Guo, Y., Wang, X., & Han, M. (2018). Surface modification of doxorubicin-loaded nanoparticles based on polydopamine with pH-sensitive property for tumor targeting therapy. *Drug Delivery, 25*(1), 564–575.
68. Han, N., Pang, L., Xu, J., Hyun, H., Park, J., & Yeo, Y. (2017). Development of surface-variable polymeric nanoparticles for drug delivery to tumors. *Molecular Pharmaceutics, 14*(5), 1538–1547.
69. Tao, W., Zeng, X., Wu, J., Zhu, X., Yu, X., Zhang, X., Zhang, J., Liu, G., & Mei, L. (2016). Polydopamine-based surface modification of novel nanoparticle-aptamer bioconjugates for in vivo breast cancer targeting and enhanced therapeutic effects. *Theranostics, 6*(4), 470–484.
70. Park, J., Kadasala, N. R., Abouelmagd, S. A., Castanares, M. A., David, S., Wei, A., Yeo, Y., Pharmacy, P., Lafayette, W., Lilly, E., Lafayette, W., & Lafayette, W. (2016, September). Polymer–iron oxide composite nanoparticles for EPR-independent drug delivery. *Biomaterials, 101*, 285–295.
71. Abouelmagd, S. A., Ku, Y. J., Yeo, Y., Pharmacy, P., Lafayette, W., & Lafayette, W. (2015). Low molecular weight chitosan-coated polymeric nanoparticles for sustained and pH-sensitive delivery of paclitaxel. *Journal of Drug Targeting, 23*(7–8), 725–735.
72. Sun, Y., Deng, Y., Ye, Z., Liang, S., Tang, Z., & Wei, S. (2013, November). Peptide decorated nano-hydroxyapatite with enhanced bioactivity and osteogenic differentiation via polydopamine coating. *Colloids Surfaces B Biointerfaces, 111*, 107–116.
73. Dreyer, D. R., Miller, D. J., Freeman, B. D., Paul, D. R., & Bielawski, C. W. (2012). Elucidating the structure of poly(dopamine). *Langmuir, 28*(15), 6428–6435.
74. Hong, S., Na, Y. S., Choi, S., Song, I. T., Kim, W. Y., & Lee, H. (2012). Non-covalent self-assembly and covalent polymerization co-contribute to polydopamine formation. *Advanced Functional Materials, 22*(22), 4711–4717.
75. Liebscher, J., Mrówczyński, R., Scheidt, H. A., Filip, C., Haìdade, N. D., Turcu, R., Bende, A., & Beck, S. (2013). Structure of polydopamine: A never-ending story? *Langmuir, 29*(33), 10539–10548.
76. Ye, Q., Zhou, F., & Liu, W. (2011). Bioinspired catecholic chemistry for surface modification. *Chemical Society Reviews, 40*(7), 4244–4258.
77. Leng, C., Liu, Y., Jenkins, C., Meredith, H., Wilker, J. J., & Chen, Z. (2013). Interfacial structure of a DOPA-inspired adhesive polymer studied by sum frequency generation vibrational spectroscopy. *Langmuir, 29*(22), 6659–6664.
78. Zhang, Y., Thingholm, B., Goldie, K. N., Ogaki, R., & Städler, B. (2012). Assembly of poly(dopamine) films mixed with a nonionic polymer. *Langmuir, 28*(51), 17585–17592.
79. Lee, H., Scherer, N. F., & Messersmith, P. B. (2006). Single-molecule mechanics of mussel adhesion. *Proceedings of the National Academy of Sciences, 103*(35), 12999–13003.

80. Zhou, R., Ren, P. F., Yang, H. C., & Xu, Z. K. (2014, September). Fabrication of antifouling membrane surface by poly(sulfobetaine methacrylate)/polydopamine co-deposition. *Journal of Membrane Science, 466*, 18–25.
81. Ren, P. F., Yang, H. C., Jin, Y. N., Liang, H. Q., Wan, L. S., & Xu, Z. K. (2015). Underwater superoleophobic meshes fabricated by poly(sulfobetaine)/polydopamine co-deposition. *RSC Advances, 5*(59), 47592–47598.
82. Ren, P. F., Yang, H. C., Liang, H. Q., Xu, X. L., Wan, L. S., & Xu, Z. K. (2015). Highly stable, protein-resistant surfaces via the layer-by-layer assembly of poly(sulfobetaine methacrylate) and tannic acid. *Langmuir, 31*(21), 5851–5858.
83. Chang, C. C., Kolewe, K. W., Li, Y., Kosif, I., Freeman, B. D., Carter, K. R., Schiffman, J. D., & Emrick, T. (2016). Underwater superoleophobic surfaces prepared from polymer zwitterion/dopamine composite coatings. *Advanced Materials Interfaces, 3*(6), 1–9.
84. Yang, H. C., Liao, K. J., Huang, H., Wu, Q. Y., Wan, L. S., & Xu, Z. K. (2014). Mussel-inspired modification of a polymer membrane for ultra-high water permeability and oil-in-water emulsion separation. *Journal of Materials Chemistry A, 2*(26), 10225–10230.
85. Yang, H. C., Xu, W., Du, Y., Wu, J., & Xu, Z. K. (2014). Composite free-standing films of polydopamine/polyethyleneimine grown at the air/water interface. *RSC Advances, 4*(85), 45415–45418.
86. Zhao, C., Zuo, F., Liao, Z., Qin, Z., Du, S., & Zhao, Z. (2015). Mussel-inspired one-pot synthesis of a fluorescent and water-soluble polydopamine-polyethyleneimine copolymer. *Macromolecular Rapid Communications, 36*(10), 909–915.
87. Quan, S., Li, S., Wang, Z., Yan, X., Guo, Z., & Shao, L. (2015). A bio-inspired CO_2-philic network membrane for enhanced sustainable gas separation. *Journal of Materials Chemistry A, 3*(26), 13758–13766.
88. Karkhanechi, H., Takagi, R., & Matsuyama, H. (2014). Enhanced antibiofouling of RO membranes via polydopamine coating and polyzwitterion immobilization. *Desalination, 337*(1), 23–30.
89. Wu, T. F., & Hong, J. D. (2015). Dopamine-melanin nanofilms for biomimetic structural coloration. *Biomacromolecules, 16*(2), 660–666.
90. Zhang, C., Lv, Y., Qiu, W. Z., He, A., & Xu, Z. K. (2017). Polydopamine coatings with nanopores for versatile molecular separation. *ACS Applied Materials & Interfaces, 9*(16), 14437–14444.
91. Zhang, L., Shi, J., Jiang, Z., Jiang, Y., Qiao, S., Li, J., Wang, R., Meng, R., Zhu, Y., & Zheng, Y. (2011). Bioinspired preparation of polydopamine microcapsule for multienzyme system construction. *Green Chemistry, 13*(2), 300–306.
92. Ball, V., Del Frari, D., Toniazzo, V., & Ruch, D. (2012). Kinetics of polydopamine film deposition as a function of pH and dopamine concentration: Insights in the polydopamine deposition mechanism. *Journal of Colloid and Interface Science, 386*(1), 366–372.
93. Shin, Y. M., Jun, I., Lim, Y. M., Rhim, T., & Shin, H. (2013). Bio-inspired immobilization of cell-adhesive ligands on electrospun nanofibrous patches for cell delivery. *Macromolecular Materials and Engineering, 298*(5), 555–564.
94. Zhou, P., Deng, Y., Lyu, B., Zhang, R., Zhang, H., Ma, H., Lyu, Y., & Wei, S. (2014). Rapidly-deposited polydopamine coating via high temperature and vigorous stirring: Formation, characterization and biofunctional evaluation. *PLoS One, 9*(11), 1–10.
95. Sheng, W., Li, B., Wang, X., Dai, B., Yu, B., Jia, X., & Zhou, F. (2015). Brushing up from 'anywhere' under sunlight: A universal surface-initiated polymerization from polydopamine-coated surfaces. *Chemical Science, 6*(3), 2068–2073.
96. Ball, V. (2010). Impedance spectroscopy and zeta potential titration of dopa-melanin films produced by oxidation of dopamine. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 363*(1–3), 92–97.
97. Mack, F., & Bönisch, H. (1979). Dissociation constants and lipophilicity of catecholamines and related compounds. *Naunyn-Schmiedeberg's Archives of Pharmacology, 310*(1), 1–9.

98. Klosterman, L., Riley, J. K., & Bettinger, C. J. (2015). Control of heterogeneous nucleation and growth kinetics of dopamine-melanin by altering substrate chemistry. *Langmuir, 31*(11), 3451–3458.
99. Xiong, W., Peng, L., Chen, H., & Li, Q. (2015). Surface modification of MPEG-b-PCL-based nanoparticles via oxidative self-polymerization of dopamine for malignant melanoma therapy. *International Journal of Nanomedicine, 10*, 2985–2996.