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Review article

Applications of polydopaminic nanomaterials in mucosal drug delivery

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ABSTRACT

Polydopamine (PDA) is a biopolymer with unique physicochemical properties, including free-radical scavenging, high photothermal conversion efficiency, biocompatibility, biodegradability, excellent fluorescent and theranostic capacity due to their abundant surface chemistry. Thus, PDA is used for a myriad of applications including drug delivery, biosensing, imaging and cancer therapy. Recent reports present a new functionality of PDA as a coating nanomaterial, with major implications in mucosal drug delivery applications, particularly muco-adhesion and muco-penetration. However, this application has received minimal traction in the literature. In this review, we present the physicochemical and functional properties of PDA and highlight its key biomedical applications, especially in cancer therapy. A detailed presentation of the role of PDA as a promising coating material for nanoparticulate carriers intended for mucosal delivery forms the core aspect of the review. Finally, a reflection on key considerations and challenges in the utilizing PDA for mucosal drug delivery, along with the possibilities of translation to clinical studies is expounded.

1. Introduction

Nanomaterials have become pivotal in several medical applications, paving a way for successful diagnosis and treatment of diseases previously insurmountable. Polydopamine (PDA) is formed via autoxidation of dopamine and has found use in chemistry, biology, biomedicine and material sciences [1–3]. A snapshot of some PDA applications utilized as nanomaterials is shown in Fig. 1. PDA is relatively easy to formulate and can be functionalized with relevant chemical moieties [4–6] for targeting specific sites. For example, when constructed as nanoparticles, and due to its biocompatibility and mucoadhesivity, PDA nanomaterials can be made to target malenoma cell adhesion molecule (MUC18), which causes disruption of the actin cytoskeleton in cancer cells and thus inhibits metastasis [7]. MUC18 is a transmembrane glycoprotein highly expressed in several cancers [4]. More interestingly, PDA can be coated on nanomaterials to effect advanced properties such as non-toxicity, biocompatibility, thermal stability and strong near infrared (NIR) absorption capability [5–8]. With regard to NIR functionality, PDA quenches florescence in chromophores and thus, manifests luminescence, which is desirable in imaging and sensing of nanomaterials in biological milieu [9,10]. Polydopamine nanoparticles (PDA-NPs) exhibits photothermal proprieties, making them ideal for photothermal

Abbreviations: ACE2, Angiotensin-converting enzyme 2; **BET**, Bromodomain and extra-terminal; **BRD4-c-MYC**, Bromodomain-containing protein 4- c-Myelocytomatosis; **BTZ**, Bortezomib; **CDs**, Carbon dots; **CT**, Chemotherapy; **COVID 19**, Coronavirus disease of 2019; **DHI**, 5,6-dihydroxyindole; **DHICA**, 2-carboxy derivative; **GIT**, Gastrointestinal tract; **GNPs**, Gold nanoparticles; **GQD**, graphene quantum dots; **IDO**, Indoleamine 2,3-dioxygenase; **IFN-γ**, Interferon gamma; **L-DOPA**, L-3,4-dihydroxyphenylalanine; **NIR**, Near-infrared; **NTs**, Nanotubes; **PD-1**, Programmed death 1; **PDA**, Polydopamine; **PDA-NPs**, Polydopamine nanoparticules; **PD-L1**, Programmed death-ligand 1; **PEG**, Poly (ethylene) glycol; **PEI**, Polyethylene imine; **PTT**, Photothermal therapy; **PTX**, Paclitaxel; **ROS**, Reactive oxygen species; ***SARS-CoV-2***, Severe acute respiratory syndrome *coronavirus 2*; **SOD-2**, Superoxide dismutase 2; **TLR7**, Toll-like receptor 7; **TLR9**, Toll-like receptor 9; **TNF-α**, Tumor necrosis factor alpha.

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therapy (PTT) [11–13]. In PTT, photosensitive chemicals (photosensitizers), are activated via energy transfer to form a singlet oxygen ($^1O_2$) and reactive oxygen species (ROS). These in turn inactivate several cellular activities and eventually causes cell death [14,15]. Aptly, PDA-NPs have been widely used in cancer therapy due to their high photothermal conversion efficiency, which directly suppresses cancer cell growth through autophagy and apoptosis [16–18]. When targeted to specific cancer tissue, PDA PDA-NP has been projected to decrease tumor development synergistically [7,16]. With regards to mucosal drug delivery, two nanomaterial-based strategies have emerged formidable and include i) muco-adhesive and ii) muco-penetrative systems [19]. Indeed, muco-penetration of nanoparticles through epithelia can be facilitated via polymeric coatings such as poly (ethylene) glycol (PEG), due to their charge neutrality and hydrophobicity, however this surface neutrality limits the propensity of the coatings to interact with the cell membrane, resulting in poor cellular uptake of nanoparticles [20]. To improve uptake of nanoparticles, across mucosal barriers, PDA coating has been shown to promote interaction the mucosa, resulting in muco-penetration and cellular uptake both in vivo and in vitro [21,22]. These recent studies are promising insomuch as they open the door to clinical investigations involving PDA nanomedicines, with improved clinical outcomes in the management of several diseases. We must however be cognizant that mucosal barriers present physical challenges that must be surmounted prior to nanoparticle internalization in cells [23]. Some of these challenges are species and disease state-dependent. In this review, we present the functionalities of PDA-coated nanomedicines with relevance to biomedical applications, specifically, anticancer therapy. The review also covers important considerations and challenges of using PDA in sustained mucosal drug delivery and how this might translate to clinical use.

2. Properties of PDA nanomaterials

PDA is a black biopolymer formed by self-polymerization of dopamine (which is white) and colorless in alkaline media and molecular oxygen. It comprises of covalently linked dihydroxyindole, indoledione and dopamine monomers [24]. As a flexible coating material, PDA can be customized as a conformal layer of up to 100 nm [25], which allows surface modification with relevant chemical moieties to elicit desired responses [25]. The binding properties of PDA to substrates was inspired by mussel foot proteins, which explains its versatility in binding with almost any substrate and wide appeal in pharmaceutical and chemical industrial applications [26,27]. PDA rose to prominence as a coating material, where for example, it was used to change the surface properties of Teflon® microchannel walls, allowing for the fabrication of PDA-modified Teflon chips [28,29]. Understanding the toxicity of PDA is a crucial assessment to evaluate its applications in nanomedicine. In this regard, Hong et al. have studied the biocompatibility of PDA coating through in vivo assays, and it was found that PDA works as a biocompatible layer that reduced significantly the inflammatory responses due to exposure to poly-L-lactic acid surfaces as well as reducing the immunological responses in blood to quantum dots [30]. In drug delivery research, it was observed that among the available polymeric carriers, PDA is considered the most suitable carrier for drug delivery applications. To serve this point, Städler et al. showed that PDA-coated-liposomes have promoted the adhesion and proliferation of myoblast cells, and large thickness of PDA coatings induced less fluorescent intensity of the cells [31]. Thus, the cellular uptake of PDA could be controlled by the polymerization time, suggesting PDA to serves as a potential delivery system to cells and other PDA applications as cell imaging and sensing. In another study, doxorubicin, which is a chemotherapeutic agent, was loaded inside PDA capsules as a proposed drug carrier, and an improved effect of eradicating HeLa cancer cells compared to free drug was reposted [32]. Additionally, PDA coating gold nanorods conjugated to anti- epidermal growth factor receptor antibodies selectively bound to breast and oral cancer cells, which overexpressed epidermal growth factor receptor and enhanced the dell death after exposure to NIR light [33]. Liu et al. discovered that dopamine-coated melanin colloidal nano-spheres could be used as an effective NIR photothermal therapeutic agent for cancer therapy [34]. In

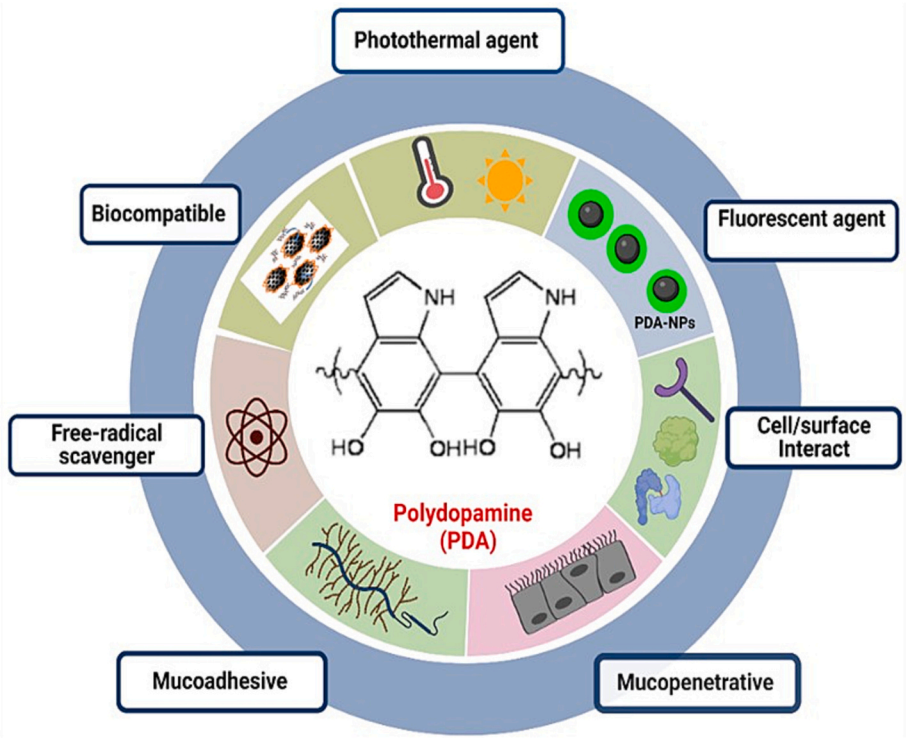

Fig. 1. Applications of PDA nanomaterials, including excellent biocompatibility, high photothermal performance, mucoadhesion, biodegradability, drug delivery system.

terms of degradability, PDA breaks down oxidatively in strongly alkaline media or peroxides [35]. Bettinger et al. demonstrated that PDA-coated melanin implants appear to degrade in tissues during eight-week storage and attributed this to the stiff features of melanin implants, following administration in the host [36]. Recently, PDA-NPs showed potent ROS scavenging proprieties, whereby the catechol group in PDA is able to quench various free radicals [37]. Moreover, PDA-based nanomaterials exhibits powerful antioxidant properties by eliminating ROS and thus can be used for further biomedical applications with ideal outcomes [38,39].

3. PDA-based multifunctional platform for combined therapy

As mentioned earlier, PDA has excellent photothermal properties, which has led to its use in PPT in conjunction with other therapeutic approaches. The following sections are dedicated to some of the key findings where PDA is utilized in combinational therapy.

3.1. Combinational photothermal therapy and chemotherapy

Utilization of PDA-NPs in conjunction with chemotherapy has proven successful in eradicating cancer via various modalities as illustrated in Fig. 2. For example, Zhu and Su synthesized PDA-polyethylene glycol-cisplatin nanoparticles that showed a pH-dependent drug release profile with remarkable synergistic effects due to PDA and cisplatin [40]. Similarly, Banstola et al. formulated PDA-coated gold nanoparticles (GNPs) encapsulating paclitaxel (PTX), (GNPs-PDA-PTX) which is activated by NIR irradiation. Synergism resulting from the photothermal effect and the anticancer properties of PTX provided a successful platform for the treatment of pancreatic cancer, whereby the GNPs-PDA-PTX produced a three-fold higher cytotoxicity compared to controls. In addition, more ROS were produced with a downregulation of expressed antioxidant enzymes such as superoxide dismutase 2 (SOD-2) and catalase [41]. Tiwari et al. showed that PDA coated polycaprolactone-doxorubicin nanoparticles exhibited a pH and NIR irradiation responsive behavior, prompting an improved drug release profile in acidic media compared to physiological pH condition (pH 7.4). In this regard, the combined effects of NIR irradiation and pH-mediated chemo-release induced hyperthermia, causing cell death [42]. In another study, PDA-functionalized nanoparticles crossed the endo/lysosomal cellular barrier, with enhanced cytosolic deployment of bortezomib (BTZ), triggered by NIR irradiation. Here again, synergy through photothermal effect and chemotherapy caused tumor regression [43]. During PTT or chemotherapy, cancer cells exhibit pro-survival autophagy to protect them from further damage, which results in poor treatment outcomes. To overcome this phenomenon, Lu et al. highlighted the use of PDA-NPs in PPT and chemotherapy coupled with autophagy inhibitors to enhance the antitumor effect [44].

3.2. Combinational photothermal therapy and immunotherapy

Immunotherapy remains as an effective cancer treatment modality,

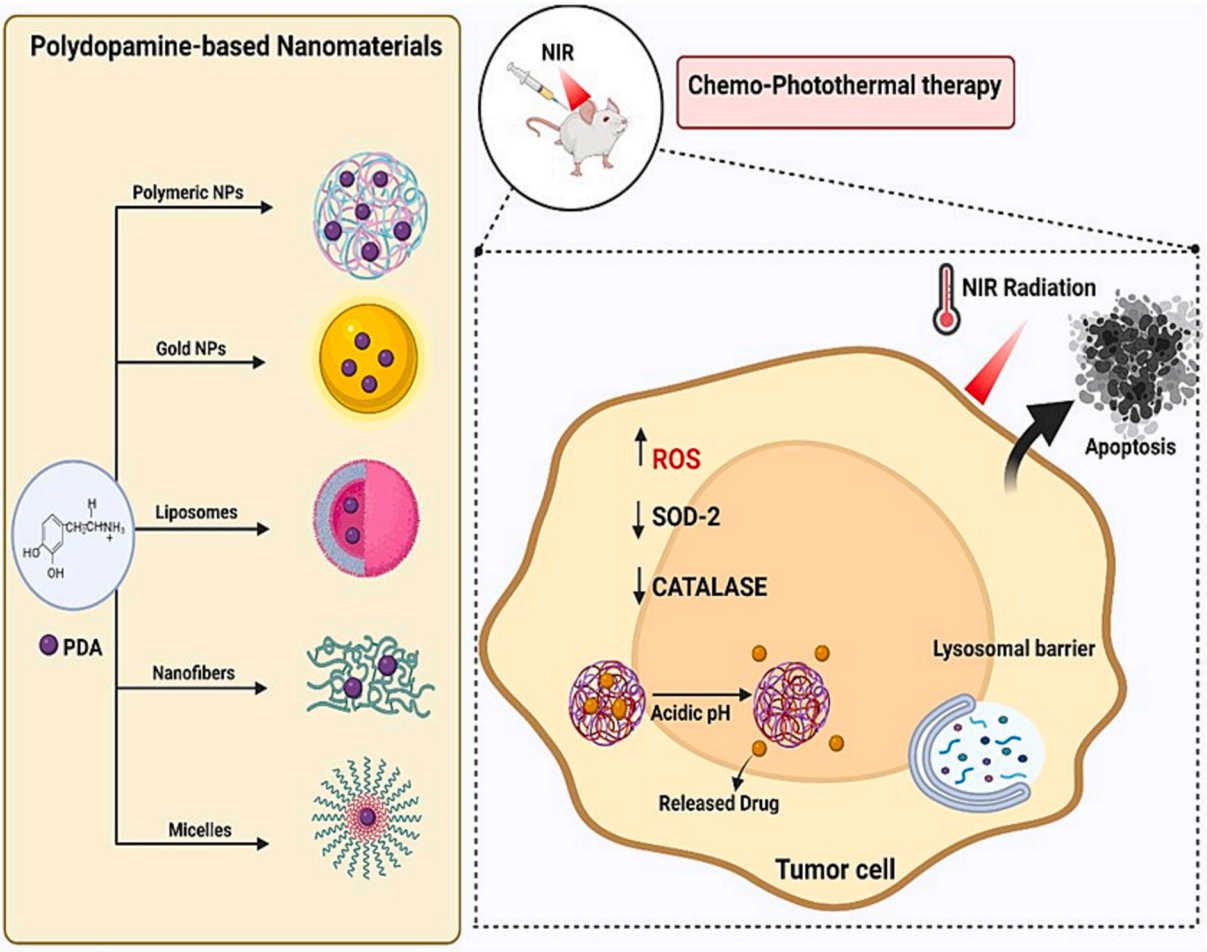

Fig. 2. Polydopamine-based nanomaterials for near-infrared light-triggered synergistic chemo-photothermal therapy. Polydopamine nanoparticles loaded with chemotherapeutic drugs (eg; Doxorubixin, paclitaxel and bortezomib) exhibited a pH, near infrared irradiation responsive behavior, and prompted an improved drug release profile in acidic media causing cell death.

since it relies on the patient's immune system to target and ward-off tumor cells. PTT on the other hand, relies on IR irradiation and temperature to ablate or regress tumors. However, PTT offers a low toxicity regimen, which sometimes does not completely eradicate the tumor cells, leading to possible relapse or metastasis. To overcome this drawback, PTT may be used in conjunction with immunotherapy. Here, we discuss synergies derived from application of PDA-NPs in combinational therapies based on immune responses (Fig. 3). Specifically, in a study by Li et al. encapsulation of toll-like receptor agonists and indoleamine 2, 3-dioxygenase (IDO) inhibitors in PDA-NPs coated with polyethylene imine (PEI) exhibited a good stability and low in toxicity [45]. The delivery system was shown to effectively inhibit the proliferation of breast carcinoma in mice and trigger apoptosis. Furthermore, in-vivo analyses in mouse models showed an arrested growth of breast carcinoma cells and an acceleration in T lymphocytes differentiation. An improved maturation of antigen presenting cells was also observed, attributed to immune-activation [45]. In another study, nanocarriers coated with Al_2O_3 and biodegradable PDA destroyed the majority of the tumor tissues after NIR, leading to the release of tumor antigens that are capable of eliciting robust immune responses [46]. The group of Wu et al. engineered nanoassemblies denoted as **PC@GCpD(Gd), which** destroyed tumor cells through photothermal effects mediated by graphene quantum dots (GQD)-photosensitizer nanocomposites (GCpD), whilst the immunostimulatory polycationic polymer/CpG oligodeoxynucleotide (CpD OND), targeted endosomal Toll-like receptor 9 (TLR9), which stimulated the secretion of pro-inflammatory cytokines, dendritic cells maturation and activation and infiltration of T lymphocytes [47]. In another study, a NIR-activated core-shell PDA nanoparticle generated tumor associated antigens through photothermal ablation of cancer cells as well as immunological activation of antigen presenting cells due to gardiquimod (located in the mesoporous silica shell). This combinational therapy resulted in tumor regression, inhibition of metastasis and tumor motility in mouse melanoma models [48].

Targeting inhibitory immune checkpoints such as the programmed death ligand 1 (PDL1) using specific monoclonal antibodies called immune checkpoint inhibitors (ICIs) has significantly improved cancer therapy [49]. The Bromo-domain and extra-terminal (BET) inhibitor (JQ1) was used to downregulate the PDL1 expression and blocks BRD4-c-MYC axis (Bromodomain-containing protein 4- c-Myelocytomatosis), with the aim of eliciting immune responses to triple-negative breast cancer. Here, JQ1 was encapsulated in PDA-NPs, which in turn enhanced PTT effect. The continuous release of JQ1 from this combinational therapy led to an enhanced activation of cytotoxic T lymphocytes, with pronounced immune-memory effects that prevented tumor relapse in mice [50]. In another study, a combinatorial approach involving blockade of immune checkpoint inhibitors (PD-L1) and PTT, whereby the PDA nanoparticles were loaded with resiquimod (R848) as Toll-like receptor 7 (TLR7) agonist. The nano-assembly eliminated 4 T1 breast tumors due to photothermal energy. Furthermore, the release of R848 induced strong anti-tumor immune responses by impeding the saturation of cytotoxic lymphocytes and increasing the secretion of the

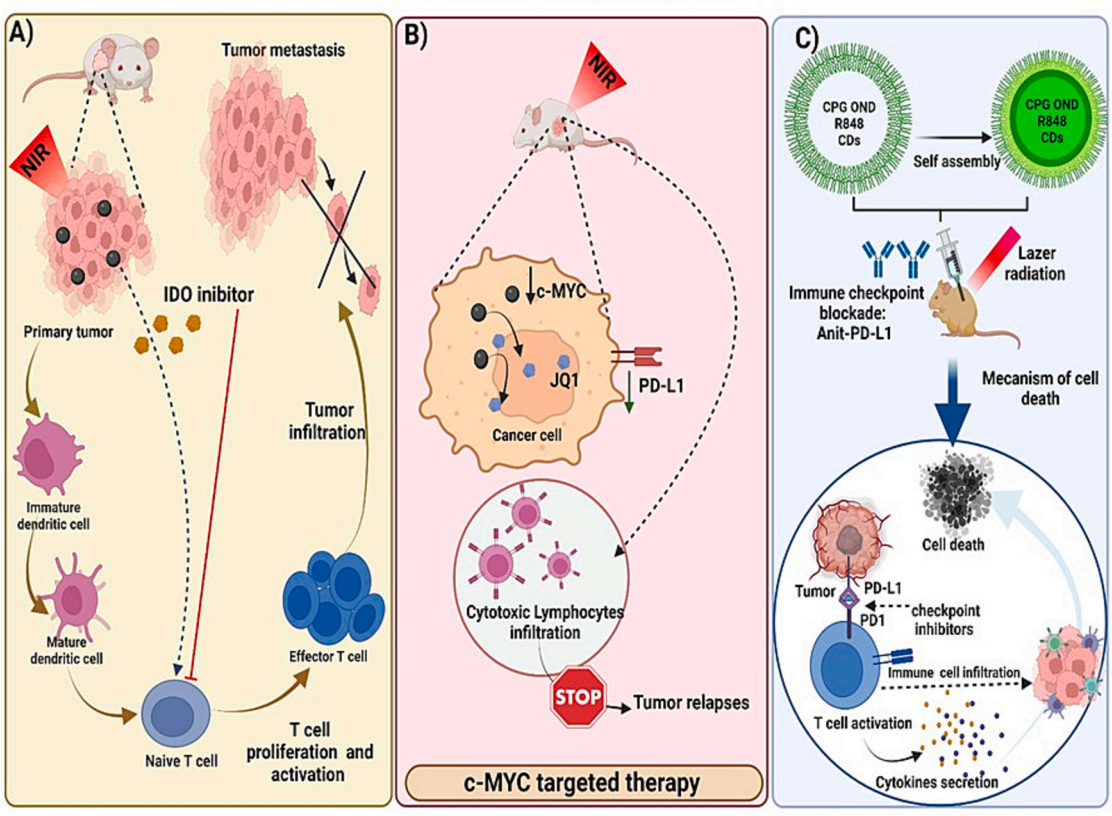

Fig. 3. Exemplars of PDA-nanoplatforms for photothermal therapy combined with immunotherapy. **A) PDA-TLR-IDO-PEI-NPs:** Polydopamine nanoparticles loaded with indoleamine 2,3-dioxygenase (IDO) inhibitors/Toll-like receptor inhibited the proliferation of breast carcinoma cells and induced antigen-presenting cell maturation and T lymphocyte differentiation. **B) PDA-JQ1-NPs:** Polydopamine nanoparticles loaded with JQ1 triggering photothermal therapy could inhibit PD-L1 and generate an immune response on triple negative breast cancer. JQ1 down-regulates the PD-L1 expression and blocks BRD4-c-MYC axis in triple negative breast cancer. **C) PDA-PEG-R848-CDs-NPs:** Polydopamine nanoparticles encapsulated resiquimod (R848) in conjunction with PD-L1 immune checkpoint inhibitors eradicates primary tumor cells and enhances immune responses to abolish metastatic tumors.
Abbreviations: PDA-TLR-IDO-PEI-NPs: Polydopamine-toll-like receptor-indoleamine 2, 3-dioxygenase polyethylene imine- nanoparticles; PDA-JQ1-NPs: Polydpamine bromo-domain and extra-terminal (BET) inhibitor-nanopartcicules; PDA-PEG-R848-CDs-NPs: Polydopamine-resiquimod (*R*848)- carbon dots–nanoparticles. PD-L1; programmed cell death-ligand 1; JQ1: The bromodomain and extra-terminal inhibitor

necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) [51]. Another study reported that PDA-NPs surface-decorated with checkpoint blocking antibodies and tumor-specific antigens caused repolarization of tumor-associated macrophages. An enhanced tumor-targeting immune response and dendritic cell maturation was observed when applied to tumors. The antibodies were able to activate cytotoxic T lymphocytes, which blocked immune checkpoints [54].

4. PDA-based nano-platform in mucosal drug delivery

The following section reviews applications of PDA nanoparticles in conjunction with mucosal drug delivery, noting that the mucosa presents a structural barrier prior to traversing the cell membrane.

4.1. Mucosal barrier and drug delivery

Crude mucus is a complex secretion comprising of water, lipids, proteins, cell debris, nucleic acids, ions and mucins, all of which contribute to its gel-like consistency [52]. Several epithelia are protected by mucus, providing physical protection to the underlying tissue [53]. Moreover, it protects the epithelium from toxins, pathogens, and exogenous substances [54].

The oral route of administration is most favored because it is non-invasive and ensures patient compliance, with cost-effectiveness in production lines [55]. Drug administered orally must traverse the epithelia prior to arrival in systemic circulation [52]. The mucus layer serves as the initial physical barrier, whereby the hydrophilicity and viscosity properties of mucus impedes the diffusion of hydrophobic molecules [53]. Prior to systemic entry, drug molecules or delivery systems, particularly nanoparticle delivery systems must first interact with the mucus layer before traversing the plasma membrane. The mucus layer is dynamic [60] and comprises of uninterrupted secretion of mucus, a mucosal unstirred layer [53], which is an interactive steric barrier, with high viscosity [54,56,57]. Successful deployment of nanoparticulate delivery system across the epithelium is dependent on favorable interactions (muco-adhesion and muco-penetration) with the mucus layer. In the next section, we review the physicochemical basis mucus interactions with PDA.

4.2. Mucopenetrative propensity of PDA

Muco-adhesive drug delivery systems have been successfully employed to enhance systemic bioavailability of the cargo following oral administration [58,59]. This has been attributed to sluggish transit of the delivery systems within the gastrointestinal tract due to muco-adhesive interactions with the epithelia. In this regard, particles with positive surface charges interact with the sialic acid moieties in mucin, which is negatively charged [60]. However, muco-adhesive interactions on its own is insufficient to ensure mass transfer of the delivery system across the mucus layer. Both muco-adhesive and muco-penetrating particles guarantees a high local concentration within epithelia that drives uptake through the mucus. PDA-nano-formulation technology offers advantages of facile delivery of drugs while leveraging the natural properties of the mucus layer for decreased muco-adhesion and increased muco-penetration [61] (Fig. 4).

Not much has been explored in the realm of PDA-NPs mucosal drug delivery. An overview of PDA-NPs and derivatives applied for mucosal drug delivery is summarized in Table 1. Key examples that stand out include the work by Poinard et al. showed that PDA coating improves both muco-penetration and cell uptake of carboxylated polystyrene nanoparticles [21]. The same group showed an improved muco-penetration of carboxylated polystyrene nanoparticles with PDA

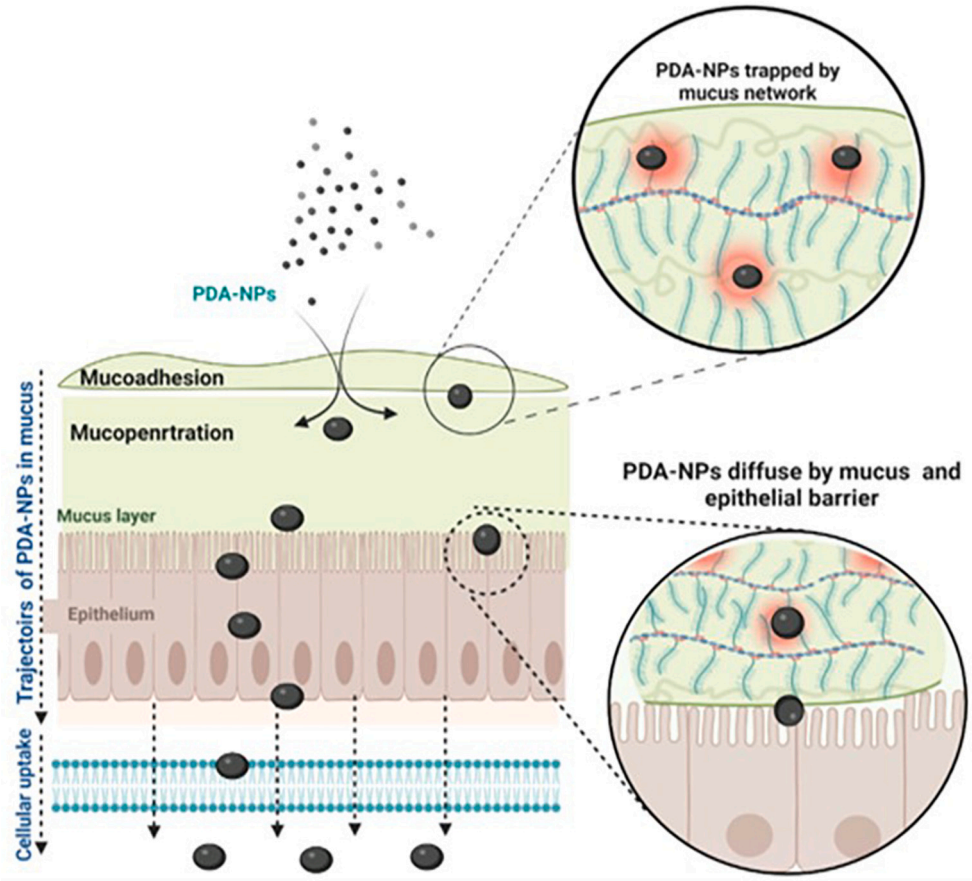

Fig. 4. Schematic illustration of muco-adhesive and muco-penetrative PDA-NPs. "PDA-NPs binds to mucus network and traverses the mucus and epithelial barrier.

Table 1
Overview of PDA-NPs and its derivate applied for mucosal drug delivery.

Dopamine materiel	Preparation technique	Application	References
Polydopamine	Polymerization method	Attenuation of Radiation-Induced Gastrointestinal Syndrome	[64]
Polydopamine	Polymerization method	Polymer matrix of Polydopamine NPs for alkali-sensitive curcumin encapsulation	[65]
Dopamine	Dopamine oxidative polymerization	Toxicity on colonic cancer cell lines	[66]
Melanin-inspired polydopamine	Water-in-oil micro-emulsion method	Photoacoustic contrast agent for non-invasive visualization of gastrointestinal tract system	[67]
Zein–polydopamine–lecithin	One-pot phase separation technique	Preparation of multi-functional nanoparticles of resveratrol	[68]
Polystyrene- polydopamine	Polymerization method	Enhancement of muco-penetration and cell uptake of PEGylated nanoparticles	[21]
Polydopamine	Polymerization method	Protection of irradiation-induced intestinal injury	[69]
Dopamine hydrochloride	Polymerization method	pH responsive cargo release from mesoporous silica nanoparticles	[70]
Catechol- succinyl chitosan	Polymerization method	Muco-adhesive drug delivery system	[71]
Tannic acid-*graft*-poly (ethylene glycol	Complexing aqueous solution	Long-lasting esophageal muco-adhesion	[72]
Zwitterionic polydopamine	Polymerization method	Evaluation of mucus penetrability and cellular uptake of nanoparticles	[73]

coated surface similar to PEG. The polystyrene-PDA diffusion was 6-fold slower in mucus than water, compared to polystyrene-NPs, which was retarded by 1000-fold [22]. In a study using oral mucositis models, Hu et al. showed that PDA-coated nanoparticles was superior in transport across the mucosal barrier, with improved drug bioavailability and therapeutic efficacy compared to controls [62]. More recently, Soto et al. showed that coating glycan particles with PDA increases uptake into Peyer's patches [63].

5. PDA nanomaterials: challenges and opportunities

Potential applications of PDA nanomaterials have expanded in the past decade, motivated by the quest for efficient therapeutics, primarily via manipulation of surface chemistry. PDA coating is an easy and simple way to functionalize the surfaces of materials based on catechol and phenethylamine groups. Such PDA-coated materials manifest positive charge dispensation and has been effectively used to surface modify several types of nanoparticles, including polymeric [74], liposomes [75], magnetic NPs [76], and gold nanoparticles [33]. To formulate PDA-based nanomaterials, several factors must be taken into consideration, including monomer concentration, pH, temperature, reaction time, and presence of metal ions [77]. Due to the complex interplay between these factors, the exact mechanisms of PDA polymerization have been rarely elucidated. Furthermore, dopamine itself has anticancer effects and is biodegradable, which reflects its release in biological systems [78]. As discussed earlier co-assembly of PDA with other functional moieties can be used to achieve synergism and improve antitumor-selectivity [79,80]. Although PDA-NPs have proven biocompatibility with human and experimental animal tissue, data on clinical trials aimed at demonstrating muco-penetrability of dosage forms is lacking and it is the view of the authors that this be given precedence. Furthermore, evaluation of biosafety and toxicity of PDA-NPs should be also examined in human tissue. PDA-based nanomaterials may be fabricated through polymerization of dopamine [77], where muco-adhesion improves the residence times of dosage forms and thereby increases the local gastrointestinal tract concentration and flux across the epithelia. Muco-adhesion to the outermost mucus layers, present challenges due to high turnover. Furthermore, muco-adhesion between PDA and mucus is affected by the swelling factors, spatial polymer conformation, plasticity, molecular weight, surface charge, hydrogen bonding sites within PDA, and the milieu pH [81,82]. Each of these factors in turn affects muco-penetration. Thus, in developing PDA-NPs, formulation and processing variables are to be carefully tuned in order to achieve muco-adhesive and muco-penetrative, properties, which will serve well in the treatment of various diseases. Furthermore, the mucus layer shows interspecies variation [23], inter-mucosal and trans-mucosal distinctions in structure and composition [83]. The impact of such variability on PDA muco-adhesion and muco-penetration warrants more investigation. The physical integrity of the carrier system must also be taken into account with regard to effective muco-adhesion or muco-penetration. For example, the charge and the size of PDA nanoformulation plays a crucial role in the chemical interaction with mucus [66,73]. Finally, mucosa is a promising delivery site in several diseases. We hope this review would motivate research in the development of PDA-based nanoparticulate delivery systems that display muco-adhesive and muco-penetrative since these will provide a formidable frontier in the deployment of drugs across epithelia or indeed in local mucosal infections such as COVID 19. Ma et al. (2022) have demonstrated that SARS-CoV-2 infection can be inhibited using an exosome-sheathed PDA nanoformulation (PDA@Exosome). The PDA@Exosomes are generated by exocytosis of PDA nanoparticles from H293T cell lines whereby, they display expression of ACE2, the protein that provides the entry point for the coronavirus (COVID-19), to attach and infect human epithelial cells. Thus, the PDA@Exosome are able to compete with ACE2-expressed epithelial cells for S protein binding. Furthermore, the PDA@Exosome may intercept and deactivate free radicals and thereby, attenuate the level of cytokines. The authors conclude that, due its high mediatory interception and antioxidant properties, the PDA@Exosome may be a promising candidate in antiviral therapeutics for the COVID-19 pandemic [84].

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Author's contribution

TB, SI, AA, QF, HI and RB wrote the initial draft. TB and SI prepared the figs. TB, SI, SD, SU, MM and NB revised the manuscript.NB provided intellectual input and critical review of the manuscript.

Declaration of Competing Interest

The authors declare no potential conflicts of interest with respect to

the research, authorship, and/or publication of this article.

Data availability

No data was used for the research described in the article.

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