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Review Article

Utilization of Multilayering as a Drug Release Platform

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Abstract

Finding a method for drug delivery that is safe, effective, and sustainable has always been a challenge. However, one novel approach is the utilization of polyelectrolyte multilayering as a drug release platform. This method has been incorporated in not only chronic, but also, acute disease states. In this article, acute disease states such as cancer, microbials, inflammatory, and immunosuppressants are discussed; as well as chronic disease states such as hypertensives, coagulants, and diabetes. Some successes are shown with bases made of chitosan nanofilms, a combination of chitosan and alginate, gold nanorods, magnetic hollow nanospheres, pluronic nanoparticles, liposomal vesicles, phospholipids, superparamagnetic iron oxide, gelatin, and more. Additionally, a wide range of advanced technological methods were employed to observe and analyze any changes in their morphology, physicochemical properties, and drug release rates. Some challenges faced when integrating this specific drug delivery approach varied per study and are highlighted within this review.

Keywords: Multilayering; drug release; chronic disease; acute diseases

Introduction

The classification, therapeutic use, and frequency of a drug being administered to a patient are all determined by the pharmacodynamic and pharmacokinetic properties, formulation, and the delivery route of the drug itself [1]. The route of delivery can vary from oral, intranasal, topical, vaginal, or rectal [2]. For nasal and pulmonary delivery, peptide, and protein therapeutics such as gels, liposomes, microspheres, proliposomes, and cyclodextrins have been investigated [1]. The destination of where the drug will have its therapeutic effects is also vital. For example, when targeting the brain, the need to cross the blood brain barrier is a crucial aspect [2]. Nanotechnology has become more commonly used within anticancer medications for combatting angiogenesis, inflammatory, and tumor progression [3]. Likewise, depending on the diagnosis and treatment, some medications can have more of a targeted intracellular delivery [2]. Different drug classifications, such as analgesics, antimicrobials, antidepressants, sedatives, etc., can determine the type of coating, formulation, and excipients [4] that are associated with the drug itself [1]. Multifunctional excipients can consist of cyclodextrins, disintegrants, surfactants, sugars, soluble and insoluble filler materials, amorphous solid dispersions, and self-emulsifying drug delivery systems [4]. Apart from the existing drug release systems, a relatively new approach of drug delivery is with the use of multilayered thin films. Multilayering is typically composed of polyelectrolytes, which are formed using the layer-by-layer (LbL) assembly technique [5]. Polyelectrolyte Multilayers (PEMs) are essentially nanostructured polymeric systems that can be formed by LbL deposition, enabling the desired agent to be incorporated into a coating in a simple, versatile, and cost-effective manner [6]. These polyelectrolyte multilayers have been investigated as electronically conductive polymers [7], membrane filtration [8], light-emitting diodes [9-16], carboxymethyl cellulose and chitosan layering [17], antimicrobial coatings [18-20]anticorrosive coatings [21-23], small molecule delivery vehicles [24,25], anticancer agents [26-30], as well as a means for reducing failure in medical devices [31].These polymer multilayers are held together via intermolecular interactions such as hydrogen bonding, electrostatics, bio-specific interactions, as well as covalent bonding [17]. Park et al looked at chitosan and carboxymethyl cellulose by cross-linking the two molecules to form a multilayer, which was then evaluated for small-molecule release. In order to measure the release, they incorporated a photoluminescence process which varied based on the film stability.

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Various factors are used in multilayer design such as the layer thickness, drug dispersion homogeneity, polymer configuration, particle size, and more [32]. To investigate drug release, properties such as pulsatile, burst, zero-order, time-order, and multiple-drug release are utilized [32]. For example, pulsatile-release kinetics was used for radiosensitizers, local tumor therapies, and vaccinations [32]. Additionally, the solvent evaporation technique has been used to dissolve the polymers and analyze the specific drug's release. To measure the stability and release from the multilayering, drugs are placed in solutions of different pH [33,34], temperatures [35], or incorporated into biodegradable polymers to form the layers [36]. Herein is a review of multilayer drug release as it has been explored in acute disease states such as cancer, microbials, inflammatory, and immunosuppressants; as well as chronic disease states such as hypertensives, coagulants, and diabetics.

Acute Disease States

Anti-Cancer

Multiple ways of administering drugs, utilizing the multilayering technique, have been attempted; one in particular, is targeting against cancers.

Doxorubicin

Sun et al evaluated the controlled-release rate of chitosan-based multilayer nanofilms composed of hyaluronic acid, tannic acid, and/or alginic acid [37]. They integrated doxorubicin hydrochloride, ovalbumin, and fluorescein isothiocyanate and observed at the variable combinations tested, a thirty-minute drug-release rate. Drug release was determined by how quickly the film had degraded, which within the first 30 min of being in the phosphate buffer solution, they saw the most rapid drug release. When a multilayer was composed of a drug and film with favorable interactions between each another, an accurate, sustainable, and controlled release formulation for anticancer therapy was formed [37].Similarly, Prasad et al examined a biodegradable, nanoparticle multilayer composed of chitosan as the outer layer and doxorubicin or methotrexate as the inner core layer, for treating osteosarcoma [38]. When these formulations were placed in differing pH environments, it was observed that in lower pH environments, 1.5 times greater amount of the drug was released. When tested on the human osteosarcoma MG 63 cell lines to compare cytotoxicity, the cell death increased by 50% as drug concentration increased after a 24 hour-incubation period. They concluded that combination multilayer delivery with biodegradable carriers showed more effective results in the treatment of osteosarcoma [38].

In a study targeted on the treatment of ovarian cancer, Liu et al integrated positively charged doxorubicin into a multilayer system with gold nanorods, coated with poly-glutamic acid (PGA), poly-L-Lysine (PLL), and hyaluronic acid (HA), for photothermal and chemotherapy [39]. This combination provided a synergistic effect in ovarian cancer (SKOV3) cell death when the near-infrared (NIR) laser irradiation triggered the doxorubicin release. Similar to Prasad and Sun's works, lower pH environments led to an increase in doxorubicin release from the encapsulated multilayer composition. In addition to the presence of the NIR laser irradiation and acidic environments, an increase in temperature also compounded to a greater amount of drug release, resulting in a higher synergistic antitumor effect on the ovarian cancer cells [39].A study by Nozohouri et al focused on the combination of doxorubicin and methotrexate in the creation of a multilayered dry powder inhalation for the treatment of lung cancer [40]. This unique multilayer system was composed of a magnetic hollow-nanosphere coated in a polyethylene glycol polymer, integrated with doxorubicin and methotrexate. The nanosphere itself was composed of amino-acrylate coated magnetic-silica nanoparticles (Am-Ac-MNPs). When analyzing the drug release, they tested the in vitro cytotoxicity against A549 cell lines, and the cytotoxicity level was not substantial. Additionally, they observed the overall reduction in the drugs' adverse effects, as this multilayer inhalation formulation was designed to be delivered directly into the lungs. Due to this design's effectiveness in destroying A549 cancer cells, its aerosolization property, its drug-loading capability of both hydrophilic and hydrophobic molecules, it was concluded that this composition was safe to be used as a drug carrier for anticancer therapy [40].

Another approach studied by Xu et al focused on a multilayer formulation of a non-vascular stent coat on antitumor and antibacterial treatment [41]. The difficult aspect of this process was to achieve the most effective loading of the drugs into the multilayer films in order to obtain long-term drug release. The integrated hydrophobic and hydrophilic small-molecule drugs varied in their release rates based on their physicochemical properties. The weak oxidized alginate sodium and doxorubicin (O-Alg-DOX) bond released rapidly at the early stage, in comparison to the more stable polyethyleneimine-cis-aconitic anhydride-doxorubicin (PEI-CA-DOX) bond, which varied based on their different pH levels. In addition, after a ten-day incubation period in an acidic environment, a doubling in the drug release rates was observed. When comparing drug release rates, they concluded that the polyelectrolyte multilayer film composition resulted in a more long-term controlled release rate. Ultimately, it was concluded that when combining the positively charged polyelectrolyte complex of polyethyleneimine, cis-aconitic anhydride, and doxorubicin (PEI-CA-DOX), with the negatively charged polyelectrolyte complex of oxidized alginate sodium and doxorubicin (O-Alg-DOX) multilayer films, the most effective antitumor and antibacterial properties were observed due to the design's sustained drug release rates and the precise drug loading capability [41].

Likewise, Chai et al focused on the utilization of alginate and chitosan bio-polyelectrolytes for the incorporation of doxorubicin into multilayers and analyzed the initial burst release and the overall drug-release rates [42]. This study was inspired by Adibikia et al who determined that when naproxen was placed in a multilayer as naproxen-eudragit RS 100 nanoparticles (NPs), there was a reduction in the initial burst release and a slow drug release overall, in comparison to naproxen on its own. However, the polymers had low biodegradability and the methods used to control the drug release included the addition of unnecessary additives, such as surfactant [42-44] microspheres. Thus, Chai et al proposed a more efficient method. By utilizing alginate and chitosan coating with a doxorubicin and poly lactic-co-glycolic acid complex of nanoparticles (DOX-PLGA NPs), there was a tenfold reduction in the initial burst release percentage compared to that of the PLGA NPs (55.12% vs. 5.78%). They analyzed that the extension of half release time from 0.78 to 61.58 hours lengthened due to the increase in thickness of the layer, which ultimately provided a slower release rate. They concluded that adding the alginate and chitosan coating to doxorubicin, with the PLGA NPs, was advantageous with regards to time and control of drug release. Furthermore, they interpreted that this would lead to less adverse reactions relating to drug resistance, decreased toxicity, and more therapeutic effectiveness, making it an optimum therapy for treating cancer [42].

Xiao et al examined the effects of the laponite-doxorubicin nanohybrid at varying pH levels when placed in a multilayer coating design [45]. Similar to those investigating chlorhexidine and gentamycin, this doxorubicin formulation also incorporates cationic poly(allylamine) hydrochloride. Since doxorubicin itself is a cationic molecule, it was seen to have a faster release rate in lower pH solutions. Therefore, the anionic poly(sodium styrene sulfonate) was unique to this design, forming integrated layers of PAH/PSS with doxorubicin-loaded laponite nanoparticles. With the help of these additional layers, it resulted with an enhanced sustained release. Additionally, the level of cytotoxicity was tested with the drug's effect on a human breast adenocarcinoma cell line (MCF-7). When observing the cell viability with the (PAH/PSS)1-Dox/Laponite formulation, there was a 57.8% to 16.1% reduction and with the (PAH/PSS)3-Dox/Laponite nanohybrid formulation, there was a 62.4% to 24.1% reduction. Drug release rates were tested by placing the sample in a phosphate buffer solution (PBS) or an acetic acid-sodium acetate buffer solution, incubated, centrifuged, and examined via a UV-vis spectroscopy. They concluded that this multilayer drug carrier, incorporating laponite and doxorubicin integrated with PAH/PSS layers, successfully proved a sustainable controlled release which has potential for anticancer therapy [45-47]. Finally, a study by Sharma, et al, used a similar multilayering techniques to incorporate a natural hydrophobic compound, nimbin (NB), in a dual-drug loaded capsule with doxorubicin for optimal and synergistic chemo-photothermal therapy [48]. Their formulation of hollow poly-allylamine hydrochloride and poly-methacrylic acid (PAH/PMA) microcapsules was designed for the release to occur simultaneously to yield enhanced effective therapeutic results. In addition, they also added gold nanorods (NR) as a dual drug-loaded capsule for increased efficiency in drug delivery, catalysis, and bioimaging. Drug release was tested through NIR laser irradiation and varying pH conditions. Both resulted in a higher percentage release with laser irradiation than when placed in an acidic pH environment. When testing the anti-cancer activity on THP-1 human monocytic cell lines, they observed ~99% cell death. They concluded that this dual-drug multilayer formulation was optimal for chemo-photothermal anticancer treatment [48].

Docetaxels

Sang Oh et al observed the intermolecular interactions of lipid bilayers and Pluronic membranes, using Pluronic nanoparticles (NPs) or molecular imaging probes as a prototype [35]. When utilizing the temperature-induced phase transition and vesicle fusion for the docetaxel-loaded Pluronic NPs, they observed how the varied ratio of vesicles placed in the aqueous media affected both their attraction to one another, as well as their integration of NPs within the vesicles themselves. They also noted that freeze-drying affected the interaction between liposomes and Pluronic NPs when placed in an aqueous solution. Ultimately, the hydrophobic interactions helped create the multilayer formation in the nano-sized powdered form. Additionally, it was observed that Pluronic NPs were unstable, resulting in its rapid-release profile. It was concluded that this property was influenced by the presence of an extra Pluronic layer on its surface. Furthermore, cells without multilayer NPs were seen to have significantly higher viability. This discovery was beneficial in terms of determining a formulation which may impact the reduction of hypersensitivity and anaphylaxis [49-51] adverse effects; and as a result, increase the antitumor efficacy when administering docetaxel. The multilayering technique of accumulating NPs in the tissue caused an exponential increase in the magnetic resonance (MR) intensity present at the tumor site, which ultimately increased the precision of tumor-targeted therapy. As a result, this enhanced the therapeutic effectiveness of utilizing multilayering NPs for anti-cancer therapy [35,45]. Additionally, Nagpal et al analyzed the multilayered controlled-release drug delivery of docetaxel placed in a liposome and coated with chitosan [52]. The use of chitosan became crucial when they determined its efficiency in obtaining a high drug entrapment due to the lipid layers having opposite charges. Docetaxel is typically delivered intravenously with ethanol to improve the solubility of the drug. In order to create the composition, thin-film hydration and ethanol injection methods were used; however, the method which produced the most stability and a macroscopically homogenous suspension, was through ethanol injection. Placing the cholesterol molecule in temperatures higher than phase transition guided

its slow drug release. Nagpal et al ultimately concluded that this liposomal encapsulation provided an optimal form of sustainable drug delivery for cancer treatment [52].

Similarly, Khaliq et al used liposomal vesicles in which they integrated nanoparticles and layered them with docetaxel through Forster Resonance Energy Transfer (FRET) [53]. In order to achieve the targeted drug delivery, temperature-induced phase transition was incorporated into the formulation. They created a homogenous phase of 20mg docetaxel and 350mg solutol, which was then dissolved with 150mg of Pluronic F-68. Magnetic stirring was then utilized for a phase transition, followed by a cooling down phase, and incubation. They then combined equivalent amounts of the L-α-phosphatidylcholine aqueous vesicle solution and docetaxel-loaded Pluronic NPs and used an ultrasonic wave probe-type homogenizer to form the vesicle NPs. For the polymeric shell, the vesicle NPs and Pluronic F-68 solution (with trehalose as a preservative) were freeze-dried together. Additionally, dynamic light scattering, and transmittance electron microscopy techniques were utilized to observe the nanoparticles' size distribution and morphology. A challenge they faced with this preparation was the oxidation of docetaxel at high temperatures over the thirty-minutes. To overcome this and stabilize the formulation, Solutol was added as a lipophilic active ingredient [54,55]. For the in vitro drug release, they observed release rates to be 2- and 2.4-fold increased for the DTX-loaded Pluronic NPs, in comparison to the multilayer and vesicle forms of NPs. As a result, it was concluded that this multilayer drug delivery formulation positively enhanced the efficacy of the drug being used for anticancer treatment [53].

Furthermore, a study by Kusi-Appiah et al focused on a small-molecule microarray approach for designing a lipid multilayer structure for delivering docetaxel to prevent mitosis progression in cancer cells [56]. They employed phospholipids with fluorescent labels to test the dosage control. The composition consisted of various plating patterns such as lipid-encapsulated docetaxel, lipid-encapsulated valinomycin, and a lipid-only layer, which were then layered on the same glass slide and kept in incubation for 48 hours. They observed that as time progressed, there was an increase in cell death. Additionally, it was noticed that docetaxel had greater toxicity in comparison to valinomycin. Unlike in other multilayer designs discussed above, where the drugs are dissolved into the solution and have an effect on the nearby cells, this formulation was confined within the multilayer drops. Keeping the drug confined increased the efficacy of the drug's effects since the concentration remained high. A constraint faced was the difficulty in layering thousands of different compounds into one array [56,57]. They discovered a method in which liposome mixtures are distributed to a structure polymer stamp, which ultimately helped with forming a thick homogenous multilayer design. Furthermore, utilization of a polylysine surface avoided the creation of a single bilayer due to the possibility of water immersion with the lipid multilayer array. Ultimately, with these changes, it was concluded that for delivering small-molecular drugs locally, the lipid multilayer microarray design was the most efficient method and it minimized neighboring cells from up-taking drugs [56].

Xin Gao et al created a multilayer drug design made of a superparamagnetic iron oxide/docetaxel-poly(D,L-lactic-co-glycolic acid)-carboxylic acid (SPIO/docetaxel-PLGA-COOH) nanoparticle formulation targeted against prostate cancer, which was also seen to be beneficial for cell-targeted magnetic resonance imaging (MRI) scanning [58]. They evaluated the toxicity and efficacy levels against the PC3M tumors in mice, by comparing the effects of the surface-localized scAb antibody- poly(D,L-lactic-co-glycolic acid)-superparamagnetic iron oxide (scAb-PLGA-SPIO) design, the docetaxel-integrated design, and the design with docetaxel by itself. The change or loss in body weight and white blood cell (WBC) count were both key factors in determining cytotoxicity and these levels were also compared in the two groups. The scAb-PLGA-SPIO/docetaxel system showed the least percentage of decrease (8.38% + 5.12%) in body weight. In terms of the WBC count, all three designs were observed to be within the same normal range. Additionally, during the comparison, it was forecasted that reticuloendothelial system cells may steer PLGA-SPIO/docetaxel to be phagocytosed or guided away from the tumor site or release docetaxel prematurely to other organs, resulting in more toxicity than efficacy. As a result, it was concluded that the scAb-PLGGA-SPIO/docetaxel would be more effective in prostate tumor-targeting anticancer therapy and tumor imaging [58].

Dexamethasone

Dexamethasone is a multifaceted drug with an anti-inflammatory, immunosuppressive, and anti-cancerous effects, as well as prevention against retinal diseases [59]. A study by Pargaonkar et al demonstrates the use of a polyelectrolyte multilayer nano-assembly in producing a controlled-release dexamethasone in the form of microcapsules [59]. Prior work by Qui et al and Ai et al examined the multilayer drug design of encapsulated microcrystal drugs to form stable nanoshells [60,61]. Factors such as the shell's thickness, poly-ion type, microcrystal size, number of layers, and solubility all contributed to determining the drug release rate [59]. Antipov et al demonstrated an optimal version of the multilayer drug delivery with dexamethasone [62,63]. It was formulated to have a low molecular weight core surrounded by a polyelectrolyte shell. Pargaonkar et al created a drug design with the use of gelatin A, polyelectrolyte solutions, and heat adsorption [59]. The first layer of the assembly was produced by suspending dexamethasone into a poly-dimethyldiallyl ammonium chloride (PDDA) solution. Due to the high pH of the solution, there was a net positive charge after immersing the dexamethasone. After 15 minutes of sonication, the suspension was then centrifuged for 5 minutes, followed by it being washed with gelatin-infused phosphate buffer solution

(PBS) to separate the drug particles. This process was repeated with either PSS or gelatin A to form the multiple layers consisting of dexamethasone core/(PDDA/ polystyrenesulfonate (PSS))$_4$, dexamethasone core/(PDDA/gelatin A)$_4$/PDDA, dexamethasone core/(PDDA/gelatin B)$_4$/ PDDA, and dexamethasone core/ PDDA/(PSS/gelatin A)$_4$/(PSS/PDDA)$_1$. The Vertical Franz-type Diffusion cell system was used to determine the in vitro release of dexamethasone. A rapid release of dexamethasone when placed in an ethanol/water solution or when placed in the presence of PDDA was observed. Additionally, a sustained drug release for systems that incorporated gelatin A was observed. Furthermore, they determined that monodispersed molecular suspensions would be useful in reducing irritation while administering suspensions into the eye [59].

A study by Birhanu et al, observed how utilizing the multilayering for dexamethasone drug delivery was advantageous via the implantation of the nanofiber scaffolds, which allowed for the controlled drug-release of dexamethasone [64]. Poly-l-lactic acid (PLLA), Pluronic scaffolds (P123), and dexamethasone were multilayered with electrospinning and analyzed using Fourier Transform Infrared Radiation (FTIR) Spectrophotometer and Scanning Electron Microscopy (SEM) to confirm accuracy of the scaffold composition. Similar to the study by Pargoankar et al, an ultraviolet spectrophotometer was used in determining the amount of dexamethasone released in vitro when placed in a PBS solution and incubated in a shaker for 23 days. The multilayer scaffolds consisting of the two-layer P123 blend had a much higher burst release in comparison to the three-layer P123 blend. When comparing the general P123 combination scaffold composition with that of the plasma-treated PLLA scaffold composition, the former displayed a higher drug-release rate. Additionally, they were able to analyze the different factors that play a role in the variable drug release rates, such as the stability of the backbone, solubility of the water, chemical composition, matrix architecture and interaction, as well as the drug loading capacity. It was then concluded that placing dexamethasone in PLLA-P123 multilayer electro-spun nanofiber scaffolds assisted in creating a successful bone repair and bone tissue engineering application [64].

Additionally, Jing Zhou et al performed a study incorporating a dual-solvent evaporation technique [65] to formulate the multilayering drug delivery design with dexamethasone nanoparticles (DXM NPs) [66]. To test the stability of the design, they compared the effects of altering the ionic strengths of the assembly solution, the release of dexamethasone outermost layer, different temperatures, and the number of layers. After testing the drug delivery system, a reduced level in toxicity and a positive outcome with thermo responsiveness was noted, when utilizing the poly-diallyl dimethylammonium chloride/poly-styrene sulfonate (PDAC/ PSS) 8.5 multilayer assembly for the shell, without any salt, and dexamethasone for the core. The concentration and size of the free volume cavities determined the varying drug release and diffusion rates. As a result, to improve biocompatibility, incorporation of natural polymers was suggested. For a more localized release, metallic nanoparticles were recommended as they are observed to be more effective in that nature [66]. Furthermore, Nikkola et al formulated a triple layer drug delivery carrier incorporating a dexamethasone fiber grid with poly (80D,L-lactide-co-80 glycolide (PLGA) as the first layer, a membrane carrying etidronate with poly (95ε-capro/5D, L-lactide) (PCL95/5) as the second layer, and diclofenac sodium-carrying nanofibers with poly (95ε-capro/5D, L-lactide) (PCL) as the third layer [67]. They utilized methods such as melt extrusion, solvent casting, and electrospinning to produce the three layers. UV/Vis-spectrophotometer was used to determine the drug release rates, along with their pH levels. The maximum absorbance of dexamethasone and diclofenac were measured to be 242nm and 276nm, respectively, and their pH values were measured weekly based on the amount of drug released the previous week. Each layer is released at a different stage which is seen to be beneficial due to the impact it can have at the varying stages of tissue regeneration and repair. It was concluded that this nanofibrous triple-drug multilayer design is pertinent in treating anti-inflammatory conditions [67].

Castagnola and Carli et al utilized electrodes coated with poly (3,4-ethylenedioxythiophene) (PEDOT) that are bioactive polymers, integrated with glassy carbon (GC) as a substrate and dexamethasone as the drug, to create a multilayer drug delivery design. From previous studies, the PEDOT coating was known to have enhanced stability, reproducibility, morphological control, and electrochemical properties, in comparison to other methods of electrodeposition [68]. However, their unique approach of forming a poly-carbon-dexamethasone (PCD) coating made of two different PEDOT layers was shown to stabilize the neural interface simultaneously with enhanced electrochemical and electrical properties. The in vitro drug release rate of dexamethasone was determined by placing the PCD-coated GC electrode into a NaCl water solution and observing the results. Dexamethasone's absorbance value of 242nm was also utilized. When comparing the amount of dexamethasone being released at the first 100 pulses to that of 400 pulses, the value increased from an average of 91.8μg/cm2 to 140μg/cm2; however, it increased at a slower rate than it did from 0 to 100 pulses. It was concluded that this design, with control of its electrical impulses, has the ability to reduce the inflammation of the brain tissue after the implantation process and can further reduce the adverse effects due to the added layer of free dexamethasone. Additionally, this will be beneficial in averting potential immune reactions that may develop [68,69].

Anti-Microbials

Possible implementation of multilayer surface coatings designed using multilayer deposition are comprised of leaching,

contact killing, and anti-adhesion approaches which are all suitable in obtaining an antimicrobial surface [70]. Leaching coatings function by releasing a high concentration of antibacterial agents from its assembly. Contact killing coatings work against bacterium when the assembly is directly applied to applicable surfaces. Anti-adhesion coatings aim to repel bacteria from its surface, preventing biofilm formation entirely. Antibacterial agents can either be trapped between layers or constitute an integral part of the coating. Suitable carrier coatings for the delivery of antibacterial compounds are comprised of hydrogels, ceramics, and plasma-deposited polymers. The choice of coating materials depends on the chemical compatibility between the multilayer agent, in conjunction with the antibacterial agent, and the required matrix functionalities such as bio-integration or wear-resistance [70]. Each assembly can have a unique set of properties depending on its composition, thus the requirements needed for a target application must be analyzed before designing a release based antibacterial coating [70].

Chlorhexidine

A study by Luo et al explored the benefits of using chlorhexidine, as seen in dentistry to reduce infections, when incorporated into a multilayer sustained-release capsule [24, 71-73]. The system was obtained by precipitating $CaCl_2$, adjusting temperature levels of both chlorhexidine and $CaCl_2$ solutions (to control the size of the chlorhexidine spheres) to ultimately form a homogenous mixture, thus intertwining the spherical chlorhexidine together with $CaCl_2$ [72]. To make the microcapsules, they deposited bilayers of polyelectrolytes such as polystyrene sulfonate (PSS) and poly(allylamine hydrochloride (PAH) to stabilize the chlorhexidine molecules. It was observed that the shape of the drug colloids varied based on the process of the encapsulation, and this ultimately determined the efficacy of this multilayer design. It was further concluded that the drug release kinetics and concentration were dependent on the route and location of where the drug had to be released [72].

Gentamicin

Zhao et al examined a multilayer drug design focused on the drug release and resistance in corrosion of gentamicin integrated in magnesium alloys [74]. This design was formed by immersing the magnesium substrates in polyethyleneimine (PEI) solution, utilizing spin-assisted multilayer assembly, followed by washing, drying, and finally treating the substrates with poly(acrylic acid) (PAA) and poly(allylamine hydrochloride) PAH. The thermal cross-linking technique was then utilized by heating the samples at 150°C to form the heat-treated poly(allylamine hydrochloride)/poly(acrylic acid)-gentamycin sulfate (HT-(PAH/PAA-GS)n) multilayer films. By utilizing the plate-counting method, antibacterial effects of the systems were comparing Gram-positive Staphylococcus aureus. It was concluded that the process of cross-linking determined good resistance in corrosion and overtime the multilayer could form hydroxyapatite (HA) when placed in Hank's Balanced Salt Solution (HBSS). These results portrayed the benefits of using this drug delivery design in magnesium alloy implants for anticorrosive and antibacterial coatings [74]. Another study, one by Pavlukhina et al, examined the leaching capabilities of several multilayer films loaded with antibacterial agents [75]. They primarily focused on films made of adipic acid dihydrazide (AADH) and ethylenediamine (EDA), which were loaded with guest molecules, including peptide L5, gentamicin, and lysozyme. The prepared assemblies were then examined based upon their release capabilities as well as bactericidal activity. The positive charges exhibited by peptide L5 and gentamicin were integral to the initial electrostatic attraction of antimicrobial peptides to the negatively charged phospholipid bacterial membranes, ultimately resulting in this peptide being highly active against Escherichia coli and Staphylococcus aureus [75].

Isoniazid (anti-tuberculosis)

Tiwari and Mishra performed a study focusing on the controlled delivery of isoniazid integrated within sodium alginate (NaALG) and chitosan (CHI) polyelectrolyte multilayers [76]. Through colloidal crystallization of combining calcium chloride ($CaCl_2$) and sodium bicarbonate (Na_2CO_3), they formed calcium carbonate micro templates for layering with CHI and NaALG [76]. To determine the drug concentration, they utilized the eggshell membrane process by Philip et al. This was followed by a stirring process, which involved that the system be placed in either the phosphate or acetic acid buffer solution. Then, a spectrophotometer was used to determine the drug release rates [77,76]. Within a 24-hour observation period, they noticed that as the number of bilayers increased and polyelectrolyte cross-linking was performed, there was an immense improvement in the drug release rate as well. As a result, it was concluded that this drug design would be successful in the use of site-specific targeted therapy [76].

Anti-fungal β-peptide

Raman et al created a multilayer-coating design made of antifungal β-peptide, integrated between polyelectrolyte multilayers of chitosan (CH) and hyaluronic acid (HA) or poly-L-lysine (PLL) and poly-L-glutamic acid (PGA) to compare the effects of prevention or reduction in Candida albicans, a hospital-acquired infection [78]. Drug release rates were determined by immersing the β-peptide-filled test tubes reversibly into phosphate buffer solutions. Ultimately, they noted that the polysaccharide-based HA/CH β-peptide polyelectrolyte multilayer (PEM) coatings presented a more effective antifungal effect and exemplified a reduction in Candida albicans, in comparison to the polypeptide-based PGA/PLL β-peptide PEM coating which lacked any effects against Candida albicans [78].

Antimicrobial Peptides

Kazemzadeh-Narbat et al studied the controlled release of an antimicrobial peptide (AMP) from a non-cytotoxic multilayered

coating [79]. The coating itself was comprised of three layers of vertically oriented TiO_2 nanotubes, a calcium phosphate coating, and a phospholipid (POPC) film which were constructed in the LbL fashion with the AMP, HHC-36, begin deposited into each subsequent layer. The phospholipid layer was introduced into the structure in an attempt to enable the film to provide a more sustained release of the AMP. The combined structure was found to be highly efficacious against S. aureus and P. aeruginosa. Furthermore, this coating was found to exhibit no cytotoxicity upon osteoblast-like cells, in this case, MG-63. Hemocompatibility was also examined as demonstrating moderate platelet activation and low red blood cell lysis on implant surfaces but was also found to have no platelet activation in the solution [79]. A study conducted by Cado et al designed a self-defensive polysaccharide multilayer film with the antimicrobial peptide, bovine cateslytin (CTL), embedded within the final assembly [80]. The resulting system used polysaccharide multilayer films based on CTL-C functionalized hyaluronic acid as the polyanion and chitosan as the polycation (HA-CTL-C/CHI). The release of the antimicrobial peptide, CTL, was triggered by the enzymatic degradation of the film by the pathogens. The secretion of hyaluronidase, excreted by pathogens, released HA-CTL-C from the film, inducing an antimicrobial effect. CTL also exhibited a broad spectrum of antimicrobial activity against Gram-positive bacteria, yeasts, and filamentous fungi. The antibacterial and antifungal efficacy of HA-CTL-C/CHI films were tested against two Gram-positive strains, S. aureus and M. luteus and one yeast strain, C. albicans. The results specified that a decrease in microbial growth was congruent with an increasing number of HA-CTL-C/CHI bilayers. The assembly with 15 bilayers exhibited a 70% inhibition of all microbials occuring after 6 hours of incubation. However, all assemblies including the 5, 15, and 30 HA-CTL-C/CHI bilayer groups exhibited a complete inhibition of all microbials after 24 hours of incubation [80]. Etienne et al developed a multilayer coating which incorporated an antimicrobial peptide, defensin into alternating layers of polyanions and polycations [81]. The resulting assembly was studied for its antimicrobial efficacy against broad spectrum bacteria, by using two different strains of bacterium: Micrococcus luteus (a gram-positive bacterium) and Escherichia coli D22 (a gram-negative bacterium). Results were promising as a defensin-functionalized multilayer coating with 10 antimicrobial peptide layers which exhibited a 98% inhibition of E. coli D22 [81]. However, functionalization could only be achieved when the positively charged poly(L-lysine) was found to be the outermost layer of the film. There is a high chance that this may be due to the interaction that the positively charged ends of the films have with bacteria, facilitating defensin to interact with the bacterial membrane structure, and in turn, preventing bacterial adhesion [81].

Antibiotics

A study conducted by Guillaume et al. evaluated a degradable multilayer coating comprised of a biocompatible and biodegradable PCL and PLA based polymeric coating that served as a reservoir for two antibiotics, ofloxacin and rifampicin. The assembly consisted of three antibiotic layers and a topcoat of polymeric drug-free PCL-PLA to allow for controlled drug release [82]. The resulting multilayer was found to inhibit bacterial adhesion against, E. coli and S. epidermidis, while impeding biofilm formation and preventing bacterial proliferation. Additionally, the antibacterial effect against, E. coli and S. epidermidis was apparent for 72 hours. Furthermore, the incorporation of ofloxacin and rifampicin reduced in vitro fibroblast proliferation compared to polypropylene (PP) and drug free coated meshes [82].

Immunosuppressants

Heparin-Sirolimus

Liang-Cheng Su et al designed a polyelectrolyte multilayer coated stent made of the hydrophobic drugs, Duraflo heparin and sirolimus, and examined their antithrombotic and antiproliferative effects by utilizing an airbrush to spray the multilayer coating onto the stent [83]. To observe the drug release rate of this dual drug-eluting stent (DES), the coated stent was placed in ethanol [84] or a phosphate buffer solution [83, 85,86]. They noticed that the lower-dose stents displayed a two times higher drug-release percentage, in comparison to that of the higher-dose stents. For future drug designs, it was suggested that incorporating solvents or surfactants would be beneficial and would maintain an infinite sink condition when using drugs that have a low solubility. It was concluded that this dual DES of heparin and sirolimus was an effective candidate to be used in preventing adverse effects caused by induced polymers and be an essential alternative treatment for coronary artery stenosis [83].

Chronic Disease States

Anti-Coagulants

Heparin-Collagen

Zhang et al. created a multilayer system incorporating poly-L-lactide (PLLA) nanofibrous scaffolds into a dual-drug encapsulation of heparin and collagen [87]. With the nerve growth factor (NGF) multilayers, they observed a sustained release and regeneration in the peripheral nerve up until two weeks after the initial coating of 5.5 bilayers. This was observed when the formulation was tested on Schwann and PC12 cells. Methods utilized for measuring the efficacy were immunofluorescence imaging and laser scanning confocal microscopy. It was concluded that this technique could be an effective method for peripheral nerve regeneration when used in vivo [87].

Anti-Hypertensives

Felodipine

Hu et al created a multilayer system for oral sustained drug delivery system at the anti-hypertensive medication, felodipine

[88]. Due to felodipine's poor water solubility, it was integrated into layers of mesoporous silica nanospheres (MSN), chitosan (CHI), and acacia (ACA). Transmission electron microscopy (TEM), scanning electron microscopy (SEM), and nitrogen adsorption methods were utilized to examine the morphological changes to the structures. Additionally, x-ray diffractometry (XRD) and differential scanning calorimetry (DSC) were used to observe the physicochemical properties. Furthermore, surface tension measurement and thermal gravimetric analysis (TGA) were used to determine how varying the number of layers impacted the integrated drug. To evaluate the drug release kinetics, they first used the USP II paddle method, by placing the sample into a sodium dodecyl sulfate (SDS) solution which was taken out periodically and placed into a new medium. Finally, UV spectrophotometry was used to measure the actual drug release rate. It was concluded that using 5 bilayers of CHI/ACA within the Fel-MSN layers showed an enhanced sustained drug-release characteristic. Therefore, they forecasted this multilayer design as a beneficial one for other drugs with poor water solubility [88].

Asthma

Dexamethasone (in Nebulizer formulation)

Unlike the previous studies which mentioned the involvement of dexamethasone, this multilayering assembly formulation designed by Stewart-Clark et al explores dexamethasone for its use in ultrasonic nebulization [89]. This design consisted of poly(dimethyl diallyl ammonium chloride) (PDDA), poly(styrene sulfonate) sodium salt (PSS), and dexamethasone immersed in a deionized (DI) H_2O solution, which was then diluted to create the formulation. They also integrated the TiO_2 nanoparticles with dexamethasone to increase the film thickness. Using the nebulization technique increased the rate of film fabrication [90] and was suggested to be used for implanting coatings and similar biomaterials [89,90].

Inflammatory Bowel Disease

Dexamethasone

Oshi [91] et al focus on a treatment targeted for inflammatory bowel disease (IBD) by multilayering dexamethasone microcrystals (DXMCs) with pH-sensitive chitosan (CH) and alginate (AG) with Eudragit S (ES) layers [91]. They noted that the ES1AG4CH5-DXMCs design exhibited a sustained release at colon pH values and an enhanced protection against being dissolved in areas with pH levels similar to that of the upper gastrointestinal tract. However, they observed that the AG5CH5-DXMCs system's drug release rate was unfortunately too similar to that of the small intestine and stomach. As a result, they concluded that the pH sensitive DXMC multilayer drug delivery design is only highly effective when targeting colon IBD treatment [91-93].

Conclusion

As discussed in this review, there are a vast number of varying applications through the utilization of a multilayer drug delivery system. Each study described their own unique integration of layers which was implemented in their design and ultimately influences the outcome of the design's use. Benefits range from obtaining controlled drug release rates, sustainability, safety, biocompatibility, reduction in adverse effects relating but not limited to drug resistance and toxicity, to ultimately finding an effective treatment for specific medical conditions. Based on the varying environments of different pH levels, temperatures, constituents added to the design and each of their properties, varying drug release rates are shown. Challenges faced with this multilayer formulation varied per study based on the specific drug, solutions, polymers, technology, materials, and techniques utilized. Ultimately, with the benefits outweighing the challenges, this novel approach of utilizing a multilayer drug release platform is currently, and is forecasted to be, one of the optimal drug delivery designs for specific acute and chronic disease states, such as the ones mentioned in this review.

Declaration of competing interest

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

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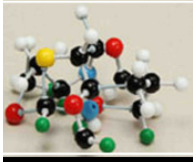

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