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Polymer assemblies for controlled delivery of bioactive molecules from surfaces ☆

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ABSTRACT

Localized delivery of bioactive compounds from surfaces of biomedical devices affords significant therapeutic benefits, and often relies on the capability of surface coatings to provide spatial and temporal control over release rate. The layer-by-layer technique presents a unique means to construct surface coatings that can conform to a variety of biomaterial surfaces and serve as matrices enabling controlled delivery of bioactive molecules from surfaces. The versatility of layer-by-layer assembly enables construction of surface coatings of diverse chemistry and internal architecture with controlled release properties. This review focuses on recent developments in constructing such layered matrices using linear polymers, polymer nanoparticles and block copolymer micelles, including micelles with stimuli-responsive cores, as film building blocks and in controlling release rate of therapeutics from these matrices via degradation, application of pH, ionic strength, temperature, light, electric field and chemical or biological stimuli. Challenges and opportunities associated with fabrication of stratified multilayer films capable of multi-stage delivery of multiple drugs are also discussed.

Contents

1. Introduction

Synthesis and design of materials for safe and effective drug delivery play an important role in modern biomedical science and medicine. Preventing degradation of therapeutic compounds and controlling their delivery rate are two central material properties that

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increase drug effectiveness and diminish adverse side effects. Yet another desired material properties includes the capability of a biomaterial to control delivery of multiple biological compounds at independent time scales. The layer-by-layer (LbL) technique, capable of depositing functional polymer coatings at surfaces of various chemistry and shape [1], is now viewed as a promising candidate for achieving a combination of these material properties.

Important applications of LbL coatings include controlling cellular and bacterial adhesion, as well as in delivery of bioactive molecules at the interface of a biomedical device and biological tissue, such as surfaces of orthopedic implants, urinary catheters or cardiovascular stents. Significant efforts have been made to design LbL structures as coatings to deliver small molecules, drugs and biomolecules from the surfaces of biomedical devices. The potential of drug-loaded polyelectrolyte multilayers as antimicrobial, anti-inflammatory, and anticancer coatings has already been demonstrated [2–5].

LbL deposition leads to construction of 3D or 2D polyelectrolyte multilayer (PEM) materials, i.e. capsules or thin films. PEMs in both 3D and 2D geometries have been explored as carriers of bioactive molecules. In the 3D case, functional compounds are encapsulated by the PEM wall; in the 2D case, functional molecules are included within the PEM film itself. The latter approach is receiving growing attention and has been discussed in several recent reviews [6–12]. While these two approaches target different applications, i.e. targeted systemic delivery or controlled delivery from the surfaces of biomedical devices for the 3D and 2D cases, respectively, we focus this review on recent advances, challenges and opportunities in using 2D PEM films as matrices for controlled release of therapeutics from surfaces.

The focus on the PEM film itself emphasizes the importance of chemical and physical properties of LbL films, such as the nature of interpolymer interactions, film hydrophobicity, nature and number of functional groups available for binding with guest molecules, and internal structure of the film. Multiple ways of binding polymer building blocks within LbL films have been explored, including non-covalent electrostatic [13,14], hydrogen bonding [15], charge transfer [16], recently reported halogen interactions [17], or covalent binding using click chemistry [18]. The LbL technique is highly suitable for immobilization of biomolecules with preserved activity, since LbL film fabrication is performed under mild conditions, often in an aqueous environment. It has been demonstrated that a variety of functional molecules, such as dyes, drugs, proteins, polysaccharides, enzymes, nucleic acids, can be incorporated within LbL films, and that these components retain their biological activity. The loaded amount of functional molecules may vary from 0.1 to several micrograms per layer, and can be often controlled at the step of film deposition by varying pH or ionic strength [19]. Higher total loaded amounts can be simply achieved by an increase in number of deposited layers. Importantly, the rate of drug release from PEM films can be controlled in a wide range from several seconds to several weeks by changing the nature of biodegradable building blocks, or by applying environmental cues, including temperature [20], pH [21], ionic strength [19], light [22] or electrochemical stimuli [23,24]. Importantly, recent years have seen increased interest in incorporating biodegradable components within LbL films [25], as well as in using other biologically relevant stimuli, such as the reducing environment of the cell membrane [26] or localized enzymatic film degradation [27].

Probably one of the most attractive features of LbL films for their biological and drug delivery applications is the potential capability of fabricating stratified films for multi-stage, multi-agent delivery of therapeutic compounds. While in certain cases the rate and time schedule for delivery of functional compounds can be controlled by the embedding depth of functional molecules within the film [27], it is not unusual to observe that strong interdiffusion of film components hinders film stratification [28]. In this respect, controlling internal structure and stratification of LbL films becomes of paramount importance. Interpenetration of polymer layers within the film and the surface morphology has been shown to be affected, to a certain degree, by the technique used for film deposition, i.e. dipping, spin coating or spraying. More dramatic are the effects of polymer nature and deposition conditions on the mode of PEM film growth and polymer intermixing. Specifically, strong intermolecular binding usually leads to linear film growth and results in stratified film structure, while weak interpolymer binding results in an exponential increase in film thickness with layer number and strong interdiffusion of polymers within the film [29].

In this review, we discuss recent developments in fabricating functional, LbL surface coatings with advanced controlled release capabilities, and discuss correlation between film architecture and release modes of single or multiple drugs. A great deal of attention is focused on the last four years achievements in constructing responsive LbL matrices for controlled release of functional molecules, which is enabled by chemical crosslinking routes of hydrogen bonded films, as well as by new strategies of inclusion of biodegradable nanoparticles or responsive-core block copolymer micelles within LbL assemblies.

2. Diversity of layer-by-layer (LbL) polymer film architectures

Fig. 1 shows a few examples of film architectures that can be constructed using the LbL technique. Below, we briefly describe selected types of LbL films whose application for controlled delivery is discussed in this review.

2.1. Homopolymer and random copolymer assemblies: non-crosslinked films versus LbL surface hydrogels

LbL films deposited 'as-is' are stitched together by interacting pairs of functional groups, and contain small or moderate amounts of water (Fig. 1a). Such structures can be used for controlled delivery of therapeutics if, for example, one of the film components contains a biologically active compound, and another film component is biodegradable. This type of film has demonstrated a strong potential for localized delivery of therapeutics and will be discussed below. Another route of incorporating biologically active compounds within LbL films is saturating PEM films with bioactive molecules post-assembly. While the capacity of as-deposited LbL matrices to absorb functional molecules from solution is usually relatively low, the use of weak polyelectrolytes (wPE) as film components enables a significant increase of capacity by using post-assembly pH variations which increase the number of ionic centers for guest molecule binding. Non-crosslinked wPE LbL films, however, often lose their structure upon long-term exposure to extreme values of pH and/or ionic strength [30,31]. This significantly limits potential applications of LbL as matrices for loading and releasing guest therapeutic compounds. Therefore, cross-linking is often applied to convert LbL films to surface hydrogels.

To stabilize deposited PEM films, different types of crosslinking, including thermal, photo, or chemical crosslinking based on carbodiimide chemistry [32], or formation of disulfide bonds [33] have been explored. Surface hydrogels can also be fabricated using sequential chemical crosslinking during self-assembly [34]. Recent examples of such an approach involve azide-alkyne and thiol-ene click chemistry approaches [35,36]. As illustrated in Fig. 1(b) and (c), cross-linking can be performed between self-assembled polymers of the same type (b), or different types (c), resulting in single-component or two-component surface hydrogels. Surface hydrogel PEM films with structure shown in Fig. 1b can be derived from either electrostatically assembled, or hydrogen bonded LbL films [37]. In the case of electrostatic self-assembly, amino-containing polycations (such as poly(allyl amine) (PAH), poly(ethyleneimine) (PEI), or chitosan (CHI)), glutaraldehyde was used to selectively crosslink polyamines within polyamine/polyacid multilayers [38], and a non-crosslinked polyacid can then be partially or completely removed from the film by exposure to basic pH [39,40]. As compared to their electrostatically assembled counterparts, hydrogen-