Journal of Controlled Release 158 (2012) 2–14

Contents lists available at SciVerse ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Responsive layer-by-layer materials for drug delivery

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ARTICLE INFO

Article history:
Received 27 June 2011
Accepted 23 August 2011
Available online 6 September 2011

Keywords:
Layer-by-layer
LbL
Responsive polymers
Polyelectrolyte multilayers
Drug delivery
Triggered release

ABSTRACT

Due to its versatility and ease of use the layer-by-layer (LbL) assembly technique has been under intensive investigation for drug and gene delivery applications. Especially the development of responsive LbL materials has advanced significantly in recent years. Responsiveness plays an important role in many delivery applications, either for loading of therapeutics or controlled and triggered release. In general four basic mechanisms within responsive LbL films have been identified: disruption of layer interactions, degradation of the LbL film, multilayer destruction via physical stimuli, and phase transitions or polymer rearrangements within the LbL film. This review will outline these different mechanisms and highlight recent advances in these fields.

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1. Introduction

The progress of synthetic polymers has been an enormous success story. Being initially developed as basic materials, they have advanced to a class of highly versatile and diverse materials, with applications in

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doi:10.1016/j.jconrel.2011.08.035

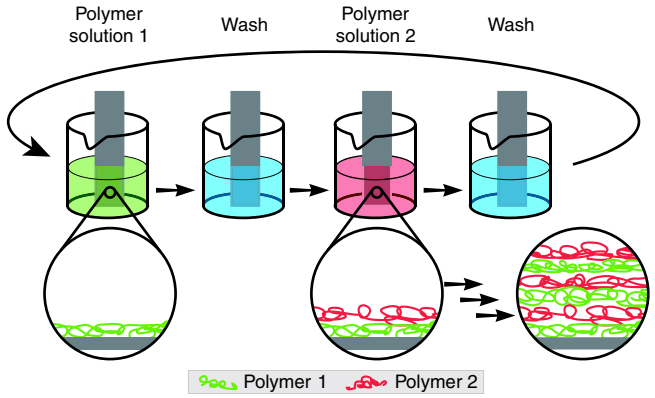

Fig. 1. Basic principle of the layer-by-layer technique. A template is alternatingly immersed in solutions of two interacting polymers. The template is washed in between the immersion steps in order to remove weakly bound macromolecules.

essentially every aspect of our lives. Due to the shear infinite variability of polymers, they have been prepared with a wide range of properties and functions. Especially in the last few decades stimuli-responsive polymers have helped to advance so-called "smart materials", which can change their properties in response to the environment or by external stimuli. But not only polymer materials themselves have progressed, also the techniques to (self) assemble them into functional materials have been under vigorous research [1]. Of these assembling techniques, especially the layer-by-layer (LbL) technique has attracted considerable attention. LbL assemblies were first reported by Decher et al. in 1992, who deposited alternating layers of anionic and cationic polyelectrolytes from solution onto a charged planar substrate [2,3] (Fig. 1).

The general concept of multilayer formation by electrostatic attraction has been expanded to alternating films stabilized by hydrogen bonding [4–6], hydrophobic interactions [7], covalent bonding [8–11], DNA base pair hybridization [12–14], and molecular recognition [15,16] (see Quinn et al. [17] for a review on these types of multilayers). The large interest in this technique becomes self-evident when further considering the possibilities to assemble films from a wide range of components: synthetic polymers (including dendrimers [18]), natural polymers (i.e. DNA, RNA, proteins, peptides, polysaccharides) [14,19–22], macromolecular assemblies (i.e. polymeric micelles, polyplexes) [23,24], (metal-) nanoparticles [25,26], viruses [27] and liposomes [28,29]. A list of polymer abbreviations, which also reflects commonly used LbL components, can be found at the end of this review. The LbL film properties (e.g. size, structure, stability) are readily tailored to specific needs during the assembly process, by adjusting the number of bilayers, concentration of the film components in solution or assembly conditions (e.g. solvent, temperature, pH, salt concentrations, time) [30–33].

Quinn et al. have also studied the assembly of blend multilayers via concurrent absorption of multiple film components. They showed that by incorporating multiple components into one layer, film stability could either be enhanced or decreased. Furthermore, this technique allows for the inclusion of a large number of species whose film loading can be tailored by varying solution composition and experimental conditions [34–36]. In contrast single component LbL films have also been reported by removing one of the film components subsequent to cross-linking of the second component (see section on reducible disulfide links and Fig. 12 for details), thus effectively creating a hydrogel film [37–39].

As the LbL technique allows for film assembly on virtually any template morphology, even complex surfaces can be modified and/or functionalized; a good example being controlled DNA release from LbL-modified stainless steel stents [40–43]. In general utilizing the LbL technique for surface-mediated drug delivery holds great potential, not only to modulate surface properties, but also as drug reservoir [44,45]. Furthermore, due to the step-wise structure of LbL assemblies, parallel and/or temporally spaced release of multiple therapeutics from one surface can be achieved [46–48]. It has to be noted however, that a large degree of cross-layer interdigitation and diffusion is often observed, thus complicating exact control over temporal release [49]. In addition, a trade off of step-wise assembly is that it is a rather time consuming process, especially when working with colloidal systems (Fig. 2). Although this may be of less concern in current research, it will become important should LbL move from the lab to large scale applications.

Nevertheless, another important area where the LbL technique has been utilized is the construction of multilayer films on sacrificial templates to obtain free-standing structures of various morphologies [40]. This has first been demonstrated by Caruso et al. in 1998, by the construction of novel hollow capsules via LbL assembly on colloidal templates which were subsequently removed [50–52] (Fig. 2).

In general, such capsules obtained by LbL deposition show great promise especially for drug and gene delivery, as the therapeutic payload can be encapsulated both in the shell and the interior, and the composition of the capsules can be tailored for controlled or triggered release [53–58]. Besides incorporating therapeutics during the assembly process as film component (e.g. DNA), there are generally three approaches to incorporate therapeutics or other active agents into LbL capsules: 1) post-production loading by reversibly enhancing the capsule permeability, 2) LbL assembly on therapeutic crystals, and 3) absorption

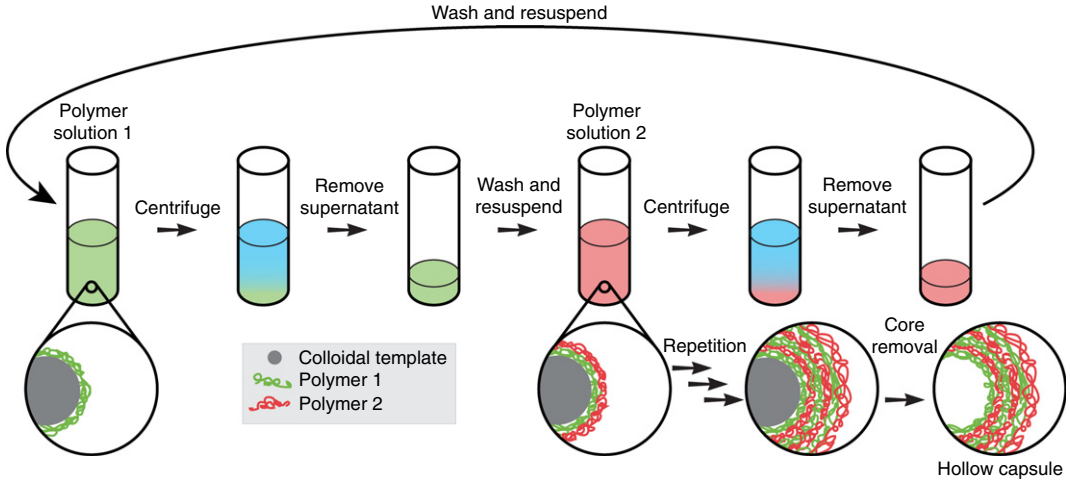

Fig. 2. Layer-by-layer assembly on colloidal templates is achieved by suspending the templates alternately in solutions of two interacting polymers. After each assembly step the templates are isolated via centrifugation and washed to remove weakly bound macromolecules. Dissolution of the colloidal template affords hollow LbL capsules.