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Review

Layer-by-layer deposited nano- and micro-assemblies for insulin delivery: A review

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ABSTRACT

We present an overview of the recent progress in the development of layer-by-layer (LbL) assembled thin films and microcapsules for insulin delivery. The LbL deposition of insulin-containing thin films on the surfaces of flat substrates or microparticles has been investigated for orally administered insulin formulations. The amount of insulin in the LbL films can be precisely controlled by altering the number of layers in the films. As-prepared LbL films and microcapsules can be loaded with insulin by exposing the films and microcapsules to an insulin solution. The insulin can be released by pH-induced decomposition or permeability changes in the LbL films and microcapsules. Closed-loop insulin delivery systems that can release insulin in response to changes in glucose concentration have also been constructed with LbL films and microcapsules. Glucose-sensitive materials, such as glucose oxidase, concanavalin A, and phenylboronic acid, have been incorporated into insulin-containing LbL assemblies. In addition, LbL film-coated pancreatic islet cells have recently been developed as a bio-artificial pancreas, in which the islet cells are isolated from the recipient's immune system by the LbL coatings. Thus, LbL films and microcapsules could make a significant contribution to the further development of patient-friendly insulin delivery systems.

Contents

1. Introduction

Non-invasive routes for insulin administration, such as oral, pulmonary, nasal, and transdermal routes, offer promising alternatives to subcutaneous injection [1–5]. Oral administration is the safest route

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and thus is effective for improving patient compliance. However, oral formulations of insulin are not currently used, because insulin is decomposed by proteolytic enzymes in the stomach and duodenum, the acidic conditions in the stomach destabilize insulin during transit, and only a small percentage of orally administered insulin is absorbed from the small intestine. Consequently, many approaches have been proposed for enhancing the bioavailability of oral formulations of insulin, including nanoparticles, microspheres, microcapsules, and liposomes [6–11]. In particular, insulin-loaded nanoparticles have recently attracted intense interest, because nanoparticle-based formulations enhance the stability of insulin in the gastrointestinal tract, which improves the pharmacological availability of insulin [5,9–11]. The insulin-loaded nanoparticles are usually pH-sensitive; insulin is released from the nanoparticles in the neutral environment in the small intestine, but not under acidic conditions in the stomach. For example, orally administering insulin-loaded nanoparticles composed of chitosan (CHI) and alginic acid (ALG) effectively lowered the blood glucose level of diabetic rats, suggesting that nanoparticles could be used for the oral delivery of insulin [11]. A variety of materials are currently used for preparing insulin-loaded nanoparticles, including CHI [7,12], ALG [13], dextran sulfate (DS) [13], phospholipids [14], synthetic polymers [15,16], poly(lactic acid) (PLA) [17,18], poly(lactic acid-glycolic acid) (PLGA) [18], and zirconium phosphate [19]. However, the pharmacological activity of the insulin in orally administered nanoparticles is generally still less than 10% that of the subcutaneous dose of free insulin.

Closed-loop insulin delivery systems, which contain an electromechanical artificial pancreas consisting of an electrochemical glucose sensor and an insulin infusion pump, have been extensively studied [20,21]. However, the performance of the implanted glucose sensors for continuously monitoring glucose levels is not sufficiently reliable, limiting the routine operation of artificial pancreases. Therefore, alternative systems in which insulin release is directly coupled with glucose monitoring via a chemical interface are highly desirable. Insulin-loaded chemical devices that can release insulin in response to elevated blood glucose levels have been studied [22]. Glucose-responsive materials such as glucose oxidase (GOx), lectin, and phenylboronic acid derivatives (PBA) have been employed for monitoring the glucose level in blood.

The layer-by-layer (LbL) deposition technique has been used to construct insulin-containing nano- and micro-assemblies that are suitable for oral insulin formulations and glucose-dependent insulin release systems. LbL deposition is a bottom–up nanofabrication technique that was first developed by Decher and co-workers [23–25]. They found that alternating the adsorption of cationic and anionic polyelectrolytes from their aqueous solutions produced thin films composed of oppositely charged polymers on a solid surface. A variety of materials, including synthetic polymers, dendrimers, polysaccharides, DNA, and proteins, have subsequently been used to construct LbL films on the surfaces of flat substrates and colloidal particles [26–29]. Insulin-loaded microparticles can be prepared by the LbL deposition of insulin and oppositely charged polymers on the surface of microparticles. The loading of insulin on microparticles can be precisely controlled by changing the number of layers in the film. In addition, hollow microcapsules can be prepared by the LbL deposition of synthetic polymers on the surface of a microparticle core, followed by dissolving the core material [30]. Another advantage of the LbL deposition protocol is that whole process is carried out in aqueous media under mild conditions. Therefore, LbL deposition is considered to be an ideal protocol for preparing delivery systems for unstable protein drugs, including insulin. LBL deposition has widely been used for preparing protein-loaded thin films and microcapsules. The synthesis and applications of LbL assemblies in drug delivery have been comprehensively reviewed [31–34]. The present review focuses on insulin-loaded LbL films and microcapsules suitable for developing oral insulin formulations and glucose-dependent insulin release systems. We will briefly review the synthesis and properties of LbL films and microcapsules in the next section.

2. Synthesis and properties of LbL films and microcapsules

2.1. LbL films composed of synthetic polymers

LbL films were first prepared by the alternate deposition of oppositely charged synthetic polymers, and the film formation relied on the electrostatic binding of the polymers [23–25]. The chemical structures of polymers frequently used as components of LbL films are shown in Fig. 1. In a typical procedure, a solid support is alternately immersed in aqueous solutions of positively and negatively charged polymers for 15–30 min to deposit the polymers on the support, followed by rinsing for 5–10 min. In this procedure, the positively and negatively charged polymers are alternately adsorbed on the surface of a support to form nanometer-thick layered films. A spray deposition protocol can also be used for the fast fabrication of LbL films [35]. A variety of substrates, including metals, ceramics, polymers, and glass, with hydrophilic, hydrophobic, charged, or uncharged surfaces can be used as solid supports on which LbL films are deposited. An advantage of the LbL deposition technique is that the thickness of films can be precisely controlled by the number of deposited layers. The thickness of LbL films also depends on the pH and ionic strength of the polymer solutions, because the conformation of the polymer chains depends on the pH- and ionic strength [36]. Highly charged polymers form a stretched conformation in solution, whereas weakly charged polymers tend to adopt a globular conformation. Aqueous media with a high ionic strength forces polymers to adopt globular forms through shielding the electrostatic repulsion within the polymer chains. Consequently, the pH and salt concentration of the polymer solutions must be carefully considered for LbL films. The electrostatic bonding of synthetic polymer LbL films is usually stable over a wide pH range, even if the environmental pH is more acidic or basic than the apparent pK_a of the polymers, because the polymer chains are connected through multiple binding sites.

Hydrogen bonding can also be used for constructing LbL films. Synthetic polymers bearing carboxylic acid side chains are often used in combination with hydrogen bond acceptor polymers, such as poly(vinylpyridine), poly(vinylpyrrolidone), and poly(ethyleneglycol) [37–40]. The alternate deposition of the hydrogen-bonding donor and acceptor polymers affords hydrogen-bonded LbL films. Hydrogen-bonded LbL films are usually stable in acidic media, whereas they often decompose in neutral or basic solutions because the hydrogen bonds are broken as a result of the deprotonation of carboxylic acid residues. Therefore, hydrogen-bonded LbL films are useful in the construction of pH-sensitive devices [41]. LbL film building blocks are not limited to polymers; small ions and molecules can also be used under appropriate conditions [42–45].

2.2. LbL films composed of biopolymers

Charged biopolymers, such as polysaccharides [29,46–49], DNA [50,51], and proteins [30,52–55], can also be used as building blocks for LbL films. The biological activities of the biopolymers are preserved in the LbL films, thus the biopolymer films can be used as an active component in biosensors [53], bioreactors [52], and catalysts [54]. Binding proteins, such as antibodies [56,57], avidin [58,59], and lectin [59–61], can also be used for constructing LbL films based on antibody–antigen, avidin–biotin, and lectin–sugar interactions. For instance, catalytically active LbL films have been prepared by the alternate deposition of lectin, and concanavalin A (Con A), with glycoproteins, such as GOx, and horseradish peroxidase (HRP) [62]. The LbL deposition protocol is suitable for preparing protein films, because the whole process can be carried out in aqueous media under physiological conditions.

2.3. Microcapsules prepared by LbL deposition

LbL microcapsules can be directly constructed by coating colloidal particles with LbL films, to produce a core–shell structure. Nanocrystals