Advanced Drug Delivery Reviews 63 (2011) 809–821

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

pH- and sugar-sensitive layer-by-layer films and microcapsules for drug delivery ☆

Katsuhiko Sato, Kentaro Yoshida, Shigehiro Takahashi, Jun-ichi Anzai *

Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki, Aoba-ku, Sendai 980-8578, Japan

ARTICLE INFO

Article history:
Received 1 October 2010
Accepted 30 March 2011
Available online 12 April 2011

Keywords:
LbL film
LbL microcapsule
pH-sensitive release
Sugar-sensitive release
Insulin release
Drug delivery

ABSTRACT

The present review provides an overview on the recent progress in the development of pH- and sugar-sensitive layer-by-layer (LbL) thin films and microcapsules in relation to their potential applications in drug delivery. pH-sensitive LbL films and microcapsules have been studied for the development of peptide and protein drug delivery systems to the gastrointestinal tract, anti-cancer drugs to tumor cells, anti-inflammatory drugs to inflamed tissues, and the intracellular delivery of DNA, where pH is shifted from neutral to acidic. pH-induced decomposition or permeability changes of LbL films and microcapsules form the basis for the pH-sensitive release of drugs. Sugar-sensitive LbL films and microcapsules have been studied mainly for the development of an artificial pancreas that can release insulin in response to the presence of glucose. Therefore, glucose oxidase, lectin, and phenylboronic acid have been used for the construction of glucose-sensitive LbL films and microcapsules. LbL film-coated islet cells are also candidates for an artificial pancreas. An artificial pancreas would make a significant contribution to improving the quality of life of diabetic patients by replacing repeated subcutaneous insulin injections.

Contents

1. Introduction

Drug delivery systems are an effective way to control the concentration of therapeutic agents in blood and to improve their bioavailability. The blood level of a drug is known to rapidly increase after administration and gradually decreases below the lowest level required for therapeutic action. Consequently, repeated administration of a drug is often required for patients to maintain the blood level of the drug within the range of effective therapeutic action. However, in controlled delivery systems, drug molecules are embedded in gel matrices that can control the release rate of the drug, which results in sustained drug release. Furthermore, systems for stimuli-sensitive drug release can be constructed if the gel materials are endowed with sensitivity to specific

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Layer-by-Layer Self-Assembled Nanoshells for Drug Delivery".

* Corresponding author. Tel.: +81 22 795 6841; fax: +81 22 795 6840.
E-mail address: junanzai@mail.pharm.tohoku.ac.jp (J. Anzai).

0169-409X/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2011.03.015

stimuli. External stimuli such as temperature, light, and electric and magnetic fields, and internal stimuli including pH and biological ions and molecules are often used as the stimuli by which drug release is triggered [1–6]. In stimuli-sensitive drug delivery, required amounts of the drug can be released at the site of drug action in response to stimuli.

A typical example of stimuli-sensitive drug delivery can be seen in the development of insulin formulations for the treatment of diabetic mellitus, in which much effort has been devoted to the development of glucose-sensitive microspheres or micropaticles that release insulin in response to the elevated level of blood glucose. To develop glucose-triggered insulin release, glucose-sensitive materials such as glucose oxidase, lectins, and phenylboronic acid derivatives have currently been employed [7–9]. Glucose-sensitive formulations of insulin could serve as an artificial pancreas, which would eliminate the necessity of repeated insulin injection. Another insulin formulation under extensive study is one that can be orally administrated as an alternative to subcutaneous injection [10,11]. However, the oral delivery of insulin is not presently realistic, because insulin is decomposed into peptide fragments by proteolytic enzymes in the stomach. The bioavailability of orally administrated insulin can be improved to some extent by coating the formulations with polymer films that are stable in acidic environments but are dissolved in neutral media (i.e., enteric coating). The use of enteric coatings is known to be effective for protecting insulin as well as other protein drugs from enzymatic digestion in the stomach and the drugs are then released in the small intestine at neutral pH. Synthetic polymers such as poly(acrylic acid) and cellulose derivatives with carboxyl side chains are often used for this purpose. Thus, enteric coatings open an opportunity for developing oral administrations of peptide and protein drugs including insulin, which in turn would significantly improve patient compliance.

Targeted drug delivery has also been attracting much attention, due to its therapeutic advantages in improving bioavailability and minimizing systemic side effects [12]. Drug-embedded microparticles can be targeted to specific cells or tissues by modifying the particle surface with a ligand that exhibits affinity to the target cells or tissues. Recently, sugar derivatives have been explored for targeting drugs by taking advantage of the high affinity of specific sugars to lectins or sugar receptors on cell surfaces. For this goal, sugar-labeled polymers, liposomes, and microparticles have extensively been studied. For example, galactose-labeled microparticles have been developed for drugs targeting the liver (hepatocyte cells) through asialoglycoprotein receptors present on the surface of hepatocyte cells [13]. Therefore, different types of natural or synthetic materials are widely employed for the construction of devices for controlled drug delivery.

Recently, layer-by-layer (LbL) deposited thin films and microcapsules have attracted much attention for the development of drug delivery systems [14–22]. This review focuses on the recent developments of LbL films and microcapsules for pH- and sugar-sensitive drug delivery. LbL-deposited thin films were first developed by Decher and co-workers [23]. They proposed a protocol for the preparation of thin films based on alternate and repeated adsorption of polycations and polyanions on the surface of a solid substrate from solution, as schematically illustrated in Fig. 1. LbL thin films with desired components can be prepared using appropriate types of cationic and anionic polyelectrolytes. The driving force of LbL deposition is not limited to attraction by electrostatic force, but other binding interactions such as hydrogen bonding, covalent bonding, and biological affinity can also be used. A diversity of materials have been employed as building blocks for LbL films, including synthetic polymers, biopolymers (proteins, polysaccharides, DNA, etc.), inorganic nanoparticles, carbon nanotubes, and even viruses [24]. Consequently, a variety of components and functionality can be incorporated into LbL films, which forms the basis for the development of stimuli-sensitive LbL films for drug delivery. Another advantage of LbL films is that the film thickness can be regulated at the nanometer level by simply changing the number of deposited layers, which enables precise control of the drug loading in the film.

Möhwald and co-workers fabricated polyelectrolyte hollow microcapsules in 1998 by LbL deposition of polyelectrolytes on the surface of colloidal particles, followed by dissolution of the core material (Fig. 2) [25]. The combination of poly(allylamine hydrochloride) (PAH) and poly (styrene sulfonate) (PSS) is a polyelectrolyte pair frequently used for microcapsule construction. Organic (polystyrene and melamine formaldehyde) and inorganic microparticles ($CaCO_3$ and $MnCO_3$) with diameters of a few micrometers have often been employed as core materials. With respect to drug delivery applications, the use of inorganic microparticles is plausible, because dissolution of these inorganic materials can be conducted in mild aqueous media (such as ethylenediaminetetraacetic acid (EDTA) solution) compared to the harsh conditions required for dissolution of the organic microparticles (i.e., organic solvent or strong acid). $CaCO_3$ particles are often used recently for the preparation of polyelectrolyte microcapsules, especially for biomedical applications [26]. This is because biologically active peptides and proteins are easily incorporated in $CaCO_3$ particles by co-precipitation upon synthesis of $CaCO_3$ particles from a mixture of $CaCl_2$ and $(NH_3)_2CO_3$ solutions. Two distinct sites exist where drugs can be accommodated in polyelectrolyte microcapsules; the polyelectrolyte shell and the internal cavity. It is envisaged that drug molecules encapsulated in the cavity of microcapsules are released in response to chemical or physical stimuli that is detected by a receptor located on the polyelectrolyte shell. This strategy is widely adopted for the development of stimuli-sensitive drug delivery systems, as discussed in the following sections.

The synthesis and properties of LbL films and microcapsules, including their applications to drug delivery, have been comprehensively reviewed by many authors [14–22,27–30]. Therefore, this review focuses on recent progress in the preparation and concepts of LbL films and microcapsules for pH- and sugar-sensitive drug delivery.

2. pH-sensitive LbL films and microcapsules

The physiological pH in tissues and cells has been summarized in recent reviews in relation to drug delivery [1–5]. The pH variation along the gastrointestinal (GI) tract is well known and should be taken into consideration when developing oral administrations. The stomach has a strongly acidic pH of ca. 1.5, while the pH in the small intestine and colon is almost neutral. Therefore, acid-sensitive drugs such as peptides and proteins should not be delivered through the oral route. The extracellular pH of tumor cells slightly deviates to the acidic region from pH 7.4, by which pH-sensitive delivery of anti-cancer drugs may be developed. The pH of inflammatory tissues is also known to be acidic.

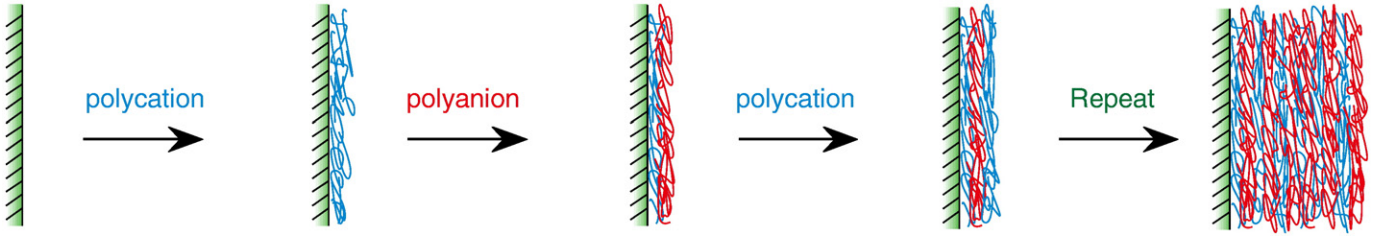

Fig. 1. Preparation of LbL thin films.