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Layer-by-layer polyelectrolyte coating of alginate microgels for sustained release of sodium benzoate and zosteric acid

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ABSTRACT

The potential of sustaining release of very small (Mw < 250 g/mol) hydrophilic drugs up to several days from layer-by-layer (LbL) polyelectrolyte coated alginate microgels (Alg-Ms) was investigated. One purpose is to minimize post-surgical adhesions, which develop in 12 h to 3 days after surgery. The LbL polyelectrolyte layer would serve as a diffusion barrier for their release. The LbL polyelectrolyte bilayers were prepared using poly (allylamine) (PAH) and poly(styrene sulfonate) (PSS). Sodium benzoate (NaB, Mw = 144 g/mol) and zosteric acid (ZA, Mw = 244 g/mol), two anti-inflammatory and anti-microbial compounds, were used as model drugs. A higher number of PAH/PSS bilayer lead to a greater sustained release of both drugs, and with 4 bilayers, the release of NaB and ZA was prolonged from 24 h to 72 h and 120 h, respectively. Fitting the data to the Ritger-Peppas' equation showed that as the bilayer number increased, the release constant and/or exponent decreased, indicating the LbL PAH/PSS bilayer effectively reduced the permeability of these two very small hydrophilic drugs. The ability to prolong the release of such small hydrophilic molecules, which has rarely been investigated previously, would find broad applications in fields such as anti-adhesion treatment and antifouling coatings.

1. Introduction

One major aim for developing drug delivery systems is to achieve greater drug effectiveness with sustained release and reduced toxicity [1–3]. Such system is critical when the drug is designated for local delivery on the surface of an organ. An example is the application of anti-adhesion drugs for preventing post-operative adhesions, which normally develop in 12 h to 3 days after a surgery [4–6]. In an effort to prevent surgical adhesions, numerous pharmacological and barrier-based approaches have been reported [7–10]. When pharmacological agents are applied, the rapid clearance of drugs from the peritoneum leads to limited effectiveness of the intraperitoneally applied drugs [4,6]. Instead of burst release, a sustained release would be more suitable for delivering certain therapeutics to local target sites.

Some of the anti-adhesion drugs of interests are low molecular weight (Mw < 500 g/mol) hydrophilic (solubility in water > 33 mg/mL) compounds [11–13]. One group of these hydrophilic drugs is defined as nonsteroidal anti-inflammatory drugs, which are commonly used for treating inflammation, pain, and fever [14,15]. They can also regulate cell growth and reduce inflammatory activities when applied to a wound [4,5]. One of the challenges for delivering such small hydrophilic drug is their high initial burst release on the target sites and their quick depletion [16–21]. Various drug carriers including micelles, liposomes, and nano/micro-particles have been designed to achieve sustained release [22–24]. However, these systems still suffer from some drawbacks such as poor drug release control, weak chemical stability, or low drug loading.

In recent years, the particulates made of hydrogels (i.e., nano-or microgels) with a size ranging from 50 nm to 500 μm have been widely recognized as promising drug carriers for controlled drug delivery. The main advantages of hydrogel based drug carriers include easy synthesis with precise size control, long-term stability, and biocompatibility [25]. However, the ease and high permeability of small molecules in hydrogels are problematic for them to serve as sustained release drug carriers. A potential approach to reduce drug permeability is to create a barrier over the hydrogels that carry hydrophilic drugs [11,26,27]. In this regard, the layer-by-layer (LbL) deposition of alternating cationic and anionic polyelectrolytes to form a barrier coating for sustaining drug delivery has been actively investigated [28,29] primarily due to the process being simple, cost-effective and safe [29,30].

The LbL coatings have been utilized for sustaining the delivery of various biomolecules including DNA, proteins and peptides, particles, and small hydrophobic drugs [31–35]. Several recent studies have also examined the release of small (Mw: 300–500 g/mol) hydrophilic compounds (e.g., fluorescein, ciprofloxacin hydrochloride, rhodamine B) utilizing LbL polyelectrolyte bilayers as the barrier. The total release of

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these drugs, however, still occurs within minutes to a few hours [29,30,36,37], and a faster depletion is expected when the molecule is smaller and/or more soluble in water [35]. However, the release, especially sustaining the release, of very small (Mw < 250 g/mol) hydrophilic drugs from LbL polyelectrolyte coated hydrogel based carriers has rarely been investigated [33]. In order to expand the applications of this class of drugs (e.g., for anti-adhesion treatment), investigations into designing suitable carriers that prolong (e.g., up to 72 h) their release are needed.

In our study, we created LbL deposited polyelectrolyte bilayers on alginate microgels (LbL-Alg-Ms) as drug carriers. Alginate, a linear anionic polysaccharide, has been widely investigated as a carrier material for drug delivery [38–40]. The LbL deposited polyelectrolyte bilayers were hypothesized to serve as a diffusion barrier that would significantly retard the release of very small hydrophilic drugs (Mw < 250 g/mol, solubility in water > 33 mg/mL) by increasing the diffusion path and potentially introducing molecular interactions, such as electrostatic interactions and hydrogen-bonding, between drug molecules and the bilayers. The primary goal of this study was to evaluate the effectiveness of the LbL Poly (allylamine)/Poly (sodium 4-styrenesulfonate) (PAH/PSS) bilayers in retarding the release of small hydrophilic drugs from alginate microgels, and desirably to prolong their release up to three days, the critical period for the development of post-surgical adhesions. PAH/PSS is the most commonly used and well-studied polyelectrolyte pair for LbL deposition in drug delivery applications [29,30,36,41–44]. The two drugs to be evaluated were sodium benzoate (NaB, Mw = 144 g/mol, solubility in water = 630 mg/mL) and zosteric acid (ZA, Mw = 244 g/mol, solubility in water = 300 mg/mL). They are potential anti-microbial and anti-inflammatory compounds [45–47] that would reduce inflammatory activities and be beneficial in post-surgical adhesions' management. The release was monitored via a topical Franz diffusion cell to mimic the conditions where the drugs would be mixed in a gel to be applied on the surgical sites. Our results showed that the LbL PAH/PSS bilayers were effective barriers in slowing down the release of these two very small hydrophilic drugs and sustained the release of NaB and ZA up to 3 days and 5 days, respectively, sufficiently long enough for treating potential adhesions post-surgery.

2. Experimental section

2.1. Materials

Most of the starting materials were purchased commercially and used as received. All reagents and solvents were of ACS or HPLC grade. Sodium alginate, sodium benzoate (NaB), phosphate buffered saline (PBS) and sodium chloride (NaCl) were obtained from Sigma-Aldrich. Calcium chloride ($CaCl_2$) anhydrous was purchased from EMD. Zosteric acid (ZA), with a purity > 95%, was synthesized in house by using p-coumaric acid (98% pure) and chlorosulphonic acid (99% pure) [48] – both purchased from Sigma-Aldrich – as the reactants. Crocein orange G (CG) was obtained from TCI. Poly (allylamine) (PAH) (average M_w ~ 15,000, 15 wt % solution in water) was purchased from Polysciences, Inc. Poly (sodium 4-styrenesulfonate) (PSS) (average M_w ~ 70,000) and acridine orange (AO) were purchased from Sigma-Aldrich. Deionized water (DI) was purified in house and had a conductivity of ~1 μS/cm or less. Some main materials used in this study and their properties are summarized in Table 1.

2.2. Preparation of alginate microgels (Alg-Ms)

Alg-Ms were produced by a special air droplet generator. The drug, either NaB or ZA, was added into both alginate solution and gelation solution for microgels preparation. Briefly, calcium chloride (1.5% w/v) and the drug (3% w/v) were dissolved in DI water (200 mL) as the gelling medium. Alginate (2% w/v) and the drug (4% w/v) were dissolved in DI water (8 mL) and co-axial extruded as droplets through a 25-gauge needle using a 10-mL syringe barrel. The droplets formed on the needle tip were sheared off by the air flow at a rate of 5 LPM. The gelation process took place in the gelling medium for 30 min under gentle stirring using a magnetic stirring bar. Eventually, the Alg-Ms were collected by filtering the Alg-Ms containing gelling solution through a stainless-steel mash with a grid size of ~100 μm.

2.3. Deposition of polyelectrolyte bilayer(s) on Alg-Ms

The PAH solution was prepared at a concentration of 2 mg/mL in DI water containing 0.1 M NaCl, and the PSS solution was also prepared at a concentration of 2 mg/mL in DI water and contained either 0.1 M NaCl or 1.5–2 wt% of the drug (NaB or ZA). For deposition of the first layer, 1 mL of PAH solution was added to a 2 mL micro-centrifuge tube containing 270 mg of negatively charged alginate microgels. Adsorption was allowed to proceed for 2 min. After the microgels settled, the solution was removed, and the microgels were washed, twice, by adding DI water to the centrifuge tube followed with gentle shaking and discarding of the liquid to remove free polyelectrolytes on the surface. A 1 mL aliquot of PSS solution was then added to the PAH-coated alginate microgels and allowed to interact for 2 min, followed by the removal of the solution and washing with DI water. The process was repeated to deposit polyelectrolyte multilayers onto Alg-Ms with a desired number of PAH/PSS bilayers.

2.4. Determination of drug loading

For drug loading in the carriers (Alg-Ms and LbL-Alg-Ms), ~200 mg of each carrier-drug pair was used. The polyelectrolyte bilayers were dissembled and the alginate cores were de-gelled by using 40 mL 1 M NaOH solution at 80 °C under stirring for 2 h. After vortexing and centrifuging the solution, the supernatant was collected and diluted 20 × using 1 × PBS to measure the sodium benzoate (NaB) or zosteric acid (ZA) concentration by using UV–vis spectroscopy (Model UV-1601, Shimadzu Corporation, Columbia, MD) at 225 nm or 273 nm, respectively. The exact concentration of each drug was determining by using a pre-constructed calibration curve of absorbance intensity vs. concentrations (0–20 mg/mL) of the drug. All measurements were performed in triplicate. The amount of drug loaded is estimated using:

$$\text{Drug loading (\%)} = \frac{\text{mass of NaB or ZA from LbL−Alg−Ms}}{\text{total mass of LbL−Alg−Ms with drug}} \times 100\%$$

2.5. Characterizations of microgels: morphology and size

A drop of Alg-Ms or LbL-Alg-Ms suspended in DI water was placed on a glass slide and observed with an inverted IX-70 microscope (Olympus IX71, B&B Microscope, Pittsburg, PA) equipped with a differential interference contrast (DIC) slider (U-DICT, Olympus). Bright field images were taken using either 4 × (Olympus, PLAN4/0.1 NA) or 10× (Olympus, UPLFLN10 × PH/0.3 NA, W.D. 10) objective lens with the DIC slider in. For fluorescence images, the LbL-Alg-Ms spread on glass slide were illuminated with a Xenon light passing through a blue/green fluorescent filter. The images were viewed by an eye-piece digital camera (HDCB-90D) connected to the microscope, and captured by the YAWCAM software (version 0.5.0, Magnus Lundvall). The size, in term of radius, of the microgels, and the fluorescence intensity of LbL-Alg-Ms were measured using ImageJ (Version 1.43t, National Institute of Health) from the captured images. To obtain reliable values, images of at least 30 microgels were measured for each sample.

2.6. In vitro release of NaB or ZA from Alg-Ms and LbL-Alg-Ms

In vitro drug release from LbL-Alg-Ms was followed using a Franz-