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Chemical and physical modification of layer-by-layer assembled nanofilms composed of block copolymer micelles and graphene oxide for controlled drug release

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ABSTRACT

In this study, multilayer films with two components, block copolymer micelles (BCM) and graphene oxide were prepared. To adjust the ratio of the model drugs (coumarin-6) loaded in the BCMs, we used BCM at pH values of 5.5 and 8.5. However, the release behavior of a model drugs was rapid, and most of drugs was released within 24 h. Therefore, to control the release rate of the drugs, we used two methods to modify the films: chemical modification of the inner structure and modification of the external structure. These two modifications were achieved by crosslinking and the addition of external layers, respectively, and we investigated the effects of these modifications on the release of the model drug. We observed a slow release profile, from 24 to almost 70 h, in the film modified with an external layer. In contrast, the crosslinked film showed different release profile that was dependent on the pH of the BCMs in the film. When the pH of the BCMs in the film was 5.5, the release of the drug was rapid, more so than the unmodified film. When the pH of the BCM in the film was 8.5, the drug release was similar to that of the unmodified film.

Introduction

In the past few decades, the design and manufacture of nanostructured materials have become of immense interest for the preparation of drug delivery systems [1–3]. This interest has arisen because nanomaterials can overcome the short half-lives, poor stabilities, and toxic side effects [4] that affect current drug delivery systems. These nanostructured materials include nanoparticles, nanowires, and micelles [5,6]. Among the many methods of preparing nanostructured materials, the layer-by-layer (LbL) assembly method is one of the most important techniques, allowing the fabrication of multilayered thin films, and has considerable applications in the preparation of drug delivery carriers [7]. In particular, the LbL method is simple and amenable to modification [8]. The LbL technique can be accomplished by using various techniques such as dipping, spinning, and spraying [9–11]. LbL-assembled nanofilms can be composed of various materials, for example, polyelectrolytes [12], nanoparticles [13], and micelles [14]. The multilayers are formed continuously by electrostatic forces, hydrogen bonding interactions, or covalent bonding between the materials [15,16]. Advantageously, multilayer thin films can be used to control the drug release rate by tailoring the film composition, thickness, and porosity [17,18]. However, multilayer thin films have many limitations; for example, the limited number of charged ions in each layer result in limited assembly of film causing poor drug loading amounts [19]. Therefore, block copolymer micelles were used to prepare a film to solve the limitations of multilayer films with low drug loading [20].

Amphiphilic block copolymer micelles are nanosized polymeric nano-sized particles. These have been used widely because of their unique structures, properties, and potential applications [20–22]. Their peculiar structure gives them unique properties, such as self-assembly and self-organization in various solutions, and the micelle cores can be loaded with various drugs. For instance, several studies have applied polymeric micelles to drug delivery systems [23–25]. A common disadvantage of LbL films containing micelles is that they have low structural stabilities. However, graphene oxide can be used to increase film stability [26]. Graphene oxide (GO) is a polymer with a 2D sheet structure,

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and it has been applied in various fields because of its simple structure and the easy modification of its charge [26,27]. Several studies concerning the fabrication of multilayer thin films using GO as drug carriers have been carried out [28–30]. In addition, the use of GO and BCM to fabricate multilayer films has also been studied [31]. However, if the loading amount with GO sheets is too high, the release of the loaded drug is rapid. Therefore, careful film modification is required.

Recently, various surface modification methods have been investigated, including both chemical and physical methods [32,33]. These methods can change and improve the surface roughness, hydrophilicity, surface charge, biocompatibility, reactivity, and controlled release of drugs [34,35]. Among the various modification methods, crosslinking has been used as a modification method in many fields. Richert et al. crosslinked poly(L-lysine)/hyaluronan films with an 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride/*N*-hydroxysulfosuccinimide (EDC/NHS) solution to improve the stability and cell adhesion properties of multilayer films [36]. In addition to crosslinking, we have also attempted to achieve the sustained release of drugs from films by fabricating a cover layer on the film surface. The cover layer can be fabricated on the film surface and is expected to trap the model drug in the film. After the fabrication of cover layers, not only mechanical modification, but also pH-responsive properties have been studied [37].

The release of drugs from LbL films containing GO and BCM has already been studied [31,38]. However, the release profiles of the films are not perfect. For example, some films suffered from burst release behavior. In this study, we modified the films in two ways to regulate the rapid and significant release of the drug, problems that affect existing unmodified GO/BCM films. Interestingly, we found that the drug release rate was affected by the pH of the BCMs, film modification method, and composition of the cover layer. Additionally, the quantity of drug released was reduced in all kinds of modified films. In conclusion, we successfully adjusted the release through film modification and confirmed that the release performance varies with the method of film modification. Thus, we could control the release of model drugs, preventing the rapid and significant loss of the drug from the film, which is the main problem of using GO for the drug carrier in the film based delivery. We expect that these findings will find application in various drug delivery systems.

Experimental

Materials

Amphiphilic block copolymer polystyrene-*b*-poly(acrylic acid) (PS-*b*-PAA), graphite powder (<20 μm), coumarin-6 (C-6, M_w = 350.44), chitosan (Chi, medium M_w), 2-(*N*-morpholino)ethanesulfonic acid hydrate (MES, M_w = 195.24), *N*-hydroxysulfosuccinimide (NHS), and glutaraldehyde 25% solution (M_w = 25000) were purchased from Sigma–Aldrich. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride (EDC, M_w = 191.71) was obtained from Daejung (South Korea).

Preparation of the C-6-loaded BCMs

The formation of block copolymer micelles of PS-*b*-PAA and the encapsulation of C-6 in the micelles has already been reported [39]. In brief, the PS-*b*-PAA and C-6 solutions were prepared to concentrations of 25 and 2 mg/mL, respectively, in 2 mL of *N*,*N*-dimethylmethanamide (DMF). Subsequently, the C-6 and PS-*b*-PAA solutions (2 mL each) were added to 48 mL of DI water (pH 10) with stirring. As a result, PS-*b*-PAA micelles with a hydrophobic core, which consists of PS and C-6, surrounded by a PAA hydrophilic corona were prepared. The resulting solution was stirred for 6 h and subjected to dialysis in water for 48 h to remove any remaining DMF solvent.

Synthesis of GO and ethylenediamine functionalized GO

We synthesized GO from graphite powder using the widely used Hummers method [26]. The GO formed by this method has a negative surface charge, so it was modified using ethylenediamine, resulting in a positive surface charge. The ethylenediamine functionalized GO (GO^+) solution has pH of 8.4.

Film fabrication on a flat silicon substrate

We fabricated the multilayer thin films using the LbL method with GO^+ (pH 9) and BCM at two pH conditions: 5.5 and 8.5. The concentrations of the GO^+ and BCM solutions were set at 1 mg/mL. First, we obtained a negatively charged silicon substrate by treatment for 2 min with oxygen plasma. Then, the treated silicon substrates were dipped in the GO^+ solution for 10 min. After dipping, the substrates were rinsed with DI at pH 8.4 (the same pH as the GO^+ solution) in three steps (2, 2, and 1 min) and dried in air. Subsequently, the substrates were then immersed in a BCM solution, where the pH was either 5.5 or 8.5, followed by rinsing three times, as described previously, and drying. The above dipping steps were repeated until the desired number of bilayers had been obtained. The resulting bilayer films are denoted as $(GO/BCM)_n$, and we fabricated bilayer films until fourteen layers had formed $(GO/BCM)_{14}$. All films were fabricated at room temperature (27 °C).

Film characterization

The film thickness was measured by using a profilometer (Dektak 150, Veeco, Plainview, NY, USA). It is equipped with a tip running on the object surface and estimating surface height differences. Therefore, we made a scratch on the film, then estimated the thickness of the film. The film morphologies were confirmed using a field-emission scanning electron microscope (FE-SEM) (Carl Zeiss, Oberkochen, Germany) and an atomic force microscope (AFM) (X-10, Park Systems, Santa Clara, CA, USA).

Measurement of the release profiles of the multilayer thin films

To determine the release profile of C-6 (model drug), the multilayer thin films (1 cm × 1 cm) were immersed in 10 mL of a mixed solution of phosphate buffer saline (PBS, 1×) and ethanol (EtOH) (PBS:EtOH = 1:1). We added EtOH to the PBS buffer because C-6 is hydrophobic and insoluble in PBS. The PBS buffer containing the thin films was placed in an incubator at 37 °C for the release process. Subsequently, 0.1 mL portions of the solution were drawn off at predetermined times, and 0.1 mL of pure PBS/EtOH solution was added to the sample. After removal of the sample, to prevent the evaporation of ethanol, the release sample was kept in a 1.5 mL Eppendorf tube at 4 °C. The fluorescence spectra of the removed samples were measured using a microplate reader (Synergy H1 Hybrid Multimode Microplate Reader, Bio-tek, USA). In addition, we also measured the degradation of the multilayer thin films at the same times and conditions used for the measurement of the release profiles. The degradation of the films was measured using a profilometer.

Modifying the multilayer film

We modified the multilayer films using two different methods: modification of the inner structure by crosslinking and fabrication of a cover layer on the film. For the crosslinking (modifying inner

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