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Hypromellose-*graft*-chitosan and Its Polyelectrolyte Complex as Novel Systems for Sustained Drug Delivery

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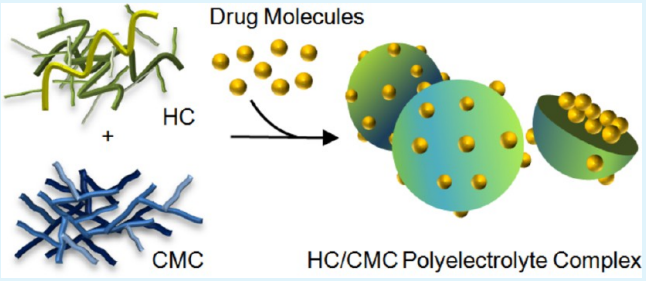
Supporting Information

ABSTRACT: Polyelectrolyte complexes formed between chitosan (CS) and anionic polymers have attracted increasing interest in drug delivery. In this study, CS is copolymerized with hypromellose via a coupling reagent-mediated approach to form a water-soluble, nontoxic CS derivative, namely hypromellose-*graft*-CS (HC), which is subsequently complexed with carboxymethylcellulose (CMC) to generate a polyampholytic hydrogel. When compared with conventional CS, HC is highly water-soluble across a wide pH range, and has a substantially higher pH buffering capacity to provide a pH-stable environment for delivery of drugs. In addition, the polyelectrolyte complex of HC exhibits a drug encapsulation efficiency of over 90% in all drugs tested, which is 1−2 fold higher than the efficiency attainable by the polyelectrolyte complex of conventional CS, with a 2−3 fold longer duration of sustained drug release. Our results indicate that as a novel polymer, HC has excellent promise for future pharmaceutical applications.



KEYWORDS: *chitosan, drug release, drug delivery, hypromellose, polyelectrolyte complex*

INTRODUCTION

As far as drug therapy is concerned, one of the most important factors to be considered is drug bioavailability,[1−6] which has often been reduced by various factors (particularly the physiological barriers and blood clearance) after drug administration. This has not only limited the sustainability of the therapeutic effect but has also made repeated drug administration necessary.[7] Over the last several decades, increasing efforts have been directed to develop drug carriers for more sustained drug action;[8−12] because of the ease of functionalization, low cost, and the possibility of mass production, polymers have become one of the promising candidates for development of drug delivery systems. Among different polymers studied, chitosan (CS) is one of the polymers that have received the most interest. CS is a linear polysaccharide consisting of $\beta(1 \rightarrow 4)$-linked D-glucosamine residues with a variable number of randomly distributed N-acetyl-D-glucosamine units.[13] Because of its biocompatibility, biodegradability, mucoadhesive properties, slow biodegradability, and nontoxicity, applications of CS have spanned areas including food, cosmetics, regenerative engineering, and environmental protection over the years.[14−18] Not surprisingly, CS has also become one of the most extensively studied polymers in drug delivery. Despite the promise, CS has poor solubility in physiological solvents, low drug encapsulation capacity and limited drug release sustainability. CS-based systems are also ineffective for delivering pH-sensitive drugs because of the need for acidic media to dissolve.[19,20] These restrict the wider applications of CS.

Since the turn of the last century, polyelectrolyte complexes formed by CS and anionic polymers have been extensively exploited in drug delivery as an alternative to pristine CS.[21−24] One earlier study has demonstrated that when compared to CS alone, CS/pectin complexes (molar ratio 1:9) show higher mucoadhesive properties.[25] This helps to increase the residence time experienced by the drug in the gastro-intestinal tract. Another study has reported that upon complexation with alginate, the swelling and erosion of CS can be retarded, resulting in a higher retardant capacity of drug release.[26] Even though the drug delivery capacities of CS have been improved through polyelectrolyte complexation with oppositely charged polymers, the application of these complexes still has been limited by the inherent properties of CS, including the low aqueous solubility and drug encapsulation capacity.

To address the aforementioned limitations, we introduce a novel CS-based copolymer, which when complexed with a polyelectrolyte achieves more effective drug encapsulation and more sustained drug release than the conventional CS. The copolymer, namely hypromellose-*graft*-CS (HC), is synthesized by copolymerizing CS with hypromellose via a coupling reagent-mediated approach. This highly water-soluble, biocompatible and nontoxic copolymer provides a pH-stable environment for drug delivery. In addition, it complexes with carboxymethylcellulose (CMC) via electrostatic interactions. The polyelectrolyte

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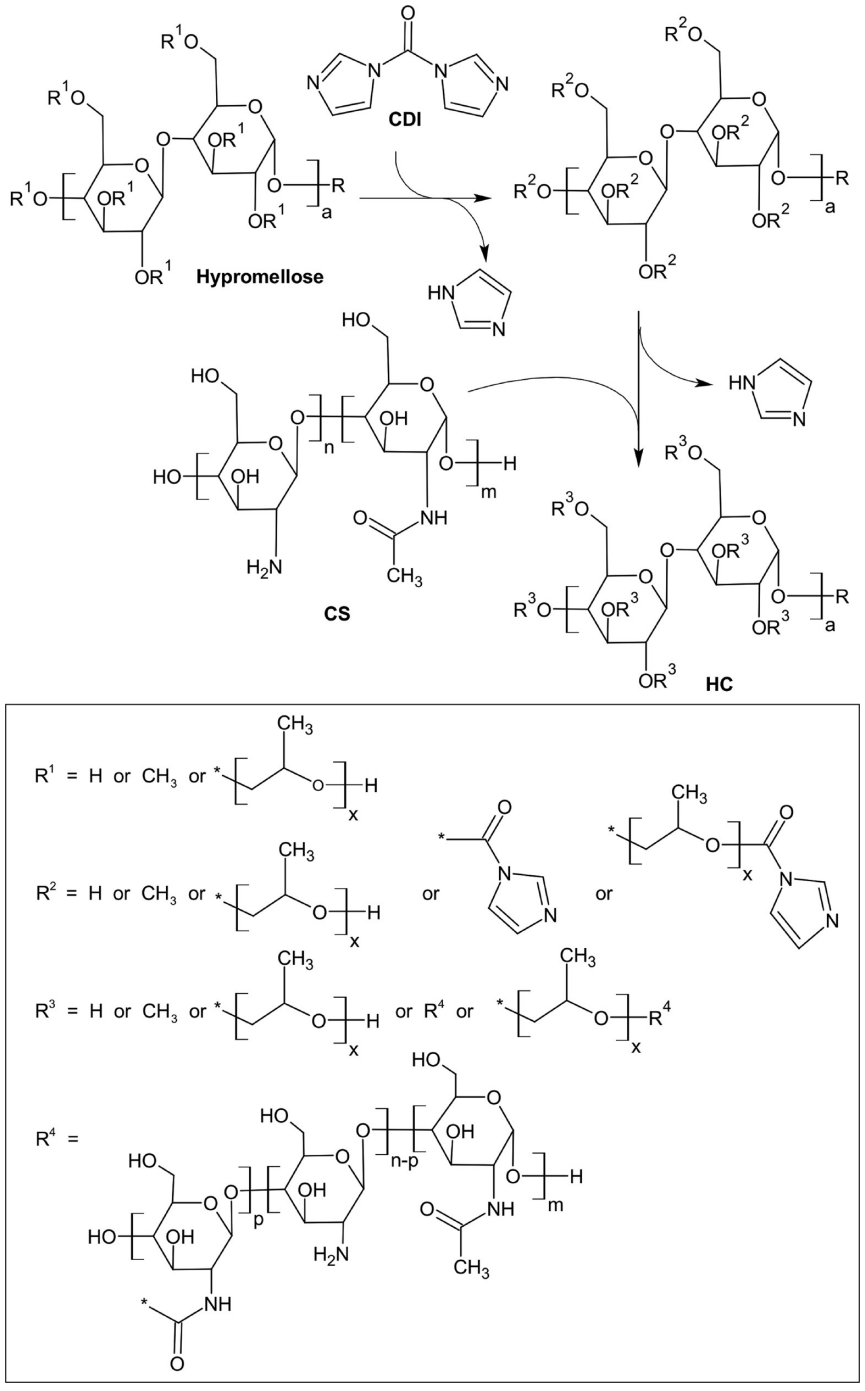

Figure 1. Synthesis and putative structure of HC.

complex formed by HC gives a drug encapsulation efficiency of over 90% in a few representative drugs tested, with a 2−3 fold longer duration of sustained drug release as compared to that formed by unmodified CS. Our results indicate that HC exhibits future potential for drug delivery, in particular, for localized drug delivery to the skin, intestinal environment and other similar sites of interest.

2. EXPERIMENTAL SECTION

2.1. Materials. Mometasone furoate (MF) was purchased from United States Pharmacopeia (Rockville, MD). CS, hypromellose and CMC (degree of substitution = 1.2) were obtained from Aladdin (Shanghai, China). Methylene blue (MB), tetracycline hydrochloride (TH), metronidazole (MT), dimethyl sulfoxide (DMSO), triethylamine (Et_3N), 1,1′-carbonyldiimidazole (CDI), sodium chloride (NaCl) and various other chemicals were purchased from Sigma−Aldrich (St. Louis, MO, USA). Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Grand Island,), penicillin G−streptomycin sulfate (Life Technologies Corporation. USA) and fetal bovine serum (FBS, Hangzhou Sijiqing Biological Engineering Materials Co, CHN) were used as the cell culture medium. Trypsin−EDTA (0.25% trypsin−EDTA) was obtained from Invitrogen.

2.2. Synthesis of the HC Graft Copolymer. Hypromellose was dissolved in degassed DMSO at a concentration of 0.1 g/mL, and mixed with a DMSO solution (0.1 g/mL) of CDI. Et_3N was added to the reaction mixture at a concentration of 4.5 μL/mL. The reaction was conducted in the dark for 3 h under an inert nitrogen atmosphere. The activated hypromellose was then added to CS, which was dissolved in

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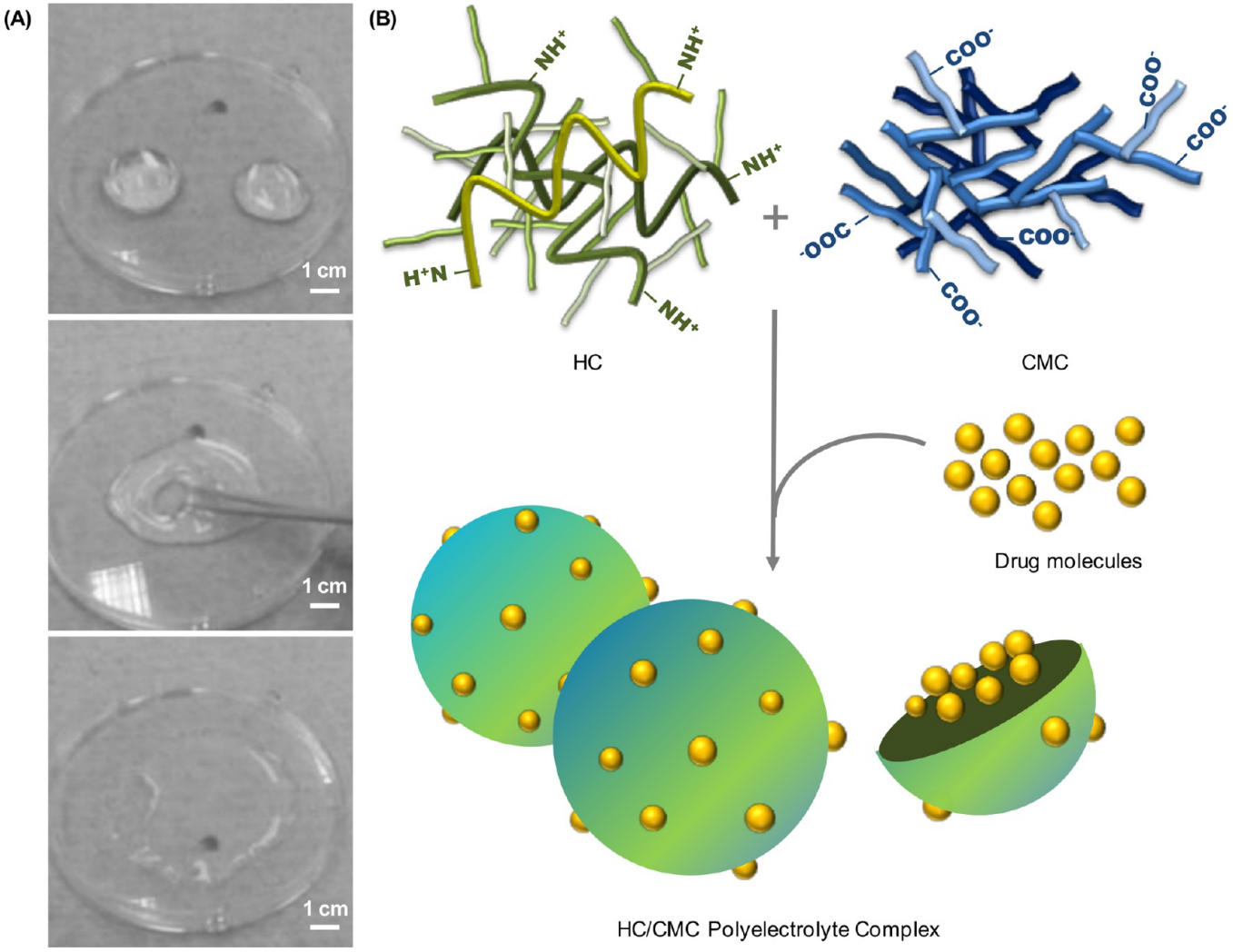

Figure 2. Preparation of the HC/CMC polyelectrolyte complex. (A) Procedures for complex formation. (B) Schematic diagram showing complexation of HC with CMC via electrostatic interactions for encapsulation of drug molecules.

10% acetic acid at a concentration of 0.05 g/mL. The reaction was carried out for 16 h in the dark at 37 °C under an inert nitrogen atmosphere. The crude reaction mixture was dialyzed against triple-distilled water at 4 °C for 3 days with a molecular weight cutoff of 12 kDa. The solution was then lyophilized for 2 days to obtain HC. The synthetic mechanism of HC is shown in Figure 1.

2.3. Morphological Examination. The surface morphology of CS and HC was observed by scanning electron microscopy (SEM). For SEM analysis, CS and HC were sputter-coated with gold, and their surface morphology was observed using a JEOL JSM-6380 (Japan) microscope.

2.4. Proton Nuclear Magnetic Resonance (^{1}H NMR). Hypromellose and HC were solubilized in deuterium oxide (D_2O), whereas CS was dissolved in DCl/D_2O 1:100 (v/v). ^{1}H NMR spectra were recorded using an NMR spectrometer (500 MHz; Bruker Corporation, Germany).

2.5. Fourier-Transform Infrared (FT-IR) Spectroscopy. FT-IR spectroscopy was performed using an FT-IR spectrometer (Spectrum 2000, PERKIN ELMER) at ambient conditions. The potassium bromide (KBr) disk technique was used for analysis. Spectra were obtained at a resolution of 2 cm^{-1}, and reported as an average of 16 scans.

2.6. Solubility Test. Excess amount of the polymer was dissolved in 10 mL of the buffer solution at different pH values (pH 1.2, 7.4, and 10), and agitated at ambient conditions for 30 min. After that, the setup was centrifuged at a relative centrifugal force of 16 000 × g for 5 min, where g refers to the standard acceleration due to gravity. The supernatant was removed, and the pellet was dried in an oven at 65 °C for 2 days. The aqueous solubility of the polymer was determined by subtracting the mass retained from the mass originally added.

2.7. Buffering Capacity Assay. CS, hypromellose and HC were dissolved in 150 mM NaCl solution at a concentration of 0.2 mg/mL. Their pH buffering capacities were evaluated as previously reported.[27] The NaCl solution alone was used as a control.

2.8. Cytotoxicity Assay. Rat retinal Müller rMC-1 cells were cultured in DMEM medium containing 10% FBS,100 UI/mL penicillin, 100 μg/mL streptomycin, and 2 mM L-glutamine. One day before the assay, the cells were seeded separately in 96-well plates at an initial density of 5,000 cells per well, and incubated at 37 °C for 24 h. The growth medium was replaced with 100 μL of fresh cell culture medium with or without 10% FBS. Ten μL of the polymer solution (CS, HC or CMC) were added to each well. After 5 and 24 h incubation at 37 °C, the polymer-containing medium was replaced with 100 μL of fresh cell culture medium. The cytotoxicity of the polymer was evaluated using the Cell Titer 96 Aqueous One solution cell proliferation assay (MTS assay; Promega Corp., Madison, WI). Assays were performed according to the manufacturer's instructions. Cell viability (%) in each well was determined by using the following formula as previously described[28−30]

$$\text{cell viability}(\%) = \frac{A_{\text{test}}}{A_{\text{ctrl}}} \times 100\% \quad (1)$$

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where A_{test} and A_{ctrl} represent the absorbance values of the test well and the control well, respectively.

2.9. Preparation of the HC/CMC Polyelectrolyte Complex. The HC/CMC polyelectrolyte complex was prepared by mixing 1% (w/v) HC solution with an equal volume of 1% (w/v) CMC solution. The mixture was then left at ambient conditions for 10 min to give more time for gelation. Figure 2 shows the gelation mechanism of the HC/CMC polyelectrolyte complex. The same approach was also used to prepare the CS/CMC polyelectrolyte hydrogel complex, but the HC solution was replaced by 1% (w/v) acetic acid solution of CS.

2.10. Determination of the Drug Encapsulation Efficiency. MT, MB, TH, and MF were used as drug models. Basic information on these models, together with their molecular weights, was provided in Table 1. To prepare the drug-loaded HC/CMC polyelectrolyte complex, the drug was first mixed thoroughly with 1% (w/v) HC solution at a concentration of 1 mg/mL, and then mixed with an equal volume of 1% (w/v) CMC solution. The mixture was left at ambient conditions for 10 min for gelation. The same approach was adopted to prepare the drug-loaded CS/CMC complex, but the HC solution was replaced by 1% (w/v) acetic acid solution of CS. Once the complex was made, 5 mL of distilled water was added to the drug-loaded polyelectrolyte complex. The mixture was gently agitated for 30 s, and centrifuged at a relative centrifugal force of 16,000 × g for 1 min. The supernatant was removed. The concentrations of unloaded MB, TH and MF were determined at 665, 360 and 297 nm, respectively, via ultraviolet−visible (UV−vis) spectroscopy (Supporting Information, Figure 1). Determination of the concentration of MT was performed according to a method modified from Simões et al.[31] In brief, the supernatant was mixed with an equal volume of 20% sodium hydroxide solution. The mixture was incubated for 10 min at ambient conditions for developing the color before the concentration of the drug was determined at 500 nm.

2.11. Drug Release Evaluation. Drug-loaded HC/CMC and CS/CMC polyelectrolyte complexes were prepared as described above. After that, 5 mL of the buffer solutions at the pH of 7.4 was added to the drug-loaded complex. The setup was incubated at 37° and 5% CO_2 with saturating humidity. At a predetermined time interval, 1 mL of the buffer solution was removed for testing, and replaced with 1 mL of the fresh buffer solution. The amount of the drug released from the complex was determined via UV−vis spectroscopy as delineated above. The cumulative drug release was calculated by using the following formula:

$$\text{cumulative drug release}(\%) = \frac{M_t}{M_\infty} \times 100\% \quad (2)$$

where M_t is the amount of the drug released from the complex at time t, and M_∞ is the amount of the drug loaded in the complex.

2.12. Determination of the Equilibrium Water Content. The equilibrium water content (EWC) of the polyelectrolyte complex was used as an indicator of the swelling capacity of the complex.[32] It was determined as described in earlier studies.[33−35] In brief, a buffer solution at the physiological pH of 7.4 was prepared by mixing the aqueous solutions of potassium chloride, hydrochloric acid, potassium dihydrogen phosphate and sodium hydroxide. The pH value was measured using a pH meter (ELICO digital pH meter, model LI 614, equipped with calomel glass electrode having accuracy ±0.01). The dried and preweighed polyelectrolyte complex (0.05 g) was immersed in 100 mL of the buffer solution, and was then incubated at 37 °C. To remove the surface water on the swollen complex, we centrifuged the buffer-immersed sample at a relative centrifugal force of 16,000 × g for 1 min, followed by the removal of the supernatant. The EWC was calculated using the following equation as previously reported[35]

$$\text{EWC}(\%) = \frac{M_w - M_d}{M_d} \times 100\% \quad (3)$$

where M_d and M_w represent the dry and wet weights of the sample, respectively.

2.13. Examination of the Erosion Behavior. The erosion behavior of the polyelectrolyte complex was examined based on a method modified from von Burkersroda et al.[36] In brief, the

Table 1. Details of the Drug Models

name	abbr.	other names	IUPAC name	CAS	formula	M_w
metronidazole	MT	443−48−1, Flagyl, Anagiardil, Metronidazol, Trichopol, Vagilen	2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol	443−48−1	$C_6H_9N_3O_3$	171.15
methylene blue	MB	Methylthioninium chloride, Basic blue 9, Chromosmon, Swiss Blue, Methylene Blue N, 61−73−4	3,7-bis(dimethylamino)-phenothiazin-5-ium chloride	61−73−4	$C_{16}H_{18}ClN_3S$	319.85
tetracycline hydrochloride	TH	Supramycin, Sustamycin, Artomycin, Subamycin, Tetracycline chloride, Panmycin hydrochloride	(4*S*,4a*S*,6*S*,12a*R*)-4-(dimethylamino)-1,6,10,11,12a-pentahydroxy-6-methyl-3,12-dioxo-4,4a,5,5a-tetrahydrotetracene-2-carboxamide hydrochloride	64−75−5	$C_{22}H_{25}ClN_2O_8$	480.90
mometasone furoate	MF	83919−23−7, Nasonex, Twisthaler, Elocon, Danitin, Sch32088	[(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-chloro-17-(2-chloroacetyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[*a*]phenanthren-17-yl] furan-2-carboxylate	83919−23−7	$C_{27}H_{30}Cl_2O_6$	521.43

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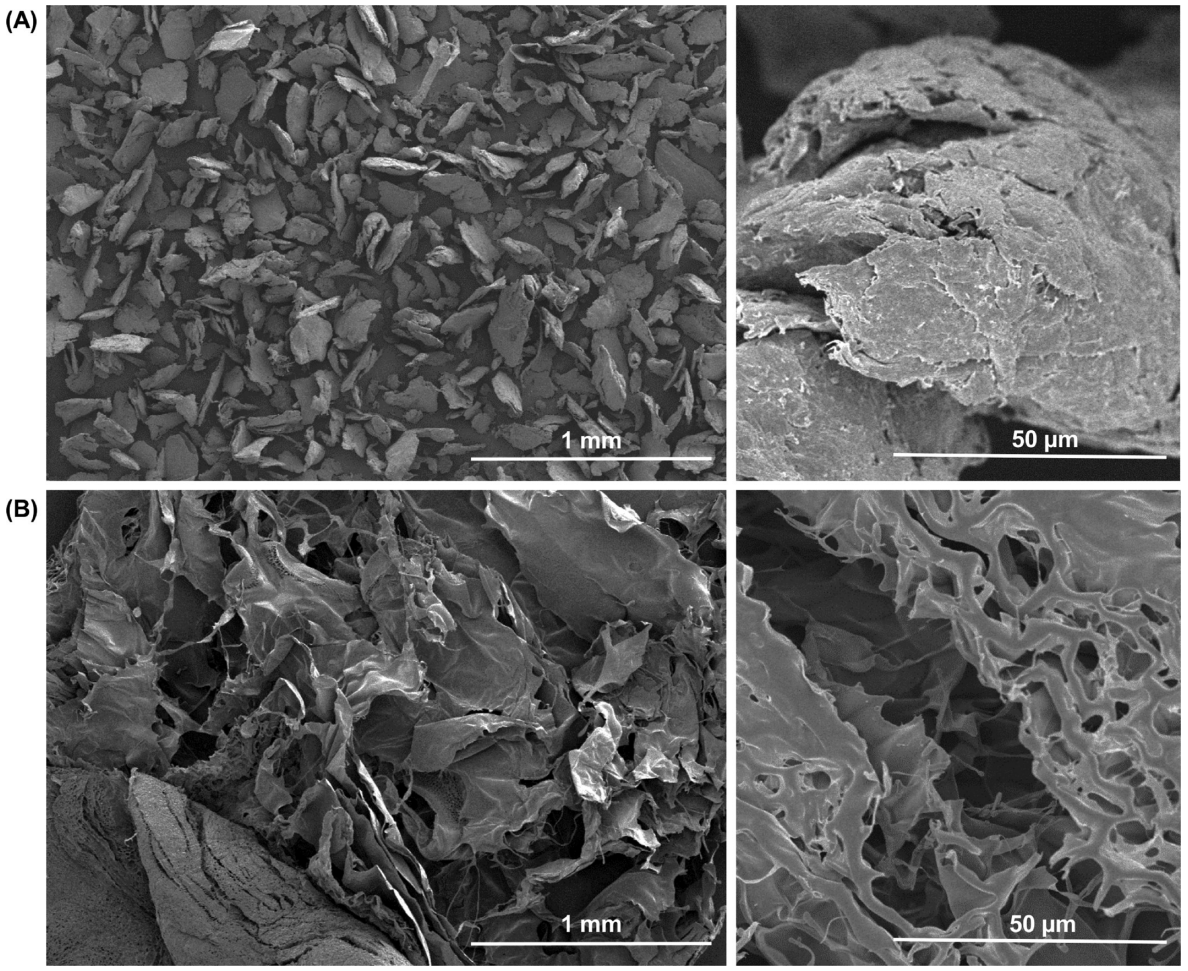

Figure 3. SEM micrographs of (A) CS and (B) HC.

polyelectrolyte complex with a known initial dry mass was immersed in PBS at the physiological pH of 7.4, and was incubated at 37 °C. At predetermined time intervals, the buffer-immersed sample was centrifuged at a relative centrifugal force of 16,000 × g for 1 min, followed by the removal of the supernatant. The sample was dried in an oven at 65 °C, and the ratio between the final dry mass (m) and the initial dry mass (m_0) was determined.

3. RESULTS AND DISCUSSION

3.1. Polymer Synthesis and Morphological Analysis. CS is a biocompatible, biodegradable and nontoxic biopolymer that has been widely exploited as a carrier for controlled drug release.[14] However, CS is basically hydrophobic. This, together with its low drug encapsulation capacity and poor drug release sustainability, has limited the use of CS in drug delivery. Moreover, failure to deliver pH-sensitive drugs due to the need of acidic media for dissolution has also restricted the processing and wide pharmaceutical uses of CS. In this study, we have employed a coupling reagent-mediated approach to copolymerize CS with hypromellose. During synthesis, the hydroxyl groups of hypromellose molecules are activated by CDI to form active imidazolyl carbamate intermediates, which are then attacked by primary amine groups from CS, with imidazole being released as a byproduct. Unreacted reactants are removed by dialysis against water.

The surface morphologies of CS and HC have been examined by SEM. As shown in Figure 3A, conventional CS shows a granular surface morphology. In Figure 3B, the granular morphology of CS is shown to be distorted, and a transition from the granular to fibrillar morphology can be observed. Such a distortion has also been reported to occur during other graft copolymerization processes,[37,38] and is attributed to the presence of the grafted chains, which agglomerate to make the morphology of the graft copolymer fibrillar.

3.2. Structural Characterization of HC. The success of CS/hypromellose graft copolymerization has been verified by ^{1}H NMR (Figure 4A). A characteristic signal from CS at 1.97 ppm ($NCOCH_3$) is present in the spectrum of HC, in which the signal from hypromellose at 1.2 ppm, which is attributed to the methyl protons from the hydroxypropyl group, can also be observed. This suggests the successful grafting of hypromellose onto CS chain molecules. The molar ratio of CS to hypromellose in HC has been calculated based on the proton integral values of the ^{1}H NMR spectrum at 1.97 and 1.2 ppm. The molar ratio is approximated to be between 1:1 and 1:2.

Grafting of hypromellose onto CS has been further verified by FT-IR (Figure 4B). The spectrum of hypromellose exhibits an absorption band at 2,936 cm^{-1}, which is assigned to C−H stretching of methyl and hydroxypropyl groups. A distinctive signal can also be observed at 1458 cm^{-1}, which comes from the asymmetric bending vibration of the methyl group in CH_3O. All these signals can be found in the spectrum of HC. On the other hand, distinctive absorption bands at 1598 cm^{-1} and 1650 cm^{-1} are detected in the spectra of HC and CS but not in the spectrum of hypromellose. These peaks are attributed to the N−H bending

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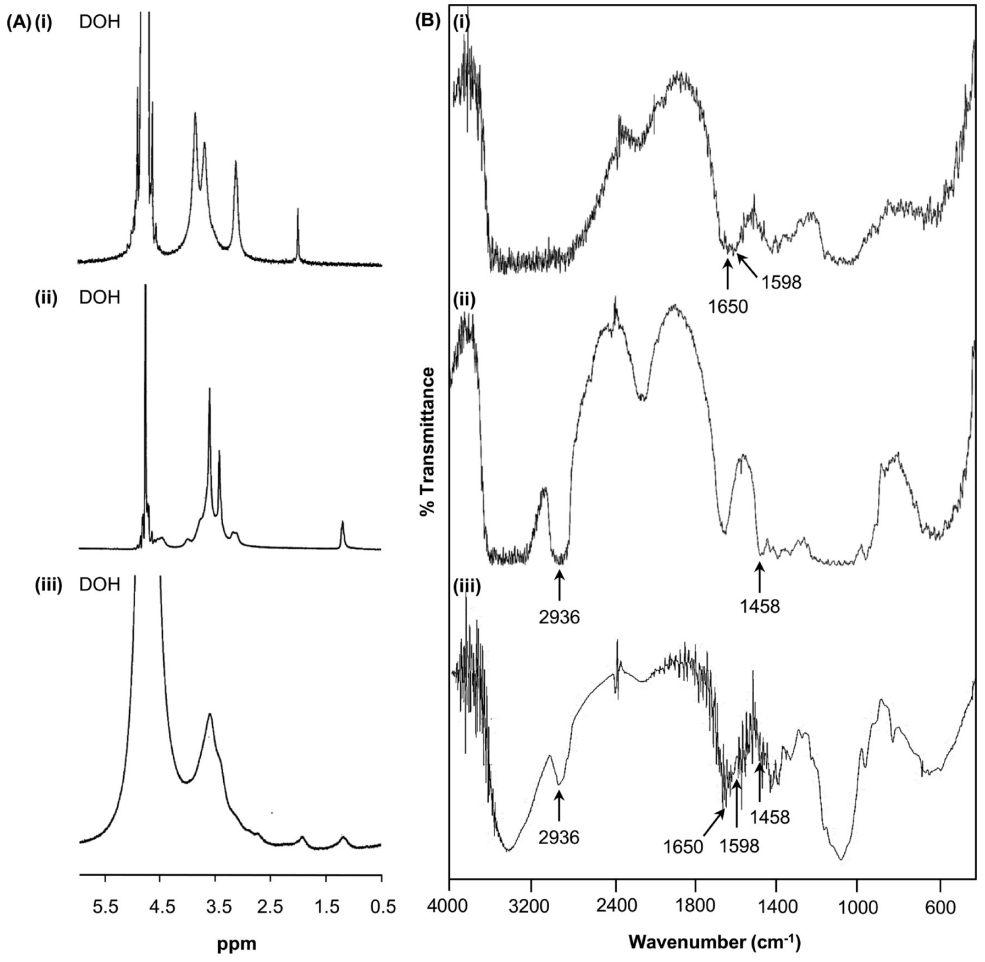

Figure 4. Structure characterization of HC. (A) ^{1}H NMR spectra and (B) FT-IR spectra of (i) CS, (ii) hypromellose, and (iii) HC.

vibration (amide II) and the carbonyl stretching vibration (amide I), respectively.[39]

3.3. Evaluation of Physical-Chemical and In Vitro Properties. As hypromellose is a cellulose ether commonly used in the fabrication of hydrophilic matrices, incorporation of Hypromellose to the hydrophobic CS molecules is expected to enhance the aqueous solubility of the resulting product. When compared to conventional CS, the aqueous solubility of HC is 2.01-, 2.26- and 2.95-fold higher at pH values of 1.2, 7.4 and 10, respectively (Figure 5A). The higher aqueous solubility of HC is attributed to the loss of some primary amine groups during copolymerization of hypromellose onto CS, and this weakens the intermolecular hydrogen bonds between CS molecules. The higher aqueous solubility of HC has allowed it to be dissolved in neutral solutions, and hence is more compatible with delivery of pH-sensitive drugs than conventional CS. In addition, due to the higher aqueous solubility of HC, formulation preparation can be done in aqueous solution without the need for any organic solvents. This reduces some clinical concerns on conventional CS capsules, which often requires approaches involving the use of aqueous/organic systems to generate.[40]

The pH buffering capacities of HC and CS are demonstrated by the acid−base titration profiles shown in Figure 5B. The results show that HC has a higher buffering capacity than CS. This is considered to be due to the higher aqueous solubility of HC, which gives HC a higher number of available amine groups in solutions to buffer changes in pH. The higher pH buffering capacity of HC can protect the loaded drug from drastic changes in pH (e.g., when reaching the acidic conditions of the stomach) and can hence provide a more pH-stable environment for drug encapsulation and drug delivery in practice.

Finally, one of the factors determining the practical potential of a drug delivery system is the toxicity of the system. The toxicity of HC, CS and CMC in vitro has been evaluated by the MTS assay in this study. No significant toxicity of HC, CS and CMC has been observed in vitro in all concentrations tested, as shown in Figure 6. This illustrates the high safety profile of HC in biological use.

3.4. HC/CMC Polyelectrolyte Complex as Drug Carriers. Since the turn of the last century, CS has begun to be exploited for formation of polyampholytic hydrogels, which are polymeric networks consisting of both positive and negative segments, via complexation with CMC.[33,34,41,42] A similar formulation has also been used for cutaneous administration of vitamin E, with an aim to protect the skin tissue from UV damage, to delay the photoaging process and to obtain a moisturizing effect.[43] When compared to CS alone, polyelectrolyte complexes formed between CS and anionic polymers achieve a better drug encapsulation efficiency and more tunable drug release sustainability.[44] Physical entrapment of drugs in hydrogels is one of the common approaches used in drug delivery. Another common approach to load drugs is via chemical cross-linking.[45−47] Recently, physical entrapment has sparked a great interest because on the one hand, it can avoid chemical or biochemical interferences with cell activity, when compared to chemical cross-linking;[48] on the other hand, it can also minimize

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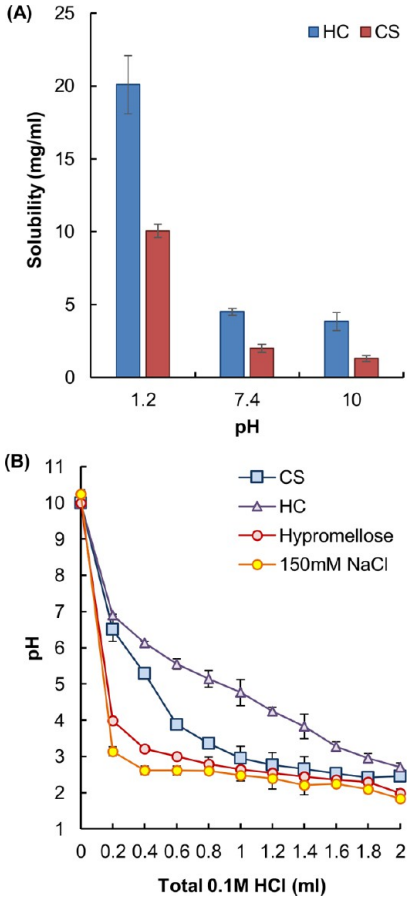

Figure 5. (A) Solubility of CS and HC at different pH values. (B) Buffering capacity profiles of CS, hypromellose, and HC.

structural changes possibly introduced to the loaded drug.[48,49] Moreover, drug loading by physical entrapment does not require any chemical or photochemical triggering and as a result, it can usually be done in a simpler and faster manner.[49] These advantages are particularly important in delivering fragile drugs, such as proteins, peptides, and nucleic acids.[48]

In this study, the polyelectrolyte complexes are formed via electrostatic interactions by mixing the positively charged CS or HC molecules with the negatively charged CMC chains. As shown in Figure 7, the drug encapsulation efficiency varies between 60 and 70% for CS/CMC and 90−95% for HC/CMC.

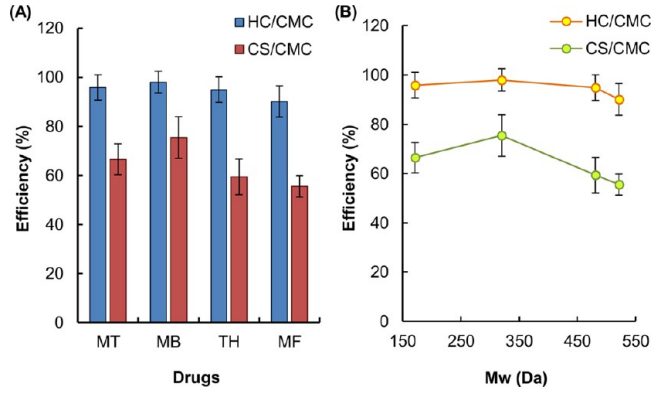

Figure 7. Drug encapsulation capacities of the HC/CMC and CS/CMC polyelectrolyte complexes. (A) Efficiencies of HC/CMC and CS/CMC in drug encapsulation. (B) Effect of the molecular weight of drug molecules on the encapsulation efficiencies of HC/CMC and CS/CMC.

The lower encapsulation efficiency of CS reflects a greater drug loss during polyelectrolyte complexation. In the range of molecular weights examined, the effect of the size of the drug molecules on the encapsulation efficiency is not significant in both CS/CMC and HC/CMC complexes. The higher drug encapsulation capacity of HC/CMC is partially attributed to the alteration of CS upon graft copolymerization as shown in Figure 3 in earlier parts of this section. Because of the transition from the granular to fibrillar morphology upon hypromellose graft copolymerization, the fibrillar structure of HC presumably plays a role in increasing the entrapment of molecules, including drugs, when the drug-loaded HC/CMC complex is prepared.

Although drug encapsulation capacity is important to development of drug carriers, the ability to limit drug release is also required for maintaining constant therapeutic levels for prolonged periods and thereby reducing the total dose of administration. According to our results, HC/CMC shows an improvement in the sustainability of drug release (Figure 8). Although CS/CMC leads to a release of 80% of the encapsulated MT on day 3 and TH on day 4, HC/CMC releases the same amount of drugs only on day 7 for MT and day 9 for TH. The drug release sustainability of HC/CMC is thus 2−3.5 times higher than that of CS/CMC.

3.5. Analysis of Complex Swelling and Erosion Behavior. To obtain a better understanding of the higher drug release sustainability of HC/CMC over CS/CMC, we have

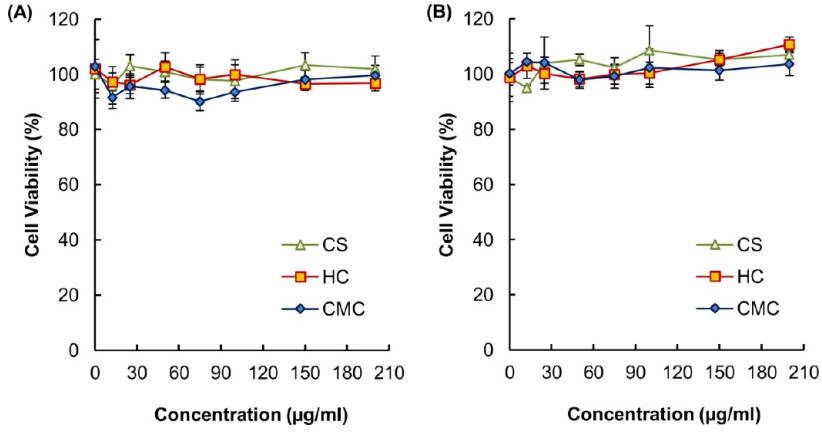

Figure 6. Cytotoxicity of CS, HC, and CMC in rat retinal Müller rMC-1 cells after (A) 5 h and (B) 24 h incubation.

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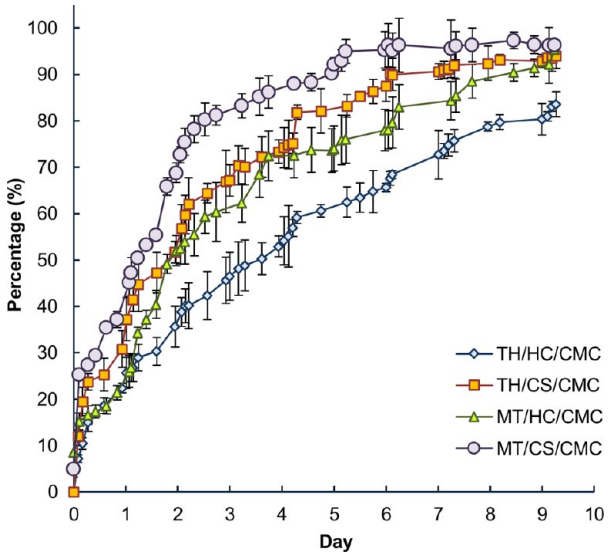

Figure 8. Drug release profiles of HC/CMC and CS/CMC at 37 °C.

examined the swelling capacities of both polyelectrolyte complexes. The swelling capacity has been recognized as one of the important factors determining the release rate of the encapsulated drug because water in the matrix is the medium through which the drug will diffuse.[32] The swelling capacity of the polyelectrolyte hydrogel complex depends largely on the amount of water the complex can take up upon hydration, and is closely related to the EWC of the complex.[32,35] When compared with CS/CMC, HC/CMC has a much lower EWC (Figure 9A).

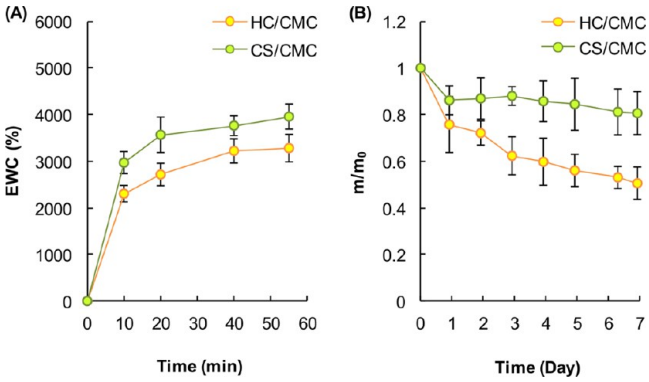

Figure 9. Swelling and erosion behavior of the HC/CMC and CS/CMC polyelectrolyte complexes. (A) Changes in the EWC as a function of time for HC/CMC and CS/CMC at the pH of 7.4. (B) Erosion of HC/CMC and CS/CMC at the pH of 7.4.

This suggests a lower swelling capacity of the HC/CMC complex than CS/CMC. Such lower swelling capacity of HC/CMC is proposed to be due to the copolymerization of hypromellose onto CS, and the consequent cross-linking of the CS molecules. This cross-linking may restrict the mobility of polymer chains in the polyelectrolyte complex, thereby reducing the swelling capacity. Apart from cross-linking, the number of available amine groups from CS has been reduced after graft copolymerization. The osmotic pressure built up inside the complex can therefore be reduced because of the discounted ability of HC as compared to CS to form hydrogen bonds with water molecules. This may also explain the lower swelling capacity of the HC/CMC polyelectrolyte complex.

Apart from swelling, drug release can be affected by erosion of the complex. Erosion is a process resulted from hydrogel degradation, which leads to bond cleavage and cross-link dissolution.[50] According to an earlier study, while both surface erosion and bulk erosion occur in hydrogels, surface erosion will be favored by increasing the molecular weight and degradability of the polymeric matrix.[36] As HC has a higher molecular weight than CS, along with its higher aqueous solubility that makes HC more susceptible to hydrolytic degradation, surface erosion is expected to be favored in the HC/CMC complex. This is consistent with the largely linear erosion profile of HC/CMC (Figure 9B), which is typical of surface eroding polymers.[51] Although HC/CMC has a higher erosion rate than CS/CMC (Figure 9B), its lower swelling capacity (Figure 9A), together with the dominance of surface erosion over bulk erosion, may account for the ability of the polyelectrolyte complex to limit drug release.

4. CONCLUSIONS

CS is a polymeric system showing great potential for drug applications; however, its wide pharmaceutical uses have been impeded by its poor aqueous solubility. In this study, we have introduced a CS-based copolymer, namely HC, which is highly water-soluble across a wide range of pH values and hence can provide a pH-stable environment for delivery of even pH-sensitive drugs. In addition, the drug encapsulation efficiency and drug release sustainability of the polyelectrolyte complex formed by HC are substantially higher than those achievable by the polyelectrolyte complex formed by conventional CS. Regarding the promise of our polymer, it is anticipated that with further optimization and research, HC will have the potential to be a promising system for drug development and drug administration both industrially and clinically.

■ ASSOCIATED CONTENT

Supporting Information

The absorbance−concentration curves of MT, MB, TH, and MF. Supplementary Figure 1: The absorbance−concentration curves of (A) MT, (B) MB, (C) TH, and (D) MF. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.5b01984.

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Notes

The authors declare no competing financial interest.

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