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Original Article

Tunable drug loading and release from blended chitosan/silk fibroin-based daily disposable contact lenses

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Abstract

Recently, chitosan/regenerated silk fibroin (CS/SF) films have been developed for daily disposable contact lenses. This study further explored the versatility of using CS/SF films in contact-lens-based ophthalmic delivery for multiple charged drugs. The selected model drugs, the negatively charged 5(6)-carboxyfluorescein (CF), the zwitterion rhodamine B (RB), and the non-charged acetaminophen (APAP), were individually loaded into the CS/RSF films by soaking. The non-charged APAP could not be loaded into the CS/SF films, whereas the charged CF and RB were successfully loaded. The drug loading capacity increased with soaking time and reached its equilibrium at 3 h. Furthermore, the drug loading capacity and release characteristics could be controlled by adjusting the CS/SF ratio in the film, which is useful for tailoring various treatments. The loading capacity and release duration of the negatively charged CF increased with CS content, while those of the zwitterion RB increased with SF content. In addition, a prolonged drug release exceeding 12 h could be obtained for both drugs. In summary, the CS/SF films are promising biomaterials for contact-lens-based ophthalmic delivery of various charged drugs, which is beneficial for reducing the drug side effects and administration frequency.

Keywords: tunable drug release, contact lenses, chitosan, silk fibroin

1. Introduction

Worldwide, most eye drop formulations (> 90%) are either solution or suspension systems for convenience of administration (Clotilde, Shima, Nasim, & Reza, 2020). However, in clinical use they suffer from a short contact time on the eye surface due to precorneal barriers such as blinking, rapid tear turnover, and tear drainage into the nasolacrimal system. Therefore, the ocular bioavailability of a conventional eye drop is typically poor (< 5% of the total drug dose can get into the intraocular tissues). As a result, frequent instillation is needed to achieve therapeutic efficiency, which may lead to poor patient compliance and increase systemic side effects (Els, Christophe, Luc Van, Inge Van, Jean Paul, & Koen, 2020).

To overcome these obstacles, contact lenses are a topic of increasing interest as a potential new carrier for ocular drug delivery. The main concept in using contact-lens-based ocular drug delivery system is to minimize the drug loss from

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the precorneal area, while increasing its residence time on the ocular surface. Contact lenses are commonly positioned on the cornea with a thin 5-to-10-micron-thick post-lens tear film (POLTF) layer in between, making them a suitable option for delivering drugs to the cornea. Moreover, the POLTF could possibly trap the released drugs for a longer time, which further enhances the drug bioavailability to ~50% (Gause, Hsu, Shafor, Dixon, Powell, & Chauhan, 2016).

Most commercial contact lenses are hydrogels fabricated from two types of synthetic polymers, namely the poly (2-hydroxyethyl methacrylate) (pHEMA)-based hydrogels and the silicone-based hydrogels (SiH). Despite possessing high oxygen permeability, SiH contact lenses generally have a low water content with a hydration ability below 45% (Horst, Brodland, Jones, & Brodland, 2012; Lee, Kim, & Park, 2015; Tighe, 2013). On the other hand, pHEMA-based hydrogel contact lenses have a high water content reaching up to 80% (Lee *et al*., 2015): therefore, prior studies have focused on these contact lenses for hydrophilic ocular drug delivery of diclofenac sodium, cysteamine, brimonidine, fluconazole, and moxifloxacin hydrochloride (Lee, Cho, Park, & Kwon, 2016; Peng, Kim, & Chauhan, 2010; Sharma, 2018). Unfortunately, these contact lenses released the drugs rapidly within 3 h, which requires repeated dosing, and thus reduces the viability of this approach. It remains a crucial challenge to develop novel daily disposable contact lens materials for the sustainable (at least prolonged) delivery of hydrophilic drugs.

In our previous study, we successfully developed daily disposable contact lenses using natural polymers, the chitosan/silk fibroin (CS/SF) blended films (Jeencham, Sutheerawattananonda, & Tiyaboonchai, 2019). The films pass all requirements for contact lens material. Consequently, in this work, we have assessed the potential of CS/SF films for ophthalmic delivery in broader applications. Generally, topical ophthalmic delivery systems are formulated with various charged drugs (Sharma, 2008; Suzuki, Yamamoto, & Ohashi, 2016). Therefore, we hypothesized that the CS/SF films could provide drug loading capacity and prolonged release of oppositely charged drugs by ionic interactions between the negatively charged SF and positively charged drugs, or between the positively charged CS and negatively charged drugs. To test this hypothesis, the negatively charged 5(6)-carboxyfluorescein (CF), the zwitterion rhodamine B (RB), and the non-charged acetaminophen (APAP) were employed as model hydrophilic drugs. The formulation factors and CS/SF ratios affecting the drug loading capacity and release characteristics were examined. Lastly, the drug loading effect on the intrinsic properties of a contact lens were also investigated.

2. Materials and Methods

2.1 Materials

SF was sourced and extracted following our previous report (Jeencham *et al*., 2019). CS, originated from shrimp (> 90% deacetylation, MW 250 kDa), was purchased from Marine Bio Resources Co., Ltd (Samutsakhon, Thailand). Polyethylene glycol 400 (PEG400), APAP, and CF were bought from Merck KGaA (Darmstadt, Germany) and from Sigma-Aldrich Chemie GmbH (Munich, Germany), respectively. RB was acquired from Carl Roth GmbH & Co. KG (Karlsruhe, Germany). All solvents and chemicals were of analytical grade.

2.2 Preparation of CS/SF films

CS/SF films were prepared using the casting method at its optimal conditions, as demonstrated in our previous study (Jeencham, Sutheerawattananonda, & Tiyaboonchai, 2019). Briefly, 2% (w/v) SF solution, 2% (w/v) CS in acetic acid, and 25% (w/w) PEG400 were blended thoroughly at 200 rpm for 30 min, and dried at 60°C. The CS/SF ratio was varied among 100/0, 90/10, 80/20, and 70/30 (v/v). Subsequently**,** the formulations were immersed in 1M NaOH solution for 15 min and repeatedly rinsed with deionized water until neutral pH. Lastly, the films were immersed in 0.01M phosphate buffer saline (PBS, pH 7.4) for 24 h, followed by autoclaving (121°C, 15 psi, 20 min) to obtain the final products.

2.3 Drug loading procedure

APAP, CF, and RB were used as model drugs, see Figure 1. The film (10 × 10 × 0.1 mm^3) was soaked in 1 ml of drug solution (125 µg/ml in 0.01M PBS) at room temperature for a predetermined time. The drug loading capacity was determined by an indirect method, in which the unloaded drug amount in the aqueous solution was measured using UV-VIS spectrophotometer at 241, 493, and 553 nm for APAP, CF, and RB, respectively (Maulvi *et al*., 2016a). The loading time (2 to 24 h) and the solution pH (6.5 to 8.5) were varied.

Scanning electron microscopy (SEM, Carl Zeiss AURIGA®, Thuringia, Germany) was utilized to inspect the cross-section and surface morphology of the drug loaded CS/SF films. The sample was sputter-coated with platinum before imaging with SEM.

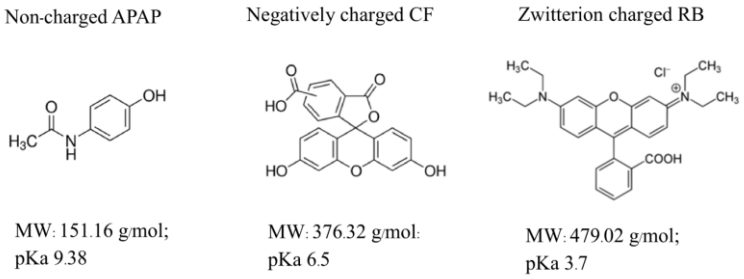

Figure 1. Chemical structures of the model drugs

2.4 *In vitro* drug release

Prior to the release test, the drug-loaded CS/SF films (10 × 10 × 0.1 mm^3) were prepared by soaking the films in drug solutions at pH 6.5 for 3 h. Then, the drug loaded films were placed into a 30-µl-cavity micropipette tip**,** followed by tip insertion into a tube. Simulated tear fluid (STF, pH 7.4, 34 ± 1°C, flow rate 10 µl/min) was used as a continuous flow dissolution medium. At each time interval, the tube was removed (for drug release measurements) and newly replaced. The amount of released drug was determined by UV-VIS spectroscopy. All experiments were carried out in triplicates.

Fickian diffusion model was then utilized to determine the diffusion coefficient (D) of the model drugs in the films. Considering that the films were slab-shaped, with a surface-diameter-to-thickness ratio of > 10, the drug diffusion was assumed to be one-dimensional. Moreover, as the films were immersed in the aqueous environment, the bulk fluid surrounding the contact lenses did not significantly affect the diffusing drug concentration. Equation (1) was used to calculate the drug diffusion (Rungchang, Numthuam, Qiu, Li, & Satake, 2013).

$$M = 2AC_{p,o}\sqrt{Dt/\pi} \quad (1)$$

in which M is the drug mass leached from the film to STF medium (µg); A is the film area in contact with the medium (cm^2); $C_{p,o}$ is the initial drug concentration (µg/cm^3); D is the drug diffusion coefficient (cm^2/s); and t is the migration time (s).

2.5 Physical properties of drug loaded CS/SF films

A thickness gauge (Holex Digital Micrometer, Munich, Germany) was used to determine the film thickness at 5 positions, including the center and around the film's perimeter (Jeencham, Sutheerawattananonda, & Tiyaboon chai, 2019).

For Young's modulus and elongation at break, the films (width 3 mm; thickness 0.1 mm) were measured using a universal testing machine (Zwick/Roell Z2.5, Ulm, Germany) with a 2-kg load cell, a 20 mm/min crosshead speed, and a 10-mm gauge length (Jeencham, Sutheerawattananonda, & Tiyaboonchai, 2019).

To determine the film water content, a weighing method was utilized. The weights of hydrated films (W_{wet}) and of dried films (drying at 105°C until constant weight) (W_{dried}) were measured, respectively (Jung, Abou-Jaoude, Carbia, Plummer, & Chauhan, 2013). The water contents of CS/SF films were then calculated based on equation (2)

$$\text{Water content (\%)} = [(W_{wet} - W_{dried})/W_{wet}] \times 100 \quad (2)$$

Similarly, the water contents of the drug loaded films were determined using equation (3), with the amount of drug in the films (W_{drug}) obtained from the drug loading study (section 2.3) (Jung, Abou-Jaoude, Carbia, Plummer, & Chauhan, (2013).

$$\text{Water content (\%)} = [(W_{wet} - W_{dried} - W_{drug})/W_{wet}] \times 100 \quad (3)$$

2.6 Statistical analysis

Mean ± standard deviation (SD) is reported for all quantitative results. In all comparisons, statistical analysis was performed using a paired t-test or one-way ANOVA followed by Tukey's post hoc test, with $P < 0.05$ required for significance.

3. Results and Discussion

Currently, the topical ophthalmic drugs for the ocular treatments possess various charges, such as the negatively charged cefazolin sodium, the zwitterion ciprofloxacin, and the zwitterion diclofenac sodium (Jeencham, Sutheerawattananonda, Rungchang, & Tiyaboonchai, 2020; Suzuki, Yamamoto, & Ohashi, 2016). Therefore, it is a challenging task to develop contact lens materials that are suitable for delivery of the differently charged drugs. In our previous study, CS/SF films have been developed to satisfy all standards for daily disposable contact lenses (Jeencham, Sutheerawattananonda, Rungchang, & Tiyaboonchai, 2020; Jeencham, Sutheerawattananonda, & Tiyaboonchai, 2019). These films manifested outstanding visible light transparency (> 90%), smooth surface, softness, high strength characteristics, high oxygen permeability (22-26 Barrers), and suitable water content (59-65% w/w). Importantly, the films were stable and safe as they showed no degradation in STF and no cellular cytotoxicity. Therefore, in this study, we further investigated the effects of formulation parameters on the drug loading capacity of various charged drug models. Furthermore, the effects of CS/SF proportions in the film on the drug loading and drug release characteristic were also studied.

3.1 Drug loading

Soaking is a simple and cost-effective approach to loading a drug into contact lenses (Bengani, Hsu, Gause, & Chauhan, 2013). On using this technique, the drug loading capacity depends on several factors including the drug solution pH, the loading time, and the interactions between the contact lens matrix and the drug (Maulvi, Soni, & Shah, 2016b).

Despite a long soaking time of 24 h, APAP could not be loaded in the CS/SF films. Thus, these films are not a suitable for contact-lens-based ophthalmic delivery of a non-charged drug. In theory, the non-charged APAP could interact with CS/SF films via hydrogen bonding or by hydrophobic interactions, but not by ionic interactions. Thus, this result suggested that the interactions between film matrix and drug via hydrogen bonding and hydrophobic interactions were weak and insignificant.

On the other hand, the negatively charged CF and zwitterion RB could be successfully incorporated in the CS/SF films. This could be explained by the ionic interactions between CS or SF matrix and the oppositely charged drug (Lammel, Hu, Park, Kaplan, & Scheibel, 2010). Thus, the effects of drug loading parameters, loading time, drug solution pH, and CS/SF ratio, on CF and RB loading capacities, were further studied.

To investigate the drug loading time effect, films were soaked in CF or RB solution (125 µg/ml, pH 6.5) for various times. For all film blend ratios, the amount of CF and RB loading increased proportionally with time and reached equilibrium at 3 h (Table 1). The rapid loading time of 3 h is good for commercial potential of the production process, giving an advantage over the conventional contact lenses that need a loading time of 12-24 h (Lee, Cho, Park, & Kwon, 2016; Maulvi, 2014).

Regarding the effects of pH on the drug loading capacity, the films were soaked in CF or RB solutions of various pH for 3 h. Table 2 shows that all the CS/SF ratios gave the highest drug loading at pH 6.5 and the least loading at pH 8.5 (>> pKa of CF (6.5) or RB (3.7)). As the pH of the drug loading solution exceeded the pKa for the drug, the CF or RB carboxylic group became more ionized, leading to more drug being dissolved in the medium (Sharma, 2018). Therefore, using drug loading solutions with pH similar to the pKa of the drug would increase the loading capacity. In addition, when employing the CF solution at pH greater than its pKa of 6.5, CF loading capacity was decreased due to the deprotonation of the positively charged CS amine group in the CS matrix, which reduced the ionic interactions with the negatively charged CF.

The effects of film CS ratio on the drug loading capacity are shown in Table 1-2. The negatively charged CF loading capacity increased with the film CS ratio. Thus, the CS/SF: 100/0 films showed the highest loading capacity. This could be explained by the high content of positively charged CS that had ionic interactions with the negatively charged CF. These results matched well the SEM micrographs (Figure 2) illustrating that CF was found both on the film surface and in the film inner core. On the other hand, when increasing the film SF ratio, CF could repel the negatively charged SF, leading to a lower drug loading. Consequently, the SEM micrographs of the CS/SF = 70/30 film revealed CF only on the outer surface.

In contrast, the zwitterion RB loading capacity increased with SF content, Table 1-2. Thus, the CS/SF = 70/30 film yielded the highest RB loading capacity, whereas the CS/SF=90/10 film demonstrated the lowest RB loading capacity. These results agree with the SEM micrographs, which illustrate that the higher the film SF proportion, the more RB was located in the film's inner core, Figure 3. The films with high SF content could have strong ionic interactions between the negatively charged SF and the RB amine group; and the positively charged CS interacted with the RB carboxylic group. However, RB could not be loaded in the CS/SF = 100/0 film, even at the longest loading time of 24 h. This could be due to the repulsive forces between the positively charged CS and the RB amine group, that overcame the attractive forces between the positively charged CS and the RB carboxylic groups.

Table 1. Effects of soaking time on drug loading

CS/SF ratio	Drug loading (µg)/10 mm^3 of film			
	2h	3h	4h	24h
CF				
100/0	41.31 ± 1.73	60.74 ± 3.23	60.73 ± 3.18	60.95 ± 3.86
90/10	31.18 ± 1.45	55.74 ± 3.07	54.27 ± 0.87	54.56 ± 1.29
80/20	23.15 ± 1.58	37.88 ± 0.89	37.13 ± 1.05	37.30 ± 1.06
70/30	20.43 ± 1.78	34.40 ± 1.66	34.68 ± 1.34	34.78 ± 1.93
RB				
100/0		Not detected		
90/10	17.20 ± 1.31	24.92 ± 0.81	24.74 ± 1.43	25.04 ± 1.16
80/20	40.76 ± 4.64	52.61 ± 1.00	52.07 ± 1.28	52.65 ± 1.08
70/30	46.72 ± 1.31	61.27 ± 1.45	61.15 ± 1.27	60.89 ± 2.57

Condition: drug solution pH 6.5; SD is standard deviation, *n = 3*.

Table 2. Effects of pH of drug solution on loading

CS/SF ratio	Drug loading (µg)/10 mm^3 of film		
	pH 6.5	pH 7.4	pH 8.5
CF			
100/0	60.74 ± 3.23	41.58 ± 1.15	19.93 ± 0.88
90/10	55.74 ± 3.07	33.58 ± 1.50	16.80 ± 0.86
80/20	37.88 ± 0.89	25.09 ± 2.63	16.57 ± 1.56
70/30	34.40 ± 1.66	19.68 ± 0.70	13.61 ± 1.13
RB			
100/0		Not detected	
90/10	24.92 ± 0.81	18.54 ± 1.42	16.31 ± 1.49
80/20	52.61 ± 1.00	47.24 ± 2.52	45.37 ± 1.22
70/30	61.27 ± 1.45	54.81 ± 0.71	50.47 ± 1.08

Condition: loading time 3 h; SD is standard deviation, *n = 3*.

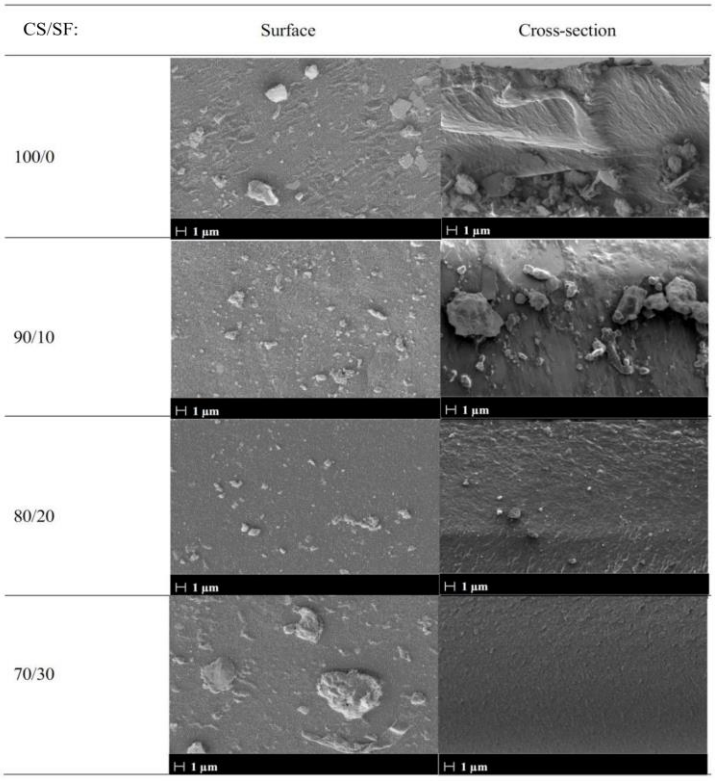

Figure 2. SEM micrographs of the surfaces and cross-sections of negatively charged CF loaded CS/SF films, pH 6.5, soaked for 3 h (×3000 magnification)

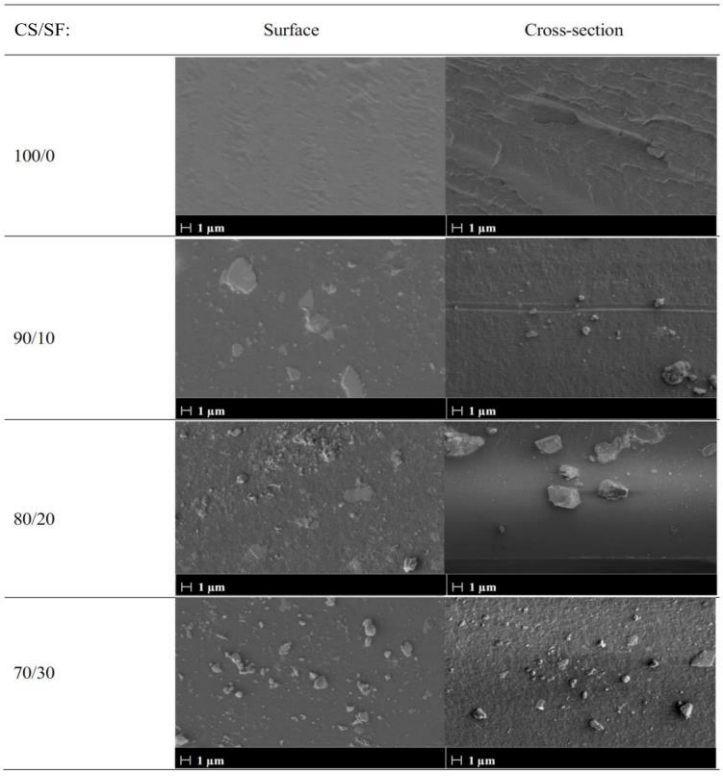

Figure 3. SEM micrographs of the surfaces and cross-sections of zwitterion RB loaded CS/SF films, pH 6.5, soaked for 3 h (×3000 magnification)

3.2 *In vitro* drug release from CS/SF films

The developed CS/SF films aimed to prolong the drug release on the ocular surface to exceed 8 h, which would benefit by reducing administration frequency and drug side effects. Hence, an *in vitro* drug release study with the eye hydrodynamic conditions, low liquid volume of 30 µl and a tear flow rate of 10 µl/ml, was used to determine the drug release characteristics (Mahomed, Wolffsohn, & Tighe, 2016).

The cumulative release of CF and RB from CS/SF films of varied proportions were examined. All the formulations showed similar prolonged release characteristics, Figure 4A-B, and were best fit by Higuchi's model giving R^2 of 0.97 - 0.99, Figure 5A-B. This implied that the drug release from the films occurred by a diffusion-controlled mechanism.

For the negatively charged CF, the larger the proportion of CS in the film, the lower the drug release rate that was observed, Figure 4A. The film CS/SF= 100/0 manifested the least diffusion coefficient of 42×10^{-11} cm^2/s, Table 3, and showed prolonged CF release past 12 h, Figure 4A. On increasing SF proportion, a higher diffusion coefficient was obtained. CS/SF films at the ratios 90/10, 80/20, and 70/30 showed diffusion coefficients of 70×10^{-11}, 148×10^{-11}, and 157×10^{-11} cm^2/s, respectively, Table 3. Consequently, they showed a prolonged CF release of nearly 95% within 12, 8, and 7 h, respectively, Figure 4A. The opposite trend was observed for the zwitterion RB loaded CS/SF films. The higher the amount of SF in the film, the lower diffusion coefficient of RB was observed. The diffusion coefficients of CS/SF films at ratios of 90/10, 80/20, and 70/30 (w/w) were 38×10^{-11}, 27×10^{-11}, and 22×10^{-11} cm^2/s, respectively, Table 3. Thus, the RB release levels at 12 h were 74%, 65%, and 55%, in the same order (Figure 4B). Although the tested formulations showed a prolonged RB release exceeding 12 h, the CS/SF= 70/30 showed the slowest drug release rate.

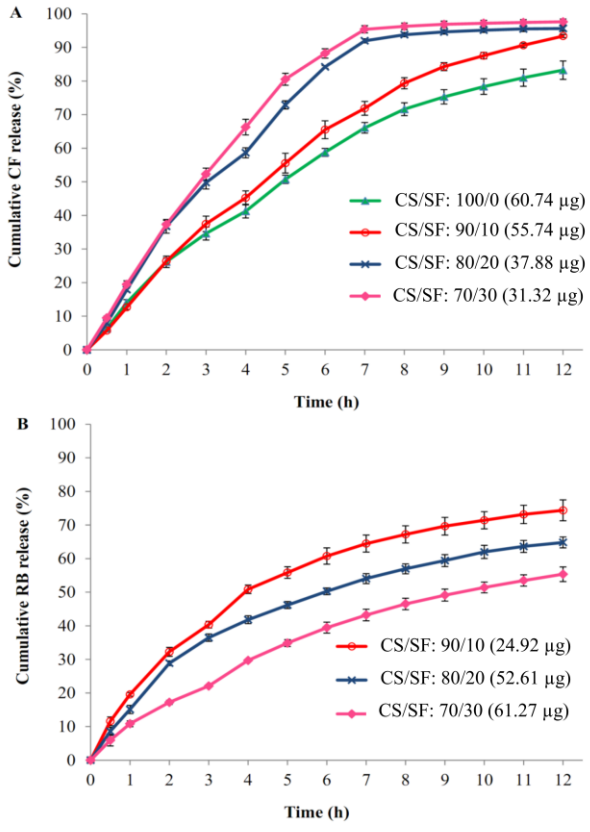

Figure 4. (A) Cumulative negatively charged CF release from CS/SF films, and (B) cumulative charged zwitterion RB release from CS/SF films

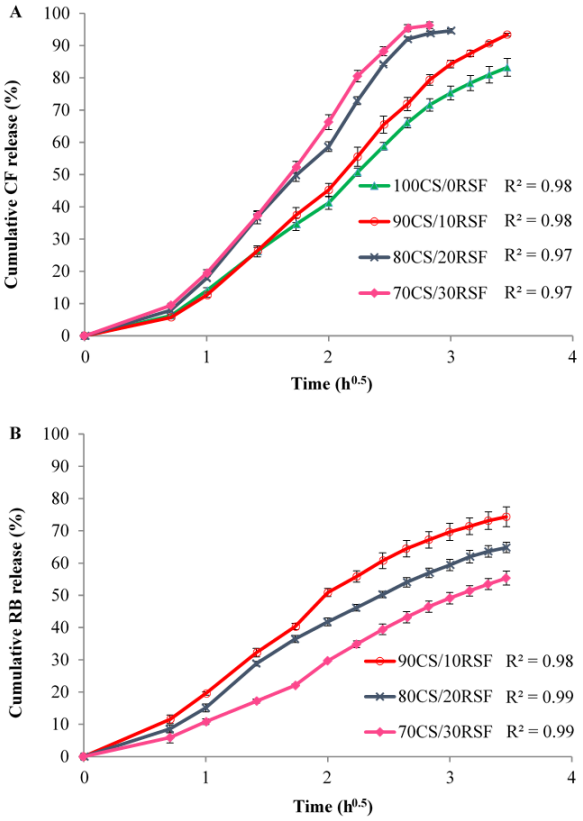

Figure 5. (A) Higuchi model kinetics for cumulative negatively charged CF release from CS/SF films vs square root of time, and (B) Higuchi model kinetics for cumulative zwitterion charged RB release from CS/SF films vs square root of time

Table 3. Drug release kinetic data of drug-loaded CS/SF films

CS/SF ratio	Diffusion coefficient ($\times 10^{-11}$ cm^2/s)
CF	
100/0	42
90/10	70
80/20	148
70/30	157
RB	
90/10	38
80/20	27
70/30	22

SD is standard deviation, $n = 3$

Table 4. Physical properties of CS/SF films and drug-loaded CS/SF films

Formulation	Young's modulus (Mpa) ± SD	Elongation at break (%) ± SD	Water content (%) ± SD
CS/SF: 100/0	7.17 ± 0.89	104 ± 20	61 ± 0.50
CF loaded CS/SF: 100/0	7.08 ± 0.73	101 ± 20	60 ± 0.64
CS/SF: 70/30	6.43 ± 1.00	72 ± 14	58 ± 0.84
RB loaded CS/SF: 70/30	6.52 ± 1.00	72 ± 18	58 ± 1.36

SD is standard deviation, $n = 3$.

The drug release rate was found to be affected by the CS/SF ratio in the film and by the charge of drug, which provides useful information for designing the drug control-release characteristics for a specific treatment. The release rate of the negatively charged CF decreased with the CS proportion, while the release rate of the zwitterion RB decreased with SF proportion. Apart from the ionic interactions between the CS/SF matrix and the drugs, as extensively discussed above, the adsorbed drug location also significantly affected the drug release rate. Typically, a larger amount of a drug in the film inner core would take a longer time for dissolving and diffusing to the outer surface, inducing a slower drug release rate. These results are in accordance with the SEM micrographs in Figures 2 and 3. On increasing the proportion of CS or SF in the films, more CF or RB was observed in the film inner core, respectively. In addition, in our previous study, the zwitterion diclofenac loaded CS/SF film showed similar drug release behavior as RB, but with a slightly faster release rate (Jeencham, Sutheerawattananonda, Rungchang, & Tiyaboonchai, 2020). Therefore, these results confirm that the CS/SF contact lens material is compatible with various charged drugs, namely zwitterion, and in general with negatively charged or positively charged molecules. Nevertheless, the drug loading time, drug loading capacity, and drug release characteristics also depend on the physical properties of drugs, such as charge density, pKa, and molecular weight.

It is worth noting that the stronger ionic interactions in RB loaded CS/SF films resulted in slower drug release rate than that of the CF loaded in CS/SF films. The zwitterion RB loaded CS/SF= 70/30 film manifested a lower diffusion coefficient than that of the negatively charged CF loaded in CS/SF=100/0 film (22×10^{-11} and 42×10^{-11} cm^2/s, respectively). Another factor involved is that at pH 7.4, CF had an 88% ionized form, while RB presented a 100% ionized form, suggesting that the ionic interactions between the CS/SF: 70/30 film and the zwitterion RB should be stronger than that of the CS/SF: 100/0 film with the negatively charged CF.

3.3 Physical properties

Based on the drug release results, the CF loaded CS/SF= 100/0 film and RB loaded CS/SF= 70/30 films were selected for studying the film physical properties. The physical properties of the drug loaded-films showed no significant differences compared to the blank films, Figure 4. The films had similar thickness of ~100 µm, matching typical commercial contact lenses that have thicknesses of 50-200 µm (Lee, Kim, & Park, 2015). Moreover, possessing a Young's modulus of > 1.5 Mpa and an elongation at break of > 50%, these films satisfied the flexibility and stiffness requirements (Horst, Brodland, Jones, & Brodland, 2012; Selby, Maldonado-Codina, & Derby, 2014; Tighe, 2013). Based on the FDA's classification (Elshaer, 2017), the films showed high water content, which implies that they could be worn comfortably. Conclusively, the results indicate that the intrinsic contact lens physical properties of the CS/SF films were unaffected by their drug loading, and these films have met all the requirements of daily disposable contact lenses.

4. Conclusions

Daily disposable contact lenses made of CS/SF films as a biomaterial were successfully demonstrated to enable an ophthalmic drug delivery system. They have been proven to meet all the contact lens property requirements. Importantly, only charged drug molecules could be incorporated into the CS/SF film by soaking. The drug loading capacity as well as its release profile could be sufficiently controlled by varying the proportions of CS/SF in the film blend, enabling the tailoring of specific characteristic for various treatments. The rapid drug loading time of 3 h is beneficial for eventual manufacturing. The drug loading capacity was obviously enhanced when the drug loading solution pH was near the pKa of the loaded drug. In addition, these systems offer a prolonged drug release up to and even exceeding 12 h. The ionic interactions are the main type between the CS/SF film and the drugs. Therefore, the higher the film CS proportion, the more drug loading capacity and the longer the release of a negatively charged drug. On the other hand, the higher the film SF proportion, the more drug loading capacity and the longer release of the zwitterion drug. In conclusion, the CS/SF film blends are beneficial for decreasing both the drug administration frequency and its side effects, thus they are potential candidates for contact-lens-based ophthalmic delivery of several charged pharmaceutical active ingredients.

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