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Research Article

A Facile Route to Fabricate CS/GO Composite Film for the Application of Therapeutic Contact Lenses

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Traditional contact lenses bring convenience for ophthalmic drug delivery. However, either as contact lenses or as drug carriers, traditional materials have still some drawbacks in the field. Therefore, a transparent film was designed and investigated for the application of therapeutic contact lenses. Chitosan (CS)/graphene oxide (GO) composite film and CS film were fabricated with acceptable transparent and tensile properties by simple casting flow method. Although swelling ratio of CS/GO composite film was higher than that of CS film with significant difference, both formed films had suitable swelling ratio for contact lens application. Both CS/GO composite film and CS film exhibited typical CS infrared characteristic peaks. CS/GO composite film had significant greater breaking strength than CS film, but its elongation at break was a little lower than CS film. Either CS/GO composite film or CS film exhibited good hydrophilic property with a contact angle of around 20 degree. Ofloxacin as a model drug was loaded into films by adsorption diffusion method. Loaded drug amount in CS/GO composite film was a little larger than that in CS film, but without significant difference. The drug release behaviors from CS/GO composite film or CS film were investigated and revealed that the loaded drug could be controlled to release in the first hour. Two kinds of cells were used to evaluate the biocompatibility of films by in vitro method. It was found that both CS/GO composite film and CS film could support human umbilical vein endothelial cell (HUVEC) growth. But for human epidermal fibroblasts (HSF) cells, CS/GO composite film could promote HSF cells growth and proliferation much better than CS film.

1. Introduction

Contact lenses emerged in response to request of cosmetology in 1960s, which was quite popular with young people. Traditional soft contact lenses were composed of poly (hydroxyethyl methylacrylate) (pHEMA) hydrogel, which also opened the field of hydrogel research works and applications [1]. Since then, pHEMA hydrogel as a soft material with aqueous environment attracted intensively attention in the biomedical field including drug delivery and tissue engineering on account of similar environment to physiological environment [2–7]. Due to lack of protection from skin, eyes become one kind of vulnerable tissues. Since drug therapy was a main manner for eye disease treatment, low effectiveness and efficiency of eyes drops for treatment of eye diseases disturbed patients with eye disease. With the development of modern medicine, chemicals, and materials science, the emergence of drug carrier solved the problem partly. Among numerous carriers, contact lenses were especially impressed by researchers for the reason that it directly contacted with cornea and bridged between drugs and tissues [2, 4, 7–9]. These contact lenses were considered to be therapeutic contact lenses.

Although pHEMA hydrogel had been made to commercial contact lenses, some problems could not be neglected including protein deposition [10–12]. Moreover, environment of pHEMA hydrogel was very suitable for bacterial growth, which easily caused infection of eyes. In order to solve the problem, contact lens care solution was used to wash contact lens for getting rid of absorbed proteins as well as absorbed bacteria [10–12]. Recently, some measures of pHEMA hydrogel modification were made to improve antiprotein adsorption property and antibacterial property. These measures included surface modification by

chitosan (CS)/hyaluronic acid (HA) layer-by-layer technique to decrease protein absorption and improve antibacterial property, introduction of crosslinkable chitosan in polymerization to enhance hydrophilic property and improve antibacterial property for hydrogel matrix, and introduction of antiadhesion monomer in polymerization to improve hydrogel properties [3–8, 13, 14]. Although these measures succeeded to some extent to improve hydrogel properties, the problem was not solved completely. Another way to design a practical contact lens was still needed. Chitosan, a kind of polysaccharide, had been made all kinds of carriers and scaffolds on account of good biocompatibility and excellent antibacterial property [3, 15–19]. But chitosan film was too fragile to processing. Graphene family, as a new favorite in the file of material, is famous for its excellent mechanical properties including toughness in the field of composite material. Due to its single layer structure, transparency and large specific surface area of graphene also provide its potential application in optical device and drug delivery field [20–22]. Therefore, we designed a tough and tensile chitosan film for contact lens processing in the research, which was strengthened by graphene oxide.

Besides abovementioned characteristics, drug delivery property and biocompatibility were also essential properties for therapeutic contact lenses as drug carriers. In order to enhance the drug encapsulated and controlled capacity, surface modification as well as bulk modified technique was performed to introduce functional domains into hydrogel. Previously, cyclodextrin domain possessing hydrophobic cavity, which could accommodate drug molecules, was incorporated into hydrogel contact lenses by copolymerization as well as surface modification for improving drug loading and releasing property [3, 6, 7]. Moreover, some charged polysaccharides such as chitosan, hyaluronic acid, and chondroitin sulfate could have interactions with oppositely charged drug molecules, which could also help to control drug loading and releasing [5, 18]. Additionally, graphene family materials have a conjugated structure, which can absorb drug molecule through π-π interactions [18, 23–28]. Moreover, the oxygen permeability of CS film had been confirmed by previous research [29]. Therefore, two involved materials in the research had been proven to be effective and efficient carrier materials. Finally, the drug delivery was evaluated using ofloxacin as a model drug, and biocompatibility was evaluated by in vitro endothelial cells and fibroblast cells.

Although CS material including hydrogels, films, particles, even fibers had been intensively investigated, the material in the research for contact lens application was not intensively concerned. Thus, the research broadened the range of CS material's application and simultaneously provided an available choice for soft contact lens.

2. Experiment Section

2.1. Materials. Chitosan (CS, $\overline{M}_W$: 620 kDa) with deacetylation of 85% was purchased from Haidebei Marine Bioengineering Company, Ji'nan, China. Acetic acid, glycerol, ethyl alcohol, and sodium hydroxide were obtained from Shanghai Chemical Industries Co. Ltd. (Shanghai, China). Graphene oxide (GO) was purchased from XF nano Co. Ltd. (Nanjing, China). Dulbecco's modified Eagle's medium (DMEM) and 3-(4, 5-dimethyl) thiazol-2, 5-dimethyl tetrazolium bromide (MTT) were obtained from Sigma. Ofloxacin was purchased from Jinling Pharmacy Industries Co. Ltd., (Nanjing, China). All other reagents and solvents were of analytical grade and used as received.

2.2. Preparation of CS/GO Composite Film. CS/GO composite film was prepared by casting flow method, and simultaneously CS film without GO was also prepared by casting flow method as a control. For CS film, 1 g chitosan was dissolved in 20 mL 2% acetic acid solution, into which 2 mL glycerol was added. After the mixture was incubated in 30°C and degassed to get rid of bubbles, it was poured to mold for casting films. Then, the mold was incubated in 50°C for 6 h for solvent evaporation. Finally, 5 mL 1 M sodium hydroxide solution was added to mold for assisting CS film fabrication. The film was obtained after washing with water and vacuum drying. For CS/GO composite film, 2 mL 5 mg/mL GO was first dropped into 20 mL 2% acetic acid solution, which was used to dissolve 1 g chitosan. Then, 2 mL glycerol was added into the mixture. The mixed CS/GO/glycerol solution was brown transparent. Similarly, the degassed mixture was poured to mold for casting films. After solvent was evaporated in 50°C for 6 h, 5 mL 1 M sodium hydroxide solution was added to mold for assisting CS film fabrication. Finally, the film was obtained after washing with water and vacuum drying. The thickness of the final film was about 2 mm.

2.3. Characterization of CS/GO Composite Film. Films were characterized by infrared spectrum (IR spectrum, IS 10) by the attenuated total reflection (ATR) technique. The equilibrium swelling ratio of films was detected by weight fraction. Briefly, dried films were weighed (W_0), which were subsequently submerged in water at 37°C for 24 h and weighed (W_1). The swelling ratio of films was defined as W_1/W_0. Mechanical properties of films were characterized by universal material testing machine (Instron 5543) using the stretch mode. The contact angle of dried films was tracked by the contact angle meter (Kruss, DSA 100). In the measurements, water drop was fixed at 20 μL. The degradation of films was detected by weight fraction. In brief, swollen films were weighed (W_0) and put in PBS at 37°C. at every interval, and the films were taken out and weighed (W_1). The remaining ratio of films was defined as W_1/W_0. For swelling ratio, mechanical properties, contact angle test, and degradation test, at least 5 parallel samples were detected and statistically calculated and analyzed for getting credible results.

2.4. Drug Loading and Releasing Behaviors. Ofloxacin with the structure of Scheme1 was loaded into films as a model drug. The films were cut to $10 \times 10\,\text{mm}^2$ size, which were submerged in 3 mL 1 mg/mL ofloxacin solution to load the

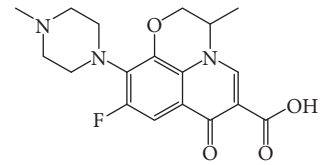
drug for 24 h to absorb drugs. The drug-loaded films were submerged in 4 mL PBS at 5 mL centrifugal tubes. At specified times, 2 mL released solution was moved from a centrifugal tube and recorded by ultraviolet-visible (UV-vis) spectroscopy (Varian, Cary 50). At the same time, 2 mL fresh PBS was added into a centrifugal tube. The drug concentration at specified times was then obtained, and the cumulative released amount was calculated according to the drug concentration and volume. At last, the residual drug in films was extracted by ethyl alcohol, which was quantified using the abovementioned method. The total loaded drug amount was obtained by the cumulative released amount and residual amount.

2.5. In Vitro Evaluation. Two kinds of cells were used in the research. One was human umbilical vein endothelial cells (HUVEC cells), and the other was human skin fibroblasts (HSF cells), which were obtained from Shanghai Enzyme-linked Biotechnology Co., Ltd. Both kinds of cells were incubated in a humidified atmosphere of 95% air and 5% CO_2 at 37°C. The used cells were detached using 0.25% trypsin in PBS for the experiment. The dried CS/GO composite films and CS films were cut into small pieces, disinfected with UV, and then put into a 96-well culture plate. 200 μL cell suspension containing a certain number of cells was added to each well. The cells were cultured at 37°C in a humidified atmosphere of 95% air and 5% CO_2. For HUVEC cells, the cell seeding density is 5000 cells/well. For HSF cells, cell seeding density is 1, 6000 cells/well. Cells were observed by microscope (Zeiss Axovert 200) and characterized by MTT assay for their viability after they had been cultured for 1 d, 2 d, and 3 d. For MTT assay, 20 μL MTT was first supplemented to each well under test for another 4 h culture. 200 μL dimethyl sulphoxide was added to dissolve the formed formazan pigment. The absorbance of 150 μL above solution at 570 nm was recorded by a microplate reader in a 96-well TCPS plate. Moreover, the cell number was also characterized. For cell statistics, cells in each well were first detached by 100 μL 0.25% trypsin in PBS for 5 min. Then, 100 μL culture medium was added to terminate trypsin action. Finally, detached cells were counted by hemacytometer.

2.6. Statistical Analysis. Data were analyzed using one-way ANOVA for differences. Results are reported as mean±standard deviation. The significant level was set at $p < 0.05$, and the great significant level was set at $p < 0.01$.

3. Results and Discussions

3.1. Characterization of CS/GO Composite Film. Either CS/GO composite film or CS film was fabricated by simple casting flow method using glycerol as a flexibilizer and crosslinker, as shown in Figure 1. The formed film exhibited good transparent and tensile characteristic, which confirmed by their flat and curving photos in Figure 1. Generally, CS film without glycerol was transparent and fragile, which prevented the material from processing to specific shape.



Scheme 1: The chemical structure of ofloxacin.

The addition of glycerol solved the problem. From film appearance, no significant difference was found between CS/GO composite film and CS film. Moreover, little CS and GO left after film was fabricated, and the pH value of soak solution of CS and CS/GO film was between 7 and 8.

As a contact lens, light transmittance performance and water content were very important since the material should contact with soft cornea without hindering the visual. Transparency of either CS/GO composite film or CS film was verified by either their digital photos (Figure 1) and UV-vis spectra of Figure 2(c). According to our previous research [3], the light (range from 450 nm to 800 nm) transmittance of commercial is 60–98% dependent on many factors such as film thickness, morphology characteristic, and color. Although light transmittance was different, the vision transparency could be ensured according to digital photo including our films in Figure 1.

In other aspects, swelling ratio of material reflected water content, which is related to wearing comfortability of contact lens. Hence, the swelling ratio of materials was characterized in Figure 2(a). The swelling ratio of CS/GO composite film (1.8) was a little lower than that of the CS film (2.1) with significant difference. Not surprisingly, the addition of GO made the swelling ratio of the film decrease a little since GO could not be swollen in water. Although the water content of CS/GO composite film was relatively low (45 wt.% calculated from swelling ratio), the value actually approached the water content of commercial soft contact lens material according to our previous research [2, 3, 8]. Therefore, these properties confirmed that CS/GO composite film was suitable for contact lens fabrication.

In order to clarify chemical structure of films, FTIR spectra of both CS/GO composite film and CS film are characterized in Figure 2(b) using ATR mode. The typical peaks of 1534 cm^{-1}, 1624 cm^{-1}, and 1730 cm^{-1} emerged in their FTIR spectrum, which belonged to the amide group and amino group of CS. Naturally, the CS film exhibited CS characteristic peaks since it was mainly composed of CS. For CS/GO composite film, CS was still a main component of films since GO addition was much less than CS component in film processing. Moreover, GO had little other specific infrared characteristic peaks apart from the same infrared characteristic peaks to CS. Therefore, CS/GO composite film possessed similar FTIR spectrum with the CS film.

As a kind of film material, its tensile strength is an important factor that cannot be neglected for its application. Stress curves as a function of strain are shown in Figure 3(a). It was found that the breaking strength of CS/GO composite film was higher than that of CS film, but the elongation at break for CS/GO composite film was lower than that for CS film. The result could be further verified by statistical data of

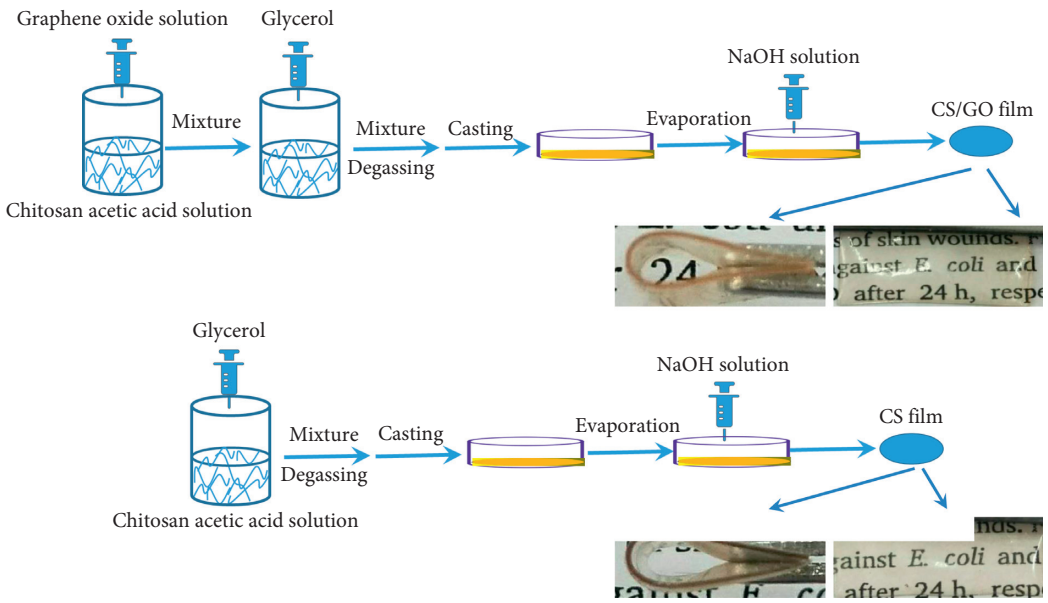


Figure 1: Schematic illustration to show films preparation and their digital photos to show the transparency and toughness.

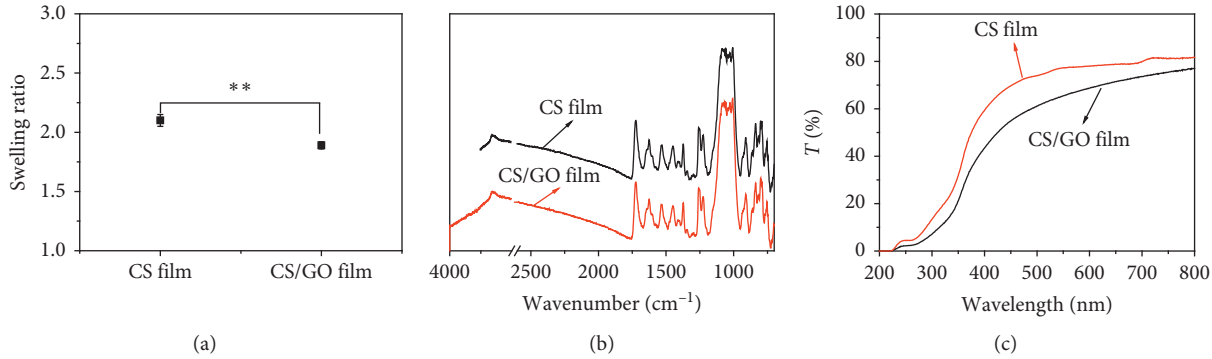


Figure 2: (a) Swelling ratio of CS film and CS/GO film $^{*}p < 0.05$ and $^{**}p < 0.01$; (b) FTIR spectra of CS film and CS/GO film; (c) transparency of CS film and CS/GO film.

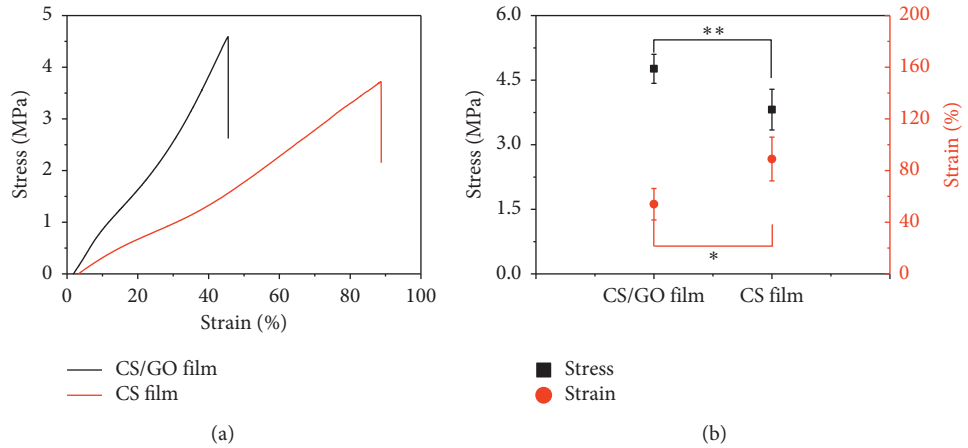


Figure 3: (a) Stress of CS film and CS/GO composite film as a function of strain; (b) stress and strain of CS film and CS/GO film just before fracture. $^{*}p < 0.05$ and $^{**}p < 0.01$.

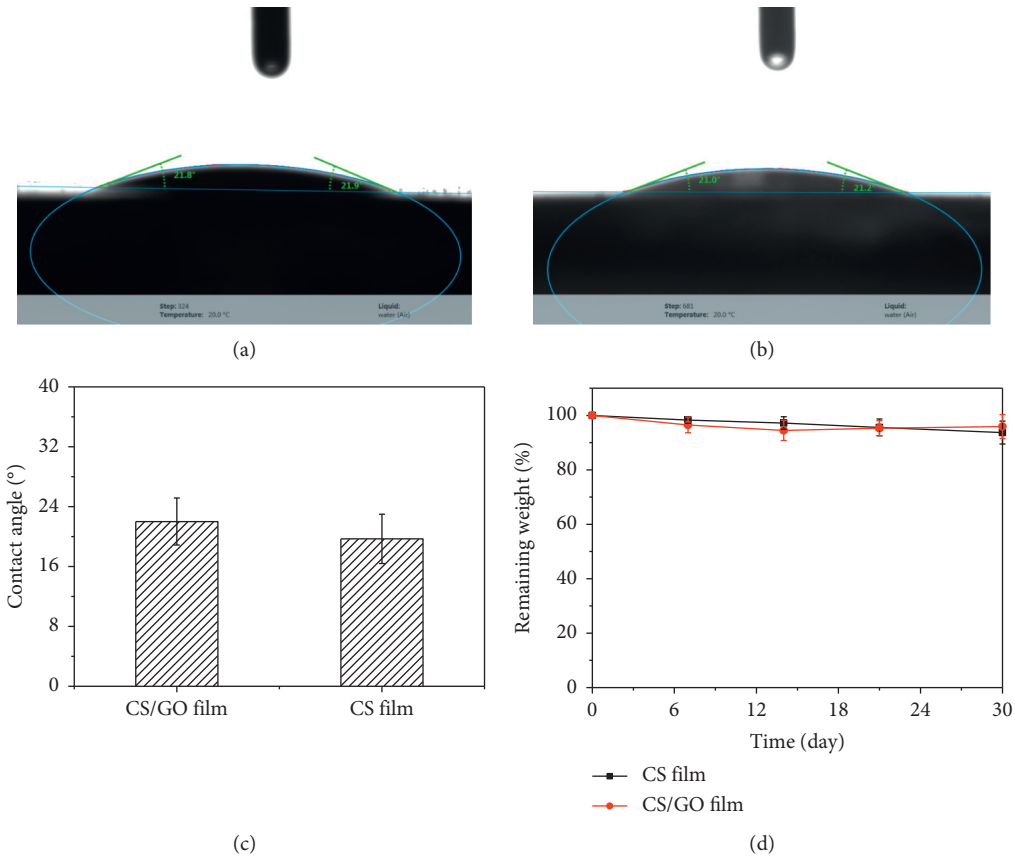


Figure 4: Photo of contact angle for (a) CS/GO film and (b) CS film; (c) contact angle value for CS/GO film and CS film $^{*}p < 0.05$, $^{**}p < 0.01$; (d) the remaining weight of CS film and CS/GO film as a function of degradation time.

Figure 3(b). Especially for breaking strength, great significant difference existed between them. Since the enhance effect of GO had been proven from previous research, the result was expectable. At the same time, toughness was slightly influenced by GO addition due to toughness for GO itself.

In addition, contact angle of films was characterized in Figure 4, which reflected the hydrophilic property of material surface. When a drop of water fell on the surface of either CS/GO composite film or CS film, it became flat with a contact angle of around 20 degree from the photo of contact angle in Figures 4(a) and 4(b). The statistic value of contact angle for CS/GO composite film was about 22 degree, which was little higher than that of CS film. But the difference had no statistic significant meaning. However, the contact angle of either CS film or CS/GO composite film is lower than traditional contact lens materials. These results showed that either CS/GO composite film or CS film had good hydrophilicity, which was suitable for contact lens usage [2, 3, 5, 7, 8].

Since CS is biodegradable, the degradation of film will affect the properties of either CS film or CS/GO composite film. The degradation of CS film and CS/GO composite film is shown in Figure 4(d). It was found that either CS film or CS/GO composite film could not be degraded along with time within one month from our experiment though degradation for long time has not been detected.

3.2. Drug Loading and Releasing Behaviors. Since ofloxacin were commonly used drugs, it was used as a model drug to evaluate the drug loading and releasing behavior. The drug was loaded into films by adsorption diffusion method. Loaded drug amount in every CS/GO composite film was 2.3 ± 0.5 mg/g, which was larger than that in every CS film (2.1 ± 0.3 mg/g) without significant difference (Figure 5(a)). Since GO had some interactions with drug molecules, the addition of GO in film would help to absorb more drug molecules.

The release behaviors of drug in PBS are investigated in Figure 5(b). In the procedure, the pH of releasing media during in-vitro drug release study has been measured to be stabilized to 7.2–7.4 without any variation. About 90% ofloxacin was linearly released from either CS/GO composite film or CS film along with time during the first hour, and the release equilibrium was reached. The results of Figure 5(b) show that either CS/GO composite film or CS film could control drug release in the first hour. However, there was no significant difference between CS film and CS/GO composite film. It was inferred from the results that the release of drug was controlled mainly by diffusion.

From results, GO addition seemed to have no significant beneficial effect for drug (ofloxacin) encapsulation and its release control. The driving force of either drug loading or drug releasing was the diffusion. Furthermore, equilibrium time was relatively short compared with our previous

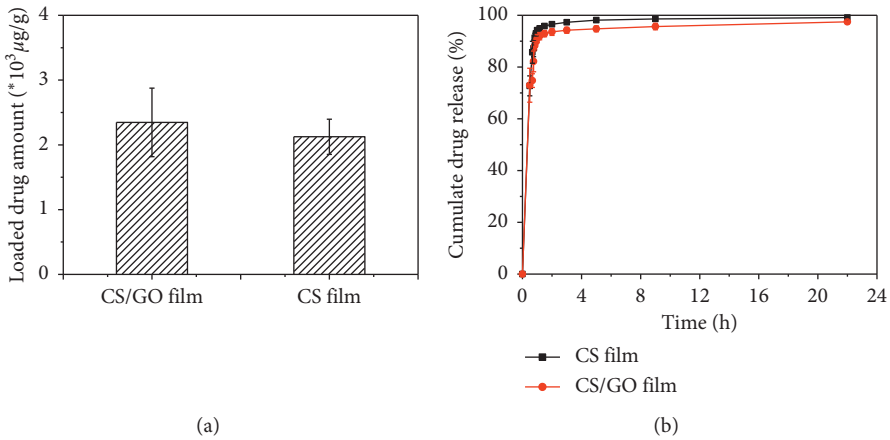


Figure 5: (a) Loaded drug amount of CS film and CS/GO film; (b) cumulative drug release of CS film and CS/GO film as a function of time. $^{*}p < 0.05$ and $^{**}p < 0.01$.

research [5–7]. Therefore, it was inferred that ofloxacin did not enter the inner part of film, which might shield the effect of GO component in composite film. Since ofloxacin was also a small molecule, its conjugated structure might prevent it going across the crosslinked CS network with soft domains. Moreover, crosslinked density might too large to accommodate the molecule of that size.

3.3. In Vitro Evaluation. In vitro culture of HUVEC cells and HSF cells was performed to preliminarily assess the biocompatibility of CS/GO composite film and CS film. As shown in Figure 6(a), the viability of HUVEC cells on two kinds of films monotonously increased significantly along with the culture time from 1 d to 3 d. Furthermore, the viability of HUVEC cells on CS film was higher than that on CS/GO composite film, but without significant difference (Figure 6(a)). Similarly, cell number on two kinds of films also monotonously increased significantly along with the culture time from 1 d to 3 d. Differently, cell number on CS/GO composite film was higher than that on CS film without significant difference (Figure 6(b)). These results indicated that either CS/GO composite film or CS film could support HUVEC cell growth, and no obvious difference of the supporting role was found between the two films. Cell microscopy images revealed similar results (Figure 7). At day 1, cells uniformly spread on both film surfaces with some antennas (Figures 7(a) and 7(d)). No significant difference was found for cells on between CS/GO composite film and CS film. At day 2, the cell number obviously increased with similar morphology on both CS/GO composite film and CS film (Figures 7(b) and 7(e)) compared with that of day 1. At day 3, the number of cells on both surfaces increased significantly, forming confluence cell clusters at some places (Figures 7(c) and 7(f)). These results confirmed the biocompatibility of both films for HUVEC cells.

However, results were different for HSF cells compared with EC cells in Figures 8 and 9. The viability of HSF cells on two kinds of films also monotonously increased from 1 d to 3 d, simultaneously cell number exhibited the same trend

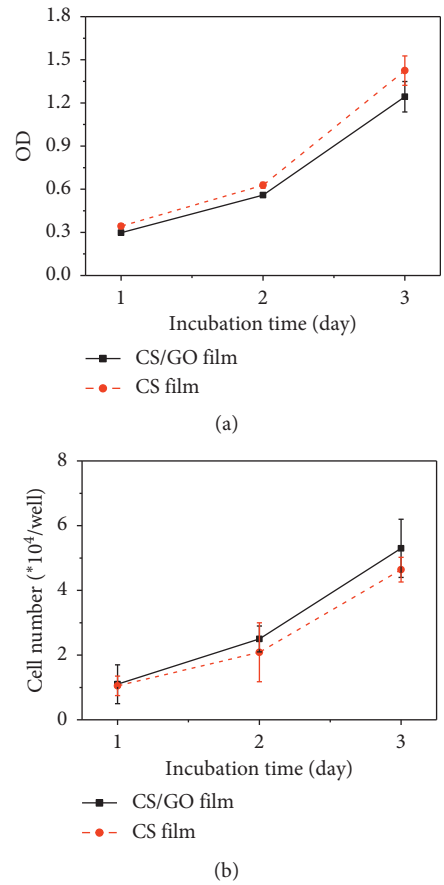


Figure 6: Cell viability (a) and cell number (b) as a function of incubation time on CS/GO films and CS films. $^{*}p < 0.05$ and $^{**}p < 0.01$.

from 1 d to 3 d (Figure 8). Differently, either viability of HSF cells or cell number on CS/GO composite film was significantly higher than that on CS film with great significant difference (Figure 8). Cell microscopy images revealed similar results (Figure 9). At day 1, certain HSF cells uniformly spread on CS/GO composite film with stretching

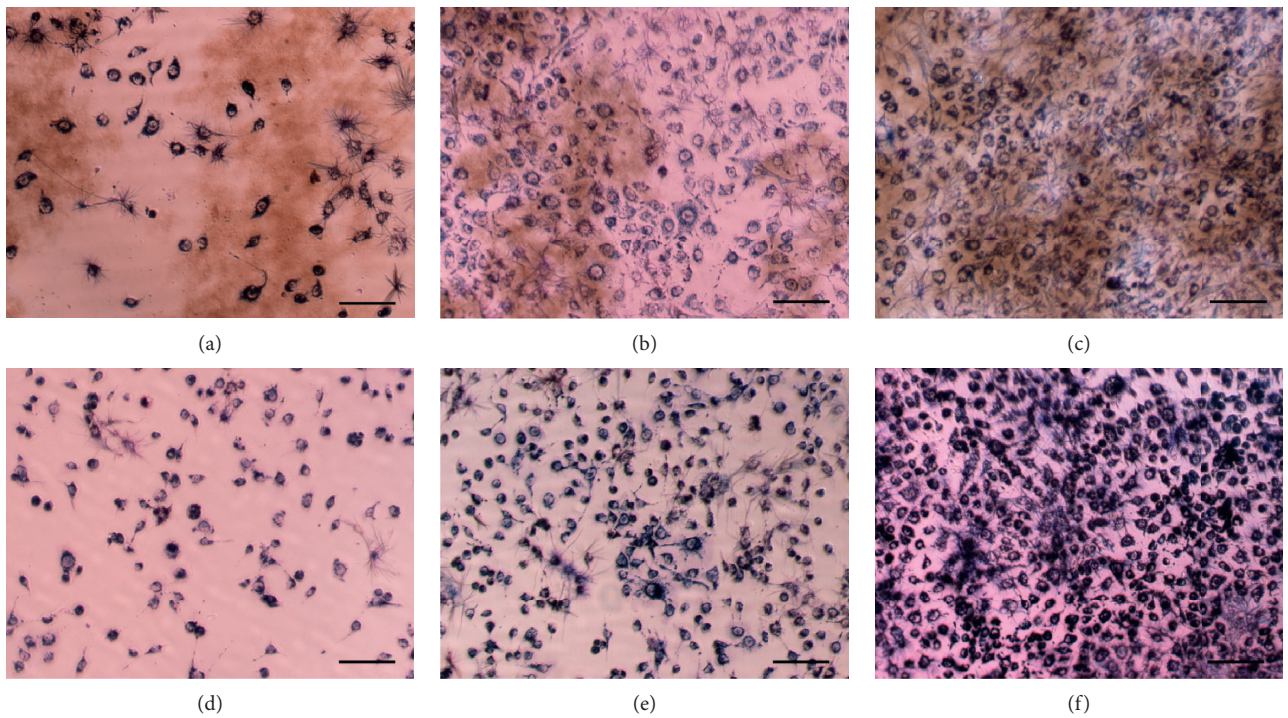


Figure 7: Optical images of HUVEC cells on CS/GO films (a, b, c) and CS films (d, e, f) after cultured 1 d (a, d), 2 d (b, e), and 3 d (c, f). Cell seeding density is 5000 cells/well. Cells were stained by MTT. The scale is 100 μm.

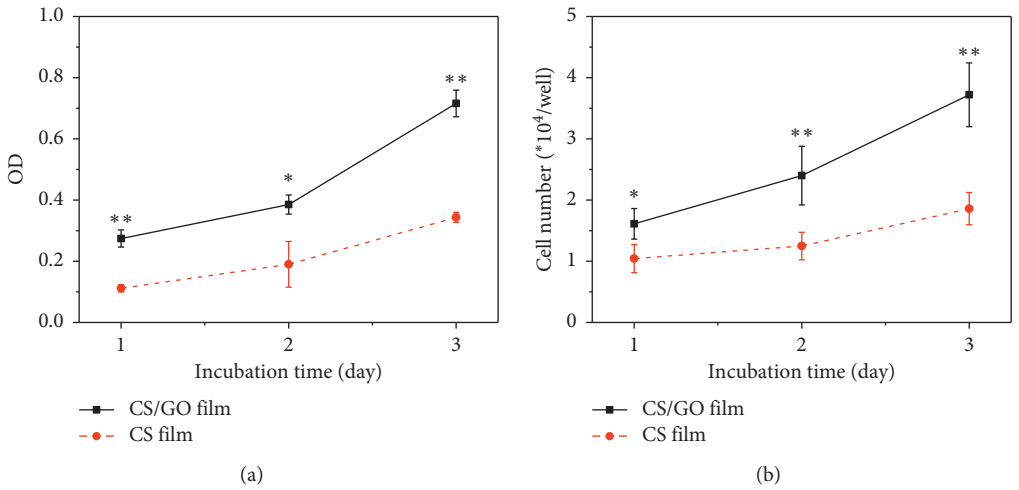


Figure 8: Cell viability (a) and cell number (b) as a function of incubation time on CS/GO films and CS films. $^{*}p < 0.05$ and $^{**}p < 0.01$.

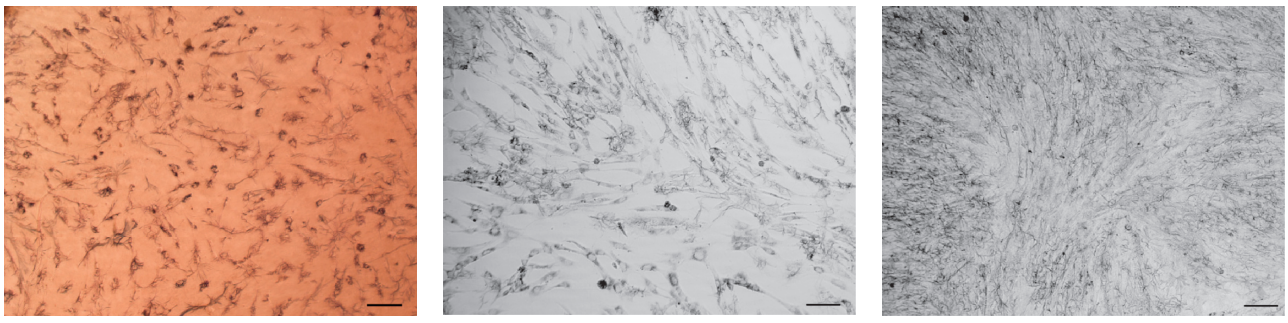
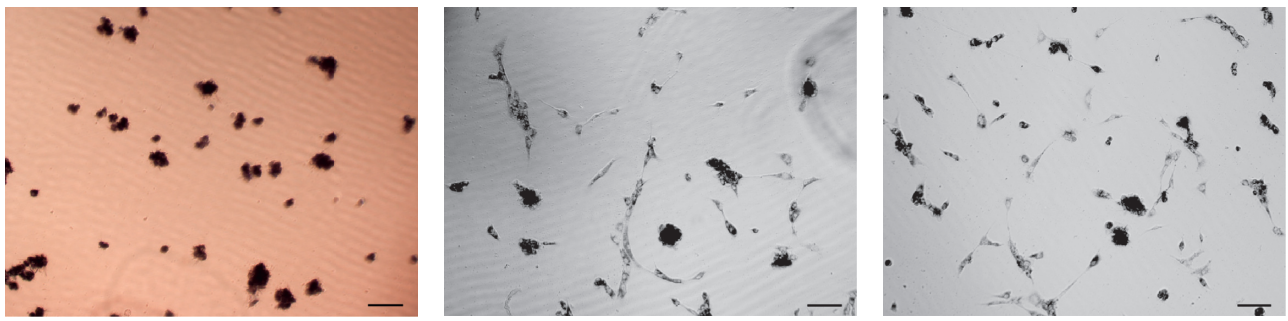


Figure 9: Continued.



(d) (e) (f)

Figure 9: Optical images of HSF cells on CS/GO films (a, b, c) and CS films (d, e, f) after cultured 1 d (a, d), 2 d (b, e) and 3 d (c, f). Cell seeding density is 1,6000 cells/well. Cells were stained by MTT. The scale is 100 μm.

morphology (Figure 9(a)), but only a small round HSF cells scattered on CS film (Figure 9(d)). At day 2, cells obviously grew and fused with elongated morphology on CS/GO composite film (Figure 9(b)). At day 3, further cell fusion was found on CS/GO composite film (Figure 9(c)). Although HSF cell on CS film become elongated state and the number of HSF cells increased a little at day 2 and day 3, no obvious proliferation was found (Figures 9(e) and 9(f)). These results indicated that CS/GO composite film could promote HSF cells growth and proliferation than CS film.

4. Conclusion

CS/GO composite film and CS film could be successfully fabricated by the simple casting flow method. The formed films exhibited acceptable transparent and tensile characteristic. The films possessed suitable swelling ratio for contact lens application. The swelling ratio of CS/GO composite film was higher than that of CS film with significant difference. Both CS/GO composite film and CS film exhibited typical CS infrared characteristic peaks, which indicated that two kinds of films possessed similar chemical structure. CS/GO composite film had significant greater tensile modulus than CS film, but its elongation at break was a little lower than CS film. Either CS/GO composite film or CS film had good hydrophilic property with a contact angle of around 20 degree. Ofloxacin could be loaded into CS/GO composite film and CS film by adsorption diffusion method. Loaded drug amount in CS/GO composite film was a little larger than that in CS film, but without significant difference. CS/GO composite film or CS film could control drug linearly release during the first hour by diffusion mechanism. In vitro evaluation revealed that either CS/GO composite film or CS film could support HUVEC cell growth, and no obvious difference of the supporting role was found between the two films. But for HSF cells, results were different. Although both films could support HSF cells survival and growth, CS/GO composite film could promote HSF cells growth and proliferation much better than CS film. In all, the formed materials satisfied the fundamental request of contact lens and exhibited good prospect for the application of therapeutic contact lenses.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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