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Improved properties of incorporated chitosan film with ethyl cellulose microspheres for controlled release

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ABSTRACT

In this article, to discover an innovative drug release system, ciprofloxacin hydrochloride-loaded blending films of chitosan (CS)/ethyl cellulose (EC) microspheres were prepared. Two steps were adopted in the film forming process. The first was formation of the drug-loaded EC microspheres in CS solution by solvent remove/solvent evaporation methods; then, the composite films were made by casting and solvent evaporation. The results were that the drug-loaded round EC microspheres dispersed asymmetrically in the CS films and largely improved the release time. Moreover, the drug-loaded blending film containing 0.5 g EC microspheres prepared at 90 °C showed highlighted extended release property. The drug was stable in the blending films, which expressed good cytocompatibility proved by MTT test. The film should be a promising carrier for controlled and extended drug release system in pharmaceutical applications.
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1. Introduction

In pharmaceutical industry, CS has been researched broadly because of its potential usage in the development of controlled drug release systems (Karlsen and Skaugrud, 1991; Aspden et al., 1997; Oungbho and Muller, 1997; Mao et al., 2001). Moreover, CS also has other powerful abilities, such as biodegradability, antimicrobial activity, biocompatibility and acceleration of wound-healing (Malette et al., 1983; Qurashi et al., 1992; Wei et al., 1992). Chitosan with a structure of Fig. 1a is the derivative of chitin and one of the most abundant polysaccharides, whose amino groups exhibit protonation under acidic condition (pH < 7). It has good gel and film forming properties. With respect to the excellent film forming property of CS, many original films have been obtained, such as CS/polyethylene glycol blending film with extended drug release (Wang et al., 2007), asymmetric CS membrane of antibacterial release in wound dressing area (Mi et al., 2003) and citrate cross-linked CS film for improving drug release property (Shu et al., 2001). In addition, various extended or sustained-delivery systems with dissolved or dispersed ingredients have been described (Blanco et al., 2000; Li et al., 2002). Therefore, CS demonstrates obvious potential in film formation and drug release.

As shown in Fig. 1b, ethyl cellulose is one kind of water-insoluble cellulose ether and has been widely studied for pharmaceutical purposes (Porter, 1980; Rowe et al., 1984). EC films and microspheres show good extended drug release properties, especially for those drugs that were highly soluble in liquids (Gunder et al., 1995; Jani and Gohel, 1997; Ofori-Kwakye and Fell, 2001; Puttipipatkhachorn et al., 2001; Anal et al., 2006; Desai et al., 2006). EC is also a kind of polymer with excellent membrane-forming ability, durability and low cost. However its flexibility is relatively inferior.

As mentioned above, it is now well accepted that CS appears to pose excellent film forming ability, which is combined with other components to shape various kinds of films with extended drug release properties. However, these blending films do not show satisfactory controlled release properties to the water-soluble drugs, such as ciprofloxacin hydrochloride (Fig. 1c). On the other hand, EC microspheres show preferable release properties for water-soluble drugs.

Hence the aim of the paper is to prepare a novel film with outstanding controlled release properties for water-soluble drugs, the incorporated CS films with EC microspheres containing ciprofloxacin hydrochloride are prepared in this research. Moreover, the chemical, morphological and release properties of ciprofloxacin hydrochloride-loaded CS/EC microsphere blending films are investigated.

2. Materials and methods

2.1. Materials

EC was purchased from Niansha Chemical Reagent Company of Kunshan, China. CS was from Haidebei Technological Co. Ltd. of Shandong, China. Ciprofloxacin hydrochloride was supplied by

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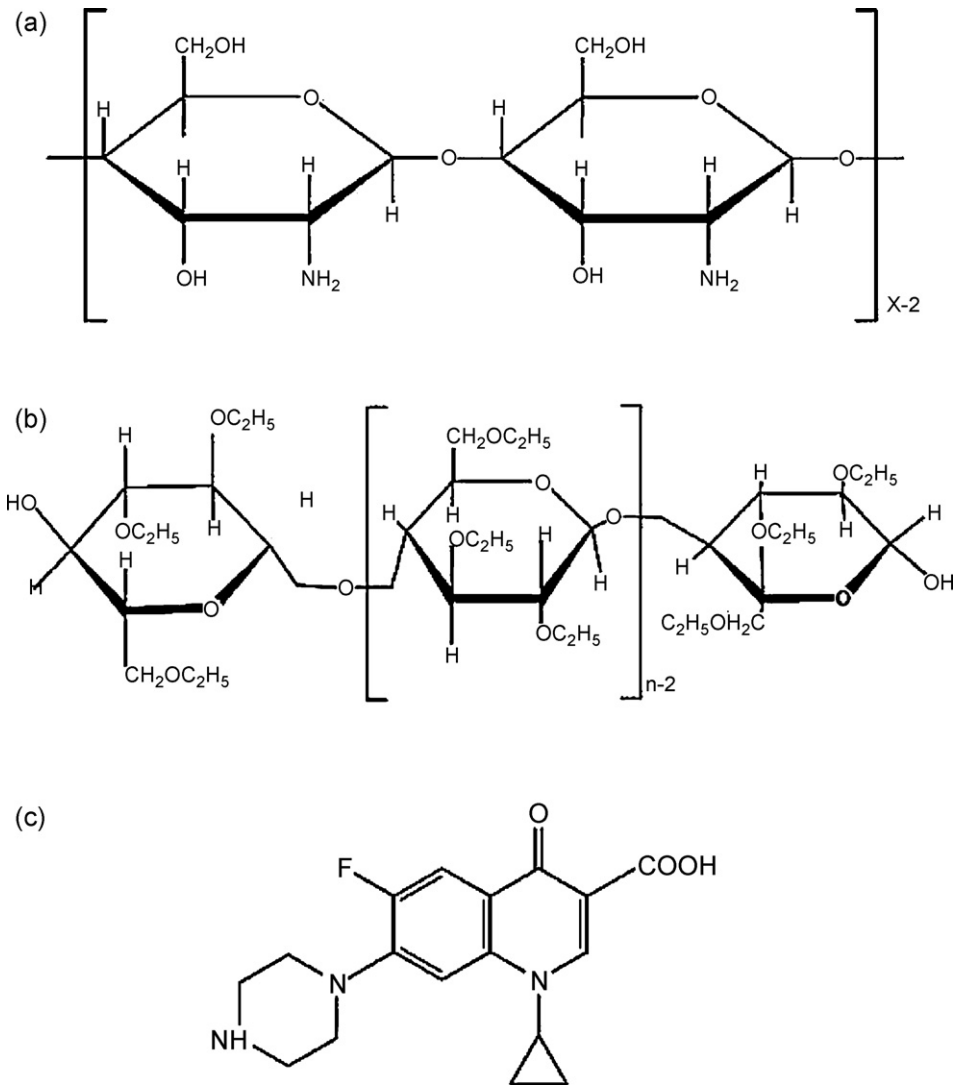

Fig. 1. Chemical structure of chitosan (a), ethyl cellulose (b) and ciprofloxacin (c).

Maidesheng Medical Company of Chengdu, China. All the reagents used here were analytical grade.

2.2. Preparation of drug-loaded EC microspheres

In our analysis, various factors in the process of microspheres fabrication were taken into account, such as the different mass of EC in CS solution, the incubation time and temperature. In this paper, 6% CS solution was used to form the drug-loaded EC microspheres and the films. Chitosan solution (6%, w/v) was prepared by dissolving 6 g chitosan in 100 ml diluted acetic acid (3%, v/v) (Shi et al., 2008).

At first, 0.5, 0.7 and 0.9 g EC, respectively, were dissolved in the ternary mixture (40 ml) consisted of CH_2Cl_2, methanol and acetone to form each EC solution. All the EC solutions were mixed with 200 mg ciprofloxacin hydrochloride, ultrasonically treated for 5 min. Then, EC solution was injected in 100 ml 6% CS solution at room temperature to form the primary o/w emulsion. Later, the emulsion was put in water incubator for 1 h at 70 °C. After the organic solvent was evaporated, the microspheres were centrifugated from CS solution, fully washed with distilled water and freeze-dried. Conversely, the primary o/w emulsions were also put in a water incubator for 0.5 h at 90 °C using the same methods.

2.3. Fabrication of CS films with drug-loaded EC microspheres

At first, the EC solutions were prepared by dissolving 0.1, 0.3, 0.5, 0.7 and 0.9 g EC in the ternary mixture (40 ml) of CH_2Cl_2, methanol and acetone, respectively. Then, 200 mg ciprofloxacin hydrochloride powders were added into the five EC solutions separately marked as solution $E_{0.1}$, $E_{0.3}$, $E_{0.5}$, $E_{0.7}$ and $E_{0.9}$. Then, $E_{0.1} \rightarrow E_{0.9}$ were dripped into 100 ml 6% CS solution respectively, and the emulsions were stirred at 1000 rpm at 70 °C for 1 h. After the organic solvent was removed, the CS solution containing EC microspheres (co-solution) was together poured on glass plate and dehydrated at room temperature as well as freeze-dried. The five drug-loaded CS/EC microspheres films were marked as $F_{0.1}$, $F_{0.3}$, $F_{0.5}$, $F_{0.7}$ and $F_{0.9}$. On the other hand, other samples whose microspheres were formed at 90 °C for 0.5 h were also prepared and marked as $F_{t0.1}$, $F_{t0.3}$, $F_{t0.5}$, $F_{t0.7}$ and $F_{t0.9}$.

The area of glass plates was kept invariable, the amount of the co-solution pouring on the plate could determine the thickness of the drug-loaded blending films and their thickness was tested by electronic digital outside micrometer (Chengliang Co. Ltd., Chengdu, China), five tests were taken for each sample. In this article, 7.107 ± 0.095 and 30 ± 0.137 μm films were made to test their drug release properties. In addition, sodium alginate solutions (0.1 and 0.3 wt%) used for coating the films were prepared by dissolving

0.1 and 0.3 g sodium alginate in 100 ml distilled water, respectively. The sodium alginate solution was sprayed on the $F_{t0.3}$ films and dried to prepare the drug-loaded CS/EC microspheres blending films with alginate coating. The thickness of coating was also tested by digital micrometer, five tests were taken for each sample.

2.4. Fabrication of CS film containing ciprofloxacin hydrochloride

To investigate the efficient release of ciprofloxacin hydrochloride-loaded CS film, 200 mg ciprofloxacin hydrochloride was mixed with 100 ml 6% CS solution, then the solution was cast on glass plate, dehydrated at room temperature and freeze-dried.

2.5. Characterization analyses

2.5.1. SEM observation

The morphologies of drug-loaded microspheres and drug-loaded blending films were characterized by SEM (Jeol Ltd., Tokyo, Japan). Samples were sputter-coated with a layer of Au under argon atmosphere, and 20 and 5 kV acceleration voltages were used.

2.5.2. FT-IR analysis

Infrared (IR) spectra of samples were recorded with a FT-IR spectrophotometer (PerkinElmer Co., USA). Film samples were scanned from 500 to 4000 cm^{-1}.

2.5.3. Drug release properties

The Na_2HPO_4–NaH_2PO_4 solution with pH 7.6 was mainly used to evaluate the release properties of the blending films. The ionic strength of all the above-mentioned solutions was carefully adjusted to a relatively level by adding appropriate amount of NaCl. In addition, appropriate amount of NaCl was added in Na_2HPO_4–NaH_2PO_4 buffer (pH 7.6) to produce three different release mediums with different ionic strength (0.5, 1 and 1.5 M) for the tests of drug release properties.

The drug-loaded blending films were suspended in glass vessels containing 100 ml mediums and incubated in a shaking instrument (SHA-C, Fuhua Co. Ltd., Jiangsu, China) at 37 °C and 100 rpm. At proper interval times, aliquots of the solutions were withdrawn and an equal volume of the same solution was added back to maintain a constant volume. The amount of ciprofloxacin hydrochloride released from the samples was evaluated by UV spectrophotometry (SP-754PC, Shanghai Spectrum Instruments Co. Ltd., China) at 277 nm (Mao et al., 2005; Wang et al., 2007), and the data including the drug loss were recorded. Three tests were taken for each sample.

2.6. Cell viability

The tests of cell viability were used to investigate the biological properties of the drug-loaded blending films.

2.6.1. Cells and culture conditions

MG63 cells, obtained from West China Hospital of Sichuan University, were used to assay the cellular effect on the drug-loaded blending films. The cells were thawed from the frozen stock and seeded in the F12 culture medium containing osteogenic factors (50 μg/l L-ascorbic acid, 10–8 mol/l dexamethasone and 10 mmol/l b-glycerophosphate, 10 mmol/l VitD3, 100 μg/ml penicillium and 100 μg/ml streptomycin, 0.3 μg/ml amphotericin, 2.2 g/l sodium bicarbonate and 10% fetal bovine serum) under standard culture conditions. The medium was regularly substituted twice a week.

$F_{t0.3}$ film was chosen to perform the biological evaluations, which were shaped into 5 mm in diameter and sterilized with 70% alcohol three times. The samples were put in 12-well polystyrene plates and pre-wetted using medium for 24 h. Then, 1 ml cell suspension (20,000 cells/ml) was seeded on the top surface of each sample. As the control, the cell suspension was distributed with the same medium in the blank 12-well plates. All the samples were cultured in a humidified incubator at 37 °C with 95% air and 5% CO_2 for 11 days. The medium was changed every 3 days.

2.6.2. MTT assay

3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrasodium bromide (MTT) having a purple formazan reaction with the mitochondria of living cells was used to estimate cell viability or proliferation. Control cultures and the seeded specimens were incubated with 0.5 mg/ml MTT for 4 h. The medium was then discarded. Formazan salts were dissolved with dimethylsulphoxide and the absorbance (A) of optical density of the solutions was measured at 570 nm.

2.6.3. Statistical analysis

Triplicate experiments were performed. Statistical analysis was assessed using SPSS (v10.0). The results were shown as the arithmetic means ± standard deviation (±SD). Analysis of the results was carried out using the t-test, with a significance level of $p < 0.05$.

3. Results and discussion

3.1. SEM observation

As shown in Fig. 2a and b, 0.5 and 0.7 g EC could produce microspheres in 6% CS solution at 70 °C (Fig. 2a and b). However 0.9 g EC formed smaller microspheres with obvious conglomeration, and some of which were not round and smooth (Fig. 2c). At 90 °C, 0.5 g EC formed microspheres similar to those at 70 °C with larger size. Moreover, 0.7 and 0.9 g EC could form both large and small microspheres with obvious conglomeration (Fig. 2b1 and c1) which indicated that high temperature can accelerate the evaporation of organic solvent and leave less time for the formation of EC microspheres. In other words, when the temperature of the continuous phase was going up too quickly, the inner phase would be solidified immediately before dispersed equally. Therefore, the concentration of the internal phase (EC solution) and temperature played a significant role in the preparation of EC microspheres (Freiberg and Zhu, 2004). Moreover, the shape change of microspheres would make a huge influence on their drug release properties, which also been proved as described below. Furthermore, as the viscosity of EC solution increases, to disperse the EC solution in the continuous phase (6% CS solution) became harder. Note that it was harder to get a fully emulsified solution if the viscosity of the inner phase was high. So, as can be seen from Fig. 2, when the concentration of EC solution was increasing, the EC microspheres became agglomerative and distorted.

As can be seen from Fig. 2d and f, the EC microspheres dispersed uniformly in CS film without conglomeration with even film thickness. Moreover, Fig. 2d shows that there were lots of microspheres on the upper surface of the CS film, but nothing on the underside surface (Fig. 2e). So, the film had asymmetrical surfaces. If the drug-loaded CS/EC microspheres film was used in traumatic dressing, the drug concentration of microspheres side would be higher than the smooth side; on the other hand, if the microspheres in the CS film was used to carry growth factors, such as BMP, the blending film could be used in covering the defect sites to keep the higher growth factor concentration in the defective place than the surrounding tissue. In addition, at higher voltage (25 kV), the microspheres which were embedded/penetrated in the upper surface, can be observed (Fig. 2g). Moreover, it was worthy mentioning that the higher acceleration voltage would let the SEM photos be provided with further

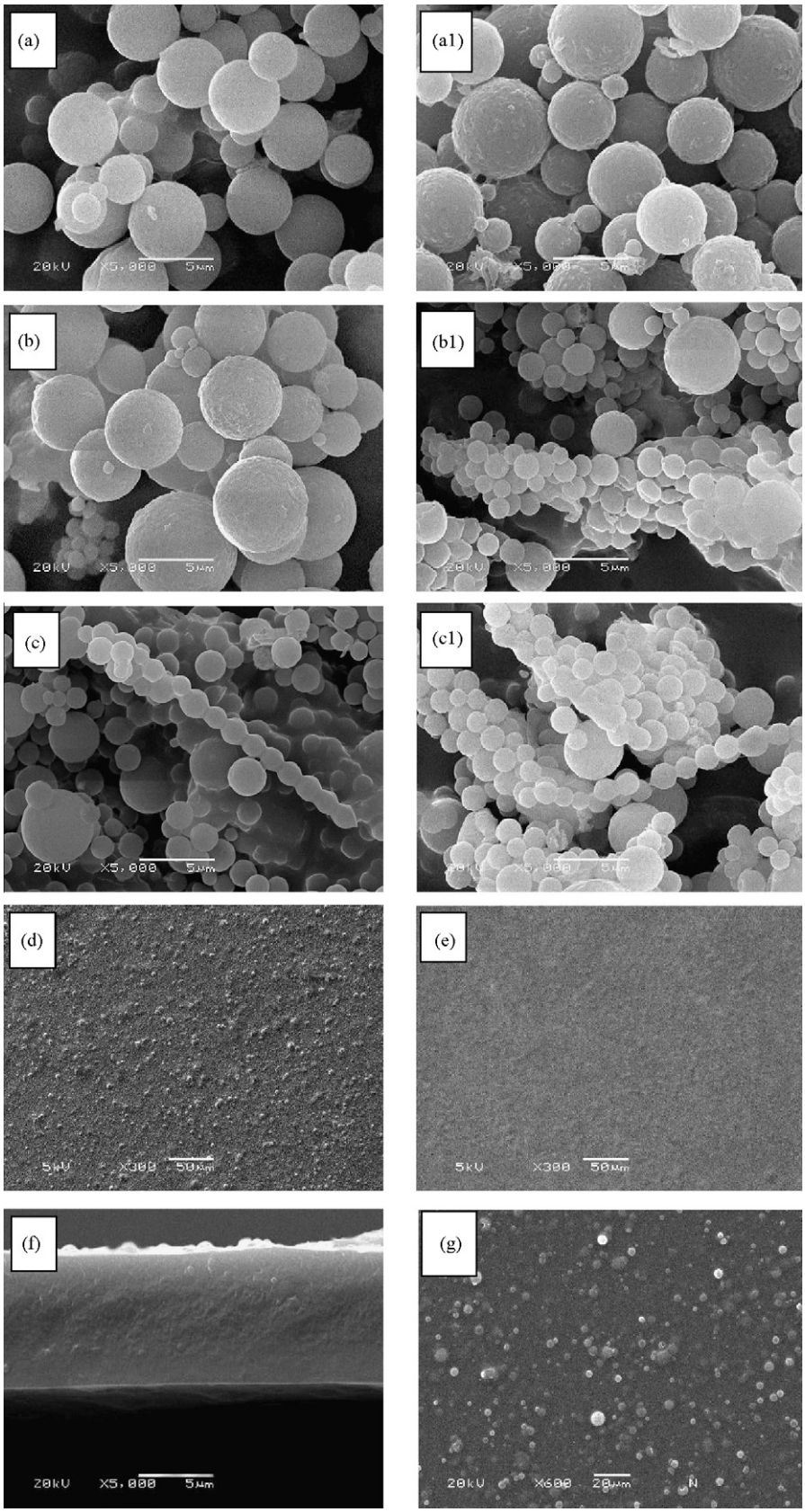

Fig. 2. SEM images of EC microspheres (a and a1: 0.5 g; b and b1: 0.7 g; c and c1: 0.9 g) carrying drug prepared in 6% CS solution at 70 °C (a–c) and 90 °C (a1–c1); and photos of CS/EC microspheres films (0.5 g EC in 6% CS solution at 90 °C) carrying drug: upper surface (d and g), underside surface (e) and section of the film (f).

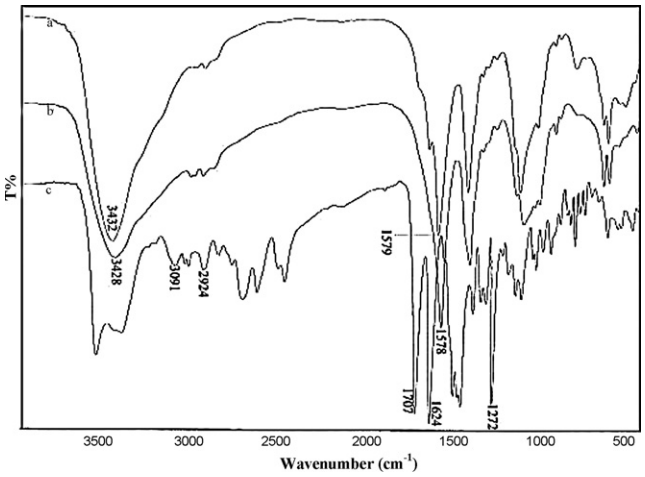

Fig. 3. FT-IR spectra of the drug-loaded CS/EC microspheres blending films prepared at 70 °C (a) and 90 °C (b), and the ciprofloxacin hydrochloride (c).

depth of field (Johari and Bhattacharyya, 1969; Rotermund et al., 1990; Cowley, 1992).

3.2. FT-IR analysis

In our work, we proved that the EC and CS had strong evidence for the intermolecular interactions and good molecular compatibility (Shi et al., 2008). In Fig. 3, the characteristic absorption bands of ciprofloxacin hydrochloride at 1272 and 1624 cm^{-1} (Fig. 3c) were due to the stretching vibration of C–F bond and the vibration of phenyl framework conjugated to –COOH, respectively. The stretching vibration at 1707 cm^{-1} was due to –COOH and the stretching vibrations of C–H from the phenyl framework at 3091 and 2924 cm^{-1} were also observed. The characteristic absorption band at 1598 cm^{-1} of the CS/EC microspheres blending film without drug (Shi et al., 2008) shifted here to lower wavenumber at 1579 and 1578 cm^{-1} (Fig. 3a and b), respectively. Moreover, the characteristic absorption band at 3424 cm^{-1} of the blending film without drug (Shi et al., 2008) shifted to 3432 and 3428 cm^{-1}, respectively. The results indicated that the model drug, ciprofloxacin hydrochloride, formed hydrogen bonds and ionic bonds with the matrix of the film. At the same time, there were no new characteristic absorption bands of the drug-loaded film, there was no obvious chemical reaction between the drug and the film matrix, and the drug was stable in the film.

In addition, in the drug-loaded fabrication process, the preparation parameters were not mild. Therefore, the FT-IR was employed here to test the possible properties that change in the materials and medicine in the preparation process. As a matter of fact, all their chemical properties do not change, especially the ciprofloxacin hydrochloride is thermostable in the preparation process. Moreover, more mild preparation needs to be examined.

3.3. Release properties

Herein the films used in Sections 3.3.1 and 3.3.3–3.3.4 have a thickness of about 7 μm, the films used in Section 3.3.2 is about 30 μm.

3.3.1. Effect of the amount of EC microspheres and temperature

The release property of the drug-loaded CS film with ciprofloxacin hydrochloride was tested in 100 ml sodium phosphate buffer at pH 7.6 and 37 °C. Fig. 4a showed that the ciprofloxacin hydrochloride released quickly from the film. Most of the drug

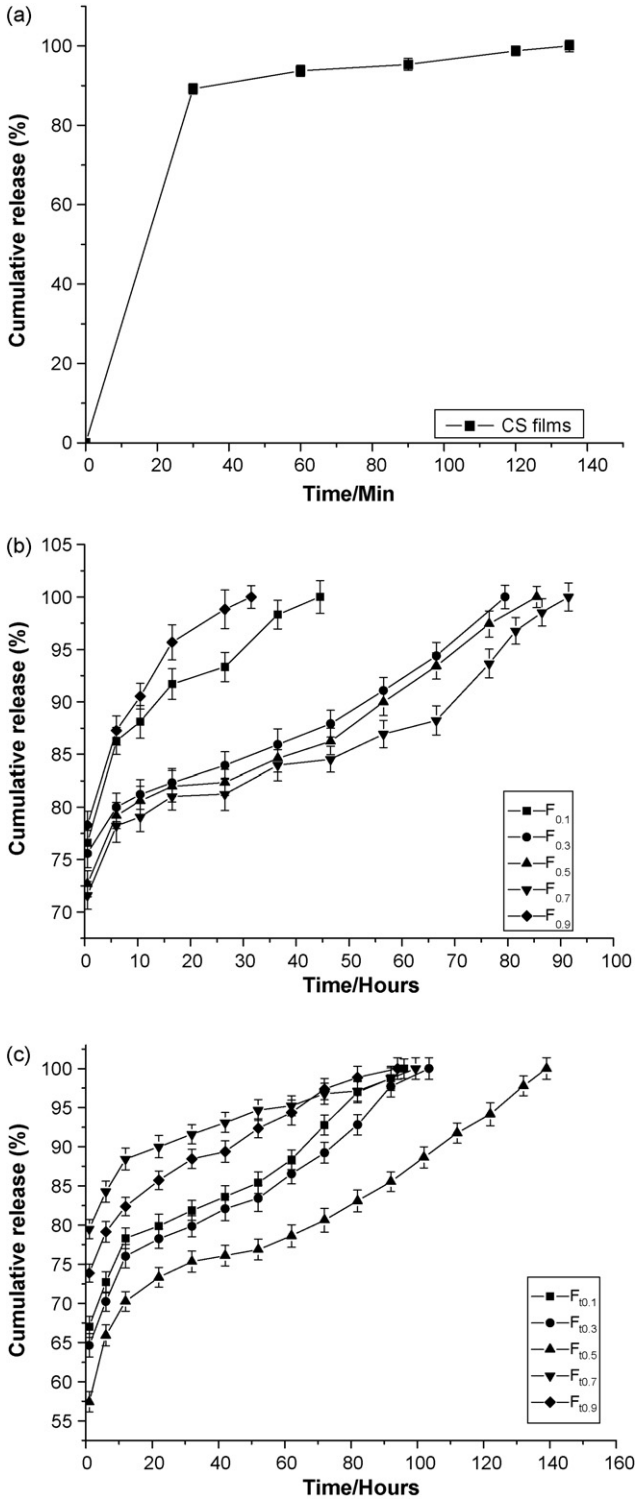

Fig. 4. Release properties of drug-loaded CS film without EC microspheres (a), the drug-loaded blending films with different amounts of EC microspheres prepared at 70 °C (b) and 90 °C (c) in 100 ml sodium phosphate buffer at pH 7.6 and 37 °C.

(89.19%) had released from the film at the first half hour, and the cumulative release can reach 100% at about 135 min. The pure CS film used in the experiments was thin and hydrophilic. It is easy for the water to penetrate the film after their contact, and the ciprofloxacin hydrochloride was also soluble in the liquid water. So, the drug in the film was diffusing quickly and easily from the film to the water, and releasing almost 100% drug in 135 min.

The curves in Fig. 4b show that only 0.1 g EC microspheres in the blending film can decrease the release rate, the fully release time was about 45 h. From $F_{0.1}$ to $F_{0.7}$, the drug release time increased with the amount of EC microspheres, more EC microspheres correspond to containing more ciprofloxacin hydrochloride. So, $F_{0.7}$ sample showed the longest release time, more than 90 h. However, for $F_{0.9}$ sample, its fully release time was relatively short, only about 35 h. This may be attributed to the fact that the EC microspheres in this film were agglomerate obviously (Fig. 2c) and the drug was releasing abnormally.

When the EC microspheres were put in the CS film, they became the major carrier of the drug compared with the CS matrix. In addition, the EC was not hydrophilic, it was some kind of hydrophobic and the liquid water was hard to penetrate the EC matrix, so the drug was not dissolving easily when it was covered by EC, so it was why after EC microspheres were incorporated in the films whose release time was extended magnificently. Furthermore, more EC in the blending film meant more drug been covered, or more drug in the EC microspheres, so the drug release rate decreased after the EC amount been increased resulting in the extension of the releasing time (Fig. 4b).

As it can be seen in Fig. 4c, the samples of $F_{t0.1}$–$F_{t0.9}$ prepared at 90 °C showed better extended drug release properties than the corresponding samples prepared at 70 °C, in which $F_{t0.5}$ had the longest release time of more than 140 h. One reason was that the formation of EC microspheres at 90 °C (0.5 h) was faster than that at 70°C (1 h), this made EC microspheres carry more drugs; the other was due to the bigger size or conglomeration of microspheres resulting in abnormal drug release properties. From the trend of drug release in Fig. 4, the samples of $F_{0.3}$, $F_{0.5}$, $F_{0.7}$ and $F_{t0.1}$, $F_{t0.3}$, $F_{t0.5}$ may be suitable for extended or controlled drug release systems. From these tests, it was also proved that the temperature was a vital parameter in the preparation of EC microspheres. Higher temperature can led microspheres to be solidified quickly and contain more drugs. On the other hand, higher temperature led the solvent of inner phase to be evaporated quickly even before the formation of emulsification. The EC solution did not disperse uniformly in the CS continuous phase.

In addition, the total release time of the blending films was longer than alginate/gelatin blending films given by Dong et al. (2006). Wang et al. (2007) reported the release properties of chitosan/polyethylene glycol blend films (55 μm in thickness), which fully released ciprofloxacin hydrochloride in 5 h. The results of their researches testify that achieving better release property for water-soluble drugs was a difficult task, so the CS/EC microspheres blending films had exhibited significant improvement in controlled release, especially extended release.

3.3.2. Effect of thickness of the drug-loaded films

Compared with blending films with a thickness of 7 μm, the 30 μm films can extend drug release time obviously, as shown in Fig. 5. The thickness of the film changed the rate of drug diffusion from the microspheres and the film matrix into the solution. When compared with the two kinds of blending films reported by Dong et al. (2006) and Wang et al. (2007), the 30 μm CS/EC microspheres blending films had the most advantaged release properties and released 25% of total drugs approximately in the first 24 h.

After the thickness has been increased, there were more EC microspheres, more drugs and more CS to form the film. The ratio of superficial area of the film to the volume of the film decreased obviously, so the drug release rate decreased. Moreover, the drug releasing from the core of the film became difficult because of the augment of the diffusion path from the film to the water. Finally, more microspheres in the film, which contained more drugs, also contributed to increase the time of the drug release.

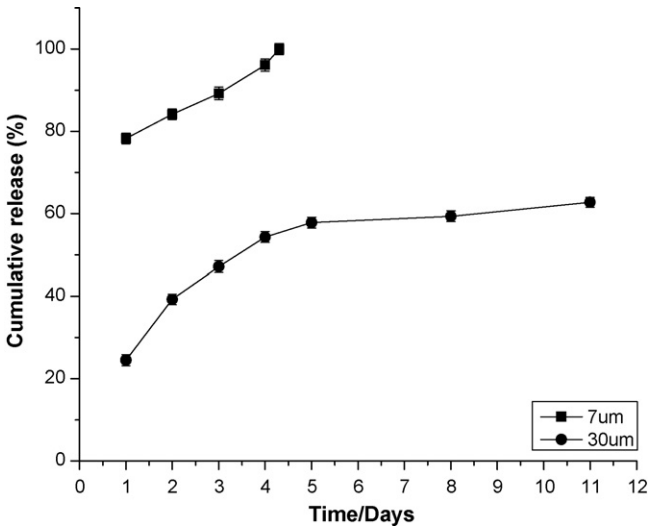

Fig. 5. Influence of thickness of the drug-loaded $F_{t0.3}$ films on the property of drug release in 100 ml sodium phosphate buffer at pH 7.6 and 37 °C.

3.3.3. Effect of ionic strength

With the decrease of the ionic strength of mediums, the drug release rate will decrease, as shown in Fig. 6. These results were in line with the outcomes reported by Dong et al. (2006) and Wang et al. (2007) and was caused by the osmotic pressure inside the film, which decreased with the increase of the salt concentration in the release medium and the weakened salt-bond between ciprofloxacin hydrochloride and film matrix by salt ions. On the other words, the Na^+ and Cl^- may aggregate around the NH^+ of CS and weak the interaction between NH^+ and ciprofloxacin hydrochloride, so the release rate of ciprofloxacin hydrochloride become quick. When the osmotic pressure inside the film was going down, the pressure difference between the outside and inside of the film increased, so the increased pressure difference which may act as a kind of "strength" to push or accelerate drug release.

3.3.4. Effect of thickness of sodium alginate coating

Fig. 7 shows that the thick coating of sodium alginate (5 μm) on the blending films can reduce the release rate of ciprofloxacin hydrochloride more obviously than that of the thin coating (1 μm) and elongate the total release time. Because the increased coat-

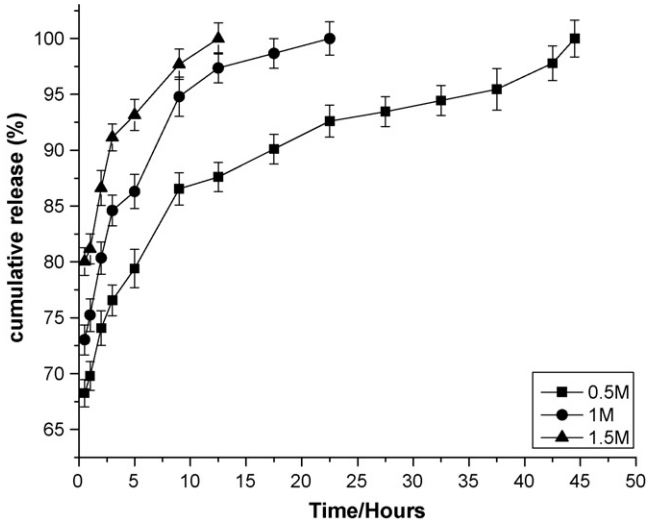

Fig. 6. Influence of ionic strength of the mediums on drug release properties of the $F_{t0.3}$ blending films in 100 ml sodium phosphate buffer at pH 7.6 and 37 °C.

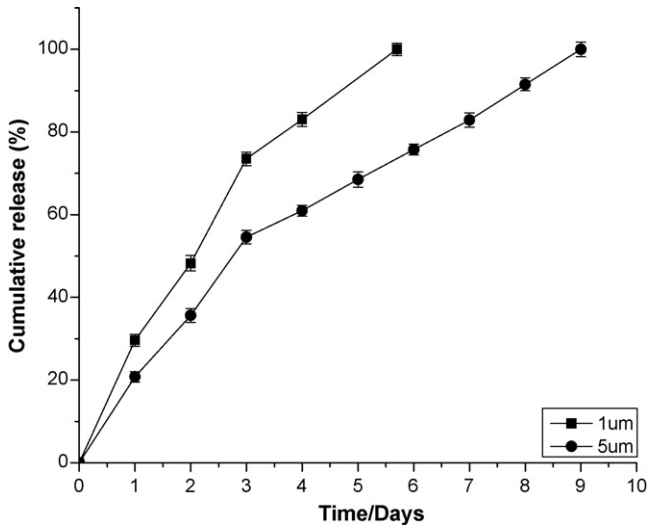

Fig. 7. Influence of thickness of sodium alginate coatings on ciprofloxacin hydrochloride release of $F_{t0.3}$ films in 100 ml sodium phosphate buffer at pH 7.6 and 37 °C.

ing thickness and the strong electrostatic interactions between the molecules of CS and sodium alginate made more barriers for the drug diffusion. Compared with the release curve of $F_{t0.3}$ in Fig. 4c, the alginate coating had significantly positive effect on the elongation of total drug release time.

The polyelectrolyte complex was formed when the blending film touched with alginate solution, especially on the surface of the film. The polyelectrolyte complex formation was firm which was hard to be washed out by water. So the alginate coating may help the blending films to modify their release rate and release time not only in short time but in a long time.

CS was soluble in acidic condition, which made the blending films dissolve in the acidic release mediums when pH < 7. After the blending films were coated with the alginate, the drug release rate decreased. So, the alginate coating or thick blending films could be used to diminish the burst release effect of these films.

3.4. Cell viability

The cytocompatibility of the drug-loaded blending films was evaluated *in vitro* by the living morphology of the MG63 cells cultured with the films using phase-contrast microscopy. Fig. 8a and b shows the cells cultured with the films for 4 and 11 days. At 4 days, cells proliferate normally and at 11 days, the population of MG63 cells increases abundantly. The cell viability in each group was evaluated by MTT test. The data were plotted in Fig. 8c. The cell number increased with the culture time for both groups. Statistical analysis indicated that there was no significant difference ($p > 0.05$) in the cell number between the blending films and the control in the osteogenic condition. Moreover, the MG63 cells grew dramatically at 11 days in both groups. So, it indicated that the drug-loaded blending films have good compatibility with cells.

Moreover, methanol, acetone and CH_2Cl_2 were used in this experiment to prepare the EC microspheres, so it was critical to test the cytocompatibility of the blending films made by organic solvent. From the MTT data, it was obvious that there were not any

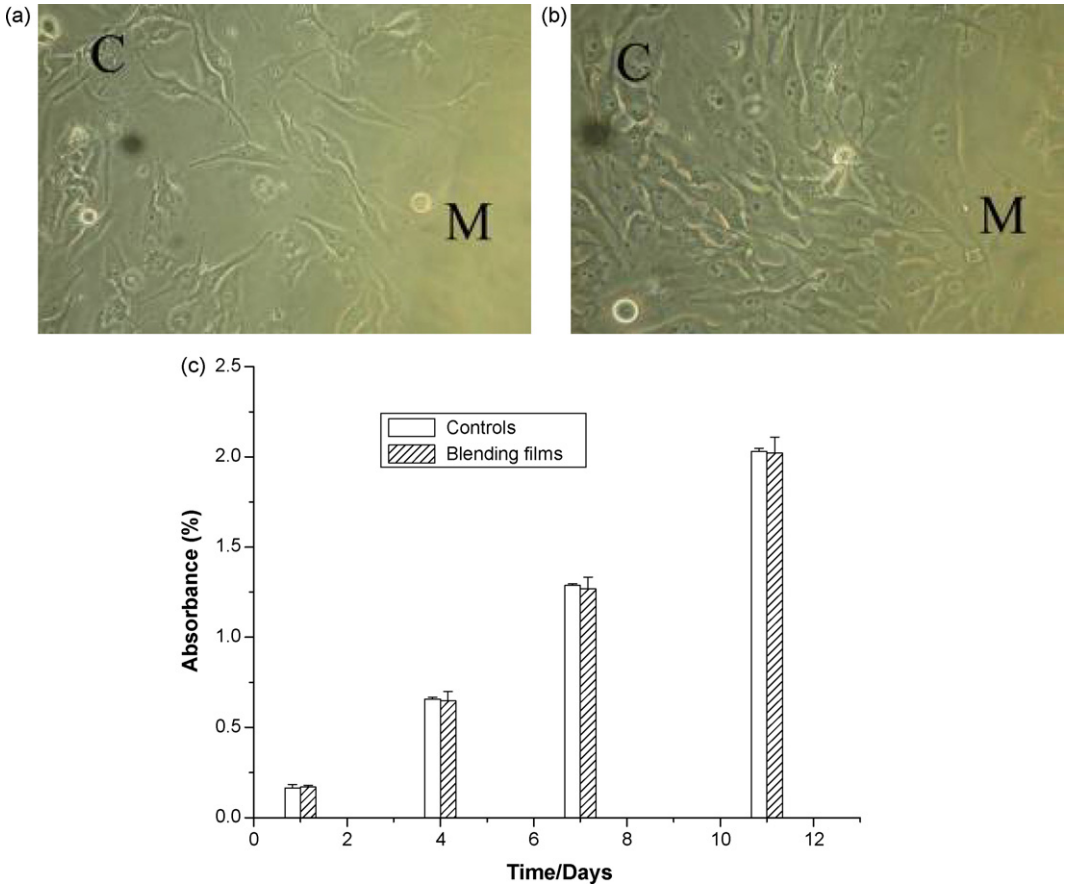

Fig. 8. Phase-contrast microscopy images of the MG63 cells (marked as C) cultured with the drug-loaded blending films (marked as M) in osteogenic medium for 4 days (a) and 11 days (b); and the proliferation/viability of MG63 cells cultured on samples surface ($F_{t0.3}$) and control (c). Error bars represent means ± SD for $n = 5$. No significant difference between samples and control ($p > 0.05$).

adverse effects left by organic solvent. The blending film showed excellent cytocompatibility. In addition, based on the IR analysis, there were not any peaks of methanol, acetone and CH_2Cl_2.

4. Conclusions

Ciprofloxacin hydrochloride-loaded films based on CS and EC microspheres were prepared by solvent remove/solvent evaporation and casting/solvent evaporation methods. The chemical and morphological properties showed that there were good compatibility between the film matrices and the drug due to hydrogen bonds and ionic interactions. The release time of ciprofloxacin hydrochloride increased after the EC microspheres were incorporated in the CS film. The release properties of CS/EC microspheres blending films were also sensitive to the film thickness and the alginate coating on them. In addition, the blending film exhibited excellent cytocompatibility. So, the drug release rate could be controlled by changing the influential factors of the drug-loaded blending films, which would be a successful drug carrier in pharmaceutical applications with diversified usage.

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