Chitosan-Grafted Multi-Walled Carbon Nanotubes for Sustained Releasing of Pazufloxacin Mesilate

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Abstract: Chitosan modified multiple-walled carbon nanotubes (MWCNT-CS) and chitosan (CS) semi-interpenetrating (semi-IPN) hydrogels were prepared according to different contents of MWCNT-CS in MWCNT-CS/CS. The so prepared semi-IPN hydrogels were used as drug carriers. Pazufloxacin mesilate (PZFX) was loaded to the semi-IPN hydrogels, and the effects of the contents of MWCNT-CS in MWCNT-CS/CS and the pH values of the buffers to the loading and releasing ability of semi-IPN hydrogels were further studied. The mechanism of PZFX releasing from the hydrogels was also discussed.

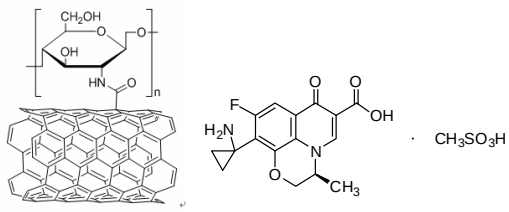
Keywords: chitosan; multi-walled carbon nanotubes; hydrogel; sustained releasing; pazufloxacin mesilate

1. Introduction

In recent years, carbon nanotubes (CNTs) have attracted a considerable attention as potential carriers for their sustained delivery of drugs [1, 2]. Functionalized carbon nanotubes (*f*-CNTs) loaded with different peptides, proteins and nucleic acids are even able to deliver them into cells [3]. As a consequence, *f*-CNTs are emerging as novel carriers for the delivery of therapeutic molecules [4]. Similarly, controlled drug delivery technology using biodegradable polymers as carriers is also one of the most rapidly advancing areas for such delivery systems offer numerous advantages in contrast to conventional dosage forms, including improved efficacy, reduced toxicity and improved patient compliance and convenience. Chitosan (CS) is known as such a biocompatible, biodegradable, and nontoxic natural polymer, which has already been extensively used in medical and pharmaceutical areas. By grafting the hydrophobic and hydrophilic segments to chitosan would give rise to the amphiphilic graft copolymers [5], CS modified CNTs were prepared accordingly [6-9].

Nowadays, hydrogels based on chitosan have been investigated for its special properties and thus potential utilization as drug delivery [10-12]. In contrast with the normal CS hydrogel, CS modified multiple-walled carbon nanotubes (MWCNT-CS) (Fig. 1) and chitosan (CS) semi-interpenetrating (semi-IPN) hydrogels have been found with higher mechanical strength and well preserved pH sensitivity [13].

The model drug selected, pazufloxacian mesilate (PZFX) (Fig. 1) is a novel injectable quinolone antibacterial agent, which has excellent therapeutic effects against a broad spectrum of bacterial infection, was primarily came into the drug market by Toyama Chemical Co., Tokyo, Japan in the year of 2002. The use of extended-release products offers potential advantages like sustained blood levels, attenuation of adverse effects and improved patient compliance. Hence, its formulation in controlled release form is very important. In this paper, MWCNT-CS/CS semi-IPN hydrogels were prepared according to different contents of MWCNT-CS in MWCNT-CS/CS. PZFX was loaded to the so prepared semi-IPN hydrogels by a soaking method. The effects of the contents of MWCNT-CS in MWCNT-CS/CS and the pH values of buffer solutions to the loading and releasing ability of the semi-IPN hydrogels were further studied. The mechanism of PZFX releasing from the drug-loaded hydrogels was also discussed.



(A) MWCNT-CS. (B) PZFX.

Figure 1. Chemical scheme drawing of: (A) MWCNT-CS; (B) PZFX.

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2. Experimentals

2.1. Reagents

Pristine MWCNTs (purity≥95%; diameter: 10−20 nm; length: 2−20 μ m) were purchased from Shenzhen Nanotech Port Co. Ltd. Biochemical reagent grade chitosan (deacetylation degree≥90%) was obtained from Shanghai Bo'ao Biological Technology Co., Ltd. MWCNT-CS were prepared and fully characterized in our lab according to a previously described method [8].

2.2. Preparation of MWCNT-CS/CS semi-IPN hydrogels

MWCNT-CS/CS semi-IPN hydrogels were prepared according to different contents of MWCNT-CS and CS in MWCNT-CS/CS as we have reported before [13]. When the contents of MWCNT-CS in hydrogels are 0, 2.5% or 10% (weight percent), the hydrogel are assigned a sample number C0, C1 or C10, respectively (Table 1).

Table 1. Loading ratios of different hydrogels

Number of Semi-IPN hydrogels samples	*The amount of MWCNT-CS in hydrogels/ %*	*The weight of dry semi-IPN hydrogels / g*	*Drug load ratio / %*
C0	0	0.024	126.7
C1	2.5	0.021	99.4
C10	10	0.025	87.4

2.3. Loading of PZFX to MWCNT-CS/CS semi-IPN hydrogels

The MWCNT-CS/CS semi-IPN hydrogels were dried to constant weight, which were dipped in a solution (containing 0.1 g/mL PZFX) for 48 hours. The semi-IPN hydrogels were then dried under vacuum to constant weight and dried drug-loaded MWCNT-CS/CS semi-IPN hydrogels were obtained. Drug load ratio (L) was obtained using the following formula (Table 1):

$$L = \frac{W_f - W_s}{W_s} \times 100\%$$

Where W_s is the weight of the dried MWCNT-CS/CS semi-IPN hydrogels; W_f is the weight of the dried MWCNT-CS/CS semi-IPN hydrogels after loading of PZFX.

2.4. Loading of PZFX to MWCNT-CS/CS semi-IPN hydrogels

The dried drug-loaded MWCNT-CS/CS semi-IPN hydrogels were dipped in 5 mL buffer solution with different pH values (1.2 or 7.4) and oscillated (100 r/min) at 37 °C. One milliliter testing samples was obtained every few hours and buffer solution of same volume was added to balance volume of the solution.

3. Results and disscussion

3.1. Loading ratios of different MWCNT-CS/CS semi-IPN hydrogels

As shown in Table 1, L decreases with the contents of MWCNT-CS increase in the MWCNT-CS/CS semi-IPN hydrogels, which is probably due to the hydrophilicity of CS and hydrophobicity of CNTs in MWCNT-CS. As a matter of fact, when 100% CS was used to prepare semi-IPN hydrogel, its hydrophilic network structure allowed more PZFX to enter in.

3.2. The effects of the contents of MWCNT-CS in drug-loaded MWCNT-CS/CS hydrogels

As shown in Fig. 2, in contrast to C0 and C1, C10 has better sustained-releasing ability when drug-loaded semi-IPN hydrogels were dipped in a buffer solution (pH= 7.4) at 37 °C, which is probably due to the CNT parts of MWCNT-CS in MWCNT-CS/CS semi-IPN hydrogels. The opened tubes of CNTs introduced by oxidation of CNTs [14] during the modification process can provide effective space to contain PZFX and their slower speed releasing ability prolongs the releasing time. And we have found previously [13] that the swelling rate of MWCNT-CS/CS semi-IPN hydrogels decreased with contents of MWCNT-CS increased in hydrogels, hence we can also ascribe the higher speed releasing ability to the higher swelling rate of MWCNT-CS/CS semi-IPN hydrogels.

3.3. The effects of the pH values of the buffer solution to drug-loaded MWCNT-CS/CS semi-IPN hydrogels

As shown in Fig. 3, when C0 and C10 were dipped in buffer solutions with different pH values (pH= 1.2 or 7.4), the effect of pH value to releasing ability of C0 was more prominent. As we have reported previously [13], pH value of buffer solution affected the deswelling and swelling behavior of semi-IPN hydrogels apparently. Herein, we ascribed the releasing difference of the semi-IPN hydrogels to their deswelling and swelling behavior in buffer solutions.

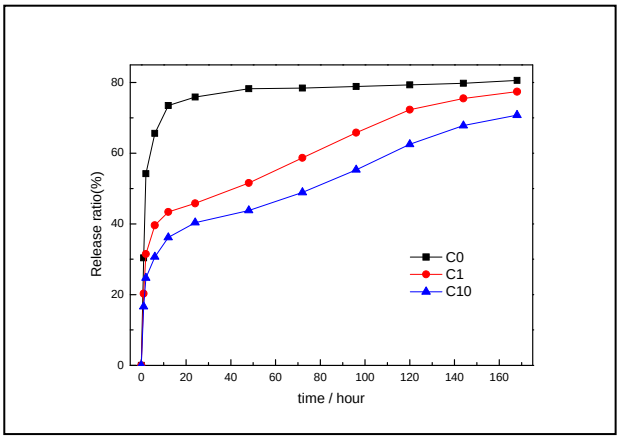

Figure 2. Eeffet of the amounts of MWCNT-CS in hydrogels on the releasing Ratio of PZFX from hydrogels (37℃、PH=7.4).

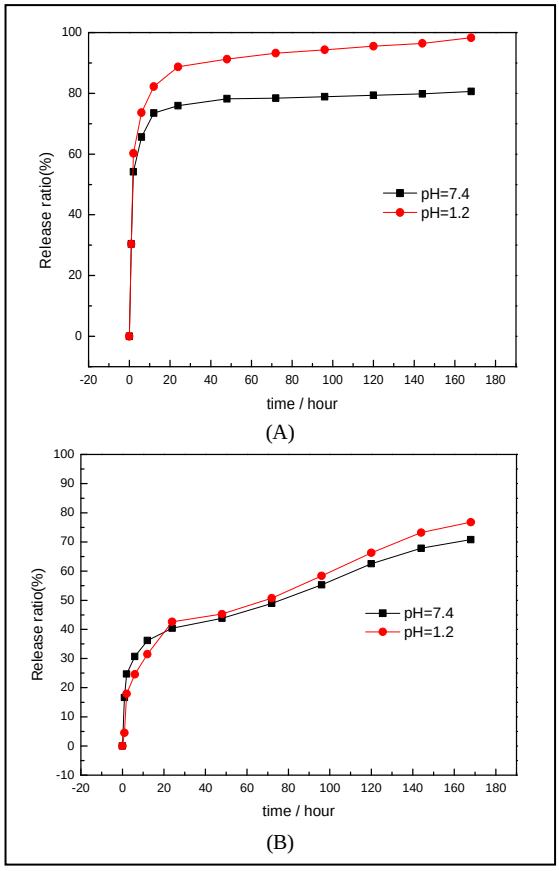

Figure 3. PZFX releasing curves at different pH values: (A) C0; (B) C10.

3.4. The mechanism of sustained-releasing

From Fig. 2 and Fig. 3, we could find a flashy high speed releasing of PZFX from drug-loaded MWCNT-CS/CS semi-IPN hydrogels in the initial several hours, and then slowed down by degrees, and finally reached a balance rate.

Accoding to the releasing rate change, when dried drug-loaded MWCNT-CS/CS semi-IPN hydrogels were dipped in buffer solutions, there might be three steps for their releasing adsorbates: Firstly, the surface of hydrogels was swelled and adsorbates on the surface was released instantaneously, and the adsorbates inside was diffused to outside (Fig. 4B); Secondly, the dried parts of the drug-loaded MWCNT-CS/CS semi-IPN hydrogels was totally immersed and disappeared, the adsorbates from inside of semi-IPN hydrogels was released slowly (Fig. 4C); finally, the semi-IPN hydrogels were totally swelled, releasing of the adsorbates was slowly but stable (Fig. 4D).

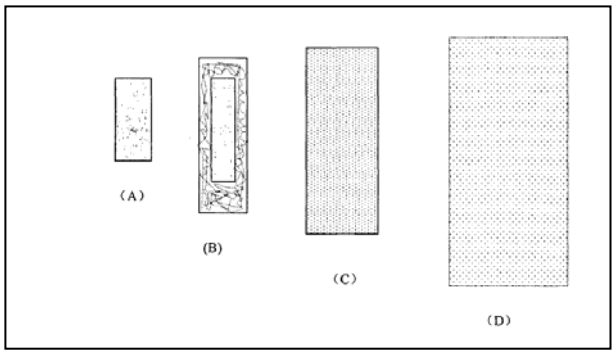

Figure 4. The mechanism of PZFX releasing from hydrogel: (A) Drug-loaded hydrogel; (B) Outermost surface was swelled along with subsequent releasing of PZFX, and some dried region of drug-loaded hydrogel began to be immersed; (C) Dried drug-loaded hydrogel was totally immersed; (D) Drug-loaded hydrogel was further relaxed and swelled.

4. Conclusions

Novel type of MWCNT-CS/CS semi-IPN hydrogels with controlled drug releasing capability was prepared and their loading and releasing ability were further studied. The semi-IPN hydrogels can be loaded with active agents (e.g.,drugs, etc.), which are sustained-released in their environment during use, and therefore can provide a healthy environment. The MWCNT-CS/CS semi-IPN hydrogels with more contents of MWCNT-CS have higher sustained-releasing ability in buffer solutions.

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