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# Sustained release of 5-fluorouracil by incorporation into sodium carboxymethylcellulose sub-micron fibers

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ABSTRACT

This work introduces a novel route to the sodium carboxymethylcellulose sub-micron fibers loaded with hydrophilic anticancer drug, 5-fluorouracil (5-Fu). The results show that 5-Fu is successfully incorporated into the biocompatible polymer, sodium carboxymethylcellulose (NaCMC)-based fibers with good stability, desired drug loading content and 100% entrapment efficiency. Furthermore, the drug release rate of the as-prepared drug-loaded fibers could be well controlled. The drug release behavior of the 5-Fu-loaded NaCMC fibers shows a diffusion mechanism, obeying Ritger–Peppas kinetics model. The drug release behavior of the as-prepared products demonstrates their promising application in drug delivery system.



## 1. Introduction

Many of the pharmacological properties of conventional drugs can be improved through the use of drug delivery systems (DDS), composed primarily of lipids and/or polymers. Therefore, various DDS are designed to alter the pharmacokinetics (PK) and biodistribution (BD) of their associated drugs, or to function as drug reservoirs (i.e., as sustained release systems), or both (Allen and Cullis, 2004). In general, the drug delivery platforms of choice have been spherical particles such as liposomes, polymeric micelles, polymeric solid particles, and lipid nanocarriers (Shin et al., 2010). These platforms, especially solid particles, yield polydisperse particles with sizes that usually span a wide range and with a tendency aggregation (Heslinga et al., 2009). In addition, these particulate carriers usually have rather low drug-loading capacity (Leo et al., 2006). Therefore, current efforts in developing drug delivery systems have focused on controlling the particle size, shape and drug loading capacity (Shin et al., 2010). Based on the drawbacks of the particulate carriers, the fibers, which are thought to be the new type of DDS for in vivo delivery of drugs, have attracted much attention (Xu et al., 2008).

Polymeric fibers, whose diameter ranges from nanometer to millimeter (Cronin et al., 2004), have been widely researched for various applications such as tissue engineering (Loh et al., 2010), hydrogen storage (Chambers et al., 1998), drug delivery carrier (Xu et al., 2009) due to their excellent characteristics, such as high surface area, softness, absorbency (Knill et al., 2004) and so on. Up to now, a number of methods have been developed for fabrication of nano/micro polymer fibers. These nanofiber fabrication techniques include self-assembly (Gelain et al., 2010), melt-spinning (Ahuja et al., 2003), wet-spinning (Gao et al., 2007) and electro-spinning techniques (Taepaiboon et al., 2007; Verreck et al., 2003). However, some problems still exist in fiber fabrication concerning the reported routes. Furthermore, most of the developed methods for fabrication of polymer fibers are usually time- and energy-consuming and sometimes the special apparatus and organic solvents are usually utilized in these processing methods. Therefore, it is still a great challenge for developing a versatile and simple route to polymer fibers.

In recent years, freeze-drying has been used to produce a range of aligned porous structures (Zhang and Cooper, 2007; Qian et al., 2009). In a typical process, an aqueous solution or dispersion is quickly frozen using a cryogenic liquid and the ice crystals are removed by sublimation through freeze drying (Qian et al., 2009). However, to the best of our knowledge, there is no report on the synthesis of drug-loaded polymer fibers for controlled drug release by this method.

NaCMC is non-toxic, biodegradable and commonly used in the controlled release systems (Podczeck et al., 2008). For example, Boateng et al. (2009) studied the paracetamol release characteristics from NaCMC wafers and films. It demonstrates that both formulations show sustained type drug release determined largely by matrix swelling and drug diffusion through the matrix. Conti et al. (2007) used NaCMC and hydroxypropylmethylcellulose (HPMC) as polymeric carriers to improve controlled release performances of matrix tablets containing a soluble drug. The results show the two

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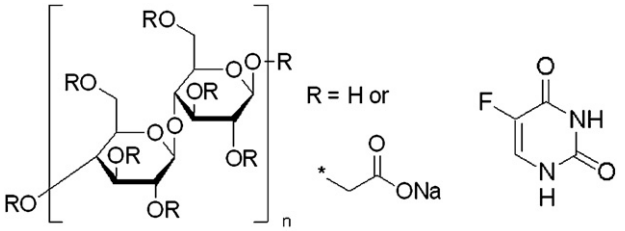


**Scheme 1.** The molecular structures of NaCMC and 5-Fu.

polymers mixture systems maintain a constant drug release rate coupling diffusion and erosion mechanism. In the present work, NaCMC is chosen as the drug carrier. 5-Fluorouracil, a hydrophilic anticancer drug, which is more effective when administrated at lower doses for a longer period of time (Anthony et al., 2006), is chosen as the model drug. The aim of the present work is to report a new method for preparing drug-loaded biocompatible polymer sub-micron fibers which shows promising application in drug delivery system. Freezing the aqueous solution with liquid nitrogen is the key for the formation of drug-loaded polymer fibers. The quick freezing avoids the individual phase separation of the drug and polymer, and therefore the drug and polymer separate out simultaneously to form the fibers.

## 2. Experimental

### 2.1. Materials

Sodium carboxymethylcellulose (NaCMC, MW = 250,000, DS = 0.9) was purchased from Acros, USA. 5-Fluorouracil (5-Fu) was bought from Aldrich. Double-distilled water was used in all the experiments. The molecular structures of NaCMC and 5-Fu are schematically shown in Scheme 1.

### 2.2. Preparation of 5-Fu and NaCMC Solution

Initially, NaCMC aqueous solution (2 wt.%, 1 wt.%, 0.1 wt.%) was prepared by dissolving the required amount of polymer in the stirred water maintained at a temperature of 60 °C. The mixture was then stirred for 2 h. The beaker containing the solution was further ultrasonicated for 5 min to remove all bubbles at room temperature. For the preparation of 5-Fu loaded NaCMC solution, certain amount of the drug was added into the NaCMC aqueous solution. The weight ratio of the 5-Fu to NaCMC ($W_{drug}$:$W_{polymer}$) is fixed to 1:2, 1:3, 1:6, respectively. Then, the mixture was stirred for 10 min. After this, the mixture becomes a transparent solution, which indicates that the 5-Fu dissolves in the NaCMC solution.

### 2.3. Preparation of drug-loaded NaCMC composite

The drug-loaded polymer composite was prepared by freeze-drying the solution of 5-Fu and NaCMC in a VirTis Advantage Freeze-Drier (VirTis 2K-ES from USA). Firstly, certain amount of the solution of 5-Fu and NaCMC was put in a glass beaker. Then, the glass beaker with the solution was frozen in liquid nitrogen. The glass beaker was kept in the liquid nitrogen for 5 min to make it completely frozen. Finally, the frozen sample was completely freeze-dried in a freeze drier for 24 h. The freeze-dried samples were recovered and kept in a clean sample container for further characterizations.

### 2.4. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was done using a Hitachi SU-70 FESEM scanning electron microscope operated at 3 kV. Samples were sputtered with Au prior to imaging. The size of the sputtered Au is about 5 nm.

### 2.5. Powder X-ray diffraction (XRD)

XRD measurements were done on a Rigaku Dmax-rc X-ray diffractometer with Ni filtered Cu $K_\alpha$ radiation. The angular range was from 10° to 80°.

### 2.6. Differential scanning calorimetry (DSC)

DSC measurements were performed using CDR-4P (Shanghai Precision and Scientific Instrument Co., Ltd., China). Weighed samples of 10 mg were placed in aluminum pans and the samples were scanned from 30 °C to 350 °C with a heating rate of 10 °C/min.

### 2.7. Drug loading determination

The drug loading content (DLC) was defined as follows:

$$\text{DLC}\ (\%) = \frac{\text{amount of 5-Fu}}{\text{amount of 5-Fu and NaCMC}} \times 100\%$$

According to above formula, the DLC are 33%, 25% and 14% for $W_{drug}$:$W_{polymer}$ = 1:2, 1:3 and 1:6, respectively. The entrapment efficiency of all the samples is 100%.

### 2.8. In vitro release studies

The dialysis bag has been widely used to evaluate the in vitro release of drugs. Small 5-Fu molecules can diffuse into the release medium through the dialysis membranes while large molecules (NaCMC) cannot. The released drug in the medium outside the dialysis bag makes it easy for analysis (Luo et al., 2006). The in vitro release of 5-Fu-loaded NaCMC was investigated in different release medium with a dialysis bag (MW = 3500, Solarbio) at 37 °C. A certain amount of freeze-dried samples in release medium (2 ml) was sealed in the dialysis bag, and incubated in release (198 ml) medium. The solution was continuously shaken in a shaker (100 rpm $min^{-1}$) during the drug release study at 37 ± 0.5 °C. At given intervals, 5 ml of the release solution was withdrawn from the container. Then, an equal amount of fresh release medium was added to replenish the sample to maintain the original volume. The release solution was measured by a UV spectrophotometer (WFZ UV-2102pcs, UNICO) at a wavelength of 266 nm which was a typical absorbance peak of 5-Fu. For comparison, the release of the pure 5-Fu in release medium was also investigated. The procedure was the same as described above. The cumulative amount of 5-Fu released from the freeze-dried NaCMC fibers was calculated using the following equation:

$$\text{Cumulative amount released}\,(\%) = \frac{M_t}{M_{\text{total}}}$$

where $M_t$ is the amount of 5-Fu released from the freeze-dried NaCMC fibers at time $t$ and $M_{total}$ is the total amount of 5-Fu loaded in the NaCMC fibers.

### 2.9. Drug release kinetics

The kinetics of 5-Fu release from the 5-Fu-loaded NaCMC products was determined by fitting the curves (% release against time)

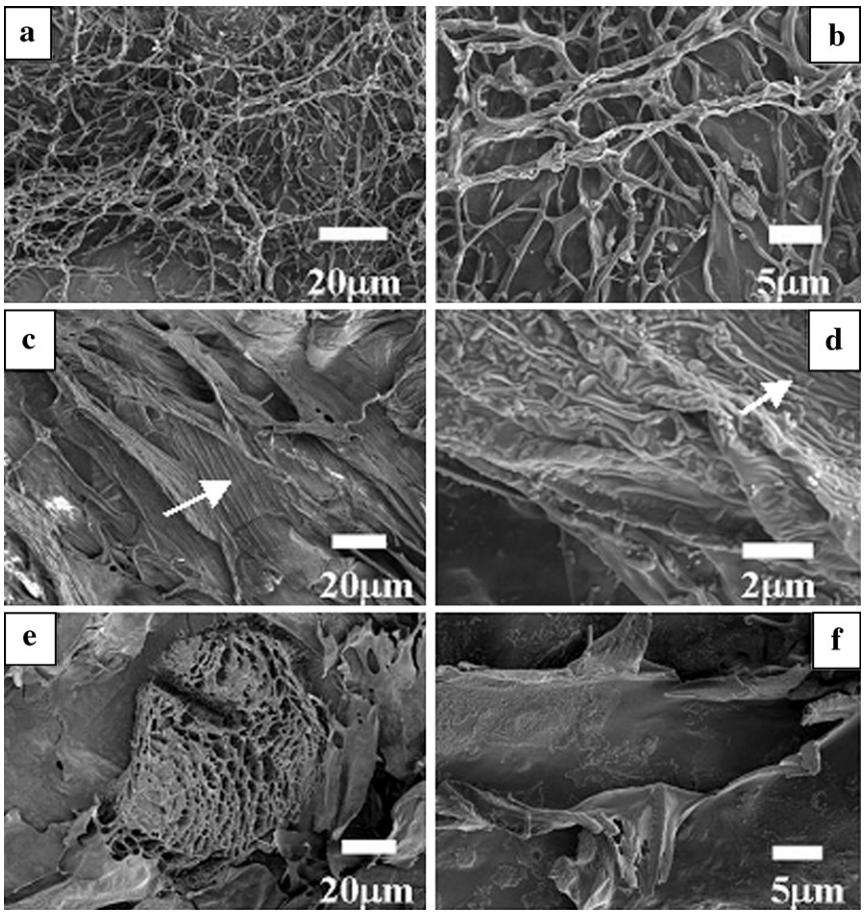


**Fig. 1.** SEM images of the 5-Fu-loaded NaCMC composites prepared with different NaCMC concentration at $W_{drug}$:$W_{polymer}$ = 1:3. (a and b) 0.1 wt.%, (c and d) 1 wt.%, (e and f) 2 wt.%.

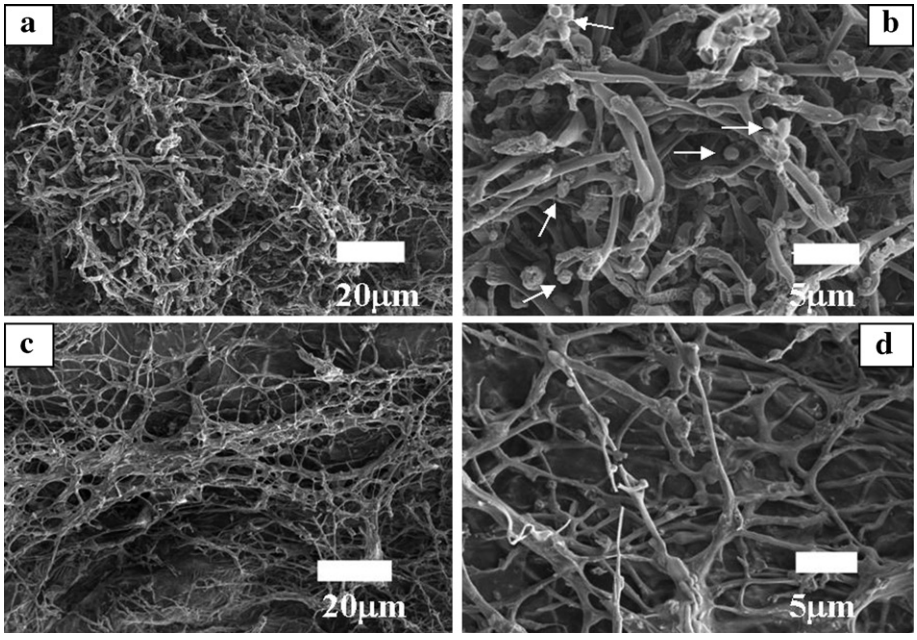


**Fig. 2.** SEM images of 5-Fu-loaded NaCMC composites prepared with 0.1 wt.% NaCMC solution containing different concentration of 5-Fu. The weight ratio of 5-Fu to NaCMC is fixed to 1:2 (a and b) and 1:6 (c and d).

to distinct models. Data were fitted using Origin 7.5 (Microcal Software, Inc., MA, USA) and the linearised form of each function was evaluated using *R* regression analysis.

## 3. Results and discussion

### 3.1. Scanning electron microscopy (SEM)

Fig. 1 shows the low and high magnification SEM images of the freeze-dried products prepared with different concentration of NaCMC with $W_{drug}$:$W_{polymer}$ = 1:3. At the low concentration of NaCMC (0.1 wt.%), it shows that the diameter of the fibers is 851 ± 328 nm, as shown in Fig. 1a. Fig. 1b is the high magnification SEM image for the fibers in Fig. 1a, which shows the fibers are well-defined. With the increase of NaCMC concentration to 1 wt.%, the drug-loaded NaCMC composites are in sheet shape (Fig. 1c and d). On the surface of the sheets it shows some fibers starts to form at this condition (see the arrow part in Fig. 1c and d). Further increasing the NaCMC concentration to 2%, part of the products is in porous state besides the formation of sheet product (Fig. 1e and f).

For the formation mechanism of the 5-Fu-loaded NaCMC composites, it can be explained based on the mathematical model of the unidirectional solidification of a suspension of hard-sphere colloids which is recently developed and demonstrated by an experimental test (Qian et al., 2009; Peppin et al., 2008). For small particles, Brownian diffusion dominates and the constitutional supercooling occurs at the interface under certain conditions, potentially leading to instability in the shape of the interface. When the solidification rate is slow, the interface remains planar and rejects all of the particles, leaving behind a layer of pure ice. The NaCMC polymer molecules in this study could be regarded as small particles. Therefore, drug-loaded sheets or wafers form due to the fast freezing rate with liquid nitrogen at higher concentration of NaCMC (2%, 1%). When a dilute NaCMC solution (0.1%) was used, the polymer molecules are excluded to form fibers due to the small number of polymer molecules available. The quick freezing avoids the individual phase separation of the drug and polymer, and therefore the drug and polymer separate out simultaneously to form the composites.

To further study the influence of 5-Fu concentration on the morphology of the final products, we perform the experiments on drug-loaded composites with different 5-Fu concentration while at the same NaCMC concentration (0.1 wt.%), shown in Fig. 2. It can be seen that independent of drug concentration the fibers form in all the studied samples. There are no obvious differences in the diameter of the fibers prepared with different amount of 5-Fu. The diameter of the fibers is 860 ± 351 nm. However, there appears more spherical particles (see the arrows in Fig. 2b) in the fibers with the increase of drug concentration, varying from $W_{drug}$:$W_{polymer}$ = 1:6 (Fig. 2c and d) to $W_{drug}$:$W_{polymer}$ = 1:2 (Fig. 2a and b). These spherical particles are possibly to be drug particles according to the reference Gao et al. (2007). The surface of the fibers are smooth with the smaller $W_{drug}$:$W_{polymer}$ (1:6), as shown in Fig. 2c and d, indicating that the drug is finely incorporated onto the fibers. While for the higher $W_{drug}$:$W_{polymer}$ (1:2), there are spherical particles in the fibers, as shown in Fig. 2a and b, suggesting that there have more 5-Fu molecules adsorbed or trapped near the fibers surface. This result is in agreement with the report for hydrophilic drug-loaded fibers prepared with electrospin technique (Gao et al., 2007).

### 3.2. Powder X-ray diffraction measurements

X-ray diffraction (XRD) patterns of the pure 5-Fu, pure NaCMC and the 5-Fu-loaded NaCMC fibers are tested to study the physical state of these systems. As shown in Fig. 3a, 5-Fu shows characteristic intense peaks at 2$\theta$ of 16.2°, 19.0°, 20.5° and 28.6°, indicating the typical crystalline structure. For the pure NaCMC powder, there only exists a broad XRD peak around 2$\theta$ = 20.68° (Fig. 3b), indicating an amorphous structure. The 5-Fu-loaded NaCMC fibers show the broad peak at 20.68° of NaCMC and the peaks at 16.2°, 28.6° and 32.1° of 5-Fu (Fig. 3c), which suggests the good compatibility between 5-Fu and NaCMC molecules and the frozen process does not change the physical state in the formation of 5-Fu-loaded NaCMC fibers.

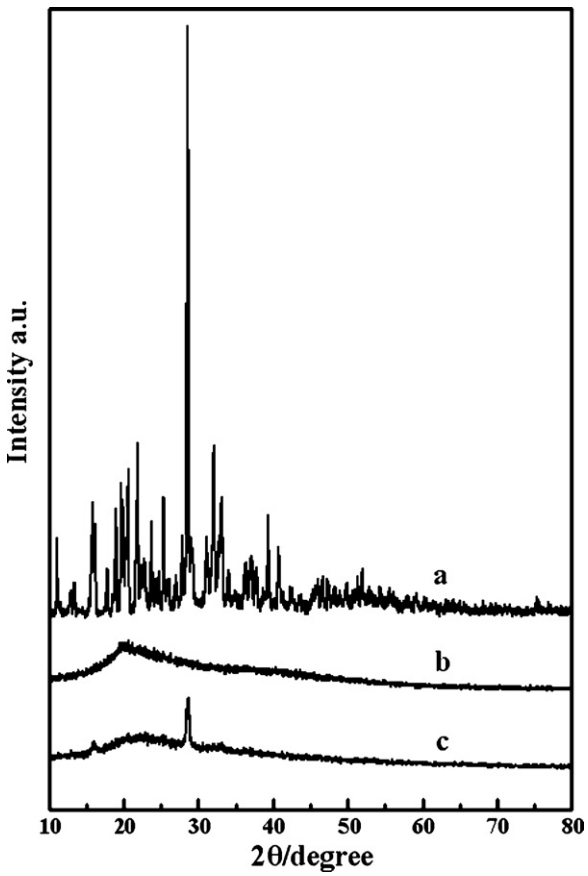


**Fig. 3.** XRD pattern of pure 5-Fu (a), pure NaCMC (b), and the 5-Fu-loaded NaCMC fibers prepared with 0.1 wt.% NaCMC solution ($W_{drug}$:$W_{polymer}$ = 1:3) (c).

### 3.3. Differential scanning calorimetry measurements

DSC is performed for pure 5-Fu, pure NaCMC as well as 5-Fu-loaded NaCMC fibers. The concentration of NaCMC and the $W_{drug}$:$W_{polymer}$ of drug-loaded polymer fibers are 0.1 wt.% and 1:3, respectively. As shown in Fig. 4, the pure 5-Fu shows a endothermic peak with onset melt temperature about 287 °C, which is in good agreement with the report of 285 °C (Bilensoy et al., 2007). The pure NaCMC shows a exothermic peak with the temperature of 293 °C assigned to its decomposition. However, two peaks are observed in the drug-loaded polymer composite with the temperature of 283.6 °C and 307 °C, which indicates that the melting temperature of 5-Fu and the decomposition temperature NaCMC are shifted. The shift of melting temperature of 5-Fu indicates that the regenerated 5-Fu in the fibers is not crystallized as well as the raw one.

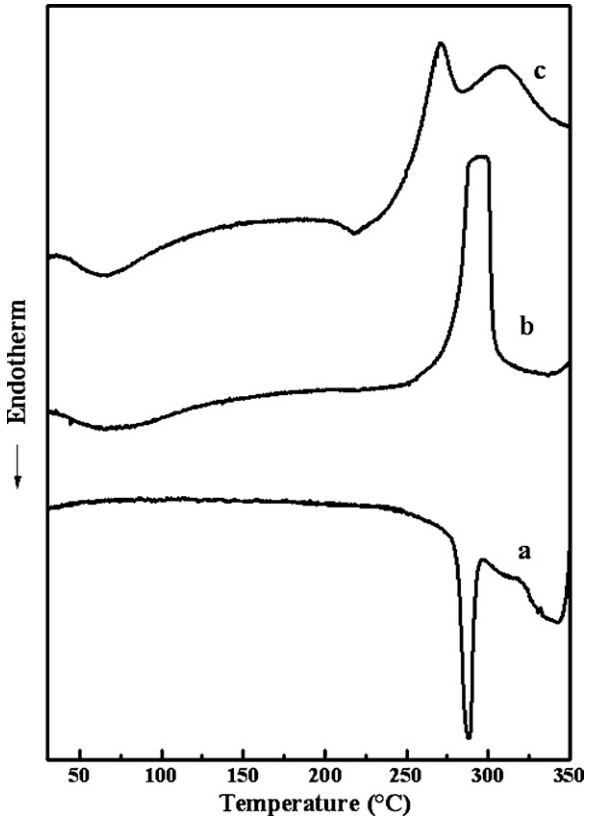


**Fig. 4.** DSC curves of pure 5-Fu (a), pure NaCMC (b), and 5-Fu-loaded NaCMC fibers prepared with 0.1 wt.% NaCMC solution ($W_{drug}$:$W_{polymer}$ = 1:3) (c).

### 3.4. In vitro release studies

#### 3.4.1. Effect of polymer concentration on drug release

The drug release was monitored with UV absorbance of the release medium (PBS, pH = 7.4) at 37 °C. Firstly, a series of standard drug solutions are prepared. The standard solution is the one in which the 5-Fu concentration is accurately known. The absorbances of the standard 5-Fu solutions are measured and used to prepare a calibration curve, which shows how the absorbance varies with the drug concentration. For this experiment, the calibration curve of 5-Fu in phosphate-buffered saline (PBS) yields a straight line (Beer's Law, results are not shown). The slope and intercept of the line provide a relationship between absorbance and concentration:

$$A = \text{slope}\, c + \text{intercept}$$

The absorbance of the unknown drug solution, $A_u$, is then obtained with the slope and intercept from the calibration curve to calculate the concentration of the unknown solution, $c_u$.

$$c_u = \frac{A_u - \text{intercept}}{\text{slope}}$$

The cumulative release profiles of 5-Fu from drug-loaded composites containing different concentration of NaCMC and the pure 5-Fu in a phosphate buffered solution (PBS pH = 7.4) are shown in Fig. 5. The amount of 5-Fu is the same for all samples during the release experiments. As shown in Fig. 5, the pure 5-Fu is rapidly dissolved and released and the release amount reached 93% within 120 min. However, for the release of 5-Fu-loaded NaCMC composites, approximately 67% and 65% of 5-Fu is released within the first 120 min in 2 wt.% and 1 wt.% of NaCMC products, respectively. The cumulative release percent of drug-loaded fibers prepared with 0.1 wt.% NaCMC is less than that prepared with 2 wt.% and 1 wt.%

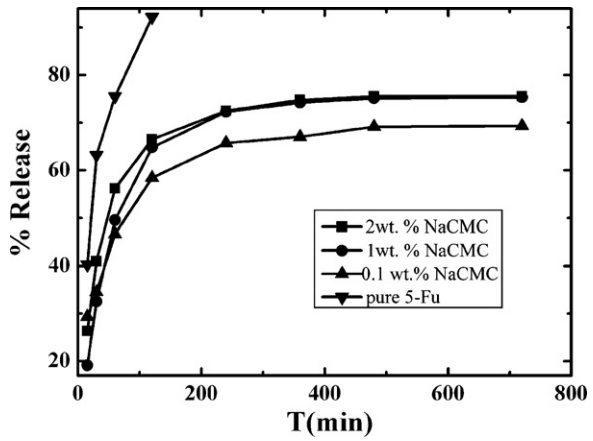


**Fig. 5.** Percent cumulative drug release of drug-loaded polymer composites with different concentration of NaCMC with $W_{drug}$:$W_{polymer}$ = 1:3 (PBS with pH = 7.4).

NaCMC. It shows only about 58% release during the same period of time. It is clear that the release of 5-Fu-loaded NaCMC composites is much slower than that of pure 5-Fu. It has been reported that the rate of drug release is affected by the amount and type of polymer (Williams et al., 2002). The release profile for the drug-loaded composites can be described as follows. At the beginning, there is a faster release. The faster release of 5-Fu is associated with those 5-Fu molecules adsorbed or trapped near the surface of or close to the products surface, which diffuse out easily in the initial incubation time. The release of these molecules creates a concentration gradient, which favors the transportation of drug molecules toward this release boundary. The drug molecules from the other side have to travel a longer distance, and therefore the release rate decreases with time. As the increase of the time, the inner drugs diffused to the buffer solutions through the carrier gradually and it reached release equilibrium in the end. Moreover, composites prepared with 1–2 wt.% NaCMC release the drug relatively faster than that prepared with 0.1 wt.% NaCMC solution. This can be understood as follows. As the NaCMC content in the polymer products increases, swelling of the products increases due to the hydrophilic nature of NaCMC (Rokhade et al., 2006). Therefore, it is clear that the release of 5-Fu-loaded NaCMC fibers is much slower than that of 5-Fu-loaded NaCMC sheets or wafers. After 720 min, the cumulative releases of 5-Fu-loaded NaCMC fibers reaches 70%. The result clearly reveals that these fibers could be a suitable polymeric carrier for drug release in vitro.

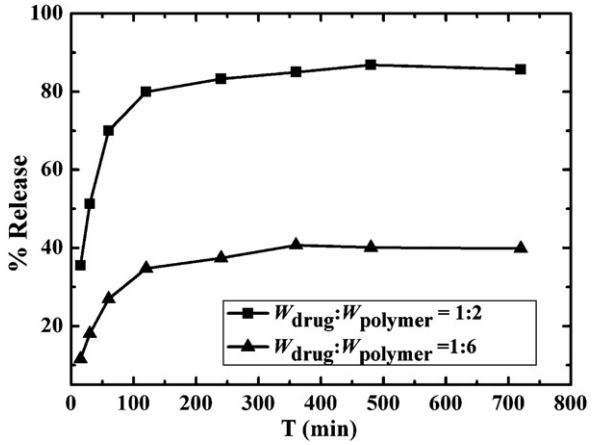


**Fig. 6.** Percent cumulative drug release from 5-Fu-loaded NaCMC (0.1 wt.%) fibers containing different concentration of 5-Fu in PBS with pH = 7.4.

### 3.4.2. Effect of drug loading on drug release

The percentage cumulative release profiles of 5-Fu from drug-loaded NaCMC products containing different concentration of drug ($W_{drug}$:$W_{polymer}$ = 1:2 and $W_{drug}$:$W_{polymer}$ = 1:6) are shown in Fig. 6. It is clearly seen that the release of 5-Fu is faster for the higher drug concentration in the freeze-dried composites ($W_{drug}$:$W_{polymer}$ = 1:2) although the two plots have the similar shape. For example, the release amount of 5-Fu within 120 min reaches about 79% and 34% for $W_{drug}$:$W_{polymer}$ = 1:2 and $W_{drug}$:$W_{polymer}$ = 1:6, respectively. Comparing Fig. 6 and the release behavior of 5-Fu-loaded fibers with $W_{drug}$:$W_{polymer}$ = 1:3 in Fig. 5, it can be concluded that the decrease of drug loading causes a more slowly release of the fibers. As shown in Figs. 5 and 6, the burst effect of the sample of $W_{drug}$:$W_{polymer}$ = 1:6 is smaller than that of the samples of $W_{drug}$:$W_{polymer}$ = 1:2 and $W_{drug}$:$W_{polymer}$ = 1:3. This suggests that drug release behavior is more sensitive to high drug loading in these systems. It is known that the high drug loading fibers have a high concentration gradient during the process of drug release, and have more 5-Fu molecules adsorbed or trapped near the surface of or close to the fibers surface, which could shorten the diffusion distance. Thus, it leads to the faster release of fibers with high drug loading.

### 3.4.3. Effect of medium pH on drug release

In order to better understand the release behaviors of the prepared drug-loaded fibers, the in vitro release pattern of 5-Fu-loaded NaCMC fibers in different release medium are studied. In drug release studies, HCl aqueous solution (pH = 1.2) is the typical medium to mimic gastric fluid while phosphate buffered solution (PBS, pH = 6.8) is the typical medium to mimic intestinal fluid. And therefore the release mediums with HCl aqueous solution (pH = 1.2) and PBS (pH = 6.8) are used for the present study. The percent cumulative drug release from 5-Fu-loaded NaCMC (0.1 wt.%) fibers ($W_{drug}$:$W_{polymer}$ = 1:3) in different release medium with pH = 6.8 and pH = 1.2 are shown in Fig. 7. It can be seen that the drug release pattern is not affected much by the pH (and composition) of the release medium. The cumulative release percent of 5-Fu from the drug-loaded sub-micron fibers is about 60% after 720 min both in PBS (pH = 6.8) and in HCl aqueous solution (pH = 1.2). However, comparing the plots in Figs. 7 and 5 with the same NaCMC concentration (0.1 wt.%) and the same drug to polymer weight ratio ($W_{drug}$:$W_{polymer}$ = 1:3), it is found that the release rate is faster in PBS (pH = 7.4) solution than that in PBS (pH = 6.8) and in HCl aqueous solutions (pH = 1.2). This is mainly caused by the following reasons. Firstly, 5-Fu is an acidic drug and the pH of medium has much effect on the solubility of the drug. The solubility of the 5-Fu is smaller in the acidic medium than that in the alkali medium. Secondly, most of the carboxyl groups of NaCMC exist in the form of carboxylic acid in the low pH solution. Thus there are more hydrogen bonds formed between the hydroxyl group of 5-Fu molecules and carboxylic acid group of NaCMC molecules. As a result, the release rate of 5-Fu from the fibers in the acidic medium is smaller than that in the alkaline medium.

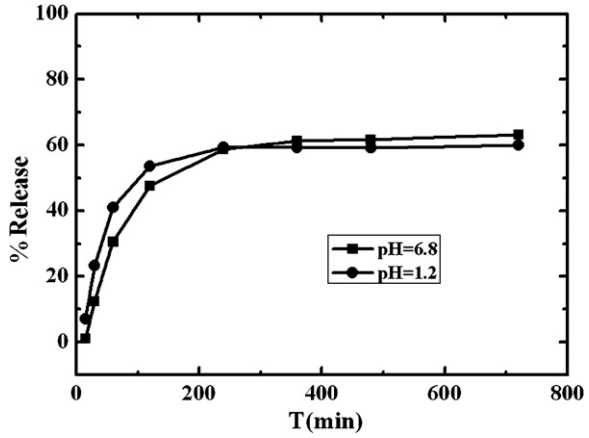


**Fig. 7.** Percent cumulative drug release from 5-Fu-loaded NaCMC (0.1 wt.%) fibers ($W_{drug}$:$W_{polymer}$ = 1:3) in PBS (pH = 6.8) and HCl aqueous solution (pH 1.2) medium.

### 3.5. Drug release kinetics

Representative regression coefficient ($R$) obtained by fitting experimental release data to zero order, first order, Higuchi release model, Ritger–Peppas (Ritger and Peppas, 1987) are shown in Table 1. It is observed that $R$ value is the largest when fitted to Peppas equation compared to other equations of 5-Fu-loaded NaCMC composites, which indicates a Peppas release from the optimized 5-Fu-loaded NaCMC composites. Similar studies have been reported in literatures (Boateng et al., 2009). It is known that drug release from swellable matrices is usually complex. Although some processes may be distinctly classified as either diffusion or erosion controlled, drug release is mostly governed by both mechanisms. Analysis of the experimental data using Peppas equation and interpretation of the release exponent ($n$), provides a better understanding of the mechanisms controlling release. The value of $n$ = 0.5 indicates Fickian Diffusion, while $0.5 < n < 1$ indicates Anomalous Transport (Singh et al., 2006). As shown in Table 1, the release exponents were 0.285, 0.378, 0.265, respectively. These values of release exponents show an Fick transport for the 5-Fu-loaded NaCMC products, suggesting that the release of 5-Fu through the freeze-dried

**Table 1**
The regression equation of 5-Fu-loaded NaCMC composites ($W_{drug}$:$W_{polymer}$ = 1:3) release in vitro.

| | Model | Equation | $R$ |
|---|---|---|---|
| 2 wt.% NaCMC | Zero-order kinetics | $Q = 42.991t + 0.086$ | 0.811 |
| | First-order kinetics | $\ln(100 - Q) = 4.024 - 0.00212t$ | 0.875 |
| | Higuchi | $Q = 29.197 + 2.469t^{1/2}$ | 0.899 |
| | Ritger–Peppas | $\ln Q = 2.695 + 0.285 \ln t$ | 0.940 |
| 1 wt.% NaCMC | Zero-order kinetics | $Q = 36.238t + 0.103$ | 0.826 |
| | First-order kinetics | $\ln(100 - Q) = 4.138 - 0.00237t$ | 0.839 |
| | Higuchi | $Q = 19.859 + 2.947t^{1/2}$ | 0.911 |
| | Ritger–Peppas | $\ln Q = 2.158 + 0.378 \ln t$ | 0.946 |
| 0.1 wt.% NaCMC | Zero-order kinetics | $Q = 36.956t + 0.0517$ | 0.805 |
| | First-order kinetics | $\ln(100 - Q) = 4.129 - 0.00103t$ | 0.841 |
| | Higuchi | $Q = 25.362 + 1.775t^{1/2}$ | 0.908 |
| | Ritger–Peppas | $\ln Q = 2.561 + 0.265 \ln t$ | 0.964 |
| Pure 5-Fu | Zero-order kinetics | $Q = 42.463t + 0.459$ | 0.942 |
| | First-order kinetics | $\ln(100 - Q) = 4.376 - 0.0216t$ | 0.995 |
| | Higuchi equation | $Q = 17.875 + 7.191t^{1/2}$ | 0.975 |

$Q$ is the fraction of drug release, $t$ is the time, $R$ is the regression coefficient.

NaCMC products are largely based on diffusion. In addition, NaCMC concentration does not alter the mechanism of 5-Fu release from drug-loaded NaCMC products. The *R* value is the highest when fitted to First-order kinetics equation compared to other equations for pure 5-Fu, which indicates a first order release kinetics from the pure 5-Fu.

## 4. Conclusions

A simple and generic method is demonstrated to prepare drug-loaded polymeric submicron fibers by freeze-drying dilute polymer solution with the desired content of drug. In this study, a hydrophilic anticancer drug, 5-Fu, is successfully incorporated into the NaCMC fibers with good stability, desired drug loading content and 100% entrapment efficiency. Polymer concentration is an important factor effecting the formation of the sub-micron drug-loaded fibers. However, the formation of the fibers is independent of drug concentration. The drug release rate of the fibers could be controlled by the drug loading content, polymer concentration and the release medium. The drug release behavior of the 5-Fu-loaded fibers shows a diffusion mechanism, obeying Ritger–Peppas kinetics model. The present method can be easily scaled up for large quantity production of drug-loaded polymer fibers and it has the potential to extend to the fabrication of other drug-loaded polymer composites for their applications in drug delivery systems.

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