Materials Research Express

PAPER

Loading and sustained release of sodium alginate membranes on pyridirubicin chloride

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Keywords: sustained drug release, alginate, disorption kinetics, ion exchange

Supplementary material for this article is available online

Abstract

To develop diversified drug carriers for local treatment of cancer, three types of alginate membranes were fabricated by spin-coating, freeze drying and electrospinning. The uniaxial tensile test is shown that spin-coated membranes possess the maximum tensile strength. All the three types of membranes present excellent adsorption performance toward pyridirubicin chloride (THP) and the electrospinning membranes exhibit the maximum adsorption mass of 144.13 mg g⁻¹. The pseudo-first order, pseudo-second order, and intra-particle diffusion equation were used to evaluate the kinetic data and the drug adsorption process followed the pseudo-first-order model well. The drug releasing mechanism was studied by using different release medium, and it shows that the release process was undertaken by ions exchange reaction. The result shows that the three types of membranes are promising materials for the local treatment of cancer such as local cancers of the pancreas and trachea.

1. Introduction

In 2015, over 17.5 million cancer cases were reported worldwide with over 8.7 million deaths, making cancer the second leading cause of death, after cardiovascular diseases [1]. Chemotherapy is a major component of cancer therapy; however, the drugs used in chemotherapy can influence the cells in the normal tissues and lead to many side effects [2]. For some cancers, such as local cancers of the pancreas, surgery is usually impossible and the patient is completely dependent on radiotherapy and/or chemotherapy-based treatment options [3]. Thus, local treatment may provide more effective treatments for such inaccessible cancers [4].

The use of drug-eluting polymer implants can increase and control the drug dose at the tumor site. Compared with traditional systemic administration and local chemotherapy injection/infusion, it can provide many advantages such as minimal side effects and long-term efficacy. Also, this technology is available in a variety of forms such as drug-eluting films, [5] gels,[6–9] microspheres, [10, 11] and particles, [12–14] and features predictable and prolonged drug release kinetics. However, a majority of the sample preparation and the drug loading processes is carried out simultaneously, which is not suitable for Pirarubicin hydrochloride for injection(THP) due to THP cannot be placed at room temperature for more than 6 h according to the drug instruction. When choosing THP as a chemotherapy drug, the only strategy is using microspheres to deliver it and embolize tumor vessels for local cancer chemotherapy, which cannot meet the needs of clinical applications. The diameter of the microspheres is generally 1–500 μm. When the microspheres are injected into vessels, it will flow with the blood. But the microspheres cannot pass through the capillaries, causing the blood vessels to be...
embolized, and the blood supply of the nearby tissues was cut off. With the accumulation of microspheres at capillaries near the tumor, THP in the microspheres was released out to kill tumor cells. While not all of tumors are well vascularized, leading to that microspheres is not applicable in all cases. Develop new strategy of drug delivery can broaden the clinical applications of THP and provide more choice for patients.

Alginate is a natural polymer purified from brown seaweed, which possesses good biocompatibility, relatively low cost, and low toxicity; therefore, it has been wildly used in drug delivery, wound healing, and tissue engineering [15–17]. Alginate is a random block copolymer mainly composed of β-D-mannuronic acid (M unit) and α-L-guluronic acid (G unit) connected by 1, 4-glycosidic bonds. The rich carboxyl groups of alginate can capture drugs with positive charges, which makes it a promising material for controlling drug release [18].

In this work, different methods have been applied to form alginate membranes, including spin-coating, freeze-drying, and electrospinning, which provided membranes with different structures. The membranes with different structures showed different adsorption performances [19–22]. Pirarubicin hydrochloride for injection (THP) was used as the model drug to study the adsorption kinetics and release kinetics of the three types of membranes, and the loading and release mechanism were discussed accordingly, providing theoretical support for further applications.

2. Materials and methods

2.1. Chemicals and materials

Sodium alginate (SA) was provided by Kangtong Marine Fiber Corporation, which had a weight-average molecular weight (Mw) of 323 kDa and an M/G ratio of 1.25, as determined byGPC and solid-state 13C NMR spectroscopy, respectively [23]. Poly(ethylene oxide) (PEO, Mw = 5000 kDa) and calcium chloride (CaCl2) were purchased from Aladdin, Tianjin, China. TritonX-100 is a product of Solarbio Life Science (China). Normal saline was provided by Kelun Pharmaceutical, Henan, China. Sodium chloride (NaCl) and magnesium chloride (MgCl2) were purchased from Cool Chemistry, Beijing, China. Pirarubicin hydrochloride for injection is a product of Wanle Pharmaceutical, Shenzhen, China. All materials were used as received without further purification.

2.2. Preparation of the alginate membrane

2.2.1. Spin-coating

The spin-coating of alginate membranes was performed using a MODEL WS-650MZ-23NPPB spin-coater (Mycro technology) using a 4% solution of SA in deionized water (Milli-Q Direct 16). PTFE sheets (R = 8 cm) with a thickness of 2.7 mm as the substrate. The SA solution was supplied to the substrate at a constant temperature of 25 °C. The experiment included the following steps: [24] rotating the substrate at a speed of 150 RPM; application of 10 ml SA solution on the rotating substrate; exposure for 10 min; accelerating the speed of the rotating substrate to 250 RPM; holding the sample in steady state rotation for 10 min. Finally, the substrate was removed to the fume hood for further drying.

2.2.2. Freeze-drying

SA was put into deionized water and stirred by a mechanical agitator until it was completely dissolved. The weight ratio was 4%. The solution was set for 10 h to remove the bubbles. Then, the solution was put in a 6-well cell culture plate and frozen in a Thermo refrigerator (Thermo Form 900 series, USA). To avoid uneven surface of the samples caused by rapid cooling, the plate was put at 4 °C for 4 h and at −20 °C for 6 h; the plate was then transferred to −80 °C overnight. Subsequently, it was dried in a vacuum freeze-drying machine (Labconco Missouri 64132, USA) for 2 days.

2.2.3. Electrospinning

Electrospinning is a popular technique to fabricate fibrous membranes due to the high porosity and large specific surface areas of the resultant products [25, 24, 26]. The process parameters have been investigated by many researchers [27–31]. The aqueous solution used for electrospinning was prepared by dissolving SA powder and PEO powder in deionized water. The alginate and PEO solutions were then mixed. The total polymer concentration was fixed at 4 wt. % and the mass ratio of SA/PEO was 90/10 [22]. 1 wt.% Triton X-100 was added to the mixtures to reduce the surface tension of the solution. The resultant mixtures were stirred for 6 h to attain a homogenous solution. Then, the solution was set for another 6 h to remove the air bubbles before electrospinning. The resulting solution was ultrasonicated for 10 min before electrospinning. The mixed solution was loaded in a 10 ml syringe with a stainless-steel 20 gauge needle and connected to a syringe pump (NE-1000, New Era Pump Systems, Inc.) working at a constant flow rate of 1 ml/h. The distance from the end of the needle to the collector was kept at 18 cm. The collector was an iron drum with a diameter of 15 cm. The needle was clamped to the positive electrode of a high-voltage power supply (EH40R2.5, Glassman High V Power Supplies, USA) at a voltage of 10 kV and a frequency of 50 Hz. The collector was moved upward by a stepping motor to ensure that the coating process was uniform.

The resulting membranes were dried in a vacuum freeze-drying machine (Thermo Form 900 series, USA) at a temperature of −40 °C for 4 h and at −80 °C overnight. Subsequently, they were transferred to a drying cabinet at 4 °C for 2 days. The membranes were then transferred to an infrared dryer at 60 °C for 4 h to remove the residual moisture.
Voltage, Inc.), generating 20 kV to obtain a stable jet. Electrospinning was conducted at ambient temperature (25 °C–30 °C) and relative humidity of 35%–40%.

2.3. Crosslinking of alginate membranes
Alginate is a linear block copolymer containing 1, 4-linked β-D mannuronic acid (M) and α-L-guluronic acid (G) residues with the structural characteristics of rich carboxyl groups. This block copolymer forms crosslinks via ionic interactions between the G residues on the chains and chelating ions such as Ca\(^{2+}\), which is termed as the ‘egg-box’ model of crosslinking [32]. The three types of membranes were soaked in ethanol for 2 min for pre-crosslinking and then immersed in 2 wt% CaCl\(_2\) solution for 30 s. After that, they were washed with deionized water twice, which removed PEO and Triton X-100 from the alginate nanofiber. Finally, the membranes were placed in a dryer at 50 °C for 3 h.

2.4. Characterization of the alginate membranes
Field emission scanning electron microscopy (SEM) (FEI Quanta 250 FEG, U.S.A.) was used to characterize the surface morphology of the three types of alginate membranes before and after crosslinking, and their morphological changes before and after THP adsorption. The membranes were coated with gold via sputter coating and the acceleration voltage of the SEM was 10 kV. The average fiber diameters of the electrospinning membranes were determined by measuring the fibers randomly selected from the SEM images by the ImageJ software. N\(_2\) adsorption-desorption isotherms (ASAP 2460) was used to analyze the specific surface area of the three membranes. The mechanical properties of the membranes were tested using a uniaxial mechanical testing machine (UTM2203, Shenzhen Suns Technology Co., Ltd, Shenzhen, China). Specimens were cut into a rectangular shape (20 mm × 10 mm) and dried in a vacuum oven at 50 °C for 24 h before testing. Measurements were carried out with a 100 N load sensor at a strain rate of 1 mm min\(^{-1}\) until failure occurred.

2.5. THP adsorption study
THP was dissolved in normal saline to obtain the solution for drug loading. A certain amount of the THP solution was injected into a 24-well cell culture plate with a pipette. The three types of membranes were cut into an appropriate size and put into the 24-well cell culture plate to load THP. The concentration of the drugs was measured at different time intervals to carry out the kinetic study. The 24-well cell culture plate was maintained at 25 °C. The concentration of THP was calculated by measuring the absorbance at 490 nm using a microplate reader (Thermo scientific, Multiskan FC).

The mass of THP loading was calculated using the following equation

\[ q_t = \left( \frac{C_0 - C_t}{m} \right) \times V \]  

where \(C_0\) (mg L\(^{-1}\)) and \(C_t\) (mg L\(^{-1}\)) are the concentrations of THP in the solution before and after THP loading at time \(t\), respectively, \(m\) (g) is the mass of loading, and \(V\) (L) is the volume of the THP solution. \(C_0\) (mg L\(^{-1}\)) and \(C_t\) (mg L\(^{-1}\)) were calculated from the standard curve, which was pre-made by measuring the absorbance of different concentrations of THP solutions from 0.1 mg ml\(^{-1}\) to 1 mg ml\(^{-1}\).

The adsorbed amount of THP at equilibrium, \(q_e\) (mg g\(^{-1}\)), was calculated by:

\[ q_e = \left( \frac{C_0 - C_e}{m} \right) \times V \]  

where \(q_e\) (mg g\(^{-1}\)) and \(C_e\) (mg L\(^{-1}\)) are the mass of THP and the concentration of THP solution at adsorption equilibrium, respectively. The meaning of \(C_0\) (mg L\(^{-1}\)), \(m\) (g), and \(V\) (L) are the same as that in equation (1).
The drug encapsulation rate (DER) of THP was calculated by:

\[
\text{DER\%} = \left( \frac{C_0 - C_e}{C_0} \right) \times 100\% \quad (3)
\]

where \(C_0 (mg L^{-1})\) and \(C_e (mg L^{-1})\) are the concentration of the THP solution at the beginning of adsorption and at adsorption equilibrium, respectively.

2.6. THP release study

To investigate the THP elution kinetics, the three types of membranes with THP loaded on them were immersed in normal saline. Then, 100 \(\mu\)L of the release medium was extracted to determine the concentration of the drug in the solution at set intervals. The solutions of NaCl, CaCl\(_2\), and MgCl\(_2\) was used as the release media to explore the mechanism of drug release for the three membranes, respectively. All the processes took place in a rotating shaker set to 60 rpm at 37 °C.

Figure 1 shows the schematic of membrane preparation and drug loading.

3. Results and discussion

3.1. Characterization of the alginate membranes

The SEM images of the three types of alginate membranes are shown in figure 2. The membranes fabricated by the spin-coating (SP) possess a relatively smooth surface with some cracks (figure 2(a1)). Alginate is brittle and the fracture may be caused by the plastic shrinkage of the alginate surface. The crosslinked membrane fabricated by spin-coating (SP-C) shows a rougher surface than that of the SP membranes (figure 2(a2)). During the process of crosslinking in CaCl\(_2\) solution, the calcium ions not only form eggshell structures with alginate but also displace sodium ions by ion exchange, [19] i.e., the membranes crosslinked by CaCl\(_2\) are a mixture of SA and calcium alginate. The surface of alginate was reconstructed by ion exchange, which gave a rough surface. The membranes fabricated by freeze-drying (FR) present a lamellar structure with cracks in the sheet (figure 2(b1)). However, after crosslinking, the membranes (FR-C) shrank and exhibited a porous structure (figure 2(b2)). The solution of alginate is 4%; ice in the membrane was sublimed to form loose membranes in the process of freeze-drying. Therefore, the membranes possess several pores. In the process of drying the membrane after crosslinking, the mass of alginate is too low to maintain a lamellar structure. Thus, the membranes shrank to a smaller shape. Non-crosslinked electrospinning membranes (EL) composed of smooth nanofibers (figure 2(c1)) with an average diameter of about 123 nm were obtained (figures 2(d1) and (c2)). The average diameter of the crosslinked electrospinning nanofiber (EL-C) reduced to about 110 nm (figure 2(d2)). Also, some interconnections were observed at the junctions of the nanofibers, which were attributed to ion exchange in the process of crosslinking. The removal of PEO and Triton X-100 is the main reason for the reduction of the fiber diameter after crosslinking [15].

3.2. Specific surface area and mechanical properties

The specific surface areas of the three types of samples before and after crosslinking were examined by the BET adsorption isotherms (Figure S2 (available online at stacks.iop.org/MRX/8/065402/mmedia)). The values of the specific surface area of the alginate membranes before and after crosslinking are shown in table 1. It is obvious that the SP samples have the smallest specific surface area, followed by FR membranes, and the EL membranes have the largest specific surface area. The SP membrane possessed the smallest specific surface area of 0.9706 m\(^2\) g\(^{-1}\), which increased to 1.0440 m\(^2\) g\(^{-1}\) after crosslinking. This may be because the SPC membranes possess a rougher surface than the SP membranes. The specific surface area was 2.0619 m\(^2\) g\(^{-1}\) for the FR membranes, which decreased to 1.4726 m\(^2\) g\(^{-1}\) for FR-C membranes. Also, the decrease in the specific surface area was attributed to the shrinkage of the lamellar structure. As for the electrospinning membranes, the surface area reduced to 3.2030 m\(^2\) g\(^{-1}\) from 3.7599 m\(^2\) g\(^{-1}\) after crosslinking, which was caused by the fusion of nanofibers at the junctions.

In the application process, the mechanical properties are one of the guarantees that make the drug carriers smoothly arrive at the lesions and continue to play a role. If the mechanical properties are insufficient, may cause it to deform during use and fail to achieve the desired effect. A universal testing machine was used to study the mechanical properties of the three types of membranes before and after crosslinking. The tensile strength and the elongation at break of three membranes before and after crosslinking are presented in table 1. Also, the stress-strain curves are shown in figure 3. The SP membranes have the highest tensile strength, followed by EL membranes, and the FR membranes have the smallest value of tensile strength. After crosslinking, all the membranes showed an enhancement in the tensile strength, which indicated that the crosslinking process was effective; thus, the mechanical performance of the membranes was enhanced. The elongation at break for the SP and FR membranes was slightly enhanced after crosslinking, while that of the EL membranes reduced from
10.2% to 6.6%. Alginate is brittle and an increase in the tensile strength is often accompanied with a decrease in the elongation at break. However, for the SP and FR membranes, the wrinkles formed by drying after crosslinking was the main reason for the slight enhancement in the elongation at break.

3.3. THP adsorption rate and kinetics

3.3.1. THP adsorption rate

The adsorption performance of the three types of alginate membranes toward THP was examined by checking the adsorption kinetics of the membranes with an initial THP concentration of 1 mg ml⁻¹, as suggested in the

Figure 2. SEM images of different samples with or without crosslinking (a1) SP, (a2) SP-C, (b1) FR, (b2) FR-C, (c1) EL, (c2) EL-C, and the fiber diameter distribution of the EL samples without crosslinking (d1) and with crosslinking (d2).
The morphology of the THP-loaded membranes is shown in figure 4. The THP-loaded membranes fabricated by spin-coating (SP-T) show the roughest surface because THP displaces sodium ions in the process of THP loading (figure 4(a)). However, the ring structure on the surface was not destroyed (Figure S1). Also, the THP-loaded membranes fabricated by freeze-drying (FR-T) further contracted and the volume of the membranes reduced significantly (figure 4(b)). Figure 4(c) shows that the process of THP loading leads to the fusion of SA nanofibers at the junctions, which is consistent with the results of long-term crosslinking of alginate that have been reported before [33].

Figure 5(a) shows the changes in the mass of THP adsorbed by the three types of alginate membranes over time. The three types of membranes showed the same tendency for adsorbing THP. In the first 5 h, rapid adsorption was observed for the three types of alginate membranes; then, the adsorption rate gradually decreased. The THP loading process reaches equilibrium in 24 h for the spin-coated and electrospinning membranes. The freeze-dried membranes adsorbed THP after 24 h, which was attributed to the 3D structure that make it difficult for THP to diffuse in the membranes. THP is a modified adriamycin, which has little solubility in water. It is difficult for THP to diffuse inside the 3D structure of the FR-C membranes and it takes more time to reach equilibrium for the FRC membranes. For the adsorption ratio, the electrospinning
membranes exhibit the largest adsorption rate of the three types of membranes due to the largest specific surface area. The specific surface area of the FR-C membranes was larger than that of the SPC membranes; thus, the adsorption rate of the FR-C membranes was larger than that of the SPC membranes. The adsorption rate gradually decreased over time. Due to the 3D structure of the FRC membranes, the adsorption rate of the FRC membranes became smaller than that of the spin-coated membranes after 5 h. The adsorption efficiency and adsorption capacity of the three types of membranes are shown in figure 5 (b); the adsorption efficiency of the three membranes was more than 70%, especially for the electrospinning membranes with an efficiency of 86.4%. Also, the electrospinning membranes show the largest adsorption capacity of 144.13 mg g\(^{-1}\).

3.3.2. Adsorption kinetics

It is very important to analyze the kinetics curve for figuring out the mechanism of THP loading in the membranes, which can help us in practical applications [34]. The pseudo-first-order model, pseudo-second-order model, and intra-particle diffusion model were applied to study the adsorption kinetics behavior.

The pseudo-first-order model can be written as

\[
\ln(q_e - q_t) = \ln q_e - k_1 t \tag{4}
\]

where \(q_e\) (mg/g) is the mass of THP loaded in the membranes at equilibrium, \(q_t\) (mg/g) is the mass of THP loaded in the membranes at time \(t\), and \(k_1\) (min\(^{-1}\)) is the first order rate constant, which can be attained from slope of the \(\ln(q_e - q_t)\) versus \(t\) plots. The plot of \(\ln(q_e - q_t)\) versus \(t\) should be a straight line and the intercept of the plots represents the value of \(q_e\) (mg/g).

The pseudo-second-order model can be written as

\[
\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e} \tag{5}
\]

where the meaning of \(q_e\) and \(q_t\) are same as that in equation (4). \(k_2\) is the second-order rate constant. The parameters \(q_e\) and \(k_2\) were calculated from the intercept and slope of the \(\frac{t}{q_t}\) versus \(t\) plot, respectively.

The intra-particle diffusion model can be expressed as

\[
q_t = K_{id}t^{1/2} + C \tag{6}
\]

where \(C\) represents the greater effect of the boundary layer on molecular diffusion, which is calculated by the intercept of the plot, and \(K_{id}\) is the intra-particle diffusion rate, which is determined by the slope of the plot of \(q_t\) versus \(t^{1/2}\).

Figure 6 shows the plots of \(\ln(q_e - q_t)\) versus \(t\), \(\frac{t}{q_t}\) versus \(t\), and \(q_t\) versus \(t^{1/2}\) for the pseudo-first-order model, the pseudo-second-order model, and the intra-particle diffusion model, respectively. The \(R^2\) values of the models are close to one (table 2), and the \(q_t\) of the pseudo-first-order model is closer to the actual value than the pseudo-second-order model, indicating that the adsorption fit with the pseudo-first-order model is better than the pseudo-second-order model, especially for the spin-coated membranes. As for the intra-particle diffusion model, the plots are linear but do not pass through the origin (figures 5(g)–(i)), indicating that the adsorption process is a complex process and involves more than one diffusive resistance.[21]
3.4. THP release rate and impact factors

3.4.1. THP release rate

To study the process of the THP release rate for the three types of membranes, the membranes with THP loaded in the adsorption study were placed in normal saline in order to determine the concentration to study the release process of the THP-loaded membranes. Figure 7(a) shows the release curve of the THP-loaded membranes. The three types of samples show similar release kinetics. In the first 5 h, it shows a quick release of drugs for the three types of membranes, and the release process reaches equilibrium in 24 h for the spin-coated membranes and the electrospinning membranes. The FR membranes showed the sustained release of THP after 24 h. However, the mass of the released drug was different, i.e., 0.04299 mg for the spin-coated membranes, 0.05826 mg for the freeze-dried membranes, and 0.06324 mg for the electrospinning membranes.

3.4.2. Impact factors on the release rate

3.4.2.1. Initial drug loading mass

We investigated the effect of different loading masses of THP on the THP release with electrospinning membranes, which showed that these membranes can load more drugs than the other two membranes. Figure 7(c) shows that different initial drug loading had different release behaviors in releasing the drugs. The released mass at the equilibrium increases with the increase in initial drug loading (figure 7(d)) but the released ratio declines.

3.4.2.2. Salt concentration of the release medium

The effect of the salt concentration of the release medium on the release mass and release ratio was investigated by immersing the drug-loaded electrospinning membranes in NaCl solutions with weight ratios of 1%, 2%, and 3% (figure 7(e)). With the increase in the concentration of NaCl in the release medium, both the released mass at
equilibrium and the release ratio increased (figure 7(f)); however, the increase is not linear, indicating that drug release is a complex process.

### 3.4.2.3. Different ions in the release medium

For the process of drug release, the release behavior not only relies on the solute concentration of the releasing environment but is also determined by the solution properties. Figure 6(g) shows the release curve of the THP-loaded electrospinning membranes in different ion media. From figure 6(h), we can see the difference between the groups. In a brief, the amount of drug released in CaCl$_2$ solutions was the most, reaching 0.03396 mg, followed by the amount of drug released in MgCl$_2$. The released drug mass in NaCl solutions was the least, even if the ionic strength was controlled.

### 3.4.3. Release behavior after changing the release medium continuously

When the release equilibrium was reached, the drugs loaded in the membranes will no longer be released. Therefore, after the release process reaches equilibrium, we transferred the drug-loaded membranes to a new release medium to study the sustained release of the drug-loaded membranes. Figure 8(a) shows the release curves of the three types of membranes before and after changing the release medium. The media were replaced with normal saline at 110 h and 134 h, and when the media are replaced, the drug release process, which had reached equilibrium before, is restarted. However, the THP mass of the membranes released was less than that before for the three types of membranes, especially for the third change of the release medium. We also studied the accumulated mass of THP released in 35 d by changing the release medium everyday (figure 8(b)). Alginate can be easily crosslinked by divalent cations but the process is reversible. When the concentration of calcium ions was too low to crosslink alginate, the membranes gradually dissolved in the medium. In the 8th change of the release medium, the spin-coated membranes and the electrospinning membranes could not maintain the shape and became fragments; thus, the experiment could not go on. Also, it is obvious that THP was still being released. Though swelling was observed for the membranes fabricated by freeze-drying, the drug release experiment could still go on. Figure 8(c) shows the total mass of released THP and the release ratio. The THP-loaded freeze-dried membranes showed sustained release of THP during the experiment for 35 d and 46.1% of the loaded drugs were released into the medium.

As the results show, alginate has a high loading capacity for THP and shows sustained release of the drugs. Alginate can absorb THP by ion exchange reaction and physical adsorption, and the section of THP absorbed by physical interaction is released rapidly in the medium. Sustained release was attributed to the section absorbed by ion exchange. The ion exchange reaction can be described by the figure 9.

The release of THP from alginate membranes is a reverse process to drug loading, involving ions competing for the binding site and physical adsorption and desorption. Therefore, the concentration and kinds of cations in the release medium play an important role in the drug release process. The electrospinning membranes have the maximum adsorption mass of THP among the three types of membranes, which is due to the larger specific surface area and more binding sites, resulting in more THP being adsorbed by physical adsorption. The part adsorbed by physical adsorption is released fast, resulting in a decrease in the release ratio with the increase in the initial drug loading, as described in 3.4.1. Also, the released THP mass increases disproportionately in different concentrations of NaCl solutions, as described in 3.4.2. After refreshing the release medium, the gap between the released drug mass of the three types of membranes decreases, which indicates that a certain degree of drugs adsorbed by physical adsorption was released before refreshing the medium. The released amount from the third equilibrium is only slightly less than the second release amount at equilibrium, indicating that only a few
Drug molecules are bound by physical adsorption. In other words, most of the released drugs were bound via ion exchange after refreshing the release medium.

The sustained release process occurred through ion exchange and the released amount of THP depends on the cationic strength in the release medium. The competitiveness of sodium ions for the binding sites in alginate can be reinforced by increasing the concentration of sodium ions in the release medium, which leads to more THP being released. The binding force between the carboxylate groups and the divalent cations was stronger.
than the monovalent cation. Therefore, the released amount of THP in CaCl₂ solution and MgCl₂ solution is higher than that in NaCl solutions, even if the ionic strength of the media are the same. In addition, the affinity of calcium ions to carboxylic acid groups is stronger than that of magnesium ions, resulting in more THP being released in CaCl₂ solution than that in MgCl₂ solution.

By refreshing the release medium of normal saline, the three types of membranes can release THP for several days. However, the spin-coated membranes and electrospinning membranes get degraded because the calcium ions are diluted in the 8th change of the refreshing medium. The freeze-dried membranes showed sustained release of THP for 35 d, indicating that the membranes are promising materials in the field of sustained drug release for the local treatment of cancer.

4. Conclusions

In this study, three types of alginate membranes were fabricated by spin-coating, freeze-drying, and electrospinning. 2% CaCl₂ solution was used to crosslink the membranes to obtain the water-insoluble membranes. Also, the three membranes were immersed in THP solution to study the drug loading process. In comparison, the electrospinning membranes exhibited the maximum adsorption mass of the three types of membranes and the value was 144.13 mg g⁻¹ due to the highest specific surface area, which can provide more binding site for physical adsorption. Also, the analysis of adsorption kinetics indicates that the adsorption process followed the pseudo-first-order model well. The release process occurred via ion exchange and the amount of released THP was related to the ionic strength of the release medium, including the type and concentration of ions. The three types of membranes are promising materials for the local treatment of cancer such as local cancers of the pancreas and trachea. Our next work is to conduct cell culture tests or injections at different concentrations and rates to establish a good release kinetics, and prepare drug-loading covered airway stents. Then animal experiments need to be conducted to verify the safety and effectiveness of the prepared drug-loading covered airway stents, for the treatment of malignant non-vascular stenosis caused by lung cancer or tracheal cancer, which are promising for overcoming the limitations of existing therapies such as higher restenosis rate and tissue necrosis caused by multiple operations, etc.

Acknowledgments

This work was supported by the International Science & Technology Cooperation Program of China (2015DFA30550), the ‘111’ Project of Henan Province, the key scientific and technological project of Henan Province(162102210159, 172102210489), the Scientific Research and Innovation Platform of Fuzhou University of Technology (KF-C19009), and the Key Science & Technology Project for Institutions of Higher Education of Henan Province(19A430003).
Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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