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Alginate/starch blend fibers and their properties for drug controlled release

Qun Wang[a], Xianwen Hu[b], Yumin Du[a,*], John F. Kennedy[c]

[a] Department of Environmental Science, Wuhan University, Wuhan 430072, China
[b] Department of Chemistry, College of Science, Huazhong Agricultural University, Wuhan 430070, China
[c] Chembiotech Laboratories, Institute of Advanced Science and Technology, 5 The Croft, Buntsford Drive, Stoke Heath, Bromsgrove, Worcestershire B60 4JE, UK

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ABSTRACT

Fibers of alginate and starch, with salicylic acid (SA) as model drug incorporated in different concentrations, were obtained by spinning their solution through a viscose-type spinneret into a coagulating bath containing aqueous $CaCl_2$ and ethanol. Chemical, morphological and mechanical properties characterization was carried out, as well as the studies of the factors that influence the drug releasing from alginate/starch fibers. The results of controlled release tests showed that the amount of SA released increased with an increase in the proportion of starch present in the fiber. Moreover, the release rate of drug decreased as the amount of drug loaded in the fiber increased, but the cumulative release amount is increasing. The alginate/starch fibers were also sensitive to pH and ionic strength. All the results indicated that the alginate/starch fiber was potentially useful in drug delivery systems.

1. Introduction

Sodium alginate, widely used in food and pharmaceutical industries, is a water soluble salt of alginic acid, a naturally occurring non-toxic polysaccharide found in all species of brown algae (Musa, Fara, & Badwan, 1999; Rubio & Ghaly, 1994). It contains two uronic acids, (1-4)-linked β-D-mannuronic acid (M) and (1–4) linked α-L-guluronic acid (G), and is composed of homopolymeric blocks M–M or G–G, and blocks with an alternating sequence of M–G blocks (Yotsuyanagi, Yoshioka, Segi, & Ikeda, 1991). In addition, sodium alginate has a unique property of cross-linking in the presence of multivalent cations, such as calcium ions in aqueous media, which rather complex with G–G sequences in the polymer chain to form the 'egg box junctions' (Smidsrod, Glover, & Whittington, 1973; Smidsrod & Skjak, 1990) and insoluble calcium alginate. Depending on the degree of cross-linking, alginate will significantly reduce its swelling in the presence of the solvent, generally resulting in a reduction of the permeability of different solutes. As a consequence, the release of embodied drugs in alginate matrices will be delayed, allowing these systems to be used in drug controlled release (Aslani & Kennedy, 1996; Badwan, Abumalooh, Sallam, Abukalaf, & Jawan, 1983; Knill et al., 2004; Mi, Sung, & Shyu, 2002). Alginate fibers can be prepared by extruding solutions of sodium alginate into a bath of calcium ions. The resultant calcium alginate fibers are then dried to give tough fibers that can be collected on spools for knitted fabrics or directly chopped for applications in non-woven materials. Alginate fibers, typically as a calcium salt, interact with the wound exudates to form a moist gel, as a result of the ion exchange between the calcium ions in the fiber and sodium ions in the exudates. This in situ generation of a moist healing environment and the consequent high absorbency of the alginate dressings are two of the outstanding properties which make the alginate dressing one of the most versatile wound dressings available today (Qin, Agboh, Wang, & Gilding, 1996). In addition, alginate containing dressings have been demonstrated to activate macrophages within the chronic wound bed and generate a pro-inflammatory signal which may initiate a resolving inflammation characteristic of healing wounds (Thomas, Harding, & Moore, 2000). As a result, many commercially available wound dressings contain calcium alginate fibers.

Starch is a biodegradable polymer with excellent biocompatibility and non-toxicity (Herman, Remon, & De Velder, 1989). It is often compounded with other polymers or used alone in the fields of drug controlled release (Pohja, Suihko, Vidgren, Paronen, & Ketolainen, 2004; Rahmouni, Chouinard, Nekka, Lenaerts, & Leroux, 2001; Wierik et al., 1996).

With regard to the excellent fiber forming properties of alginate, many new and original fiber materials have been achieved (Fan et al., 2005; Wang et al., 2005). Drug loaded fiber is one of the applications by those fibers in pharmaceutical technology. In addition, numerous controlled or sustained-delivery systems have been described in the literature, whereby the active ingredient has been dissolved or dispersed within these matrixes (Carmen & Roland, 1997). For the development of fiber devices to be used in controlled release, tests carried out with them are very important

* Corresponding author. Tel.: +86 27 68778501; fax: +86 27 68778501.
E-mail address: duyumin@whu.edu.cn (Y. Du).

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(Musa et al., 1999). And it is well known that blending is effective and convenient method to improve the performance of polymer materials. In the present study, we prepared alginate/starch blend fibers. To use these fibers in several controlled release applications, it was necessary to have an overall understanding of their properties. Using salicylic acid (SA), as a model drug, we studied some factors that may have influence on the drug release from alginate/starch fibers. Such as the ratio of alginate and starch used, the loaded amount of SA, the pH and ionic strength of the release solution, etc. We wish this fiber can lead to a successful application for localized drug delivery in vivo or in vitro environment.

2. Materials and methods

2.1. Materials

Sodium alginate ($M_v = 1.2 \times 10^5$, $\mu = 280$ MPa s), Starch and SA were all purchased from Shanghai Chemical Reagent Co., Ltd. (Shanghai, China). Other reagents were all analytical grade and all commercially available and used as received.

2.2. Preparation of drug loaded fibers

Alginate/starch drug loaded fibers were obtained by spinning their solution through a viscose-type spinneret into a coagulating bath. Solutions of alginate and starch, 5 wt.%, were both prepared with distilled water respectively; and the later one is dissolved in higher temperature. These solutions were mixed in different proportions to obtain final starch weight ratio (dry state) of 10 wt.%, 30 wt.%, 50 wt.% and 70 wt.%. The four solutions were made completely homogeneous under stirring, and then filtered through a 200 mesh filter cloth under pressure. After that, the filtrate was sonicated in sonication bath (FS-20, Jingrong Sonic Electronics Co. Ltd., Beijing, China), left to stand until trapped air bubbles were removed. Finally the clear solution as a spinning solution was poured into the spinning tank, and extruded at 25 °C from a 30-hole (0.08 mm diameter) viscose-type spinneret into a coagulating bath containing 10 wt% $CaCl_2$ aqueous solutions with ethanol to form fibers. The volume ratio of $CaCl_2$ aqueous solution to ethanol was 50:50. The as-spun fibers were washed and stretched (stretching ratio was 20%) in distilled water, then were dried in an oven (GDW-250, Saiou Test Machine Co. Ltd., Shanghai, China) at 37 °C for 48 h, and finally dried under vacuum at room temperature until constant weight. The several alginate/starch fibers, without drug, were designated as AS-1, AS-2, AS-3 and AS-4 (A—alginate; S—starch; weight ratio of alginate: starch were 90:10, 70:30, 50:50 and 30:70, respectively).

To make drug loaded fibers, 2.0 g SA was dissolved, under stirring, in 500 ml of each one of those four above solutions to make them completely homogeneous. And applied the same method to make fibers, we can get the drug loaded ones and designated them as ASS-1, ASS-2, ASS-3 and ASS-4 (A—alginate; S—starch; S-SA, weight ratio of alginate: starch were 90:10, 70:30, 50:50 and 30:70, respectively). Then 1.0 g or 3.0 g of SA was dissolved in a solution of alginate and starch (starch was 30 wt.%, dry state), producing drug loaded fibers designed as ASS-2(−) and ASS-2(+), respectively.

2.3. FT-IR analysis

The FT-IR spectra of pure alginate, starch, AS-1 and AS-3 fibers were recorded with KBr pellets on a Nicolet FT-IR spectrometer, Model 170SX (USA).

2.4. X-ray diffraction studies

The X-ray diffraction patterns of pure alginate, starch, AS-1 and AS-3 fibers were carried on a Shimadzu Lab-XRD-6000X diffractometer (Japan), using Nickel-filtered Cu Kα radiation at 40 kV and 50 mA in the 2θ range of 8–40°.

2.5. Morphology observations

The morphologies of the AS-1 and AS-3 fibers were examined using scanning electron microscopy (SEM) Hitachi S-570 (Japan). Cross-sectional samples were prepared by fracturing fibers in liquid nitrogen. Prior to observation, samples were arranged on metal grids, using double-sided adhesive tape, and coated with gold under vacuum before observation.

2.6. Atomic absorption spectrum analysis

The amount of Ca^{2+} cross-linked on the blend fibers was evaluated by a Xintian WF-5 (Tianjin, China) atomic absorption spectrophotometer at 422.7 nm. All the experiments were done in triplicates.

2.7. Mechanical properties

The tensile strength (σ_b) and the elongation at break (ε_b) for fibers were determined on an electronic tester machine (CMT8502, Shenzhen SANS Test Machine Co. Ltd., China). The gauge length was 90 mm and crosshead speed was 50 mm/min. All samples were preconditioned at 20 °C and 65% relative humidity, for 24 h prior to mechanical testing. All the experiments were done in five times.

2.8. Water swelling ratio

The water swelling ratio (WSR) of fibers was calculated as follows:

$$\mathrm{WSR} = \frac{W_1 - W_0}{W_0} \times 100\%$$

where W_0 denote the weight (g) of fiber which was dried at 80 °C until a constant weight achieved; W_1 is the weight of fully swollen fiber that was centrifuged at 4000 rev/min for 10 min. All the experiments were done in triplicates.

2.9. Release studies

0.3 g drug loaded fibers were suspended in glass vessels containing 50 ml of medium, and incubated on a shaking bed (HS-150, Saiou Test Machine Co. Ltd., Shanghai, China) at 37 °C, 130 rpm. At appropriate time intervals the solutions were withdrawn and the amount of SA released from the drug loaded fibers were evaluated by UV spectrophotometer (UV-721, Shanghai Analytical Instrument Co., China) at 300 nm. Then an equal volume of the fresh medium was added back to maintain a constant volume. The medium conditions for the controlled release studies were four typical solutions: pH 1.0 (0.1 N HCl solution, acts as simulated gastric fluid), pH 3.6 and pH 5.0 (10 mM HAc–NaAc buffered solution), and pH 7.4 (10 mM NaH_2PO_4–Na_2HPO_4 buffered solution, acts as simulated intestinal fluid). The ionic strength of above buffered solutions can be carefully adjusted to a relatively level by adding an appropriate amount of NaCl. All the experiments were done in triplicates.

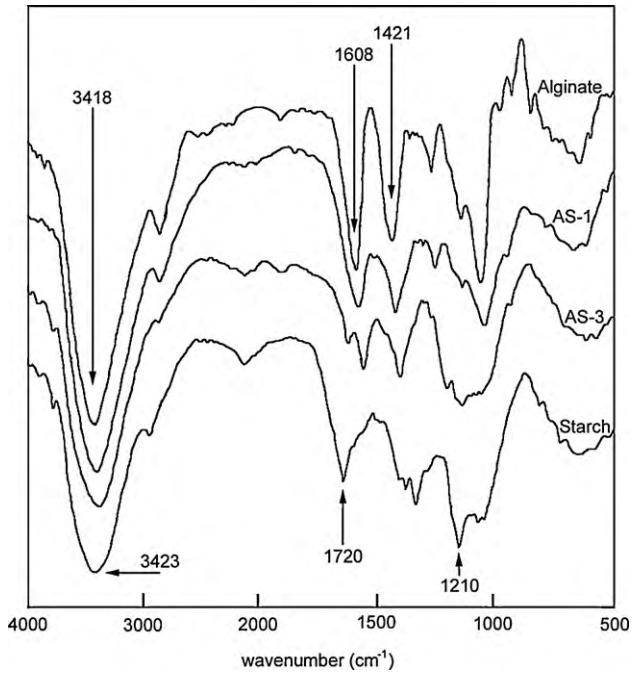

Fig. 1. IR spectra of alginate, starch, and blank matrix fibers AS-1 and AS-3.

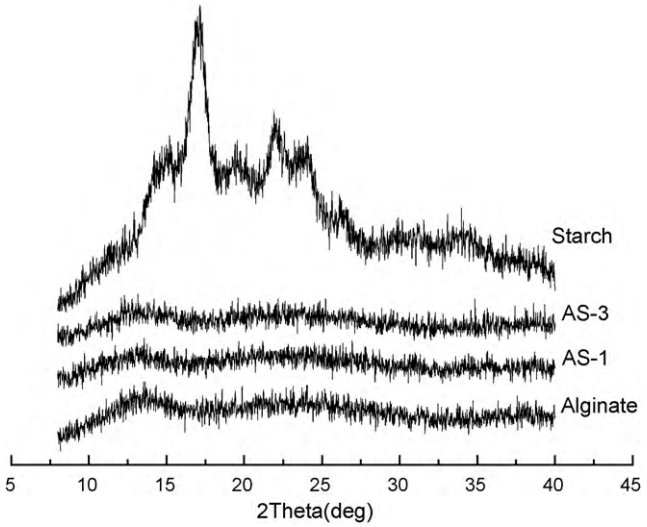

Fig. 2. XRD patterns of alginate, starch, and blank matrix fibers AS-1 and AS-3.

3. Results and discussion

3.1. Structure and morphology characterization

3.1.1. FT-IR analysis

Fig. 1 revealed the FT-IR spectra of alginate, starch and blank matrix fibers AS-1 and AS-3. About pure alginate, two characteristic absorption bands at 1608 cm^{-1} and 1421 cm^{-1} were detected and attributed to the asymmetric stretching vibration and symmetric stretching vibration of –COO group, respectively (Huang, Pal, & Moon, 1999). The characteristic absorption bands at 1210 cm^{-1} and 1720 cm^{-1} of starch were attributed to the bending vibration and stretching vibration of C–O, respectively. Finally, the wide absorption band around 3423 cm^{-1} was due to the stretching vibration of O–H.

From the FT-IR spectra of blend fibers AS-1 and AS-3, we can see that the characteristic absorption bands at 1608 cm^{-1} and 1421 cm^{-1} of alginate shifted to lower wave number at 1594 cm^{-1} and 1409 cm^{-1}. At the same time, the absorption band around 3418 cm^{-1}, concerned the stretching vibration of N–H group bonded to O–H group, shifted to a lower wave number at 3410 cm^{-1}, suggesting an increase in the hydrogen bonding (Yu, Du, & Zheng, 1999). All those changes demonstrated a strong evidence of the intermolecular interactions and good molecular compatibility between alginate and starch.

3.1.2. X-ray diffraction studies

It may be seen, in Fig. 2, the X-ray diffraction patterns of alginate, starch and blank matrix fibers AS-1 and AS-3. The diffractogram of alginate consisted of two crystalline peaks at $2\theta = 13.7^\circ$ and 23.0° (Yang, Zhang, Peng, & Zhong, 2000). Starch had typical crystalline peaks at $2\theta = 17.1^\circ$ and 22.0° because of its close molecular packing and regular crystallization. From the X-ray diffraction patterns of blend fibers AS-1 and AS-3, Fig. 2, it may be seen that the diffraction peaks of alginate decreased at 13.7° and 23.0°, with the increasing of starch content. This can be explained by the strong interaction between alginate and starch which has destroyed the close packing of the alginate molecules for the formation of regular crystallites. In other words, the results of X-ray diffraction could reinforce the existence of good compatibility between alginate and starch due to both kind of strong interactions like hydrogen bonds and ionic interactions.

3.1.3. Morphology observations

Analysis of the morphologies of blank matrix fibers AS-1 and AS-3 obtained by Scanning Electron Microscopy (SEM), in Fig. 3, demonstrated that the cross-section of both is smooth and homogeneous, with absence of micro-phase separation. Again, the result obtained here also indicated good compatibility between alginate and starch.

3.2. Atomic absorption spectrum analysis

The amount of Ca^{2+} which was cross-linked on the fibers alginate, AS-1, AS-2, AS-3 and AS-4 were shown in Fig. 4. This change can be explained that the strong intermolecular interactions between alginate and starch remarkably decrease the possibilities of Ca^{2+} cross-linking to the carboxyl groups of alginate. So the amount of Ca^{2+} cross-linked on the blend fibers decreased greatly as the amount of starch was raised. This result could also reinforce the existence of strong interactions between alginate and starch molecules.

3.3. Mechanical properties

Fig. 5 revealed the mechanical properties of the blend fibers. From the figure, it may be seen that the maximum value of tensile strength and elongation at breaking were observed when the content of starch was 10 wt.% and 30 wt.%, respectively. The results indicated that blending is effective in improving the mechanical properties of the drug loaded fibers.

3.4. Release studies

3.4.1. Effect of the composition ratio of drug loaded fiber

The influence of the different composition ratios of alginate and starch in the drug loaded fibers ASS-1, ASS-2, ASS-3 and ASS-4 (10 wt.%, 30 wt.%, 50 wt.% and 70 wt.% of starch, respectively) was investigated in this experiment. The release medium conditions, as mentioned before, were 10 mM NaH_2PO_4–Na_2HPO_4 buffered solution with pH 7.4 and ionic strength of 0.145 M. As Fig. 6 demonstrated, the release of SA increased as the content of starch increased. In other words, as starch is a kind of water soluble macro-

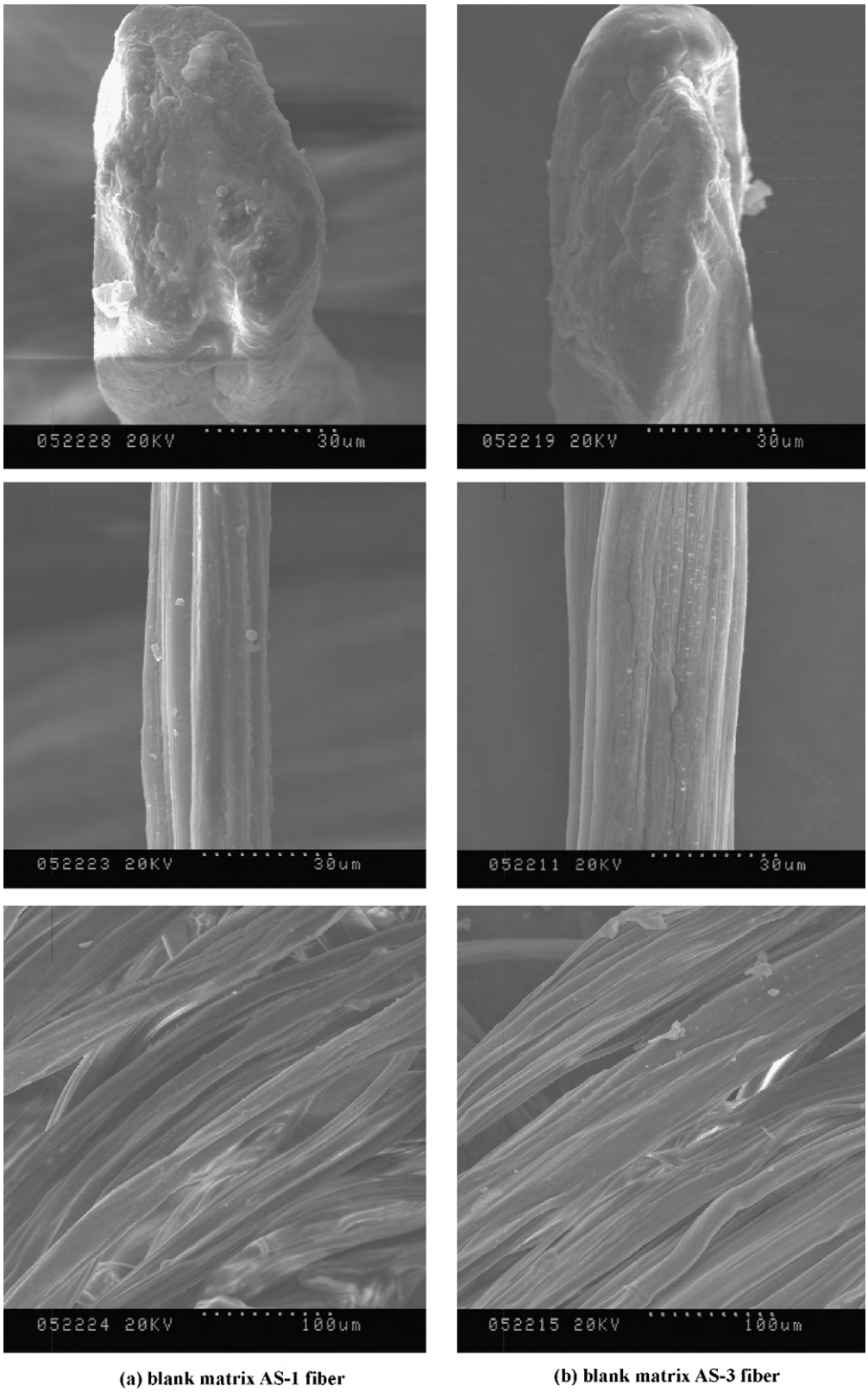

Fig. 3. SEM photographs of alginate, starch, and blank matrix fibers AS-1 and AS-3.

molecule, it dissolves and leaves pores that accelerate the release of the drug from the matrix fiber.

3.4.2. Effect of the drug loaded amount

Fibers ASS-2(−), ASS-2 and ASS-2(+), with different drug loaded amount (1.0, 2.0 and 3.0 g, respectively) were studied in the same release solution cited in Section 3.4.1. From Fig. 7, it may be concluded that the more drugs loaded, the lower the drug release rate was; but according to the fact that more drugs were loaded, the cumulative release amount is increasing. So we can get a more persistent release by increasing the drug loaded amount.

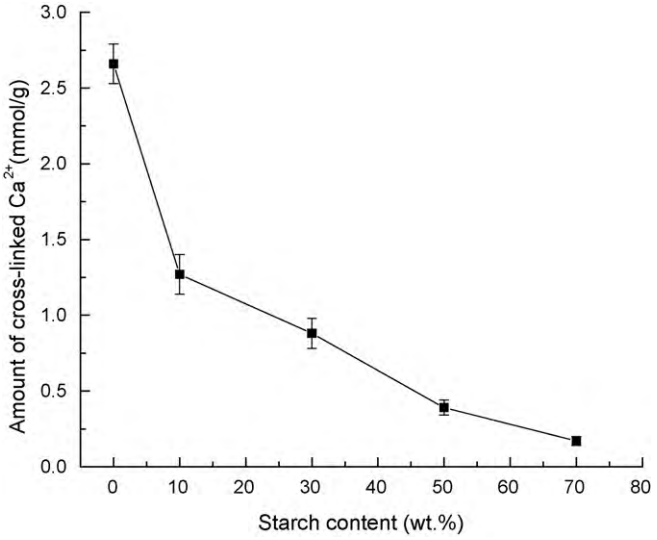

Fig. 4. Amount of cross-linked Ca^{2+} in blank alginate/starch fibers with different composition.

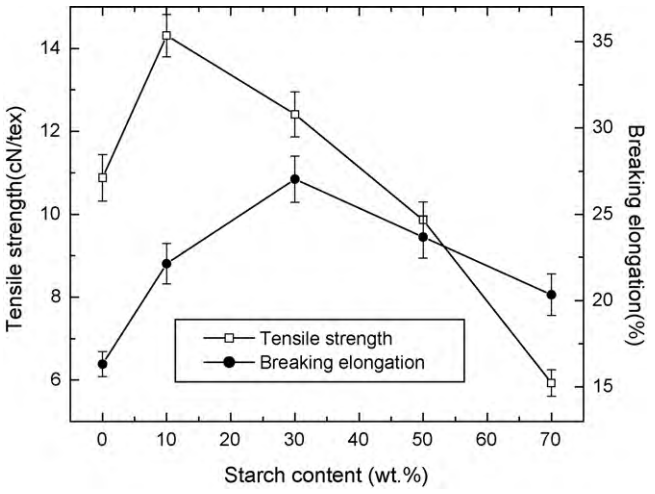

Fig. 5. Mechanical properties of blank alginate/starch fibers with different composition.

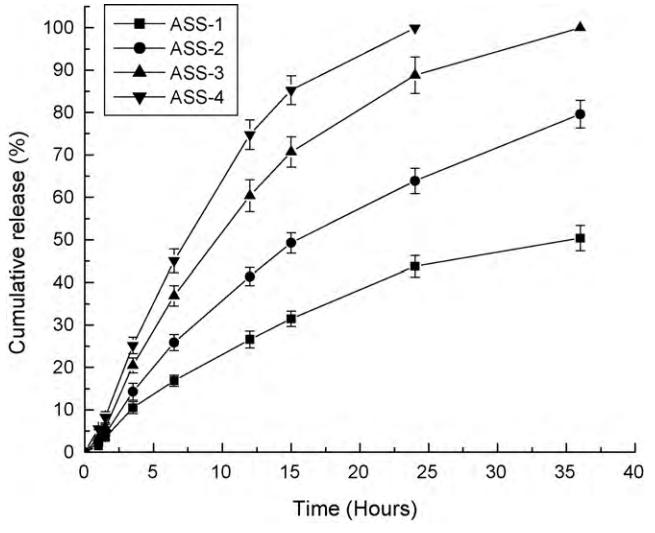

Fig. 6. Influence of the composition of the drug loaded in alginate/starch fibers on the controlled drug release process.

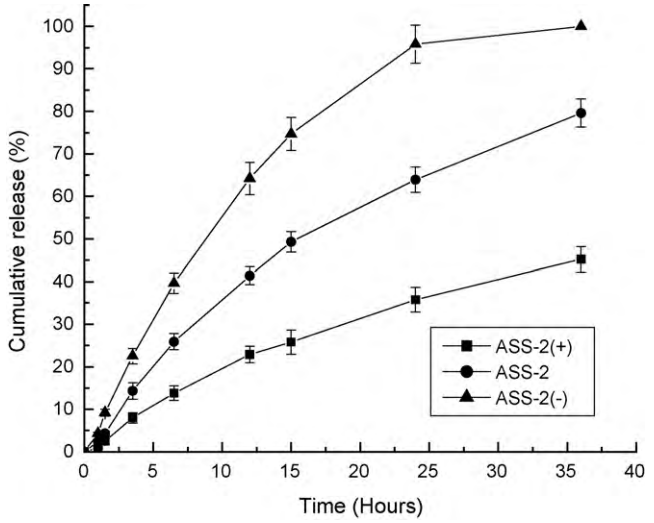

Fig. 7. Influence of the amount of drug loaded in ASS-2 fibers on the controlled drug release process.

3.4.3. *Effect of pH*

The drug release from loaded fiber ASS-2, in four different buffered solutions with pH 1.0, 3.6, 5.0 and 7.4, was studied. The ionic strength of those solutions was all adjusted to 0.145 M, by adding an appropriate amount of NaCl. Fig. 8 demonstrated that the drug release from loaded fibers was very sensitive to the pH of the medium. The release rate was maximal at pH 7.4 and minimum at pH 1.0. The result was consistent with the value of water swelling ratio of blank matrix fiber AS-2 in Fig. 9. As $-COO^-$ on alginate will changes to –COOH at low pH, this will reduce the swelling ability of alginate. Furthermore, the pH also has a slight effect on the solubility of SA. A higher pH leads to a better solubility of SA, which results in higher drug release rate.

3.4.4. *Effect of ionic strength*

Drug loaded fiber ASS-2 was used in this experiment as release matrix. Adding an appropriate amount NaCl to the 10 mM NaH_2PO_4–Na_2HPO_4 buffered solution with pH 7.4 produced the four different release mediums. In Fig. 10, higher ionic strength seemed to accelerate the drug release process; however, the dif-

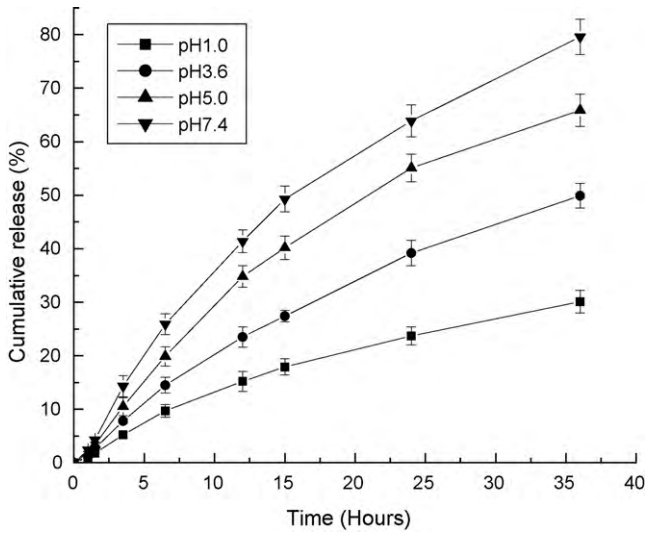

Fig. 8. pH influence of the release medium on the controlled drug release process from ASS-2 fiber.

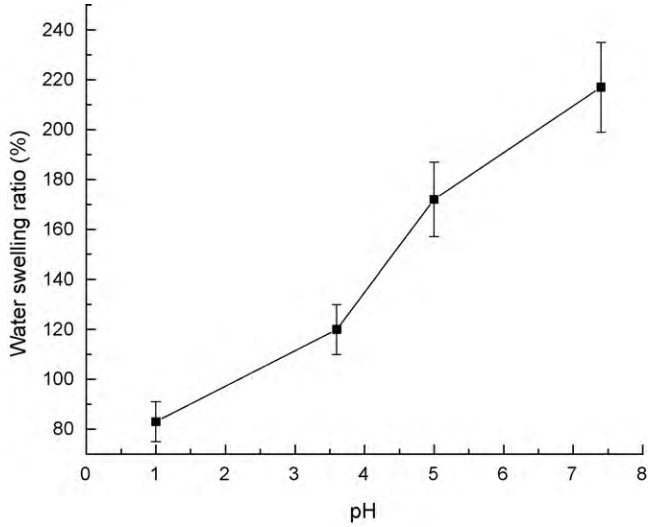

Fig. 9. pH influence of the release medium on the water swelling ratio of blank matrix fiber AS-2.

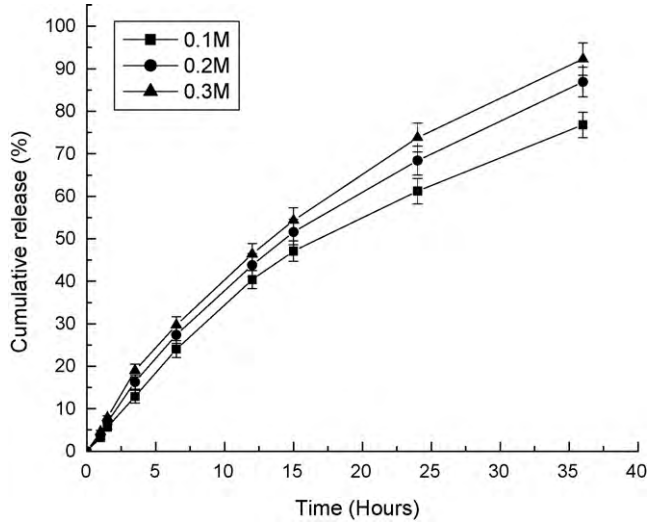

Fig. 10. Influence of the ionic strength of the release medium on controlled drug release from ASS-2 fiber.

ferences were not statistically significant. The result was possibly related to the decrease of osmotic pressure inside the fiber with the increase of the salt concentration and the weakened salt-bond between Ca^{2+} and alginate, SA and fiber matrix by salt ion (Yin & Prudhomme, 1992).

4. Conclusions

Drug loaded fiber based on alginate and starch was obtained by spinning their solution through a viscose-type spinneret into a coagulating bath containing aqueous $CaCl_2$ and ethanol. With SA as a model drug, we studied the fiber's structures and characterizations, especially its potential capacity in drug delivery system. The results indicated that the blended fiber was sensitive to pH and ionic strength of the release medium. However, the effect of pH is stronger. Furthermore, the fiber's composition and drug loaded amount both had relevant influence on the release properties of the fiber. Thus, we can control the drug release rate through changing some influential factors of the drug loaded fiber. The fiber can lead to a successful application for localized drug delivery in vivo or in vitro.

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