Front. Chem. Eng. China 2010, 4(1): 102–108
DOI 10.1007/s11705-009-0299-x

RESEARCH ARTICLE

Konjac glucomannan and xanthan gum as compression coat for colonic drug delivery: experimental and theoretical evaluations

Kang WANG (✉), Jiangyang FAN, Yanjun LIU, Zhimin HE

Enzyme Technology Laboratory, Chemical Engineering Research Center, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China

Abstract Compression coated tablets for oral colon specific delivery systems were developed with a mixture polysaccharide of konjac glucomannan (KGM) and xanthan gum (XG) as the compression coat. Diffusion of cimetidine from compression coated tablets was investigated by release experiment *in Vitro*. 0.22 U/mL β-mannanase was applied in the mimic colon solution. The structure of the mixture polysaccharide was studied by an atomic force microscope (AFM). The experimental results indicate that a KGM70 tablet with a 0.4 g coat is of good design, due to a less than 5% drug loss in the mimic upper gastrointestinal solution by the synergistic interaction between XG and KGM, and due to about 50% cumulative release in the mimic colon solution by degradation after 24 hours. The release mechanism and model are discussed based on different periods of drug release including the delay of the drug, the constant release without an enzyme and the delay of degradation. Under hydrolysis by β-mannanase, drug release from the tablet with KGM coat shows an exponential increase, while that from the dosage with the mixture polysaccharide coat is an approximately zero-order process in which the constant release rate relates to the release velocity of a non-degraded system, the content of KGM within the coat and the average molecular weight ratio of KGM to XG. It was found that XG was the framework of the polysaccharide mixtures by AFM, which is similar to the analysis results from experiments on drug release.

Keywords colon specific delivery, compression coated tablet, konjac glucomannan, xanthan gum, synergistic interaction, release mechanism and model, different period of release, structure of mixture polysaccharide

Received November 4, 2009; accepted November 30, 2009

E-mail: wangk72@tju.edu.cn

1 Introduction

The colon and rectum, which are susceptible to some diseases such as colorectal cancer, inflammatory bowel disease (IBD), Crohn's disease (CD), and infectious diseases, are located at the end of humans' digestive systems. The traditional oral dosage forms may cause unwanted systemic side effects, even toxicity, due to the absorption and/or degradation of the active ingredient in the upper gastrointestinal tract (GIT). Therefore, it is necessary to highly concentrate on drugs for the colon for disease therapy. Various approaches have been used for targeting drugs to the colon [1]. Chourasia and Jain indicated that a large number of polysaccharides already have been studied for their potential as colon-specific drug carrier systems, such as pectin, amylase, chondroitin sulphate, inulin, guar gum, dextran, chitosan, cyclodextrin, alginate, and locust bean gum [2]. Among them, glucomannan has become a particularly attractive polymer in the biomedical and drug delivery fields [3].

Konjac glucomannan (KGM), a water-soluble and high-molecular weight polysaccharide, is extracted from tubers of the *Amorphophallus Konjac* plant, consisting of 1,4-linked D-mannose and D-glucose in the ratio of 1.6∶1, with about 1 in 19 units being acetylated. It can be hydrolyzed by β-mannanase to manufacture manno-oligosaccharides which play important roles in biological systems [4,5,6]. In recent years, KGM gel, as a drug delivery matrix, has shown promising applications. Strong, elastic, heat-stable KGM gels can be formed with heating and mild alkali [7] and can be used as a drug carrier [8]. Wang and He reported on alginate-KGM-chitosan beads as a controlled release matrix [9]. Hydrogel systems of KGM cross-linked with trisodium trimetaphosphate were prepared for colon targeting drug delivery [10].

It has also been reported that xanthan gum (XG) has a

greater drug release retarding property and synergistically enhances gel properties in the presence of galactomannan like guar gum [11]. It was shown that the synergistic interaction between KGM and XG in the gel phase affects drug diffusion, which can effectively retard drug release from the matrix tablets [12,13]. Rheological measurements of KGM and KGM/XG systems incubated with and without *Aspergillusniger* β-mannanase (used to mimic colonic enzymes) showed that KGM was degraded by the enzyme even when interacting with XG [14].

Furthermore, compression coating has been found to be useful for colonic drug delivery. In order to evaluate a formulation with a considerably reduced coat weight and gum concentration for colonic drug delivery in vivo using gamma scintigraphy, rapidly disintegrating core tablets containing 99mTc-DTPA have been prepared and compression coated with 150 mg of granules containing a mixture of xanthan (XG), guar gum (GG) and starch [15]. It has also been reported that the use of konjac glucomannan-hydroxypropyl methylcellulose (HPMC) compression coated tablets is a promising delivery system for drug delivery in the colon [16]. A pectin-hydroxypropyl methylcellulose coating has been compressed onto core tablets labelled with 4MBq 99mTc-DTPA [17]. Though some attempts have been made to use compression coating to get the targeting release of drugs to the colon, the release mechanism, the theoretical model and the structure of the mixture polysaccharide have hardly been discussed in published papers.

In this paper, compression coated tablets with polysaccharide mixtures of KGM and XG as the controlled release materials were investigated and the release mechanism was analyzed. Cimetidine was used as the model drug in this paper. β-mannanase was employed to mimic the enzymatic attack of the bacterial enzymes in the colon. The structure of the mixture polysaccharide was studied by an atomic force microscope (AFM). The polysaccharide morphology was observed directly by AFM with adopting tapping, and the molecular chain was not destroyed [18]. The aim of our work was to describe the release process of the drug from compression coated tablets and the degradation properties of polysaccharide mixtures.

2 Materials and methods

2.1 Materials

Cimetidine was purchased from Baozhong Company (Shanghai, China). Multi-ring Co., Ltd (Hainan, China) provided the konjac glucomannan powder (the viscosity of 1% konjac powder solution was 30000 mPa·s). Xanthan gum (the viscosity of 1% xanthan gum powder solution was 20000 mPa·s) was obtained from Jinsu Co., Ltd (Shandong, China). Carboxymethyl starch sodium, lactose, talc and magnesium stearate used for the preparation of tablets were of pharmacopoeial grade. All the above materials were passed through a 154 μm mesh. β-mannanase was produced through published methods [19].

2.2 Preparation of cimetidine core tablets

Cimetidine and super-disintegrant carboxymethyl starch sodium (CMS) were mixed by wet granulation method with a certain volume of deionized water employed as the moistening agent. The wet mass was passed through a 900 μm mesh and the granules were dried to constant weight at 60°C. Then magnesium stearate 1% (w/w) was mixed with the dry granules. Conducting content uniformity tests on the samples of the mixture assessed the uniformity of the mixture. 220 mg mixed granule was compressed using 6 mm flat plain punches on a single punch tabletting machine (Guoyao Longli Co., Ltd, Beijing, China) with a compression force of 3500 kg. The compression core tablets of cimetidine had a diameter of 6.0±0.05 mm and a height of 2.5±0.02 mm. Their hardness was controlled within the range of 2.0 – 3.0 kg/cm^2. The content of cimetidine within the core tablet was controlled to be (90±1)% (w/w). The amount of drug and the weight of the core are shown in Table 1.

Table 1 Description of a compression coated tablet

amount of drug/g	weight of core/g	weight of coat/g	diameter/mm	height/mm
0.198±0.002	0.220±0.005	0.40	10.0±0.05	8.2±0.05
0.198±0.002	0.220±0.005	0.60	14.0±0.05	7.2±0.05

2.3 Preparation of compression coated tablets

The compression coat material containing polysaccharides 43% (w/w) and lactose 56% (w/w) were mixed by wet granulation method with a certain volume of deionized water employed as the moistening agent. The wet mass was passed through a 900 μm mesh and the granules were dried to constant weight at 60°C. Then the dry granules were mixed with magnesium stearate 1% (w/w). Different proportions of the KGM & XG are outlined in Table 2.

Table 2 Proportions of KGM and XG in the polysaccharide mixtures of the compression coat

code name	KGM0	KGM 30	KGM 50	KGM 70	KGM 90	KGM 100
KGM/(w/w, %)	0	30	50	70	90	100

In the coating progress, 43% (w/w) of the coat material was placed in the die cavity followed by carefully centering the core tablet and adding the remainder of the coating material. The coating material was compressed

around the core tablet using 10 mm or 12 mm round concave punches with a force of 5000 kg. Then, the hardness, shape, drug content, uniformity and drug release characteristics of the compression coated tablets with different compositions were tested on more than 5 tablets for each test.

The hardness of the compression coated tablets was controlled in the range of 7.0 – 9.0 kg/cm^2. The punches of two sizes were used in the studies due to the weight changes of the coating material. The diameters of the tablets with different outer compression coat weights are shown in Table 1.

2.4 Drug release studies *in vitro*

The compression coated tablets were evaluated for their drug release properties in the physiological environment under conditions mimicking mouth to colon transit. These studies were carried out using a USP XXIII dissolution test apparatus (apparatus 1100 rpm, 37°C) (Tianfa Instrument Co., Ltd. Tianjin China). The tablets were tested for drug release for 2 hours in 0.1 mol·L^{-1} HCl (900 mL), as the average gastric emptying time is about 2 hours. Then the dissolution media were replaced by pH 7.4 phosphate buffers (900 mL) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours. At the end of a certain time period, the tablets were assessed by continuing the drug release studies in media of pH 6.8 phosphate buffers with and without β-mannanase content. The medium of 0.220 U/mL β-mannanase should be employed to mimic the colonic environment in further studies in vitro [12]. The dissolution method was similar to that reported earlier [20]. Samples of a certain volume were taken and analyzed to find the amount of drug released from the tablets by an ultraviolet-visible spectrophotometer at a wavelength of 218 nm. The drug release data was then calculated.

2.5 Atomic force microscopy of polysaccharides

KGM and XG, at a concentration of 0.02% (w/v) with 0.1 mol·L^{-1} NaCl as solvent, were prepared by the methods of Kirby [21]. Drops of the solution (2 μL) were applied to freshly cleaved mica surfaces, which were dried in air for about 10 min, and then became images in air at room temperature.

The atomic force microscope used in the study was the Nanoscope IIIa mmspm type (Digital Instrument Inc., USA) The Nanoprobe™ (Digital Instrument Inc., USA) cantilevers were used. Sample size ⩽ 10 mm, scan range 6 μm × 6 – 20 μm × 20 μm, ability to distinguish (based on the crystal lattice of mica surface): *X*-axis and *Y*-axis 0.4 nm, *Z*-axis < 0.1 nm, needlepoint approaching range ⩾ 20 mm, precision ⩽ 0.1 μm. The images were obtained under tapping mode and the touch force was controlled in the range of 3 – 4 nN.

3 Results and discussion

3.1 Drug release from system without enzyme

The drug release from KGM30, KGM50, KGM70, KGM100 and KGM0 tablets are given respectively in Fig. 1. For the first 5 hours of drug release, all of the release media have no enzymes. The delay of drug release can be found at the initial stage and the delay time is shown in Table 3.

Table 3 Delay time of the drug release from different systems (the percentage of cumulative release of drug is < 1%)

name	KGM0	KGM30	KGM50	KGM70	KGM100
0.4 g of coating/h	—	2	4	3	—
0.6 g of coating/h	2	4	5	5	2

Once tablets are put into the dissolution media, the compression coat begins to absorb water. When the compression coat is swelled to certain degree, the solution diffuses into the core tablet and the drug is dissolved and released. The delay time of KGM 50 is longer due to the strong interaction between KGM and XG. It was reported that the evaluated Japanese and the European KGM show a synergistic interaction with XG at the ratio of one to one, leading to strong gels when the total polysaccharide concentration is 0.5% (w/v) [22]. The delay time of KGM 70 is similar to that of KGM50 because the swelling volume of KGM 70 is bigger than that of KGM50 and the diffusion path is prolonged.

After the delay of drug release, the coating gel continues swelling. The stable structure of coating is obtained. At this stage, the drug release without an enzyme is assumed to be in accord with Fick's first law:

$$\frac{\mathrm{d}Q_t}{\mathrm{d}t} = D_a, \tag{1}$$

and after integration

$$Q_t = D_a t + c, \tag{2}$$

where Q_t is the percentage of cumulative release, D_a is the apparent diffusion parameter, h^{-1}, t is the release time, h, c is the constant.

The calculated results are shown in Table 4. It is indicated from Table 4 that Fick's first law can be applied to describe the release process for a period of time due to the parameter of linear regression $R^2 > 0.90$. Moreover, a multi-constant release stage can be found, such as in KGM50 with 0.4 g coating. Furthermore, the thicker the coat used, the lower the D_a and a longer duration is obtained owing to increase of the diffusion path and the tablet stability. In addition, it is shown from Table 4 that D_a of a single polysaccharide (KGM100 and KGM0 system) is bigger than that of a mixture polysaccharide due to the strong interaction between KGM and XG.

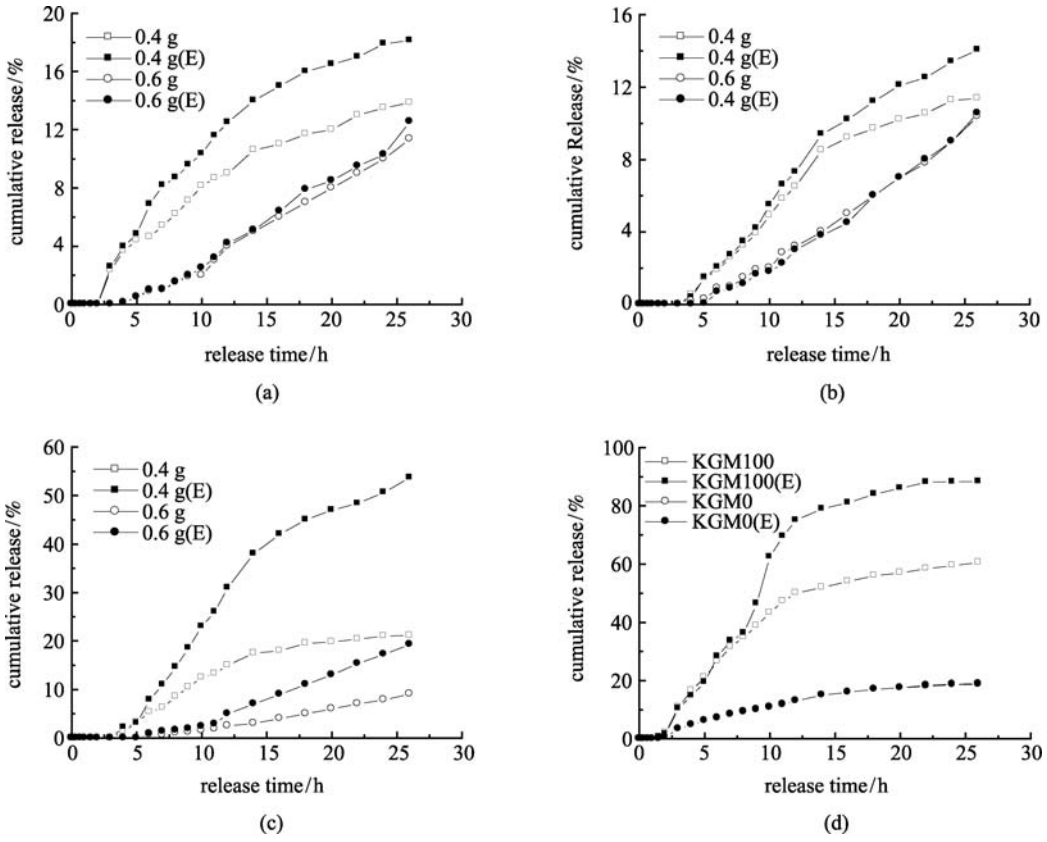

Fig. 1 Drug release from cimetidine compression coated tablets. (a) KGM30; (b) KGM 50; (c) KGM70; (d) KGM100 and KGM 0 with 0.6 g coating; (E) denotes the dissolution media containing 0.220 U/mL β-mannanase. Drug release for 2 hours in 0.1 mol·L^{-1} HCl, then for 3 hours in pH 7.4 phosphate buffers (900 mL), at the end of time in media of pH 6.8 phosphate buffers with or without 0.220 U/mL β-mannanase content

Table 4 Calculated results of the constant release rate without enzyme

coating	name	D_a/h^{-1}	c/h^{-1}	R^2	release time/h	n
0.4 g	KGM30	0.730	0.472	0.9911	3–14	11
	KGM50	0.789	−2.88	0.9907	5–14	9
		0.262	4.93	0.9904	14–24	6
	KGM70	1.66	−4.38	0.9919	4–14	10
0.6 g	KGM0	1.01	0.878	0.9950	3–14	11
	KGM30	0.546	−2.91	0.9957	7–26	13
	KGM50	0.484	−2.63	0.9958	8–26	12
	KGM70	0.452	−2.98	0.9940	8–26	12
	KGM100	4.35	−0.498	0.9938	3–12	10

3.2 Drug release from KGM100 with enzyme

It is seen from Fig. 1 (d) that the KGM100 system has a good response to hydrolysis of the enzyme, but the drug leak within 5 hours reaches 20%. However, XG (KGM0) has a good ability to restrain the drug release but has no response to β-mannanase. It is well known that XG is non-digestible in humans and is used to lower the calorific content of foods [23].

It has been reported that the theoretical model for drug release from a biodegradable matrix is proposed with two assumptions: correlation of the diffusion coefficient with the average polymer molecular weight and existence of a first order degradation kinetic [24]

$$\frac{D_t}{D_0} = \frac{\overline{M_0}}{\overline{M_t}} = \mathrm{e}^{kt}, \tag{3}$$

where D_t and D_0 are the diffusion coefficient at time t and initially, and $\overline{M_t}$ and $\overline{M_0}$ are the average polymer molecular weights at time t and initially, where k is the constant of degradation. A comparison between Eqs. (1) and (3) leads to

$$\frac{\mathrm{d}Q_t}{\mathrm{d}t} = D_0\mathrm{e}^{kt}. \tag{4}$$

If $t = 0$ and $Q_{t=0} = 0$, this leads to the expression of the amount of drug release as a function of time:

$$Q_t = \frac{D_0}{k} \times \mathrm{e}^{kt}. \tag{5}$$

The concentration of drug is zero at the initial time tablets are put into the mimic colon solution. Regression results from Eq. (5) are displayed in Table 5 and Fig. 2. We can see that this model presents a good representation from 0 to 6 hours of degradation time. For the corresponding period of KGM100 without enzyme, the apparent diffusion parameter D_a is constant. D_0 should be equal to D_a. However, the value of D_0 is obviously lower than the value of D_a (Table 4, D_a of KGM100 = 4.35). The reasons should be further discussed. Furthermore, an obvious error appears at the initial time (Fig. 2), because the diffusion of the enzyme into the coat needs time. After 6 hours of degradation, the drug content of the core tablet is reduced quickly, which leads to a decrease in the diffusion drive, and then Eq. (5) can not be applied.

Table 5 Regressive results by Eq. (5) (KGM100, 0.6 g coating)

D_0	k	R^2	degradation time/h	release time/h	n
2.24	0.357	0.9562	0–6	5–11	7

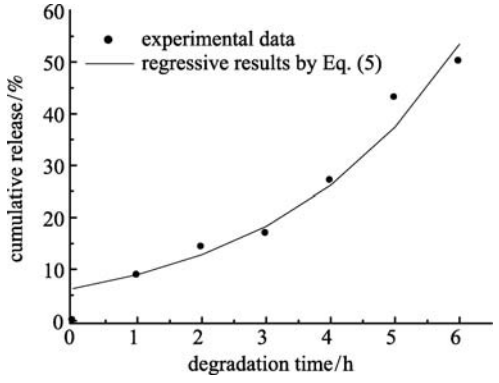

Fig. 2 Experimental data and regressive curve by Eq. (5) (KGM100, 0.6 g coating)

3.3 Drug release from mixture polysaccharide with enzyme

Comparing with KGM30 (Fig. 1(a)) and KGM 70 (Fig. 1(c)), the increase of drug release by degradation from the KGM 50 system (Fig. 1(b)) is the least for the strong interaction between KGM and XG. A good colon drug delivery system should have lower drug loss in mimicking upper gastrointestinal media, better triggering of drug release under the action of the colon enzymes, smaller diameter of tablets, and so on. In this paper, for KGM70 tablets with a 0.4 g coat (Fig. 1(c)), cumulative drug release did not exceed 5% after the first 5 hours but rose up to 50% through the action of β-mannanase after 24 hours. Furthermore, patients could accept the 10 mm diameter tablets. Therefore, the KGM70 tablets with a 0.4 g coat weight percentage should be the best dosage design for colon drug delivery in studies.

When the coat is thicker (0.6 coat) or contains less KGM, an obvious delay time of degradation is presented, as seen in Table 5. In this case, the concentration of enzyme within the coat gel is very low and there is no obvious rise of drug release through degradation of β-mannanase (the difference of percentage of cumulative release between with and without enzyme is $< 1\%$).

Furthermore, it is seen that the application of Eq. (5) to the mixture polysaccharide system is not good because the average polymer molecular weight of XG is unchangeable. If we assume

$$\overline{M_0} = A_X\overline{M_{X0}} + A_K\overline{M_{K0}}, \tag{6}$$

$$\overline{M_t} = A_X\overline{M_{X0}} + A_K\overline{M_{K0}}\mathrm{e}^{-kt}, \tag{7}$$

where $\overline{M_{X0}}$ and $\overline{M_{K0}}$ is, respectively, the average polymer molecular weight of XG and KGM, where A_X and A_K is, respectively, the mass ratio of XG and KGM. B is defined as

$$B = \frac{A_K\overline{M_{K0}}}{A_X\overline{M_{X0}}}. \tag{8}$$

Introduce Eqs. (6), (7) and (8) into Eq. (3)

$$\frac{D_t}{D_0} = \frac{1+B}{1+B\mathrm{e}^{-kt}}. \tag{9}$$

Assume

$$B\mathrm{e}^{-kt} \ll 1, \tag{10}$$

then

$$\frac{D_t}{D_0} \approx 1 + B. \tag{11}$$

It is demonstrated that the diffusion coefficient by degradation of the enzyme is approximately constant. D_0 is equal to D_a, then D_{tcal} is defined as

$$D_{tcal} = D_a(1+B). \tag{12}$$

D_{treg} is obtained from experimental data by linear representation. The error is defined as

$$E = \frac{|D_{Treg} - D_{Tcal}|}{D_{Treg}} \times 100. \tag{13}$$

We have known $\overline{M_{K0}} = 1.05 \times 10^6$, $\overline{M_{X0}} = 2.13 \times 10^6$ by static laser light scattering, then

$$\frac{\overline{M_{K0}}}{\overline{M_{X0}}} \approx 0.5. \tag{14}$$

Regression and calculation results are shown in Table 6. A good representation appeared for the polysaccharide mixture coat. Under degradation, the drug diffusion coefficient of the KGM system is a function of time,

while that of the mixture polysaccharide system is approximately constant. This is a very interesting result.

It is very important how to control the drug release. If we want to get a period of zero-order drug release, firstly, the main structure of the coating gel must remain stable, namely, XG is the framework of the mixture polysaccharide gel. The KGM between two macromolecular chains of XG is hydrolyzed by the enzyme, which forms release pores. It is an adequate content of XG within the coat gel that can maintain coat structure stability, which can be used to explain the experimental results from Table 6 that E is decreased with the increase in XG.

Table 6 Regression results from the mixture polysaccharide system

coating	name	D_a	$1+B$	D_{Tcal}	D_{Treg}	release time/h	E/%	R^2	n
0.4 g	KGM30	0.730	1.15	0.840	0.886	6–14	0.34	0.9948	8
	KGM50	0.262	1.5	0.393	0.397	14–24	1.01	0.9899	6
	KGM70	1.66	2.17	3.60	3.84	6–14	6.25	0.9978	8
0.6 g	KGM70	0.452	2.17	0.981	1.06	10–26	7.45	0.9972	10

Second, the degradation rate of the coating gel is proper. When the concentration of the enzyme within the coating is very low, there is no obvious rise of drug release by the enzyme and the delay of degradation emerges such as seen in the result from Table 7. If the faster degradation rate appears and Eq. (10) $Be^{-kt} \ll 1$ is satisfied, constant release is gained. In case of a very high degradation rate, the network of the coating gel is destroyed quickly and the burst release like the KGM100 system takes place. In a reported paper [16], the enzyme concentration in the mimic colon solution was higher than that in this paper (0.22 U/mL β-mannanase), which showed drug release presenting an exponential increase similar to Eq. (5).

Table 7 The delay time of degradation (the difference of percentage of cumulative release from solution with and without enzyme is $< 1\%$)

name	KGM30	KGM50	KGM70
0.4 g of coating	< 1 h	9 h	< 1 h
0.6 g of coating	19 h	> 21 h	5 h

3.4 AFM images of polysaccharides

In order to prove the above results, the structure of the mixture polysaccharide was studied by AFM. It can be found from Fig. 3(a) that the molecular chains of KGM are disordered. The chain length of KGM is 260–700 nm, which is less than the reported value (982.82 nm) [25] due to the winding molecular chains. The width of KGM is 17.5 nm, which is much greater than the theoretical width (0.1–1 nm) due to probe broadening by the finite curvature of the probe. Molecular chains of XG present a straight chain structure (Fig. 3(a)). The length and the width of the chain are, respectively, 1080 nm and 4.8 nm, which are similar to the reported values [21].

The AFM image of the polysaccharide mixtures is revealed in Fig. 3(c). A clear three-dimensional network is formed by KGM and XG molecular chains. The width of the inner chain of the network is within the range of 15–20 nm, close to the width of KGM. In addition, the width of the outer extended molecular chain is 39.1 nm, approaching the width of XG. It is demonstrated that XG is the framework of the polysaccharide mixtures, which resembles the analysis results from 3.3.

4 Conclusions

In this paper, compression coated tablets with polysaccharide mixtures of KGM and XG as the controlled release materials were investigated. The experimental results indicate that the polysaccharide mixtures of KGM and XG as the compression coat have a great potential in the application of colonic drug delivery systems. The synergistic interaction between XG and KGM reduces drug loss in the mimic upper gastrointestinal solution. At the same time, the coat maintains a good response to degradation due to the hydrolysis of KGM.

Furthermore, the release mechanism was analyzed based on different periods of drug release, including drug delay, a constant release rate without an enzyme and the delay of degradation by an enzyme. It is notable that the degradation model is different between the KGM100 system and the mixture polysaccharide. The stable network structure and the proper degradation rate results in a

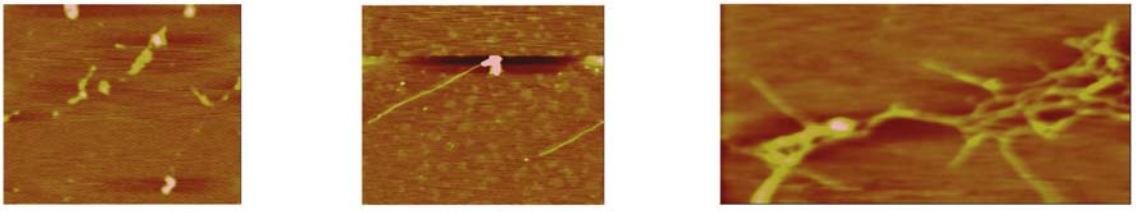

Fig. 3 AFM image of KGM (a), XG (b) and network of mixture polysaccharide (c)

constant release velocity which relates to the drug release speed of a non-degraded system, the content of KGM within the mixture polysaccharide and the average molecular weigh ratio of KGM to XG.

Moreover, the structure of the mixture polysaccharide was researched by AFM, which is helpful to understand the mechanism of drug release. XG is the framework of polysaccharide mixtures and KGM is embedded in this network.

These results could be used for the front stages of the drug release process. The back stages of drug release are very complicated and are not discussed in this paper. Of course, further improvements are necessary for the application of KGM to the oral colon drug delivery systems and the validation of the release mechanism and models.

Acknowledgements The authors are grateful for the financial support from Grand project of Tianjin City, China (No. 07ZCZDGX19600).

References

1. Kinget R, Kalala W, Vervoort L, Mooter G V. Colonic drug targeting. J Drug Target, 1988, 6(2): 129–149
2. Vandamme T F, Lenourry A, Charrueau C, Chaumeil J. The use of polysaccharides to target drugs to the colon. Carbohyd Polym, 2000, 48(3): 219–231
3. Alonso-Sande M, Teijeiro-Osorio D, Remunan-Lopez C, Alonso M J. Glucomannan, a promising polysaccharide for biopharmaceutical purposes. European Journal of Pharmaceutics and Biopharmaceutics, 2009, 72: 453–462
4. He Z M, Zhang J, Huang D P. A kinetic correlation for konjac powder hydrolysis by β-mannanase from *Bacillus licheniformis*. Biotechnol Lett, 2001, 23(5): 389–393
5. Huang C Y, Zhang M Y, Peng S S. Effect of konjac food on blood glucose level in patients with diabetes. Biomed Environ Sci, 1990, 3 (2): 123–131
6. Vuksan V, Jenkins D J, Spadafora P. Konjac-mannan (glucomannan) improves glycemia and other associated risk factors for coronary heart disease in type 2 diabetes. A randomized controlled metabolic trial. Diabetes Care, 1999, 22(6): 913–919
7. Dave V, Sheth M, McCarthy S P, Ratto J A, Kaplan D L. Liquid crystalline, rheological and thermal properties of konjac glucomannan. Polymer, 1998, 39(5): 1139–1148
8. Nakano M, Takikawa K, Arita T. Release characteristics of dibucaine dispersed in konjac gels. J Biomed Mater Res,1979, 13: 811–819
9. Wang K, He Z M. Alginate-konjac glucomannan-chitosan beads as controlled release matrix. Int J Pharm, 2002, 244(2): 117–126
10. Liu M M, Fan J Y, Wang K, He Z M. Synthesis, characterization, and evaluation of phosphated cross-linked konjac glucomannan hydrogels for colon-targeted drug delivery. Drug Delivery, 2007, 14 (6): 397–402
11. Sinha V R, Mittal B R, Bhutani K K, Kumria R. Colonic drug delivery of 5-fluorouracil: an in vitro evaluation. Int J Pharm, 2004, 269(1): 101–108
12. Fan J Y, Wang K, Liu M M, He Z M. In vitro evaluations of konjac glucomannan and xanthan gum mixture as the sustained release material of matrix tablet. Carbohydrate Polymers, 2008, (73): 241–247
13. Paradossi G, Chiessi E, Barbiroli A, Fessas D. Xanthan and glucomannan mixtures: synergistic interactions and gelation. Biomacromolecules, 2002, 3(3) : 498–504
14. Alvarez-Mancenido F, Landin M, Martinez-Pacheco R. Konjac glucomannan/xanthan gum enzyme sensitive binary mixtures for colonic drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 2008, 69: 573–581
15. Sinha V R, Mittal B R, Kumria R. In vivo evaluation of time and site of disintegration of polysaccharide tablet prepared for colon-specific drug delivery. Int J Pharm, 2005, 289(1–2): 79–85
16. Zhang Y, Hou S X, Lu Y, Chen G, Ju J H. Study on preparation of konjac glucomannan-hydroxypropyl methyl cellulose compression coated tablets for colonic delivery and in vitro release. China Journal of Chinese Materia Medica (Zhongguo Zhong Yao Za Zhi), 2006, 31(8): 642–645 (in Chinese)
17. Hodgesa L A, Connollya S M, Banda J. Scintigraphic evaluation of colon targeting pectin-HPMC tablets in healthy volunteers. International Journal of Pharmaceutics, 2009, 370: 144–150
18. Rief M, Oesterhelt F, Heymann B, Gaub H E. AFM, a tool for single-molecule experiments. Science, 1997, 275(21): 1295–1297
19. Feng Y Y, He Z M, Ong S L, Hu J Y, Zhang Z G, Ng W J. Optimization of agitation, aeration, and temperature conditions for maximum β-mannanase production. Enzyme Microb Tech, 2003, 32 (2): 282–289
20. Krishnaiah Y S R, Satyanarayana V, Dinesh Kumar B, Karthikeyan R S. In vitro drug release studies on guar gum-based colon targeted oral drug delivery systems of 5-fluorouracil. Eur J Pharm Sci, 2002, 16(3): 185–192
21. Kirby A R, Gunning A P, Morris V J. Imaging xanthan gum by atomic force microscopy. Carbohyd Res, 1995, 267(1): 161–166
22. Alvarez-Manceñido F, Landin M, Lacik I, Martínez-Pacheco R. Konjac glucomannan and konjac glucomannan/xanthan gum mixtures as excipients for controlled drug delivery systems. Diffusion of small drugs. International Journal of Pharmaceutics, 2008, 349:11–18
23. Whistler R L, Bemiller J N. Xanthan, Gellan, Welan, and Rhamsan. In: Whistler R L, Bemiller J N, eds. Industrial Gums. Polysaccharides and Their Derivatives. 3rd ed. New York: Academic Press, 1993, 341–371
24. Charlier A, Leclerc B, Couarraze G. Release of mifepristone from biodegradable matrices: experimental and theoretical evaluations. Int J Pharm, 2000, 200(2): 115–120
25. Li B, Xie B J, John F K. Studies on the molecular chain morphology of kongjac glucomannan. Carbohydr Polym, 2006, 64(4): 510–515