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In vitro evaluations of konjac glucomannan and xanthan gum mixture as the sustained release material of matrix tablet

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Abstract

The objective of the present investigations was to develop sustained release matrix tablets with a mixture of the polysaccharides, konjac glucomannan (KGM) and xanthan gum (XG), as the sustained release material. A simple enzymatic procedure was selected to mimic the environment of colon in vitro assessments. The concentration of β-mannanase solution in mimic colon media was determined by comparing the hydrolytic ability of the mimic colon solution with that of 4% (w/v) rat cecal content media. In vitro, investigations were carried out to characterize the drug release process. The model drug cimetidine released from polysaccharides gel layer of matrix tablets over 10 h. It was shown that the synergistic interaction between konjac glucomannan and xanthan gum in the gel phase affects on the drug diffusion, which can effectively retard the drug release from the matrix tablets. Further research on the mixed polysaccharides indicated that there was a strong synergistic interaction between KGM and XG in solution and in the gel phase. The experimental results predicted that the polysaccharide mixtures of konjac glucomannan and xanthan gum has a good potential to be applied to sustained release drug delivery systems.

Keywords: Konjac glucomannan; Xanthan gum; Sustained release matrix tablet; Synergistic interaction

1. Introduction

Naturally occurring polysaccharides have been paid a lot of attention in drug controlled release as these polymers are nontoxic, safe, hydrophilic and biodegradable. These polymers have found potential applications as carriers for the development of novel pharmaceutical formulations and the delivery of drugs. As they are not metabolised in the upper gastrointestinal tract (GIT), some studies were carried out based on the activity of colonic bacterial enzymes that are capable of degrading a variety of polysaccharides present in the diet (Sinha & Kumria, 2003).

Konjac glucomannan (KGM) is a high-molecular weight polysaccharide that is extracted from tubers of the *Amorphophallus konjac* plant. It has the structure of a linear random copolymer of $\beta(1 \rightarrow 4)$ linking D-mannose and D-glucose in the ratio of 1.6:1, with approximately one in nineteen of the sugar units being acetylated. KGM can not be hydrolyzed by digestive enzymes in the human upper gastrointestinal tract and is considered as an indigestible dietary fiber that can reduce the risk of developing diabetes and heart disease (Huang, Zhang, & Peng, 1990; Vuksan, Jenkins, & Spadafora, 1999). It can be hydrolyzed by β-mannanase to produce manno-oligosaccharides which play an important role in biological systems (He, Zhang, & Huang, 2001). Strong, elastic, heat-stable gels are formed when heated with mild alkali (Dave, Sheth, McCarthy, Ratto, & Kaplan, 1998) and also used as drug carrier (Nakano, Takikawa, & Arita, 1979). Some studies revealed that the graft copolymers of KGM and acrylic acid retained the enzymatic degradable specificity and had the potential for the colon-specific delivery of protein or peptide drugs (Liu, Hu, & Zhuo, 2004). Alginate–konjac glucomannan–

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chitosan beads was used as controlled release matrix (Wang & He, 2002). There were some other attempts to use KGM in drug delivery (Zhang, Xie, & Gan, 2005).

Xanthan gum (XG) is known to retard drug release considerably (Talukdar & Kinget, 1995). It is reported that XG has a greater drug release retarding property and synergistically enhanced gel property in the presence of galactomannan gums. It is well known that xanthan gum is non-digestible in humans and serves to lower the calorific content of food and improve their passage through the upper gastrointestinal tract (Kang & Pettitt, 1993). The polysaccharide composition consisting of XG as a drug release retarding agent combined with colon degradable polysaccharides, guar and starch could be successfully used to protect drug from releasing under conditions mimicking mouth-to-colon transit (Sinha, Mittal, Bhutani, & Kumria, 2004). The strong synergistic interaction between KGM and XG had been studied intensively (Annable, Williams, & Nishinari, 1994; Goycoolea, Richardson, Morris, & Gidley, 1995).

Cimetidine is used as the model drug in this paper. It is a histamine type-2-receptor antagonist that is commonly prescribed to treat gastro-esophageal reflux diseases as well as gastric and duodenal ulcer (Freston, 1982). Accumulated evidence suggests that cimetidine may improve the survival of patients with malignant tumor, including gastric and colorectal carcinomas (Burtin et al., 1988; Tonnesen et al., 1988). Further investigation shows that cimetidine suppresses tumor growth by inhibiting tumor-associated angiogenesis (Takeshi, Masataka, Ryozo, & Masatoshi, 2005). Therefore, it is necessary to sustain the release of cimetidine over a long period to treat diseases.

It was the aim of the present investigation to develop new materials for sustained drug release. The drug release profiles of the matrix tablets with polysaccharide mixtures of KGM and XG as a sustained release material and the potential application of KGM for oral sustained release drug delivery were studied. The matrix tablets with cimetidine as the model drug were made with the mixture of KGM and XG as drug release-retarding ingredients, which were proposed to sustain drug release more significantly in the condition of the upper GIT but still retain the biodegradability due to the presence of KGM. β-mannanase was employed to mimic the hydrolyzation of colon bacterial enzymes to polysaccharides. The concentration of β-mannanase solution in mimic colon media was determined by comparing the hydrolytic ability of mimic colon solution with that of 4% (w/v) rat cecal content media.

2. Materials and methods

2.1. Materials

Cimetidine (98–101% purity) was purchased from Baozhong pharmaceutical factory (Shanghai, China). Multiring Co., Ltd. (Hainan, China) provided the konjac glucomannan powder (the viscosity of 1% konjac powder solution was 30,000 mPa s). Xanthan gum was obtained from Jinsu Co., Ltd. (Shandong, China) (the viscosity of 1% xanthan gum powder solution was 20,000 mPa s). The viscosities of the solutions were tested by a DV-II+ Pro revolving viscosity meter (Brookfield Asset Management Inc. USA) with a rotational speed of 30 rpm at 25 ± 1 °C. Carboxymethyl starch sodium, lactose, talc and magnesium stearate used for the preparation of tablets were Pharmacopoeial grade. All the above materials were passed through a 154 μm mesh. β-Mannanase was prepared from *Bacillus licheniformis* as described by the published methods (Feng et al., 2003).

2.2. Preparation of matrix tablets of cimetidine

Matrix tablets of cimetidine were prepared by the wet granulation method. Lactose was used as diluent and a mixture of talc – magnesium stearate (3:1) was used as lubricant. KGM and XG were included in the formulations of various proportions which are shown in Table 1. The polysaccharide mixtures content was 20% (w/w) of the total formulations weight. The composition of different formulations used in the study containing 50% (w/w) of cimetidine in each case is shown in Table 1. In all formulations, the powders of polysaccharides were mixed with cimetidine by sieving with a 450 μm mesh. The powders were blended and granulated with lactose at a weight content of 26% (w/w) with a certain volume of deionized water as the moistening agent. The wet mass was passed through a mesh (900 μm) and the granules were dried to constant weight at 60 °C. The particle size distributions of the mixed material were measured by a sieving method. Then, the dried granules were mixed with a mixture of talc and magnesium stearate (3:1). The mixture was compressed into tablets using 10 mm round arc punches on a single station tabletting machine (Guoyao Longli Co., Ltd., Beijing, China) with the hardness between 3 and 5 kg/cm^2. The hardness of the matrix tablets was determined by the hardness tester (Xintianguang instrument Co., Ltd. Tianjin China). Matrix tablets were tested for their drug content, uniformity and drug release characteristics with a suitable number of tablets for each test. The amount of cimetidine in matrix tablet was determined to be 505 ± 5 mg, and the cimetidine content was 50 ± 1% (w/w). The tablets used in the same studies were made in the same batch and the uniformity of the tablets was tested.

2.3. Determination of model drug content

The drug content of the matrix tablets was decided. The tablets were grinded to fine powder and a certain amount of the powder was weighed exactly and transferred to volumetric flasks, which were then filled to scale with pH 7.4 phosphate buffers. After complete drug dissolution, the solutions were filtered through 0.8 μm membrane and analyzed using No. 752 ultraviolet–visible spectrophotometer

Table 1
Proportions of the KGM and XG in the polysaccharide mixtures of the formulations

Code name	KGM0	KGM 30	KGM 50	KGM 70	KGM 90	KGM 100
KGM (%)	0	30	50	70	90	100
XG (%)	100	70	50	30	10	0

(Precision & Scientific instrument Co., Ltd. Shanghai China) at 218 nm for the content of cimetidine.

2.4. Preparation of mimic enzymatic media of colon

The mimic enzymatic media of colon was prepared for β-mannanase and cecal content of rats. Male wistar rats fed by a normal diet were used in the test. The weight of the rats was controlled within 200–250 g. Eight rats were killed by spinal traction. The abdomens of the rats were opened and the cecal were found, ligated at both ends, dissected, and immediately transferred into, pH 6.8, phosphate buffers bubbled with nitrogen to keep anaerobic conditions. After that, the cecal bag was opened and the content was put into the solutions. The dissolution media was then diluted to 4% (w/v). The care of the rats was in accordance with the European convention for the protection of vertebrate animals used for Experimental and other Scientific Purposes (Council of Europe No. 123, Strasbourg 1986).

2.5. In vitro drug release studies

The matrix tablets of cimetidine were evaluated for their drug release ability in the physiological environment under conditions mimicking mouth to colon transit. There studies were carried out using a USP XXIII dissolution rate test apparatus (apparatus 1, 100 rpm, 37 °C). The tablets were tested for drug release for 2 h in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced by, pH 7.4, phosphate buffers (900 ml) and tested for drug release for 3 h, as the average small intestinal transit time is about 3 h. The ability of the matrix tablets of cimetidine to release in the physiological environment of the colon was assessed by continuing the drug release studies in a medium of, pH 6.8, phosphate buffers with and without β-mannanase content. At the end of this time, samples of a certain volume were taken and analyzed to find the amount of drug released from the tablets by ultraviolet–visible spectrophotometer at a wavelength of 218 nm. The drug release data was then calculated. The cumulative percentage of cimetidine released from the tablets ($n = 3$) in the dissolution medium with and without enzyme contents was compared, and the statistical significance was tested by a Student's t-test. A value of $P < 0.05$ was considered statistically significant.

2.6. Viscosity test of the mixed polysaccharides solutions

The solutions of separate 0.5% KGM and XG were mixed in different proportions. The viscosities of the polysaccharide mixtures solutions were tested by a DV-II+ Pro revolving viscosity meter (Brookfield Asset Management Inc. USA) with different rates of shear at 25 ± 1 °C.

2.7. IR studies of the mixed polysaccharides

The powder of KGM, XG and the mixtures of the polysaccharide were dispersed in water, and then dried at 60 °C to make sample films. The films were blended with potassium bromide and laminated, and their IR spectra were studied by an FTS3000 Fourier transform infrared spectrophotometer (Bio-Rad Co., Ltd. USA).

3. Results and discussion

3.1. Particle size distributions of the mixed granules

In the process of the wet granulation, the same weight of water was sprayed to the mixtures at the same time intervals, which were composed of cimetidine, lactose, KGM and XG in different ratios. The particle size distributions of the mixed material were measured by sieving after being dried at 60 °C to constant weight and the results are shown in Table 2.

It can be found from Table 2 that the granules with different compositions of KGM and XG have different particle size distributions as mixed with the same mass of water over the same interval. The result may depend on the different absorbed abilities of the polysaccharide mixtures. The mixture of KGM100 (without XG) had a higher rate of gel formation, and could not adhere to other powders to form granules. The granules of KGM100 therefore have the finest powder distribution after the wet granulation, but may not meet the requirements of tablet preparation. It can be found that the addition of XG could increase the adhesive performance of the polysaccharides gel, and the proportion of fine powder decreased effectively with the increase of XG content. In the first instance, the absorptive and swollen performance of XG is different from that of KGM. Secondly, there was no interaction between KGM and XG powder in the dry blend before the addition of water, and then, some polysaccharide mixture hydrogel was formed with water in the process of wet granulation, the synergetic interactions between KGM and XG caused the hydrogel of mixture to have a different absorptive and swollen capability from either KGM or XG. Both of them were likely to contribute to the wide distribution of particle size for tablet preparation in the process of the wet granulation. The formulation of KGM30 had the least fine powder content of all formulations and by far the largest content of particles was found in the size

Table 2
The Particle size distributions of the mixed materials

Particle size distributions (%)	KGM0	KGM10	KGM30	KGM50	KGM70	KGM90	KGM100
⩾900 μm	0.01	0.34	0	1.47	0.23	0.05	0
450–900 μm	19.47	17.29	17.46	23.17	16.86	21.89	16.48
280–450 μm	13.71	15.70	26.59	36.58	22.92	17.45	14.22
180–280 μm	29.90	22.18	41.62	17.03	32.33	25.28	14.65
154–180 μm	24.10	37.62	12.71	12.01	18.17	25.48	28.81
⩽154 μm	12.69	6.86	1.62	8.74	9.48	9.84	25.82

of 180–280 μm. The distribution of it may be more appropriate for the preparation of tablets.

3.2. Determination of the concentration of β-mannanase solution to mimic colon solution

Enzymes were used for drug release in vitro to mimic the colon conditions in previous studies (Chen, Liu, & Zhuo, 2005; Gliko-Kabir, Yagen, Baluom, & Rubinstein, 2000). However, they did not discussed how to determine the amount of enzyme closing to the hydrolyzation ability of microflora in the colon. In this study, matrix tablets of cimetidine with KGM as a sustained release material were employed in dissolution studies in order to compare the hydrolyzation ability of media containing different amounts of β-mannanase with that of 4% (w/v) rat cecal solutions.

It is found from Fig. 1 that the KGM matrix tablets had a good response to the β-mannanase and the microflora of rat cecal. It showed the obvious variety of drug release rates among the media containing different quantities of β-mannanase. When the concentration of enzyme increased, the release rate of drug from matrix tablets accelerated. It can be found that the release rate of the drug in the media of 0.220 U/ml β-mannanase was similar with that in the 4% (w/v) rat cecal content solution. The media of 0.220 U/ml β-mannanase should be employed to mimic the colon environment in the following studies in vitro.

It was reported that the proper concentration of the β-mannanase solution simulating colon condition was 0.166 U/ml (Burke, Park, Srinivasarao, & Khan, 2005). The drug released in vitro in the presence of a certain amount of α-galactosidase could predict performance in vivo more accurately (Wong, Larrabee, Clifford, Tremblay, & Friend, 1997). Based on the different hydrolysis abilities between β-mannanase and α-galactosidase, the activity of β-mannanase was calculated. The results in this paper were similar to the open reference. Differences in the data may result from the different experimental methods employed.

3.3. Drug release from the matrix tablets with KGM or XG as sustained release materials

The ability of the polysaccharides to retain the release of cimetidine in the physiological environment of stomach and small intestine was assessed by drug release studies in mimic stomach, small intestinal and colon environments. The profiles of drug release from the tablets with single polysaccharide (KGM or XG) as sustained release materials were shown in Fig. 2.

It can be seen from Fig. 2 that the drug release rates of the matrix tablets with KGM and XG were different in various dissolution media. In the first 2 h, more drugs were released from the tablets using XG as sustained release materials than using KGM over the same time interval. However, the cumulative drug release data at the end of 2 h were similar. The drug release rate of KGM100 was faster than that of KGM0 in the dissolution media mimicking small intestine and colon. It was found that β-mannanase had clear accelerative effect on drug release from KGM100 tablets. There was an obvious difference between

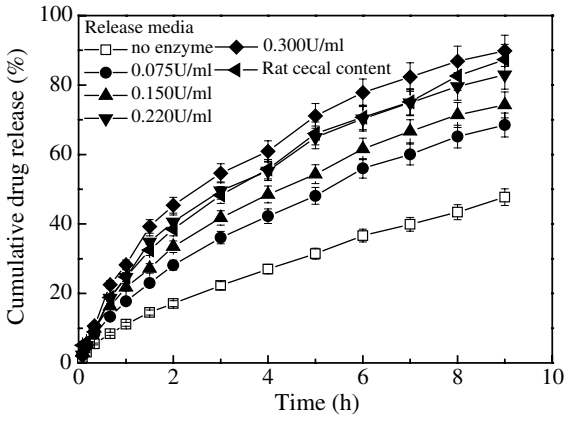

Fig. 1. Drug release from matrix tablets of KGM100 in different mimic colon media.

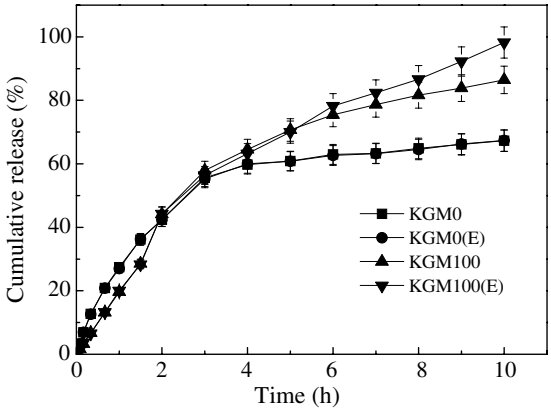

Fig. 2. Drug release from cimetidine matrix tablets of KGM or XG, (E) denotes the mimic colon dissolution media containing 0.220 U/ml β-mannanase.

the drug release profiles of KGM100 tablets in the media with and without the enzyme to mimic colon environment; KGM showed a good response to hydrolysis of enzymes in the colon, which demonstrated that it has a good potential application for colon drug delivery. It can also be found that XG has the ability to restrain drug release, but no response was found for to β-mannanase. In 10 h, the cumulative drug releases were 98.24% from KGM100 in media containing β-mannanase and 86.44% in medium without enzyme; drug release percentages from KGM0 showed little difference in media with and without enzyme (67.33% and 67.28%, respectively). Similar results that xanthan gum is non-digestible in the human alimentary tract have been reported early (Sinha, Mittal, & Kumria, 2005). After the dissolution studies, it could be seen that the tablets of KGM0 swelled to a certain extent and still kept good shape and gel strength. The tablets of KGM100, however, were strongly hydrophilic to fill the baskets and the viscosity of the swollen tablet matrix was low, which couldn't keep the shape of the tablet, especially in the media with enzyme. A highly swollen degree appears when the tablets of KGM100 meet water, which may prolong the diffusion path and leads to the relative slow release in the first 2 h. Then, the weak strength of the matrix gel resulted in the fast drug release from KGM100 afterwards.

3.4. Drug release from the matrix tablets with polysaccharide mixtures as sustained release materials

As the weak gel strength of KGM100 and the premature release phenomenon of KGM0 in the dissolution studies, the mixtures of two polysaccharides were employed as sustained release materials in the matrix. Different drug release profiles were resulted in different formulations. The dissolution results were shown in Fig. 3.

It can be seen in Fig. 3 that the mixtures of KGM and XG were capable of sustaining the drug from being released in the physiological environment of stomach and small intestine. The drug release rates were different as the different polysaccharides proportions in the matrix. The drug release rate was near constant as the accelerated effect of the hydrolyzation of enzyme to polysaccharide mixtures hydrogel in mimicking colon environment, which may meet the requirement of the sustained drug release. In addition, the drug release rate from tablets can be adjusted by the ratios of KGM and XG. In 10 h of dissolution, the cumulative drug release of KGM30 was the lowest of all formulations studied. There is a strong synergistic interaction between KGM and XG in solution and in the gel phase, with the structure stabilized by favorable van der Waals interactions and a network of intermolecular hydrogen bonds between KGM and XG backbones to effectively retard the drug release (Paradossi, Chiessi, Barbiroli, & Fessas, 2002). On exposure to the dissolution fluids, the mixed polysaccharide matrices sopped up solvent and a viscous gel layer was formed to delay the solvent penetrating toward the core of the matrix, slowing down further release

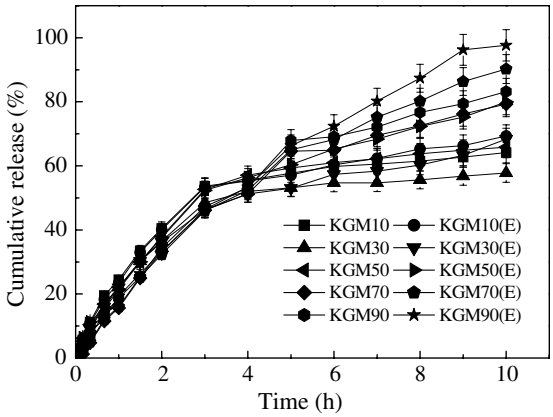

Fig. 3. Drug release from cimetidine matrix tablets of polysaccharide mixtures, (E) denotes the mimic colon dissolution media containing 0.220 U/ml β-mannanase.

of the drug in the matrix. The enzyme generated by microflora in the colon can hydrolyze KGM in the matrix gel and accelerate the drug release, which was propitious to keep a near steady drug release in the second half of dissolution study. The initial drug release may be attributed to the dissolution of the drug present on the surface of the tablet and the solubility of the drug is higher in acidic solvent than that in neutral or basic solvent.

3.5. Drug release from the tablets of different drug content

In order to elucidate the influence of drug content on the drug release, the drug release from matrix tablets of KGM30 with different drug content was investigated.

It is found in Fig. 4 that the drug release rate and the cumulative release experienced no marked increase or decrease when the range of the drug content was between 40% and 60%.

3.6. The viscosity of the polysaccharide mixtures solution

The 0.5% (w/w) solutions of single KGM and XG were mixed in different proportions, and the viscosity of the mixed polysaccharides solutions at different rate of shear was investigated. The results are shown in Fig. 5. The strong synergistic interaction indicated that the mixed solution of KGM:XG = 3:7 had the highest viscosity at all shear rates in all solutions. There is a good correlation with the trend of matrix tablets' drug release profiles, which is probably due to the stronger interaction between the molecules of KGM and XG in the solution at the mixing ratio of 3:7. There were more crosslinked points between molecular chains of KGM and XG in mixed solution of this ratio and more energy was therefore needed to open them.

3.7. IR characterization analysis of the mixed polysaccharides

It can be seen from IR spectra of KGM and XG (Fig. 6) that the absorption band of carbonyl of acetyl groups was

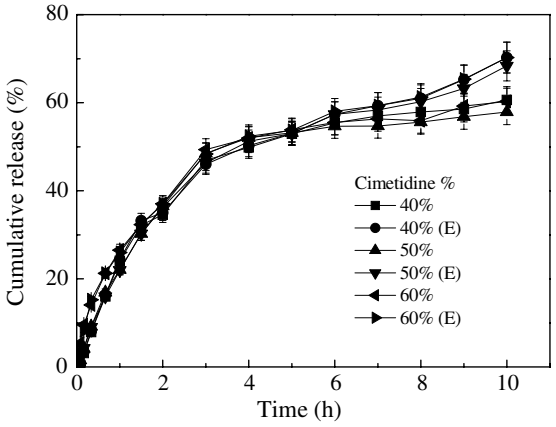

Fig. 4. Drug release from tablets with different drug content, (E) denotes the mimic colon dissolution media containing 0.220 U/ml β-mannanase.

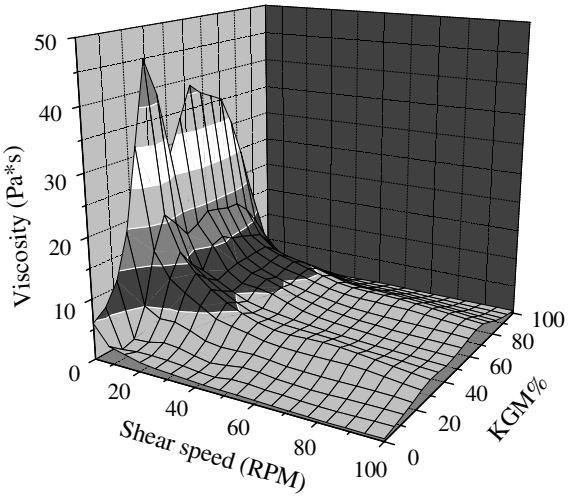

Fig. 5. Viscosity of KGM, XG and mixed polysaccharides solution.

at 1730 cm^{-1}, and the absorption band of C–H bond of the macromolecule hexatomic ring was at 2940 cm^{-1}. The band at 1240 cm^{-1} was characterized by the absorption of C–O stretching, and the peak at 1450 cm^{-1} was the absorption band of $-CH_2^-$. For the IR spectrum of the polysaccharides matrix without drug, the peaks at 3700–3200, 2940, 1726, 1240 and 1450 cm^{-1} became stronger due to the interaction of KGM and XG on hydration, compared with that of KGM. The peaks of KGM at 1640 cm^{-1} and XG at 1620 cm^{-1} were moved to 1630 cm^{-1} in the mixture because of the strong intermolecular hydrogen bond interaction between KGM and XG.

4. Conclusions

In this study, the sustained release matrix tablets were prepared together with the polysaccharide mixtures of konjac glucomannan (KGM) and xanthan gum (XG) as the sustained release materials. Lactose was selected as a diluent in the matrix tablets. Cimetidine was used as the model drug for in vitro assessments. Different

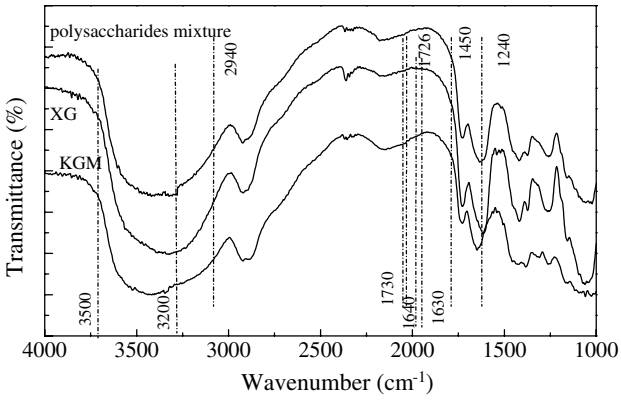

Fig. 6. FT-IR spectra of konjac glucomannan, xanthan gum and the mixed polysaccharides.

polysaccharide proportions had different dry particle size distribution in the process of wet granulation due to the different absorbed abilities of KGM, XG and the polysaccharide mixtures. In dissolution studies, β-mannanase was used to mimic the environment of the colon in vitro. It was shown in the dissolution studies that KGM had a good response to hydrolysis of enzyme in the colon, while the matrix tablets with a single polysaccharide (either KGM or XG) as the sustained release material could not retard drug release from the tablets effectively. Then, the mixtures of polysaccharide were employed. The drug release results showed that the synergistic interaction between KGM and XG in the gel phase could retard the drug diffusion effectively. Different ratios of KGM and XG led to different drug release profiles in the dissolution studies. The addition of β-mannanase can accelerate the drug release rate because of the existence of KGM in the matrix.

The rotary viscosity of the mixed polysaccharides solutions and IR spectra of mixed polysaccharides were investigated. The studies on the polysaccharide mixtures revealed that there was a strong synergistic interaction between KGM and XG in certain order.

The mixture of konjac glucomannan and xanthan gum may be considered to have potential as the new material to sustain and control the release of drugs. It is necessary that more studies in vivo should be carried out for the application of KGM to oral drug delivery systems.

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