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Konjac glucomannan and konjac glucomannan/xanthan gum mixtures as excipients for controlled drug delivery systems. Diffusion of small drugs

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Abstract

Konjac glucomannan (KGM), alone or in combination with xanthan gum (XG), was evaluated as main component of systems capable of controlling the diffusion of small molecules with a view of their use in drug delivery. To provide the study with enough general character, KGM batches were obtained from the three main areas of excipient harmonization (Europe, USA and Japan). The rheological evaluation at physiological temperature of KGM (0.5%, w/v) aqueous dispersions, with or without XG at different ratios, showed significant variability among the three KGMs owing to differences in the acetylation degree. The Japanese and European varieties of KGM synergically interact with XG giving rise to gel formation; the synergism being maximum at a 1:1 ratio. By contrast, the American KGM does not show such effect forming only viscous solutions. Drug diffusion coefficients of theophylline and diltiazem HCl, with different molecular size and net charge, were evaluated in systems containing KGM/XG ratio 1:1. KGM/XG systems were more efficient than the XG alone dispersion for controlling drug diffusion of small molecules because of the gel formation. These results point out the potential of mixtures of some KGM types with XG to develop delivery systems capable of maintaining physical integrity and drug release control for up to 8-h period.

Keywords: Konjac glucomannan; Xanthan gum; Synergistic interaction; Diffusion coefficient; Microviscosity; Rheology

1. Introduction

Many attempts have been carried out in order to explore the potential of some polysaccharides of different origins such as pectins, galactomannans, dextrans, chitosan, condroitin sulphate or alginates, both individually or combined, as sustained release carriers (Bhardwaj et al., 2000). Natural polysaccharides are non-toxic, inexpensive, biodegradable and freely available. As a disadvantage their usually high aqueous solubility makes the maintenance of the integrity of the formulation and the control of drug release difficult. Chemical cross-linking (Liu et al., 2004) and blending of different polysaccharides (Sinha and Kumria, 2001; Chourasia and Jain, 2003) have been proposed to overcome these problems while maintaining biodegradability. Blends of polysaccharides in which synergistic interactions occur provide a valuable approach to obtain systems that combine sufficient mechanical stability and resistance towards diffusion of solutes (Vendruscolo et al., 2005; Alonso-Sande et al., 2006).

Konjac glucomannan (KGM) is a natural neutral polysaccharide commonly used as gelling agent or thickener in the food industry. Although KGM was already shown as efficient component of dibucaine and theophylline gels some years ago (Nakano et al., 1979a,b,c), its use was discontinued for decades. Recent studies on KGM have demonstrated its potential for the controlled release of hormones (Gonzalez et al., 2004) and other macromolecules such as dextran, insuline and bovine serum albumine (Wang and He, 2002; Liu et al., 2004; Alvarez-Manceñido et al., 2006; Alonso-Sande et al., 2006).

The synergistic interaction between KGM and other gelling polysaccharides (agarose, κ-carrageenan and gellan gum) or non-gelling polysaccharides (xanthan gum and acetan) has been pointed out by different authors (Goycoolea et al., 1995a; Miyoshi et al., 1996, 1997; Ridout et al., 1998; Chandrasekaran et al., 2003; Penroj et al., 2005). Those combinations yield the formation of strong and thermoreversible hydrogels even under conditions at which the components alone do not gel (Morris, 1995). Among those polysaccharides, xanthan gum

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(XG) is particularly attractive due to its well-established properties as pharmaceutical excipient, especially as component of hydrophilic matrices able to provide zero-order profiles (Talukdar and Kinget, 1995, 1997; Talukdar et al., 1996). To optimize the development of drug delivery systems based on KGM and XG synergistic interaction, a key aspect is to understand how the diffusion of the drug is influenced by the structure of the polymer network, hitherto unexplored aspect for KGM and KGM/XG systems. In a previous paper (Alvarez-Manceñido et al., 2006), the diffusion of macromolecules as dextrans in KGM and KGM/XG systems was evaluated by fluorescence recovery using the photobleaching technique. Results indicated that macroscopic rheological properties cannot be used to predict changes in the diffusivities of large molecules through KGM/XG systems and that the size of the diffusing molecule is an important factor. A crowding or a sieving mechanism was involved in controlling macromolecules diffusion.

The goals of the present study were: (a) to investigate KGM intermanufacturing variability by using konjac glucomannan from the three main areas for excipient harmonization: Japan, Europe and America; (b) to evaluate, from the rheological point of view, the interactions of KGM from different sources with XG in order to establish the optimum ratio of KGM/XG to produce the strongest gels at physiological temperature, and (c) to study the effect of the interaction between KGM/XG polysaccharides on the diffusion process of two small model drugs, theophilline and diltiazem HCl, different in net charge and molecular weight.

2. Materials and methods

2.1. Raw materials

Konjac glucomannans from different suppliers and geographical origins: American (Triple Crown America Inc. Lot. 3500C), European (Escuder, Spain, Lot. 019), Japanese (Propol A®, Lot. AKG07) and Xanthan gum (Guinama, Spain, Lot: 016) were studied as received.

Theophylline anhydrous (Lot. 102K0547) was supplied by Sigma, USA and Diltiazem hydrochloride European Pharmacopoeia compliant (Lot. 0307362) was provided by Roig-Farma, Spain.

2.2. Gel permeation chromatography (GPC)

Molecular weight distributions of KGMs, being neutral polysaccharides, were analyzed by employing the aqueous-phase gel permeation chromatography (GPC). Samples at a concentration of ~1 mg/mL were prepared in 0.1 M Na_2HPO_4 and injected onto Waters GPC setup consisting of degasser, 515 pump, Rheodyne injector 7725i with 200 μL loop, and differential refractive detector DRI 2400. Separation was performed on Suprema column system using 8 mm × 50 mm guard column and 8 mm × 300 mm Suprema 1000 and 3000 Å columns (PSS Germany) with particle sizes 10 μm. Eluent of composition 0.1 M Na_2HPO_4 with 100 ppm NaN_3 was flowing at 1 ml/min and flow rate was controlled by ethylene glycol added to each sample in a minute amount used as a flow standard. The GPC system was calibrated using the 3rd polynomial fit to calibration curve made of dextran standards from American Polymer Standards Corp. (Ohio, USA) with the weight average molecular weights between 3500 and 2,200,000 g/mol. Thus the molecular weight of KGMs reported in this work should be considered as the effective ones towards the dextran standards. Data acquisition and evaluation was performed by means of PSS WinGPC7.0 (PSS Germany).

2.3. Fourier transform infrared spectroscopy (FTIR)

Transmittance spectra from KGM samples in KBr disks were recorded by a Bruker IFS-66v (Germany) in the range from 400 to 4000 cm^{-1}.

2.4. Preparation and rheological characterization of the KGM, XG and KGM/XG systems

Polysaccharide systems were prepared in distilled water at a total concentration of 0.5% (w/v) by mechanical stirring for 1 h at 85 °C in an hermetic container. In order to evaluate the interaction between KGM and XG, several weight ratios (1:0 3:1, 1:1, 1:3, and 0:1) were prepared keeping total polysaccharide concentration at 0.5% (w/v). Solutions were left to cool and equilibrate overnight and its rheological properties characterized using a rheometer AR1000-N (TA instruments, Newcastle, UK) fitted with a cone and plate geometry (2° cone angle, 60 mm diameter, 59 μm gap).

Steady-shear measurements and dynamic rheological characterization were carried out at least in triplicate at 37 °C.

Macroviscosities of glucomannan dispersions were determined from steady-shear measurements using a logarithmic torque ramp in order to decrease the initial acceleration and the effects of inertia.

Experimental data were fitted to the Newtonian or the Cross model (Barnes, 2000) from which viscosity or zero-shear rate viscosity (η_0), consistency (K) and shear rate index (m) were obtained, respectively, as previously described (Alvarez-Manceñido et al., 2006).

Dynamic rheological characterization started with torque sweeps to ensure operation within the linear viscoelastic region of the viscoelastic samples. The extension of the linear viscoelastic regime has been determined under oscillatory shear conditions at a frequency of 1 rad/s. Dynamic frequency sweep experiments were carried out at a constant strain amplitude within the limits of the linear viscoelastic region in the range of 0.1–100 rad/s.

For the gel systems preheating of the rheometer peltier plate above gel temperature was needed to avoid the appearance of harmonic signals.

Samples were covered with a thin layer of paraffin oil to limit evaporation.

2.5. Drug diffusion measurements on KGM, XG and KGM/XG systems

Diffusion coefficients of two different drugs, anhydrous theophylline and diltiazem hydrochloride, were estimated as

previously described (Alvarez-Lorenzo et al., 1999). Diltiazem hydrochloride or anhydrous theophylline were added to the prepared KGM or KGM/XG systems at a total drug concentration of 0.05% (w/v) and 0.02% (w/v), respectively. Drug loaded systems were stirred at 85 °C for five extra minutes in order to ensure homogenous drug distribution and allowed to cool and equilibrate in a water bath at 37 °C.

Assays for the characterization of the diltiazem or theophylline release from the studied systems were performed in triplicate in Franz-Chien vertical diffusion cells (Vidra Foc, Spain) fitted with 0.45 μm pore size cellulose acetate membrane filters (Albet AC-045-25-BL, Spain) between the donor and the recipient compartments. A test formulation sample of 2.0 mL was placed at the donor compartment. The recipient compartment, containing 5.8 mL of distilled water or isoosmotic NaCl solution, was thermostated at 37 °C and stirred with a magnetic bar. The surface available for diffusion was 0.785 cm^2. Samples of 0.5 mL were taken from the recipient compartment at given intervals over the 8-h period and immediately replaced with the same volume of fresh thermostated medium, which assures full contact between the test formulation and receptor liquid. Samples were analyzed spectrophotometrically in a diode array spectrophotometer (Agilent Technologies 8453, Germany) at 272 and 237 nm for theoplylline and diltiazem, respectively. For each experiment, the cumulative percentage of drug released was calculated using validated calibration curves and diffusion coefficients estimated by fitting the experimental data to the Higuchi equation (Higuchi, 1962):

$$\frac{Q}{A} = 2C_0\sqrt{\frac{Dt}{\pi}} \quad (1)$$

Q is the amount of drug (theophylline or diltiazem) in milligrams released by time t (s), A the diffusion area (cm^2), C_0 the initial concentration of drug in the formulation (mg/mL) and D is the diffusion coefficient (cm^2/s).

The microviscosities of these systems were calculated using the Stokes–Einstein relation (Armstrong et al., 1987):

$$\frac{D_0}{D} = \frac{\eta}{\eta_0} \quad (2)$$

where D and D_0 are diffusion coefficients (cm^2/s) of the drug in the presence and absence of polymer, respectively, and η and η_0 are the viscosities (mPa s) of the polysaccharide dispersion (microviscosity) and medium without polymer, respectively.

2.6. Statistical analysis

The statistical package SPSS 13.0 for Windows was used to study the variability among the different KGM formulations by the analysis of variance (ANOVA) test and *post hoc* comparisons among pairs by Scheffé tests ($\alpha < 0.05$) (Bolton, 1997).

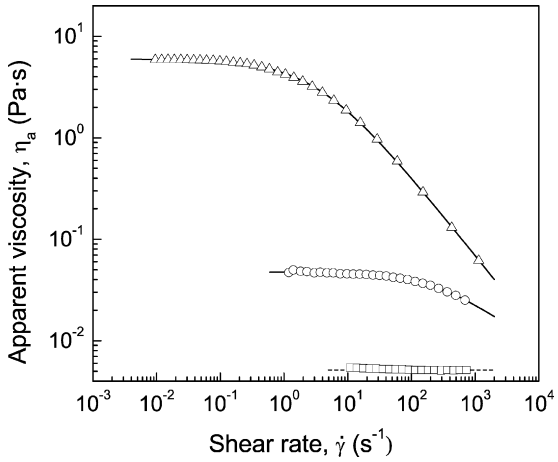

Fig. 1. Flow curves for 0.5% konjac glucomannan solutions at 37 °C. Symbols: Japanese KGM (triangles), European KGM (circles) and American KGM (squares). Full lines represent cross model predictions and dashed line Newtonian model prediction.

3. Results and discussion

3.1. Characterization of the KGM or XG single systems at physiological temperature

In order to explore the utility of KGM and KGM/XG systems as components of controlled delivery systems, it is necessary to characterize their rheological behaviour at physiological temperature and to establish its influence on the diffusion of small molecules through them.

Flow experiments, shown in Fig. 1, were carried out at 37 °C for the solutions of the American, European and Japanese KGMs at a concentration of 0.5% (w/v). Flow profiles of KGM systems at 37 °C were similar to those previously obtained at 25 °C (Alvarez-Manceñido et al., 2006). European and Japanese (0.5%, w/v) KGMs clearly show a shear thinning behaviour at high shear rates after the initial Newtonian region at low shear rates, which is in agreement with previous findings (Jacon et al., 1993). On the other hand, the American KGM shows a non-typical (for KGMs) Newtonian behaviour with a constant apparent viscosity indicating that the shear stress is proportional to the shear rate.

Table 1 presents the parameters derived from fitting Newtonian and Cross models to the rheological data at 37 °C and, for comparison, also the viscosities determined at 25 °C in our previous work (Alvarez-Manceñido et al., 2006). This 12 °C increase in temperature causes an important reduction in the viscosity values for all glucomannans studied and especially for the XG system.

It has been reported that rheological properties of KGM strongly depend on the methods of preparation, the strain and the producing areas of *Amorphophallus k.* tubers (Kishida, 1979). The different rheological properties have been either related to the molecular weight variability (Zhang et al., 2001) or to the acetylation degree of KGMs (Maekaji, 1974). The GPC elution curves (and, derived effective molecular weight distributions) in Fig. 2 show a close agreement among all the KGMs

Table 1
Zero-shear rate viscosity (η_0), shear rate index (m) and consistency (K) obtained by fitting steady-shear measurements to Newtonian or cross model parameters for the American, European and Japanese KGMs and XG solutions (0.5%, w/v) at 37 °C

Samples	Model	η_0 (Pa s)	K (s)	m	Standard error[a]	η_0 (Pa s) at 25 °C[b]
American KGM	Newtonian	0.005 (0.000)	–	–	2.410	0.007
European KGM	Cross	0.046 (0.001)	0.003 (0.000)	0.953 (0.011)	5.739	0.103
Japanese KGM	Cross	5.651 (0.474)	0.286 (0.006)	0.779 (0.009)	3.556	9.471
XG	Cross	10.442 (0.766)	11.95 (1.107)	0.753 (0.004)	4.720	32.25

Standard deviations in parentheses.

[a] Standard error $= \left(\left[\sum_{i=1}^{i=n} (x_{\exp,i} - x_{\mathrm{cal},i})^2 / n - 2 \right]^{1/2} / \mathrm{range}(x_{\exp}) \right) \times 1000$.

[b] From Alvarez-Manceñido et al. (2006).

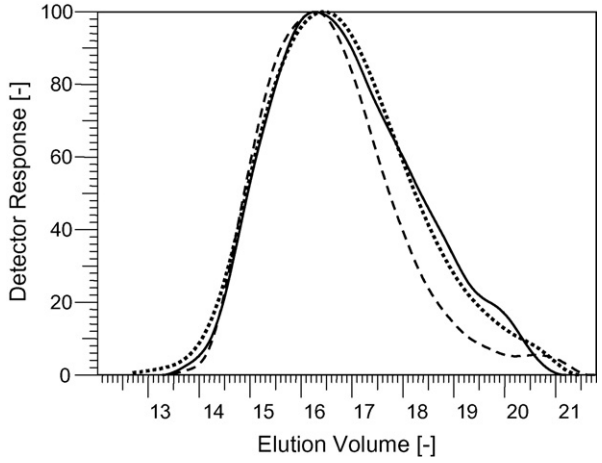

Fig. 2. Elution curves for Japanese-KGM (solid line), European-KGM (dashed line) and American-KGM (dotted line) at 25 °C in 0.1 M Na_2HPO_4.

(American KGM: $\overline{M_w} \sim 5.4 \times 10^6$ g mol, polydispersity ~8; European KGM: $\overline{M_w} \sim 5.3 \times 10^6$ g mol, polydispersity ~7, Japanese KGM: $\overline{M_w} \sim 4.7 \times 10^6$ g mol, polydispersity ~7), which suggests that the variation in molecular weight cannot explain the strong variability in rheological profiles seen in Fig. 1. Therefore the differences among the KGMs should be dominated by their chemical composition, particularly to the content of acetyl groups. Fourier transform infrared spectroscopy (FTIR) spectra show (Fig. 3) the absence of the peak at 1730 cm^{-1} for the American variety as the main difference with the other KGMs. This band corresponds to the acetyl group (Zhang et al., 2001), which actively participates in the water absorption and the gel formation (Williams et al., 2000).

The differences on rheological behaviour among KGMs may be determinant of its performance as components of controlled delivery systems. In fact, the magnitude of zero-shear rate viscosity is a macroscopic index of the microstructural conformation of biopolymers. Diffusion coefficient (D) and dynamic viscosity (η) are inversely related through the well-known Stokes–Einstein equation (Cheng et al., 2002). If diffusion of diltiazem and theophyline through this type of systems is governed just by Stokes–Einstein equation, significant differences in diffusion coefficients should be expected when viscosity changes. Additionally, the highest value found for the XG system (Table 1) suggests that diffusion of small molecules should be highly influenced by the presence of XG in the mixtures.

The frequency dependence of the elastic (G') and viscous (G'') moduli obtained for the solutions of individual polysaccharides at 0.5% (w/v) at physiological temperature (Fig. 4) is typical for polymer solutions in the diluted (circles and squares of Fig. 4a; negligible G' values) or concentrated (triangles of Fig. 4a and b) regimes (Nishinari, 2000). Compared to our previous results at 25 °C (Alvarez-Manceñido et al., 2006), lower values of elastic and viscous moduli were obtained at 37 °C. At physiological temperature, none of the solutions of individual polysaccharides can be considered as gels from the rheological point of view. This statement follows the Almdal et al.'s considerations (Almdal et al., 1993).

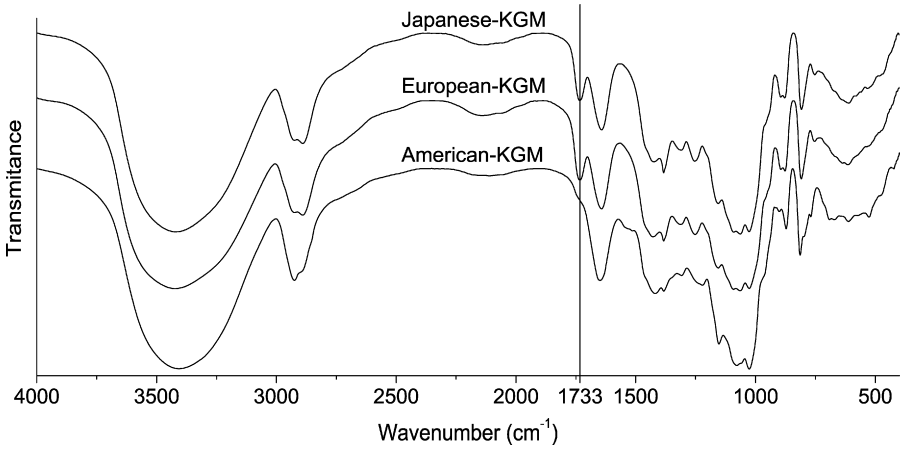

Fig. 3. FTIR spectra of KGM samples from different suppliers.

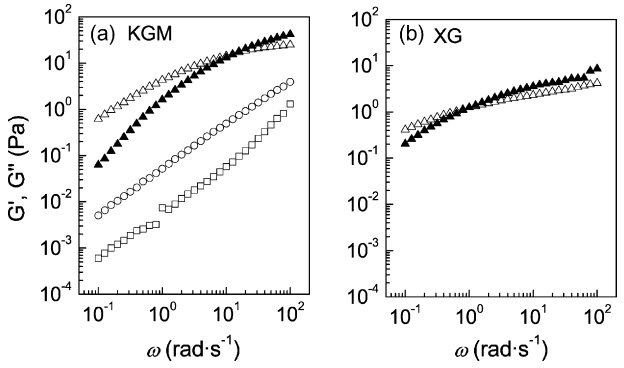

Fig. 4. Dynamic elastic (G') and viscous (G'') moduli at 37 °C as a function of frequency of (a) 0.5% (w/v) KGM systems: (triangles) Japanese KGM, (circles) European KGM, (squares) American KGM and (b) 0.5% (w/v) xanthan gum system (closed symbols, G'; open symbols, G'').

3.2. Characterization of the KGM/XG binary systems at physiological temperature

When XG is added to KGM solutions, the rheological properties undergo a great change. Fig. 5 depicts the mechanical spectra for different KGM/XG ratios, keeping constant the total polysaccharide concentration (0.5%, w/v). It has been described that synergistic effect between polysaccharides can be recognised as an enhancement in the viscosity values in dilute solutions or even as an unexpected gelation at higher polysaccharide concentrations (Morris, 1995). The Japanese and the European KGM/XG systems showed a well-defined profile showing a clear synergistic effect for all the compositions studied (Fig. 5A and B). G' exceeds G'' in the frequency range evaluated and the relative magnitude of both moduli is roughly independent of the frequency within a few orders of magnitude. From a rheological point of view, they can be considered as true gels (Almdal et al., 1993).

Interactions between KGM and other anionic polysaccharides similar to XG have generated great scientific interest and discussion (Ridout et al., 1998, 2004; Chandrasekaran et al., 2003). The synergistic interaction is manifested as a maximum value in both G' (Fig. 6a) and G'' (Fig. 6b) at a mixing ratio 1:1 for the Japanese and the European KGMs. Evidence for the intermolecular binding in xanthan–konjac mannan gels with maximum in the enthalpy change and the storage modulus at the 1:1 stoichiometry ratio has been previously elucidated through DSC and rheological measurements (Tako, 1993; Goycoolea et al., 1995b; Paradossi et al., 2002).

By contrast, blending of XG and the American KGM results in an important increase in both G'' and G' compared to the solution of this KGM alone (Fig. 4). However, they cannot be considered as true gels at any ratio because G'' and G' showed a strong frequency dependence in almost the whole frequency range and G' does not exceed G''; both features being characteristic for the non-gelled systems. American-KGM/XG systems (Fig. 6a and b) did not show a maximum G' or G'' at any composition studied suggesting that there is no positive deviation from additivity.

The variation in the relative contributions of the liquid-like and solid-like responses with increasing the ratio of KGM in the binary mixtures can be evaluated through the tan δ parameter showed in Fig. 6c. For the Japanese KGM/XG and the European KGM/XG blends, the gel-like character is manifested by tan δ values lower than 0.1; the minimum value at 1:1 ratio being 0.034 and 0.037, respectively. For the American-KGM/XG systems, however, tan δ values lie around 1 for all proportions indicating that the values of G' and G'' are very close to each other and that these systems do not behave as true gels at any ratio. Again, the possible explanation for the different behaviour of the American KGM could lie in its lower acetylation degree compared to the Japanese and the European KGMs as detected by FTIR (Maekaji, 1974; Zhang et al., 2001).

Importantly, the differences between American KGM/XG (1:1) system properties at 25 °C (Alvarez-Manceñido et al., 2006) and 37 °C (from gel-like to liquid-like) reveal the strong influence of temperature in this range of values, especially for the American KGM/XG combinations. This aspect should be taken into account when this KGM is used in the development of drug delivery systems.

Our rheological findings prompted us to choose the KGM:XG 1:1 systems for the drug diffusion studies, since their consistency as hydrogels or physically cross-linked networks is enough to maintain their structure under small stress (Eros et al., 2003).

3.3. Drug release from single KGM or XG systems

A key-factor in determining the drug release rate from pharmaceutical preparations is the drug diffusion rate through the hydrated polymer gel (Alvarez-Lorenzo et al., 1999). Among the models developed to describe the time course of the release process (Costa et al., 2001), the simplified Higuchi model (Eq. (1)) allows to directly compare drug diffusion coefficients (D) in different systems. Diltiazem HCl and theophylline release profiles fit Higuchi equation ($r^2 > 0.99, \alpha < 0.05$), which is indicative of Fickian diffusion, enabling the estimation of the diffusion coefficients for both drugs in KGM, XG and KGM/XG systems (Table 2). As an example, two diltiazem HCl release profiles from European KGM and European KGM/XG systems are shown in Fig. 7.

Microviscosity values were estimated from the diffusion coefficients applying the Stokes–Einstein equation (Eq. (2)). This parameter is an index of the resistance of the medium surrounding the drug to the diffusion (Alvarez-Lorenzo et al., 1999). Theophylline diffusion coefficient values are greater than for diltiazem HCl (Table 2) which may be related to their different molecular weight and radius: 450.98 g/mol and 4.24 Å for diltiazem HCl, and 180.17 g/mol and 3.78 Å for theophylline (Peppas et al., 1999). Additionally, the interaction between the net positive charge of dilitiazem and the negative charge of some groups of the polysaccharide network should contribute to the lower drug diffusion rate for this molecule. The delay in release rate due to ion–ion interactions between charged polymers and drugs has been previously reported by different authors (Seki et al., 2003; Bonferoni et al., 2000; Sousa et al., 2005; Cornejo-

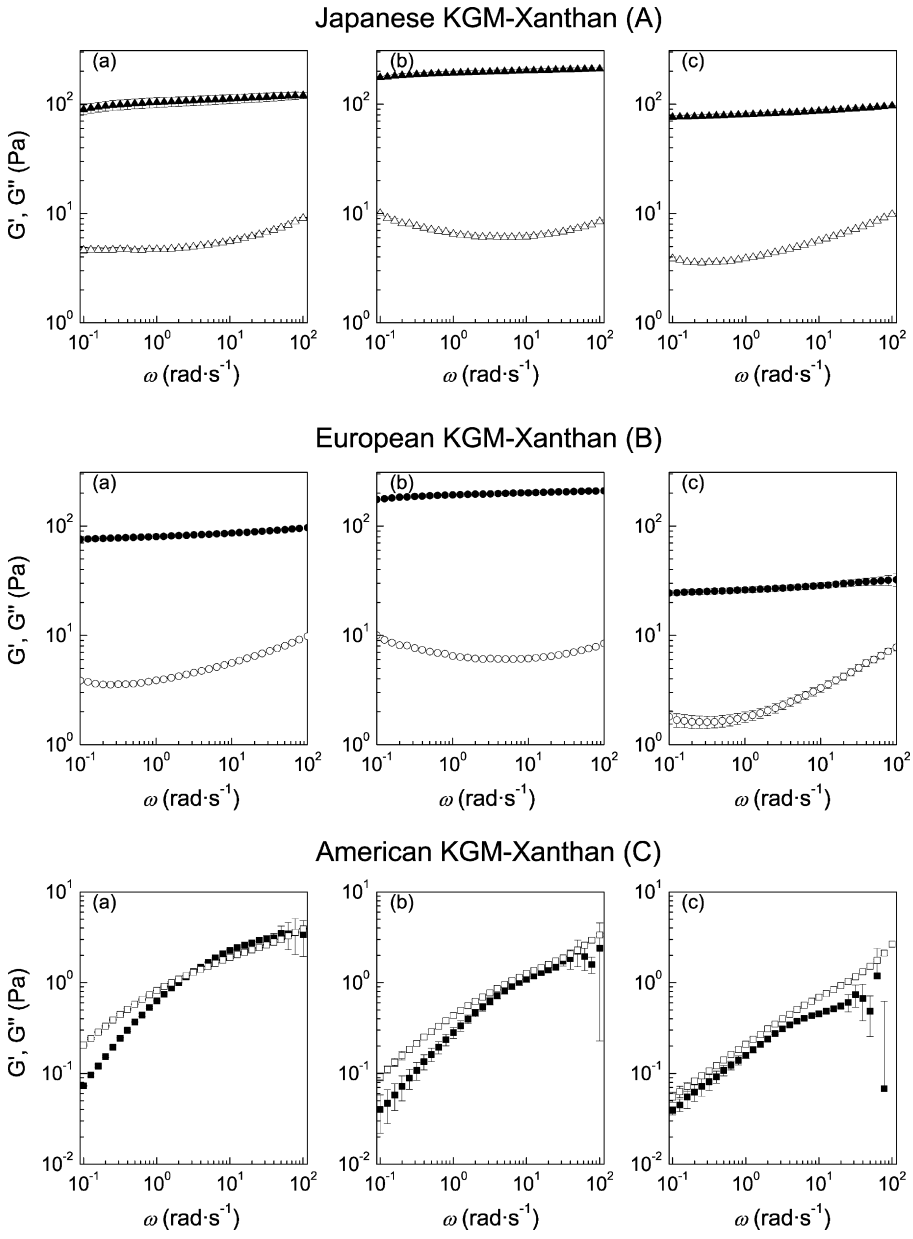

Fig. 5. Dynamic elastic (G'; closed symbols) and viscous (G''; open symbols) moduli as a function of frequency for 0.5% (w/v) KGM/XG systems at 37 °C for the different KGMs studied. (a) KGM/XG ratio 3:1; (b) KGM/XG ratio 1:1 and (c) KGM/XG ratio 1:3.

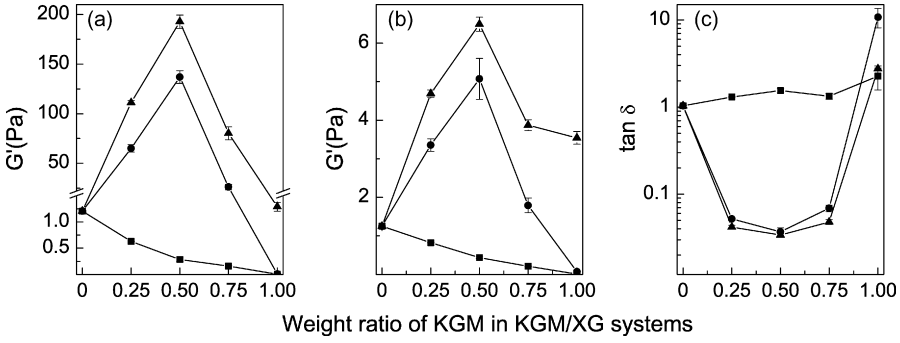

Fig. 6. Dynamic elastic (G'), viscous (G'') moduli and tan δ as function of the mixing ratio in 0.5% w/v KGM/XG systems at 1 rad/s for the three varieties of KGM studied at 37 °C: (triangles) Japanese KGM, (circles) European KGM, and (squares) American KGM.

Table 2
Diffusion coefficients (D) (cm^2/s) and microviscosities (η) (mPa s) for diltiazem HCl and theophylline through the polysaccharide systems studied at 37 °C (0.5%, w/v total polysaccharide concentration) standard deviations in parentheses

	Diltiazem HCl		Theophylline	
	D ($\times 10^6$) (cm^2/s)	η (mPa s)	D ($\times 10^6$) (cm^2/s)	η (mPa s)
Single system				
Japanese-KGM	11.15 (3.26)	6.49 (1.85)	13.62 (3.57)	6.69 (1.76)
European-KGM	29.87 (4.33)	2.33 (0.33)	56.19 (6.84)	1.55 (0.18)
American-KGM	25.39 (2.12)	2.70 (0.24)	35.24 (7.89)	2.55 (0.55)
XG	3.65 (0.30)	18.81 (1.50)	9.72 (0.48)	8.91 (0.45)
Binary system				
Japanese-KGM/XG	3.49 (0.48)	19.86 (2.65)	8.72 (0.38)	9.93 (0.43)
European-KGM/XG	4.05 (0.33)	16.98 (1.34)	9.70 (0.14)	8.92 (0.13)
American-KGM/XG	5.18 (0.84)	13.43 (1.99)	14.74 (0.56)	5.87 (0.22)

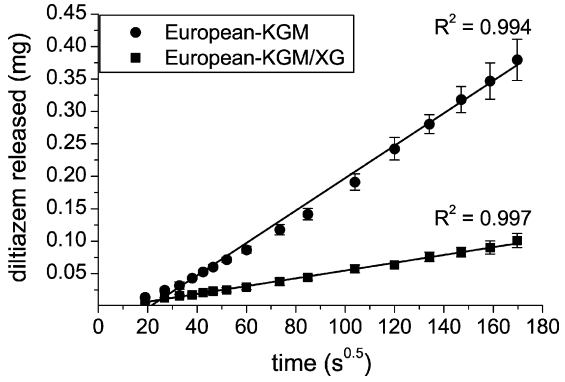

Fig. 7. Squared root fitting for diltiazem HCl release profile at 37 °C for the European-KGM and European KGM/XG systems.

Bravo et al., 2005), and should be taken also into account when design KGM/XG-based delivery systems.

The microviscosity values obtained in KGMs and XG solutions from the diltiazem and theophylline diffusion coefficients (Table 2) were in all cases lower than the corresponding macroviscosities (Table 1); similar findings have been reported for hydroxypropylcellulose gels (Alvarez-Lorenzo et al., 1999) and chondroitin sulphate solutions (Seki et al., 2003). No linear correlation between macroviscosities from flow rheology experiments (Table 1) and microviscosities (Table 2) was found for the solutions of individual polysaccharides. Therefore, macroviscosity values widely used as routine predictor of drug mobility, cannot explain drug diffusion results as previously reported by other authors for hydroxypropyl methylcellulose and polyvinylpyrrolidone solutions (Desmidt et al., 1986; Alvarez-Lorenzo et al., 1999).

It is interesting to note that among the individual polysaccharides evaluated, XG solutions exhibit the highest resistance to drug molecule diffusion.

3.4. Drug release from KGM/XG binary systems

In the KGM/XG dispersions, the diffusion coefficients were significantly lower ($\alpha < 0.01$) than those obtained for the KGM solutions and close to the D values found for the XG solutions. This clearly indicates that drug mobility is mainly determined by the structure of XG.

The source of KGM also played a significant role on the diffusion coefficients. The results of the Scheffé tests indicated that the American-KGM/XG systems, which do form gels, provide the highest drug diffusion coefficients. This suggests that either more entanglement points or a stronger gel network (when the Japanese or the European KGM is used) improve the control over drug release by a crowding or a sieving mechanism; in a similar way to that described for the macromolecules diffusion through this kind of systems (Alvarez-Manceñido et al., 2006).

KGM/XG gels elaborated with the Japanese or the European KGM variety are able to control drug release as efficiently as XG systems, with the advantage of having improved consistency and physical strength.

4. Conclusions

Rheological characterization of glucomannans of a different origin at physiological temperature highlights the importance of having into account the intermanufacturing variability of KGM and of establishing detailed specifications mainly about the degree of acetylation. This parameter strongly influences the interactions between KGM and XG. The Japanese and the European KGMs evaluated show a synergistic interaction with XG at a 1:1 ratio and 37 °C leading to strong gels when the total polysaccharide concentration is 0.5% (w/v). By contrast, the American KGM does not show such a synergistic effect and the systems behave as viscous solutions at any KGM:XG ratio. Drug diffusion experiments demonstrate that XG proportion and its synergistic interaction with KGM are the main responsible for the control of diffusion in the binary systems. Gels based on XG and the Japanese or the European KGM were found useful to develop theophylline or diltiazem delivery systems capable to maintain physical integrity and to control the release for 8 h.

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References

Almdal, K., Dyre, J., Hvidt, S., Kramer, O., 1993. Towards a phenomenological definition of the term 'gel'. Polym. Gels Networks 1, 5–17.

Alonso-Sande, M., Cuna, M., Remunan-Lopez, C., 2006. Formation of new glucomannan–chitosan nanoparticles and study of their ability to associate and deliver proteins. Macromolecules 39, 4152–4158.

Alvarez-Lorenzo, C., Gomez-Amoza, J.L., Martinez-Pacheco, R., Souto, C., Concheiro, A., 1999. Microviscosity of hydroxypropylcellulose gels as a basis for prediction of drug diffusion rates. Int. J. Pharm. 180, 91–103.

Alvarez-Manceñido, F., Braeckmans, K., De Smedt, S.C., Demeester, J., Landin, M., Martinez-Pacheco, R., 2006. Characterization of diffusion of macromolecules in konjac glucomannan solutions and gels by fluorescence recovery after photobleaching technique. Int. J. Pharm. 316, 37–46.

Armstrong, N.A., Gebremariam, T., James, K.C., Kearney, P., 1987. The influence of viscosity on the migration of chloramphenicol and 4-hydroxybenzoic acid through glycerogelatin gels. J. Pharm. Pharmacol. 39, 583–586.

Barnes, H.A., 2000. A handbook of elementary rheology. In: The University of Wales Institute on Non-Newtonian Fluid Mechanics, 1st ed. Aberystwyth, Wales.

Bhardwaj, T.R., Kanwar, M., Lal, R., Gupta, A., 2000. Natural gums and modified natural gums as sustained-release carriers. Drug Dev. Ind. Pharm. 26, 1025–1038.

Bolton, S., 1997. In: Swarbrick, J. (Ed.), Pharmaceutical Statistics: Practical and Clinical Applications, 3rd ed. Marcel Dekker Inc., New York, pp. 265–325.

Bonferoni, M.C., Rossi, S., Ferrari, F., Bettinetti, G.P., Caramella, C., 2000. Characterization of a diltiazem-lambda carrageenan complex. Int. J. Pharm. 200, 207–216.

Chandrasekaran, R., Janaswamy, S., Morris, V.J., 2003. Acetan: glucomannan interactions—a molecular modeling study. Carbohydr. Res. 338, 2889–2898.

Cheng, Y., Prud'homme, R.K., Thomas, J.L., 2002. Diffusion of mesoscopic probes in aqueous polymer solutions measured by fluorescence recovery after photobleaching. Macromolecules 35, 8111–8121.

Chourasia, M.K., Jain, S.K., 2003. Pharmaceutical approaches to colon targeted drug delivery systems. J. Pharm. Pharm. Sci. 6, 33–66.

Cornejo-Bravo, J.M., Flores-Guillen, M.E., Lugo-Medina, E., Licea-Claverie, A., 2005. Drug release from complexes with a series of poly(carboxyalkyl methacrylates), a new class of weak polyelectrolytes. Int. J. Pharm. 305, 52–60.

Costa, P., Manuel, J., Lobo, S., 2001. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 13, 123–133.

Desmidt, J.H., Fokkens, J.G., Grijseels, H., Crommelin, D.J.A., 1986. Dissolution of theophylline monohydrate and anhydrous theophylline in buffer solutions. J. Pharm. Sci. 75, 497–501.

Eros, I., Csoka, I., Csanyi, E., Takacs-Wormsdorff, T., 2003. Examination of drug release from hydrogels. Polym. Adv. Technol. 14, 847–853.

Gonzalez, A., Fernandez, N., Sahagun, A., Garcia, J.J., Diez, M.J., Castro, L.J., Sierra, M., 2004. Effect of glucomannan and the dosage form on ethinylestradiol oral absorption in rabbits. Contraception 70, 423–427.

Goycoolea, F.M., Morris, E.R., Gidley, M.J., 1995a. Screening for synergistic interactions in dilute polysaccharide solutions. Carbohydr. Polym. 28, 351–358.

Goycoolea, F.M., Richardson, R.K., Morris, E.R., Gidley, M.J., 1995b. Stoichiometry and conformation of xanthan in synergistic gelation with locust bean gum or konjac glucomannan—evidence for heterotypic binding. Macromolecules 28, 8308–8320.

Higuchi, W.I., 1962. Analysis of data on medicament release from ointments. Pharm. Sci. 51, 802–804.

Jacon, S.A., Rao, M.A., Cooley, H.J., Walter, R.H., 1993. The isolation and characterization of a water extract of konjac flour gum. Carbohydr. Polym. 20, 35–41.

Kishida, N., 1979. Relationship between the quality of konjac flour and the molecular matter nature of konjac mannan. Agr. Biol. Chem. 43, 2391–2392.

Liu, Z.L., Hu, H., Zhuo, R.X., 2004. Konjac glucomannan-graft-acrylic acid hydrogels containing azo crosslinker for colon-specific delivery. J. Polym. Sci. Pol. Chem. 42, 4370–4378.

Maekaji, K., 1974. The mechanism of gelation of konjac mannan. Agr. Biol. Chem. 38, 315–321.

Miyoshi, E., Takaya, T., Williams, P.A., Nishinari, K., 1996. Effects of sodium chloride and calcium chloride on the interaction between gellan gum and konjac glucomannan. J. Agric. Food Chem. 44, 2486–2495.

Miyoshi, E., Takaya, T., Williams, P.A., Nishinari, K., 1997. Rheological and DSC studies of mixtures of gellan gum and konjac glucomannan. Macromol. Symp. 120, 271–280.

Morris, V.J., 1995. Synergistic interactions with galactomannans and glucomannans. In: Harding, S.E., Hill, S.E., Mitchell, J.R. (Eds.), Biopolymer Mixtures. Nottingham University Press, Nottingham, pp. 289–313.

Nakano, M., Takikawa, K., Arita, T., 1979a. Sustained-release of dibucaine from konjac gels after rectal administration to rats. Chem. Pharm. Bull. 27, 2501–2503.

Nakano, M., Takikawa, K., Arita, T., 1979b. Release characteristics of dibucaine dispersed in konjac gels. J. Biomed. Mater. Res. 13, 811–819.

Nakano, M., Takikawa, K., Juni, K., Arita, T., 1979c. Sustained-release of drugs from konjac gels. 4. Sustained-release of theophylline from konjac gels. Chem. Pharm. Bull. 27, 2834–2837.

Nishinari, K., 2000. Konjac glucomannan. In: Doxastakis, G., Kiosseoglou, V. (Eds.), Novel Macromolecules in Food Systems. Elsevier, pp. 309–330.

Paradossi, G., Chiessi, E., Barbiroli, A., Fessas, D., 2002. Xanthan and glucomannan mixtures: synergistic interactions and gelation. Biomacromolecules 3, 498–504.

Penroj, P., Mitchell, J.R., Hill, S.E., Ganjanagunchorn, W., 2005. Effect of konjac glucomannan deacetylation on the properties of gels formed from mixtures of kappa carrageenan and konjac glucomannan. Carbohydr. Polym. 59, 367–376.

Peppas, N.A., Keys, K.B., Torres-Lugo, M., Lowman, A.M., 1999. Poly(ethylene glycol)-containing hydrogels in drug delivery. J. Control. Release 62, 81–87.

Ridout, M.J., Brownsey, G.J., Morris, V.J., 1998. Synergistic interactions of acetan with carob or konjac mannan. Macromolecules 31, 2539–2544.

Ridout, M., Cairns, P., Brownsey, G., Morris, V., 2004. Synergistic interactions between the genetically modified bacterial polysaccharide P2 and carob or konjac mannan. Carbohydr. Res. 339, 2233–2239.

Seki, T., Okamoto, M., Hosoya, O., Aiba, D., Morimoto, K., Juni, K., 2003. Effect of chondroitin sulfate on the diffusion coefficients of drugs in aqueous solutions. STP Pharma Sci. 13, 215–218.

Sinha, V.R., Kumria, R., 2001. Polysaccharides in colon-specific drug delivery. Int. J. Pharm. 224, 19–38.

Sousa, R.G., Prior-Cabanillas, A., Quijada-Garrido, I., Barrales-Rienda, J.M., 2005. Dependence of copolymer composition, swelling history, and drug concentration on the loading of diltiazem hydrochloride (DIL.HCl) into poly [(*N*-isopropylacrylamide)-*co*-(methacrylic acid)] hydrogels and its release behaviour from hydrogel slabs. J. Control. Release 102, 595–606.

Tako, M., 1993. Binding sites for mannose-specific interaction between xanthan and galactomannan, and glucomannan. Colloid Surf. B-Biointerfaces 1, 125–131.

Talukdar, M.M., Kinget, R., 1995. Swelling and drug-release behavior of xanthan gum matrix tablets. Int. J. Pharm. 120, 63–72.

Talukdar, M.M., Kinget, R., 1997. Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery. 2. Drug diffusion in hydrated matrices. Int. J. Pharm. 151, 99–107.

Talukdar, M.M., Michoel, A., Rombaut, P., Kinget, R., 1996. Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery. 1. Compaction and in vitro drug release behaviour. Int. J. Pharm. 129, 233–241.

Vendruscolo, C.W., Andreazza, I.F., Ganter, J.L.M.S., Ferrero, C., Bresolin, T.M.B., 2005. Xanthan and galactomannan (from M-scabrella) matrix tablets for oral controlled delivery of theophylline. Int. J. Pharm. 296, 1–11.

Wang, K., He, Z.M., 2002. Alginate–konjac glucomannan–chitosan beads as controlled release matrix. Int. J. Pharm. 244, 117–126.

Williams, M.A.K., Foster, T.J., Martin, D.R., Norton, I.T., Yoshimura, M., Nishinari, K., 2000. A molecular description of the gelation mechanism of konjac mannan. Biomacromolecules 1, 440–450.

Zhang, H., Yoshimura, M., Nishinari, K., Williams, M.A.K., Foster, T.J., Norton, I.T., 2001. Gelation behaviour of konjac glucomannan with different molecular weights. Biopolymers 59, 38–50.