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Research paper

Effect of calcium ions on the gelling and drug release characteristics of xanthan matrix tablets

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Abstract

Xanthan is a well-known biopolymer. It is an anionic polysaccharide, whose primary structure depends on the bacterial strain and fermentation conditions. Xanthan was extensively studied in combination with galactomannans, and over 90 patents cover the technology of this preparation. Our aim was to investigate the relation between the physical properties of a xanthan matrix in the absence or presence of calcium ions and its influence on the release of pentoxifylline. The release of pentoxifylline from xanthan tablets in purified water was shown to be very slow and governed by the process of polymer relaxation. The presence of calcium ions significantly increased the drug release, changing the release mechanism into a more diffusion controlled one. Xanthan matrices showed substantially faster and more extensive swelling in water than in the presence of Ca^{2+} ions. Surprisingly, negative correlation between drug release and degree of swelling was obtained for xanthan: the higher the swelling, the slower the drug release. Higher ionic strength led to lower erosion of xanthan tablets, and the gel layers formed were more rigid and of firmer texture, as shown by rheological experiments and textural profiling. The results indicate that the presence of Ca^{2+} ions in the solution or in matrices does not cause crosslinking of xanthan polymers, but causes charge screening of ionized groups on the trisaccharide side chains of xanthan, leading to lower inter-molecular repulsion and changing water arrangement. The understanding of the parameters influencing drug release leads to the conclusion that xanthan is suitable for controlled release formulations, especially with the incorporation of certain small counterions.

Keywords: Polysaccharide; Controlled release; Rheology; Texture analyzer; Polymer hydration

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1. Introduction

Xanthan is an extracellular heteropolysaccharide produced by fermentation of the bacterium *Xanthomonas campestris*. It consists of a β,1-4-D-glucose backbone, which is the same as for cellulose. Every alternate glucose unit has a three sugar side chain consisting of two mannose residues separated by a glucuronic acid. The mannose closest to the backbone can carry an acetyl group, and the terminal mannose a pyruvate group (Fig. 1) [1]. The degree of acetylation and pyruvylation varies, depending on fermentation conditions. Typically, pyruvate residues are found on 30–40% of the terminal mannose residues, and 60–70% of the internal mannose residues carry acetate groups.

Bacterial polysaccharides are stereoregular and can adopt an ordered conformation under given conditions. The native ordered and rigid conformation has been reported to exist as a double-strand helix [2] although a single helical conformation has also been proposed [3]. A helix-coil transition in solution has been demonstrated by NMR, microcalorimetry and circular dichroism [4] and the stability and physical properties of the helix are strongly affected by the ionic environment. The ordered xanthan structure can dissociate into flexible coils, the disordered state, on heating above 50 °C in 0.01 M sodium chloride [2]. The temperature for the conformational change depends strongly on the polymer concentration

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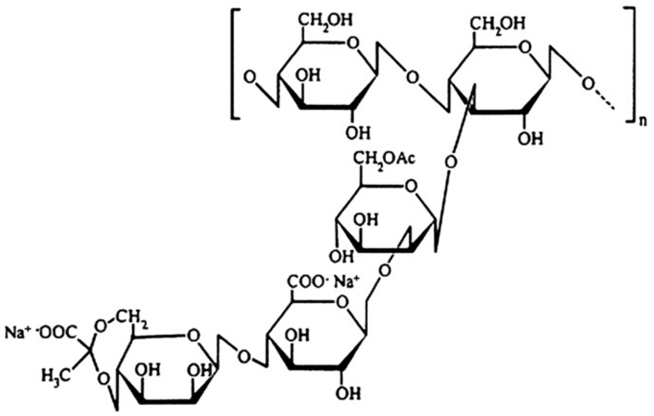

Fig. 1. Molecular structure of xanthan.

and the salt concentration. On cooling to room temperature, the disordered xanthan molecule adopts its reordered structure [2] (Fig. 2).

Xanthan is highly soluble in cold and hot water and this behaviour is related to the polyelectrolyte nature of the xanthan molecule. The behaviour of polyelectrolytes is complicated by charge densities influencing the polymer-solvent and polymer counter-ion interactions that lead to significant changes in their characteristic properties. Xanthan solutions are highly viscous, even at low concentrations. This property is useful in many industrial applications, especially in the food and cosmetic industries, where it is used as a thickener and stabilizer of suspensions and emulsions [1]. Furthermore, xanthan is a useful pharmaceutical excipient, since it is of natural origin, biocompatible and safe – it is assigned the GRAS (generally recognized as safe) label – as well as being relatively cheap to produce. It is used as a tablet excipient to increase or decrease the drug release rate but not much has been reported concerning its use for sustained drug release [5].

In addition, it has been reported that xanthan forms polyelectrolyte complexes with the polymer chains of chitosan, which is used for biomedical applications [6]. The most studied xanthan formulations are hydrophilic matrix systems consisting of xanthan and galactomannans like locust bean gum, guar gum and carob gum. The principle of such formulations is that the strong, elastic gel produced by direct interaction between the polymeric chains in the presence of a ternary component (dextrose) can control the drug-release process. Drug release from these systems is less sensitive to the presence of ions in the release medium than are the systems prepared from each polymer separately [7]. The technology of preparing blends composed of synergistic heterodisperse polysaccharides, together with a small saccharide component, known as the TIMERx drug delivery system, is well protected with over 90 patents issued worldwide [8].

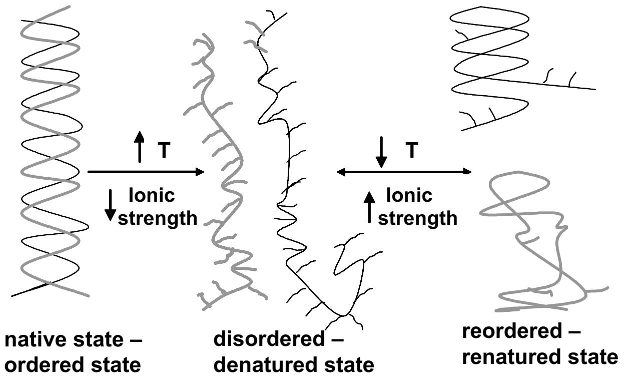

Fig. 2. Schematic illustration of the effect of ionic strength and temperature on xanthan structural changes.

Since xanthan is an anionic polyelectrolyte with a semi-rigid chain structure, we expected that the xanthan matrix would result in fundamentally different release behaviour from those of semi-synthetic polymers with flexible chains, like the cellulose ethers which we studied previously [9–13]. Compared to hydroxypropylmethylcellulose, xanthan has the potential advantage of drug release with zero order release kinetics; however its major drawback is that the drug release is influenced by the pH and the presence of ions in the medium. For example, drug release has been shown to be faster at higher electrolyte concentrations (sodium or potassium chloride) [14–16].

The behaviour of xanthan in multicomponent systems like matrix tablets is relatively difficult to predict due to the complex mutual interactions of the components. An understanding of these interactions is important for predicting the effects of drug release in vivo. The aim of this paper is therefore focused on the relation between the physical properties of a xanthan matrix in the absence and presence of calcium ions and the release of pentoxifylline as a model drug. Pentoxifylline is highly soluble in water, so its release depends predominantly on structural changes in the xanthan matrix. The original behaviour that occurs in specific cases when xanthan is mixed with divalent counterions, giving rise to new properties, is also investigated.

2. Experimental

2.1. Materials

Xanthan with MW 2×10^6 g/mol was obtained from Sigma–Aldrich Chemie, Germany, and lactose monohydrate from Lex d.o.o., Slovenia. Pentoxifylline, with MW 278.31 and solubility in water at 37 °C of 191 mg/ml, was supplied by Krka, d.d., Slovenia. Calcium chloride dihydrate ($CaCl_2{\cdot}2H_2O$) and sodium chloride (NaCl) were from Riedl-de-Haen, Germany, and were of analytical grade.

2.2. Preparation of tablets

Different types of tablets were prepared (Table 1). Xanthan and the drug were mixed homogeneously using a laboratory model drum blender. Crystals of $CaCl_2{\cdot}2H_2O$ were powdered before addition to the mixture. As a control, tablets with immediate release were prepared from lactose and pentoxifylline in the ratio 1:1. Predetermined amounts of

Table 1
Composition of tablet formulations investigated in the present study

Tablet type	Xanthan (mg)	Pentoxifylline (mg)	Lactose monohydrate (mg)	$CaCl_2 \cdot 2H_2O$ (mg)
XAN	400	0	0	0
XAN-50%	200	200	0	0
XAN-75%	300	100	0	0
LAC-50%	0	200	200	0
XAN-25-$CaCl_2$	275	100	0	25
XAN-50-$CaCl_2$	250	100	0	50
XAN-100-$CaCl_2$	200	100	0	100

blend were fed manually into the die of a flat-surface punch, 13 mm in diameter, and compressed in a tabletting machine (Graseby Specac, UK). Hardness for all the formulations was adjusted to within the range of 80–110 N (VanKel VK 200, USA; hardness tester; $n = 6$). The weight of each tablet was 400 ± 10 mg. For swelling and erosion experiments and for textural profiling of hydrated tablets XAN alone was compressed to tablets under the same procedure.

2.3. Drug release

Dissolution was studied on a fully calibrated dissolution apparatus using the paddle method (Apparatus II, VanKel Dissolution Apparatus, model VK 7000, USA). In addition to the standard apparatus II arrangement, further variations were made as described in the literature [17]. These involve the inclusion of a ring/mesh stainless steel device, which fits precisely under the paddle into the lower portion of the standard dissolution vessel. Paddle speed was kept at 50 rpm. The dissolution medium was 900 ml of purified water or water with $CaCl_2$ in a range of ionic strength from 0.00 to 0.20 M.

Sixty-three milliliters of 1 M hydrochloric acid was diluted to 1 L of the total solution (pH 1.2) and 1 M hydrochloric acid was diluted 1:1000 (pH 3.0). pH 1.2, pH 3.0 solutions and simulated intestinal fluid (SIF) pH 6.8 without pancreas powder (Ph. Eur., 5th ed., suppl. 3) were used to evaluate the influence of pH on release from xanthan tablets. The ionic strength was varied by adding $CaCl_2$ to 0.20 M.

The temperature was maintained at 37 ± 0.5 °C. At predetermined time intervals, 10 ml samples (not replaced) were withdrawn and analyzed UV spectrophotometrically at 274 nm (HP diode array UV spectrophotometer, 8453, Germany). All dissolution studies were performed at least in triplicate.

2.4. Dissolution data analysis

The dissolution profiles were fitted to the simple power law expression which best describes the kinetics of drug release from swollen tablet matrices [18]:

$$\frac{M_t}{M_\infty} = k \cdot t^n, \tag{1}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released at infinite time, k is the rate constant, n is the diffusion exponent that indicates the general release mechanism, and can range from 0.43 to 1; it depends on the shape of the drug delivery system. Based on the value of the diffusion exponent, drug transport in slab geometry is classified either as Fickian drug release ($n = 0.5$), non-Fickian or anomalous transport ($0.5 < n < 1$), or Case II transport ($n = 1$). Fickian diffusion release occurs by molecular diffusion of the drug due to a chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stresses and transition from glassy to rubbery states of polymers, which swell in water or physiological fluids. Anomalous transport occurs due to a coupling of Fickian diffusion and polymer relaxation [19]. Dissolution data up to 60% drug release were fitted to Eq. (1), using least-squares nonlinear regression.

2.5. Determination of the swelling degree and erosion

Swelling and erosion studies were performed in 900 ml of purified water, with or without $CaCl_2$ from 0.00 to 0.20 M. All other conditions were the same as those described above for dissolution testing. Three tablets were used per experiment. After 1, 3, 5 and 8 h the ring mesh assemblies supporting the partially hydrated tablets were carefully removed and the tablets lightly dried with tissue paper to remove excess surface water and weighted. The swelling degree was calculated using Eq. (2):

$$\text{swelling degree}(\%) = \frac{m_t - m_r}{m_r} \times 100 \tag{2}$$

where m_t, is the mass of hydrated tablet after the determined time of swelling (g); m_r, is the mass of remaining dry tablet after the swelling (g).

After determining the weight of the hydrated tablets, they were dried at 70 °C in a vacuum oven for 2 days, before reweighing to determine the remaining dry weight. The percent erosion was calculated as

$$\%\ \text{erosion} = \frac{m_0 - m_r}{m_0} \times 100 \tag{3}$$

where m_0, is the mass of dry tablet before swelling (g)

2.6. Preparation of xanthan hydrogel

To simulate swollen xanthan matrix layers, gels of xanthan were prepared by thoroughly dispersing 3 w/w% polymer in purified water at 40 °C. Gels were stored at 4 °C for

48 h to ensure complete hydration. To study the effect of Na^+ and Ca^{2+} ions on the gel behaviour, sodium or calcium salts were first dissolved in water at an ionic strength of 0.01 or 0.20 M and xanthan then added.

2.7. Rheological characterization of hydrogels

Viscoelasticity of previously prepared 3 w/w% hydrogels was measured at 20 °C ± 0.5 with an oscillatory viscometer Rheolab MC 100 (Physica, Germany) using a cone-plate measuring system. After determination of the linear viscoelastic region, frequency tests were performed at a constant strain of 0.2. Storage (G') and loss (G'') moduli were calculated using Physica software. The mean of at least three replicates was taken to calculate each modulus. In the preliminary tests the sinusoidal changing frequency range was stated from 0.05 to 5 Hz. However, at frequencies lower than 0.5 the cone slept over the sample, therefore standard deviations were very high. Consequently the measurements were performed at frequencies 1–50 Hz. The tendency of G' and G'' curves was the same in whole measuring range.

2.8. Texture profiling of swollen matrix tablets

Gel layer formation and its dynamics were evaluated as a function of time by texture profiling analysis (Zwick, Germany). Each tablet was placed on a stainless steel mesh device in the standard dissolution vessel containing the medium with or without Ca^{2+} ions. This allows medium ingress from all directions and simulates the actual process of gel dynamics that occurs in the dissolution process, as the tablets move freely in the vessel. Tablets were removed at determined time intervals and subjected to texture analysis. A flat-tipped steel sensor, 2 mm in diameter, was connected to a force transducer that measured the force of resistance encountered by the sensor during advancement through the swollen matrix. During a typical test, the sensor was advanced at a predetermined velocity into the sample in accordance with the following parameters: pre-test speed, 1 mm/s; test speed and post-test speeds, 5 mm/min; maximum compression force, 35 N, and auto trigger force, 1 mN. Data were captured at a rate of 200 points/s using the Texture Expert for Windows software, Version 1.20. The Texture Analyzer instrument can capture stress–strain profiles with a high degree of accuracy.

2.9. Evaluation of similarity factor (f_2) of release profiles

In order to compare the release profiles of pentoxifylline in different media as well as from different xanthan tablet formulations, the similarity factor (f_2) was calculated from the mean dissolution data according to Eq. (4):

$$f_2 = 50 \log \left\{ \left[1 + (1/n) \sum_{t=1}^{n} |R_t - T_t|^2 \right]^{-0.5} \times 100 \right\} \quad (4)$$

where n is the number of pull points, R_t is the reference profile at time point t and T_t is the test profile at the same time point. For a dissolution profile to be considered similar, the value of f_2 should be between 50 and 100.

An f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases [20].

3. Results and discussion

3.1. The release of pentoxifylline from xanthan tablets in purified water with and without Ca^{2+}

Release of pentoxifylline (PF) from different xanthan tablets was followed initially in water, where PF release was prolonged by more than 24 h, while release from the control lactose formulation was completed within 30 min (Fig. 3). Increasing the content of xanthan in the tablets from 50% to 75% did not change the release profiles significantly which was also confirmed by calculating similarity factor between these two release profiles ($f_2 = 81.13$). The slowing of release was accompanied by evident swelling of matrix tablet. The process of swelling generally starts when a dry matrix tablet is placed in water, which penetrates into the free spaces between the polymer chains. Polymers would hydrate and as a result gel-like network is formed around the dry tablet core. The formation of hydrogel on the surface of a matrix tablet generally undergoes a transition phase, i.e., from a dry (glassy) stage, where polymer is in a solid and compressed form, to a wet (rubbery) stage, where diffusion takes place [19]. The structural arrangement of water molecules within hydrophilic polymers is very important because it influences the formation of polymeric gel-like network as well as diffusion of the drug. Within the gel layer water can be present as bound or free [13,21]. The amount of free water is crucial for the drug dissolution and its diffusion. On the other hand during the hydration process, the matrix volume

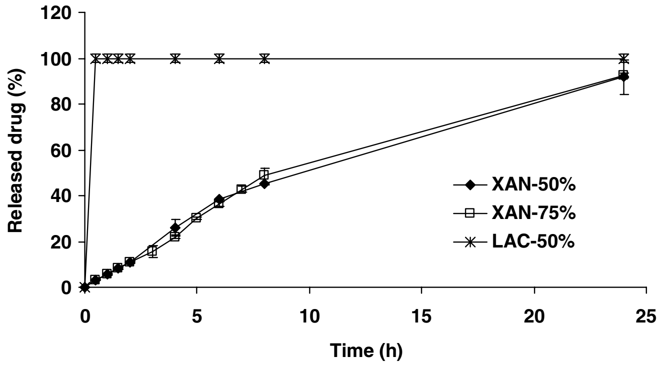

Fig. 3. The release profiles of pentoxifylline (PF) in purified water from xanthan tablets in comparison with the control tablets containing lactose and PF in the ratio 1:1 (LAC-50%). The ratio between XAN and PF was 1:1 (XAN-50%) and 3:1 (XAN-75%). Each data point represents the means ± SD of at least six measurements.

increases because of the polymer relaxation, creating pathways for diffusion of the dissolved drug.

To investigate the influence of Ca^{2+}ions on the release of PF from xanthan tablets, a range of ionic strength from 0.00 to 0.20 M was chosen for this study, what is within the physiological interval of the ionic strengths in gastrointestinal fluids [14]. Ca^{2+} ions are present in the gastrointestinal tract at 0.1 M ionic strength [22], but this concentration may be increased by food intake.

The release rate of pentoxifylline from xanthan tablets was significantly increased by the presence of calcium ions in media (Fig. 4A). The higher the concentration of Ca^{2+} ions, the faster the release, which was also shown by obvious differences in release profiles according to calculated similarity factor ($f_2 = 41.30$) for minimal (0.02 M) and maximal (0.20 M) ionic strength used. Again, the difference in rate of release in medium with Ca^{2+} from tablets with 50% or 75% xanthan is not significant, $f_2 = 70.25$ (Fig. 4B).

From the obtained release profiles the diffusion exponent n was calculated according to Eq. (1) (Table 2). It is evident that the presence of calcium ions changes the release mechanism. The release of pentoxifylline from xanthan tablets in purified water is described as Case II transport, i.e., relaxational release. Increasing the ionic strength in the release medium by adding $CaCl_2$ decreases the diffusion exponent, meaning that the influence of Fickian diffusion is more and more pronounced. Thus the drug release mechanism is changing with the increasing concentration of Ca^{2+} ions from purely relaxational to anomalous transport.

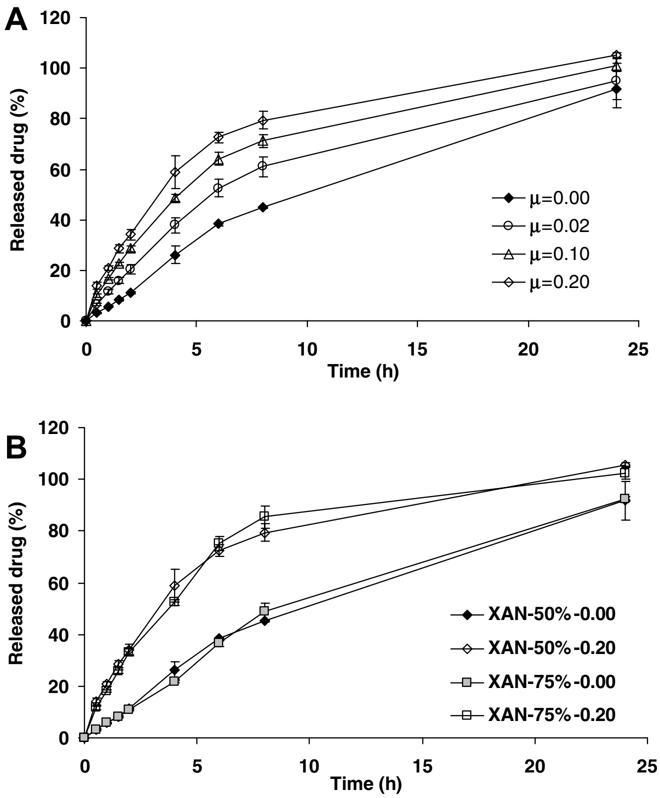

Fig. 4. (A) The release profiles of pentoxifylline from xanthan tablets (XAN-50%) in media with added $CaCl_2$ at ionic strengths from 0.00 to 0.20 M. (B) Comparison of the release profiles from xanthan tablets with different proportions of XAN polymer in tablet in purified water and medium with $CaCl_2$ at ionic strength of 0.20 M. The data points represent means ± SD of six measurements.

The influence of monovalent cations on the drug release from xanthan tablets has been studied [14–16]. These results and ours both show that monovalent and divalent ions increase the drug release rate. In contrast, the cross-linking of some polyanionic polymers by Ca^{2+} ions decreases the drug release rate [23–25].

Further, we checked the effect of Ca^{2+} ions on the release profile, by incorporating three different amounts of $CaCl_2$ in xanthan tablet matrices (Table 1). Drug release was performed in water (Fig. 5A) and in medium with ionic strength of 0.20 M (Fig. 5B). The effect of incorporated $CaCl_2$ on the drug release in water was similar to the effect of Ca^{2+} ions from medium. However, release rate in water was influenced by the amount of $CaCl_2$ in tablets, hence the higher was the amount of incorporated $CaCl_2$ the faster was the release. This effect in water was more pronounced in the first two hours, when local ionic strengths were relatively higher than later (Fig. 5A). But, with the release of pentoxifylline, $CaCl_2$ was also dissolved and the local ionic strength decreased. At the end of the experiment performed in water, when all the $CaCl_2$ was released from tablets with 100 mg of salt, the ionic strength of the medium reached only about 0.002 M. Therefore it is not surprising that in the medium with Ca^{2+} ions at an ionic strength of 0.20 M the effect of incorporated $CaCl_2$ in xanthan tablets is less pronounced (Fig. 5B). According to calculated similarity factor it can be seen that dissolution profiles of pentoxifylline from xanthan tablets with different incorporated amounts of $CaCl_2$ are similar in both media (values of f_2 from 58.43 to 80.51), but no one of them is similar to dissolution profile from xanthan tablet without $CaCl_2$ (values of f_2 from 38.48 to 47.51).

The findings from the release data of PF from xanthan tablets confirm that the higher the concentration of Ca^{2+} ions in media or in tablet, the faster the release.

3.2. Swelling and erosion studies of xanthan matrices in water with and without Ca^{2+}-ions

To investigate the changes in hydration ability of xanthan matrices, swelling and erosion studies were performed in purified water in the absence and presence of calcium ions at different ionic strengths (Fig. 6A). Xanthan matrices showed substantially faster and more extensive swelling in water than in the presence of Ca^{2+} ions. The difference in swelling of xanthan matrices in media with ionic strengths of 0.10 and 0.20 M is less than the difference between 0.02 and 0.10 M. Increase of ionic strength above 0.20 M would have even smaller effect. These results are in agreement with observations that an increase of ionic strength above

Table 2
The diffusion exponent *n* for release profiles for pentoxifylline from xanthan tablets in different media

Tablet type	μ of the medium (M)	pH of the medium	*n*	*k*	R^2
XAN-50%	0.00	5.672	1.0120	1.235	0.9956
	0.02	5.697	0.8199	0.933	0.9985
	0.10	5.708	0.7285	0.773	0.9968
	0.20	5.798	0.6575	0.662	0.9942
XAN-75%	0.00	5.672	0.9944	1.233	0.9929
	0.20	5.798	0.7383	0.719	0.9970

where *n* is calculated using Eq. (1). μ, is the ionic strength of the medium; *k*, the rate constant and R^2, is the Pearson coefficient.

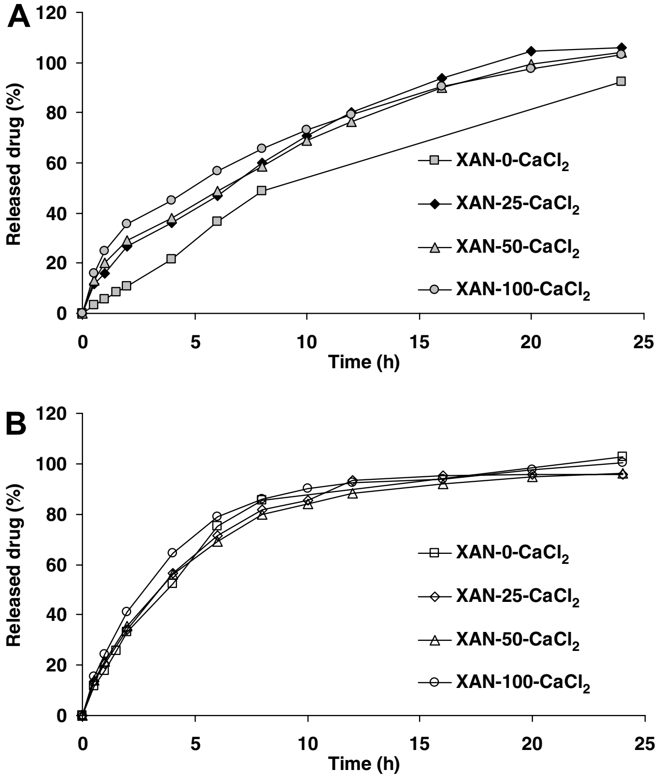

Fig. 5. The release profiles of pentoxifylline from xanthan tablets with various amounts of incorporated $CaCl_2{\cdot}2H_2O$ (0, 25, 50 or 100 mg): (A) in purified water and (B) in media with $CaCl_2$ at ionic strength of 0.20 M. The composition of tablets is presented in Table 1. The data points represent the mean of six measurements; error bars are omitted for better resolution.

0.10 M does not lead to any significant difference in the swelling of the xanthan [15].

In purified water at pH 5.5–5.7 carboxylic groups on the trisaccharide side chains of xanthan are ionized and repel each other. The polymer is a random coil (disordered state) and presents many hydrophilic groups exposed to the water. The interactions between xanthan and water molecules are favourable and the degree of swelling is thus high.

It is known that a divalent counter-ion (Ca^{2+}) strengthens the electrostatic interaction between a counter-ion and a polyion [26,27]. Polyanionic behaviour of xanthan in our experimental conditions is obviously influenced by addition of Ca^{2+} ions. According to the Manning's condensation theory of counterions [28,29] it can be assumed that in the investigated system Ca^{2+} ions condense on ionized carboxyl moieties of xanthan and reduce repulsive forces between polyelectrolyte chains. Since polyelectrolyte conformations are controlled by the fraction of ionized groups, the charge screening by Ca^{2+} ions results in the conformational changes. The trisaccharide side chains of xanthan in the presence of Ca^{2+} ions presumably collapse down to the backbone driving a transition in the structure which gives the xanthan molecule a rigid rod-like shape (and reduces its hydrodynamic size) [30] and attractive inter-polymer interactions between xanthan polymer chains are enhanced. These conformational changes result in reduced ability of xanthan molecules for interactions with water, therefore swelling is decreased with increasing concentration of Ca^{2+} ions (Fig. 6A). Subsequently, the degree of erosion is expected to be lower than in purified water, as is confirmed experimentally (Fig. 6B).

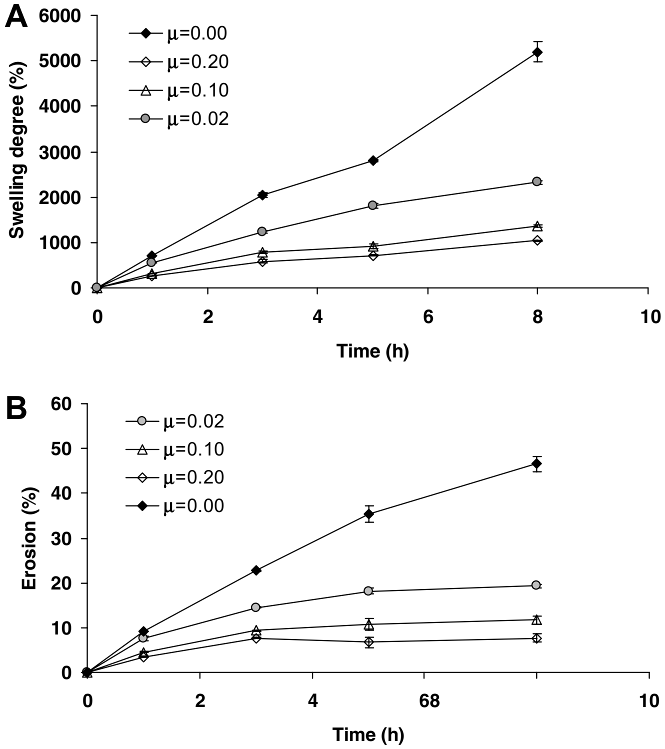

Fig. 6. Influence of calcium ions in the medium on: (A) swelling and (B) erosion of matrix tablets composed of xanthan/pentoxifylline 1:1. Swelling was studied in water without or with $CaCl_2$ added to ionic strengths from 0.00 to 0.20 M. The data points represent means ± SD of six measurements.

Swelling and drug release from cellulose ethers matrices have been shown to be positively correlated [9,31]. Surprisingly, negative correlation is seen with xanthan: the greater the swelling, the slower the drug release. Drug release kinetics is strictly associated with the structure of the polymer network in the gel layer and arrangement of water molecules within it. The release mechanism of pentoxifylline, as a water soluble molecule, from xanthan in purified water is controlled mainly by macromolecular relaxation or swelling (Table 2), which determines the volume increase of the matrix. Water molecules are arranged around negatively charged carboxyl moieties of xanthan. The thickness of xanthan gel layer and water arrangement cause slower release of PF in purified water.

In the presence of Ca^{2+} influence of diffusion on the drug release mechanism is more and more pronounced (Table 2). Charge screening of xanthan with Ca^{2+} increases the inter-polymer interactions and decreases the interactions with water molecules, therefore water ingress into the tablet matrix is more restricted, swelling is lower and gel layer is thinner. Besides, water molecules inside the xanthan gel in the presence of Ca^{2+} ions are not bounded in such an amount as in purified water. Consequently relatively larger amount of free water molecules is within hydrogel. Thinner gel layer and less ordered water molecules within it cause faster release of PF from xanthan tablet in the presence of Ca^{2+} ions.

The effect of charge screening of Ca^{2+} ions on the drug release was confirmed by additional drug release studies. Under simulated physiological conditions we measured drug release for two hours at pH 1.2 or pH 3.0 before transferring the tablet to water or to simulated intestinal fluid at pH 6.8. (Fig. 7). At pH 1.2 the drug release was very fast. When pH 1.2 medium was replaced by water, polymer started to swell more and drug release was decreased. At low pH carboxylic groups are less ionized, the repulsion between xanthan chains and the interaction of water with xanthan chains are lower. Therefore swelling is lower, and drug release is faster and controlled by diffusion (Table 3).

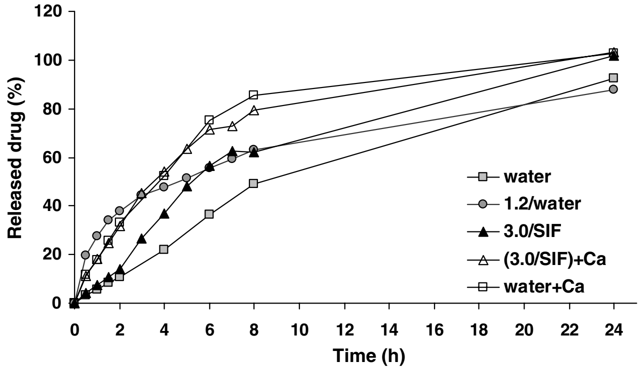

Fig. 7. The release of pentoxifylline from xanthan tablets in different media: purified water; solution, pH 1.2, which was replaced by water after 2 h; solution, pH 3.0, replaced by simulated intestinal fluid (SIF) after 2 hours; medium pH 3.0/SIF with $CaCl_2$, $\mu = 0.2$ M and purified water with $CaCl_2$, $\mu = 0.2$ M. Each data point represents the mean of six measurements; however the error bars were omitted for better resolution.

When the drug release was performed at pH 3.0 and after two hours in simulated intestinal fluid (SIF) with pH 6.8, apparently contradictory results were obtained. At pH 3.0 the release is slow and after replacement of solution the release was increased. SIF possessed an ionic strength of 0.035 M and, even if pH of 6.8 enables ionization of carboxylic groups, increased ionic strength (provided by Na^+ and K^+ ions) causes a partial charge screening effect and, from known reasons, faster drug release. The same was observed in medium pH 3.0/SIF with addition of $CaCl_2$ (Fig. 7), where the drug release constants k and n are very similar to those of xanthan tablets in media with ionic strength of 0.20 M (calculated $f_2 = 73.38$). Increased ionic strength or low pH exerts the same effect on the hydration of xanthan chains, and thus the same effects on drug release and degree of swelling. From the obtained results it can be concluded, that the higher the concentration of Ca^{2+} ions in media, the lower the swelling degree as well as polymer erosion.

3.3. Viscoelasticity of swollen xanthan layers

The effect of Ca^{2+} ions on the structure of the xanthan network was investigated by oscillatory rheometry. The critical deformation point below which the linear viscoelastic region is obtained was determined by the amplitude sweep test. The determined deformation was 0.2. The loss and elastic moduli increased dramatically when the polymer was hydrated in water containing calcium salts (Fig. 8A). The same was observed in medium with added NaCl (Fig. 8B).

In water the carboxylic groups on the trisaccharide side chains of xanthan are ionized and highly solvated, causing the expansion of polymer chains. Negatively charged xanthan chains are stretched out due to mutual charge repulsion, interactions between polymer chains are lower, G' and G'' are lower and swelling/erosion is increased. On addition of small counterions like Ca^{2+} the effective charge of xanthan is reduced and the chains contract. With charge screening the intra- and intermolecular attraction between the polymer segments is greater than the segment-water affinity and the xanthan chain will tend to coil up or adopt a more rigid structure (increasing G').

An additional argument supporting the last statement can also be that the xanthan structure determined rheologically in the presence of Na^+, which cannot crosslink xanthan molecules, differs very little from that in the presence of Ca^{2+} ions (Fig. 8A and B). As already noted, multivalent cations can physically crosslink some polyanions like alginates [5,32]. However, for xanthan this is apparently not the case. Alginates are unbranched binary co-polymers with carboxyl groups located on the polymer backbone and therefore calcium can crosslink the chains through carboxyl groups.

Similar approaches with xanthan have been used by other investigators [33,34]. Their studies had focused on

Table 3
The diffusion exponent *n* for release profiles for pentoxifylline from xanthan tablets in different media

Tablet type	μ of the medium (M)	pH of the medium	*n*	*k*	R^2
XAN-75%	0.08/0.00	1.2/water*	0.4029	0.5604	0.9912
	0.001/0.035	3.0/SIF**	1.0795	1.1071	0.9891
	0.201/0.235	3.0/SIF**	0.7679	0.7321	0.9984

n is calculated using Eq. (1). μ, the ionic strength of the medium; *k*, the rate constant and R^2, the Pearson coefficient; *, medium pH 1.2 was replaced by purified water after 2 h; **, medium pH 3.0 was replaced by SIF after 2 h.

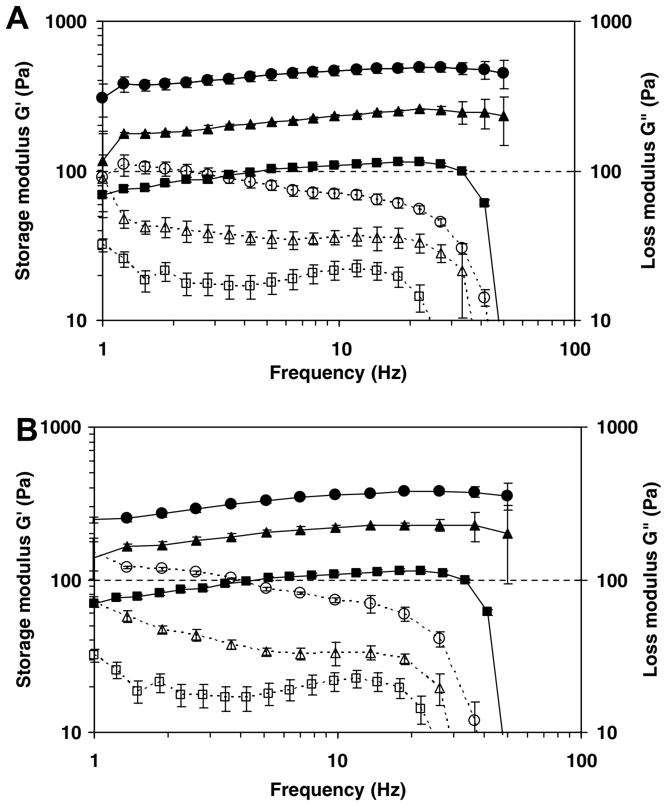

Fig. 8. Dependence of viscoelastic properties (expressed as G′ and G″) of a 3% xanthan dispersion on (A) added $CaCl_2$ or (B) NaCl to ionic strengths from 0.00 to 0.20 M. Each data point represents means ± SD of three measurements. G′-full line and G″-dashed line: ■□, purified water, ▲△, $\mu = 0.01$ M, ●○, $\mu = 0.20$ M.

ideal systems and conditions; where small structural differences are easier to determine. But those differences do not necessarily reflect the behaviour of real systems that do not involve extra purified excipient, low concentration of polymers, unphysiological environment, etc.

On the basis of the obtained rheological data it can be stated that Ca^{2+} ions did not crosslink xanthan chains, however the elastic and plastic moduli of formed structures are more expressed.

3.4. Texture profiling and gel layer dynamics of swollen tablets

The dynamic structural changes of the gel layer formed during swelling of tablets were followed by force-displacement measurements (Figs. 9 and 10). After 30 min of swelling the core of a xanthan tablet in Ca^{2+} media was still dry (Fig. 10), and the measured forces were higher than those determined for xanthan in water, in which the core was little hydrated (Fig. 9).

The charge on the trisaccharide side chains of xanthan is partially screened in the presence of Ca^{2+} ions, as was demonstrated previously, and this is the reason why water enters more slowly into the polymer matrix. After 2 h of swelling the differences between the measured penetrating forces are minor, but remain during whole experiment. Xanthan tablets in water become very thick (Fig. 9) – more than 10 mm – but after 8 h the gel layer could not be determined because the structure was too weak. This was confirmed by calculating the mass percentage of xanthan in a swollen tablet from swelling and erosion data. After 8 h of swelling the mass percentage of xanthan in the tablet was reduced from 100 w/w% to only around 1.9 w/w%. In contrast, the thickness of xanthan tablets in media with Ca^{2+} was lower and the tablet shape was clearly observed even after 8 h of swelling (Fig. 10). The calculated mass percentage of xanthan in the remaining tablet was around 8.8 w/w%. On the basis of the results of measured penetrating forces through the swollen tablets, the gel layers were very weak in both media (Table 4). It was surprising that, after 8 h of swelling in water, when the mass percentage of xanthan in a swollen tablet is only around 1.9 w/w% and the structure of the tablet could no longer be determined by texture analyzer, only around 40% of pentoxifylline was released. On the other hand, at the same time in medium with Ca^{2+}, almost 3 times higher mass percentage of xanthan remained in a more structured form, but drug release was less sustained, since around 80% of the pentoxifylline was already released. Thus, Ca^{2+} induces more highly ordered molecules whose intermolecular interaction is different from that of the less ordered molecules in the absence of Ca^{2+}. This interaction together with differently ordered water molecules leads to a more open gel structure which allows more rapid drug release.

4. Conclusions

The physical structure of xanthan matrix tablet in water was strongly affected by the presence of Ca^{2+} ions and by pH, which was reflected in the release profiles of an incorporated drug. Increasing the ionic strength of the medium causes charge screening of carboxylic groups on the trisaccharide side chains of xanthan, leading to reduced intermo-

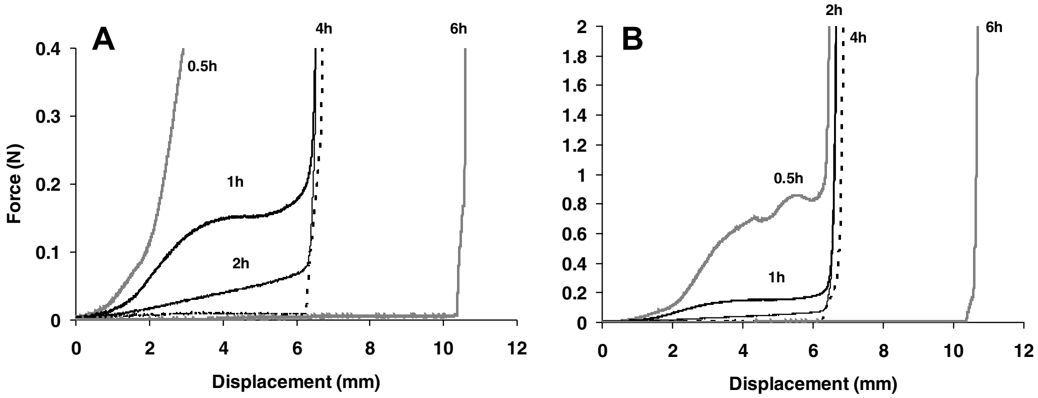

Fig. 9. Texture profiling of xanthan tablets after different times of swelling (hours) in purified water ($n = 3$). (A) Range of forces from 0 to 0.4 N, (B) range of forces from 0 to 2.0 N.

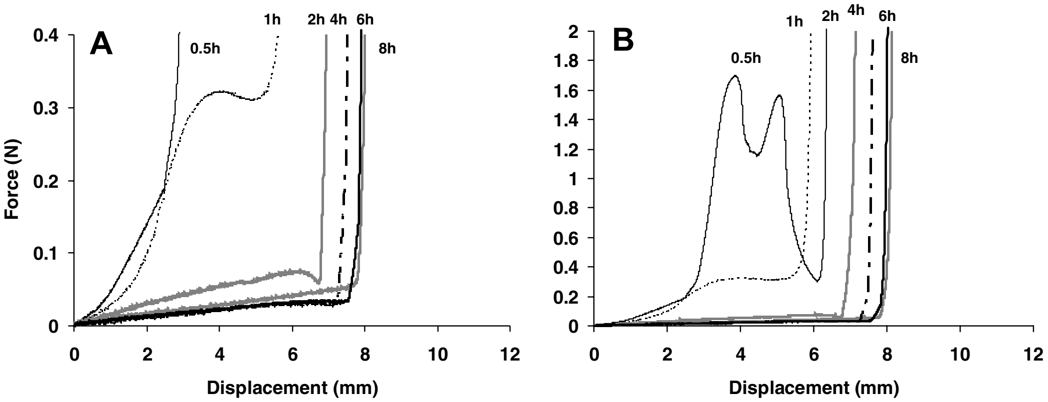

Fig. 10. Texture profiling of xanthan tablets after different times of swelling (hours) in medium with $CaCl_2$ at an ionic strength of 0.20 M ($n = 3$). (A) Range of forces from 0 to 0.4 N, (B) range of forces from 0 to 2.0 N.

Table 4
The mass percentage of xanthan in tablets swollen in different solutions calculated from swelling and erosion data and the penetrating force (mN) of the gel layer measured at a distance of 4 mm

Swelling time (h)	Purified water		$CaCl_2$ ($\mu = 0.20$ M)	
	w/w% xanthan in swollen tablet	Force (mN) at distance of 4 mm	w/w% xanthan in swollen tablet	Force (*N*) at distance of 4 mm
1	12.0	151.2	23.9	322.3
2	8.3	40.6	19.3	52.1
4	4.1	10.2	12.9	28.5
6	3.0	2.4	10.1	23.1
8	1.9	–	8.8	22.5

lecular repulsion rather than crosslinking. Consequently, swelling and erosion were lower, the gel structure formed was more rigid, and the texture was shown to be firmer by force-displacement studies. Faster drug release was confirmed by incorporating $CaCl_2$ into the tablet. The higher the amount of incorporated salt, the faster the release in purified water.

The question remains as to whether xanthan alone is suitable for the formulation of tablets with controlled release. Xanthan tablets in water possess limited mechanical stability, and the drug release is too slow. However, the drug release experiments performed in simulated physiological media and at moderate ionic strength indicated the formation of a firmer gel structure and increased drug release rate. Thus, taking into account all the parameters that influence the drug release, xanthan is a suitable candidate for controlled release formulations, especially with the incorporation into the tablet of some small counterions.

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