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Influence of hydrogel structure on the processes of water penetration and drug release from mixed hydroxypropylmethyl cellulose/thermally pregelatinized waxy maize starch hydrophilic matrices

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Abstract

The kinetics of water penetration and molsidomine release from both hydroxypropylmethyl cellulose (HPMC) and mixed HPMC/thermally pregelatinized waxy maize starch (SDWMT) hydrophilic matrices has been examined in 0.1 mol dm^{-3} HCl (pH 1.0) and 0.06 mol dm^{-3} Na_3PO_4/HCl buffer (pH 6.8). The rheological oscillatory test parameters of their gel layers obtained by swelling of the matrices in the two aqueous media have been observed. The kinetic swelling properties of mixed HPMC/SDWMT hydrogels (i.e. degree and velocity of both water penetration and swelling, transport mechanism which controls solvent sorption) directly influence the drug release behaviour and the structural features of the formed gel layer. Both diffusion processes are diffusion-controlled ones, their mechanisms being influenced insignificantly by the relaxation properties of the hydrated macromolecules. It has been established by means of comparative viscoelastic analysis, that mixed HPMC/SDWMT hydrogels demonstrate the typical behaviour of 'filled' composite systems having poor adhesion between the surface of the elastic SDWMT 'filler' and the continuous HPMC phase. Due to the inter-phase relations between the swollen starch granules and the linear cellulose derivative as well as to the specific structure of amylopectin molecule, the pregelatinized waxy maize starch shows a stronger influence on the velocities of both water penetration and drug release from mixed HPMC/SDWMT matrices. © 2001 Published by Elsevier Science B.V.

Keywords: Thermally pregelatinized waxy maize starch; Hydroxypropylmethyl cellulose; Mixed hydrophilic matrices; Water penetration; Rheology

1. Introduction

Thermally pregelatinized starches prove to be very suitable for formulating of hydrophilic ma-

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trix systems (Mohile, 1986; Herman and Remon, 1989; Sánchez et al., 1995) because their technological and physicochemical properties are rather similar to those of the commonly used cellulose derivatives, i.e. hydroxypropylmethyl cellulose (HPMC), HPC, HEC. The native starch consists of two macromolecular structural analogues, i.e. a branched amylopectin and a linear amylose, whose content can vary between 0 and 80% according to the starch genotype (Young, 1984). Thermally pregelatinized starches are produced by gelatinization of the native starches followed by a process of thermal dehydration like extrusion, drum-drying, roll-drying, spray-drying, freeze-drying (Snyder, 1984; Sánchez et al., 1995). In vitro biopharmaceutical studies of pregelatinized starch hydrophilic matrices show that the main factors controlling their drug release behaviour are the starch chemical composition, i.e. amylose/amylopectin proportion, the degree of pregelatinization and the starch concentration in the gel. It has been established that waxy maize starch (containing 100% amylopectin) has the best potential for drug release retardation which progressively decreases with the increase of amylose content (Herman and Remon, 1989). Like most unlimited swelling hydrogels matrices, the drug release mechanism from these hydrogels is a diffusion-controlled one. It is determined by the structural characteristics of the gel layer (structural organization, diffusion capability, gel strength), and by the processes of both polymer swelling and gel layer erosion (Herman and Remon, 1989).

The structural characteristics of starch gels have been investigated extensively by means of the experimental and theoretical rheology methods (Eliasson, 1986; Doublier et al., 1987; Ellis et al., 1989). The rheological properties of starch pastes and gels are strongly dependent on the techniques of pregelatinization and especially on the temperatures and processing parameters, as well as on the amylose/amylopectin ratio, the swelling degree of starch granules and their concentration in the gel (Bagley and Christianson, 1982; Doublier et al., 1987; Dintzis and Bagley, 1995). According to the modern view starch gels containing amylose are composite materials, consisting of an amylose network reinforced by the swollen starch granules (Ott and Hester, 1965; Carnali and Zhou, 1996). Their swelling degree, their compressibility, and the adhesion between the continuous and dispersed phase control the rheological behaviour of the starch gels (Eliasson and Bohlin, 1982; Ring and Stainsby, 1982). The structural and rheological properties of pregelatinized waxy maize starch hydrogels (100% amylopectin) differ considerably from those of the highly elastic amylose containing gels. Their concentrated dispersions possess weaker gel structures, which depend on the concentration of whole or partially destroyed starch granules and on the dissolved amylopectin quantity (Bagley and Christianson, 1982; Evans and Lips, 1990). In vivo the erosion of such a gel layer may accelerate the drug release from pregelatinized waxy maize starch matrices (Herman and Remon, 1989). Starch gel strength can be increased by means of chemical crosslinking (Gluck-Hirsh and Kokini, 1997), enzymatic hydrolysis and retrogradation (Te Wierik et al., 1997), and addition of macromolecular hydrophilic polymers (Sánchez et al., 1995) or complexing emulsifiers (Conde-Petit and Escher, 1995). Some of these methods have been used for modifying the drug release kinetics from pregelatinized starch hydrogels (Sánchez et al., 1995; Te Wierik et al., 1997). For this reason we used HPMC, which is able to form elastic gels (Michailova et al., 1999), for developing of mixed matrix systems containing pregelatinized waxy maize starch.

In this work, we evaluate the processes of both water penetration and molsidomine release from mixed hydrophilic HPMC/thermally pregelatinized waxy maize starch (SDWMT) matrices in 0.1 mol dm^{-3} HCl (pH 1.0) and 0.06 mol dm^{-3} Na_3PO_4/HCl buffer (pH 6.8). A comparative rheological analysis of the mechanical spectra of the mixed hydrogels is made using a dynamic oscillatory viscoelastic test. The structural features of the gel layer are related to the kinetics and mechanism of both water uptake and drug release.

2. Materials and methods

2.1. Materials

HPMC (Methocel K15M Premium, Colorcon, UK) and HPMC/SDWMT mixtures of the following ratios were used: 80/20, 60/40, 40/60 and 20/80. Methocel K15M has 22% methoxy and 8.1% hydroxypropyl content; a 2% w/v aqueous solution has a viscosity of ≈15 000 mPa s at 20°C (Doelker, 1987). SDWMT consists of 100% amylopectin; its 14% w/v aqueous dispersion has a viscosity of 287 mPa s at 20°C (Herman et al., 1989). The pregelatinized waxy maize starch was produced by spray-drying technique at the Pharmaceutical Technology Laboratory of the State University of Gent, Belgium. Molsidomine (*N*-ethoxycarbonyl-3-morpholinosydnonimine) was supplied by Sopharma Ltd., Bulgaria.

2.2. Preparation of hydrophilic matrix tablets

Matrix tablets containing 8 mg molsidomine and HPMC/SDWMT in the proportion ratios mentioned above were directly compressed on an eccentric tablet-press machine (Erweka, Germany) equipped with 8 mm flat punches at a pressure of 150 MPa. The weight of each tablet was 200 ± 1 mg.

2.3. Liquid penetration study

The process of liquid penetration into the hydrophilic matrix tablets was examined gravimetrically by means of Stamberg and Sevcik method. The dry matrix tablet was weighed accurately in a tarred glass column consisting of a funnel of 4 cm^3 volume, sintered filter and a tube taking the surplus of water away (Stamberg and Sevcik, 1966). The liquid penetration was studied using the following aqueous phase: (a) 0.1 mol dm^{-3} HCl solution (pH 1.0), and (b) 0.06 mol dm^{-3} Na_3PO_4/HCl buffer (pH 6.8). The Na_3PO_4/HCl buffer is prepared by mixing of 800 cm^3 0.1 mol dm^{-3} HCl solution and 100 cm^3 0.6 mol dm^{-3} Na_3PO_4 (Lehmann et al., 1999). The sample was soaked into the aqueous phase tested for a given period of time (1, 2, 3, 4 and 5 h) at a temperature of 37 ± 0.5°C. Then the excess liquid was removed by centrifugation at 2500 min^{-1} for 10 min and the swelled hydrogel was weighed again. For the weight of each swelled matrix, the mean value of six measurements was taken. The dynamics of the liquid uptake was expressed as a weight gain (w_p) of the swelled matrix, in g penetrant/g dry polymer (Davidson and Peppas, 1986), calculated as a ratio between the amount of the aqueous phase remaining in the swollen matrix for a given period of time and the initial weight of the dry matrix tablet.

2.4. In vitro dissolution study

The dissolution testing was performed using a USP XXIII rotating paddle apparatus (Erweka DT6) at a rotation speed of 100 ± 1 min^{-1} and a temperature of 37 ± 0.5°C. The dissolution medium (900 cm^3) was identical to that used in the liquid penetration studies, i.e. 0.1 mol dm^{-3} HCl solution (pH 1.0) and 0.06 mol dm^{-3} Na_3PO_4/HCl buffer (pH 6.8). The quantity of molsidomine released was measured spectrophotometrically using a Hewlett Packard 8452A apparatus at 285 and 310 nm for pH 1.0 and 6.8, respectively. The mean value of three determinations is taken into account. The mean cumulative percentages of drug released were calculated (± S.D.).

2.5. Preparation of hydrogel systems

The highly concentrated HPMC and mixed gels were obtained by swelling of the matrix tablets in the above mentioned aqueous phases, i.e. 0.1 mol dm^{-3} HCl solution (pH 1.0) and 0.06 mol dm^{-3} Na_3PO_4/HCl buffer (pH 6.8), at a temperature of 37 ± 0.5°C for 7 h. The gel layer formed around the matrix was carefully separated from the unswollen core and then it was immediately tested rheologically. The swelling time (7 h) was selected having in mind the in vitro evaluation of molsidomine release processes from the hydrophilic matrices. The polymer concentration of the hydrogels was between 18 and 25% w/w. It was determined by means of DTA (Mettler TA3000, Switzerland) over a temperature range from 35 to

170°C at a standard heating rate of 10°C per minute.

2.6. Rheological studies

Rheological studies of the hydrogel systems were performed with a Rheotron Brabender rheometer equipped with cone-plate systems (P8/B, P8/C). All measurements were carried out at a temperature of 37 ± 0.5°C. The storage (G') and the loss (G'') moduli, as well as the dynamic viscosity (η') were obtained under the dynamic conditions of non-destructive oscillatory tests in a frequency range from 0.06 to 31.95 rad s^{-1}.

2.7. Data analysis

The kinetics of liquid penetration into the hydrophilic matrices was analysed according to Eq. (1) (Michailova et al., 2000):

$$w_p = K_p t^{n_p}, \tag{1}$$

where w_p is the weight gain of the swelled matrix; K_p is the kinetic constant of water penetration; t is penetration time; n_p is an exponent which depends on the water penetration mechanism.

The evaluation of molsidomine release kinetics is based on Peppas' equation (Peppas, 1985):

$$M_t/M_\infty = kt^n, \tag{2}$$

where M_t/M_∞ is the fraction of the drug released at time t, k is the kinetic constant of drug release, and n is a release exponent whose values for a cylindrical geometry range between 0.45 and 0.89 depending on Fickian or anomalous release kinetics.

The values of K_p, n_p, k and n for all tested hydrophilic matrices were calculated by regression analysis (values ± 95% confidence limits).

3. Results and discussion

3.1. Evaluation of water penetration and drug release processes from mixed HPMC/SDWMT hydrogels

The penetration profiles of 0.1 mol dm^{-3} HCl (pH 1.0) and 0.06 mol dm^{-3} Na_3PO_4/HCl buffer (pH 6.8) into pure HPMC and mixed HPMC/SDWMT hydrophilic matrices are shown in Fig. 1(a) and (b). The ionic strength of the aqueous phases and their pH values influence the processes of water uptake into the hydrogels insignificantly. For the media tested, the degree of water penetration is the highest for the pure HPMC. It diminishes with the increase of the pregelatinized starch quantity (20–60%), a slight minimum being observed with the system containing 40% SDWMT. With the 20/80 HPMC/SDWMT matrices, the degree of water sorption greatly decreases. That dependence indicates the water-absorption and swelling capabilities of the two polymers (Gehrke, 1992). In comparison with the cellulose derivative,

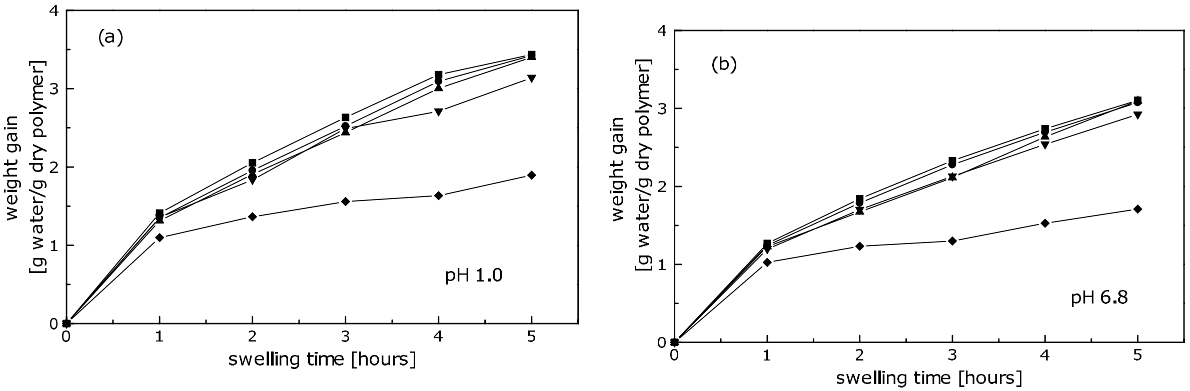

Fig. 1. Weight gain of HPMC and mixed hydrophilic matrices as a function of the swelling time. (a) 0.1 mol dm^{-3} HCl medium; and (b) pH 6.8 phosphate buffer. (■) HPMC; and mixed HPMC/SDWMT matrices: (●) 80/20, (▲) 60/40, (▼) 40/60, (◆) 20/80.

Table 1
Values of kinetic parameters of both water penetration (K_p and n_p) and drug release (k and n) processes of HPMC and mixed HPMC/SDWMT hydrogels in 0.1 mol dm^{-3} HCl

HPMC/SDWMT ratio	Water penetration			Drug release		
	K_p (h^{-n})	n_p	r	k (h^{-n})	n	r
100/0	1.4065 ± 0.0295	0.5678 ± 0.0175	0.9986	0.2303 ± 0.0039	0.5361 ± 0.0138	0.9991
80/20	1.3343 ± 0.0247	0.5829 ± 0.0183	0.9993	0.2778 ± 0.0026	0.5496 ± 0.0064	0.9996
60/40	1.2949 ± 0.0231	0.5889 ± 0.0188	0.9986	0.3655 ± 0.0048	0.4683 ± 0.0093	0.9990
40/60	1.3201 ± 0.0404	0.5354 ± 0.0319	0.9981	0.3998 ± 0.0046	0.4293 ± 0.0076	0.9992
20/80	1.0919 ± 0.0346	0.3213 ± 0.0247	0.9980	0.4642 ± 0.0032	0.3867 ± 0.0044	0.9997

Table 2
Values of kinetic parameters of both water penetration (K_p and n_p) and drug release (k and n) processes of HPMC and mixed HPMC/SDWMT hydrogels in Na_3PO_4/HCl buffer (pH 6.8)

HPMC/SDWMT ratio	Water penetration			Drug release		
	K_p (h^{-n})	n_p	r	k (h^{-n})	n	r
100/0	1.2646 ± 0.0049	0.5601 ± 0.0049	0.9999	0.1682 ± 0.0009	0.6206 ± 0.0039	0.9999
80/20	1.2285 ± 0.0101	0.5651 ± 0.0102	0.9995	0.2096 ± 0.0034	0.5922 ± 0.0146	0.9983
60/40	1.1189 ± 0.0431	0.5826 ± 0.0404	0.9926	0.2468 ± 0.0029	0.5537 ± 0.0086	0.9994
40/60	1.1796 ± 0.0178	0.5529 ± 0.0151	0.9989	0.2678 ± 0.0025	0.4962 ± 0.0097	0.9990
20/80	1.0140 ± 0.0456	0.3566 ± 0.0241	0.9908	0.3151 ± 0.0029	0.4423 ± 0.0058	0.9996

the pregelatinized starch hydrates to a considerable lower degree although its swelling characteristics, such as swelling and water retention capacities, are enhanced as a consequence of the preliminarily physical modification of the native waxy maize starch (Herman et al., 1989). The lower ability of SDWMT to swell may be explained by the formation of intra-molecular hydrogen bonds in the highly branched amylopectin (Hanselmann et al., 1996). Stabilizing and fixing the starch granules during the process of swelling, the bonds lead to preservation of their integrity and determine their high rigidity. The topological constraints exerted by the branches of the adjacent molecules suppress the polymer segments' mobility and also diminish the degree of SDWMT hydration (Ferri and Lomellini, 1999). Such inter- and intra-molecular relations of amylopectin molecules suggest a reduced gel layer diffusivity and a decreased drug release velocity from HPMC/SDWMT matrices containing higher pregelatinized starch quantity.

The kinetic parameters of penetration, i.e. kinetic penetration constant, K_p, and penetration exponent, n_p of 0.1 mol dm^{-3} HCl and phosphate buffer into the pure HPMC and mixed HPMC/SDWMT matrices are presented in Tables 1 and 2, respectively. With both solvents, the values of n_p, ranging between 0.53 and 0.59 for all hydrogels examined, determine a diffusion-controlled water sorption whose mechanism depending mainly on the hydrogel structure is influenced insignificantly by the relaxation properties of hydrated macromolecules. As an exception, the HPMC/SDWMT 20/80 formulation displays a non-Fickian penetration behaviour ($n_p = 0.32$ and 0.35 for pH 1.0 and 6.8, respectively). It is probably due to the hydrogel structural characteristics, the lower swelling degree of pregelatinized starch and the slow erosion of the hydrated matrix.

The molsidomine release profiles of the pure HPMC and mixed HPMC/SDWMT hydrogels in acid medium (pH 1.0) and phosphate buffer (pH 6.8) are shown in Fig. 2(a) and (b), respectively.

In both dissolution media, the degree of drug release is the lowest with the HPMC matrices, the release rate being gradually enhanced with the increase of the pregelatinized starch fraction (Tables 1 and 2, respectively). An inverse proportion is observed between the velocities of both water penetration and drug release. The proportion suggests that the gel layers formed probably possess a heterogeneous microporous structure and a high diffusion capability. With all mixed HPMC/SDWMT hydrogels, the values of the release exponent, *n*, are close to 0.45 (0.42–0.59) which is typical of a diffusion-controlled drug release process. The increase of the amount of pregelatinized starch in the tablets leads to a decrease in the values of *n* down to 0.45, which describes the systems rather as porous matrices.

The usual kinetic swelling properties determined for solvent-activated controlled-release systems (i.e. degree and velocity of both water penetration and swelling, transport mechanism which controls solvent sorption) are directly related to the drug release behaviour but they are insufficient for prediction purposes regarding unlimited swelling hydrogels. The dependence between the velocities of both water penetration and drug release processes as well as their identical mechanism show that the structural features of mixed HPMC/pregelatinized waxy maize starch hydrogels are the major factor controlling the drug release kinetics. To examine their inherent structure a comparative rheological analysis of hydrogel viscoelastic properties is used.

3.2. Viscoelastic properties of mixed HPMC/SDWMT hydrogel systems

The mechanical spectrum of both HPMC and mixed HPMC/SDWMT hydrogels in 0.1 mol dm^{-3} HCl obtained by means of a dynamic oscillation program are shown in Fig. 3(a)–(e). The pure HPMC keeps its elastic character ($G' > G''$), G' and G'' increasing as a function of frequency (Fig. 3(a)), which determines the gel's ability to maintain a comparatively strong network structure (Michailova et al., 1999). Adding pregelatinized starch to the hydrogel changes the viscoelastic response. At low SDWMT percentage (20%) in the system, the elastic behaviour of the pure HPMC transforms into a viscoelastic one ($G' \approx G''$) which is typical of weak structure hydrogels in solid-to-liquid transition state (Fig. 3(b)). With mixtures containing 40% starch, the relaxation spectrum suddenly changes its character (Fig. 3(c)); the system is in liquid-like state ($G' < G''$) which is observed with concentrated polymer solutions under their critical gel concentration and with composite polymer systems filled with elastic fillers at their maximum packing (Ferry, 1980). The increase of pregelatinized starch quantity up to 60% reinforces the hydrogel structure modifying its liquid-like properties into viscoelastic ones (Fig. 3(d)). With mixed hydrogels containing 80% starch, the elastic behaviour dominates throughout all the frequency ranges applied and there is a clearly expressed

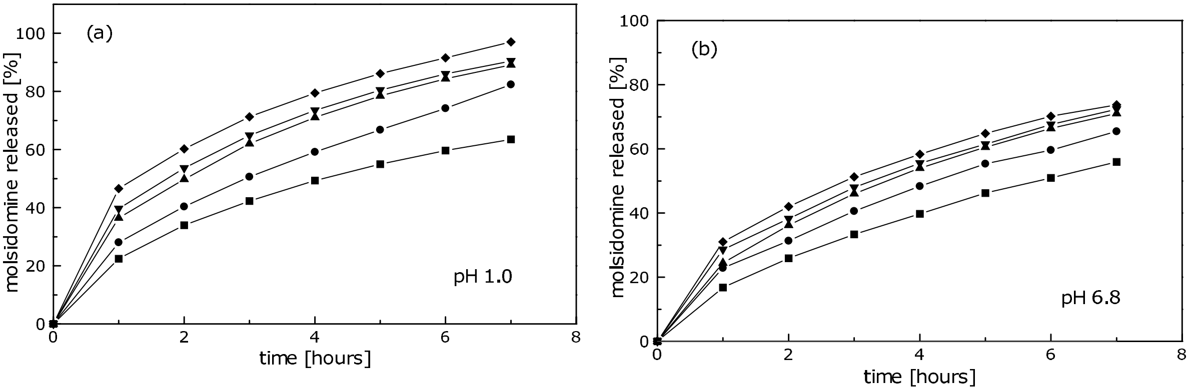

Fig. 2. Molsidomine release profiles of HPMC and mixed hydrophilic matrices. (a) 0.1 mol dm^{-3} HCl medium; and (b) pH 6.8 phosphate buffer. (■) HPMC; and mixed HPMC/SDWMT matrices: (●) 80/20, (▲) 60/40, (▼) 40/60, (◆) 20/80.

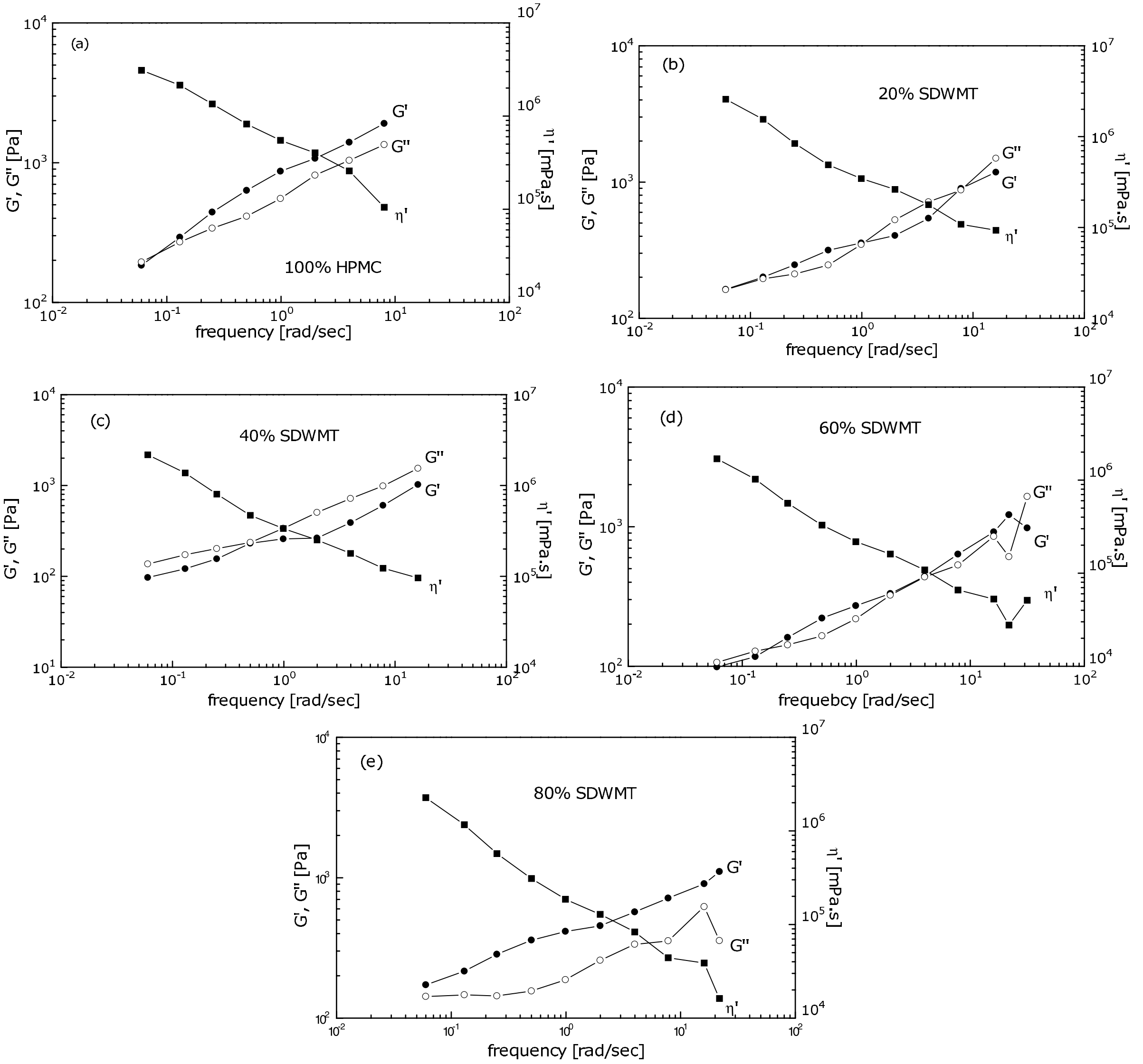

Fig. 3. Mechanical spectrum of HPMC and mixed HPMC/SDWMT hydrogels in 0.1 mol dm^{-3} HCl medium. (a) HPMC; and mixed HPMC/SDWMT hydrogels: (b) 80/20; (c) 60/40; (d) 40/60; (e) 20/80. G' (●), G'' (○), η' (■).

plateau zone in the elastic modulus curve (Fig. 3(e)). The mechanical spectrum obtained is typical of strong physical gels which is probably due to the highly-branched structure of the amylopectin molecule, its restricted mobility and low water-retaining capacity (Hanselmann et al., 1996). In a phosphate buffer, the viscoelastic behaviour of the mixed HPMC/SDWMT hydrogels is similar to that of the acid medium (Fig. 4(a)–(e)). The presence of 20–40% starch in the systems leads to weakening of the gel structure (Fig. 4(a)–(c)). Its liquid-like properties ($G' < G''$) change into viscoelastic and elastic ones with the increase of the amount of SDWMT (60 and 80%, respectively; Fig. 4(d) and (e)).

The rheograms of the hydrogel systems studied show that there is a sharply outlined boundary-line between the rheological behaviour of the hydrogels containing up to 60% pregelatinized starch and the 20/80 HPMC/SDWMT system. With hydrogels containing up to 60% SDWMT, the viscoelastic responses are situated in neighbouring, close-lying regions of the mechanical spectrum (i.e. in the beginning of the viscoelastic region, in the transition zone, and in the end of the terminal region), a fact which indicates swelled polymer systems having gel-like properties. Their comparatively weak intra-molecular links facilitate the processes of both the aqueous penetration and the acceleration of the macromolecular relaxation, which results in a higher hydration velocity of the mixed matrices. The weaker gel structure is probably a cause of the similarity in the water penetration rate constants because it gives one and the same relaxation opportunities to the molecules of the two polymers during the process of swelling. As different from the rheological response of the pure HPMC

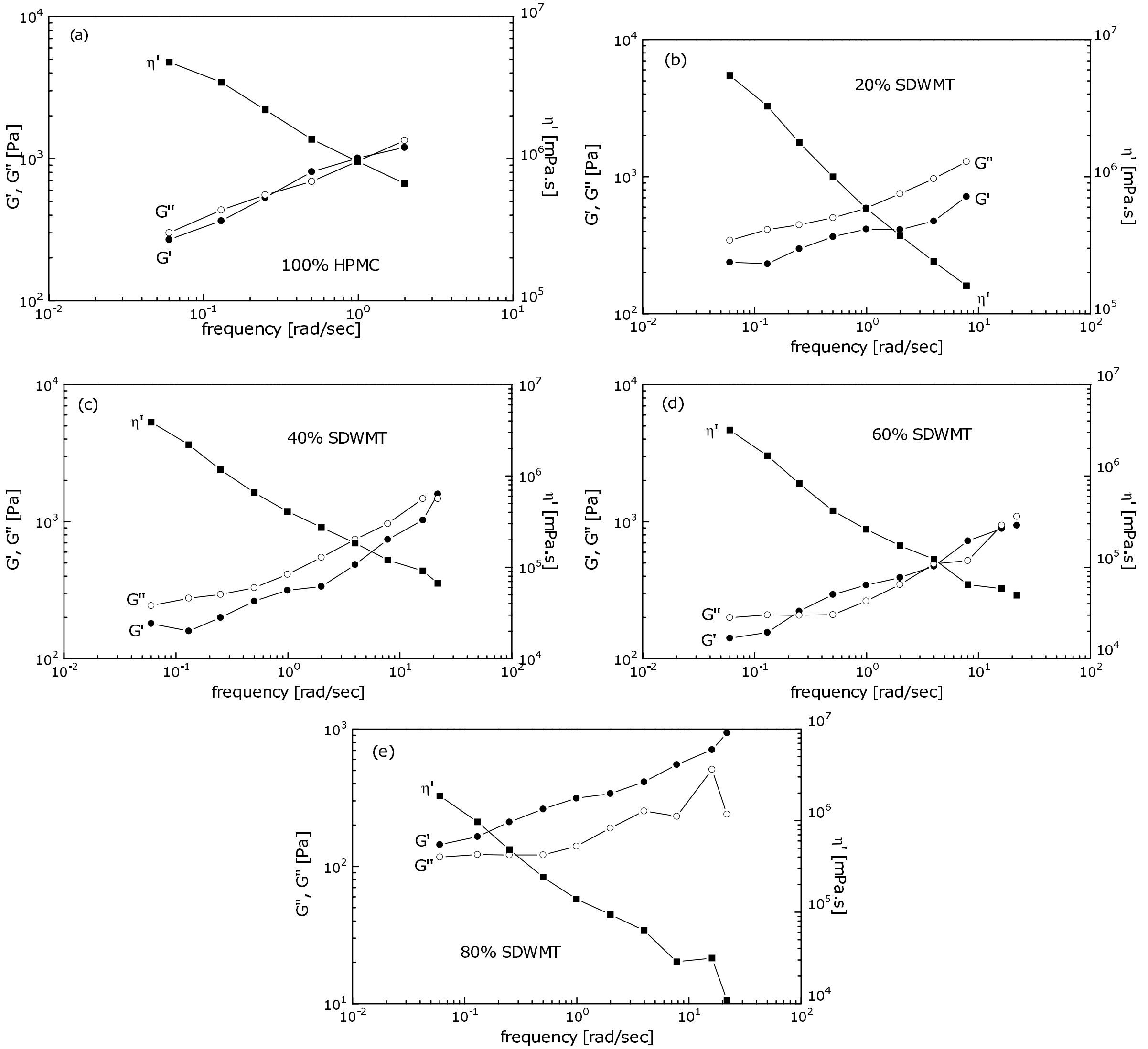

Fig. 4. Mechanical spectrum of HPMC and mixed HPMC/SDWMT hydrogels in pH 6.8 phosphate buffer. (a) HPMC; and mixed HPMC/SDWMT hydrogels: (b) 80/20; (c) 60/40; (d) 40/60; (e) 20/80. G' (●), G'' (○), η' (■).

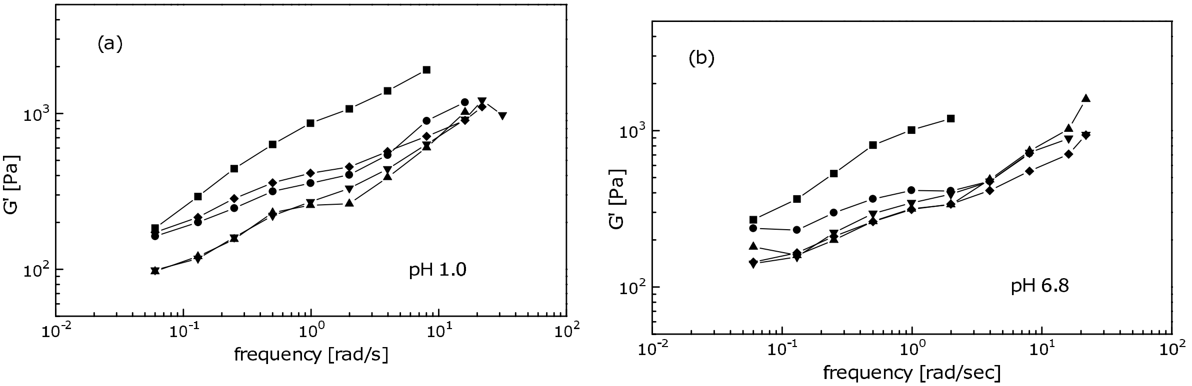

Fig. 5. Comparison of storage modulus (G') curves of the gel systems as a function of the angular frequency in (a) 0.1 mol dm^{-3} HCl medium and (b) pH 6.8 phosphate buffer. (■) HPMC; and mixed HPMC/SDWMT hydrogels: (●) 80/20, (▲) 60/40, (▼) 40/60, (◆) 20/80.

located at the beginning of the viscoelastic region, the one of the mixed hydrogel containing 80% SDWMT lies in the plateau zone of the mechanical spectrum which reveals an enhanced elasticity, a greater density of the network, and a stronger hydrogel structure. Such a highly elastic system resists the penetrant uptake to a significant degree (Gehrke, 1992) and determines the considerably lower swelling extent of the hydrogel.

Fig. 5(a) and (b) represents the elastic moduli curves (G') of the pure HPMC and mixed HPMC/SDWMT systems in acid medium and phosphate buffer, respectively, as a function of the angular frequency. Similar change of the gel strength is obtained in both media tested. Regardless of the quantitative proportion of the two polymer components, the shape of the G' curves of all mixed hydrogels and their slopes look the same but they differ from those of the pure HPMC considerably. This fact indicates that the rheological behaviour of the swelled starch grains determines both the elastic response and the gel strength of the mixed systems.

The morphological analysis of mixed HPMC/SDWMT hydrogels and the dependence between their viscoelastic behaviour and polymers proportions characterize them as ‘filled’ composite systems having poor adhesion between the surface of the elastic ‘filler’ and the continuous phase (Schultz, 1974). With such systems, the disperse phase of the elastic SDWMT filler functions as a supporting structure, while the linear HPMC forms the disperse medium but it has no supporting capability because of its weaker structure. For this reason, at low concentrations of the pregelatinized starch, a common homogeneous HPMC network cannot be formed which suggests the existence of a porous gel structure and an increased diffusion capability. With the increase of the starch volume fraction (60–80%), a phase inversion occurs. The swelled starch particles form strong supporting structure whose comparatively high rigidity causes the solid-like behaviour observed. The porous structure of the gel layer is probably preserved because the low mobility of amylopectin molecule confines the formation of inter-penetrating network at the starch granule surfaces. Those features of the inherent hydrogel structure of mixed HPMC/SDWMT hydrophilic matrices explain the direct proportion between molsidomine release velocity and the pregelatinized waxy maize starch content.

4. Conclusions

The kinetic swelling properties of both mixed HPMC/SDWMT hydrogels (i.e. degree and velocity of both water penetration and swelling, transport mechanism which controls solvent sorption) directly influence the drug release behaviour and the structural features of the formed gel layer. The processes of both water penetration and drug release from the mixed hydrogels are diffusion-controlled ones, their mechanisms being influenced insignificantly by the relaxation properties of the hydrated macromolecules. The specific structural dependence obtained for mixed HPMC/SDWMT hydrogels defines them as 'filled' composite systems with poor adhesion between the surface of the elastic SDWMT 'filler' and the continuous HPMC phase. Due to the inter-phase relations between the swollen starch granules and the linear cellulose derivative as well as to the specific structure of amylopectin molecule, the pregelatinized waxy maize starch shows a stronger influence on the velocities of both water penetration and drug release from mixed HPMC/SD-WMT matrices.

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