

Water uptake and relaxation processes in mixed unlimited swelling hydrogels

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Abstract

The rheological oscillatory test parameters have been observed for highly concentrated hydroxypropylmethyl cellulose (HPMC), carboxymethylcellulose-sodium (NaCMC) and mixed HPMC/NaCMC hydrogels obtained by swelling of matrix tablets in 0.1 mol cm⁻³ HCl and pH 6.8 phosphate buffer. The mechanical spectra of the gels have been analysed using theoretical models, i.e. a generalised Maxwell model and an adapted Maxwell model, both based on Ferry and Williams approximations. The relaxation time spectra as well as the parameters characteristic of linear viscoelastic behaviour have been calculated: zero shear viscosity (η_0), plateau moduli (G_N^0 , G_0' and G_0''), zero-relaxation time (τ_0) and mean relaxation time (θ). The mechanical spectra of mixed HPMC/NaCMC hydrogels differ considerably from those of the pure ones, the type of the spectrum depending on the two polymers' ratios. In both media, the rheological models applied define the HPMC gels as homogeneous entangled networks, and those of NaCMC and mixed HPMC/NaCMC as heterogeneous physical gels. The relationship between the kinetic constants of water penetration and the mean relaxation times suggests that the molecular relaxation controls the water uptake velocity. With all the systems tested irrespective of pH of the aqueous phase, an inversely proportional dependence between the viscosity and the water penetration velocity has been noted. Since the degree of hydration is one of the factors determining the degree and velocity of drug release from the hydrogel matrices, the relation between the kinetic parameters of water penetration and the viscosity is a characteristic indicator for the gel structure, the degree of swelling and the drug release rate. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Mixtures of neutral hydroxypropylmethyl cellulose (HPMC) and polyelectrolyte carboxymethylcellulose-sodium (NaCMC) have long been used as excipients for formulation of controlled-release matrix tablets which show nearly zero-order ki-

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netics of drug release under given conditions (pH of dissolution medium, polymer/polymer ratio) (Rao and Devi, 1988). Their drug-release kinetics can be determined by both the hydrogel erosion behaviour and the processes of water and drug diffusion through the formed gel (Rao et al., 1990; Bonferoni et al., 1995; Reynolds et al., 1998). They depend on the synergistic macromolecular interactions and the polymer chains' relaxation (Walker and Wells, 1982). Such relaxation-diffusion dependence (Doi, 1996; Lustig, 1996) can be evaluated in terms of both kinetic parameters of water penetration into hydrophilic matrices and rheological peculiarities of their gel layers.

Viscoelastic properties of mixed versus pure polymer gels differ from one another significantly because of their additional intermolecular interactions and the possible formation of an interpenetrating network. Dynamic tests applied under small deformation conditions at low frequencies are convenient when studying the degree of structural organization of polymer systems and the inter- and intramolecular links in entanglement networks, strong and weak physical gels (Ross-Murphy, 1995). The rheological experiments can also help in the evaluation of both liquid- and/or solid-like thermodynamic states which define the kinetics of drug release from hydrogel matrix tablets (Talucdar et al., 1996).

Different rheological models are proposed to predict the linear viscoelastic behaviour of polymer gels, and specifically, the mechanical spectra obtained from small deformation oscillatory tests (Graessley, 1974; Ferry, 1980; Tschoegl, 1989). The models give us the opportunity to estimate the relaxation capability of the entangled macromolecules in gels and to describe more correctly the complex rheological behaviour which is a result of the inherent macro- and/or microheterogeneity of swelled matrices.

The mechanical spectra of mixed HPMC/NaCMC hydrogel matrices swelled in 0.1 mol cm⁻³ HCl and pH 6.8 phosphate buffer have been analyzed below using rheological models based on Ferry and Williams approximations (Ferry, 1980; Kotsilkova et al., 1999). The dependence between the discrete rheological characteris-

tics and the kinetic parameters of the water penetration processes has also been examined.

2. Materials and methods

2.1. Materials

Hydroxypropylmethyl cellulose (HPMC, Methocel K4M Premium, Colorcon, UK), carboxymethylcellulose-sodium (NaCMC, Blanose 7H4FD, Aqualon, Milan, Italy), and HPMC/NaCMC mixtures with the following ratios were used: 15/85, 40/60, 44/56 and 50/50. Methocel K4M has 22% methoxy and 8% hydroxypropyl content; its gelation temperature and degree of methoxy substitution are 85°C and 1.4, respectively; a 2% w/v aqueous solution has a viscosity of approximately 4000 mPa s at 20°C (Doelker, 1987). Blanose 7H4FD has 0.65–0.90 as a substitution range and 7.0–8.9% sodium content; a 1% w/v aqueous solution has viscosity in the range from 2500 to 4000 mPa s at 25°C (Doelker, 1987).

2.2. Preparation of hydrophilic matrix tablets

Matrix tablets containing HPMC/NaCMC in proportion ratios mentioned above were directly compressed on an eccentric tablet-press (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. Preparation of hydrogel systems

The highly concentrated NaCMC, HPMC and mixed gels were obtained by swelling of the matrix tablets in a 0.1 mol cm⁻³ HCl solution (pH 1.0) and Na₃PO₄/HCl buffer (pH 6.8) at a temperature of 37 ± 0.5°C for 7 h. The Na₃PO₄/HCl buffer was prepared by mixing of 800 ml 0.1 mol cm⁻³ HCl and 100 ml 0.6 mol cm⁻³ Na₃PO₄ (Lehmann et al., 1986). The swelling time (7 h) was selected having in mind an *in vitro* evaluation of molsidomine release processes from the same hydrophilic matrices we recently tested (Michailova et al., 2000). The polymer concentration of the hydrogels examined was between 18

and 22% 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 min⁻¹.

2.4. 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 dynamic conditions of non-destructive oscillatory tests in the frequency range from 0.06 to 31.95 rad s⁻¹. To analyse the relaxation spectra of HPMC, NaCMC and mixed HPMC/NaCMC gels, we used the following models: (1) a generalised Maxwell model (Ferry, 1980) and (2) an adapted Maxwell model (Kotsilkova et al., 1999). By means of a software package and the G' and G'' values for all experimental points, we calculated the components of the relaxation time spectra ($G_1\tau_1$) and the theoretical functions $G'(\omega)$, $G''(\omega)$ and $\eta'(\omega)$, according to the rheological models applied, i.e. Eqs. (2)–(6). Using the mean statistical error values which did not exceed 7%, we selected the theoretical model for each particular hydrogel tested. By means of extrapolation of Eqs. (2)–(6), the following constants characteristic of linear viscoelastic behaviour were calculated:

1. The generalised Maxwell model gave the plateau modulus (G_N^0), calculated according to Eq. (2) at $\omega \rightarrow \infty$, zero shear viscosity (η_0) and zero-relaxation time (τ_0) (both η_0 and τ_0 were obtained from the terminal region of the relaxation spectrum);
2. The adapted Maxwell mode gave the second plateau moduli (G'_0 and G''_0) determined from the second plateau at low frequencies of oscillation in the terminal region of the relaxation spectrum, and the mean relaxation time (θ).

2.5. Liquid penetration study

The process of liquid penetration into the hydrophilic matrix tablets was examined gravimetri-

cally using the method of Stamberg and Sevcik. The dry matrix was weighed accurately in a tarred glass column consisting of a funnel of 4 cm³ volume, sintered filter and a tube taking the surplus of water away (Stamberg and Sevcik, 1966). The sample was then 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. The excess liquid was removed by centrifugation at 2500 min⁻¹ for 10 min and the swelled hydrogel was then weighed again. For the weight of each swelled matrix, the mean value of six measurements was taken. The dynamics of the water uptake was expressed as the weight gain (w_p) of the swelled matrix, in g penetrant/g dry polymer, (Davidson III 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 dried matrix tablet. The kinetics of the liquid penetration into all hydrophilic matrices studied was analysed according to Eq. (1):

$$w_p = K_p t^{n_p} \quad (1)$$

where w_p is the weight gain of the swelled matrix (g penetrant/g dry polymer); K_p , kinetic constant of water penetration; t , penetration time; n_p , exponent which depends on the water penetration mechanism.

The values of K_p and n_p for all tested matrix models were calculated by regression analysis (values ± 95% confidence limits). They are shown in Tables 2 and 3.

3. Results and discussion

In our previous study, we determined the viscoelastic characteristics of pure hydrogels, i.e. HPMC and NaCMC, in 0.1 mol cm⁻³ HCl and Na₃PO₄/HCl buffer (pH 6.8). In acid medium, both hydrogels behave like elastic solids, the elastic properties of NaCMC being better expressed. In phosphate buffer, the polyelectrolyte gel has a liquid-like character throughout all the frequency range applied while the HPMC system is in a transition solid-to-liquid state and has tighter networks (Michailova et al., 1999). The mechanical

properties specifically determine the drug release behaviour of HPMC and NaCMC matrices. The noticeable difference in the drug release kinetics at different HPMC/NaCMC ratios (Michailova et al., 2000) enabled us to try to establish the interdependence between the gel structure and the ratio of the two components in the mixed systems.

To analyse the mechanical (relaxation) spectra of mixed HPMC/NaCMC gels obtained by means of small deformation oscillatory tests, we use the following models: (1) a generalised Maxwell model and (2) an adapted Maxwell model. Both models relate the discrete spectrum of relaxation times with the material viscoelastic functions (G' and G'') in the mathematical expressions given below:

1. Generalised Maxwell model

$$G'(\omega) = \sum_n G_i \omega^2 \tau_i^2 / (1 + \omega^2 \tau_i^2) \quad (2)$$

$$G''(\omega) = \sum_n G_i \omega \tau_i / (1 + \omega^2 \tau_i^2) \quad (3)$$

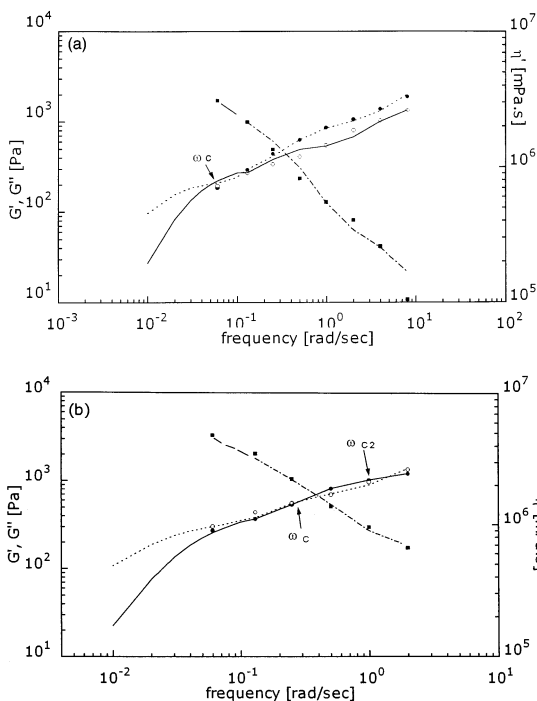


Fig. 1. Theoretical and experimental mechanical spectra of HPMC hydrogels. (a) 0.1 mol cm⁻³ HCl medium; (b) pH 6.8 phosphate buffer. Model parameters: G' (straight line), G'' (dotted line), η' (dot-dashed line); Experimental data: G' (●), G'' (○), η' (■).

$$\eta'(\omega) = \sum_n G_i \tau_i / (1 + \omega^2 \tau_i^2) \quad (4)$$

2. Adapted Maxwell model

$$G'(\omega) = G'_0 + \sum_n G_i \omega^2 \tau_i^2 / (1 + \omega^2 \tau_i^2) \quad (5)$$

$$G''(\omega) = G''_0 + \sum_n G_i \omega \tau_i / (1 + \omega^2 \tau_i^2) \quad (6)$$

where G' and G'' are the storage and the loss moduli, respectively, obtained as a function of the angular frequency, ω ; G_i and τ_i are the parameters of the relaxation spectrum, i.e. the modulus and relaxation time, of the i th-member of n -Maxwell elements, respectively; G'_0 and G''_0 are the second plateau moduli at the low frequencies of the G' and G'' curves, respectively.

The zero-relaxation time (τ_0) and the mean relaxation time (θ) are calculated based on the discrete characteristics of the relaxation spectrum using the following equations:

$$\tau_0 = \lim_{\omega \rightarrow 0} \eta_i / G_i = \lim_{\omega \rightarrow 0} \tau_i \quad (7)$$

$$\theta = \frac{\sum_n G_i \tau_i^2}{\sum_n G_i \tau_i} \quad (8)$$

3.1. Application of the generalised Maxwell model

For both media, the mechanical spectra of pure HPMC hydrogels are best fitted by the generalised Maxwell model (Eqs. (2)–(4)). It describes homogeneous gel systems in which the thermodynamic compatibility of the solvent and the polymer is observed (Fig. 1a,b). The model can be extrapolated towards very low frequencies showing the flow curve in the terminal region based on which the following constants characterising the entangled gel network can be calculated: zero shear viscosity (η_0); plateau modulus (G_N^0); zero-relaxation time (τ_0) (Graessley, 1974). Applying the generalised Maxwell model to HPMC gels gives us the opportunity to define them as homogeneous entangled networks. The values of parameters calculated by means of the generalised Maxwell model and the cross points of G' and G'' experimental curves (ω_c and ω_{c2}) are shown in Table 1. Except for the plateau modulus (G_N^0), the values of the discrete characteristics of HPMC gel

Table 1

Values of the rheological parameters, i.e. plateau modulus (G_N^0), zero shear viscosity (η_0), zero-relaxation time (τ_0), calculated by means of the generalised Maxwell model, and the cross points (ω_C and ω_{C2}) of G' and G'' experimental curves for HPMC gels in 0.1 mol cm⁻³ HCl (pH 1.0) and Na₃PO₄/HCl buffer (pH 6.8)

Parameter	pH 1.0	pH 6.8
G_N^0 (Pa)	3654.04	11 515.10
η_0 (Pa s ⁻¹)	10.56	11.35
τ_0 (s)	28.57	21.18
ω_C (rad s ⁻¹)	0.08	–
ω_{C2} (rad s ⁻¹)	0.27	1.32

systems, i.e. η_0 and τ_0 , are influenced insignificantly by the pH of the swelling media. The higher plateau modulus obtained in pH 6.8 phosphate buffer defines a stronger network structure. The comparatively longer zero-relaxation times observed in both media suggest a decreased mobility of the hydrated macromolecules, which is related to the lower quantity of the solvent in the swollen matrix system. A system of that type could demonstrate slower rates of both water penetration and hydrogel erosion/dissolution.

3.2. Application of the adapted Maxwell model

The generalised Maxwell model was not appropriate for the description of mixed HPMC/NaCMC gels because the hydrophilic matrices are highly inhomogeneous during the process of swelling due to the presence of particles of different degrees of hydration. The mixing of polymers of different chemical compositions and viscoelastic behaviour increases the gel heterogeneity. With highly swelling and quickly relaxing cellulose derivatives, it is possible that an interpenetrating network should form as a third gel-phase with its own rheological properties. Such hydrogels show a second plateau in the loss modulus curves G'' , inhomogeneity in the process of polymer chain oscillation, low coefficient of relaxation and residual stress and can be described using the adapted Maxwell model (Eqs. (5) and (6)). It gives a good correlation of the theoretical and experimental mechanical spectra of NaCMC and mixed

NaCMC/HPMC gels tested in 0.1 mol cm⁻³ HCl and pH 6.8 phosphate buffer as shown in Figs. 2 and 4, respectively.

The rheological behaviour of the mixed matrices swelled in 0.1 mol cm⁻³ HCl (Fig. 2a–e) depends on the ratio between the two polymers. For systems containing up to 60% NaCMC, the curves of G' modulus show a plateau zone revealing a predominantly solid-like response ($G' > G''$) which indicates both a stronger link at entanglement points and/or a greater density of the network. The slight slope of their G' and G'' curves defines them as strong physical gels (Ross-Murphy, 1995). With the decrease of the NaCMC content, the frequency range of the plateau zone diminishes. The curves of G' consist of two slopes: a steeper one at low frequencies and a less steep one at high frequencies. The inclination of the slopes depends on regions with different densities, which dominate the response at different frequencies (Stading et al., 1995). With the experimentally obtained curves (G' and G''), the cross points (ω_C and ω_{C2}) showing the transition of the systems from viscoelastic to terminal zone and from viscoelastic to glassy state, respectively, shift towards lower frequencies. The further increase of the quantity of the neutral HPMC transforms the elastic characteristics of the systems into characteristics of the transitional state, i.e. liquid–solid like, which can be observed throughout all the frequency range. Such an extended transition zone is mainly due to the inhomogeneous macrostructure of the gels. Almost all systems tested in acid medium do not show a terminal zone. However, the mechanical spectrum of the hydrogel containing the highest HPMC quantity, i.e. 1:1 HPMC/NaCMC mixture, demonstrates a terminal zone. Since at low frequencies the gel flows as high viscosity liquid, we may conclude that the intermolecular links are weak which could lead to a more facilitated dissolution of the polymer chains of the gel surface. A nearly linear relationship is observed between G'_0 and NaCMC percentage in the gels (Fig. 3) which suggests that the plateau storage moduli, G'_0 , are additive magnitude taking into account the elastic responses of the particles of stronger structure, i.e. NaCMC (Ferry, 1980). In this case, the formation of an interpenetrating

network at the hydrated particles' interface of the two polymers should be neglected since the great rigidity of NaCMC gel restricts the processes of disentanglement of its chains and their diffusion into swelled HPMC phases. In phosphate buffer, viscoelastic behaviour of all mixed HPMC/NaCMC systems is the same as the pure NaCMC one (Fig. 4) and differs significantly from that observed in acid medium. Irrespective of the polymer ratio, all hydrogels we studied behave as liquid-like systems possessing a weak structure.

Their viscous properties ($G'' > G'$) are well delineated all over the frequency range and the ω_c cross points are located at the highest frequency applied, if any.

The tendency in the viscoelastic behaviour of both 0.1 mol cm⁻³ HCl and pH 6.8 phosphate buffer hydrogels expressed by the storage moduli (G') and dynamic viscosity (η') values is shown in Fig. 5a,b. Regardless of the type of system, the elastic modulus values in acid medium are a lot higher than the ones obtained in the phosphate

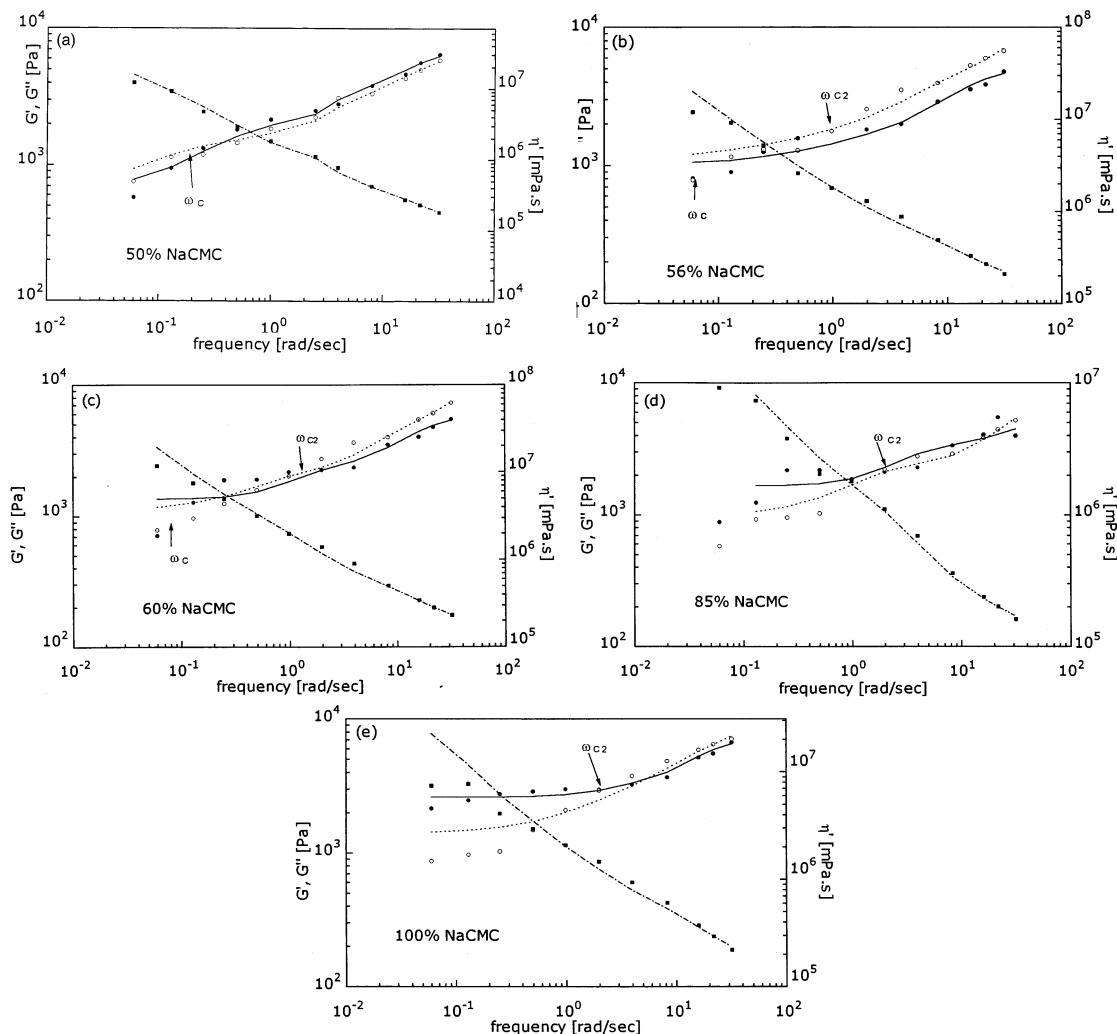


Fig. 2. Theoretical and experimental mechanical spectra of NaCMC and mixed HPMC/NaCMC hydrogels in 0.1 mol cm⁻³ HCl. Model parameters: G' (straight line), G'' (dot line), η' (dot-dashed line); Experimental data: G' (●), G'' (○), η' (■).

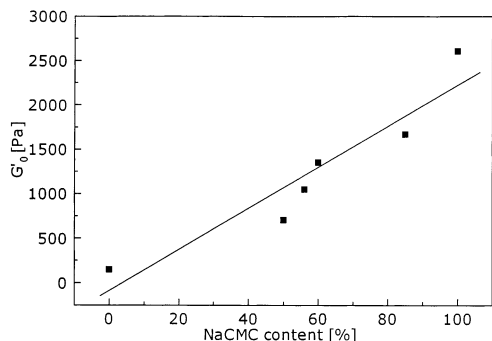


Fig. 3. Plateau storage modulus (G'_0) as a function of the NaCMC percentage in the gels obtained in 0.1 mol cm^{-3} HCl medium.

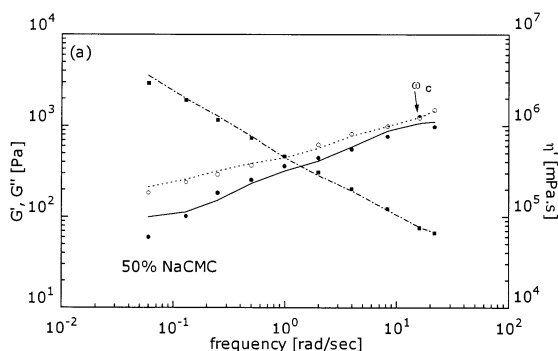


Fig. 4. Theoretical and experimental mechanical spectra of NaCMC and mixed HPMC/NaCMC hydrogels in pH 6.8 phosphate buffer. Model parameters: G' (straight line), G'' (dotted line), η' (dot-dashed line); Experimental data: G' (●), G'' (○), η' (■).

buffer. The modulus curves of the pure HPMC represent the boundary between the G' profiles established for the two media. The change of the gel system viscosity follows the same dependence of the G' curves mentioned above (Fig. 5b). In acid medium, the viscosity rises with the increase of NaCMC percentage in the gel; in pH 6.8 phosphate buffer, the viscosity diminishes under the same conditions.

3.3. Relation between the rheological characteristics and the kinetic parameters of water penetration

A number of authors have researched the processes of hydrogel swelling and polymer relax-

ation with respect to controlled-release drug delivery systems (Vrentas and Duda, 1977; Davidson III and Peppas, 1986; Peppas et al., 1994). With chemically cross-linked hydrogels, they determine the relaxation phenomenon quantitatively, and relate it to both the penetrant transport mechanism and the concurrent drug release mechanism assuming the relaxation time for the hydrogels as a characteristic time for sorption (because it is related to the mobility of the polymer chains and the gel capability and assures the advancement of the water penetration front into the glassy matrix region). With unlimited swelling hydrophilic matrices, as different from chemically cross-linked hydrogels, not only the relaxation behaviour of the hydrated macromolecules but also the structure of the gel layer influence the degree and the velocity of water penetration considerably. To find the dependence between the structures of the hydrogel matrices, their relaxation behaviour and degree of hydration, the rheological parameters (i.e. second plateau storage (G'_0) and loss (G''_0) moduli and mean relaxation time (θ), all calculated by means of the adapted Maxwell model, and the dynamic viscosity at $\omega = 0.06 \text{ rad s}^{-1}$ ($\eta'_{\omega 0.06}$)) are compared with the kinetic constants of water penetration (K_p) for pure and mixed polymer systems tested in 0.1 mol cm^{-3} HCl and pH 6.8 phosphate buffer (Tables 2 and 3, respectively).

3.3.1. In acid medium (0.1 mol cm^{-3} HCl)

The pure HPMC gels, having a comparatively weak, elastic structure and low dynamic viscosity at $\omega = 0.06 \text{ rad s}^{-1}$, are characterised by the highest value of the mean relaxation time which corresponds to low values of the kinetic constant of water penetration (Table 2). The elastic nature of the system is considered to resist to a significant degree against the penetrant uptake (Gehrke, 1992); a longer period of time is required for the disentanglement of the macromolecule chains. For pure NaCMC system, with its strong elastic structures, too high a kinetic constant of water penetration and a shorter mean relaxation time are unexpectedly observed. The discrepancy found out between G'_0 and the water penetration velocity may be due to the polyelectrolyte state and the

Table 2

Values of the rheological parameters, i.e. plateau storage (G'_0) and loss (G''_0) moduli and mean relaxation time (θ), calculated by means of the adapted Maxwell model, the dynamic viscosity at $\omega = 0.06$ ($\eta'_{\omega,0.06}$) and the kinetic constants of water penetration (K_p and n_p) for HPMC, NaCMC and mixed HPMC/NaCMC hydrogels in 0.1 mol cm⁻³ HCl

HPMC/NaCMC ratio	G'_0 (Pa)	G''_0 (Pa)	$\eta'_{\omega,0.06}$ (Pa s)	θ (s)	ω_c (rad s ⁻¹)	ω_{s2} (rad s ⁻¹)	(K_p) (h ^{-n_p})	n_p	r
100/0	149.8	10.3	3.1 E3	26.07	0.082	–	1.4066 ± 0.0295	0.5678 ± 0.0175	0.9974
50/50	703.8	627.7	1.2 E4	8.91	0.189	–	1.0744 ± 0.0759	0.6704 ± 0.1008	0.9879
44/56	1045.5	1114.2	1.2 E4	7.92	0.062	0.974	1.5753 ± 0.0117	0.5492 ± 0.0496	0.9999
40/60	1353.5	1092.2	1.2 E4	2.56	0.081	1.332	1.3967 ± 0.0440	0.5560 ± 0.0322	0.9957
15/85	1667.9	954.0	9.2 E3	0.38	–	2.055	1.9378 ± 0.0645	0.7931 ± 0.0356	0.9962
0/100	2608.5	1388.3	7.4 E3	0.49	–	2.432	2.6914 ± 0.1135	0.5567 ± 0.0458	0.9888

Table 3

Values of the rheological parameters, i.e. plateau storage (G'_0) and loss (G''_0) moduli and mean relaxation time (θ), calculated by means of the adapted Maxwell model, the dynamic viscosity at $\omega = 0.06$ ($\eta'_{\omega,0.06}$) and the kinetic constants of water penetration (K_p and n_p) for HPMC, NaCMC and mixed HPMC/NaCMC hydrogels in $\text{Na}_3\text{PO}_4/\text{HCl}$ buffer (pH 6.8)

HPMC/NaCMC ratio	G'_0 (Pa)	G''_0 (Pa)	$\eta'_{\omega,0.06}$ (Pa s)	θ (s)	ω_c (rad s $^{-1}$)	ω_{c2} (rad s $^{-1}$)	(K_p) (h $^{-n}$)	n_p	r
100/0	204.3	66.8	4.8 E3	9.96	0.273	1.325	1.2646 \pm 0.0049	0.5601 \pm 0.0049	0.9999
50/50	94.8	169.9	2.9 E3	2.37	15.163	–	2.1860 \pm 0.1998	0.6662 \pm 0.0788	0.9889
44/56	106.2	192.5	2.8 E3	2.55	–	–	2.7077 \pm 0.0697	0.4934 \pm 0.0266	0.9991
40/60	132.0	242.4	3.3 E3	3.35	–	–	2.1079 \pm 0.0020	0.6301 \pm 0.0039	0.9987
0/100	78.1	124.8	1.9 E3	2.25	15.242	–	4.3842 \pm 0.1554	0.5365 \pm 0.0369	0.9924

texture of the gel layer in acid medium. The uncharged NaCMC possesses strong intermolecular links, an enhanced elasticity and a diffusive inhomogeneous structure. The system offers insignificant resistance against the penetrant uptake and it relaxes quickly embedding a great quantity of water.

With mixed HPMC/NaCMC systems, the percentage of polyelectrolyte polymer delineates the relationship between the rheological parameters and the water penetration velocity (Fig. 6a). The values of both the plateau storage modulus and the kinetic constants of water uptake increase while those of the mean relaxation time diminish.

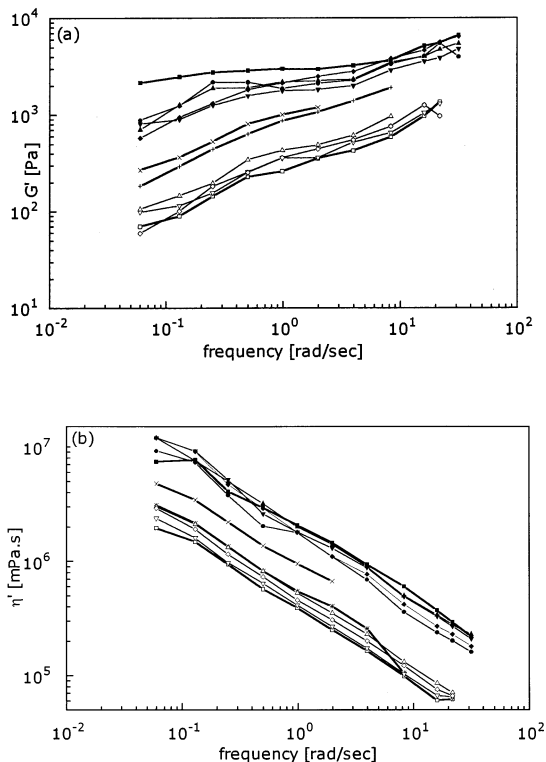


Fig. 5. Comparison of storage modulus (G') curves and dynamic viscosity (η') curves of the gel systems as a function of the angular frequency in acid medium (closed symbol) and pH 6.8 phosphate buffer (open symbol). (a) G' curves; (b) η' curves. (\times , $+$) HPMC; (\blacksquare , \square) NaCMC; and mixed HPMC/NaCMC gels: (\bullet , \circ) 15/85; (\blacktriangle , \triangle) 40/60; (\blacktriangledown , \triangledown) 44/56; (\blacklozenge , \lozenge) 50/50.

The dynamic viscosity of mixed hydrogels with polymer ratios in the limits from 50 to 60%, is considerably higher than that of each of the pure polymers which could be explained by means of a possible synergism between the two components. Regardless of the relationship established between the relaxation time and the kinetic constants, the viscosity also greatly influences the penetration process of the mixed systems. The higher viscosity values concur with the lower values of the kinetic constants and with the longer relaxation times.

3.3.2. In phosphate buffer (pH 6.8)

The relation between the rheological behaviour of a HPMC matrix and its kinetic parameters of water penetration is similar to that obtained in acid medium (Fig. 6b, Table 3). The elastic structure of HPMC gels, their high values of $\eta'_{\omega 0.06}$ and long mean relaxation time determine the low velocity of water penetration. The ionized and highly hydrated NaCMC system has a weak, viscous structure ($G''_0 > G'_0$) which logically explains the great values of the kinetic constants of penetration.

Although the gel structure in the mixed systems depends predominantly on the NaCMC properties, no considerable divergencies are observed between the parameters of the gels under investigation. The variation in both dynamic viscosity and penetration velocities conforms with the polymer ratio of the two components. The almost equal values of the mean relaxation time of pure NaCMC and mixed systems are probably due to the weak structure giving one and the same relaxation opportunity to the molecules of the two polymers.

4. Conclusions

The theoretical rheological models we applied give more details about the intermolecular interactions and hydrogels' texture and permit some characteristic peculiarities of the mechanical spectra of the systems to be explained. In both media, they define the HPMC gels as homogeneous en-

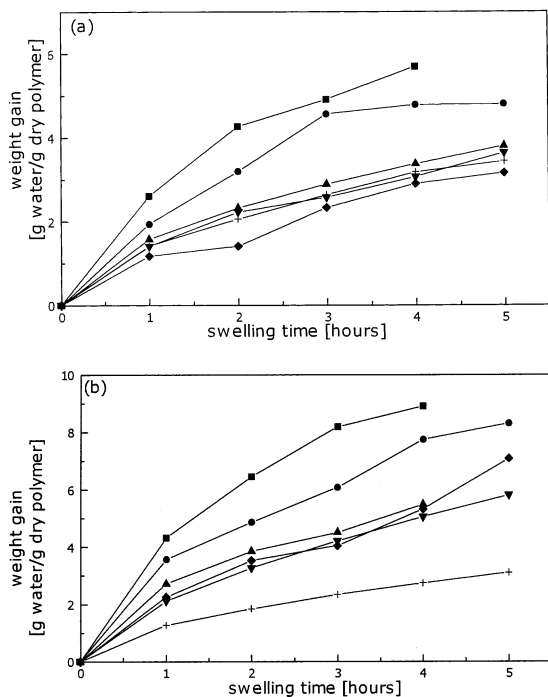


Fig. 6. Weight gain of the gel systems as a function of swelling time. (a) 0.1 mol cm⁻³ HCl medium; (b) pH 6.8 phosphate buffer. (+) HPMC; (■) NaCMC; and mixed HPMC/NaCMC gels: (●) 15/85; (▲) 40/60; (▼) 44/56; (◆) 50/50.

tangled networks, and those of NaCMC and mixed HPMC/NaCMC as heterogeneous strong physical gels. The mechanical spectra of mixed HPMC/NaCMC hydrogels differ considerably from those of the pure ones, the type of the spectrum depending on the two polymers' ratios. The anionic polymer NaCMC influences the viscoelastic properties more strongly since its hydration is a function of the pH of the medium. The relationship between the kinetic constants of water penetration and the mean relaxation times suggests that the molecular relaxation controls the water uptake velocity. With all the systems tested irrespective of pH of the aqueous phase, an inversely proportional dependence between the viscosity and the water penetration velocity has been determined. Since the degree of hydration is one of the factors determining the degree and velocity of drug release from the hydrogel matrices, the relation between the kinetic parameters of water penetration and the viscosity

is a characteristic indicator for the gel structure, the degree of swelling and the drug release rate.

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