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Influence of medium on dissolution-erosion behaviour of Na carboxymethylcellulose and on viscoelastic properties of gels

M.C. Bonferoni, S. Rossi, F. Ferrari, M. Bertoni, C. Caramella *

Department of Pharmaceutical Chemistry, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy

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Abstract

The relevance of the rheological properties of a gelled polymer on its dissolution behaviour was investigated in the case of a high viscosity grade Na carboxymethylcellulose (NaCMC). Creep viscosity and oscillatory test parameters were measured on NaCMC gels in distilled water and in pH 6.8 phosphate buffer. Gel concentration ranged between 2.5 and 4.0% w/w. Polymer erosion from gels and from tablets was also tested in the same media and the results were in line with rheological data. Moreover, the effect of ionic strength and ion type on both rheological properties of gels and erosion from tablets was assessed. A relationship was also found in this case between rheological parameters and erosion rates. The importance of ionic strength on the rheological and erosion behaviour of polyelectrolytes such as NaCMC is highlighted.

Keywords: Sodium carboxymethylcellulose; Viscoelasticity; Erosion; Hydrophilic matrix

1. Introduction

It is well known that the behaviour of the gellified layer that is formed around hydrophilic matrices after water intake is of major importance for drug release profiles. In particular slowly erodible gel layers result in diffusional release, while, when significant erosion occurs, the increase in diffusional path length is prevented and the profiles that are obtained are often close to linearity. This encourages efforts toward a thorough characterization of gelled polymers and a better understanding of erosion phenomenon (Skoug et al., 1993).

Some authors have suggested (albeit not directly evidenced) the relevance of the strength of gellified layer to the resistance of the matrix against gastrointestinal attrition (Alderman, 1984; Mitchell et al., 1993). Some of them measured gel strength by means of a penetrometer (Mitchell et al., 1993), others by means of an Instron Universal testing machine (Herman and Remon, 1989).

Another approach to the characterization of gelled polymers is based on rheological measurements. In general, the rheological behaviour of polymer solutions and gels is sensitive to interchain interactions and entanglements, and to the influence of the medium on swelling or shrinking

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* Corresponding author.

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of the polymeric coil. In the particular case of ionized polymeric chains, the conformation and the rheological behaviour of the polymer can also be affected by its ionization grade. This in turn depends on both pH and ionic strength.

Since erosion can be described as the disentanglement and dissolution of polymeric chains at the surface of the hydrated gel layer, it is likely affected by the same conformational features, polymer-polymer and polymer-solvent interactions that are involved in rheological behaviour.

In a previous work (Caramella et al., 1989), the concentration at which polymeric chains can be considered disentangled, as demonstrated by an abrupt change in rheological properties, has been measured for a few polymers. This concentration was found in line with that deduced from drug release models (Harland et al., 1988). More recently, an attempt was made to relate the viscosity of the gel layer with drug release from erodible matrices: the viscosity gradient inside the gel layer was correlated to the ability of the polymer to build up a thicker and therefore less erodible gel layer (Bonferoni et al., 1992).

However, the complexity of matrix systems, influenced by excipients and technological factors, often makes it difficult to determine simple and reliable relationships between rheological properties and erosion; in fact, erosion from matrices can be affected by many factors others than the intrinsic dissolution of the polymer.

Moreover, in classical viscosity measurements, the sample is made to flow and is therefore destroyed during rheological analysis. Therefore, these tests may be not suitable to characterize samples having concentrations as high as those present in the gel layer around the matrix. More useful information on the entanglement of polymer chains especially in gels or highly concentrated solutions is provided by viscoelasticity tests. These allow in fact a deeper insight into the intimate structure of polymeric network, that is not destroyed but only flexed under the experimental conditions. This approach has already been suggested by some authors: for example, viscoelastic parameters were related to drug release in the case of matrices based on xanthan gum and locust bean gum mixtures, where the importance of erosion was pointed out, albeit indirectly (Mannion et al., 1991).

Given these premises, the aim of this work was to investigate more extensively the relationship between the viscoelastic parameters of polymeric gels and the sensitivity to erosion of both gels and tablets made of pure polymer. (for the purpose of the present work, the term 'erosion' in the case of polymeric gels indicates the process of getting into solution of the disentangled polymeric chains). Na carboxymethylcellulose (NaCMC) was chosen as a model polymer, since it is described in the literature as subject to the phenomenon of erosion (Ranga Rao et al., 1990; Bonferoni et al., 1992).

Since it is known that ionic strength influences the behaviour of polyelectrolytes such as NaCMC, rheological properties of NaCMC gels and erosion from gels and tablets were investigated in two different media: distilled water and pH 6.8 phosphate buffer. Rheological characterization was based on both creep and oscillation tests. Creep and oscillatory tests were performed on gels ranging in concentration between 2.5 and 4.0% w/w. The sensitivity to erosion was examined by assaying the NaCMC released in dissolution apparatus. Moreover, the influence of ionic strength and of the ion type on polymer properties was investigated. For this purpose, 3.0% w/w NaCMC gels were prepared in 0.2 M NaCl solution and 0.05, 0.1 and 0.2 M phosphate buffers at pH 6.8 and evaluated for viscoelastic properties. NaCMC tablet erosion was also measured in the same media.

2. Materials and methods

2.1. Materials

The NaCMC employed was Blanose 7HFD (1.5–2.5 Pa s in 1% w/v solutions at 25°C) (Aqualon GmbH, Dusseldorf, Germany).

Polymer gels for rheological analysis were prepared in the following media: distilled water; 0.2 M NaCl (ionic strength 0.2); KH_2PO_4/Na_2HPO_4 buffers at pH 6.8 and at differing concentrations: 0.05 M (ionic strength 0.1), 0.1 M (ionic strength

0.2) and 0.2 M (ionic strength 0.4); and a Na_3PO_4/HCl buffer at pH 6.8 obtained by mixing 750 ml of 0.1 M HCl and about 250 ml of Na_3PO_4 0.2 M according to the USP XXII method for pH change in drug release evaluation from enteric forms (calculated ionic strength 0.18).

The same media were used for erosion studies.

2.2. Rheological studies

Polymer gels were prepared by thorough dispersion, under agitation, until complete hydration. The content in water of the polymer was measured and taken into account to prepare the samples. The following concentrations were analysed: 2.5, 3.0, 3.5 and 4.0% w/w in distilled water and in Na_3PO_4/HCl buffer. 3.0% w/w gels were also prepared in 0.1 M NaCl solution and in the three KH_2PO_4/Na_2HPO_4 buffers.

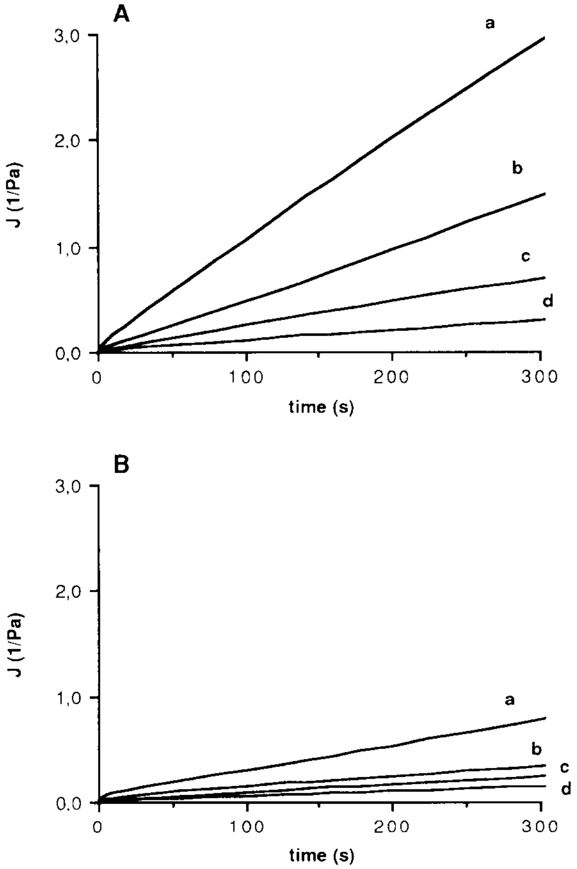

Fig. 1. Creep curves of NaCMC gels in distilled water (A) and in Na_3PO_4/HCl buffer (B) at different concentrations (% w/w): (a) 2.5%; (b) 3.0%; (c) 3.5%; (d) 4.0%.

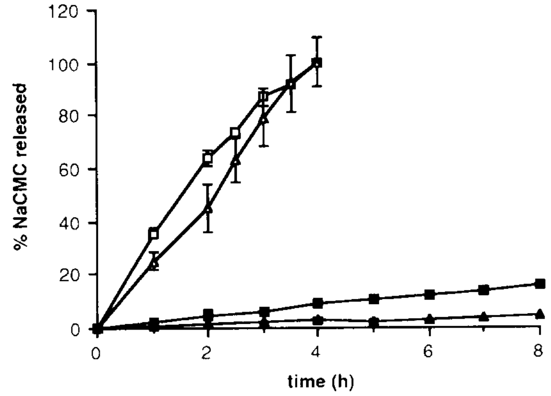

Fig. 2. Release profiles of NaCMC from 3.0% and 4.0% (w/w) gels in distilled water ((□) 3.0%; (▲) 4.0%) and in Na_3PO_4/HCl buffer ((■) 3.0%; (▲) 4.0%) (mean ± SD; n = 3).

Rheological studies were performed with a Bohlin CS rheometer (Bohlin Reologi AB, Lund, Sweden) equipped with cone-plate systems (CP 4/20, CP 4/40). All the measurements were carried out at 37 ± 0.2°C.

Creep curves (compliance J as a function of time) were registered; since the compliance is defined as the ratio between the strain measured at each time and the constant stress, higher values of compliance characterize samples that are more easily subject to deformation. The slope of the linear portion of a creep curve is inversely related to the residual viscosity of the sample.

From the dynamic oscillation programme at frequencies ranging between 0.1 and 4.0 Hz the elastic (G') and the viscous modulus (G'') were obtained; the tangent of the phase angle (tan ∂) was therefore calculated as the G''/G' ratio: the lower the tan ∂ value, the more pronounced is the elastic nature of the sample with respect to the viscous character.

2.3. Erosion studies

Erosion studies were performed by measuring the amount of NaCMC dissolved from both tablets and gels.

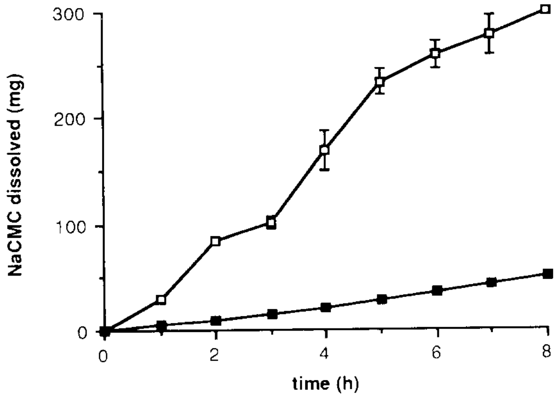

Fig. 3. Release profiles of NaCMC from tablets made of pure polymer in distilled water (□) and in Na_3PO_4/HCl buffer (■) (mean ± SD; $n = 3$).

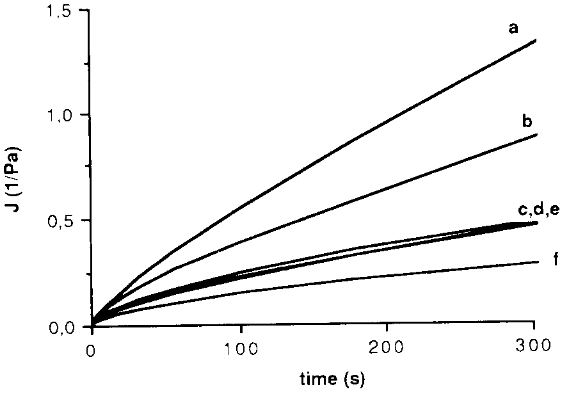

Fig. 4. Creep curves of 3.0% (w/w) NaCMC gels in different media: (a) distilled water; (b) 0.05 M KH_2PO_4-Na_2HPO_4 buffer; (c) Na_3PO_4/HCl buffer; (d) 0.1 M KH_2PO_4-Na_2HPO_4 buffer; (e) 0.2 M NaCl solution; (f) 0.2 M KH_2PO_4-Na_2HPO_4 buffer.

To measure erosion from gels, cylindrical holders (41 mm diameter and 12 mm height) were filled with accurately weighed samples, in either distilled water or Na_3PO_4/HCl buffer, at 3.0 and 4.0% w/w concentration; air bubbles were removed by centrifugation. The holders were placed in USP XXII vessels containing 500 ml of deaerated dissolution medium (either distilled water or Na_3PO_4/HCl buffer) at 37°C; the paddle apparatus (at 25 mm above the gel surface) was used at 50 rpm. 5-ml samples were withdrawn at defined times and replaced with fresh medium.

Tablets of 300 mg of pure NaCMC were prepared at 5 tons for 2 min by means of a hydraulic press for KBr discs (Perkin Elmer), equipped with a manometer; a flat punch of 13 mm diameter was used. The tablets were glued at rotating discs (at 25 mm from the bottom of the vessel) whose rotation speed was 100 rpm; 400 ml of deaerated medium were used in USP XXII vessels.

All the dissolution tests were performed at 37°C. The samples were filtered before being analysed by means of the anthrone method.

The erosion rate (mg h^{-1}) was calculated as the slope of the line that fitted the release profile.

2.4. Anthrone method

The amount of NaCMC dissolved was quantified by means of the anthrone method (Morris, 1948). The reagent was prepared by dissolving 50 mg of anthrone in a mixture of 28 ml water and 72 ml concentrated sulfuric acid. A mixture of 0.5 ml of sample and 2.5 ml of reagent was heated in

Table 1

G' (Pa), G'' (Pa) and tan ∂ values obtained at 0.1 Hz frequency for NaCMC gels at different concentrations (% w/w) in distilled water and Na_3PO_4/HCl buffer (mean ± SD, $n = 3$)

Concentration (% w/w)	Distilled water			Na_3PO_4/HCl buffer		
	G'	G''	tan ∂	G'	G''	tan ∂
2.5	10.7 (±0.54)	15.3 (±0.69)	1.43 (±0.036)	23.1 (±1.11)	19.2 (±0.98)	0.83 (±0.029)
3.0	26.6 (±1.06)	28.3 (±1.33)	0.98 (±0.031)	48.5 (±2.42)	33.6 (±1.78)	0.71 (±0.036)
3.5	51.9 (±2.75)	41.1 (±2.01)	0.79 (±0.025)	80.8 (±4.20)	48.6 (±2.23)	0.60 (±0.035)
4.0	135.0 (±7.15)	77.0 (±3.77)	0.57 (±0.015)	173.0 (±9.34)	84.6 (±4.06)	0.49 (±0.018)

boiling water for 15 min, refrigerated and spectrophotometrically read at 625 nm. Four standard solutions (0.05, 0.1, 0.15 and 0.2 mg/ml) were analysed together with the samples to calculate a calibration line.

3. Results and discussion

Fig. 1A and B illustrates the creep curves of NaCMC gels at different concentrations ranging from 2.5 and 4.0% w/w, in distilled water and in Na_3PO_4/HCl buffer. As expected, the compliance is always higher for lower concentrations. At each concentration, the compliance values in distilled water are greater than those in buffer, and the residual viscosities (as demonstrated by the slopes of the curves) are lower.

Table 1 gives the values of G', G'' and tan ∂ at 0.1 Hz frequency for the same samples in distilled water and Na_3PO_4/HCl buffer. Both moduli have higher values in buffer than in distilled water, indicating that both elastic and viscous character increase when salts are present. The tan ∂ values are always lower in buffer than in distilled water. This suggests that the presence of salts increases the elastic more than the viscous behaviour. The rheological data indicate therefore that the polymer network structure is looser in distilled water than in presence of salts.

The erosion profiles of NaCMC from 3.0 and 4.0% w/w gels in distilled water and in Na_3PO_4/HCl buffer are given in Fig. 2; Fig. 3 demonstrates the erosion of the polymer from NaCMC tablets in the two media. The erosion rate from both gels and tablets is higher in distilled water than in buffer. This confirms a relationship between the rheological properties of gels and the ability of the polymer chains to disentangle from the polymeric network and get into solution.

Fig. 4 shows the creep curves of NaCMC 3.0% w/w gels in 0.2 M NaCl solution and in phosphate buffers (0.05, 0.1 and 0.2 M). For ease of comparison, the curves in distilled water and in Na_3PO_4/HCl buffer are also given. It can be appreciated that the residual viscosities (as demonstrated by the slopes of the curves) increase on increasing the ionic strength of the medium. The ionic composition of the medium (NaCl or phosphate salts) does not influence creep behaviour, since very similar curves are obtained in 0.2 M NaCl solution, 0.1 M KH_2PO_4-Na_2HPO_4 buffer, or Na_3PO_4/HCl buffer (all having very similar ionic strength). In Table 2 the oscillation parameters for the same samples are listed. Both elastic and viscous moduli increase with increasing ionic strength, whereas the loss tangent decreases. These results are in line with creep tests and indicate that the polymer network becomes tighter at high ionic strengths; this can be explained by the fact that the neutralization of charges by counterions affects polymer chain conformation.

The relationships between ionic strength and oscillation parameters (G', G'' and loss tangent) are illustrated in Fig. 5 (A–C, respectively). A direct relationship can be seen in the case of G' and G''; in particular, the variation of G' with ionic strength is close to linear. The decrease of loss tangent is not linear since smaller variations in tan ∂ occur at higher ionic strength values.

Fig. 6 illustrates the dissolution profiles of NaCMC from tablets made of pure polymer, in

Table 2
G' (Pa), G'' (Pa) and tan ∂ values, at 0.1 Hz frequency for 3.0% (w/w) NaCMC gels in different media (mean ± SD, $n = 3$)

	G'	G''	tan ∂
H_2O	26.6 (±1.06)	28.3 (±1.33)	0.98 (±0.031)
KH_2PO_4-Na_2HPO_4 (0.05 M)	35.3 (±1.70)	29.3 (±1.16)	0.83 (±0.018)
HCl-Na_3PO_4	48.5 (±2.42)	33.6 (±1.78)	0.71 (±0.036)
KH_2PO_4-Na_2HPO_4 (0.1 M)	49.3 (±3.05)	35.6 (±2.04)	0.72 (±0.015)
NaCl (0.2 M)	47.7 (±3.10)	33.5 (±3.74)	0.70 (±0.022)
KH_2PO_4-Na_2HPO_4 (0.2 M)	66.7 (±5.26)	44.6 (±4.12)	0.67 (±0.033)

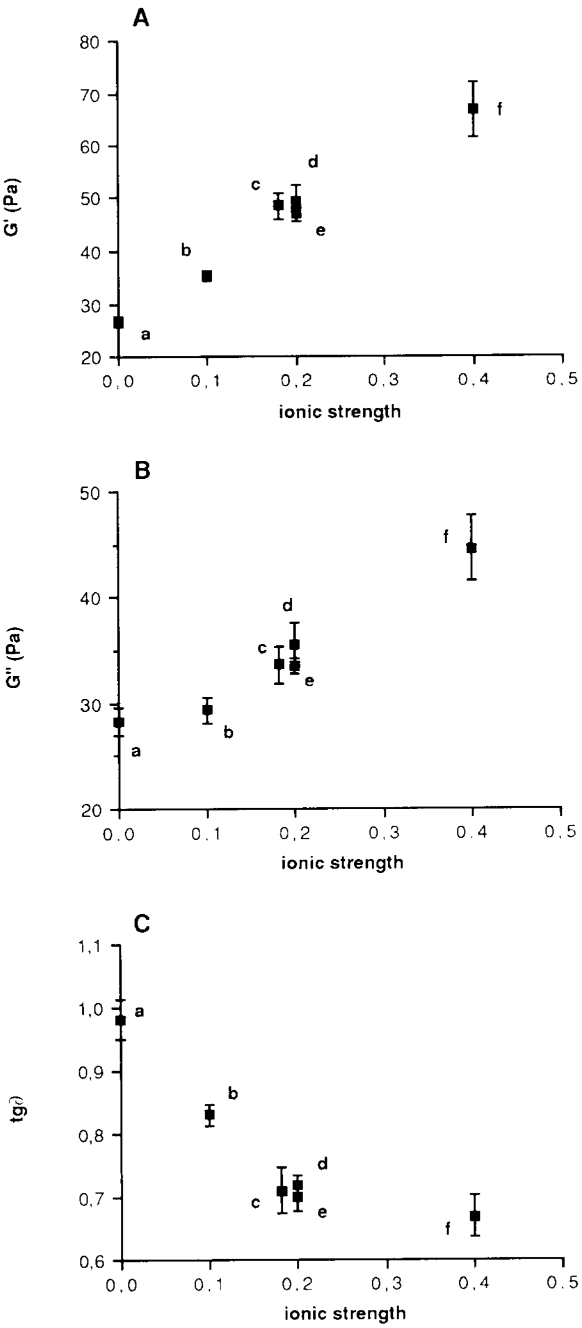

Fig. 5. Influence of ionic strength on viscoelastic parameters G', G'' and tan δ (A–C, respectively) of 3.0% w/w NaCMC gels in different media: (a) distilled water; (b) 0.05 M KH_2PO_4-Na_2HPO_4 buffer; (c) Na_3PO_4/HCl buffer; (d) 0.1 M KH_2PO_4-Na_2HPO_4 buffer; (e) 0.2 M NaCl solution; (f) 0.2 M KH_2PO_4-Na_2HPO_4 buffer.

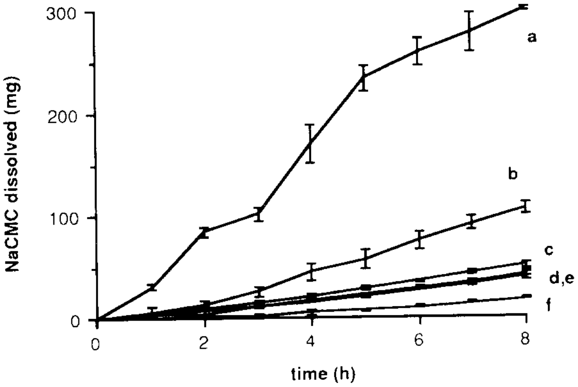

Fig. 6. Erosion profiles of NaCMC from tablets made of pure polymer in different media: (a) distilled water; (b) 0.05 M KH_2PO_4-Na_2HPO_4 buffer; (c) Na_3PO_4/HCl buffer; (d) 0.1 M KH_2PO_4-Na_2HPO_4 buffer; (e) 0.2 M NaCl solution; (f) 0.2 M KH_2PO_4-Na_2HPO_4 buffer (mean ± SD; $n = 3$).

0.2 M NaCl solution and in pH 6.8 phosphate buffers (0.05, 0.1 and 0.2 M). For ease of comparison the profiles in distilled water and in Na_3PO_4/HCl buffer are also given. The dissolution profiles clearly show the relevance of ionic strength on polymer erodibility. The profiles are quite linear, so that the polymer dissolution rate can be calculated as the slope of the regression line.

In Fig. 7A–C the NaCMC erosion rates in different media are related to the oscillation parameters G', G'' and tan δ, respectively. Although the rheological parameters refer only to one concentration (3.0% w/w gels) and only to one frequency value (0.1 Hz) quite good correlation can be seen between rheological parameters and the erosion rate. The relationships are not generally linear over the whole range of ionic strengths examined.

4. Conclusions

The results here obtained confirm that viscoelastic tests can give reliable and complete information about polymer network structure. They are therefore especially suitable to characterize polymer and polymer-solvent properties that may have a relevance in matrix systems. In

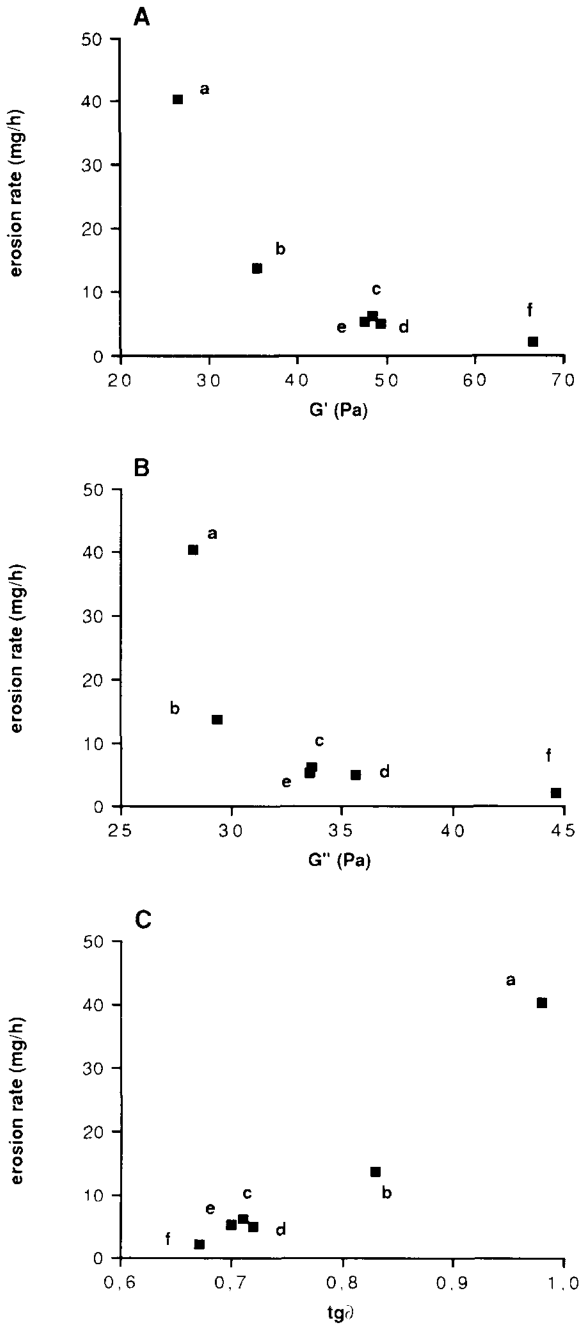

Fig. 7. Relationship between polymer erosion rate from NaCMC tablets in different media and viscoelastic parameters G', G'' and tan δ (A–C, respectively) of 3.0% w/w NaCMC gels in the same media: (a) distilled water; (b) 0.05 M KH_2PO_4-Na_2HPO_4 buffer; (c) Na_3PO_4/HCl buffer; (d) 0.1 M KH_2PO_4-Na_2HPO_4 buffer; (e) 0.2 M NaCl solution; (f) 0.2 M KH_2PO_4-Na_2HPO_4 buffer.

particular, they describe both the resistance of chains to undergo unrecoverable, viscous deformations and their ability to elastically rebuild their structure. These two characteristics are responsible for a more or less easy disentanglement of the polymer chains from the matrix surface to get into solution. This is confirmed by the good correlation between rheological parameters and sensitivity to erosion of NaCMC gels.

Both the elastic and viscous behaviours of NaCMC gels are significantly modified by the ionic strength of the medium. The influence of the ionic strength of the medium on viscoelastic parameters paralleled quite well its influence on the polymer sensitivity to erosion from gels and from tablets.

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