Rheological Destructuring of Aqueous Gels Composed of Cellulose Ethers Following Storage in the Presence of Redox Agents

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Received 4 August 2004; accepted 28 February 2005
DOI 10.1002/app.22180
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Despite their widespread use, there is a paucity of information concerning the effect of storage on the rheological properties of pharmaceutical gels that contain organic and inorganic additives. Therefore, this study examined the effect of storage (1 month at either 4 or 37°C) on the rheological and mechanical properties of gels composed of either hydroxypropylmethylcellulose (3–5% w/w, HPMC) or hydroxyethylcellulose (3–5% w/w, HEC) and containing or devoid of dispersed organic (tetracycline hydrochloride 2% w/w) or inorganic (iron oxide 0.1% w/w) agents. The mechanical properties were measured using texture profile analysis whereas the rheological properties were analyzed using continuous shear rheometry and modeled using the Power Law model. All formulations exhibited pseudoplastic flow with minimal thixotropy. Increasing polymer concentration (3–5% w/w) significantly increased the consistency, hardness, compressibility, and adhesiveness of the formulations due to increased polymer chain entanglement. Following storage (1 month at 4 and 37°C) the consistency and mechanical properties of additive free HPMC gels (but not HEC gels) increased, due to the time-dependent development of polymer chain entanglements. Incorporation of tetracycline hydrochloride significantly decreased and increased the rheological and mechanical properties of HPMC and HEC gels, respectively. Conversely, the incorporation of iron oxide did not affect these properties. Following storage, the rheological and mechanical properties of HPMC and HEC formulations were markedly compromised. This effect was greater following storage at 37 than at 4°C and, additionally, greater in the presence of tetracycline hydrochloride than iron oxide. It is suggested that the loss of rheological/mechanical structure was due to chain depolymerization, facilitated by the redox properties of tetracycline hydrochloride and iron oxide. These observations have direct implications for the design and formulation of gels containing an active pharmaceutical ingredient. J Appl Polym Sci 98: 852–859, 2005

Key words: cellulose ethers; gels; flow rheometry; texture profile analysis; redox; stability

INTRODUCTION

Etherification of cellulose provides a broad spectrum of polymers that dissolve in water and/or organic solvents depending upon the chemical nature of the substitution.[1] The physicochemical properties of cellulose ether polymers render them suitable for use in a broad range of applications in such diverse industries as food, construction, paint, oil recovery, paper, cosmetics, adhesives, printing, agriculture, and pharmaceuticals.[1] Within the pharmaceutical industry cellulose ethers are used as viscosity modifying agents in ophthalmic and topical formulations and, additionally, as tablet binders, controlled release matrices, and film coating agents.[1–6] Examples of commercially available nonionic cellulose ethers include methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and hydroxyethylcellulose.

It is accepted that product rheology directly influences the clinical and nonclinical properties of pharmaceutical systems.[7,8] Due to their acceptable rheological properties, one of the primary pharmaceutical applications of cellulose ethers is in the formulation of topical pharmaceutical products.[9–11] The rheological properties of these systems are dependent on both the chemical nature and the concentration of the chosen cellulose ether.[1,11] At low concentrations Newtonian flow may be observed. However, if the concentration exceeds a defined critical concentration, gels composed of cellulose ethers exhibit pseudoplastic flow.[1,12,13] The viscosity of these systems has been reported to be stable over a wide pH range (typically, between pH 2 and 12). However, under more acidic

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conditions, acid-catalyzed hydrolysis results in rapid molecular weight degradation. Furthermore, in the presence of molecular oxygen with solution at high pH, a base-catalyzed oxidation mechanism may reduce the polymer molecular weight.[1,14]

In the design of topical gel formulations the therapeutic agent is either dissolved or dispersed within the gel/semisolid matrix. However, while it has been accepted that the presence of the therapeutic agent may affect the rheological properties of the resultant formulation, it is assumed that the incorporated drug will not affect the rheological properties of the formulation upon storage and, thus, product stability. Interestingly, we have observed time-dependent changes in the rheological properties of ternary polymeric systems composed of cellulose ethers and containing tetracycline hydrochloride. Tetracycline may undergo redox reactions and this ability may be one source of the observed rheological instability. Therefore, the aim of this study was to investigate the effect of model redox substances, namely, iron-2-oxide and tetracycline hydrochloride, on the rheological stability of hydroxyethylcellulose (HEC) and hydroxypropylmethylcellulose (HPMC) aqueous gels following storage under defined conditions. The information generated will both provide an insight into the effects of redox agents on the stability of aqueous cellulose ether gels and highlight the pharmaceutical implications of such interactions.

METHODS

Materials

Hydroxyethylcellulose (Natrosol HHX 250 Pharm) was a gift from Aqualon Ltd. (Warrington, UK). HPMC (100 000 cps) tetracycline hydrochloride, and iron-2-oxide were purchased from Sigma-Aldrich (Dorset, England). All other chemicals were purchased from BDH Chemicals Ltd. (Gillingham, Dorset, UK) and were of AnalaR or equivalent quality.

Manufacture of aqueous gels composed of cellulose ethers

Aqueous gels composed of either HEC or HPMC were manufactured by the addition of the appropriate amount of polymer (3, 4, or 5% w/w) to the vortex produced by mechanical agitation of distilled water.[11] Gels were also prepared containing 2% w/w tetracycline hydrochloride and 0.1% w/w iron-2-oxide. These were dispersed into HEC and HPMC gels by agitation using a Heidolph mechanical stirrer. Each formulation was examined following 48 h of manufacture and in addition after storage for 1 month at both 4 and 37°C.

Continuous shear analysis

Flow rheograms were obtained using a Carri-Med CSL^2 100 continuous shear rheometer (T.A. Instruments, Surrey, England) in flow mode at 20 ± 0.1°C in conjunction with parallel plate geometry (4 cm diameter, 1 mm plate gap). Samples were applied to the lower plate and allowed 20-min equilibration for induced stresses to relax. Rheograms were produced using the loop test, whereby the shearing stress was increased gradually from a minimum up to a predetermined maximum within 60 s and then returned to the starting point under the same conditions. Shearing stresses were selected according to formulation consistency.[7,8] The range of shearing stresses employed for continuous shear analysis is presented in Table I. In all cases at least five replicates were examined.

Modeling of the flow properties of the various formulations was performed using the Power Law model (Eq. (1))[15] and the Cross model (Eq. (2)),[16] presented below.

$$\sigma = K\dot{\gamma}^n, \tag{1}$$

where σ is the shearing stress, $\dot{\gamma}$ is the rate of shear, K is the consistency, and n is a rheological exponent;

$$\eta = \eta_\infty + \left(\frac{\eta_0 - \eta_\infty}{1 + (k\gamma)^n}\right), \tag{2}$$

where η is the dynamic viscosity, η_∞ is the infinite viscosity, η_0 is the zero rate viscosity, k is the frequency at which formulation first displays shear-rate-dependent viscosity, n is the slope of the shear rate dependent region, and γ is the rate of shear.

Texture profile analysis

Texture profile analysis (TPA) was performed using a TA-XT2 Texture Analyser (Stable Micro Systems, Surrey, England). Formulations were transferred into McCartney bottles to a fixed height and centrifuged to remove entrapped air. In TPA a polycarbonate probe (10 mm diameter) was depressed twice into each sample to a depth of 15 mm with a 15-s delay between depressions. At least five replicate analyses were performed for each formulation at ambient temperature. From the resulting force–time plots the following parameters were determined:[7]

- hardness: the force required to attain a given deformation;
- compressibility: the work required to deform the product during the first compression of the probe;
- adhesiveness: the work required to overcome the attractive forces between the surface of the probe and the sample. This parameter encompasses the

TABLE I
Shear Stresses Employed in the Continuous Shear Analysis of HEC- and HPMC-Based Gel Systems

Formulation	Additives	Shear stress (Pa)
3% HEC	NA[a]	100–250
	Iron-2-oxide (0.1% w/w)	100–250
	Tetracycline hydrochloride (2% w/w)	200–500
4% HEC	NA	250–600
	Iron-2-oxide (0.1% w/w)	250–600
	Tetracycline hydrochloride (2% w/w)	200–500
5% HEC	NA	600–795
	Iron-2-oxide (0.1% w/w)	600–795
	Tetracycline hydrochloride (2% w/w)	600–795
3% HPMC	NA	100–300
	Iron-2-oxide (0.1% w/w)	400–700
	Tetracycline hydrochloride (2% w/w)	400–700
4% HPMC	NA	100–300
	Iron-2-oxide (0.1% w/w)	400–700
	Tetracycline hydrochloride (2% w/w)	400–700
5% HPMC	NA	100–300
	Iron-2-oxide (0.1% w/w)	400–700
	Tetracycline hydrochloride (2% w/w)	400–700

[a] NA, no additive.

breakage of either polymer–polymer bonds or polymer–probe bonds.

Statistical analysis

Modeling of the flow rheograms of each formulation was performed using the Power Law and Cross models. The quality of each model was assessed using regression and correlation analyses, the most appropriate model being that which exhibited the greatest correlation coefficient and lowest standard deviation.[17] The effects of polymer concentration (3, 4, or 5% w/w), type of additive (i.e., tetracycline hydrochloride, iron-2-oxide, and no additives), and storage temperature (freshly prepared or stored at either 4 or 37°C) on formulation consistency and textural properties (i.e., hardness, compressibility, and adhesiveness) were statistically examined using a three-way ANOVA. Post hoc comparisons of individual means were performed using Tukey's HSD test.[17] At least five replicates of each formulation were examined and in all cases $P < 0.05$ denoted significance.

RESULTS

In this study all gels, both devoid of or containing additives (2% w/w tetracycline hydrochloride, 0.1% w/w iron oxide) and independent of the storage conditions (freshly prepared or stored at either 37 or 4°C for 1 month), were pseudoplastic. In addition, several gels displayed thixotropy, although the extent of this was frequently minimal and no relationships between gel formulation/storage conditions and thixotropy were observed. Examples of flow rheograms of gels of HEC and HPMC, either devoid of or containing 2% w/w tetracycline hydrochloride that had been stored at 37°C for 1 month, are displayed in Figures 1–4. Mathematical modeling of the flow curves was performed using the Power Law and the Cross models, from which it was shown that both the quality of the regression and the significance of the analysis of variance associated with the former model were greater. Accordingly, the Power Law model was employed to describe the rheological properties of the various gel systems (Table II). As may be observed, increasing the concentration of HEC or HPMC sequentially from 3 to 5% w/w, either in the presence or in the absence of

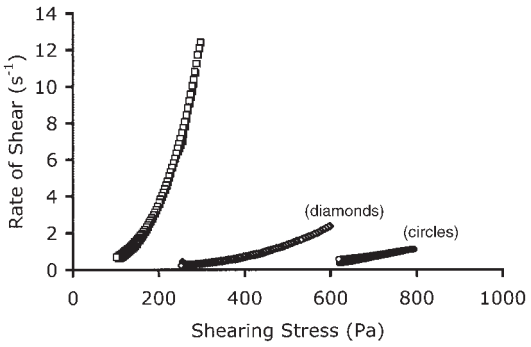

Figure 1 Flow rheograms of aqueous gels of hydroxyethylcellulose following storage at 37°C for 1 month. Squares depict gels composed of 3% w/w HEC; diamonds depict gels composed of 4% w/w HEC; circles depict gels composed of 5% w/w HEC. Open symbols refer to the up flow curve whereas closed symbols refer to the down flow curve. The rheograms presents mean values. Standard deviations have been omitted for clarity; however, the coefficient of variation was less than 6% for all measurements.

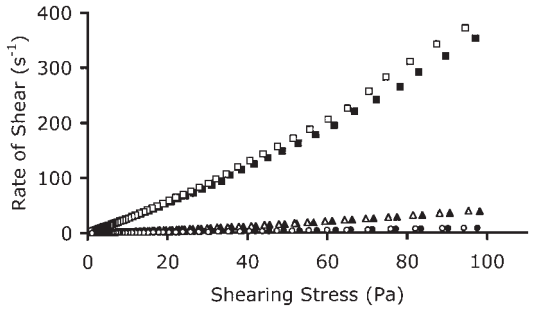

Figure 2 Flow rheograms of aqueous gels of hydroxyethylcellulose containing 2% w/w tetracycline hydrochloride following storage at 37°C for 1 month. Squares depict gels composed of 3% w/w HEC; diamonds depict gels composed of 4% w/w HEC; circles depict gels composed of 5% w/w HEC. Open symbols refer to the up flow curve, whereas closed symbols refer to the down flow curve. The rheograms presents mean values. Standard deviations have been omitted for clarity; however, the coefficient of variation was less than 8% for all measurements.

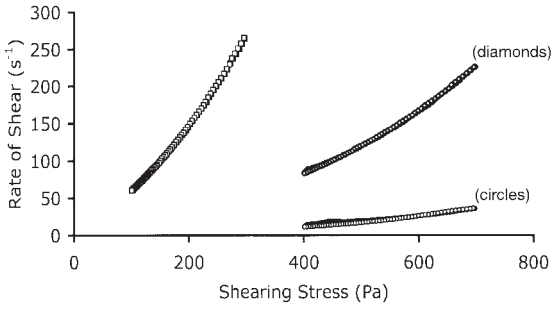

Figure 4 Flow rheograms of aqueous gels of hydroxypropylmethylcellulose containing 2% w/w tetracycline hydrochloride following storage at 37°C for 1 month. Squares depict gels composed of 3% w/w HPMC; diamonds depict gels composed of 4% w/w HPMC; circles depict gels composed of 5% w/w HPMC. Open symbols refer to the up flow curve whereas closed symbols refer to the down flow curve. The rheograms presents mean values. Standard deviations have been omitted for clarity; however, the coefficient of variation was less than 8% for all measurements.

additives and independent of storage conditions, significantly increased the consistencies of the gel formulations. The effect of storage on the consistencies of the various gels was dependent on both the absence and the presence (and type) of additive and the temperature at which the formulations were stored (Tables II and III). In the absence of either tetracycline hydrochloride or iron oxide, storage conditions did not significantly affect the consistency of HEC gels (3, 4, or 5% w/w) but the consistency of HPMC gels at each polymer concentration was seen to increase. The incorporation of tetracycline hydrochloride (2% w/w) significantly increased the consistency of HEC gels, but decreased the consistency of gels composed of HPMC. Conversely, with the exception of 3% w/w HEC, the presence of iron oxide did not affect the consistency of either aqueous gel system.

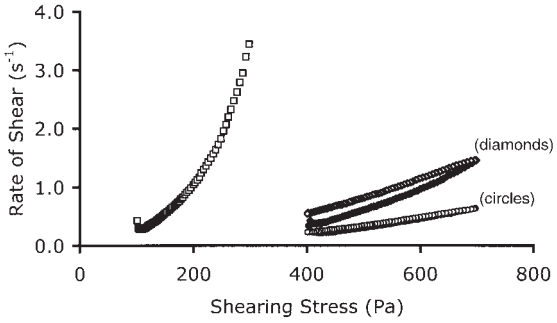

Figure 3 Flow rheograms of aqueous gels of hydroxypropylmethylcellulose following storage at 37°C for 1 month. Squares depict gels composed of 3% w/w HPMC; diamonds depict gels composed of 4% w/w HPMC; circles depict gels composed of 5% w/w HPMC. Open symbols refer to the up flow curve, whereas closed symbols refer to the down flow curve. The rheograms presents mean values. Standard deviations have been omitted for clarity; however, the coefficient of variation was less than 6% for all measurements.

Following storage for 1 month, the consistencies of gels containing tetracycline hydrochloride or iron oxide were reduced in comparison to their additive-free counterparts. Furthermore, lower consistencies were associated with formulations that had been stored at the higher storage temperature (37°C). For example, the consistency of HEC gel (5% w/w) that was devoid of additives following storage at 37°C for 1 month was 722.1 ± 20.6 $(Pa.s)^n$, whereas the consistencies of comparator formulations containing iron oxide and tetracycline hydrochloride were 587.2 ± 16.0 and 18.5 ± 0.6 $(Pa.s)^n$, respectively. Similarly, the consistencies of the additive-free HPMC (5% w/w) gel following storage at 37°C for 1 month was 857.5 ± 24.8 $(Pa.s)^n$, which, following the incorporation of iron oxide and tetracycline hydrochloride, reduced to 680.6 ± 18.8 and 127.6 ± 8.5 $(Pa.s)^n$, respectively. Interestingly, the detrimental effects of storage and the presence of additives on gel consistency were greater for systems composed of HEC than for those composed of HPMC.

The effect of storage conditions and the absence or presence of iron oxide or tetracycline hydrochloride on the mechanical (textural) properties of gels composed of HEC or HPMC are presented in Tables IV and V, respectively. Increasing the concentration of each polymer significantly increased the hardness, compressibility, and adhesiveness of each polymer system, independent of storage conditions or the presence or absence of additives. The mechanical properties of HEC gels that were devoid of either tetracycline hydrochloride or iron oxide were unaffected following storage at either 4 or 37°C for 1 month. However, following storage, the hardness, compressibility, and adhesiveness of HPMC gels increased. Incorporation

TABLE II
The Effect of Storage on the Consistency of HEC Gels either Devoid of or Containing Tetracycline Hydrochloride or Iron-2-oxide

HEC (% w/w)	Additive	Mean (±SD) consistency of HEC formulations (Pa·s)^n		
		Freshly prepared	One month stored at 4°C	One month stored at 37°C
3	NA[a]	149.5 ± 12.1	140.3 ± 9.9	158.4 ± 16.6
4	NA	457.4 ± 9.3	468.0 ± 25.1	457.3 ± 17.4
5	NA	738.7 ± 28.2	770.1 ± 14.3	722.1 ± 20.6
3	Iron oxide	203.1 ± 15.3	190.0 ± 13.3	178.9 ± 9.8
4	Iron oxide	452.4 ± 13.9	417.0 ± 12.4	375.6 ± 21.5
5	Iron oxide	728.2 ± 15.5	699.5 ± 21.2	587.2 ± 16.0
3	Tetracycline hydrochloride	232.0 ± 16.2	229.4 ± 12.4	0.7 ± 0.0
4	Tetracycline hydrochloride	537.4 ± 28.6	478.5 ± 11.8	5.8 ± 0.2
5	Tetracycline hydrochloride	838.6 ± 24.1	475.5 ± 13.8	18.5 ± 0.6

[a] NA, no additive.

of iron oxide into each gel system was not observed to alter the mechanical properties, whereas the presence of tetracycline hydrochloride increased and decreased the mechanical properties of HEC and HPMC gels, respectively. For example, the hardness and compressibility of freshly prepared gels composed of 5% w/w HEC were 2.20 ± 0.09 *N* and 21.94 ± 0.24 *N* mm, respectively, which, following the incorporation of tetracycline hydrochloride increased to 2.42 ± 0.03 *N* and 24.35 ± 0.59 *N* mm. Conversely, the hardness and compressibility of HPMC (5% w/w) containing tetracycline hydrochloride (2% w/w) were 1.73 ± 0.05 *N* and 15.41 ± 0.50 *N* mm, a significant decrease from 2.05 ± 0.07 *N* and 18.36 ± 0.79, the values associated with the drug-free gel.

Following storage, the mechanical properties of HEC and HPMC gels containing iron oxide or tetracycline hydrochloride decreased, the extent of which was greater following storage at the higher temperature. In particular, dramatic reductions in the hardness, compressibility, and adhesiveness of the various tetracycline-hydrochloride-containing formulations were observed.

DISCUSSION

In the formulation of pharmaceutical gels designed for the controlled topical release of therapeutic agents several design criteria may be defined. These include ease of removal from the container; excellent spreadability; retention on the host substrate; and controlled delivery of the therapeutic agent either to the host mucosa or into the surrounding biological fluids.[8,18,19] Accordingly, an understanding of the rheological/mechanical properties is essential to ensure optimum product performance.[18,19] While the effects of the concentration and type of polymer on the rheological properties of pharmaceutical gel systems have been documented, e.g., Refs. [18–22], comparatively little attention has been paid to the possible effects of the

TABLE III
The Effect of Storage on the Consistency of HPMC Gels either Devoid of or Containing Tetracycline Hydrochloride or Iron-2-oxide

HPMC (% w/w)	Additive	Mean (±s.d) consistency of HPMC formulations (Pa·s)^n		
		Freshly Prepared	One month stored at 4°C	One month stored at 37°C
3	NA[a]	177.2 ± 14.3	207.8 ± 20.4	188.6 ± 9.5
4	NA	445.2 ± 17.2	493.1 ± 14.9	548.1 ± 13.8
5	NA	783.2 ± 28.9	832.6 ± 10.6	857.5 ± 24.8
3	Iron oxide	175.4 ± 14.6	147.1 ± 10.4	123.7 ± 5.1
4	Iron oxide	465.2 ± 16.2	423.7 ± 8.4	276.8 ± 13.4
5	Iron oxide	719.2 ± 16.3	677.3 ± 23.6	680.6 ± 18.8
3	Tetracycline hydrochloride	157.7 ± 11.7	126.7 ± 5.2	5.6 ± 0.2
4	Tetracycline hydrochloride	389.0 ± 28.2	270.1 ± 17.4	35.8 ± 2.4
5	Tetracycline hydrochloride	616.1 ± 9.9	451.1 ± 15.2	127.6 ± 8.5

[a] NA, no additive.

TABLE IV
The Effect of Storage on the Textural/Mechanical Properties of HEC Gels either Devoid of or Containing Tetracycline Hydrochloride (Tet. HCl) or Iron-2-oxide

Conc. of HEC (% w/w)	Additive	Textural/mechanical properties of HEC gels (mean ± SD)								
		Compressibility (N mm)			Hardness (N)			Adhesiveness (N mm)		
		Freshly prepared	1 month at 4°C	1 month at 37°C	Freshly prepared	1 month at 4°C	1 month at 37°C	Freshly prepared	1 month at 4°C	1 month at 37°C
3	NA[a]	6.17 ± 0.20	6.23 ± 0.19	6.33 ± 0.16	0.68 ± 0.01	0.71 ± 0.02	0.74 ± 0.02	4.80 ± 0.22	4.50 ± 0.60	4.49 ± 0.17
3	Iron oxide	6.88 ± 0.24	6.25 ± 0.19	5.54 ± 0.37	0.73 ± 0.04	0.67 ± 0.01	0.58 ± 0.01	4.32 ± 0.10	3.73 ± 0.01	3.04 ± 0.12
3	Tet. HCl	6.43 ± 0.05	5.38 ± 0.21	ND[b]	0.71 ± 0.01	0.58 ± 0.05	ND	5.23 ± 0.25	3.40 ± 0.29	ND
4	NA	13.18 ± 0.23	13.58 ± 0.40	13.70 ± 0.24	1.43 ± 0.04	1.74 ± 0.05	1.69 ± 0.03	7.68 ± 0.30	8.72 ± 0.19	8.67 ± 0.13
4	Iron oxide	12.10 ± 0.25	10.46 ± 0.16	7.25 ± 0.60	1.27 ± 0.09	1.08 ± 0.02	0.80 ± 0.10	7.36 ± 0.36	6.42 ± 0.13	4.71 ± 0.38
4	Tet. HCl	15.11 ± 0.40	9.63 ± 0.22	0.62 ± 0.12	1.53 ± 0.03	1.17 ± 0.12	0.09 ± 0.00	7.88 ± 0.09	6.06 ± 0.52	ND
5	NA	22.94 ± 0.24	23.97 ± 0.16	24.71 ± 0.52	2.20 ± 0.09	2.32 ± 0.18	2.43 ± 0.12	11.93 ± 0.24	12.56 ± 0.15	12.56 ± 0.17
5	Iron oxide	22.78 ± 0.40	19.87 ± 0.98	9.68 ± 0.59	2.28 ± 0.17	1.89 ± 0.18	1.02 ± 0.11	10.98 ± 0.52	9.21 ± 0.04	7.99 ± 0.17
5	Tet. HCl	23.35 ± 0.19	14.68 ± 1.41	1.29 ± 0.11	2.52 ± 0.03	1.64 ± 0.13	0.19 ± 0.01	13.29 ± 0.23	8.32 ± 0.45	0.97 ± 0.10

[a] NA, no additive.
[b] ND, not detectable.

incorporation of drugs on the rheological properties of gel systems. In particular, there is a paucity of reports concerning the effects of therapeutic agents on the rheological stability of aqueous gel systems. This study was therefore designed to address some of these deficiencies. The additives used in this study were known to undergo redox reactions and a saturation concentration of each was employed within the gel systems to ensure that no significant depletion of either occurred following possible interactions with the polymer matrix.

In this study both the consistency and the mechanical properties (hardness, compressibility, and adhesiveness) of the gels increased as the concentration of polymer was sequentially increased. Consistency is a measure of resistance to flow following the application of a torsional stress, whereas hardness and compressibility are measurements of the resistance to flow following the application of a compressional stress.[8] Similarly, in light of the limited interaction of the gels with the probe following application of a tensional stress in texture profile analysis, it may be concluded that adhesiveness was primarily a measure of the resistance to tensional deformation following the prior application of a compressional stress. The effect of polymer concentration on torsional, tensional, and compressional flow may be accredited to enhanced polymer entanglement due to the closer proximity of adjacent polymer chains and has been reported in several studies.[7,8,11,12,18,19,21]

Incorporation of tetracycline hydrochloride (but not iron oxide) significantly affected the rheological and mechanical properties of the two parent gel systems, reflecting differences in the abilities of these two agents to interact with the gel matrix. The solubility of tetracycline hydrochloride and iron oxide within the gel matrices differs, with tetracycline hydrochloride possessing a markedly greater aqueous solubility. The incorporation of therapeutic agents into hydrophilic gels has been reported to affect the rheological prop-

TABLE V
The Effect of Storage on the Textural/Mechanical Properties of HPMC Gels either Devoid of or Containing Tetracycline Hydrochloride (Tet. HCl) or Iron-2-oxide

Conc. of HEC (% w/w)	Additive	Textural/mechanical properties of HPMC gels (mean ± SD)								
		Compressibility (*N* mm)			Hardness (*N*)			Adhesiveness (*N* mm)		
		Freshly prepared	1 month at 4°C	1 month at 37°C	Freshly prepared	1 month at 4°C	1 month at 37°C	Freshly prepared	1 month at 4°C	1 month at 37°C
3	NA[a]	5.06 ± 0.28	5.83 ± 0.43	6.73 ± 0.17	0.58 ± 0.04	0.65 ± 0.03	0.74 ± 0.02	4.47 ± 0.31	5.27 ± 0.28	6.40 ± 0.21
3	Iron oxide	4.84 ± 0.34	3.98 ± 0.16	3.67 ± 0.17	0.54 ± 0.04	0.49 ± 0.01	0.42 ± 0.01	4.10 ± 0.34	3.51 ± 0.08	3.20 ± 0.20
3	Tet. HCl	4.36 ± 0.30	3.18 ± 0.07	0.50 ± 0.04	0.50 ± 0.03	0.33 ± 0.01	0.05 ± 0.00	3.82 ± 0.40	2.75 ± 0.12	ND[b]
4	NA	11.00 ± 0.99	12.16 ± 0.69	16.18 ± 0.18	1.26 ± 0.08	1.29 ± 0.11	1.70 ± 0.02	9.69 ± 0.95	10.56 ± 1.00	13.84 ± 0.04
4	Iron oxide	10.09 ± 0.38	9.49 ± 0.24	7.04 ± 0.15	1.15 ± 0.10	0.84 ± 0.48	0.69 ± 0.09	9.44 ± 0.47	7.98 ± 0.48	6.99 ± 0.46
4	Tet. HCl	8.80 ± 0.32	7.50 ± 0.36	1.06 ± 0.12	1.03 ± 0.07	0.84 ± 0.05	0.14 ± 0.02	8.13 ± 0.39	6.94 ± 0.35	0.67 ± 0.10
5	NA	18.36 ± 0.79	20.95 ± 1.34	21.29 ± 1.62	2.05 ± 0.97	2.25 ± 0.15	2.28 ± 0.17	12.84 ± 0.73	15.99 ± 1.68	17.40 ± 1.09
5	Iron oxide	17.76 ± 1.05	16.87 ± 1.01	14.03 ± 0.87	1.89 ± 0.90	1.78 ± 0.58	1.38 ± 0.81	11.58 ± 0.87	10.05 ± 0.52	9.25 ± 0.23
5	Tet. HCl	15.41 ± 0.50	13.43 ± 0.79	1.35 ± 0.18	1.73 ± 0.05	1.47 ± 0.08	0.19 ± 0.01	1.38 ± 0.06	1.20 ± 0.03	0.74 ± 0.04

[a] NA, no additive.
[b] ND, not detectable.

erties. For example, the dispersion of tetracycline hydrochloride into binary aqueous polymer networks significantly increased the viscoelastic properties[8,15] due to the effects of the dispersed solids on the overall semisolid character. In this study the incorporation of tetracycline hydrochloride within gels composed of HEC significantly increased both the consistency and the mechanical properties. Considering the concentration of drug employed it is proposed that, in line with previous studies,[8,15] this increase in rheological structuring may be explained, at least in part, by the effect of dispersed solid on the resultant flow properties. Conversely, the rheological properties of HPMC gels were compromised by the presence of tetracycline hydrochloride, inferring that this therapeutic agent interfered with polymer–polymer interactions. The ability of organic agents to interfere with polymer–polymer interactions and, in so doing, modify the rheological properties of pharmaceutical gels, has been documented. For example, Craig et al.[23] reported that the inclusion of a chlorhexidine gluconate into poly(acrylic acid) gels reduced their viscoelastic properties, whereas Jones et al. [18] illustrated the interaction between chlorhexidine and poly(acrylic acid) and the enhanced solubility of the complex in the presence of HEC. The lack of effect of iron oxide on the rheological properties of the two gel matrices may be due to both the limited ability of this inorganic agent to interfere with polymer–polymer interactions and the low concentration under examination, the latter being unable to alter the semisolid character of the gels. Therefore, this study has served to illustrate the ability of model additives to alter the rheological properties of polymeric gel systems on storage.

In light of the widespread pharmaceutical use of HPMC and HEC polymers for the formulation of pharmaceutical gels, the results presented herein have direct implications for product stability. Remarkably, there have been few reports that have examined the effects of ageing on the rheological properties of gels. However, Tamburic and Craig[24] described a loss of viscoelastic structure in poly(acrylic acid) gels, which was accredited to the redistribution of cations between the polymer chains and the bulk of the gel. More recently, Tosh et al.[25] described the polymer chain rearrangement and rheological structuring of gelatin during aging. Interestingly, in the present study, the two gels differed in their aging properties, with HPMC displaying enhanced rheological structure following storage. The greater resistance to deformation of this system infers that the density of polymer–polymer interactions has increased as a function of time. The greater rheological structuring at the higher storage temperature serves to highlight the ability of this polymer to undergo thermally induced interactions.[26,27] Significantly, this study has illustrated the complete loss of gel structure of tetracycline-containing gels (composed of either HPMC or HEC) following storage at 37°C for 1 month. In addition, following storage for 1 month at 4°C, the gel structure of these systems was also markedly reduced. Similarly, the structure of HPMC or HEC gels that contained iron oxide following storage for 1 month, particularly at 37°C, was compromised. There are few studies that have examined the effects of organic and inorganic additives on the rheological properties of aqueous gels. However, in one study the rheological stability of a series of cellulose ethers gels that contained Hamamelis was examined following storage under different light and temperature conditions.[28] The authors reported that following storage at 30°C, the viscosities of gels composed of methylcellulose, carboxymethylcellulose, or hydroxypropylmethylcellulose were dramatically affected. It is understood that cellulose derivatives, e.g., HPMC, HEC, may undergo oxidative depolymerization reactions in which free radicals may be formed by several mechanisms including hydrogen abstraction and electron transfer.[14] The model additives employed in this study are redox agents[29,30] and accordingly may participate in electron transfer and general oxidative processes. The dramatic loss of the gel structure (particularly in the presence of tetracycline hydrochloride) may, therefore, be due to a reduction in the molecular weight of the polymer. Similarly Knapczyk[31] reported a reduction in rheological structure following storage of chitosan gels containing therapeutic agents (e.g., metronidazole) and concluded that depolymerization of chitosan had occurred in the presence of these additives. The present study illustrates the differing abilities of iron oxide and tetracycline hydrochloride to alter the rheological structure of the aqueous gels under examination. One possible explanation for this disparity is the greater aqueous solubility of tetracycline hydrochloride and, thus, the greater number of molecules available in solution to participate in the depolymerization process.

In conclusion, it is apparent that the outcomes of this study have direct consequences to the formulation of drug-containing gels composed of cellulose ethers. First, in light of the structural similarities of the cellulose ethers and the known ability of cellulose (the parent backbone) to undergo depolymerization,[14] it may be speculated that the phenomena reported in this study would extend to other cellulose ethers, e.g., carboxymethylcellulose, methylcellulose. Furthermore, the rheological instability described in this study may translate to pharmaceutical products and, in this scenario, the clinical and nonclinical performance of aqueous gels of cellulose ethers, which contain certain therapeutic agents, will be inadequate. Under these circumstances the use of other hydrophilic polymers may be essential or, alternatively, the

inclusion of other ancillary agents, e.g., antioxidants, may be necessary.

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