

RESEARCH PAPER

Rheological Characterization of Hydroxypropylcellulose Gels

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ABSTRACT

The present paper describes the rheological properties of hydroxypropylcellulose (HPC) gels formulated in propylene glycol (PG), water, ethanol, and mixtures of these components. The effects of molecular weight, polymer concentration, and solvent composition on the apparent viscosity and flow characteristics have been studied by continuous shear rheometry. The HPC gels are shear thinning and do not exhibit significant yield or hysteresis in their rheograms. The apparent viscosity increases with increasing molecular weight and concentration of the polymer, as expected. Although not so pronounced at lower concentrations ($\leq 1.5\%$), HPC gels tend to become increasingly non-Newtonian with increasing molecular weight at higher polymer concentrations (3%). A mathematical model has been proposed for the prediction of viscosities of HPC gels. There exists a high degree of dependence on molecular interactions between various solvent molecules in the prediction of mixture viscosities in ternary systems. The effects of solvent composition on the viscoelastic behavior of these gels have also been examined by dynamic mechanical analysis. The HPC gels are highly viscoelastic and exhibit greater degrees of elasticity with increased PG content in ternary solvent mixtures with water and ethanol. The study also suggests that dynamic mechanical analysis could prove to be a useful tool in the determination of zero-shear viscosities, viscosities that are representative of most realistic situations.

Key Words: Dynamic mechanical analysis; Hydroxypropylcellulose; Rheology; Solvent effects.

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INTRODUCTION

Hydroxypropylcellulose (HPC), a nonionic, water-soluble polymer, is widely used in pharmaceutical and cosmetic formulations. In tablets, it is used as a binder, and it is also commonly used as a thickening agent in many topical products. Although rheological properties of pharmaceutical semisolids have been the subject of considerable interest for the last few decades (1–4), little is known about the rheological properties of HPC. Rheological characterization of such polymeric materials can be of importance as it provides fundamental information required for assessment of some of the final properties of a product, such as quality, storage stability, effect of formulation variables on product characteristics such as consistency (5–8), correlation of consumer evaluation with consistency (9,10), and so on. Rheology can also become extremely critical when the release of an entrapped medicament is affected by the viscosity of the formulation (11).

Another key point of polymer rheology is the concept of viscoelasticity (12–16). This property is important in polymeric solutions as they exhibit both liquid and solidlike properties. The relative contributions of the elastic and viscous elements within a polymer solution are governed by the extent of intermolecular association/aggregation and chain entanglement, respectively. A practical implication of this concept is that a viscoelastic fluid with a high elastic modulus will exhibit excellent suspending properties as dispersed particles will be effectively trapped within a quasi gel. In the case of solid dosages that are in the form of hydrophilic matrices, drug release occurs immediately from the surface, followed by diffusion through, and/or erosion of, the hydrated layer. In this context, viscoelastic characterization of polymers used to form hydrophilic matrix systems is very important. Practically speaking, a high elastic modulus is likely to provide erosion resistance to the hydrated gel, whereas a purely viscous material is likely to be washed away more quickly by the dissolution medium (17).

Typically, for a complete understanding of the rheological behavior of a given material, three different types of tests are generally performed: oscillation measurements, creep measurements, and steady shear measurements. Most commonly, steady shear methods are used to determine non-Newtonian viscosity. Although steady shear methods form a useful technique, they generally destroy the underlying structure that imparts a certain viscoelastic characteristic to the material. Useful as they may be, steady shear measurements do not completely describe a material in its rheological ground state. This

warrants the further use of oscillation or creep measurements to investigate the material rheologically in full.

The primary objective of the present work is to characterize the flow behavior and the effects of molecular weight and polymer concentration on the apparent viscosity and flow characteristics of HPC gels formed in propylene glycol (PG), water, ethanol, and mixtures of these components. This study also investigates the properties of these gels in their undisturbed state by dynamic mechanical analysis.

MATERIALS AND METHODS

Materials

Hydroxypropylcellulose (Klucel NF) of three different molecular weights (1,150,000, 850,000, and 370,000 daltons) was obtained from Aqualon (Wilmington, DE) and was used as received. The PG and ethanol (200 proof) were obtained from Aldrich Chemical Company (Milwaukee, WI). Dionized water filtered using a Milli-Q system was used.

Gel Preparation

A preweighed amount of HPC (1–3% w/w) was slowly dissolved in PG, ethanol, water, or a mixture of these components using a Lightnin mixer at a stirring speed of 300–400 rpm until an optically clear gel was formed. Care was taken to avoid the formation of lumps. Entrapped air was removed by keeping the gel undisturbed or by centrifuging at 1000 rpm for 5 min. The air-free gel was then kept at least 12 hr before any rheological measurements were made. Ethanolic gels were kept tightly sealed to prevent evaporation.

Steady Shear Measurements

The flow curves for HPC gels were determined using a Haake RS100 (Haake, Paramus, NJ) cone-and-plate rheometer at 25°C. Up and down portions of the flow curve were determined using a C20/1 cone (20 mm diameter and 1° cone angle) in the controlled-rate mode, with the shear rate ranging from 0.6 sec⁻¹ to 1000 sec⁻¹ on the up curve and back to 0.6 sec⁻¹ on the down curve. The limits on the shear rates were chosen as they are representative of some typical pharmaceutical operations such as spreading on skin (18), pouring from a bottle, and the like.

Dynamic Mechanical Analysis

The dynamic viscoelastic parameters were determined using a Haake RS 100 cone-and-plate viscometer in the oscillatory mode. The rheometer was equipped with oscillation software (Haake, Paramus, NJ) that was used to process data. Oscillation measurements were conducted in the linear viscoelastic range using a 35-mm cone with a 4° cone angle. The frequency of oscillation was varied over four decades, from 0.00251 Hz to 25.1 Hz. Confirmation of linear viscoelastic behavior was achieved by duplicating results at various stress levels. All the measurements were then conducted at a stress level of 2 Pa, at which all the gels seemed to lie in the region of linear viscoelasticity. A solvent trap was used around the cone to minimize solvent evaporation during experiments.

Data Analysis

Model building and error analysis were performed on Mathcad. Sigmaplot 4.0 was employed to generate ternary contour diagrams.

RESULTS AND DISCUSSION

Effect of Polymer Molecular Weight and Concentration on Apparent Viscosity and Flow Behavior in Single-Solvent Systems

Flow curves were generated for HPC gels of different molecular weights formulated in water, PG, and ethanol using a polymer concentration range of 1–3% w/w. A typical flow curve for a 1.5% (w/w) HPC gel formulated in PG is shown in Fig. 1. All HPC gels formulated are

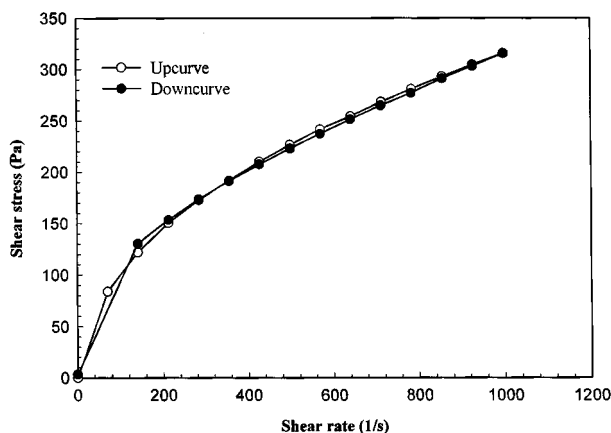


Figure 1. A typical flow curve for a 1.5% (w/w) HPC gel in propylene glycol.

shear thinning and do not exhibit significant yield or hysteresis in their rheograms as the up and down portions of the flow curve overlay. The flow curves for these gels are well described by the Herschel-Bulkley model, in which the shear stress τ is related to the shear rate $d\gamma/dt$ by

$$\tau = \tau_0 + K(d\gamma/dt)^n \quad (1)$$

where τ_0 is the yield stress, n is the non-Newtonian index ($0 < n < 1$), and K is a factor related to the apparent viscosity of the gel.

Figures 2 and 3 show the dependence of the apparent viscosity and non-Newtonian index n on polymer concentration and molecular weight, respectively. For HPC gels in single-solvent systems, the apparent viscosity of the gels is in the order PG > water > ethanol at a given polymer concentration. As expected, the increase in apparent viscosity is observed with increasing molecular weight.

For a given molecular weight, the non-Newtonian index decreases with increasing concentration, suggesting that the gels exhibit a greater degree of shear thinning at higher concentrations. Although not so pronounced at low polymer concentrations (1–1.5% w/w), HPC gels tend to become increasingly non-Newtonian with an increase in molecular weight at higher concentrations. A lower non-Newtonian index can sometimes be desirable as it facilitates processing the gel during manufacture and spreading the gel during application.

Effect of Solvent Composition on the Apparent Viscosity of Hydroxypropylcellulose Gels in Ternary Solvent Systems

The effect of solvent composition on the apparent viscosities of 3% HPC gels in a ternary solvent system at a shear rate of 500 sec^{-1} is shown in Table 1. An empirical relation between excess viscosity and solvent weight fraction based loosely on regular solution theory has been shown to describe the data collected. This relation is given below.

The excess viscosity η^E is defined as

$$\eta^E = \eta - [x_1 \cdot \eta_1 + x_2 \cdot \eta_2 + x_3 \cdot \eta_3] \quad (2)$$

where η is the mixture viscosity, and η_1 , η_2 , and η_3 are the apparent viscosities of HPC in pure solvents, PG, ethanol, and water, respectively. In Eq. 2, x_1 , x_2 , and x_3 are the weight fractions of PG, ethanol, and water, respectively, and η^E is related to the solvent composition via the following relation:

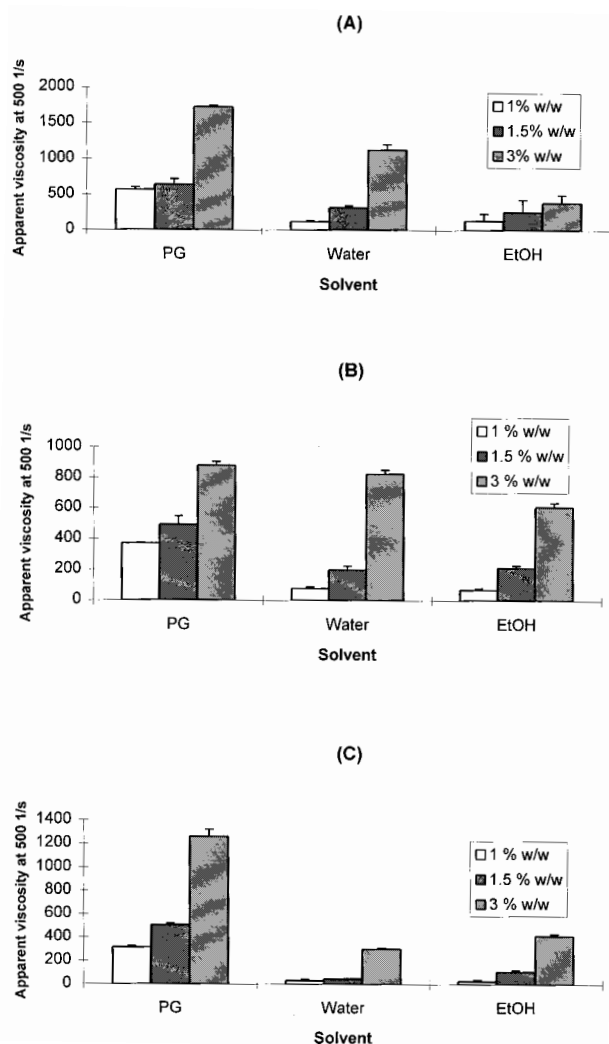


Figure 2. Solvent effect on the apparent viscosity of HPC gels: (A) MW = 370,000; (B) MW = 850,000; (C) MW = 1150,000. Each data point represents the mean \pm SD ($n = 2-3$).

$$\begin{aligned} \eta^E = & 989.7 x_1 x_2 + 1706 x_1 x_3 + 1671 x_2 x_3 \\ & - 18,340 x_1 x_2 x_3 - 95,690 x_1^8 x_2 x_3 \\ & + 18,840 x_1 x_2^8 x_3 - 185,000 x_1 x_2 x_3^8 \end{aligned} \quad (3)$$

Figure 4 shows the agreement between experimental observation and model predictions. Figure 5 shows contours of constant viscosity as predicted by the model in Eq. 3. The model appears to predict the system behavior in a reasonable manner and can therefore be used as a pre-

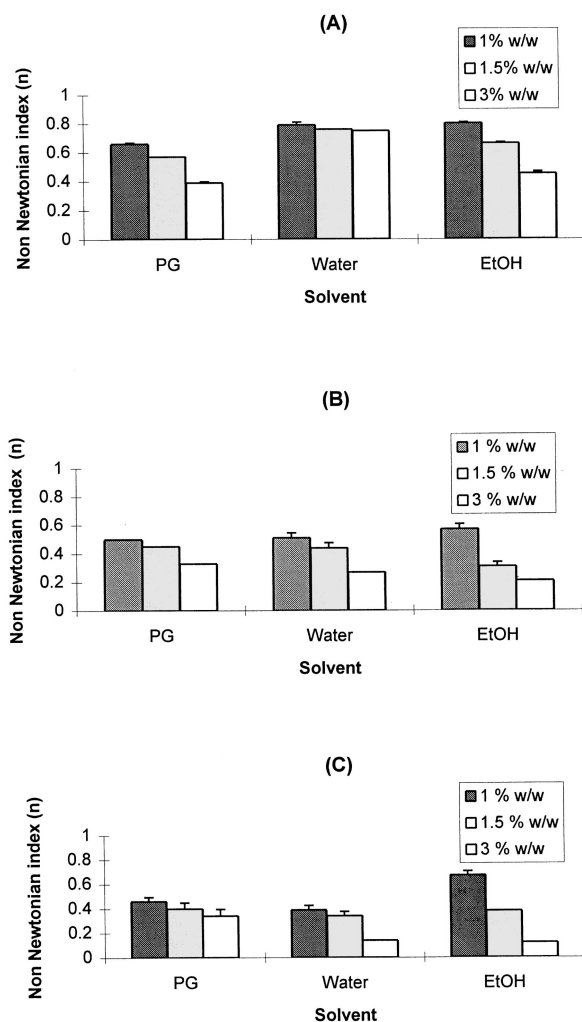


Figure 3. Effect of polymer concentration on the non-Newtonian index of HPC gels: (A) MW = 370,000; (B) MW = 850,000; (C) MW = 1150,000. Each data point represents the mean \pm SD ($n = 2-3$).

dictive relationship to predict viscosities of HPC gels formulated in a solvent mixture of PG, ethanol, and water.

As expected with mixtures of this nature, there is a high degree of dependence on the intermolecular interactions between various solvent molecules, as represented by the product terms and the indices in Eq. 3. This type of empirical relationship has been found to exist in literature and has been explained by the use of four-body, eight-body, and higher-order interactions in aqueous and nonaqueous mixtures (19).

Table 1
Effect of Solvent Composition on the Apparent Viscosity of 3% Hydroxypropylcellulose Gels Formulated in Mixtures of Propylene Glycol, Water, and Ethanol

Formulation Number	Composition (% w/w)			Apparent Viscosity ± SD (CP)
	PG	Ethanol	Water	
1	100	0	0	880 ± 23
2	0	100	0	609 ± 57
3	0	0	100	825 ± 4
4	50	50	0	973 ± 67
5	50	0	50	1278 ± 47
6	0	50	50	1148 ± 101
7	66.6	16.7	16.7	766 ± 32
8	16.7	66.7	16.7	538 ± 22
9	16.7	16.7	66.7	697 ± 11
10	75	12.5	12.5	726 ± 33
11	12.5	75	12.5	402 ± 21
12	12.5	12.5	75	609 ± 4
13	25	37.5	37.5	487 ± 3
14	37.5	25	37.5	611 ± 12
15	37.5	37.5	25	642 ± 7

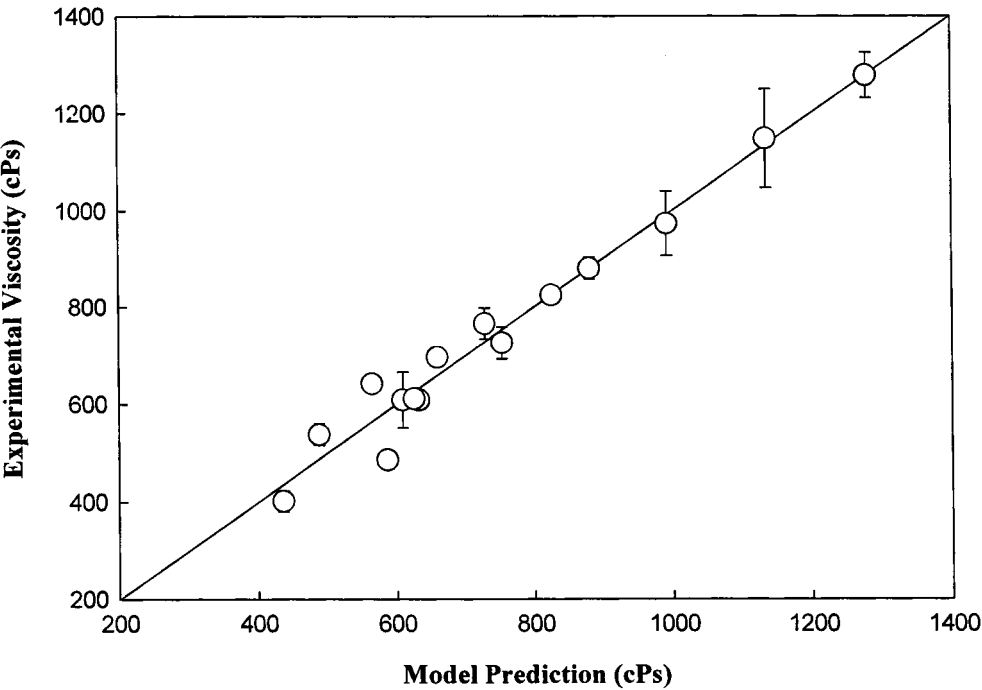


Figure 4. Comparison of calculated versus experimentally observed viscosity.

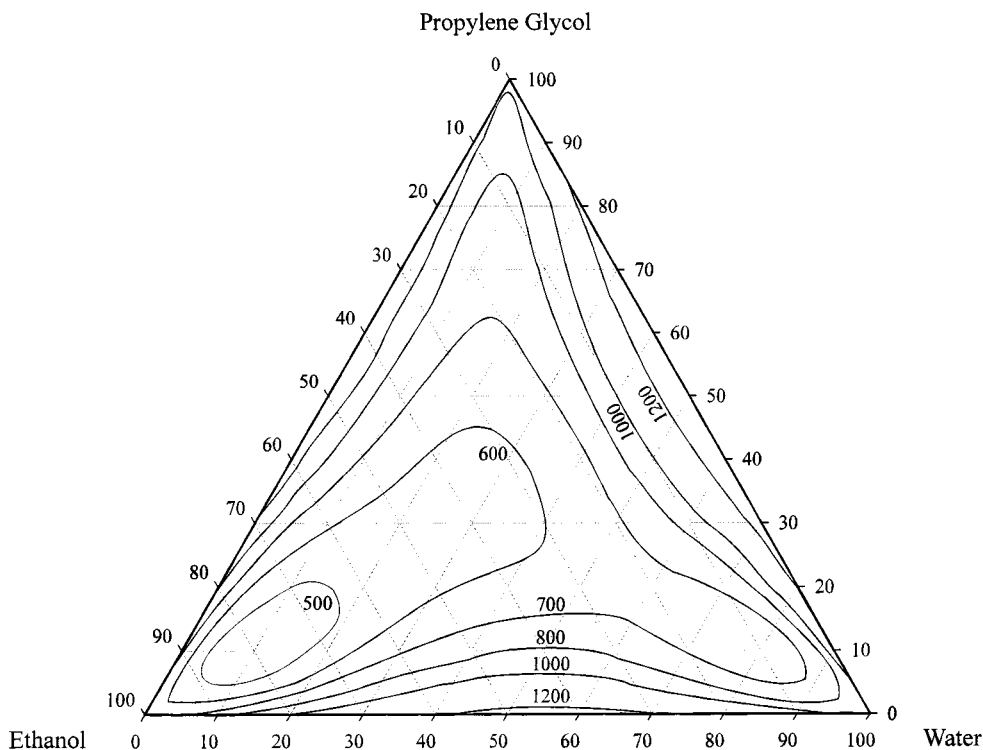


Figure 5. Ternary viscosity contour diagram generated using the model (Eq. 3).

Effect of Solvent Composition on Gel Viscoelasticity in Ternary Solvent Systems

Viscoelastic properties of HPC gels (MW = 850,000, 3% w/w) were investigated by oscillation. In a typical oscillation measurement, the sample is subjected to a sinusoidal strain γ_0 with respect to time t , and the resulting stress σ_0 is measured in terms of a complex modulus G^* that, when resolved into real G' (elastic or storage modulus) and imaginary G'' (viscous or loss modulus) components, gives a complete understanding of the sample's viscoelasticity. The elastic modulus is associated with the energy stored in elastic deformation, while the viscous modulus is associated with the energy associated with viscous dissipation effects. As most polymeric solutions exhibit a certain degree of viscoelasticity, the stress and the strain are not in phase with one another. Therefore, the angle between the stress and the strain vector is defined by a phase angle δ . The interrelationships can be defined as follows:

$$\gamma_0 = \sigma_0 (G' \sin \omega t + G'' \cos \omega t) \quad (4)$$

and

$$\tan(\delta) = G''/G' \quad (5)$$

where ω is the angular frequency in radians per second. The loss tangent $\tan(\delta)$ is a dimensionless parameter that compares the relative importance of the elastic contributions to the viscous contributions in a viscoelastic material.

As an alternative, these relationships can be expressed equally well by a complex viscosity (η^*),

$$\eta^* = \eta' - i\eta'' \quad (6)$$

where

$$\eta' = G''/\omega \text{ and } \eta'' = G'/\omega \quad (7)$$

In the above equation, η' and η'' represent the dynamic and complex viscosities, respectively.

Gels formulated using HPC exhibited linear viscoelastic behavior over the frequency range studied. Figure 6 shows a representative response of the viscoelastic moduli (G' and G'') and viscosities (η' and η'') generated

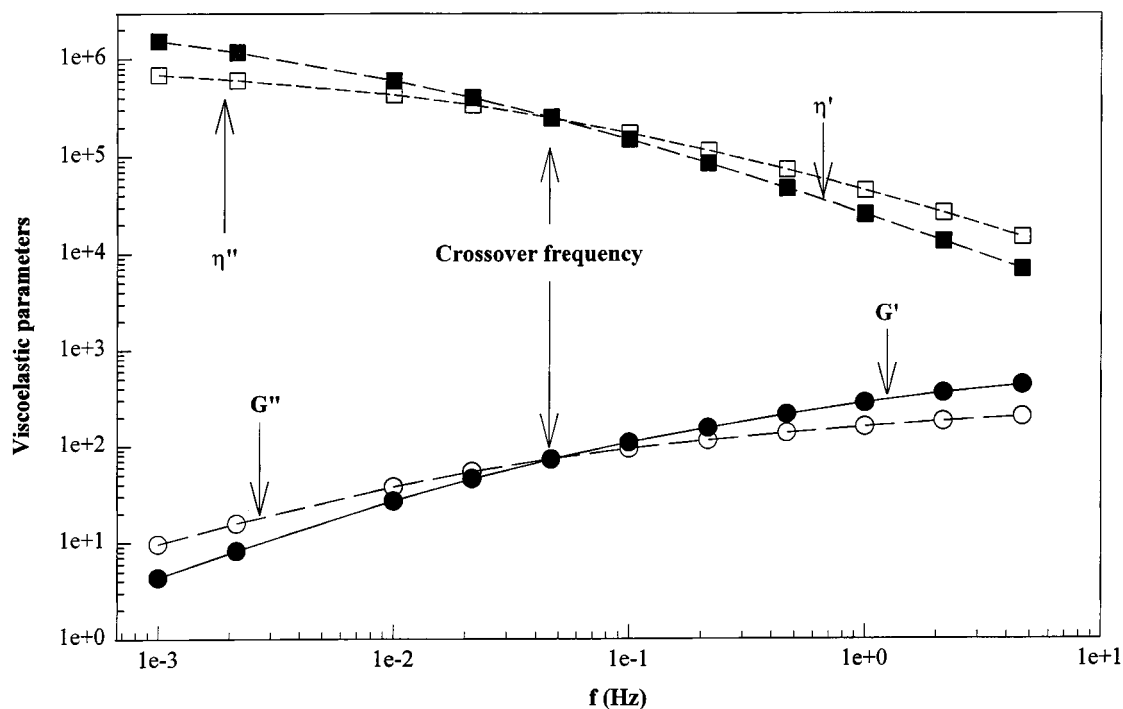


Figure 6. A typical plot illustrating the frequency response of viscoelastic moduli and viscosities for an HPC gel (solvent composition: 75/25 propylene glycol/water).

from oscillation measurements for an HPC gel in PG/water (75:25 w/w). The plots of η' versus frequency are of particular interest as η' should approach η_0 , the residual Newtonian viscosity or zero-shear viscosity, at low frequencies. As observed in Fig. 7, the plot shows a near-plateau region in η' at low frequencies, indicating that the approach to zero shear has been reached at a frequency of 0.00251 Hz. Thus, for all the HPC gels used in this study, it is fair to assume the value of η' at 0.00251 Hz is the zero-shear value for all practical purposes as it becomes extremely difficult and time consuming to probe the material at frequencies lower than 0.00251 Hz.

The effect of frequency on the loss tangent $\tan(\delta)$ is also shown in Fig. 7. It is clear from Figs. 6 and 7 that HPC gels are highly viscoelastic in nature. In other words, they simultaneously exhibit viscous and elastic properties. The loss tangent in Fig. 7 drops continuously with an increase in oscillation frequency, implying that the polymer imparts a certain degree of viscoelasticity to the gel.

As shown in Fig. 6, there is a point on the graphs of moduli and viscosities at which the curves intersect each other. At this point, the elastic and viscous contributions match one another. The frequency corresponding to this

point is defined as the *crossover frequency*. In Fig. 7, this frequency is indicated by the point at which the loss tangent assumes a value of 1. Thus, the crossover frequency provides a good indication of the elastic behavior of a certain material. The lower the crossover value is, the greater is the elastic contribution in the material. It is generally known that the extent of elasticity in a semi-solid preparation is a good indicator of some of the physical properties of the formulation, such as spreadability (20), pourability, processability, and so on. For example, a more-elastic semisolid would tend to roll up rather than to spread when applied to skin. On the other hand, a viscous gel would tend to flow away from the site of action and reduce the availability of the compound at the intended site of action.

Figure 8 is a ternary diagram showing the effect of solvent composition on the crossover frequency of HPC gels. It is apparent that an increase in PG content in the solvent mixture results in decreased values of the crossover frequency. This drop does not exist in ethanol-water systems, suggesting that the increased PG content in the solvent mixture translates into an increased elasticity of the final formulation. In ethanol-rich regions, a small inclusion of PG or ethanol to water could significantly re-

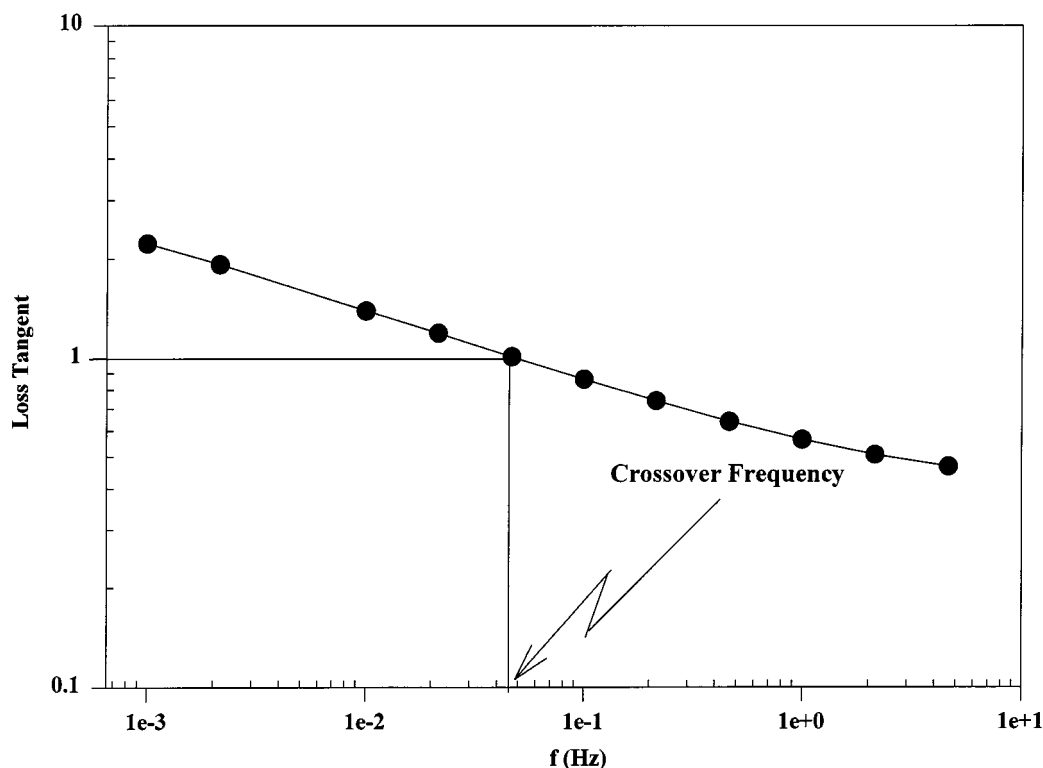


Figure 7. Frequency response of the loss tangent for an HPC gel (solvent composition: 75/25 propylene glycol/water).

duce the elastic nature of the gel. Regions of high elasticity are observed close to ethanol and PG in the ternary diagram.

It is deduced, therefore, that the viscoelastic nature of HPC gels can be varied significantly by adjusting the

solvent composition. The viscoelasticity exhibited by HPC further supports its use as a mucoadhesive polymer in the formulation of gelling systems that prolong drug residence time in the nasal passage (21) for nasal drug delivery or in the precorneal region (22) for ocularly administered drugs. Thus, understanding the viscoelastic characteristics of a polymeric system is critical and could provide the basic framework and insight in the rational design and development of an optimal rheology-based polymeric drug delivery system.

CONCLUSIONS

Hydroxypropylcellulose gels formulated in PG, water, ethanol, or mixtures of these components are shear thinning and do not exhibit hysteresis. As expected, the viscosity increases with increasing molecular weight and concentration. Although not so pronounced at lower polymer concentrations (1–1.5%), HPC gels tend to become increasingly non-Newtonian with increasing molecular weight at higher concentrations. The mathematical model that has been developed for apparent viscosity

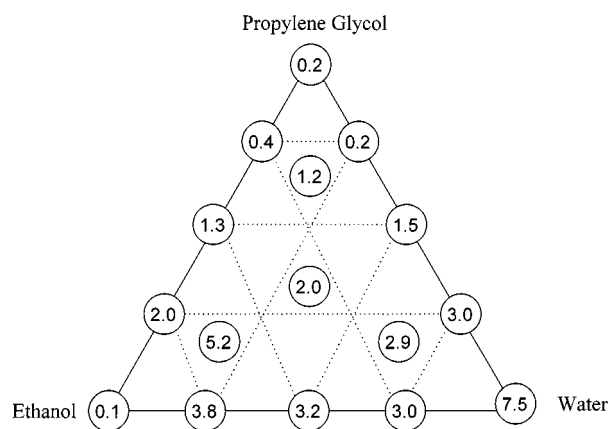


Figure 8. Crossover frequency (rad/sec) for HPC gels in ternary solvent mixtures.

of HPC gels in solvent mixtures of PG, ethanol, and water seems to predict values within experimental bounds reasonably. Increasing PG content in the solvent mixture favors the formation of a more-elastic gel. Although highly desirable from a solubility standpoint for many lipophilic drugs, this property may not be so desirable from a spreadability or processability viewpoint. Thus, a compromise has to be struck between these two properties when optimizing a formula.

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