Viscoelastic Properties of Polyacrylic Acid Gels in Mixed Solvents

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The objective of this study is to investigate the viscoelastic properties of Carbopol 934P polymeric systems in a variety of mixtures of pharmaceutical solvents. Carbopol 934P neutralized with a 1:1 equivalent ratio of triethanolamine was dissolved in various binary or ternary solvent mixtures consisting of propylene glycol, glycerol formal, and water. Dynamic moduli G' and G'', complex viscosities, η' and η'', and loss tangent, $\tan\delta$, were examined over a frequency range of 10^{-3} to 10 Hz using an oscillatory viscoelastic rheometer at 30°C. The results indicated that for 0.5–1.5 wt% neutralized Carbopol in ternary mixtures, G' and G'' increased by 3–4 orders of magnitude and the phase angle decreased from 80 to 25° when the water content in the solvent mixture increased from 10 to 80 wt%. These studies also indicated that the addition of water to nonaqueous Carbopol 934P polymer systems transforms them from low-viscosity solutions to gels with significant elastic behavior involving physical interaction and entanglement of polymer segments with solvents.

INTRODUCTION

The study of the rheological behavior of pharmaceutical formulations containing polymers is necessary to ascertain their stability and underlying structure for quality control during and after their manufacture (1,2). Such studies involved the use of viscoelastic property evaluation of the formulation to test the consistency and durability of ointments or topical suspensions (3–5); in most cases the domains of the drug formulations were limited to solid-like gels or moderately dilute polymeric solutions within a specific solvent. However, it is still not clear how the viscoelastic properties of the formulations are related to phase changes of the polymeric systems induced by changes in solvent composition over a suitable polymeric concentration range. If such patterns of viscoelastic behavior were known, one could effectively understand the dependence of rheological variation on changes in solvent composition.

The objective of the current study is to determine the rheological properties of Carbopol 934P polymeric formulations in mixed solvents consisting of propylene glycol, glyc-erol formal, and water. The viscoelastic analysis is based on the mechanical properties of materials that exhibit both viscous properties of liquids and elastic properties of solids. Oscillatory assessment here is therefore designed not to destroy the underlying structure of such polymeric formulations, so that the viscoelastic measurement can provide useful information on the intermolecular and interparticle interactions within the material. This information is believed important to the study of contemporary development for a mucoadhesive drug delivery formulation using the viscoelastic rheology concepts of polymeric gels to prolong its residence at the application site for improving drug bioavailability (6).

MATERIALS AND METHODS

Materials

Carbopol 934P (B. F. Goodrich Chemical Co., Cleveland, OH), with an average molecular weight of approximately 3,000,000, was used as received. Polymer equivalent weight as determined by potentiometric titration was 76.32 ± 0.80, in agreement with the manufacturer's reported value. Triethanolamine (TEA) was obtained from Sigma Chemical Co. (St. Louis, MO). Propylene glycol (PG) and glycerol formal (GF) were obtained from Fisher Chemical Company. Distilled water (W) filtered using a Milli-Q system was used. The solubility parameter of glycerol formal was estimated to be 8.1 $(cal/cm^3)^{1/2}$ using the enthalpy of vaporization at its boiling point from DSC studies. The literature solubility parameter values of 23.4 and 12.6 $(cal/cm^3)^{1/2}$ for water and propylene glycol, respectively, were reported (7).

Preparation of Polymer Gels or Dispersions

Accurately weighed amounts of Carbopol 934P were added slowly into the vortex of pure solvents or solvent mixtures and stirred at 500 rpm, in tightly capped bottles, overnight, to obtain homogeneous dispersions. If partially wetted polymer lumps remained, the system was not studied. The concentrations of stock dispersions prepared were 1.5% by weight. Lower concentrations of polymer dispersions were prepared by dilution of the stock solutions with appropriate amounts of pure solvents or solvent mixtures. For each concentration of Carbopol, 31 samples with uniformly varying solvent composition were analyzed. The polymer systems were then neutralized by adding TEA at a 1:1 equivalent ratio of TEA:Carbopol and mixing the systems thoroughly. All systems were stored overnight to ensure the maximum dissolution. Entrapped air was removed by centrifuging at 3000 rpm for 15 min. After centrifugation, the gels were allowed to rest for 24 hr before rheological measurement. The final pH of each polymer gel or dispersion was determined using a pH meter (Model 61, Beckman Co., Irvine, CA) at 25°C.

Viscoelastic Measurements

The dynamic moduli of Carbopol dispersions or gels were determined with a Rheo-Tech ViscoElastic Rheometer (Contraves Co., Cincinnati, OH) over a frequency range of

1.0×10^{-3} to 10 Hz at $30.0 \pm 0.5°C$ using a cone and plate measuring system (CC05, 5.0-cm diameter, 1° angle). A major advantage of the cone and plate system is a constant shear rate being applied throughout the sample. To ensure that the Carbopol gels were examined in their linear viscoelastic region, amplitude sweep at a fixed frequency value (0.1 or 1.0 Hz) was first carried out to identify the region in which the complex moduli were independent of stress amplitude. A stress amplitude was selected in the linear region with a strain amplitude of sufficient magnitude above the sensitivity limit of the instrument to ensure a good signal-to-noise ratio. Frequency scans were then obtained with this stress amplitude as applied oscillatory shear stress, σ_0, on the material and measuring the strain response, γ. A thin layer of mineral oil was applied along the edges of the cone and plate device to prevent excessive solvent evaporation especially during low frequency scans.

The dynamic moduli G' (storage modulus) and G'' (loss modulus) and the phase angle, δ, between the stress (σ) and the strain (γ) vector were calculated using a computer program developed by Rheo-Tech Co. In general, the sinusoidal shear stress can be resolved into a component in phase with strain (which defines the storage modulus) and a component 90° out of phase with strain (which defines the loss modulus G''). The angle between the stress and the strain vector is the phase angle, δ. These interrelationships can be defined as follows;

$$\gamma = \sigma_0(G'\sin\omega t + G''\cos\omega t)$$

and

$$\tan\delta = G''/G'$$

where ω is the angular frequency as radians per second.

It is usually convenient to express the sinusoidally varying stress as a complex quantity. Thus the modulus is also complex, given by

$$G^* = G' + iG'' \quad \text{and} \quad |G^*| = \sqrt{G'^2 + G''^2}$$

and yields the information on the ability of the Carbopol 934P dispersions or gels to store elastic energy associated with the recoverable elastic response (as described by storage modulus, G') or to dissipate friction energy associated with the unrecoverable viscous loss (as described by loss modulus, G''). Loss tangent, $\tan\delta$, is a dimensionless measure of the ratio of energy lost to energy stored in a cycle of deformation and provides a comparative parameter that combines both the elastic and viscous contributions to the systems (8).

As an alternative to G^*, the phase relationships can equally well be expressed by a complex viscosity,

$$\eta^* = \eta' - \eta''$$

which is frequently used to describe viscoelastic liquids: η' is the ratio of stress in phase with rate of strain to the rate of strain and η'' is the stress 90° out of phase with the rate of strain divided by the rate of strain. Thus the phase relation-

ships are the opposite of those for G^* and the individual components are related as follows:

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

RESULTS AND DISCUSSION

The changes in dynamic moduli were studied for 0.5–1.5 wt% neutralized Carbopol 934P in binary or ternary solvent mixtures of PG, GF, and water at 30°C over the frequency range of 1.0×10^{-3} to 10 Hz. Figures 1a–f present the contour variation of G' and G'' determined at 10 Hz for Carbopol systems with solvent composition. The results indicate that for all concentrations of Carbopol studied, G' and G'' are extremely low or negligible when the Carbopol system is dispersed in a nonaqueous mixture or in mixtures containing low water contents. However, upon increasing the water content in the solvent mixtures, both the elastic and the viscous moduli of neutralized Carbopol increased dramatically. For example, G' and G'' for 1.5 wt% Carbopol systems increased about 3 to 4 orders of magnitude when the water content increased from 10 to 80% in either binary or ternary solvent mixtures. This suggests that a stiffer viscoelastic gel is obtained when the solvent environment becomes highly aqueous in nature.

Figures 2–5 show plots of the viscoelastic parameters G', G'', $\tan\delta$, and η' for neutralized 1.5 wt% Carbopol 934P systems as a function of frequency in ternary solvent systems defined by the tie-line AW in the phase diagram as shown in Fig. 1a. As shown, with increasing amounts of water in the solvent mixture, both the storage and the loss modulus (Figs. 2 and 3) for neutralized Carbopol 934P gels increased over the frequency range of 10^{-3} to 10 Hz. However, both dynamic moduli change little over the frequency range for the gels, which indicates that the gels show solid-like behavior and are in their plateau region of viscoelastic behavior as reported by Barry and Meyer (9,10). The plateau region is exhibited because of the suppression of long-range configurational rearrangement of the polymer segments by cross-links or entanglements.

Furthermore, from the loss tangent profiles shown in Fig. 4 for neutralized Carbopol systems, the phase angle δ was found to decrease from 80 to 25° upon inclusion of increasing amounts of water in the solvent mixtures. This corresponds to an increase in elastic behavior with increasing water content. It is also elucidated from Fig. 5 that η', the dynamic viscosity, increases with water content. The results for 0.5 and 1.0 wt% Carbopol also show that in ternary mixtures containing 20 to 80 wt% water, G' increased from about 0.01 to 1400 Pa and the phase angle decreased significantly. All the oscillatory data for neutralized Carbopol systems indicate that the addition of water content to nonaqueous Carbopol 934P polymer systems transforms them from low-viscosity solutions to gels with significant elastic behavior involving physical interaction and entanglement of polymer segments within solvents.

It is apparent that the solubility parameter, ϕ, of the solvent mixture and polymer should be a good indicator for the above viscoelastic behavior in different solvent compositions. The correlation of G' with mixture solvent ϕ, calculated based on the volume fraction of solvent blends, shown in Fig. 6 indicates that there is a sharp increase in G' from
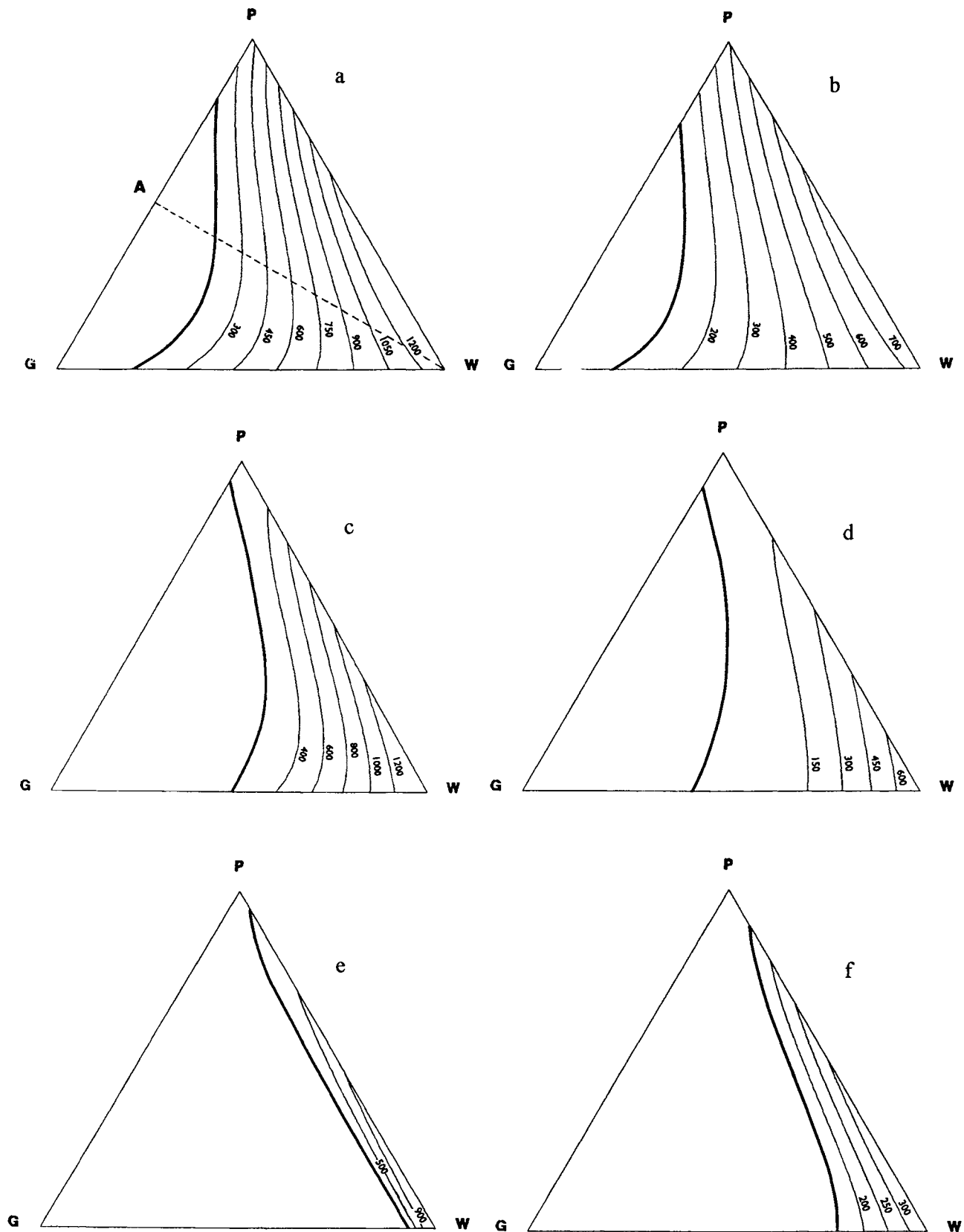
Fig. 1. Contour of storage (G') and loss (G'') modulus as a function of solvent composition for 1:1 equivalent triethanolamine-neutralized Carbopol 934P at 10 Hz and 30°C. P, propylene glycol; G, glycerol formal; W, water. (a) G' for 1.5 wt%; (b) G'' for 1.5 wt%; (c) G' for 1.0 wt%; (d) G'' for 1.0 wt%; (e) G' for 0.5 wt%; (f) G'' for 0.5 wt%.
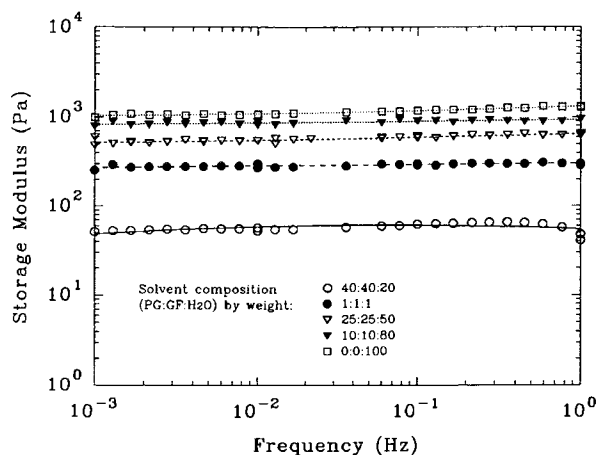
Fig. 2. Storage modulus (G') for 1:1 equivalent triethanolamine-neutralized 1.5 wt% Carbopol 934P in ternary solvents systems at 30°C along the tie line "AW" as indicated in Fig. 1a.

0.01 to 1500 Pa at ϕ about 11 to 13 for 1.5 wt% Carbopol systems and from 0.01 to 1200 Pa at ϕ about 13 to 16 for 1.0 wt% Carbopol systems.

For neutralized Carbopol polymers, viscoelasticity is obviously affected by the degree of entanglement between different polymer chains, which is higher when the polymer chains are in a more extended form. Substances that have nearly the same solubility parameter will be mutually soluble. In a "good" solvent composition with a higher water content, polymer–solvent interactions are favored over the polymer chain–chain interactions, thus polymer chains are well expanded. In a "poor" solvent composition, the intermolecular interactions between the polymer segments are greater than the segment–solvent affinity, and the molecular chains would thus tend to be more contracted, resulting in the formation of uniform suspension particles. Thus, when the solvent composition is varied from poor solvent systems with less water to good solvent systems with more water, the neutralized Carbopol polymer chain is more extended and
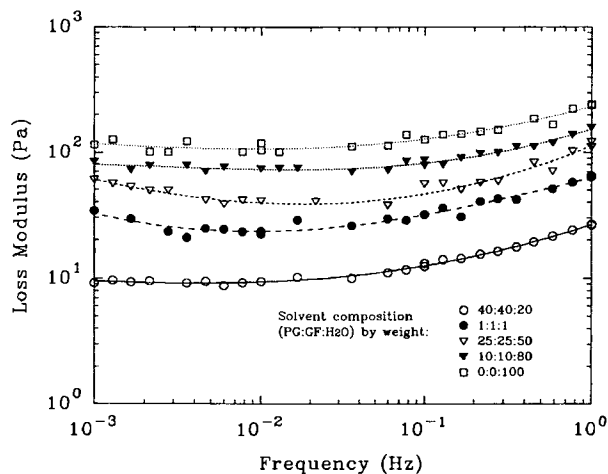

Fig. 4. Loss tangent (tan δ) for 1:1 equivalent triethanolamine-neutralized 1.5 wt% Carbopol 934P in ternary solvents systems at 30°C along the tie line "AW" as indicated in Fig. 1a.
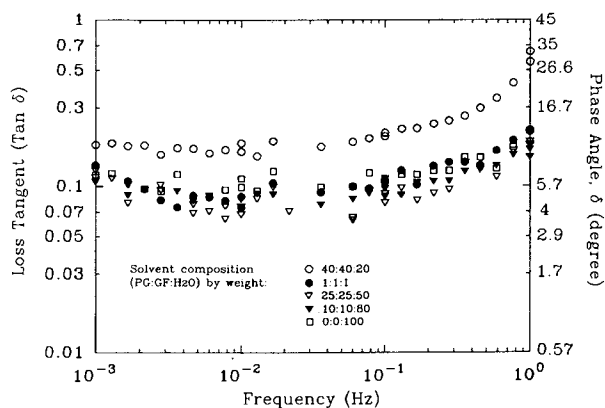

Fig. 5. Dynamic viscosity (η') for 1:1 equivalent triethanolamine-neutralized 1.5 wt% Carbopol 934P in ternary solvents systems at 30°C along the tie line "AW" as indicated in Fig. 1a.
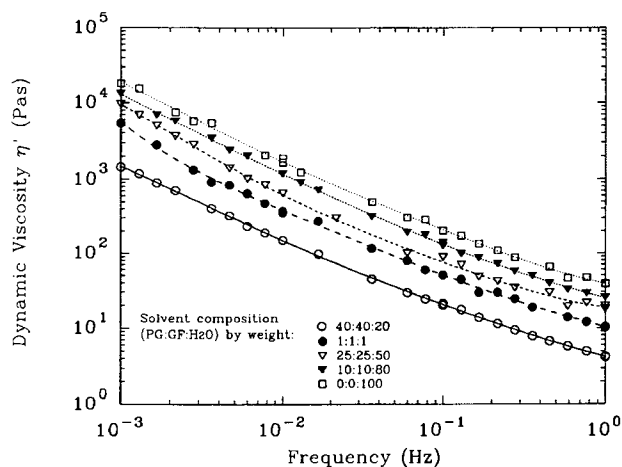

Fig. 3. Loss modulus (G'') for 1:1 equivalent triethanolamine-neutralized 1.5 wt% Carbopol 934P in ternary solvents systems at 30°C along the tie line "AW" as indicated in Fig. 1a.
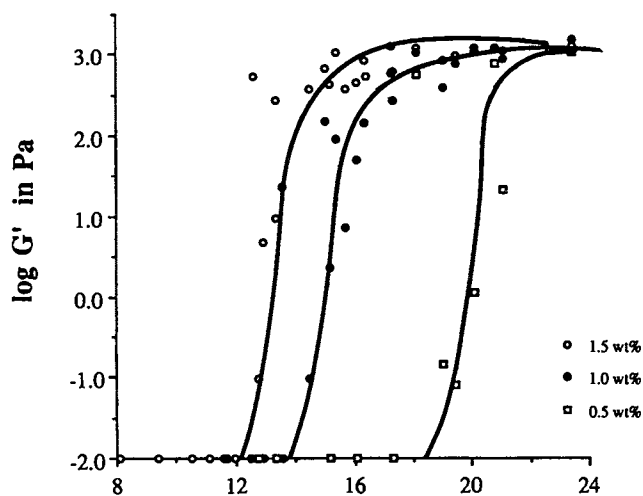

Fig. 6. Correlation of G' with mixed solubility parameter based on the volume fraction of solvent blends.

the viscoelastic behavior of the polymer increases. Further, the fact that at higher concentrations, a solvent mixture with lower ϕ is required to obtain a given viscoelastic behavior (Fig. 6) indicates that the entanglement of the polymer molecules increases as the amount of Carbopol increased.

The viscoelastic behavior of Carbopol 934P in mixed solvents suggests that such dispersions may be useful as mucoadhesive delivery systems to prolong drug residence time at the site of application. Such enhancements in residence times are expected to allow an enhancement in absorption of the drug. Further correlations of viscoelastic properties with in vivo bioavailabilities and residence times studies can then provide the basic framework for the design of optimal drug delivery systems. In light of the tremendous potential usage of the Carbopol polymeric gelling systems to pharmaceutical applications, this information should allow us to optimize its application in the drug delivery applications.

ACKNOWLEDGMENTS

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