

Rheological Characterization of Topical Carbomer Gels Neutralized to Different pH

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Purpose. The primary objective of this study is to perform detailed and extensive rheological characterization of rheology of carbomer (Carbopol) microgels formulated using a solvent system typically used in topical gel formulations. Solvents like glycerin and propylene glycol can alter rheology and drug delivery characteristics of topical gels owing to their different viscosities and due to the change in solvent-polymer and solvent-solvent interactions.

Methods. Aqueous gels with different pH were prepared by dissolving cross-linked Carbopol polymers in a co-solvent system comprising water, propylene glycol, and glycerol and subsequently neutralizing the carboxylic groups of the polymers with triethanolamine (TEA). Oscillatory, steady, and transient shear measurements were performed to measure viscoelastic properties, temperature dependency, yield strength, and thixotropy of carbomer pharmaceutical gels.

Results. The topical pharmaceutical gels exhibit remarkable temperature stability. Flow curves obtained at different temperatures indicate Carbopol microgels show much more pseudoplastic behavior (lower power law index) compared to Carbopol gels dissolved only in water. Substantial yield strength is required to break the microgel network of the topical gels. The gel samples exhibit modest thixotropy at higher deformation rates.

Conclusions. The rheological behavior of the Carbopol microgels do not change appreciably in the pH range 5.0–8.0, and the gels can be used as effective dermatological base for topical applications.

KEY WORDS: Carbopol; constitutive model; microgel; pharmaceutical gel formulation; rheology; thixotropy; topical gel; viscoelasticity; yield stress.

INTRODUCTION

Aqueous polymeric dispersions are used extensively as thickeners in cosmetics and pharmaceutical products to improve their rheological properties (1–3). The cross-linked thickeners can form a networked microgel structure in solutions and are very useful as platforms in drug delivery applications because controlled release of medicaments are possible (4,5). Also, the microgel network can resist the physiological stress caused by body or skin movement and can adopt the shape of the application area (4).

The carbomer microparticles (Carbopol 980 NF) used in this study are acrylic acid polymers cross-linked with polyalkenyl polyethers or divinyl glycol (5). The anionic polymers expand upon neutralization in aqueous medium and form gel

networks. By employing organic amines as neutralizing agents, it is possible to jellify Carbopol particles in many semi-polar liquids or in mixtures of these liquids with water. Compatibility of the polymer with solvents depends on the formation of ion pairs with the amines. Carbomer polymers have a potential wide range of applicability in the pharmaceutical and dermocosmetic fields. Some advantages of using aqueous carbomer gels are i) high viscosity at low concentration, ii) wide viscosity interval and characteristic flow behavior, iii) compatibility with many active ingredients, iv) bioadhesive properties, v) good thermal stability and vi) excellent organoleptic characteristics and good patient acceptance (6–8).

Knowledge of the rheological properties is very important because the microstructural environment or mobility, responsible for drug diffusion and compatibility, can be indirectly probed using these measurements. Extensive study may lead to the possible employment of rheological parameters and models to optimize topical drug delivery from dermatological formulations. Due to their paramount importance, the rheological properties of carbomer gels have extensively been investigated as a function of concentration, pH, and cross-link density (7,9–11). Most of the studies use water as the solvent with a few reports about hydroalcoholic systems. To our knowledge, no study has reported extensive rheological characterization of carbomers in a solvent system typically used in pharmaceutical applications. The choice of solvent(s) is important because solvents like glycerin and propylene glycol can modify hydrogen bonding characteristics between water, solvent, and polymer, thereby affecting the swelling and viscoelastic properties of the polymers (12).

Carbopol is very useful as a major component of drug delivery gel systems for buccal, transdermal, ocular, rectal, and nasal applications (8). The physical properties of the Carbopol gels, the time they remain on the application area, and the drug release rates are extremely sensitive to the rheological behavior of the topical gel formulations. Therefore, exhaustive characterization of the flow behavior of these systems as a function of neutralization and polymer concentration is essential to evaluate the ability of Carbopol polymers to jellify for a range of pH values and their potential uses as dermatological bases (13,14). The aim of the current work was to study the rheological behavior of topical Carbopol gels in the pH range 5.0–8.0.

To obtain information about viscous and elastic behavior as well as microstructure of the topical gels, flow viscometry, oscillatory rheometry, and transient measurements were conducted. Experiments were designed to probe the strength, stability, deformation, and evolution of the microgel networks during a wide range of flow and deformation conditions. The specific objectives are outlined below. First: To measure the linear viscoelastic properties such as elastic modulus (G_N) and zero shear viscosity (η_0) of the Carbopol gels in the co-solvent system. Second: To estimate yield strengths of the materials in terms of stress and strain using a variety of techniques. Third: To construct flow curves for a range of temperatures and to model the temperature dependence of the viscosity. Fourth: To determine whether these topical gels exhibit thixotropy and if so to what extent. Fifth: To determine the applicability of the simple and well-known constitutive models in describing the flow properties of the microgels. All the experimental findings were explained in terms of de-

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formation and evolution of the microstructure of the Carbopol gel dispersions.

MATERIALS AND METHODS

Materials

Some reagents were obtained through generous donation from Pfizer. Carbopol 980 was obtained from Noveon (Cleveland, OH, USA); all other reagents were of analytical grade. Distilled deionized water was used to prepare gels. The triethanolamine (TEA) 98% solution was purchased from Sigma-Aldrich (Milwaukee, WI, USA). Anhydrous glycerol (99.9% purity) was acquired from J. T. Baker (Phillipsburg, NJ, USA), whereas propylene glycol was obtained from Sigma.

Gel Preparation

Appropriate quantity of Carbopol 980 NF was added to deionized water and mixed using Omni Mixer Homogenizer (Model M50). This mixture was agitated at setting 4 for 30 min. Appropriate and preweighed amounts of propylene glycol and glycerol were then added to the mixture and agitated at a setting of 4 for additional 20 min. The dispersion was then allowed to hydrate and swell for 60 min. The pH of the unneutralized sample was then measured to be 3.1. The Carbopol dispersion was then neutralized with 98% TEA until the desired pH value was approximately reached (5.0, 6.0, 8.0). During neutralization, the mixture was stirred gently with a spatula until homogeneous gel was formed. All the samples were allowed to equilibrate for at least 120 h at room temperature prior to performing rheological measurements. The concentrations (weight fractions) of different components as well as the pH values (after 120 h) of the products are given in Table I.

Rheological Measurements

Rheological behavior was evaluated at 25.0°C (unless otherwise mentioned) in Rheometric Scientific ARES and AR2000 rheometers (TA Instruments, New Castle, DE, USA) equipped with Peltier plate temperature control (RTE 130 temperature controller). Two cone and plate fixtures, i) a 25-mm diameter cone with an angle of 2.3° and ii) a 60 mm diameter with 2.0° cone angle, were used to perform the experiments.

Measurements as a function of temperature were performed for a range of 5–75°C at 10°C increments. At high temperatures, water evaporation posed difficulty for measurements for an extended period of time. To help minimize water evaporation, the free surface between cone and plate was coated with low viscosity mineral oil which formed an

occlusive layer. Although this technique reduced water loss, experiments could not be performed for extended periods at temperatures above 60°C. The solvent trap used in conjunction with the 60-mm cone made it possible to perform experiments up to a temperature of 75°C.

Oscillatory shear responses (G' or elastic modulus, and G'' or loss/viscous modulus) were determined at low strains over the frequency range 0.001–100 rad/s. The linearity of viscoelastic properties was verified for all samples.

RESULTS AND DISCUSSION

Low Amplitude Oscillatory Shear Measurements

Figure 1a shows the elastic and loss moduli of sample AQ8 as a function frequency. For all gel systems, G' is higher than G'' indicating that the systems are very elastic. Two factors contribute to the elasticity of the microgel structures. When neutralized with TEA, the swelled microgel particles form a closely packed structure thus forming an elastic network (15,16). Entanglement between the long chain segments and side chains of the neighboring microparticles also help to form the network structure (17).

The plateau elastic moduli (G_N) of the aqueous gels were determined from the value of the storage modulus where the loss moduli exhibit a minimum (18) (Table II). For sample AQ8, the crossover frequency (the frequency at which G' and G'' cross each other) is identified as 0.00158 rad/s from which a longest relaxation time of 3960 s (relaxation time, $\lambda_0 \sim 2\pi/\omega_c$) can be evaluated (18). For other samples, the crossover frequencies could not be accessed within the frequency range for which measurements were conducted. But the longest relaxation times of AQ5 and AQ6 are of the same order of magnitude as for sample AQ8. The longest relaxation time can be viewed as the lifetime of the junction of networks. Once the networks break, this long reorganization period is required for the system to reach equilibrium and form close-packed entangled structure. For 0.5% Carbopol microgels neutralized in solvent water, Barreiro-Iglesis *et al.* (19) reported relaxation times longer than and of the order of 100 s. The increased relaxation times ($\lambda_0 > 1000$ s) of topical formulations are due to the fact that co-solvent glycerin slowed down the rearrangement processes due to its higher viscosity. Also favorable polymer-cosolvent interactions may cause relaxation time to increase.

Flow Curve

The viscosity profiles of two microgel samples are plotted in Fig. 1b along with their complex viscosities evaluated from oscillatory shear experiments. Each curve exhibits a power

Table I. Composition and pH of Different Microgel Samples

Sample	Water % (w/w)	Glycerin % (w/w)	Propylene glycol % (w/w)	TEA % (w/w)	Carbopol 980 NF % (w/w)	pH
AQ5	68.37	1.0	30.0	0.13	0.5	5.1
AQ6	68.5	1.0	30.0	0.5	0.5	6.3
AQ8	67.6	1.0	30.0	0.9	0.5	8.0

TEA, triethanolamine.

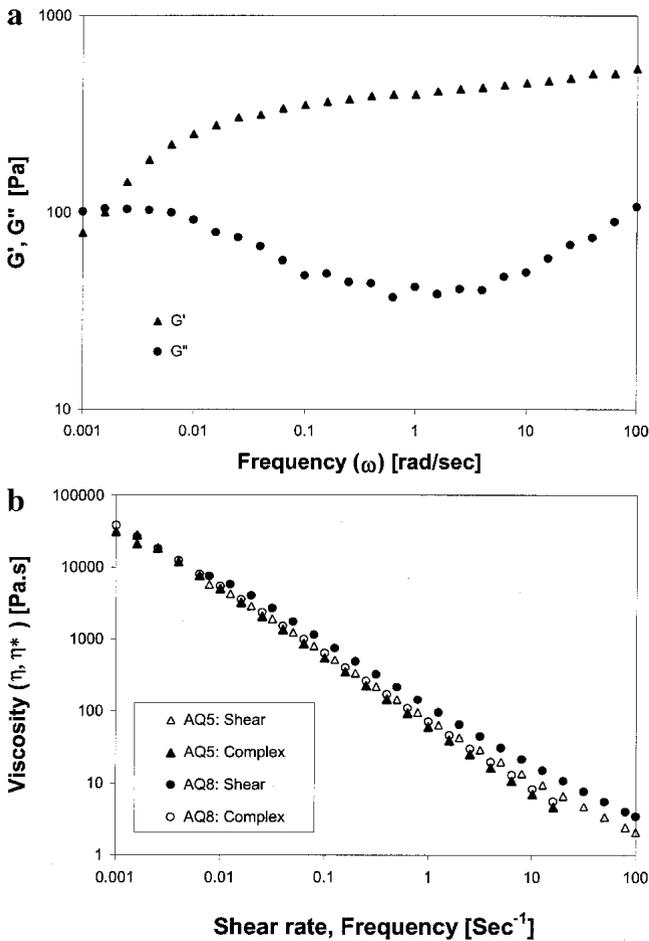


Fig. 1. Frequency-dependent properties of aqueous microgels: (a) storage and loss moduli for sample AQ8; (b) comparison of complex and shear viscosities.

law relationship between viscosity (η) and shear rate ($\dot{\gamma}$). No Newtonian flow regime (i.e., constant viscosity region) has been observed either at higher or lower $\dot{\gamma}$. The absence of a low shear rate plateau can be attributed to the longer relaxation times ($\lambda_0 \sim O <1000>$ s) of the gels. The plateau in viscosity is expected to occur at shear rates lower than 0.001 s^{-1} ($\dot{\gamma} < 1/\lambda_0$) (18), whereas reproducible measurements could be performed down to shear rates of 0.005 s^{-1} . At higher shear rates, Carbopol particles as a whole and polymer chain segments deform and align themselves in the direction of flow, and the topical gels exhibit pseudoplastic behavior.

Comparison of shear and complex viscosities for the gel samples indicates relatively good match between the viscosities at least similar trends can be observed (Fig. 1b). This suggests that the empirical Cox-Merz rule (18,20) can be used with some accuracy where high shear rate measurements of Carbopol dispersions may not be possible due to practical problems such as slip, edge fracture, and other instrument limitations. In general, the Cox-Merz rule holds for simple polymeric fluids but is not reliable for complex structured fluids such as concentrated colloidal dispersions or gels (21). The deviation from the Cox-Merz rule is more apparent at high shear rates where departure from linearity is more. Also the deviation is most for sample AQ8 and least for sample AQ5 suggesting that the associative nature or complexity of

the structure is increases at higher pH. Repulsion between like negative charges at higher pH values causes maximum uncoiling and the dispersions become more closely packed and entangled.

Strain Sweep Tests

Strain sweep experiments were typically performed at constant oscillating frequencies with increased strain from 0.001 to 10. Little differences in the G' and $\tan(\delta)$ [$\tan(\delta) = G''/G'$] profiles of these materials were observed at different constant frequencies (0.01 Hz, 1 Hz, 100 Hz) (Fig. 2a). The observations further substantiates that the gels' responses are elastic in the frequency range 0.01 to 100 Hz.

As evident from Fig. 2a, the complex modulus is dominated by the elastic contribution at low strains. For sample AQ8, up to a strain of about 10%, the loss modulus (G'') is less than 20% of the elastic modulus indicating full elasticity of the system. In this regime, the gel network can be considered as closely packed hard sphere dispersion. At higher strains, the elastic structure breaks down and consequently the elastic modulus decreases steeply with increasing strain (Fig. 2a). A crossover strain (γ_c) can be identified above which the gels behave predominantly as liquid because G'' becomes greater than G' [$\tan(\delta) > 1$]. Because Carbopol concentration is same in all three samples, the breakdown strain is similar ($\gamma_c = 0.8 \pm 0.2$). The collapse of the gel structure at such low strains is indicative of a closer packing of the microgel particles. As indicated by Ketz *et al.* (15), smaller spheres lead to a lower breakdown strain.

Yield Stress Determination

Yield stress can be defined as the minimum stress that must be applied before the material really starts to flow (22). This is an important parameter for topical gels. Yield stress of these materials should be high enough so that they do not flow out of their container due to their own weight if the container is placed in upside down position. It should not be too high to offer significant resistance during application on skin. The cross-linked microgel structure where individual particles are closely packed with their neighbors is responsible for the yield stress. The magnitude of the yield stress is a measure of the strength of the closed-pack structure that must be exceeded for the material to flow appreciably. Four different methods were explored to measure the yield stress of these materials. The most convenient method for determining yield stress is from stress sweep test (21). Figure 2b shows shear stress sweep measurements for sample AQ5. The magnitude of the yield stress is determined from the intersection of the straight lines shown in the figure. The values of the yield stress (τ_0) for the carbomer gel samples determined using this technique are between 28 and 37 Pa (Table II). The yield stresses obtained are much higher than the reported values for TEA neutralized Carbopol gels in water (3). For carbopol concentrations between 0.1% and 2.0%, Kim *et al.* (3) observed the yield stress ranges between 1.59 Pa and 6.0 Pa. However, the values of our τ_0 are comparable to the values reported by Atapattu *et al.* (23) and Nguyen and Boger (24). The authors performed extrapolation of the flow curves at low shear rates ($\dot{\gamma} \approx 0.1 \text{ s}^{-1}$) to zero shear rate to obtain the yield stress values. Using the same method and performing

Table II. Rheological Properties of Aqueous Gels: Linear Viscoelastic and Yield Properties

Sample	Plateau modulus (G_N) (Pa)		Zero shear viscosity (η_0) (Pa·s)	Yield stress (Pa)			
	Frequency sweep	Stress sweep		Shear sweep	Oscillator y sweep	Low shear rate extrapolation	Bingham method
AQ5	345	376	9.5×10^5	28.0	61	52.2	116.8
AQ6	379	423	1.5×10^6	33.3	86	61.4	163.9
AQ8	398	436	*	36.8	89	70.3	187.5

* For this sample, the viscosity did not reach a constant plateau value even at the lowest accessible shear stress.

extrapolation of data points between $\dot{\gamma} = 0.05 \text{ s}^{-1}$ and $\dot{\gamma} = 0.01 \text{ s}^{-1}$ to zero shear rates, we obtained yield stresses that are about 2 times higher than those obtained using shear stress sweep tests (Table II). However, the trend with respect to pH of the gels is similar.

Although unconventional, oscillatory stress sweep tests were also performed on the microgel samples (Fig. 2c) to determine yield stress using the same procedure as in shear sweep tests. The τ_0 values obtained using this procedure are about 2–2.5 times the values from shear stress sweep experiments. Finally, Bingham yield stress (τ_B) was determined using the Bingham equation for shear stress (25): $\tau = \tau_B + \eta_P \dot{\gamma}$. The τ - $\dot{\gamma}$ relationship at highest shear rates ($\dot{\gamma} \approx 19.9$ to 100 s^{-1}) was found to be linear. By extrapolating this linear relationship to zero shear-rate, τ_B was determined as equal to the intercept. As described by other authors (3,21), the magnitudes of yield stress (τ_B) derived using this technique are much higher than those determined from other methods. Our findings summarized in Table II are in agreement with the literature. The salient point is that the τ_B values obtained for our samples (116–188 Pa) are again much higher than those measured by Kim *et al.* (10–66 Pa) (3).

The higher observed yield stress values in the current study is due to the higher solvent viscosity caused by the addition of glycerol and higher attraction forces between dispersed particles due to favorable solvent-polymer interactions. In solvent water it would require much higher carbopol concentration to obtain similar τ_0 .

Zero shear viscosity (η_0) values reported in Table II were also evaluated from the low shear stress plateau values of the viscosity obtained during stress sweep experiments (Fig. 2b). This seems to be the best way to determine η_0 as during shear rate sweep experiments, low shear rate plateau in viscosity could not be observed even at the lowest measurable shear rates.

Temperature Dependence of Viscosity

Steady state viscosities of all the three samples were measured for a temperature range covering 5 to 75°C at 10°C increments. For clarity, the flow curves at only three different temperatures for sample AQ8 are shown in Fig. 3a. It is apparent from Fig. 3a that carbomer gels exhibit remarkable temperature stability. For a particular shear rate, viscosity of these materials do not change appreciably with change in temperature. Weak temperature dependency of carbomer gels is also supported by experimental literature (3,16). The temperature stability or insensitivity can be explained in terms of the elastic or cross-link structure of the microgels.

Thermal fluctuation or increased thermal mobility of the polymer chain strands are suppressed by the cross-link junctions. Therefore viscosity does not change appreciably with temperature.

The flow curves for different temperatures were fitted with Ostwald's model (25): $\tau = K\dot{\gamma}^n$. The fluidity or power law index n in this equation represents departure from Newtonian behavior ($n = 1$ for Newtonian fluids) and is a measure of pseudoplastic or shear thinning extent of the fluid. It can be interpreted as the rate of change of structure with shear rate ($\dot{\gamma}$) (26). The gel network structure can be changed due to deformation induced changes in shapes of the microgel particles, alignment of polymer chain segments, and decrease in the number of entanglements between polymer chain segments and side chains. In accordance with this argument, the values of n will be lower in case of stronger gels due to increased noncovalent forces of attraction between neighboring particles, which increase lifetime of the temporary entanglement junctions.

As shown in Table III, the values of n remain almost constant (0.14–0.16 at 25°C) and independent of the pH of the topical gel formulations. This range for n is much lower than the values reported by Kim *et al.* (3) (0.48–0.62) for Carbopol gels of comparable concentration in water neutralized with TEA. This suggests increased attraction forces between the microgel particles in topical gel formulations due to enhancement in viscosity and hydrogen bonding caused by the addition of co-solvents glycerin and propylene glycol. Our values are also lower but comparable to the n values (0.25–0.40) obtained by Ramirez *et al.* (26) for hydroalcoholic gels, further confirming the viewpoint that co-solvents contribute to the stronger gel formation. Due to higher glycerin viscosity and polymer-cosolvent interactions, the topical gels of the current study form stronger attractions among particles than the hydroalcoholic (30% ethanol) solvent systems used in the work of Ramirez *et al.* (26). For all aqueous gel samples investigated, the fluidity index (n) values decrease slightly at higher temperatures (Table III).

Viscosities at any particular shear rate (e.g., $\dot{\gamma} = 100 \text{ s}^{-1}$) can be used to quantify the temperature dependency of the viscosity using Arrhenius (Arrhenius-Frenkel-Eyring) (27) and WLF (Williams-Landel-Ferry) (18) types of relations and to determine physical processes responsible for the observed changes. The Arrhenius formula assumes the exponential form of temperature dependency (27):

$$\eta = A \exp\left(\frac{E_\gamma}{RT}\right),$$

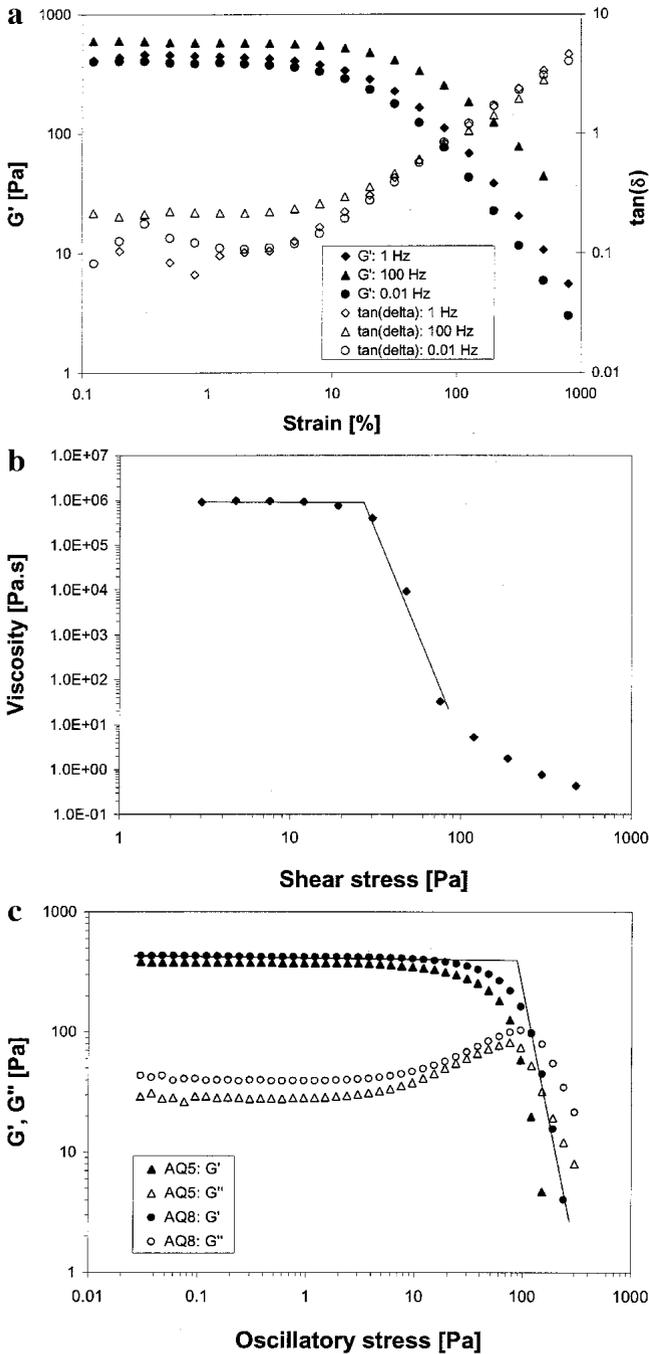


Fig. 2. Sweep experiments of Carbopol gels: (a) oscillatory strain sweep test for sample AQ8 at constant frequencies; (b) stress sweep experiments to measure yield stress of AQ5; (c) determination of yield stress from oscillatory stress sweep measurements.

where E_γ is the activation energy of the flow process at constant shear rate, A is the pre-exponential factor, T is the absolute temperature, and R is the gas constant.

On the other hand, the WLF equation is based on the free volume concept, and the change in viscosity is modeled according to the empirical relation (18):

$$\log(a_T) \equiv \log\left(\frac{\eta}{\eta_0}\right) = \frac{-C_1(T - T_0)}{C_2 + T - T_0},$$

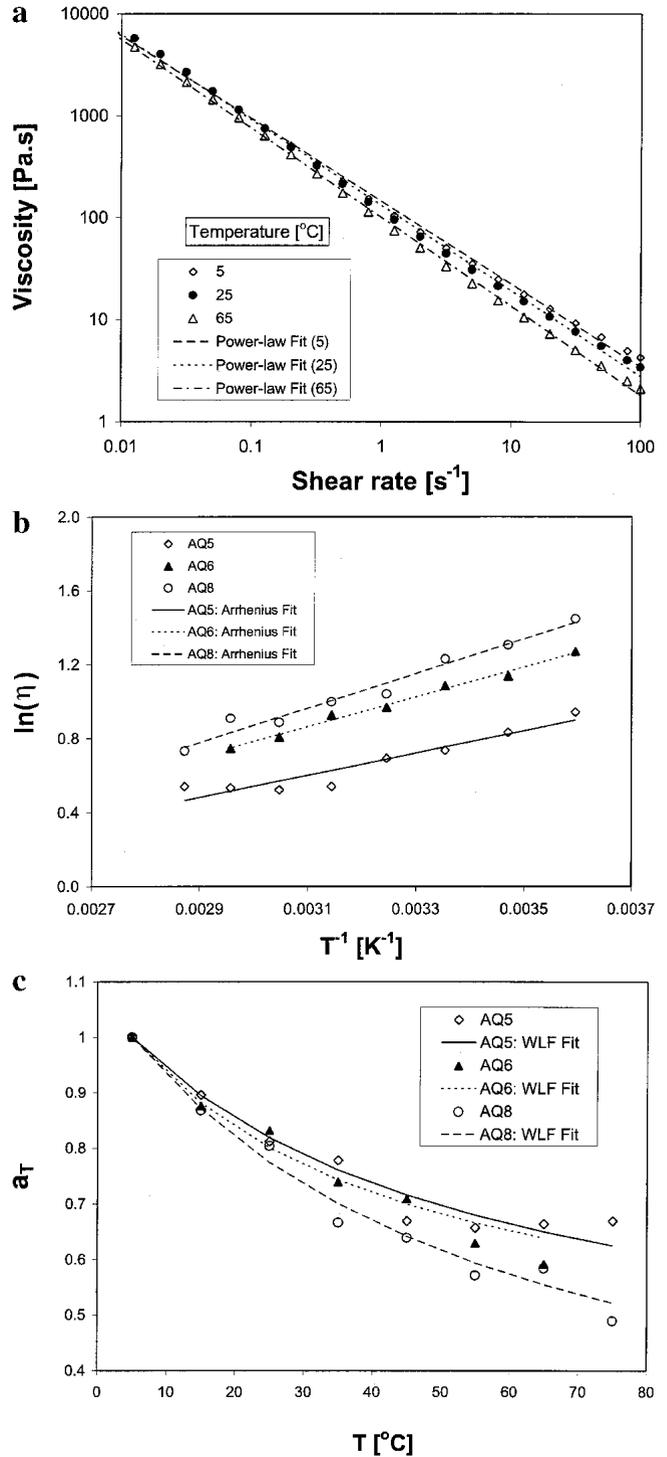


Fig. 3. Temperature dependency of aqueous microgels: (a) steady shear viscosity of AQ8 as a function of shear rate at different temperatures; (b) modeling of the viscosities of gel samples at 100 s^{-1} using Arrhenius equation; (c) modeling of shift factors with Williams-Landel-Ferry (WLF) formalism.

where a_T is the temperature dependence shift factor defined here as the ratio of viscosity (η) at temperature T to that of a viscosity (η_0) at a reference temperature T_0 , and C_1 and C_2 are constants.

Figures 3b and 3c show the Arrhenius and WLF model-

Table III. Rheological Properties of Aqueous Gels: Thermorheological Properties

Sample	Power law index (n)			Consistency (K) (Pa·s ⁿ)			Correlation coefficient		Activation energy (E _a) (kJ/mol)
	5°C	25°C	65°C	5°C	25°C	65°C	WLF	Arrhenius	
AQ5	0.17	0.14	0.11	93.0	87.7	85.7	0.9837	0.8987	4.99
AQ6	0.18	0.16	0.13	124.2	116.6	100.2	0.9513	0.9900	6.70
AQ8	0.19	0.16	0.13	144.0	131.4	100.1	0.9732	0.9703	7.77

WLF, Williams-Landel-Ferry.

ing of the experimental data for the three microgel samples. The correlation coefficient (R^2) values are tabulated in Table III. It can be inferred from Figs. 3b and 3c as well as Table III that the temperature dependence of shear viscosity of these aqueous gels can be explained equally well by the Arrhenius and WLF relations.

From Fig. 3b, the activation energies (E_a) of AQ5, AQ6, and AQ8 samples were estimated to be 4.99, 6.70, and 7.77 kJ/mol, respectively (Table III). The increase in activation energy with increasing pH is in accordance with the findings of Fresno Contreras *et al.* (28) and Ramirez *et al.* (29). However, the activation energies of our samples are higher than the values obtained by the authors for same Carbopol concentration (0.5%): 0.98–2.34 kJ/mol (29) and 1.49–3.02 kJ/mol (28). The higher values of E_a of our samples can be explained in terms of an increase in the polymer chain rigidity and intermolecular forces of attraction in the co-solvent system composed of water, propylene glycol, and glycerol. The same argument can be used to explain the increase in E_a with increasing pH.

Thixotropy Determination

In dispersed systems, thixotropy arises when shear stress (viscosity) values measured by progressively increasing the shear rate are higher from those measured when one progressively decreases it (26). Thixotropy is a kind of viscoelasticity that has a very long relaxation time caused by flow induced changes in structure that are generally erased after hours of quiescence (21). With relaxation times of the order of an hour (for AQ8, $\lambda_0 \sim 2\pi/\omega_c \sim 3960$ s), the topical gels are good candidates for investigating thixotropy. In general, thixotropy has two main components: the shear thinning effect and the time dependence of viscosity (26).

Figure 4a confirms that the topical gels show thixotropy only at very high shear rates. However, the amount of thixotropy is very low as evidenced by the proximity of the curves, although it has to be noted that at such high shear rates, measurements become difficult and less reliable due to edge fracture and/or sample expulsion owing to high centrifugal forces. When the topical gels experience high shear rates, the network structure between neighboring microgel particles as well as the entanglements between long polymer chain segments break down. Therefore, the shear stresses or viscosities in decreasing shear rate curve are lower. The lower curve represents apparent shear stresses or viscosities of a long-lived metastable state induced by the highest shear rate in the samples recent past (21).

Transient Experiments

Start-up of steady shear experiments were performed to probe the time dependence of viscosity, which contributes to

the thixotropy of the particulate dispersions. Once shear is applied to the samples, the gel network breaks down and re-forms again because of shear-induced collisions. After some time, a steady-state will be attained when a dynamic equilibrium is reached between the process of breakdown and re-formation of interparticle bonds, which depends on thermal motion and shear rate (26). For a thixotropic particulate gel, the recovery takes longer, and initially an overshoot in viscosity is observed. For the topical microgels, an overshoot in the shear stress or apparent viscosity is observed only at high shear rates as shown in Fig. 4b. However, in all cases and up to a shear rate of 200 s^{-1} , the ratio of the steady-state viscosity to the maximum viscosity was above 0.9 indicating no significant thixotropic behavior. Therefore, it can be in-

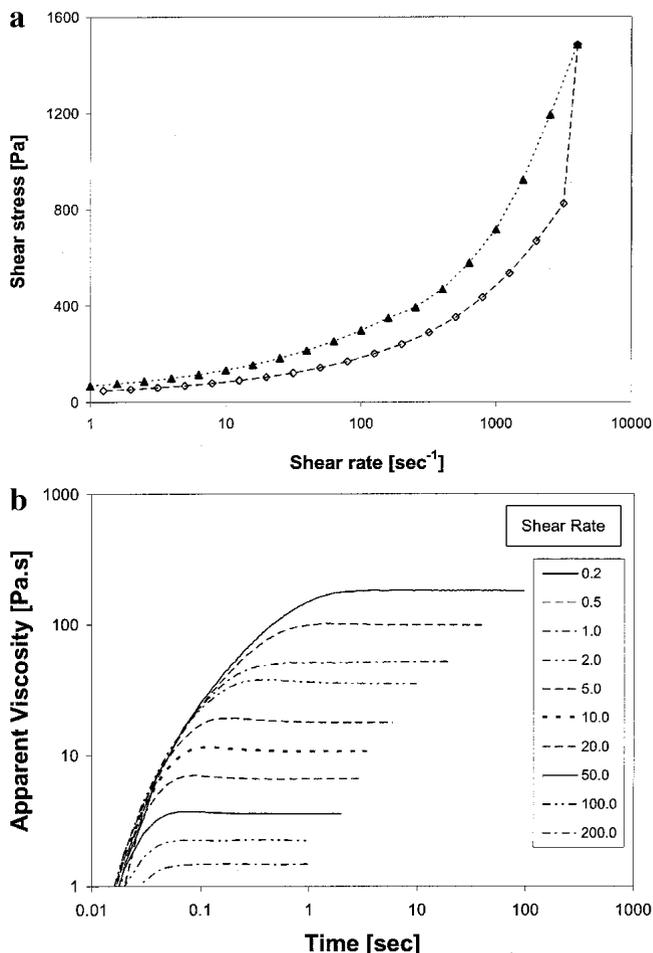


Fig. 4. Determination of thixotropy: (a) thixotropic loop of shear stress vs. shear rate for AQ8; (b) transient viscosities of AQ6 during start-up of steady shear.

ferred that the co-solvents propylene glycol and glycerin do not induce significant thixotropy to the aqueous dispersions.

The start-up of steady shear experiments was also used to determine the approach time for reaching steady-state. These times were subsequently used during steady shear measurements to identify the steady-states. This is very important because approach time to steady-state is a strong function of shear rate.

Flow Curve Modeling

The flow behavior of the aqueous microgels is compared with the predictions of some well-known constitutive models to determine their validity. Figure 3a clearly indicates a power law relationship between viscosity (η) and shear rate ($\dot{\gamma}$), at least for a range of shear rates, which is the prediction of Ostwald's model: $\tau = K_o \dot{\gamma}^n$ [here, τ is the shear stress, K_o is the consistency ($\text{Pa}\cdot\text{s}^n$), and n is the power law or fluidity index] (25). From the viscosity (η) against shear rate ($\dot{\gamma}$) plot at 25°C, the magnitude of n can be estimated to be 0.14–0.16 ($\eta_{\text{app}} = \tau/\dot{\gamma} = K_o \dot{\gamma}^{n-1}$). However, the Ostwald model assumes no yield stress, which is not certainly the case for these topical gels. Among the constitutive models that explicitly include yield stress, Bingham model (25) [$\tau = \tau_B + \eta_P \dot{\gamma}$] can be ruled out as it assumes a linear relationship between τ and $\dot{\gamma}$ (i.e., $\eta_{\text{app}} \approx \tau/\dot{\gamma} \approx \text{constant}$). For the same reason, Casson model (25) [$\tau^{0.5} = \tau_0^{0.5} + \eta^{0.5} \dot{\gamma}^{0.5}$] is also not appropriate as this model assumes the fluidity exponent to be a constant equal to "0.5." The Hershel-Berkley model (25) seems to be the one that most closely resembles the flow behavior of the topical gels: $\tau = \tau_0 + K \dot{\gamma}^n$, where τ is the shear stress, τ_0 represents yield stress, K is the consistency ($\text{Pa}\cdot\text{s}^n$), and n is the power law or fluidity index.

However, modeling the data using Fig. 3a can sometimes be misleading because of the log-log scale used to cover the entire range. In these plots, experimental data points and fitted lines appear closer. A more revealing plot between shear stress and shear rate as shown in Fig. 5 underlines the limitations of all the simple models. Clearly, the match is not

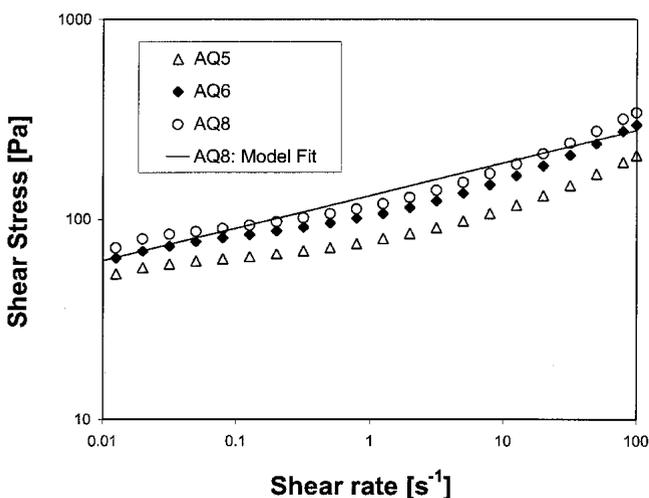


Fig. 5. Flow curves of the gel samples plotted as shear stress against shear rate. It is obvious from the trends in the data that a single straight line is inadequate to fit the data for the entire shear rate range. A sample best fit line for AQ8 is plotted beside the experimental data to demonstrate the point.

as good as it appeared in the flow curve (Fig. 3a). It is readily apparent that at least two regions with different power-law exponents can be identified. Hence, it can be concluded that a constitutive model with yield stress (τ_0) and single fluidity index (n) is inadequate to model the entire flow curves of the topical gels.

CONCLUSIONS

All the Carbopol gel samples show viscoelasticity with long relaxation times and substantial plateau moduli (345–435 Pa). In general, the viscoelasticity increases with increasing pH but the change is not significant. The topical gels exhibit remarkable temperature stability. Flow curves obtained at different temperatures indicate Carbopol microgels show significant pseudoplastic behavior with a power law exponent ranging from 0.10 to 0.20, which is substantially lower from literature reported values of 0.48–0.68 for Carbopol gels in water (3) and 0.25–0.40 for Carbopol gels in hydroalcoholic solvent system (26). The enhanced non-Newtonian trends in topical formulations can be attributed to the increased solvent-solvent and polymer-solvent attractions and higher viscosity of co-solvent glycerol. The index n decreases slightly at higher temperatures, from 0.17 to 0.19 at 5°C to 0.11 to 0.13 at 65°C. The temperature dependency of the gels can be explained equally well by Arrhenius and WLF models. Several rheological techniques confirm that substantial amounts of stress greater than the yield values of the topical gels are required before the topical gels can start to flow. The yield stress values depend on the method used and range from 28 Pa to 188 Pa. In terms of strain, the required values to break the gel networks are within $80 \pm 20\%$. The pharmaceutical gel samples exhibit thixotropy but only at higher deformation rates. However, the amount of thixotropy is not significant, suggesting stability of gels at high shear rates comparable to those experienced in physiological processes when gels are applied over skin. Comparisons of the flow curves were performed with the simple well-known constitutive models to determine their applicability. The three-parameter Hershel-Berkley model better describes the experimental flow curves, although a single fluidity index is inadequate to describe the flow behavior in the entire regime. The viscoelastic nature of Carbopol dispersions with substantial yield strength suggests that such aqueous gels may be useful as topical and mucoadhesive delivery systems. The long relaxation time, remarkable temperature stability, and low thixotropy of the gels make them amenable in delivery systems requiring prolonged drug residence time with enhanced absorption at the application areas. The rheological parameters can be used along with other studies such as bioavailability and residence time of drugs to construct a framework for designing optimal drug delivery systems.

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