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Research Paper

Viscoelastic Properties of Carbopol 940 Gels and Their Relationships to Piroxicam Diffusion Coefficients in Gel Bases

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Purpose. This study was conducted to determine the effect of formula compositions on viscoelastic properties of piroxicam gels using Carbopol 940 as a gelling agent and to determine the relationships between viscoelastic properties of Carbopol 940 gel bases and diffusion coefficients of piroxicam in gel bases.
Methods. Piroxicam gels (1.0% w/w) were prepared by using Carbopol 940 as a gelling agent and varying Carbopol 940 concentrations, glycerin, and sodium chloride contents. The *in vitro* release of piroxicam from gel bases to the receiving media, isotonic phosphate buffer solution (pH 7.4), were carried out using Franz-modified cell. The piroxicam diffusion coefficients were obtained by Higuchi's equation. Rheological property measurements of gel samples were performed via a cone and plate fluid rheometer. Relationships between viscoelastic properties of gel samples and piroxicam diffusion in gel bases were analyzed by Pearson's test at a p value of less than 0.05.
Results. All piroxicam gels exhibited predominantly elastic solid behavior whose magnitude depended on Carbopol 940 concentration. Preparations containing good solvent exhibited more elastic solid characters. In contrast, the piroxicam gels containing higher sodium chloride contents possessed more viscous fluid behavior. Analyzed by Pearson's test at a p value of less than 0.05, piroxicam diffusion coefficients were directly proportional to loss tangent, but were inversely proportional to storage modulus, loss modulus, complex modulus, and viscosity.
Conclusions. There is a potential for predicting drug diffusion coefficients from their correlations to rheological parameters. This could be beneficial to the formulation design of transdermal drug delivery systems including mucoadhesive drug delivery systems.

KEY WORDS: Carbopol 940; diffusion coefficients; piroxicam; rheology; viscoelastic.

INTRODUCTION

Viscoelasticity is a mechanical property of materials that possess a combined behavior of elastic solid and viscous fluid. These materials include melt polymers, food, and pharmaceutical semisolid dosage forms such as cream, ointment, and gels. One of the accepted techniques in investigating viscoelastic behaviors of materials is "dynamic mechanical testing," which is based on the fundamentally different responses of viscous and elastic elements to a sinusoidally varying stress or strain.

Sinusoidal shear stress (τ) can be resolved into a component in phase with strain, γ (which defines the storage modulus, G'), and a component 90° out of phase with strain (which defines the loss modulus, G''). The angle between the stress and strain vector is the phase angle, δ (1). These interrelationships can be defined as

$$\gamma = \tau(G' \sin \omega t + G'' \cos \omega t) \tag{1}$$

$$\tan \delta = G''/G'' \tag{2}$$

where ω is the angular frequency (rad/s). It usually expresses the sinusoidally varying stress as a complex quantity. The modulus is also complex, given by

$$G^* = G' + iG'' \text{ and } |G^*| = \left(G'^2 + G''^2\right)^{1/2} \tag{3}$$

Viscoelastic properties of pharmaceutical semisolid dosage forms affect the physical appearance of preparations that may influence patient or consumer perceptions (2). Viscoelastic properties also affect the contact times of an ophthalmic gel that are related to bioavailability and therapeutic efficacy of the preparations (3). Semenzato *et al.* (4) found that the viscoelastic properties of vitamin A palmitate emulsion were related to their chemical and physical stability. In addition, Bonferoni *et al.* (5) pointed

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out that there were relationships between drug release from gel matrices by a mechanism of gel erosion and viscoelastic properties.

Carbopol, a synthetic polymer, has been often used recently as a component of drug delivery systems. As its rheological properties are usually explored by a technique of continuous shear, which can deform the gel structure, the obtained data do not really represent the intact gel structure.

Many researchers have tried to investigate the effect of viscosity obtained by continuous shear methods on drug release (6–8). Some of them found inverse relationships between viscosity of preparations and diffusion coefficients of diffusant consistent with the Stoke–Einstein equation

$$D = k_B T / 6\P\eta R \quad (4)$$

where D is the diffusion coefficient, k_B is Boltzmann's constant, T is the absolute temperature, η is the viscosity of solvent, and R is the radius of diffusant (9). Because viscoelastic properties are more related to the intact structure of products than the viscosity, the correlation of viscoelastic properties to release characteristics of a drug should be more accurate.

In this study, rheological properties of gel preparations using Carbopol 940 as a gelling agent were determined by methods of continuous shear and dynamic shear. Piroxicam was used as a model to study drug release.

This study was conducted (1) to determine the effect of formula compositions on viscoelastic properties of piroxicam gels using Carbopol 940 as a gelling agent and (2) to determine the relationship between viscoelastic properties of Carbopol 940 gel bases and diffusion coefficients of piroxicam in gel bases.

MATERIALS AND METHODS

Materials

Carbopol 940 (Goodrich Co., Ltd., Cleveland, OH, USA), piroxicam, sodium chloride (NaCl; Merck, Darmstadt, Germany), disodium hydrogen phosphate (APS Finechem, Sydney, Australia), and potassium dihydrogen phosphate (Carlo Erba, Milan, Italy) were purchased from Tong Chemical Co., Ltd. Glycerin, propylene glycol (PG), triethanolamine (TEA), methyl paraben (MP), and propyl paraben (PP) and cellulose dialysis tubing with a molecular weight cutoff of 12,000 (Sigma, St. Louis, MO, USA) were obtained from Srichand United Dispensing Co., Ltd.; (Bangkok, Thailand) and Sac-science Co., Ltd., (Bangkok, Thailand); respectively.

Preparations of 1.0% w/w Piroxicam Gel

An accurately weighed amount of Carbopol 940 (0.4, 0.6, and 1.0 g) was dispersed in an appropriate amount of water with continuous stirring using porcelain mortar and pestle until uniform consistency was achieved. An accurate amount of TEA at a 2 mL:1 g ratio of TEA/Carbopol 940 was slowly added to the dispersion with continuous stirring thus resulting in a stiff gel. The piroxicam solution prepared by dispersing 1 g of piroxicam powder in a mixture of 10 mL of PG, a portion of water, 1 mL of paraben concentrate, 2 mL of TEA, glycerin (5.0, 10.0, and 15.0 mL in the case of C.6/G5, C.6/G10, and C.6/G15, respectively), and sodium chloride (0.09, 0.9 g in the case of C.6/S.09, C1/S.09 and C.6/S.9, C1/S.9, respectively) (Table 1) was incorporated to the Carbopol 940 gel base, and the mixture was stirred continuously until it was homogeneous. Purified water was added to attain the total weight of 100 g with continuous stirring. The gel was stored in an airtight glass jar wrapped with aluminum foil to protect it from light. Their pH values were slightly basic to provide a complete dissolution of piroxicam (in the range of 7.98–8.11).

All gels were analyzed spectrophotometrically in triplicate for piroxicam content using a wavelength of 355 nm and having 20.0% v/v PG in isotonic phosphate buffer, pH 7.4 [the composition of pH 7.4 isotonic phosphate buffer is shown in (9)], as a blank. Only samples with a piroxicam content of within 100 ± 10% of the labeled amount were accepted.

Samples were taken within 14 days after they were prepared to avoid the aging time effect.

Rheological Property Measurements

Measurements were performed via a fluid rheometer Model ARES (Rheometric Scientific Inc.) using the cone and plate geometry with a cone angle of 0.04 rad and a diameter of 25 mm. The gap range was 0.051 ± 0.001 mm. The determination of the rheological characteristics of all samples was performed by applying about 0.5 g of the samples to the lower plate of the rheometer. The gap between cone and plate was adjusted to 0.051 ± 0.001 mm. A thin layer of silicone oil was applied along the edges of the cone and plate device to prevent excessive solvent evaporation especially

Table I. 1.0% w/w Piroxicam Gel Formulae

Formula	Piroxicam (g)	Carbopol 940 (g)	Paraben conc. (mL)	PG (mL)	NaCl (g)	Glycerin (mL)	TEA (mL)
C.4	1.0	0.4	1.0	10.0	–	–	2.8
C.6	1.0	0.6	1.0	10.0	–	–	3.2
C.6/S.09	1.0	0.6	1.0	10.0	0.09	–	3.2
C.6/S.9	1.0	0.6	1.0	10.0	0.9	–	3.2
C.6/G5	1.0	0.6	1.0	10.0	–	5.0	3.2
C.6/G10	1.0	0.6	1.0	10.0	–	10.0	3.2
C.6/G15	1.0	0.6	1.0	10.0	–	15.0	3.2
C1	1.0	1.0	1.0	10.0	–	–	4.0
C1/S.09	1.0	1.0	1.0	10.0	0.09	–	4.0
C1/S.9	1.0	1.0	1.0	10.0	0.9	–	4.0

during low-frequency scans. Rheological properties of all samples were measured in triplicate.

Dynamic Strain Sweep Test

The experiments were carried out at a frequency of 1.0 rad/s at 27 ± 1°C. The initial and final strain values were set at 0.05 and 500%, respectively.

Dynamic Frequency Sweep Test

The measurements were performed at 27 ± 1°C for the study of formula composition effects and at 33 ± 1°C for the study of relationship between viscoelastic properties of gel bases and piroxicam diffusion. The initial and final frequencies were set at 100 and 0.1 rad/s, respectively. The value of strain used was chosen to be within the linear viscoelastic regime.

Steady Rate Sweep Test

The experiments were carried out at 33 ± 1°C for the study of relationship between rheological properties of gel bases and piroxicam diffusion. The initial and final shear rates were set at 0.05 and 100 s^{-1}, respectively.

Piroxicam Diffusion Coefficient Determination

A semipermeable cellulose membrane with a molecular weight cutoff of 12,000 was soaked overnight in isotonic phosphate buffer solution (pH 7.4). The membrane was placed between the donor and receptor units of a modified Franz diffusion cell. The receptor part was filled with isotonic phosphate buffer solution (pH 7.4) maintained at 37 ± 1°C. The system was equilibrated for 30 min. Then, about 5 g of the gel preparation was placed over the membrane in the donor part. An accurate amount of the receiving solution was withdrawn at 15, 30, 60, 90, 120, 150, and 180 min, respectively. The volume of the receiving solution was maintained by replacing the amount withdrawn with an equal volume of isotonic phosphate buffer solution (pH 7.4). The receiving solution was kept well stirred with a magnetic stirrer throughout the time of diffusion studies. All piroxicam diffusion studies were carried out in triplicate. The receiving solution withdrawn was analyzed spectrophotometrically at a wavelength of 355 nm. Diffusion coefficients were calculated from the slope of cumulative amount released *vs.* square root of time plot.

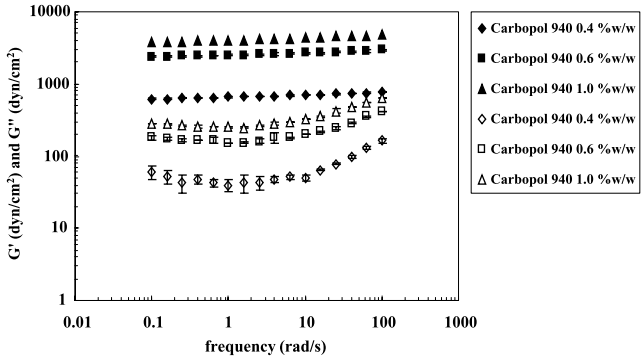

Fig. 1. Double logarithmic plot of storage modulus (filled symbol) and loss modulus (unfilled symbol) against frequency of piroxicam gels with varied Carbopol 940 concentrations at 27°C (mean ± SD, $n = 3$).

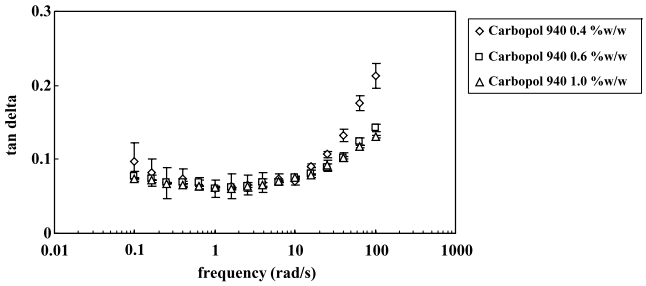

Fig. 2. Semilogarithmic plot of tan delta against frequency of piroxicam gels with varied Carbopol 940 concentrations at 27°C (mean ± SD, $n = 3$).

RESULT AND DISCUSSION

Effect of Formula Compositions on Rheological Parameters

Effect of Carbopol 940 Concentrations

For dynamic measurements, the level of strain was determined at a fixed frequency to ensure that all dynamic measurements were carried out within a linear viscoelastic regime, wherein viscoelastic parameters were independent of strain amplitude (10). In these studies, the strain of 1.0% was chosen for the subsequent dynamic test.

Gel formulae C.4, C.6, and C1, containing 0.4, 0.6, and 1.0% w/w Carbopol 940, respectively, had a predominant elastic solid behavior as the magnitude of their storage moduli (G') was greater than that of loss moduli (G'') (Fig. 1). In addition, tan δ, which is commonly described as the ratio of the energy lost (G'') to energy stored (G'), was less than 0.5 (Fig. 2). The value of both moduli increases with an increment in Carbopol 940 concentration, and tan δ values tended to decrease. This suggests that the gel samples would demonstrate a predominantly elastic solid behavior when the concentration of gelling agent increased. It is possible that the more the polymer content, the more entanglements and more interactions in the polymer chains.

Effect of Solvent Composition

The solvent composition studied included water, propylene glycol, and glycerin (formulae C.6, C.6/G5, C.6/G10, and C.6/G15) as shown in Table II. Carbopol 940 at a concentration of 0.6% w/w was used throughout this study. The storage

Table II. Ratios of Solvent Compositions

Formula	Water/Propylene glycol/Glycerin
C.6	90:10:0
C.6/G5	85:10:5
C.6/G10	80:10:10
C.6/G15	75:10:15

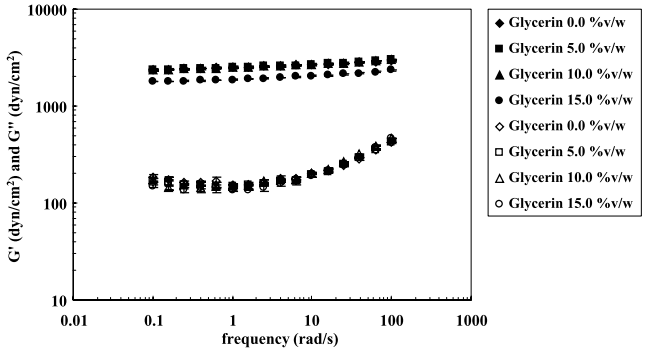

Fig. 3. Double logarithmic plot of storage modulus (filled symbol) and loss modulus (unfilled symbol) against frequency of piroxicam gels containing 0.6% w/w Carbopol 940 and varied concentrations of glycerin at 27°C (mean ± SD, $n = 3$).

modulus and loss modulus values of gel formulae C.6, C.6/G5, and C.6/G10 containing 0.0, 5.0, and 10.0% v/w glycerin, respectively, were comparable (Fig. 3). However, the gel formula C.6/G15 containing 15.0% v/w glycerin had lower storage moduli and a decreasing tendency of loss moduli values. Furthermore, the tan δ profiles shown in Fig. 4 of gel formulae C.6, C.6/G5, and C.6/G10 showed that their tan δ values were comparable, but those of C.6/G15 were higher. This indicates that C.6/G15 had a more viscous fluid behavior than the others.

From the dynamic testing data, the decrease in water content of the solvent mixtures to lower than 80% with an increase in glycerin content to over than 10% would yield a more viscous fluid behavior of the gel structure. Generally, the viscoelasticity of neutralized carbopol polymers is markedly affected by the degree of entanglement between different polymer chains; the entanglement is greater when the polymer chains are more extended. In a "good" solvent composition, such as a solvent 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 chain would tend to be more contracted. Thus in a good solvent, the neutralized carbopol polymer chain is more extended and the elastic solid behavior of the polymer is more obvious (1,11). In addition, the added glycerin can act as a platicizer, which increases the flexibility of polymer chains, and therefore the gel elastic behavior decreases.

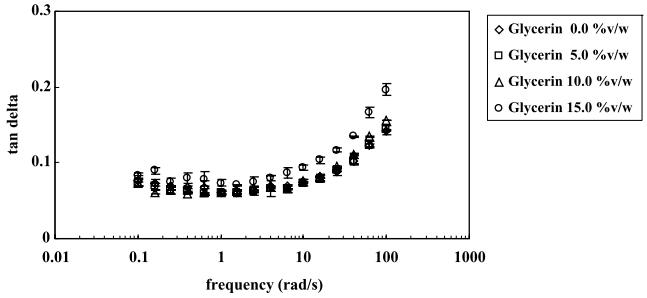

Fig. 4. Semilogarithmic plot of tan delta against frequency of piroxicam gels containing 0.6% w/w Carbopol 940 and varied concentrations of glycerin at 27°C (mean ± SD, $n = 3$).

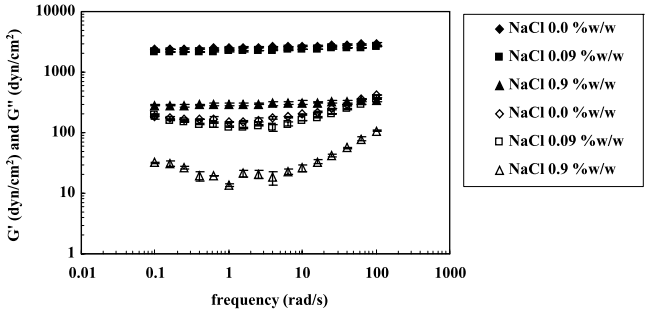

Fig. 5. Double logarithmic plot of storage modulus (filled symbol) and loss modulus (unfilled symbol) against frequency of piroxicam gels containing 0.6% w/w Carbopol 940 and varied concentrations of sodium chloride at 27°C (mean ± SD, $n = 3$).

Effect of Electrolyte

The rheological properties of preparations containing sodium chloride were thus examined. Sodium chloride markedly influenced the carbopol gel structure and induced a slightly cloudy appearance in the preparations. The storage modulus and loss modulus values of the preparations under study decreased with increments of sodium chloride content; the effect was greater in the case of formulation containing a lower concentration of Carbopol 940 (Figs. 5–8). Tan δ profiles (Fig. 7) show that the structure of the gel containing 0.6% w/w Carbopol 940 with 0.9% w/w sodium chloride possessed a more viscous fluid behavior. However, the structure of the gel containing higher concentrations of Carbopol 940, i.e., 1.0% w/w, had a slight change in its behavior as its tan δ values did not change as much as those of 0.6% w/w Carbopol 940 (Fig. 8).

Sodium chloride could affect the hydration of Carbopol 940 due to its greater solubilizing power. Thus the polymer-solvent interactions were lessened and the polymer chains tended to contract. Consequently, the preparations tended to lose their elastic solid characters—particularly the preparation containing a lower concentration of Carbopol 940 (0.6% w/w) and a high concentration of sodium chloride (0.9% w/w), which became slightly turbid. This might occur as a result of polymer flocculation. In conclusion, the preparations containing high concentrations of Carbopol 940 were more

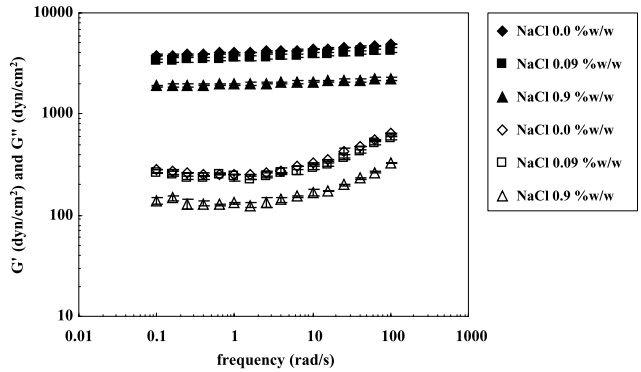

Fig. 6. Double logarithmic plot of storage modulus (filled symbol) and loss modulus (unfilled symbol) against frequency of piroxicam gels containing 1.0% w/w Carbopol 940 and varied concentrations of sodium chloride at 27°C (mean ± SD, $n = 3$).

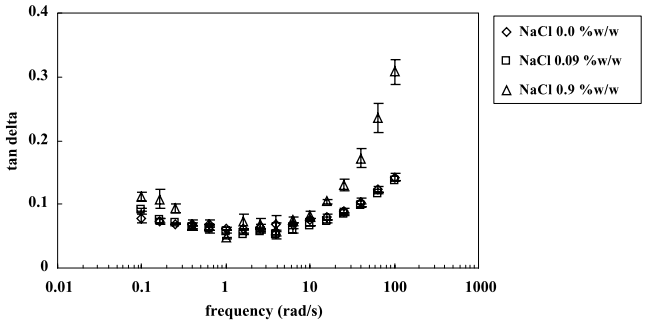

Fig. 7. Semilogarithmic plot of tan delta against frequency of piroxicam gels containing 0.6% w/w Carbopol 940 and varied concentrations of sodium chloride at 27°C (mean ± SD, $n = 3$).

tolerant to electrolyte than the preparations containing low concentrations of Carbopol 940.

Edsman *et al.* (3) found that there was a good correlation between the human ocular contact time and the elastic solid properties of ophthalmic gels using carbopol as a gelling agent. Thus, preparations containing high Carbopol 940 concentrations should be chosen for use in ocular drug delivery dosage forms and mucoadhesive dosage forms because they would prolong the contact time and are tolerant of electrolyte in biological fluids such as tear, saliva, and mucus. The increment of contact time would result in an increase in drug bioavailability. However, the gel structure should be optimally strong because too strong a gel structure could result in irritation.

Piroxicam Diffusion Coefficient Determination

Diffusion coefficients of piroxicam in several preparations possessing different viscoelastic behaviors were calculated from the slopes of plots of cumulative amount released *vs.* square root of time according to Higuchi's equation [Eq. (5)], which is valid when the release of the diffusant from base is less than 30%. They are presented in Table III.

$$Q = 2C_0(Dt/\P)^{1/2} \tag{5}$$

where Q is the amount of material flowing through a unit cross-section of a barrier in a unit time, t; C_0 is the initial drug concentration in the gel; and D is the diffusion coefficient of a diffusant (12).

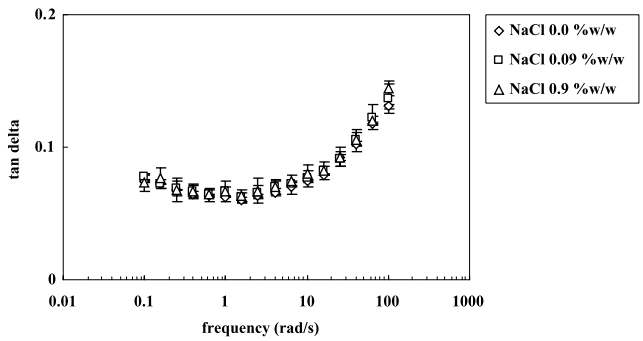

Fig. 8. Semilogarithmic plot of tan delta against frequency of piroxicam gels containing 1.0% w/w Carbopol 940 and varied concentrations of sodium chloride at 27°C (mean ± SD, $n = 3$).

Table III. Diffusion Coefficients of Piroxicam in Carbopol 940 Gel Bases at 33°C

Formula	Diffusion coefficient[a] (cm^2/min)
C.4	$1.17\times10^{-4} \pm 7.99\times10^{-6}$
C.6	$9.07\times10^{-5} \pm 1.97\times10^{-6}$
C1	$8.58\times10^{-5} \pm 1.54\times10^{-6}$
C.6/G10	$8.86\times10^{-5} \pm 2.29\times10^{-6}$
C.6/G15	$7.45\times10^{-5} \pm 4.88\times10^{-6}$
C.6/S.09	$1.13\times10^{-4} \pm 3.69\times10^{-6}$
C.6/S.9	$1.48\times10^{-4} \pm 1.88\times10^{-6}$
C1/S.9	$1.00\times10^{-4} \pm 7.01\times10^{-6}$

[a] Mean ± SD ($n = 3$).

Piroxicam diffusion coefficients in gel bases are ranked in the following order: C.6/S.9 > C.4 > C.6/S.09 > C1/S.9 > C.6 > C.6/G10 > C1 > C.6/G15. However, using one-way ANOVA with Tukey's multiple comparison at a p value of less than 0.05, the diffusion coefficients of piroxicam of formulae C.6 and C.6/G10 were not different significantly; those of formula C.6/G10 and C1 were also not different significantly.

The rheological properties of these formulations were examined at low frequency (0.1 rad/s) and minimum shear rate (0.05 s^{-1}) (Table IV) so as to minimize interference with the gel structure.

Generally, drug mobility in aqueous dispersions of polymers is basically restricted by mechanical impediments of polymers and reductions in free volume with increases in medium viscosity (13). Thus, there is an inverse relationship between diffusion coefficient and gel viscosity as predicted by the Stokes–Einstein equation [Eq. (4)]. In this study, the order of viscosity of test products was as follows: C.6/S.9 < C.4 < C.6/G15 < C1/S.9 < C.6/S.09 < C.6/G10 < C.6 < C1. Because there was a trend of inverse relationship between piroxicam diffusion coefficients (D) in Carbopol 940 gel bases and their viscosity, simple regression with Pearson's test at a p value of less than 0.05 was performed. Equation (6) was obtained with the correlation coefficient (r) of 0.8835 ($p = 0.004$) and its plot is shown in Fig. 9.

$$D = 0.0659/\eta + 9 \times 10^{-5} \tag{6}$$

Table IV. Rheological Data of the Test Products at 33°C (mean, $n = 3$)

	Viscoelastic parameters[a]				
Formula	G' (dyn cm^{-2})	G'' (dyn cm^{-2})	tan δ[b]	G^* (dyn cm^{-2})	Viscosity[c] (P)
C.4	608.78	58.55	0.0965	611.70	1986.61
C.6	2365.59	180.14	0.0762	2372.48	10,108.05
C1	3799.99	280.72	0.0739	3809.35	20,452.20
C.6/G10	2348.25	170.62	0.0727	2339.08	10,018.18
C.6/G15	1773.69	144.60	0.0816	1779.69	7997.01
C.6/S.09	2120.43	192.61	0.0908	2129.16	9179.54
C.6/S.9	279.81	29.83	0.1067	281.40	1060.90
C1/S.9	1897.29	135.08	0.0713	1902.10	8158.80

[a] Viscoelastic parameters were obtained at the frequency of 0.1 rad/s.
[b] tan δ is dimensionless.
[c] Viscosity was obtained at the shear rate of 0.05 s^{-1}.

Despite the trend of inverse relationship, the correlation coefficient of this relationship was quite far from ±1. Thus gel viscosity was not the only parameter affecting the diffusion coefficients. The plot of *D vs.* viscosity in Fig. 9 shows some deviations. Addition of glycerin could reduce gel viscosity as seen in the cases of C.6, C.6/G10, and C.6/G15. However, decrease in viscosity did not induce increases in piroxicam diffusion coefficients. The diffusion coefficient of formula C.6/G15 was the lowest although its viscosity was in the middle region. The polymer concentrations of formulae C.6 and C.6/G15 were the same; the only difference was the glycerin content, which could increase vehicle lipophilicity. Thus piroxicam tended to stay in the donor part and diffused less to the hydrophilic receiving solution. This could be confirmed by the increase in piroxicam solubility by an addition of glycerin as shown in Table V. The solubility rate of piroxicam in isotonic phosphate buffer (pH 7.4) used as a receiving medium is 0.48 ± 0.07 mg/mL at 37°C (14). Therefore, piroxicam was more likely to stay in the donor part because its solubility in the donor part was greater than that in the receiving solution.

The effect of glycerin on viscosity was less than that on diffusion coefficient. This was even more prominent in the case of C1 and C.6/G10. The viscosity of gel base C1 was about twice as that of C.6/G10 because C1 contained a greater amount of Carbopol 940. However, the diffusion coefficients of piroxicam in both gel bases were not significantly different. This should be because the increase in lipophilicity of glycerin-added gel base would induce more drug molecule to stay in the donor part or would lessen the diffusion coefficient of the drug.

Carbopol 940 was very sensitive to sodium chloride. This was obvious in the case of C.6/S.09 and C.6/S.9. The increase in Carbopol 940 could reduce the salt effect as seen in the case of C.6/S.9 and C1/S.9. The diffusion coefficient of C1/S.9 was less than that of C.6/S.09 although its viscosity was less. Barry (15) explained that the polymer can impede the movement of drug molecules by adsorbing them on the polymer surface and/or modify the observed diffusivity of solute by a mechanical obstruction effect, which depended on the size of the solute molecule. In this case, piroxicam should have negative charge in the solution pH studied. Thus the adsorption of drug molecules on carbopol chain should not be significant because charges on polymer were also negative.

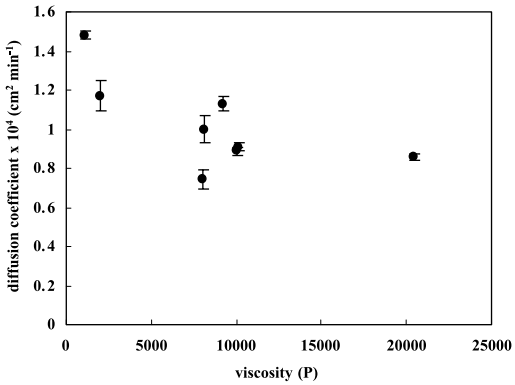

Fig. 9. Plot of piroxicam diffusion coefficients in Carbopol 940 gel bases against viscosity at a shear rate of 0.05 s^{-1} of piroxicam gel at 33°C (mean ± SD, $n = 3$).

Table 5. The Solubility of Piroxicam in the Vehicles of Formulae C.6 and C.6/G15 at 33°C

Formula	Solubility[a] (mg/mL)
C.6	12.32 ± 0.17
C.6/G15	15.64 ± 0.42

[a] Mean ± SD, $n = 4$.

The relationships between D and viscoelastic parameters were studied by using simple regression with Pearson's test at a p value of less than 0.05 as shown in Eqs. (7)–(10).

$$D = 0.0181/G' + 8 \times 10^{-5} \quad r = 0.8787\ (p = 0.004) \tag{7}$$

$$D = 0.002/G'' + 8 \times 10^{-5} \quad r = 0.8721\ (p = 0.005) \tag{8}$$

$$D = 0.0015(\tan\delta) - 3 \times 10^{-5} \quad r = 0.8525\ (p = 0.007) \tag{9}$$

$$D = 0.0182/G^* + 8 \times 10^{-5} \quad r = 0.8787\ (p = 0.004) \tag{10}$$

Moduli G', G'', and G^* were inversely proportional to D, whereas tan δ was directly proportional to D. Because the coefficient value of Eq. (7) was greater than that of Eq. (8), the effect of G' on D was greater than that of G''. This was also confirmed by the small value of coefficient in Eq. (9). Therefore, the Carbopol 940 gel structure possessing predominantly elastic solid behavior and showing extensive entanglements between different polymer chains could act as a fine mesh impeding the diffusant's movement. Thus, G' was inversely proportional to D. Because G^* was dominated by the modulus that had greater effect (which was G' in this case), the coefficient of Eq. (10) was very close to that of Eq. (4).

The correlation coefficients of Eqs. (7)–(10) that were not close to ±1 meant that the linear regression equations describing the relationships between viscoelastic parameters and D were not optimum. Walkow and McGinity (16) proposed that it was not possible to correlate any single physical or chemical property of either the drug or the vehicle with the resulting diffusion profiles. Instead, it seemed that a combination of factors were responsible for the unique diffusion of the diffusant. Thus, to construct equations that would describe the diffusivity of the diffusant, more than one independent variable should be considered, such as parameters describing vehicle structure, solubility of diffusant in the vehicle, and interactions between vehicle components and the diffusant.

CONCLUSIONS

Increases in Carbopol 940 concentrations induced the preparations to exhibit a more elastic solid behavior. Preparations containing optimum water and glycerin contents showed a more elastic solid behavior than preparations containing lower water contents with higher glycerin concentrations. The addition of sodium chloride affected the viscoelastic properties of piroxicam gels containing Carbopol 940. Higher concentrations of Carbopol 940 could help build tolerance against concentrated electrolytes.

We found correlations between viscoelastic parameters of Carbopol 940 gel bases and piroxicam diffusion coeffi-

cients in gel bases, as analyzed by using Pearson's test at a p value of less than 0.05. These correlations indicated that the effect of G' on D was greater than that of G'', and tan δ on D, respectively, and the influence of G^* on D was about the same as that of G'. Viscosity exerted its greatest effect on D.

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