

## Viscoelasticity of Anionic Polymers and Their Mucociliary Transport on the Frog Palate

Shun Y. Lin,<sup>1</sup> Gordon L. Amidon,<sup>1,3</sup>  
Norman D. Weiner,<sup>1</sup> and Arthur H. Goldberg<sup>1,2</sup>

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The influence of formulation variables on the rheology of polyanionic formulations and the relationships between viscoelastic properties and mucociliary transport rate were investigated. Polymeric samples were oscillated from 0.001 to 5 Hz using either a "cone and plate" or a "coaxial cylinder" measuring system. The mucociliary transport rates of polymeric samples were determined and compared movement of charcoal powder on the frog palate. For the linear polymeric solutions, sodium carboxymethylcellulose and sodium alginate, the elastic modulus ( $G'$ ) increased with increasing amplitudes during frequency scan. However, the  $G'$  or viscous modulus ( $G''$ ) of partially cross-linked polyacrylic acid (cPAA) samples did not change significantly under oscillation. Both  $G'$  and  $G''$  of cPAA samples were significantly influenced by the amount of salt present in the formulation. The rheology of 2% (w/w) cPAA in 90:10 (w/w) propylene glycol:alcohol changed from a viscous fluid to a coarse suspension after neutralization. The pH increased gradually when the nonaqueous formulation reacted with water and the maximum dynamic moduli were obtained after incorporating 20% (w/w) water in the formulation. A negative correlation was found between the  $G'$  of linear polyanionic samples and the relative transport rate. However, the lowest mucociliary transport rate was observed when the loss tangent ( $G''/G'$ ) was around 0.4–0.5.

**KEY WORDS:** anionic polymer; rheology; nonaqueous solvent; frog palate; mucociliary transport.

### INTRODUCTION

Polymers that swell in an aqueous medium have often been used for the preparation of controlled-release dosage forms. Several natural and synthetic polymers have been screened for their capacity to adhere to the mucin-epithelial surface. Robinson *et al.* (1) examined a broad range of polymers as to their binding affinity to a mucin-epithelial surface and observed that polyanions with a high charge density were good mucoadhesives. They concluded that a polyanionic polymer is preferred over a neutral or polycationic polymer and that a water-insoluble polymer would offer advantages over a water-soluble polymer for mucoadhesive dosage forms. Anionic polymers such as carboxymethylcellulose, polyacrylic acid, and alginate are suitable for use in preparations with prolonged release of a drug at the mucosal surface. Solutions of anionic polymers are suscep-

tible to chemical interaction with pharmaceutical cationic compounds, usually forming complexes in the preparation.

Using the frog palate model to study the mechanism of mucociliary transport began with Stewart in 1948 (2). Because of the variations in preparing and handling the excised frog palate, conflicting results may exist in comparing the mucociliary clearance rate between the mucus-depleted and the nondepleted frog palate models (3). The rheologic requirement for mucociliary transport is specific to the viscoelasticity of substances but not to their chemical structure (4). Many hydrophilic macromolecular materials including guaran, polyacrylamide, agarose, and gelatin, which are chemically quite dissimilar to mucus, are capable of performing the transport function on a mucus-depleted ciliated epithelium from frog palate (3). An optimal mucociliary flow takes place when the mucus concentrations and viscoelastic properties are within a specific range (5).

In recent years, drugs administered by the intranasal route have attracted much attention, especially when systemic availability can be improved. Several techniques to determine the bioadhesive potential of anionic polymers in the nasal cavity have been recently reviewed (1,2,4). Factors affecting the rate of drug absorption from various preparations in the nasal cavity include the rate of mucociliary clearance, which can vary the site of drug disposition and resident time. The epithelium of the mammalian nasal cavity is covered by mucus, which serves as a coupling agent to transport airborne and other particles. Cilia are beating in a low viscosity medium (water-like periciliary fluid) with a micron-thin mucus blanket (5 to 10  $\mu\text{m}$ ) on top of the medium (6). Solid substances such as charcoal powder with a high elastic modulus are cleared at the same transport rate as mucus in the nasal cavity. This mucociliary system represents an obstacle in nasal delivery. Since most of the surface of the nasal cavity is covered by mucin with cilia beating underneath, polymers used to deliver drugs to these areas are subjected to cyclic shear deformation generated by cilia movement. The purposes of this study are (a) to understand the rheological changes of polyanionic formulations under cyclic shear deformation with varying polymer concentrations, solution pH's, salt concentrations, solvent compositions, and neutralizing agents and (b) to evaluate the relationships between the viscoelastic properties of polyanionic formulations and their mucociliary transport rate using the nondepleted frog palate model.

### MATERIALS AND METHODS

#### Preparation of Polymeric Sample

The anionic polymers tested were partially cross-linked polyacrylic acid (cPAA; Carbopol-934P from BF Goodrich, Cleveland, OH), sodium carboxymethyl-cellulose (Na-CMC; cellulose gum 7HF from Aqualon, Hopewell, VA), and sodium alginate (Na-ALG; Kelcosol from Kelco, Chicago, IL). Samples were prepared by dispersing polymers in deionized water, except where mentioned otherwise. Different amounts of polymer were mixed with water to yield concentrations of 0.5, 1.0, 1.5, 2.0, 3.8, and 5.7% (w/w). Triethanolamine (TEA), ethanolamine (EA), and diisopropanol-

<sup>1</sup> College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48109-1065.

<sup>2</sup> Rugby-Darby Group Companies, Inc., Rockville Centre, New York 11570.

<sup>3</sup> To whom correspondence should be addressed.

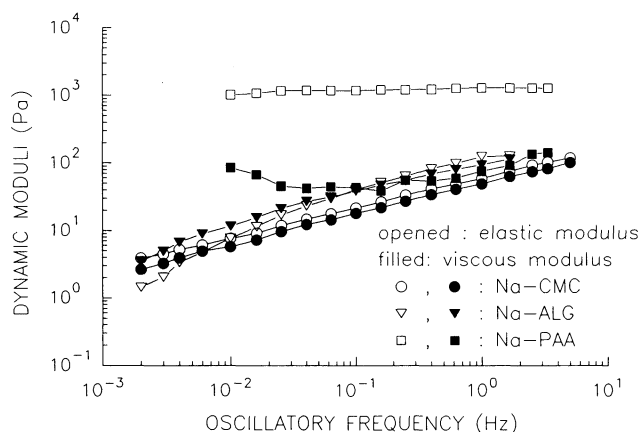


Fig. 1. Behavior of dynamic moduli of 2% (w/w) sodium anionic polymer in water under oscillatory deformation. CMC, carboxymethylcellulose; ALG, alginic acid; PAA, polyacrylic acid.

amine (DIPA) were used as neutralizing agents for cPAA samples. Some cPAA samples were neutralized with 16% (w/v) NaOH to produce sodium cPAA samples for comparing the effect of concentration on the rheology of anionic polymers in sodium form. The influence of electrolytes on viscoelasticity of cPAA samples was evaluated using 0.6, 0.9, and 1.2% (w/v) NaCl and Ringer solutions as swelling agents.

The ability of thickening cPAA samples with three organic amines, TEA, EA, and DIPA, was studied. Because DIPA is in a solid form, a small portion of water was used to dissolve calculated amounts of DIPA and mixed with cPAA to give final concentrations of cPAA of 0.5, 1.0, 1.5, and 2.0% (w/v). Several nonaqueous swelling agents, such as propylene glycol (PG; Fisher Sciences, Pittsburgh, PA), dimethylacetamide (DMA; Sigma), *N*-methylpyrrolidone (PYR; Sigma), dehydrated ethyl alcohol (ALC; Aaper Alco-

hol and Chemical Co., Shelbyville, KY), solketal (SOL; Sigma), glycerol formal (GF; Sigma), propylene carbonate (CAR; Sigma), and ethyl lactate (LAC; EM Sciences, Gibbstown, NJ), were introduced as potential swelling agents for cPAA samples. Some 1% (w/w) cPAA samples were first mixed with binary nonaqueous swelling agents and then neutralized with TEA before mixing with water. Others were prepared by dispersing cPAA in ternary swelling agents mixtures before neutralization. The amounts of the individual swelling agents in each mixture were at equal portions weight by weight. The effects of dilution with water on 2% (w/w) cPAA in 90:10 PG:ALC were determined by measuring the changes of solution pH, apparent viscosity, and viscoelastic properties.

All polymeric samples were stirred vigorously and stored overnight at room temperature. Samples were stirred again and centrifuged for 20 min at 2500 rpm on the second day, except cPAA samples, which were neutralized on the second day and centrifuged on the third day. Samples were used at least 4 hr after centrifugation and tested in 2 days.

#### Measurement of Viscoelasticity

The rheological changes of the polymeric samples were measured at 30°C with a Rheo-Tech viscoelastic rheometer (Contraves Co., Cincinnati, OH), using either a "cone and plate" or a "coaxial cylinder" measuring system. Sample was oscillated from frequencies 0.001 to 5 Hz at a fixed shear stress selected from the linear region where the dynamic moduli did not change with varying stress. The viscoelastic properties of each sample (storage modulus or elastic modulus,  $G'$ , loss modulus or viscous modulus,  $G''$ , and complex viscosity,  $\eta^*$ ) were calculated by computer software developed for the rheometer. The apparent viscosity of each polymeric sample was also measured using the equilibrium flow curve test at 30°C. The pH of the polymeric samples were

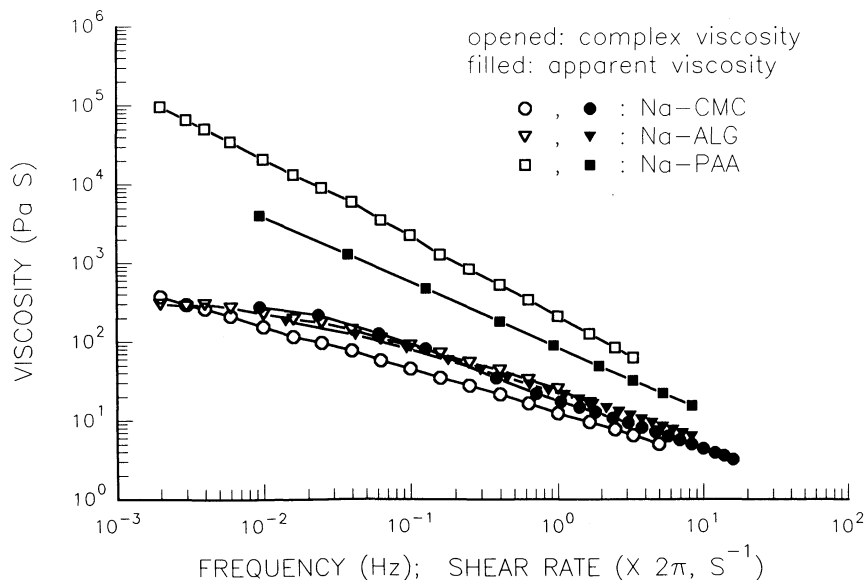


Fig. 2. Influence of oscillatory frequency on the viscosity of 2% (w/w) sodium anionic polymers in water. CMC, carboxymethylcellulose; ALG, alginic acid; PAA, polyacrylic acid.

**Table I.** The Viscoelasticity of Polyanionic Samples as a Function of Polymer Concentration<sup>a</sup>

Polymer conc. (% w/w) in water	Na-CMC		Na-ALG		cPAA with NaOH	
	G'	η*	G'	η*	G'	η*
0.5	ND	ND	ND	ND	653	104.4
1.0	ND	ND	ND	ND	1030	164.7
1.5	31	7.5	39	8.8	1120	178.5
2.0	55	12.4	118	24.4	1310	209.0
3.8	667	116.1	1050	179.0	ND	ND
5.7	2630	438.2	3800	625.6	ND	ND

<sup>a</sup> The viscoelastic properties of samples are determined at 1 Hz, 30°C. CMC, carboxymethylcellulose; ALG, alginate; cPAA, polyacrylic acid neutralized with 16% (w/v) NaOH; G', elastic modulus (Pa); η\*, complex viscosity (Pa S); ND, not determined.

measured using a Beckman Φ40 pH meter (Fullerton, CA) at room temperature.

### Rheology and Mucociliary Transport

Bullfrogs (*Rana catesbiana*), 5 in. or larger, were sacrificed using a beheading method. The nervous system was destroyed by inserting a sharp bamboo stick into the brain and spinal cord. The lower jaw was removed with scissors and the upper palate was washed with frog Ringer solution (90 mM NaCl, 3 mM KCl, 2 mM CaCl<sub>2</sub> · 2H<sub>2</sub>O, and 15 mM NaHCO<sub>3</sub>, pH 8) and transferred to an 8 × 4-cm glass petri dish covered with a 16.5 × 16.5-cm glass plate. The dish was filled with 10–15 mL of frog Ringer solution (the upper palate was not immersed in the solution) and the temperature was kept between 25 and 28°C with circulating water. The mucociliary transport of each sample was measured using an eyepiece micrometer set in a stereomicroscope at ×20 magnification (Stereo 2, Cambridge Instruments) with activated charcoal powder (100 mesh, 150 μm) as the indicator. Since this preparation is designed to utilize the mucus secreted by the frog's mucosal glands as a control baseline, the surface of the palate has to be washed and wiped clear after each comparison (charcoal powder vs sample) to remove any buildup of mucus. Without this treatment, the movement of the mucus blanket stops within hours. Whenever the baseline clearance rate of the charcoal powder was less than 10% of the initial clearance rate measured after excision, the pal-

ate was rested in a plastic container filled with cold frog Ringer solution and stored for 45 min at 4°C before reuse. An excised frog palate could be used for at least 2 days under these conditions.

Polymers tested for their mucociliary transport rate included (a) Na-ALG, 2 and 4%, w/w, (b) Na-CMC, 2 and 4%, w/w, and (c) cPAA, 1 and 2%, w/w, neutralized with triethanolamine. Each sample was divided into two portions; one was mixed with charcoal powder for studying mucociliary transport rate and the other portion was used to determine the viscoelastic properties. For testing the transport rate of polymeric samples on the frog palate, a small quantity (about 3 to 5 mg) of sample was placed either two-thirds from the palate front on the center line or near the edge of the ear. A baseline reading was established each time a polymeric sample was added to the surface of the palate. The samples were loaded on the palate within 1 min after taking the baseline reading, and the transport rate was measured within 3 min. The ratio of the sample's transport rate to its own baseline reading was calculated as the relative transport rate (RTR) and correlated to the sample's viscoelastic properties as determined by the rheometer. The measurement of transport rate was repeated at least five times for each sample to ensure the reproducibility of the results.

### RESULTS AND DISCUSSION

Three anionic polymers were studied for their viscoelastic properties. For the linear polymers such as sodium alginate (Na-ALG) and sodium carboxymethylcellulose (Na-CMC), the elastic modulus (G') and viscous modulus (G'') increase with the frequencies scanned at the terminal region (Fig. 1). Both G' and G'' of Na-ALG or Na-CMC shown in Fig. 1 are typical behaviors of a linear polymeric solution examined at low oscillating frequencies. The complex viscosity (η\*) measured at frequencies higher than 1 Hz is well correlated with its apparent viscosity (η) at the coordinating steady-state shear rate for these linear polymers (Fig. 2). This empirical correlation of η\* to η permits the prediction of η from viscoelasticity data. Because of partial cross-linking of cPAA samples, G' becomes flat from 0.001 to 5 Hz, which introduces a deviation of η\* from η (Figs. 1 and 2). Since η\* is calculated from G' and G'' for linear polymeric solution (7),

$$G^* = (\sigma_0/\gamma_0)\exp(i\delta) = (\sigma_0/\gamma_0)\cos\delta + i(\sigma_0/\gamma_0)\sin\delta$$

**Table II.** The Effects of Ionic Strength on the Rheology of Partially Cross-Linked Polyacrylic Acid Samples<sup>a</sup>

Swelling agent	cPAA							
	0.5% (w/w)		1.0% (w/w)		1.5% (w/w)		2.0% (w/w)	
	G'	η*	G'	η*	G'	η*	G'	η*
0% NaCl	890	143.4	1550	248.2	1780	284.1	1820	290.1
0.6% NaCl	ND	ND	179	29.0	769	122.7	1190	189.7
0.9% NaCl	ND	ND	85	14.3	586	93.5	1080	172.2
1.2% NaCl	ND	ND	61	10.0	433	69.3	943	150.3
Ringer	ND	ND	99	16.4	525	83.7	1040	165.8

<sup>a</sup> Samples are neutralized with triethanolamine. For cPAA, G', η\*, and ND, see footnote a, Table I. Ringer: 8.6 g NaCl, 0.3 g KCl, and 0.3 g CaCl<sub>2</sub> dissolved in 1 L water.

Table III. The Thickening Ability of Water-Soluble Amines on Partially Cross-Linked Polyacrylic Acid Samples<sup>a</sup>

Neutralizing agent	cPAA							
	0.5% (w/w)		1.0% (w/w)		1.5% (w/w)		2.0% (w/w)	
	$G'$	$\eta^*$	$G'$	$\eta^*$	$G'$	$\eta^*$	$G'$	$\eta^*$
EA	748	120.4	1470	234.4	1680	268.0	1730	275.8
DIPA	934	149.3	1580	253.0	1690	269.7	1890	301.3
TEA	894	143.9	1560	250.0	1780	284.0	1810	288.7
16% (w/w) NaOH	528	86.0	1030	164.7	1120	178.4	1400	223.2

<sup>a</sup> For cPAA,  $G'$ , and  $\eta^*$ , see footnote a, Table I. EA, ethanolamine; DIPA, diisopropanolamine; TEA, triethanolamine. The pH of samples was adjusted to 7–7.5.

generally,  $G^*$  is expressed as the mixture of ( $G' + iG''$ ), where

$$\begin{aligned} G' &= (\sigma_0/\gamma_0)\cos\delta, & G'' &= (\sigma_0/\gamma_0)\sin\delta, \\ \tan\delta &= G''/G', & \text{and} & |G^*| &= (G'^2 + G''^2)^{1/2} \end{aligned}$$

and  $\eta^*$  is expressed as the mixture of ( $\eta' - i\eta''$ ), where

$$|\eta^*| = (\eta'^2 + \eta''^2)^{1/2} = (G'^2 + G''^2)^{1/2}/2\pi\nu = \eta/2\pi$$

$G^*$  is the complex modulus;  $\sigma_0$  the initial stress amplitude;  $\gamma_0$  the initial strain amplitude,  $\delta$  the phase angle between stress and strain,  $\eta'$  the dynamic viscosity,  $\eta''$  related to the dynamic rigidity, and  $\nu$  the shear frequency (Hz); a significant change in  $G'$  will influence  $\eta^*$  behavior. However, the differences between  $\eta^*$  and  $\eta$  of cPAA samples became smaller at higher shearing rates. This result suggests the breakdown of the cross-linked structure. It seems there exists a critical point where the dynamic moduli of linear polymeric solution increase dramatically with increasing polymer concentrations (Table I). It is expected that a plot of  $G'$  (or  $\eta^*$ ) against the polymer concentration on a normal scale will reveal a curve relationship between  $G'$  and polymer concentration. This is because polymers are not fully hydrated or extended at higher concentrations, resulting in an upper limit of the viscoelastic profile.

Adding salts to an aqueous polymeric formulation will change its rheology, depending on the ionic strength. This effect is especially significant when cPAA concentrations are lower than 0.5% (w/w). With only 0.6% (w/v) NaCl in

Table IV. The Viscoelasticity of Partially Cross-Linked Polyacrylic Acid Samples as a Function of the Solution pH Adjusted with Ethanolamine<sup>a</sup>

pH	cPAA							
	0.5% (w/w)		1.0% (w/w)		1.5% (w/w)		2.0% (w/w)	
	$G'$	$\eta^*$	$G'$	$\eta^*$	$G'$	$\eta^*$	$G'$	$\eta^*$
4	185	30	1030	165	1310	211	1590	253
5	698	112	1420	227	1580	252	1430	227
6	783	126	1460	234	1650	263	1500	239
7	748	120	1470	234	1680	268	1730	275
8	738	119	1450	231	1650	264	1830	292
9	744	123	1400	223	1530	244	1740	277

<sup>a</sup> Samples are neutralized with ethanolamine. For cPAA,  $G'$ , and  $\eta^*$ , see footnote a, Table I.

water, the rheology of 0.5% (w/w) cPAA sample changes from gel-like to liquid-like (Table II). A gel structure was obtained after increasing the cPAA concentration to 1% (w/w). This result suggests that the adhesiveness of polyanionic formulations should be tested in a simulated physiologic fluid instead of water. There are no significant differences in viscoelastic properties among cPAA samples neutralized with different organic amines at the same molar ratio (Table III). The rheology of 0.5 to 2.0% cPAA samples does not change significantly when the pH was adjusted from 5 to 9 with ethanolamine (Table IV). A small decrease in the moduli was observed at pH 4 for both 1.0 and 2.0% cPAA samples. However, the effective pH range of thickening cPAA sample becomes wider as the cPAA concentration increases (Table IV).

The procedure of dispersing cPAA into ternary solvent systems did not vary the  $G'$  and  $\eta^*$  after neutralization. However, using TEA as neutralizing agent caused different degrees of precipitation in the nonaqueous swelling agent systems. Precipitation occurs when adding TEA to a nonaqueous swelling agent system (without water) and these precipitates could redisperse in the system after mixing with

Table V. The Viscoelastic Behavior of 1% (w/w) Partially Cross-Linked Polyacrylic Acid in Mixed Swelling Agent Systems<sup>a</sup>

Solvent (at equal portions, w/w)	Phase	$G'$ -A	$G'$ -B	$\eta^*$ -A	$\eta^*$ -B
PG:DMA:H <sub>2</sub> O	Gel	1070	1090	171	174
PG:PYR:H <sub>2</sub> O	PPT	1030	1090	165	174
PG:ALC:H <sub>2</sub> O	PPT	842	860	135	138
PG:SOL:H <sub>2</sub> O	PPT	550	486	90	79
PG:GF:H <sub>2</sub> O	PPT	404	309	65	50
PG:CAR:H <sub>2</sub> O	Gel	315	323	52	53
PG:LAC:H <sub>2</sub> O	PPT	ND	ND	ND	ND

<sup>a</sup> The pH of preparations was adjusted to  $7.5 \pm 0.3$  with triethanolamine. Phase: reaction of adding neutralizing agent into nonaqueous polymeric preparation. For cPAA,  $G'$ ,  $\eta^*$ , and ND, see footnote a, Table I. A, pH of polymer in nonaqueous swelling agent system adjusted before mixing with water; B, polymer dispersed in mixed ternary swelling agents system and then neutralized. PG, propylene glycol; PYR, 1-methyl-2-pyrrolidinone; DMA, *N,N*-dimethylacetamide; ALC, ethyl alcohol; SOL, solketal; 1,2-*o*-isopropylidene-*rac*-glycerol; CAR, propylene carbonate; GF, glycerol formal; LAC, ethyl lactate; PPT, precipitation.

**Table VI.** The Viscoelasticity of 2% (w/w) Partially Cross-Linked Polyacrylic Acid in Propylene Glycol:Ethyl Alcohol (90:10, w/w) After Dilution with Water<sup>a</sup>

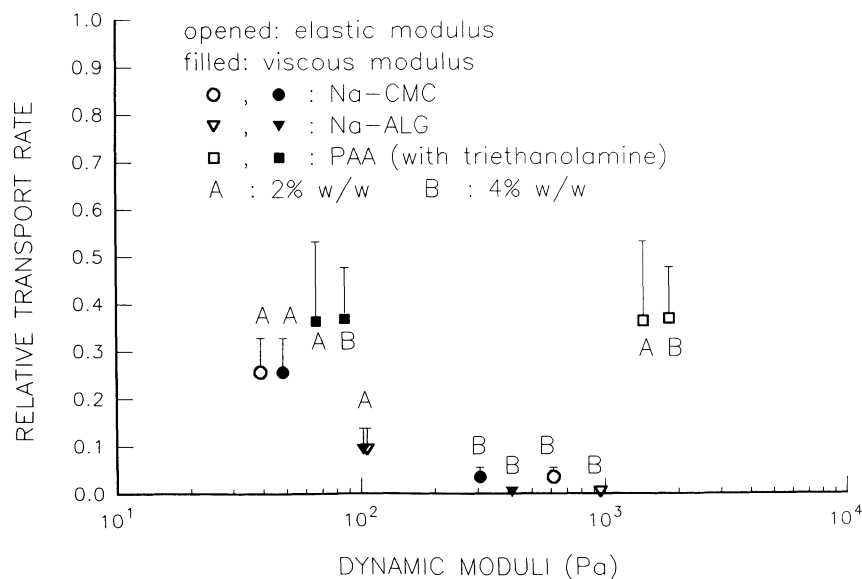
Water added (mL)	pH	$G'$	$G''/G'$	$\eta^*$	$\eta$
0	7.87	ND	ND	ND	ND
1.1	7.31	596	0.150	96	42
2.2	7.08	989	0.143	127	66
5.0	6.86	1270	0.142	204	82
8.6	6.71	1280	0.100	204	78
13.3	6.58	1270	0.120	204	76
20.0	6.44	1150	0.147	186	65
30.0	6.26	993	0.182	161	49
46.7	5.94	703	0.218	115	30

<sup>a</sup> The dynamic moduli are determined at 1 Hz, 30°C. For cPAA,  $G'$ ,  $\eta^*$ , and ND, see footnote *a*, Table I.  $G''$ , loss modulus (Pa);  $\eta$ , apparent viscosity at 6.24/sec (Pa S).

water (Table V). Only the cPAA in the dimethylacetamide and in propylene carbonate systems was compatible with TEA. However, the ternary swelling agent system containing propylene carbonate was not stable at room temperature, producing air bubbles during storage, making the determination of viscoelasticity difficult. Loss of dynamic moduli in the ethyl lactate system could result from the amount of lactate (electrolyte) inhibiting the formation of PAA gel structure. The theory of thickening PAA samples is complex and is governed by factors such as solubility parameters, dielectric constants, and hydrogen bonding properties of the swelling agent(s). When 2% (w/w) cPAA was dispersed in 90:10 (w/w) propylene glycol:ethyl alcohol, a viscous sample was formed. After increasing the pH with triethanolamine, the viscous cPAA sample became a coarse suspension with some degree of sedimentation. By adding a small amount of

water into the nonaqueous suspension, the particles redispersed and the system became gel-like. The pH of the preparation changed gradually with the amount of water incorporated, and the dynamic moduli reach their peaks after adding 20% (w/w) of water (Table VI). A nonlinear relationship existed between the amount of water added and the loss tangent ( $G''/G'$ ). The lowest loss tangent was 0.1 with 8.6 mL water, and the rheology of cPAA samples showed a pseudo-plastic behavior.

Because of differences in the experimental methodology, the mucus-depleted frog palate model vs the nondepleted frog palate model, it is difficult to compare results among reports. The influences of viscoelastic properties of the polymeric samples on mucociliary transport rate were studied using nondepleted frog palate model. It has been shown that mucus from bullfrog (*Rana catesbiana*) has viscoelastic properties similar to those of normal mammalian respiratory mucus (2). The frequency of the cilia beats ranged from 9 to 15 beats/sec for bullfrog, which is close to the cilia beat frequency in the human nasal cavity (8 to 13 beats/sec). However, the bullfrog has a faster mucociliary transport rate compared to the human nasal clearance rate, normally 8–12 to 5–10 mm/min, respectively (8). To identify a cilia active region on the frog palate for the baseline measurement, a light source was applied to the palate, and the intensity of ciliary beating was judged by light flickering. The average mucociliary transport rate after excision was 10 to 15 mm/min. After placing polymeric samples with elasticity varying from 39 Pa (2% Na-CMC) to 1800 Pa (2% cPAA), a negative correlation is found between the relative transport rate (RTR) and the dynamic moduli of linear polymeric formulations (Fig. 3). The deviation of cPAA data could be attributed to the partial cross-linking of gel structure, resulting in a high elastic modulus. A greater scattering between RTR and apparent viscosity is found in Fig. 4. A three-dimensional structure (cross-linked gel) was required for mucus to be transported on mucus-depleted frog palate (4). An



**Fig. 3.** The relationship between dynamic moduli of anionic polymer and mucociliary transport on frog palate. CMC, carboxymethylcellulose, 2 and 4%, w/w; Alg, alginic acid, 2 and 4%, w/w; PAA, polyacrylic acid, 1 and 2%, w/w.

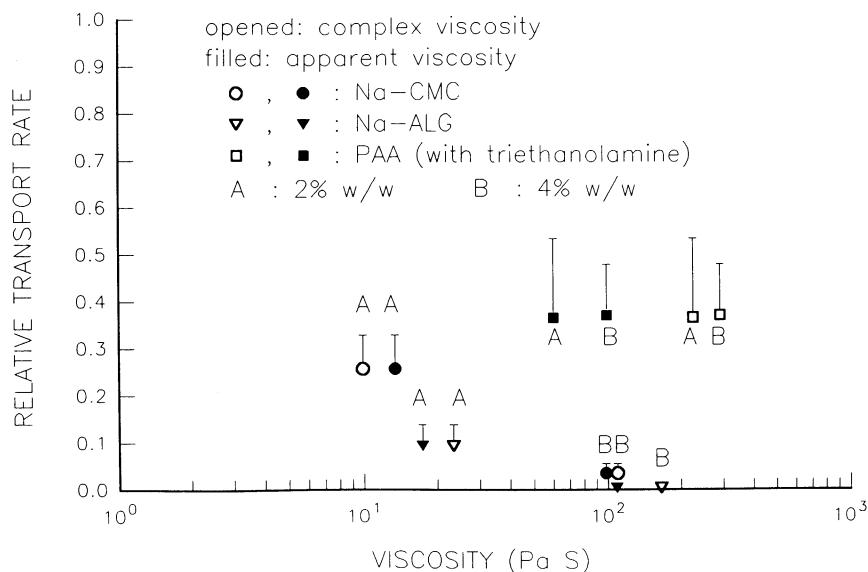


Fig. 4. The effect of viscosity on mucociliary transport rate. CMC, carboxymethylcellulose, 2 and 4%, w/w; ALG, alginic acid, 2 and 4%, w/w; PAA, polyacrylic acid, 1 and 2%, w/w.

optimal transport rate is found with a mucus elasticity of 1 to 2 Pa, whereas the clearance rate decreased dramatically below 1 Pa and decreased slowly above 2 Pa (9). It is not clear whether these polymers interacted with the mucus or was just loaded on top of the mucus layer. It was recognized that the interfacial layer between periciliary fluid and the transported medium should have viscoelastic properties similar to those of frog mucus to be transported by cilia movement (2-4). This indicates that the residence time of a drug in the nasal cavity depends on the degree of the rheologic alteration in the interfacial layer by the polymer. Figure 5 shows a concave curve between RTR and loss tangent. A sharp

decrease in RTR occurs when the loss tangent increased from 0.05 to 0.5, and a slow recovery of RTR when the loss tangent was above 0.5. This concave curve is consistent with results from charcoal powder (loss tangent was around zero; RTR = 1) and dimethyl-polysiloxane (loss tangent was around 10; RTR = 0.6). However, the nonsterilized alginate samples which had a low loss tangent were not stable at room temperature and the apparent viscosity dropped dramatically in 10 days of storage. Since polymeric formulations are subjected to dilution in the nasal cavity, samples with pseudoplastic behavior will increase their loss tangent upon dilution with water, therefore formulations with high dy-

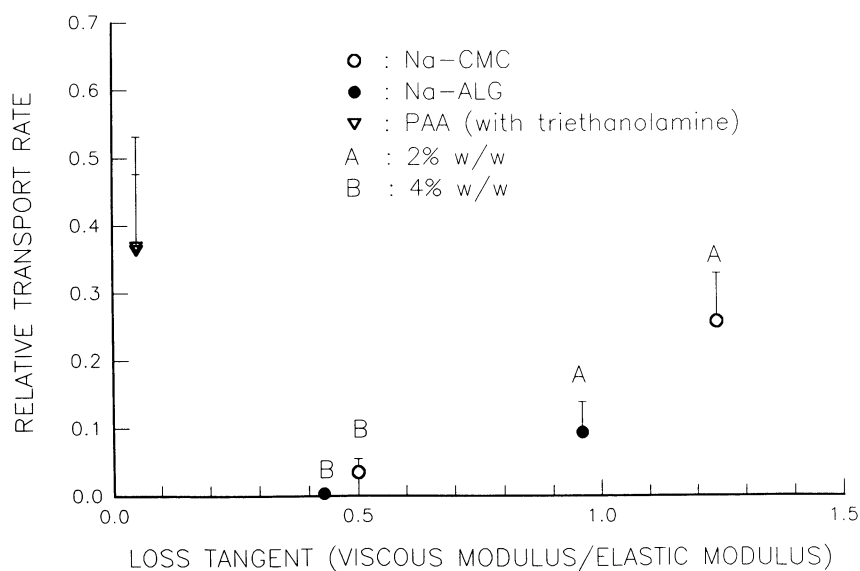


Fig. 5. Correlation between polymer's loss tangent and mucociliary transport rate. CMC, carboxymethylcellulose, 2 and 4%, w/w; ALG, alginic acid, 2 and 4%, w/w; PAA, polyacrylic acid, 1 and 2%, w/w.

namic moduli and with a loss tangent of 0.4 to 0.5 will be preferable to enhance the nasal resident time of drugs.

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