Rheological Properties and Drug Release Characteristics of pH-Responsive Hydrogels

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ABSTRACT: Rheological properties, blend compatibility, and gel-forming capacity of carbopol 940 (CP-940), sodium alginate (NaAlg), and guar gum (GG) have been studied. These matrices have been used in delivery of timolol maleate for ophthalmic applications. Aqueous solutions of CP-940, NaAlg, and GG in concentrations between 0.1 and 1% (wt/vol) and their blends have been prepared. *In situ* gel forming polymeric solutions have shown an increase in viscosity upon exposure to specific pH, ions, and temperature of the eyeball. Blend miscibility was studied by calculating polymer–polymer interaction parameters using viscosity data. Rheological properties viz., torque, viscosity, shear stress, and shear rate were obtained using a Brookfield rheometer. Viscosities of polymer solutions were obtained by a Schott Gerate viscometer. Rheological data were analyzed using Bingham, Casson Standard, and Casson Chocolate equations. The hydrogels were subjected to *ex vivo* release studies on timolol maleate through the excised bovine cornea using a modified Franz diffusion cell. Results were compared with the conventional drug solution. The release could be extended when the drug is incorporated into hydrogel-forming solution. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 94: 2057–2064, 2004

Key words: rheology; hydrogels; blends; drug delivery systems

INTRODUCTION

Hydrogels are used in a wide variety of pharmaceutical and agricultural applications.[1–3] In particular, use of *in situ* forming hydrogels from solutions for ophthalmic drug delivery offers many advantages over conventional eye drops, mainly due to their prolonged corneal contact time.[4,5] Many biocompatible polymers that are capable of forming *in situ* hydrogels are used in ophthalmic applications[6–10] due to their low viscosity during formulation and high gelling capacity in the eye environment.[11,12] Aminabhavi and coworkers[13–15] developed several polymers and blends that are capable of forming hydrogels. For ophthalmic applications, polymers should have optimum viscosity for easy instillation into the eye, which in turn should undergo rapid sol-gel transition at specific pH, ions, and temperature of the eyeball.[6–9] Thus, evaluation of rheological properties of *in situ* gelling polymers is important to predict their *in vivo* drug release characteristics.[16] The ocular residence time depends upon the rheological properties and viscosity of the hydrogels.[17,18]

In the present investigation, blends of carbopol 940 (CP-940), sodium alginate (NaAlg), and guar gum (GG) are used for ophthalmic delivery of timolol maleate. CP-940 contains an acrylic acid moiety and is hydrophilic,[19] having good gel-forming and bioadhesive properties. Upon exposure to water or alkaline media, the polymer begins to uncoil due to increased viscosity and gel-forming capacity. NaAlg is a naturally occurring polysaccharide,[20] which forms hydrogel in the presence of specific ions. GG is a naturally occurring polysaccharide[21] obtained from the ground endosperm of *Cyamposis tetragonolobus* (Leguminosae family). It is widely used as an excipient in pharmaceutical applications.[22] GG exhibits gelling characteristics in the presence of water or biological fluids.

No attempts have yet been made on the rheological properties of blends of CP-940, NaAlg, and GG in both solution and gel forms at the physiological temperature (i.e., 37°C) and artificial tear fluid conditions. In an effort to search for new polymers for ophthalmic *in situ* hydrogel forming solutions, we have selected blends of CP-940, NaAlg, and GG. Their viscosity, shear stress, and shear rate have been measured. Blend compatibility of these polymers at low polymer concentrations in water and in acidic pH conditions have been studied. At higher polymer concentrations, in the presence of basic pH and specific ions, they show different gel-forming characteristics. The rheo-

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logical data at higher polymer concentration and in basic pH solutions were examined using Casson Standard,[23] Casson Chocolate,[23] and Bingham[24–26] equations to obtain the desired parameters. Timolol maleate (TM) is used for the treatment of open-angle glaucoma. Since systemic absorption of TM causes respiratory and cardiovascular side effects, one can minimize these effects and increase its ocular bioavailability. However, efforts[27,28] have been made in the earlier literature to develop ophthalmic delivery systems using liposomes, niosomes, nanoparticles, implantable systems, collagen shields, etc., but *in situ* gelling systems of the kind used here are quite rare.

EXPERIMENTAL

Materials

Carbopol-940 was received as a gift sample from Eros Pharma, Bangalore, India (courtesy of Mr. M. K. Sreevalsan). Sodium alginate (approximate molecular weight 240,000), guar gum (approximate molecular weight 220,000), sodium hydroxide, hydrochloric acid, and the salts used to prepare buffer solutions were all of analytical grade samples, purchased from S.D. Fine Chemicals Ltd., Mumbai, India. Double distilled water was used throughout the study.

Preparation of polymer solutions

Stock solutions of CP-940, NaAlg, and GG were prepared by dissolving an exactly weighed quantity (1 g) of polymer in 100 mL of either distilled water or pH 6 phosphate buffer. These solutions were stirred for 6 h on a magnetic stirrer. From the 1% (wt/vol) stock solution of each polymer, dilutions were made using either water or phosphate buffer in concentrations ranging from 0.1 to 1%. Polymer blend solutions were prepared by diluting stock solutions of different polymers using distilled water or buffer solution. These solutions were stirred on a magnetic stirrer for 15 min and stored in closed containers to prevent evaporation of water. Polymer blend solutions were prepared by mixing equal volumes of solutions of respective polymer concentrations.

Compatibility of polymer blend solutions

The solutions of 0.25 mass % of NaAlg, GG, and CP-940 were prepared in 200 mL distilled water separately in three different 250-mL stoppered conical flasks from standard solutions. Three different mass ratios of the blend solutions of NaAlg, GG, and CP-940 were prepared by mixing NaAlg, GG, and CP-940 in the ratios of 20/20/60, 20/60/20, and 60/20/20. From these blend solutions, 0.05, 0.10, 0.15, 0.20, and 0.25 mass % solutions were prepared.

Solution viscosity measurements

Viscosities were measured[29] using a Schott Gerate viscometer, model AVS 350 (Hofheim, Germany) equipped with an Ubbelohde capillary viscometer at 37°C. In this instrument, time measurement was fully automatic. The change in light intensity was converted to a digital electrical signal and efflux times were determined on a digital display within an uncertainty of ±0.01 s. The viscometer was immersed in a thermostatic bath, Schott Gerate, model CT 050/2 (Hofheim, Germany), which was electronically controlled to the set temperature. The uncertainty in temperature was ±0.1°C, while the uncertainty in viscosity was ± 0.001 cP. Approximately 5 mL of liquid was placed in the viscometer. The liquid was allowed to equilibrate to the desired bath temperature for about 10 min and flow times were measured.

Rheological measurements

Viscosities of CP-940, NaAlg, and GG hydrogels at concentrations of 0.1 to 1% (wt/vol) and their blends at different ratios were measured by using a Brookfield rheometer, model DV-III (Stoughton, MA) by taking 8 mL of the sample into a removable sample chamber equipped with a temperature probe within an accuracy of ±0.1°C. The removable sample chamber was then inserted into the water jacket assembly; an insulation cap was placed on the chamber to minimize the heat loss during measurements. Spindle SC-21 was used with the % torque in the range of 10 to 90 (i.e., within the recommended optimum range). Before taking readings, the rheometer scale was autozeroed and data were collected at 37°C. The temperature was maintained constant (±0.1°C) by circulating water into the water jacket using a stirred circulator bath Grant, model GR 150 (Cambridgeshire, UK). All calculations were done using the RHEOCALC software supplied with the instrument. Before the actual measurements, calibration of the rheometer was checked by using a standard fluid #1000 supplied with the instrument.

Gel persistence capacity

Gel persistence capacity (GPC) of different polymer solutions is defined as the time required to dissolve the hydrogel formed by the polymer solution in an artificial tear fluid. The hydrogel dissolving times of the polymer and blend solutions were determined by placing a drop of the polymer solution in 2 mL of freshly prepared artificial tear fluid. A modified watch glass loop assembly, surrounded by a water jacket to maintain the constant temperature of 37°C (see Fig. 1), was used for visual assessment of the gel formation. Time taken for complete dissolution of the gel was

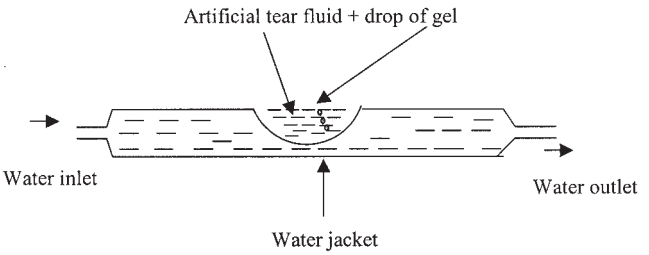

Figure 1 Modified watch glass loop assembly for determination of gel persistence capacity.

recorded. Artificial tear fluid was prepared by dissolving sodium chloride (0.670 g), sodium bicarbonate (0.200 g), and calcium chloride.$2H_2O$ (0.008 g) in 100 g of purified water.[19]

Determination of pH

The pH of polymer solution and their blends prepared in distilled water as well as in pH 6 phosphate buffer were measured using a Jenway, model 4330 (Dunmow, UK) combined conductivity and pH meter. The pH measurements were carried out in a beaker kept in water bath maintained at 37°C.

Ex vivo drug release

Three different polymer solutions were blended with different concentrations of solutions and studied for GPC. After performing several trial experiments, four blend solutions were finally selected for drug release studies. The selection was based on viscosity, GPC, and pH of the polymer blends. Four different formulations of TM in blend solutions of CP-940 : NaAlg : GG in different concentrations viz., 0.3 : 0.6 : 0.3, 0.5 : 0.2 : 0.2, 0.6 : 0.3 : 0.3, and 0.5 : 1.0 : 0.2 were prepared and designated as F1, F2, F3, and F4, respectively, and pure TM solution was designated as D.

The e*x vivo* drug release studies have been carried out in modified Franz diffusion cells using freshly excised bovine cornea[27] as a barrier membrane. Bovine eyeball was collected from the local slaughterhouse. The cornea was removed, washed with saline solution, and mounted on the donor compartment of the diffusion cell. Absence of leakage after mounting the cornea was confirmed by placement of 2 mL of distilled water and consistently observing for possible leakage. Known amounts of either formulations or conventional drug solution prepared in distilled water were added in the donor compartment of the diffusion cell containing 1 mL of the tear fluid. When the formulation touched the tear fluid in the donor compartment, it was readily converted into hydrogel. Diffusion of TM through the cornea into the receiver compartment was measured by collecting aliquot samples at definite time intervals and estimated by a UV spectrophotometer, Secomam, model Anthelie (Dumont, France) at 294 nm.

RESULTS AND DISCUSSION

pH versus viscosity of hydrogels

An ideal *in situ* gelling drug delivery system should be a free flowing liquid with low viscosity under non-physiological conditions (pH 4.0) to allow reproducible administration into the eye as drops. It should also undergo *in situ* phase transition to form a gel capable of withstanding shear forces in the cul-de-sac and to sustain the drug release at physiological conditions (pH 7.4). Several *in situ* gel forming systems have been developed to prolong the precorneal residence time of a drug to improve the bioavailability. Polymers employed in the present study demonstrate a transition from sol (liquid) to gel state once instilled in the cul-de-sac of the eye.

Various mechanisms are involved in the phase transition of the chosen polymers. Viscosities of NaAlg solutions (see Table I) increase when the pH is raised from its native value to the eye environment (pH 7.4). To reduce the total polymer content and to improve gelling properties, we have used a judicial combination of polymers to develop the suitable delivery system. CP-940 is a polyacrylic acid, which shows a sol-to-gel transition[30] in aqueous solution when the pH is raised above its pK_a value of about 5.5. GG, a viscosity-enhancing polymer, exhibits the sol-gel transition upon changing the pH of the solution. Kumar and Himmelstein[31] also developed a similar system by combining carbopol with hydroxypropylmethylcellulose, wherein it was observed that a reduction in carbopol concentration without compromising the *in situ* as well as rheological properties can be achieved by adding a suitable viscosity enhancer. Among the polymers studied here, CP-940 is pH sensitive and its sol-gel transformation occurs at pH 7.4. However, NaAlg is sensitive to divalent ions, such as Ca^{2+}, in the presence of which it can be converted into hydrogel. When both CP-940 and GG are present in the hydrogel matrix, an increase in viscosity is observed with a decrease in pH.

Table I presents the pH values of all the polymers and blend solutions prepared in distilled water and phosphate buffer (pH 6) at different polymer concentrations. Polymer solutions were prepared in phosphate buffer to avoid variations of pH in the final formulations. Polymer solutions prepared in distilled water showed wide-ranging pH values from 2.8 to 7.65. This difference in pH is due to the change in pK_a of the ionizing moiety of each polymer. Increase in the concentration of CP-940 and GG resulted in a decrease of pH of the polymer solution, whereas for NaAlg, pH

TABLE I
Results of pH, Viscosity, and Gel Persistence Capacity in Artificial Tear Fluid of Various Polymers/Blends Prepared in Different Media at Different Concentrations

Polymer / blends	Concentration in % (w/v)	pH of solution prepared in		Viscosity (cP) of solution prepared in buffer (6.0 pH)	GPC in ATF[a] (min)
		Water	Buffer (6.0 pH)		
NaAlg	0.1	6.64	6.03	1.38	1
	0.2	6.69	6.09	2.51	1
	0.3	6.96	6.12	3.60	2
	0.4	7.14	6.17	6.05	2
	0.5	7.30	6.18	9.61	2
	0.6	7.44	6.20	14.97	>2
	0.7	7.58	6.20	19.59	>2
	0.8	7.60	6.22	27.88	>2
	0.9	7.65	6.23	38.00	>2
CP-940	0.1	3.31	5.85	1.10	1
	0.2	3.13	5.66	1.75	1
	0.3	3.01	5.50	2.12	2
	0.4	2.97	5.46	2.53	2
	0.5	2.93	5.39	3.40	>2
	0.6	2.88	5.01	4.20	>2
	0.7	2.87	4.82	6.85	>2
	0.8	2.85	4.55	7.86	>2
	0.9	2.82	4.46	9.60	>2
GG	0.1	5.8	6.07	1.51	1
	0.2	5.71	6.04	2.51	1
	0.3	5.69	6.00	5.66	1
	0.4	5.67	5.98	9.17	2
	0.5	5.38	5.97	27.8[b]	>2
	0.6	5.34	5.60	41.0[b]	>2
	0.7	4.99	5.98	54.3[b]	>2
	0.8	4.97	5.93	82.8[b]	>2
	0.9	4.81	5.91	155.8[b]	>2
CP-940 : NaAlg : GG	0.3 : 0.6 : 0.3	5.31	6.08	18.22[b]	>2
	0.5 : 0.2 : 0.2	5.12	6.00	21.63[b]	>2
	0.6 : 0.3 : 0.3	5.01	5.98	26.01[b]	>60
	0.5 : 1.0 : 0.2	4.98	5.73	29.28[b]	>60

[a] Artificial tear fluid.
[b] Data generated using rheometer at 200 rpm.

increases with increasing polymer concentration. Such a concentration dependency on the pH of the solution was avoided by preparing polymer solutions in buffer media of pH 6. Those polymer solutions prepared in phosphate buffer showed a narrow pH range between 4.46 and 6.23 compared to polymer solutions prepared in water (see data displayed in Fig. 2). Hydrogel formation and dissolution of the individual polymers and their blends depend upon their concentrations and the responsive nature of the polymer to the artificial tear fluid. Further, it also depends on the pH of the original polymer solution. To compare the gelling property of three different polymers, solutions were prepared in phosphate buffer at pH 6.

Results of viscosity of all the polymer/blend solutions prepared in phosphate buffer at different concentrations are included in Table I. The viscosity of polymer solutions increases with increasing polymer concentration in NaAlg and GG, whereas for CP-940 increase in viscosity is not very significant compared to NaAlg and GG polymers. For instance, with an increase in concentration of polymer solutions from 0.1 to 0.9% (wt/vol), there was an increase in viscosity. At 0.9% (wt/vol), NaAlg has a viscosity of 38 cP while

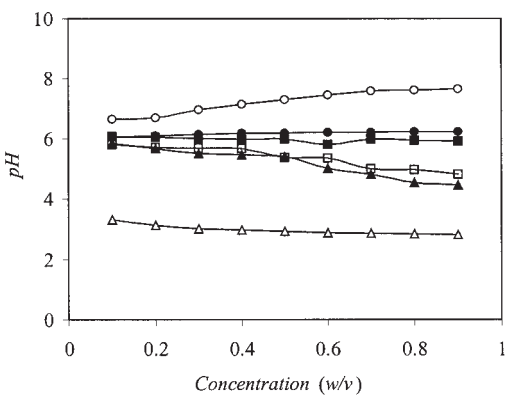

Figure 2 pH of different polymer solutions prepared in water (open symbols) and buffer (closed symbols) solutions at different concentrations at 37°C. ○, NaAlg; □, GG; △, CP-940

GG has a viscosity of 156 cP, whereas CP-940 shows a viscosity of only 9.6 cP. Thus, GG exhibits the highest viscosity compared to NaAlg and CP-940. All the viscosity measurements were carried out in a Schott Gerate viscometer equipped with an Ubbelohde capillary viscometer, but for GG at concentrations more than 0.5% (w/v), the rheometer was used to measure the viscosity at 200 rpm spindle speed because it formed a hydrogel at this concentration.

The GPC of polymers and their blends in artificial tear fluid at 37°C was determined using a specially designed glass apparatus shown in Figure 1. Results of GPC of all the individual polymer solutions and their blends are also included in Table I. GPC of the solution is measured for 1, 2, > 2, and > 60 min. These data suggest that CP-940 and NaAlg exhibited a higher GPC (i.e., more than 2 min) at a concentration of more than 0.3%, whereas GG exhibited higher GPC at the concentration of 0.4%. However, all the blends exhibited comparable GPC at the selected compositions. From the sample preparation procedures, it was observed that GPC increases with increasing concentration of the polymer solution. However, these concentrations could not form strong hydrogels under the physiological condition, but GG alone could form a stiff hydrogel even at pH 4.81 due to its high viscosity. On the other hand, with CP-940, with increasing concentration, the solution becomes more acidic and, hence, it cannot be readily neutralized by the buffering action of the tear fluid. CP-940 solution retained the liquid state at pH 5.85, but gelled upon exposure to physiological conditions. At any rate, the GPC data of this study are appropriate for ocular applications by using blend solutions of CP-940, NaAlg, and GG.

Rheological data

Rheological properties influence the drug release characteristics of the polymer solutions and hydrogels. Effect of rheological data of hydrogels and polymer solutions as well as blend solutions have been analyzed using empirical viscosity equations. According to Newton's law of viscosity, we have

$$\eta = \frac{\sigma}{D} \tag{1}$$

where σ is shear stress (N/m^2) (Pa) and D is shear rate (s^{-1}). If viscosity is independent of rate of shear, then the material is called Newtonian or it exhibits an ideal flow behavior. If viscosity increases by increasing the shear rate, then the material is said to be shear thickening or to follow the dilatant behavior. However, an opposite effect is known as shear thinning or pseudoplastic, in which a reversible decrease in viscosity can be obtained by increasing the shear rate. To calculate plastic viscosity, η, the Casson Standard equation was used:[23]

$$\sqrt{\sigma} = \sqrt{\sigma_0} + \sqrt{\eta D} \tag{2}$$

where σ and σ_0 are, respectively, the shear stress and yield stress, i.e., shear stress or zero shear rate. When the square root of shear stress is plotted versus the square root of shear rate, a straight line is obtained with an intercept equal to the square root of yield stress; the slope of the plot gives η. Values of η and σ_0 decide the blend performance and its composition.

An improved version of the Casson Standard equation is that of the Casson Chocolate equation[28] given in the form

$$(1 + a)\sqrt{\sigma} = 2\sqrt{\sigma_0} + (1 + a)\sqrt{\eta D} \tag{3}$$

where a is the spindle (or bob) radius/inner cap radius. Plotting $(1 + a)\sqrt{\sigma}$ vs $(1 + a)\sqrt{D}$, values of σ_0 and η can be calculated. For the yield value at complete rest, materials behave like semisolids and flow after certain shear stress, especially if the yield value has been exceeded. In such cases, the Bingham plastic equation[24,25] in the following form is used to compute the values of η and σ_0.

$$\sigma = \sigma_0 + \eta D \tag{4}$$

Values of plastic viscosity and yield stress for Casson's Standard and Casson's Chocolate and that of Bingham equations calculated for polymer solutions and hydrogels produced from the same solutions in artificial tear fluids are presented in Table II. Plastic viscosity data of all the blends in both the cases calculated from Bingham equation are higher than those calculated from Casson's Standard and Chocolate equations. There is no difference in plastic viscosity calculated from Casson's Standard and Chocolate equations. But, the values of yield stress calculated from Casson's Standard and Chocolate equations are different. Smaller values of yield stress are obtained for Casson's Chocolate equation than Casson's Standard equation. These results support that mixed polymer solutions or hydrogels might have higher strength to withstand the low shear forces likely to be encountered in the cul-de-sac of the eye as well as to prolong the residence time of the drug in the eye. The present rheological data suggest that the mixed systems exhibit psuedoplastic or Newtonian flow behavior.

Blend compatibility

Miscibility of polymeric blends is important if one is interested in developing such materials for controlled release applications. In the present study, blend com-

TABLE II
Results of Plastic Viscosity and Yield Stress Value Calculated from Different Equations

Blends CP-940:NaAlg: GG	Plastic viscosity (cP) calculated by			Yield stress (N/m^2) calculated by		
	Bingham	Casson (Standard)	Casson (Chocolate)	Bingham	Casson (Standard)	Casson (Chocolate)
Polymer solutions						
0.3 : 0.6 : 0.3	28.7	20.5	20.5	1.06	0.31	0.27
0.5 : 0.2 : 0.2	30.7	20.9	20.9	1.30	0.42	0.37
0.6 : 0.3 : 0.3	58.4	52.1	52.1	0.65	0.07	0.06
0.5 : 1.0 : 0.2	41.5	31.7	31.7	0.75	0.20	0.18
Gels produced in artificial tear fluid						
0.3 : 0.6 : 0.3	391.0	210.0	210.0	9.15	4.27	3.77
0.5 : 0.2 : 0.2	68.6	43.7	43.7	4.55	1.66	1.46
0.6 : 0.3 : 0.3	322.0	145.7	145.7	14.3	7.87	6.95
0.5 : 1.0 : 0.2	411.2	223.6	223.6	10.2	5.12	4.65

patibility has been investigated at lower polymer concentrations by calculating the reduced viscosity (η_{sp}/c) and then by judging the nature of the plot of (η_{sp}/c) versus concentration, c. In general, a linear relationship exists for miscible blends.[32] Miscibility of polymer blends in solution was also investigated by calculating the polymer–polymer interaction parameter, Δb of the blends using the general relation[33,34] given by eq. (5) and modified for the ternary systems as per eq. (6).

$$b_m = x_1^2 b_1 + x_2^2 b_2 + 2x_1 x_2 b_{12} \quad (5)$$

$$b_m = x_1^2 b_{11} + x_2^2 b_{22} + x_3^2 b_{33} + 2x_1 x_2 x_3 b_{123}\left(\frac{1}{x_1 b_{11}} + \frac{1}{x_2 b_{22}} + \frac{1}{x_3 b_{33}}\right) \quad (6)$$

In the above equations, x_1, x_2, and x_3 refer to mass fractions of polymers 1, 2, and 3; b_{11}, b_{22}, and b_{33} are the respective interaction parameters; b_{123} is the ternary interaction parameter of the blend system, and b_m defines the global interaction between all the polymers. Interaction parameters, b_{11}, b_{22}, b_{33}, and b_m have been calculated from the slopes of the plot of reduced viscosity of polymer solutions and their blend solutions versus concentration.

Intrinsic viscosity values have been calculated for the three individual polymers and their blends from the intercepts calculated by extrapolating straight lines of the reduced viscosity versus concentration plot. Values of $[\eta]_m$ have been obtained from such plots for noninteracting blends using[32,35]

$$[\eta]_m = x_1[\eta]_1 + x_2[\eta]_2 + x_3[\eta]_3 \quad (7)$$

Interaction parameter, b_{123}* can be calculated theoretically using the modified original equation

$$b_{12}^* = (b_{11} b_{22})^{1/2}(\text{Original}) \quad (8a)$$

$$b_{123}^* = (b_{11} b_{22} b_{33})^{1/3} \quad (8b)$$

Here, the values of b_{11}, b_{22}, and b_{33} are slopes of the plots of reduced viscosity versus concentration of the individual polymers calculated using the classical Huggins equation.[34,35]

$$[\eta]_{sp}/c = [\eta]_0 + bc \quad (9)$$

Thus, the difference, Δb between the theoretically calculated b^*_{123} from eq. (8b) and that of experimental b_{123} calculated from eq. (6) is given as

$$\Delta b = (b_{123} - b_{123}^*) \quad (10)$$

It has been stated[34,36] that if $\Delta b > 0$, then the polymer blends are miscible and if $\Delta b < 0$, phase separation occurs. The calculated Δb values along with experi-

TABLE III
Experimental and Theoretical Intrinsic Viscosity and Interaction Parameters of the Blends at 37°C

GG–NaAlg–CP-940 blend	Intrinsic viscosity		Parameter b_{123} calculated		Δb
	Experimental	Theoretical	Experimental	Theoretical	
20 : 20 : 60	30.36	6.33	16,296	92.5	16,203
20 : 60 : 20	27.18	7.77	5,399	92.5	5,306
60 : 20 : 20	11.31	6.86	13,570	92.5	13,478

mental, theoretical intrinsic viscosities, and b_{123} values are presented in Table III. Positive values of Δb suggest that the blends are compatible.

Ex vivo release study

Formulations giving acceptable values of GPC (i.e., > 10 h) have been selected for *ex vivo* drug diffusion in the modified Franz diffusion cells using freshly excised bovine cornea as a barrier membrane. When the definite amount of formulation was added in the donor compartment of the diffusion cell containing 1 mL of artificial tear fluid, the solution was readily converted into a hydrogel. Results of *ex vivo* release data of formulations F1 to F4 are compared with the pure drug in Figure 3. Triplicate release data were reproducible within 3% SD, but the release curves are drawn through the average data points. The release of pure drug solution is higher than all formulations through the bovine cornea. Among all the formulations studied, drug release was slow for formulation F4, due to its high viscosity. In the formulations studied, CP-940 is sensitive to pH of the tear fluid, i.e., it becomes a hydrogel at pH 6.0, but NaAlg is sensitive to Ca^{2+} ions of the tear fluid, while GG acts as a viscolyser and enhances the gelation of other polymers.

Time required for 50% of drug release (T_{50}) was calculated from the plot of % drug release versus time as shown in Figure 3 by extrapolating the data to time axis. These results are presented in Table IV. Formulations F1 and F2 have the same T_{50} values even though the hydrogel viscosity is different. Hence, the release is not only dependent on the viscosity of the hydrogel, but also on the composition of the formulation. The highest T_{50} observed for formulation F4 is 300 min. This suggests that, when the drug is incorporated into hydrogel-forming solutions, 50% of drug release could be extended up to 300 min, whereas 50% of drug release from the conventional solution could occur at 60 min.

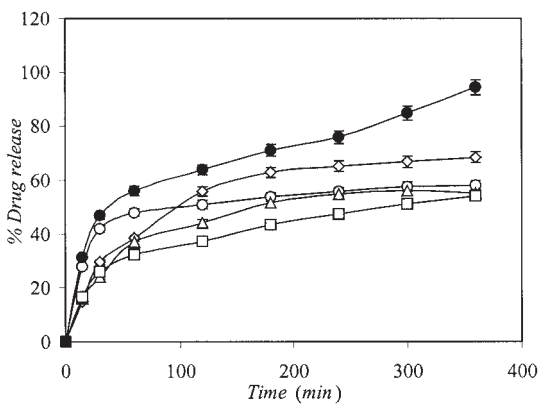

Figure 3 Release data of timolol maleate from different gel forming formulations and pure drug solution in distilled water at 37°C. ◇, F1; ○, F2; △, F3; □, F4; ●, D.

TABLE IV
Results of T-50 for Different Formulations

Formulation code	Polymers CP-940 : NaAlg : GG	T_{50} (min)
F1	0.6 : 0.3 : 0.3	120
F2	0.3 : 0.6 : 0.3	120
F3	0.5 : 0.2 : 0.2	180
F4	0.5 : 1.0 : 0.2	300
D	Drug solution (0.25% in distilled water)	60

CONCLUSION

This study demonstrates the advantages of *in situ* gelling polymers in ophthalmic drug delivery applications. Aqueous solutions of different compositions containing individual and blend polymer solutions have been studied to seek their suitability as *in situ* hydrogel forming systems. Results obtained for carbopol-940, sodium alginate, and guar gum and their blends demonstrate the importance of pH-responsive ocular gel forming solutions to slow the release of timolol maleate. Blending of three polymers is effective to obtain a mixed hydrogel for the effective release of timolol maleate. Drug release could be extended five times more when it was incorporated in hydrogel-forming solutions than conventional eye drops. Results of this study demonstrate the usefulness of the systems developed. These can be administered in the eye as drops to form hydrogels, which could withstand the shear force in the cul-de-sac.

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References

1. Hoffman, A. S. Adv Drug Delivery Rev 2002, 43, 3.
2. Hennink, W. W.; van Nostrum, C. F. Adv Drug Delivery Rev 2002, 53, 13.
3. Rudzinski, W. E.; Dave, A. M.; Vaishnav, U. H.; Kumbar, S. G.; Kulkarni, A. R.; Aminabhavi, T. M. Designed Monom Polym 2002, 5, 39.
4. Meseguer, G.; Gurny, R.; Rozier, A.; Plazonnet, B. Int J Pharm 1993, 57, 163.
5. Sanzgiri, Y. D.; Maschi, V.; Crescenzi, L.; Topp, E. M.; Stella, V. J. J Controlled Release 1993, 26, 195.
6. Srividya, B.; Cardoza, R. M.; Amin, P. D. J Controlled Release 2001, 73, 205.
7. Lin, H. R.; Sung, K. C. J Controlled Release 2000, 69, 379.

8. Miyazaki, S.; Suzuki, S.; Kawasaki, N.; Endo, K.; Takahashi, A.; Attwood, D. Int J Pharm 2001, 229, 29.
9. Paulsson, M.; Hagerstrom, H.; Edsman, K. Eur J Pharm Sci 1999, 9, 99.
10. El-Kamel, A. H. Int J Pharm 2002, 241, 47.
11. Aminabhavi, T. M.; Yenkar, P. S.; Kulkarni, A. R. Polym News 2003, 28, 150.
12. Zignani, M.; Tabatabay, C.; Gurny R. Adv Drug Del Rev 1995, 16, 51.
13. Kumbar, S. G.; Dave, A. M.; Aminabhavi, T. M. J Appl Polym Sci 2003, 90, 451.
14. Rudzinski, W. E.; Chipuk, T.; Dave, A. M.; Kumbar, S. G.; Aminabhavi, T. M. J Appl Polym Sci 2003, 87, 394.
15. Kumbar, S. G.; Soppimath, K. S.; Aminabhavi, T. M. J Appl Polym Sci 2003, 87, 1525.
16. Hartmann, V.; Keipert, S. Die Pharm 2000, 55, 440.
17. Wilson, C. G.; Zhu, Y. P.; Frier, M.; Rao, L. S.; Gilchrist, P.; Perkins, A. C. Br J Ophthalmol 1998, 82, 1131.
18. Chang, J. Y.; Oh, Y.; Choi, H.; Kim, Y. B.; Kim, C. Int J Pharm 2002, 241, 155.
19. Hooper, H. H. Macromolecules 1990, 23, 1096.
20. Draget, K. I.; Skjak-Braek, G.; Smidsroed, O. Int J Biol Macromol 1997, 21, 47.
21. Goldstein, A. M.; Alter, E. N.; Seaman, J. K. In Industrial Gums; Whilster, R. L.; BeMiller, J. N., Eds.; Academic Press: New York, 1973; 2nd ed., Chap. 14.
22. Bhardwaj, T. R.; Kanwar, M.; Lal, R.; Gupta, A. Drug Dev Ind Pharm 2000, 26, 1025.
23. Casson, N. In Rheology of Dispersed Systems; Mills, C. C. Ed.; Pergamon Press: New York, 1959.
24. Bingham, E. C. J Am Ceram Soc 1924, 7, 430.
25. Bingham, E. C. J Franklin Inst 1924, 197, 99.
26. Pierce, P. E.; Schoff, C. K. In Kirk-Othmer Encyclopedia of Chem Technology; John Wiley & Sons: New York, 1980; 3rd ed., vol. 20, p. 259.
27. Le Bourlais, C.; Acar, L.; Zia, H.; Sado, P. A.; Needham, T.; Leverge, R. Progr Retinal Eye Res 1998, 17, 33.
28. Kaur, I. P.; Kanwar, M. Drug Dev Ind Pharm 2002, 28, 473.
29. Aminabhavi, T. M.; Banerjee, K. J Chem Eng Data 1998, 43, 509.
30. Davies, N. M.; Farr, S. J.; Hadgraft, J.; Kellaway, I. W. Pharm Res 1991, 8, 1039.
31. Kumar, S.; Himmelstein, K. J. J Pharm Sci 1995, 84, 344.
32. Kurkuri M. D.; Kulkarni A. R.; Aminabhavi T. M. Polym Plast Tech Eng 2002, 41, 469.
33. Van Oene, H. Rheology of Polymer Blends and Dispersions, Polymer Blends; Paul, D. R.; Newman, S., Eds.; Academic Press: Orlando, 1978.
34. Singh, Y. P.; Singh, R. P. Eur Polym Mater 1983, 19, 535.
35. Toti, U. S.; Amur, K. S.; Kariduraganavar, M. Y.; Manjeshwar, L. S.; Aralaguppi, M. I.; Aminabhavi, T. M. J Appl Polym Sci 2002, 83, 283.
36. Chee, K. K. Eur Polym Mater 1990, 26, 423.