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Mixture Experimental Design in the Development of a Mucoadhesive Gel Formulation

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The objective of the present study is to apply response surface methodology to the design and analysis of composite experiments containing independent covariate(s). The approach is illustrated here by the study of viscosity characteristics of a polymeric mucoadhesive formulation in multicomponent solvent vehicles. The nonaqueous formulation will produce a gel network with significant rheological change when in contact with body fluids. The process of water inclusion will induce not only solvent compositional change of the mixture but also concomitant dilution of the polymer concentration. To study the viscosity change over the solvent compositions and polymeric concentrations of interest, an experimental design is utilized consisting of a 10-point simplex-centroid lattice augmented with three interior points at each polymeric concentration. The contour patterns are compared with the experimental data using the variance and lack of fit, starting with the Scheffe linear model and building up to the full cubic model including the covariate terms. The fitted model provides information needed to predict optimum formulations, i.e., initial viscosity of less than 100 cP, but yielding rheological profiles commensurate with high degrees of substantivity when diluted with water. For illustrative purposes, the Carbopol resins neutralized with a 1:1 molar equivalent ratio of triethanolamine in three primary solvents, propylene glycol, glycerol formal, and water, were chosen for this study.

KEY WORDS: mixture model; pharmaceutical gel formulation; Carbopol gel; viscosity; solvent effects on polymer gel rheology.

INTRODUCTION

Nasal delivery of drugs from solution or suspension is very difficult to achieve, primarily because of the lack of retention of applied formulation in the nasal cavity. Highly viscous, mucoadhesive formulations having required substantivity could easily be formulated, but such systems would not be amenable to insertion into the nasal cavity as a nasal spray. A unique polymeric formulation with a low viscous fluid-like property in nonaqueous solvent mixtures (e.g., propylene glycol and glycerol formal) has therefore been developed in our laboratories. The formulation can easily be sprayed into the nasal cavity but quickly obtains a rheological profile yielding a high degree of substantivity upon dilution with the water present in the nasal cavity.

The optimization of such a formulation is extremely difficult since (a) a rheological profile must be obtained (prior to and after insertion into the nasal cavity); (b) the solvent composition is continuously changing upon insertion into the nasal cavity, resulting in dramatic changes in rheological behavior and solubility of the polymer; and (c) the polymer is being continuously diluted with moisture in the nasal passage, upon changing the rheological profile.

To facilitate optimization we have attempted to apply the response surface methodology (RSM) to the design and analysis of the above mucoadhesive formulation with composite experiments containing independent covariates. Statistically, the interpretation of the data in composite experiments where the compositional components represent proportionate amounts of the mixture differs from those of classical factorial experiments where the responses vary depending on the actual amounts of each of the input variables. The experimental design to study such mixtures has been the subject of many studies (1) and has enjoyed extensive application in chemicals, geology, petroleum, foods, tobaccos, and many other areas (2–5).

Optimization of response of interest for any mixture or combination of the ingredients in composite experiments can be made quantitatively by appropriate statistical response surface methodology such as steepest ascent (6), sequential simplex search (7), or extreme vertices design (8). To complicate further the optimization process for the design and analysis, the effect of independent or concomitant variables such as total irritation response, dose loading, temperature, cost, or reaction time should also be considered. When including one or more covariates in mixture experiments, a more complex design strategy is required (9). Relatively little has been done to include covariates in the mixture designs in pharmaceutical formulations.

The objective of this study is to present methodologies for design and analysis of mixture experiments containing covariate(s) that will yield a better understanding of the statistical approach to experimentation with mixtures. The approach is illustrated in this work by the study of viscometric behavior of polymeric mucoadhesive formulations in multicomponent solvent vehicles.

EXPERIMENTAL DESIGN

In this study, RSM modified for mixture experiments including independent covariates is employed to estimate the rheological response variations during water inclusion and, from this information, to predict the most feasible self-gelling formulation compositions. At the beginning of the study a screening design was run first to identify the significant factors in order to simplify the system. The neutralizing effect by several low molecular weight amines was evaluated. A list of candidate pharmaceutical solvents was screened for the mixture component in the vehicle mixture given the rheological and physicochemical considerations (10). For illustrative purposes, the Carbopol resins neutralized with a 1:1 molar equivalent ratio of triethanolamine in three primary solvents, propylene glycol (P), glycerol formal (G), and water (W), were chosen for the polymeric gel systems in this study. The process of water inclusion with the polymeric formulation will induce not only the solvent com-

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positional change of the mixture but also the concomitant dilution of the polymer concentration, the independent covariate which is the factor believed to affect significantly the viscosity response of the systems.

To simulate the dilution processes during the inclusion of water, the response surface of viscosity contours over the solvent compositions of the P-G-W system were first investigated as a function of polymer concentration. The augmented simplex-centroid design with a 10-point arrangement was used for design lattices as shown in the weight fraction ternary diagram in Fig. 1 for each individual polymer concentration (1). The experimental lattices consist of six equispaced points on the boundary of the triangle and four interior points strategically positioned to provide greater flexibility when modeling a mixture surface (12). A three-dimensional display such as the triangular bar in Fig. 2 can then be constructed. The viscosity change over the polymer concentration may be fully represented by placing the ternary diagram of individual polymer concentration as the cross section of the bar at the appropriate depth for that concentration. To obtain the most desired set of formulations, any systematic trend of viscosity changes in the representational points along the length of the bar such as the contour from point A to point B in Fig. 2 should be optimized.

The influence on the response of each component singly or in combination with the other components can be obtained by expressing the blending properties of the mixture components with Scheffe-type polynomial models (13) with q components ($q = 3$ in this case) as equations.

Linear:

$$\text{response} = \sum_{i=1}^{q} \beta_i X_i \tag{1a}$$

Quadratic:

$$\text{response} = \sum_{i=1}^{q} \beta_i X_i + \sum_{i<j}\sum^{q} \beta_{ij} X_i X_j \tag{1b}$$

If the linear or quadratic formula is deemed inadequate for graduating the response, the remedy would be progressing up to special forms or even higher orders of polynomial models as following.

Special cubic:

$$\text{response} = \sum_{i=1}^{q} \beta_i X + \sum_{i<j}\sum^{q} \beta_{ij} X_i X_j$$

$$+ \sum_{i<j<k}\sum\sum^{q} \beta_{ijk} X_i X_j X_k \tag{1c}$$

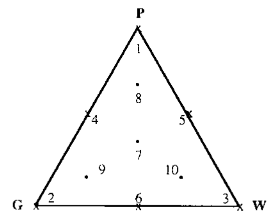

Fig. 1. Augmented simplex-centroid design with a 10-point arrangement in the weight fraction ternary diagram. P, propylene glycol; G, glycerol formal; W, water.

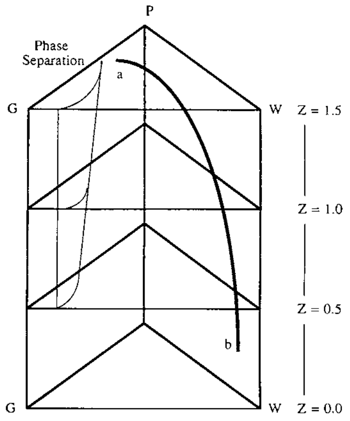

Fig. 2. Triangular bar diagram for representation of solvent compositions and concentration depths. Z, polymeric concentration as wt% of total.

Special quartic:

$$\text{response} = \sum_{i=1}^{q} \beta_i X_i + \sum_{i<j}\sum^{q} \beta_{ij} X_i X_j$$

$$+ \sum_{m=1}\sum \sum_{i<j<k}\sum^{q} \beta_{ijkm} X_i X_j X_k X_m \tag{1d}$$

Full cubic:

$$\text{response} = \sum_{i=1}^{q} \beta_i X_i + \sum_{i<j}\sum^{q} \beta_{ij} X_i X_j$$

$$+ \sum_{i<j}\sum^{q} \delta_{ij} X_i X_j (X_i - X_j)$$

$$+ \sum_{i<j<k}\sum\sum^{q} \beta_{ijk} X_i X_j X_k \tag{1e}$$

where β or δ values are the fitted regression coefficients for each term and the X values are the proportions of the formulation components in the mixture, and they should all account for the compositional restraints (2).

$$\sum_{i=1}^{q} X_i = 1 \quad \text{and} \quad 0 \le X_i \le 1, \quad i = 1, 2, \ldots, q \tag{2}$$

On the other hand, the effects of linear and blending on the response of interest for the independent covariates are expressed by a standard polynomial for (9) that consists of n covariates ($n = 1$ in this case) as the equation

$$\text{response} = \alpha_0 + \sum_{l=1}^{n} \alpha_l Z_l + \sum_{l<m}\sum^{n} \alpha_{lm} Z_l Z_m + \ldots \tag{3}$$

If the independent covariates are quantitative factors and curvature in the response is to be modeled across three or more continuous levels, then higher-order terms such as $\alpha_{ll}Z_l^2$, $\alpha_{lll}Z_l^3$, $l = 1, 2, \ldots, n$, are added to Eq. (3).

The terms in the most complete combined model are obtained by taking the product of the polynomial equation modeling for the mixture components and the equation describing the covariates. For instance, the modeling equation for a system of three mixture components in quadratic term and one independent covariate in second order with continuous level is expressed as

$$\text{response} = \left(\sum_{i=1}^{3} \beta_i X_i + \sum_{i<j}^{3} \sum \beta_{ij} X_i X_j \right) \left(\alpha_0 + \sum_{l=1} \alpha_l Z_l + \sum_{l=1} \alpha_{ll} Z_l^2 \right) \quad (4)$$

The search for the adequacy of the fitted model by analyzing the lack of fit and residuals is initiated from linear term and sequentially increases to a higher order in both compartments. The goodness of fit is determined by the experimental errors which are available from replicated observations at one or more design lattices and the sum of the squares of the residual differences between experimental observations and model predictions as described in the Appendix. To increase the sampling size and randomness of the data set, the appropriate number of simulated data calculated from the fitted model equations of each level may be randomly selected in order to augment the analysis. The additional degrees of freedom are used to obtain estimates of sufficient precision and to allow the fitting of a more elaborate approximating function which can cover a wider experimental region.

MATERIALS AND METHODS

Preparation of Polymer Gels or Dispersions

Carbopol 934P polymer resin was supplied by B. F. Goodrich Chemical Co. Triethanolamine (TEA), used as the neutralizing agent, was obtained from Sigma Chemical Co. Propylene glycol (P), glycerol formal (G), and deionized water (W) were used as vehicle solvents. Known amounts of Carbopol 934P were slowly added to the stirring vortexed solvents of P, G, and W, respectively, to make 0.5, 1.0, and 1.5 wt% polymer solutions. The solutions were lightly shaken with a shaker (Orbit Shaker, Lab-Line Instruments Inc., Melrose Park, IL) overnight to assure the complete dissolution of the polymer. Solutions of known composition in different solvents were mixed uniformly from the above stock solutions in glass vials and adequate amounts of TEA were added. The particle size distribution of dispersions with low viscosity was measured by a particle sizer (Nicomp 370, Pacific Scientific Instrumental Co., Silver Springs, MD). The polymeric gels with a high consistency were vigorously shaken for 3 min with a mixer (VWR Scientific Industries Inc., Bohemia, NY) and then centrifuged for 15 min at 3,000 rpm to remove the entrapped air in the gel, which was then stored overnight before the viscosity was measured.

Viscosity Measurements

All viscosity studies were carried out using a Rheomat 135S (Contraves Co., Cincinnati, OH) viscometer with suitable measuring attachment at temperature 30°C. For dispersions with viscosities lower than 100 cP, double coaxial measuring systems (MS-115) were used. For gels with a higher viscosity, concentric cylinder measuring systems (DIN-125) were used. A shear rate of 100 $\sec^{-1}$ was chosen for all studies.

Data Analysis

Analysis of variance and the regression coefficients for the linear, quadratic, and higher-order interaction terms of the polynomial model were calculated by computer software developed by SAS Institute Inc. Sygraph (Systat Inc., Evanston, IL) was employed to produce the ternary diagram contour plots.

RESULTS AND DISCUSSION

The results clearly indicate that the Carbopol resins show different phenomenological behavior in various compositions of nonaqueous solvent mixtures such as propylene glycol (P) and glycerol formal (G). Figure 3 shows the phase diagram for neutralized Carbopol dispersed in a wide range of solvent compositions of P and G at 30°C. It is interesting to note that Carbopol was completely dispersible in P/G mixtures having weight fraction ratios ranging from 75/25 to 60/40 (for 0.5 wt% of Carbopol or higher). The formation of the uniform dispersions (particle sizes distributed around 1–5 μm) significantly decrease the viscosities of the solutions to a sprayable scale of less than 50–100 cP. It is also apparent that the phase separation of the polymeric resins from the dispersions will occur for higher contents of G in the solvent mixtures (more than 45 wt% of G in 0.5 wt% or higher of Carbopol). The observation is important because the dispersion with a low viscosity in the solvent composition of P/G mixture could be easily sprayed by commercial dispensers without the need of additives, e.g., oils or surfactants.

Besides showing low viscosity characteristics in the polymeric solvent mixture, significant enhancement in viscosity occurs when the formulation is diluted with water and the viscosity continues to increase regardless of the polymer

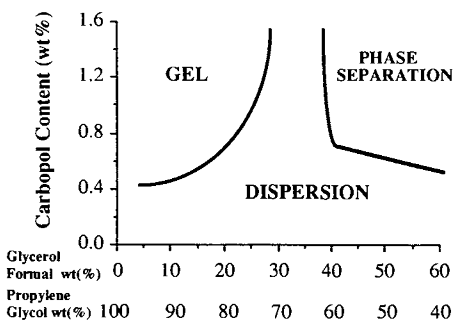

Fig. 3. Phase diagram for neutralized Carbopol with a 1:1 molar equivalent ratio of TEA in a mixture of P and G at 30°C.

concentration decreasing (10). It is important to note that both polymer concentration and solvent compositions have significant influence on the rheological behavior of the systems during inclusion of water.

In this study, the viscosity behavior for the solvent composition as the mixture component and the polymer concentration as the independent covariate was examined by RSM with a 10-point simplex-centroid design. The solvent compositions for the design lattices of four levels of polymer concentrations over the P-G-W mixtures and the corresponding viscosity experimental data are listed in Table I. For the proper experimental region, the transformation of viscosity data was made by logarithmic transformation. The transformed data were then used to fit the models defined by Eqs. (1a)–(1e) from the simplest linear model up to the full cubic model in the component proportions. A summary of pertinent model and regression coefficient over each term in the model for the individual polymer concentration is given in Table II. The postulated models were chosen based on the adequate lack of fit with significant confidence level of 95% and the analysis of variance with satisfactory values of R^2. Figures 4 a–d show the ternary contour diagrams with changes in apparent viscosity at shear rate of 100 $\sec^{-1}$ for 1.5, 1.0, 0.5, and 0 wt% Carbopol 934P, respectively.

As can be seen in these figures the viscosity increased with increasing polymer concentration and water content in the solvent mixtures. Obviously, the polymer concentration has significant effect on viscosity change over the solvent composition at lower polymer concentrations. From the linear regression coefficients of the postulated models in Table

Table I. Design Lattices for Solvent Compositions and Corresponding Experimental Viscosity Data

Design lattice	Carbopol content (wt% of total)	Propylene glycol (wt fr)[a]	Glycerol formal (wt fr)[a]	Water (wt fr)[a]	Viscosity (cP)	
1	0.0	1.000	0	0	34.34	
2	0.0	0	1.000	0	10.53	
3	0.0	0	0	1.000	0.98	
4	0.0	0.500	0.500	0	17.20	
5	0.0	0.500	0	0.500	5.19	
6	0.0	0	0.500	0.500	3.18	
7	0.0	0.333	0.333	0.333	6.27	7.25
8	0.0	0.667	0.167	0.167	13.69	11.85
9	0.0	0.167	0.667	0.167	7.84	8.54
10	0.0	0.167	0.167	0.667	2.75	2.05
1	0.5	1.000	0	0	869.10	
2	0.5	0	1.000	0	13.00	
3	0.5	0	0	1.000	2557.54	
4	0.5	0.500	0.500	0	17.78	
5	0.5	0.500	0	0.500	2192.30	
6	0.5	0	0.500	0.500	72.73	
7	0.5	0.333	0.333	0.333	133.11	125.60
8	0.5	0.667	0.167	0.167	209.29	198.20
9	0.5	0.167	0.667	0.167	27.50	21.50
10	0.5	0.167	0.167	0.667	621.66	605.51
1	1.0	1.000	0	0	2431.00	
2	1.0	0	1.000	0	13.42	
3	1.0	0	0	1.000	5102.00	
4	1.0	0.500	0.500	0	19.02	
5	1.0	0.500	0	0.500	3145.72	
6	1.0	0	0.500	0.500	488.29	
7	1.0	0.333	0.333	0.333	1289.00	1201.21
8	1.0	0.667	0.167	0.167	1865.00	1782.00
9	1.0	0.167	0.667	0.167	98.00	81.00
10	1.0	0.167	0.167	0.667	2941.00	2715.00
1	1.5	1.000	0	0	3385.65	
2	1.5	0	1.000	0	20.54	
3	1.5	0	0	1.000	6211.14	
4	1.5	0.500	0.500	0	35.65	
5	1.5	0.500	0	0.500	6016.00	
6	1.5	0	0.500	0.500	3008.00	
7	1.5	0.333	0.333	0.333	2941.00	2798.00
8	1.5	0.667	0.167	0.167	3615.00	3654.00
9	1.5	0.167	0.667	0.167	201.15	225.12
10	1.5	0.167	0.167	0.667	4550.00	4647.00

[a] All values for the components are weight fractions of the mixture.

Table II. Summary of Pertinent Response Surface Models for Individual Polymer Concentration[a]

Response surface model	Significance (α)	Adjusted R^2
0.0 wt% Carbopol solution—linear model		
$\ln(\eta) = 3.39\ P + 2.33\ G - 0.08\ W$	0.05	0.988
0.5 wt% Carbopol solution—quadratic model		
$\ln(\eta) = 6.64\ P + 2.63\ G + 7.85\ W - 6.93\ P * G - 3.20\ G * W + 1.64\ W * P$	0.05	0.992
1.0 wt% Carbopol solution—special quartic model		
$\ln(\eta) = 7.82\ P + 2.62\ G + 8.56\ W - 8.92\ P * G + 2.58\ G * W - 0.37\ W * P$		
$+ 100.19\ P * P * G * W + 28.01\ P * G * G * W + 4.05\ P * G * W * W$	0.05	0.996
1.5 wt% Carbopol solution—special quartic model		
$\ln(\eta) = 8.13\ P + 3.02\ G + 8.73\ W - 8.01\ P * G + 8.52\ G * W + 1.08\ W * P$		
$+ 115.85\ P * P * G * W + 17.63\ P * G * G * W - 40.21\ P * G * W * W$	0.05	1.000

[a] P = weight fraction of propylene glycol of the mixture; G = weight fraction of glycerol formal of the mixture; W = weight fraction of water of the mixture; η = apparent viscosity as centipoises; adjusted $R^2 = 1 - \{[(N - 1)/(N - p)][SSE/(SSE + SSR)]\}$; SSR, regression sum of squares; SSE, residual sum of squares.

II, it is revealed that water is the most influential solvent among the three solvent components affecting the response variables.

The influence of increasing water content in solvent mixtures on rheological properties of Carbopol polymer can be described by the changes in alternating the solvation ability of the polymer chains with solvents and the extent of physical entanglement among polymer segments. For neutralized Carbopol polyacrylic resins, the viscosity is significantly affected by the degree of entanglement between

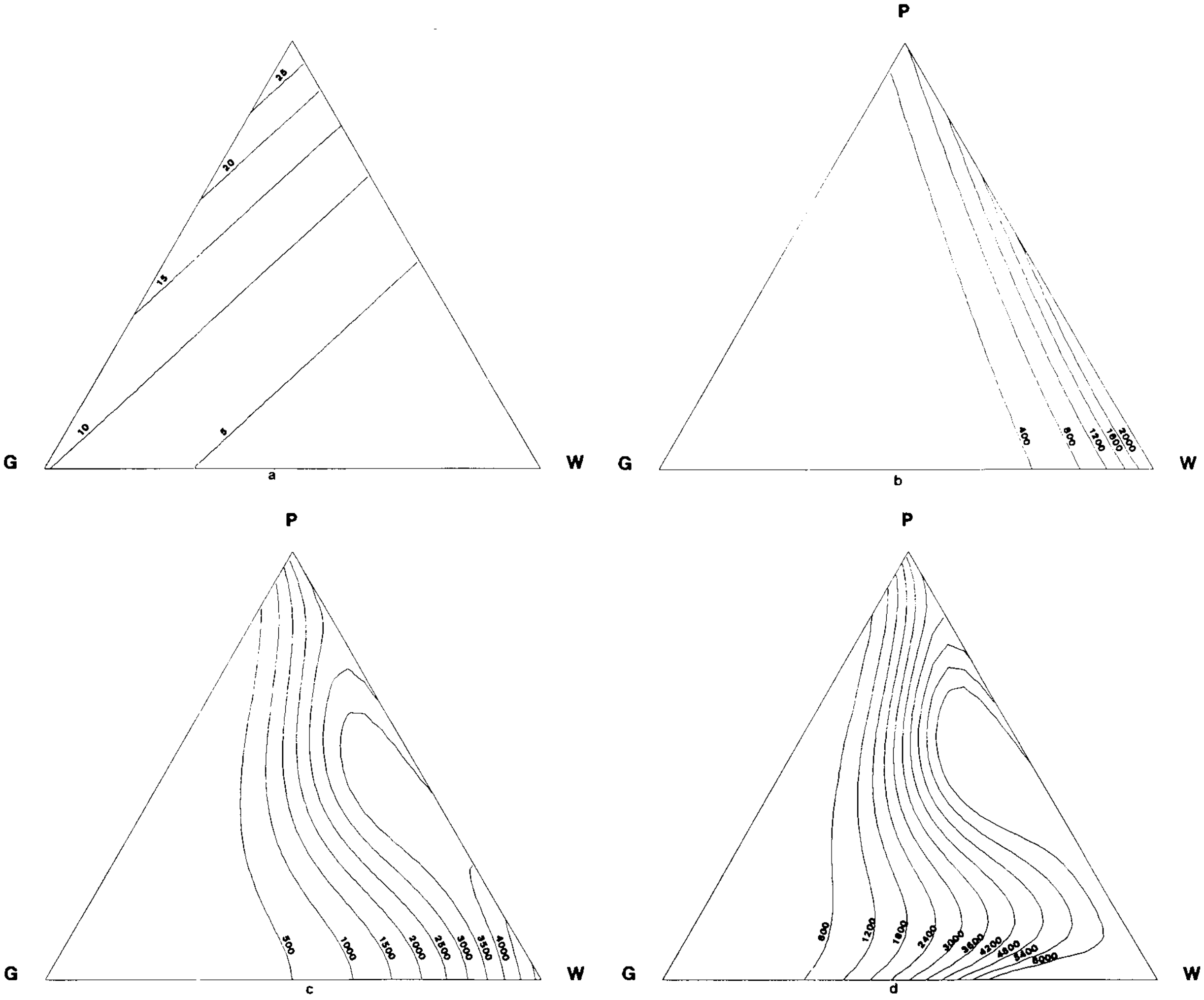

Fig. 4. Ternary contour diagrams with changes in apparent viscosity calculated from the fitted model equations listed in Table II for (a) 0.0, (b) 0.5, (c) 1.0, and (d) 1.5 wt% Carbopol 934P solutions.

Table III. Regression Parameters for the Most Fitted Model in the Form of Solvent Components and Polymer Concentration Covariate

Variable[a]	Regression coefficient	SE	Probability >F
P	3.53	0.10	0.0001
G	2.39	0.08	0.0001
W	0.69	0.10	0.0001
P * G	−0.40	0.44	0.3673
G * W	−1.14	0.45	0.0121
W * P	−0.82	0.50	0.1006
P * G * W	−4.81	2.42	0.0472
P * Z	7.70	0.31	0.0001
G * Z	0.13	0.28	0.6480
W * Z	15.78	0.33	0.0001
P * G * Z	−17.12	1.43	0.0001
G * W * Z	−4.68	1.45	0.0013
W * P * Z	4.77	1.61	0.0030
P * G * W * Z	46.83	7.77	0.0001
P * Z * Z	−3.08	0.20	0.0001
G * Z * Z	0.17	0.18	0.3438
W * Z * Z	−7.12	0.21	0.0001
P * G * Z * Z	8.77	0.91	0.0001
G * W * Z * Z	6.52	0.93	0.0001
W * P * Z * Z	−2.92	1.06	0.0045
P * G * W * Z * Z	−14.13	4.97	0.0045

[a] P = weight fraction of propylene glycol of the mixture; G = weight fraction of glycerol formal of the mixture; W = weight fraction of water of the mixture; Z = Carbopol concentration as wt% of total; adjusted $R^2 = 0.9979$.

neighboring polymer chains, which is higher at a high polymer concentration or in the extended form of polymer chains associated with the more hydrophilic solvents. When the solvent composition is shifted from a poor solvent mixture such as P or G to a good solvent mixture with a higher water content, the polymer–solvent interactions are favored over the polymer chain–chain interactions. Thus polymer chains are expanded from the contracted forms of polymeric particles in the dispersion and result in higher viscosities.

When considering the effects of both solvent composition and polymer concentration together, a more complex analysis strategy is employed for this four-variable system. The strategy attempts to increase the size of the experimental program so that a complete randomization in execution of the final model is possible. Besides the experimental data in Table I as the input, a set of 200 viscosity data points was generated randomly from each postulated equation listed in Table II. The variances and the regression coefficients in the combined model were tested using regression analysis. Table III lists the regression coefficients for the best model in the form of special cubic equation in solvent components and of parabola in polymer concentration covariate. The 21-term model was chosen as a final model because most of its parameters had substantial F-test values and adequacy of fit.

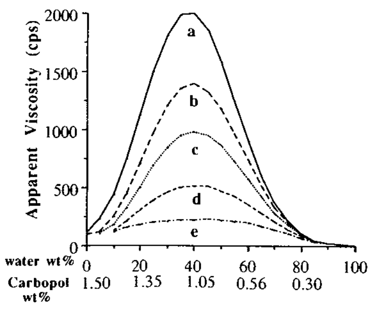

Fig. 5. Predicted viscosity changes calculated by the final model equation of Table III for a set of 1.5 wt% Carbopol with viscosities of 100 cP toward dilution path. Solvent composition for a–e listed in Table IV.

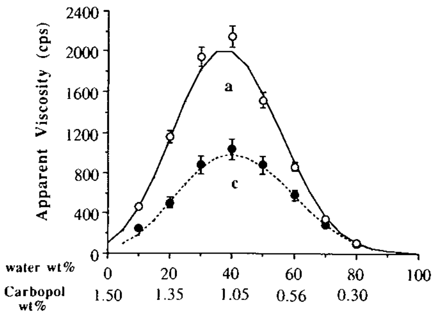

Fig. 6. Comparison of calculated versus experimentally observed viscosity changes for optimum formulation regions predicted by the RSM. Solvent composition for a and c Listed in Table IV.

Figure 5 shows the predicted viscosity changes calculated by the final model equation for a set of 1.5 wt% Carbopol in different solvent compositions with a viscosity of 100 cP toward the dilution path, with water resulting in a decreasing polymer concentration. The enhancement factor (EF) at maximum viscosity and the area under the curve (V_{AUC}) during water inclusion are listed in Table IV. It is apparent that, at higher P regions rather than at higher G regions, the viscosity increase is more pronounced and spans over a wide range of water content of the systems. Therefore, it is expected that the optimal formulations for the system are around the regions where the solvent composition is close to a mixture of 60 wt% P and 40 wt% G. However, when changing this mixture by replacing with G and water to 40 wt% P, there are only half the changes in EF and V_{AUC}. This information could be useful if one is concerned with the irritation response of the solution. Since P is significantly more irritating than G and W, the irritating response may be decreased without compromising the viscosity significantly when the solvent composition is changed to different regions.

Figure 6 shows the comparison of calculated versus experimentally observed viscosity changes for optimum formulation predicted by the SRM. The agreement is excellent over the entire viscosity range, suggesting that the strategy for development of response surface model is of considerable value in formula optimization. This study is presently extending to determine the viscoelastic properties of the gels with drugs incorporated and correlate these data with the *in vivo* bioavailability in these formulations.

APPENDIX

For testing lack of fit of the proposed model, an F ratio would be calculated by

$$F\ \mathrm{ratio}_{\alpha,c-p,N-c} = \frac{\mathrm{SSLF}/(c - p)}{\mathrm{SSPE}/(N - c)} \tag{A1}$$

Table IV. Enhancement Factor (EF) and Area Under the Curve (V_{AUC}) During Water Inclusion for a Set of 1.5 wt% Carbopol in Solvent Compositions with a Viscosity of 100 cP

	Formulation composition				
	Propylene glycol (wt fraction)	Glycerol formal (wt fraction)	Water (wt fraction)	EF[a]	V_{AUC}
a	0.68	0.32	0	20.01	842.97
b	0.52	0.44	0.04	14.10	591.38
c	0.40	0.54	0.06	9.87	432.65
d	0.20	0.72	0.08	4.58	238.33
e	0.02	0.90	0.08	2.00	129.16

[a] The ratio of maximum viscosity during water inclusion and the initial viscosity of formulations, i.e., 100 cP.

and the adequacy of fit for the model is compared the F ratio with tabulated F value for $c - p$ and $N - c$ degrees of freedom at the desired α level of significance (15). In the equation, the pure error sum of squares (SSPE) is the variation of experimental error and can be achieved by collecting at least two replicate observations at one or more of the design lattices. Denote the ith observation at the jth design lattice by Y_{ij}, where $i = 1, 2, 3, \ldots, n_j \geq 1, j = 1, 2, \ldots, c$. Define Y_j to be the average of the n_j observations at the jth design lattice. Then the sum of squares for pure error is

$$\text{SSPE} = \sum_{j=1}^{c} \sum_{i=1}^{n_j} (Y_{ij} - Y_j) \tag{A2}$$

The degrees of freedom associated with SSPE in Eq. (A2) is $N - c$, where N is the total number of observations. The residuals sum of square associated with the difference between experimental observations Y_{ij} and model predictions y_{ij} can be calculated by

$$\text{SSE} = \sum_{j=1}^{c} \sum_{i=1}^{n_j} (Y_{ij} - y_{ij}) \tag{A3}$$

If the fitted model contains p parameters, then the number of degrees of freedom for SSE is $N - p$. The lack of fit sum of squares (SSLF) is found by subtraction as

$$\text{SSLF} = \text{SSE} - \text{SSPE} \tag{A4}$$

with the degrees of freedom $c - p$.

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