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Application of a factorial design to the study of specific parameters of a Carbopol ETD 2020 gel. Part I. Viscoelastic parameters

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Abstract

This work studies the application of a 2^3 factorial design to a cosmetic gel with the aim of simplifying the analysis of the influence of the concentration of Carbopol ETD 2020 (cb), of ethanol (et) and of glycerin (gl) on the viscoelastic parameters: equilibrium modulus (Gn), critical molecular weight (M_c), degree of structuring ($\log G'/\log \nu$) and viscous modulus (G''). We have obtained high linear polynomial correlations among the components and the response factors determined. The results obtained evidence the usefulness of this type of technique in detecting interactions among the components that would be difficult to foresee otherwise. M_c, $\log G'/\log \nu$ and G'' depend on the interaction cb–et. Gn depends on the interaction of cb–et–gl. That is, an increase in gl can increase or decrease the elasticity (Gn) of the gels, depending on the concentrations of cb and et. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Carbopol ETD 2020; Cosmetic; Factorial design; Gels; Viscoelasticity

1. Introduction

In preformulation studies, it is difficult to predict the final characteristics of the product being studied. Trial and error is generally used, with the subsequent drawbacks of numerous assays, time and money, in addition to the lack of precision in determining how a factor or an interaction of factors influences the response analyzed. With the aim of simplifying these studies and obtaining more conclusive results, the experimental design technique has been applied in the last decade, particularly to tablets. Although the results have been acceptable, this technique has only infrequently been applied to semisolids (Takaya et al., 1995; Simovic et al., 1999).

Carbopol polymers are commonly used for obtaining therapeutic and cosmetic gels. Their aqueous dispersions form three-dimensional network structures, like a gel, by neutralization of its charges or by adding hydrogen-bond donor substances. The latter property is found in ethanol

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and glycerin, hence their frequent inclusion as cosolvents, antiseptics, moisturizers, etc. The effect of ethanol has been shown to depend on the rate of carbopol and ethanol (Pena, 1990), whereas the effect of glycerin has been little examined. Systems containing both ethanol and glycerin have unpredictable effects, thus complicating the analysis of the preformulation assays.

The aim of this work is to study the possible use of an experimental design for a cosmetic gel, with the aim of simplifying the analysis of the influence of some of the components on the specific characteristics of the product.

The components and their proportions are the normal ones for an after-shave gel (Pons and Parra, 1995), including allantoin (keratoplastic properties), menthol and ethanol (antiseptics), and glycerin (moisturizer). The gelling agent is Carbopol ETD 2020, a copolymer of acrylic acid and alkyl acrylate with long chains linked by transverse bonds with allyl pentaeritrithol ether or sucrose. It was initially chosen due to its interesting characteristics (BF Goodrich, 1993): (a) It is easy to manage industrially since, although its aqueous dispersions are of low viscosity, once neutralized, it is an effective gelling agent. (b) It synthesizes in a cosolvent medium of lower toxicity than other polymers of the series, thus conforming to the European regulations regarding toxic residues (Reynier et al., 1998).

Based on a general formula and using a 2^3 factorial design, we have studied the influence of the concentration of the polymer, ethanol and glycerin on viscoelastic parameters (Part I) and flow behavior, spreadability, and transparency (Part II, submitted), factors that are often decisive in the acceptance or rejection of a product by consumers.

2. Materials and methods

2.1. Materials

Menthol, allantoin, ethanol, glycerin and triethanolamine were provided by Henkel (Barcelona, Spain), Carbopol ETD 2020 by BF Goodrich (Germany), and methyl parahydroxybenzoate and propyl parahydroxybenzoate by Aldabo Julia, S.A. (Barcelona, Spain). All were used as received.

2.2. Experiment

The influence of three factors (the concentration of the polymer, ethanol and glycerin) on the viscoelastic parameters of the samples was studied. A 2^3 factorial design was applied, to which two central points were added to estimate the error. The amount of each component in each sample, the order of elaboration and the analysis of the results were all performed with the statistical program STATGRAPHICS PLUS v. 4.1 (Statgraphics Plus, 1999).

The resolution of the design is V+, which shows the main effects and the interactions of two and three factors and allows a first-order polynomial predictive equation to be obtained:

$$y = \text{bo} + \sum \text{bi xi} + \sum \text{bii xi xj} + \sum \text{biii xi xj xz}$$

Analysis of variance (ANOVA) was used to analyze the significance of the terms of the complete equation, for a level of $\alpha = 0.05$ and 0.1. The terms that are not significant are eliminated from the equation in successive stages one-by-one and in decreasing order of the P-value (level of significance attained by the test) up until the statistic r^2 fitted to the degrees of freedom (r^2 adjusted for d.f.) nears unity, the maximum fit allowed. r^2 adjusted for d.f. was chosen as it is more suitable for comparing models with different numbers of independent variables.

For each of the response factors examined, the definitive predictive equation (in which all of its terms are not always significant, though they may be necessary to describe the effect; Bolton, 1990), the standard error of the estimate (S.E.E.) and the mean standard error (M.S.E.) are included. The Duban–Wanson coefficient, the correlation matrix, and the normal probability fit are within the normal limits for accepting the results of the analysis and are not included.

2.3. Formulations

To develop the factorial design, ten different samples (2^3+2) were prepared. The samples have. (a) Constant concentrations of menthol (0.3% m/m), allantoin (0.2% m/m), methylparaben (0.075% m/m) and propylparaben (0.025% m/m). (b) Variable concentrations (Table 1) of Carbopol ETD 2020 (cb; 0.5–1% m/m) within the recommended limits for a gel, glycerin (gl; 2–5% m/m) according to the recommendations for this type of preparation, and ethanol (et; 5–30% m/m) up to the upper limit determined by its compatibility with the polymer. Triethanolamine was used as neutralizer (all the samples have pH 7) and de-ionized water was added to obtain a total sample amount of 100 g.

We prepared 200 g of each formula, dissolving the menthol, allantoin and preservatives in the ethanol. Independently, the polymer was dispersed in the water and the glycerin was added. The two mixtures were then mixed, neutralized and homogenized by hand stirring. The samples were kept at rest at 25 °C in hermetically sealed containers for 24 h before testing.

2.4. Response factors

We have used dynamic parameters characteristic of the microstructure of the samples, as follows. Equilibrium modulus (Gn): elastic modulus (G') characteristics of the plateau zone of a weak gel. It is associated with the energy recovered by the system in each oscillation cycle. A higher Gn represents greater elasticity. Ross-Murphy and McEvoy (1986) attributed its value to the number of chains in the elastically active networks, that is, to the number of chains forming the three-dimensional infinite network and that are available to permanently or nearly permanently withstand mechanical stresses. Its approximate value is obtained from the value of G' associated to the minimum value of the phase angle ($\delta_{\min}$; Alfaro et al., 1998; Wu, 1989):

$$\mathrm{Gn} = [G']_{\tan\delta\to\min} \tag{1}$$

Critical molecular weight (M_c): characterizes the space between two points of physical contact (entanglement) between the polymer chains forming the three-dimensional network (Ferry, 1980). High values of M_c are related to fewer contact points. Ferry (1980), Vinogradov and Malkin (1980), among others, describe the following relationship:

$$\tan\delta_{\min} = 1.04\left(\frac{M}{M_c}\right)^{-0.8} \qquad \frac{M}{M_c} = \left(\frac{1.04}{\tan\delta_{\min}}\right)^{1/0.8} \tag{2}$$

where $\tan\delta_{\min}$ is the tangent of the phase angle at minimum and M is the molecular weight of the polymer, value unknown. The M/M_c ratio, chosen as the factor response, is determined from the Eq. (2).

Table 1
The concentrations of samples and the response factors

Sample	Carbopol (% m/m)	Ethanol (% m/m)	Glycerin (% m/m)	Gn (Pa)	$\delta_{\min}$	M/M_c	log G'/log v (Pa Hz)	G'' (Pa)
1	0.5	30	5	70	4.8	23.00	0.079	10.5
2	0.5	10	2	153	3.0	40.87	0.045	15.5
3	1	30	5	120	4.6	23.92	0.068	17.7
4	0.5	30	2	66.5	4.9	22.10	0.073	11.3
5	0.75	20	3.5	150	3.9	29.42	0.058	18.8
6	0.75	20	3.5	130	4.1	27.63	0.053	17.8
7	1	10	2	166	4.3	26.03	0.061	23.0
8	1	10	5	233	4.3	26.03	0.059	28.8
9	1	30	2	121	4.7	23.28	0.069	17.7
10	0.5	10	5	125	3.5	33.70	0.054	14.9

Gn, equilibrium modulus; $\delta_{\min}$, minimum phase angle; M/M_c, ratio polymer molecular weight and critical molecular weight; log G'/log v, degree of structuring; G'', viscous modulus.

Degree of structuring of the samples: this is obtained from the analysis of the variation of G' with the frequency (ν) ($\log G'/\log \nu$) (Alfaro et al. 1997).

The viscous modulus (G'') associated with the energy which has been used to initiate flow is irreversibly lost into shear heat (Schramm, 1994). Although it has not been studied in as much detail as other viscoelastic parameters, this modulus is thought to be related to the molecular interactions in the formulations (Doublier et al., 1992).

2.5. Viscoelasticity assays

Mechanical spectra at 25 °C were obtained via dynamic tests with a Bolhin CS and a 4° cone in the linear viscoelastic range, which was previously determined by stress sweep tests at a fixed frequency (1 Hz).

3. Results and discussion

3.1. Prior tests

Prior tests determined the degree of stickiness and the compatibility of the polymer with the ethanol.

(a) Formulas of the same composition as those analyzed were prepared with different types of Carbopol, including Carbopol ETD 2020. Except for the latter, all the Carbopols left some amount of sticky residue on the skin. According to Brand-Garnys et al. (1994), a characteristic of Carbopol ETD 2020 is the ratio of the particle surface with the porosity, which favors its complete hydration and eliminates the sensation of stickiness. This property influenced the choice of this particular Carbopol given its end use as a facial formulation.

(b) In general, Carbopols are characterized by their variable compatibility with ethanol. We verified that, within the range of concentrations (0.5–1% m/m) and formulas analyzed, the compatibility of Carbopol ETD 2020 was 30% (m/m). Above these proportions, the polymer clearly precipitates within 48 h in some of the formulations. In the tests and over long periods at 25 °C, no polymer precipitation was visible.

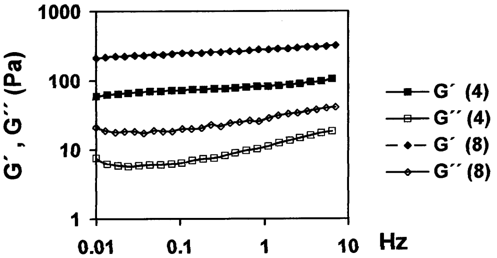


Fig. 1. Mechanical spectra of the samples numbers 4 and 8. Mechanical spectra of the samples are between those of samples numbers 4 and 8.

3.2. Macroscopic appearance

All the preparations appear to be consistent and homogeneous, some clear and transparent, others white and opaque. Spreadability on the skin was smooth and agreeable with no sticky residue.

3.3. Viscoelasticity

The assays were performed in a linear viscoelastic range, previously determined by a stress amplitude sweep at 1 Hz. Outside of the linear viscoelastic range, G' falls and G'' initially increases and then drops.

The mechanical spectra (Fig. 1) were obtained in the 0.01–8 Hz range. The values of G' were nearly independent of ν and higher by one order of magnitude than G'', which has a greater dependency on the frequency. In all samples, G'' had a minimum ($G''_{\min}$). The phase angle (δ) ranged from 5 to 10, was more dependent on the frequency and presented a minimum ($\delta_{\min}$) closely related to $G''_{\min}$. These mechanical spectra are characteristic of the 'plateau zone' of weak gels (Ross-Murphy and McEvoy, 1986; Kleck, 1992; Kavanagh and Ross-Murphy, 1998) and indicate the existence of an internal network with linked zones, stable over the time of the test (Doublier et al., 1992).

Irreversible destruction of the structure is not caused upon obtaining the spectra in the linear viscoelastic range. Any change in the ratios of the components affecting the internal structure is reflected in the dynamic parameters (G', G'' and

δ). As response factors we analyzed the equilibrium modulus (Gn), the critical molecular weight (M_c), the degree of structuring ($\log G'/\log \nu$) and the viscous modulus (G'').

3.3.1. Gn

The independence of G' and ν allows the equilibrium modulus (Gn) be defined. Gn is obtained from the Eq. (1) and ranges from 273 to 70 Pa (Table 1). The internal structures of the systems are highly distinct.

The ANOVA results indicate that two main factors significantly influence the value of Gn: Carbopol and ethanol and the Carbopol–ethanol–glycerin interaction for a level of $\alpha = 0.05$ and the Carbopol–glycerin interaction for a level of $\alpha = 0.1$. The predictive linear equation fits the proposed model very well, accounting for 95% of the observed variability.

$$\begin{aligned}\text{Gn (Pa)} &= 343.679 - 225.0 \times \text{cb} - 11.385 \times \text{et} - 62.830 \times \text{gl} \\ &\quad + 11.608 \times \text{cb} \times \text{et} + 99.50 \times \text{cb} \times \text{gl} + 2.183 \times \text{et} \\ &\quad \times \text{gl} - 3.316 \times \text{cb} \times \text{et} \times \text{gl}\end{aligned}$$

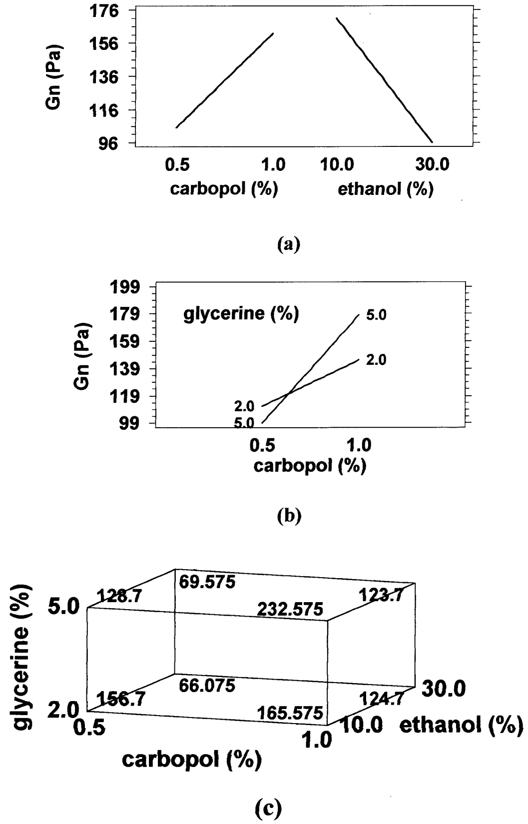
r^2 (adjusted for d.f.) = 95.0185%;

SEE = 10.666; MAE = 3.65

In Fig. 2a, it can be seen that Gn is directly related to the concentration of Carbopol and inversely related to that of ethanol.

Carbopol is a polyelectrolitic copolymer. The gelling mechanism by neutralizing (all the samples have pH 7) is based on the ionic repulsion of their charges. The long chains are forced through the domains of others, originating networks by simple entanglement (physical contact between the chains; Warburton, 1996). However, the affinity of the polymer for the solvent also influences the network structure as the polymer has less affinity for water than for ethanol (Pena, 1990). An increase in ethanol gives rise to an adverse solvent for the polymer, which contracts and decreases the number of elastically active cross-links.

Gn is directly related to the polymer concentration, which increases the number of elastically active bonds. Nonetheless, the effect of the polymer depends on the concentration of glycerin (Fig. 2b). Therefore, for high concentrations of polymer (1%), there is a direct relationship between the glycerin concentration and elasticity due to the formation of the hydrogen bonds between the polymer and the glycerin. This phenomenon is not observed when the polymer concentration is lower (0.5%). The elasticity diminishes still further when the glycerin concentration increases. The system behaves as though an excess of glycerin existed and shows dehydrating effects, similar to those caused by ethanol. This effect can be better seen if the interaction of the three main factors is observed (Fig. 2c). The increase in the concentration of Carbopol and glycerin and the decrease in ethanol leads to systems with a greater density of elastically active cross-links.



(a)

(b)

(c)

Fig. 2. The effect on Gn (equilibrium modulus) of: (a) concentration of Carbopol and ethanol, (b) Carbopol–glycerin interaction, and (c) Carbopol–ethanol–glycerin interaction.

3.3.2. M_c

The M/M_c ratio, chosen as the factor response, is determined from the $\delta_{\min}$ value of each mechanical spectrum (Table 1) and by using Eq. (2). A lower value of M/M_c indicates less entanglement, or fewer points of physical contact, between the polymer molecules comprising the three-dimensional network of the gel.

In the systems analyzed, M/M_c (Table 1) ranges from 41 (sample 4, the most entangled system) to 22 (sample 2, the least entangled systems) and reflects the variations in the states of the polymer.

Three effects (Carbopol, ethanol and their interaction) significantly influence a level of $\alpha = 0.05$. The predictive linear equation fits the proposed model very well, accounting for 94.5% of the observed variability.

$$\frac{M}{M_c} = 88.064 - 60.208 \times \text{cb} - 2.256 \times \text{et} - 7.364 \times \text{gl} + 2.097 \times \text{cb} \times \text{et} + 7.258 \times \text{cb} \times \text{gl} + 0.258 \times \text{et} \times \text{gl} - 0.248 \times \text{cb} \times \text{et} \times \text{gl}$$

$$r^2 \text{ (adjusted for d.f.)} = 94.472\%; \quad \text{SEE} = 1.369 \quad \text{MAE} = 0.370$$

Less entangled systems (a lower M/M_c ratio) are obtained by increasing the concentration of the polymer or by increasing the ethanol concentration (Fig. 3a), although the causes are different. A rise in the Carbopol concentration increases the number of charges of equal sign and the repulsion between the chains, decreases the entanglement and increases the distance between the contact points. In contrast, a rise in the ethanol concentration favors the contraction of the polymer, decreases the concentration of elastically active chains and the entanglement, and increases the distance between them. Both processes increase M_c.

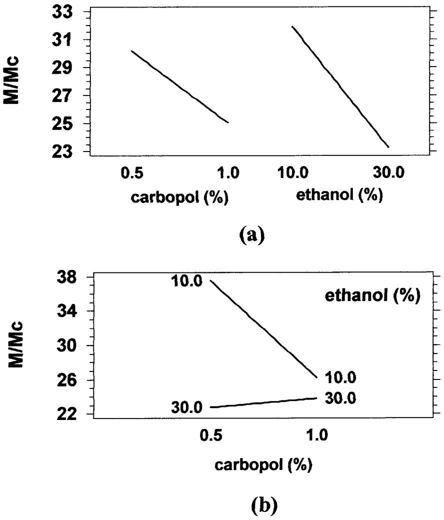


Fig. 3. The effect on M/M_c (the ratio of the molecular weight of the polymer and the critical molecular weight) of: (a) the Carbopol and ethanol concentration and (b) the Carbopol–ethanol interaction. A lower M/M_c indicates lower entanglement of the polymer.

These effects are more evident when the Carbopol–ethanol interaction is analyzed (Fig. 3b). For low Carbopol concentrations (0.5%), both the intermolecular bonds and the cross-links are evident for low ethanol concentrations (10%), and the cross-linking drops with an increase in ethanol (30%), at the limit of polymer-alcohol compatibility. When the polymer concentration increases (1%), the electrostatic repulsion between the chains also increases, and M/M_c is independent of the ethanol concentration.

From the combined analysis of the results obtained for the Gn and M/M_c parameters, and especially from Fig. 2a and Fig. 3a, it is difficult to deduce that these two parameters express the same quality of the network and that the two are closely related (Ferry, 1980). A detailed analysis suggests that the rise in the Carbopol concentration increases the number of elastically active filaments, even though the network is less entangled. However, an increase in ethanol always produces contraction of the polymer chains. Therefore, Gn and M/M_c are directly related ($r^2 = 89.95$).

3.3.3. Degree of structuring

The slope of the doubly logarithmic ratio between G' and the frequency (ν) ($\log G'/\log \nu$) in the linear range allows the determination of the degree of structuring or entanglement between the flow units of the systems. Greater structuring is associated with a lower $\log G'/\log \nu$ ratio (Alfaro et al. 1997).

The values obtained (Table 1) range from 0.045 (sample 2, greater structuring) and 0.078 (sample 4, less structuring).

The ethanol concentration and the Carbopol–ethanol interaction significantly influence this parameter (level of significance, $\alpha = 0.05$).

$$\frac{\log G'}{\log v} = 0.0037 + 0.0540 \times \text{cb} + 0.00223 \times \text{et} + 0.00383 \times \text{gl} - 0.001807 \times \text{cb} \times \text{et} - 0.00511 \times \text{cb} \times \text{gl}$$

r^2 (adjusted for d.f.) = 77.865%;

SEE = 0.00483; MAE = 0.00286

The ethanol decreases the degree of structuring of the systems (Fig. 4a), although its influence depends on the polymer concentration (Fig. 4b). Low Carbopol concentrations (0.5%) result in more structured systems as long as the ethanol concentration is low (10%), since when it increases (30%) its dehydrating effect dominates to produce less structured systems. An increase in the Carbopol concentration (1%) leads to systems with an intermediate degree of structuring. Such marked influences are not seen when the ethanol concentration is modified, as the repulsion effect between the neutralized charges of the polymer seems to dominate. All the samples have the same pH value and the glycerin did not appear to affect it.

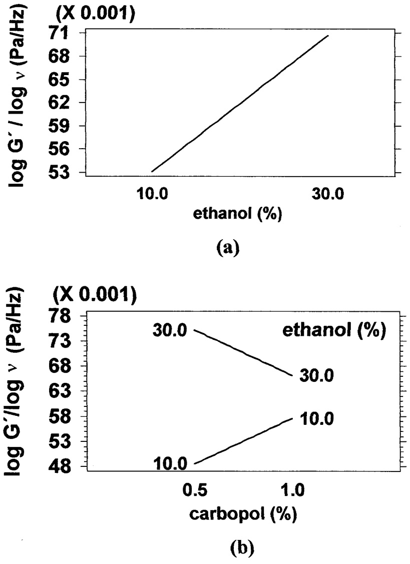


Fig. 4. The effect on log G'/log v (degree of structuring of the gel) of: (a) ethanol and (b) Carbopol–ethanol interaction.

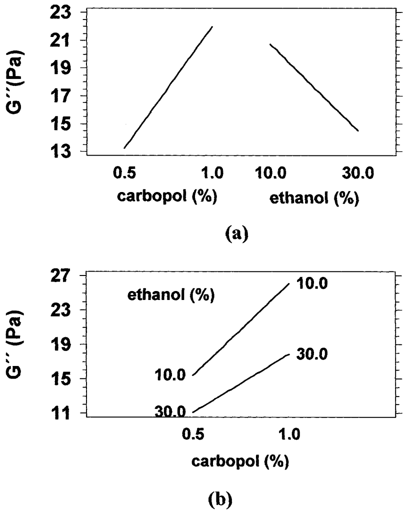


Fig. 5. The effect on G'' (viscous modulus) of: (a) Carbopol and ethanol concentration and (b) Carbopol–ethanol interaction.

3.3.4. G''

In the samples studied, G'' ranges from 10 to 28 Pa at 1 Hz (Table 1) and is significantly influenced by the concentrations of Carbopol and ethanol ($\alpha = 0.05$) and the Carbopol–ethanol interaction ($\alpha = 0.1$).

The fitted linear equation accounts for the observed variability quite well (96%).

$$G'' \text{ (Pa)} = 16.192 + 3.833 \times \text{cb} - 0.335 \times \text{et} - 3.233 \times \text{gl} + 0.263 \times \text{cb} \times \text{et} + 6.133 \times \text{cb} \times \text{gl} + 0.090 \times \text{et} \times \text{gl} - 0.187 \times \text{cb} \times \text{et} \times \text{gl}$$

r^2 (adjusted for d.f.) = 96.990%; SEE = 0.929;

MAE = 0.280

The increase in G'' (Fig. 5a) is related to a rise in the concentration of Carbopol or a decrease in ethanol due to the dominance of charge repulsion between the polymer chains. Moreover, for any concentration of Carbopol, it depends on the ethanol concentration (Fig. 5b). The greatest loss of energy (higher-viscosity systems, greater G'') is always associated with a lower ethanol concentration. An increase in ethanol and the contraction of the polymer chains gives rise to less 'viscous' systems.

4. Conclusions

We have applied a 2^3 factorial design to the study of the influence of the concentrations of carbopol, ethanol and glycerin on the structure of a gel. The dynamic parameters analyzed are: Gn, M/M_c, $\log G'/\log v$ and G''.

The sensitivity of these dynamic parameters to structural changes in a gel qualifies them as ideal response factors. In this study, they have shown good fits to linear polynomial equations, which can be used in future predictions. The results obtained indicate that the application of experimental design techniques to preformulation studies of a gel can be very effective. The formulator can easily determine the relationship between the composition and properties of a gel. In this experiment only ten tests sufficed to provide a great deal of information, especially on the interactions between two or three components, which would otherwise have been difficult to foresee.

Thus, it has been shown that the incorporation of ethanol to a carbopol gel (Pena, 1990) decreases the affinity of the polymer for the solvent and makes it more difficult to obtain a gel. This effect can be observed from the decrease in the M/M_c ratio (less entanglement), the increase in $\log G'/\log$ (degree of structuring), and the decrease in G''. The effect of glycerin is more difficult to study. In cosmetic preparations of this type (after-shave), glycerin is generally used in low concentrations ($< 5\%$), its effect on the gel structure is usually ignored. Nevertheless, glycerin has been shown to influence the elastic properties (Gn) of such systems. A small increase in glycerin (2–5%) can produce different effects depending on the carbopol and ethanol ratio: there is an increase in the affinity of the polymer for the solvent and of the elasticity of the gel (higher Gn) or there can be a decrease in the affinity of the polymer for the solvent and in the elasticity of the gel (Gn drops).

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