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European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 329–335

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

Systematic study of the flow behaviour and mechanical properties of Carbopol® Ultrez™ 10 hydroalcoholic gels

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Received 19 February 2002; accepted in revised form 3 June 2002

Abstract

Flow behaviour and mechanical properties of 0:100, 15:85, and 30:70 v/v gelled ethanol:water mixtures are studied as a function of pH (4.0–7.0) and Carbopol® Ultrez™ 10 concentration (0.1–0.5%). As previously reported individually for 30% v/v alcoholic Ultrez™ 10 gels, flow curves were adjusted to the Ostwald's model, and similar sigmoidal dose response functions were obtained to describe the pH dependence of consistency index and mechanical properties of the systems. The concentration dependence of flow indexes was also best adjusted to one-phase exponential decay functions. As a result, the influence of ethanol content on polymer network is meaningfully assessed by means of the obtained empirical parameters: bottom value of each variable (Y_{max}), pH value required for a 50% polymer network development (pH_{50}), and asymptotic flow index value for the fully structured gels (n_{min}). Also, it is assessed the influence of cosolvent on the above-mentioned empirical variables, by studying pH-dependence of gelation in methanol:water, 1-propanol:water and 1-butanol:water 15:85% v/v mixtures. As a result, the alcohol induced variations in consistency and mechanical properties of hydroalcoholic gels were well correlated to modifications in the solubility parameter (δ_T). © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Carbopol® Ultrez™ 10; Hydroalcoholic gels; Flow behaviour; Ostwald model; Mechanical properties; Empirical models

1. Introduction

Aqueous gel vehicles containing water, alcohol, propylene glycol and/or polyethylene glycol, and gelled with Carbopols or cellulose derivatives, are classed as water-soluble bases [1]. Simple gelled mixtures of water and alcohol, in proportions varying to suit specific cases, are also extensively used, and are often referred to as hydroalcoholic gels. Bases of this kind may be formulated to optimise non-polar drug delivery [2]. However, although alcohols are useful to increase solubility of non-polar drugs, their use as cosolvents with hydrophilic polymers is often limited. The rheological behaviour of polymer solutions is determined not only by polymer–polymer conformation and entanglement, but also by concentration and polymer–solvent effects. Therefore, gelation process in hydroalcoholic mixtures is also a function of the alcohol–polymer intermolecular interactions, and consequently, the alcohol content used in the design and development of technologically adequate hydroalcoholic gelled bases is often limited by the compatibility of the gelling agent with the non-aqueous solvent [3].

Carbopols are insoluble acrylic acid polymers, which became stiff gels upon neutralisation in aqueous medium. By employing organic amines as neutralising agent, it is possible to gel many semipolar liquids or mixtures of these liquids with water. Compatibility of the polymer with non-aqueous liquids depends on the formation of ion pairs with the amine [4]. Actually, Ultrez™ 10 is a new member of the Carbopols family, it can be considered a hybrid between Carbopol® 940 and Carbopol® 934, with better dispersion properties and a potential wide range of applicability in the pharmaceutical and cosmetic fields [5]. Like in the case of other Carbopol resins, neutralisation of Ultrez™ 10 dispersions is essential to develop the rheological, and consequently, the mechanical properties of the polymer, since hardness (H) and compressibility (A) are components of shearing stress too. Therefore, the exhaustive characterisation of flow behaviour and mechanical properties of these systems as a function of neutralisation and polymer concentration, especially when solubilising cosolvents like alcohols are employed, is essential to evaluate the

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PII: S0939-6411(02)00080-2

ability of Carbopol® Ultrez™ 10 to jellify ethanol:water mixtures and their potential uses as dermatological bases [6–9].

In recent years many gelled water-soluble bases have been formulated to optimise topical drug delivery without an exhaustive rheological study [10]. Nevertheless, acknowledge of the rheological and mechanical properties have an outstanding importance, and may lead to the possible employ of rheological parameters and empirical models to optimise topical non-polar drug delivery from dermatological formulations. Particularly, the study of the influence of alcoholic cosolvents on the rheological and mechanical properties of Ultrez™ 10 gels, is an important feature in their exhaustive characterisation as topical delivery systems [9–13]. With this in mind, the aim of the present work was to study the flow behaviour and mechanical properties of Carbopol® Ultrez™ 10 hydroalcoholic gels as a function of the following variables: pH (4.0–7.0), polymer concentration (0.1–0.5%), ethanol concentration (0.0, 15.0 and 30.0% v/v) and alcohol polarity. Results and models obtained are to be used in forthcoming studies of non-polar drug release from these polymeric systems.

2. Materials and methods

2.1. Materials

Carbopol® Ultrez™ 10 was purchased from BF Goodrich Chemical Co. (Cleveland, OH, USA); all other reagents were of analytical grade: triethanolamine was obtained from E. Merck, Darmstadt; ethanol was supplied by Panreac Química SA, Barcelona, Spain; methanol, 2-propanol and *n*-butanol were furnished by Scharlau, Barcelona, Spain.

2.2. Hydroalcoholic gel elaboration

Appropriate quantities of Carbopol® Ultrez™ 10 were added to 0:100, 15:85 and 30:70% v/v ethanol/deionized water mixtures, to obtain the following polymer concentrations: 0.1, 0.2, 0.3, 0.4 and 0.5% w/w. These mixtures were agitated at 2000 rpm for 10 min with a Silverson L4R agitator, equipped with an axial flow head in conjunction with a disintegrating head. Polymer dispersions after 1 h were neutralised with triethanolamine 50% until the desired apparent pH value (4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0), measured 'in situ' with a digital Crison 2000 pH-meter. In order to evaluate the influence of alcohol polarity, 0.5% w/w Carbopol® Ultrez™ 10 dispersions were also prepared in 15:85 v/v methanol:water, 2-propanol:water and *n*-butanol:water mixtures, and neutralised to the desired apparent pH value (4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0), as described previously. All the samples were allowed to equilibrate for 72 h at room temperature prior to the evaluation of their rheological properties.

2.3. Viscosity measurements

Rheograms were determined with a cone and plate Brookfield Digital Viscometer DV III, equipped with a recirculating water-bath Brookfield TC 200 for control of sample-container temperature. The data obtained were analysed and adjusted to Ostwald's model by Rheocalc for Windows 1.01 software, that permits us to select from among all the flow models which is the one that is more approximated to the behaviour of the system. The viscosity determinations were done in 0.5 ml of sample, for 21 sequentially increasing and decreasing values of shear rate in the range 2–200 l/s. The temperature was kept constant at 20 ± 0.1°C, and all samples were equilibrated at each run temperature on the plate for 5 min prior to viscosity measurements. The influence of agitation time was determined by recording viscosity for decreasing values of shear rate after constant agitation at 200 l/s for 1, 2, 5, 10, 20 and 30 min. Thixotropic area values were determined by numerical integration as the difference between the areas enclosed by the 'up' and 'down' curves of rheograms.

2.4. Compression study

Compression study was performed using a Load and Tensile Penetrometer Model PNR 20 fitted with a 20 N sensor and cylindrical aluminium holed disk 18-0254 (plate diameter 55 mm, diameter of holes 4–5 mm/30°). Determinations were done in the following conditions: speed of travel 1.0 mm/s and compression depth 40 mm. The gels were analysed in its original containers (500 ml) without stirring or shaking.

3. Results and discussion

3.1. Flow behaviour of hydroalcoholic gels

The flow curves of all the 105 ethanol:water hydroalcoholic gels studied were characteristic of viscoelastic systems with pseudoplastic and shear thinning behaviour. These rheograms were adjusted to Ostwald's model ($\tau = kD^n$), obtaining correlation coefficients in excess of 0.9900 and good reproducibility in triplicate, with standard deviations (SD) within 4.0%. Correlation parameters demonstrate that the Power Law reproduces adequately the rheological behaviour of Ultrez™ 10 hydroalcoholic gels in the pH, polymer and alcohol concentration range evaluated [14]. Furthermore, the study of the influence of agitation time demonstrated that, in general, Carbopol® Ultrez™ 10 hydroalcoholic gels show high stability against agitation and exhibit no significant thixotropic behaviour under the test conditions and range evaluated [15].

3.1.1. Consistency indexes

As previously reported [16], good correlations were obtained between calculated power law consistency (k)

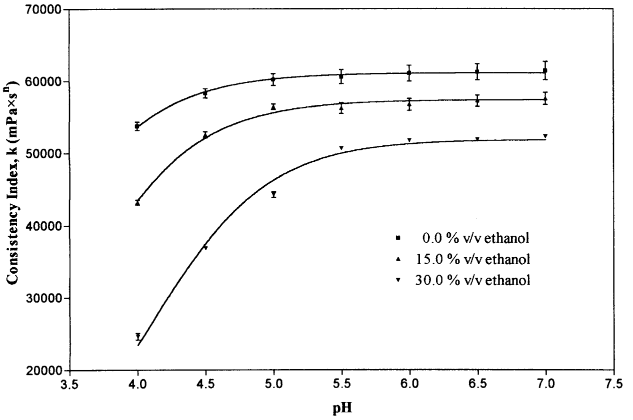

Fig. 1. Dependence of consistency indexes (k) of 0.5% w/w Carbopol® Ultrez™ 10 hydroalcoholic gels with pH at different ethanol concentrations. Theoretical curves obtained by Eq. (1).

and flow (n) indexes with polymer concentration and pH. In that experimental work, the mean values of k, obtained for 30% alcoholic gels, were well correlated with the pH according to a sigmoidal dose response function of the type:

$$k = \frac{k_{\max}}{1 + 10^{(\mathrm{pH}_{50} - \mathrm{pH})}} \tag{1}$$

According to this expression, consistency of hydroalcoholic gels increased with pH and tended to a maximum value ($k_{\max}$) at neutral pH, which was in agreement with the general behaviour of acrylic acid polymers upon neutralisation. Furthermore, the variable pH_{50} introduced in Eq. (1), determined the rate at which the system reached its maximum consistency ($k_{\max}$). In general, this empirical model was able to adequately describe the variation of consistency indexes as a function of pH, including variables with physical meaning. Considering the importance of cosolvents in developing dermatological bases, we extended the application of the model to a wider range of alcohol content.

As an example, Fig. 1 shows experimental k values plotted as a function of pH, for gels of 0.5% w/w polymer concentration at different ethanol concentrations. Correlation parameters obtained from Eq. (1), between consistency indexes and pH, are given in Table 1. As it can be stated from correlation coefficients and theoretical curves shown in Fig. 1, Eq. (1) is able to adequately describe the variation of consistency indexes as a function of pH in the ethanol concentration range evaluated (0.0–30.0% v/v).

The structure of Carbopol gels in solution is determined by the extent to which the macromolecules associate and form entanglement networks. In aqueous media, the polymer is mainly in the free acid form, and the pH-induced generation of negative charges along the polymer chain, causes it to uncoil and expand. Subsequently, the value of the variable pH_{50} can be assessed as an inflection point in the structure forming effect of pH, i.e. pH_{50} is the pH value required to generate half of the neutral gel's structure, expressed as $k_{\max}/2$. From this pH value onward, the increase of consistency index with neutralisation is less pronounced, asymptotically reaching the maximum consistency ($k_{\max}$) of the fully structured polymer network [17].

Calculated maximum consistency indexes ($k_{\max}$) were found to be directly related to polymer concentration, and inversely related to ethanol content. On the other hand, as previously reported for 30% hydroalcoholic gels, a characteristic feature of the variable pH_{50} is the inverse relationship with polymer concentration (Table 1). Thereafter, for higher polymer contents, a more significant network development can be obtained at lower pH values. Another outstanding feature is the dependence of this variable with the alcohol content. Fig. 2 shows the dependence of calculated pH_{50} values with polymer concentration in the three ethanol:water mixtures evaluated as jellying medium. At constant polymer concentration, an increase in ethanol content tends to increase the value of pH_{50}, i.e. to increase the degree of neutralisation required to obtain half structure development (Table 1, Fig. 2). This increase is more pronounced between 15.0 and 30.0% v/v ethanol concentrations, than between 0.0 and 15.0% v/v concentrations. For higher ethanol contents (>40% v/v) random, not reliable values are obtained, due to change in the flow mechanism (data not shown). Furthermore, the influence of ethanol concentration on pH_{50} is more pronounced at higher polymer concentrations.

The above-mentioned features are related to changes in polymer hydration and solubility parameter induced by the addition of ethanol. The ionised chains of Ultrez™ 10 polymer are extended in good solvents, as would be the case in aqueous media, due to hydrogen bond formation between water and hydroxyl groups of the gelling agent. In a poor

Table 1
Correlation parameters obtained from Eq. (1), between Carbopol® Ultrez™ 10 gel's consistency indexes (k) and pH

Ethanol content (%, v/v)	Polymer concentration (%,w/w)	Correlation parameters $k = f(\mathrm{pH})$		
		$k_{\max}$	pH_{50}	r
0.0	0.1	13,130	5.723	0.9914
	0.2	26,480	4.867	0.9953
	0.3	36,790	4.012	0.9971
	0.4	47,860	3.416	0.9926
	0.5	66,190	3.192	0.9885
15.0	0.1	8628	5.865	0.9923
	0.2	27,130	4.984	0.9961
	0.3	35,800	4.155	0.9946
	0.4	45,730	3.757	0.9979
	0.5	56,900	3.593	0.9994
30.0	0.1	6410	6.226	0.9995
	0.2	21,720	5.031	0.9983
	0.3	30,070	4.667	0.9996
	0.4	40,750	4.287	0.9981
	0.5	51,880	4.084	0.9983

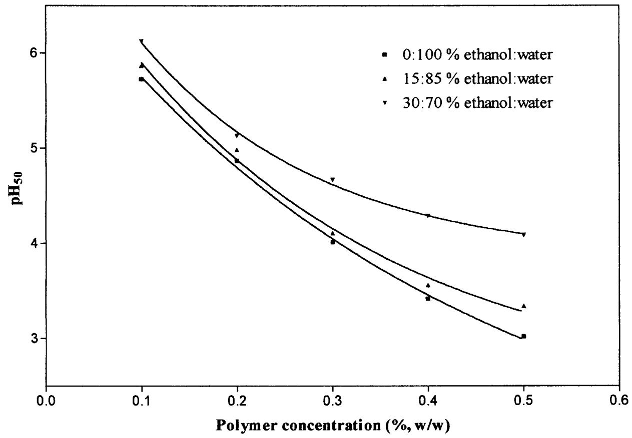

Fig. 2. Relationship between calculated pH_{50} values and polymer concentration as a function of ethanol content.

solvent, the polymer chain would be more or less tightly coiled, preferring self-interactions to interaction with the solvent. The degree of hydration will hence determine the extent of formation of weak secondary bonds between polymer strands. Addition of alcohols may attract part of the water of hydration of the polymer, allowing the formation of more intermolecular secondary bonds, leading to precipitation [3]. Furthermore, alcohols alter the solvent's characteristics, changing the solubility parameter; the p*K*a-values of Carbopol (p*K*a = 6) are changed due to the increasing alcoholic concentration, and so less dissociated product of Carbopol is formed, influencing also the hydration and viscosity of the polymer. By these mechanisms, the increment of ethanol concentration decreases the maximum consistency, and increases the polymer neutralisation degree required to jelly the medium.

On the other hand, it is accepted that the addition of ethanol often brings about coacervation rather than gelation, i.e. the production of viscous, solvated polymer-rich phase, leaving behind a polymer poor phase [2]. This process abruptly changes the physical state and the flow mechanism of the system, which is the case of gels having ethanol concentrations higher than 40% v/v. In general, it is the case for all the empirical functions obtained in the present study, and consequently limit its applicability to the pH and ethanol concentration ranges evaluated (pH ≤ 7.0, ethanol concentration ≤ 30.0% v/v).

3.1.2. Flow indexes

Power law flow indexes were also examined as a function of pH and polymer concentration at 0.0, 15.0 and 30.0% ethanol concentrations. In all cases, the increase in pH at constant polymer concentration was found to induce a nearly linear decrease in flow indexes, i.e. an increase in the pseudoplastic and shear thinning character of non-alcoholic and hydroalcoholic gels [15]. Also it is observed a lesser dependence between *n* and pH as polymer concentration increases. Consequently the effect of the final pH value of gels upon flow index decreases at higher polymer concentrations. It is generally accepted that although the power law index *n* measures departure from Newtonian flow, one of the best way to view it is a function of the rate of change of structure with shear rate or shear stress [17]. The structure can be altered on deformation by change in the shape of polymer molecules and in the number of molecular entanglements, possibly by straining a network of temporary junctions. As a result entanglement lifetimes determines changes in molecular shape and flow. On the basis of this, neutralisation will tend to decrease *n* by increasing intermolecular forces of attraction, and hence increasing lifetime of junctions to produce a straining of the chain approaching that of a permanent network.

On the other hand, an exponential decrease of the intercepts of the linear functions $n = f(\mathrm{pH})$ with polymer concentration was observed, as shown in Fig. 3. The decrease in calculated *n*-intercept values also indicates an increased departure of gels from the Newtonian flow behaviour with concentration. As in the case of 30.0% alcoholic gels [16], *n*-intercept values of non alcoholic and 15.0% hydroalcoholic gels [18], were also well fitted by least-squares to one-phase exponential decay function of the type (*C* is concentration, expressed in% w/w):

$$n = (n_{\max} - n_{\min})e^{-AC} + n_{\min} \tag{2}$$

Correlation parameters obtained from Eq. (2) are given in Table 2. Eq. (2) describes the exponential decrease of *n*, at a rate *A*, with polymer concentration to a constant minimum value ($n_{\min}$). As shown in Fig. 3, this behaviour is qualitatively similar at the different ethanol contents studied. The existence of an asymptotic value as a bottom flow index for all the gels, demonstrates that the three-dimensional polymer lattice gradually becomes fully structured with increasing polymer concentration, both in the non-alcoholic and the hydroalcoholic mixtures evaluated as jellifying mediums. Nevertheless, as it is shown in Fig. 3, at constant polymer concentration $n_{\min}$ increases with ethanol concentration,

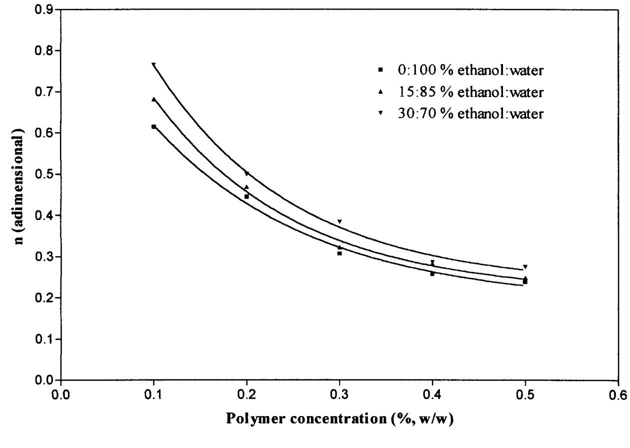

Fig. 3. One-phase exponential decay correlation of intercept flow index (*n*) values and polymer concentration for different ethanol contents. Theoretical curves obtained by Eq. (2).

Table 2
Correlation parameters obtained from Eq. (2), between *n*-intercepts and polymer concentration

Correlation parameters	Ethanol concentration (%, v/v)		
	0.0	15.0	30.0
n_{max}	0.9583	1.1260	1.2750
n_{min}	0.1873	0.2117	0.2311
A	5.8210	6.5930	6.7110
R	0.9902	0.9931	0.9928

since the addition of a poor solvent reduces polymer chain–solvent interactions. For ethanol concentrations higher than 30% v/v, the poor solvent effect reduces lifetime of junctions and straining of the polymer chains to an extent that affect the formation of a permanent like network, and Eq. (2) is no longer valid. As in the case of the previously discussed limitation of the empirical equation of consistency indexes, abrupt changes in the physical state and the flow mechanism of the system limit its applicability to the alcohol concentration range evaluated (alcohol concentration ≤ 30.0% v/v).

3.2. *Influence of cosolvents on the consistency of hydroalcoholic gels*

Cosolvents are widely used in semisolid bases formulation, and usually have greater influence on the resultant rheological properties of the systems. So, we intended to extend the application of the models previously discussed to a series of decreasing polarity alcohols. To assess the influence of alcohol quality on the above-discussed empirical variables, the pH-dependence of gelation in methanol:-water, 1-propanol:water and 1-butanol:water 15:85 v/v mixtures was evaluated.

The flow curves of the gels were also characteristic of viscoelastic systems with pseudoplastic and shear thinning behaviour, and were adjusted to Ostwald's model, with correlation coefficients in excess of 0.9850. This behaviour demonstrates the consistency of flow mechanism in all the alcoholic mixtures evaluated as jellifying media, since power law still reproduces adequately their rheological behaviour. Furthermore, calculated power law consistency indexes (*k*) were also well correlated with pH by Eq. (1). As an example, Fig. 4 shows experimental *k* values plotted as a function of pH, for gels of 0.5% w/w polymer concentration in methanol:water, ethanol:water, 1-propanol:water and 1-butanol:water 15:85 v/v mixtures. Correlation parameters obtained from Eq. (1), between consistency indexes and pH, are given in Table 3.

Calculated maximum consistency indexes (k_{max}) were found to be directly related to the alcohol polarity and solubility parameter, since the value of k_{max} decreases from methanol to 1-buthanol at constant pH and polymer concentration (Fig. 4, Table 3). On the other hand, as previously reported for increasing ethanol concentration, an inverse relationship between pH_{50} and cosolvent polarity and solubility parameter is observed (Table 3). A decrease in alcohol polarity tends to increase the value of pH_{50}, i.e. to increase the degree of neutralisation required to obtain half structure development in the respective cosolvent:water mixture. Furthermore, in the case *n*-butyl alcohol gels some degree of syneresis was observed, i.e. expression of interstitial liquid to the surface of the gel. The mechanism of syneresis has been related to the relaxation of elastic stresses during the setting of the gel, and the consequent reduction in the available interstitial spaces, which forces the expression of fluid [2].

The factors that influence hydrophilic polymeric gel's viscosity are molecular size and shape, concentration, temperature and intermolecular forces of attraction of solvent and polymer. Other variables being constant, the above-described features can be related to changes in intermolecular forces of attraction, through variations in polymer hydration and solubility parameter induced by the alcohols. Addition of alcohols of decreasing polarity change the solvent's characteristics, reducing the total solubility parameter of the jellifying medium, as demonstrated by the direct second-order polynomial relationship obtained between k_{max} and δ_T (Fig. 5, $k_{max} = -68870 + 1449\delta_T - 1449(\delta_T)^2$, $r^2 = 0.9963$). At the same time, the decrease in the solvent solubility parameter induces an increase in pH_{50}, as demonstrated by the inverse second-order polynomial relationship obtained between pH_{50} and δ_T (Fig. 5, $pH_{50} = 16.90 - 1.446\ \delta_T + 0.038(\delta_T)^2$, $r^2 = 0.8857$). This findings point to the importance of the specific effect of the solvent on the conformational characteristics of the macromolecules, which determines the formation of the entanglement network, and the influence of this network on the viscosity of gels and empirical variables introduced in Eq. (1).

3.3. *Mechanical properties of hydroalcoholic gels*

Formulations designed for topical application may exhibit acceptable mechanical characteristics such as easy removal of product from container, easy application, and

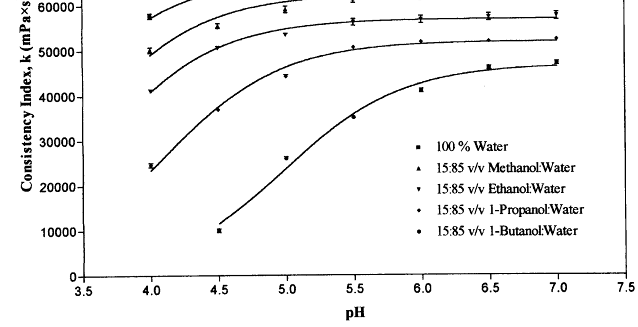

Fig. 4. Influence of alcoholic cosolvent on the pH dependence of consistency indexes (*k*) of 0.5% w/w Carbopol® Ultrez™ 10 gels. Theoretical curves obtained by Eq. (1).

Table 3
Empirical variables (k_{max} and pH$_{50}$) obtained from Eq. (1) for 0.5% w/w gels in 15:85 v/v alcoholic mixtures, together with the cosolvent total solubility parameters [δ_T, (cal/cm^3)$^{1/2}$]

Cosolvent	k_{max}	pH$_{50}$	r	δ_T
Water	66,190	3.192	0.9885	23.4
Methanol	62,480	3.441	0.9893	14.5
Ethanol	56,900	3.593	0.9994	13.0
1-Propanol	51,880	4.084	0.9926	12.0
1-Butanol	46,710	4.982	0.9901	11.3

low hardness. Texture profile analysis has been proven as an adequate method for the determination of the most important mechanical properties of polymeric systems, such as hardness and compressibility [13,19].

These two parameters, hardness A (the force required to attain a given deformation) and compressibility H (the work required to deform the product during a first compression cycle), were evaluated as a function of pH (4.0–7.0), polymer concentration (0.1–0.5% w/w), ethanol content (0.0, 15.0 and 30% v/v) and cosolvent polarity in a series of alcohol:water mixtures. Both parameters were found to be dependent on the variables evaluated, since increments in polymer concentration produced a resultant linear enhancement in hardness and compressibility, while the pH dependence was better accomplished by a sigmoidal function with a top value at neutral pH. On the other hand, ethanol content and lower polarity were found to affect mechanical properties of gels by limiting polymer chain interactions.

The evolution of mechanical properties (MP) as a function of pH in all the alcoholic mixtures studied showed a marked similarity with the previously obtained pH profile of consistency index. Similarities observed with k–pH profile are also confirmed by the good correlations obtained ($r > 0.9800$) between hardness, compressibility and pH with a sigmoidal function (Eq. (1)):

$$MP = \frac{MP_{max}}{1 + 10^{(pH_{50} - pH)}} \tag{3}$$

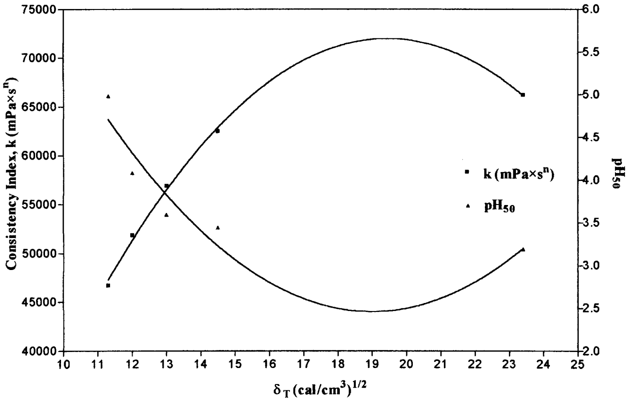

Fig. 5. Second-order polynomial correlation of the empirical variables k_{max} and pH$_{50}$ of 0.5% w/w Carbopol® Ultrez™ 10 gels with the cosolvent total solubility parameter (cal/cm^3)$^{1/2}$.

Correlation parameters are shown in Table 4. According to Eq. (3) both mechanical properties of hydroalcoholic gels increase with pH and tend to a maximum value (MP$_{max}$) at neutral pH, which is in agreement with the evolution of consistency index of acrylic acid polymers upon neutralisation. From analogy with the consistency index–pH profile, Eq. (3) predicts an erroneous nearly constant maximum of the mechanical properties for pH > 7.0, since obviously it is unable to account for any change that may occur in the physical state and flow mechanism of gels at pH > 8.0.

The effect of changing polymer concentration on the mechanical properties of hydroalcoholic gels was also analysed. An increase in the Carbopol® Ultrez™ 10 concentration, while keeping constant the pH, results in a linear increase of H_{max} and A_{max}, with correlation coefficients in excess of 0.9750 [20]. Furthermore, calculated maximum mechanical properties (MP$_{max}$) were found to be directly related to the alcohol polarity and solubility parameter, since the values of A_{max} and H_{max} decreased from methanol to 1-buthanol at constant pH and polymer concentration (Table 4). On the other hand, as previously reported for consistency, an inverse relationship between pH$_{50}$ – related to MP, Eq. (3) – and cosolvent polarity and solubility parameter is also observed (Table 4).

In general, the above-described characteristic features and similarities between consistency and mechanical properties point to the fundamental role of viscosity on compres-

Table 4
Values of the variables H_{max} (N), A_{max} (N·mm) and pH$_{50}$ obtained from Eq. (3) as a function of polymer and alcohol content

Alcohol content (%, v/v)	Ultrez™ 10 (%, w/w)	Correlation parameters		
		H_{max}	A_{max}	pH$_{50}$
0.0%	0.1	1.40	12.76	4.53
	0.2	2.91	26.29	4.4
	0.3	3.93	35.3	4.02
	0.4	4.92	44.36	3.76
	0.5	6.06	54.35	3.68
15.0% Ethanol	0.1	1.18	10.78	4.72
	0.2	2.4	22.22	4.59
	0.3	3.32	29.83	4.19
	0.4	4.16	37.48	3.93
	0.5	5.12	45.93	3.84
30.0% Ethanol	0.1	0.99	8.99	5.01
	0.2	2.05	18.52	4.86
	0.3	2.77	24.86	4.44
	0.4	3.47	31.24	4.16
	0.5	4.27	38.28	4.07
15.0% Methanol	0.5	5.64	50.32	3.71
15.0% 1-Propanol	0.5	4.33	36.76	4.19
15.0% 1-Butanol	0.5	3.95	29.12	4.86

sion characteristics of all the gels studied. This interrelation is demonstrated by the statistically significant linear correlation obtained between hardness, compressibility and consistency index (k) for the same polymer concentration and pH, regardless the composition of the jellifying medium:

$$H = (0.072 \pm 1.14 \times 10^{-3})k + 0.53 \pm 0.019$$

$$(r = 0.9873,\ \ n = 96,\ \ F = 9027)$$

$$A = (0.632 \pm 1.20 \times 10^{-2})k + 5.33 \pm 0.23$$

$$(r = 0.9745,\ \ n = 96,\ \ F = 9687)$$

This finding agrees with the previously reported studies on compression characteristics of other polymers [21,22]. Recently, Jones et al. reported significant correlations between product hardness and compressibility and the viscosity enhancement effect of a series of polymer including hydroxyethylcellulose, polyvinylpyrrolidone and polycarbophil. Linear models obtained with our polymer confirm those results, since the hardness and compression properties of all the hydroalcoholic gels express as a function of the viscosity enhancement effect of Carbopol® Ultrez™ 10.

Finally, it can be concluded that, the influence of polymer concentration, pH and cosolvent on polymer network development, and consequently on the flow behaviour and mechanical properties of Carbopol® Ultrez™ 10 hydroalcoholic gels, can be assessed by means of empirical parameters. The alcohol induced variations in consistency and mechanical properties of hydroalcoholic gels were correlated to modifications in the solubility parameter (δ_T). Furthermore, these empirical parameters (Y_{max}, pH$_{50}$ and n_{min}) can be used to evaluate *the ability of Carbopol® Ultrez™ 10* to jellify cosolvent:water mixtures, and have a wide potential to be used as optimisation parameters in topical drug delivery formulation development.

Acknowledgements

Authors acknowledge the financial support received from the research project (Ref.: E044/2001) forwarded by the University of Alcalá, Spain.

References

[1] R. Rodríguez, C. Alvárez-Lorenzo, A. Concheiro, Rheological evaluation of the interactions between cationic celluloses and Carbopol 974P in water, Biomacromolecules 2 (2001) 886–893.

[2] J.L. Zatz, G.P. Kushla, in: H.A. Lieberman, M.M. Rieger (Eds.), Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, Inc., New York, 1989, pp. 495–510.

[3] G.V. Vinogradov, A.Y. Malkin, Rheology of Polymers, Mir Publishers: Moscow/Springer: Berlin, 1980 (Chapter 2).

[4] S. Anlar, Y. Capan, A.A. Hincal, Physico-chemical and bioadhesive properties of polyacrylic acid polymers, Pharmazie 48 (1993) 285–287.

[5] F. Ferrari, S. Rossi, M.C. Bonferoni, C. Caramella, Rheological and mechanical properties of pharmaceutical gels. Part I: non-medicated systems , Boll. Chim. Farm. 140 (2001) 329–336.

[6] H.O. Ho, F.C. Huang, T.D. Sokoloski, M.T. Sheu, The influence of cosolvents on the in-vitro percutaneous penetration of diclofenac sodium from a gel system , J. Pharm. Pharmacol. 46 (1994) 636–642.

[7] C.H. Liu, H.O. Ho, M.C. Hsieh, T.D. Sokoloski, M.T. Sheu, Studies on the in-vitro percutaneous penetration of indomethacin from gel systems in hairless mice, J. Pharm. Pharmacol. 47 (1995) 365–372.

[8] L. Montenegro, A.M. Panico, A. Ventimiglia, F.P. Bonina, In vitro retinoic acid release and skin permeation from different liposome formulations, Int. J. Pharm. 133 (1996) 89–96.

[9] A. Arellano, S. Santoyo, C. Martin, P. Ygartua, Influence of propylene glycol and isopropyl myristate on the in vitro percutaneous penetration of diclofenac sodium from carbopol gels, Eur. J. Pharm. Sci. 7 (1999) 129–135.

[10] S. Rossi, F. Ferrari, M.C. Bonferoni, C. Caramella, Rheological and mechanical properties of pharmaceutical gels. Part II: medicated systems: relevance to hydration properties and drug release, Boll. Chim. Farm. 140 (2001) 337–344.

[11] B.W. Barry, in: J. Swarbrik (Ed.), Dermatological Formulations. Percutaneous Absorption, Marcel Dekker Inc., New York, 1983, pp. 301–304.

[12] H.B. Arnardóttir, S.J. Sveinsson, T. Kristmundsdóttir, The release of clindamycin from a suspension of different types of liposomes and selected topical dosage forms, Int. J. Pharm. 134 (1996) 71–77.

[13] D.S. Jones, Dynamic mechanical analysis of polymeric systems of pharmaceutical and biomedical significance, Int. J. Pharm. 179 (1999) 167–178.

[14] J.V. Herráez, M. Dolz, P. Sobrino, R. Belda, F. González, Modification of rheological behaviour of cellulose gels with sodium chloride concentration. Application of Ostwald's model, Pharmazie 48 (1993) 359–362.

[15] M. Dolz, M. Herráez, F. González, O. Díez, J. Delegido, M. Hernández, Flow behaviour of Carbopol-940 hydrogels. The influence of concentration and agitation time, Pharmazie 53 (1998) 126–130.

[16] A. Ramírez, M.J. Fresno, M.M. Jiménez, E. Sellés, Rheological study of *Carbopol® Ultrez™ 10* hydroalcoholic gels. I: flow and thixotropic behaviour as a function of pH and polymer concentration, Pharmazie 54 (1999) 444–447.

[17] J. Ferguson, Z. Kemblowski, Applied Fluid Rheology, Elsevier, London/New York, 1992 (Chapter 2, 5).

[18] M.J. Fresno, A. Ramírez, M.M. Jiménez, Rheological characterization of hydroalcoholic gels – 15% ethanol – of Carbopol Ultrez 10, Farmaco 56 (2001) 437–441.

[19] N.A. Peppas, J.J. Sahlin, Hydrogels as mucoadhesive and bioadhesive materials: a review, Biomaterials 17 (1996) 1553–1559.

[20] A. Ramírez, M.J. Fresno, M.M. Jiménez, E. Sellés, Rheological study of *Carbopol® Ultrez™ 10* hydroalcoholic gels. II: thermal and mechanical properties as a function of pH and polymer concentration, Pharmazie 54 (1999) 531–533.

[21] D.S. Jones, A.D. Woolfson, A.F. Brown, Textural analysis and flow rheometry of novel, bioadhesive antimicrobial gels, Pharm. Res. 14 (1997) 450–457.

[22] B. Vennat, F. Lardy, A. Arvouet-Grand, A. Pourrat, Comparative texturometric analysis of hydrogels based on cellulose derivatives, carraghenates, and alginates: evaluation of adhesiveness, Drug Dev. Ind. Pharm. 24 (1998) 27–35.