ELSEVIER

www.elsevier.nl/locate/farmac

Il Farmaco 56 (2001) 437–441

IL FARMACO

Rheological characterization of hydroalcoholic gels — 15% ethanol — of Carbopol® Ultrez™ 10[☆]

M.J. Fresno Contreras *, A. Ramírez Diéguez, M.M. Jiménez Soriano

Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Alcalá University, Madrid, Spain

Received 31 October 2000; accepted 10 January 2001

Abstract

The rheological behaviour of Carbopol® Ultrez™ 10 ethanolic (15%) gels was studied as a function of two main variables: pH (4.0–7.0) and the polymer concentration (0.1–0.5%). Flow curves of all hydroalcoholic gels were adjusted to the Ostwald model. Sigmoidal dose response functions were obtained to describe the pH dependence of consistency index of the systems. The concentration dependence of flow indexes was best adjusted to one-phase exponential decay functions. Finally, by substituting in the power law expression, an empirical model is given to estimate viscosities of gels for any value of pH and polymer concentration in the ranges evaluated. As a result, the influence of the variables on polymer network is meaningfully assessed by means of the obtained empirical parameters: bottom value (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}). © 2001 Éditions scientifiques et médicales Elsevier SAS

Keywords: Carbopol® Ultrez™ 10; Hydroalcoholic gels (15:85, ethanol:water, % v/v); Rheological behaviour; Power law; Empirical models

1. Introduction

Aqueous gel vehicles containing water, alcohol, propylene glycol and/or polyethylene glycol, and gelled with Carbopols or cellulose derivatives are classified as water-soluble bases. 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. 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, the gelation process in hydroalcoholic mixtures is also a function of the alcohol–polymer intermolecular interactions, and consequently, the alcohol content used in design and development of technologically adequate hydroalcoholic gelled bases is often limited by the compatibility of the gelling agent with the non-aqueous solvent [1].

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. Actually, Carbopol® Ultrez™ 10 is a new member of the Carbopols family, with better dispersion properties and a potential wide range of applicability in the pharmaceutical and dermocosmetic fields. Some advantages that have propitiated this development are: (1) high viscosity at low concentration; (2) wide viscosity interval and characteristic flow behaviour; (3) compatibility with many active ingredients; (4) bioadhesive properties; (5) low termosensitivity; and (6) excellent organoleptic characteristics and good patient acceptance [2–4].

As 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.

[☆] XXIV International Congress of the Latin-Mediterranean Pharmaceutical Society, Assisi, Italy, 20–23 September 2000.

* Corresponding author.

E-mail address: mjose.fresno@uah.es (M.J. Fresno Contreras).

0014-827X/01/$ - see front matter
PII: S0014-827X(01)01057-6

Therefore, the exhaustive characterisation of flow behaviour of these systems as a function of neutralisation and polymer concentration, specially when solubilising cosolvents like alcohols are employed, is essential to evaluate the ability of Carbopol® Ultrez™ 10 to jellify ethanol/water mixtures and their potential uses as dermatological bases [5–7].

In recent years many gelled water-soluble bases has been formulated to optimise topical drug delivery without an exhaustive rheological study. Nevertheless, knowledge of the rheological and mechanical properties are very important, and may lead to the possible employment 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 properties of Ultrez™ 10 gels is an important feature in their exhaustive characterisation as topical delivery systems [8–10]. With this in mind, the aim of the present work was to study the flow behaviour of Carbopol® Ultrez™ 10 hydroalcoholic gels as a function of the following variables: pH (4.0–7.0) and polymer concentration (0.1–0.5%). 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); all other reagents were of analytical grade.

To elaborate the gelification medium, double distilled deionised Milli-Q® water and ethanol 96° PA (Panreac Quimica S.A., Barcelona, Spain) were utilised. The triethanolamine (TEA) 50% solution was obtained by dissolution of TEA PA (E. Merck, Darmstadt) in Milli-Q® water.

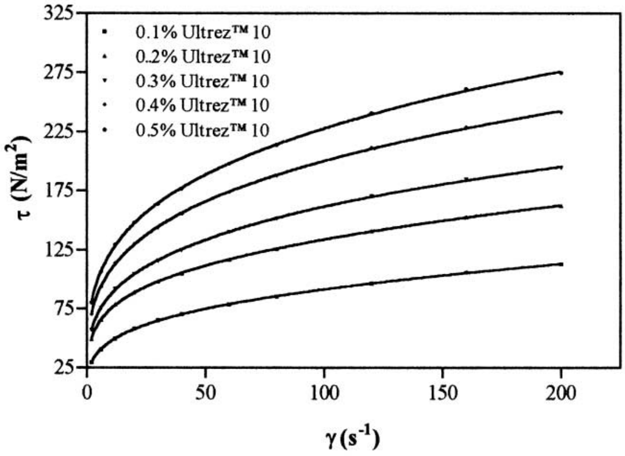

Fig. 1. Characteristic rheograms (shear stress (τ, N/m^2) vs shear rate (γ, s^{-1})) of different polymer concentration gels at constant pH = 7.

2.2. Hydroalcoholic gel elaboration

Appropriate quantities of Carbopol® Ultrez™ 10 were added to 15:85 v/v ethanol:deionised 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 were immediately neutralised with 50% TEA until the desired pH value was reached (4.0, 4.5, 5.0, 5.5, 6.0, 6.5 and 7.0), measured in situ with a digital Crison 2000 pH-meter. 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 with Rheocalc for Windows 1.01 software. 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 s^{-1}. 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.

3. Results and discussion

3.1. Flow behaviour of hydroalcoholic gels

The flow curves of all ethanol/water hydroalcoholic gels studied were characteristic of viscoelastic systems with pseudoplastic and shear thinning behaviour. These rheograms were adjusted to Ostwald's model ($\tau = k\gamma^n$), 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 and polymer concentration range evaluated [11].

As examples Figs. 1 and 2 show characteristic rheograms of hydroalcoholic gels for varying polymer concentration at constant pH and for increasing neutralisation pH at a constant polymer concentration, respectively.

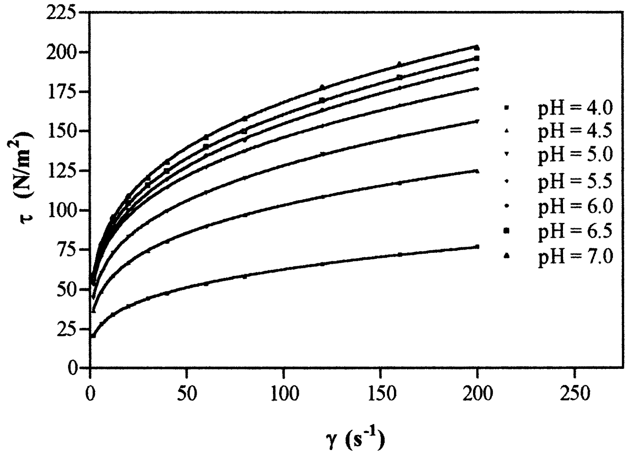

Fig. 2. Characteristic rheograms (shear stress (τ, N/m^2) vs shear rate (γ, s^{-1})) of 0.3% Carbopol® Ultrez™ 10 hydroalcoholic gels as a function of pH.

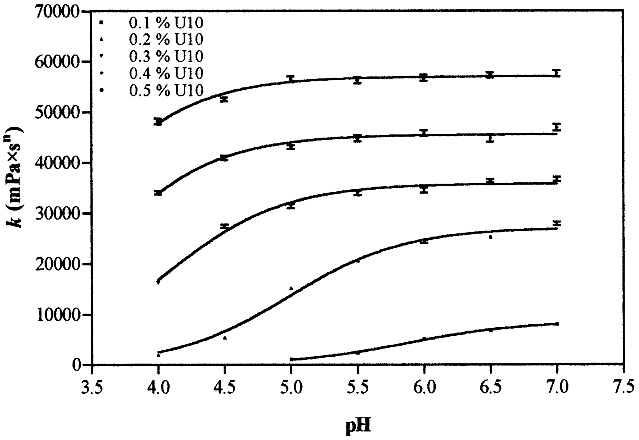

Fig. 3. Consistency indexes (k) of (15:85 ethanol:water) hydroalcoholic gels as a function of pH at different polymer concentrations (% w/w Ultrez™ 10 — U10).

3.1.1. Consistency indexes

The calculated power law consistency indexes (k) and flow indexes (n) were correlated to polymer concentration and pH. The graphical representation of the relationship between consistency index of hydroalcoholic gels and pH for the five polymer concentrations studied is given in Fig. 3.

The k-values show an initial pronounced increase with increasing pH (in the range 4.0–5.5) and a further stabilisation or reduced increment for pH values between 5.5 and 7.0 (Fig. 3). This behaviour indicates an initial more noticeable progressive development of polymer network with increasing pH, which attenuates for pH increments in the range 5.5–7.0. The mean values of k were thus correlated with pH according to a sigmoidal dose response function of the type:

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

obtaining the following empirical equation (correlation parameters are shown in Table 1):

$$k_{15} = \frac{112500c + 273.4}{1 + 10^{(-6.60c - \mathrm{pH} + 6.36)}} \tag{2}$$

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.

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 consis-

Table 1
Correlation parameters between consistency indexes ($\bar{k}$, mPa s^n) and pH (Eq. (1)) [a]

Ultrez™ 10 (% w/w)	$k = f$(pH)				
	$k_{\max}$ (±SE)	pH$_{50}$ (±SE)	r	$S_{x,y}$	ASS
0.1	8628 ± 178.8	5.865 ± 0.033	0.9991	38.6	4478
0.2	27130 ± 697.3	4.984 ± 0.056	0.9995	254.2	232000
0.3	35800 ± 460.7	4.055 ± 0.040	0.9982	219.3	240400
0.4	45540 ± 405.0	3.540 ± 0.045	0.9981	206.6	213300
0.5	57000 ± 316.9	3.287 ± 0.041	0.9971	164.4	135100

[a] SE, standard error; $S_{x,y}$, typical error; and ASS, absolute square sum.

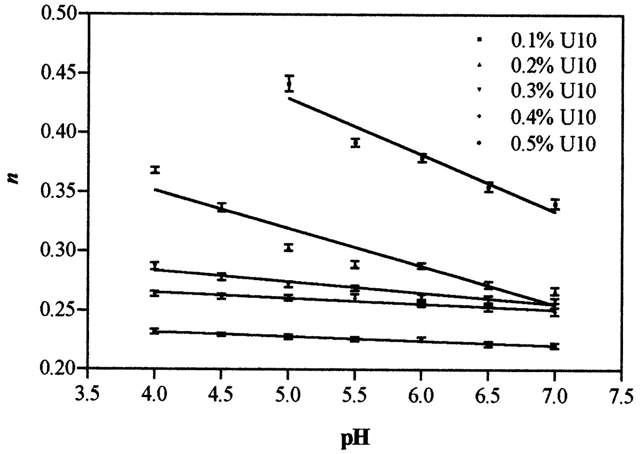

Fig. 4. Flow indexes (n) of (15:85 ethanol:water) hydroalcoholic gels as a function of pH at different polymer concentrations (% w/w Ultrez™ 10 — U10).

tency (k_{max}) of the fully structured polymer network [12].

3.1.2. Flow indexes

Power law flow indexes were also examined as a function of pH and polymer concentration. In all cases, the increase of pH at constant polymer concentration was found to induce a nearly linear decrease of flow indexes, i.e. an increase in the pseudoplastic and shear thinning character of hydroalcoholic gels, as can be observed in Fig. 4 [13]. Also, a lesser dependence is observed 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 measure departure from Newtonian flow, one of the best way to view it is as a function of the rate of change of structure with shear rate or shear stress [12]. 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 determine changes in molecular shape and flow. On this basis, 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 $n = f(\text{pH})$ with polymer concentration was observed, as is shown in Table 2. The decrease of calculated n-intercept values also indicate an increased departure of gels from the Newtonian flow behaviour with concentration. As in the case of 30.0% alcoholic gels [14], n-intercept values of 15.0% hydroalcoholic gels were also well fitted by least-squares to one-phase exponential decay function of the type (c, concentration; expressed in % w/w):

$$n = (n_{\max} - n_{\min})\,\mathrm{e}^{-Ac} + n_{\min} \tag{3}$$

obtaining the following empirical equation:

$$n_{15} = 0.857\,\mathrm{e}^{-5.889c} + 0.197 \tag{4}$$

Correlation parameters obtained with Eq. (3) describes the exponential decrease of n, at a rate A, with polymer concentration to a constant minimum value ($n_{\min}$). The theoretical curve obtained with Eq. (4) is shown in Fig. 5. 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.

Finally, by replacing Eqs. (1) and (3) in the general expression of the Ostwald model ($\eta = k\gamma^{n-1}$) we can obtain an empirical model for the apparent viscosity of hydroalcoholic gels as a function of the two main variables considered in our study:

$$\eta = \frac{k_{\max}\gamma^{[(n_{\max} - n_{\min})\,\mathrm{e}^{-Ac} + n_{\min}] - 1}}{1 + 10^{(\mathrm{pH}_{50} - \mathrm{pH})}} \tag{5}$$

Subsequently, substituting Eqs. (2) and (4) in the general model (5) we can obtain the empirical equation for the 15% ethanolic gels:

$$\eta = \frac{(112500c + 273.4)\gamma^{(0.857\,\mathrm{e}^{-5.889} + 0.197) - 1}}{1 + 10^{(-6.60c - \mathrm{pH} + 6.36)}} \tag{6}$$

Table 2
Correlation parameters between flow indexes and pH (Eq. (3)) [a]

Ultrez™ 10 (% w/w)	Statistical parameters					
	m (±SE)	b (±SE)	r	$S_{x,y}$	F	P
0.1	−0.0478 ± 0.0074	0.669 ± 0.0445	0.9335	0.0116	42.13	0.0074
0.2	−0.0320 ± 0.0051	0.479 ± 0.0282	0.8896	0.0133	40.28	0.0014
0.3	−0.0093 ± 0.0010	0.321 ± 0.0058	0.9406	0.0028	79.12	0.0003
0.4	−0.0046 ± 0.0006	0.284 ± 0.0033	0.9265	0.0016	63.06	0.0005
0.5	−0.0036 ± 0.0003	0.247 ± 0.0016	0.9705	0.0008	164.6	< 0.0001

[a] m, linear regression slope; b, y-intercept; SE, standard error; $S_{x,y}$, typical error; F of Snedecor; and P, correlation probability.

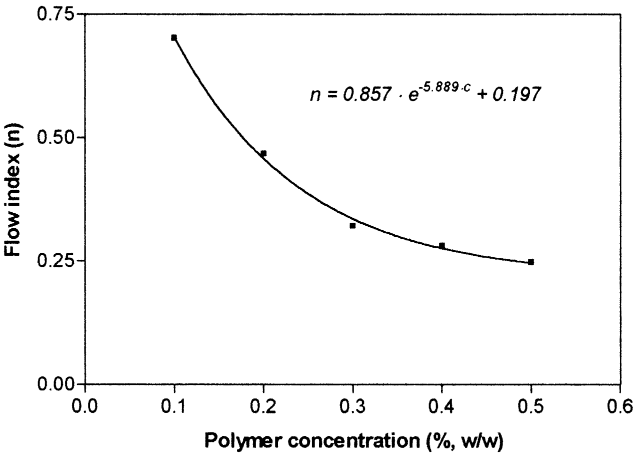

Fig. 5. Correlation between *n*-intercepts and polymer concentration with Eq. (3).

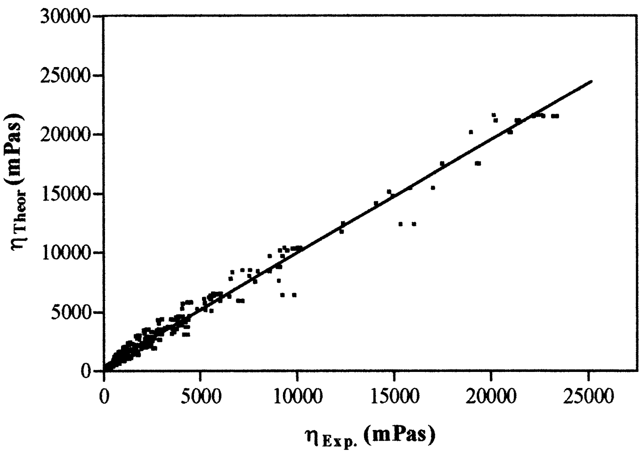

Fig. 6. Linear correlation obtained between calculated viscosity values (Eq. (6)) (η_{Theor}) and experimental viscosity values (η_{exp}).

The theoretical apparent viscosities calculated from Eq. (6) were correlated with the corresponding experimental values by linear regression, obtaining the following linear equation:

$$\eta_{\mathrm{Theor}} = (0.995 \pm 0.005)\eta_{\mathrm{exp}} + (437.8 \pm 18.9)$$

$$(r = 0.9860;\ F = 26220;\ n = 363) \qquad (7)$$

The graphical representation of theoretical apparent viscosity values plotted against experimental values is given in Fig. 6.

Based on the statistical parameters the obtained empirical model (Eq. (6)) is valid to calculate the theoretical apparent viscosity of the Carbopol® Ultrez™ 10 hydroalcoholic gels (15:85, ethanol:water, % v/v) for any pH and polymer concentration in the range investigated (*c*, 0.1–0.5% w/w; pH, 4.0–7.0). It should be noted that, although the validity of this type of empirical models is strictly limited to the region of deformation conditions tested, Eq. (6) could be useful in pharmacochemical and quality control processes [14].

Acknowledgements

The authors acknowledge the financial support received from the research project (E043/2000) forwarded by the University of Alcalá, Madrid, Spain.

References

[1] G.V. Vinogradov, A.Y Malkin, Rheology of Polymers, Mir/Springer, Moscow/Berlin, 1980.
[2] B.F. Goodrich, Polymers for pharmaceutical applications, I. General Overview, (Literatura técnica), 1997.
[3] S. Tamburic, D.Q.M. Craig, An investigation into the rheological, dielectric and mucoadhesive properties of poly(acrylic acid) gel systems, J. Controlled Release 32 (1995) 59–68.
[4] S. Tamburic, D.Q.M. Craig, Rheological evaluation of polyacrylic acid hydrogels, Pharm. Sci. 1 (1995) 107–109.
[5] 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.
[6] 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.
[7] 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.
[8] B.W. Barry, Dermatological Formulations, Marcel Dekker, New York, 1983.
[9] 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.
[10] D.S. Jones, Dynamic mechanical analysis of polymeric systems of pharmaceutical and biomedical significance, Int. J. Pharm. 179 (1999) 167–178.
[11] J.V. Herráez, M. Dolz, P. Sobrino, R. Belda, F. González, Modification of rheological behavior of cellulose gels with sodium chloride concentration. Application of Ostwald's model, Die Pharmazie 48 (1993) 359–362.
[12] J. Ferguson, Z. Kemblowski, Applied Fluid Rheology, Elsevier, London, 1992.
[13] M. Dolz, M. Herráez, F. González, O. Díez, J. Delegido, M. Hernández, Flow behavior of Carbopol 940 hydrogels. The influence of concentration and agitation time, Die Pharmazie 53 (1998) 126–131.
[14] A. Ramírez, M.J. Fresno, M.M. Jiménez, E. Sellés, Rheological study of Carbopol® Ultrez™ 10 hydroalcoholic gels. I: flow and thixotropic behavior as a function of pH and polymer concentration, Die Pharmazie 54 (1999) 444–447.