

## Rheological study of Carbopol<sup>®</sup> Ultrez<sup>™</sup> 10 hydroalcoholic gels, I: Flow and thixotropic behavior as a function of pH and polymer concentration

A. RAMÍREZ, M. J. FRESNO, M. M. JIMÉNEZ and E. SELLES

The rheological behavior of Carbopol<sup>®</sup> Ultrez<sup>™</sup> 10 alcoholic (30%) gels was studied as a function of two main variables: pH (4.0–7.0) and polymer concentration (0.1–0.5%). Flow curves of all hydroalcoholic gels were adjusted to the Ostwald model. Empirical functions are obtained to describe the individual dependence of calculated consistency and flow index, and hence of the structural development of the polymer network, on the variables studied. Finally, by substituting in the power law expression, an empirical model is given to estimate viscosities of gels for any pH value and polymer concentration in the ranges evaluated. The results of a further study are given, performed to assess the effect of shear time on gel viscosity and thixotropic properties. In general, the hydroalcoholic gels showed no significant thixotropic behavior, with a remarkable stability under the shear conditions evaluated.

### 1. Introduction

Ultrez<sup>™</sup> 10 is a new member of the Carbopol<sup>®</sup> acrylic acid polymers family, with better dispersion properties and a potential wide range of applicability in the pharmaceutical and cosmetic fields. According to flow properties Carbopol<sup>®</sup> Ultrez<sup>™</sup> 10 may be considered a hybrid between Carbopol 940 and Carbopol 934 type resins. This polymer has some advantages, mainly because of its dispersion properties: due to low viscosity of unneutralized dispersions requires a less time and effort consuming elaboration process, allowing to make more concentrated dispersions and offering greater versatility in formulating and processing.

Like in the case of other Carbopol resins, neutralization of Ultrez<sup>™</sup> 10 dispersions is essential to develop the rheological properties of the polymer. Nearly any required value of viscosity can be achieved by adjusting the polymer concentration and the final pH of the gels [1, 2]. Therefore the exhaustive characterization of the rheological behavior of this systems as a function of neutralization and polymer concentration, especially when solubilizing cosolvents like ethanol are employed, is essential to evaluate their potential uses as dermatological bases [3].

In recent years many gelled water-soluble bases were formulated to optimize topical drug delivery, without an exhaustive rheological study of this systems. In our opinion acknowledge of the rheological properties of this systems is of greater importance, and may lead to the possible employ of rheological parameters to optimize topical drug delivery from dermatological formulations [4–7].

The aim of the present work was to study the rheological behavior of 30% hydroalcoholic gels of Carbopol<sup>®</sup> Ultrez<sup>™</sup> as a function of the following variables: pH (4.0 to 7.0), polymer concentration (0.1–0.5%) and agitation time (1–30 min). The results and models obtained are to be used in forthcoming studies of drug release from this polymeric systems.

### 2. Investigations, results and discussion

#### 2.1. Rheological behavior as a function of pH and polymer concentration

The flow curves (rheograms) obtained for the 35 hydroalcoholic gels studied were qualitatively similar, and are characteristic of viscoelastic systems with pseudoplastic and shear thinning behavior (i.e., a decrease in viscosity

as the shear rate is increased). As examples Figs. 1 and 2 show characteristic rheograms of hydroalcoholic gels for increasing neutralization pH at a constant polymer concentration and for varying polymer concentrations at constant pH, respectively. The reproducibility in triplicate runs was good and the standard deviations (SD) were within 3%. All the rheograms obtained were adjusted to Ostwald's model ( $\tau = k \cdot D^n$ ) with correlation coefficients in excess of 0.9930, showing that the power law reproduce adequately the rheological behavior of Ultrez 10 hydroalcoholic gels [8]. 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 the consistency index of hydroalcoholic gels and the pH for the five polymer concentrations studied is given in Fig. 3. The  $k$  values show an initially pronounced increase with increasing pH (in the range 4.0–5.5) and a further stabilization or reduced increment for pH values between 5.5 and 7.0. This behavior indicates a more noticeable progressive development of the 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:

$$k = \frac{k_{\max}}{1 + 10^{(\text{pH}_{\text{struc}} - \text{pH})}} \quad (1)$$

whose correlation parameters are shown in Table 1. As it can be deduced from statistical parameters and theoretical curves shown in Fig. 3., Eq. (1) is able to adequately describe the variation of consistency indexes as a function of pH in the concentration range investigated (0.1–0.5% w/w). According to this expression, the consistency of hydroalcoholic gels increases with pH and tends to a maximum value ( $k_{\max}$ ) at neutral pH, which is in agreement with the general behavior of acrylic acid polymers upon neutralization. The variable  $\text{pH}_{\text{struc}}$  in eq. (1) determines the rate at which the system reaches its maximum consistency ( $k_{\max}$ ). It should be noted that eq. (1) is unable to account for the characteristic decrease of consistency due to an excessive neutralization of these systems. For pH values greater than 8.0 in the gels under study a coacervation process may take place, which abruptly changes the physical state and the flow mechanism of these system. In general, this is the case for all the empirical functions obtained in the present study, and consequently limits its applicability to the pH range evaluated ( $\text{pH} < 7.0$ ).

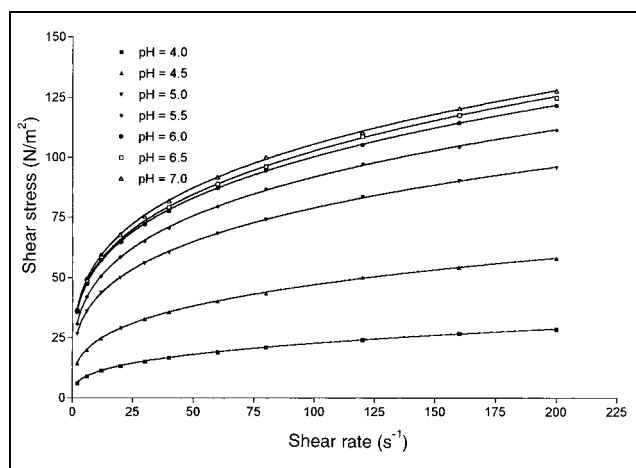


Fig. 1: Characteristic rheograms (shear stress vs. shear rate) of 0.3% Carbopol® Ultrez™ 10 hydroalcoholic gels as a function of pH

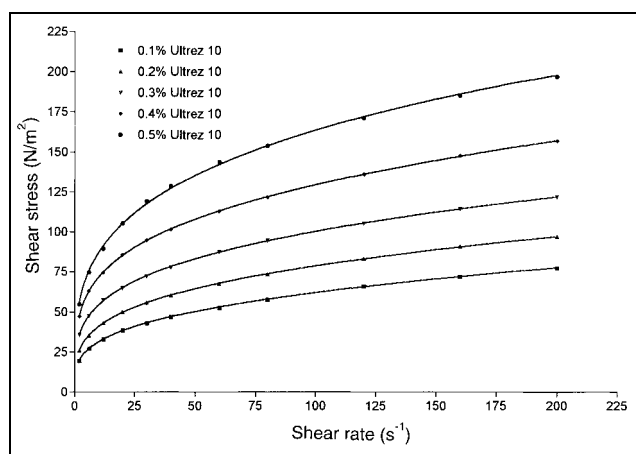


Fig. 2: Characteristic rheograms (shear stress vs. shear rate) of different polymer concentration gels at constant pH = 7

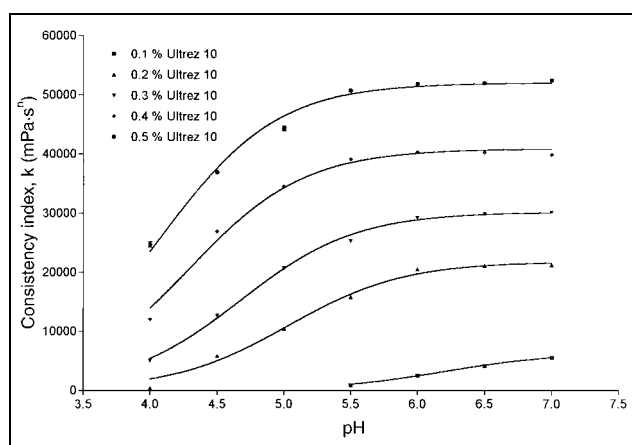


Fig. 3: Consistency indexes ( $k$ ) of hydroalcoholic gels as a function of pH at different polymer concentrations. Theoretical curves obtained by eq. (1)

In general, the structure of Carbopols in solution depends on the extent to which the macromolecules associate and form entanglement networks. Because of their molecular structure, and specially due to the dissociation process induced by pH, non covalent binding plays a dominant role in forming the gel structure. In aqueous media the polymer is mainly in the free acid form, and the generation of negative charges along the polymer chain causes it to uncoil and expand. Therefore, in agreement with the above

Table 1: Correlation parameters of consistency ( $k$ ) and flow ( $n$ ) index of Carbopol® Ultrez™ 10 hydroalcoholic gels as a function of pH

Conc.	Correlation Parameters					
	$k = f(\text{pH})$			$n = f(\text{pH})$		
	$k_{\max}$	$\text{pH}_{\text{struc.}}$	$r^2$	A	B	$r^2$
0.1%	6410	6.226	0.9995	-0.06200	0.7650	0.9936
0.2%	21720	5.031	0.9983	-0.03286	0.4993	0.8845
0.3%	30070	4.667	0.9996	-0.01786	0.3839	0.8712
0.4%	40750	4.287	0.9981	-0.00250	0.2854	0.7562
0.5%	51880	4.084	0.9983	-0.00250	0.2749	0.8703

mentioned characteristic and progressive evolution of consistency indexes, the values obtained for the variable  $\text{pH}_{\text{struc}}$  (Table 1) can be interpreted as an inflection point. From this pH value onwards, the polymer network is practically structured and the increase of the consistency index with neutralization is less pronounced. This characteristic pH value decreased with polymer concentration, indicating that for higher polymer contents, a more significant network development can be obtained at lower neutralization pH values.

The effect of changing polymer concentration on the consistency of hydroalcoholic gels was also analyzed. An increase in the Carbopol® Ultrez™ 10 concentration, while keeping pH constant, results in a linear increase in viscosity. In the low concentration range evaluated there are no strong interactions between polymer chains, and consequently the physical properties of this systems change in direct proportion to the concentration. With the aim of include the concentration dependence of  $k_{\max}$  and  $\text{pH}_{\text{struc}}$ , both parameters were correlated with polymer concentration, obtaining linear models with correlation coefficients in excess of 0.990. By replacing linear expressions of  $k_{\max}$  and  $\text{pH}_{\text{struc}}$  as a function of concentration in Eq. (1), the final mathematical expression of the function  $k = f(\text{pH}, C)$  is obtained ( $C$ : concentration, expressed in % w/w):

$$k = \frac{110000 \cdot C - 2885}{1 + 10^{(-5.03 \cdot C - \text{pH} + 6.37)}} \quad (2)$$

Power law flow indexes were also examined as a function of pH and polymer concentration. An increase in pH of the hydroalcoholic gels, while keeping the polymer concentration constant, results in a nearly linear decrease of flow indexes as shown in Fig. 4. The equation parameters of the linear correlations between  $n$  and pH are shown in Table 1. The negative slope values obtained in each linear equation demonstrate the increasing pseudoplastic and shear thinning character of hydroalcoholic gels when pH increases.

It is generally accepted that although the power law index  $n$  measures departure from Newtonian flow, one of the best ways to view it is a function of the rate of change of structure with shear rate or shear stress [9, 10]. 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 this basis neutralization 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. Also, a less dependence between  $n$  and pH is observed as polymer concentration increase. Consequently the effect of the final

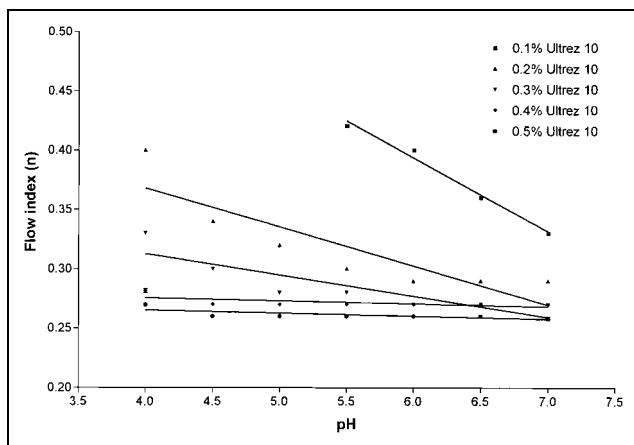


Fig. 4: Power law flow index ( $n$ , adimensional) of hydroalcoholic gels as a function of pH at different polymer concentrations

pH value of the gels upon flow index decreases at higher polymer concentrations.

Another feature of the obtained flow index-pH profile is the dependence existing between intercepts of the linear functions  $n = f(\text{pH})$  and polymer concentration (Table 1). The calculated  $n$ -intercept values show a progressive decrease with polymer content, indicating a progressive increase in shear thinning behavior of the hydroalcoholic gels with concentration. This data was best fitted by least-squares to one phase exponential decay function ( $r = 0.9967$ ) of the type:

$$n = (n_{\max} - n_{\min}) \cdot e^{-A \cdot C} + n_{\min} \quad (3)$$

obtaining the following equation ( $C$ : concentration, expressed in % w/w):

$$n = 1.04 \cdot e^{-6.71 \cdot C} + 0.231 \quad (4)$$

A theoretical curve obtained with Eq. (4) is shown in Fig. 5, which in general confirms the increasing shear thinning and progressive development of a polymer network with increasing polymer concentration. Eq. (4) describes the exponential decrease of  $n$  at a rate of  $A = -6.71$ , with polymer concentration to a constant minimum value. The existence of an asymptote ( $n_{\min} = 0.231$ ) as a bottom flow index value for hydroalcoholic gels demonstrates that the three dimensional polymer lattice gradually becomes fully structured with increasing polymer concentration [9–11].

Finally, by replacing Eqs. (2) and (4) in the general expression of the Ostwald model ( $\eta = k \cdot D^{n-1}$ ) we can ob-

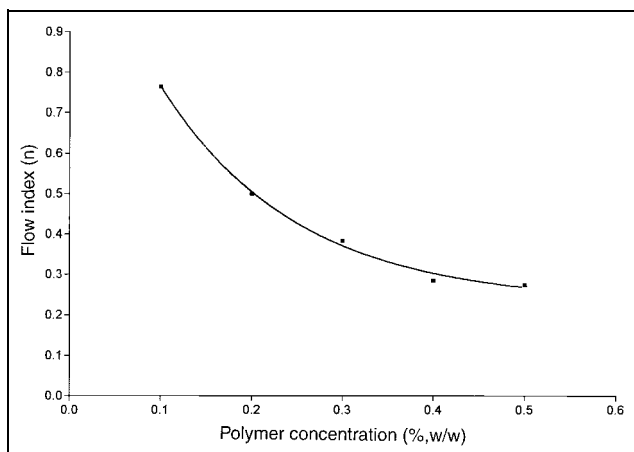


Fig. 5: One phase exponential decay correlation of intercept flow indexes and polymer concentration

tain an empirical model for the apparent viscosity of hydroalcoholic gels as a function of the two main variables considered in our study:

$$\eta = \frac{k_{\max} \cdot D^{((n_{\max} - n_{\min}) \cdot e^{-A \cdot C} + n_{\min}) - 1}}{1 + 10(\text{pH}_{\text{struc}} - \text{pH})} \quad (5)$$

$$\eta = \frac{(110000 \cdot C - 2885) \cdot D^{(1.04 \cdot e^{-6.71 \cdot C} + 0.231) - 1}}{1 + 10(-5.03 \cdot C - \text{pH} + 6.37)} \quad (6)$$

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

$$\eta_{\text{Theor}} = (0.983 \pm 0.006) \cdot \eta_{\text{exp}} + (46.1 \pm 3.4) \quad (7)$$

$$(r = 0.991, \quad F = 28970, \quad n = 560)$$

The graphical representation of theoretical apparent viscosity values plotted against experimental values is given in Fig. 6. Based in its statistical parameters the obtained empirical model (eq. 6) is valid to calculate the theoretical apparent viscosity of the Carbopol<sup>®</sup> Ultrez<sup>™</sup> 10 hydroalcoholic gels 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 pharmaceutical and quality control processes.

## 2.2. Thixotropic behavior of hydroalcoholic gels

Thixotropy of dispersed systems arises from the progressive decrease in viscosity, and hence of shear stress, due to application of a shear rate for a given period of time. In order to evaluate the thixotropic behavior of Carbopol<sup>®</sup> Ultrez<sup>™</sup> 10 30% alcoholic gels, product samples were subjected to a maximum shear rate ( $200 \text{ s}^{-1}$ ) for different agitation times.

Due to the wide range of viscosities covered by the hydroalcoholic gels under study it was necessary to employ the relative thixotropic area concept ( $S_R$ ) [12], with the aim of comparing the thixotropic behavior of gels as a function of pH and polymer concentration:

$$S_R = \frac{S_T}{S_{\max}} \cdot 100 = \frac{S_{\max} - S_{\text{ta}}}{S_{\max}} \cdot 100 \quad (8)$$

where  $S_{\max}$  is the total area enclosed by the “Up” curve in the rheogram and  $S_{\text{ta}}$  is the area enclosed by the corresponding “down” curve after an agitation time ( $t_a$ ), calculated by numerical integration (in  $\text{Nm}^{-2} \text{ s}^{-1}$ ).

Fig. 7 shows characteristic rheograms obtained as a function of the applied agitation time corresponding to 0.4% Ultrez<sup>™</sup> 10 hydroalcoholic gels at pH 7. The  $S_{\text{ta}}$  areas enclosed by rheograms tend to a minimum with agitation time. This behavior was described by Dolz et al. [13] for highly viscous sodium (carbox methyl)cellulose hydrogels, fitting the thixotropic areas ( $S_T$ ) as a function of agitation time by the following equation:

$$S_{\text{ta}} = (S_{\max} - S_{\min}) \cdot e^{-A \cdot \sqrt{t_a}} + S_{\min} \quad (9)$$

where  $S_{\min}$  is the limiting area value for a very long agitation time and  $A$  is the decrease rate of  $S_{\text{ta}}$  with agitation time. The phenomenon of thixotropy have two main characteristics: the shear thinning effect and the time-dependence of viscosity. The later may be explained on the basis

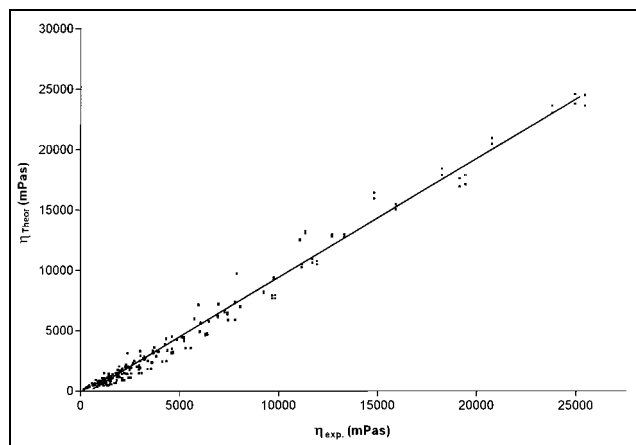


Fig. 6: Linear correlation between theoretical apparent viscosities ( $\eta_{Theor}$ ) calculated from eq. (6) and the experimental viscosities ( $\eta_{exp}$ ) for the same pH and polymer concentration

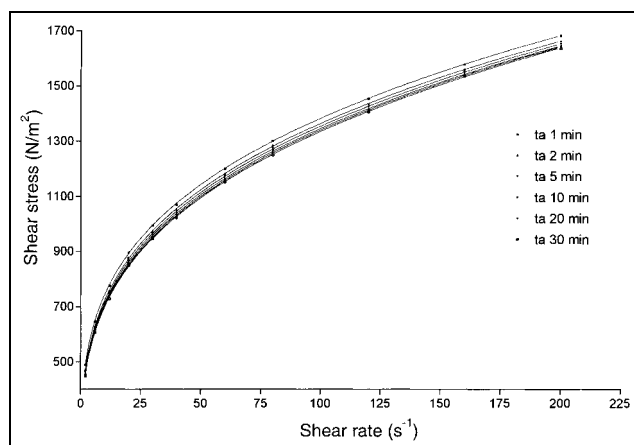


Fig. 7: Characteristic flow curves of 0.4% Carbopol Ultrez 10 hydroalcoholic gels as a function of agitation time (constant pH = 7)

of the dynamic equilibrium between the process of breakdown and recovery of structure, which depends on thermal motion and shear stress. Since the viscosity of the system is determined by the number of bonds retained at a given time, in steady flow conditions, when an equilibrium exist between process of formation and breakdown of interparticle bonds, this parameter will also approach an equilibrium value. Hence, the value of  $A$  in eq. (9) can be assessed as to include the time-dependence of the viscosity in terms of a delayed adjustment of the hydroalcoholic gel structure to the shear conditions.

In our case only the  $S_{ta}$  values of high pH and polymer concentration hydroalcoholic gels were well correlated to agitation time by eq. (9). For gels of low pH (<5.0) and polymer concentration (<0.3%) the experimental values of  $S_{ta}$  varied in a random basis with agitation time (data not shown). This result can be explained by the low sensitivity of the viscometer employed in conjunction with the limited thixotropic properties exhibited by the studied hydroalcoholic gels.

On the basis of the above mentioned time-dependence of hydroalcoholic gel viscosities, relative thixotropic areas ( $S_R$ ) were calculated by employing the  $S_{min}$  values estimated with eq. (9) for  $t_a \rightarrow \infty$ , and are given in Table 2 as a function of pH and polymer concentration. These results indicate an increase in the thixotropy of hydroalcoholic gels with increasing pH and polymer concentration, in agreement with the above mentioned progressive development of polymer network. However, in general, Carbo-

**Table 2: Calculated relative thixotropic areas ( $S_R$ , %,  $t_a \rightarrow \infty$ ) of Carbopol<sup>®</sup> Ultrez<sup>™</sup> 10 gels as a function of pH and polymer concentration**

Conc. (%, w/w)	pH				
	5	5.5	6	6.5	7.0
0.3	1.08	1.27	1.40	1.70	1.85
0.4	1.45	1.76	1.98	2.15	2.28
0.5	1.70	1.97	2.36	2.79	2.97

pol<sup>®</sup> Ultrez<sup>™</sup> 10 hydroalcoholic gels show high stability against agitation and exhibit no significant thixotropic behavior under the test conditions.

### 3. Experimental

#### 3.1. Hydroalcoholic gel elaboration

Appropriate quantities of Carbopol<sup>®</sup> Ultrez<sup>™</sup> 10 (B. F. Goodrich Chemical Co.) were added to 30:70 ethanol/deionized water mixtures to obtain the following polymer concentrations: 0.1, 0.2, 0.3, 0.4 and 0.5% w/w. The mixture was agitated at 2000 r.p.m for 10 min with a Silverson L4R agitator equipped with an axial flow head in conjunction with a disintegrating head. Polymer dispersions were immediately neutralized with Triethanolamine 50% until the desired 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. The samples were allowed to equilibrate for 72 h at room temperature prior to the evaluation of their rheological properties.

#### 3.2. 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 the sample-container temperature. The data obtained was analyzed and adjusted to the Ostwald model with the Rheocalc for Windows 1.01 software. The viscosity determinations were done in 0.5 ml of sample, for twenty-one sequentially increasing and decreasing values of shear rate in the range 2–200 1/s. The temperature was kept constant at  $20 \pm 0.1$  °C and all samples were equilibrated at each run temperature on the plate for 5 min prior to the viscosity measurements. The influence of agitation time was determined by recording viscosity for decreasing values of shear rate after constant agitation at 200 1/s for 1, 2, 5, 10, 20 and 30 min. The thixotropic area values were determined by numerical integration as the difference between the areas enclosed by the "up" and "Down" curves of the rheograms.

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Dr. M. J. Fresno Contreras  
Departamento de Farmacia  
y Tecnología Farmacéutica  
Campus Universitario  
Ctra. de Barcelona Km 33.600  
E-28871 Alcalá de Henares, Madrid  
Spain