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Rheological Study of Binary Gels with Carbopol® Ultrez™ 10 and Hyaluronic Acid

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The objective of this study is to provide a rheological characterization of binary hydroalcoholic gels made with Carbopol® Ultrez™ 10 (U10) and Hyaluronic Acid (HA) as a function of polymer concentration: U10 (0.0—2.0% w/w) and HA (0.00—0.20% w/w), and to determine the influence of this combination on the thixotropic properties of the resulting binary systems. Interaction of the two polymers was measured using the Viscose Synergy Index (I_S) and thixotropic analysis, which indicate the structural changes that take place in binary gels attributable to molecular interactions between the gelling agents. The maximum values for viscose synergy ($I_S = 1.22$—1.44) are obtained for the U10 : HA mixtures with a polymer proportion of 10 : 1. The behavior of the binary gels studied is the result of the formation of a more structured three-dimensional network between the U10 and HA molecules. Shearing of this polymer network requires application of a greater force than is needed to shear the structure of the separate gels. Inclusion of HA in a proportion of 1 : 10 has a fixing effect on the polymer network, resulting in greater resistance to shearing in the compound gel. The relative thixotropic area —A_R— shows maximum values ($A_R = 17.215\%$) for the same polymer composition. The evolution of the two parameters indicates that restructuring of the molecular interactions for this polymer proportion (10 : 1) takes place; the result is a reinforced three-dimensional structure in the gelled system, which increases the thixotropic properties. The same composition leads to a maximum of thixotropic properties as well as viscose synergy because both characteristics are closely related to structural changes observed in the binary systems of this composition. Thixotropic systems have a very wide area of application in the pharmaceutical industry. For this reason, the results obtained here considerably increase the use of the gels studied. In fact, incorporation of HA significantly improves a property of acrylic gels which has direct repercussions on the ease and efficiency of their application to the skin.

Key words Carbopol® Ultrez™ 10; hyaluronic acid; binary gel; viscose synergy index; relative thixotropic area

Many products containing natural, semi-synthetic and synthetic polymers are used in the pharmaceutical industry as agents for gelling, thickening, stabilizing and modification of viscosity. The polymer materials used to develop pharmaceutical vehicles of topical application must have the appropriate physical, chemical and mechanical properties. Generally, commercialized synthetic polymers comply with these requirements and they are widely used as bases for topical application, but they are not sufficiently biocompatible. The properties of these materials can be improved by combining biological macromolecules such as collagen, elastin and glycosaminoglycans.[1,2]

Many semi-solid pharmaceutical vehicles include more than one polymer in the formulation in order to obtain the appropriate properties for topical application. The properties of most of these systems correspond to those of the individual polymers. However, in some cases, the characteristics of the compound systems are superior to those of each of the separate components or they are even qualitatively different. Specifically, the combination of certain synthetic and natural polymers can lead to significant synergistic effects as a result of interaction between the different polymer chains and the formation of mixed bonding areas.[3,4]

Mixtures of two or more polymers can show complex properties that depend on the total polymer concentration, the relative proportion of each of the components, the characteristics of the dissolution medium and the temperature. The causes of this non-additive behavior are directly related to the efficiency of the interactions observed among the polymer molecules and to the balance of interaction between the molecules in the same polymer and in different polymers, which depend on the primary and secondary structures in the chains.[5,6]

This behavior leads to a wide variety of structural conditions and to the nonlinearity of the macroscopic properties observed in certain compound systems. In fact, the combination of two polymers can produce gels characterized by a higher degree of rigidity than is calculated using a linear combination of rigidity values for gels formed by each of the individual polymers. Many polymers show this non-additive behavior, which is called synergy.[7—9]

The combination of specific synthetic and natural polymers can create significant synergistic effects as a result of interaction between different polymeric chains and the formation of mixed bonding areas.[10]

Synthetic polymers are widely used in pharmaceutical and biomedical applications. However, mixtures of synthetic and natural polymers are increasingly used as a complementary alternative in these areas. Characterization of these mixtures reveals the existence of synergistic effects that can be used to optimize drug delivery. The advantage of these systems is that the kinetics of drug release from the matrix can be adjusted by varying the composition of the components.[11] However, some types of restructuring observed in some compound polymer systems cause a nonlinear decrease in the resulting properties, that is, negative synergy.[1]

This study examines the rheological behavior of binary hydroalcoholic gels made with the synthetic polymer Carbopol® Ultrez™ 10 —U10— and the natural polymer Hyaluronic Acid —HA—. Each of the two components has

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specific advantages.

Carbopol® Ultrez™ 10, a carbomer polymer, is considered to be a universal polymer capable of replacing two or more carbomer polymer grades currently in use to formulate lotions, creams and gels.[12]

Hyaluronic acid (HA) has recently been introduced as a vehicle for topical application of drugs to the skin. Specifically, recent studies have propitiated its use in the development of new pharmaceutical dosage delivery forms.[13—15]

One of the most important technical considerations in the galenic development of gelled water soluble bases designed specifically for topical use is the exhaustive rheological characterization of the systems studied and optimization of the rheological parameters related directly to application and topical delivery. Increased interest in these polymers for elaboration of cosmetic and pharmaceutical formulations justifies a complete rheological study of these gelled topical forms. Hence, the objective of this study is to examine the rheological behavior of binary hydroalcoholic gels formulated using Carbopol® Ultrez™ 10 —U10— and Hyaluronic Acid —HA—. In order to determine the extent of a possible interaction and viscose synergy existing between U10 and HA, the two polymers are combined in different proportions —U10–0.0; 0.1; 0.5; 1.0; 1.5; 2.0 and HA–0.00; 0.01; 0.05; 0.10; 0.15; 0.20% w/w — to study the influence of the final polymer composition of the gel on the rheological properties of the compound systems[2,16,17] and agitation time (t_a): 0, 1, 2, 5, 10, 15 and 20 min.

Experimental

Materials Carbopol® Ultrez™ 10 was purchased from BF Goodrich Chemical Co. (Cleveland, U.S.A.) and cross-linked hyaluronic acid was obtained from Sigma Chem. Co. (St. Louis, U.S.A.). Hyaluronic acid must be cross-linked or mixed with acrylic hydrogels to increase stability.[18] To elaborate the gelification medium, double distilled-deionized Milli-Q® water and ethanol 96° PA (Panreac Química S.A., Barcelona, Spain) were utilized. The triethanolamine (TEA) 50% solution was obtained by dissolution of TEA PA (E. Merck, Darmstadt) in Milli-Q® water.

Composition of the Formulations Table 1 lists the composition of the 35 binary hydroalcoholic gels (F1—F35) as a function of the partial concentrations of the two polymers: U10–0.0; 0.1; 0.5; 1.0; 1.5; 2.0 and HA–0.00; 0.01; 0.05; 0.10; 0.15; 0.20% w/w. The intervals of polymer concentration assayed were selected based on the results of a preliminary study of the rheological parameters (viscosity and the indexes for consistency and flow) of the binary gels.

Procedure Appropriate amounts of Carbopol® Ultrez™ 10 were weighed to obtain the partial concentrations of polymer described in Table 1 and added to 100 ml of ethanol : Milli-Q® water mixtures prepared in the proportion of 15 : 85% v/v. The mixtures were agitated at 2000 rpm for 10 min with a Silverson L4R agitator equipped with an axial flow head and disintegrating head. The dispersions were then set aside for 2 h in order to eliminate any air and to guarantee a complete humectation of the polymer. In the meantime, exact quantities of hyaluronic acid sodic salt were weighed to obtain the partial concentrations of the polymer listed in Table 1 and then dissolved in 100 ml of ethanol : Milli-Q® water mixtures in the proportion 15 : 85% v/v. These solutions were also set aside for 2 h. After this rest time, the U10 dispersions and HA solutions were interposed and then neutralized with a 50% triethanolamine solution to obtain a pH value of 7.0. Homogenization during neutralization was carried out at a continuous flow of 1000 rpm to prevent air from entering the gelled mass. The pH measurements were taken *in situ* with a digital Crison 2001 micro pH-meter, previously calibrated and equipped with an electrode for emulsions. The samples were allowed to equilibrate for 72 h prior to evaluation of their rheological properties.[19—22]

Determination of Viscosity and Viscose Synergy Index Viscosity was determined using a cone and plate Brookfield Digital Viscometer DV-III, equipped with a recirculating Brookfield TC 200 bath to control the sample-container temperature. Reproducibility of the data was assessed by deter-

Table 1. Composition of the Binary Hydroalcoholic Gels Made with Carbopol® Ultrez™ 10 (U10) and Hyaluronic Acid (HA)

HA (%, w/w)	U10 (%, w/w)					
	0.0	0.1	0.5	1.0	1.5	2.0
0.00	—	F-1	F-2	F-3	F-4	F-5
0.01	F-6	F-7	F-8	F-9	F-10	F-11
0.05	F-12	F-13	F-14	F-15	F-16	F-17
0.10	F-18	F-19	F-20	F-21	F-22	F-23
0.15	F-24	F-25	F-26	F-27	F-28	F-29
0.20	F-30	F-31	F-32	F-33	F-34	F-35

mining the rheograms at 20.0±0.1 °C for 0.5 ml of each sample ($n=5$). The temperature of each sample on the rheometer plate was allowed to stabilize for 5 min before the viscosity measurement was taken. Rheograms were obtained for 11 decreasing shear rates (D, s^{-1}): 50.0; 40.0; 30.0; 20.0; 14.0; 10.0; 6.0; 4.0; 3.0; 2.0; 1.0; 0.2 s^{-1} using the CP-52 cone (angle=3.0° and diameter=2.4 cm). The rheograms obtained were analyzed and adjusted to the Ostwald model using Rheocalc for Windows, version 1.01.[23—25] The interaction between the two polymers was quantified with the Viscose Synergy Index.[7,26—28]

Influence of Hyaluronic Acid on the Thixotropic Properties Another aspect of the structural modifications measured using the viscose synergy index is their possible effect on the thixotropic properties of the dispersions. The objective of this part of the present study is to determine the effect of agitation time on the flow behavior of binary gels formulated using different polymer proportions of U10 : HA. In order to quantify the effect of each polymer individually, the compositions of the formulations assayed were selected according to the following criteria[7,28,29]:

Binary U10 : HA gels formulated using increasing values of HA concentration (0.00; 0.01; 0.05; 0.10; 0.15; 0.20%, w/w) with a constant U10 concentration (0.5% w/w). (Formulations F-2, F-8, F-14, F-20, F-26, F-32, described in Table 1).

Binary U10 : HA gels formulated using increasing values of U10 (0.00; 0.10; 0.50; 1.0; 1.5; 2.0%, w/w) with a constant HA concentration (0.05% w/w) (Formulations F12—F17, described in Table 1).

The effect of agitation time (t_a) on the thixotropic area values of the binary gels was determined by measuring the viscosity of the down curve of the rheogram (D, s^{-1}: 50.0; 40.0; 30.0; 20.0; 14.0; 10.0; 6.0; 4.0; 3.0; 2.0; 1.0; 0.2 s^{-1}) after subjecting the sample to a constant agitation speed of 50.0 s^{-1} for 0, 1, 2, 5, 10, 15 and 20 min. Viscosity was measured using 0.5 ml of each sample at a constant temperature of 20.0±0.1 °C. The values for areas under the curve were calculated using numerical integration of the minimum (0.2 s^{-1}) and maximum (50.0 s^{-1}) shear rate values from the rheograms [$\tau=f(D)$] for the different agitation times (t_a) applied to the systems.[30]

Results and Discussion

Interaction of Carbopol® Ultrez™ 10 and Hyaluronic Acid: Viscose Synergy Index The experimental values of shear stress (τ, N m^{-2}) as a function of shear rate [D, s^{-1}] for the 35 binary hydroalcoholic gels yielded flow curves that adjust to the Ostwald model ($\tau=k \cdot D^n$), with correlation coefficients above 0.990. The statistical parameters show that the power law adequately reproduces the pseudoplastic behavior of binary hydroalcoholic gels with U10 and HA. The average values of the consistency index ($\bar{k}$) and flow index ($\bar{n}$), calculated using the Ostwald de Waele model, appear in Table 2.

In order to determine the influence of the factors of U10 concentration (c_U, 5 levels) and HA concentration (c_H, 5 levels), the —k— values were compared using a multifactorial analysis of variance (Two-way Anova; GraphPad Prism 2.0). The results obtained show that the two affect consistency of the gelled binary systems both systematically and significantly ($p<0.001$). In addition, interaction of the two vari-

Table 2.   Average Consistency Index ($\bar{k}$, mPa s^n±S.D.) and flow index ($\bar{n}$, Adimensional±S.D.) Values of the Binary Gels as a Function of U10 and HA Concentration [$\bar{k}, \bar{n}, f(c_{U10}, c_{HA})$]

HA (%, w/w)	U10 (%, w/w)											
	0.0		0.1		0.5		1.0		1.5		2.0	
	$\bar{k}$±S.D.	$\bar{n}$±S.D.	$\bar{k}$±S.D.	$\bar{n}$±S.D.	$\bar{k}$±S.D.	$\bar{n}$±S.D.	$\bar{k}$±S.D.	$\bar{n}$±S.D.	$\bar{k}$±S.D.	$\bar{n}$±S.D.	$\bar{k}$±S.D.	$\bar{n}$±S.D.
0.00	—	—	8597.7 ±43.11	0.3270 ±0.008219	30893.3 ±833.1	0.2551 ±0.01064	59036.7 ±1605.8	0.2136 ±0.003735	73383.3 ±1806.7	0.1890 ±0.004007	100790.0 ±1667.7	0.1715 ±0.002816
0.01	63.64 ±1.81	0.4851 ±0.007345	12106.7 ±402.4	0.3741 ±0.005670	37166.7 ±1797.3	0.2671 ±0.005537	59320.0 ±1171.2	0.2231 ±0.003878	74783.3 ±1864.1	0.1934 ±0.002721	100420.0 ±3533.4	0.1711 ±0.004206
0.05	214.07 ±6.25	0.4551 ±0.004251	10363.3 ±375.3	0.3538 ±0.005369	44926.7 ±1286.2	0.2835 ±0.004191	68526.7 ±1284.6	0.2290 ±0.003248	77480.0 ±2316.2	0.1913 ±0.004386	103100.0 ±2088.1	0.1689 ±0.003353
0.10	357.03 ±3.78	0.4233 ±0.003608	9302.0 ±399.4	0.3407 ±0.005583	36373.3 ±410.5	0.2614 ±0.004444	83933.3 ±2137.8	0.2420 ±0.004047	88120.0 ±1775.4	0.1890 ±0.005897	107733.3 ±1106.0	0.1710 ±0.003055
0.15	549.00 ±26.48	0.3924 ±0.005306	8900.0 ±219.3	0.3340 ±0.007034	32216.7 ±618.6	0.2633 ±0.003713	66450.0 ±805.5	0.2294 ±0.002792	103066.7 ±404.15	0.2023 ±0.003054	111300.0 ±4326.7	0.1689 ±0.004062
0.20	707.73 ±25.37	0.3535 ±0.005901	8653.3 ±176.2	0.3420 ±0.003734	30843.3 ±1049.8	0.2628 ±0.004491	59083.3 ±1412.3	0.2306 ±0.004044	85526.7 ±2592.8	0.1893 ±0.005565	123933.3 ±1616.6	0.1795 ±0.002845

ables is statistically significant ($p<0.001$).[31] Interaction was measured using the Viscose Synergy Index (I_S), defined as:

$$I_S = \frac{k_{U+H}}{k_U + k_H} \tag{1}$$

in which: k_{U+H}, (mPa s^n) is the average consistency index for the binary hydroalcoholic gel made with U10 and HA at concentrations c_{U+H} (U10 : HA, % w/w); and —k_U— and —k_H— (mPa s^n) are the average consistency indexes for the individual U10 and HA gels at the concentrations c_U and c_H (%, w/w), respectively.

According to this definition, synergy exists when $I_S>1$. On the contrary, if $I_S<1$, the binary gel shows lower consistency values than the sum of the consistency indexes for the two separate gels. In this case, it can be said that there is antagonism, which may be caused by a reordering of the molecular bonds that leads to weakening of the three-dimensional structure in the compound. Thus, measurement of the viscose synergy index can show structural changes that take place in binary gels and are attributable to molecular interactions between the gelling agents.[32,33]

Synergy formation in a gel can take place through different mechanisms. Intermolecular interactions can be chemical in origin and involve formation of covalent bonds between the polymer chains, as is the case of propylene glycol alginate and gelatine in a slightly alkaline medium.[27] In these cases, the result is formation of a chemical network. However, in most cases, synergy is related to intermolecular interactions of a physical nature, either through a cooperative association between chains of different polymers to form mixed bonding areas similar to bonding areas in single-component gels, or through chain-to-chain associations due to attraction between opposite charges.

In other cases, behavior of compound gelled systems is governed by thermodynamically unfavorable interactions ($\Delta H<0$) between the chain segments, which may cause mutual exclusion of each of the components and thus increase the effective concentration of the two polymers. When thermodynamic incompatibility is the basis of the structural state in the system, an increase in concentration of one of the components above a specific value can lead to separation of the system into two phases.[34]

Table 3.   Values of Viscose Synergy Indexes (I_S) of the Binary Gels as a Function of U10 and HA Concentration [$I_S, f(c_{U10}, c_{HA})$]

HA (%, w/w)	U10 (%, w/w)				
	0.1	0.5	1.0	1.5	2.0
0.01	1.398	1.201	1.004	1.018	0.996
0.05	1.176	1.444	1.157	1.053	1.021
0.10	1.039	1.164	1.413	1.195	1.065
0.15	0.973	1.025	1.115	1.394	1.098
0.20	0.930	0.976	0.989	1.154	1.221

The average values of the synergy indexes (I_S) for the U10 and HA binary gels are found in Table 3. The experimental results indicate that the maximum synergy values were obtained for the U10 and HA mixtures in a proportion of 10 : 1. Specifically, with this U10/HA polymer proportion, the binary gels show viscose synergy indexes that vary from 1.22 to 1.44. In practice, these synergy values suggest that the consistency of the compound gels ranges from 122 to 144% more than the sum of the consistency for the individually formed gels.

The hydroalcoholic systems of these two polymers have somewhat similar rheological properties: hyaluronic acid behaves like tightly-coiled macromolecular solutions, while the flow characteristics of Carbopol® Ultrez™ 10 correspond to gelled intermediate networks. When the two polymers are combined, their interaction produces a more rigid gel, characterized initially by cooperative transitions and bonding through non-covalent ordered associations. The mechanism for synergistic gelling of the two polymers can take place presumably through formation of mixed bonding areas.

Based on the general considerations mentioned above related to the definition of the viscose synergy index, the behavior of the binary gels studied may be a result of the formation of a more structured three-dimensional network between the U10 and HA molecules. Shearing of this polymer network requires greater force than is needed to shear the structure of the individual gels. Apparently, incorporation of HA in a proportion of 1 : 10 serves to set the polymer network, and therefore the compound gel becomes more resistant to shearing.

The results in Table 3 show that the polymer compositions whose U10/HA proportions differ from 10:1 have significantly lower viscose synergy indexes. In particular, the binary gels with a low U10/HA proportion (0.1% U10:0.2% HA; 0.1% U10:0.15% HA) have lower —I_S— values than the unit. This behavior suggests that incorporation of HA in relative amounts greater than 10% of the U10 content may produce a certain degree of structural antagonism. An excess of HA possibly causes a restructuring of the molecular interactions, which leads to weakening of the three-dimensional structure in the binary systems, with a resulting decrease in viscosity compared to the sum of the viscosity values for the systems with only one of the components.

The structural changes observed as a result of the combination of a synthetic polymer and another polymer of natural origin are most likely to have a direct effect on the thixotropic properties of the systems. It is of major importance to study the thixotropic properties of binary gels and their correlation with the evolution of viscose synergy given the importance of thixotropy in the pharmaceutical industry and the low values inherent in simple U10[35] aqueous and hydroalcoholic gels.

Influence of Hyaluronic Acid on the Thixotropic Properties of Binary Gels The pharmaceutical industry can benefit highly from systems that are capable of experiencing isothermic transitions from a gel state to a colloid state as a result of shearing forces and are then able to go back to a gel when left to rest. However, Carbopol® gels in general, and Carbopol® Ultrez™ 10 hydroalcoholic gels in particular, have highly limited thixotropic properties. Nevertheless, as shown above in the application of the viscose synergy index, incorporation of Hyaluronic Acid to these gelled systems brings about structural variations which will most likely affect their thixotropic behavior.

Consequently, this section examines the influence of the combination of U10 and low molecular weight HA on the thixotropic properties of the resulting binary systems. Specifically, the effect of agitation time (t_a) on the flow behavior of binary gels formulated using different polymer concentrations of U10:HA will be studied. To measure the effect of each polymer individually, the compositions of the formulations were designed according to the following criteria: 1) increasing concentrations of HA (0.00; 0.01; 0.05; 0.10; 0.15; 0.20% w/w) with a constant U10 concentration (0.5% w/w); 2) varying concentrations of U10 (0.00; 0.10; 0.50; 1.0; 1.5; 2.0% w/w) with a constant HA concentration (0.05% w/w).

Thixotropic behavior is generally measured, among other methods, by determining the thixotropic areas —A—, that is, the areas enclosed between the up curve in the rheogram $\tau = f(D)$ (increasing values of D) and each of the down curves (decreasing values of D) obtained after subjecting samples to different agitation times. Experimentation is used to obtain the rheograms [$\tau = f(D, t_a)$; t_a: 0, 1, 2, 5, 10, 15, 20 min] and the corresponding areas under the curve of the U10 and HA binary gels for each of the polymer compositions (U10:HA) assayed. Figures 1—3 are examples which show the rheograms [$\tau = f(D, t_a)$] for the HA gels (U10:HA–0.0:0.05%), the U10 gels (U10:HA–0.5:0.0%) and the binary gels (U10:HA–0.5:0.05%), respectively.

Comparison of the graphs reveals that the hydroalcoholic gels made from one or the other of the polymers do not show
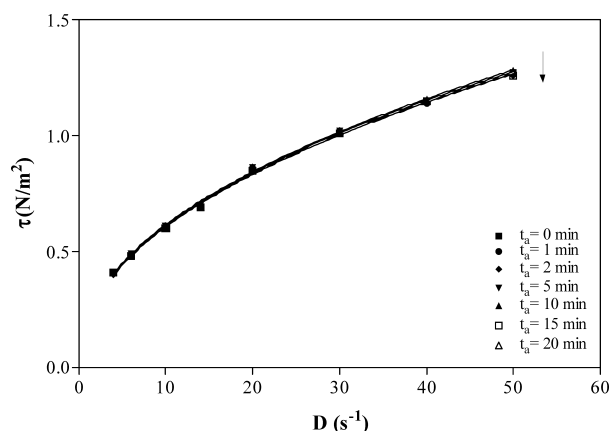

Fig. 1. Flow curves [$\tau = f(D)$] for the Hydroalcoholic Gels with HA (U10:HA–0.0:0.05%) at Different Agitation Times (t_a)
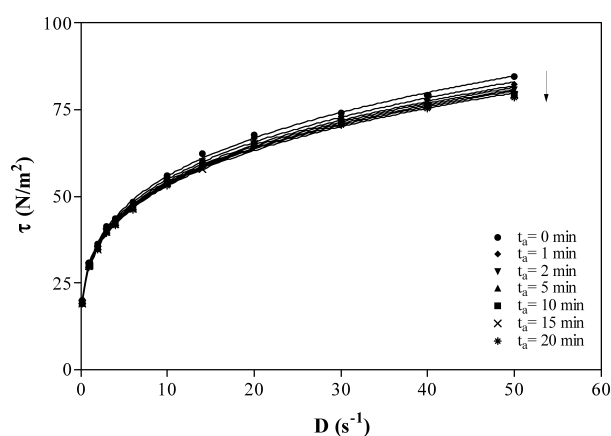

Fig. 2. Flow Curves [$\tau = f(D)$] for the Hydroalcoholic Gels with U10 (U10:HA–0.5:0.00%) at Different Agitation Times (t_a)
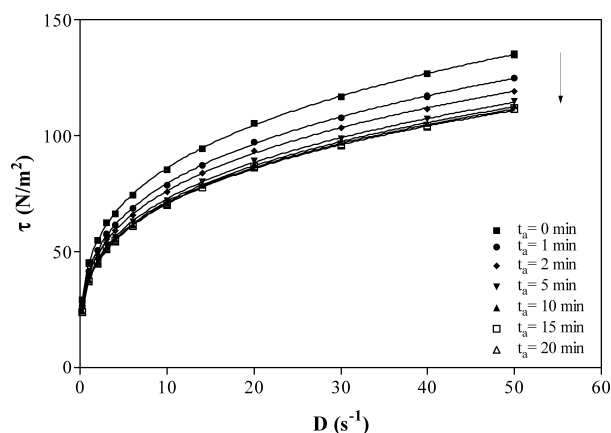

Fig. 3. Flow Curves [$\tau = f(D)$] for the Binary Hydroalcoholic Gels with U10 and HA (U10:HA–0.5:0.05%) at Different Agitation Times (t_a)

significant thixotropic behavior (Figs. 1, 2). That is, they do not experience an appreciable change in shearing force in relation to agitation time. On the contrary, Fig. 3 shows that the combination of Carbopol® Ultrez™ 10 and Hyaluronic Acid (U10:HA) creates a binary dispersion with a progressive, significant decrease in shearing force related to increased agitation time, a common characteristic of thixotropic systems.

The decrease is most pronounced in the first 2—5 min and is less appreciable as agitation time is increased. This behavior may explain the irregular distribution observed for the values of areas under the curve when they are correlated with agitation time, particularly with prolonged agitation conditions.[31]

An additional difficulty in the experimental study of these dispersions is related to their few thixotropic properties, that is, from the low values of area enclosed by the hysteresis cycle (A) compared to the total area determined by the up curve of the rheogram. In these cases, study of thixotropy requires prior determination using linear regression of the function $A=A(t_a)$, in which —A— is the area under the curve calculated for each of the rheograms $\tau=f(D)$ using the minimum and maximum shearing rate values applied to the system during agitation time —t_a—.

Dolz *et al.*, 1991, proposed the following mathematical function, which meets the limits required to describe the thixotropic behavior of the systems studied ($A=A_{max}$ for $t_a=0$; $A=A_{min}$ for $t_a=\rightarrow\infty$):

$$A(t_a) = A_{min} + (A_{max} - A_{min}) \cdot e^{K \cdot \sqrt{t}} \tag{2}$$

The area values, calculated using numerical integration of the flow curves $\tau=f(D)$ using the values $D_0=0.2\,s^{-1}$ and $D_1=50.0\,s^{-1}$, corresponding to each of the polymer compositions (U10 : HA) examined, were correlated with agitation time using this empirical model (Eq. 2). Functions $A=A(t_a)$ for the U10 : HA binary systems studied appear in graph form in Fig. 4.

The statistical parameters of the correlations obtained through linear regression using Eq. 2 are listed in Table 4.

According to the empirical model used to obtain the functions $A=A(t_a)$, intersection of the different curves and the A-axis determines the maximum area values (A_{max}). At the same time, the limit values for area when $t_a\rightarrow\infty$ correspond to the maximum degree of rheodestruction (A_{min}). In addition, the parameter —K— characterizes time variation of the area —A. If the system in question is thixotropic, then $K>0$ because the value of —A— decreases when agitation time is extended. Moreover, —K— must be finite for only in this case does the area depend on agitation time. Finally, the influence of —K— on $A(t_a)$ is clearly conditioned by the value of ($A_{max}-A_{min}$), which depends in turn on the polymer concentration of the gel (Table 4).

As can be observed in Table 4, an increase in U10 concentration ($c_{HA}=0.05\%$; constant) produces a progressive increase in the maximum area and the total thixotropic area. On the contrary, for higher HA concentration ($c_U=0.5\%$; constant) Table 4 shows an initial rise and a later fall in the values for —A_{max}— and —A_T—. The maximum area of the binary hydroalcoholic gels is mainly determined by the viscosity of the system, so the difference in ability to enhance viscosity on the part of the two polymers conditions the relationship $A_{max}=f(c)$. The relative increase in viscosity and, thus, the maximum thixotropic area for the U10 concentration is significantly greater than the result obtained for the HA concentration.

Another significant result obtained by using Eq. 2 regards parameter —K—. The relationship between viscosity and time is normally determined by the dynamic balance existing between the processes of breaking and recovery of the structure, both of which depend on thermal movement and on shearing stress. Because the viscosity of the systems is related to the number of bonds maintained for a specific period of time when flow is kept stationary, if there is a balance between the processes of shearing and breaking of bonds between particles, —K— also tends to reach a balanced value. Consequently, it can be suggested that the value for —K— used in Eq. 2 represents the dependence of viscosity on time,
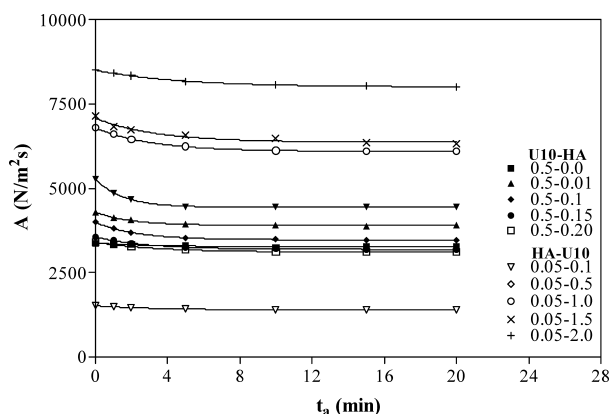

Fig. 4.   Values of Area (A) as a Function of Agitation Time (t_a) for the Binary Hydroalcoholic Gels with U10 and HA (U10 : HA, % w/w) (Theoretical Curves Obtained Using Eq. 2)

Table 4.   Statistical Parameters of the Correlations $A=A(t_a)$ (Eq. 2), Total Thixotropic Area Values —A_T (N/m^2 s)— and Relative Thixotropic Area Values —A_R (%)— for the Binary Gels Studied (U10 : HA)

Composition		Statistical parameters						Areas	
U10 (%, w/w)	HA (%, w/w)	A_{max} (±S.E.)	A_{min} (±S.E.)	K	r	ASS	$S_{x,y}$	A_T	A_R
0.5	0.00	3375.0±17.36	3225.0±71.53	0.321±0.288	0.9407	1301.0	18.04	150.0	4.450
0.5	0.01	4307.0±21.57	3854.0±27.92	0.617±0.108	0.9930	1922.0	21.92	453.0	10.518
0.5	0.05	5292.0±57.57	4381.0±54.62	0.779±0.155	0.9888	13510.0	58.12	911.0	17.215
0.5	0.10	4004.0±40.27	3373.0±73.34	0.498±0.144	0.9862	6788.0	41.19	631.0	15.759
0.5	0.15	3575.0±29.16	3087.0±77.86	0.401±0.139	0.9859	3612.0	30.05	488.0	13.650
0.5	0.20	3410.0±23.76	2976.0±109.2	0.302±0.140	0.9849	2447.0	24.73	434.0	12.727
0.0	0.05	43.52±0.2276	41.87±90.98	−0.033±1.71	0.4271	0.251	0.251	1.65	3.791
0.1	0.05	1526.0±10.42	1347.0±38.50	0.338±0.142	0.9848	466.8	10.80	179.00	11.730
1.0	0.05	6819.0±55.38	5867.0±178.8	0.363±0.139	0.9855	13120.0	57.28	992.00	13.961
1.5	0.05	7129.0±20.27	6103.0±71.49	0.346±0.048	0.9982	1764.0	21.00	1126.00	14.392
2.0	0.05	8527.0±39.00	7484.0±597.5	0.165±0.135	0.9854	6840.0	41.35	1183.00	12.232

S.E.: standard error; ASS: absolute sum of squares; $S_{x,y}$: typical error.

that is, the period of time which this parameter of the binary hydroalcoholic gels requires to adjust to the shearing conditions.

The correlations of $K = f(c)$ for each of the polymers, appearing in Table 4, show initial increases related to concentration with a maximum value of $0.779\,\mathrm{min}^{-1/2}$ at 0.5% U10 and 0.05% HA, respectively. The gels with more polymer concentration than the samples indicated here lead to progressive drops in —K— value. This result indicates that the binary gel with 0.5% U10 and 0.05% HA (U10 : HA polymer proportion 10/1) showed a larger degree of dependence of —A— on agitation time (t_a). Consequently, it can be said that the gelled system with a U10 : HA polymer relation of 10 : 1 is the most thixotropic of all the binary gels studied.

However, in Table 4 it can be seen that the maximum values of parameter —K— and the total thixotropic area —A_T—, are not obtained by the same polymer composition. In other words, the binary gel which shows more thixotropy, as measured by the sensitivity of area —A— compared to —t_a— through parameter —K— does not have a greater total thixotropic area. This apparent contradiction can be resolved bearing in mind that a higher value for thixotropic area does not necessarily imply greater thixotropy. In fact, comparison of the thixotropic properties of systems with different viscosities must be carried out using the relative thixotropic area (A_R), defined as[26]:

$$A_R = 100 \cdot \frac{A_T}{A_{max}} \tag{3}$$

This equation enables calculation of the percentage of area rheodestroyed ($A_T = A_{max} - A_{min}$) during agitation compared to the initial maximum area as determined by the up curve of the rheogram (A_{max}). In this case, a system is more thixotropic when it has a larger value for relative thixotropic area (A_R). If Eq. 3 is incorporated into Eq. 2, the result is as follows:

$$A_R(t_a) = \{(A_R)_{min} + [100 - (A_R)_{min}]\} \cdot e^{K \cdot \sqrt{t}} \tag{4}$$

in which:

$$(A_R)_{min} = 100 \cdot \frac{A_{min}}{A_{max}} \tag{5}$$

Equations 2 and 4 are formally identical and can be applied indistinctly to measure the thixotropic behavior of the U10 and HA binary gels studied in this section. The relative thixotropic area values for the systems are listed in Table 4.

Table 4 shows the dependence of relative thixotropic area and parameter —K— of the binary gels on U10 content with a constant HA concentration. The data in Table 4 suggest that, unlike the values for total thixotropic area, the maximum values for relative thixotropic area are obtained for the same polymer concentration (0.5% U10 and 0.05% HA), which have the maximum value of —K—. Following this procedure, the binary gel that has a more thixotropy according to the definition of —K— in the equation also has a larger relative thixotropic area (Table 4). The evolution of the two parameters confirms that restructuring of the molecular interaction has taken place with this polymer proportion (10 : 1), which produces a reinforced three-dimensional structure of the gelled system, thus increasing its thixotropic properties.

This result corrects the apparent contradiction which arose when total thixotropic area was considered to indicate the degree of thixotropy in the systems. Evidently, when gels show the same total thixotropic area values, the system whose rheogram up curve determines a smaller initial area under the curve experiences more rheodestruction (Table 4).

Finally, it should be highlighted that the maximum values for the relative thixotropic area (A_R) and the Viscose Synergy Indexes (I_S) coincide at the same U10 : HA polymer composition. This coincidence in composition which obtains the maximum value for both thixotropic properties as well as viscose synergy is a result of the fact that the two characteristics are closely related to the structural changes observed in the binary systems with this composition.

Conclusion

The area of application of thixotropic systems in the pharmaceutical industry is wide, so the results obtained here increase considerably the use of the gels studied. In fact, incorporation of Hyaluronic Acid significantly improves a property of acrylic gels which has direct repercussions on the ease and efficiency of their application to the skin.

Binary gels show complex rheological properties which depend on the total and relative concentration of each of the polymers. The maximum values for viscose synergy ($I_S = 1.22$—1.44) and the relative thixotropic area are obtained in the mixtures of Ultrez™ 10/Hyaluronic Acid in a 10 : 1 polymer proportion.

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