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A study of shear and compression deformations on hydrophilic gels of tretinoin

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Abstract

A rheological study of hydrophilic gels of Carbomer® 940 with tretinoin as the drug, and ascorbic acid as an antioxidant, has been carried out. At the same time, the effect of storage time has been determined. Both shear and compression deformations were applied. From the results obtained, correlations between both types of deformation have been established. The results were statistically significant between shear and compression stresses, and between shear stress and area of spreading.

Key words: Shear deformation; Compression deformation; pH; Tretinoin; Ascorbic acid; Carbomer® 940

1. Introduction

The basic rheological properties of materials can be described by at least three parameters: stress, shear rate and time. A knowledge of these and their interaction is essential for the measurement and interpretation of rheological data (Deem, 1988; Lucero et al., 1991).

When a material is subjected to a force, it deforms to a greater or lesser degree (Dolz et al., 1988). Therefore, the fundamental factors are the deformation and its rate.

It is interesting that most suppositions are made on the basis that the material is continuous – i.e., on the assumption that all the properties of the system are uniform at each point. From this, a series of rheological equations has been derived that can be applied to the resolution of problems of deformation and flow. In fact, the rheological properties of a material can be best understood considering their behaviour in a particular simplified state, called simple shear (Banker and Chalmers, 1981; García et al., 1987).

Fluid material can be deformed by both shear and compression. In the former case, a tangential force is applied to the material, while in the latter the force is perpendicular to the direction of fluid movement.

In the bibliography consulted, few works have been found on flow by compression from a rheological point of view, except those of Campanella and Peleg (1987) and DeMartine and Cussles (1975). In contrast, there are works on spreadabil-

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Table 1
Components of the dermatological bases assayed

	Gel G	Gel AA	Gel T	Gel TAA
Carbomer® 940	1 g	1 g	1 g	1 g
Ethanol 96%	15 ml	15 ml	15 ml	15 ml
Triethanolamine	3 ml	3 ml	3 ml	3 ml
Tretinoin	–	–	0.025 g	0.025 g
Ascorbic acid	–	0.1 g	–	0.1 g
Distilled water	85 ml	85 ml	85 ml	85 ml

ity as a parameter to measure the capacity of bodies to spread under weight (Buenestado and Suñé, 1972a,b; Del Pozo et al., 1987; Jiménez-Castellanos et al., 1982; León et al., 1982; 1991).

The present work aims to study the rheology of semisolid preparations of tretinoin made with the polymer Carbomer® 940 – in particular, the determination of pH and shear and compression deformations. At the same time, it will establish the correlation between rheological parameters, with the object of incorporating new criteria into the traditional studies of viscosity and spreadability.

2. Materials and methods

2.1. Semisolid preparations

Dermatological hydrophilic gels, prepared with the components listed in Table 1, were used as base (Vigo, 1993).

Excipient gel G: Carbomer® 940 (Acofarma, Tarrasa, Spain) was sprinkled on distilled water (without stirring) and left to settle for 24 h. Triethanolamine (TEA) (Acofarma, Tarrasa, Spain) was added and stirred slowly to avoid the inclusion of air (BF Goodrich, 1981). Ethanol was added to complete the formula.

Gels AA, T and TAA were obtained by solution of tretinoin (T) (*trans*-retinoic acid, Merck, Darmstadt, Germany) in ethanol, with or without the antioxidant ascorbic acid (AA) (Merck, Darmstadt, Germany), followed by incorporation into the rest of the formula.

Before preparation of the excipient (gel G), the amount of TEA necessary to neutralize the gels (BF Goodrich, 1981) and yield a pH of around 5.4 units (ideal for the stability of AA (Derriter, 1982)) was determined.

The different formulations prepared were kept at ambient temperature for 24 h before the assays.

2.2. Study of pH

pH in the semisolid preparations was studied as an indicator of their stability with respect to time and oxidation of the components of the formulations. At the same time, as these preparations are intended for application to the skin, this parameter should be between 4 and 6.5 units to avoid the risk of irritations or alterations of the cutaneous tegmentum (Clearly, 1984).

The study was carried out exhaustively on gel G, as AA has a narrow pH range of maximum stability. Otherwise, there would be early oxidation of AA favouring oxidation of the drug (T).

The assay was performed using a pH-meter (MicropH 2001, Crison). Measurement was by direct contact of the electrode with the different formulations.

To detect possible pH variations with time, samples were assayed at 1, 30 and 60 days after their preparation.

2.3. Shear deformation

This assay was carried out using a Searle rotary viscosimeter (Brookfield Model RVT) with spindle no. 7. The deformation rates (D) used were 0.5, 1, 2.5, 5, 10, 20, 50 and 100 rpm.

The Brookfield viscosimeter (Ball et al., 1982; Pugnetti, 1982; Barraco et al., 1985; Deem, 1988; Dolz et al., 1988; Lucero et al., 1991), based on the Searle system, measures the viscous traction exerted on a spindle rotating in a fluid in a vessel, with the slip rate being very variable throughout the sample. The spindle is rotated by a synchronized rotor via a beryllium-copper torsion wire of 7187 dyn/cm. The degree to which this spring achieves a determinate number of rpm is indicated on a dial calibrated in units of rotational force (Wood, 1986; Lucero et al., 1991). For this apparatus, shear rate and stress are determined as:

$$\dot{\gamma} = \frac{2\omega R_c^2 R_b^2}{X\left(R_c^2 - R_b^2\right)} \tag{1}$$

$$\tau = \frac{T}{2\pi R_b^2 L} \tag{2}$$

where ω is the angular velocity of the spindle, R_c the radius of the container, R_b the radius of the spindle (0.15 cm), X the radius of the determined point, T the torsion (7187 dyn/cm) and L the effective length of the spindle (5.5 cm).

Non-Newtonian behaviour can be determined applying the model of Ostwald-De Waele (Shotton and Ridgway, 1974; Pugnetti, 1982; Schramm, 1984; Sherman, 1983; Wood, 1986; Deem, 1988; Opota et al., 1988; Lucero et al., 1991):

$$\tau = K\dot{\gamma}^n \tag{3}$$

$$M = KD^n \tag{4}$$

where n is the index of flow, K the index of consistency, M the moment of rotation and D the deformation rate.

Finally, apparent viscosity can be defined as:

$$\eta = K\dot{\gamma}^{n-1} \tag{5}$$

The methodology for the assay was standardized. In each case, the viscosimeter rotated for 1 min and was still for 30 s. After reaching maximum speed (100 rpm), each preparation was left to settle (15 min) to recover its initial structure. The measurement was then repeated, beginning with the highest deformation rate and ending with the lowest. The temperature was kept at 22 ± 1°C.

The apparent viscosities were determined by calculating the following parameters: moment of rotation (M) from the dial reading and the torsion of the viscosimeter; indices of flow (n) and consistency (K) (Eq. 4); shear stresses (τ) (Eq. 2); shear rate ($\dot{\gamma}$) (Eq. 3); and apparent viscosities (η) (Eq. 5).

The selection of deformation rates between 5 and 50 rpm is important, as measurements at higher or lower speeds lead to instrumental errors (Brookfield).

Times of 1, 30 and 60 days from preparation of the excipient and semisolid preparations were established to determine the rheological changes provoked by storage time.

2.4. Compression deformation

The method chosen was that described previously by certain authors (Buenestado and Suñé, 1972b) and modified by Jiménez-Castellanos et al. (1982). A manual microtome (Ranvier) was used with the following characteristics: perfectly flat plate of 5 cm diameter; screw bore of 1.2 cm diameter; and thread of 0.68 mm.

The micrometer screw was placed in position 1, corresponding to one complete turn from position 0. The cavity produced was filled with each of the formulations. After smoothing the surface and cleaning the plate of product, the screw was returned to position 0, so that it and the plate were at the same level, forming a cylinder of product (77 mm^3) above the level of the plate. Next, a sequence of masses of 80, 150, 300 and 500 g, equivalent to compression stresses of 3302, 6191, 12383 and 20638 dyn cm^{-2}, respectively, was placed on the cylinder of sample, under normal conditions of temperature (22 ± 1°C). The duration of each force was 1 min of compression with intervals of 30 s of rest between each.

To evaluate the deformation caused in the different formulations by each of these stresses, photographic plates (Kodak Tmax 400) were printed with the areas of spreading produced (Nikon 501, close-up lens +5), using a lamp of constant situation and intensity. Lastly, these areas were determined by direct reading of the perimeters using a planimeter (Staedtler Mars 927).

The same times as in the assay of shear deformation – 1, 30 and 60 days – were used to determine rheological changes provoked by storage time.

3. Results

3.1. Study of pH

Table 2 shows the results obtained for pH in all the formulations.

Table 2
pH values of the gels indicated

Gel	Time (days)	pH $\bar{x}$	SD	CV
G	1	5.82	0.045	0.77
	30	5.82	0.058	0.99
	60	5.81	0.051	0.87
AA	1	5.46	0.086	1.58
	30	4.64	0.102	2.19
	60	4.46	0.016	0.37
T	1	5.30	0.061	1.14
	30	5.15	0.104	2.02
	60	5.12	0.038	0.75
TAA	1	5.05	0.066	1.31
	30	4.55	0.086	1.89
	60	4.79	0.089	1.86

3.2. *Shear deformation: fluidity curves*

Fig. 1 and 2 show the fluidity curves of the gels assayed for the indicated times.

The flow and consistency indices were determined by applying the model of Ostwald-De Waele (Eq. 4) (Table 3), using the descending legs of the rheograms (Lucero, 1989).

3.3. *Shear deformation: viscosity curves*

Fig. 3 and 4 show the viscosity curves obtained for each gel studied. The shear rate ($\dot{\gamma}$) was taken as that at 20 rpm (USP, 1990) for the rheological study.

3.4. *Compression deformation*

Table 4 shows the areas of spreading obtained subjecting the semisolid preparations to compression. The relationship between the applied compression stress and the measured area of spreading can be observed.

3.5. *Correlation between rheological parameters*

All possible correlations between the data obtained by shearing and those by compression have been established. Of these, those that relate shear stresses with compression stresses (Table 5), and shear stresses with areas of spreading (Table 6), are those showing the best statistical parameters.

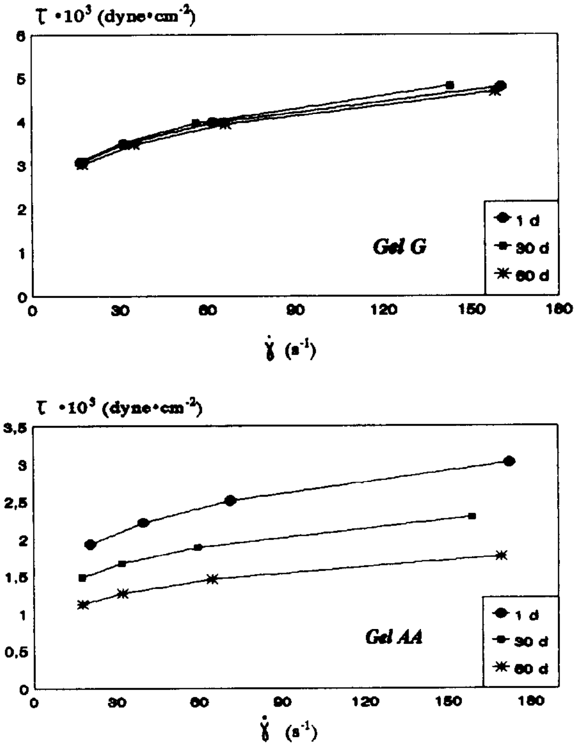

Fig. 1. Fluidity curves of gels G and AA for the indicated times.

Table 3
Indices of flow (n) and consistency (K)

Gel	Time (days)	n	K
G	1	0.20	1737.8
	30	0.21	1698.2
	60	0.20	1698.2
AA	1	0.21	1023.3
	30	0.20	831.8
	60	0.20	631.0
T	1	0.18	1819.7
	30	0.17	1819.7
	60	0.17	1862.1
TAA	1	0.17	1349.0
	30	0.17	871.0
	60	0.19	489.8

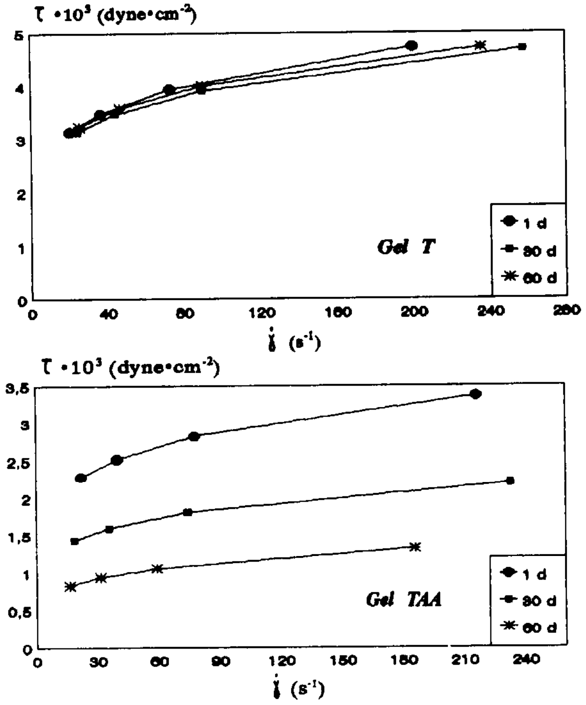

Fig. 2. Fluidity curves of gels T and TAA for the indicated times.

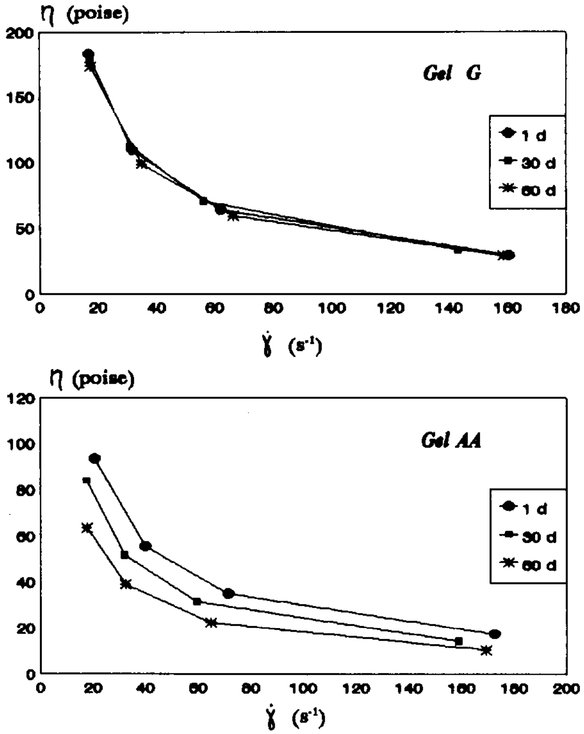

Fig. 3. Viscosity curves of gels G and AA for the indicated times.

4. Discussion

From the fluidity curves (Fig. 1 and 2), non-Newtonian behaviour of pseudoplastic flow is observed in all the gels. At the same time, no thixotropic phenomenon was detected experimentally. The causes of pseudoplastic flow may be due to progressive rupture of the internal structure of the preparation (by increasing shear) and its later reconstruction by means of Brownian movement (Vemuri, 1988). Applying the model of Ostwald-De Waele (Table 3) – in particular the flow index (n) – corroborates the type of flow found from the rheograms.

Various factors participate in the formation of gel G. On the one hand, the concentration of the polymer (1% w/w), and on the other, the amount of TEA added to decrease the initial acidity of this formulation (pH ≈ 3). Consequently, in order to be able to explain the rheological behaviour of these semisolid preparations, it is necessary to monitor the pH. According to the literature, Carbomer® 940 (BF Goodrich, 1981) in water has a pH range of maximum stability between 6 and 8 units. Independently of this factor, gel G

Table 4
Areas of spreading obtained from compression deformation

Gel	Time (days)	Area of spreading (cm^2) [compression stress (dyn cm^{-2})]			
		3302	6191	12383	20638
G	1	3.30	3.80	4.90	6.20
	30	2.80	3.70	4.70	5.40
	60	2.70	3.50	4.30	5.10
AA	1	2.82	3.67	4.69	5.63
	30	3.28	4.61	5.52	6.04
	60	3.73	4.76	6.17	6.67
T	1	2.68	3.58	4.50	5.09
	30	2.64	3.31	4.04	4.96
	60	2.66	3.40	4.58	5.90
TAA	1	2.94	3.71	4.97	5.80
	30	4.07	5.34	6.19	6.73
	60	4.67	6.15	7.03	7.69

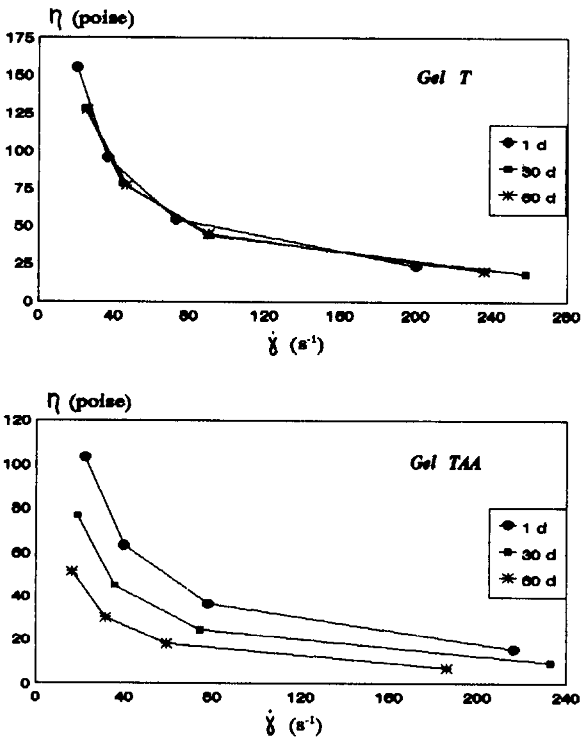

Fig. 4. Viscosity curves of gels T and TAA for the indicated times.

was given a final pH close to 5.4 to achieve maximum stability of one of the components present in the formulations, AA (Deritter, 1982).

Gel G has a tridimensional structure. Its pH of 5.82 (Table 2) is very close to the pH range mentioned above. No variations were found in either this parameter or the apparent viscosity with storage time (Fig. 3). In contrast, the area of spreading decreased slightly (Table 4). This phenomenon may be explained by the fact that the excipient is very viscous, and while neither the shear applied nor the storage time is sufficient to show changes of viscosity, the application of an increasing tangential force on small samples at different times is sufficient.

Ascorbic acid (AA) has a pK_{a1} of 4.18 and a pK_{a2} of 11.6, with maximum degradation at pH 4 and minimum at pH 5.6 (Deritter, 1982). For this reason gel G, to which AA would later be added, was prepared with a pH close to that of maximum stability of both excipient and antioxidant.

With storage time, the pH of gel AA decreased (Table 2). This was due to oxidation of AA to form the ascorbyl radical which, although not reacting normally, can do so with itself, giving rise to dehydroascorbic acid (Burton et al., 1983;

Table 5
Parameters of correlation between shear stress (τ_s) and compression stress (τ_c)

Gel	Time (days)	r_{xy}	$F_{(1,22)}$	Probability	Equation
G	1	0.9923	2817.6	< 0.0001	$\tau_s = 0.0945\ \tau_c + 2758.5$
	30	0.9798	1066.4	< 0.0001	$\tau_s = 0.0901\ \tau_c + 2801.2$
	60	0.9712	742.2	< 0.0001	$\tau_s = 0.0949\ \tau_c + 2714.4$
AA	1	0.8594	134.5	< 0.0001	$\tau_s = 0.0602\ \tau_c + 1776.7$
	30	0.8729	151.1	< 0.0001	$\tau_s = 0.0455\ \tau_c + 1343.3$
	60	0.8890	176.2	< 0.0001	$\tau_s = 0.0358\ \tau_c + 1017.1$
T	1	0.8866	172.1	< 0.0001	$\tau_s = 0.0934\ \tau_c + 2777.9$
	30	0.9878	1780.7	< 0.0001	$\tau_s = 0.0866\ \tau_c + 2872.8$
	60	0.7927	84.1	< 0.0001	$\tau_s = 0.0826\ \tau_c + 2999.8$
TAA	1	0.8565	131.3	< 0.0001	$\tau_s = 0.0608\ \tau_c + 2101.3$
	30	0.5163	23.5	< 0.0001	$\tau_s = 0.0406\ \tau_c + 1225.2$
	60	0.9464	388.8	< 0.0001	$\tau_s = 0.0269\ \tau_c + 752.6$

Table 6
Parameters of correlation between shear stress (log τ_s) and area of spread (S)

Gel	Time (days)	r_{xy}	$F_{(1,22)}$	Probability	Equation
G	1	0.9913	1244.7	< 0.0001	$\log \tau_s = 0.0634S + 3.2813$
	30	0.9715	369.1	< 0.0001	$\log \tau_s = 0.0689S + 3.2822$
	60	0.9916	1296.0	< 0.0001	$\log \tau_s = 0.0818S + 3.2459$
AA	1	0.8827	77.6	< 0.0001	$\log \tau_s = 0.0603S + 3.1235$
	30	0.6884	19.8	< 0.0001	$\log \tau_s = 0.0422S + 3.0510$
	60	0.8026	39.8	< 0.0001	$\log \tau_s = 0.0502S + 2.8713$
T	1	0.9464	189.1	< 0.0001	$\log \tau_s = 0.0670S + 3.3107$
	30	0.9501	204.3	< 0.0001	$\log \tau_s = 0.0693S + 3.3147$
	60	0.7432	27.1	< 0.0001	$\log \tau_s = 0.0395S + 3.4204$
TAA	1	0.8597	62.3	< 0.0001	$\log \tau_s = 0.0531S + 3.2016$
	30	0.5337	8.8	0.0070	$\log \tau_s = 0.0527S + 2.9150$
	60	0.7950	37.8	< 0.0001	$\log \tau_s = 0.0462S + 2.7218$

Willson, 1983). Apparent viscosity diminished with decreasing pH (Fig. 3). This can be explained by the fact that the pH zone is not one of maximum stability, so that a slight decrease in pH causes coiling of the polymer molecule (BF Goodrich, 1981), diminishing the viscosity. The areas of spreading increased with time (Table 4). This is logical considering that the viscosity is also lower.

Compared with gel G, AA presented lower pH and apparent viscosity values, while the areas of spreading were greater. These results were independent of storage time.

Tretinoin (T) is an acid substance ($pK_a = 6.0$) (Vahlquist, 1992). This acidity is shown by the initial pH of the formulation, which is lower than that of gel G (Table 2). With storage time, it decreases slightly to 30 days and remains constant during the final period. The apparent viscosities also show a slight decrease with respect to both gel G and with time, concretely to 30 days, remaining constant until 60 days (Fig. 4). Thus, the relationship between apparent viscosity and pH seems obvious.

Finally, the results obtained for compression deformation (Table 4) reflect a phenomenon contrary to that expected. At 60 days the areas of spreading found are similar to the initial ones, overcoming the decrease produced at 30 days, while the apparent viscosity decreases in the first period of study and then remains constant to the end.

These results could be explained by oxidation. Tretinoin has a chemical structure with one functional acid group which obviously cannot be oxidized, but also has four double bonds in the side-chain, disposed to free radical reactions. This would lead to rupture of these bonds and saturation of the molecule. Such a modification could be responsible for the phenomena observed in gel T. It should be added that these small modifications in the basic structure of T give rise to the same rheological behaviour, but with different apparent viscosities and areas of spreading from those expected.

Gel TAA yielded a lower initial pH than gels G, AA and T (Table 2) as a consequence of the combination of these two acid substances. The parameter decreased with time. The apparent viscosity (Fig. 4) on the first day of study was lower than that of gels G and T and similar to that of gel AA. With storage time, the apparent viscosity decreased, with the descending legs of the rheograms presenting a behaviour similar to that found in gel AA.

The areas of spreading (Table 4) were always greater compared with gels T and AA.

Detailed study of the different gels indicates that AA provokes a decrease of pH with storage time, as a consequence of the oxidative reactions it undergoes. This phenomenon is shown by the decrease in apparent viscosity of the gels. In contrast, the surfaces of deformation are greater. However, there is no obvious correlation between these parameters and pH. Gel T shows superimposible fluidity curves and non-significant variations in the areas of spreading with time.

Until now spreadability has been considered as a parameter indicating stability (Lucero et al., 1993) in its widest sense, and even, in some works (Shama and Sherman, 1973; Kokini et al., 1977; Kokini and Cussler, 1983; Kokini et al, 1984) as a sensorial property of semisolid preparations. However, in no case has it been included in rheological studies of fluids, perhaps because the methodology is not universally standardized, or because properly rheological concepts, such as force, stress, deformation, etc., are not used. Two types of stress are known: normal and shear. The former is a force that acts on the component perpendicular to the plane (tension outward and compression on the plane), while a stress on the component tangential to the plane is the shear stress.

It seems obvious that there must be some type of relationship between shear and compression. Correlations have been established between the different parameters of shear deformation (shear stress, shear rate and apparent viscosity) and compression deformation (compression stress, area of spread and masses). Of these, the best statistical results have been obtained comparing the two types of stress and from the semilogarithmic relationship between shear stress and area of spread.

Table 5 shows the results obtained in the correlation between the shear and compression stresses. There is a significant statistical difference in all the gels assayed, independently of the composition of the formulation. Thus, the shear stress can be calculated that would have to be applied to a fluid to achieve a tangential deformation equal to a perpendicular deformation obtained by subjecting the sample to a concrete compression stress. This explains the decision to use the compression stress of 12383 dyn/cm^2 to relate with the shear stresses resulting from application of a deformation rate of 20 rpm, following the indications of the USP XXII (1990).

At the same time, the shear stresses have been related with the areas of spreading obtained from compression. The results obtained (Table 6) also indicate significant statistical correlation, permitting calculation of the shear stress corresponding to a determinate area of spreading.

Consequently, this work indicates that to carry out a complete rheological study it is necessary to follow the deformations, both tangential and longitudinal, and not as has been done up to now – to make only a viscosimetric study. In this way, the traditional concept of spreadability, of little importance in semisolids, would become a parameter that, together with viscosity, would define the rheology of gellified disperse systems.

5. Conclusions

pH and the presence of AA in the final formula determine the stability of the tridimensional structure of hydrophilic gels, and their rheological behaviour with storage time.

Correlations have been established between shear and compression stresses, and between shear stress and the area of spread. These relationships are independent of the components of the gellified disperse systems assayed.

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