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COMMUNICATION

Galenic and Dermopharmaceutical Effectiveness Study of an Emulsified Pharmaceutical Form with Retinoic Acid

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ABSTRACT

Retinoic acid constitutes an active that is already being used extensively in the fight against cutaneous aging. After a period in which certain scientific publications questioned its use, today there is no doubt that retinoic acid continues to be an active with wide possibilities of use when it is formulated and administered correctly.

In this work we propose a new formulation that, on the basis of a modern self-emulsifying excipient, incorporates retinoic acid in its composition.

The work protocol is structured in the following points of study. Rheological assay: Shear rate, shear stress, viscosity, thixotropy, rheodestruction, and extensibility measurements were carried out. Other pharmacotechnical assays: External appearance, interposition type, and pH control were studied. Dermopharmaceutical effectiveness study: Biophysical non-invasive techniques were applied, according to a standardized work method.

The following considerations can be made from the results: the layout of the rheograms could fit, in principle, inside a non-Newtonian–shear-thinning flow behavior, with similar rheodestruction profiles. The hysteresis values, as well as the extensibility indexes that were obtained, determined a good degree of applicability.

From the whole of results, we could conclude that the formulation proposed is profiled like an emulsified pharmaceutical form with an excellent cosmetological adaptation, eudermic pH, and soft emollient action, which prohibits the loss of superficial water that maintains the retinoic acid action.

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INTRODUCTION

Vulgar acne is a frequently occurring cutaneous illness (1). The implementation of an acne treatment plan should be made early, combining the dermatological and dermopharmaceutical therapies as a function, logically, of the specific individual diagnosis.

The topical treatment of this follicular illness is presently carried out with success by the application of products containing retinoids (2–4).

For this purpose, a new formulation based on tretinoin was designed, typified, and studied from a pharmacotechnical point of view in order to obtain a galenic vehicle suitable for this medical active, and to maximize its therapeutical effectiveness in the topical treatment of cutaneous acne.

MATERIALS AND METHODS

Formulation

The formula is an emulsion formulated on the base of a modern self-emulsifying excipient with the following composition: (*a*) oil phase (o): base F-2230®, 10.00%; Miglyol 812, 12.00%; cethylic alcohol, 0.50%; and tretinoin, 0.025%. (*b*) water phase (w): Sodium chloride, 1.00%; glycerine, 3.00%; quaternium 15, 0.10%; and distilled water, to 100.00%.

Modus Operandi (5)

Fatty phase o and watery phase w were separately weighed. Phase o was obtained by melting the cethylic alcohol and posterior addition to the rest of the components. Phase w was then poured over o little by little, with constant stirring until the emulsion had a uniform appearance. Once all the watery phase w was added, the emulsion was mixed with a mechanical stirrer between 800 and 1200 rpm. (Silverson Model L4R Turbine Mixer).

Rheological Study (6)

Rheological study was based on the determination of two fundamental parameters, viscosity and extensibility.

Viscosity (7)

Rheograms and rheological parameters were obtained to characterize the flow, its structural profile, and the stability and applicability of the proposed formulation. Instrumentation used included a Brookfield digital RVTD viscometer (precision ± 5%); a Helipath stand (F/T-shaped spindle); and a Brookfield bath model TC 200 with a sensitivity of ± 0.01°C.

Extensibility

To quantify the extensibility properties, the surface of the ellipse described by the tested cream was calculated as follows:

$$S = \pi \cdot d/2 \cdot d'/2$$

where d and d' are the dimensions of the extension of the sample on the graduated medians.
An extensometer of our own design was used (precision ± 0.5 mm).

Other Pharmacotechnical Assays

Organoleptic characteristics were studied by periodic *de visu* observation. The interposition type was determined by the Robertson method (8). The pH was determined by potentiometry (9) with a Crison 2001 Micro-pH-Metre (precision ± 0.1). Stability was studied by subjecting homogeneous formulation samples to the following conditions: assay temperatures of 4, 20, 30, and 45°C; assay time of 3 months.

Dermopharmaceutical Effectiveness Study

To evaluate the dermopharmaceutical efficacy of the formulation, non-invasive tests were performed (10,11). A Corneometer, model CM 820, was used for conductimetric analysis. A Sebumeter, model SM 810, was used for photometric analysis of luminescent transmittance. Measurement conditions were temperature 20°C and relative humidity 60%. Determinations were performed in 15 healthy volunteers ranging in age between 25 and 35 years old.

RESULTS

Rheological Study

Viscosity

Initial Rheogram and Rheological Parameters

Shear stress values T ($N \cdot m^{-2}$) are obtained at $t = 0$, to allow the design of the initial rheograms as indicated in Fig. 1.

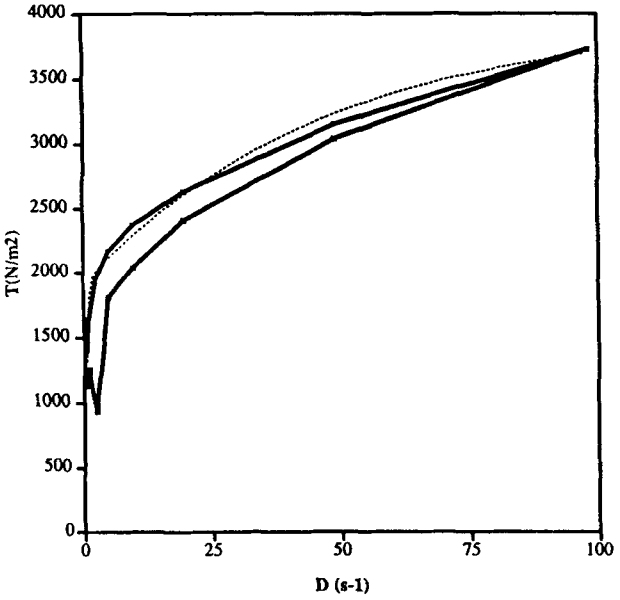

Figure 1. Initial rheogram.

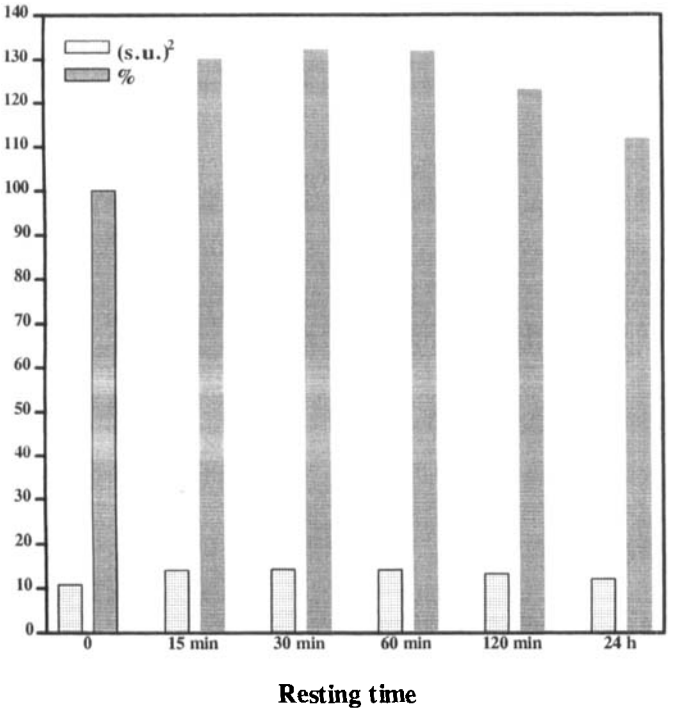

Figure 2. Hysteresis loop area evolution over time.

The rheogram shows a pseudoplastic behavior that adjusts to an Ostwald de Waele type. Adjusting this mathematic model gives the following equation:

$$T = 1613.3841 \cdot D^{0.1760} \quad (r = 0.9970)$$

Comparing the correlation coefficient with the corresponding value (with a probability of 95% and $n - 2 = 6$ degrees of freedom) from the literature (12) ($r^6_{0.05} = 0.7070$), we obtain an acceptable correlation value, so that these results are validated.

The presence of the initial thixotropy as well as the appearance of the hysteresis cycle in the initial rheogram—with an initial hysteresis loop area value (A_0) of 10.84 square surface units [(su)²]—(Fig. 1), justifies a thorough study of the thixotropic parameters.

Structural Recuperation

Successive rheograms were obtained in order to estimate the degree of restructurization undergone by the system after longer rest periods. In order to obtain a better interpretation of the hysteresis thixotropic results, the quantification of the degree of hysteresis is expressed also in percentages, in relation with the initial area, that we will consider as relative thixotropic surface (RTS). These values are represented by comparison in the histograms in Fig. 2.

Evolution of Viscosity as a Function of Shear Time

To study the relationship between viscosities and shear times, we apply for two maxima shear rate values ($D_1 = 98$ sec^{-1} and $D_2 = 49$ sec^{-1}), the following agitation times (t_a): 0, 60, 120, 300, and 600 sec. The corresponding viscosity values are reflected in Table 1.

Evolution of Viscosity as a Function of Shear Rate

In this test we adjusted a maximum shear rate value ($D_1 = 98$ sec^{-1} and $D_2 = 49$ sec^{-1}) and at the same time

Table 1

Evolution of Viscosity as a Function of the Shear Time

t (sec)	η_{98} (Pa·sec)	η_{49} (Pa·sec)
0	7.1444	10.7786
60	8.5603	11.1406
120	8.4533	11.2474
300	8.1455	11.2387
600	6.7773	8.7387

fit some very low shear times (15 sec) so that this parameter do not affect the experimental values. The corresponding viscosities are put in order in Table 2.

Extensibility

The extensibility measurements (average surface) and the variability coefficients (*Vc*) that correspond to the five tests carried out for $t = 0$, are shown in Table 3. If we consider that the variability coefficient for an acceptance interval (95–105%) and $n = 5$ presents a theoretical value of 4.2 (13), we can observe (Table 3) that, in fact, all the values are lower than the maximum acceptable *Vc* (%) value.

The mathematical treatment of the extensometric data, linear and potential adjustment, is expressed in Table 4.

Table 2

Evolution of the Viscosity as a Function of the Shear Rate

D (sec^{-1})	η_{98} (Pa·sec)	η_{49} (Pa·sec)
0.49	534.6138	498.8706
0.98	297.4367	276.8909
2.45	137.0104	127.1590
4.90	76.2280	70.5998
9.80	42.4102	39.1755
19.60	23.5954	21.7444
49.00	10.8696	9.9857
98.00	6.0474	–

Table 3

Extensometric Measures and Variability Coefficients of Five Tests

Weights (g)	S (mm^2)	*Vc*(%)
$W_0 = 27.6$	352.9580	2.56
$W_0 + 50$	555.9049	4.10
$W_0 + 100$	712.1990	4.13
$W_0 + 200$	915.7742	3.88
$W_0 + 300$	1065.3141	3.96

Table 4

Mathematical Adjustment—Both Linear and Potential—of Extensibility Test Results

Linear	Potential
$y = 2.3015x + 357.7199$ ($r = 0.9809$)	$y = 79.3284x^{0.4498}$ ($r = 0.9997$)

Other Pharmacotechnical Assays

Organoleptic Characteristics

The formulation is a shiny, soft, yellow emulsified cream, homogenous, non-greasy, smooth, and fine to the touch, and easy to extend.

Determination of the Interposition Type

The results corresponding to the Robertson test indicate that all formulations are a water-in-oil (w/o) system.

pH Determination

The average pH ($n = 5$) at 20°C presents a value of 7.26.

Stability

The corresponding results are shown in Table 5.

Dermopharmaceutical Effectiveness Study

These results are represented by relative and not absolute values. The values for the corneometric and sebumetric assays, the average of 15 measurements each, are given graphically in Figs. 3 and 4.

DISCUSSION

Rheological Study

Viscosity Measurements

From the results we can deduce that the system shows a non-Newtonian flow behavior which adjusts to the Ostwald de Waele model. The mathematical expression shows a flow index ($n = 0.17$) that, being less than one, reflects its pseudoplastic behavior. This is a desirable rheological behavior in these types of formulations.

The initial hysteresis loop value $A_0 = 10.84$ $(su)^2$, indicates the existence of a certain degree of initial thixotropy.

The test carried out to study the degree of structural recuperation as a function of hysteresis areas led us, generally, to an increase with regard to the initial value. This means a positive behavior as to skin applicability.

From the study of the viscosity evolution it would be possible for us to make the following considerations: As a function of the shear time, very similar rheological data profiles are obtained. The viscosity values do not show any significant rheological difference for each maximum shear rate applied. We can observe a logical

Table 5

Organoleptic Characteristic Evolution During the Stability Study

Time (days)	Temperature (°C)	Organoleptic Characteristics
0		Pale yelow, brilliant; non-scented; homogeneous soft, spreadable, oleaginous washable residue
1	4	Changes were not observed
	20	
	30	
	45	
7	4	Changes were not observed
	20	
	30	
	45	
15	4	A little bit more consistent
	20	Changes were not observed
	30	
	45	A little bit more fluid
30	4	Changes were not observed with regard to $t = 15$
	20	
	30	
	45	
60	4	Changes were not observed
	20	
	30	
	45	Slightly creamy
90	4	Changes were not observed
	20	
	30	
	45	Lightly exudated

relationship as a function of the punctual shear rate assayed. From a rheological point of view, it does not offer, in any case, significant differences.

Extensibility Measurements

With regard to the extensometric data, we have obtained high extensibility indexes (14) in all assays, which guaranteed a perfect degree of applicability on the skin; they were perfectly valid in order to guarantee an excellent adherence for better penetration of tretinoin through the skin.

On the other hand, the method is validated by a kind of adjustment which is preferably potential. In fact, for a significance level of $p < 0.05$ and $(n - 2) = 3$ degrees of freedom, we found that the theoretic value of the coefficient r was 0.8780 (12); so that the experimental values of Table 4 remained within the allowed limits, and the equations were perfectly validated.

Other Pharmacotechnical Assays

Organoleptic Characteristics, Emulsion Sign, and pH

The proposed formulation corresponds to an emulsified system with very pleasant organoleptic properties. The neutral pH of this pharmaceutical form of topical application maintains the stability of the active principle.

The formulation on the base of a water-in-oil system would increase its emollient/moisturizing power. This produces a higher degree of adherence and substantivity to the skin, and also favors the degree of penetration and bioavailability of the active principle.

Stability (Table 5)

After a 3-month storage at different temperatures, we can affirm that there were no significant changes, either in the texture or in the external appearance of the preparations. Samples were always a water-in-oil system.

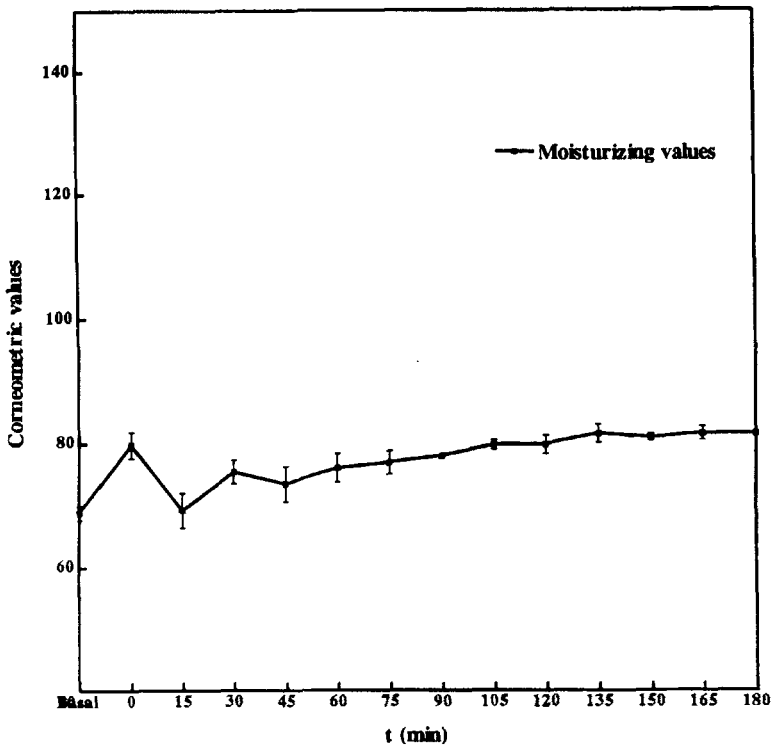

Figure 3. Moisturizing degree evolution over time at 20°C and 60% RH.

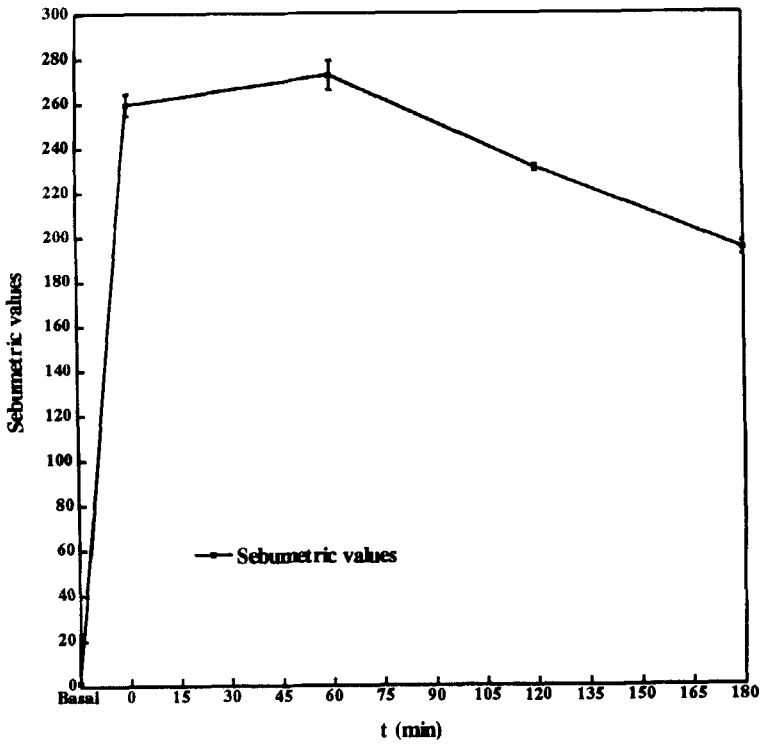

Figure 4. Emollient power degree evolution over time at 20°C and 60% RH.

Therefore, we can deduce that the stability of the systems was enough to guarantee their efficacy during the conservation time studied.

Dermopharmaceutical Effectiveness Study

Figure 3 shows that the moisture level was above 80.63, which means that this preparation offers an effective moisturizing power.

On the other hand, Fig. 4 shows that the sebumetric values during the practical application time were above 234.46, which means that the preparation has a very high degree of emollient power. This pharmacotechnical test allowed us to relate its specific action with the potential emolliency/moisturizing power that we supposed, *a priori*, our emulsion had, due to its specific composition. This means that the formulation we proposed was perfectly qualified as a vehicle for the retinoic acid, which normally requires a certain degree of occlusivity.

CONCLUSIONS

In summary, we can conclude that the proposed formulation with tretinoin (stable, active, and perfectly typified from a pharmaceutical point of view) has a high degree of emollient/moisturizing power, and a notable degree of occlusivity. All these qualities and properties make it a very adequate pharmaceutical form for use as a treatment in acne therapy.

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