ELSEVIER

www.elsevier.nl/locate/farmac

Il Farmaco 56 (2001) 513–522

IL FARMACO

Development of a cream from a self-emulsifying base and moisturizing actives☆

M.M. Jiménez Soriano, M.J. Fresno Contreras *, E. Sellés Flores

Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Alcalá University, 28871 Alcala de Henares, Madrid, Spain

Received 31 October 2000; accepted 10 January 2001

Abstract

This research study is based on the design and development of a semisolid emulsion system whose novel self-emulsifying base and preferentially moisturizing actives were investigated to find out whether the system mentioned could be used as a dermatological treatment for highly sensitive skins, including atopic ones. Thus, one of the main objectives of the present study consisted of in vivo evaluation of its effectiveness by means of non-invasive assessment techniques currently employed in cosmetology. Due to the fact that the new formula is, in principle, designed for skins that could present any kind of alteration, the current study was focused on rheological parameters of viscosity, thixotropy, and extensibility to guarantee not only an accurate assessment of composition but also a comfortable and safe application on skin. © 2001 Éditions scientifiques et médicales Elsevier SAS

Keywords: Dermopharmaceutical form; Pharmacotechnical study; Rheology (thixotropy); Stability; Effectiveness assays

1. Introduction

Semisolid emulsion systems are used widely in the formulation of topical pharmaceutical and cosmetic preparations. Rheological properties of semisolids are highly important physical parameters in both technical (manufacturing, filling, storage) and esthetic terms. The evaluation of semisolid emulsion structure and consistency is, therefore, essential in order to determine, adjust, and perhaps predict the performance of newly designed products [1].

The rheological properties of an emulsified system significantly determine its quality, usefulness, and purpose. Therefore, rheology always played and will play a role in the preparation, development, and manufacture of any formula. For that matter, rheological determinations are indispensable in the analysis of its properties. The importance of the rheological properties in emulsified pharmaceutical and cosmetic forms is such that rheological and thixotropic studies have became crucial tools from both pharmacotechnical and galenic points of view [2]. In a similar way, it can deduce the possible modifications of the system, expressed as a function of time and temperature, from the variation in the hysteresis areas (area under the curve, AUC) [3]. Thus, pharmacotechnical tests that include the determination of organoleptic properties, pH, sign, macroscopic and microscopic examination allow us to evaluate the evolution of the properties of the formulations mentioned, according to the time, temperature, and gravity.

By definition, the emulsions are thermodynamically unstable; thus, their lifetime is inexorably finite. In consequence, the formula-designers have to evaluate and predict how these preparations will behave in terms of stability.

Among the more frequently used methods to evaluate the physical stability of an emulsion, which involves both its structural and thixotropic features, are the accelerated aging tests [4] and their rheological counterparts, which become almost indispensable in these types of assessment. As a rule, the rheological study and, more precisely, the evaluation of thixotropic properties, allow us to obtain a correct picture of the physical

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

* Corresponding author.

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

0014-827X/01/$ - see front matter © 2001 Éditions scientifiques et médicales Elsevier SAS
PII: S0014-827X(01)01087-4

properties and structural stability of semisolid systems [5,6]. Among the systems mentioned are the dermocosmetic emulsified formulas that have gained importance in modern pharmacy, being indispensable in all types of skin-applications and formulas.

2. Materials and methods

The aim of this study was to design and develop a binary emulsion which, based on novel self-emulsifying base and moisturizing actives, would serve as a treatment for sensitive, atopic, and otherwise reactive skins. For this purpose, the formula for a hydrated emulsified system, to which rosemary honey and lactil have been added, was proposed and investigated thoroughly because of its possible advantages. The new emulsion suggested includes the following components:

Oil phase (O)		%
Self-emulsifying base[1] [7]		25.0
Phenonip™[2]		0.4
Water phase (W)		
Glycerine		3.0
Lactil™[3]		5.0
Rosemary honey[4]		7.0
Distilled water	to	100.0

2.1. Experimental procedure

The oily phase was melted (O) using a double boiler at temperatures between 75 and 80°C. The aqueous phase (W) was then heated up to sub-boiling point that never exceeded 75°C. In continuation, the aqueous phase was added to the oily phase when both phases were at the same temperature (60°C). Subsequently, the pre-emulsion was mixed thoroughly by continuous agitation with a turbine homogenizer — Silverson mod. L4R. The use of the controlled-speed homogenizer was indicated specially since it prevented the intake of air into the final emulsion [8]. At the end of the homogenization cycle, both phases were interposed completely. In order to obtain homogeneous samples, 4 kg batches were prepared and stored at room temperature (20°C) for 48 h in order to stabilize the whole mixture. The study and characterization of the system from the pharmacotechnical point of view is schematized in a working protocol contained in Table 1.

Table 1
Working scheme

Assays	Parameters and equipment
Pharmacotechnical	
Organoleptic characteristics	De visu and application appearance
Photomicrograph study	analysis of particle size photomicroscopy mod. Axiophot
Type of interposition	emulsion sign Robertson and Briggs methods [9,10]
pH-determination	potentiometry measurements [11] pH-cream-electrode of Crison 2001 Micro-pH-Metre (Precision ± 0.1) (20°C)
Rheological study	viscosimetric determinations [12,13] Brookfield digital rheometer mod. DV-III viscometer (CP-40 cone) [14] Rheocalc software version 1.2 Brookfield mod. TC 200 bath. IBM computer mod. 80486 extensometric measurements [15] extensometer of own design (Precision ± 0.5 mm)
Stability: physical assays [16]	conditions of storage: 6 months at room temperature (20°C), 30 and 45°C
Effectiveness [17]	corneometric or moisturizing measurements [18] Corneometer CM 820 sebumetric or emollient measurements [19] Sebumeter SM 810 experimental conditions: $T = 20 \pm 1$°C; RH = 60 ± 5%; 0.5 ml sample (15 healthy volunteers); three prefixed points on the forearm

3. Results

3.1. Pharmacotechnical assays

3.1.1. Organoleptic characteristics

The formulation had the consistency of a cream with a gleaming and lustrous tone of beige. It was homogenous, non-greasy, smooth in texture, and it did not form a greasy film on the skin upon application. The emulsified system was slightly evanescent, easily washable and agreeably honey-scented.

[1] CTFA adopted name of Neo PCL O/W: ceteareth-10 (and) beeswax (and) stearyl heptanoate (and) cetyl octanoate (and) spermaceti (and) myristoyl (and) dimethicone (and) mineral oil (and) lanolin oil.

[2] Phenotip™ (preservative); CTFA composition: phenoxyethanol (and) methylparaben (and) butylparaben (and) ethylparaben (and) propylparaben.

[3] Lactil™ composition — NMF®: sodium lactate, sodium PCA, glycine, fructose, urea, niacinamide, inositol and water.

[4] *Rosemary Honey*, known as *Miel de La Alcarria* — Spain, according to the regulations of the Governing Council.

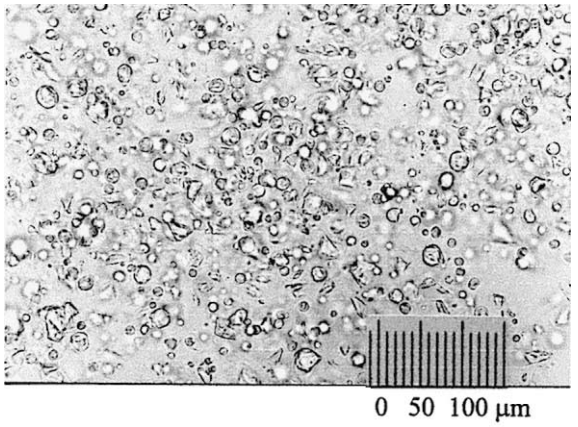

Fig. 1. Photomicrography at $t = 0$.

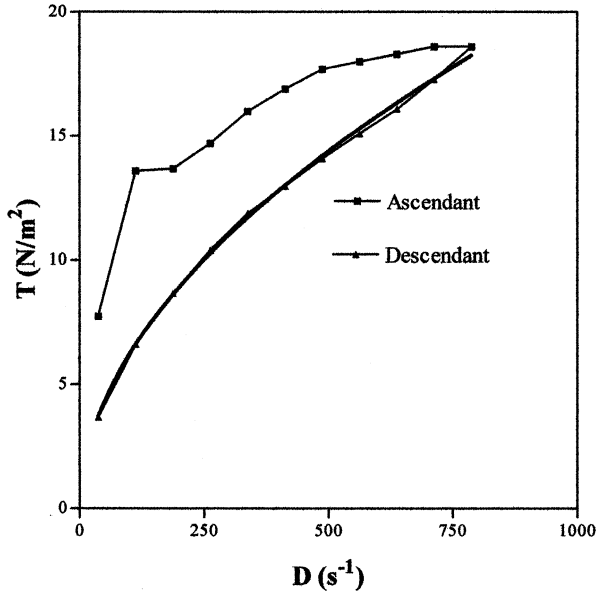

Fig. 2. Initial rheogram at $t = 0$. Shear stress versus shear rate.

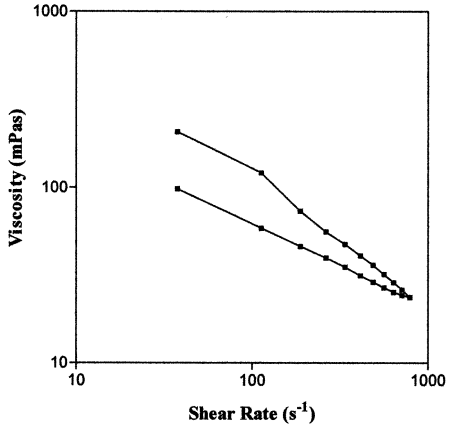

Fig. 3. Viscosity, η (mPa s), versus shear rate, D (s^{-1}).

3.1.2. Photomicrographic examination

Fig. 1 includes the microphotography of the obtained formulation (40 ×).

3.1.3. Type of interposition

The results from Robertson and Briggs tests indicated that all formula samples belonged to an oil-in-water system (O/W).

3.1.4. pH-Determination

The average pH ($n = 5$) at 20°C was 5.40.

3.1.5. Rheological assays

3.1.5.1. Viscosity determination

Initial rheological study. The initial rheogram and more significant rheological parameters are indicated in Fig. 2. The mathematical adjustment is also represented on the descending curve of the initial rheogram.

The data obtained were analyzed and adjusted to Ostwald's model with Rheocalc for Windows 1.01 software.

$$T = 555.3D^{0.524} \quad (r = 0.9987)$$

By comparing the correlation coefficient with the theoretical value (95% probability and $n - 2 = 9$ degrees of freedom) secured from the literature — $r^9_{0.05} = 0.6020$ — [20], we have obtained a satisfactory correlation value, which validated our experimental results.

The rheograms from Figs. 3 and 4 were used to express graphically the viscosity evolution as a function of shear rate and shear time, respectively, in the preliminary testing.

The presence of the initial thixotropy, the appearance of the hysteresis cycle in the rheogram — with a hysteresis loop area value (S_0) of 2726 $(s.u.)^2$ (Fig. 2, as well as the evolutive profiles from Figs. 3 and 4) — completely justified the complementary study of the thixotropic parameters.

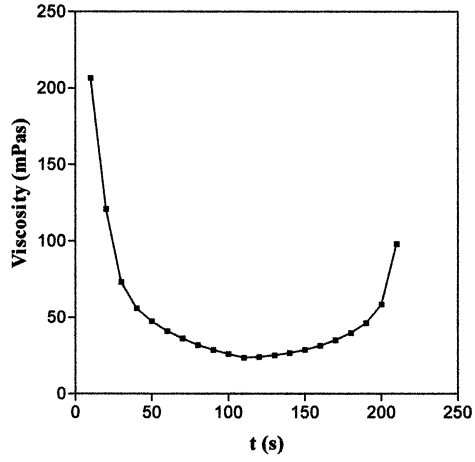

Fig. 4. Viscosity, η (mPa s), versus shear time, t (s).

Table 2
Mathematical equations

Resting time (min)	Equation	r^2	Confidence of fit (%)	Hysteresis surface (s.u.)^2	TRS (%)
0	$T = 555.3D^{0.524}$	0.9987	99.0	2726	100.00
15	$T = 521.7D^{0.503}$	0.9993	99.1	1168	42.85
30	$T = 490.0D^{0.497}$	0.9992	99.1	961	35.25
60	$T = 605.1D^{0.462}$	0.9988	98.9	972	35.66
120	$T = 621.9D^{0.456}$	0.9983	98.7	1037	38.04

Table 3
Mathematical adjustments and area under curve values (AUC) for $D = 787.5\ s^{-1}$

T_s (min)	Equation	r^2	Confidence of fit (%)	Area (s.u.)^2	TRS (%)
0	$T = 658.7D^{0.521}$	0.9994	98.9	10 880	100.00
1	$T = 662.8D^{0.490}$	0.9990	99.0	9075	83.41
2	$T = 665.8D^{0.456}$	0.9991	99.1	7433	68.32
5	$T = 530.2D^{0.478}$	0.9992	99.0	6762	62.15
10	$T = 385.1D^{0.504}$	0.9994	98.9	5736	52.72

Table 4
Mathematical adjustments and area under curve values (AUC) for $D = 562.5\ s^{-1}$

T_s (min)	Equation	r^2	Confidence of fit (%)	Area (s.u.)^2	TRS (%)
0	$T = 682.2D^{0.504}$	0.9994	99.0	6075	100.00
1	$T = 608.1D^{0.505}$	0.9990	98.9	5439	89.53
2	$T = 548.4D^{0.503}$	0.9994	98.9	4862	80.03
5	$T = 525.5D^{0.495}$	0.9989	99.0	4456	73.35
10	$T = 447.1D^{0.506}$	0.9979	98.8	4041	66.52

Hysteresis loop area evolution over time. Successive rheograms were plotted in order to estimate the degree of restructuring undergone by the system after longer resting time. In order to obtain a better interpretation of the hysteresis, thixotropic results and the flow behavior adjustment were estimated mathematically with the corresponding equations, confidence fit (%) and the r^2-values. Subsequently, we have quantified the thixotropic degree and expressed it by hysteresis loop area values as well as in percentages with respect to the initial surface (S_0), which was denoted thixotropic relative surface — TRS. These results are listed in Table 2.

Viscosity evolution as a function of the shear time. In order to study the relationship between viscosity and shear time, we have applied the shear rate values for two maximums ($D_1 = 787.5$ and $D_2 = 562.5\ s^{-1}$) during the following shear times, t_s: 0, 60, 120, 300, and 600 s. The flow behavior adjustment was estimated mathematically by relevant equations, based on the confidence fit (%) and the r^2-values. Thus, we have quantified the thixotropic degree and expressed it in terms of hysteresis loop area values as well as in percentages. The adjustments with the mathematical parameters are listed in Tables 3 and 4 for the maximum shear rate value, respectively, whereas the viscosity values are represented in Fig. 5.

Viscosity evolution as a function of the shear rate. In this assay, the maximum shear rate value ($D_1 = 787.5$ and $D_2 = 562.5\ s^{-1}$) was adjusted and, at the same time, some very low shear-times (30 s) were fitted in such a way that the ensuing parameter would not affect the experimental results. The values, as well as the regression models are represented graphically in Fig. 6. The adjustments with the mathematical parameters are listed in Table 5, whereas the viscosity values are represented in Table 6.

In the same way, the analysis of the thixotropic parameters are very interesting (Table 5): AUC and the relation between the two maximum rates of assay (D_1/D_2) being introduced by the thixotropic index ($TI = A_{D_1}/A_{D_2}$).

3.1.5.2. Extensibility measuring. Extensibility experimental values for mean surface ($S = \pi \times d/2 \times d'/2$) as well as the standard error of the mean (SEM) for five repeated measurements are listed in Fig. 7. The mathematical adjustment of the extensometric data by linear and potential models is shown in Fig. 8. The results from the pharmacotechnical study — point of reference for the stability study — are specified in Table 7.

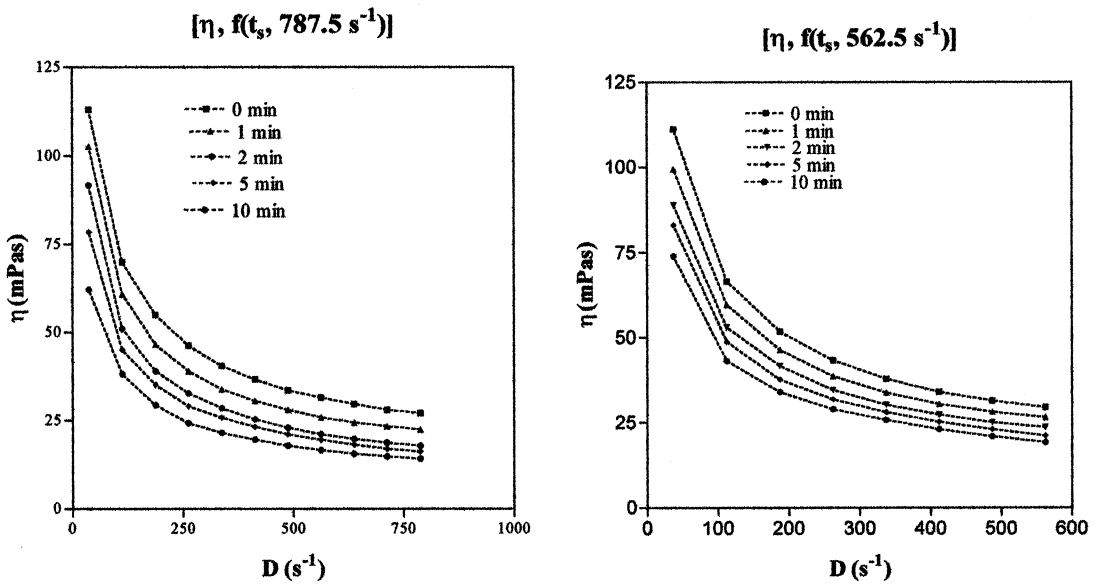

Fig. 5. Evolutive profiles of viscosity $[\eta, f(t_s,D)]$.

3.1.6. Stability: physical assays

None of the formula samples previously subjected to different experimental conditions presented organoleptically appreciable differences in texture or external appearance (Table 8). As a matter of fact, they have always appeared as an oil-in-water system.

3.1.6.1. Photomicrograph examination. The microphotographs (40 ×) obtained after 180 days of storage at room temperature are posted in Fig. 9, while those of the centrifuged sample can be found in Fig. 10.

3.1.6.2. pH. The results from pH-evolution under experimental conditions are represented in Fig. 11.

3.1.6.3. Rheological assays

Viscosity. Rheograms were secured from the whole range of experimental conditions with their corresponding adjustments for the flow behavior. The principal rheological parameters were calculated and statistically analyzed (Tables 9 and 10). The values of one of the most significant rheological parameters — the apparent viscosity (η_{ap}) — that refer to the highest point of the corresponding rheograms are also represented in Fig. 12.

Extensibility. Because of its relevance, from all the extensometric measurements carried out, the extensibility index ($EI\ S_{200g}$) was selected and represented graphically in Fig. 13 as a function of time and temperature.

3.2. Effectiveness assays

Two of the most representative non-invasive biophysical techniques [21] — electrical capacitance measurements and light transmission photometric analysis — were applied to evaluate the dermopharmaceutical effectiveness of the studied system [22,23]. The hydration of the epidermis was measured using Corneometer mod. CM 820 [24]. The lipid content of the skin surface, resulting from cream lipids spread over the skin, was measured using Sebumeter mod. SM 810.

The corneometric and sebumetric values obtained from effectiveness assays are represented graphically in Figs. 14 and 15, respectively. In both graphs, each point corresponds to the average numerical value of the three measurement points on the forearm with their corresponding values for the standard error of the mean (SEM).

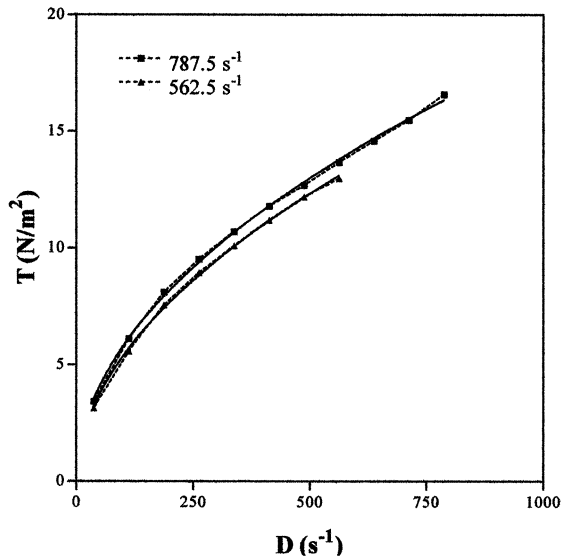

Fig. 6. Shear stress versus shear rate: mathematical adjustments.

Table 5
Mathematical adjustments, area under curve values (AUC) and thixotropic index

D (s^{-1})	Equation	r^2	Confidence of fit (%)	Area (s.u.)^2	D_1/D_2	A_{D_1}/A_{D_2}
787.5	$T = 551.5D^{0.509}$	0.9990	99.0	8457	1.40	1.7718
562.5	$T = 464.2D^{0.529}$	0.9992	99.0	4773		

4. Discussion

A stable dermopharmaceutical formula was obtained successfully. The new system established on the base of a binary emulsion O/W, presented a pH value of 5.4 that resembled a closely eudermic value (pH 5.5), in itself considered [25] the ideal physiological pH of the skin. Thus, we have deduced the NMF® contribution to achieve this experimental pH value as adequate to match the eudermic value.

The formula is adjusted for a rheological pseudoplastic behavior ($T = 555.3D^{0.524}$) with the following features: consistency index, $k = 555.3$ mPa s, flow index, $n = 0.524$, and structural recuperation about 43%. These results confirmed the suitability of our formula for its safe application on the skin.

The study of viscosity evolution as a function of the shear time, t_s, has yielded satisfactory rheological profiles. The evolutive viscosity profiles have shown a decrease with the experimental shear time. The viscosity values also decreased during study as a function of the shear stress, D, yielding a TI ($A_{D_1}/A_{D_2} = 1.77$) close to the constant relation of shear stresses $D_1/D_2 = 1.40$.

The extensibility results with a significant value of $EI = 1825.89$ mm^2 proved to be adequate for comfortable application on the skin. The variation of the extensibility surfaces was adjusted to the exponential model ($S_{ext} = kP^n$). After conducting the study on stability, the system showed no significant physical changes.

The comparative study of the microphotographs provides a priori information relative to the stability of an emulsified system. Thus, in the photograph taken for $t = 0$ in addition to the presence of some waxen briquette, the size of the initial droplet (30 μm [26]) was maintained. However, in the aged sample, we could observe the absence of big briquettes and also, a homogenous distribution. This particular configuration was preserved in the samples throughout the centrifuge stage, although some other structure was observed among the droplets, probably due to the solidification of dispersed components in the aqueous phase.

The evolution of the pH was not significant (0.06–0.27 units of pH). Therefore, we could deduce that both honey and NMF® exerted a positive influence on this important parameter.

With respect to the rheological stability, it was possible to prove that all samples maintained the same flow behavior as typified by Ostwald de Waele, presenting a degree of thixotropy of 73% after 6 months at room temperature.

The pursued analysis of the variance of one factor for the viscosity ($\eta_{787.5}$ mPa s) and the area of hysteresis (TRS, %) as a function of time and storage temperature indicated statistically significant variations ($P < 0.01$).

The similar analysis of the variance of one factor for the EI as a function of the storage time yielded a significant variation of this parameter ($P < 0.01$) from the 60th day on of storage; the same statistical analysis as a function of temperature showed significant variation ($P < 0.01$) that translated into an increase of the

Table 6
Viscosity values as a function of the shear rate [η, $f(D)$]

D (s^{-1})	$\eta_{787.5}$ (mPa s)	$\eta_{562.5}$ (mPa s)
787.5	21.0	
712.5	21.8	
637.5	22.9	
562.5	24.4	23.1
487.5	26.1	25.1
412.5	28.5	27.2
337.5	31.6	30.0
262.5	36.3	34.1
187.5	43.3	40.3
112.5	54.3	49.5
37.5	91.6	83.7

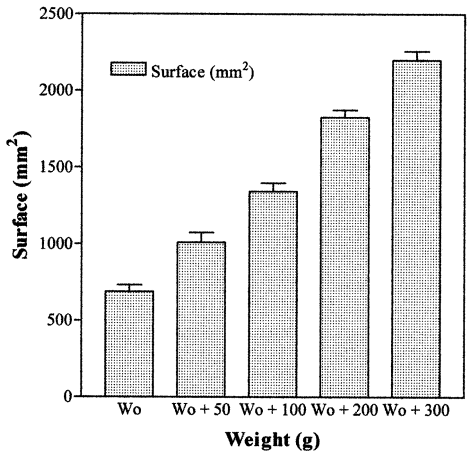

Fig. 7. Results of the extensometric study and SEM values.

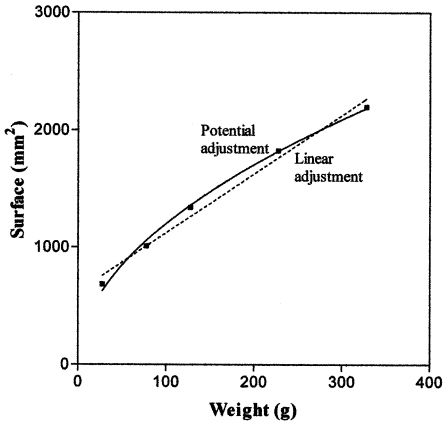

Fig. 8. Mathematical adjustment of the extensibility results — linear and potential.

Table 7
Summary scheme of the results

Assay	Results
Organoleptic characteristics	shiny soft cream with an agreeable honey scent
Photomicrograph examination	Fig. 1
Type of interposition	oil-in-water system (O/W)
pH-determination	5.40
Rheological study	
Viscosity determination	
Initial rheological study	flow index: 0.524 consistency index: 555.3 mPa s $S_0 = 2726$ (s.u.)^2
Hysteresis loop area evolution over time	$TRS_{120} = 38.04\%$
Viscosity evolution as a function of shear time	$\eta_{787.5} = 27.1$ and $\eta_{562.5} = 29.4$ mPa s
Viscosity evolution as a function of shear rate	$TI = 1.7718$
Extensibility measuring	$EI = 1825.893$ mm^2

average values influenced by the temperature and the storage time.

In order to obtain more precise information and secure a better understanding of the system's physical–structural stability as a function of the rheological parameters studied, we have decided to extrapolate the possible correlations among them. Consequently, the existence of linear correlations among these parameters was established as follows.

- *Viscosity–TRS*:

  As a function of time:

  $y = 152.1x - 1005 \quad (r^2 = 0.9908)$

  As a function of temperature:

  $y = 143.3x - 827.9 \quad (r^2 = 0.9996)$

- *Viscosity–extensibility*:

  As a function of time:

  $y = -45.78x + 3067 \quad (r^2 = 0.9281)$

Table 8
Organoleptic characteristics evolution during the stability study

Storage conditions		Organoleptic characteristics
t (days)	T (°C)	
0		shiny soft beige color, homogenous, non-greasy, easily washable and with an agreeable honey scent
1	20	no change observed
	30	no change observed
	45	no change observed
7	20	no change observed
	30	no change observed
	45	no change observed
15	20	no change observed
	30	no change observed
	45	minor modification in consistency; slightly more fluid
30	20	no change observed
	30	no change observed
	45	minor modification in consistency; slightly more fluid
60	20	no change observed
	30	no change observed
	45	the initial tonality begins to change; minor modification in consistency; slightly more fluid
90	20	no change observed
	30	no change observed
	45	change of color to a tint of caramel; minor modification in consistency; slightly more fluid
180	20	no change observed
	30	no change observed
	45	darker color; moderate melting

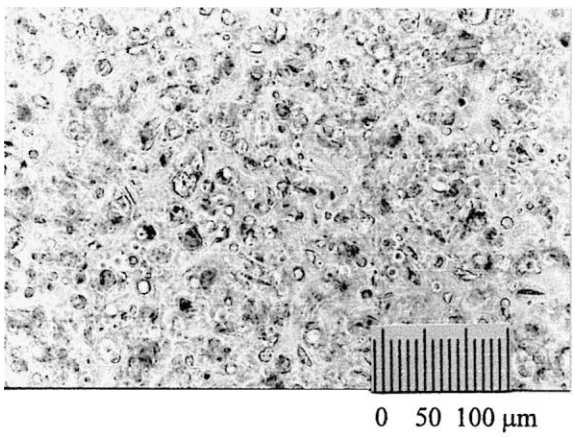

Fig. 9. Photomicrography at $t = 180$ days and $T = 20$°C.

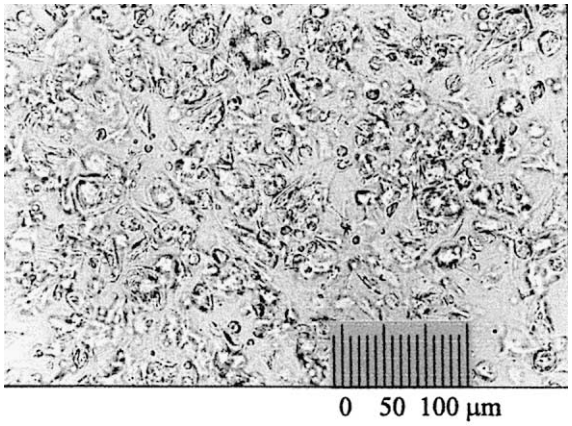

Fig. 10. Photomicrography of centrifuged sample.

As a function of temperature:

$y = -39.32x + 2904 \quad (r^2 = 0.9643)$

- *TRS–extensibility*:

As a function of time:

$y = -0.3006x + 2764 \quad (r^2 = 0.9343)$

As a function of temperature:

$y = -0.2747x + 2677 \quad (r^2 = 0.9668)$

By relying on a similar approach, we have observed the following correlations of rheological parameters with temperature:

- *Viscosity–temperature*

$\eta = -0.4181T + 28.26 \quad (r^2 = 0.9868)$

- *TRS–temperature*

$\mathrm{TRS} = -59.77T + 3217 \quad (r^2 = 0.9819)$

- *Extensibility–temperature*

$EI = 15.38T + 1795 \quad (r^2 = 0.9444)$

Based on the corneometric results, an average increase of 33.8% was observed, which is a more than acceptable value, basically due to the presence of the NMF® in the formula. The sebumetric study yielded

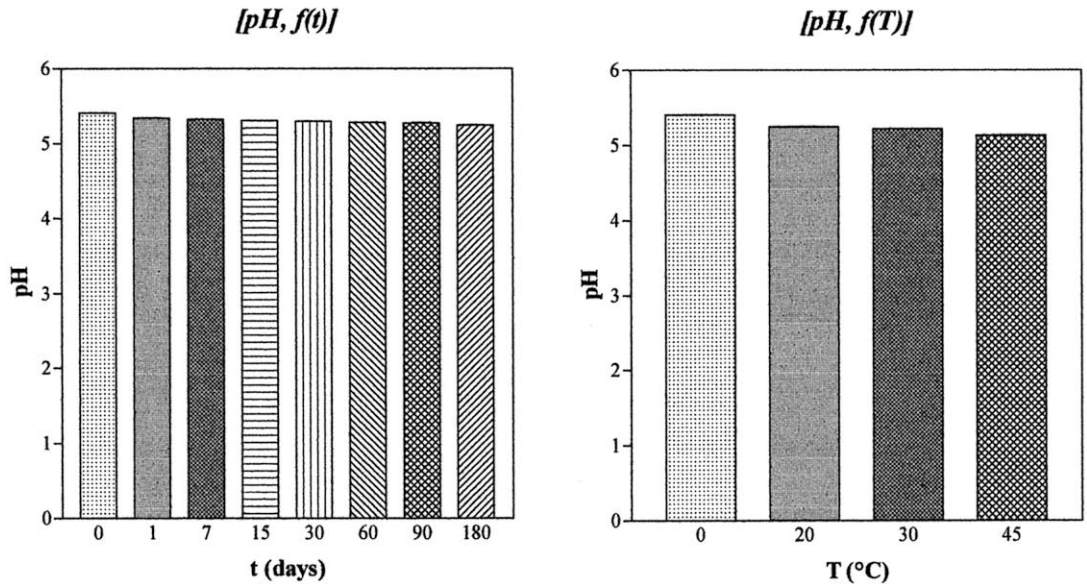

Fig. 11. Evolution of pH.

Table 9
Stability study over time: mathematical adjustments

t (days)	Equation	r^2	Confidence of fit (%)	Area (s.u.)^2	TRS (%)
0	$T = 555.3D^{0.524}$	0.9987	99.0	2726	100.00
1	$T = 703.3D^{0.519}$	0.9984	98.7	2920	107.12
7	$T = 429.8D^{0.586}$	0.9990	98.9	3020	110.78
15	$T = 278.2D^{0.643}$	0.9990	98.6	2982	109.39
30	$T = 684.3D^{0.476}$	0.9980	98.9	1902	69.77
60	$T = 451.4D^{0.525}$	0.9979	98.8	1941	71.20
90	$T = 549.2D^{0.496}$	0.9987	98.8	1718	63.02
180	$T = 608.2D^{0.481}$	0.9992	98.9	1993	73.11

Table 10
Stability studied as a function of temperature: mathematical adjustments

T (°C)	Equation	r^2	Confidence of fit (%)	Area (s.u.)^2	TRS (%)
0	$T = 555.3D^{0.524}$	0.9987	99.0	2726	100.00
20	$T = 608.2D^{0.481}$	0.9992	98.9	1993	73.11
30	$T = 316.4D^{0.542}$	0.9989	98.9	1365	50.07
45	$T = 327.0D^{0.477}$	0.9990	98.8	849	31.14
c.s.	$T = 464.9D^{0.517}$	0.9987	98.6	1926	70.65

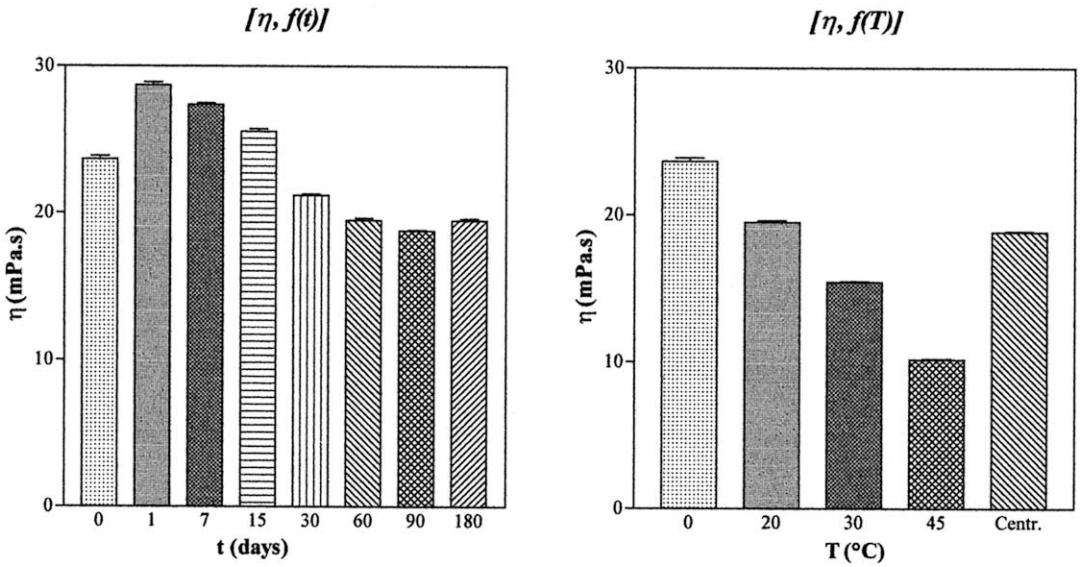

Fig. 12. Evolution of the viscosity.

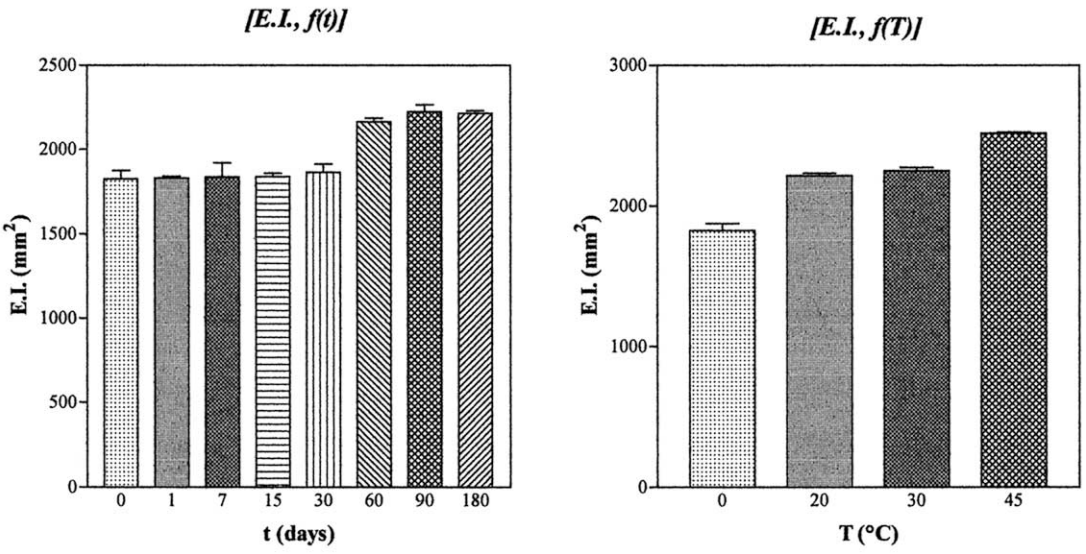

Fig. 13. Evolution of the *EI*.

results that ranged between 44 and 155 μg/cm^2 with regard to the normolipic interval (90–100 μg/cm^2). These results finally confirmed a satisfactory degree of hydration, which may be attributed to the synergic action existing among actives in the experimental emulsion.

We have, therefore, concluded that the suggested formula is a creamy emulsion for easy application and

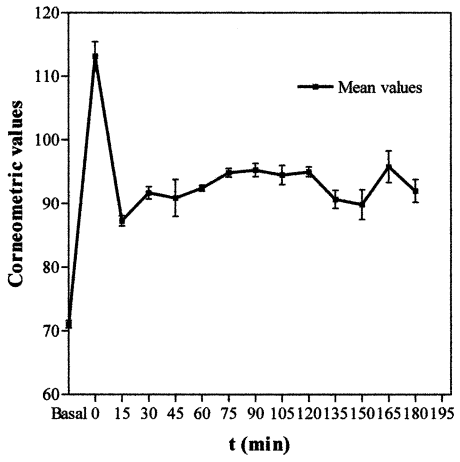

Fig. 14. Study of hydration.

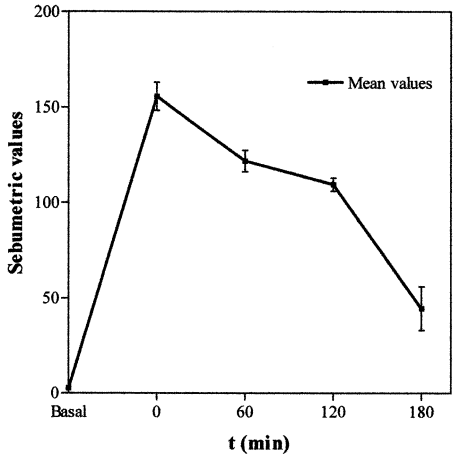

Fig. 15. Study of emolliency.

comfortable wear. Furthermore, the newly designed formula proved to be completely stable, hypoallergenic, and satisfactory from the pharmacotechnical point of view. In addition, the preparation mentioned is characterized by a favorable dermocosmetic profile because of its scientifically proven hydrating and emollient actions, insomuch that the newly designed and thoroughly scrutinized skin-prescription has satisfied exigencies of eudermic and moisturizing dermopharmaceutical application, a formula that hydrates and humidifies all types of skin. We therefore strongly recommend our recently described ointment for cases of extremely dry and desquamated skins.

Acknowledgements

We thank Jerry Keller of the Instituto de Ciencias de la Educación (ICE) of the University of Alcalá for his help with the translation.

References

[1] B.W. Barry, Dermatological Formulations. Percutaneous absorption, Marcel Dekker, New York, 1983.
[2] M.M. Jiménez, M.J. Fresno, E. Sellés, A. Reíllo, Stability and rheology of a dermopharmaceutical excipient formulated with honey, STP Pharma Sci. 5 (1995) 216–224.
[3] F.B. Ahmad, P.A. Williams, Effect of sugars on the thermal and rheological properties of sago starch, Biopolymers 50 (1999) 401–412.
[4] C. Michon, G. Cuvelier, P. Relkin, B. Launay, Influence of thermal history on the stability of gelatin gels, Int. J. Biol. Macromol. 20 (1997) 259–264.
[5] R.I. Tanner, Rheology and computation, Theor. Appl. Rheol. 1 (1992) 12–15.
[6] S.B. Ross-Murphy, Structure and rheology of gelatin gels: recent progress, Polymers 33 (1992) 2622–2627.
[7] S.A. Dragoco, Technical specification of the Neo PCL O/W Base, Barcelona, 1995.
[8] M.H. Rubinstein, Pharmaceutical Technology. Drug Stability, Ellis Horwood, New York, 1989.
[9] E. Sellés, Farmacia Galénica General, El Autor, Madrid, 1995.
[10] C. Faulí, Tratado de Farmacia Galénica, Luzán 5 S.A., Madrid, 1993.
[11] A. Le Hir, Farmacia Galénica, Masson, Barcelona, 1995.
[12] S. Ramachandran, S. Chen, F. Etzler, Rheological characterization of hydroxypropylcellulose gels, Drug Dev. Ind. Pharm. 25 (1999) 153–161.
[13] T.M. Bresolin, P.C. Sander, F. Reicher, M.R. Sierakowski, M. Rinaudo, J.L.M.S. Ganter, Viscometric studies on xanthan and galactomannan systems, Carbohydr. Polym. 33 (1997) 131–138.
[14] Manual de Instrucciones del Reómetro Brookfield Digital Rheometer mod. DV-III, Massachusetts, USA, 1995.
[15] D. Amdidouche, C. Poisson, M.C. Polman, J.C. Chaumeil, Rhéologie et extensometrie de préparations ophtalmiques à base d'huiles végétales, Pharmazie 47 (1992) 207–210.
[16] P.E. Miner, Emulsion rheology: creams and lotions, in: D. Laba (Ed.), Rheological Properties of Cosmetics and Toiletries, vol. 13, Marcel Dekker, New York, 1993, pp. 313–370.
[17] D. Salter, Non-invasive cosmetic efficacy testing in human volunteers: some general principles, Skin Res. Technol. 2 (1996) 59–63.
[18] J. Moss, The effect of 3 moisturizers on skin surface hydration. Electrical conductance (Skicon-200), capacitance (Corneometer CM420), and transepidermal water loss (TEWL), Skin Res. Technol. 2 (1996) 32–36.
[19] E.A. Olsen, Sustained improvement in photodamaged skin with reduced tretinoin emollient cream treatment regimen: effect of once-weekly and three-times-weekly applications, J. Am. Acad. Dermatol. 37 (1997) 227–230.
[20] M. Castro, Validation of analytic methods, Industrial Pharmaceutics Spanish Association (IPSA) Monography, Barcelona, 1989.
[21] A. Lassus, The effect of Silicol gel compared with placebo on papulopustular acne and sebum production. A double-blind study, J. Int. Med. Res. 24 (1996) 340–344.
[22] R.S. Sparacio, Non invasive evaluation of cosmetic products, Cosmet. Toil. 111 (1996) 47–52.
[23] E. Berardesca, N. Farinelli, H.I. Maibach, Statum corneum water content and TEWL, in: R. Baran, H.I. Maibach (Eds.), Cosmetic Dermatology, Martin Dunitz, London, 1994, pp. 383–388.
[24] M. Lodén, E. Hagforsen, M. Lindberg, The presence of body hair influences the measurement of skin hydration with the corneometer, Acta Derm. Venereol. (Stockh.) 75 (1995) 449–450.
[25] G. Yosipovitch, I. Maibach, Skin surface pH: a protective acid mantle, Cosmet. Toil. 111 (1996) 101–103.
[26] M.J. Fresno, M.M. Jiménez, E. Sellés, Aplicación de técnicas reológicas al estudio de estabilidad de una crema dermofarmacéutica hidratante, in: IX National Congress of Dermopharmacy Book, Granada, Spain, 1998, pp. 292–300.