Available online at www.sciencedirect.com
SCIENCE DIRECT
Il Farmaco 58 (2003) 1289–1294
IL FARMACO
www.elsevier.com/locate/farmac

Influence of the concentration of a gelling agent and the type of surfactant on the rheological characteristics of oleogels

Mª.A. Ruíz Martínez *, M. Muñoz de Benavides, Mª.E. Morales Hernández, V. Gallardo Lara

Facultad de Farmacia, Dpto. Farmacia y Tecnología Farmacéutica, Universidad de Granada, Campus Universitario de Cartuja, Granada, Spain

Received 3 February 2003; accepted 20 March 2003

Abstract

The investigation on the influence of components that contribute diverse degrees of viscosity to the formulations is of great interest in medicines for topical use. It is such the case of a derivative of the cellulose—ethylcellulose—that participates in the formula of the oleogels of olive oil as a gelificant agent. Surfactant agents—Olivem—can also modify the rheological characteristics of oil gels. In this work, it is studied how the variation of the concentration of ethylcellulose (3–5%) notably changes the viscosity of the prepared ones. The most concentrated preparations in gelling agent are the most viscous and also present a plastic material, whereas the minor concentration awards a Newtonian character to the prepared ones. On the other hand, the influence of the temperature has been investigated—25 and 37 °C—verifying that the viscosity of the samples diminishes with the increase of temperature. The influence of the addition of surfactant products—Olivem 900, 700 and 300—has given a result that prepared with major viscosity are those which include Olivem 900 that can be qualified like plastic. The most fluid prepared are those which have been elaborated with Olivem 300, and their liquid character has been confirmed by rheological measurements—viscometry, oscillometry and creep-recovery. Many applications can be foreseen in pharmaceutical as well as in the cosmetic area where the use of natural vegetable oils as vehicles for drugs is large.

Keywords: Ethylcellulose; Oleogel; Olivem; Viscosity

1. Introduction

A gel which is an intermediate state between solid and liquid could be defined as a dispersed system that has a colloidal structure with a particle diameter varying from 1 to 100 nm. The gelling process of vegetable or mineral oils has been studied by different authors, who have determined the nature of the oleogel structure.

The investigation on the influence of components that contribute diverse degrees of viscosity to the formulations is of great interest in medicines for topical use [1,2]. It is such the case of a derivative of the cellulose—ethylcellulose—which participates in the formula of the oleogels [3] of olive oil as a gelifying agent [4]. The recent appearance on the market of products derived from olive oil with surfactant characteristics—called "Olivem" [5,6]—has also encouraged our investigation on the rheological characteristics of diverse formulations of oil gels [7]. The influence of the addition of one type or another of these products—Olivem 300, 700 and 900—in the formulations has given as result different values of viscosity and other physical characteristics—limpidity, colour and smell. There is also another parameter that is directly involved with the viscosity: the temperature.

In this work, it is studied how the variation in the concentration of ethylcellulose (3–5%) notably changes the viscosity of the preparations as well as the influence of the type of surfactant included in the composition of formulae. Rheological parameters [8] at room temperature—25 °C—and at the physiological one—37 °C—are also studied [9,10]. The aim has been to determine their organoleptic [11] and rheological [12–15] characteristics in order to find the most suitable

* Corresponding author.
E-mail address: adolfina@ugr.es (M.A. Ruíz Martínez).

0014-827X/03/$ - see front matter
doi:10.1016/S0014-827X(03)00180-0

formulation for the incorporation of a drug and its subsequent topical administration [16].

2. Materials and methods

The components of the formulae are as follows:

– Olive oil, Pharmacopaea Europaea; acidity 1.1, water content $<0.1\%$, supplied by Fluka® (Spain).
– Ethylcellulose; ethoxyl content from 48 to 49.5% and viscosity of toluene or alcohol (5% solution) of 45 cP, supplied by ICN (Spain).
– Olivem® products: Olivem 300 (PEG-7 Olive oil), Olivem 700 (PEG-4 Olivate), Olivem 900 (Sorbitan Olivate); surfactants supplied by Quimibios S.L. (Spain).

In the elaboration of these formulations, we have been guided by the research on gelling methods of vegetable oils carried out by Fukasawa and Aiache, although some changes have been introduced to adapt the synthesis methods to our needs.

Our aim has been to design a series of formulations with qualitative and quantitative differences in some of their components. These formulations were then subjected to different temperatures in order to note any changes in their stability, consistency and other organoleptic properties.

We have prepared oleogels that include olive oil [17] with each of the surfactants listed in Table 1 in their composition as well as a gelifying agent—ethylcellulose at different proportions, 3 or 5% [9].

The gelification process is as follows: the surfactant agent and ethylcellulose are added to the oil phase and heated to 100 °C with constant stirring. After a clear mixture has been obtained, the formulation is removed from the heat but the stirring is maintained until the mixture returns to room temperature and solidifies. After 48 h at rest, the definite internal reticulate structure of the oleogels becomes consolidated. It is advisable to slightly stir the mixture by hand to confirm the homogeneity of the formula and check that there is no oil exudate within the gel or granules that would indicate incomplete melting of the ethylcellulose. The main issue in the preparation of these gels was the fate of ethylcellulose in the oil phase. This material does not melt at the temperature used in the manufacturing process (melting point is 260 °C) but, on the contrary, seems to dissolve in the oil phase and disappear totally.

The parameters determining the organoleptic and rheological study are thus:

- the concentrations of the gelling agent, 3 and 5%;
- the temperatures, 25 and 37 °C; and
- the type of surfactant included.

Table 1
Composition of oleogels formulae: olive oil is the major component; ethylcellulose is the gelling agent and Olivem products have surfactant characteristics

	Sample **1**		Sample **2**		Sample **3**	
	1a	**1b**	**2a**	**2b**	**3a**	**3b**
Olive oil (%)	92	90	92	90	92	90
Ethylcellulose (%)	3	5	3	5	3	5
Olivem 300 (%)	5	5				
Olivem 700 (%)			5	5		
Olivem 900 (%)					5	5

2.1. Organoleptic study

The organoleptic characteristics of the preparations vary depending on their composition. The parameters analysed were colour, scent, texture and consistency. Taste was not determined since these formulae are destined for topical use.

The texture of the preparations is determined by the suitable interposition of the cellulose derivative in the oily matrix. If the melting has been inadequate, granules would appear, thus diminishing the cosmetic quality of the preparation. During storage, an oily exudate may appear in the gel matrix, indicating instability of the formula.

2.2. Rheological measurements

The rheological analysis [18] was performed, for different values of temperature, in a controlled stress (Bohlin CS-10, UK) rheometer with a cone-plate (CP 4/40) measuring system. This configuration has been chosen because of the high consistency of the samples.

Prior to each experiment, samples were pre-sheared with a 100 Pa stress for 3 min and left to equilibrate for the same time.

The following types of experiments were performed.

2.2.1. Steady flow (viscometry)

In this method, samples were subjected to a shear stress ramp between ca. 0.1 and 50 Pa and the corresponding shear rate, $d\gamma/dt$, and dynamic viscosity η were measured for two values of temperature: 25 ± 0.1 and 37 ± 0.1 °C.

The stress was applied in 30 linearly spaced steps.

2.2.2. Oscillatory stress

Another type of dynamic measurements for studying the viscoelastic properties of the formulations consists in obtaining the mechanical oscillograms of the samples. This can be done by application of an oscillatory shear stress of frequency w. The elastic, $G'(w)$, and viscous, $G''(w)$, moduli were obtained for frequencies ranging between 10^{-2} and 100 Hz. Prior to those experiments, the maximum shear stress amplitude, σ_0, below which a viscoelastic linear behaviour is expected, was determined. The viscoelastic linear region (VLR) was determined as a fixed frequency of 1 Hz. These experiments were performed at different values of temperature (25 ± 0.1 and 37 ± 0.1 °C).

2.2.3. Creep-recovery tests

In these measurements, the viscoelastic properties of the formulations were studied in the time domain. A constant stress, $\sigma=1$ Pa, was applied and the compliance or stain per unit stress, $J(t)=\gamma(t)/\sigma$, is measured during $T=60$ s. At $t=T$, the stress is removed and the recovery curve is also determined until $t=60$ s.

The experiments have been performed for the two different temperatures (25 ± 0.1 and 37 ± 0.1 °C).

3. Results and discussion

3.1. Organoleptic study

The preparations formulated with Olivem 700 and 900 had the best appearance based on homogeneity and texture. Their colour and smell were similar to the original raw material: they seemed to be a "solid oil". In contrast, Olivem 300 did not provide these desirable qualities or stability. Their viscosity depended on the percentage of ethylcellulose used. The visual aspect of the samples reveals that with a higher proportion of gelling agent the consistency is more solid but the spreadability of the gel which was correct at lower percentages disappears partially. These results are confirmed by those of the rheological studies shown below.

As far as the relationship between viscosity and temperature is concerned, all the samples behave in the same way: they present a more solid-like aspect for the lowest temperature (25 °C) while these textures go to liquid-like for the highest one (37 °C).

Formulae are opaque and greenish-yellow in colour.

They have a slight scent of olive oil, which could be corrected by a suitable scenting agent. As regards the texture, preparations that include Olivem 300 in their composition contain granules indicating incomplete melting of the ethylcellulose and thus rendering them unsuitable. Every formulae remained homogenous during storage. Therefore, those elaborated with Olivem 700 and 900 result the most ideal formulae for topical administration, given their homogeneity, stability, appearance and texture.

3.2. Rheological study

3.2.1. Viscometric measurements

Figs. 1 and 2 show the results obtained in steady flow measurements. The applied shear stress is presented as a function of the resulting shear rate. The rheograms indicate that sample **a**—with less proportion of gelling agent—show a Newtonian liquid behaviour giving the lowest viscosity values, except for sample **3a** that

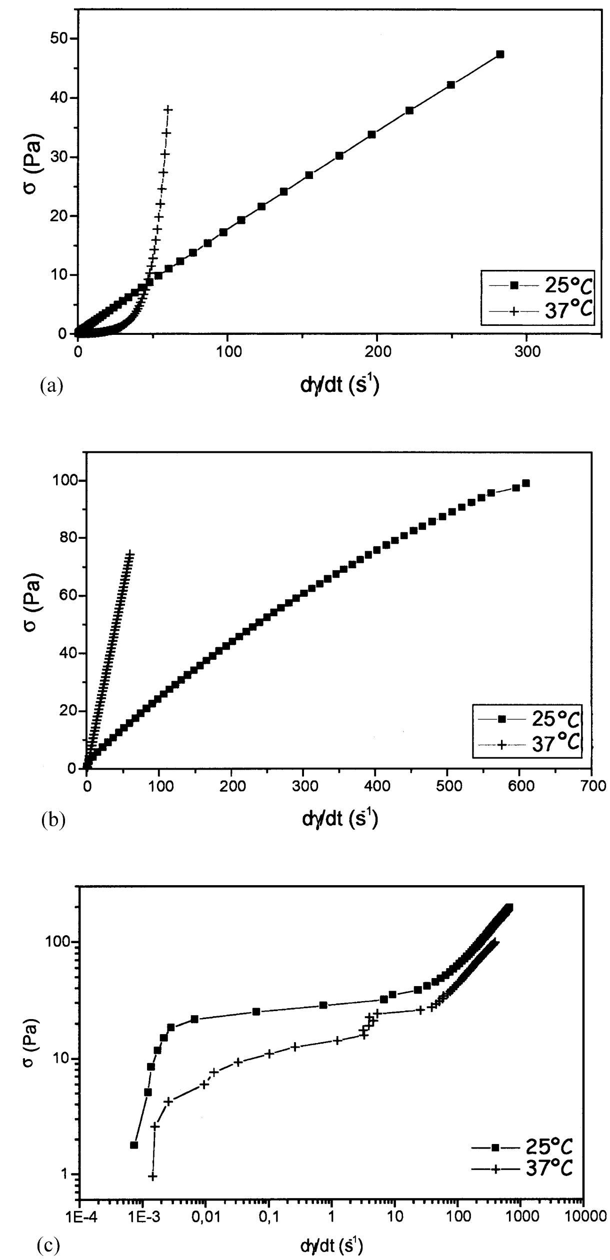

Fig. 1. (a) Shear stress range for two temperatures (25 and 37 °C) as a function of shear rate for sample **1a** that contains Olivem 300 and 3% of gelling agent. (b) Influence of the temperature (25 and 37 °C) on the rheograms of sample **2a** that includes Olivem 700 and 3% of gelling agent. (c) Influence of the temperature (25 and 37 °C) on the rheograms of sample **3a**—elaborated with Olivem 900 and 3% of ethylcellulose.

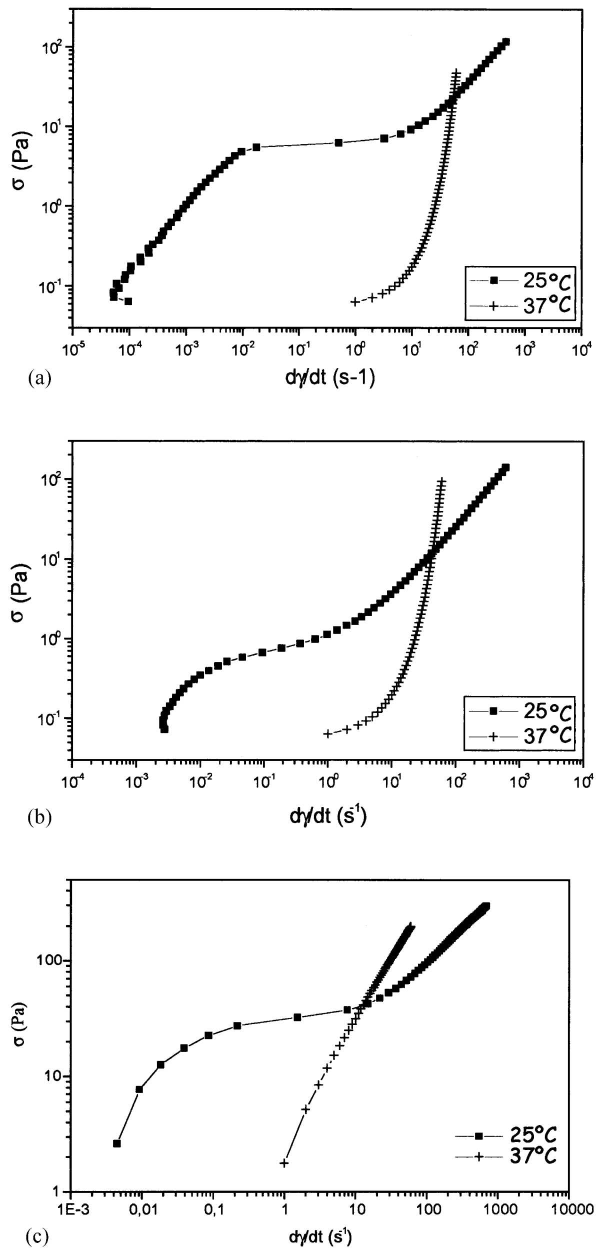

Fig. 2. (a) Influence of the temperature (25 and 37 °C) on the rheograms of sample **1b**—with Olivem 300 and 5% of ethylcellulose. (b) Influence of the temperature (25 and 37 °C) on the rheograms of sample **2b**. (c) Influence of the temperature (25 and 37 °C) on the rheograms of sample **3b**, which includes Olivem 900 and 5% of gelling agent.

behaves as sample **b**, whereas these ones indicate a plastic behaviour. Fig. 1 shows the rheograms corresponding to the first ones and Fig. 2 shows the other rheograms. Rheograms show an increase in the viscosity in parallel with the increasing amount of ethylcellulose dissolved in olive oil when equal forces are applied. There is a linearity in the relationship between the amount of ethylcellulose and the viscosity of the gels obtained. In addition, the behaviour of sample **a** can be classified as that of a viscous liquid obeying Newton's

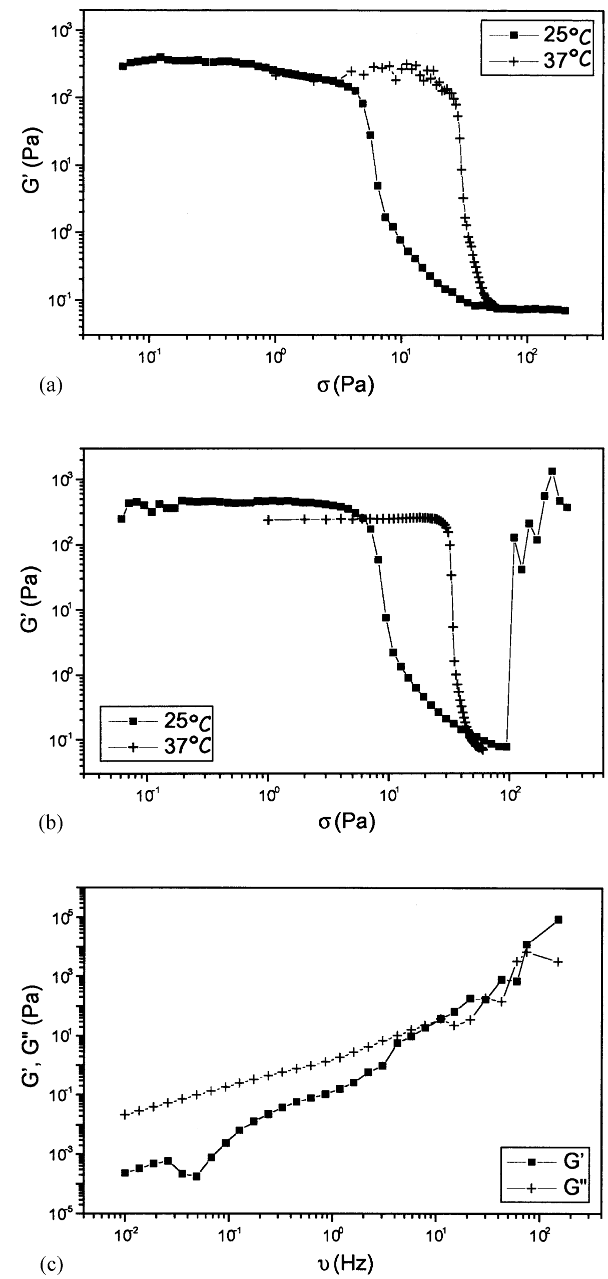

Fig. 3. (a) Elastic modulus G' as a function of shear stress amplitude σ applied in oscillatory tests on sample **3a**. VLR is obtained for different temperatures (25 and 37 °C). Measurements were taken 3 min after pre-shear. Frequency: 1 Hz. (b) Oscillometric measurements to study the influence of the temperature on VLR of sample **3b**—that includes Olivem 900 and 5% of gelling agent. (c) Oscillometry test to study the dependence between G' and G'' with the frequency at a constant shear stress of 1 Pa on sample **2b** at 25 °C.

law, which says that the shear rate increases proportionally to the applied stress (shear stress). Sample **b**, however, behaves like plastic materials, which require a certain force (the threshold force) to begin to flow. At rest, the cohesive forces produce the characteristics of a solid, but when the fluidity limit is exceeded, the bonds break and the product behaves like a fluid, flowing with ease.

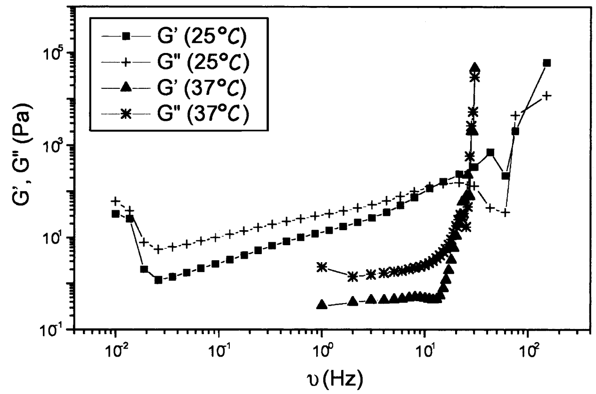

Fig. 4. Influence of the temperature (25 and 37 °C) on an oscillometry study of sample **3b**. Elastic (G') and viscous (G'') moduli obtained for sample **3b** as a function of the frequency of the oscillatory stress applied. The experiments were performed at two temperatures (25 and 37±0.1 °C).

This physical behaviour seems to indicate that the colloidal particles or molecules of the polymer form secondary valence bonds with each other, originating a reticulate network. This makes it necessary for there to be an initial force to weaken these bonds in the face of electrostatic cohesive forces or van der Waals forces. Thus, the threshold stress (σ_0) serves to characterise the rheology of the formulations.

A mathematical method can be used to calculate the value of σ_0 applying logarithmic scales in each axis so that the function has a plateau with the value located at midpoint. These values range from 0.764 Pa for formula **2b** to 32.609 Pa for formula **3b** at a temperature of 25 °C. With regard to the influence of the temperature on the viscosity values of the samples, it can be noted that an increase in temperature contributes to a decrease in the viscosity of the preparations due to the weakening of the bond forces between particles. For instance, formula **3a**, at room temperature, has a σ_0 value of 25.088 Pa, whereas at body temperature (37 °C) this value is 10.948 Pa.

3.2.2. *Oscillometric measurements*

The determination of the viscoelasticity of the preparations by application of an oscillatory shear stress involved first of all the determinations of the range of stress amplitudes (σ) for which a linear viscoelastic behaviour is observed. That range is known as VLR and it can be found by measuring the elastic modulus G' as a function of σ at constant frequency (1 Hz in our experiments).

Results like those in Fig. 3 can be found corresponding to essays performed for samples **3a** and **3b** at different temperatures.

In Fig. 3a, as observed, at 25 °C for $\sigma < 0.9$ Pa, G' maintains an approximately constant value (that we will call G'_{VLR}) that corresponds to VLR of each preparation.

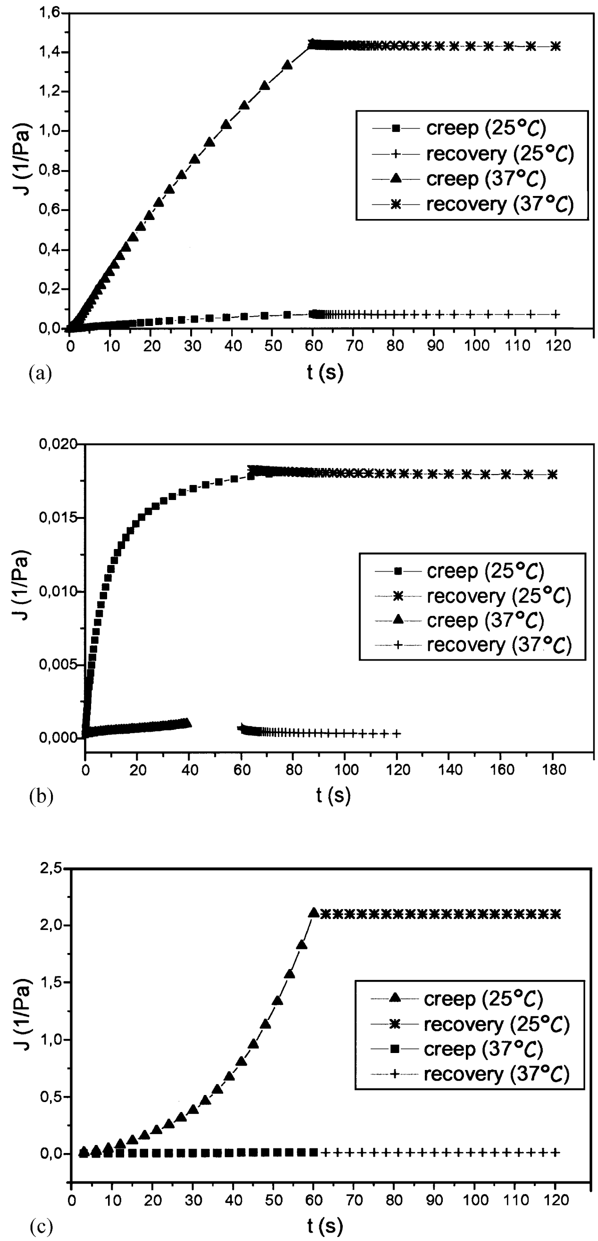

Fig. 5. (a) Influence of the temperature (25 and 37 °C) on a creep-recovery study of sample **1b** that includes Olivem 300 and 5% of gelling agent. (b) Study of the influence of the temperature (25 and 37 °C) on creep-recovery diagrams of sample **2b**, which includes Olivem 700 and 5% of ethylcellulose. (c) Influence of the temperature (25 and 37 °C) on a creep-recovery study of sample **3b** that contains Olivem 900 and 5% of ethylcellulose.

Data in Fig. 3 demonstrate that G'_{VLR} is slightly larger and the temperature is minor, no matter the proportion of gelling agent they contain; again, this demonstrates that low temperature (25 °C in this essay) implies a more elastic behaviour than for the highest one (37 °C). Thus, G' is larger when the proportion of gelling agent (ethylcellulose) is higher (5%; Fig. 3b) and also for the lowest temperature (25 °C).

Moreover, sample **3**—which contains 900 as a surfactant—showed the highest values for the elastic modulus G' in comparison with samples **1** and **2** that include Olivem 300 and 700. This indicates a greater degree of internal structure as confirmed by the viscometric studies.

Having determined the VLR, we can proceed with obtaining $G'(w)$ and $G''(w)$ by the application of an oscillatory stress with an amplitude below the limit of the linear region. These experiments were carried out in the oil gels under two conditions of temperature.

We have measured G' and G'' applying a frequency scan at a constant shearing amplitude: the preparations were sheared (always with the same stress amplitude) with increasing frequencies (0.01–100 Hz).

The most interesting feature of Fig. 4 is the significant effect of the applied frequencies and the temperature on both G' and G'', since both quantities are larger at 25 °C and, furthermore, values for G' are lower than G'' at frequencies under 15 Hz but there is an inversion of the tendency at frequencies upon that value. In the first range of frequencies, the relationship between moduli involves a viscous behaviour while in the second one G' modulus values are the highest, signifying a more elastic character than viscous character.

3.2.3. Creep-recovery

We have subjected the samples to a constant shear stress (1 Pa) for a period of 60 s, measuring the compliance modulus (J) during that time. After stopping the stress, we measured the recovery for another 60 s. The results have shown that there is no structural recovering after ceasing the application of stress to the systems. Figs. 5a–c, thus, point to a viscous behaviour, in agreement with the oscillometry results at certain range of frequencies, which indicated lower G' than G'' values at certain frequencies. Figs. 5a–c show the creep-recovery diagrams for sample **b**—that contain 5% of gelling agent—as an example. The tests were performed under the same conditions at two temperatures. Compliance modulus values (proportionally related with those for the shear rate) were always greater for the highest temperature; that is, the shear rate diminishes as the temperature falls.

4. Concluding remarks

- Oleogels with higher proportion of ethylcellulose present greater consistency.
- Viscosity values diminish with the increasing temperature.
- The least viscous oleogels show a Newtonian liquid behaviour, whereas the most viscous ones present a plastic behaviour.
- Many applications can be foreseen in pharmaceutical as well as in the cosmetic area where the use of natural vegetable oils as vehicles for drugs is large.

Acknowledgements

Financial support by Caja Rural, Spain, for part of this work is gratefully acknowledged.

References

[1] L. Pena, Gel Dosage Forms: Theory, Formulations and Processing. Topical Drug Delivery Formulations, Marcel Dekker, New York, 1990, p. 381.
[2] R. Voigt, M. Bornschein, Ungüentos y pomadas, in: Tratado de Tecnología Farmacéutica, Acribia, Zaragoza, 1982, p. 297.
[3] A. Del Pozo, Pomadas, lipogeles, cremas y pastas, in: C. Faulí i Trillo (Ed.), Tratado de Farmacia Galénica. Luzón 5, S.A. de Ediciones, Madrid, 1993, pp. 625–630.
[4] M. Paulisch, Pomadas, in: Tecnología Farmacéutica, Acribia, Zaragoza, 1981, p. 176.
[5] S. Amari, V. Orta, Derivados del aceite de oliva: nuevos componentes de aplicación en fórmulas cosméticas, NCP Documenta, 1998, p. 236, 11–13.
[6] L. Rigano, R. Trenti, Giada Maramaldi, Ottimizzazione applicativa di un emulsionante derivato d'all olio di oliva, Cosmetic News, XXII, 1999, p. 124, 42–46.
[7] N. Realdon, M. Dal zotto, E. Ragazzi, G. Dalla Fini, Drug release form lipogels according to gelling conditions and mechanical treatment, Drug Dev. Ind. Pharm. 22 (1996) 125–134.
[8] A.R. Gennaro, G.D. Chase, A.D. Marderosian, G.R. Hanson, D.A. Hussar, Remington. Farmacia, Tomo 1, 19ª Edición, Editorial Médica Panamericana, Buenos Aires, 1998, pp. 426–430.
[9] J.M. Aiache, P. Gauthier, S. Aiache, New gelification method for vegetable oils I: cosmetic application, Int. J. Cosmet. Sci. 14 (1992) 228–234.
[10] J. Fukasawa, H. Tsutsumi, A. Ishida, New oil-gelling agents for cosmetics: formation mechanisms of oil gels, Int. J. Cosmet. Sci. 11 (1989) 153–165.
[11] H. García, Valoración sensorial de los aceites de oliva vírgenes, in: J. Mataix (Ed.), Aceite de oliva virgen: nuestro patrimonio alimentario, Vol. 1, Editorial Universidad de Granada, Granada, 2001, pp. 137–145.
[12] V. Gallardo, N. Aybar, A. Hernández, Mª.A. Ruíz, Sunscreen formulation: a study of silicone-emulsifiant concentration, J. Appl. Cosmetol. 16 (1998) 37–44.
[13] R. Howink, Elasticity, Plasticity and Structure of Matter, 2nd ed., Harren Press, Washington, DC, 1953.
[14] T. Ree, H. Eyring, Rheology, vol. 2, Academic Press, New York, 1958.
[15] M. Reiner, Deformation, Strain and Flow, 2nd ed., Interscience, New York, 1960.
[16] Mª.A. Ruíz, J.de.D. Navarro, V. Gallardo, Dermatological applications of olive oil, J. Appl. Cosmetol. 17 (1999) 19–22.
[17] D.D. Ben Miled, A. Smaoui, M. Zarrouk, A. Chérif, Do extraction procedures affect olive oil quality and stability?, Biochem. Soc. Trans. 28 (2000) 929–933.
[18] J. De Vicente, J. Durán, A. Delgado, Electrokinetic and viscoelastic properties of magnetorheological suspensions of cobalt ferrite, Colloid. Surf. A: Physicochem. Eng. Aspects 195 (2001) 181–188.