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Rheological behavior of gels and meloxicam release

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Abstract

The aim of this work was to identify a gel with suitable organoleptic and rheological properties (spreadability, texture and viscosity) for topical administration, designed to allow fast release of the active principle. The release of Meloxicam (anti-inflammatory agent) from olive oil lipogels was compared with a Carbopol hydrophilic prepared gel. In order to improve the diffusion of the active principle, two different artificial membranes with different pore size were used, before release assays in diffusion cells were compared. Drug released rate were obtained by Higuchi's model. Release rate and rheological properties relations were studied, and the best results were obtained for the gel prepared with an olive oil emulgent (Olivem 900).

Keywords: Meloxicam; Carbopol; Olive oil; Viscometry; Creep recovery; Oscillometry

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the long-term treatment of chronic rheumatic diseases such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Meloxicam is a new NSAID of the enolic acid class of compounds.

In recent years, it was selected for pharmaceutical development because it exhibits a high potency in animal tests as potential anti-arthritic action, and has a wide spectrum of anti-inflammatory activity, combined with less gastric and local tissue (e.g., dermal, rectal, ocular) irritation (Luger et al., 1996; Hanft et al., 2001).

Research on the transdermal absorption of drugs (Barry, 1990) requires the use of devices that can record the release and absorption of the active principle in vitro, such as the Franz cell, along with analytical methods (Hassan, 2002) able to quantify the drug released, the amount that accumulates in different layers of the skin and the amount that reaches the dermal microcirculation. Release assays are performed with artificial membranes, whereas permeation assays involve the use of natural membranes such as human skin (Smith and Irwin, 2000), or split layers of animal skin, or artificial membranes such as Spectra/Por®, whose hydrolipid composition makes it similar to skin with regard to affinity for certain molecules.

Luger et al. (1996) studied the physicochemical properties (molecular structure, solubility, pK_a) of meloxicam at different pH conditions, and different solvents. The relative bioavailability of an oral formulation of meloxicam, evaluating its safety and efficacy in a clinical setting (Del Río and Del Río, 2000), concluding that the oral suspension was well accepted by the patients. Due to the notable influence on the drug's rate of release from a preparation for topical administration, the physicochemical properties of both the vehicle and the drug are studied. In fact, the release kinetics profile is determined by vehicle–drug interactions. The transdermal absorption of drugs administered topically depends on the rate of release and the permeability of the skin to the molecules in question, and on the viscosity.

Here we investigated the release of meloxicam, an antiinflammatory drug (Dasandi et al., 2002; Turck et al., 1997), from hydrophilic gels containing Carbopol® (Barry and Meyer, 1979; Pena, 1989; Swarbrick and Boylan, 1988) and lipogels (Aiache, 1992; Fukasawa, 1989) prepared with olive oil. Prior to the release assays in diffusion cells, we compared artificial membranes to select the one that allowed the best diffusion of the active principle. In addition, to optimizing the vehicle for

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topical application to maximize drug bioavailability, it is also important to ensure that the formulation is aesthetically acceptable to the patient, is easy to use and adheres to the treated area for the required time. Another aim of this study was therefore to identify the gel with the best organoleptic and rheological characteristics for topical application (Welin-Berger et al., 2001), i.e., with suitable spreadability and texture, that permitted the most rapid release of the active principle (and hence the shortest delay in transdermal absorption).

2. Material and methods

2.1. Materials

The organoleptic and rheological characteristics of the formulations we compared here were described in a previous study (Ruiz et al., 2003) that tested gelling polymers (ethylcellulose and the olive oil-derived products Olivem 700 and 900) at different concentrations in preparations of different consistencies and rheological behaviors. Table 1 shows the composition of the formulas chosen for the present release study.

The products used to prepare our formulations were:

- Ethylcellulose: (9004-57-3); ethoxyl content 48%-49.5%, viscosity in toluene or alcohol (5% solution) 45 cPs; supplied by ICN (Aurora, OH, USA).
- Olivem products: Olivem 700 (PEG-4 olivate), Olivem 900 (Sorbitan olivate); surfactants supplied by Quimibios S.L. (Barcelona, Spain).
- Olive oil: Pharmacopaea Europaea; acidity index 1.1, water content <0.1%, (75343); supplied by Fluka Chemica (Steinheim, Switzerland).
- Carbopol® ETD 2001: Batch EC8N1EC007; supplied by BF Goodrich (Brussels, Belgium).
- Propylene glycol USP: purity >99.5%, density 1.038, batch 1770696; supplied by Roig Farma, S.A. (Terrasa, Spain).
- Triethanolamine (TEA) 85% 181110: Batch 8290; supplied by Probus S.A. (Badalona, Spain).
- Purified water.
- Meloxicam: In this study, we used the sodium salt of meloxicam ($C_{14}H_{12}N_3O_4S_2Na$, PM 373.4), supplied by Sigma–Aldrich (St. Louis, MO, USA) as a yellowish, water-soluble photosensitive powder.

Table 1
Composition of meloxicam formulations for topical application

	Lipogel 1	Lipogel 2	Carbopol hydrogel
Ethylcellulose	3%	3%	–
Olivem 700	5%	–	–
Olivem 900	–	5%	–
Olive oil	To 100%	To 100%	–
Carbopol® ETD 2001	–	–	1%
Propylene glycol	–	–	10%
Triethanolamine 85%	–	–	To pH 7
Distilled water	–	–	To 100%
Meloxicam	0.3%	0.3%	0.3%

2.2. Methods

The methodology used to produce lipogels was based on the findings of Fukasawa (1989) and Aiache (1992) for the gelling of vegetable oils. We have modified these procedures for synthesis as necessary for our purposes (Gallardo et al., 2005).

The gelation process for lipogels began with the addition of surfactant and ethyl cellulose to the oil phase, which was heated to 100 °C under constant rate shaking. Once the mixture was homogeneous, the heat process was stopped, however, the shaking process continued until the material got cooled to room temperature. A 48-h settling period then ensued to allow the reticular structure of the lipogel to stabilize. Gentle manual shaking is recommended to verify homogeneity of the formula and check the appearance of oil exudates not fully interposes within the gel structure, or granulates that denote incomplete melting of the ethyl cellulose. The main difficulty with these gels is in melting the cellulose in the oil phase. This material does not melt at the temperatures used to produce the gel (melting point 120 °C), but instead appears to dissolve in the oil and disappear completely. Once the lipogel vehicle is prepared meloxicam can be added to perform a suspension gel system. Carbopol hydrogel can incorporate meloxicam in solution (solubility value of meloxicam: 7.5 mg/ml in water).

2.3. Rheological study

We designed a series of formulations that differed qualitatively and quantitatively in some of their components. Measurements were performed at 25 and 32 °C in order to study the possible changes in stability, consistency, and other organoleptic properties. The temperature unit had a stability of ±0.1 °C.

The rheological analysis was performed at different temperatures in a stress-controlled rheometer (Bohlin CS-10) with a CP 4/40 cone-plate geometry (cone diameter 40 mm, angle 4°). This configuration was chosen because of the high consistency of the samples.

All samples were subjected to pre-shear preconditions to impart similar history of mechanical manipulation before each rheological assay. This ensured that the internal structure of the system would break down as a result of application of a stress equal to or greater than the yield stress value for each sample. This was followed by a waiting time of the same duration for all samples, during which elastic recovery commenced. Because the preparations differed in consistency, the stress applied varied from 50 Pa for lipogel 1 to 150 Pa for more rigid (solid-like) gels: lipogel 2 and Carbopol hydrogel. The time duration of the stress was 60 s in all samples, followed by a 180-s waiting time. Preconditioning was used in all assays, i.e., viscosimetry, oscillatory measurements in stress sweep and frequency sweep modes, and creep-recovery assays.

2.3.1. Steady flow (viscometry)

The sweep stress applied to the sample depended on its consistency. Although the initial stress was the same in all assays (the lowest setting the device allowed, i.e., 0.06 Pa), the final stress ranged from 100 Pa for lipogel 1 samples (fluid consistency)

to 300 Pa for lipogel 2 (solid-like consistency). The Carbopol® hydrogel with meloxicam had a more rigid texture than both lipogels, so analytical conditions for these samples required higher shear stress values. In viscosimetric studies we used a sweep stress up to 400 Pa. The shear stress ramp was applied for 120 s, and 60 different points were recorded. Due to the strong thixotropic nature showed by the preparations, a fresh sample was used for each replication to circumvent prolonged recovery times.

2.3.2. Oscillatory stress

The viscoelasticity of the preparations was tested applying an oscillating shear stress. Previously, we determined the range of stress values (σ) for which linear viscoelastic behavior was observed. This range, known as the viscoelastic linear region (VLR), was found by measuring the storage modulus G' as a function of σ at a constant frequency (1 Hz in our experiments).

2.3.3. Creep recovery tests

All samples were subjected to a constant shear stress (1 Pa) for a period of 60 s, and the compliance modulus (J) was measured. Then the stress was removed and recovery was measured for 120 s. The experiments were performed at two different temperatures, 25 ± 0.1 °C and 32 ± 0.1 °C.

2.3.4. Artificial membrane

To compare diffusion profiles, two different types of membranes were tested with a meloxicam solution before meloxicam release from topical use formulations. The meloxicam solution used in the donor compartment was prepared by dissolving meloxicam in an appropriate amount of phosphate buffer solution (PBS) at pH 5.6 (500 μg/ml). The two types of hydrophilic artificial membrane commonly used in Franz diffusion cells were tested: mixed cellulose esters MF 0.45 μm Millex HA, and Durapore PFDF 0.45 μm Millex HV/Pb (both supplied by Millipore).

Synthetic membranes were kept immersed in PBS pH 5.5 for 24 h before they were mounted in the diffusion cell. The receptor compartment contained 17 ml PBS free of air bubbles. The sample (1.5 ml) was placed in the donor compartment to cover the surface of the membrane. It is very important to be careful in this process in order to ensure that no air bubbles were trapped under the membrane. The device was kept at constant temperature (32 ± 1 °C), under continuous magnetic shaking.

We have analysed the meloxicam content in the samples by UV spectrophotometry (Perkin-Elmer, Lambda 40) at a peak absorption wavelength of $\lambda = 362$ nm. The analytical method was validated for linearity, precission and accuracy between 30 and 75 μg/ml; the variation coefficient was <5% and the relative error was one order of magnitude lower.

2.4. Meloxicam release from gels in the Franz diffusion cell

Drug release from different formulations was tested in a Franz diffusion cell with artificial cellulose membranes to study the influence of the nature and the rheological characteristics of each vehicle on the release of the active principle in vitro (Realdon et al., 1996, 2001; Valenta and Schultz, 2004). The release profiles of the compound were then investigated as a function of the macroviscosity of the formulation.

The sample (0.3 g) was spread evenly on the membrane in the donor compartment, and the receptor compartment was filled with PBS at pH 5.5 (a value similar to that of the epicutaneous acid mantle). The receptor medium cell was shaken on a magnetic stirrer throughout the assay to ensure sink conditions. The membranes were immersed in the buffer solution for 24 h before the assay. The temperature in both compartments was kept at approximately 32 °C (USP, 2004) with a thermostated water bath circulating through the double glass walls of the jacketed diffusion cell.

Samples (0.5 ml) were withdrawn from the receptor compartment at 5, 10, 15 and 30 min and at hourly for 6 h) and the sample volume was replaced each time with fresh medium. All samples were analysed spectrophotometrically (Perkin-Elmer, Lambda 40) at the peak absorption wavelength of meloxicam, $\lambda_{max} = 362$ nm.

3. Results and discussion

3.1. Organoleptic characteristics of the preparations

Preliminary studies with these formulations (Ruiz et al., 2003) assessed their cosmetic qualities (color, scent, texture and consistency). The organoleptic characteristics of the preparations varied depending on their composition. Taste was not determined since these formulas are intended for topical use.

Lipogels containing Olivem products were opaque and greenish-yellow. They had a pleasant, smooth appearance and texture. Both formulations remained homogenous during storage. They were similar in color and smell to the original raw material and had the appearance of a solid-like gel. Carbopol hydrogel was a transparent, solid-like gel. The presence of meloxicam gave the preparation a light yellow color.

Because these preparations were intended for topical use, we evaluated their spreadability and film-forming capacity on skin. Layers of the preparations were spread at different thicknesses (200 and 300 μm) on glass plates to evaluate the formation of a continuous (Laboratorios Domca, S.A., Granada, Spain).

3.2. Rheological characteristics

3.2.1. Viscometry

Fig. 1 shows the obtained results in steady state. The applied shear stress is presented as a function of shear rate for both lipogel at 25 and 32 °C. As can be seen, lipogel 1 sample shows an almost newtonian behavior compared to the viscoplastic behavior showed by lipogel 2. An increase of the shear stress led to progressively greater breakdown of the gel structure, with a steady decrease in the slope (apparent viscosity). In addition, an increase in the temperature (from 25 to 32 °C) provokes a decrease of the viscosity and therefore reducing the yield stress (i.e., the stress value necessary to make the system flow). At rest state, the cohesion forces are the responsible of the solid-

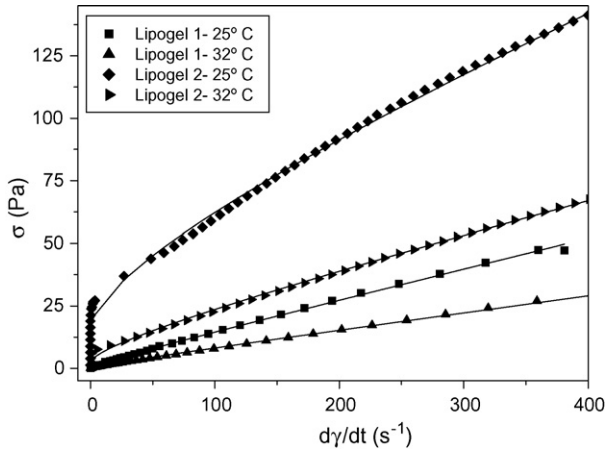

Fig. 1. Shear stress (σ) curves plotted as a function of shear rate ($d\gamma/dt$) of meloxicam lipogel 1 (■, ▲) and lipogel 2 (♦, ►) (0.3%) at 25 and 32 °C, respectively.

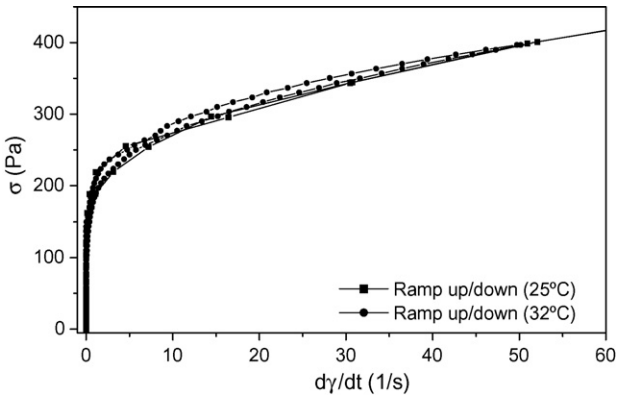

Fig. 2. Shear stress curves plotted as a function of shear rate for meloxicam hydrogel (■, ●) (0.3%) at 25 and 32 °C, respectively.

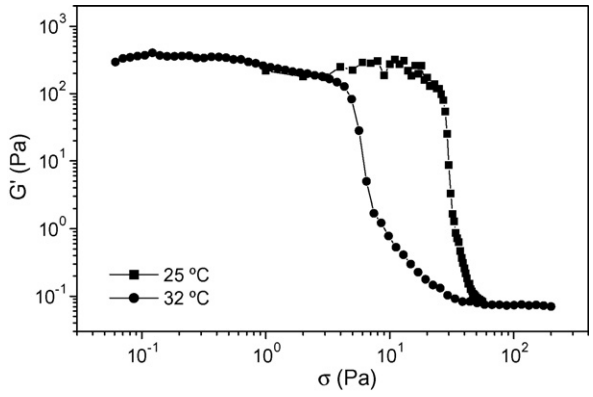

Fig. 3. Storage modulus G' as a function of shear stress amplitude σ in oscillatory tests for meloxicam lipogel 2 sample at 25 and 32 °C. Frequency: 1 Hz.

like characteristics showed by these samples, however, once the shear stress is high enough to exceed the fluidity limit (yield stress value) the bonds break down and the product behaves as a fluid.

For topical anti-inflammatory formulations, the consistency of the samples is specially an important feature, due to the fact that it must be applied to the skin in thin layers. For this reason, it is preferable to formulate plastics samples because of their low resistance to flow when they are applied under high shear conditions, whereas at rest – under the stress caused by gravity – the flow is zero. Thus, plasticity is a desirable characteristic of the consistency of topical formulations (Bousmina, 1999).

The flow curves plotted in Fig. 1 were fitted with the Casson model:

$$\tau^{1/2} = \tau_C^{1/2} + (\eta_C \dot{\gamma})^{1/2} \quad (1)$$

where τ is the shear stress [Pa], $\dot{\gamma}$ the shear rate [s^{-1}] and τ_C and η_C are the Casson yield stress and viscosity parameters, respectively. All the experimental data for both suspensions showed a good fit to the Casson model. Table 2 shows the Casson model parameters (viscosity and yield stress) as a function of the dispersant for both temperatures. As can be seen, the rheograms indicate that the apparent viscosity diminished half as the temperature increased due to the increase in fluidity.

In the case of Carbopol hydrogel, the rheological behavior is plastic, as can be seen in Fig. 2. The flow curves were also fitted to Casson model. The best fit parameters of the Carbopol solutions rheograms to the Casson model are also include in Table 2. As can be seen, according to the yield stress and viscosity values, there is no effect with the increase of the temperature. Both values are much higher compared with that obtained for both lipogels.

Finally, we have to point out that all the samples, both lipogels and Carbopol solutions, presented thixotropic behavior.

3.2.2. Oscillometric findings

Fig. 3 shows the results for lipogel 2 at different temperatures. At 25 °C for $\sigma < 0.9$ Pa, G' remained approximately constant (G'_{VLR}, i.e., the VLR of each preparation). The G'_{VLR} increased slightly as temperature decreased. Thus, at the lower temperature (25 °C in this essay) the behavior was more elastic compared to the results obtained at the higher temperature (32 °C). The lipogel 2 samples, which contained Olivem 900 as a surfactant, showed a higher storage modulus G' than the sample of lipogel 1, which contained Olivem 700. This result clearly indicate that Olivem 900 impart a more robust internal structure, as confirmed by the viscometry studies.

Table 2
Viscosity and yield stress Casson model parameters at 25 °C and 32 °C for the different formulations for topical applications

	Lipogel 1		Lipogel 2		Carbopol	
	25 °C	32 °C	25 °C	32 °C	25 °C	32 °C
τ_C (Pa)	0.16 ± 0.03	0.10 ± 0.02	14.95 ± 0.67	2.32 ± 0.08	181.8 ± 8.5	189.7 ± 5.6
η_C (Pa s)	0.12 ± 0.01	0.06 ± 0.01	0.16 ± 0.01	0.11 ± 0.01	0.77 ± 0.45	0.81 ± 0.15

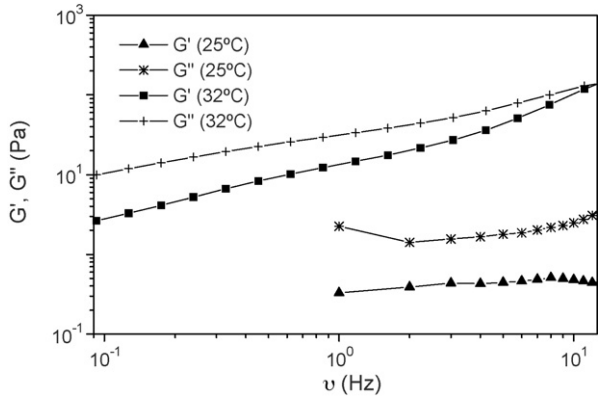

Fig. 4. Storage (G') and viscous (G'') moduli plotted as a function of the frequency for meloxicam lipogel 2, at 25 and 32 °C.

Critical stress (σ_c) was found by determining stress at the point of greatest slope in the most linear portion of the curve (VLR). For lipogel 2, σ_c was 5.652 Pa at 32 °C and 28 Pa at 25 °C (the physiological temperature of the skin) (USP, 2004). In all cases, the critical stress values are slightly higher compared to the yield stress values obtained by the Casson's model, but of the same order.

We measured storage modulus (G') and viscous modulus (G'') by frequency sweep at constant shear amplitude: the preparations were sheared (at the same stress amplitude) at increasing frequencies (0.01–100 Hz). Fig. 4 shows that at lower frequencies (0.01–75 Hz), viscous behavior predominated, whereas at higher frequencies (76–100 Hz) the storage modulus was higher, indicating a more elastic behavior in lipogel 2.

Fig. 5 shows the oscillometric study corresponding to Carbopol hydrogel. Note that both the elastic and the storage moduli, are frequency-independent. For both temperatures $G' > G''$, indicating that the samples present a more elastic than viscous behavior.

3.2.3. Creep recovery

Figs. 6–8 show, the creep-recovery diagram corresponding to lipogel 2, 1 and Carbopol hydrogel at 25 and 32 °C. The cut-off point projected from the upward-sloping part of the curve (creep) on the ordinate (6.0×10^{-5} Pa^{-1}) represents instantaneous unit deformation at $t = 0$ (J_0), or the instantaneous elastic response of the system. The lower the value of J_0, the greater the elasticity is. Greater elasticity, in turn, means greater creep recovery (compliance) of the system (δJ) after stress is removed. The creep-recovery percent can be calculated with the Eq. (2):

$$\delta J = \frac{J(120\,\text{s}) - J(240\,\text{s})}{J(120\,\text{s})} \times 100 \quad (2)$$

The δJ for lipogel 2 at 25 °C was 70.34%. At 32 °C, J_0 was 1.90×10^{-4} Pa^{-1} and δJ was 58.95%. Once again, the elastic

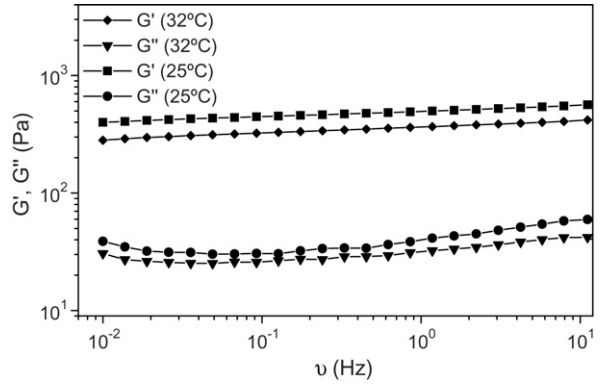

Fig. 5. Influence of the temperature (25 and 32 °C) in an oscillometry study of carbopol hydrogel. Storage (G′) and viscous (G″) moduli were obtained for the hydrogel as a function of the frequency of the oscillatory stress applied. The experiments were performed at two temperatures (25 and 32 ± 0.1 °C).

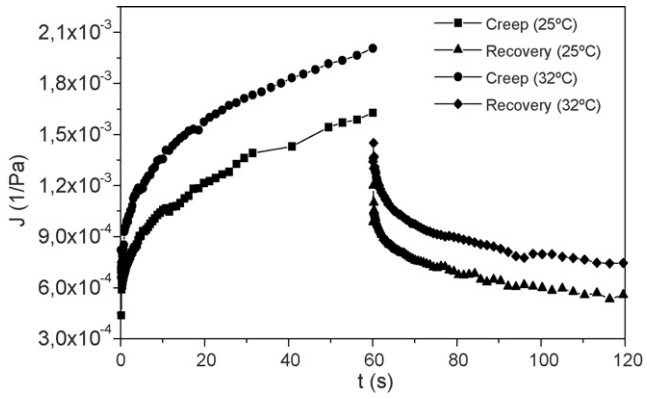

Fig. 6. Creep recovery diagrams for lipogel 2 at (25 and 32 ± 1 °C).

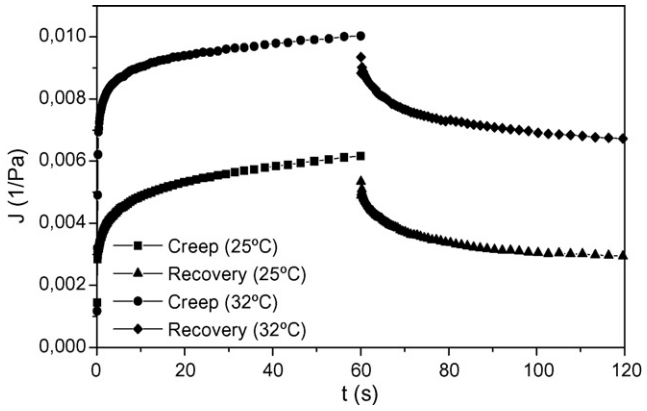

Fig. 7. As Fig. 6 for lipogel 1.

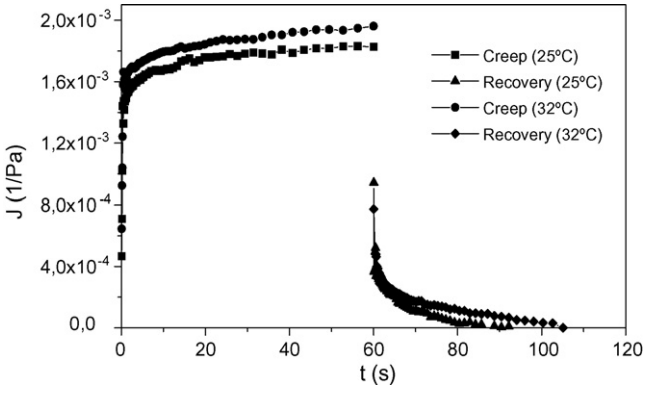

Fig. 8. As Fig. 6 for Carbopol hydrogel.

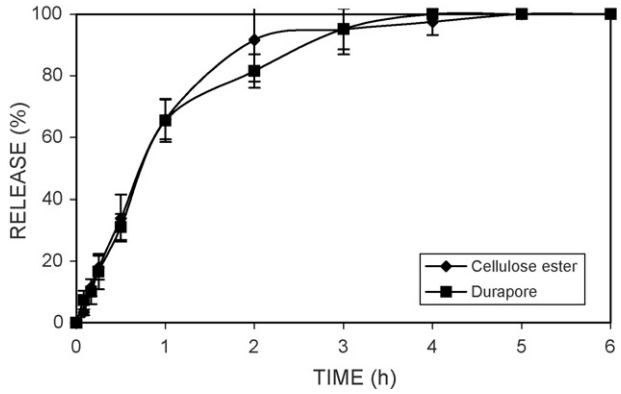

Fig. 9. Percent meloxicam release from a 500 μg/ml solution tested with both Durapore and MF cellulose membrane in a Franz diffusion cell.

behavior of lipogel 2 was confirmed by the results of rheological assays.

3.3. Artificial membranes

Drug release across artificial membranes rapidly reached a plateau. Fig. 9 shows the percent drug release of 500 (g/ml meloxicam solution tested in the receptor cell at different sampling times with both, Durapore 0.45-μm HV and MF 0.45-μm HA membranes. We therefore, chose for subsequent assays of meloxicam release the cellulose-based MF membrane on the basis of its hydrophilic nature and minimal resistance to drug release although non statistical differences between both membranes were found ($p > 0.05$). In order to obtain information about the release rate with both membranes, Higuchi equation was used. This is a useful tool for analyzing drug release data and for obtaining drug release rates. According to this model, a straight line is expected for the percent drug release versus square root of time plot, if drug release is based on a diffusion mechanism. The basic equation of the Higuchiĭs model is:

$$\frac{M_t}{A} = \sqrt{D(2c_0 - c_s)c_s t} \quad (3)$$

valid for $c_0 > c_s$, where M_t is the cumulative absolute amount of drug released at time t, A the surface area of the controlled release device exposed to the release medium, D the drug diffusivity in the polymer carrier, and c_0 and c_s are the initial drug concentration, and the solubility of the drug in the polymer, respectively. Clearly, Eq. (3) can be expressed as:

$$\frac{M_t}{M_\infty} = K\sqrt{t} \quad (4)$$

where M_∞ is the absolute cumulative amount of drug released at infinite time (which should be equal to the absolute amount of drug incorporated within the system at time $t = 0$), and K is a constant reflecting the design variables of the system. Thus, the fraction of drug released is proportional to the square root of time. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time (Siepmann and Peppas, 2001).

Table 3
(a) Higuchi rate constants of 500 mg/ml meloxicam solution tested at Durapore 0.45-μm HV and MF 0.45–μm HA membranes and (b) Higuchi rate constants of all formulations tested at MF cellulose membrane

	Rate constant
(a) Membrane	
Durapore	6.832 ± 0.333
MF-cellulose	6.594 ± 0.364
(b) Formulation	
Lipogel 1	2.10 ± 0.03
Lipogel 2	2.22 ± 0.12
Carbopol	0.75 ± 0.06

Values are mean ± S.D.

The slopes of the square root of time plots for 500 (g/ml meloxicam solution tested at different membranes are shown in Table 3a. Similar square root of time rate constants (Higuchi rate constants) were observed for the formulations at both membranes (Table 3b).

3.4. Meloxicam release from gels

Meloxicam release assays in the Franz diffusion cell made it possible to determine how the release profile of each formulation was related with its viscosity and with the aqueous or oil-based composition of the vehicle. Absorbance (determined spectrophotometrically) was converted into concentration of the drug released into the medium (μg/ml) by interpolating the value on a previously validated regression line. Fig. 10 shows the percent meloxicam released plotted as a function of time for both lipogel and Carbopol formulations. It is notable that for all the studied formulations, the experimental data fits the Higuchi model well. Higher concentration of meloxicam (0.3%) was obtained with lipogel 2 preparations. The mean value for all determinations in different assays after 6 h was 23.11 μg/ml. This result reflects a mean meloxicam percentage release of 43.49 ± 3.51%. The markedly lipophilic nature of lipogel 2 facilitated release of the water-soluble salt of the active principle; consequently the lower affinity between the vehicle and the active principle may account for the greater release from lipogel 2.

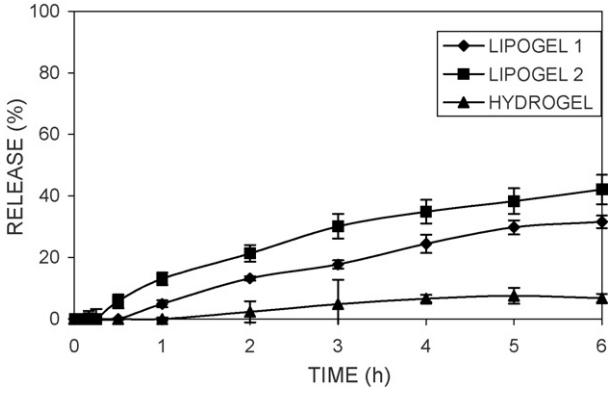

Fig. 10. Percent meloxicam release from lipogel 1, lipogel 2 and Carbopol® gel tested with an MF cellulose membrane in a Franz diffusion cell.

The next best release profile, which was only slightly slower than the release rate seen with lipogel 2, was obtained with lipogel 1. At the end of the release assay the mean concentration of meloxicam released into the medium from lipogel 1 was 20.56 μg/ml. This translated as a mean percentage release rate of 38.72 ± 2.74%.

Table 3b shows the slopes of the square root of time plots for all formulations. Greater square root of time rate constant (Higuchi rate constants) was observed for the formulations with lower viscosity. Table 3b also shows that lipogel 2 formulations have a much greater Higuhi rate constant compared with the Carbopol formulation. Lipogel 1 and lipogel 2 formulations have essentially similar rate constant, as can be expected from their viscosities values.

The rheological characteristics of the lipogels, and especially the viscosity in response to the same shear stress, were more favorable in lipogel 2, as we noted in earlier studies (Gallardo et al., 2005). Mean concentration of 0.3% meloxicam after release from the Carbopol gel was 9.18 μg/ml at the end of the assay (Fig. 8). The percentage release rate after 6 h was 14.18 ± 4.15%. The physicochemical affinity between the vehicle and the drug may have impeded release of the active molecule and thus led to the lower concentrations of the drug in the medium.

4. Conclusions

Compatibility of the oil-based vehicle with the horny layer of the skin, its texture, consistency and rheological properties of plasticity make the lipogel 2 preparation with meloxicam ideal for topical administration. Despite its high apparent viscosity, lipogel 2 more readily released the active principle than did the lipogel 1 formulation. The better release kinetics for meloxicam obtained with the lipogel 2 formula were probably a result of poor vehicle–drug affinity, which facilitated release.

The hydrophilic nature of Carbopol gel when formulated with the meloxicam salt as the active ingredient impeded release of the active molecule and may thus be a limiting factor in subsequent transdermal absorption. This effect will be tested in future assays.

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