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Evaluation of the physical stability of two oleogels

Isabel F. Almeida, M. Fernanda Bahia *

Department of Pharmaceutical Technology, Faculty of Pharmacy, Oporto University, Rua Aníbal Cunha 164, 4050-047 Porto, Portugal

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Abstract

Oleogels are semisolid systems obtained with an organogelator and a hydrophobic liquid that have been investigated over the past few years and that could play an important role as dermatological bases. Recently, we have developed an oleogel of sorbitan monostearate (19 wt.%) and sweet almond oil (SM–SAO) and another one of cholesterol (3.5 wt.%) and liquid paraffin (Ch–LP).

The aim of this work is to access their physical stability using three different methodologies. The gels were stored at different temperatures (20 and 40 °C) over a 3-month period. Appearance and textural properties were assessed on each month. An accelerated test was also performed where the temperature changed between 4 and 40 °C every 24 h, during 7 days. Rheological tests were also carried out as they could provide useful elements to predict stability. The gels were quite stable at 20 °C, being the SM–SAO gel the most stable. The textural properties of both gels were influenced by temperature. The decrease of the textural parameters, observed after storage at 40 °C and in the cycling test, was more significant for the SM–SAO gel. A good correlation was found between rheological analysis and conventional stability tests. The heating/cooling cycle test provided useful information in a short period of time.

Keywords: Stability test; Rheology; Oleogels

1. Introduction

Oleogels are gel systems obtained with a gelling agent and a hydrophobic liquid. Interest in this field has increased due to the strikingly rise of the discovery of substances that are able to gel organic solvents. Initially, organogelators were frequently discovered serendipitously while now new strategies of chemical syntheses are being explored with increasing success in the design of new gelators (Van Esch and Feringa, 2000). Terech and Weiss (1997) reviewed the different classes of organogelators. Some pharmaceutical excipients were also identified as organogelators, namely sorbitan esters (Murdan et al., 1999) and gelators with the cholesterol moiety (Terech et al., 1995).

The applications of oleogels were investigated in several areas such as organic chemistry, environmental chemistry and also in pharmaceutical and cosmetic fields. Some of these potential applications are discussed in a review by Hinze et al. (1996).

The majority of the applications reported in the pharmaceutical area were related to transdermal systems (Willimann, 1992), topical bases (Jurgens and Becker, 1974) and preparations intended for percutaneous absorption (Henmi et al., 1994; Hori et al., 1998).

In previous studies, four different organogelators (ethylcellulose, cholesterol, sorbitan monostearate and lanolin alcohols) were tested with several liquid phases, including vegetable oils (castor oil and sweet almond oil), mineral oil and synthetic esters (isopropyl miristate and isopropyl palmitate) (Almeida and Bahia, 2005). Based on the criteria of short-term stability, homogeneity, gelling ability at concentrations below 30%, and consumer preferences, the oleogels of cholesterol (3.5 wt.%) and liquid paraffin (Ch–LP) and sorbitan monostearate (19 wt.%) and sweet almond oil (SM–SAO) were selected as candidates for topical formulations. Cholesterol was able to gel liquid paraffin at concentrations as low as 1.5 wt.%, while the minimum apparent gelling concentration of sorbitan monostearate was around 17 wt.% for sweet almond oil.

These hydrophobic gel systems do not require extensive manufacturing expertise to be produced, present batch to batch consistency and can be formulated in a wide variety of viscosities,

* Corresponding author. Tel.: +351 222078949; fax: +351 222003977.
E-mail address: fgbahia@ff.up.pt (M.F. Bahia).

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from stiff solids appropriate for stick formulations to semisolid. Their physical stability is a key feature for their applicability. For pharmaceutical or personal care application, these gels must satisfy a number of criteria including long-term physical stability and rheological behaviour suitable for application, spreading and delivery of actives.

The industrial protocols (International Conference on Harmonization, ICH) foresee the storage of samples at different temperatures (room temperature and a higher temperature). Temperature has an important effect on viscosity. The temperature dependence of liquids viscosity has been correlated with intermolecular bonding similarities. Under accelerated stability conditions some systems can undergo phase transitions, and consequently there is a lack of correlation between the behaviour at room temperature and at high temperature. These accelerated tests are of limited use and the formulator faces a challenge for stability prediction.

Rheological tests have also been used to predict the behaviour of products and provide information to improve stability and general performance.

Several rheological measurements (steady state, creep and oscillatory measurements) have been used to provide information on the physical stability of emulsions. Correlations between long-term physical stability (over 6–12 months) with the short-term rheological measurements were also assessed. Low shear measurements proved to be very useful for the prediction of creaming, flocculation and coalescence of emulsions (Tadros, 2004).

In oscillatory measurements, a strain is applied in a sinusoidal manner with an angular frequency ω. The resulting shear stress wave will also be a sine-wave but differing in amplitude and phase. From the amplitudes of stress and strain and the phase angle shift, one can obtain the viscoelastic parameters: the complex modulus G^*, the storage modulus G' and the loss modulus G''.

For a purely elastic sample, the instantaneous stress will be proportional to the corresponding strain and the strain and stress waves will therefore be in phase with each other. For a viscous system, however, the stress will be proportional to the strain rate at any given time, resulting in a phase shift of $\pi/2$ radians.

G' is a measure of the energy stored in a cycle of oscillation while G'' represents the energy dissipated per cycle within the sample. The complex modulus may be defined as follows:

$$G^* = G' + iG'' \quad (1)$$

Stability tests are usually conducted at constant temperatures, but tests under conditions that are periodically changed can reveal inadequacies more quickly than can storage at a constant temperature. So, in the initial stages of the development process, for screening purposes cycling tests can provide useful information (Cannell, 1985).

In stability tests, the samples are periodically checked for changes in important features. In this work we evaluated the macroscopic appearance and the textural properties. Texture can be regarded as a manifestation of the rheological properties of a product. It is an important attribute that affects processing and handling, shelf-life and consumer acceptance of products. Formulations which have been designed for topical application must exhibit acceptable mechanical characteristics e.g. ease of application and low firmness. Considering application to the oral cavity, formulations should have good retention at the site of application. Firmness is related to the ease of product removal from a container and ease of application onto a substrate, whereas adhesiveness, a property related with bioadhesion, describes the relative adhesive properties of a formulation (Jones et al., 1997).

Textural analysis is widely used for the mechanical characterization of food products. It has also been used in the pharmaceutical and cosmetic areas (Jones et al., 1997).

One of the tests that can be performed to access textural properties is the penetration test, where an analytical probe is depressed into the sample at a defined rate to a desired depth. From the resultant force–distance curve, the mechanical parameters of firmness and adhesiveness may be derived. Firmness is defined as the force necessary to attain a given deformation and adhesiveness is regarded as the work necessary to overcome the attractive forces between the surfaces of the sample and the surface of the probe with which the sample comes to into contact (Bourne, 1978).

2. Materials and methods

Sorbitan monostearate, liquid paraffin, cholesterol and sweet almond oil were purchased from Roig Farma, Spain. They were of pharmacopeial grade.

An oleogel of sorbitan monostearate (19 wt.%) and sweet almond oil (SM–SAO) and another one of cholesterol (3.5 wt.%) and liquid paraffin (Ch–LP) were prepared by heating the liquid phase at 90 °C (liquid paraffin) or 60 °C (sweet almond oil) and adding the organogelator by stirring. After 30 min at constant agitation (300 rpm) the mixtures were stored in cylindrical recipients (Ø35 mm, 25 mm height), at 20 °C.

For the rheological analysis, after being prepared, the gels were placed on the plate of the rheometer at 80 °C (Ch–LP) or 55 °C (SM–SAO). Dynamic measurements were performed at 20 °C on a controlled stress rheometer (Haake RS 150, UK), fitted with a cone and plate geometry (diameter 35 mm, gap 0.101 mm, angle 2°). After cooling the sample from 80 or 55 to 20 °C at 1 °C/min (1 Hz, 1 Pa), the gels were allowed to rest for 2 h on the rheometer plate. Then, the time sweeps (1 Hz, 30 Pa) were carried on long enough to achieve equilibrium. Afterwards, a stress sweep from 0.3 to 1000 Pa was performed. For the evaluation of the influence of the temperature, the samples were heated from 20 to 80 °C, 1 °C/min (1 Hz, 1 Pa) after the time sweep. The apparent gel/sol transition temperature (temperature at which $G' = G''$) was determined. Dynamic tests were previously carried out to ensure that the applied stresses were within the linear viscoelastic region.

The textural analysis was performed in the compression mode in a Texturometer (Stable Micro Systems TA-XT2i, UK), by carrying out a penetration test using a cylindrical probe (13 mm diameter), a penetration depth of 10 mm and velocities of 3 mm/s. After penetrating the sample, the probe returned to a position 30 mm above the platform surface. From the graphic

Table 1
Influence of time and temperature on the appearance of the oleogels

Gel	Appearance	First month		Second month		Third month	
		20 °C	40 °C	20 °C	40 °C	20 °C	40 °C
SM–SAO	Homogeneous opaque, yellowish	No modification	Slight syneresis Darkening	No modification	Significant syneresis Darkening	No modification	Very significant syneresis Darkening
Ch–LP	Homogeneous opaque, white	No modification	No modification	No modification	No modification	No modification	No modification

force versus distance obtained, the maximum force and negative area were calculated. These parameters correlate with firmness and adhesiveness, respectively. All the measurements were performed in triplicate.

Twenty-four hours after the preparation of the gels they were placed in ovens at 20 °C and at 40 °C. Appearance and textural properties were evaluated initially and every month.

In the heating/cooling cycle test the gels were stored in a climatic oven (Astell Scientific JBH 800, UK) and temperature was changed between 4 and 40 °C every 24 h, during 7 days.

Before performing the textural measurements all samples were stored at 20 °C for 24 h.

3. Results and discussion

The texturogram of both oleogels is represented on Fig. 1. It can be observed that the SM–SAO gel exhibits higher firmness, correlated with the maximum force, (Bourne, 1978) and adhesiveness, correlated with negative area, (Bourne, 1978) than the Ch–LP gel.

At 20 °C no colour change nor syneresis were observed (Table 1) for the SM–SAO gel. For this gel, the properties firmness and adhesiveness (Figs. 2 and 3) did not change during the 3-month period storage at 20 °C. With the Ch–LP gel, a slight

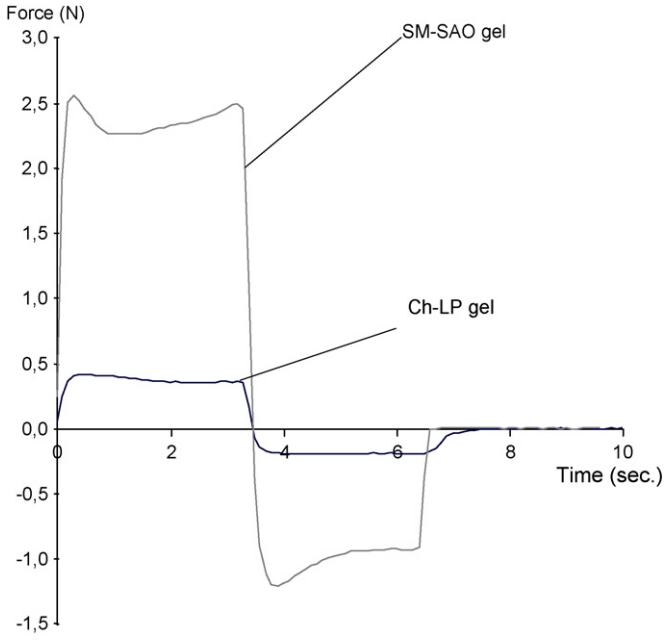

Fig. 1. Texturograms of Ch–LP and SM–SAO oleogels.

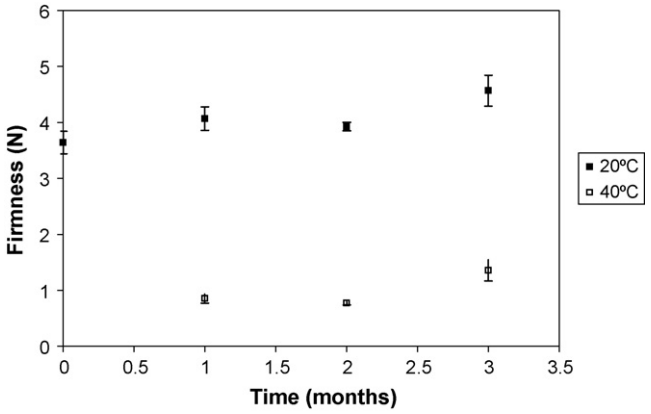

Fig. 2. Influence of storage time and temperature on the firmness of SM–SAO gels (mean±SD).

decrease (about 20%) was observed in the values of both textural properties after 1-month storage (Figs. 4 and 5), although modifications in the macroscopic appearance were not detected. These alterations did not worsen with time. These results showed that at 20 °C the SM–SAO gel is more stable than the Ch–LP gel. This behaviour could be predicted from rheological tests as in the stress sweep the linear region extends further for this gel. A 10% decrease of the value of the storage modulus (G') is observed at about 30 Pa for the Ch–LP gel and at 420 Pa for the SM–SAO oleogel (Fig. 6). This critical stress has been identified with the minimum stress above which the "structure" starts to break down (Tadros, 2004).

At 40 °C a marked decreased (around 80%) was observed in the textural parameters of the SM–SAO gels, along with sig-

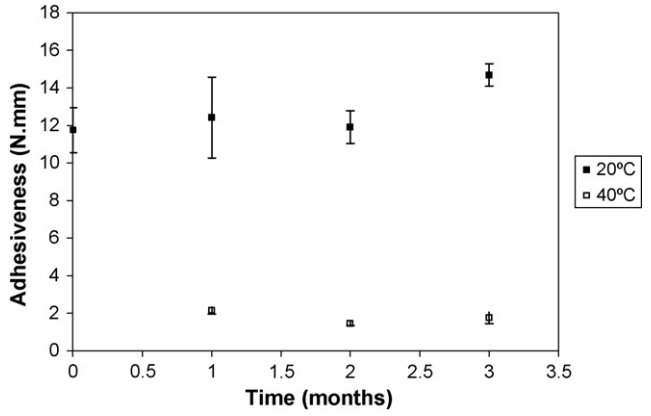

Fig. 3. Influence of storage time and temperature on the adhesiveness of SM–SAO gels (mean±SD).

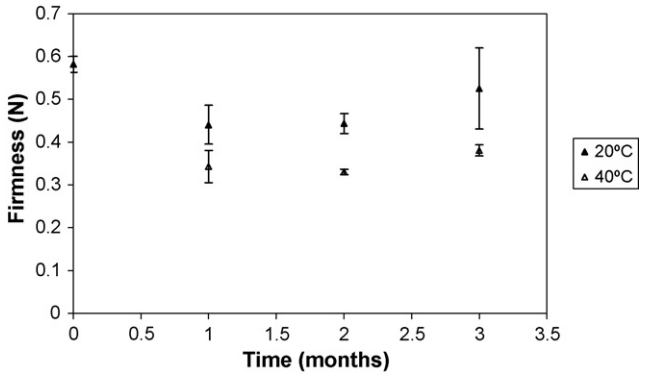

Fig. 4. Influence of storage time and temperature on the firmness of Ch–LP gels (mean±SD).

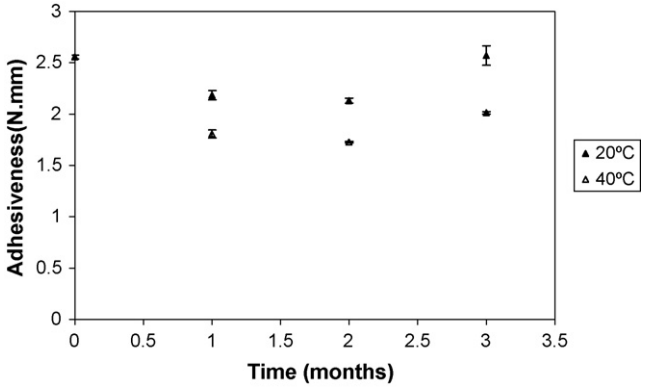

Fig. 5. Influence of storage time and temperature on the adhesiveness of Ch–LP gels (mean±SD).

nificant modifications of the appearance with the presence of syneresis and darkening, that were observable after 1-month storage. Syneresis is usually regarded as a manifestation of instability.

Although significant modifications in the textural properties of the Ch–LP gels were detected, the modifications were not as dramatic as for the SM–SAO oleogel. No apparent modifications on the appearance were observed and the decrease in firmness and adhesiveness was about 40% of the initial values. These did not change with time.

Table 2
Influence of the cycling conditions on the firmness and adhesiveness of the oleogels (mean±SD)

Oleogel	Time (days)	Firmness (N)	Adhesiveness (N mm)
SM–SAO	0	3.558 ± 0.072	12.37 ± 0.295
	7	1.508 ± 0.202	4.253 ± 0.623
Ch–LP	0	0.519 ± 0.014	2.663 ± 0.042
	7	0.307 ± 0.020	1.814 ± 0.071

The SM–SAO oleogel showed significant syneresis under the temperature cycling test, while the appearance of the Ch–LP gel remained apparently unchanged. The textural properties of both gels decreased but with different magnitudes (Table 2). The modifications of both textural parameters on the cholesterol gels were equivalent to the ones observed after storage at 40 °C for 1 month. For the SM–SAO gel it was observed a lower decrease of the firmness and adhesiveness in comparison to storage at constant temperature (40 °C). The cycling test in a short period of time demonstrated the dependence of the textural properties of these gels on thermal stress and allowed discrimination between their behaviour. A high dependence of the storage modulus on temperature was observed for both oleogels (Fig. 7). The structural constitution of these physical gels is usually considered as a heterogeneous three-dimensional network of fibers. G' exhibited a sharp decrease that has been reported to correspond mainly to the loss of interconnectivity of the cross-linked matrix. With low molecular mass gelators, such as cholesterol and sorbitan monostearate, the disaggregation of the junction zones of the network is considered to be simultaneous with that of connected fibers (Terech et al., 2000). The apparent gel/sol transition temperature is slightly higher for the Ch–LP gel (56.2 °C ± 1.6) than for the SM–SAO gel (54.8 °C ± 0.5). This could help to explain the severe alterations observed at 40 °C on the latter gel. The test temperature is closer to the phase transition temperature, so the gel exhibited higher instability. Storage at 40 °C represents accelerated conditions that are far removed from the market conditions. One approach, considered by ICH guidelines, would be to perform the tests at an intermediate temperature, like 30 °C, or considering physiology use at 32 °C (skin temperature).

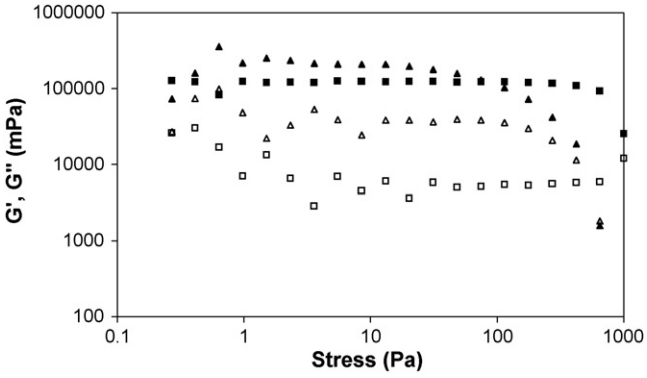

Fig. 6. Influence of stress on the elastic moduli of gels of SM–SAO [G' (■), G'' (□)] and Ch–LP [G' (▲), G'' (△)] gels; 1 Hz, 0.3–1000 Pa, 20 °C.

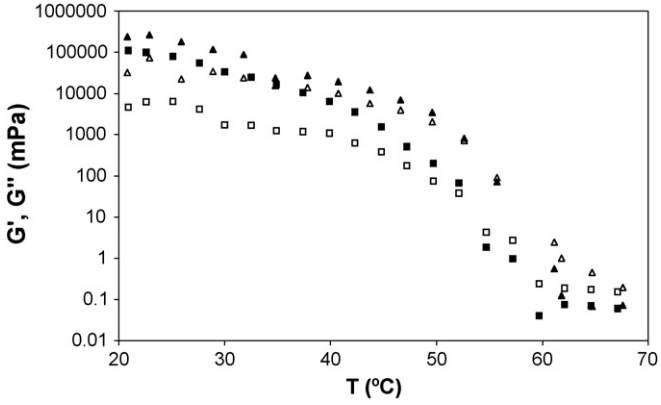

Fig. 7. Influence of temperature on the elastic moduli of gels of SM–SAO [G' (■), G'' (□)] and Ch–LP [G' (▲), G'' (△)] gels; 1 Hz, 1 Pa, 20–80 °C, 1 °C/min.

4. Conclusion

Oleogels are systems with interest as topical bases and promising mucoadhesive formulations. The stability tests performed foresee these systems to be rather stable at room temperature. The textural parameters of the SM–SAO gel were highly temperature dependent while lower changes were detected for the Ch–LP oleogel at 40 °C. The gelling capacity (higher for the Ch–LP gel) does not appear to be an indicator of physical stability. For screening purposes and in the initial phases of the formulation development rheological and cycling tests proved to be very useful.

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