Asian Journal of Pharmaceutical Technology & Innovation
ISSN: 2347-8810

Research Article

Received on: 01-09-2017
Accepted on: 05-09-2017
Published on: 15-09-2017

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Development and Characterization of Emulgels For Treatment of Chronic Wounds

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ABSTRACT

This study was conducted to develop an emulgel formulation for wound healing using Carbopol 940 as the gelling agent and isopropyl myristate as the oily phase. The prepared emulgels were evaluated regarding their rheological behavior and zeta potential. Accelerated stability analyses are a common approach for predicting the long-term stability of pharmaceutical formulations. Five formulations differing only in the proportions of the gel and emulsion were stored for 90 days under two different temperature-controlled conditions (-5 ºC ± 2 ºC/ 45 ºC ± 2 ºC). Zeta potential and rheology measurements indicated that formulations F2 and F3 showed better characteristics for use in treating chronic wounds. Stability analyses showed that the rheological behavior and zeta potential of all of the prepared emulgels remained unchanged during storage for 90 days. As a general conclusion, the results indicated that the emulgel formulations were successful concerning all of the parameters evaluated for wound healing.

Key-words: Emulgel; Chronic wounds; Rheology; Zeta potential.

Cite this article as:
Ferreira, P.G.; Souza, R.S.; Costa, V.G.; Ferreira, V.F.; Cruz, R.C.; Futuro, D.O., Development and Characterization of Emulgels For Treatment of Chronic Wounds, Asian Journal of Pharmaceutical Technology & Innovation, 05 (25); 40-48, 2017. www.asianpharmtech.com

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1. Introduction

Emulgels are emulsions of either the oil-in-water or water-in-oil type and gels that are used in combined form the dosage forms. In other words, emulgels are a class of biphasic semi-solid formulation (Mohamed 2004; Ibrahim et al. 2013; Behera et al. 2015). Emulgel preparation is performed using a gelling agent such as a carbomer responsible for converting a classic emulsion into an emulgel (Ashara et al. 2014; Preeti et al. 2013).
Emulgels for dermatological use have a several favorable properties, such as acting as an emollient, being easily removable, presenting a pleasing appearance and being bio-friendly, and due to the presence exhibiting of both aqueous and non-aqueous phases, they offer the capability of delivering both hydrophilic and lipophillic agents (Ibrahim et al. 2013; Panwar et al. 2011). Furthermore, emulgels provide the advantages of both emulsions (biphasic system) and gels (improved stability) (Behera et al. 2014).
The present study presents differences from the cited articles. Different ratios between the gel and emulsion were used to obtain several emulgels, which represents an innovation regarding both the preparation method and the application of the emulgels to tissue damage.
There are several requirements for formulations used in the treatment of wounds, such as easy application and being removable, and a high water content to maintain consistency (Harding et al. 2002). To overcome this limitation, an emulgel is the best choice due to the above-mentioned reasons.
The aim of this work was to develop an emulgel formulation for wound healing using Carbopol 940 as the gelling agent and isopropyl myristate as the oily phase. The zeta potential and rheological properties of the prepared emulgels were also evaluated.

2. Materials and methods

2.1. Materials

The following materials were used in this study: Carbopol 940, Tween 80, Span 80, butylated hydroxytoluene (BHT) and isopropyl myristate, which were purchased from Farmos (Trade and Industry Farmos Ltd., Rio de Janeiro, RJ, Brazil); methyl and propyl parabens were purchased from Fagron (Fagron of Brazil Pharmaceuticals Ltd., São Paulo, SP, Brazil); sodium hydroxide was purchased from Sigma (Sigma-Aldrich®, St. Louis, USA).

2.2. Development of emulgels

Different formulations were prepared using different proportions of the gel and emulsion. The gel phase in the formulations was prepared by dispersing Carbopol 940 and methyl paraben in purified water, with constant stirring at a moderate speed using a mechanical shaker, after which the pH was adjusted to 6-6.5 using sodium hydroxide. The oily phase of the emulsion was prepared by dissolving Span 80, propyl paraben and BHT in isopropyl myristate, while the aqueous phase was prepared by dissolving Tween 80 in purified water. The oily and aqueous phases were heated separately to 70-80 °C, and the oily phase was then added to the aqueous phase, followed by continuous stirring until the mixture cooled to room temperature. The obtained emulsion was incorporated into the gel base in different ratios with gentle stirring to obtain the emulgel. The compositions of the different formulations are discussed in Table 1 and Table 2.

Table 1: Different ratios used for obtaining emulgels (% w/w).

A (%)	90	80	70	60	50	40	30
B (%)	10	20	30	40	50	60	70

Legend: A = gel ratio; B = emulsion ratio

Table 2: Emulsion and gel bases for obtaining emulgels (% w/w).

Emulsion (O/A)	**Gel**
Isopropyl myristate – 10 1:1 ratio T 80 e S 80 – 20 Propyl paraben – 0.03 BHT – 0.06 Purified water – 79.91	Carbopol 940 – 1.0 Methyl paraben – 0.03 Purified water – 98.97

* T 80 = Tween 80; S 80 = Span 80

2.3. Evaluation of emulgels

2.3.1. Zeta potential

Zeta potential were determined using a Malvern Zetasizer. A 1.0 g sample was dissolved in purified water and agitated to obtain a homogeneous dispersion. The sample was injected into the photocell of the Zetasizer (Mei et al. 2003; Sapino et al. 2015).

2.3.2. Rheological behavior

The emulgels were subsequently transferred to a Haake Mars II Rheometer (Thermo Electron Corporation) for oscillatory and static measurements. This instrument is a rotational rheometer used to determine the rheological properties of Newtonian and non-Newtonian fluids. All parameters were established with RheoWin 4 software. A cone-and-plate geometry, with a 2º cone and 35 mm diameter plate, was used for all experiments on emulgels. Flow curves were generated using ascendant and descendant ramp rotation, with shear rates of 0-187 s^{-1} for 60 seconds in the ascending ramp and 187-0 seconds s^{-1} 60 seconds in the descending ramp. Frequency sweeps were performed at a constant stress (10 Pa) in the frequency range of 0.1 - 100 rad/sec (Pople et al. 2011; Lauterbach et al. 2014). Frequency sweeps were performed in the linear viscoelastic region of the emulgels. All analyses were conducted at temperatures of 25 °C and 36 °C, except in the stability analysis. Results were obtained from the flow curves and sweep frequency.

2.3.3. Stability analysis

The prepared emulgels were packed in glass pots covered with aluminum foil (5 g) and subjected to stability analyses at 5 ºC ± 2 ºC/45 ºC ± 2 ºC for a period of 90 days. Samples were withdrawn at zero days and time intervals of 7, 15, 30, 60 and 90 days and evaluated regarding their globule size, zeta potential and rheological properties (Pople et al. 2011; Pelagia et al. 2014).

2.3.4. Statistical analysis

The results are expressed as the mean value ± standard deviation (SD) of triplicate analyses. The data were evaluated via one-way analysis of variance (ANOVA), with the significance level set at $p \leqslant 0.05$. Tukey´s test was used to compare more than two experimental groups. All analyses were performed using Assistat software, version 7.7.

3. Results

3.1. Development of emulgels

Emulgels were prepared using different proportions of the gel and emulsion (Table 3). The tested proportions used were 90/10, 80/20, 70/30, 60/40, 50/50, 40/60 and 30/70, which correspond to F1, F2, F3, F4, F5, F6 and F7, respectively.

Table 3: Concentration (% w/w) of emulgels components

Formulations	F1	F2	F3	F4	F5	F6	F7
Gel/emulsion ratio	90/10	80/20	70/30	60/40	50/50	40/60	30/70
Components	Concentration (% w/w)						
IM	1	2	3	4	5	6	7
T 80 e S 80 ratio (1:1)	2	4	6	8	10	12	14
Propyl paraben	0.003	0.006	0.009	0.012	0.015	0.018	0.021
BHT	0.006	0.012	0.018	0.024	0.03	0.036	0.042
C 940	0.9	0.8	0.7	0.6	0.5	0.4	0.3
Methyl paraben	0.027	0.024	0.021	0.018	0.03	0.012	0.009
Water	q.s.p. 100						

*IM = Isopropyl myristate; T 80 = Tween 80; S 80 = Span 80; C 940 = Carbopol 940

3.2. Zeta potential

The electrostatic stability of emulgels is partly due to the increased solvation shell of the micelles. Adding hydrophilic gel to the emulsion (O/W) results in the aqueous phase interacting through hydrogen bonds with water in the gel composition. Therefore, emulgels with a higher gel concentration exhibit a higher solvation layer and tend to show greater stability (Figure 1).

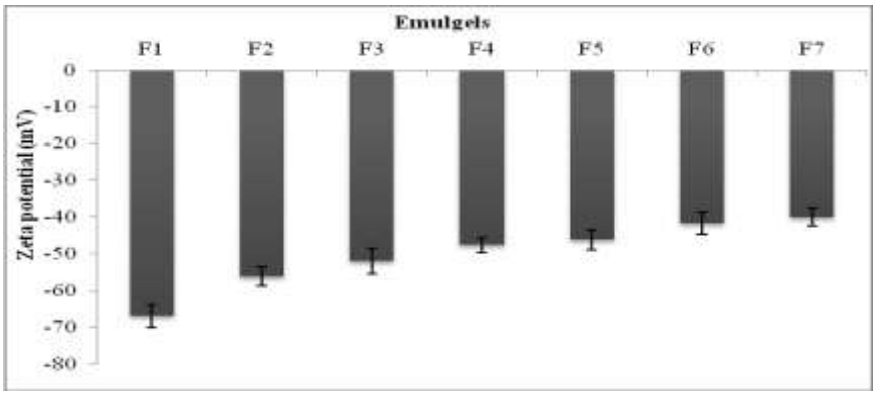


Figure 1: Graph of the zeta potential of the emulgels.

3.3. Rheological behavior

The rheological experiments performed in this study are divided into two different categories, stationary and dynamic experiments. In the first category, the system is in a stationary state, where the experiment takes place in rotational mode, and the curve obtained is referred to as a flow curve. The dynamic experiments are performed in oscillatory mode and referred to as the sweeping frequency.

Emulgels with a higher percentage of gel (F1 and F2) showed higher viscosities (Figure 2 and Figure 3), due to three-dimensional networks formed by the macromolecular colloidal structures contained in gel. Shear stress tests developed in the emulgels at two temperatures (room temperature and human body temperature) were designed to evaluate the changes in viscosity and rheological behavior that could occur during contact of the product with skin. The results showed a significant reduction in viscosity values at body temperature. Therefore, the curves retained aspects similar to those observed at room temperature, suggesting that the preparations did not lose their characteristics during application to the skin. Thixotropy of some pharmaceutical products is quite desirable; however, certain materials lose their ability to recover their properties when subjected to repetitive stress. The results regarding thixotropy were inconclusive because the hysteresis area was much smaller than the total area (Table 4 and Table 5).

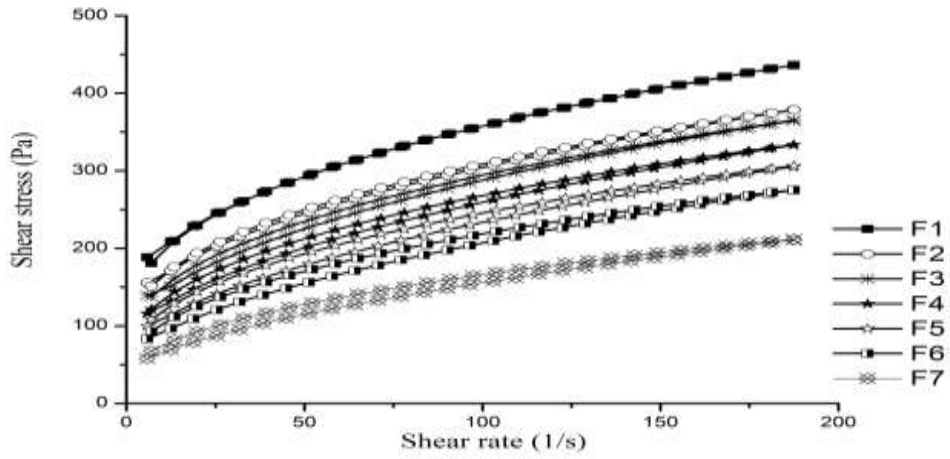


Figure 2: Emulgel flow curves at 25 ° C.

Table 4: Hysteresis values at 25 ° C.

Emulgels	Crescent area (Pa/s) (x10⁴)	Decrescent area (Pa/s) (x10⁴)	Hysteresis (Pa/s)
F1	6,214	6,211	33,34
F2	5,28	5,344	-642,9
F3	4,963	5,086	-1222
F4	4,477	4,625	-1485
F5	4,037	4,226	-1897
F6	3,571	3,763	-1922
F7	2,685	2,854	-1697

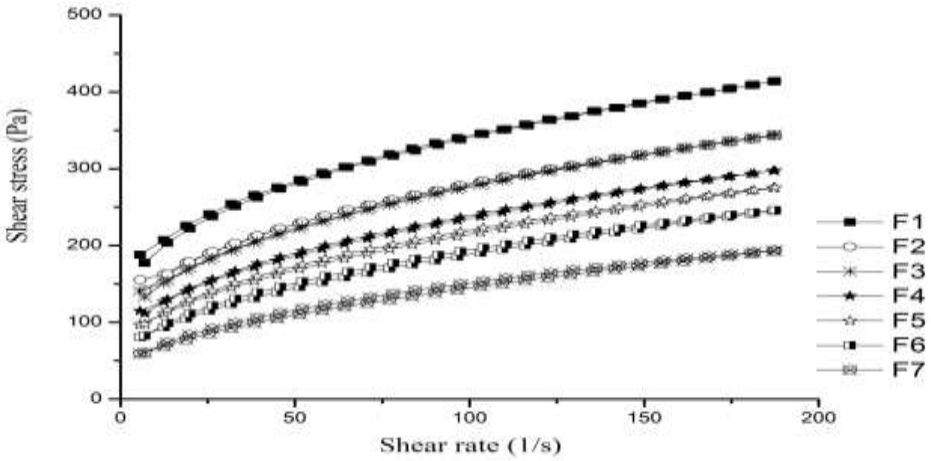
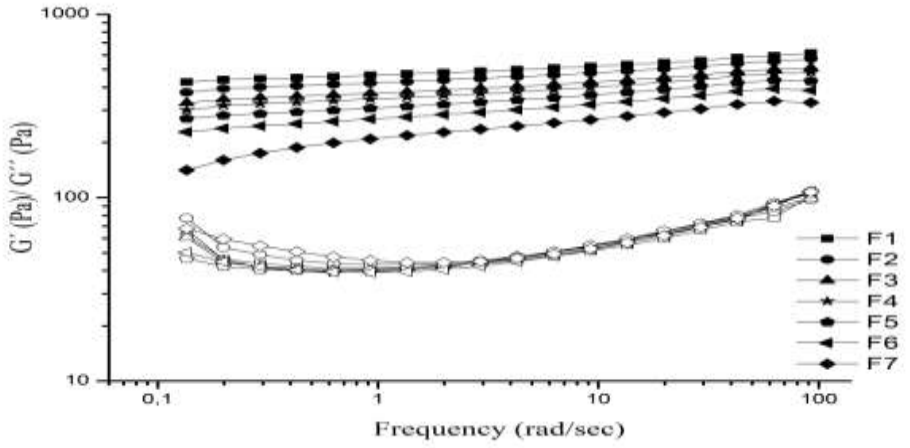


Figure 3: Emulgel flow curves at 36 ° C.

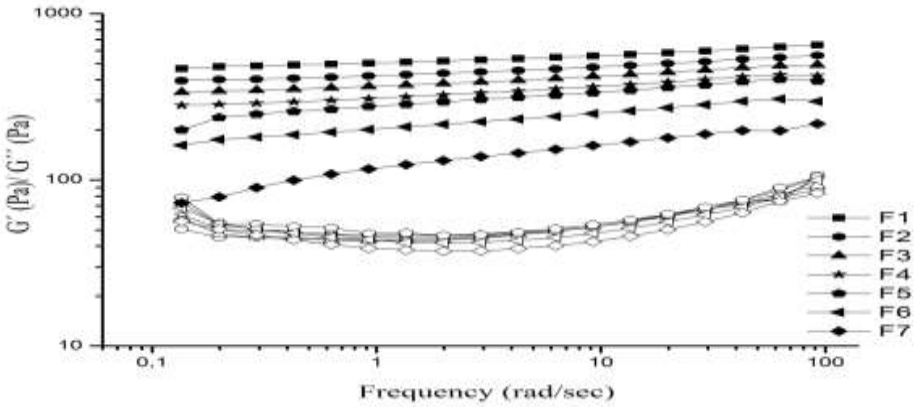
Table 5: Hysteresis values at 36 ° C.

Emulgels	Crescent area (Pa/s) (x10⁴)	Decrescent area (Pa/s) (x10⁴)	Hysteresis (Pa/s)
F1	5,948	5,923	248,3
F2	4,858	4,858	3,043
F3	4,781	4,805	-237,2
F4	4,07	4,13	-594,6
F5	3,718	3,791	-724
F6	3,26	3,345	-851,3
F7	2,499	2,597	-978,2

To comply with the objectives of this study, it is expected that the product developed must exhibit an elastic modulus (G') higher than the viscous modulus (G'') over the entire frequency range applied because it is desirable to obtain emulgels that are easy to apply and remove, without spreading beyond the limits of the lesion at the time of application of the product and thereafter. Figure 4A demonstrates that all of the emulgels showed an elastic modulus (G') higher than the viscous modulus (G'') across the frequency range applied at room temperature. Emulgels subjected to a temperature of 36 °C (Figure 4B) exhibited decreased levels of the elastic modulus, without major changes in the viscous modulus, in preparations consisting of a lower proportion of gel (F6 and F7). Emulgels F2 and F3 possessed the most features aligned with the research objectives due to presenting an appropriate consistency.



(A) 25 °C



(B) 36 °C

Figure 4: Frequency sweep of emulgels. Analysis of temperature: A = 25 ° C and B = 36 ° C.

3.4. Stability analysis

Emulgels F6 and F7 were excluded due to the changes observed in their elastic and viscous behavior during the rheological analysis. The samples were stored in sealed glass bottles, protected from the incidence of light, and subdivided based on the days of analysis (five observation times) and storage conditions (cooling and heating). The stability of colloids can be ascertained by measurement of the zeta potential. This potential reflects the actual charge on the particles, which correlates with electrostatic repulsion and, thus, with stability. Therefore, the higher the zeta potential, the more likely that the system is stable because the charged particles repel each other, and this force overcomes the natural tendency of aggregation. The ideal value should be greater than or equal to |30| mV (Roland et al. 2003). Table 6 shows that all of the formulations presented higher values across the whole stability test. There were no statistically significant differences ($p \leqslant 0.05$) at the analysis times.

Table 6: Zeta potential of the emulgels.

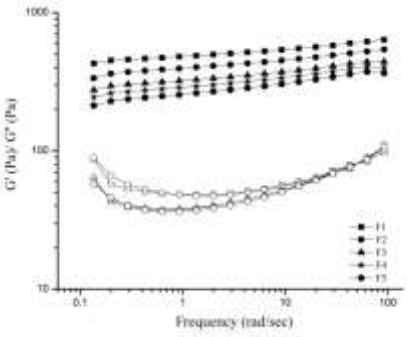
Emulgels	T0 (mV)	7 D (mV)	15 D (mV)	30 D (mV)	60 D (mV)	90 D (mV)
F1	-67.9	-65.2* -56.3**	-64.1* -67.7**	-70.5* -74.5**	-62.9* -67.3**	-63.5* -65.9**
F2	-58.6	-55.1* -57.3**	-61.6* -64.1**	-65.3* -72.1**	-66.6* -55.1**	-64.7* -58.9**
F3	-69.8	-64.2* -65.5**	-63.2* -68.4**	-68.2* -73.9**	-58.3* -67.3**	-56.1* -65.1**

F4	-58.9	-57.3* -59.3**	-60.2* -62.8**	-61.4* -71.6**	-53.1* -70.4**	-58.4* -69.2**
F5	-50.5	-57.6* -58.7**	-58.6* -63.2**	-55.4* -68.1**	-53.1* -65.4**	-58.2* -66.9**

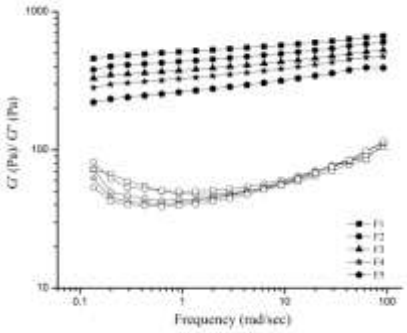
* -5 ºC ± 2 ºC; ** 45 ºC ± 2 ºC/ T0 = time zero; D = days

Emulgels tested at time zero were not subjected to heating and cooling.

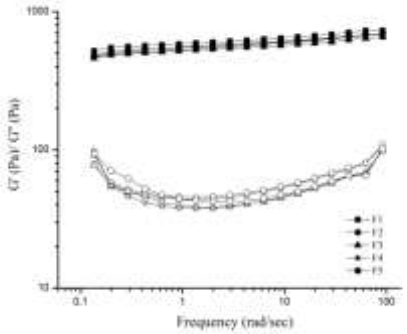
The frequency sweep of the emulgels (Figure 5) shows that the samples stored at a low temperature retained characteristics very similar to those observed in emulgels at T0. The samples stored at a higher temperature showed distinct characteristics, but they retained the same arrangement for the elastic and viscous components. It was observed that when the samples were maintained at 45 °C, the elastic component curves for all emulgels presented similar values.



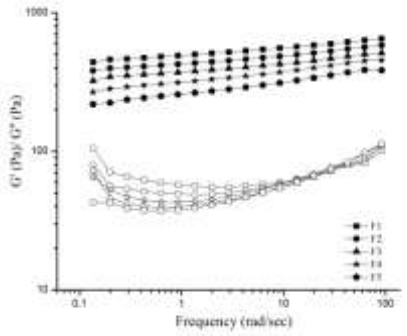
A - Time zero



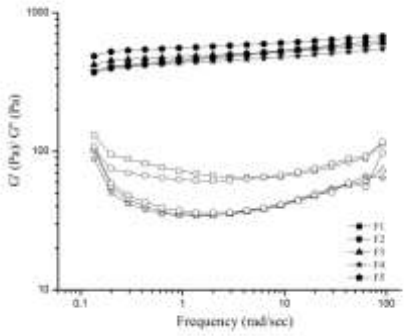
B - 30 D*



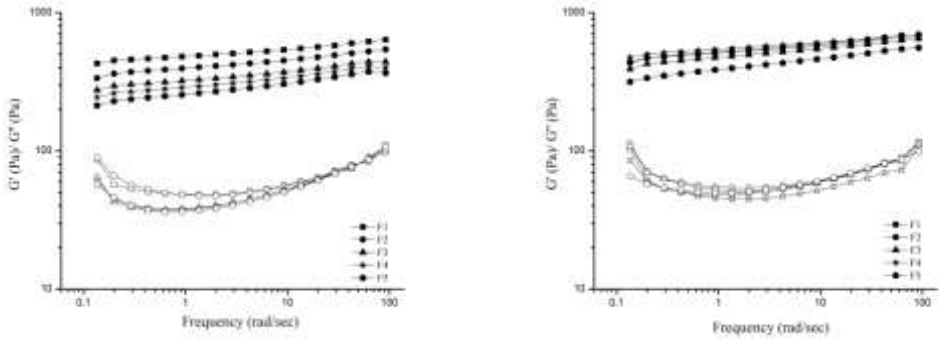
C - 30 D **



D - 60 D*



E - 60 D **



F - 90 D * **G - 90 D** **

Figure 5: Frequency sweep of the emulgels. Analysis of different temperatures: 25 °C * -5 ºC ± 2 ºC; ** 45 ºC ± 2 ºC; T0 = time zero; D = days
Emulgels tested at time zero were not subjected to heating and cooling.

4. Conclusion

This study is innovative because emulgels prepared using different proportions of gels and emulsions are not described in the literature. Furthermore, this research is aimed at the treatment of chronic wounds, and all of the requirements necessary for this type of preparation were evaluated.
The measurements of zeta potential to evaluate electrostatic stability indicated that all of the formulations showed values lower than |40| mV, which is the limit established in the literature. The rheological results indicated that the emulgels met the objectives outlined for preparations intended for the treatment of injuries, because by maintaining elastic modulus values under the conditions of use, these emulgels remain in the applied area, not exceeding the limits of injury.
In an accelerated stability test, all of the formulations designed in this study were stable regarding the zeta potential and rheology (frequency sweep) parameters, as no significant differences were observed over 90 days. Therefore, it was possible to develop emulgels with desirable characteristics for the treatment of wounds, i.e., a suitable consistency to remain in the desired location and not exceed the limits of the lesion and for ease of application and removal.

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