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Evaluation of Physical Stability of Oleogels Containing Diclofenac Diethylamine

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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 a formulation containing Diclofenac Diethylamine (1.16 % w/w) in two oleogel bases of Colloidal Silicon Dioxide (7.0 % w/w) in Sesame oil (CSD-SO) and another one of Colloidal Silicon Dioxide (7.5 % w/w) in Light liquid paraffin (CSD–LP). The aim of this study is to access their physical stability using different methodologies. The gels were stored at different temperatures (20^0 to $50\ ^0$C) over a period of six months. Appearance and textural properties were assessed on each month. An accelerated test was also performed where the temperature changed between 4^0 and $40\ ^0$C every 24 h, during 7 days. Rheological tests were also carried out as they could provide useful elements to predict stability. The textural properties of both gels were influenced by temperature. The decrease of the textural parameters, observed after storage at $40\ ^0$C and in the cycling test, were more significant in case of CSD-LP gels. The heating/cooling cycle test provided useful information in a short period of time. The gels were quite stable at $20\ ^0$C, being the CSD-SO gel the most stable.

Keywords: Physical Stability, Oleogels, Diclofenac diethylamine.

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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 [1]. Some workers reviewed the different classes of organogelators [2]. Some pharmaceutical excipients were also identified as organogelators, namely Sorbian esters [3] and gelators with the cholesterol moiety [4]. 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 [5]. The majority of the applications reported in the pharmaceutical area were related to transdermal systems [6], topical bases [7] and preparations intended for percutaneous absorption [8,9]. In previous studies, transdermal formulations containing herbal extracts were developed and optimized in oleogel bases containing vegetable oils (Sesame oil and Arachis oil) and liquid paraffin [10]. Based on the criteria of efficacy, stability, homogeneity and gelling ability at concentrations below 10% w/w, the oleogels of Colloidal Silicon Dioxide (7.0 % w/w) and Sesame oil (CSD-SO) and another one of Colloidal Silicon Dioxide (7.5 % w/w) and liquid paraffin (CSD–LP) were selected as candidates for topical formulations. Colloidal Silicon Dioxide was able to gel sesame oil and liquid paraffin at concentrations as low as 5.5 % w/w. 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, 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. Temperature has an important effect on viscosity. 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 [11]

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 [12]. 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.

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Textural analysis is widely used for the mechanical characterization of food products. It has also been used in the pharmaceutical and cosmetic areas [13]. 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 [14].

MATERIALS AND METHODS

Materials

The laboratory grade Sesame oil, liquid paraffin, Butylated hydroxyl toluene (BHT) and colloidal Silicon Dioxide were procured from CDH laboratories, Mumbai, India.. Diclofenac diethylamine was supplied by Innova Captab Ltd., Baddi, India as a gift sample. Double distilled water from an electrically heated still, having the pH 6.8 determined by the pH meter and stored in a well leached amber glass bottle, was used throughout the experiment.

Formulation of Oleogels

The oleogels were totally oil-based, and colloidal silica was used as a gelling agent. DDA and Butylated Hydroxy Toluene (BHT) were added to the oil with gentle warming to get a clear solution. The viscosity of the formulation was increased to the desired level by adding colloidal silica with continuous stirring (50 rpm) under vacuum to avoid air entrapment. The formulae for oleogels were optimized as shown in Table 1.

Table 1: Composition of CSD-SO and CSD-LP oleogels

Sl. NO.	Ingredients	Composition (%w/w)	
		CSD-SO oleogel	CSD-LP oleogel
1.	Diclofenac diethylamine	1.16	1.16
2.	BHT	0.15	0.15
3.	Colloidal Silicon Dioxide	7.00	7.50
4.	Sesame Oil	q.s	--
5.	Light Liquid Paraffin	---	q.s

Rheological Analysis

The rheological analysis, after being prepared, both the gel samples were placed in a sample holder of Brookfield Viscometer (Brookfield Engineering Laboratories, Inc., USA) at 20^0C. Dynamic measurements were performed at 20 ^{0}C on a controlled stress using spindle no.7 of the Brookfield Viscometer. For the evaluation of the influence of the temperature upon viscosity, the gel samples were stored in stability chamber (Elite Scientific Corporation, Ambala Cantt, India) at 20 ^{0}C, 30 ^{0}C, 40^0C and at 50 ^{0}C for six months duration and viscosity measurements were performed periodically.

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Textural Analysis

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 (13mm diameter), a penetration depth of 15 mm and velocities of 3 mm/s. After penetrating the sample, the probe returned to a position 30mm above the platform surface. From the graphic force versus distance obtained, the maximum force and negative force were noted. These parameters were correlated with firmness and adhesiveness, respectively. All the measurements were performed in triplicate.

For the evaluation of the influence of temperature upon firmness and adhesiveness, oleogel preparation were placed in Stability chamber at 20 ^{0}C, 30 ^{0}C 40 ^{0}C and at 50 ^{0}C. Appearance and textural properties were evaluated initially and every month up to six months. Before performing the textural measurements all samples were stored at 20 ^{0}C for 24 h.

In the heating/cooling cycle test the oleogels were stored in a Stability Chamber and temperature was changed between 4^{0}C and 40 ^{0}C every 24 h, during 7 days.

Incompatibility studies

To study incompatibility of drug with excipients at normal storage conditions, the oleogels were stored at 35 ^{0}C and humidity of 75 % RH for six months which were further subjected to IR spectroscopy using FTIR (FTIR BX-II, Perkin Elmen, USA).

RESULTS AND DISCUSSION

The rheological behavior could be predicted from flow curves of gels as shown in Figure 1, both the gels shows pseudoplastic flow, viscosity of gels decreased with an increase in shear rate. The gels showed 'shear thinning' property (when shear rate is brought back to low values gels regain their viscosities).

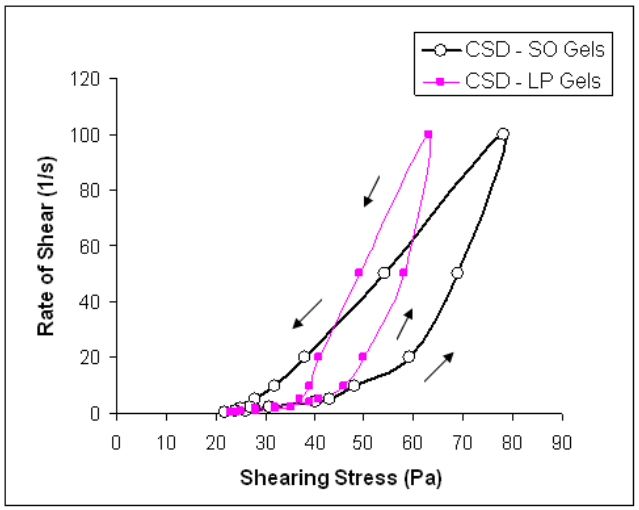

Figure 1: Flow curves of CSD-SO and CSD-LP oleogel at 20^{0}C.

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The effect of temperature upon viscosity is shown in Figure 2, gels showed about 25% decrease in viscosities after storage at 50^{0}C for six months.

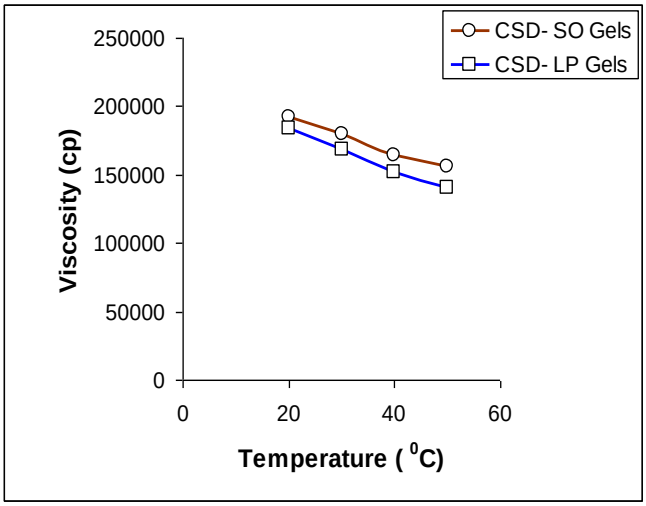

Figure 2: Influence of temperature upon the viscosity of oleogels after six months storage.

The texturogram of oleogels shows that CSD-LP gels exhibits higher firmness (correlated with the maximum force) and adhesiveness (correlated with negative force) as compared to CSD- SO gels [14]. The texturogram is shown in Figure 3.

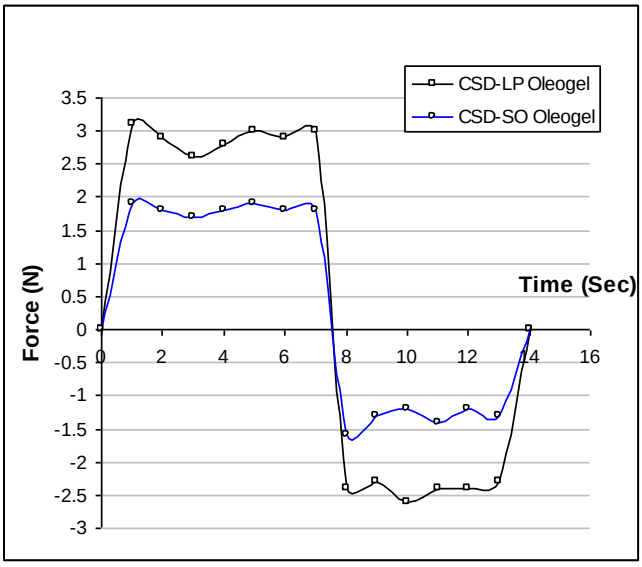

Figure 3: Texturograms of CSD- SO and CSD–LP oleogels.

The effect of temperature on firmness and adhesiveness of both the gels is shown in Table 2 and 3, it is observed that at lower temperature (20^{0}C and 30^{0}C) oleogels are texturally stable during the six months storage. Whereas at higher temperatures these gels slightly loose their textural properties.

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Table 2: Influence of storage time and temperature on the firmness of CSD- SO and CSD-LP oleogels.

Time	CSD- SO Oleogel Firmness (N)				CSD- LP Oleogels Firmness (N)			
(Months)	20 ^{0}C	30 ^{0}C	40 ^{0}C	50 ^{0}C	20 ^{0}C	30 ^{0}C	40 ^{0}C	50 ^{0}C
0	3.8 ± 0.16	3.8 ± 0.04	3.8 ± 0.21	3.8 ± 0.07	3.1 ± 0.12	3.1 ± 0.11	3.1 ± 0.07	3.1 ± 0.12
1	3.9 ± 0.09	3.1 ± 0.14	2.5 ± 0.14	2.1 ± 0.17	3.2 ± 0.15	3.1 ± 0.06	2.8 ± 0.08	2.4 ± 0.08
2	4.2 ± 0.12	2.9 ± 0.13	2.4 ± 0.06	1.8 ± 0.21	3.1 ± 0.13	3.0 ± 0.13	2.4 ± 0.16	2.2 ± 0.12
3	4.3 ± 0.18	3.1 ± 0.08	2.4 ± 0.08	1.7 ± 0.14	3.3 ± 0.09	3.1 ± 0.12	2.3 ± 0.13	1.9 ± 0.12
4	4.3 ± 0.08	3.1 ± 0.14	2.5 ± 0.18	1.8 ± 0.09	3.2 ± 0.17	3.1 ± 0.06	2.3 ± 0.11	1.8 ± 0.05
5	4.4 ± 0.11	2.9 ± 0.13	2.3 ± 0.12	1.7 ± 0.19	3.1 ± 0.07	2.9 ± 0.10	2.1 ± 0.18	1.6 ± 0.08
6	4.5 ± 0.15	3.0 ± 0.09	2.5 ± 0.14	1.7 ± 0.11	3.2 ± 0.08	2.8 ± 0.14	2.0 ± 0.17	1.4 ± 0.14

± SD, n = 3

Table 3: Influence of storage time and temperature on the adhesiveness of CSD- SO and CSD-LP oleogels.

Time	CSD- SO Oleogels Adhesiveness (N)				CSD- LP Oleogels Adhesiveness (N)			
(Months)	20 ^{0}C	30 ^{0}C	40 ^{0}C	50 ^{0}C	20 ^{0}C	30 ^{0}C	40 ^{0}C	50 ^{0}C
0	6.7 ± 0.15	6.7 ± 0.25	6.7 ± 0.13	6.7 ± 0.27	5.2 ± 0.12	5.2 ± 0.20	5.2 ± 0.21	5.2 ± 0.18
1	6.5 ± 0.21	6.5 ± 0.17	6.3 ± 0.15	6.0 ± 0.19	5.1 ± 0.14	5.0 ± 0.27	4.9 ± 0.20	4.2 ± 0.29
2	6.5 ± 0.24	6.3 ± 0.15	5.9 ± 0.22	5.7 ± 0.16	5.2 ± 0.24	5.0 ± 0.19	4.8 ± 0.16	4.1 ± 0.13
3	6.6 ± 0.18	6.4 ± 0.16	5.9 ± 0.14	5.5 ± 0.12	5.1 ± 0.14	4.9 ± 0.15	4.7 ± 0.18	3.9 ± 0.14
4	6.7 ± 0.11	6.3 ± 0.13	5.8 ± 0.15	5.4 ± 0.11	5.0 ± 0.12	4.9 ± 0.13	4.7 ± 0.14	3.4 ± 0.16
5	6.6 ± 0.20	6.2 ± 0.27	5.7 ± 0.18	5.2 ± 0.17	5.1 ± 0.13	4.9 ± 0.17	4.6 ± 0.17	3.3 ± 0.18
6	6.8 ± 0.17	6.2 ± 0.23	5.8 ± 0.18	5.1 ± 0.18	5.2 ± 0.23	5.0 ± 0.11	4.5 ± 0.25	3.1 ± 0.12

± SD, n = 3

The heating and cooling cycling test in a short period of time demonstrated the dependence of the textural properties of gels on thermal stress. The CSD-SO gels were found to be more stable as compared to CSD-LP gels for firmness and adhesiveness during heating/ cooling cycle test.

The IR spectrums of pure Diclofenac diethylamine, CSD-SO gel and CSD-LP gel are represented in Figure 4.

The spectrums of Diclofenac diethylamine exhibited distinctive peaks at 3381.57 cm^{-1} due to NH stretching of the secondary amine, at 1572.66 cm^{-1} owing to C = O stretching of the carboxyl ion and at 745.35 cm^{-1} due to C-Cl stretching. The spectrum of CSD-SO gel displayed characteristic peaks at 2981.41 due to CH aliphatic stretching and at 1724.05 due to C = O stretching. In the spectrum of the CSD-LP gel, the peak due to the drug carboxyl group was shifted to 1577.49 cm^{-1} whereas the signals resulting from the carboxyl group appeared at 1734.66 cm^{-1}. The above results of IR spectrums rules out any possibility of chemical interaction between the drug and excipients in the gel base.

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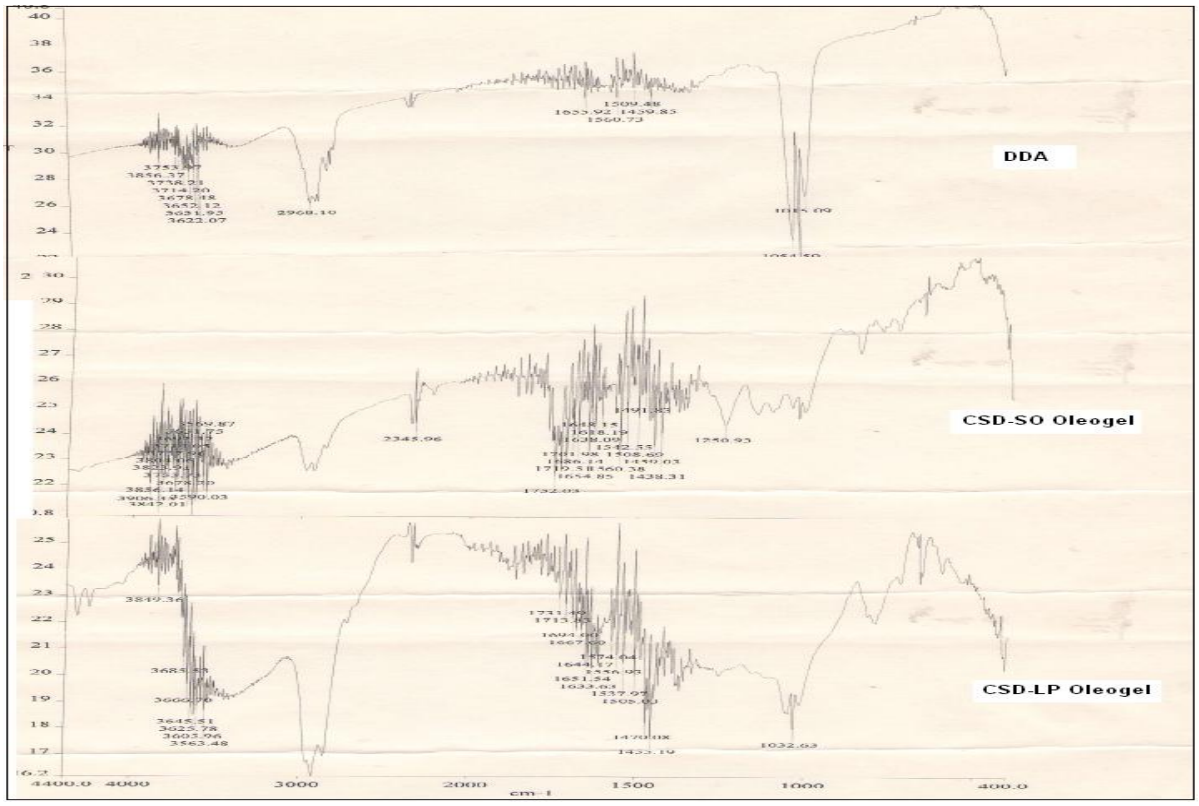

Figure 4: FTIR spectrum for pure Diclofenac Diethylamine, CSD-SO Oleogel and CSD-LP Oleogel after six months storage at 40^{0}C and humidity of 75% RH.

CONCLUSION

Oleogels are systems with interest as topical formulations. The stability tests performed foresee these systems to be rather stable at lower temperature. The textural parameters of the CSD-LP gel were temperature dependent whereas insignificant changes were detected for the CSD-SO oleogel at higher temperatures. The physical stability of CSD-SO gels was better as compared to CSD-LP gels. These oleogel bases can be utilized to formulate many topical formulations for local application. In the present study the drug Diclofenac diethylamine is formulated in oleogel bases and attempts were made to evaluate the physical stability of this formulation with positive outcome.

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