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Lanolin-Based Organogels as a Matrix for Topical Drug Delivery

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ABSTRACT: The current study deals with the development of lanolin-based emulsion gels by hot emulsification method. Bright-field, phase contrast, and fluorescent micrographs of the gels have shown the uniform distribution of circular water droplets in the formulations. Coalescence of water droplets was observed in gels containing higher proportion of water. Fourier transform infrared spectrophotometric studies indicated absence of Ln-drug chemical interactions. X-ray diffraction studies suggested an increase in amorphousness of the gels with the incorporation of water into the gel structure. The salicylic acid (SA), model drug, release from the gels was found to follow Higuchi kinetics. Krossmeyer–Peppas model fitting indicated non-Fickian release of the drug. As the water content of the gels increased, there was a corresponding increase in the rate of release of the drug. The gels showed non-Newtonian and thixotropic flow behavior. The gel to sol transition and melting temperatures of the gels were identified by differential scanning calorimetric (DSC) thermal analysis and falling ball method. DSC thermograms indicated an increase in thermal stability with the increase of water content in the gels. The gels showed sufficient spreadability and biocompatibility characteristics to be used as topical formulations. SA loaded gels showed good antimicrobial efficacy against *Bacillus subtilis*, a Gram-positive bacterium. Based on the preliminary studies, the developed gels may be regarded as carriers in topical drug delivery. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 128: 3831–3839, 2013

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INTRODUCTION

Lanolin (Ln) is an animal wax, devoid of glycerides, which is secreted from the sebaceous glands of sheep and other animals.[1] Ln coats the hair present on the body of the animals. Ln mainly consists of mono-, di-, and poly-hydroxyesters of sterols (e.g. cholesterol, dihydrocholesteol), trimethyl sterols (lanosterol and dihydrolanosterol), triterpene alcohols, aliphatic alcohols (C_{14}–C_{37}), and free hydrocarbons.[2] The biocompatibility of Ln has been attributed to its similar chemical nature as that of human sebum.[3] The significant difference between the refined Ln and human sebum is that the former is completely devoid of triglycerides and free fatty acids.[3] The increase in permeability of the bioactive agents through skin in the presence of Ln has also been related to the similar chemical properties of Ln as that of human sebum. It has found extensive applications in the formulation of moisturizers,[4] cosmetics,[5] sunscreen lotions,[5] shaving creams,[5,6] and emollient products due to its ability to incorporate large amount of water into its structure. Various pharmaceutical products meant for the topical, transdermal, subcutaneous and ophthalmic deliveries of drugs have employed Ln due to its inherent biocompatibility and water-holding capacity. The myth that Ln causes allergy in humans and animals due to sensitization of the immunological system is far from truth with no concrete scientific evidences available till date as reported by Kligman.[7] More specifically, Ln allergy amongst the general population of three European countries was calculated to be not more than 9.7 per 10^6, which is considerably very less.[8] Another study illustrated that Ln sensitization was at low even in a high-risk population suffering from deramatitis.[9] The chances of sensitization when Ln is applied, have been attributed to the presence of impurities (e.g., water soluble oxidants such as peroxides) in the Ln.[10,11]

The water-holding capacity of Ln helps formulating emulsion-based formulations having improved stability.[12] Also, Ln has been found to have good antimicrobial properties similar to vernix caseosa (VC) of new born babies.[13] Research was being carried out to develop VC substitute or synthetic VC equivalent using Ln.[13–15] Chemical composition of Ln shows 33 different hydroxy and polyhydroxy esters of alcohols (sterols) and 36 free fatty acids which can act as organogelators to form organogels

Additional Supporting Information may be found in the online version of this article.

Table I. Composition and Stability of the Formulations

	Weight (g)			
Formulation	Ln	Water	SMO	SA
L1	10	5	1	0
LD1	10	5	1	0.2
L2	10	10	1	0
LD2	10	10	1	0.2
L3	10	20	1	0
LD3	10	20	1	0.2

when polar phase was added.[16,17] In recent past, it was shown that nanoemulsions derived from the Ln carries potential drug delivery properties.[18] Taking inspiration from the above, it seems quite feasible to develop Ln-based semi-solid topical and transdermal emulsion gels. Within this framework, the objective of the current study deals with the development of novel Ln-based organogels and characterizing them to check their suitability to be used as matrices for drug delivery.

MATERIALS AND METHODS

Materials

Anhydrous Ln was procured from Loba Chemie, Mumbai, India. Span 80 (sorbitan monooleate, SMO), rhodamine B, nutrient agar, and dialysis tubing (MW cut-off 60 kDa) were purchased from Himedia, Mumbai, India. Salicylic acid (SA) was purchased from the Sara fine chemicals, Vadodhara, India. Pure microbial culture of *Bacillus subtilis* (NCIM 2699) was obtained from NCIM, Pune, India. Double distilled water was used throughout the study.

Preparation of Emulsion Gels

Ten grams of Ln were liquefied at 55°C. 0.1 g of SMO (1% wt/wt) was added to the liquefied Ln (LL) and was homogenized at 1500 rpm using an over-head stirrer (RQ-126/D, Remi Motors, India). This was followed by the drop-wise addition of double distilled water to the above mixture with continuous homogenization. The homogenization was continued till 45 min after the addition of water. The amount of double distilled water was varied so as to obtain semi-solid formulations having various proportions of Ln and water.

SA was used as the model drug. Drug containing formulations were prepared by dispersing 2% (wt/wt) of SA in the LL. The rest of the procedure was same. The composition of the formulations has been shown in Table I.

Microscopic Studies

The microstructure of the gels was studied using upright bright-field microscope (Leica DM750 equipped with ICC50 HD camera), inverted phase contrast microscope (PCM) (Olympus INVI-TR attached with SONY digital camera EPL-1), and fluorescence microscope (FM) (Carl-zeiss-HBO 50) with ProgRes capture 2.8 software. 0.5% (wt/wt) rhodamine dye solution in water was used as aqueous phase for the preparation of samples which were analyzed under FM.

FTIR Spectrophotometric Studies

Fourier transform infrared (FTIR) spectrophotometric studies of the raw materials and the formulations were carried out in attenuated total reflectance (ATR) mode using an FTIR spectrophotometer (Alpha-E Bruker, Germany) so as to understand the chemical interactions amongst the formulation components.

XRD Studies

The raw materials and the formulations were subjected to X-ray diffraction (XRD) analysis (PHILIPS, PW 1830HT diffractometer, PANanalytical B.V., Almelo, the Netherlands) to study the change in the crystallinity of the formulations as the composition of the formulations was varied. The XRD analysis was done using a Cu-anode X-ray tube in the angular range of 10°–50° 2θ. The results were analyzed using Xpert high score (version 1.0 b, Philips analytical B.V.). The % crystallinity of the samples was determined as per the equation given below[19]:

$$\% \text{ Crystallinity} = \frac{\text{Peak Area}}{\text{Background Area}} \quad (1)$$

Thermal Analysis

Gel-to-sol transition temperature (T_{gs}) of the formulations was determined using falling ball method as described in the literature.[20] In short, a SS ball (diameter 1/8 inch and weight 130 mg) was put over the 2 g formulation, kept in a 10-mL test-tube at 25°C. The formulations were heated at a rate of 1 °C/min. The temperature at which the SS ball completely submerged into the formulation was noted as T_{gs} of the formulation. The temperature at which the formulations started flow freely was recorded as melting point (T_m) of the formulation.

The thermal property of the formulations was further verified using differential scanning calorimetry (DSC-200 F3 MAIA, Netzsch, Germany). Ln (starting raw material), L3, and LD3 formulations were taken as representative samples. The samples were sealed in aluminum (Al) crucibles with pierced Al lid. An empty Al pan with lid was used as the reference. The samples were analyzed in the range of 20–150°C at a heating rate of 1 °C/min.

Accelerated Thermal Stability Studies

Accelerated thermal stability analyses of the formulations and Ln were carried out by thermo-cycling method. In the study, freshly prepared formulations were alternatively incubated at 50°C and −20°C for a period of 15 min at each temperature. The test was done for five cycles. The formulations were regarded as stable, if there was no visible separation of the formulation components.[21,22]

Rheological Studies

Rheological behavior of the prepared formulations and Ln were analyzed using a rotational cone (angle = 5.4°; diameter = 30 mm) and plate viscometer (BOHLIN VISCO-88, Malvern, UK). A gap of 0.15 mm was maintained between the cone and the plate throughout the study. Viscosity of all the formulations was measured under variable shear rates ranging from 13 s^{-1} to 95 s^{-1} in 12 min, at room-temperature (25°C, RT).[23–25]

Spreadability Studies

The spreadability of the Ln and the formulations was figured out as per the reported method.[26] In short, 0.2 g of the samples was put in between two glass slides, having equal weight and area. Thereafter, a known weight of 20 g, 50 g, or 100 g was put over

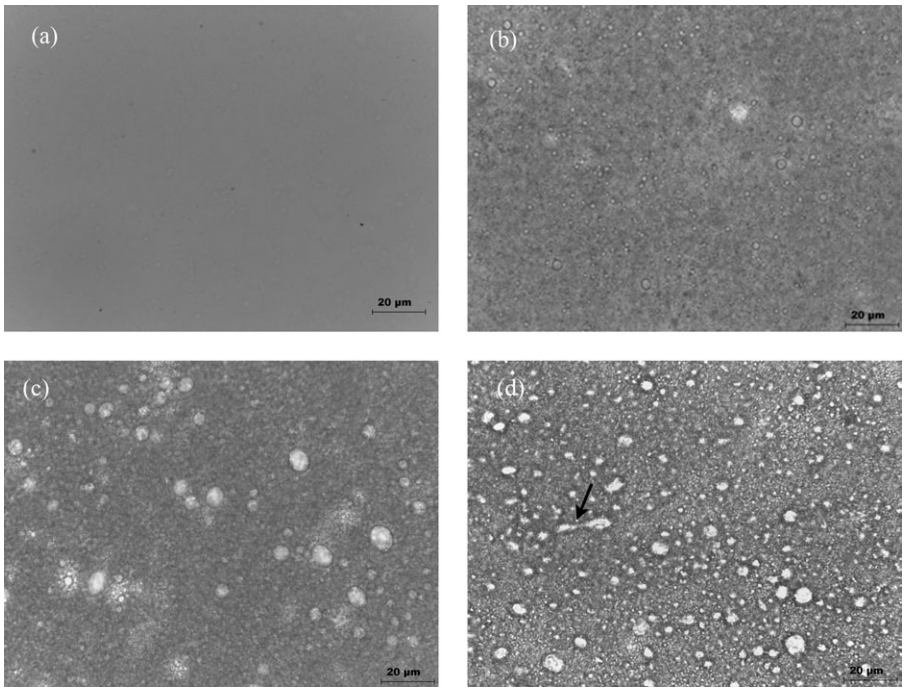

Figure 1. Bright-field microscopic images of (a) Ln, (b) L1, (c) L2, and (d) L3 gels.

the upper slide for a period of 30 s. The initial spreading diameter before the weight load and final spreading diameter after putting the weights was measured. The spreadability of the formulations was reported as % spreadability as per eq. (2):

$$\% \text{ Spreadibility} = \frac{D_2}{D_1} \times 100 \tag{2}$$

where,

D_2 = Final diameter
D_1 = Initial diameter

Antimicrobial Studies

The antimicrobial efficiency of the SA-loaded formulations was studied against *B. subtilis* (Gram positive bacteria) by bore-well method.[21] About 0.2 g of the formulations was put into the 5-mm well in a nutrient agar plate inoculated with 20 μL of microbes suspension (10^5 CFU/mL). The culture plates were incubated at (37 ± 0.5)°C for a period of 12 h. At the end of the study, zone of inhibition of the microbial growth was measured.[21]

In Vitro Drug Delivery Studies

The *in vitro* drug delivery studies were carried out using a modified Franz diffusion cell consisting of donor and receptor chambers separated by a dialysis membrane.[27,28] The receptor contained 50 mL of phosphate buffer saline, whose temperature was maintained at (37.0 ± 1.0)°C and kept on stirring at 100 rpm. The receptor fluid was replaced with fresh phosphate buffer saline at a regular interval of 15 min for the first hour and subsequently after 30 min for 17 h. The samples were analyzed by UV–visible double beam spectrophotometer (UV-3200, Labindia) at 294 nm.[29] The drug release kinetics from the gels was also evaluated using different models, viz. zero-order, Higuchi, and Krossmeyer–Peppas (KP) models.

Hemocompatibilty Studies

The hemocompatibility of the formulations was analyzed by studying the % hemolysis of the goat RBCs in the presence of the formulations, carried out as per the ASTM standard described elsewhere.[30] The percentage (%) hemolysis was calculated using eq. (3)[30]:

$$\% \text{ Hemolysis} = \frac{\text{OD}_{\text{test}} - \text{OD}_{\text{negative}}}{\text{OD}_{\text{positive}} - \text{OD}_{\text{negative}}} \times 100 \tag{3}$$

RESULTS AND DISCUSSION

Preparation of the Emulsion Gels

Water was added drop-wise to the LL with continuous homogenization, which resulted in the formation of white colored emulsion. The emulsion, so obtained, turned into pale yellow colored gels upon cooling to RT. Stable semi-solid emulsion gels were formed when the Ln : water proportions were 1 : 0.5, 1 : 1, and 1 : 2 (wt/wt) (Supporting Information Figure S1). The formulations were stable for 12 + months when stored at RT and 5°C. The samples were regarded as L1, L2, and L3, respectively. The SA loaded samples were regarded as LD1, LD2, and LD3, respectively. Since the aqueous layer formed the internal phase and Ln formed a continuous phase, the developed gels may be regarded as organogels. As the proportion of water was increased further, the formulations were found to leach water. This may be attributed to the water holding capacity of the Ln, which can absorb water only twice its original weight.[12] The prepared formulations were stored at RT for further analysis.

Microscopic Studies

The microstructural organization of the emulsion-based formulations for pharmaceutical applications may reveal important information about the stability of the formulation over a period of time. Figure 1 shows the bright-field light microscopic images of

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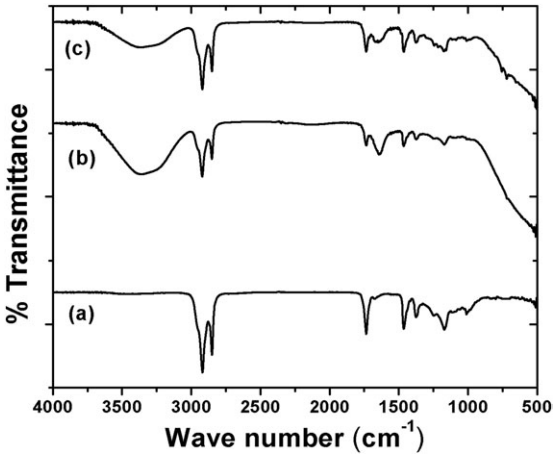

Figure 2. FTIR spectra of (a) Ln, (b) L3, and (c) LD3 gels.

the Ln and the formulations. The micrographs of the Ln did not show any visible microstructure indicating that the composition of Ln was homogenous. As water was incorporated within the Ln structure, the micrographs showed a uniform distribution of circular water droplets within the continuous phase of Ln. The size of water droplets increased with the increase in the proportion of water in the gels. Similar variation in sizes and distribution of water droplets was observed by PCM and FM techniques (Supporting Information Figures S2 and S3). The aqueous phase (containing rhodamine) appeared as red colored droplets in the Ln continuum phase when analyzed under FM. The micrographs obtained by FM technique showed the tendency of the water droplets to undergo coalescence as the proportion of the water was increased in the gels. The possible coalescence phenomenon was shown in figure 1d. The coalesced water droplets try to separate out from the continuum phase, if the water proportion increases further.[31] This phenomenon may be attributed to the phase separation of the aqueous phase and the Ln as the Ln : water ratio was increased above 1 : 2 (wt/wt).

FTIR Studies

The chemical interactions amongst the emulsion gels were studied using ATR-FTIR spectrophotometer (Figure 2). Ln, L3, and LD3 were taken as the representative formulations. Since the sample analysis was performed in the ATR mode, there was no need for sample preparation. The peaks obtained for the Ln sample were in exact match with the Ln FTIR literature data.[15] All the characteristic peaks of Ln were conserved in the L3 and LD3 samples. This suggested that there were no significant chemical alterations in the Ln molecular structure, although the other gel components were added. The shallow peak at 3361 cm^{-1} may be associated with the —OH stretching of the alcohol hydroxyl groups present in Ln. With the incorporation of water into the emulsion gels, the peak at ~3361 cm^{-1} became more prominent in L3 and LD3 which may be attributed to the intermolecular hydrogen bonding amongst the alcohol groups of Ln and the water molecules.[32] The presence of additional peaks at 1600–1500 cm^{-1} (C=C bond of aromatic ring), 1666 and 1649 cm^{-1} (C=O stretching of carboxylic acid), and 756 and 719 cm^{-1} (C—H out of plane bending in the phenol substitution ring), suggested the presence of SA in LD3.[33]

XRD Studies

Figure 3 shows the XRD diffractograms of Ln and the emulsion gels. Broad humps in the diffractograms may be attributed to the presence of isotropic liquids present within the physical structure of the formulations.[34] XRD pattern did not show any sharp diffraction peaks suggesting that the gels are amorphous or ultrafine crystalline materials where the diffraction peaks

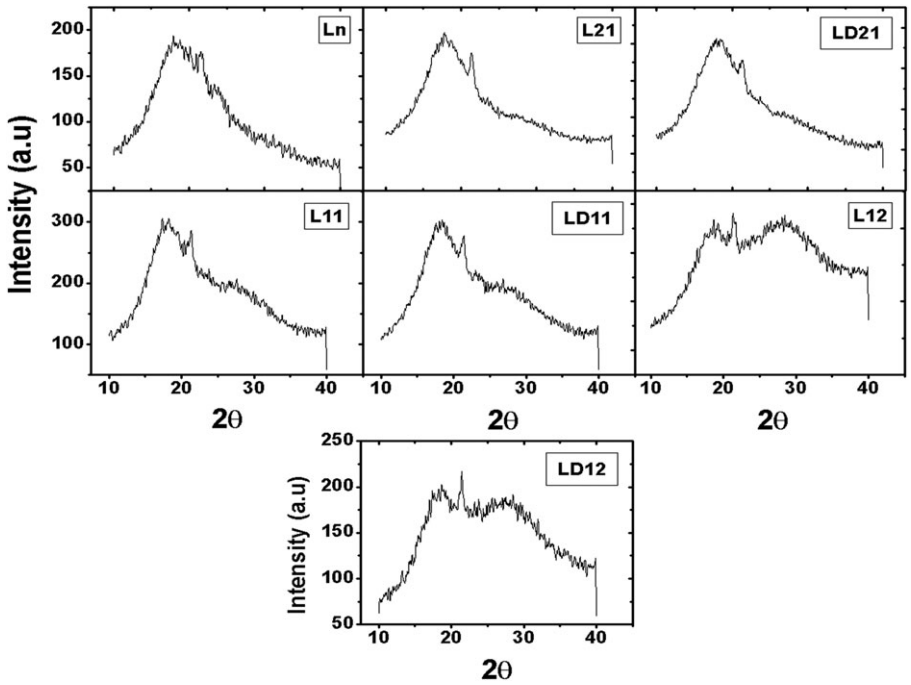

Figure 3. X-ray diffractograms of the Ln and formulations.

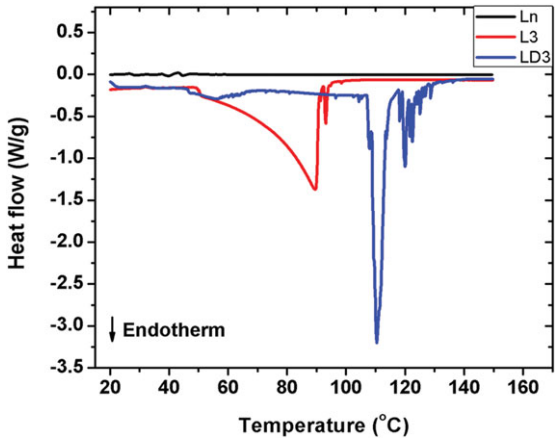

Figure 4. The DSC thermograms of the Ln and gels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

cannot be resolved.[35,36] The diffractogram analysis indicated that there was a decrease in % crystallinity of the emulsion gels as the water content in the emulsion gels increased and when SA was loaded into the emulsion gels (Supporting Information Table S1). The diffractograms of the emulsion gels showed a sharp peak at ~21.3° 2θ as compared to 21.67° 2θ in Ln. This slight shift of the peak position may be due to the change in the physical properties of the emulsion gels at the molecular level. In addition to this, the *d*-spacing of Ln (4.09 Å) was found to be lower as compared to the emulsion gels (~4.15 Å). The peak shift and increase in *d*-spacing in the diffractograms of the emulsion gels as against Ln were due to the incorporation of water.[37] The SA loaded emulsion gels did not show any characteristic peaks of SA. This indicated that SA was completely solubilized within the formulations.[38,39] In short, the change in the physical properties of the emulsion gels as the composition was varied may alter the SA release kinetics.[40–42]

Thermal Analysis

The T_{gs} (gel-to-sol transition temperature) and T_m (melting temperature) of the formulations varied in the range of 35–37°C and 47–50°C, respectively. There was no momentous variation in T_{gs} of the formulations, which may be attributed to the inherent property of Ln to undergo structural deformation at 36–42°C.[43] This signifies that the physical properties of Ln were the major factor in governing the thermal behavior of the emulsion gels. The results suggested that with the increase in the water proportion in the gel structure, there was an increase in the T_m. The increase in T_m may be correlated with the intermolecular hydrogen bonding amongst the Ln and water molecules.[44]

Differential Scanning Calorimetry

The differential scanning calorimetric thermogram of Ln showed a combination of exotherm and endotherm peaks as reported earlier.[15] The thermal profiles of the formulations were different from that of the Ln indicating that there has been a complete change in the physical properties of the Ln as water was incorporated into its structure (Figure 4, Supporting Information Table S2). Apart from the T_m and T_{gs}, the Ln thermogram had shown distinct exothermic and endothermic transitions at 25.7°C and 46.0°C. As Ln consists of many types of sterols, these peaks may be due to the non-polar lipid component and diol fractions of the Ln.[15] The obtained T_{gs} values of all the samples were found to be valid ($\Delta C_p > 0.05$ J/g K during glass transition). The T_m of formulations was higher than Ln indicating that the formulations were having higher thermal stability than the raw material.[17] The melting endotherm of the L3 gel coincided with the evaporation of water from L3. Due to this reason, a broad endotherm (peak at 89.6°C) was obtained. LD3 gel showed a distinct endothermic peak at ~108°C, which may be associated with the evaporation of water. The ΔH_m (change in enthalpy) and ΔS_m (change in entropy) values during the melting endotherm followed the same trend as that of T_m values. The ΔH_m and ΔS_m values indicate the cohesive energy for packing of the gel structure.[17] The higher ΔH_m of L3 and LD3 samples suggested the presence of higher gelator (Ln)–water interactions which may be associated to the intermolecular hydrogen bonding. The thermogram results were in accordance with the results obtained during the thermal analysis of the formulations using falling ball method.

The DSC results may also be correlated with the spreadability of the gels. As per the reported literature, higher T_m values are often associated with higher firmness or lower spreadability indices.[45]

Accelerated Thermal Stability Studies

The formulations L3, LD3, and L2 destabilized after two cycles of thermocycling, characterized by phase separation. The phase separation may be promoted due to the coalescence of the water droplets during the heating phase of the thermo-cycling. The chance of coalescence is usually more in samples containing higher proportion of water.[46] The formulations LD2, L1, and LD1 were found to be stable even after five cycles of the accelerated thermo-cycling test. The study indicated that though all the formulations were stable for 12 + months at RT, the formulations with higher proportions of water have the tendency to undergo destabilization on long-term storage.[47]

Rheological Studies

The rheological behaviors of the formulations have been shown in Figure 5. Ln showed an increase in the shear stress as the shear rate was increased. Ln showed a gradual decrease in the viscosity whereas the emulsion gels showed an exponential decrease in the viscosity as the shear rate was increased. Ln and the formulations showed higher apparent viscosities when the shear rate was increased from 13 s^{-1} to 95 s^{-1} as compared to when the shear rate was decreased from 95 s^{-1} to 13 s^{-1}. This resulted in the formation of hysteresis loop.[23,48] Decrease in the viscosity as the shear rate was increased and formation of hysteresis loop due to closed shear cycle indicate viscoelastic properties of the gels (shear thinning and thixotropy, respectively).[23,49] Though 100% structural recovery was not there, many of the junction points were recovered. The observed hysteresis loop suggested that the total structure recovery did not take place under the experimental conditions. Such profiles are very common in pharmaceutical formulations such as ointments, creams, and gels.[50,51] The non-Newtonian flow behavior of the gels were confirmed by analyzing the rheological data using power law or Ostwald–de Waelae relationship.[25]

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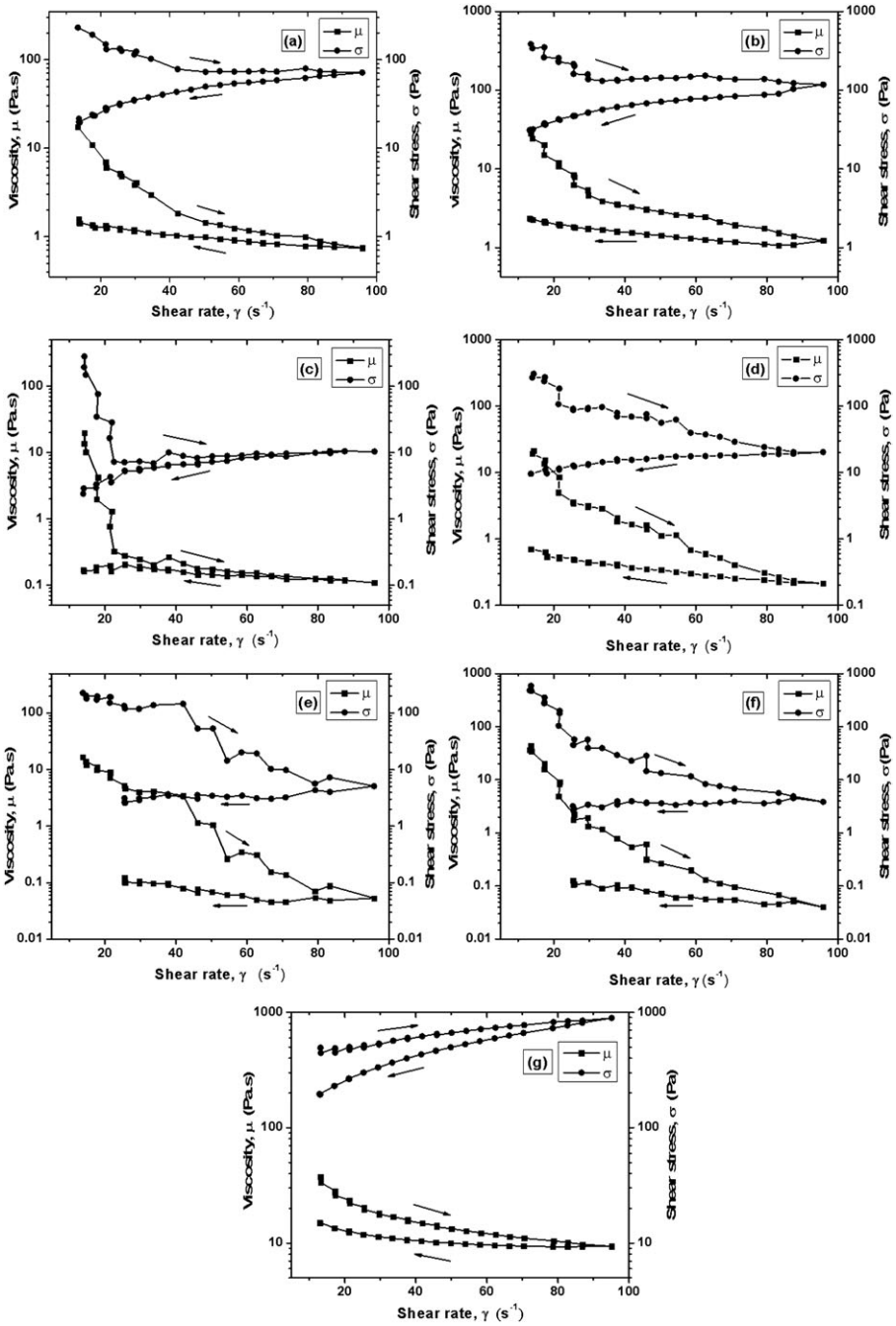

Figure 5. Plot of shear rate vs. viscosity and shear stress of (a) L1, (b) LD1, (c) L2, (d) LD2, (e)L3, (f) LD3, and (g) Ln.

$$\tau = K \cdot \gamma^n \quad (4)$$

where,

τ is the shear stress (Pa) at γ shear rate (s^{-1}),
K is the flow consistency index (Pa s), and
n is the flow behavior index.

The value of n governs the type of rheological behavior. If the value of n is <1, $= 1$, and > 1, then the flow behavior of the formulation may be regarded as pseudoplastic, Newtonian, and dilatant, respectively.[25] In the current study, the n value was determined by plotting the graph between log (shear stress) and log (shear rate) (Supporting Information Figure S4). All the n values were found to be less than 1, indicating the pseudoplastic nature of the gels.

The thixotropic behavior of the emulsion gels was evaluated by measuring the area enclosed within the hysteresis loop.[23,52] In general, the thixotropy of the emulsion gels (both blank and SA loaded) decreased non-linearly with the addition of water (Supporting Information Figure S5). The decrease in thixotropy with the increase in the water proportions in the formulations indicated that the gels would take more time to regain their initial viscosity once their internal structure was disturbed by applying

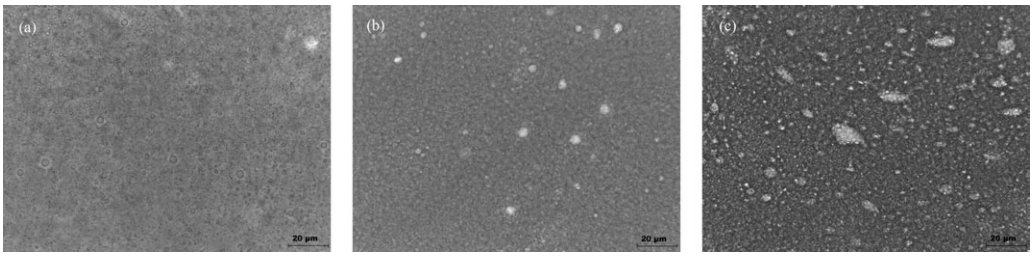

Figure 6. Bright-field microscopic images of (a) L1, (b) L2 and (c) L3 after subjecting to shear (conditions: shear cycle within the limits of 13–95 s^{-1}, in a time span of 12 min).

external shear stress. This kind of phenomenon has often been reported for topical gel formulations.[53]

The gels did not leach water even after subjecting to higher shear rates. The microscopic evaluation of the gels, subjected to shear stress (shearing conditions were maintained same as described earlier in section "Rheological Studies"), showed uniform distribution of water droplets within the gels (Figure 6) as was observed in the gels before the shearing (Figure 1). The size of the water droplets was measured using National Instruments (NI) vision assistant image analysis software. The average size of the particles before and after the shear was found to be 4.0 ± 2.2 μm and 6.0 ± 1.6 μm, respectively. The size of the water droplets did not change significantly, even after the shear stress was applied. The results suggested that the developed emulsion gels were highly stable in nature.

Gel Spreadability Studies

The extent of the spreading of the prepared formulations under different weights has been shown in Supporting Information Figure S6. The % spreadability of the formulations was calculated as the increase in the spreading diameter after loading to the initial diameter of the unloaded sample. The % spreadability of the formulations varied in the range of 30–40%, 50–63%, and 70–80% when a load of 20 g, 50 g, and 100 g, respectively, was applied. The results indicated that the spreadability of the emulsion gels were dependent on the load applied. With the increase in the load, there was an increase in the spreadability.

Also, spreadability of each sample was determined by plotting the spreading area as a function of square root of weight. The slope of the plot was taken as the response factor (Supporting Information Table S3).[54] The ratio between the area and square root of weight was determined by partial least-squares method (r^2 = 0.9). The spreadability results were in concordance with the qualitative prediction of spreadability as done by DSC analysis. The visual observation of the gels suggested that the gels were evenly spread, homogeneous, and maintained their gel integrity without any phase separation or no visible fragmentation. This indicated that the gels were having good mechanical strength under the observed range of conditions. Similar results were also observed during the rheological studies, where the gels did not lose their mechanical integrity even when high shear rates were applied.

Antimicrobial Studies

SA, being a phenolic acid, shows antibacterial activity against various microorganisms including *B. subtilis*.[55] The results of the study have been tabulated in Table II. The results indicated that the blank gels did not inhibit the growth of the bacteria. SA loaded formulations showed significant increase in the antimicrobial activity as the water content in the formulations was increased. The results suggested that the antimicrobial activity of the SA loaded gels were due to the presence of SA as the blank gels did not show any antimicrobial activity. Also, an increase in drug diffusion from the gels containing higher water content may be related to the increase in the amorphous nature of the gels, as evident from the XRD studies.

In Vitro Drug Delivery Studies

The drug release studies were conducted for 18 h in triplicates. The release profiles of SA from the formulations have been shown in Figure 7(a). The results indicated that there was 25%, 36%, 38%, and 41 % drug release from LD, LD1, LD2, and LD3 formulations, respectively, suggesting that as the water proportion was increased in the formulations the rate of release of SA was higher. This observed phenomenon of higher release rate in the formulations with higher proportions of water may be explained by the increased partition of SA into the aqueous phase of the formulations and subsequent quicker diffusion into the dissolution media. The results can be correlated with the results obtained from the XRD and antimicrobial studies. It was predicted that the increase in water content in the formulations will result in the increase in the amorphous nature of the gels and increased drug release rate.[42] This indicated that the release rate may be tailored by altering the composition of the gels.

To get an insight into the drug release mechanism, drug release kinetics from the gels was evaluated using different drug release kinetics models.[56–59] The "n" value in the KP model gives information on the mechanism of release of the drug from the delivery matrices.[56] If the n value is less than 0.45, Fickian diffusion might have occurred or else if it is between 0.45 and 0.85, non-Fickian diffusion might have happened.

Table II. Zone of Inhibition of the Formulations Against B. subtilis

Formulations	Zone of inhibition (mm)
LD1	9.0 ± 2.1
LD2	11.2 ± 1.5
LD3	13.5 ± 2.2
L1	-
L2	-
L3	-

The formulations indicated to follow Higuchi and KP drug release kinetics and have been shown in Figure 7(b, c), respectively. The data obtained from drug release profile was fit in the described models and the results have been tabulated in Supporting Information Table S4. The drug release kinetics suggested that the release of the drug from the formulations followed Higuchi model, indicating that the formulations were homogeneous–planar matrix type and did not lose their structural integrity during the course of the study.[57] The Fickian value (n) was calculated from the KP model and was found to be ~0.5 for all the formulations. This suggested that the release of SA from the gels showed non-Fickian release kinetics.

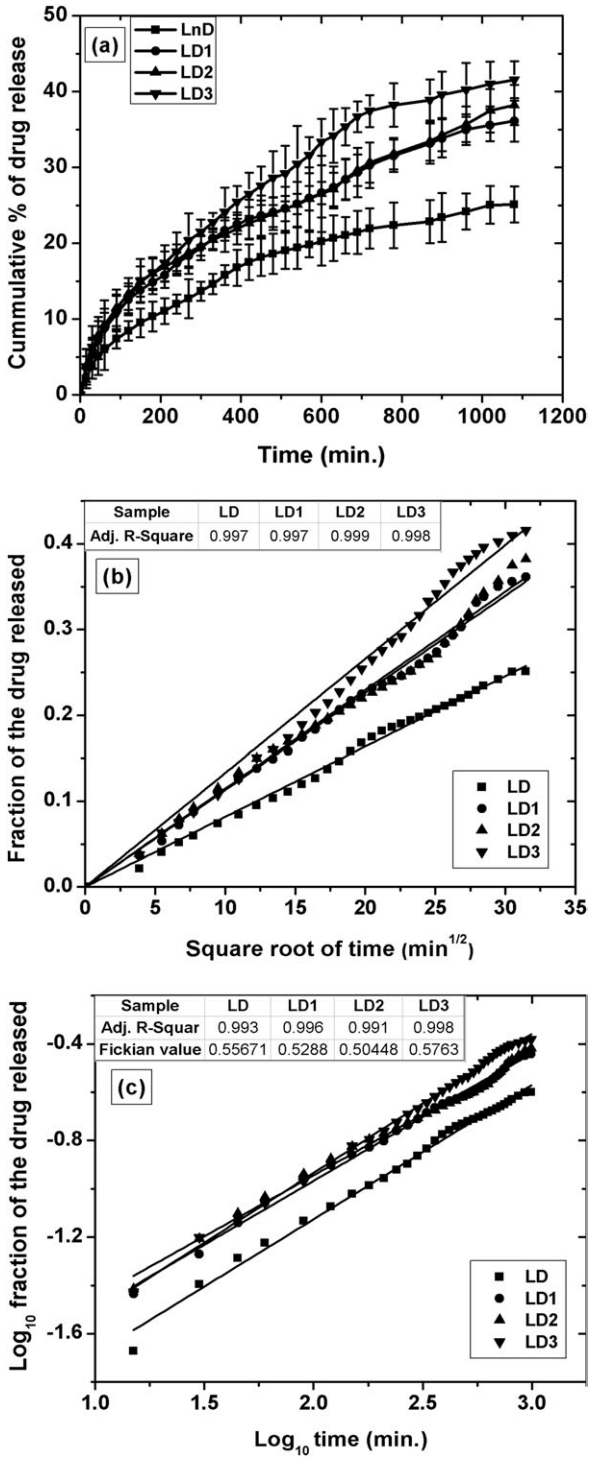

Figure 7. (a) CPDR of the formulations. Drug release kinetics showing (b) Higuchi model and (c) K-P model.

Table III. % Hemolysis of the Formulations

S. no.	Formulations	% hemolysis
1	Ln	0.928 ± 0.55
2	L21	0.809 ± 0.68
3	L11	1.206 ± 0.47
4	L12	0.803 ± 0.72

Hemocompatibility Studies

The % hemolysis of the formulations has been shown in Table III. The results showed that the % hemolysis of the blood was < 5% for Ln and the formulations. This indicated that the formulations were hemocompatible in nature and may be regarded as the biocompatible.

CONCLUSION

The present study dealt with the successful development of the Ln-based emulsion gels. There were no chemical interactions amongst SA and Ln molecules, indicating that the gel matrices were inert and may be used as carrier for various bioactive agents. The increase in amorphousness due to the addition of water has influenced the drug release pattern.[42] The developed formulations have shown increased thermal stability compared to the raw material, which suggested that the formulations may be stored for a long time. Apart from the flow behavior (thixotropic and shear thinning properties), the developed gels showed sufficient spreadability and hemocompatibility for pharmaceutical applications. This ensures a uniform application of the dosage form without any irritation to the skin during topical drug delivery. In addition, SA loaded gels showed good antimicrobial activity against *B. subtilis*. In short, the developed Ln-based gels may be tried as carrier matrices for topical drug delivery.

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