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Development of Olive Oil Based Organogels Using Sorbitan Monopalmitate and Sorbitan Monostearate: A Comparative Study

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ABSTRACT: The present work deals with preparation of the olive oil (OO) based organogels using sorbitan monostearate (SMS) and sorbitan monopalmitate (SMP) as organogelators for controlled drug delivery applications. Metronidazole (MZ) was used as the model drug. Gels were prepared by solubilizing the organogelators in OO at 60°C under stirring. As the solution was cooled down, the gelator molecules precipitate as an isotropic phase having networked structures, which immobilized OO. Formation of 3D networked structure was confirmed by light, phase contrast, and scanning electron microscopy. Accelerated thermal stability studies demonstrated the thermal stability and thermoreversibility of the organogels. DSC and gel disintegration studies suggested that the SMS based organogels were having higher thermal and physical strength as compared to the SMP based organogels. Viscometric analysis suggested the pseudoplastic flow behavior of the gels. The SMS organogels were more amorphous as compared to the SMP organogels of same composition. Drug release from the organogels followed Fickian diffusion kinetics. The drug loaded gels have shown good antimicrobial property against *Escherichia coli* and *Bacillus subtilis* and were found to be highly hemocompatible in nature. On the basis of the preliminary results, the developed organogels can be used as matrices for the topical drug delivery. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 129: 793–805, 2013

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INTRODUCTION

Gelators, considered as micro-heterogeneous solids, and organic liquid phases may form bi-continuous colloidal systems regarded as organogels.[1] Of late, the use of nonionic surfactants for immobilizing apolar phase has been gaining interest for applications in pharmaceutical, food, and cosmetic industries.[2] Sorbitan esters have been extensively used for the same due to their ready acceptability in pharmaceutical industries since long. The applications of sorbitan esters for the development of organogels have opened up a new field of study. Sorbitan esters have quite often been used as an alternative agent to phospholipids for the preparation of various formulations. This might be attributed to their low cost and stability over a wide range of temperature.[3] Sorbitan esters are generally classified based on the presence of fatty acid chains within their chemical structure. Presence of long saturated hydrocarbon chains within the sorbitan ester molecules result in the formation of solid esters [e.g., sorbitan monopalmitate (SMP) and sorbitan monostearate (SMS)] whereas, the short hydrocarbon chains results in the liquid esters (e.g., sorbitan monolaurate or span 20). SMP is an ester of palmitic acid and sorbitol whereas; SMS is an ester of stearic acid and sorbitol. Both SMP and SMS appear as yellowish-brown solid wax and are biodegradable in nature.[3] SMP and SMS have been found to be biocompatible, odorless, and form opaque, thermoreversible semi-solid oleogels with apolar liquids.[4] SMS and SMP based oleogels have potential applications as delivery vehicles for drugs and antigens.[5]

Olive oil (OO) is rich in monounsaturated fatty acids and antioxidant substances. This confers beneficial effects on the health of the consumers. Oleic acid is one of the major components of the OO. Oleic acid has been found to improve the permeation of the drugs through skin.[6] Because of the presence of oleic acid in OO, OO had been used in various transdermal formulations where there is a need for improving the drug permeation. The improvement in the skin permeation of the drug may be attributed to the alterations in the barrier properties of stratum corneum.[7] Apart from the above, OO exhibits a broad antimicrobial, antimycoplasmal, and antifungal activity which have been associated with the presence of unsaturated

aldehydes, phenolic glycoside, oleuropein, and several other phenol compounds.[8]

Taking inspiration from the above, development of OO based oleogels for transdermal applications may be justified. In the current study, attempts were made to develop SMP and SMS based OO organogels for probable transdermal applications.

MATERIALS AND METHODS

Materials

SMP and SMS were purchased from Loba chemie, Mumbai, India. Edible OO (Bertouli, New Brunswick, Canada) was purchased from the local market. Dialysis tubing (MW cut off: 12 kDa), nutrient agar were purchased from Himedia, Mumbai, India. Metronidazole (MZ) was received as a gift from the Aarti Drugs, Mumbai, India. Double distilled water (DDW) was used throughout the study.

Preparation of Organogels

Accurately weighed organogelators (SMP or SMS) was dissolved in a specified volume of OO, whose temperature was maintained at 70°C and kept on stirring at 500 rpm. The gelator molecules completely dissolved in the OO to form a clear homogenous solution. Subsequently, the solution was allowed to cool to room-temperature (RT). The formulations were considered to be gels, if they failed to flow upon inversion of the vials.[9] The critical gelator concentration of the SMP and SMS for immobilizing the OO was found out. The formed organogels were kept at RT for further analysis. Drug loaded organogels were prepared by dispersing 2% (w/w) MZ in OO.

Organoleptic Evaluation

Freshly prepared organogels were observed for their color, odor, taste, appearance, and texture.

Microscopic Studies

An upright bright-field compound microscope (LEICA-DM 750 equipped with ICC 50-HD camera, Germany) and inverted phase contrast microscope (Carl Zeiss-HBO 50, Germany) with ProgRes capture 2.8 software were used for analyzing the microstructure of the organogels.

The organogels were analyzed under scanning electron microscope (JEOL, JSM-6390, Japan). Xerogels were used for the analysis. The organogel smears were treated with a solvent mixture of acetone and hexane (7 : 3 v/v). The treated samples were dried for 24 h under vacuum so as to obtain xerogels.[10] The xerogels were subsequently sputter-coated with platinum before the analysis.

Fourier Transform Infrared (FTIR) Spectroscopy

Infrared spectroscopy of the samples were carried out by using FTIR instrument (Alpha-E by Bruker, Bellerica, MA, USA) operated in attenuated total reflectance (ATR) mode. The raw materials and the samples were scanned in the range of 3500 to 500 cm^{-1}.

XRD Analysis

The samples were subjected to XRD analysis using Philips, XRD-PW 1700, Rockville, MD. Cu-Kα was used as the X- ray source, which was operated at 35 kV and 30 mA. The organogels were scanned in the range of 5°–50° 2θ at a scanning rate of 2° 2θ/min.

Accelerated Thermal Stability Studies

The accelerated thermal stability test was done by thermo-cycling method.[10,11] In short, freshly prepared organogels were subjected to repeated freezing-thawing cycles. During the course of the study, the selected organogels were alternatively incubated at 65°C and −20°C for 15 min. The study was repeated for 5 cycles.

Thermal Analysis

Gel-to-sol transition temperature (T_{gs}) of organogels was determined by falling ball method as reported earlier.[12] Briefly, a stainless steel ball of diameter 1/8th of an inch and weight 130 mg was placed gently over the formulation in a 10 mL test tube. The test tube was placed in the melting-point determination apparatus (EI-931, Mumbai, India), which was being maintained at 25°C. Samples were then heated at the rate of 1°C/min and the temperature at which the ball started moving into the gel was noted as the T_{gs} of the gel.

Thermal properties of the gels were further examined by using a differential scanning calorimeter (DSC-200 F3, MAIA, Netzsch, Germany) over a temperature range of 25–70°C at a heating rate of 1°C/min under an inert N_2 gas atmosphere in aluminum crucibles with pierced aluminum lid.

Rheological Studies

The dynamic viscosity of the gels was examined using controlled stress rotational cone and plate viscometer (Bohlin visco 88, Malvern, UK). A gap of 0.15 mm was maintained between cone (angle 5.4°; diameter 30 mm) and plate throughout the study. During the analysis, the samples were subjected to cyclic shear rates in the range of 12 to 95 s^{-1} at RT.[13,14]

Spreadability Studies

Spreadability of the formulations was determined as per the reported method using an in-house built experimental setup.[15] In short, 0.5 g of the gel was placed between two glass slides of equal weight, area, and thickness. Thereafter, the sample was loaded with a known weight of 20, 50, or 100 g on the upper slide for 30 s. To calculate % spreadability of the gels, initial and final spreading diameters of the gels before and after the load were noted. The % spreadability was calculated as per the eq. (1).

$$\%\ \text{spreadability} = \frac{D_2 - D_1}{D_1} \times 100 \qquad (1)$$

where D_1 is the initial diameter of the organogels before the load and D_2 is the final diameter of the organogel after the load.

Gel Disintegration Study

Disintegration of SMP and SMS based organogels was conducted by using tablet-disintegration apparatus (Electronics India, model: 901, Mumbai, India). Gels (0.5 g) was placed in the basket of disintegration apparatus having 600 mL of DDW, maintained at 37°C. The time taken for the complete disintegration of the gel in the DDW was considered as the gel disintegration time.

pH Measurement

pH of the organogels was measured by using a digital ATC pH meter (EI instruments, model no-132E, Mumbai, India).

Bulk Resistance Measurement

Bulk resistance of the organogels was measured using an in-house built DC impedance analyzer whose specifications have been described in detail elsewhere.[10]

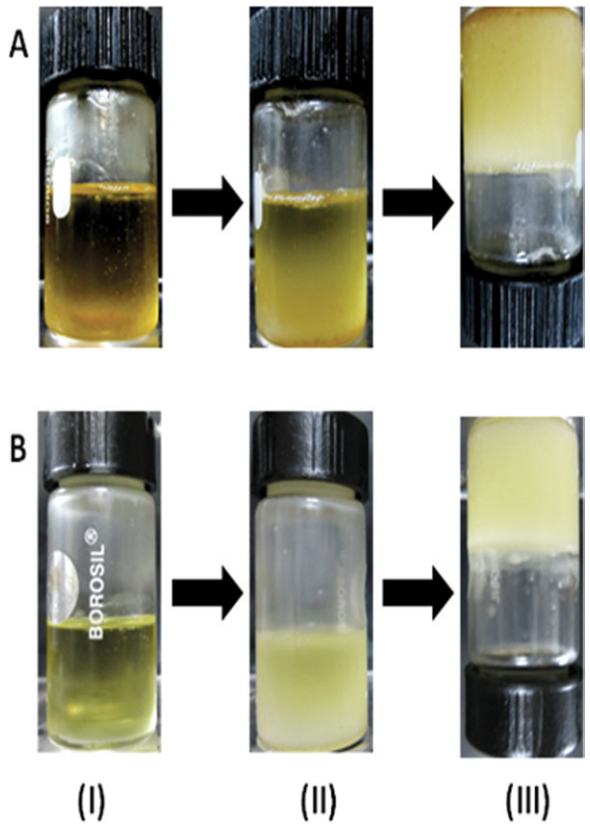

Figure 1. Gelation process of (A) SMP and (B) SMS organogels (I) clear solution after heating; (II) uniform, cloudy suspension upon cooling and standing; (III) opaque, semi-solid gel upon further cooling and inverting. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In Vitro Drug Delivery Studies

The *in vitro* drug delivery studies were performed using a modified Franz diffusion cell.[16,17] The set up consisted of a donor and receptor chamber separated by a dialysis membrane. Accurately weighed 1 g of organogel containing MZ drug was placed in the donor. The donor chamber was lowered into the receptor, containing 50 mL of DDW. The receptor solution was maintained at 37 ± 1.0°C and was kept on stirring at 100 rpm using a magnetic stirrer. Sink conditions were maintained in receptor by periodically changing the whole receptor volume with fresh DDW for every 15 min during first 1 h and subsequently, for every 30 min during next 12 h. Aliquot of 5 mL was withdrawn from the replaced fluid and analyzed by UV–visible spectrophotometer (UV-3200, Labindia, India) at a wavelength of 321 nm.[18]

Antimicrobial Studies

Antimicrobial efficacy of the gels was determined by bore-well method.[19] The samples were tested against *Escherichia coli* (gram negative bacteria) and *Bacillus subtilis* (gram positive bacteria). Thirty microliter of cell suspension containing 10^4–10^5 cfu/mL was spread on petri plates containing solid nutrient agar using a sterilized spreader. Wells of diameter 5 mm were bored in the plates using a borer followed by addition of 0.2 g of the gels into the bore. The plates were then incubated at 37°C for 24 h and zone of inhibition was measured.

Hemocompatibility Test

The biocompatibility of the developed formulations was analyzed by analyzing hemolysis of the goat blood in the presence of the sample leachate. The method has been described in detail elsewhere.[20] The % hemolysis was calculated as per the following formula:

$$\%\ \text{Hemolysis} = \frac{O.D_{Test} - O.D_{Negative}}{O.D_{Positive} - O.D_{Negative}} \times 100 \qquad (2)$$

RESULTS AND DISCUSSION

Preparation of Organogels

The dissolution of SMP and SMS in OO at 70°C resulted in the formation of a clear homogenous solution. As temperature was reduced, change in the solubility parameter of the SMP and SMS molecules resulted in the precipitation of the gelator molecules in the oil continuous phase.[21] The precipitation of gelator molecules made the solution cloudy. The precipitated gelator molecules formed self-assembled structures.[22] Depending on the concentration of the SMP and SMS in OO, the solution either remained cloudy or formed an opaque semisolid-like structure (Figure 1). The concentration of gelator at which the gelation was induced was regarded as the CGC of the organogelator.[23] The CGC of SMP and SMS was found to be 18% (w/w) and 19% (w/w), respectively. Below the CGC, the final product was a turbid solution and started flowing when the culture bottles were inverted (Figure 1). The samples were regarded as organogels, if the opaque semi-solid solution does not flow when the culture bottles were inverted (Figure 1).

SMP and SMS organogels formed below 20% (w/w) of gelator concentration became unstable within 1 month of time. The destabilization was due to the syneresis of the OO from the gelator networked structure.[24] Hence, further analyses of the gels were performed using gels having gelator concentration >20% (w/w). The gels having gelator concentration >20% (w/w) was found to be stable for more than 1 year. The composition of these organogels has been tabulated in Table I. The apparent viscosity of the turbid solution was found to be increasing as the concentration of SMP and SMS was increased.[25]

Organoleptic Evaluation

The organoleptic evaluation of the organogels has been summarized in Table II. SMP based organogels were found to be

Table I. Composition of the Organogels Used for Further Analysis

	Concentration (w/w)		
Sample	SMP	SMS	OO
SMP1	20	-	80
SMP2	23	-	77
SMP3	25	-	75
SMP4	27	-	73
SMS1	-	20	80
SMS2	-	23	77
SMS3	-	25	75
SMS4	-	27	73

Table II. Organoleptic Properties of Organogels

Properties	SMP-based organogels	SMS-based organogels
Texture	Smooth	Smooth
Odor	Odorless	Odorless
Color	Yellowish-white	Creamy-white

yellowish-white in color while SMS based gels were creamy-white in color. There was an increase in the consistency of the organogels, as the proportion of organogelators in the formulations was increased. All the samples were found to be oily to touch. The organogels were having a smooth texture.

Microscopic Studies

The mechanism of organogel formation was studied by varying the concentration of the organogelators. Figure 2 shows the light microscopic images of SMP and SMS based organogels. The microscopic studies indicated that the organogelators might have self-assembled to from bilayers, which subsequently organized to form tubular structures.[22] At lower concentration (<10%) of gelator molecules, aggregation of needle-like structure was observed. As the gelator concentration was increased to 10% (w/w), tubular structures of SMP and SMS were observed [Figure 2(a,b)]. The tubular structures did not form an interconnecting 3D network. The density of the tubular structures increased as the gelator concentration was increased and formed a network structure at CGC [Figure 2(c,d)]. With further

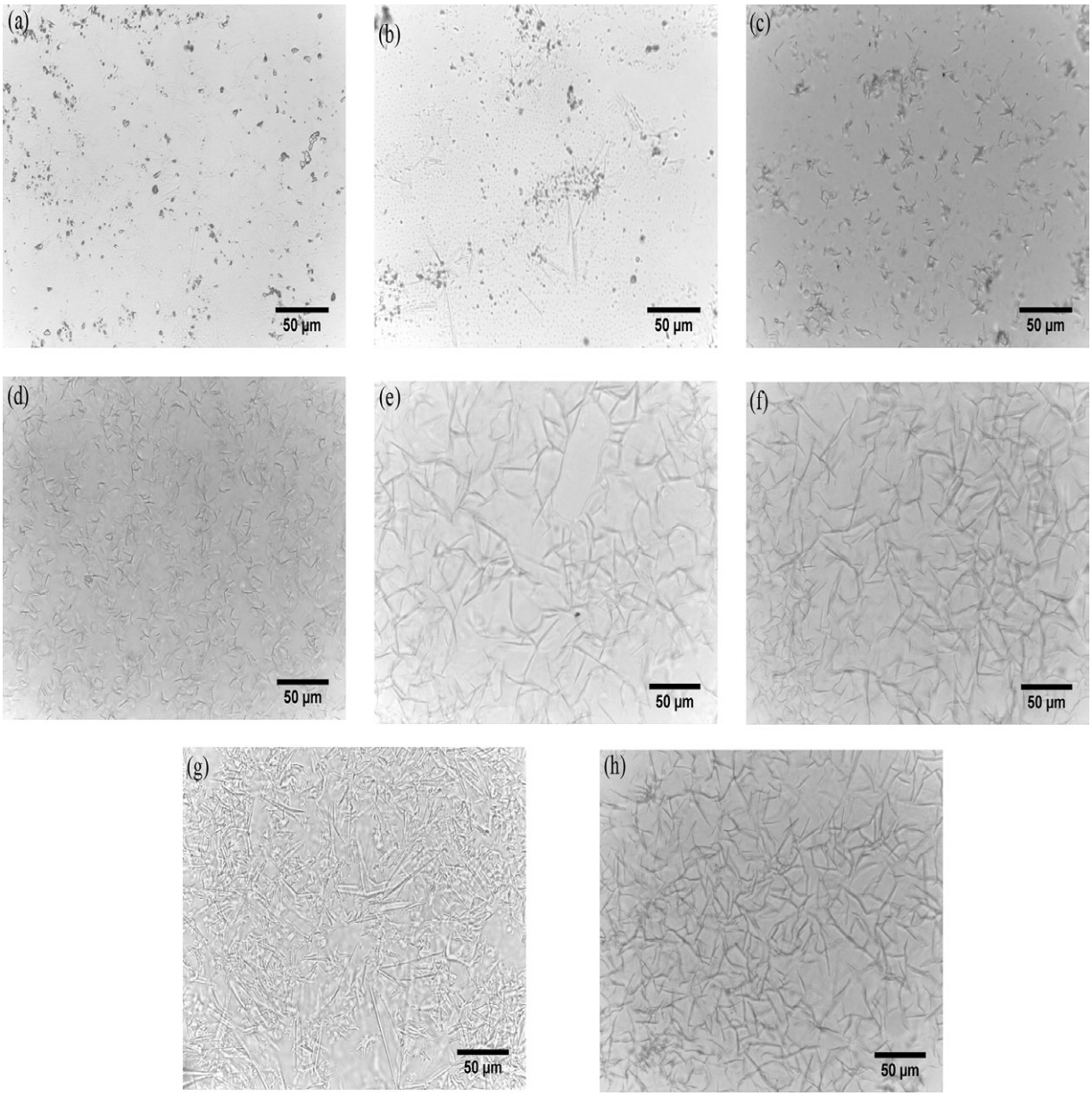

Figure 2. Micrographs of SMP and SMS based organogels at (a) 5% (w/w) SMP, (b) 5% (w/w) SMS, (c) 10% (w/w) SMP, (d) 10% (w/w) SMS, (e) CGC of SMP, (f) CGC of SMS, (g) 20% (w/w) SMP, and (h) 20% (w/w) SMS.

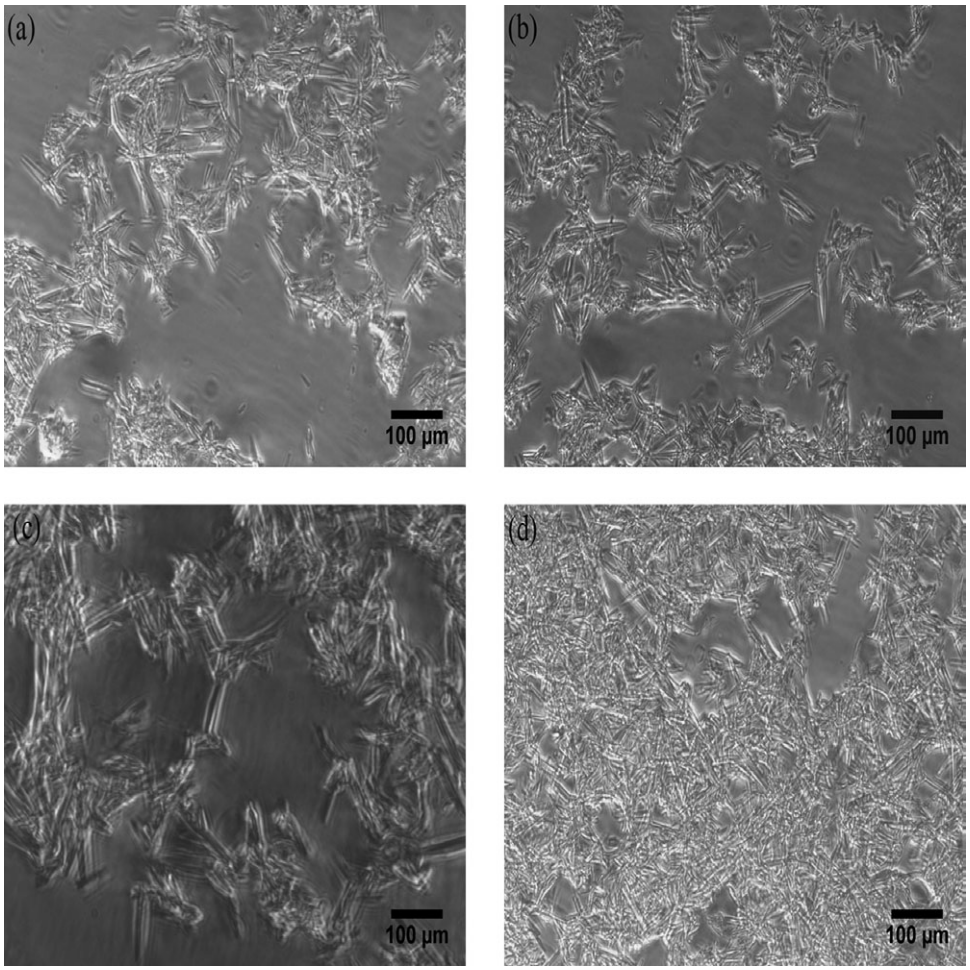

Figure 3. Phase contrast micrographs of organogels at (a) CGC of SMP, (b) CGC of SMS, (c) SMP1, and (d) SMS1.

increase in concentration of the gelator above CGC, length of the tubular structures increased and showed fibrous architecture [Figure 2(e,f)].[26] Presence of 3D networked structures was further confirmed by PCM micrographs (Figure 3). Presence of dense gelator network might be due to the apolar–apolar interactions amongst the gelator and OO molecules. In nonaqueous organogels, the enhanced hydrophobic interactions amongst gelator network and OO resulted in an increase in the stability of the organogels.[21] At CGC, the hydrophobic interactions might not be sufficient to maintain the integrity of the structure for longer duration of time, which leads to syneresis of the gels.[27] Syneresis was not observed in organogels containing higher gelator concentration $\geq$20% (w/w). This suggested that syneresis decreased with increase in the organogelator concentration.[27]

The xerogels were visualized under scanning electron microscope (Figure 4). Micrographs showed the presence of network structure of organogelator tubules, developed by the aggregation of gelator molecules in apolar liquid continuum. Increase in crosslinking density of the SMP and SMS organogelators can be seen in SMP3 and SMS3 organogels, respectively [Figure 4(b,d)]. This suggested that the SMP3 and SMS3 gels were stronger as compared to the SMP1 and SMS1 organogels, respectively.[28]

FTIR Analysis

The FTIR spectral analysis was performed for SMP, SMS, OO, SMP1, SMP1D, SMS1, and SMS1D (Figure 5). The SMP and SMS showed O—H stretching peak at ~3300 cm^{-1} whereas, SMP and SMS based organogels did not show any O—H stretching vibration. This indicated that the O—H stretching within gelator molecules have been subsided, which may be attributed to the hydrophobic interactions prevailing amongst the components of the organogels.[29] Remaining peaks of the gelator molecules were conserved in the gels. Although MZ was present in the SMP1D and SMS1D organogels, peaks corresponding to the presence of any chemical interactions between drug and gel components were absent suggesting that the drug is in its native state in the gels.

XRD Analysis

The X-ray diffractograms of the organogels have been shown in Figure 6 and the parameters of the diffractograms were tabulated in Table III. All the organogels showed a single broad peak at ~21° 2θ. The drug containing gels showed higher FWHM (full width half maximum) as compared to the blank gels. Increase in FWHM indicated that the drug loaded organogels were having more amorphous nature as compared to the blank gels.[30] Amongst the SMP1D and SMS1D organogels, the

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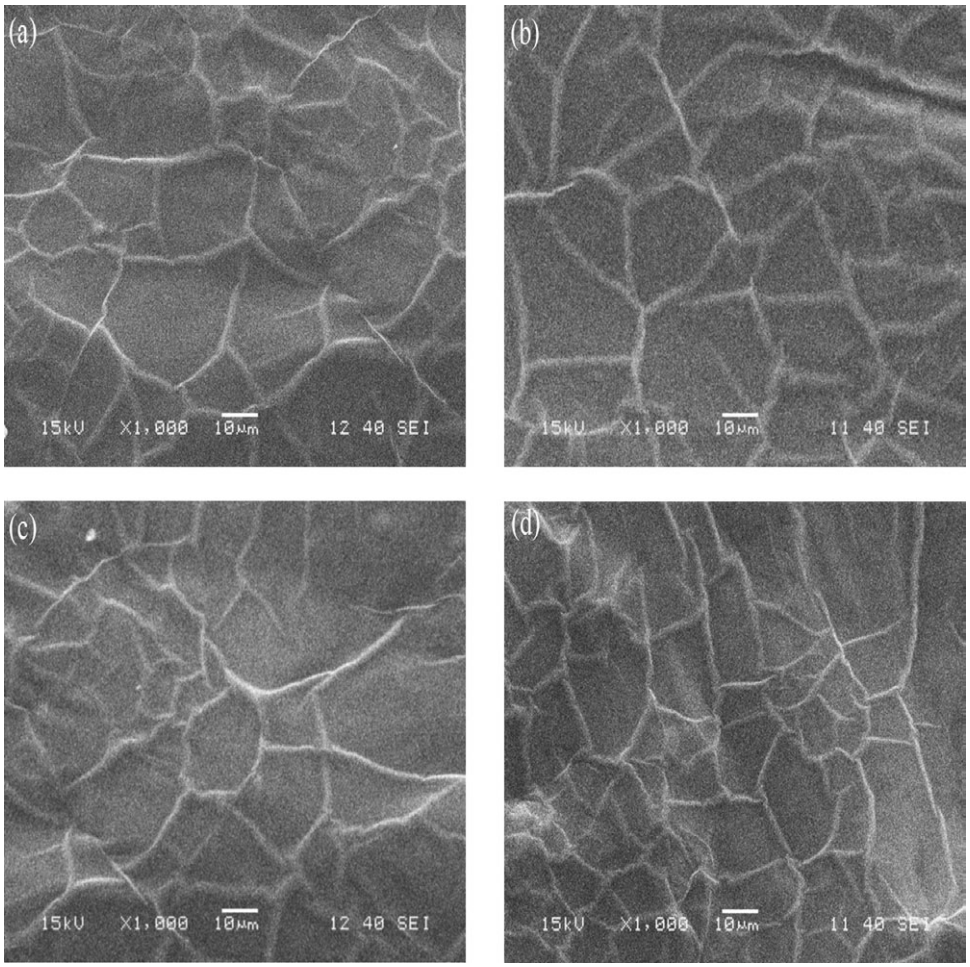

Figure 4. Scanning electron micrographs of (a) SMP1, (b) SMP3, (c) SMS1, and (d) SMS3 organogels.

SMS1D organogel showed higher FWHM, which indicated that the SMS1D organogels were more amorphous as compared to the SMP1D gels.

Accelerated Thermal Stability Studies

Accelerated thermal stability testing was carried out by continuous alternate exposure of the organogels to freeze-thaw cycles at intervals of 15 min. The thermocycling study of stability hypothesizes that the surfactant layer may get damaged due to the change in the physico-chemical properties thereby leading to the instability of the formulations.[10] In general, it is considered that the samples should withstand at least 5 cycles of freeze-thawing process. Samples were found to be stable and did not destabilize even after 8 freezing-thaw cycles showing no signs of instability. There were no major structural changes in the microstructure of both SMP and SMS based organogels after the study (Figure 7). The results suggested that the developed SMP and SMS based organogels were thermoreversible in nature and can withstand wide range of temperature conditions during their shelf-life.

Thermal Studies

The T_m (melting point) of SMP-based organogels was found to be lower as compared to SMS based organogels for a particular concentration of the gelator (Table IV). The results indicated that with the increase in the concentration of the gelator there was a slight increase in the T_m of both SMP and SMS based organogels.

The thermal properties of the SMP and SMS organogels were further studied using a differential scanning calorimeter. On the basis of the preliminary results obtained from the falling ball method, the DSC studies were carried out in the temperature range of 25–70°C. The results of the thermal scanning have been shown in Figure 8.

The SMP1 and SMP1D organogels showed melting endotherms at 47.9°C and 48.1°C, respectively whereas the SMS1 and SMS1D organogels showed melting endotherms at 51.7°C and 53°C, respectively (Table V). The results indicated that the addition of the drug has shifted the endothermic peak towards higher temperature. This suggested that the incorporation of drug into the gel structure improved the thermal stability of the gels. Both the falling ball method and DSC thermal studies indicated that the T_m of the SMS-based organogels were higher and hence the thermal stability, as compared to the SMP-based organogels. The higher thermal stability of the SMS based organogels may be due to the longer fattyacyl chain of stearic acid (C18) in SMS than the palmitic acid (C16) of the SMP.[31] Longer fattyacyl chain increases the hydrophobic interactions

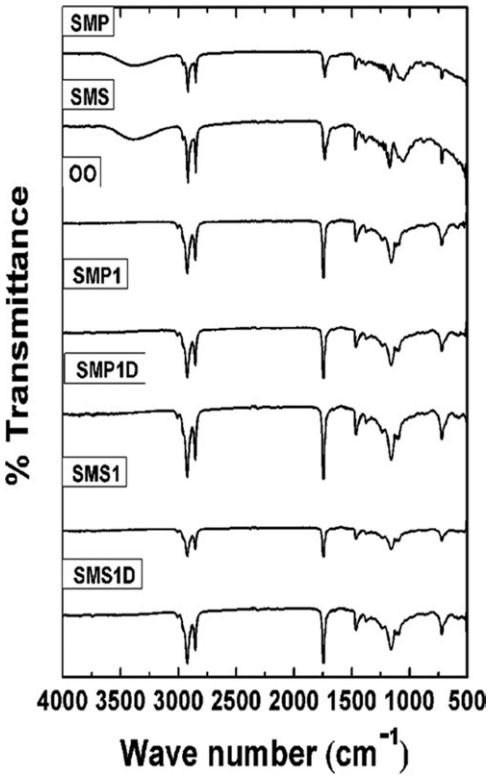

Figure 5. FTIR spectra of organogel components and organogels.

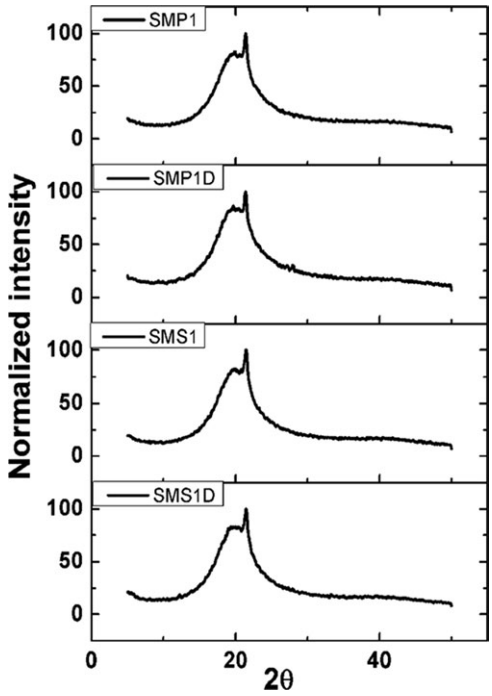

Figure 6. X-ray diffractograms of SMP1, SMP1D, SMS1, and SMS1D organogels.

amongst the gelator molecules and apolar–apolar interactions amongst the gelator and oil continuous phase.[32] The increased hydrophobic interactions of SMS based organogels as compared to SMP based organogels might have increased the thermal stability and in turn, resulted in the requirement of higher amount of energy to overcome the hydrophobic interactions. This may lead to the formation of stronger gels.

In addition to T_m, thermal stability of the organogels may also be predicted by observing the change in enthalpy (ΔH_m) and change in entropy (ΔS_m) during phase transition of the organogels (Table V). The ΔH_m was obtained by calculating the area under the endothermic curve.[33] The SMS organogels have shown higher ΔH_m and lower ΔS_m values than SMP-based organogels. The SMS organogels showed higher ΔH_m and T_m, as compared to the SMP organogels, suggesting the improved stability of the gels.[34] As entropy indicates degree of disorderness, lower entropy values is usually associated with the thermally stable organogels.[35]

Rheological Studies

The viscosity profiles of SMP and SMS based organogels have been shown in Figure 9. The viscosity of the samples decreased significantly with the increase of shear rate from 13 to 95 s^{-1}. The samples have shown higher apparent viscosities during upward curve (13 to 95 s^{-1}) of shear rate and lower apparent viscosities during downward curve (95 to 13 s^{-1}). The existence of different viscosities at a particular shear rate during upward and downward curve of shear rates resulted in the formation of hysteresis loop.[36] The decrease in viscosity with increase of shear rate is an indication of shear thinning behavior, which accompanies with the non-Newtonian, pseudoplastic fluids.[37] In addition to shear thinning behavior, gels were found to be thixotropic in nature because of the existence of hysteresis loop in the viscosity profile.[36,37] The pseudoplastic nature of the organogels was confirmed by analyzing the results using Ostwald-de waele modified power law equation [eq. (3)].[14]

$$\eta = K\gamma^{n-1} \tag{3}$$

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

The flow behavior index of the organogels was calculated by plotting the graph between log (shear rate) and log (viscosity) (Figure 10). The obtained n values were tabulated in Table VI and were found to be <1. This confirmed that the SMP and SMS-based organogels were pseudoplastic in nature having shear thinning and thixotropic properties. The gels did not lose their structural integrity even at higher shear rates.

Spreadability Studies

The % spreadability of the prepared formulations under different weights was given in Table VII. The % spreadability of the

Table III. XRD Analysis of Organogels

Sample	Peak position (2θ)	FWHM
SMP1	21.32	4.84
SMP1D	21.34	5.54
SMS1	21.49	4.98
SMS1D	21.51	5.64

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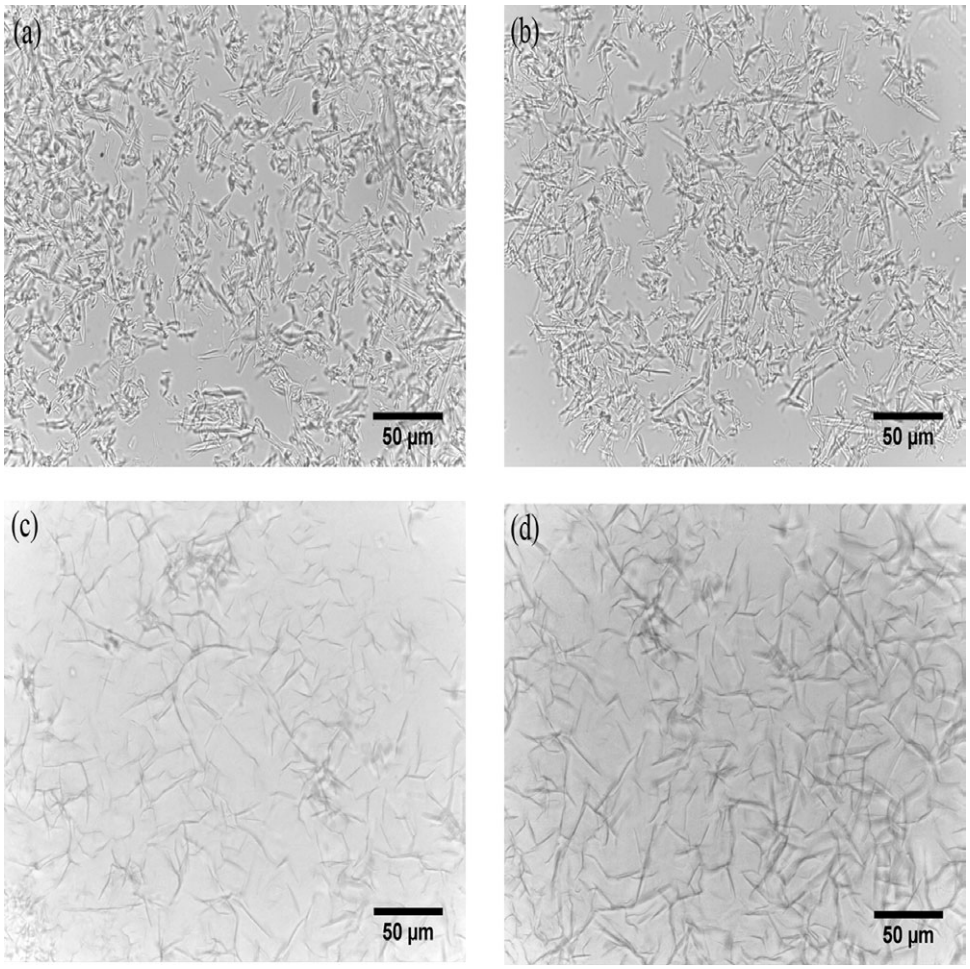

Figure 7. Micrographs of (a) SMP1, (b) SMS1, (c) SMP3, and (d) SMS3 organogels after 5th cycle of thermocycling.

formulations varied in the range of 20–75% for SMP1 gels and 8–30% in case of SMS1 gels when a load of 10, 20, 50, and 100 g was applied, respectively. With the increase in the load, a significant increase in the % spreadability was observed (Figure 11).

The gels were homogeneous, evenly spread and did not lose their structural integrity after the application of load on to the gels. This suggested that the gels were having good mechanical properties (also evident from the rheological studies). The results of the spreadability suggest that the formulations showed good spreadability properties, necessary to be used as topical or transdermal applications.

Table IV. Results of Thermal Analysis

Sample	T_m (°C)
SMP1	44.5 ± 0.70
SMP2	45.0 ± 0.00
SMP3	45.5 ± 0.70
SMP4	46.5 ± 0.70
SMS1	50.5 ± 0.70
SMS2	51.0 ± 0.00
SMS3	51.0 ± 0.00
SMS4	52.0 ± 1.41

Gel Disintegration Studies

Gel disintegration study was carried out in USP tablet disintegration apparatus. Time required for the disintegration of the gels was noted down and graph was plotted for disintegration time against corresponding gels (Figure 12). It was observed that SMS gels required more time to disintegrate completely as compared to SMP gels. This may be due to the difference in strength of the gels as observed in spreadability studies, in which SMP gels were quick to spread compared to the SMS

Table V. The T_m, Enthalpy and Entropy Data of Organogels Obtained from DSC Curves

Sample	T_m (°C)	ΔH_m[a] (J/g)	ΔS_m[a] (mJ/g K)
SMP	47.9	−6.187	−129.165
SMP1D	48.1	−10.1	−209.979
SMS	51.7	−9.95	−192.456
SMS1D	53	−9.824	−185.358

[a]Negative sign of the ΔH_m values is due to endothermic convention.

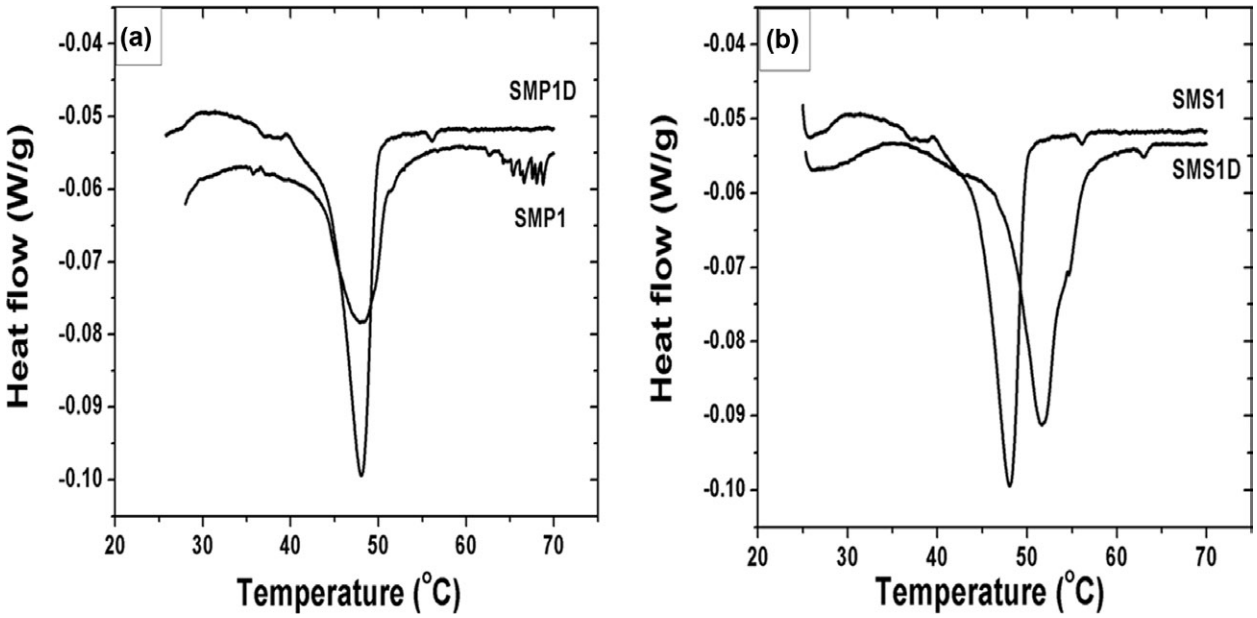

Figure 8. DSC thermograms of (a) SMP1, SMP1D and (b) SMS1, SMS1D organogels.

gels. Presence of long fatty acyl chains in SMS as compared to SMP might have contributed to the higher strength of SMS organogels.[22] This may be attributed to increased hydrophobic interactions amongst the SMS gel components, as was also evident from thermal studies. Increase in gelator concentration in organogels has direct influence on the gel disintegration time (Figure 12). Increase in gelator concentration might have increased the hydrophobic interactions amongst the organogelators, which resulted in the increase in stability of the organogels. The disintegration time of the gels was higher for the gels containing higher amount of the gelator. From the graph it was also evident that the SMS organogels were having higher disintegration time than the SMP organogels. Gel disintegration studies indicated that the SMS organogels were having higher physical strength as compared to SMP organogels.

pH Measurement

The pH of SMP and SMS based organogels was found to be in the range of 5.3 and 6.1, respectively (Table VIII). The measured pHs are in close proximity to the human skin pH indicating the probable nonirritant nature of gels.[38] pH of the formulations were in accordance to the USP guidelines for topical and

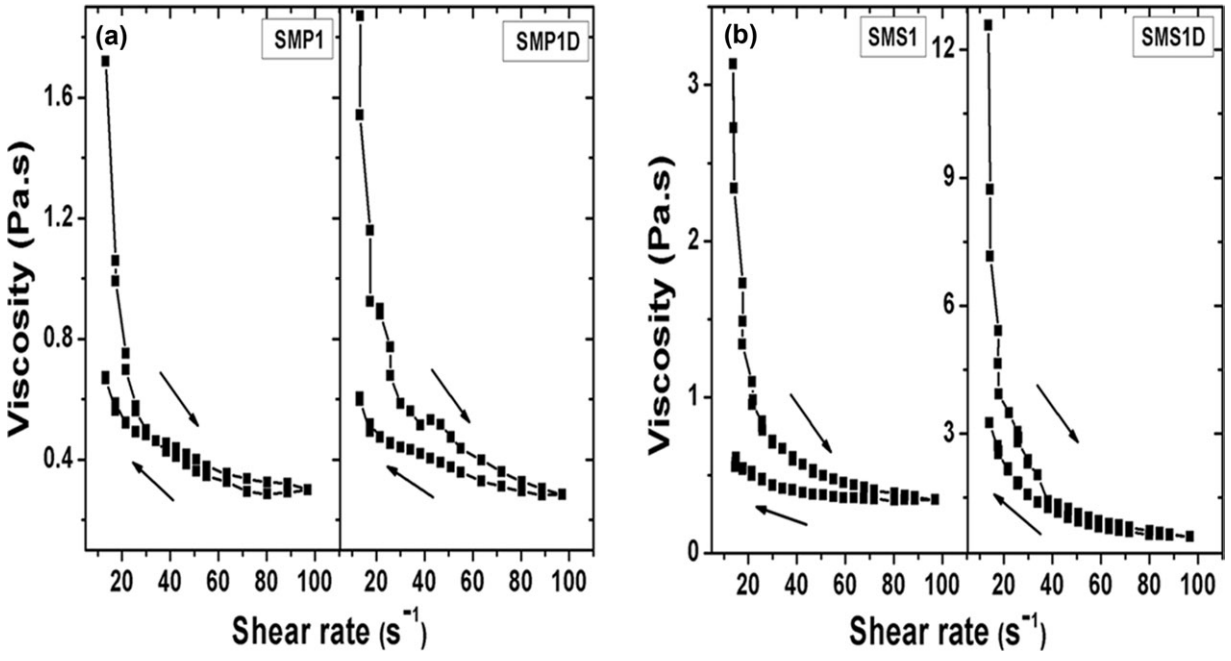

Figure 9. Viscosity profiles of (a) SMP1, SMP1D and (b) SMS, SMS1D organogels.

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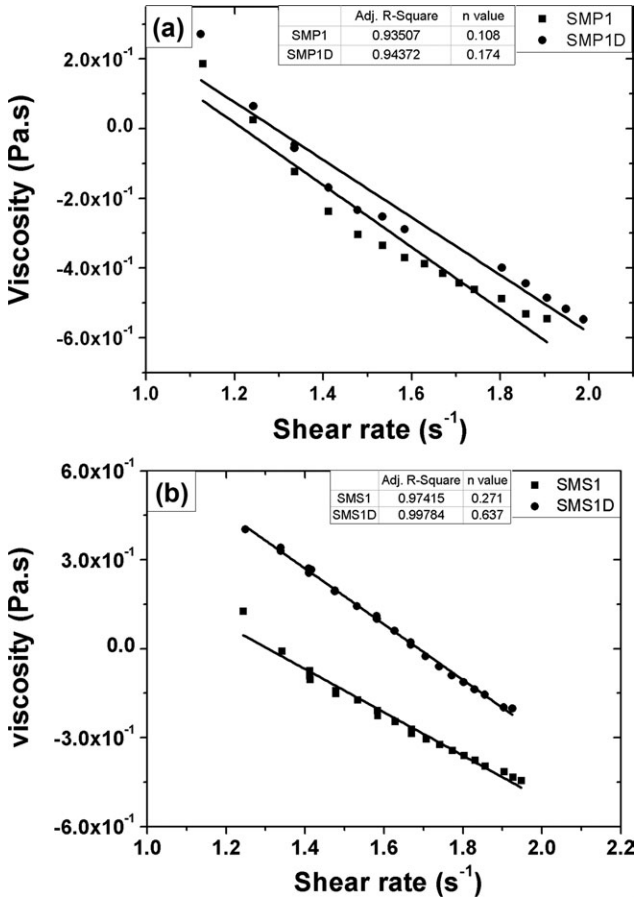

Figure 10. Graph between viscosity and shear rate (log–log scale) of (a) SMP1, SMP1D and (b) SMS1, SMS1D organogels.

transdermal formulations. According to guidelines, the pH of gels or ointments for topical or transdermal applications should lie within the limits of normal skin pH of 4.5–7.4. Any deviation will result in the immunological responses like redness, burning, and itching of the skin. The results suggested that the developed formulations may be used for topical applications.[39]

Bulk Resistance Measurement

The measurement of the bulk resistance suggested that the impedance of the gels increased as the concentration of the gelator was increased (Figure 13). The bulk resistance of the SMP organogels were lower as compared to the SMS organogels. Higher hydrophobicity of the fatty acyl chains in SMS organogels than SMP gels might have associated with less conductivity or high resistivity.[40] This may be associated to the higher hydrophobic interactions amongst the SMS organogel components.

Table VI. The Flow Behavior Indices (*n*-values) of the Organogels

Sample	*n*-value
SMP1	0.108
SMP1D	0.174
SMS1	0.271
SMS1D	0.063

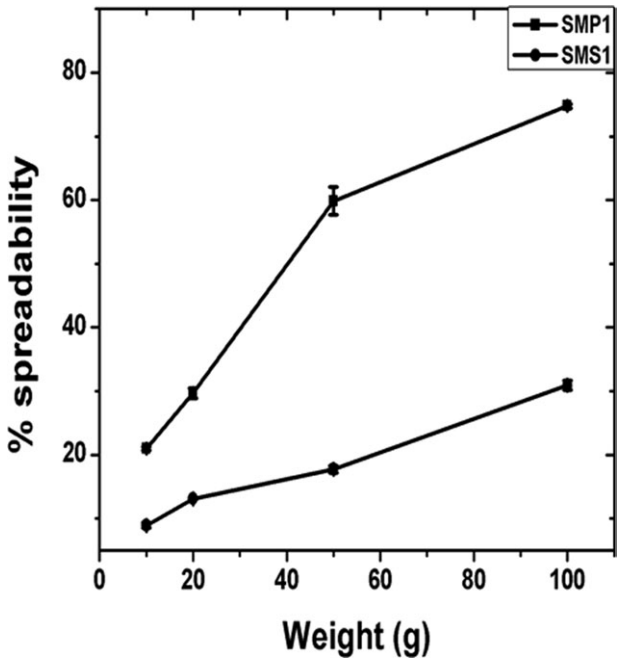

Figure 11. A plot showing spreadability of SMP1 and SMS1 organogels.

In Vitro Drug Release Studies

The SMP1D and SMS1D were chosen as the model organogels for the *in vitro* drug delivery studies. The cumulative percentage drug release (CPDR) profiles of the MZ drug from the organogels have been shown in Figure 14. The CPDR from SMP1D and SMS1D were found to be 26% and 39%, respectively, at the end of 12 h. This may be accounted to the variation in the amorphousity of the gels. The increase in amorphous nature of the organogels has a direct influence on the rate of drug delivery from the gels.[41] It was evident from the XRD results, that the SMS1D gel was more amorphous as compared to the SMP1D gels. This indicated that the increase in crystalline domains of the SMP1D organogels decreased the diffusion of MZ drug.[30] The decreased diffusion of drug from the SMP1D organogels resulted in the lower CPDR value as compared to the SMS1D organogels.

The release kinetics of the drug from the gels was studied and the parameters have been tabulated in Table IX. The results suggested that the best fit models for the drug delivery from the gels were Higuchi and KP models. Graphical representation of the Higuchi and KP models has been shown in Figure 15(a,b). The *n*-values for drug release from the SMP1D and SMS1D gels suggested that the release of the drug from the gels followed Fickian diffusion. The result indicated that the drug diffusion

Table VII. Spreadability of the Organogels

	Spreadability ($cm^2/g^{1/2}$ s)			
Sample	10 g	20 g	50 g	100 g
SMP1	0.0218	0.0225	0.0321	0.0310
SMS1	0.0079	0.0086	0.0074	0.0097

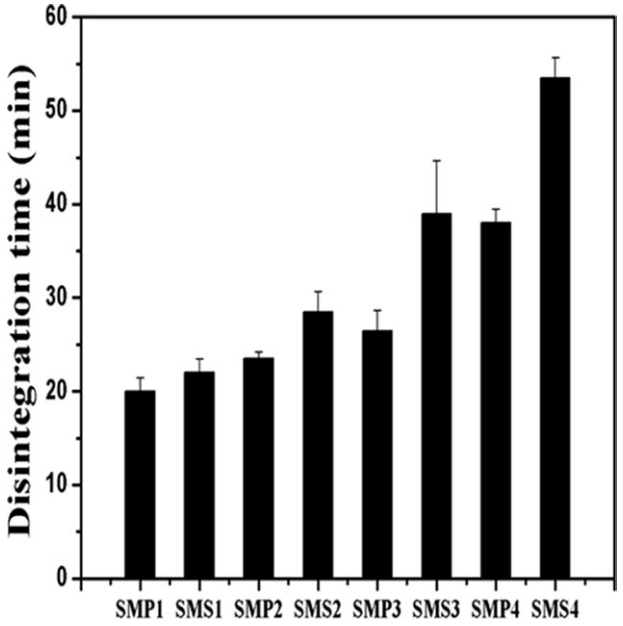

Figure 12. Disintegration times of the organogels.

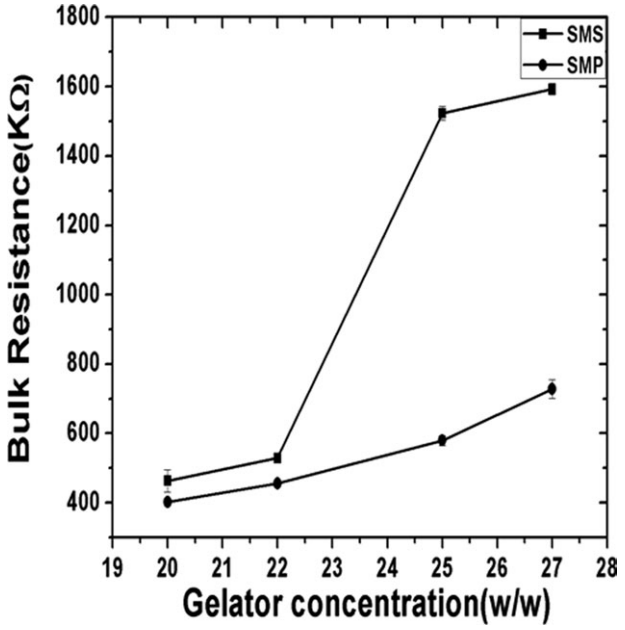

Figure 13. Bulk Resistance of SMP and SMS organogels.

was dependent on the concentration of the drug molecules in the organogel matrix with nonconstant diffusion.[42] The nonconstant diffusion is often associated with the swelling of the gel matrix.[43] The gels were found to follow Higuchian kinetics indicating that the formulations behaved as planar homogeneous matrices with no loss of structural integrity throughout the study.[44]

Antimicrobial Studies

The results of antibacterial efficiency of the developed and the marketed formulations have been tabulated in Table X. SMP1 and SMS1 organogels were used as negative controls whereas MZ was used as positive control. The antibacterial activity of SMP1D, SMS1D, and marketed formulation (MZ1) was studied against *B. subtilis* and *E. coli*. The developed formulations showed good antimicrobial activity. The antimicrobial efficiencies of the drug loaded organogels were found to be comparable with that of marketed formulation. The drug loaded organogels were able to inhibit the growth of the microorganisms even after 24 h suggesting the probable use of organogels for prolonged drug delivery.

Table VIII. pH Values of Organogel Samples

Sample	pH
SMP1	5.90 ± 0.30
SMP2	5.70 ± 0.30
SMP3	5.87 ± 0.15
SMP4	5.80 ± 0.20
SMS1	6.08 ± 0.10
SMS2	5.10 ± 0.25
SMS3	5.45 ± 0.17
SMS4	5.70 ± 0.17

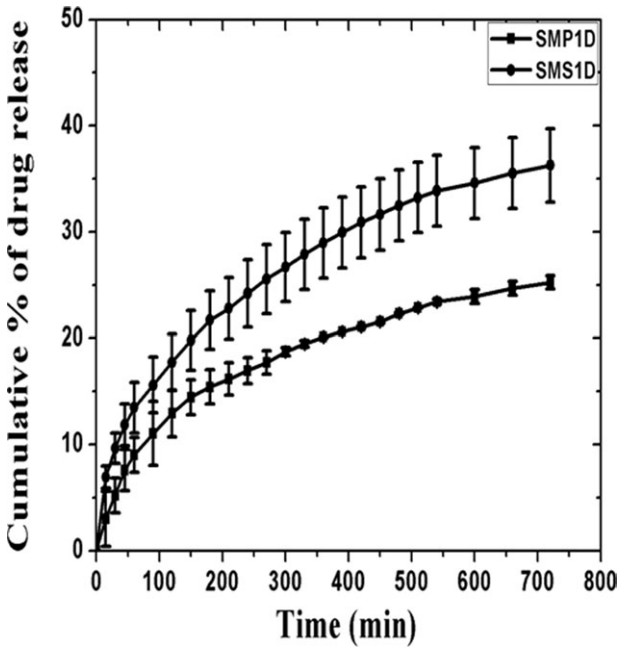

Figure 14. CPDR profile of SMP1D and SMS1D organogels as a function of time.

Table IX. Kinetics of Drug Release

Sample	Higuchi model R^2 value	K-P model		Type of release
		R^2 value	N	
SMP1D	0.99397	0.99749	0.3821	Fickian
SMS1D	0.99721	0.99562	0.2104	Fickian

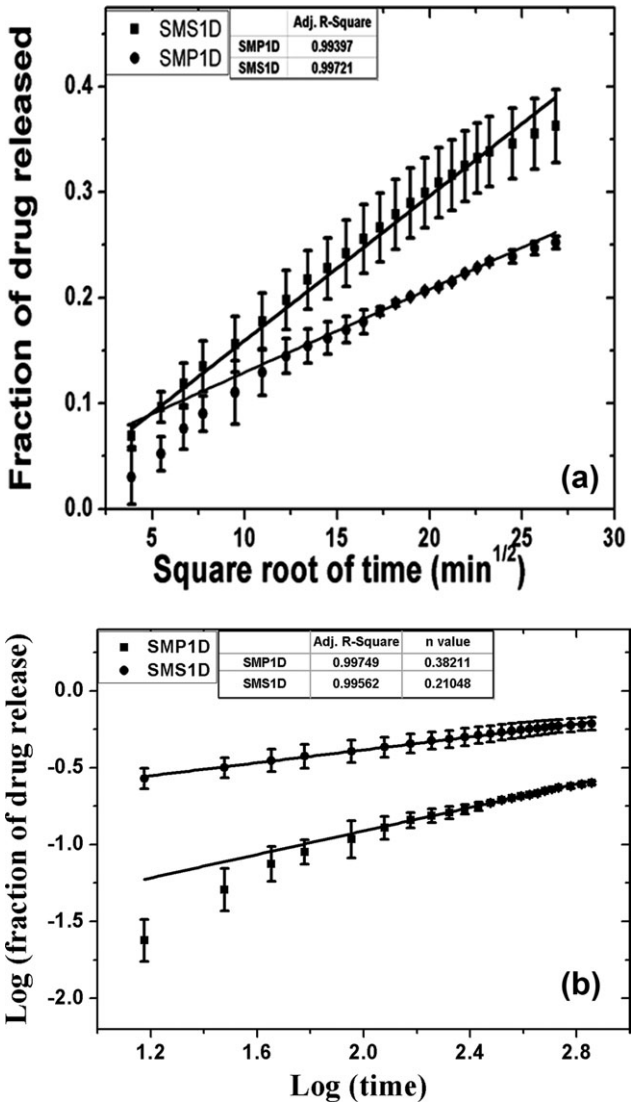

Figure 15. Drug release kinetics of organogels using (a) Higuchi model and (b) KP model.

Hemocompatibility Test

The results of the studies have been tabulated in Table XI. The results suggested that in the presence of leachate, the % hemolysis of the RBCs have been found to be <5%. Hence, the developed samples may be regarded as the hemocompatible.[20]

Table X. Antimicrobial Activity of Samples Against *B. subtilis* and *E. coli*

	Zone of inhibition (cm)	
Sample	*B. subtilis*	*E. coli*
MZ	2.7 ± 0.3	2.8 ± 0.5
MZ1	1.6 ± 0.9	1.1 ± 0.1
SMP1D	1.3 ± 0.2	1.3 ± 0.2
SMP1	0.9 ± 0.3	0.9 ± 0.2
SMS1D	1.2 ± 0.1	1.2 ± 0.3
SMS1	1.0 ± 0.2	0.9 ± 0.2

Table XI. Results of the Hemocompatibility Studies

Sample	%Hemolysis
SMP1	0.64 ± 0.35
SMP2	2.138 ± 0.28
SMP3	1.154 ± 0.24
SMP4	2.00 ± 1.22
SMS1	0.53 ± 0.48
SMS2	2.77 ± 0.61
SMS3	1.83 ± 0.84
SMS4	2.70 ± 0.38

CONCLUSION

The present study dealt with the development of OO based organogels using SMP and SMS as the gelator molecules. When the hot apolar solution of the gelator in OO was cooled down, SMS gels attained gelation sooner as compared to the SMP gels. The mechanism of gel formation was found to be because of entanglement of the tubular structure of gelator molecules to form a 3D network to immobilize the apolar phase. The gelator network of SMP and SMS in OO was clearly evident from the SEM and light microscopic studies. Gel disintegration and DSC studies have shown that the physical and thermal stability of the SMS organogels was higher than the SMP organogels.[22] Drug release kinetics study suggested that the drug loaded gels behaved as matrix type delivery system and the release mechanism of the drug was Fickian diffusion with non-constant drug release. The developed SMP and SMS gels showed mild antibacterial activity against *E. coli* and *B. subtillis* but drug loaded gels showed significant antimicrobial activity. All the gels were found to be highly hemocomptible. On the basis of the preliminary studies, the developed OO based organogels may be tried as carriers for topical drug delivery.

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