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Sorbitan Ester Organogels for Transdermal Delivery of Sumatriptan

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ABSTRACT The partial phase behavior, rheological, and drug release characteristics of an organogel (OG) composed of water, isooctane and sorbitan esters, sorbitan monopalmitate (Span-40) and poly(oxyethylene)sorbitan monostearate (Polysorbate-60) were studied. Phase diagrams showed decreasing areas of optically isotropic organogel region depending on the surfactant ratio, K_w and drug incorporation. The nonbirefringent, clear isotropic solution suggested the reverse micellar/microemulsion nature of the organogel without any molecular ordering. The increase in drug concentration in OGs leads to increase in the viscosity and sol-gel transition temperature (T_g). Fractal dimension (d_f) values calculated for different compositions suggested that the density of the tubular network increases with increasing drug concentration in OGs. The release rate of the drug from OGs was found to be non-Fickian through the dialysis membrane. The permeation rate of sumatriptan from pig skin was 0.231 mg/h/cm^2 (781.9 nmol/h/cm^2). The study indicates potential of OG as a reservoir system for transdermal drug delivery.

KEYWORDS Sumatriptan, Sorbitan esters, Organogel, Phase-behavior, Rheology, Transdermal, Fractal dimension

INTRODUCTION

In the late 1980s, a new class of formulation was described in the literature referred to as organogels (OG) that has since been applied to numerous applications such as transdermal drug delivery, separation science, templates, sensors, and so on (Hinze et al., 1996). They are thermoreversible sol-gel systems consisting of interconnected surfactant tubules (Terech, 1989). From the pharmaceutical application viewpoint, three major types of OGs have been extensively researched in last decade that include gelatin (Quellet & Eicke, 1986; Kantaria et al., 1999) and lecithin (Mahjour et al., 1990; Scartazzaini & Luisi, 1988) for the transdermal delivery of drugs (Walde et al., 1990). The use of sorbitan ester organogel for pharmaceutical use was studied by Florence and coworkers (Murdan et al., 1999a; Murdan et al., 1999b; Murdan et al., 1999c). They first showed the gelation of isopropyl myristate using sorbitan monostearate in which the aqueous phase could be incorporated in the tubular/lamellar network of the sorbitan ester. Later, they investigated the effect of types of sorbitan esters and hydrophilic additives on the gel microstructure and reported formation of toroids, tubular aggregates and

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star-shaped clusters in OGs. Optical microscopy, freeze-fracture electron microscopy and X-ray diffraction techniques were used to study their characteristics. The effect of polyoxyethylene sorbitan ester addition to sorbitan ester OGs on strength and drug release characteristics was studied by Pisal et al. (2004). The three-dimensional network of the organogel was shown to control the drug release. By the use of factorial design, optimization of the OG formulation was found to be proposed for the nasal delivery of propranolol hydrochloride. Previous experiments, however, lack evaluation of the detailed rheological characteristics of sorbitan ester OG. Knowledge of the evolution in rheological properties during sol-gel processing is useful guide to the manufacturer when formulating dispersions to optimize physical properties of the final product. Due to the complexity and poorly understood gelation behavior and the use of equipments like planetary mixers for semisolid processing that impart high shear affecting gelation (may delay or destroy gelation), a study of the rheological properties and determination of the gelation point becomes important. Thus, in this work our aim is formulate and characterize sorbitan ester OG. First, we report phase diagram for the OG formation at different ratios of hydrophobic/hydrophilic sorbitan ester surfactants and the affect of drug incorporation on the phase-behavior with the selected surfactant ratio. Then, we investigate the effect of drug incorporation on rheological characteristics of OG. From the rheological profile fractal dimensions of OGs were deduced and correlated with the observed and reported gel microstructural properties. Finally, investigation was performed of the relationship between OG microstructure and the kinetics of drug release and drug permeation through skin is also investigated.

Sumatriptan, a 5-HT receptor agonist, is chosen as a model drug because it is water insoluble in the base form hence, is expected to have good oil/water partition required for skin permeation. Besides, the absolute bioavailability of sumatriptan is approximately 15, 14, and 96% after intranasal, oral dosing and subcutaneous injection, respectively. The low bioavailabilities are primarily due to pre-systemic metabolism and partly due to incomplete absorption (Jhee et al., 2001), which also makes it a suitable candidate for transdermal delivery. From the previous reports it could be inferred that the transdermal delivery of sumatriptan is not as effective and a further assistance is required to permeate the drug into the systemic circulation. The use of penetration enhancers and iontophoresis were found to be promising (Femenia-Font et al., 2005a–c) to increase the systemic availability. In our work, we have used solvent-based penetration enhancers and surfactant micelles to assist the transdermal flux. Isoctane and DMF dissolve skin lipids therefore assist in drug penetration (Tashtoush, et al., 2004). Though the solvents reported here are not the preferred solvents, they have been used in formulating organogels (Singh et, al., 2004; Fadnavis & Koteshwar, 1999; Simmonas et al., 2001) and their use in transdermal drug delivery is also reported (Bhatnagar et al., 1994; Agrawal et al., 2004). We understand that the high loading dose required for sumatriptan is a major hurdle to develop sumatriptan transdermal system for replacement of first-line oral or nasal treatment, therefore our objective is to develop a supportive transdermal system that may avoid or prolong migraine recurrence for use along with the first line treatment.

MATERIALS AND METHODS

Materials

Span-40 and Polysorbate-60 were purchased from Fluka, Germany. Dimethylformamide (DMF), isooctane and methanol were obtained from Merck, India. Sumatriptan was a kind gift from Sun Pharma. All the buffers and other chemicals were of A.R. grade. Double distilled water was used in all experiments.

Partial Phase-behavior of Sorbitan Esters/Isooctane/Water System

Phase studies were performed by adding double distilled water to the mixture of isooctane, Span-40 and Polysorbate-60 [surfactant ratio, K_w, 1:1, 1:1.75], using a magnetic stirrer at high speed. The mixture was examined visually for optical clarity and through cross polarizers for the presence/absence of birefringent liquid crystalline phase. The appearance of turbidity was chosen as an endpoint at a particular ratio of surfactant/isooctane. The concentrations of surfactant, isooctane and water were calculated and the phase behavior of the systems was mapped on phase diagrams. The transparent, homogeneous, nonbirefringent area enclosed within the end points was considered as water in oil (w/o) microemulsion. The effect of sumatriptan solution (2 and 6% w/v) in the presence of DMF (stock solution for phase titration) on the phase behavior of a selected surfactant composition [K_w, 1:1], isooctane and water was studied. Based on the phase behavior study, OG compositions containing 1.0 or 1.4% (w/w) sumatriptan and 5% (w/w) DMF were formulated and characterized comparatively with OG containing 5% DMF without drug as explained in the following paragraphs.

Sol-gel Transition Temperature and Fractional Dimension

The rheology experiments were performed using a AR500 stress controlled rheometer (TA Instruments, U.K.). The dynamic rheology of organogel were studied by using steel parallel plate geometry of radius 20 mm and angle 0° with truncation gap 500 μm. The truncation gap was kept large to avoid breaking of the structures in the organogel sample. Frequency and strain sweep tests were performed in order to specify the viscoelastic range. Sol-gel transition studies were conducted under the temperature ramp. The OG (0.16 g) was applied on the platform of the rheometer set up at a constant angular frequency (ω = 6.283 rad/sec) and temperature was varied from 15 to 35°C. The storage modulus (elastic), G′, and the loss modulus (viscous), G″, were recorded and graphically plotted against temperature. The sol-gel transition temperature was determined as the minima of the Tan δ (G′/G″) verus temperature curve. For the determination of fractal dimension, rheometer was setup at fixed temperature (20°C) and ω was varied from 0.5 to 50 rad/sec. The relaxation exponent Δ was calculated by fitting the curve to the following power law or a linear logarithmic equation (Mohanty & Bohidar, 2005).

$$G'(\omega) = \alpha_1 \omega^{\Delta'} \quad \text{and,} \quad G''(\omega) = \alpha_2 \omega^{\Delta''} \tag{1}$$

$$\begin{aligned} &\text{Log } G'(\omega) = \text{Log } \alpha_1 + \Delta' \text{Log } \omega \\ &\text{and, Log } G''(\omega) = \text{Log } \alpha_1 + \Delta'' \text{Log } \omega \end{aligned} \tag{2}$$

where, G(ω) is the modulus, ω is the angular frequency (rad/sec), α is a constant and Δ is the relaxation exponent. After the determination of relaxation exponent, a relationship of relaxation exponent with the fractal morphology of the gel network was established as suggested by Muthkumar, 1989, in the following equation:

$$\Delta = d(d + 2 - 2d_f)/2(d + 2 - d_f) \tag{3}$$

where, d is dimension and d_f is fractal dimension. For gel, $d = 3$, therefore the equation could be simplified as:

$$d_f = (15 - 10\Delta)/(6 - 2\Delta) \tag{4}$$

In-Vitro Drug Release Studies

The formulation (1.0 g) was taken in a pretreated dialysis bag clipped on both sides. The dialysis bag was immersed in 100 mL phosphate buffered saline (PBS, pH 5.5) in a beaker maintained at 37 ± 1°C on a temperature controlled, and stirred at 50 rpm on magnetic stirrer plate. The sample from beaker were withdrawn periodically for 24 hr and replaced immediately with an equal volume of PBS, pH 5.5. The mass released (M) with time (t) was calculated according to the following power law (Peppas, 1994):

$$Mt / M_\infty = t^n \tag{5}$$

where, M_∞ is mass released after an infinite time. The in-vitro permeation of sumatriptan from the OGs through the pig abdominal skin was studied using a Franz diffusion cell. The skin was prepared by the method reported by Panigrahi et al., 2005. Briefly, it involved removal of hairs and fatty material followed by checking skin integrity by microscopy. The skin was carefully placed between the donor and receptor compartments of the cells with the stratum corneum side facing the donor compartment and dermal side bathed in receptor media. The effective area of skin available for diffusion was 2.0 cm^2. The OGs bearing sumatriptan (1 g) was placed over the skin. The receptor compartment was filled with 10ml of PBS (pH 7.4). The cell contents were maintained at 37°C using thermostatic circulating water bath and the receptor solution was stirred 50 rpm with help of magnetic stirrer. The sample (0.5 mL) was withdrawn from the receptor compartment at 1–9 h and 24 h. The withdrawn volume was replaced with fresh PBS, pH 7.4. The drug contents were determined by HPLC (Femenia-Font et al., 2005a). The diffusion coefficient, permeability coefficient and partition coefficient were determined by the reported methods (Saket et al., 1984; Aslani & Kennedy, 1996, Pefile et al., 1998).

Stability

Different formulations were subjected to mechanical stress by centrifuging (Remi Centrifuge, India) at 2000–10000 rpm for different time intervals and the volume of phase separation of OGs was noted. The OGs containing drug and respective placebos were stored for 28 days at 2–8°C and 25 ± 5°C in collapsible aluminum tubes. The drug was extracted from the formulations using 10 mL methanol with stirring and centrifugation at 3000 rpm for 10 min. The supernatant was filtered, diluted and injected in HPLC (Femenia-Font et al., 2005a). Viscosities of OG formulations were also determined at biweekly intervals (0, 14, 28 days) using a Brookfield Digital Viscometer model LVDV-I+ (Brookfield Engineering Labs. Inc., USA) with a spindle "TD". The shear rate was applied from 0.3 to 6 rpm. The viscosity was obtained by the following formula: Viscosity=TD factor×observed value. The TD factor was calculated as: TD factor=1872 n^{-1}, where, n = rpm. The shear stress was calculated by multiplying viscosity with shear rate (rpm) applied.

RESULTS AND DISCUSSION

Effect of K_w and Sumatriptan Concentration on Phase Behavior of OG

Phase behavior of OG system consisting isooctane, water and surfactant mixture (Span-40 and Polysorbate-60) was investigated by plotting the pseudo-ternary phase diagrams in which each corner of the diagram represents 100% of that particular component. The K_w was kept as 1:1 and 1:1.75. The hydrophilic-lipophilic balanced (HLB) values of Span-40/Polysorbate-60 mixtures were 10.8 and 11.9 for K_w 1:1 and 1:1.75, respectively. Fig. 1a,b show the phase diagram of isooctane, water and surfactant mixture at the two various K_w. The area of OG region decreased with the increasing K_w from 1:1 to 1:1.75. When the K_w was 1:1.75, the region of OG was too narrow, which is an indicative of low amount of water solubilized in

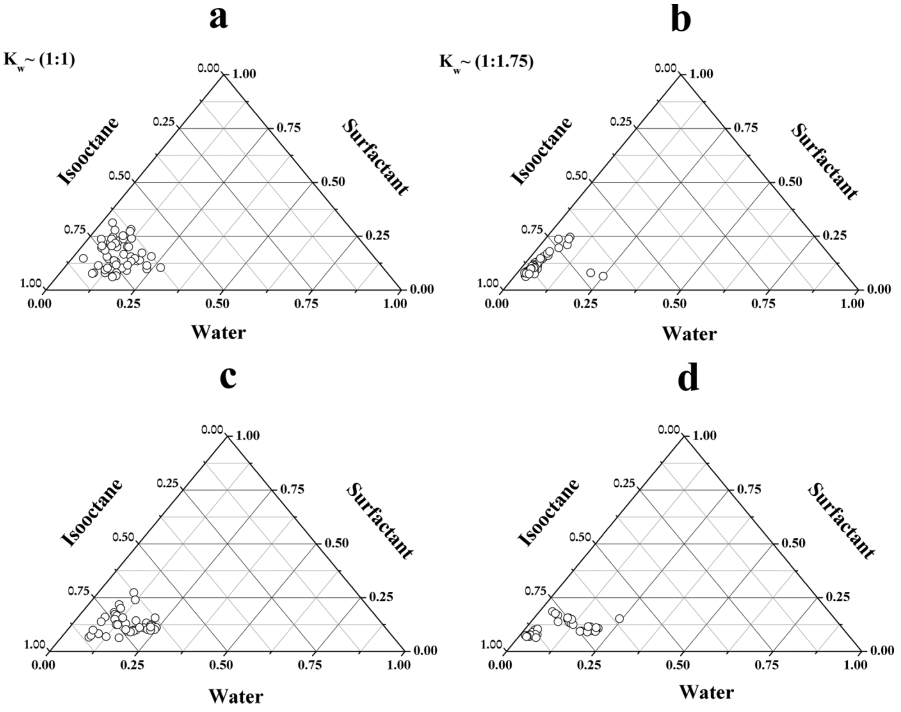

FIGURE 1 (a, b) Triangular Phase Diagram of OG Formulations Containing Different Ratios of the Surfactants, Span-40/Polysorbate-60, as Indicated in the Figure. There are 56 Data Points, Which are Clustered Over a Smaller Area With Increasing Proportion of a Polysorbate-60 in the Surfactant Mixture Indicating Less Water Incorporation. (c, d) Triangular Phase Diagram of OG Formulations Containing Different Amounts of Sumatriptan. The Phase Area is Indicated by the Data Points. The Components Indicated on the Three Sides of a Triangle are 100% at the Apex on the Anticlockwise Direction. The Base of the Triangular Diagram Indicating Water Contains ~30% DMF and 2% drug (c), and 6% drug (d).

OG. This is rather surprising as the incorporation of a hydrophilic surfactant (or high HLB value of resultant surfactant mixture) is expected to increase water incorporation, which in turn could increase the gel-phase area. It was however observed that the presence of Polysorbate-60 takes up more water and converts the system into a white, semisolid w/o emulsion (cream) rather than forming a translucent gel. The increase in HLB value of the surfactant mixture decreases the interfacial tension such that instead of forming gel structure (perhaps due to tubular channels) with increasing water content as in the case of Span-40 alone, the system forms large number of spherical droplets, i.e., w/o emulsion in case of Span-40/Polysorbate-60 mixture. The Polysorbate-60 was however, included in the gels for further studies because it increases the OG strength and storage stability (Pisal et al., 2004).

To illustrate the effect of drug on the pseudo ternary phase diagram, drug solution in 2.0 and 6.0% w/w concentrations were added to the system with K_w 1:1. As indicated in Fig. 1c,d, the area of OG decreased with the higher drug concentration in the titrating aqueous solution, i.e., lesser amounts of water could be incorporated. Increasing the water content was found cause precipitation of the drug. The OG phase area was increased in presence of DMF aqueous solution (not shown). This could be due to the reduction of interfacial tension by the co-solvency effect of DMF. The composition of OG formulations used for characterization is given in Table 1.

Rheological Characteristics of OGs

Sol-gel transition temperature (T_g) of OGs formulations was determined from the loss of storage modulus (G′) and loss modulus (G″) versus temperature curve obtained during the gelation process shown in Fig. 2a. The curves present three domains: high and nearly constant values of G″ corresponding to gel state, a sharp decrease corresponding to gel microstructure break-up and a last domain with a tendency to a plateau

TABLE 1 Composition of OGs and Their Physicochemical Characterization

Ingredients	Qty	Formulation Code		
		OG-a	OG-1	OG-3
Span-40/Polysorbate-60 (1:1)	g	24	24	24
Isooctane	g	60	61.1	64.6
Water	g	11	8.9	5
Sumatriptan (w/v)	g	–	1	1.4
Dimethyl formamide	g	5	5	5
Relaxation Exponent and Fractal Dimension of OGs*				
G′	Relaxation Exponent (Δ′)	0.34 ± 0.12	0.26 ± 0.08	0.20 ± 0.05
	Fractal Dimension (d_f)	2.18 ± 0.15	2.26 ± 0.07	2.32 ± 0.06
G″	Relaxation Exponent (Δ″)	0.27 ± 0.07	0.23 ± 0.04	0.19 ± 0.05
	Fractal Dimension (d_f)	2.25 ± 0.06	2.29 ± 0.04	2.33 ± 0.05
Release/Permeation Rate of Sumatriptan from OGs*				
Dialysis bag %/$h^{0.7}$/cm^2	–	–	7.94	6.96
Pig abdominal skin mg/h/cm^2 (nmol/h/cm^2)	–	–	0.231 (781.9)	0.102 (337.8)
Permeability coefficient, P (cm^2/h)			2.3×10^{-2}	1.02×10^{-2}
Lag time, L			30 min	45 min
Diffusion coefficient, DC (cm^2/h)			6.75×10^{-4}	4.5×10^{-4}
Percent residual Sumatriptan in OG Formulations at different storage conditions				
2–8°C	7 days	–	99.1 ± 1.2	98.4 ± 1.3
	14 days	–	98.4 ± 1.4	98.1 ± 1.2
	28 days	–	98.7 ± 0.9	97.9 ± 0.8
25 ± 5°C	7 days	–	98.9 ± 1.1	97.8 ± 1.6
	14 days	–	98.6 ± 1.3	97.3 ± 1.7
	28 days	–	98.2 ± 1.4	96.2 ± 1.7

*n = 3.

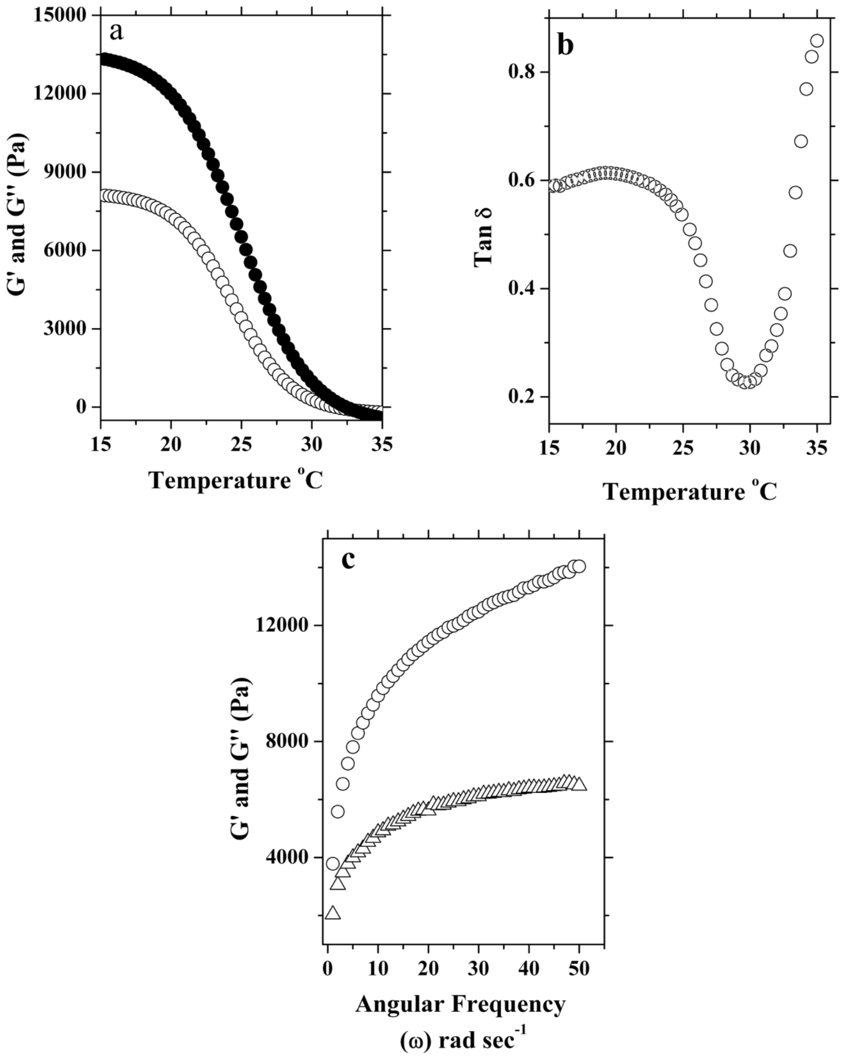

FIGURE 2 (a) The Temperature Dependent Loss of Elastic Modulus, G′ (Solid Legends), and Viscous Modulus, G″ (Open Legends), of a OG Formulation (OG-1). The Curves are Obtained From the Best Sigmoidal Fit of the Data Points. (b) Tanδ versus Temperature Curve, Showing Minima at T_g. (c) A Representative Frequency (ω) Dependence of $G'(\omega)$ (Circles) and G″(ω) (Triangles) Curves of OG Formulations. The Formulation is OG-3. Relaxation Exponents Obtained From the Slopes of the log G′ (ω) and log G″(ω) Versus log ω Curves.

that could be linked to sol formation. Both, the G′ and G″ values were slightly increased with an increase in drug concentration at a particular temperature. The curve between Tanδ(G″/G′) and T was plotted and the T_g was obtained from the minima of the curve (Fig. 2b), i.e., the point where the viscoelasticity of the gel changes abruptly. The OG-3 has highest T_g (30°C) while OG-a has lowest T_g (29.1°C). This change in T_g (sol-gel) can be explained by change in the arrangement of gel network that is affected by the incorporation of the drug. The viscoelastic nature of gels, which is a function of the microstructure network, was evaluated from the G′ and G″ versus ω curve (Fig. 2c). The elastic and viscous modulus show a apparently asymptotic increase in values with the elastic modulus component [G′(ω)] having always a higher values than the viscous modulus component [G″(ω)] suggesting predominantly elastic nature of the sorbitan ester OG within the indicated frequency range. The elastic behavior in this case reflects the presence of entangled network of aqueous domains (Murdan et al., 1999a–c).

Though the OG system is not exactly comparable to a gelling solution of a polyelectrolyte that is described through Muthukumars (1989) theoretical model. It is tempting to evaluate the value of fractal dimension (d_f). The relaxation exponent, Δ' was calculated fitting the power law equation to the G′(ω),

$G''(\omega)$ versus the power law equation to the $G'(\omega)$, $G''(\omega)$ versus ω curves or by plotting logarithm $[G'(\omega), G''(\omega)]$ versus logarithm $[\omega]$ curves and determining the slope from the linear fit equation (Fig. 2c). The d_f was calculated using a relationship given in the experimental section. The results are presented in Table 1. The OG-3 has the highest d_f value which is indicative of the formation of more dense gel structure in comparison to OG-1. It was surprising that OG-3 formulation with the less water content was denser indicating that the increasing amounts of drug affect the nature of gel. The optical microscopic observations showed that there is polydisperse clusters of short tubules in OG-3, further aggregated to form a compact structure, while relatively longer and less aggregated structures are seen in OG-1.

Drug Release and Permeation from OGs

The in-vitro drug release profile of various OGs are shown in Fig. 3a. The kinetics of drug release from OGs was established by plotting a graph between log of percent cumulative drug release against log(t) and the value of the diffusional release exponent (n) was calculated from the slope of the above plot (Fig. 3a). The value of n was found to be ~0.73 ($0.5 < n < 1$), which is an indicative of non-Fickian diffusion of the drug from the OGs (Peppas, 1994). At $n = 0.5$, the drug release is Fickian and at $n = 1$, it is zero-order. The non-Fickian diffusion of drug may be explained as follows: during the organogel release, phenomenon three moving boundaries may form. First, swelling boundary due to release medium uptake by the organogel forming a cream-like structure (note that the HLB of the Span40/Polysorbate-60 (1:1) is 10.8. Second, erosion boundary due to erosion of cream in the form of an emulsion into the bulk medium and, third a diffusion boundary due to partitioning and diffusion of the drug. A graph was plotted between percent cumulative amount of drug versus time$^{0.7}$ (not shown) and release rate was calculated from the linear curve fit. The slope of the curve gives the release rate. The in vitro drug release exhibited faster release (7.94%/h$^{0.7}$/cm^2) from the product OG-1 as it has less stiff microtubular network. The OG-3 formulation exhibited slower release (6.96%/h$^{0.7}$/cm^2), which has a stiff gel structure. These results concur with the earlier findings (Pisal et al., 2004).

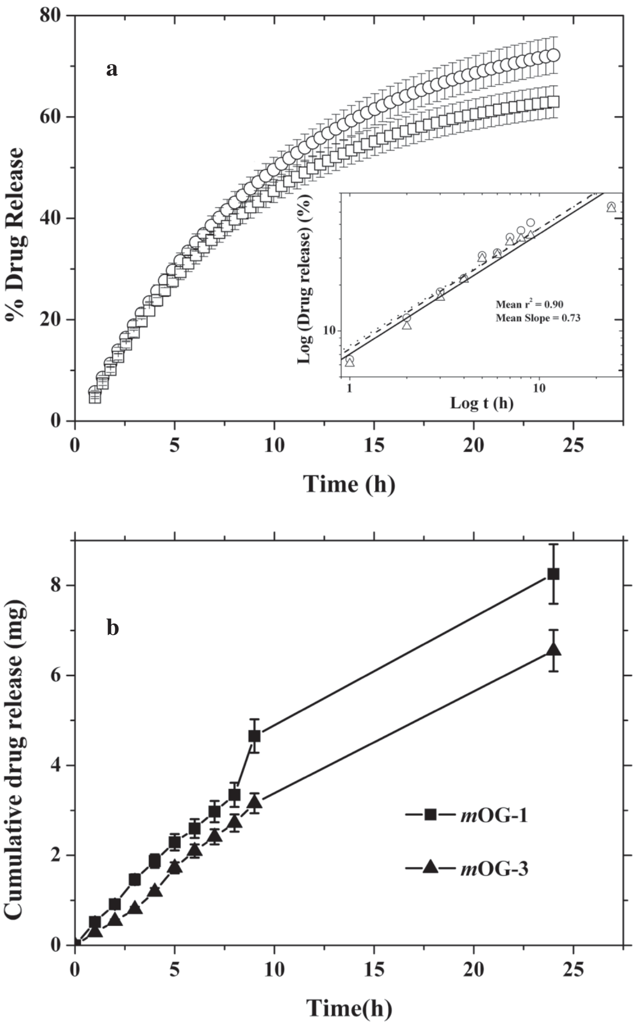

FIGURE 3 (a) Cumulative Percent Drug Released (*y*) Versus Time (*x*) Curve Fitted Using the Power Law Equation. The Inset Shows log*x* Versus log*y* to Obtain a Power Law Exponent, Which Correlates Well With Direct Fitting of the Curve to the Power Law Equation. (b) The Drug Release was Studied in PBS Buffer (pH 5.5) Using a Cellophane Membrane. Drug Permeation From Various OG Formulations Through the Pig-Skin Using a Franz-Diffusion Cell Indicating Almost Zero-Order Release. The Permeation Rate was Inversely Proportional to the Drug Concentration in the OG Formulation.

Further, the results of in-vitro skin permeation studies of sumatriptan are shown in Fig. 3b. The studies reveal that the maximum skin permeation of drug (flux) was observed with product OG-1 (0.231 mg/h/cm^2) while product OG-3 showed less drug skin permeation (0.102 mg/h/cm^2). The flux (J) was calculated from the slope of the release curve. The permeability coefficient (P) was calculated as:

$$P = J/C \tag{6}$$

where, J is steady state flux and C is concentration of drug on the skin (Aslani & Kennedy, 1996). The diffusion coefficient was calculated from the equation:

$$D = h^2 / 6L \tag{7}$$

where, h is the thickness of the skin and L is lag time. The thickness of the skin was 450 ± 30 μm. The partition coefficient between skin and vehicle can be regarded as an index of mutual drug and vehicle affinity. The partitioning of sumatriptan between skin and PBS (pH 7.4) was 2.74, which indicates that the drug has a good affinity to the skin. In addition, the penetration enhancing solvents (isooctane and DMF) present in the composition were the major factors for improved drug permeation than the reported permeation rates (Femenia-Font et al., 2005a–c).

Stability

The OG formulations were resistant to mechanical stress. No phase separation was observed even after centrifugation at 10,000 rpm for 10 min. The chemical stability of sumatriptan in OG formulations was also found to be good. The results are shown in Table 1. The assay of drug was more than 95% in all the formulations at the end of 4 weeks at room temperature (~25°C). The formulations became stiffer over a 28 days period. Hence, the viscosity studies were performed. The viscosities of the OG formulations were found to increase with time suggesting the rearrangement of the tubular network into more dense conformation. There was slight increase in the viscosity from the formulation OG-a to OG-3, i.e., with increasing drug concentration in OGs at each time point. A representative shear versus viscosity curve for OG-1 formulation is shown in Fig. 4.

CONCLUSION

Organogel system of sorbitan monopalmitate/polysorbate, isooctane and water shows phase behavior depending on hydrophobic/hydrophilic surfactant ratio and drug concentration in the composition. Increase in the drug concentration in the OG composition increases T_g due to denser network formation as a greater respective fractal dimension value was obtained. The sumatriptan permeation through biological membranes was improved from OG formulations due to combination of effects- penetration enhancing concentrations of solvent, high amounts of surfactants and high drug loading. The stress and storage stability of OGs were good for 4 weeks. The rearrangement of OG microstructural network occurs on storage making it stiffer. The properties of organogel system developed suggest its potential for transdermal delivery of sumatriptan.

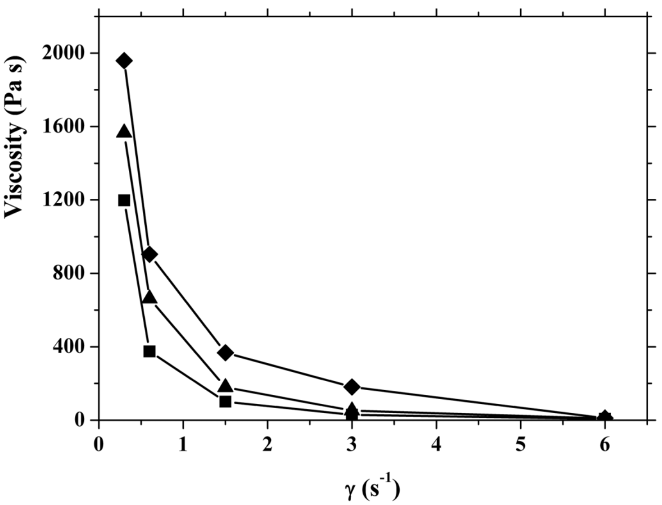

FIGURE 4 **A Representative Flow-Curves of Sumatriptan Containing OG Formulations. The Curves are Obtained for OG-1 at Initial (Squares), 14 days (Triangles) and 28 days (Diamonds) Time Points.**

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