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Drug Permeation through Skin Is Inversely Correlated with Carrier Gel Rigidity

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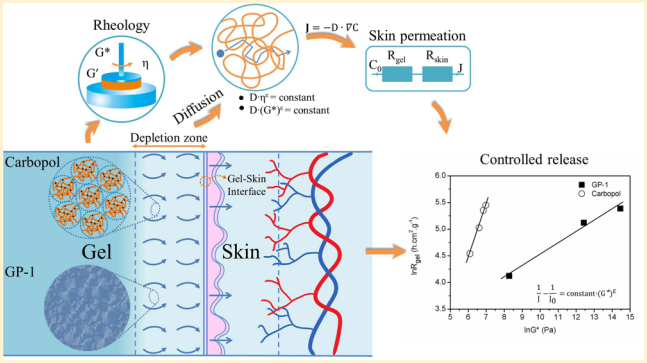
Supporting Information

ABSTRACT: Controlled release plays an essential role in formulating topical and transdermal drug delivery systems. In this study, we correlated the skin permeation of Sesamin, a lipophilic drug, with the rheological properties of two different organogel carriers, i.e., low molecular weight gelling agent *N*-lauroyl-L-glutamic acid di-*n*-butylamide (GP-1) and Carbopol polymeric gels. Although these two gels have distinct network structures, they share the same trend: the more rigid the gel network and the higher the gelator concentration, the lower the steady flux of Sesamin through skin. This negative correlation lies in the fact that organogel network hinders the diffusion of drug to the gel−skin interface; as a result, the depletion zone near the interface is non-negligible and contributes to the resistance of the whole diffusion system, and thus, the permeation flux is reduced. More interestingly, the dependence of the steady flux against gel complex modulus at the linear viscoelastic region followed a "universal" power law regardless of the gel types, i.e., $1/J = 1/J_0 + a(G^*)^{\varepsilon}/C_0$ with $a = 11.25$, $\varepsilon = 0.21 \pm 0.03$ for GP-1 gels, and $a = 0.16$, $\varepsilon = 1.05 \pm 0.06$ for Carbopol gels, J_0 is the steady flux without gel ($G^* = 0$), and C_0 is the initial concentration of drug in gels. The empirical formulae are crucial in developing transdermal organogel systems with controlled release of drug content through readily obtainable data of their rheological properties. The explanation for the power law dependence of the steady flux on gel complex modulus is discussed.



KEYWORDS: *organogel, low-molecular-weight gelator, polymeric gelator, rheological property, diffusion in organogel, Stokes−Einstein relation, skin permeation, Sesamin*

1. INTRODUCTION

Transdermal delivery has gained increasing interest as many delivery systems have passed clinical trials and were commercialized.[1] This is due in large part to their advantages over conventional routes, e.g., oral delivery, hypodermic injection, such as the reduction of first-past effects of drug components and their side effects, noninvasiveness, self-administration, painlessness, patient compliance, prolonged and sustained release.[1] Among many transdermal delivery systems, organogels have received considerable attention due to a variety of gelator−solvent systems,[2,3] skin permeability enhancement, ease of preparation, partitioning maximization of active ingredients,[3] controlled release properties.[4−6] By definition, organogels are soft materials consisting of a three-dimensional network of gelators and trapped organic liquid phase. The classification of organogel is based on gelator types or interactions among gelator molecules. For example, molecular gels or supramolecular gels are constructed by self-assembly of low molecular weight gelators (<3000) through noncovalent interactions, i.e., hydrogen bonding, $\pi-\pi$ stacking, van der Waals interaction, etc.;[7,8] while polymeric gels are either covalently cross-linked or entangled chain matrix of high molecular weight gelators (>25000). Both low molecular weight and polymeric gels are either thermo-reversible or permanent depending on the nature of network bondings.[9] Organogels have been utilized as enzyme-immobilizing medium and apolar medium for biosynthesis, enzyme-catalyzed organic reactions, bioconversion of water-insoluble substrates, separation and purification processes.[2,10] They have also found

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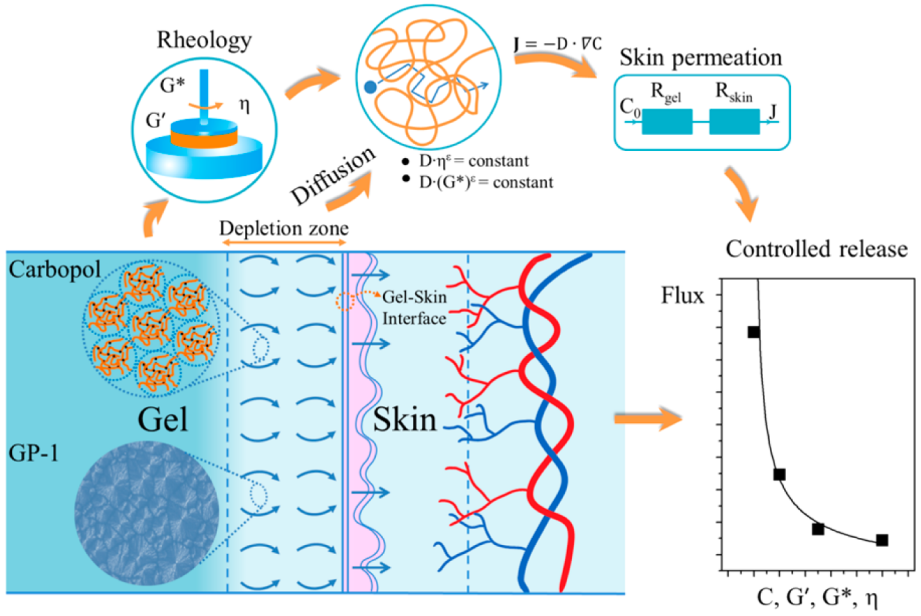

Figure 1. Schematic diagram shows the gel−skin interface with depicted Carbopol and GP-1 gel structures; the depletion zone near the interface plays as an extra layer that resists the diffusion and contributes R_{gel} to the total resistance of the whole gel-skin system.

numerous applications in food processing, cosmetic, and lubrication industries as pharmaceutical and neutraceutical controlled release carriers, apolar component delivery medium, edible oil organogels, and lubricants.[3,11,12]

The use of organogels significantly depends on their rheological properties. The deformation and flow of organogels at a range of applied stress, shear strain, shear rate, and frequency are directly related to the knowledge of how they behave at storage and application conditions, e.g., sedimentation stability, rubbing, spreading, extrusion, squeezing, pumping, pouring, pick−up, etc. This knowledge is necessary for product formation, product quality control, and customer compliance. Moreover, rheological properties of organogels, e.g., complex, storage and loss moduli, apparent viscosity, compliance, consistency, and relaxation time, are related to their mesh size, bonding, crystallinity, configurational rearrangement, modes of molecular motion, and cross-link density.[13,14] Therefore, data obtained from rheology measurement provide information on the microstructure of organogel systems, intermolecular interactions of polymer chains or gelators and polymer/gelator−solvent interactions,[15] which are indispensable for gel formation, characterization, and applications. Thus, the correlation of gelator concentration and rheological properties with drug diffusion and permeation would give us comprehensive and readily obtainable parameters for describing not only organogel network structure and their response but also transport phenomena in organogel matrix. However, which rheological properties should be correlated to the diffusion of drug content is somewhat difficult to be established.

To this end, one may recall the Stokes−Einstein (SE) relation, which describes the dependence of diffusion coefficient D on medium viscosity η, diffusant size r, and absolute temperature T as $D = kT/6\pi r\eta$ (where k is the Boltzmann constant) or $D\eta$ = constant (at constant temperature and diffusant size), for the correlation and prefer viscosity than any other bulk properties. Nevertheless either choosing a local viscosity (microviscosity η_μ) or a global viscosity (steady shear viscosity or apparent viscosity η) of the solution does matter to validate the SE equation, and many dispersion systems have been shown not to follow the SE relation but the fractional SE relation $D\eta^\varepsilon$ = constant.[16−19] Shear modulus G and storage modulus G' may be other choices as they are related to the cross-link density, mesh size, and gelator concentration, which influence the diffusion of drug in gel network.[20−22] In this study, we choose complex modulus G^* or complex viscosity η^* as a control factor over G' and η for the following reasons: The use of G^*, η^*, or η in correlation with diffusion in gel network does not matter in the linear viscoelastic limit according to Cox−Merz rule, which stated that the function of η with respect to shear rate $\dot{\gamma}$ in steady shear flow should be the same as that of complex viscosity $|\eta^*|$ with respect to frequency ω in oscillatory shear, i.e., $|\eta^*|\ (\omega \to 0) = \eta\ (\dot{\gamma} \to 0)$, and complex viscosity is proportional to complex modulus as by definition $\eta^* = \eta' - i\eta'' = G^*/i\omega = G' + IG''/i\omega$ ($i = (-1)^{1/2}$ is an imaginary unit) where $\eta' = G''/\omega$ is the dynamic viscosity, $\eta'' = G'/\omega$ is the imaginary part of complex viscosity, $G'' = |G^*| \sin \delta$ is the loss modulus, $G' = |G^*| \cos \delta$ is the storage modulus, and δ is the phase angle.[23] In addition, we can approximate $|G^*| = (G'^2 + G''^2)^{1/2} \approx G'$ with no detrimental error in solid gels with $G' \gg G''$ (from now on we refer to G^* as $|G^*|$, the module of complex modulus, unless otherwise specified). Therefore, within the linear viscoelastic limit region the fractional SE relation may be rewritten as $D(G^*)^\varepsilon$ = constant, which will be referred to as the generalized fractional SE relation. This generalized SE relation, along with the fractional SE formula, establishes the link between rheological properties and diffusion, thus they play a central role in controlled release problems.

To demonstrate the correlation of gelator concentration, complex, storage, and loss moduli with the steady flux permeated through skin, we formulated control-release systems based on two different types of organogels, i.e., GP-1 (*N*-lauroyl-L-glutamic acid di-*n*-butylamide) and Carbopol gels. GP-1 is a low molecular weight gelator, which can form a 3D fibrous network through self-assembly process. The formation

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of GP-1 network is initiated by the emergence of super nuclei followed by crystallographic mismatch branching, which results in a single or multidomain spherulitic network structure.[24] In contrast, Carbopol is a polymeric gelator, which has very high molecular weight. Carbopol gel can be considered as a dispersion of swollen microgel particles in solvent with an expanded configuration of polymer molecules due to the electrostatic repulsion of the negatively charged polymer chains.[25] As a result, Carbopol gelation largely depends on pH, ionic strength, and polymer concentrations.[14,26,27]

We used Sesamin as a model drug for skin permeation study. It is a functional lignan found in sesame seeds and can be potentially useful for the treatment of pain and inflammatory diseases such as arthritis. It has been proven to be able to inhibit inflammation responses by inhibiting ERK1/2- and NF-κB-related signaling pathways and thus is potentially useful for inflammatory diseases.[28] In addition, Sesamin has been found to reduce cytosolic reactive oxygen species levels, prevent intracellular oxidation, and maintain cell survival.[29] With its high lipophilicity (log P = 4.064) (SciFinder, calculated using Advanced Chemistry Development (ACD/Laboratories) Software V11.02), Sesamin is sparingly soluble in aqueous solutions but has higher solubility in organic solvents. For this reason, Sesamin was proposed to be formulated into organogels for topical treatment of arthritis. Propylene glycol (PG) was chosen as the solvent because Sesamin has good solubility in it, and it is commonly used in topical and transdermal formulations as both a solvent and a cosolvent type penetration enhancer.[30] Moreover, PG can be a good choice for the formation of organogel without the addition of emulsifier for lipophilic drug as compared to hydrogel systems.[31,32]

In this study, our treatment is depicted in Figure 1, which shows the gel−skin interface and the illustration of the correlation between rheology and controlled release. As discussed earlier, this correlation can be established via the fractional Stokes−Einstein relation, $D\eta^{\varepsilon}$ = constant, or the generalized fractional SE relation, $D(G^*)^{\varepsilon}$ = constant, in the viscoelastic limit region, where $0 \leq \varepsilon \leq 1$.[33]

2. MATERIALS AND METHODS

2.1. Materials. Sesamin was supplied by Dr. Prachya Kongtawelent from the Chiang Mai University, Thailand. Acetonitrile (HPLC grade) was purchased from Tedia, USA. PG, menthol, camphor, and methyl salicylate were obtained from Sigma-Aldrich, USA. Triethylamine was purchased from Alfa Aesar, U.K. Capsaicin (14% USP oleresin capsicum), lauryl lactate, and myristyl lactate were gifts from Kalsec Inc., USA. Carbopol Ultrez 21 was bought from Lubrizol, USA. GP-1 was a gift from Ajinomoto Co., Inc., Tokyo, Japan. All materials were used as supplied.

2.2. Preparation of Organogels. Camphor was found to enhance the skin permeation of Sesamin (Supporting Information 1). So it was formulated into the organogels as a penetration enhancer. To prepare GP-1 organogels, measured amounts of GP-1 (2%, 5%, or 10%, w/w), camphor (5%, w/w), and PG were put in a beaker covered by aluminum foil, vortexed, and dissolved at 90 °C. Then the solution was cooled to 70 °C and vortexed with Sesamin (0.21%, w/w) added. After Sesamin was completely dissolved, the solution was cooled at room temperature and a white, opaque gel was formed. To prepare Carbopol organogels, measured amount of Sesamin (0.21%, w/w), camphor (5%, w/w), and PG were put in a beaker covered by aluminum foil, vortexed, and dissolved. Then Carbopol (0.5%, 0.75%, 1%, or 1.5%, w/w) was added and vortexed until the viscous solution appeared visually homogeneous. An appropriate amount of neutralizer triethylamine was then added into the viscous solution to generate a transparent gel (∼pH 6).

2.3. Organogel Characterization by Optical Microscope. GP-1 organogels were prepared and transferred onto a glass slide at 90 °C, covered with a coverslip, and then observed immediately under phase contrast microscopy (Nikon Eclipse Ti, Japan) to view the gelation process of GP-1 organogel.

2.4. Rheological Study. The rheological properties of the two organogels were determined using a Bohlin Gemini rotational rheometer (Bohlin Gemini HR nano, Bohlin Co., U.K). Organogel samples were placed between two plates with adjustable gap. The lower plate was fixed; the upper plate is connected with the measuring system through a chuck. Amplitude sweep was measured using the oscillation mode with a 20 mm plane plate at controlled strain 0.1−100%, frequency 1 Hz, and gap 0.5 or 0.7 mm. GP-1 gel was first melted at 90 °C, then the clear solution was transferred immediately to the lower plate of the rheometer for *in situ* measurement of GP-1 gel formation. All other rheological measurements of GP-1 gels were conducted beyond gelation time. Carbopol gels were transferred to the lower plate using spatula to minimize preshear.

2.5. *In Vitro* Skin Permeation Study. *In vitro* skin permeation study was carried out by using horizontal diffusion cells (TK-6H1, Shanghai Kai Kai Science and Technology Co., Ltd., China) with an exposed area of 1.131 cm^2. The use of animal skin was approved by the NUS Institutional Animal Care and Use Committee. Whole thickness, intact abdominal skins were removed from rats by blunt dissection. Adhering fat and other visceral debris were carefully removed. The prepared skin sample was then mounted between donor and receptor compartments of the cells and clamped with its dermal side in contact with the receptor medium. Four milliliters of organogel was placed into the donor compartment. Four milliliters of 70% v/v ethanol solution was used as the receptor medium to ensure sink conditions.[34−36] The solubility profile of Sesamin in various solvents was tabulated in Supporting Information 2. One milliliter of samples was taken from the receptor compartments and then replaced with one milliliter of fresh receptor solution (i.e., 70% v/v ethanol). The amount of Sesamin permeated to the receptor media at predetermined time points was analyzed by using high-performance liquid chromatography (HPLC). The *in vitro* permeations of the various Sesamin formulations with different gelators and concentrations were measured in triplicates. The accumulated amount of Sesamin that permeated to the receptor media was measured as a function of time. The gradient of the linear portion of the plot yielded the steady-state flux.

2.6. HPLC Analysis of Sesamin. Sesamin quantification was done with Hitachi L2000 LaChrome Elite HPLC system using a Hypersil ODS C18 column (4.6 mm × 250 mm, 5 μm). UV detection was performed at a wavelength of 288 nm. The mobile phase consisted of water (solvent A) and acetonitrile (solvent B) with a gradient elution program of solvents A and B as follows: 50−60% B for 0−3 min, 60% B for 3−8 min, 60−50% B for 8−9 min, and 50% B for 9−14 min. The flow rate was set at 1 mL/min, and 20 μL of the samples was loaded. A calibration curve was constructed by using Sesamin standard solutions from 0.0005 to 0.25 μg/μL.

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3. RESULTS

3.1. Dynamic Formation of GP-1 Gel. The formation of GP-1 gel at different gelator concentration was captured using both optical microscope and rheometer as shown in Figure 2.

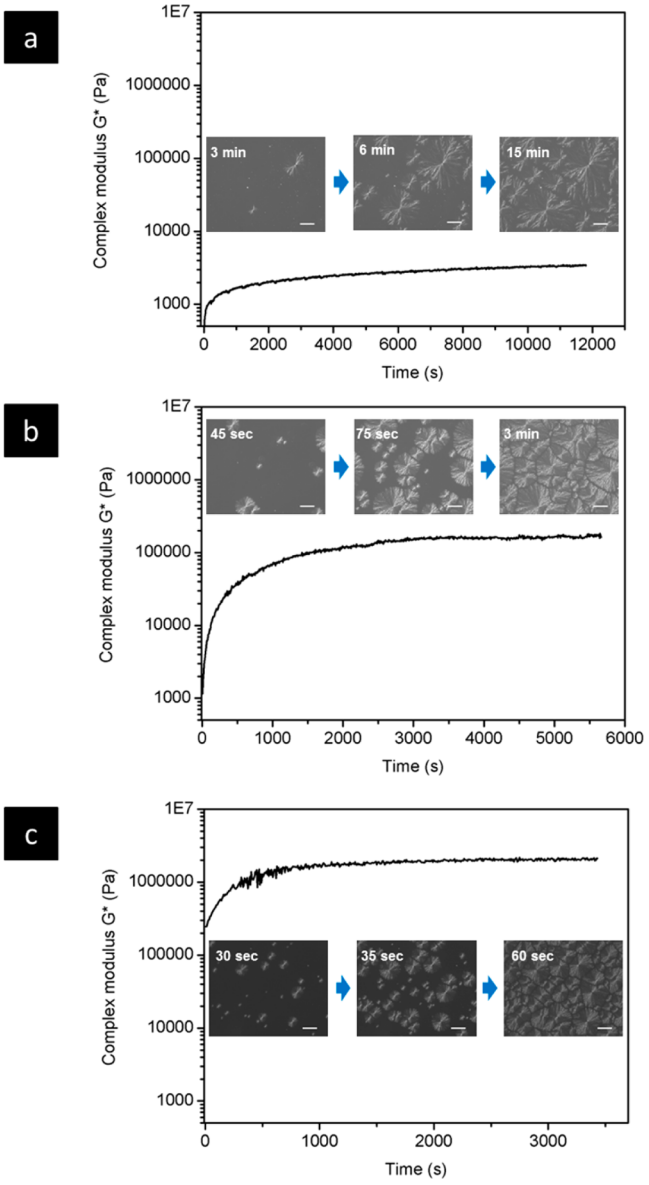

Figure 2. Network formation of GP-1 gels at different concentrations of (a) 2%, (b) 5%, and (c) 10% characterized by oscillatory measurement of complex modulus versus time and the corresponding microscopy images (scale bar 100 μm).

Nucleation centers were initially formed due to supercooling of the melt, followed by the growth of supernuclei. The increase in number and size of nuclei results in the increase of viscosity and complex modulus (or storage modulus). Thus, network formation of GP-1 is characterized by the rise of complex modulus G^* (or storage modulus G') as described in the oscillatory measurement of G^* versus time. Additionally, nucleation, growth, and branching of GP-1 gels were followed by an optical microscope as shown in the insets. The higher the GP-1 gelator concentration, the more nuclei are formed and the smaller the nuclei size. It is due to the fact that the nucleation rate is higher when the supersaturation (proportional to the gelator concentration) of the systems increases. Thus, the microscopic images in panel c show that, within less time, more nuclei but smaller size than those in panels a and b. When gel is completely formed, the system reaches equilibrium.

It follows that G^* curve reaches plateau and G^* approaches the $G^*_{plateau}$ value, as do G' and G''. For fibrous network materials, Liu's group has shown that $G'_{plateau}$ depends on the density of branching points or the average mesh size of the network characterized by the correlation length ξ in a power law $G'_{plateau} \approx \xi^{-p}$ (p is a constant ~0.5−1.7) for GP-1 and agarose gels.[22,37] The correlation length ξ is controlled by mismatch branching, which depends on the supersaturation of the system. On the basis of the nucleation kinetic model, the mismatch branching is enhanced when the supersaturation increases.[22] As a result, the gel network will become more branched and denser at increasing supersaturation; thus, it has smaller correlation length or mesh size, which results in a higher $G'_{plateau}$ and also a higher $G^*_{plateau}$. However, $G'_{plateau}$ cannot go infinity due to the competing effects of the mesh size and the number of nuclei on $G'_{plateau}$. The smaller the mesh size, the higher the $G'_{plateau}$; in constrast, the more nuclei the lower the $G'_{plateau}$. At moderate supersaturation, the effect of mesh size on $G'_{plateau}$ is dominant, which results in the increase of stiffness with gelator concentration as described in Figure 2. However, at high supersaturation, the effect of number of nuclei on $G'_{plateau}$ may be comparable with that of the mesh size; as a result, $G'_{plateau}$ will reach the maximum value at high concentration, as does $G^*_{plateau}$.[22]

3.2. Rheological Study of GP-1 and Carbopol Organogels. Figure 3 shows amplitude sweep measurements of GP-1 and Carbopol organogels. The results featured typical behavior of viscoelastic materials when they are subjected to a sinusoidal oscillation at a constant frequency (f = 1 Hz) and increased strains from 0.1−100%. At low strain, both GP-1 and Carbopol show linear viscoelastic region (LVR) at which G' and G'' remain unchanged and G' is always greater than G''. Within this region of strain, these two gels are elastic, i.e., they recover to the original shape when the shear is removed. When the strain increases beyond the critical strain (γ_C) at which plastic deformation (or nonrecoverable deformation) occurs, G' start to decrease and G'' simultaneously increase. It follows that the systems reach the nonlinear viscoelastic region and the gel network is partially broken. Before the crossover point where $G' = G''$, these two gels are solid like ($G' > G''$ or phase angle $\delta < 45°$). After the onset of the crossover point, the gel network structure is almost broken and gels will start to flow; thus, the crumbled gels behave as liquid ($G'' > G'$, $\delta > 45°$).

Although the two gels share the same viscoelastic features, they are distinct from each other due to the marked dissimilarity of their network structures. GP-1 is a crystalline gel made up of highly aligned rigid chains and thus possesses high storage modulus but small critical strain ($\gamma_C \approx 0.01$) prior to plastic deformation. In contrast, Carbopol is a polymeric gel with flexible and entangled long chains, which can resist a large deformation ($\gamma_C \approx 0.16$) before nonrecoverable change. Therefore, Carbopol gel is more ductile but has much lower storage modulus than GP-1 gel. For consistent data of measurement of flux J versus gel moduli, all permeation tests and amplitude sweep measurements were conducted on equilibrium gels, and G^*, G', and G'' were taken at plateau regions of the dynamic formation curves and the linear viscoelastic regions of G^*, G', and G'' versus strain curves.

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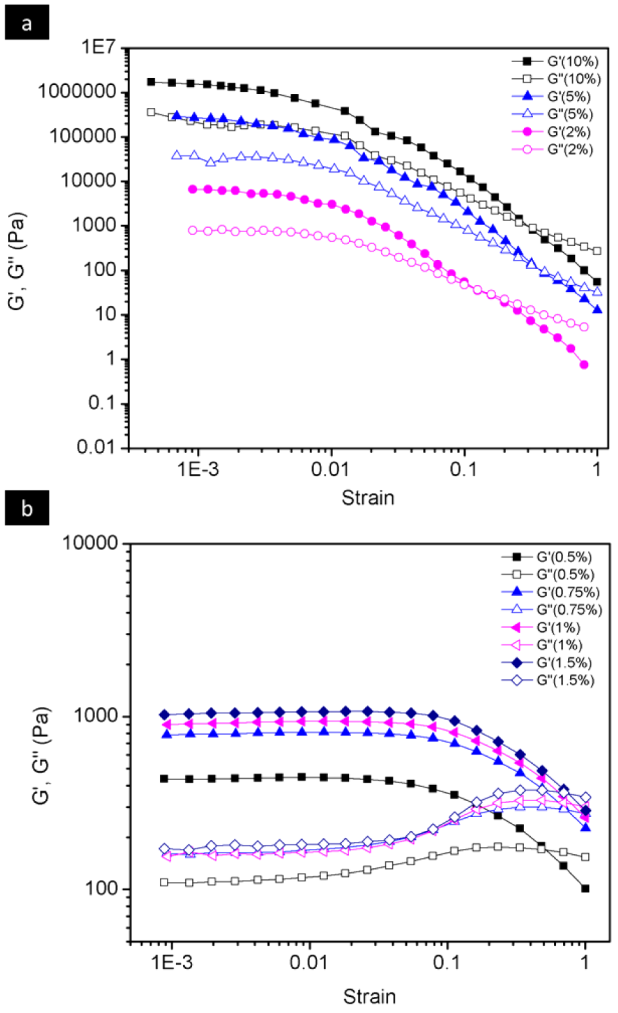

Figure 3. Amplitude sweep measurements: strain dependence of storage and loss modulus of (a) GP-1 and (b) Carbopol organogels.

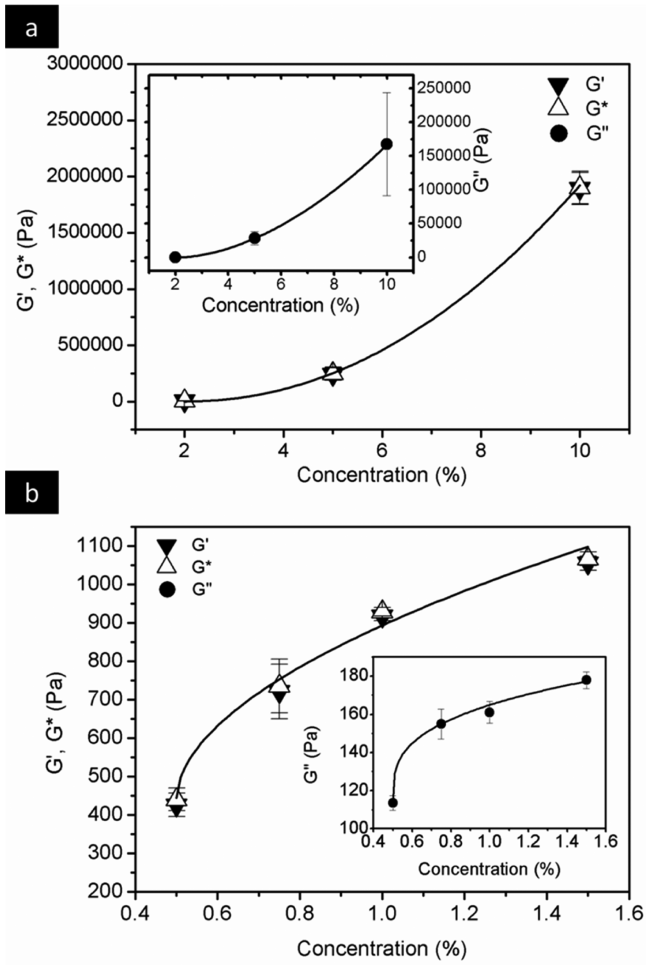

Figure 4. Dependence of complex, storage, and loss moduli on (a) GP-1 and (b) Carbopol concentration (the solid curves are guides to the eye).

The dependence of complex, storage, and loss moduli on gelator concentration for both gels is illustrated on Figure 4. The moduli of GP-1 and Carbopol increase with the gelator concentration. However, the curves of the two gels follow different functions. While the moduli versus concentration graph of GP-1 follows a convex function, that of Carbopol, in contrast, follows a concave function.

3.3. *In Vitro* Permeation Study. The amount of drug permeation through skin using two types of organogels at varied gelator concentrations is shown in Figure 5. The significance of difference was analyzed using ANOVA analysis ($p < 0.05$). All curves in Figure 5 demonstrate a lag-time profile, which is analogous with the theoretical consideration of diffusion through a membrane with drug reservoir maintained at donor side, sink condition at the receptor site, and without preloaded drug in the membrane:[38,39]

$$M(t) = A_{\text{skin}} l_{\text{skin}} C_{\text{skin0}} \left(\frac{D_{\text{skin}} t}{{l_{\text{skin}}}^2} - \frac{1}{6} - \frac{2}{\pi^2} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} e^{(-n^2 \pi^2 D_{\text{skin}} t / {l_{\text{skin}}}^2)} \right) \quad (1)$$

where $M(t)$ is a cumulative amount of drug permeated through skin at the receptor side at time t; A_{skin}, l_{skin}, and D_{skin} are the surface area, the thickness, and the diffusion coefficient of skin membrane respectively, and C_{skin0} is the concentration of drug at the surface of the skin, which is in contact with the donor compartment. At the steady state, $C_{\text{skin0}} = KC_0$ where K is the partition coefficient related to the distribution of drug content at the organogel–skin interface, C_0 is the concentration of drug

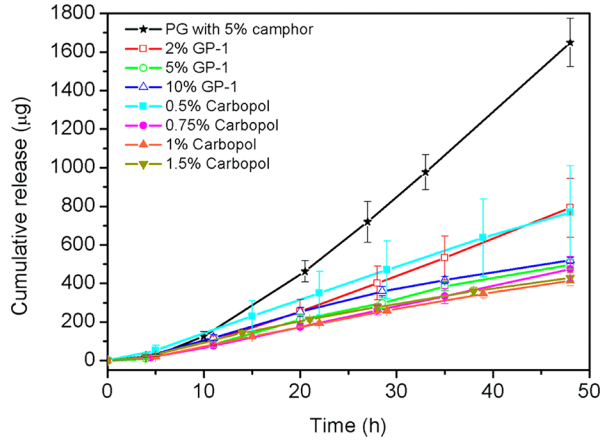

Figure 5. Time dependence of cumulative amount of Sesamin permeated through skin.

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Table 1. Flux (J), Organogel−Skin Resistance (R_{total}), Organogel Resistance (R_{gel}), and Complex Modulus (G^*)[a]

	$C_{gelator}$ (% w/w)	Flux ($\mu g \cdot cm^{-2} \cdot h^{-1}$)	R_{total} ($h \cdot cm^2 \cdot g^{-1}$)[b]	R_{gel} ($h \cdot cm^2 \cdot g^{-1}$)[c]	G^* (Pa)
Solvent	0	44.34 ± 4.20 = J_0	47.65 ± 4.50 = R_{skin}	0	
GP-1	2	19.55 ± 3.26	109.32 ± 16.91	61.67 ± 12.66	3914 ± 688
	5	10.03 ± 2.08	214.82 ± 39.79	167.17 ± 36.01	249991 ± 57440
	10	8.15 ± 1.63	265.61 ± 60.22	217.97 ± 56.48	$1.90 \times 10^6 \pm 0.14 \times 10^6$
Carbopol	0.5	15.73 ± 4.91	141.35 ± 37.56	93.70 ± 41.72	440 ± 29
	0.75	10.74 ± 1.96	199.46 ± 32.85	151.81 ± 33.10	735 ± 70
	1	8.20 ± 1.03	258.62 ± 30.17	210.97 ± 30.44	929 ± 11
	1.5	7.53 ± 0.45	279.57 ± 16.30	231.92 ± 17.53	1066 ± 18

[a] $C_{Sesamin}$ = 2.1 mg/g. Linear least-squares fit: (a) ln $R_{GP-1\ gel}$ = 2.42 (±0.32) + 0.21 (±0.03)·ln G^* (R^2 = 0.9679); (b) ln $R_{Carbopol\ gei}$ = −1.86 (±0.43) + 1.05(±0.06)·ln G^* (R^2 = 0.9886). [b] $R_{total} = C_0/J$. [c] $R_{gel} = R_{total} - R_{skin}$.

in the donor compartment. The flux of drug permeated through skin can be calculated by eq 2:

$$J(t) = \frac{1}{A_{skin}} \frac{\partial M(t)}{\partial t} \tag{2}$$

At steady state we have

$$M(t \to \infty) = \frac{A_{skin} C_{skin0} D_{skin}}{l_{skin}} \left(t - \frac{{l_{skin}}^2}{6 D_{skin}} \right) \tag{3}$$

$$J_0 = \frac{C_{skin0} D_{skin}}{l_{skin}} = \frac{K C_0 D_{skin}}{l_{skin}} = \frac{C_0}{R_{skin}} = \text{constant} \tag{4}$$

As a result, the steady flux of Sesamin permeation through skin can be obtained from the slopes of the lag-time profile curves at a sufficient long period of time. With the presence of organogels on the skin, the diffusion of the drug content to the gel−skin interface is hindered by either hydrodynamic interaction or obstruction effect of high viscosity and dense network structure of applied organogels, as a result the depletion zone near the interface play as an extra layer that resists the diffusion.[39] In this case, the nonsteady solution of the cumulative amount of drug at the receptor $M(t)$ is more complicated than that described by eq 1. However, the solution for the steady state can be easily calculated as

$$J = \frac{C_0}{R_{d\text{-}zone} + R_{skin}} = \frac{C_0}{R_{gel} + R_{skin}} = \frac{C_0}{\frac{l_{d\text{-}zone}}{D_{gel}} + \frac{l_{skin}}{K D_{skin}}} \tag{5}$$

where J is the steady flux with the presence of gels on the skin interface, $R_{d\text{-}zone} = l_{d\text{-}zone}/D_{d\text{-}zone}$, $R_{skin} = l_{skin}/KD_{skin}$ are the resistance to diffusion of the depletion zone and skin, respectively, and $D_{d\text{-}zone} = D_{organogel}$ is the diffusion coefficient of drug in the organogels.[39,40] Equation 5 shows that the steady flux is positively correlated to the diffusion coefficient of drug in gel network. If the depletion of drug content near the interface is negligible ($l_{d\text{-}zone} \approx 0$, $D_{d\text{-}zone} \gg D_{skin}$), which can be achieved by using a vigorous stirrer and solvent with low viscosity, we return to eq 4. From eqs 4 and 5 we have

$$R_{gel} = \frac{C_0}{J} - \frac{C_0}{J_0} = \frac{l_{d\text{-}zone}}{D_{gel}} \tag{6}$$

Equations 4 and 6 allow us to determine R_{skin}, R_{gel}, and the correlation between J and complex modulus using the obtained data on J, the known concentration C_0 of the drug content at the donor site, and G^*.

Table 1 shows the values of R_{skin}, R_{gel}, and R_{total} at different gelator concentrations, along with the data of permeation flux and corresponding mean values of complex modulus. The mean values and their standard deviation of G^* in Table 1 were estimated from 30 points at plateau regions and 6 points at the linear viscoelastic regions (for 3 repeated measurements). It follows from Table 1 that (i) the steady flux of Sesamin through skin is inversely correlated with gelator concentration and complex modulus of applied gels, regardless of the gel types, (ii) R_{gel} is positively related to gelator concentration and complex modulus, and (iii) within the range of studied concentration the steady flux can be controlled up to ∼6-fold difference.

3.4. Control Factors of Sesamin Drug Permeation through Skin. With the data obtained from Table 1, the steady flux of Sesamin permeation through skin was plotted against gelator concentrations and gel moduli (complex, storage, and loss moduli) as shown in Figures 6 and 7. The

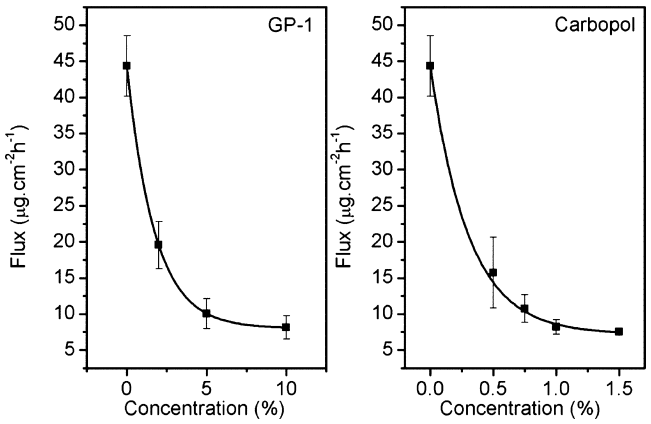

Figure 6. Dependence of flux on gellator concentration in two organogel systems (the solid curves are guides to the eye).

steady flux decreases when gelator concentration and gel moduli increase for both gels. This result is quite obvious but not easy to interpret if we neglect the depletion zone near the gel−skin interface. G' and G^* plots are almost superimposed; as a result, G' and G^* can be used interchangeably.

The plot of ln R_{gel} against ln G^* shows the straight lines that indicate a power law dependence of R_{gel} against G^* (Figure 8), i.e., $R_{gel} = A(G^*)^{\varepsilon}$ where A and ε are constant and depend on diffusant-gel types. This gives us a measurable quantity G^* that can be used to predict the Sesamin flux permeation through skin via eq 7:

$$\frac{1}{J} - \frac{1}{J_0} = \frac{A(G^*)^{\varepsilon}}{C_0} = \text{constant}(G^*)^{\varepsilon} \tag{7}$$

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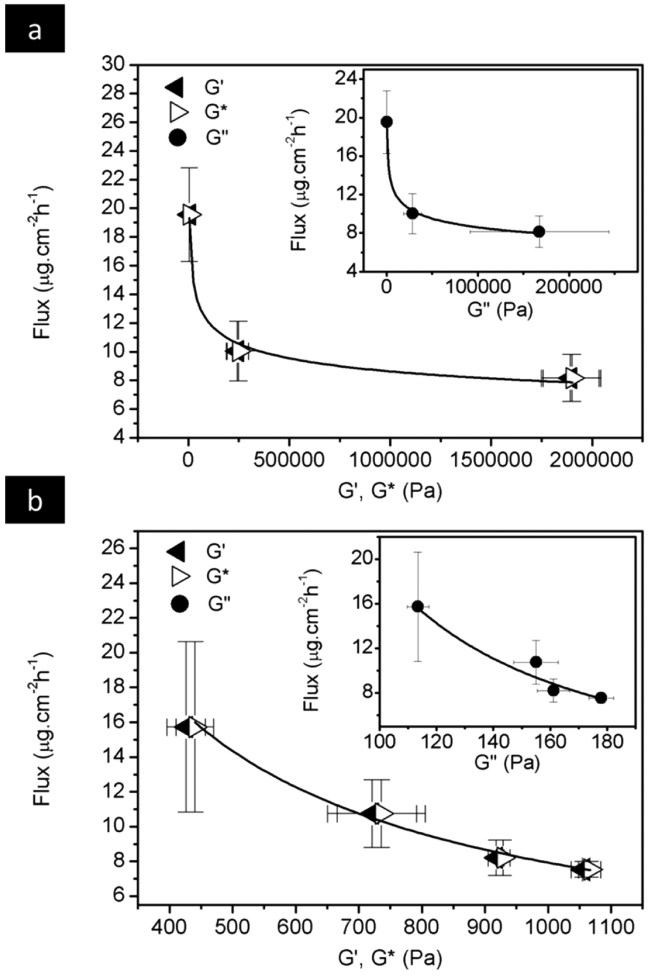

Figure 7. Correlation of flux with the complex, storage, and loss moduli of (a) GP-1 and (b) Carbopol organogels (the solid curves are guides to the eye).

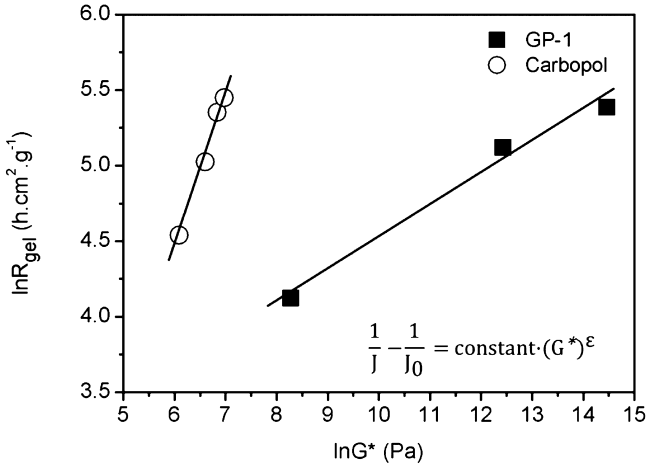

Figure 8. The plot of ln R_{gel} versus ln G^* shows power law dependence of R_{gel} or J against G^*.

The linear least-squares fitting method gave the following formulas (Table 1): $R_{GP\text{-}1} = 11.25G^{*0.21\pm0.03}$, and $R_{Carbopol} = 0.16G^{*1.05\pm0.06}$, and subsequently, the steady flux can be calculated as $J_{GP\text{-}1} = 2100/(11.25G^{*0.21} + 47.65)$ $\mu g \cdot cm^{-2} \cdot h^{-1}$) and $J_{Carbopol} = 2100/(0.16G^{*1.05} + 47.65)$ $\mu g \cdot cm^{-2} \cdot h^{-1}$).

4. DISCUSSION

Both GP-1 and Carbopol organogels showed the same trend in controlling the steady flux of Sesamin through skin: the more rigid the gel and the more concentrated the gelator, the lower the steady flux. However, Sesamin diffuses faster in GP-1 than in Carbopol, as the steady flux $J_{GP\text{-}1} > J_{Carbopol}$ at the same concentration of gelator when extrapolated from the experimental range of gelator concentration ($J_{2\%GP\text{-}1} \approx 2.7J_{1.5\%Carbopol} > 2.7J_{2\%Carbopol}$). It is probably due to the effect of gelator molecular weight on the diffusion through gel network. The increase in molecular weight results in the effectiveness of retarding the motion of diffusants. One might refer to phenomelogical scaling law model by Phillies, which has proved to fit experimental results quite well in a wide range of ternary diffusant−polymer−solvent systems, to describe the diffusion of drugs in the polymer/gel network:

$$D = D_0\, e^{-\alpha c^{\upsilon} M^{\gamma} r^{\delta}} = D_0\, e^{-\beta c^{\upsilon}} \quad (8)$$

where D_0 is the diffusion coefficient of diffusant in pure solvent, D is the diffusion coefficient of diffusant in an organogel network, c and M are the concentration and molecular weight of polymer or gelator, respectively, r is the size of diffusant, α is constant, $\upsilon = 0.6-1.0$, $\gamma = 0.8 \pm 0.1$, and $\delta = -0.1-0$ are scaling coefficients, which vary with systems and concentration range of the polymer/gelator, and $\beta = \alpha M^{\gamma} r^{\delta}$ is constant for specific gel-diffusant systems.[41,42] From eq 6 we can see that $M_{Carbopol} \gg M_{GP\text{-}1}$, then $D_{GP\text{-}1} > D_{Carbopol}$, which results in $J_{GP\text{-}1} > J_{Carbopol}$ at the same concentration of gellators. This explains the faster diffusion of drug in GP-1 gel than in Carbopol gel. From equations (a) and (b) in Table 1, we have $\Delta R_{GP\text{-}1}/R_{GP\text{-}1} = 0.21\Delta G^*/G^*$ and $\Delta R_{Carbopol}/R_{Carbopol} = 1.05\Delta G^*/G^*$. When G^* increases 1%, the diffusion resistance of GP-1 gel increases 0.21% and that of Carbopol gel increases 1.05%. It means that Carbopol gel is more effective in retarding the diffusion of Sesamin than GP-1 gel. The power law dependence of gel resistance against complex modulus may be interpreted by the fractional SE law $D\eta^{\varepsilon} \approx$ constant or the generalized fractional SE law $D(G^*)^{\varepsilon} \approx$ constant with $0 \le \varepsilon \le 1$.[33,43] With the assumption of constant $l_{d\text{-}zone}$ for the same gel systems ($l_{d\text{-}zone}$ may vary with different gel systems), we have $R_{d\text{-}zone} = R_{gel} = \text{constant}(G^*)^{\varepsilon}$, which is in good agreement with the obtained experimental data. For Carbopol gel, $\varepsilon = 1.05 \pm 0.06$ is approximately equal to 1 in our study, and we can consider the diffusion of Sesamin in Carbopol gel to follow the SE model. This remark is also in agreement with data obtained from literature.[44,45] With $\varepsilon = 0.21 \pm 0.03$, GP-1 gel thus follows the fractional SE model, and to our best knowledge, this has never been considered before. It is important to note that, in this treatment, we only take hydrodynamic interactions (frictional resistance) between drug−gelator, likely the most significant, drug−solvent, and gelator−solvent into account and assume no bonding between drug and gelator (hydrogen bond and electrostatic forces) in order to use the generalized fractional SE relation. Moreover, the activity of drug in gels was also assumed constant and equal to the drug concentration within the applied concentration range of gelators for the calculation of R_{gel} in eq 6. It would be more appropriate to take into account the effect of gels on the drug activity; however, our assumption is justifiable due to the good agreement of our experimental data. The drug permeation through skin can be enhanced by using supersaturated drug systems as they offer the highest thermodynamic activity of drug agents. However,

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the supersaturated systems are unstable due to the thermodynamic driving force to form new phases and cannot be stored for a long period of time. It is known that polymers or gels are able to maintain the metastable state of supersaturated systems for a rather long storage time due to the inhibition of nucleation and growth of new phases.[46] Therefore, understanding the effect of gels on the metastable state of supersaturated systems is also beneficial for the enhancement of skin permeation. One can easily recognize that the stiffer the gel or the more viscous the gel, the longer the metastable state since the diffusion of growth units to the nucleation sites is slower in the more viscous medium.[46]

5. CONCLUSIONS

In summary, two different types of organogel systems, namely, GP-1 and Carbopol gels, were formulated as controlled release devices for delivering Sesamin through skin. The flux of Sesamin permeating through skin was negatively correlated to the gelator concentration and the complex, storage, and loss moduli of the organogel systems regardless of organogel types. The correlation was interpreted by taking into account the depletion zone at the gel−skin interface. Diffusion of Sesamin in Carbopol gel was characterized by the generalized SE relation $D(G^*)^{1.05\pm0.06}$ = constant, while in GP-1 it was characterized by the generalized fractional SE relation $D(G^*)^{0.21\pm0.03}$ = constant. The steady flux can therefore be predicted from the value of complex modulus. Our treatment in this article can be potentially applied for a wide range of transdermal delivery systems, e.g., organogel, hydrogel, microemulsion.

■ ASSOCIATED CONTENT

Supporting Information

Permeation profile and solubility studies. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

Sesamin (PubChem CID: 72307); *N*-lauroyl-L-glutamic acid di-*n*-butylamide (PubChem CID: 13628542); Propylene glycol (PubChem CID: 1030).

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

GP-1, *N*-lauroyl-L-glutamic acid di-*n*-butylamide; G′, storage modulus; G″, loss modulus; HPLC, high-performance liquid chromatography; LVER, linear viscoelastic region; PG, propylene glycol; SE, Stokes−Einstein; ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells

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