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Research paper

Gelation of microemulsions and release behavior of sodium salicylate from gelled microemulsions

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ABSTRACT

A novel gelled microemulsion was prepared in the presence of the low molecular weight gelator *N*-stearine-*N'*-stearyl-L-phenylalanine at a very low concentration. It is completely different from the conventional microemulsion-based gels (MBGs) usually formed by polymeric gelling agents, such as gelatin, agar and κ-carrageenan. The microemulsion consists of *i*-propyl myristate, Tween 80, propylene glycol and water. The gelled microemulsions showed good thermo-reversibility. The gel-to-sol transition temperature (T_{GS}) of gelled microemulsion depends upon the concentration of gelator and the composition of the microemulsions. The gelation mechanism was investigated by polarized optical microscopy (POM) and FT-IR. POM images show elongated and strand-like crystallites formed by the aggregation of the gelator, ultimately resulting in the gelation of the microemulsion. FT-IR analysis indicates that intermolecular hydrogen bonds are responsible for the formation of gelator aggregates. Water-soluble sodium salicylate was used as a model drug for the investigation of the release from the gelled microemulsions. The release profiles exhibited a controlled release and followed the first-order release kinetics. The release rates decreased with an increase of the gelator and isopropyl myristate contents. These results reveal potential applications of gelled microemulsion in drug delivery systems.

1. Introduction

Microemulsions are thermodynamically stable, macroscopically isotropic, clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules [1]. Microemulsions are receiving considerable current attention due to their numerous applications in a wide variety of areas, such as separation [2], chemical reactions [3] and material preparation [4]. The properties of microemulsions, e.g. enhanced drug solubility, protection against enzymatic hydrolysis, ease of manufacturing and permeation enhancement ability, are often superior to those of conventional formulations and have been exploited in pharmaceutics, and they play particularly an important role in drug delivery systems [5,6]. However, most of the microemulsions possess a very low viscosity and therefore their application, especially in pharmaceutical industry may be restricted due to inconvenient use [6]. To overcome this disadvantage, some gelling agents are added into the microemulsion to form microemulsion-based gels (MBGs). Generally, the gelling agents for MBGs are polymeric materials, such as gelatin [7,8], agar and κ-carrageenan [9,10].

In the recent years, the gelation of organic or aqueous fluids by low molecular weight gelators has been the subject of increasing attention [11,12]. These gelators can self-assemble into three-dimensional network structures at a low concentration, ultimately resulting in the gelation of the fluids. Unlike polymeric gels whose three-dimensional network is based on covalent linkages, the driving forces for self-assembly of gelators are mainly intermolecular interactions, such as hydrogen bonding, π–π stacking, van der Waals interactions, coordination forces, and charge transfer interactions. These thermoreversible molecular gels show great potential applications in the field of pharmaceutics, for instance, in transdermal delivery systems and in sustained release formulations [13].

Many different types of gelators have been developed and used as gelling agents for different kinds of polar and non-polar liquids. However, little attention has been paid to the gelation of multi-component microemulsion by gelators. To our knowledge, there are only few reports that describe gelled microemulsions formed by gelators, which are mainly used to prepare functional polymers. For instance, Antonietti et al. utilized a surfactant, tetrastearylammonium bromide (TSAB), as the gelling agent of miniemulsion (aqueous droplets in a continuous monomer phase) to avoid the usual demixing upon polymerization of the continuous phase [14]. This pre-gelled system was then converted into a composite polymer with aqueous inclusions of less than 1 μm in diameter by photoinitiated free radical polymerization. Stubenrauch et al.

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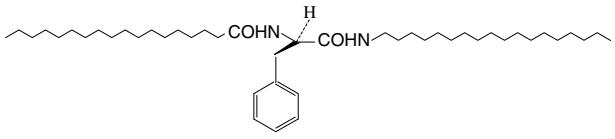

Scheme 1. Molecular structure of gelator Bis18-L-Phe.

employed 12-hydroxyoctadecanoic acid to gelatinize the oil phase of microemulsions containing the monomer *N*-*i*-propylacrylamide in the aqueous phase, and systematically investigated the phase diagrams of these gelled polymerizable microemulsions [15]. However, there are no reports that address the incorporation of drugs into the gelled microemulsion as a drug delivery system formed through the self-assembly of low molecular weight gelator.

In this work, a gelator, *N*-stearine-*N*′-stearyl-L-phenylalanine [16] (designated as Bis18-L-Phe, its molecular structure is shown in scheme 1), was used for the gelation of microemulsions. Microemulsion formulation comprises pharmaceutically permitted *i*-propyl myristate (IPM) [5], Tween 80 [17] and propylene glycol (PG). Sodium salicylate (SS) was used as a model drug. The gelation of microemulsions by Bis18-L-Phe and the release of SS from the gelled microemulsions were examined in this investigation. It is anticipated that the gelled microemulsions reported herein may lead to a potential application for localized drug delivery.

2. Materials and methods

2.1. Materials

N-Stearine-*N*′-stearyl-L-phenylalanine (designated as Bis18-L-Phe) was synthesized according to a procedure described previously [16]. *i*-Propyl myristate (IPM) and propylene glycol (PG) were purchased from Shanghai Chemical Reagent Co., Ltd. Tween 80 (98%) was purchased from Tianjin Bodi Chemical Co., Ltd. Sodium salicylate (SS) was purchased from Sinopharm Chemical Reagent Co., Ltd. All other chemicals were of analytical grade and were used as received.

2.2. Preparation of microemulsions and drug-loaded microemulsions

Microemulsions were prepared by adding weighed amounts of water to the mixtures of Tween 80, IPM, and PG under moderate magnetic stirring until transparency was obtained [18]. The compositions of the microemulsions are given in Table 1. The samples are designated as M1–M4. All samples were stable over 6 months, the remaining were clear and transparent. Alternatively, 4 wt% of SS aqueous solutions was used instead of water to prepare drug-loaded microemulsions under the same conditions.

2.3. Gelation and characterization of the microemulsions

A weighed amount of Bis18-L-Phe was mixed with a microemulsion or drug-loaded microemulsion and subsequently heated to about 75 °C under stirring until the solid was completely dissolved.

Table 1
Selected microemulsion formulations (wt%)

Sample no.	IPM	Tween 80	PG	Water or aqueous SS solution
M1	36	27	27	10
M2	27	31.5	31.5	10
M3	18	36	36	10
M4	9	40.5	40.5	10

The solution was allowed to cool to room temperature, and it exhibited no gravitational flow upon inversion of the test tube. The resulting gelled microemulsions were correspondingly designated as GM1–GM4.

The lowest concentration of Bis18-L-Phe required for gelation of the microemulsions was defined as the minimum gelation concentration (MGC). The gel-to-sol transition temperatures (T_{GS}) of the gelled microemulsions were determined by vial inverting combined with a visual method [19].

Polarized optical microscopy (POM, BH-2, Olympus): A warm (ca. 75 °C) microemulsion in the presence of 1 wt% of Bis18-L-Phe was dropped on a pre-heated glass plate, and then allowed to cool at room temperature. The samples were kept in the dark for 4 h before testing. For comparison, the microemulsion was dropped on a glass plate.

The FT-IR spectra of the microemulsions and gelled microemulsions were recorded using a spectrophotometer (EQUINOX55, Bruker). The sample was cast on a KBr slice, and then the FT-IR spectra were measured using a blank KBr slice as a background the solution spectra were obtained using a cuvette with a 1 mm path length. For the solid state measurements, the KBr disk technique was used.

2.4. Drug release from gelled microemulsions

The calibration curves were obtained by gradual dilution of SS aqueous solutions (100 mg/L). The maximum absorbance was measured at 296 nm using a UV–vis spectrometer (TU-1810, Beijing, Puxi). The curves showed excellent linear relationships between maximum absorbance and concentration in the range of 0–100 mg/L. The calibration equation was obtained as Abs = 0.02671*C* + 0.02744, where Abs is the maximum absorbance at 296 nm and *C* is the concentration of SS.

Two grams of warm (ca. 75 °C) drug-loaded (or drug free) microemulsion containing Bis18-L-Phe were placed in a cylindrical dialysis bag (synthetic cellulose membrane, MW cut-off 100,000 g/mol), and subsequently allowed to cool to room temperature. The microemulsion was gelled and allowed to stand for 2 h. The systems were equilibrated at 37 °C for 0.5 h before release measurements. Then, the dialysis bag was placed in a beaker containing 150 mL of phosphate-buffered saline (PBS, prepared with 104 mmol/L of NaH_2PO_4 and 36 mmol/L of NaCl, pH 7.4). During the release experiments, the gels in the dialysis bag were stable. No collapse of gels was observed. At convenient time intervals, 5 mL of PBS was taken from the beaker and immediately replaced by fresh PBS for maintaining sink conditions at all times. All samples were filtered using 0.45 μm MFs-millipore membrane filters (BDJK technology industry Co., Ltd., China) and assayed for SS. The amount of released SS was determined by measuring of maximum absorbance at 296 nm over a concentration range of 0–100 mg/L, using PBS from SS-free gelled microemulsions as a control to erase the disturbance of gel itself [20]. All the release experiments were carried out in triplicate.

3. Results and discussion

3.1. Preparation and characterization of the gelled microemulsions

As reported previously, Bis18-L-Phe showed an excellent ability to gelatinize a number of organic solvents [16]. Gelation experiments indicate that Bis18-L-Phe not only gelatinizes both PG and IPM to form opaque and white organogels, but also gelatinizes the microemulsion systems listed in Table 1. Gelation of microemulsions was performed by a simple method. Typically, a mixture of Bis18-L-Phe (ca. 2 wt%) and the microemulsion was heated until the solid completely dissolved and was then allowed to cool to

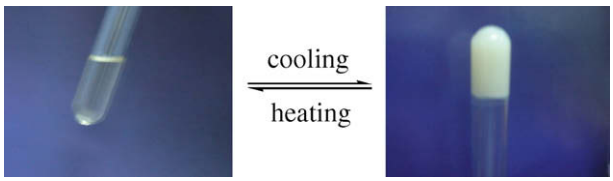

Fig. 1. Illustration of the gelation of microemulsions in the presence of Bis18-L-Phe.

room temperature (Fig. 1). Fig. 1 also indicates that the gelation of microemulsions is a typical thermally reversible process similar to that of common organogels. The gelled microemulsions show an opaque, smooth white gel at room temperature, suggesting that the gelation mechanism could be different from that of conventional MBGs, which could be ascribed to the self-assembly of Bis18-L-Phe in the organic phase [11,12].

The gelation ability of the gelator is usually characterized by the minimum gelation concentration (MGC). Table 2 lists the MGCs of Bis18-L-Phe in various microemulsions. Obviously, the MGCs of the microemulsions are much less than those of individual IPM or PG. The minimum amount of Bis18-L-Phe required for the gelation of microemulsions decreased with a decrease of the IPM content in the microemulsions. In other words, the MGCs for the microemulsions decrease with an increase of the surfactant (Tween 80) content in the microemulsions. This result can be ascribed to the cooperating effect of gelator aggregates and surfactant aggregates in the gelation of microemulsions [21,22]. Addition of Tween 80 can significantly promote the formation of three-dimensional network structures consisting of fibrillar gelator aggregates. The contribution from the surfactant could be attributed to its interfacial adsorption ability, which increases the mismatch crystallization on the fibrillar aggregates [22], leading to the lower MGCs. The gelled microemulsions exhibit an excellent stability over time, no change was found after one year of storage in a closed container.

Table 2
MGCs of Bis18-L-Phe in PG, IPM and microemulsion formulations

Sample	PG	IPM	M1	M2	M3	M4
MGCs (wt%)	1	0.9	0.5	0.45	0.3	0.15

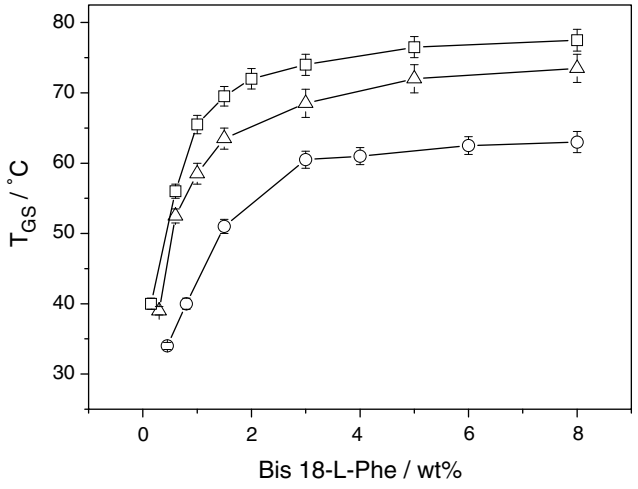

Fig. 2. The effect of Bis18-L-Phe concentration on the T_{GS} of GM2 (○), GM3 (Δ) and GM4 (□).

The thermal stability of organogels is usually characterized by the gel to sol transition temperature (T_{GS}). Fig. 2 shows the T_{GS} of gelled microemulsions as a function of the Bis18-L-Phe concentration. In general, the T_{GS} of organogels increase with an increase of gelator concentration [12]. As shown in Fig. 2, the T_{GS} of gelled microemulsions increased rapidly as the concentration of Bis18-L-Phe increased in the range of 0.5–3 wt%, indicating typical features of organogels formed primarily by the self-assembly of Bis18-L-Phe. While the concentration of Bis18-L-Phe was more than 3 wt%, the T_{GS} almost remained constant, indicating a stable and complete network structure formed within the gelled microemulsions [23]. It was found that the thermal stability of the gelled microemulsions also depends upon the composition of the microemulsions, which may be ascribed to the cooperating effect of gelator aggregates and surfactant aggregates in microemulsions as discussed above. We note that the presence of SS seems to exert no effect on the gelation ability of Bis18-L-Phe and on the thermal stability of the gelled microemulsions.

Fig. 3 shows the POM image of microemulsion and gelled microemulsion at room temperature. A distinct difference can be observed by comparing the POM images. The POM image of the microemulsion exhibits isotropy, indicating that no crystallites exist in these microemulsions. By contrast, elongated and strand-like clusters are observed from the POM image of gelled microemulsion, which can be attributed to the formation of Bis18-L-Phe aggregates. In general, the formation of gelator aggregates results in anisotropy of the organogel system. The POM observation confirms the formation of strand-like aggregates of Bis18-L-Phe in organic phase of microemulsion. The solvent molecules are immobilized by capillary forces in the three-dimensional network formed from Bis18-L-Phe aggregates [11,12,24].

To investigate the gelation mechanism of the microemulsions, an FT-IR analysis of the GM3 and solid Bis18-L-Phe was carried out. By comparison, the FT-IR spectra of M3 and a chloroform solution of Bis18-L-Phe were also recorded. As shown in Fig. 4, characteristic peaks of Bis18-L-Phe in chloroform (spectrum a) are observed at 3436, 1647 and 1523 cm^{-1}, which are assigned to

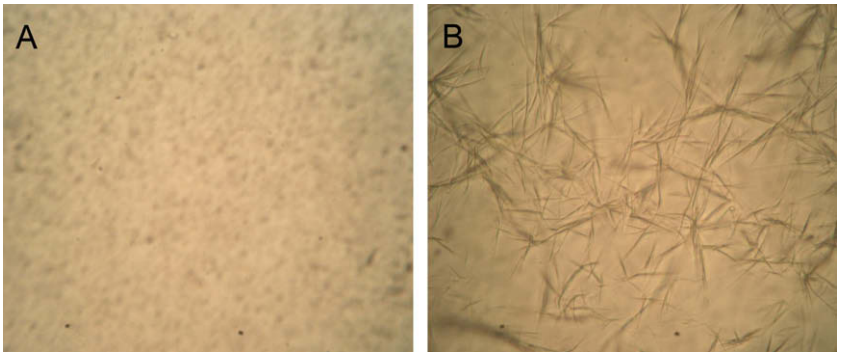

Fig. 3. Polarized optical micrographs of M3 (A) and GM3 (B).

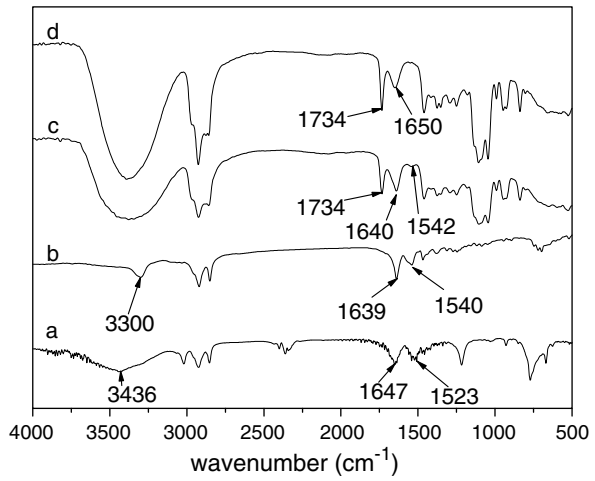

Fig. 4. FT-IR spectra of (a) Bis18-L-Phe in chloroform (4 wt%), (b) solid Bis18-L-Phe, (c) GM3 (4 wt% of Bis18-L-Phe) and (d) M3.

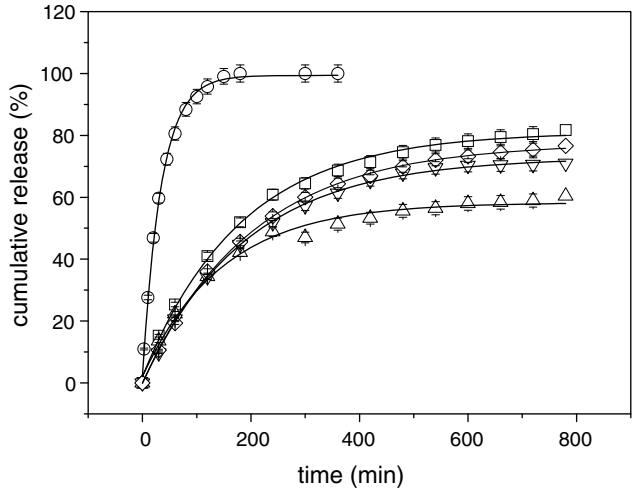

Fig. 5. Release profiles of SS from GM3 formed at 1 wt% (□), 3 wt% (◇), 5 wt% (▽) and 8 wt% (Δ) of Bis18-L-Phe, respectively. As a control, drug-loaded microemulsion (○) was tested. The lines through each set of points represent first-order kinetics fitting.

the amide N–H asymmetric stretching, the amide I and amide II bands, respectively. These characteristic peaks arise from non-hydrogen bonded amide groups of Bis18-L-Phe. However, the three peaks shift to 3300, 1639 and 1540 cm^{-1}, respectively, in the spectra of solid Bis18-L-Phe (spectrum b), indicating strong hydrogen-bonding interactions in the solid state [25,26]. Furthermore, the three typical bands corresponding to the stretching vibrations of the hydroxyl group, carbonyl group of IPM and C=C groups of Tween 80 in M3 appear at 3393, 1734 and 1650 cm^{-1} (spectrum d), respectively. In the spectrum of MG3 (spectrum c), the band corresponding to the C=C stretching is overlapped with a strong intensity band at 1640 cm^{-1} corresponding to the amide I band of Bis18-L-Phe. A new band appears at 1542 cm^{-1} corresponding to the amide II band of Bis18-L-Phe, which is similar to that in the solid state of Bis18-L-Phe. Therefore, we can conclude that the formation of intermolecular hydrogen bonds should be one of the driving forces for the formation of Bis18-L-Phe aggregates in the gelled microemulsion [27].

3.2. Drug release from gelled microemulsions

Considering that the concentration of Bis18-L-Phe has an important effect on the thermal stability and properties of the gelled microemulsions, Fig. 5 shows the release profiles of SS from the gelled microemulsions formed at several Bis18-L-Phe concentrations and from the non-gelled microemulsion as control. Since SS is highly soluble in water, SS was completely released from the non-gelled microemulsion within 2 h, displaying a typical burst release. This also indicates that the dialysis bag provides the least resistance to the diffusion of the drug [28]. By contrast, the release of SS associated within the gelled microemulsions does not exceed 50% over the same period, and displays a controlled release behavior.

Now the question is how water-soluble sodium salicylate is exactly released from the gelled microemulsion. This question involves the insight into the phase status of the microemulsion. Unlike conventional o/w or w/o microemulsion systems with a single continuous phase, we propose that the prepared microemulsions involve systems with bicontinuous phases according to the composition of microemulsion. Fig. 6 schematically shows the bicontinuous phase of a microemulsion although it could not be determined by experimental evidence. Probably, a small amount of mono-continuous phase (aqueous droplets) is also formed during the preparation of the microemulsions. The majority of the SS molecules, dissolved in aqueous phase, are released from the gelled microemulsions by the molecular diffusion. As discussed above, Bis18-L-Phe self assembles in the organic phase of the microemulsion into three-dimensional network aggregates. This may well create a physical barrier which reduces the movements of the aqueous droplets containing SS in the organic phase. Thus, part of SS cannot be released from the gelled microemulsions. For example, approximate 20% of SS is not released from the gelled microemulsion formed by 1 wt% of Bis18-L-Phe. Correspondingly, approximate 45% of SS is not released from the gelled microemulsion formed by 8 wt% of Bis18-L-Phe. This is attributed to a higher

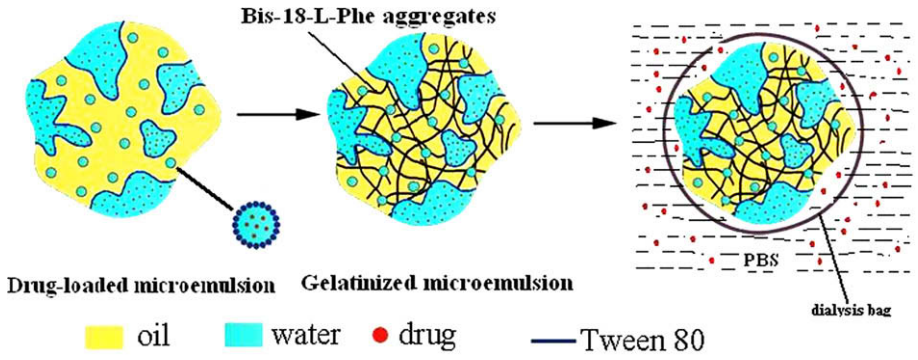

Fig. 6. Schematic representation of the release of sodium salicylate from the gelled microemulsions.

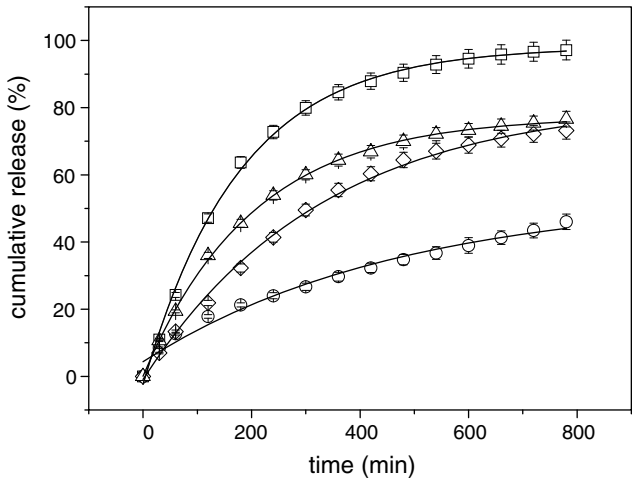

Fig. 7. Release profiles of SS from GM1 (○), GM2 (Δ), GM3 (◇) and GM4 (□) formed by 3 wt% of Bis18-L-Phe. The concentration of SS in the gelled microemulsions was 4 wt%. The lines through each set of points represent first-order kinetics fitting.

network density within the gelled microemulsion formed by 8 wt% of Bis18-L-Phe. Thus, the amount of drug release can be modulated by changing the gelator concentration.

The influence of the composition of microemulsions on the release behavior of SS was further investigated. Fig. 7 shows release rates of SS from the gelled microemulsions with varied compositions. Obviously, the release rates of SS significantly depend on the composition of the microemulsions, particularly on the content of IPM. A possible explanation involves the high hydrophilicity of SS, leading to a preferred presence of SS in the aqueous phase of the microemulsions. However, the phase status of the microemulsion can be changed from a bicontinuous phase to a water-in-oil mono-continuous phase when the IPM content is increased [6], leading to more restricted aqueous droplets, and consequently the SS molecules diffuse out of the gelled microemulsions at a longer time scale. On the other hand, the surface layer of the gelled microemulsions becomes more hydrophobic with an increase of the IPM content, restricting the diffusion of receiving medium (PBS) into the bulk gel phase, although there was no evidence of erosion of the matrices in the drug release studies.

In order to determine the release kinetics of SS from the gelled microemulsions, we assumed that the release behavior follows first-order kinetics. The release process is expressed by the following relationship [29]:

$$Q_t = Q_0(1 - e^{-kt}). \quad (1)$$

Herein, Q_t is the released amount of SS at a time t, Q_0 is the initial amount of SS in the gelled microemulsion and k is the first-order rate constant. When the sets of data points were fitted to Eq. (1) (shown as the solid lines in Figs. 5 and 7), the model fits the data accurately for all the samples and for every case the correlation coefficients were higher than 0.99. This result confirms our hypothesis about the first-order kinetics of the release of the drug.

4. Conclusions

Novel gelled microemulsions, based on self-assembly of low molecular weight Bis18-L-Phe, were prepared and used as drug delivery systems. Bis18-L-Phe exhibits an excellent ability for the gelation of microemulsions consisting of IPM, Tween 80, PG and water. The minimum gelation concentration of Bis18-L-Phe was less than or equal to 0.5 wt% according to the composition of microemulsion. T_{GS} of the gelled microemulsion is dependent on the content of Bis18-L-Phe and on the composition of the microemulsions. POM and FT-IR analysis indicated that intermolecular hydrogen bonding between the amide groups of Bis18-L-Phe should be the main driving force for the gelation of the microemulsion. Water-soluble sodium salicylate was used as a model drug to investigate release from the gelled microemulsions. The release profiles show controlled release behavior and followed first-order kinetics of release. The released amount of SS decreased with an increase in the amount of Bis18-L-Phe and IPM in the gelled microemulsions. Thus, the drug release rates can be modulated through changing the composition of the gelled microemulsions. In conclusion, the easy formation process and the controlled releasing performance should make the gelled microemulsions suitable for biomedical applications, and offer simple and safe alternatives to polymeric systems.

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