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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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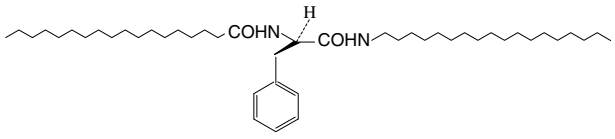

Scheme 1. Molecular structure of gelator Bis18-L-Phe.

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