Rheological properties of thermo-responsive microemulsion-based gels formed by Pluronic F68

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ABSTRACT

The thermo-responsive behavior of microemulsion-based gels (MBGs) formed by the triblock copolymer poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (F68, PEO₇₉PPO₃₀PEO₇₉) in microemulsion systems composed of isopropyl myristate (IPM)/Span20/Tween20/H₂O were characterized by rheological measurements and fluorescence spectroscopy. The results of rheological measurements indicate that the viscosities of the gels increase and the gelation temperatures decrease with increasing F68 concentration. As a model drug, chloramphenicol has little effect on the viscosities and gelation temperatures of the MBG. Moreover, chloramphenicol is sustainably released from the MBG system. Fluorescence spectroscopy was used to study the micropolarity of the hydrogel (F68/H₂O), microemulsion and MBG systems. The results show that the microstructures of microemulsion droplets are maintained in MBG after the addition of F68.

Key words: Thermo-responsive, Microemulsion-based gels, Rheological properties, Block copolymer, Drug delivery system.

INTRODUCTION

Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) [PEO₇₉PPO₃₀PEO₇₉] triblock copolymers have been widely used for controlled drug encapsulation and delivery systems, because of their amphiphilic properties and interesting temperature-induced micellization and gelation phenomena in aqueous solutions[1-5]. In the Pluronic family, the extensively studied member is F68 because F68 has a relatively long chain length (Mₘ=8400) and an appropriate n/m ratio (79/30=2.6)[6-9]. The molecular design of F68 ensures both good water solubility through the high PEO content and a high capacity for hydrophobic association through the relatively long PPO block. The unique characteristic of this copolymer is its reverse thermal gelation behavior, concentrated solutions (above 46%) of the copolymer are fluid at refrigerator temperature (4-5°C), but are soft gels at body temperature. With its relatively low toxicity and ability to form clear gels in aqueous media, the use of F68 in human skin wound cleanser has also been reported[10], and has been approved by the Food and Drug Administration. In addition, the F68 gel has been evaluated as an antibiotic carrier in wound treatment[11]. As a drug carrier, the temperature-sensitive hydrogels have many advantages, but their limitation is obvious. Such as, the solubility of oil soluble drugs in hydrogels is too low for many pharmaceutical applications. Compared with hydrogel, microemulsion-based gels can increase the solubility of oil-soluble drugs, and have good thermodynamic stability.

In this work, the MBGs which are formed by Pluronic F68 in O/W microemulsion are investigated. The objective of the present investigation is to expand on the studies previously published[12,13] in order to study in detail how the
aggregation behavior of the MBGs is affected by different PEO/PPO block ratio.

EXPERIMENTAL SECTION

Materials: Pluronic F68 (average composition, PEO<sub>79</sub>PPO<sub>30</sub>PEO<sub>79</sub>), Isopropyl myristate (IPM), Tween20 (polyethylene glycol sorbitan monolaurate) and Span20 (sorbitan monolaurate) were purchased from Sigma Chemical Co., USA. Chloramphenicol was kindly provided by FREDA BIOCHEM Co. Ltd., China. Water was purified by deionization followed by double distillation.

Sample Preparations: The phase diagram of the microemulsions (ME) was constructed and the phase transitions were investigated by electrical conductivity measurements in our previous study[14]. In this paper, the O/W microemulsion containing 3.6% Span20(concentrations reported here are expressed by percent weight), 17.1% Tween20, 2.3% IPM, and 77.0% water was chosen to form the MBG. The B.C. microemulsion containing 4.5% Span20, 27.0% Tween20, 3.5% IPM, 65.0% water was also investigated. Gels were prepared on a weight basis using the cold method[12]. In MBG systems, the concentration of F68 was kept in the range from 20.2 to 30.0%. In hydrogel systems, the concentration of F68 was fixed at 42.0%.

Rheological Measurements: The rheological properties of the gels were studied using a HAAKE RS 75 rheometer. A cone-plate sensor (20 mm diameter, 0.5˚ angle) was used. The sample thickness in the middle of the sensor was 0.052 mm. The linear viscoelastic domain was determined by shear stress sweep tests at a constant temperature of 37±0.1˚C.

In order to accurately determine the gelation temperatures, the storage modulus (G') was measured as a function of temperature at a frequency of 1.0 Hz, the temperature being increased by 1°C min<sup>-1</sup>. The transition temperature at which G' shows an abrupt increase with increasing temperature was defined as the gelation temperature[15,16].

Fluorescence Spectroscopy: Fluorescence spectra of pyrene were obtained using a Perkin-Elmer LS-55 spectrofluorometer (PE Company), at an excitation wavelength of 335 nm.

Release Test: The experiment method of release test was same as our previous study[12]. The concentration of chloramphenicol was 2.0%.

RESULTS AND DISCUSSION

Rheological Behavior
Dynamic Viscoelastic Properties
Typical results of the G’ and G” of 22.1% F68 MBG as a function of the stress at low frequency (1.0 Hz) can be seen in Fig. 1. It is observed that the sample has linear viscoelasticity up to about 100 Pa. For subsequent dynamic experiments we have chosen the stress value of 10 Pa.

Temperature Effect on Viscoelastic Behavior
The sol-gel transition temperatures of the typical samples are shown in Fig. 2. In F68+W/O microemulsion systems (curves 1-3), the samples show three distinct regions with increasing temperature. At the beginning, G’ is low but increases drastically with increasing temperature as a result of the gel forming process. The temperature at which G’ shows an abrupt increase with increasing temperature is defined as the gelation temperature[15,16]. In this region, the hydrogen bonds between central PPO blocks of F68 and water are probably destroyed, and the dehydration of PPO drives the unimers to form micelles. Beyond the transition region, the micelles are further aggregated into gels, so G' becomes independent of the temperature. The values of the G' plateau increase with the polymer concentration, whereas the gelation temperature decreases. The same phenomenon is found in hydrogels formed from F68 in aqueous solution[17]. Moreover, the G' values of the system based on the B.C. microemulsion (curve 4) are almost constant over the investigated temperature range, showing the common viscoelastic behavior of a liquid. However, the system which is based on an O/W microemulsion shows obvious temperature-sensitivity and has formed an MBG at high temperature. Not only the types of microemulsion are different, but the water contents in the formulations are different, 66.2% (curve 2) and 55.9% (curve 4). This suggests that the enough amount water is very important for forming F68 micelles and the micelles are formed in the water phase of the microemulsion.
Fig. 1 $G'$ and $G''$ of the typical MBG sample of 22.1% F68 as a function of the applied stress at a constant frequency of 1 Hz at 37.0°C

Fig. 2 $G'$ as a function of temperature at a heating rate of 1°C/min. a) Curves 1-3: F68 in W/O microemulsion systems, with F68 concentration: 20.2%, 24.0%, 28.0%, respectively; curve 4: 24.0% F68 in B.C. microemulsion; curve 5: 2% chloramphenicol in MBG and fixed concentration of F68 at 24.0%

Curve 5 shows the effect of chloramphenicol on the gelation temperature. It is observed that the effect of drug on the gelation temperature and strength is minimal, indicating that the microstructures and properties of MBGs are still...
Fluorescence Spectroscopy

Pyrene solubilization has been used previously for the determination of the cmc in block copolymer solutions[12,18,19]. In order to further investigate the microstructures of MBGs and the micropolarities of the F68 in aqueous solution, microemulsion and F68 in microemulsion, these systems were studied using pyrene as a fluorescent probe. Typical samples are shown in Fig. 3. Fig. 4 shows the $I_1/I_3$ ratios as a function of temperature. For the 42.0% F68/H$_2$O sample, at low temperature, the $I_1/I_3$ ratio is close to the value obtained from pyrene in bulk PPO 3000[18]. This indicates that micelles have been formed and that pyrene is located in the hydrophobic core of the micelles, therefore, the $I_1/I_3$ ratio should be constant with increasing temperature, once the F68 aggregates have been formed. As temperature increases, $I_1/I_3$ begin to decrease, indicating that the microenvironment around pyrene is becoming even more nonpolar. The same phenomenon was observed in aqueous PEO-PPO-PEO and bulk various organic solvents studied by Nivaggioli et al[18]. In microemulsion systems, the ratios of $I_1/I_3$ are lower than in the F68/H$_2$O system, indicating that pyrene is located in the core of the microemulsion droplets. The polarity is also affected by temperature, which causes the ratios of $I_1/I_3$ to decrease slightly with the increase of temperature. In
F68/microemulsion systems, at all temperatures investigated, the ratios of $I_1/I_3$ are constant and much closer to that in the microemulsion system, indicating that the pyrene is mostly located in the core of the microemulsion droplets, and the major structure of the microemulsion is retained after the addition of F68 into the systems.

Release Test
Fig. 5 shows a release rate graph for diffusion of chloramphenicol (2.0% concentration) from the O/W microemulsion and the 24.0% F68 MBG systems. The chloramphenicol molecules in the microemulsion show an initial fast, linear release (about 75% over the first 6 h) and then slow, but incomplete release. The chloramphenicol molecules in the MBG are sustainably released over more than 24 h. The chloramphenicol is located in the hydrophilic shells of the microemulsion droplets[12,14]. In this study, the result of fluorescence experiments indicate that the structure of the microemulsion is retained after the formation of MBG, so the drug must still be located in the hydrophilic shells of the microemulsion droplets. In both systems, the locations of the drug molecules are the same. However, the viscosity of MBG is much higher than that of the microemulsion, so the diffusion of drug molecules in the MBG is rather restricted, and the release rate is much lower.

![Graph](image)

Fig. 5 Release profiles of chloramphenicol from a microemulsion and the 24.0% F68 MBG system

CONCLUSION
In this work, thermo-sensitive microemulsion-based gels (MBGs) of Pluronic F68 have been obtained and a study of the rheological characteristics has been made. MBGs are formed in the range of F68 concentration from 22.1 to 30.0%, and the sol–gel transition temperature is decreased by increasing F68 concentration. Fluorescence spectroscopy indicates that the microemulsion structures are retained after the formation of the MBGs. The continued existence of microemulsion droplets plays an important role in enhancing the solubility and stability of oil-soluble drugs. The results of controlled release experiments show that MBG shows sustained release properties. Moreover, due to its temperature-sensitivity, MBG is superior to other drug carriers, e.g. multiple administrations are much easier to achieve at room temperature.

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REFERENCES