Controllable Preparation of 10 nm Solid Lipid Nanoparticles Based on Phase Behaviors of Drug-Loading Hot Microemulsions

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ABSTRACT

A new method was presented here for controllable preparation of 10-nm-scale solid lipid nanoparticles (SLNs). The pseudoternary phase diagram for the system polyoxyethylene(40)stearate(S-40)/ polyoxyethylene-b-poly oxypropylene(F-68)/ Glycerol monostearate(GMS)/ water was obtained at 60℃ using home-made apparatus with temperature control. Different microemulsions (W/O, B.C. and O/W) were distinguished by the conductivity measurement, and liquid crystal (LC) region was also found. The introduction of retinoic acid (RA) and temperature had little influence on the phase behaviors. RA-SLN was prepared by direct cooling of hot O/W microemulsion obtained according to the phase behavior results. The mean particle size of RA-SLN investigated by PCS was about 10 nm. TEM images indicated that RA-SLNs were spherical nanoparticles with diameter about 10 nm. It has been proved that the stability and the skin penetrating capacity of RA-SLN were very good.

Keywords: hot microemulsion, phase diagram, solid lipid nanoparticles, glycerol monostearate, retinoic acid

1 INTRODUCTION

Nanoscale drug carriers have been proved to be very promiseful drug delivery system (DDS) for certain drugs. Solid lipid nanoparticles (SLNs) have attracted much attention due to their unique properties for the preparation of suitable DDS of water-insoluble drugs since 1990s[1-3]. The main advantages of SLN include good physiology compatibility of lipids as carrier materials, good stability induced from the solid character of lipids in DDS at room temperature and feasibility of large-scale production.

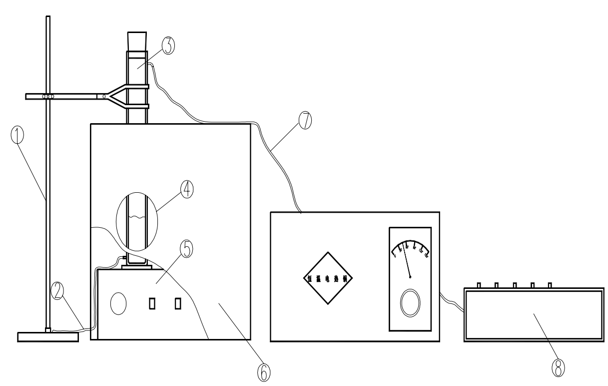
Hot drug-loading oil-in-water (O/W) microemulsions were the key intermediate product for the final preparation of many SLNs. This kind of O/W microemulsion is quite different from normal microemulsion for the solid lipid as oil phase. So it could be obtained only at the temperature 10-15 ℃ higher than the melting point of lipid. It was very meaningful to have the knowledge about the phase behaviors of these special microemulsions because the SLNs might be prepared from the O/W microemulsion based on the phase diagram.

Many researchers have focused on phase behaviors of microemulsions[4,5], including drug-loading microemulsions[6]. In order to satisfy the requirement of this kind of special microemulsion, it is necessary to make a set of instrument to acquire their phase diagram.

A new method was presented in this paper for controllable preparation of 10-nm-scale SLNs based on the phase behaviors of hot drug-loading microemulsions with the retinoic acid as model drug.

2 EXPERIMENTAL

The popular titration method was used to obtain pseudoternary phase diagram. In order to satisfy the higher temperature needed, we have made a microemulsion phase diagram detection instrument with accurate temperature control. It consists of sample cell, detection unit, thermostatic unit and control unit. The sample cell was a double-walled glass tube with the inlet and outlet on the bottom and top of the outer wall of glass tube, respectively. The temperature of sample cell was adjusted by the thermostatic unit. All the operations were directed by the control unit.



①iron stand ②infall pipe ③ sample tube ④-polarizer
⑤stirrer ⑥box ⑦-outfall pipe ⑧-controller

Figure 1: The schematic diagram of phase diagram apparatus of microemulsions with temperature control

3 RESULTS AND DISCUSSION

3.1 Phase Diagram

Figure 2 showed the pseudoternary phase diagram of S-40/F-68/GMS/water at 60℃ using home-made apparatus with temperature control. Different microemulsions (W/O, B.C. and O/W) were distinguished by the conductivity measurement (Figure 3), and liquid crystal (LC) region was also found. The mixing ratio of S-40 and F-68 was 7:3. O/W microemulsion region was found to be near the water point.

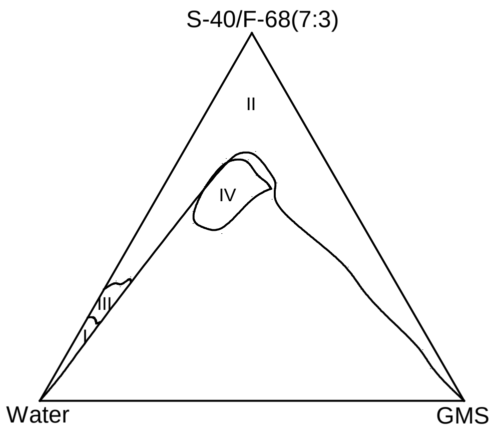


Figure 2: Phase diagram of S-40/F-68/GMS /H_2O system
I : O/W microemulsion region，II : W/O microemulsion region，III : Bicontinuous structure region， IV : Liquid Crystal region. Temperature : 60℃

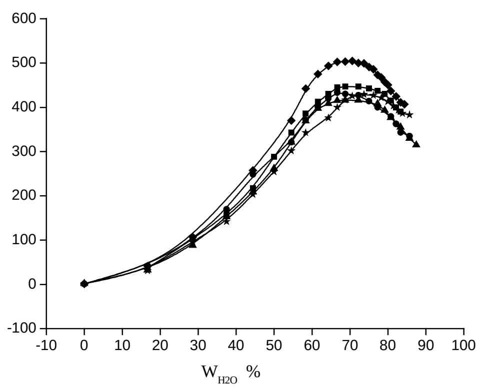


Figure 3: Relation between conductivity κ of S-40/F-68/GMS system and water content at 60℃
Mixing ratio of S-40/F-68 : GMS are: -◆- 8.6:1.4; -▲- 8.8:1.2; -■- 9:1; -●- 9.5:0.5; -★- 10:0

3.2 Influence of Temperature and Drug

The influence of temperature and drug on the phase behaviors of microemulsion was investigated. Figure 4 showed the phase diagram of S-40/F-68/GMS /H_2O system at 75 ℃. On the whole, the increase of temperature resulted in some change of the phase diagram. However, the O/W microemulsion region kept almost the same. Similarly, the introduction of retinoic acid did not influence the O/W microemulsion region evidently. It was concluded that the temperature and Retinoic Acid had little influence on the phase behaviors of drug-loading hot microemulsions.

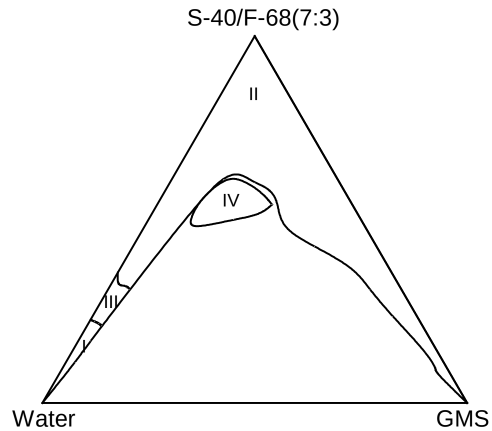


Figure 4: Phase diagram of S-40/F-68/GMS /H_2O system
I : O/W microemulsion region，II : W/O microemulsion region，III : Bicontinuous structure region， IV : Liquid Crystal region. Temperature : 75℃

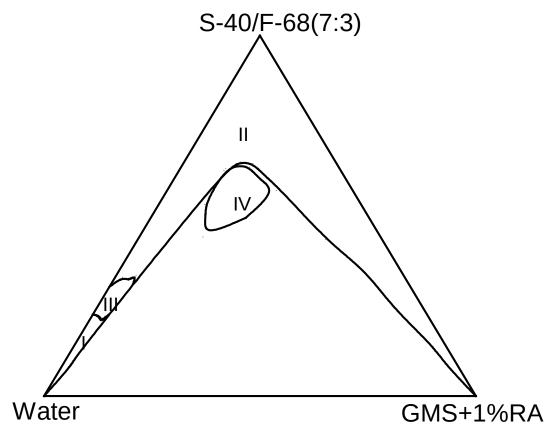


Figure 5: Phase diagram of S-40/F-68/GMS/RA/H_2O system
I : O/W microemulsion region，II : W/O microemulsion region， III : Bicontinuous microemulsion region，IV : Liquid Crystal region. Temperature : 60℃

3.3 Preparation of SLN

RA-SLN was prepared by direct cooling of hot O/W microemulsion obtained according to the phase behaviors results. The formulation was confirmed from the point in the O/W microemulsion region. As we know, any point in the phase diagram corresponded to a defined component with the content of all compounds.

3.4 Characterization of RA-SLN

The mean particle size of RA-SLN investigated by PCS was about 10 nm. TEM images (Figure 6) indicated that RA-SLNs were spherical particles with diameter about 10 nm, corresponding to the PCS results.

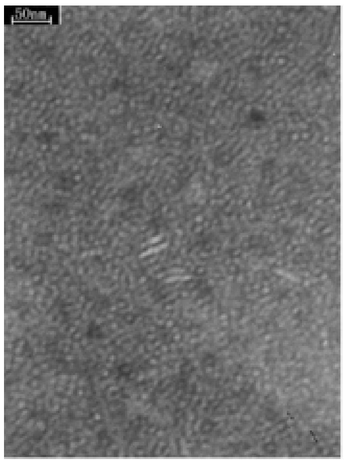


Figure 6 TEM image of RA-SLN

Table 1 gave the size results of RA-SLNs at different times after the preparation. It has been proved that the stability was very good. Further studies showed that the particle dimension was kept almost the same even after 1 year.

Tab.1 Mean particle size of RA-SLN with different time

Time (day)	Mean size (nm)	P.I.
0	13.8	0.691
10	11.1	0.613
20	11.4	0.662
30	12.2	0.594

P.I.:Polydispersity Index

3.5 Transdermal Release Behavior

RA-SLN has showed good transdermal release behavior, as shown in Figure 7.

4 CONCLUSION

The study on the phase behaviors of drug-loading hot microemulsions has been proved to be very significative for the controllable preparation of certain SLNs.

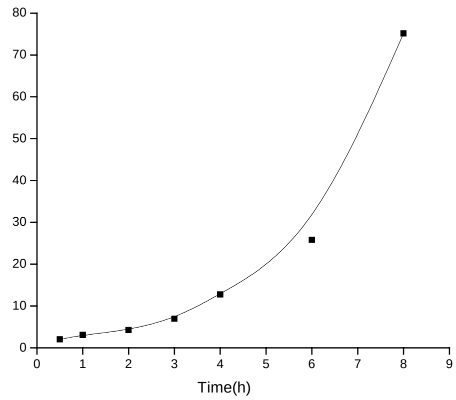


Figure 7 Transdermal release behavior of RA-SLN

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