MMP12

The Effect Of Emulsifiers And Oils On Droplet Size And Drug Loading Capacity Of Self-Emulsifying System

ผลของสารก่อมัลชันและชนิดของน้ำมันต่อขนาดหยดอิมัลชันและความสามารถในการบรรจุยาของระบบอิมัลชันที่เกิดขึ้นเอง

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Abstract

The present study was aimed to investigate the effect of emulsifiers and oils on size of self-emulsifying emulsion droplet and drug loading capacity, using fenofibrate as a model drug. The solubility of drug in oils and surfactants was determined. Two oils (Captex 200 and Captex 300), two emulsifiers (Tween 80 and Cremophor EL) and a co-emulsifier (Brij 30) were chosen to construct pseudoternary phase diagrams. Self-emulsifying efficiency, emulsion droplet size and drug loading capacity were investigated. The results showed that Captex 200 and Tween 80 provided greater number of self-emulsifying systems which could give emulsions of minimal droplet size, 11.3 ± 0.2 nm. The maximum drug loading capacity of 302.23 ± 15.3 mg/mL can be obtained with the system of Captex 200, Cremophor EL and Brij 30.

บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาผลของสารทำอิมัลชันและน้ำมันต่อขนาดหยดของอิมัลชันและความสามารถในการบรรจุยาของระบบเกิดอิมัลชันเอง โดยใช้ Fenofibrate เป็นยาต้นแบบ ใช้น้ำมันสองชนิด ได้แก่ Captex 200 และ Captex 300 สารทำอิมัลชันสองชนิดได้แก่ Tween 80 และ Cremophor EL และสารทำอิมัลชันร่วมคือ Brij 30 ในการเตรียมแผนภาพเฟสเพื่อหาสัดส่วนที่ทำให้เกิดระบบอิมัลชันเองได้ พร้อมทั้งค่าการละลายของยาในสารแต่ละชนิดข้างต้น นำระบบเกิดอิมัลชันเองที่ได้จากแผนภาพเฟสมาประเมินประสิทธิภาพในการเกิดอิมัลชันเอง ตรวจสอบขนาดหยดของอิมัลชัน และศึกษาปริมาณยาที่บรรจุได้ ผลการศึกษาพบว่าระบบที่ประกอบด้วย Captex 200 และ Tween 80 ให้ระบบเกิดอิมัลชันมากกว่าสารทำอิมัลชันและน้ำมันชนิดอื่นและสามารถให้อิมัลชันที่มีขนาดหยดเล็กที่สุดคือ 11.3 ± 0.2 นาโนเมตร ระบบที่ประกอบด้วย Captex 200 Cremophor EL และ Brij 30 สามารถบรรจุยาได้มากที่สุด คือ 302.23 ±15.3 มิลลิกรัมต่อมิลลิลิตร

Key Words: drug loading capacity, emulsion droplet size, self-emulsifying system

คำสำคัญ : ความสามารถในการบรรจุยา ขนาดหยดอิมัลชัน ระบบเกิดอิมัลชันเอง

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1. Introduction

Self-emulsifying systems are isotropic mixtures of oils, emulsifiers with or without a co-emulsifier which can form fine oil-in-water emulsions when exposed to aqueous phases with gentle agitation (Pouton, 1997; Shah et al., 1994). These systems can improve absorption of lipophilic drug by formation of small size emulsion in the gastrointestinal tract providing large interfacial surface area for absorption (Charman et al., 1992; Pouton 1997). The emulsion droplet size and the polarity of oil droplets could be affected by type and concentration of emulsifiers and oils (Shah et al., 1994). There were some studies about self-emulsifying systems of fenofibrate, for example, the system containing of C_8-C_{10} polyglycolized glycerides (Labrafac CM10), polyoxyethylene sorbitan monooleate (Tween 80) and polyethylene glycol 400 (PEG400) (Patel and Vavia, 2007) and the other systems which containing of omega-3 oil, ethanol and polyoxyl 35 castor oil (Cremophor EL) (Ratanabanangkoon et al., 2008) that showed desired results of drug release compared with plain drug or marketed products. The oils and emulsifiers in the formulation were mostly selected based on the solubility of drug in a single component. However, the solubilizing capacity might be altered in a self-emulsifying system. The purpose of this study was to investigate the effect of type and concentration of emulsifiers and oils on droplet size and drug loading capacity of self emulsifying system, using fenofibrate as a model drug.

2. Materials

Fenofibrate was obtained from Siam Bheasach Co., Ltd. (Bangkok, Thailand). Fenofibrate DMSc reference standard was purchased from the Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health (Nonthaburi, Thailand). Water was obtained from ELGA water purifier system (ELGA Maxima, ELGA LabWater Global Operations, U.K.). Propylene glycol dicaprylate/dicaprate (Captex 200) and caprylic/capric triglycerides (Captex 300) were purchased from Abitec Corporation, Janesville, USA. Polyoxyethylene 20 sorbitan monooleate (Tween 80) was purchased from Nof Corporation, Tokyo, Japan. Polyoxyl 35 castor oil (Cremophor EL) was obtained from BASF Corporation, Ludwigshafen, Germany. Polyoxyethylene (4) lauryl ether (Brij 30) was obtained from Croda (Thailand) Co., Ltd. Acetonitrile HPLC grade was purchased from RCI Labscan Limited, Bangkok, Thailand. All materials were used as received.

3. Methods

3.1 Solubility studies

The solubility of fenofibrate in oils and emulsifiers was determined. An excess of fenofibrate was added into an oil or emulsifier, then mixed by vortex mixer and shaken at ambient temperature 100 rpm for 48 hours by shaking incubator (LSI-3016A, Daihan Labtech Co., Ltd, Korea). The samples were taken at time intervals and filtered through 0.45 µm membrane. The solubilized fenofibrate was diluted by acetonitrile and the concentration of fenofibrate was quantified at ambient temperature by HPLC using a Thermo Hypersil BDS C-18 (5 µm), 250 × 4.6mm column (Thermo Fisher Scientific Inc, U.S.A.). A Shimadzu HPLC system (Shimadzu Scientific

Instruments, U.S.A.), consisting of LC-20AD pump, SIL-20A autosampler and SPD-M20A diode array detector set at a wavelength of 289 nm, was used. The injection volume was 20 µL. The mobile phase consisting of acetonitrile and water (80:20, v/v) was pumped at flow rate of 1.0 mL/min. The retention time of fenofibrate was found to be 7.8 ± 0.5 minutes. The assay of each formulation was carried out in triplicate.

3.2 Pseudoternary phase diagrams

The pseudoternary phase diagrams of oils, emulsifiers and water were constructed and used to investigate a self-emulsifying system. The mixture of oil and emulsifier at a certain weight ratio was diluted with water in dropwise manner to make 3 grams of total weight which was then mixed by vortexing at 25 Hertz for 5 minutes. The resultant mixture was kept at room temperature and observed for clarity, fluidity and phase separation at 0, 1, 3 and 7 days. The ratios of oil to emulsifier which provided clear transparent and flowable mixtures were selected for further studies.

3.3 Self-emulsification

The mixtures selected from the pseudoternary phase diagram were prepared for evaluation of self-emulsification and precipitation properties. The study was performed by using USP dissolution apparatus II (Vankel VK7000, Varian Inc, NC). One gram of each mixture was added to a dissolution vessel containing 200 mL of distilled water. The paddle speed was set to 100 rpm and medium temperature was kept at 37°C. The mixtures were categorized as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation) or unstable (showing precipitation) of the resultant emulsion observed at 0 and 24 hour.

3.4 Emulsion droplet size

Photon correlation spectroscopy (PCS) (Malvern Zetasizer nano ZS, Malvern Instuments Ltd., UK) was used for determination of emulsion droplet diameter at a backscatter angle of 173°. The stable emulsions prepared as above mentioned were subjected to particle size analysis at 37°C. Mean droplet diameter was expressed as z-average. For each emulsion, the measurement was carried out in triplicate at 0 and 24 hours after preparation.

3.5 Drug loading capacity

Five grams of the self-emulsifying mixtures which gave stable emulsion were prepared in screw cap vials. The study of drug loading capacity of the mixtures was carried out in the same manner as the solubility study, except for that one sample was taken at the end of 24 hours.

4. Results and Discussion

4.1 Solubility studies

The solubility of fenofibrate in water, Captex 200, Captex 300, Brij 30, Cremophor EL and Tween 80 were 0.04, 229.93, 187.18, 171.75, 111.27 and 170.78 mg/mL, respectively, as shown in figure 1.

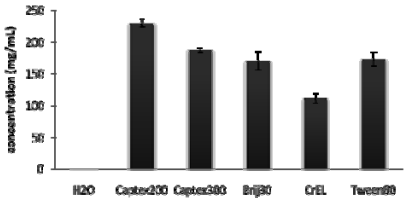
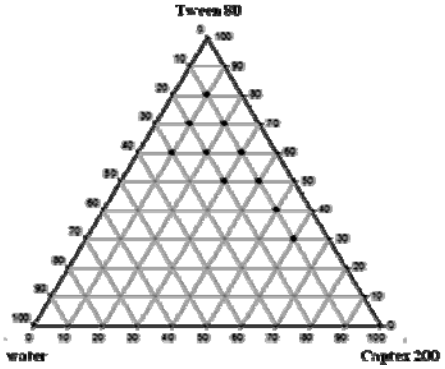


Figure 1 Solubility of fenofibrate in different oils and emulsifiers.

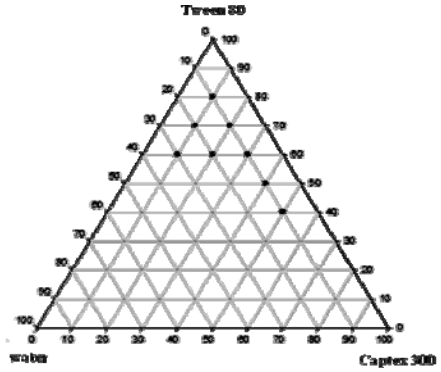
4.2 Ternary phase diagrams

The ternary phase diagrams are presented in Figure 2. The plotted area represented self-emulsifying region which gave clear transparent and flowable mixture after 7 days of preparing. The phase diagrams containing of Captex 200 and Tween 80 gave greater self-emulsifying area. The addition of Brij 30 into the phase diagram resulted in the reduced number of self-emulsifying systems.

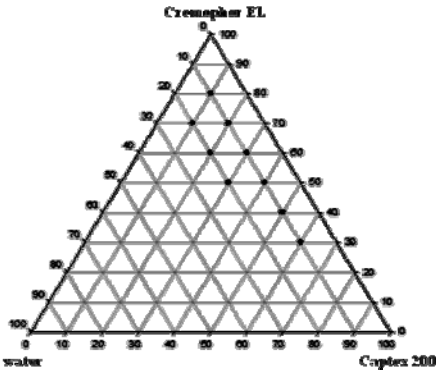
(A)



(B)



(C)



(D)

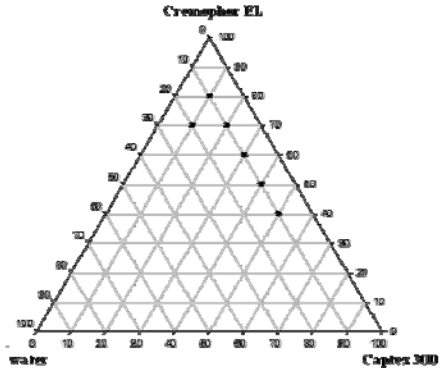
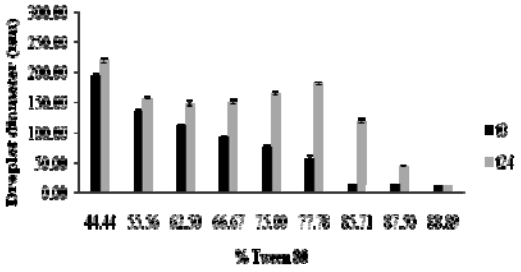


Figure 2 Phase diagrams of systems comprised (A) Captex 200 and Tween 80; (B) Captex 300 and Tween 80; (C) Captex 200 and Cremophor EL; (D) Captex 300 and Cremophor EL, with water .

4.3 Self-emulsification and emulsion droplet size

After diluting the self-emulsifying system with 200 mL of distilled water, no precipitation occurred in all formulations. Increased amounts of emulsifier tended to reduce emulsion droplet size (Figure 3). In general, Captex 200 gave emulsions of smaller size, comparing with emulsions of Captex 300 formed with the same oil to emulsifier ratio. The presence of Brij 30 in the systems provided even smaller size of emulsion. The stability of emulsion droplets observed after 24 hours of preparation relied on the type of emulsifier. Tween 80 only gave stable emulsion with Captex 300, while Cremophor EL successfully stabilized emulsion droplets with either type of oils studied.

(A)



(B)

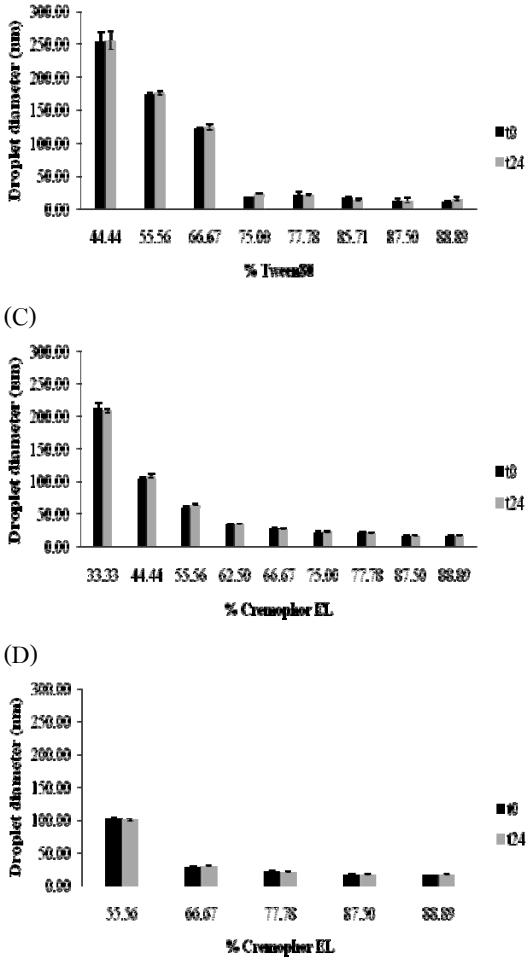


Figure 3 Emulsion droplet diameter after self-emulsification of (A) Captex 200 and Tween80; (B) Captex 300 and Tween 80; (C) Captex 200 and . Cremophor EL; (D) Captex 300 and Cremophor EL.

4.4 Drug loading capacity

Using Tween 80 as the emulsifier, Captex 200 provided higher drug loading capacity in most self emulsifying systems as shown in figure 4(A); while using Cremophor EL as an emulsifier did not give significant difference in drug loading capacity of the emulsions formed with either type of oils (figure 4B). The drug loading capacity was increased after incorporation of Brij 30 only in the systems which contained Captex 200 as the oil as shown in Figure 4(C). The system containing Captex 200, Cremophor EL and Brij 30 (5.6:2.2:2.2) gave the maximum drug loading capacity of 302.23 mg/mL. The results of drug loading capacity could depend on the solubility in the single component. Fenofibrate had better solubility in Captex 200, so the drug loading capacity would be increased when this oil was presented in the self emulsifying system. This also explains the improved drug loading capacity resulting from the addition of Brij 30.

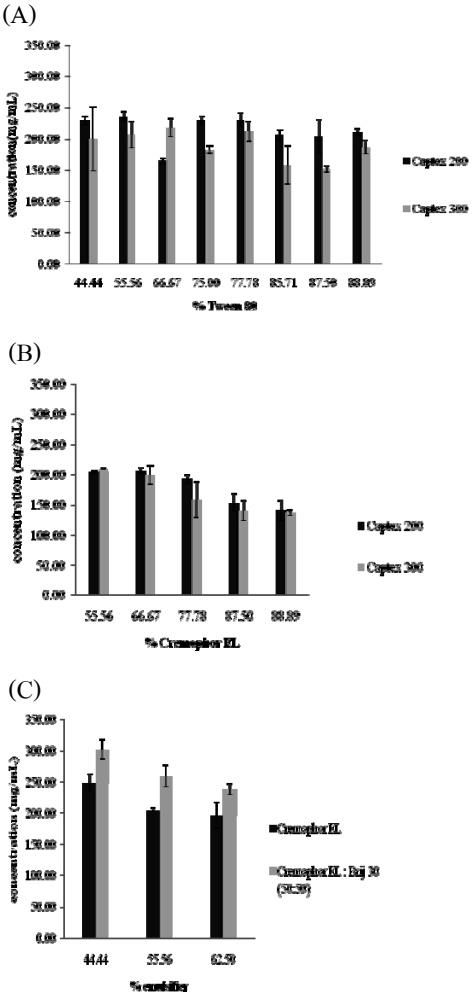


Figure 4 Drug loading capacity.

5. Conclusion

Fenofibrate loading in the self-emulsifying systems was dependent on the type of oils and emulsifiers rather than their concentrations. However, the concentration of emulsifier could affect the emulsion droplet size. The higher the concentration of emulsifier, the smaller emulsion droplet size would be.

6. Acknowledgements

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