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Thermal Reversible Microemulsion for Oral Delivery of Poorly Water-Soluble Drugs

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1. Introduction

There have been many attempts to improve absorption and bioavailability of poorly water-soluble drugs [1-3]. One of attractive systems is microemulsions which are composed of fine oil-in-water droplets in aqueous medium [4-8]. When such a formulation is released into the lumen of the gut, it disperses to form a fine emulsion, so that the drug remains in liquid state in the gut avoiding dissolution step that frequently limits the rate of absorption of liphophilic drugs [9]. The smaller sizes of droplets will have a larger interfacial surface areas per unit volume and correspondingly large free energy contribution from the liquid-liquid interfacial tension [10].

Self emulsify drug delivery system (SEDDS) is a potency microemulsions for enhancing bioavailability of poorly water soluble drugs after oral administration. Microemulsion is a system of thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water, stabilized by an interfacial film of surfactant molecules [8,9]. Microemulsion formulations are a good candidate for oral delivery of poorly water-soluble drugs, because of their ability to improve drug solubilization and potential for enhancing absorption in the gastrointestinal tract (GI), caused by surfactant-induced permeability changes [11]. After oral administration, it rapidly disperses in stomach forming small droplets (<5 μm), which promotes wide distribution of the drug throughout the GI tract. In the past decade, we have developed lipophilic drugs microemulsion [6], hydrophobic drug emulsion [12], and thermal sensitive microemulsion[13] for enhancing water insoluble drugs bioavailability. In this chapter, we discuss on the enhancing bioavailability of the poorly water soluble drugs after oral administration by using microemulsion system. Poorly water soluble drug has been designed as a thermal reversible microemulsion system, which can disperse rapidly in the aqueous contents of the stomach and form fine oil in water droplets, and thus leads to improve absorption of the poorly water soluble drugs.

2. Microemulsion system for oral delivery of lipophilic drugs

2.1 Preparation of pseudo-ternary phase diagram

Cyclosporin A as a lipophilic drug model, Caprylic/capric triglyceride (Captex 355®) as a oil, and Polyoxyethylated castor oil (Cremorphor EL®) and Transcutol® as a surfactant and cosurfactant, respectively, were used for preparation of a series of microemulsions. Surfactant

(Cremophor EL®) was mixed with cosurfactant (Transcutol®) in fixed weight ratios (0.5:1, 1:1, 2:1 and 4:1). Aliquots of each surfactant-cosurfactant mixture (S_{mix}) were then mixed with oil (Captex 355®) and finally with aqueous phase (saline or 0.1 N HCl). Mixtures were gently shaken or mixed by vortexing and kept at ambient temperature (25°C) to equilibrate. The equilibrated samples were then assessed visually and determined as being clear and transparent microemulsions, or crude emulsions or gels as shown in Figure 1.

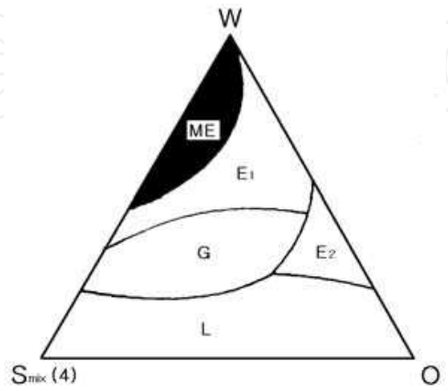


Fig. 1. Pseudo-ternary phase diagrams composed of oil (Captex 355®), Cremophor EL®-Transcutol® mixture (Smix) (Cremophor EL®: Transcutol®= 4:1) and water. Keys: G, gel; L, isotropic region ; ME, single phase o/w microemulsion; E1, crude emulsion; E2, w/o emulsion region.

Phase studies were done to investigate the effect of surfactant/cosurfactant ratio on the extent of stable o/w microemulsion region. The microemulsions in the present study were formed spontaneously at ambient temperature when their components were brought into contact. It is advantageous for developing oral dosage forms of lipophilic drugs, because easy formation at ambient temperature is particularly advantageous for thermo labile drugs such as peptides [14]. Phase study revealed that the addition of Cremophor EL®-Transcutol® mixture in a ratio 4:1 can produce clear and transparent microemulsions in the subsequent study.

2.2 Solubility of drug in the surfactants and oil

The solubility of Cyclosporin A in each component was 98.72 ± 7.75 mg/g in Captex 355®(oil), 56.51 ± 4.90 mg/g in Cremophor EL® (surfactant) and very soluble in Transcutol®(cosurfactant). The solubility of Cyclosporin A in the oil-surfactant mixture was slightly decreased with increasing the content of Cremophor EL® (Fig. 2A). In contrast, the solubility of Cyclosporin A in the oil-cosurfactant mixture was increased linearly with increasing the content of Transcutol® (Fig. 2B). Fig. 2C shows that the solubility of Cyclosporin A in the oil-S_{mix} mixture with varying surfactant-cosurfactant ratio was decreased with increasing the surfactant content. It indicates that the solubilization of Cyclosporin A was greatly affected by the cosurfactant content. After adding the aqueous phase, the solubility of Cyclosporin A in oil-surfactant-water system increased linearly with increasing the content of Cremophor EL® (Fig. 3A). The solubility of Cyclosporin A in oil-cosurfactant-water system also increased dramatically with more than 0.5% of Transcutol®

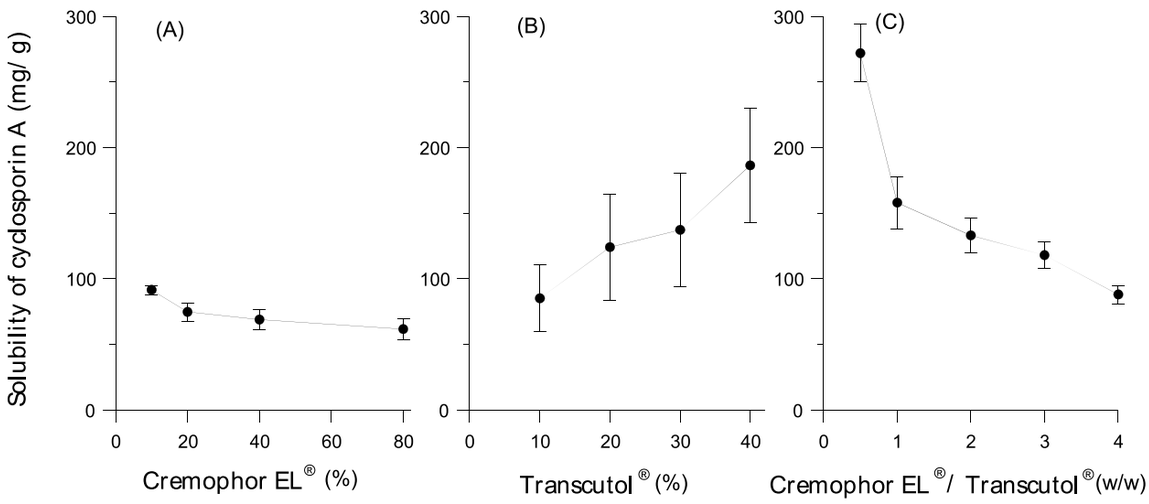


Fig. 2. (A) Effect of the content of Cremophor EL® on the solubility of Cyclosporin A in a mixture of Cremophor EL® and Captex 355®. (B) Effect of the content of Transcutol® on the solubility of Cyclosporin A in a mixture of Transcutol ®and Captex 355®. (C) Effect of the weight ratio of Cremophor EL® to Transcutol® on the solubility of Cyclosporin A in a mixture of Cremophor EL®-Transcutol® (Smix) and Captex 355 (Smix:Captex 355®=15:4).

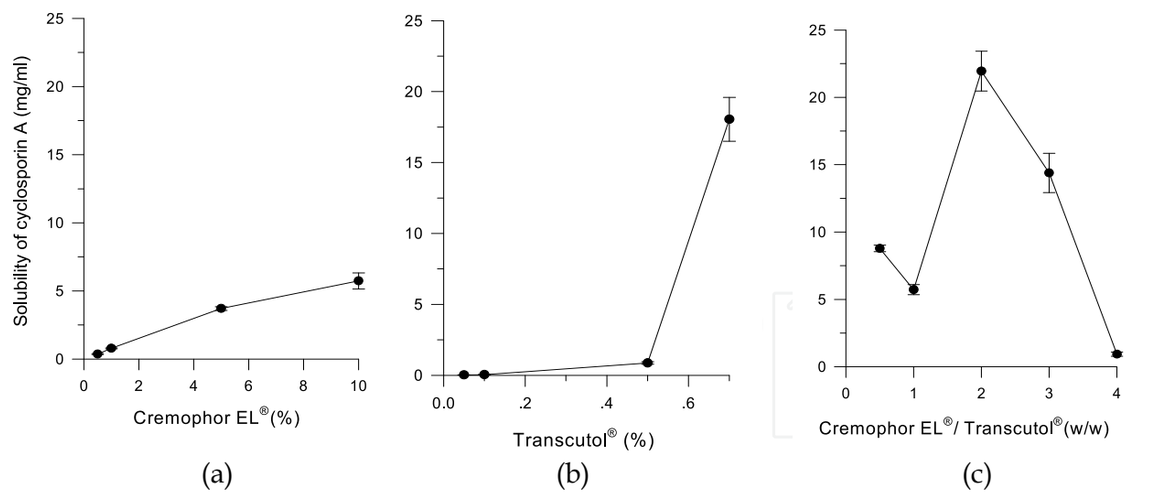


Fig. 3. (A) Effect of the content of Cremophor EL® on the solubility of Cyclosporin A in a mixture of Cremophor EL®, Captex 355® and saline (Cremophor EL®–Captex 355®: saline=19:81). (B) Effect of the content of Transcutol® on the solubility of Cyclosporin A in a mixture of Transcutol®, Captex 355® and saline (Transcutol®–Captex 355®:saline=19:81). (C) Effect of the weight ratio of Cremophor EL® to Transcutol® on the solubility of Cyclosporin A in microemulsion systems obtained by adding saline to a mixture of Cremophor EL®-Transcutol® (Smix) and Captex 355®(Smix:Captex 355®=15:4).

(Fig. 3B). The solubility of Cyclosporin A in a system containing all of the components for producing microemulsions (Fig. 3C) was increased markedly compared to those of systems without surfactant (Fig. 3B) or cosurfactant (Fig. 3A) and it reached the maximum (21.95 ± 1.48 mg/ml) when the ratio of surfactant to cosurfactant of S_{mix} was 2:1 (Fig. 3C). The maximized solubilization is thought to be achieved by the formation of transparent microemulsion with small droplets. At the ratios greater than 2:1, although these mixtures formed microemulsions, the less Transcutol® content in the microemulsion systems was caused the solubilizing capacity of microemulsion to be decreased. In contrast, at the ratio less than 2:1, the clear microemulsion cannot be produced due to the insufficient amount of surfactant. The slight increase of solubility of Cyclosporin A at the ratio of 0.5:1 is thought to be observed due to the fact that, although the clear microemulsion cannot be formed, the excess amount of cosurfactant existed in the water phase and increased the solubility of Cyclosporin A in the aqueous phase. It was also confirmed by determining the partitioning of Cyclosporin A between lipophilic and aqueous phases in the subsequent study (Fig. 4).

2.3 Partitioning of Cyclosporin A between lipophilic and aqueous phases (C_o/C_w)

Partitioning studies using the aqueous and oil phases of corresponding microemulsion are known to be correlated to the observed oral bioavailability and/or *in vitro* permeability [11]. The concentration ratio of Cyclosporin A in lipophilic phase to that in aqueous phase (C_o/C_w) was greatly affected by the ratio of surfactant to cosurfactant of S_{mix} (Fig. 4). C_o/C_w was maximized when the microemulsion system was prepared with S_{mix} at 1:1 ratio of surfactant to cosurfactant. When the ratio was at above or below 1:1, the C_o/C_w was reduced because the excess amount of surfactant or cosurfactant existed in the aqueous phase and contributed to increasing the concentration of Cyclosporin A in aqueous phase. However, if considering the absolute solubility of Cyclosporin A in the lipophilic phase, the maximized concentration of Cyclosporin A could be obtained with microemulsions containing 2:1 mixture of surfactant to cosurfactant.

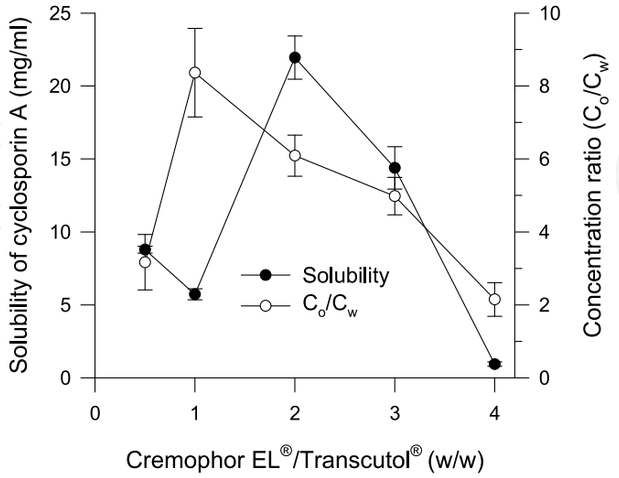


Fig. 4. Effect of the weight ratio of Cremophor EL® to Transcutol® on the concentration ratio of Cyclosporin A in lipophilic phase and that in aqueous phase of microemulsion systems (C_o/C_w).

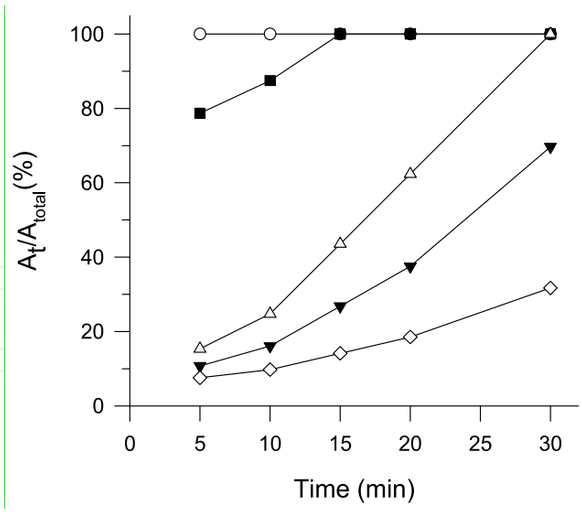


Fig. 5. Disperison rate of mixture of Cremophor/Transcutol(Smix) (Cremophor EL®/Transcutol® as 0.5:1, 1:1, 2:1, 3:1, 4:1 and Captex 355 (Smix:Captex355=15:4) into aqueous media assuming the pH condition of gastric fluid.

2.4 Dispersability and particle size determination

To use the oil-S_{mix} mixture as a pre-microemulsion concentrate, it must be readily dispersed in the stomach to form a microemulsion [10]. Thus, the dispersability of oil-S_{mix} mixture prepared with different weight ratios of surfactant to cosurfactant was compared in aqueous media assuming the pH condition of gastric fluid. The dispersion occurred more slowly with increasing the surfactant/cosurfactant ratio (Fig. 5). Too slow dispersion of pre-microemulsion concentrate prepared with S_{mix} which is greater than 3:1 ratio of surfactant to cosurfactant might retard the absorption of drugs in gastrointestinal tract and it was insisted that the ratio of surfactant to cosurfactant must not exceed 2:1 to allow use of the oil-S_{mix} mixture as a pre-microemulsion concentrate in this study.

It is known that the droplet size distribution is one of the most important characteristics of emulsion for the evaluation of its stability [15] and also *in vivo* fate of emulsion [16]. At first, the effect of each component of microemulsion systems on the resultant droplet size was investigated. The surfactant content at below 20% of mixture did not affect the droplet size significantly (Fig. 6A). However, with increasing the cosurfactant content in oil-cosurfactant-water system, the droplet size decreased linearly (Fig. 6B). The droplet size of microemulsions prepared with S_{mix} was markedly reduced compared with those prepared with surfactant or cosurfactant alone. It was demonstrated that the small and stable microemulsion was formed by the addition of both of them. The droplet size of microemulsion decreased with increasing of the surfactant to cosurfactant ratio and became constant at above 2:1 ratio of surfactant to cosurfactant (Fig. 6C). This result is in accordance with the report that the addition of surfactant on the microemulsion systems causes the interfacial film to condense and to be stable, while the addition of cosurfactant causes the film to expand [14]. The smallest droplet size of microemulsion (22 nm) was obtained from S_{mix} at more than 2:1 ratio of surfactant to cosurfactant, where it can produce clear and transparent microemulsions. However, as mentioned in the proceeding sections, S_{mix} at 3:1 or 4:1 ratio of surfactant to cosurfactant produced microemulsions with reduced drug-

solubility capacity and slow dispersion rate, which can be disadvantageous for use as an oral delivery system of Cyclosporin A.

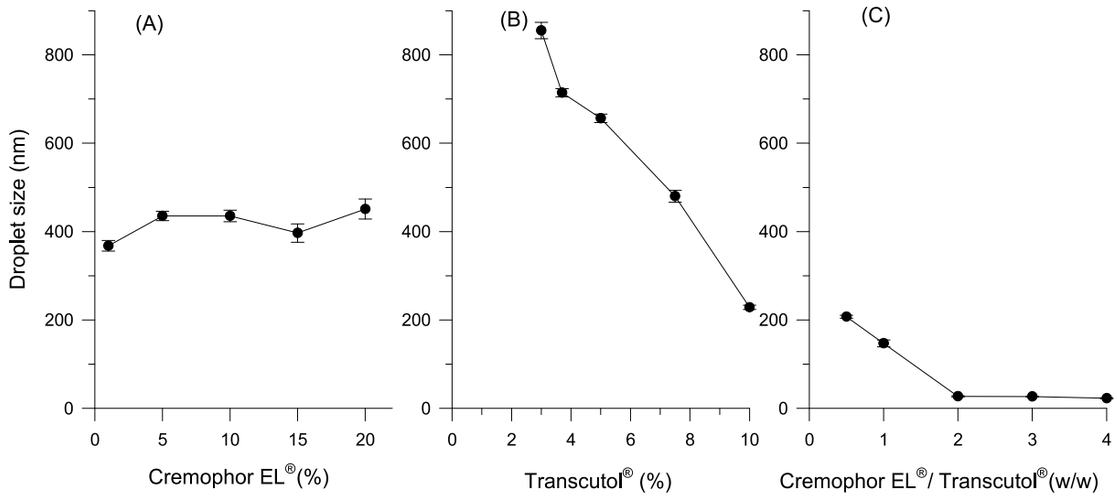


Fig. 6. (A) Effect of the content of Cremophor EL® in a mixture of Cremophor EL®, Captex 355®, and saline (Cremophor EL®–Captex 355®:saline=19:81) on the resultant mean droplet size. (B) Effect of the content of Transcutol® in a mixture of Captex 355®, Transcutol® and saline (Transcutol®–Captex 355®:saline=19:81) on the resultant mean droplet size. (C) Effect of the weight ratio of Cremophor EL® and Transcutol® in empty microemulsion obtained from a mixture of Cremophor®-Transcutol® (Smix), Captex 355® and saline (Smix:Captex 355®:saline=15:4:81) on the resultant mean droplet size.

2.5 Animal studies

The non-compartmental pharmacokinetic parameters in Table 1 were calculated based on the observed blood data. The maximal drug concentration in blood(C_{max}), time at the maximal drug concentration in blood(T_{max}) and Area Under Curve of drug concentration in blood (AUC) of Sandimmun®, Sandimmun Neoral® and microemulsion in this study were 1.285, 2.859, 3.275 (μg· ml^{-1}) and 2.333, 3.000, 3.667 (h) and 12.531, 33.171, 41.332 (μg·h/ml), respectively. The C_{max} of Cyclosporin A loaded in the microemulsion system in the present study was markedly higher compared with Sandimmun® and was not significantly different compared with Sandimmun Neoral®. The AUC of Cyclosporin A via oral administration of microemulsion in this study was significantly increased ($p<0.05$, 3.30 fold), when compared with Sandimmun®. However, no significant difference was found between the AUC of microemulsion and Sandimmun Neoral® ($p>0.05$, 1.25 fold). There was no significant change in T_{max} ($p>0.05$) among the three products. The absolute bioavailability (F) of microemulsion optimized in this study increased about 3.30 and 1.25 fold compared with Sandimmun® and Sandimmun Neoral®. The bioavailability of Cyclosporin A incorporated in microemulsion optimized did not show significant difference compared with Sandimmun Neoral® (0.416 versus 0.518) and 3.30 fold increased compared with Sandimmun® (0.157 versus 0.518). It is thought that this result support the report that for lipophilic drugs and peptides, where absorption is dissolution rate limited, a strong correlation exists between the particle size of emulsion and bioavailability because the particle size of Sandimmun®,

Sandimmun Neoral® and microemulsion (with Smix 2:1) in this study was 864, 104 nm and 22 nm, respectively, measured with Zetasizer Nano ZS90 (Malvern Instruments Ltd., UK) after diluting with water 50 times.

Parameters	Intravenous	Oral		
		Sandimmun®	Sandimmun Neoral®	Microemulsion
C_{max} (μg· ml^{-1})	–	285± 0.088	2.859± 0.322	3.275± 0.367 [a]
T_{max} (h)	–	333± 0.441	3.000± 0.354	3.667± 0.333
AUC (μg·h/ml)	390± 0.193	12.531± 0.088	33.171±5.534 [a]	41.332± 4.532 [a]
Absolute bioavailability (F) [b]		0.157	0.416	0.518

[a] $p<0.05$ by the student T-test when compared to Sandimmun®.

Table 1. Analysis of noncompartmental pharmacokinetic parameters after oral administration of cyclosporin A products to rats.

2.6 Conclusion

The surfactant to cosurfactant ratio greatly affected on the physicochemical characteristics of resultant microemulsion systems obtained by using polyoxyethylated castor oil (Cremophor EL®) as a surfactant, Transcutol® as a cosurfactant and caprylic/capric triglyceride (Captex 355®) as an oil. The stable microemulsion with high solubility of Cyclosporin A, small droplet size and fast dispersion rate was obtained from mixture composed of 10/5/4 mixture of Cremophor EL®/ Transcutol®/ Captex 355®. The enhancement of bioavailability of Cyclosporin A by using o/w microemulsion optimized in this study is thought to be due to the combination of factors including the drug solubilization effect and the increase of drug permeability to membrane. In other words, the bioavailability of drugs loaded in microemulsions was dependent on the physicochemical properties of drug and o/w microemulsions. This system might be applicable to formulate the liquid and solid dosage forms of Cyclosporin A for enhancing its bioavailability after oral administration. This formulation approach can also help to improve the oral bioavailability of other poorly soluble peptide drugs as is the case for Cyclosporin A.

3. Emulsion for hydrophobic drug oral delivery

Biphenyl dimethyl dicarboxylate (BDD) is an agent against virally induced hepatic injury and has been found to be effective in improving liver function and symptoms of patients with chronic viral hepatitis [17, 18, 19]. BDD is practically water-insoluble (3.6 μg/ml in water at 25°C) and its dissolution rate is extremely slow, resulting in very low bioavailability (20–30%) [20]. For enhancement of the solubility and bioavailability of BDD after oral administration, an Emulsion system composed of oil (Neobee M-5®), surfactant (Tween 80), and cosurfactant (Triacetin), was prepared, and its physicochemical properties and pharmacokinetic parameters were evaluated in comparison to commercial product G-cell and 0.5% calcium-carboxymethylcellulose (Ca-CMC) suspension of BDD.

3.1 Solubility of BDD in various ratios of surfactant to oil

The solubility of BDD sharply increased from 0.7 to 5.02 mg/g as the ratio of Tween 80 to Neobee M-5® increased from 1:4 to 2:1 and leveled off above the ratio of 2:1 (Fig. 7). At the ratio of 2:1, the solubility of BDD increased 7-fold compared with that at the ratio of 1:4. Hence, the ratio of 2:1 (Tween 80 to Neobee M-5®) was used for further studies.

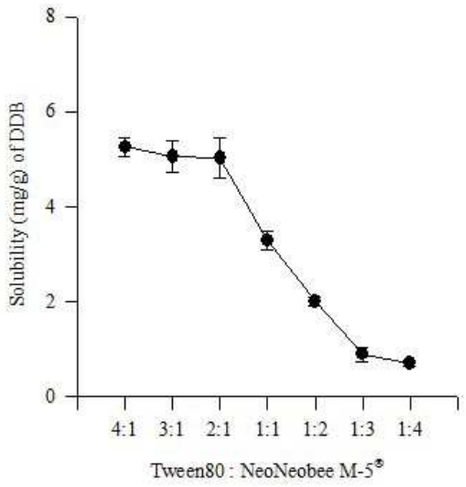


Fig. 7. Solubility of BDD in various ratios of Tween 80 to Neobee M-5®. Each point represents the mean ± SD of three experiments.

3.2 Solubility of BDD in an Emulsion system containing Triacetin

Triacetin has been used as oil to solubilize water-insoluble taxol [21] and as a food additive because of its good solubility in water and potential role as a parenteral nutrient [22]. In this study, the solubility of BDD in the absence of Tween 80 and Neobee M-5® increased proportionately with the added amount of Triacetin ranging from 0 to 50% (Fig. 8) Thus, to

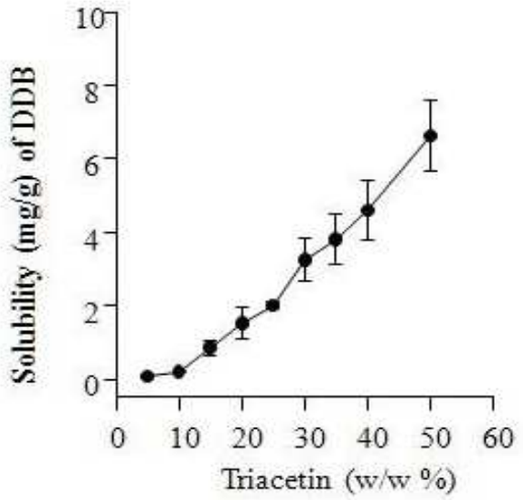


Fig. 8. Effect of Triacetin on the solubility of BDD. Each point represents the mean of four experiments.

further enhance the solubility of BDD, Triacetin was employed in a emulsion system composed of Tween 80 and Neobee M-5® at the ratio of 2:1. When the Triacetin was added to a emulsion system composed of Tween 80 and Neobee M-5® at the ratio of 2:1, the solubility of BDD gradually increased. With 55% of Triacetin, the solubility of BDD increased 40% compared to that without Triacetin, indicating the role of Triacetin as a cosurfactant in a emulsion system. Moreover, the presence of Triacetin in the emulsion system composed of Tween 80 and Neobee M-5® at the ratio of 2:1 led to the decrease in droplet size with higher physical stability and the increase in dissolution rate of BDD in aqueous media (data not shown). For further studies, 35% of Triacetin that led to 20% increase in solubility of BDD was chosen since the amount of Triacetin allowed for oral administration is less than 35%.

3.3 Droplet size of a microemulsion system

Droplet size of BDD emulsion composed of Tween 80 and Neobee M-5® at the ratio of 2:1, and 35% of Triacetin was kept constant both in distilled water and artificial gastric fluid without pepsin (pH 1.2) throughout 120 min incubation period The droplet sizes at 1 h after incubation in distilled water and artificial gastric fluid were 329.97 ± 24.31 and 284.07 ± 44.39 nm, respectively, without further changes at 2 h. This result suggests that the microemulsion system may be stable and well-dispersed in the GI tract.

3.4 Comparison of dissolution profiles among different formulations of BDD

The dissolution profiles of BDD powder, 0.5% Ca-CMC suspension of BDD, Commercial formulation G-cell and the emulsion formulation (SEDDS) of BDD composed of Tween 80 and Neobee M-5® at the ratio of 2:1, and 35% of Triacetin in distilled water were compared (Fig. 9). BDD in the emulsion formulation rapidly dissolved to a great extent whereas BDD in other formulations did hardly dissolve during 120 min incubation. About 50% of BDD in the emulsion formulation dissolved within 10 min.

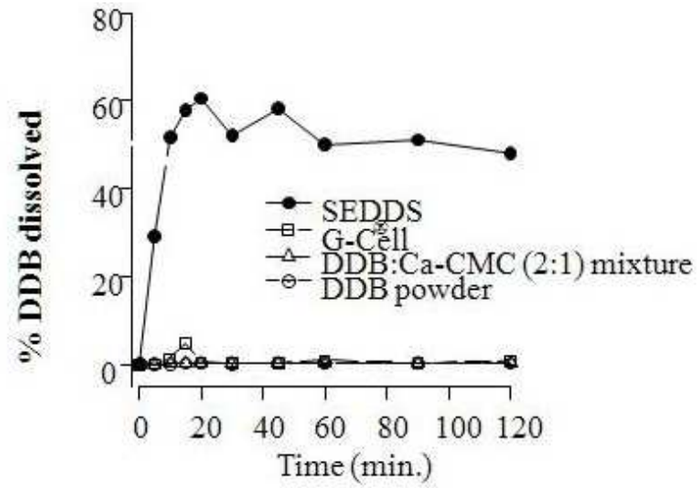


Fig. 9. Dissolution profiles of BDD from 0.5% Ca-CMC suspension of BDD, BDD powder, and the emulsion formulation of BDD (Tween 80 and Neobee M-5® at the ratio of 2:1, and 35% Triacetin; SEDDS).

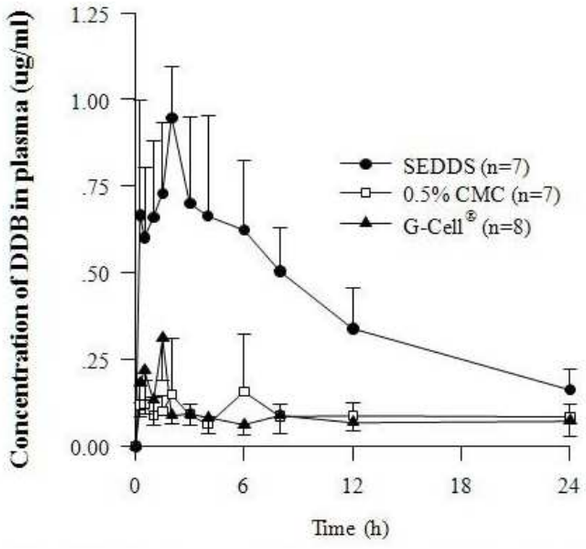


Fig. 10. Plasma concentration of BDD after oral administration to rats of 0.5% Ca-CMC suspension of BDD, BDD solution formulation and the emulsion formulation of BDD (Tween 80 and Neobee M-5® at the ratio of 2:1, and 35% Triacetin) at a dose equivalent to 12 mg of BDD/kg of body weight. Each point represents the mean ± SD of seven rats.

3.5 Pharmacokinetic analysis

An *in vivo* absorption study was undertaken to determine whether or not the enhanced solubilization and *in vitro* dissolution of BDD in a emulsion system could increase the GI absorption of drug after oral administration. Plasma concentration of BDD after oral administration of BDD in the emulsion formulation to rats increased rapidly and remarkably compared with 0.5% Ca-CMC suspension of BDD and BDD solution formulation (Fig. 10). $AUC_{0\rightarrow 24h}$ of BDD in the emulsion formulation increased 5.0-fold and 1-fold compared with that of BDD in 0.5% Ca-CMC suspension and BDD solution formulation (9.829 vs. 1.955 μg·h/ml and 1.718 vs. 1.955 μg·h/ml) (Table 2). The emulsion formulation of BDD also enhanced C_{max} of BDD by 9.8-fold and 1.1-fold compared with

Parameters	Emulsion formulation	BDD in 0.5% Ca-CMC suspension	BDD solution formulation
C_{max} (μg/ml)	1.550 ±0.706**	0.158 ±0.165	0.1412 ±0.602
T_{max} (h)	1.833 ±1.125	1.254 ±1.025	1.788 ±2.777
AUC (μg·h/ml)	9.829 ±2.255**	1.955 ±0.712	1.718 ±0.536

** $p < 0.01$ when compared with 0.5% Ca-CMC suspension and BDD solution formulation by the ANOVA test.

Table 2. Noncompartmental pharmacokinetic parameters after oral administration of BDD products to rats.

0.5% Ca-CMC suspension of BDD and BDD solution formulation (1.550 vs. 0.158 μg/ml and 0.1412 vs. 0.158 μg/ml) (Table 2). However, T_{max} was not significantly different between two formulations (Table 2). These results indicate that the emulsion system of BDD considerably increases the bioavailability of BDD compared with 0.5% Ca-CMC suspension of BDD and BDD solution formulation. The enhanced bioavailability is probably due to the increase in solubility and dispersion of the drug in the GI tract. Nerurkar reported that surfactants, which are commonly added to pharmaceutical formulations, might enhance the intestinal absorption of some drugs by inhibiting this apically polarized efflux system [23]. In this study, the presence of a surfactant, Tween 80, in the emulsion system might have caused changes in membrane permeability, which could lead to an increase in bioavailability of the drug. It is thus expected that the increased bioavailability of BDD from a emulsion system may result in improved efficacy, allowing patients to be able to take less BDD.

3.6 Conclusions

Taken together, these results demonstrate that the microemulsion formulation of BDD composed of Tween 80 and Neobee M-5® at the ratio of 2:1, and 35% of Triacetin considerably improves the bioavailability of a poorly water-soluble BDD after oral administration, possibly due to the increase in solubility and dispersion of the drug in the GI tract. Therefore, the emulsion system may provide a useful dosage form for oral intake of water-insoluble drugs such as BDD.

4. Thermal revisable microemulsion for oral delivery of poorly water-soluble drugs

To avoid the precipitation of poorly water soluble drug in the pre-microemulsion, we prepared a solid or semi-solid dosage form and it would change into liquid state at body temperature. Poorly water soluble drug YH439 was loaded in a thermal reversible microemulsion system which can disperse rapidly in the aqueous contents of the stomach and form fine oil in water droplets, and thus leads to improve absorption of the poorly water soluble drugs as indication in Figure 11.

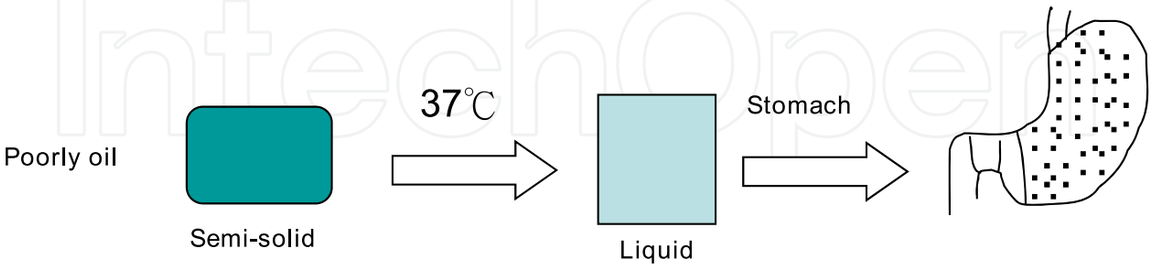


Fig. 11. Thermo sensitive SEDDS (Self-Emulsified Drug delivery System)

4.1 Effect of the composition ratio on melting point and particle size

The melting point of mixture of Pa-PEG (Palmitic-PEG400) and Ca-PEG(Capric-PEG400) was increased with increasing the composition ratio of Ca-PEG to Pa-PEG as shown in Figure 12. At the ratio of Ca-PEG to Pa-PEG was 1:3, the melting point was close to the body

temperature as 36°C. Thus, firstly, the ratio of Ca-PEG to Pa-PEG was fixed at 1:3, then the effect of Cremorphor RH40® as a surfactant and Neobee M-5® as an oil on melting point of thermal reversible microemulsions was examined and the optimal composition ratio was determined for the thermal reversible microemulsion system. The melting point of thermal reversible microemulsions was raised up with increasing the amount of oil in the formulation as shown in Figure 13(a). Whereas, the melting point of microemulsions decreased with increasing the amount of surfactant. When the microemulsion was composed of lipid matrix, surfactant and oil with a ratio of 5:4:1, its melting point was close to the body temperature as 37°C. Thus this would be considered as the pre-concentration of microemulsion since the solid state could change to liquid state around 37°C and rapidly form fine droplets microemulsion in gastrointestinal tract.

Effect of each component of microemulsion systems on the resultant droplet size was investigated as shown in Figure 13(b). In the range of surfactant with more than 0.2 g and oil with less than 0.2 g, small droplet size (< 100nm) of microemulsion was obtained in this system. The droplet size of microemulsion was significantly reduced with increasing the amount of surfactant. At the composition ratio of lipid matrices:Cremorphor RH40®:Neobee M-5® with 5:4:1, the smallest droplet with 28 nm of mean size was obtained. The smaller sizes of droplets will have a larger interfacial surface areas per unit volume and correspondingly large free energy contribution from the liquid-liquid interfacial tension. As reducing the size of droplets, a larger interfacial surface areas per unit volume could be produced.

Thus from the results, the optimal physical properties including melting point and particle size of microemulsion were produced by the composition ratio of lipid matrices:Cremorphor RH40®:Neobee M-5® with 5:4:1. This formulation would be used as a formulation of the thermal reversible microemulsion system for further study in the work.

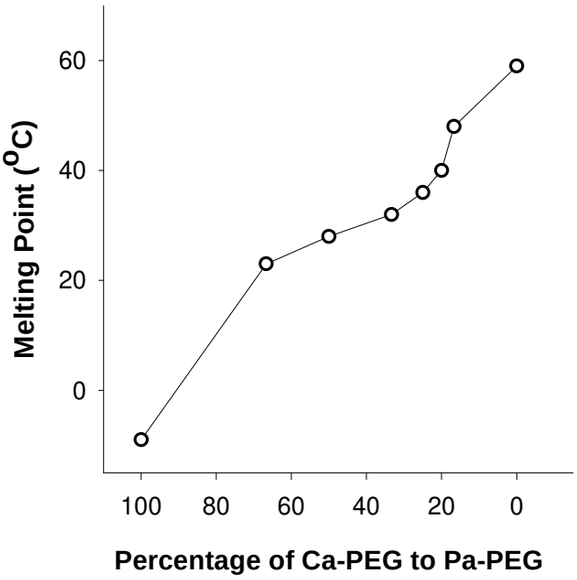
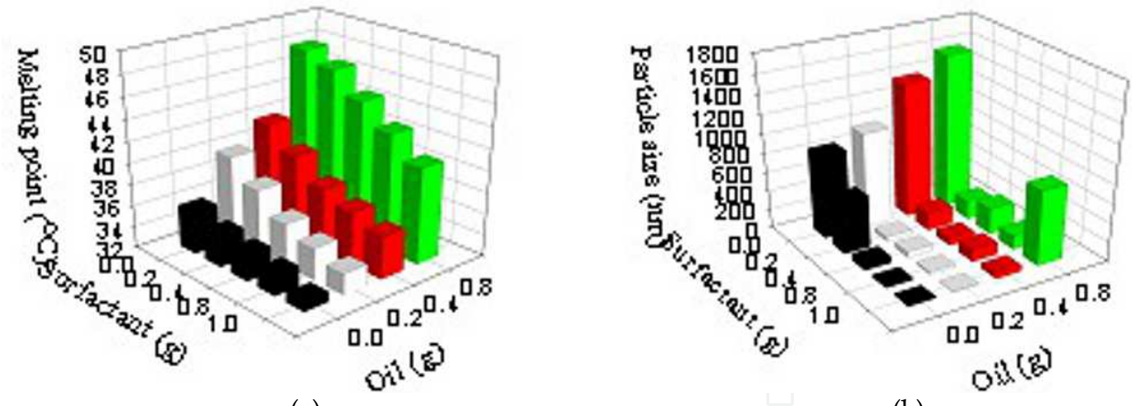


Fig. 12. The change of melting point was function of altering the composition ratio of Capric-PEG400 to Palmitic-PEG400.



(a) (b)

Fig. 13. Effect of oil and surfactant on changing melting point (a) and particle size (b) of microemulsion system. The ratio of Capric-PEG400 to Palmitic-PEG400 was fixed at 1:3 and the lipid mixture of Capric-PEG400 and Palmitic-PEG400 was equivalent to 1 g.

4.2 Release profile of YH439 from thermal reversible microemulsion

The YH439 was released from various formulations including powder form, 5% of Ca-CMC suspension, Gelucire® and the thermal reversible microemulsion prepared in this work. The powder form of YH439 was released less than 5% of initial amount and after suspending in the 5% of Ca-CMC, the YH439 was released upto 20%. However, by additions of the Gelucire® formulation and the microemulsion to YHP439, 90% of YHP439 was released until 180 min as shown in Figure 14. The systems of Gelucire® and microemulsion remarkably improved the

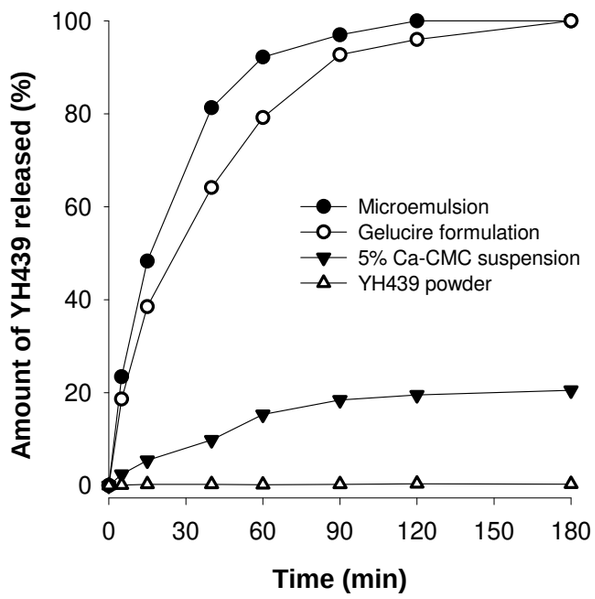


Fig. 14. Release profiles of YH439 from the thermal reversible microemulsion, Glucire® formulation, 5% Ca-CMC suspension and powder state of YH439. The thermal reversible microemulsion was composed of lipid matrices, Cremorphor RH40® and Neobee M-5® with a ratio of 5:4:1.

release property compared with powder form and 5% of Ca-CMC suspension. On the other hand, the fast release pattern was observed in the microsemulsion system compared with the Gelucire® formulation. This is desirable property since a slow dissolution rate of formulation might retard the absorption of drugs in the gastrointestinal tract.

4.3 The transport of YH439 across the caco-2 cell monolayer

The apparent permeability (Papp) of YH439 from the apical to the basolateral and basolateral to apical were calculated according the equation mentioned above. Papp of YH439 from the apical to the basolateral and basolateral to apparent direction were 2.08×10^{-5} cm/s, 4.71×10^{-5} cm/s for 0.63 uM, YH439. It was suggested YH439 was transported in the basolateral to apical direction is larger than from apical to basolateral direction in the present of a transport system as shown in Figure 4. It has been reported that the efflux of YH439 which is found in Caco-2 cells does not appear to influence the bioavailability of YH439 (Evidenced by the sufficiently high permeability in the absorption direction)[14]. YH439 was transported from microemulsion formulation larger than Gelucire® formulation and 5% Ca-CMC suspension as shown in Figure 15. The results were expected to response to *in vivo* animal experiments.

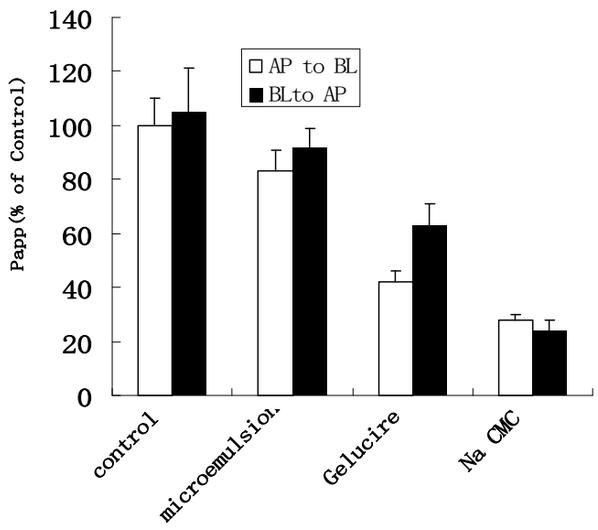


Fig. 15. Effect of YH439 transport from apical to basolateral and basolateral to apical in the microemulsion formulation, Glucire® formulation, and 5% Ca-CMC suspension (n=4).

4.4 Pharmacokinetic analysis

In vivo study was undertaken to examine the effect of a thermal reversible microemulsion system of YH439 on G.I. absorption after oral administration equivalent to 15 mg/kg of YH439 to rats. The plasma concentration of YH439 after oral administration of YH439 in the thermal reversible microemulsion formulation to rats increased compared with in the Gelucire® formulation and 5% Ca-CMC suspension as shown in Figure 5. $AUC_{0\text{-}24}$ of YH439 in the thermal reversible microemulsion formulation increased 1.17-fold and 6.91-fold compared with that of Gelucire® formulation and 5% Ca-CMC suspension (28.14 vs 24.01 μg·h/ml and 28.14 vs 4.07 μg·h/ml) as listed in Table 2. The thermal reversible

microemulsion formulation of YH439 also enhanced C_{max} of YH439 by 1.59-fold and 7.29-fold compared with Gelucire® formulation and 5% Ca-CMC suspension (2.26 vs 1.42 μg/ml and 2.26 vs 0.31) (Table 2). However, the significant difference was not observed in T_{max} value (Table 3). These results indicated that the thermal reversible microemulsion formulation of YH439 considerably increased the bioavailability of YH439 compared with Gelucire formulation and 5% Ca-CMC suspension. The enhanced bioavailability was very probably due to the increasing drug dispersion in the GI tract. Therefore, the increased solubility and enhanced bioavailability of YH439 from a thermal reversible microemulsion could result in improved drug efficacy.

Parameters	Intravenous	Oral		
		Microemulsion	Gelucire®	Suspension
C_{max} (mg/ml)	-	2.26±0.47[a,b]	1.42±0.10 [a]	0.31±0.85
T_{max} (min)	-	30	30	30
AUC (mg·h/ml)	6.11±0.28	28.14±2.89[a]	24.01±2.78 [a]	4.07±032
Absolute Bioavailability (F%)[c]	-	76.75 [a,b]	65.49 [a]	11.10

[a]P<0.001 by the AVOVA when compared to suspension
[b]P<0.05 by the AVOVA when compared to suspension
[c]$F=[AUC_{oral}/Dose_{oral}]/[AUC_{i.v}/Dose_{i.v}]$

Table 3. Plasma concentration of YH439 after oral administration of thermal reversible microemulsion, Glucire® formulation and 5% Ca-CMC suspension to rats at the dose of 15 mg/kg and after intravenous administration of thermal reversible microemulsion equivalent to 2.5 mg/kg as YH439 to rats (each group n=6).

4.5 Conclusion

The thermal reversible microemulsion system of YH439 was prepared from a lipid mixture of Ca-PEG and Pa-PEG, Cremophor RH40® and Neobee M-5® at the ratio of 5:4:1. The thermal reversible microemulsion promoted to increase the solubility of a poorly water-soluble YH439 and to enhance its bioavailability after orally administration to rat. The increased stability of poorly water-soluble YH439 by thermal reversible microemulsion system could lead to rapidly disperse as fine droplets inclusion drug in the gastrointestinal tract. Therefore, the thermal reversible microemulsion system could provide a useful dosage form for oral intake of water-insoluble YH439.

5. Acknowledgement

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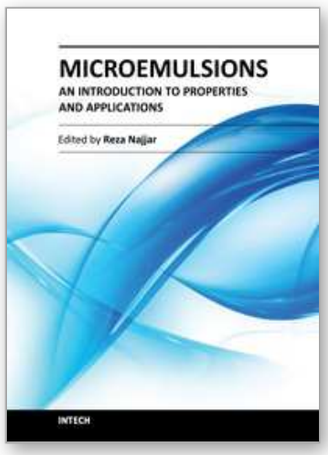

Microemulsions - An Introduction to Properties and Applications

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The rapidly increasing number of applications for microemulsions has kept this relatively old topic still at the top point of research themes. This book provides an assessment of some issues influencing the characteristics and performance of the microemulsions, as well as their main types of applications. In chapter 1 a short introduction about the background, various aspects and applications of microemulsions is given. In Part 2 some experimental and modeling investigations on microstructure and phase behavior of these systems have been discussed. The last two parts of book is devoted to discussion on different types of microemulsion's applications, namely, use in drug delivery, vaccines, oil industry, preparation of nanostructured polymeric, metallic and metal oxides materials for different applications.

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