*AAPS PharmSciTech* **2003; 4 (1) Article 10 (http://www.pharmscitech.org).**

# Study of Isopropyl Myristate Microemulsion Systems Containing Cyclodextrins to Improve the Solubility of 2 Model Hydrophobic Drugs

*Submitted: December 6, 2002; Accepted: February 6, 2003*

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## ABSTRACT

The objectives of this project were to evaluate the effect of alkanols and cyclodextrins on the phase behavior of an isopropyl myristate microemulsion system and to examine the solubility of model drugs. Triangular phase diagrams were developed for the microemulsion systems using the water titration method, and the solubility values of progesterone and indomethacin were determined using a conventional shake-flask method. The water assimilation capacities were determined to evaluate the effective microemulsion formation in different systems. The alkanols showed higher microemulsion formation rates at higher concentrations. A correlation between the carbon numbers of the alkanol and water assimilation capacity in the microemulsions studied was observed; isobutanol and isopentanol produced the best results. The addition of cyclodextrins showed no effect or had a negative effect on the microemulsion formation based on the type of cyclodextrin used. Isopropyl myristate–based microemulsion systems alone could increase the solubility values of progesterone and indomethacin up to 3300-fold and 500-fold, respectively, compared to those in water. However, the addition of cyclodextrins to the microemulsion systems did not show a synergistic effect in increasing the solubility values of the model drugs. In conclusion, microemulsion systems improve the solubility of progesterone and indomethacin. But the two types of cyclodextrins studied affected isopropyl myristate–based microemulsion systems negatively and did not improve the solubilization of 2 model drugs.

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**KEYWORDS:** phase diagram, microemulsion, solubilization, cyclodextrin, surfactant, progesterone, indomethacin

## INTRODUCTION

Solubilization of hydrophobic drugs with low aqueous solubility has been a major area of interest in recent years. Various solubilization techniques involve usage of cosolvents and surfactants along with pH adjustments. Applications of cyclodextrins (CDs) and microemulsions (MEs) have also drawn attention in the field of solubilization techniques. MEs are optically isotropic and thermodynamically stable systems of water, oil, surfactant, and cosurfactant and are known to enhance the bioavailability of drugs via topical and systemic routes. For instance, the ME formulations of cyclosporin, a highly lipophilic and poorly aqueous-soluble drug, have been shown to improve oral bioavailability and decrease absorption variation.[1,2] MEs have been considered as topical,[3,4] transdermal,[5] parenteral,[6] and vaginal[7] drug delivery systems based on their favorable solubilization and transport enhancement properties.

Recently, CDs have been used in various drug delivery systems.[1] CDs have been shown to improve the solubility, stability,[10] and bioavailability[11] of drugs. Two types of beta-hydroxy CDs—namely, Trappsol HPBCD (beta-hydroxypropyl-CD) and Captisol (sulfobutyl ether 4-beta-CD)—were examined in the current study. These 2 CDs were chosen because of their low systemic toxicity.[12]

To date, few researchers have examined a combination of ME and CD systems. Dalmora and others[13] worked on a CD-based ME system to improve the delivery of piroxicam. But no attempt has been made to fully characterize the ME systems containing CDs. One of the aims of this current project was to study the effect of CDs on ME formation.

Previous studies have examined the effects of alkanols and surfactants on various ME systems.[15,16] In this study, the effects of different alkanols and surfactants were examined in the phase behavior of isopropyl myristate–based (IPM-based) ME systems. Two hydrophobic model drugs (progesterone and indomethacin) known to form complexes with CDs were chosen. Progesterone is a neutral compound and known to form a 1:1 complex with beta-hydroxy-CD. Indomethacin is an acidic compound that also forms a 1:1 complex with beta-hydroxy-CD.[17] Recently, Trappsol and polyethylent glycol-400 (PEG-400) showed a synergistic effect on the solubilization of progesterone in an aqueous system.[18] Along the same lines, in this study the solubilization of model drugs in ME systems containing CDs was examined for synergistic effects.

## MATERIALS AND METHODS

### *Materials*

Progesterone, indomethacin, IPM, 1-propanol, 1-butanol, 1-pentanol, Tween 20, Tween 40, Tween 80, and Span 20 were purchased from Sigma Chemical Co (St Louis, MO). Ethanol was obtained from Quantum Chemical Co (Newark, NJ). Methanol and acetonitrile were obtained from J. T. Baker Chemical Co (South Plainfield, NJ). Trappsol was purchased from Cyclodextrin Technologies Development Inc (High Spring, FL). Captisol was purchased from Cydex Corp (Kansas City, KS). Soybean oil was obtained from a local vendor (Waldbaum). Water used in the study was deionized and distilled.

### *Preparation of the Phase Diagram and ME Formulations*

IPM and 1-butanol were selected as an oil component and cosurfactant, respectively, in the ME systems. The surfactants (a 1:1 mixture of Tween 80 and Span 20) were prepared separately. IPM and 1-butanol were added to the surfactant mixture. The pseudoternary phase diagrams of oil, surfactant/cosurfactant, and water were set up using the water titration method. The mixture of oil and surfactant/cosurfactant at predetermined weight ratios was diluted with water by sequential addition of 10 µL of water using a micropipette. No heating was necessary during the preparation. However, the system was stirred using a magnetic stirrer to ensure a thorough mixing. After each mixing, the sample was allowed to settle and its physical condition (clarity and flowability) was reviewed. If required, the sample was sonicated for 1 to 2 minutes to remove air bubbles and to enable a better visual examination. Mixtures that did not show a change in the meniscus after tilting to an angle of 90º were considered to be gels. Samples were examined under a microscope, if necessary.

The mixture compositions at different points in the phase diagrams were defined by the following equation:

$$\%A\ (\text{Tween 80} + \text{Span 20}) + \%B\ (\text{1-butanol} + \text{oil}) + \%C\ (\text{water}) = 100 \quad (1)$$

To study the effect of CDs on the formation of ME, a 50% wt/vol aqueous solution of each type of CD was prepared. The densities of 50% wt/vol Captisol and 50% wt/vol Trappsol aqueous solutions were 1.13 g/cc and 1.16 g/cc, respectively. Because the solutions were denser than water pipettes used in the experimentation were calibrated with CD solutions. The ME region was determined in the same way as it was determined for the ME system without CD.

### *Effects of Alkanols and Surfactants on ME Formation*

The effect of alkanol and surfactants on ME formation was evaluated by the maximum water-to-oil ratio (% wt/wt) to produce an ME.[19] To evaluate the effect of various alkanols (methanol, ethanol, isopropanol, isobutanol, and isopentanol), 0, 0.3, 0.6, and 0.9 g of each type of alkanol was mixed with the required amount of IPM to obtain a final weight of oil-alkanol mixture of 2.4 g. The amount of surfactant mixture added to the system was 6.0 g (Tween 80:Span 20, 8:1 ratio wt/wt). Water was titrated into the oil-alkanol-surfactant mixture to form the ME. Titrations were continued until an ME was converted into a different heterogeneous system, namely, an emulsion, a gel, or 2 separate phases. The endpoint of ME formation was evaluated by physical examination.

A similar procedure was followed to evaluate the effects of Tween on the ME formation. Three different Tweens—Tween 20, Tween 40, and Tween 80—were used in the study. These Tweens are liquids at room temperature. Isobutanol was selected as the alkanol, and the ratio of oil to alkanol was 8:1. The Tween:Span 20 ratios used were 0:100, 20:80, 50:50, 80:20, and 100:0 wt/wt. The titration method and the endpoint evaluation remained the same as described previously.

**Table 1.** Composition of Final ME Systems*

| Formulas | IPM† | Isobutanol† | Tween 80† | Span 20† | Tween 40† | Water† | ME Type |
|---|---|---|---|---|---|---|---|
| ME A | 36.3 | 4.5 | 20.5 | 20.5 | — | 18.2 | w/o |
| ME B | 8.6 | 5.3 | — | — | 34.5 | 51.6 | o/w |
| ME C | 36.3 | 4.5 | — | 10.2 | 30.7 | 18.3 | w/o |

*ME indicates microemulsion; IPM, isopropyl myristate; w/o, water/oil; o/w, oil/water.
†All numbers are % wt/wt basis.

### *ME Formulations*

Based on the experience in preparing phase diagrams and the effect of Tweens, 3 MEs were formulated (**Table 1**). ME A was water/oil type and contained 36.3% oil, 4.5% isobutanol, 18.2% water, and 41% surfactants (Tween 80:Span 20 1:1). ME B was oil/water type and contained 8.6% oil, 5.3% isobutanol, 51.6% water, and 34.5% surfactants (Tween 40 only). ME C was water/oil type and contained 36.3% oil, 4.5% isobutanol, 18.3% water, and 40.9% surfactants (Tween 40:Span 20 3:1). All formulations could hold 3% to 6% CD. CD-based MEs were prepared by adding a known amount of CD (either Captisol or Trappsol) in the predetermined volume of a particular ME. The system was stirred at a high rate until it formed an optically isotropic system. By dissolving all the CD in the ME system, it was possible to revert to an optically isotropic single-phase system. The physical stability of MEs, CD-containing MEs, and drug-incorporating MEs was observed for the clarity at room temperature for up to 1 month.

### *Solubility Determinations*

Progesterone and indomethacin were added in excess to various solvents. The solubilities were measured in IPM, Tween 80, Tween 40, Span 20, isobutanol, and 3% and 6% Captisol and Trappsol aqueous solutions and water. Samples were shaken at 25 ± 2ºC for 24 hours and filtered through a 0.45-µm filter. Prior to the solubility study, it was concluded that the 0.45-µm filter did not adsorb/absorb the model drugs. The drug concentrations in the filtered systems were determined using high-performance liquid chromatography (HPLC) after appropriate dilutions with methanol.

The solubility values of progesterone and indomethacin in selected ME formulations (**Table 1**) were determined by adding excess amounts of drugs to MEs. After 24 hours of shaking, the mixtures were filtered, diluted suitably, and analyzed by HPLC.

### *Analytical Methods*

An HPLC system equipped with a 600E multisolvent delivery system, a 717 Plus autoinjector, a 486-UV detector (Waters Corporation, Milford, MA), and a Turbo chrome data management system (Perkin Elmer, Shelton, Connecticut) was used to analyze progesterone and indomethacin. A reversed-phase C18 column (10 cm ´ 4.6 mm, 5 µm) was used at room temperature. For progesterone assay, the mobile phase was 50% acetonitrile/50% 0.5% acetic acid (vol/vol) at a flow rate of 1.2 mL/min and a detection wavelength of 254 nm. For indomethacin, the mobile phase remained the same as stated above but the flow rate was 1.5 mL/min with a detection wavelength of 240 nm. Under these analytical conditions, the detection limits for progesterone and indomethacin were found to be approximately 50 ng/mL.

## RESULTS AND DISCUSSION

### *Phase Behavior*

The pseudoternary phase diagrams of the different ME systems are shown in **Figures 1** and **2**. Isobutanol concentration was kept constant with respect to the oil phase (8:1) to facilitate the construction of the phase diagram. The translucent and low-viscosity area is presented in the phase diagrams as an ME area. No distinct conversion from water/oil to oil/water ME systems was observed. Therefore, this single isotropic region was considered a bicontinuous ME. The emulsion region is an area in which a milky white heterogeneous system is formed. The gel area indicates the clear and high-viscosity region. The remainder of the phase diagram represents the turbid region, repre-

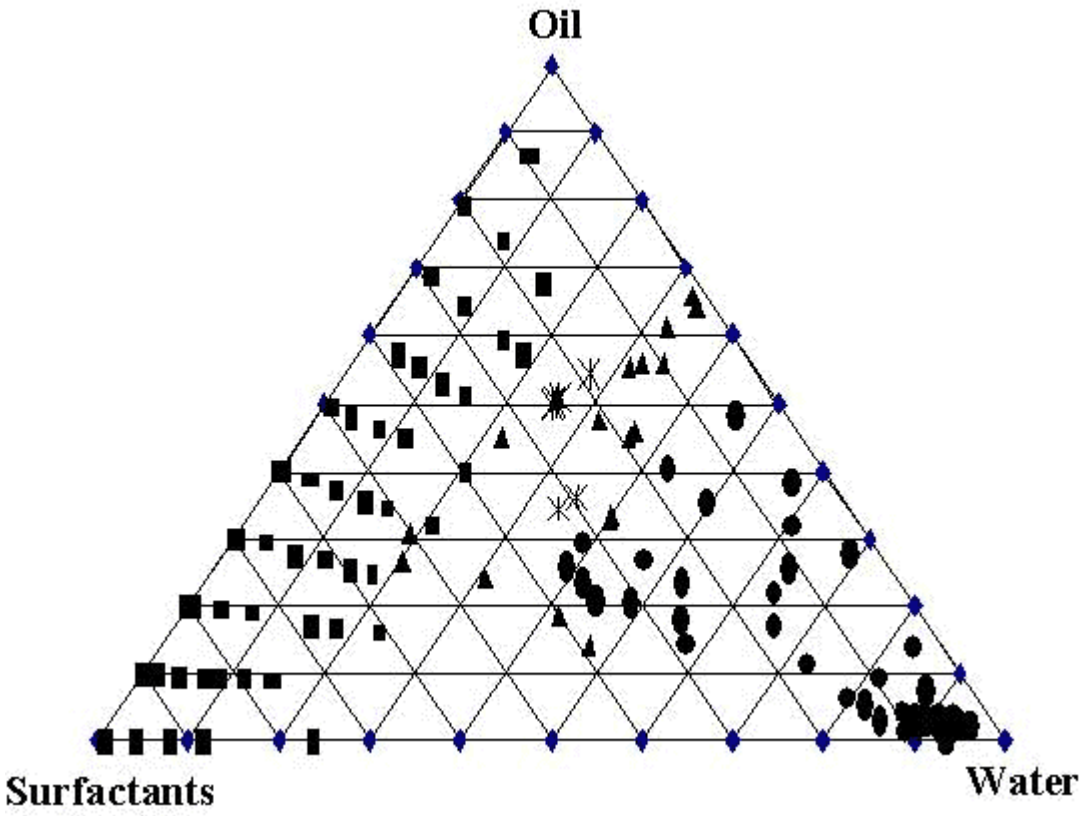


**Figure 1.** Pseudoternary phase diagrams of IPM-surfactant-water system at Tween 80:Span 20 ratios of 1:1, and IPM:1-butanol ratios of 8:1. ■ = ME, ● = emulsion, ▲ = gel, and ✳= 2 phases.

sented as 2 phases and conventional emulsions based on visual identification.

**Figure 1** shows the phase diagram of the IPM Tween 80:Span 20 pseudoternary system. The ME formation was favorable at high surfactant concentrations. At higher oil concentration, the system tended to separate into 2 phases.

The influence of CD on the ME isotropic region can be observed in **Figure 2**. The ME area decreased from about 30% in the blank ME to about 23% in the ME containing Captisol. These numbers were calculated manually by finding out the number of small triangles covered by the ME area in the phase diagram compared to the total number of small triangles in the phase diagram. On the other hand, Trappsol did not hamper the formation of ME (30% to 29%), but the shape of the ME region changed significantly. The results indicated that the formation of ME could be influenced negatively by the presence of ionic CD. Captisol has a high affinity for water, which might have affected the ME formation. The ME formation region improved at a 40% to 60% water level in the Trappsol system. The exact reason for this is not known at this time. The higher surface activity of Trappsol compared to Captisol may have played a role. Overall, from **Figure 2**, it was clear that ME could be formed in the presence of CDs, but the type of CD could alter the ME region either positively or negatively.

### *Effects of Alkanols on IPM ME Formation*

Alkanols are known to improve ME formation. Low–molecular weight alkanols affect the interfacial energy by interaction with surfactant monolayers. The lipophilic character of the nonaqueous phase would be changed by the distribution of alkanol in both aqueous and oil phases.[16] The effect of 5 different alkanols on the phase behavior was measured by the amount of water that could be incorporated into the ME per gram of oil (**Figure 3**). The effect of alkanol added in the

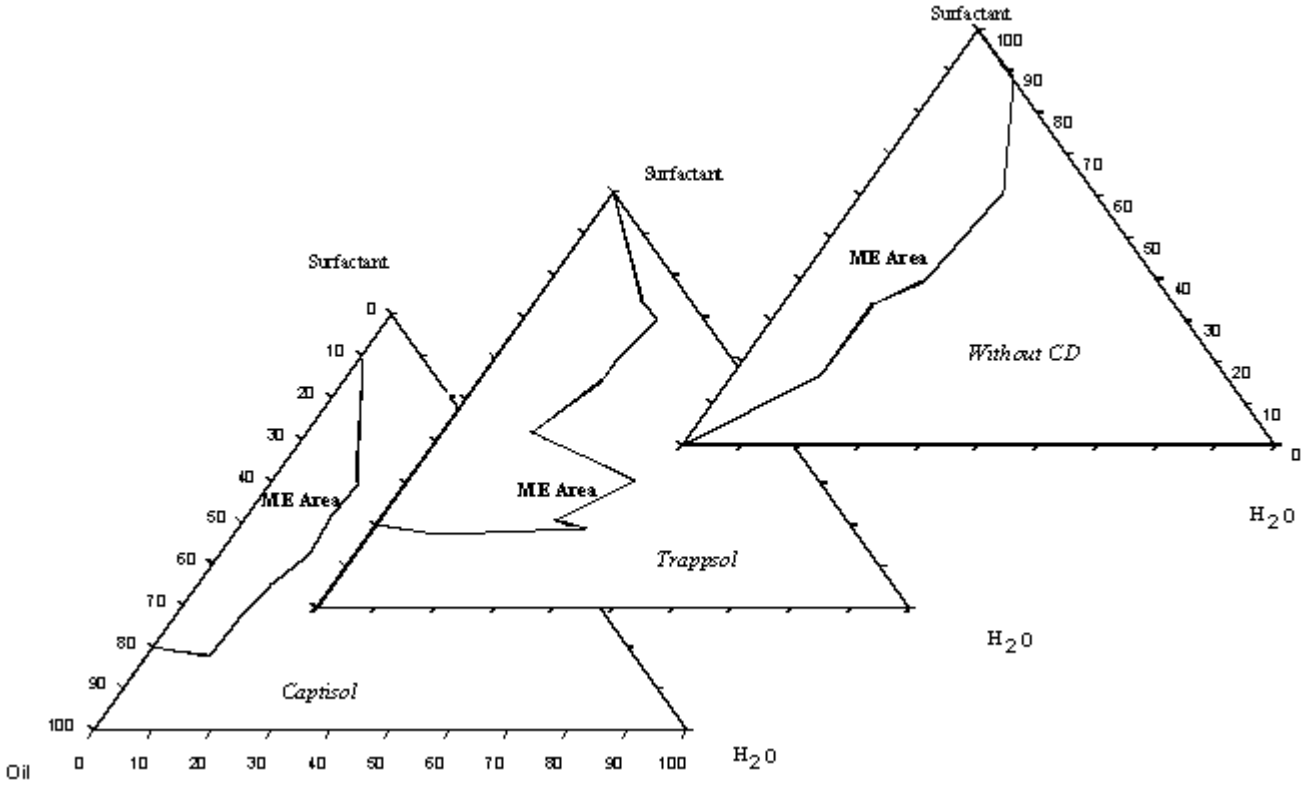


**Figure 2.** Pseudoternary phase diagrams of IPM-surfactant-water system at Tween 80:Span 20 ratios of 1:1, and IPM:1-butanol ratios of 8:1, showing effects of CDs.

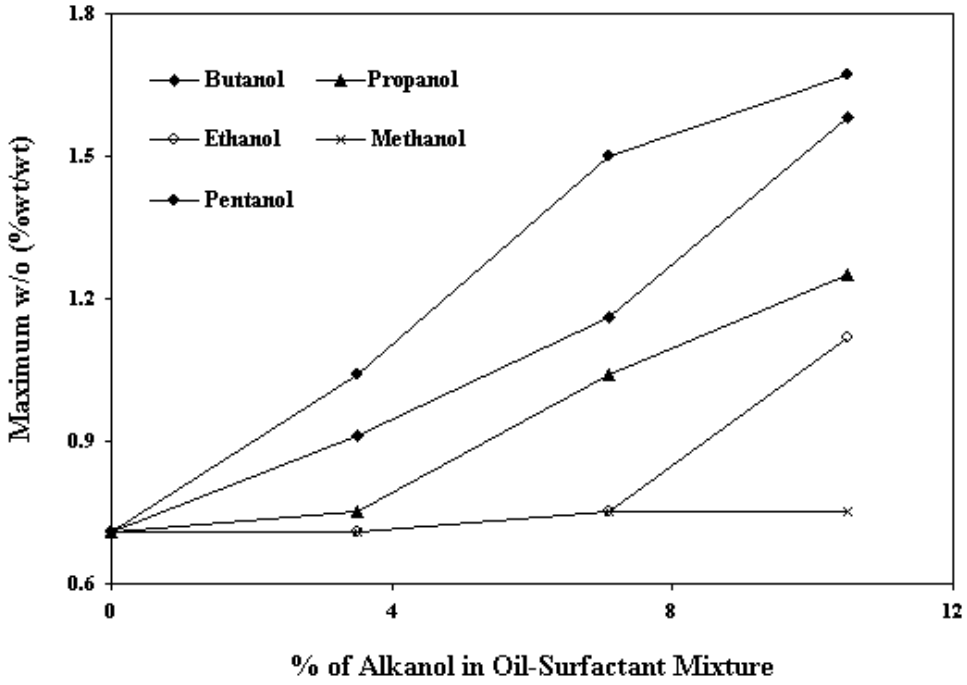


**Figure 3.** The maximum water-to-oil ratio required to produce a microemulsion as a function of the amount of alkanol in the oil-surfactant mixture.

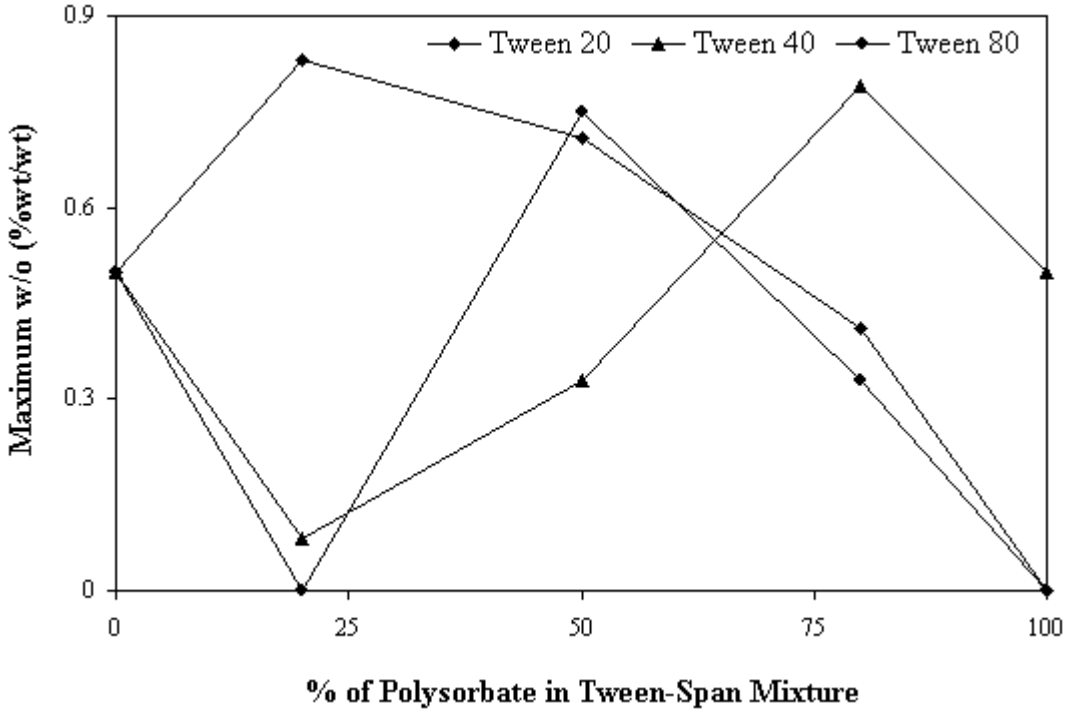


**Figure 4.** The maximum water-to-oil ratio required to produce a microemulsion as a function of the amount of polysorbate in the oil-surfactant mixture.

ME was examined at the concentrations of 0% to 10.7%. Methanol and ethanol showed no effect or very little effect. Alkanols with higher carbon numbers (isopropanol to isopentanol) facilitated the ME formation. For each alkanol, higher percentages allowed greater incorporation of water to form the MEs. Overall, the ME formation was satisfactory with the addition of 1-butanol or 1-pentanol.

### *Effects of Surfactants on ME Formation*

Spans/Tweens were used in the preparation of MEs. Out of various types of Tweens (Tween 20, 40, 60, 80, and 85), only 3 (20, 40, and 80) were selected in the present study; these were liquid at room temperature. Tweens 20, 40, and 80 are chemically known as polysorbate monolaurate, polysorbate monopalmitate, and polysorbate monooleate, respectively. Span 20 was selected as a secondary surfactant. The maximum water-to-oil ratio that could be achieved to form the ME was employed to evaluate the effects of surfactant (**Figure 4**). The number of carbons present in the fatty acid side chain of the surfactant had no direct correlation with ME formation. For example, polysorbate monopalmitate (Tween 40), which has a C16 carbon chain, showed better ME formation capacity than polysorbate monooleate (Tween 80, $C_{18}$) or polysorbate monolaurate (Tween 20, $C_{12}$). Interestingly, 2 surfactants showed similar behavior at the 100% level. As Tween was mixed with various amounts of Span, the effects varied. For Tween 80, as the percentage of Span was increased from 0% to 50% the ME formation increased linearly but later the formation reduced. Overall, there was no direct correlation between different Tween types/concentrations and ME formation.

### *Solubility of Model Drugs in Pure Vehicles*

The solubilities of the 2 model drugs, progesterone and indomethacin, were evaluated in various pure vehicles and aqueous CD solutions (**Table 2**). Water solubility values of progesterone and indomethacin were 7 and 35 µg/mL, respectively. The solubility of progesterone in nonaqueous systems improved significantly. The solubility of progesterone in IPM, Tween 80, Tween 40, isobutanol, and Span 20 was 17, 11.9, 20.7, 35.6, and 4.0 mg/mL, respectively. Indomethacin also showed marked improvement in solubility in the nonaqueous systems. The solubility

**Table 2.** Solubility of Model Drugs in Selected Vehicles

| Vehicles | Solubility (mg/mL)† | |
|---|---|---|
| | **Progesterone** | **Indomethacin** |
| Isopropyl myristate | 17.0 ± 0.0 | 1.7 ± 0.7 |
| Tween 80 | 11.9 ± 2.3 | 25.9 ± 0.5 |
| Tween 40 | 20.7 ± 1.8 | 25.5 ± 0.1 |
| Isobutanol | 35.6 ± 0.7 | 9.6 ± 0.5 |
| Span 20 | 4.0 ± 0.0 | 2.6 ± 0.1 |
| 3% Captisol aqueous solution | 1.6 ± 0.1 | 0.11 ± 0.0 |
| 3% Trappsol aqueous solution | 1.1 ± 0.0 | 0.08 ± 0.0 |
| 6% Captisol aqueous solution | 5.0 ± 0.1 | 0.27 ± 0.0 |
| 6% Trappsol aqueous solution | 1.3 ± 0.1 | 0.16 ± 0.0 |
| Water | 0.007± 0.0 | 0.035 ± 0.0 |

†All values are mean ± SD of 3 samples.

of indomethacin in IPM, Tween 80, Tween 40, isobutanol, and Span 20 was 1.7, 25.9, 25.5, 9.6, and 2.6 mg/mL, respectively. Addition of 2 types of CDs—Captisol and Trappsol—to water improved the aqueous solubility values of both the model drugs. In the case of progesterone, by the addition of 3% and 6% Captisol, the solubility values increased to 1.6 and 5.0 mg/mL, respectively. The addition of 3% and 6% Trappsol increased the solubility of progesterone to 1.1 and 1.3 mg/mL, respectively. Indomethacin aqueous solubility values improved with the addition of 3% and 6% Captisol and Trappsol, but not as significantly as observed in the cases of progesterone.

### *Solubility of Model Drugs in MEs*

Three ME formulations were selected to examine the influence of CDs on the solubility of the 2 model drugs (**Table 1**). **Figures 5** and **6** depict the solubility of progesterone and indomethacin, respectively, in various systems. In ME A, the solubility value of progesterone was 23.1 mg/mL. Addition of 3% Captisol and 3% Trappsol decreased the solubility to 21.5 and 21.1 mg/mL, respectively. For indomethacin, the solubility in ME A was 15.1 mg/mL. Addition of 3% Captisol and 3% Trappsol decreased the solubility to 12.2 and 14.3 mg/mL, respectively. Addition of 3% Captisol and 3% Trappsol had no significant effect on the solubility of progesterone in ME A. But in the case of indomethacin, an addition of 3% Captisol significantly reduced the solubility of the drug in ME A ($P$ = .0091). Addition of Trappsol did not significantly alter the solubility of indomethacin in the same ME system. The addition of 6% Captisol and 6% Trappsol did not have any positive synergistic effect on the solubility values of the model drugs.

The solubility value of progesterone was 8.5 mg/mL in ME B. Addition of 3% Captisol and 3% Trappsol resulted in solubility values of 9.1 and 6.2 mg/mL, respectively. When the concentrations of Captisol and Trappsol were increased, the solubility values increased slightly. The solubility of indomethacin in ME B was 9.7 mg/mL. Addition of 3% Captisol and 3% Trappsol decreased the solubility to 9.2 and 8.4 mg/mL, respectively.

In ME C, the solubility value of progesterone was 20.4 mg/mL. Addition of 3% Captisol and 3% Trappsol decreased the solubility to 19.4 and 17.8 mg/mL, respectively. For indomethacin, solubility in ME C was 16.7 mg/mL. Addition of 3% Captisol and 3%

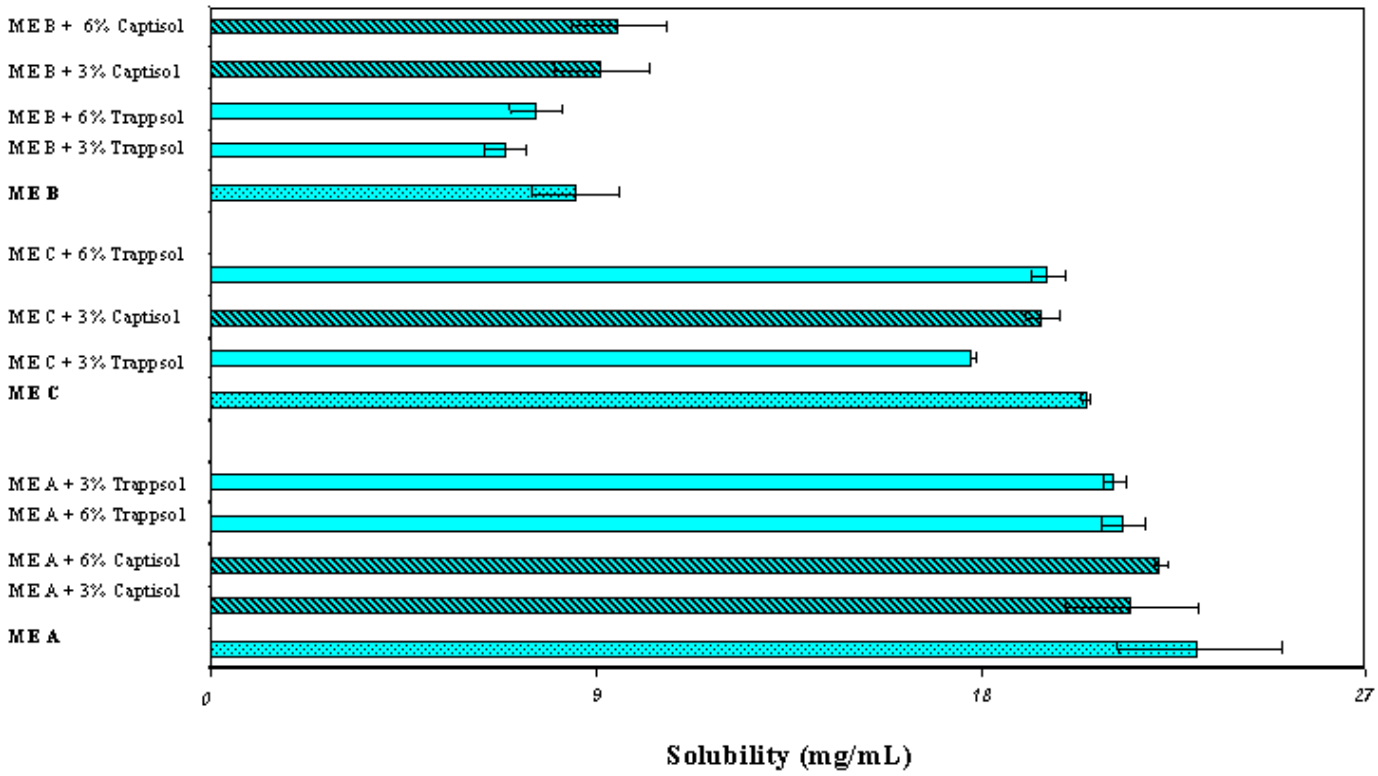


**Figure 5.** Solubility of progesterone in various MEs with or without CDs.

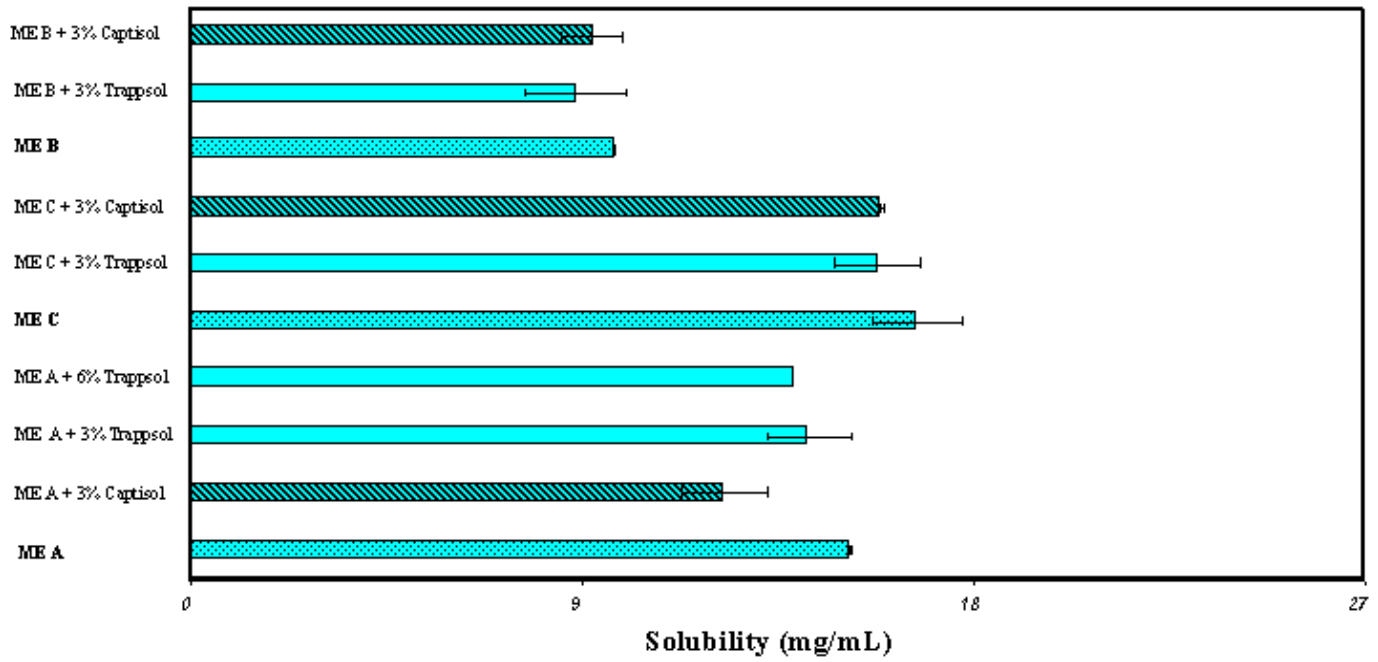


**Figure 6.** Solubility of indomethacin in various MEs with or without CDs.

Trappsol decreased the solubility to 15.9 and 15.8 mg/mL, respectively.

The low solubility of the 2 model drugs in ME B can be attributed to that formulation's higher water content. Also, MEs A and C had a combination of surfactants, which could have played a role. The difference in the effect of Captisol on the solubility of the 2 model drugs in the same MEs may be due to the ionic nature of indomethacin and Captisol. The neutral molecules may form a complex with Trappsol better than with an ionic CD.[18]

Overall, CDs failed to produce any significant additive or synergistic effects to improve the solubility of model drugs in the ME systems tested. However, it must be kept in mind that the properties of drug molecules may influence the solubilization potential of the ME and CD systems. Also, CDs may help to stabilize the drug molecules in the ME systems. In a previous study [18], Trappsol and PEG-400 were observed to have a synergistic effect on the solubilization of progesterone in an aqueous system. However, addition of Tween 80 to the system hampered the synergistic effect. ME formulations in this study had large amounts of Tweens, and the lack of improvement of solubility with CD and ME systems is consistent with the previous data.[18]

## CONCLUSION

The ME system comprising IPM, Tween 80, Span 20, isobutanol, and water showed a high solubilization capacity for 2 model drugs, progesterone and indomethacin. The addition of CDs in general affected the ME formation negatively and did not improve the solubility of hydrophobic drugs in the ME systems tested.

## REFERENCES

1. Ritschel WA, Adolph S, Ritschel GB, Schroeder T. Improvement of peroral absorption of cyclosporin A by microemulsions. Methods Find Exp Clin Pharmacol. 1990;12:127-134.

2. Kim CK, Ryuu SA, Park KM, Lim SL, Hwang SJ. Preparation and physiochemical characterization of phase inverted water/oil microemulsion containing cyclosporin A. Int J Pharm. 1996;147:131-134.

3. Linn E.E. Microemulsion for intradermal delivery of cetyl alcohol and octyl dimethyl PABA. Drug Dev Ind Pharm. 1990;16:899-920.

4. Garcia-Celma MJ, Azemar N, Pes MA, Solans C. Solubilization of antifungal drugs in water/POE (20) sorbitan monooleate/oil systems. Int J Pharm. 1994;105:77-81.

5. Thevenin MA, Grossiord JL, Poelman MC. Sucrose esters/cosurfactant microemulsion systems for transdermal delivery: assessment of bicontinuous structures. Int J Pharm. 1996;137:177-186.

6. Corswant CV, Thoren P, Engstrom S. Triglyceride-based microemulsion for intravenous administration of sparingly soluble substances. J Pharm Sci. 1998;87:200-208.

7. D'Cruz OJ, Yiv SH, Uckun FM. GM-144, a novel lipophilic vaginal contraceptive gel-microemulsion. AAPS PharmSciTech. 2001; 2(2):article 5.

8. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins, II: in vivo drug delivery. J Pharm Sci. 1996;85:1142-1169.

9. Piel G, Evrad B, Fillet M, Labres G, Dellatre L. Development of a non-surfactant parenteral formulation of miconazole by use of cyclodextrins. Int J Pharm. 1998;169:15-22.

10. Loftsson T, Brewster ME. Pharmaceutical application of cyclodextrins, I: drug solubilization and stabilization. J Pharm Sci. 1996;85:1017-1025.

11. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. Pharm Res. 1997;14:556-567.

12. Szente L, Szejtli J. Highly soluble cyclodextrin derivatives: chemistry, properties and trends in development. Adv Drug Deliv Rev. 1999;36:17-28.

13. Dalmora ME, Oliveria AG. Inclusion complex of piroxicam with β-cyclodextrin and incorporation in hexadecyltrimethylammonium bromide based microemulsion. Int J Pharm. 1999;184:157-164.

14. Dalmora ME, Dalmora SL, Oliveria AG. Inclusion complex with piroxicam with β-cyclodextrin and incorporation in cationic microemulsion: in vitro drug release and in vivo topical anti-inflammatory effect. Int J Pharm. 2001;222:45-55.

15. Attwood D, Mallon C, Kristis G, Taylor CJ. A study of factors influencing the droplet size in nonionic oil-in-water microemulsions. Int J Pharm. 1992;88:417-422.

16. Alany RG, Rades T, Agatonovic-Kustrin S, Davies NM, Tucker IG. Effects of alcohols and diols on phase behavior of quaternary systems. Int J Pharm. 2000;191:141-145.

17. Pitha J, Milecki J, Fales H, Pannell L, Uekema K. Hydroxypropyl-β-cyclodextrin: preparation and characterization; effects on solubility of drugs. Int J Pharm. 1986;29:73-82.

18. Nandi I, Bateson M, Bari M, Joshi H. Synergistic effect of PEG-400 and cyclodextrin to enhance solubility of progesterone. AAPS PharmSciTech. 2003; 4 (1):article 1.

19. Johnson KA, Shah DO. Effect of oil chain length and electrolytes on water solubilization in alcohol-free pharmaceutical microemulsions. J Colloid Interface Sci. 1985;107(1):269-271.