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Physical characterizations of microemulsion systems using tocopheryl polyethylene glycol 1000 succinate (TPGS) as a surfactant for the oral delivery of protein drugs

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Abstract

Attempts were to develop microemulsion systems using medium chain triglyceride, deionized water, and TPGS as surfactant for the oral delivery of protein drugs or poorly water-soluble drugs. Phase diagrams were constructed to elucidate the phase behavior of systems composed of Captex 300 and water with D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) as main surfactant, polysorbates (Tween 20, Tween 40, Tween 60 and Tween 80) as adjuvant surfactants, and polyethylene glycols (PEG 400 and PEG 600) and polyols (ethanediol, 1,2-propanediol, 1,3-propanediol, 1,3-butanediol, 1,4-butanediol and glycerin) as cosurfactants. The ratios of TPGS to Tweens, PEGs or polyols (K_m) were set at 4/1, 2/1, 1/1, 1/2, and 1/4. The phase diagram for H_2O/Captex 300/TPGS system reveals that when TPGS was used as a sole surfactant, it is not capable of producing isotropic solutions of water and oil over a wide range of the compositions. H_2O/Captex 300/TPGS/Tweens systems with various K_m, regardless of the adjuvant surfactant used were capable of producing an isotropic phase. The extension of microemulsion phase and the presence and extension of the gel phase were found to be dependent on the surfactant mixture. The phase diagrams of H_2O/Captex 300/TPGS systems using polyols as cosurfactants demonstrate that the types of polyols have a slight effect on the region of existence of the microemulsions. Comparison between the isotropic regions for the polyols system reveals that as the relative concentration of polyols increase, the isotropic region decrease in size. This decrease is towards the S_{mix}–water axis indicating that as the relative concentration of polyols increases the maximum amount of oil solubilized decreases. The gel region decreased in size with the increase of polyols weight ratio. All polyols do not solubilized Captex 300 without using TPGS as surfactant.

Keywords: Microemulsions; TPGS; Phase diagrams; Protein drugs; Oral delivery

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1. Introduction

Microemulsions were first introduced by Hoar and Schulman in 1943 [1]: they are isotropically clear, and thermodynamically stable dispersions of two immiscible liquids such as oil and water, stabilized by relatively large amount of surfactant and usually in conjugation with a cosurfactant, typically a short to medium chain alcohols [2]. Microemulsions are clear fluids of low viscosity and may form a number of different structures, e.g., oil-in-water (o/w) or water-in-oil (w/o) droplets, and bicontinuous structures, over a wide range of compositions dependent on the properties of the oil and the surfactant. Usually, the interfacial tension of microemulsions is ultralow ($\sim 10^{-2}$ mN/m), and the size of droplets in microemulsions is less than 100 nm, smaller than the wavelength of light, which is the reason for their transparency [3].

Microemulsions have attracted much interest for several years in terms of their drug delivery potentials. Part of this interest as consequences of their transparency, high solubilizing capacity, ease of preparation, long-term stability, and may be sterilized by filtration. Microemulsions have a higher drug loading capacity than simple micellar solutions, and their thermodynamic stability offers advantages over unstable dispersions, such as traditional emulsions and suspensions, because they can be manufactured with little energy input (heat or mixing) and have a long-term shelf life. Water-in-oil and oil-in-water microemulsions have been shown to enhance the oral bioavailability of drugs. Although the mechanism of absorption enhancement is still largely unknown, drug delivery advantages offered by microemulsions include: improved drug solubilization and protection against enzymatic hydrolysis, as well as the potential for enhanced absorption largely due to the inclusion of absorption afforded by surfactant-induced membrane fluidity and thus permeability changes [4]. Formulation with suitable excipients, microemulsions may also prove to be suitable vehicles for delivery for labile (peptide or protein) and poorly soluble drugs [5,6]. So far, microemulsions have been used mainly for the oral delivery of peptide [7], and water-insoluble drugs, but microemulsions have also been reported as drug carriers for topical [8], dermal, transdermal [9,10], pulmonary, nasal [11], periodontal [12], and intravenous [13] administration of drugs.

D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of the lipid-soluble natural Vitamin E, which is formed by esterification of vitamin E succinate with polyethylene glycol 1000, has been utilized for numerous applications in pharmaceutical dosage forms. The chemical structure of TPGS contains both a lipophilic and hydrophilic moiety, making it similar to a conventional surface-active agent. Moreover, its lipophilic alkyl tail (tocopherol succinate) and hydrophilic polar head portion (polyethylene glycol) are bulky and have large surface areas. The hydrophile–lipophile balance (HLB) of TPGS is about 13.2. The chemical properties of this distinctive compound have suggested its use as a solubilizer, an emulsifier, an absorption enhancer [14], a plasticizer [15], and as a water-soluble source of vitamin E [16]. The mechanism of action for increasing the bioavailability of poorly absorbed drugs of TPGS can be explained by its solubilizing effect through improved micelle formation, inhibitory effect on the *p*-glycoprotein efflux pump, or its protective effect against intestinal metabolism [17,18]. TPGS is a waxy solid at room temperature that forms micelles above its critical micelle concentration (0.02%), and continues to form low viscosity solutions with water until concentration of about 20%. The structure of TPGS/water liquid crystalline phase evolves form isotropic globular micellar to hexagonal to lamellar with increasing concentration.

The aim of the present study was to characterize the phase behaviors of various pseudo-ternary system containing Captex 300 as the oil phase, deionized water as the aqueous phase, TPGS as the main surfactant combined with other additives, such as polysorbates (Tween 20, Tween 40, Tween 60, and Tween 80) as the adjuvant surfactants, PEGs (PEG 400, and PEG 600) or polyols (ethanediol, 1,2-propanediol, 1,3-propanediol, 1,3-buanediol, 1,4-butanediol, and glycerin) as the cosurfactants. Captex 300 belongs to medium chain triglyceride was selected as oil phase because it has been shown to improve intestinal absorption of various active compounds [4,19].

2. Materials and methods

2.1. Materials

Captex 300 (C_8/C_{10} triglycerides) was obtained from Abitec (Columbus, MO, USA). D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) was purchased from Eastman Chemical (Kingsport, TN, USA). Polysorbates (Tween 20, Tween 40, Tween 60, and Tween 80), poly(ethylene glycol) with an average molecular weight of 400 (PEG 400) and 600 (PEG 600), ethanediol, 1,2-propanediol, and glycerin were purchased from E. Merck (Schuchardt, Germany). 1,3-Propandiol, 1,3-butandiol, and 1,4-butanediol were purchased from Acros Organics (New Jersey, USA). All these materials were used directly as obtained.

2.2. Construction of pseudo-ternary phase diagrams

To investigate the microemulsion region, pseudo-ternary phase diagrams were constructed by titration of a series of mixtures of oil (Captex 300) and surfactant (TPGS) with or without other adjuvant surfactants (Tween 20, Tween 40, Tween 60, and Tween 80), or cosurfactants (PEG 400, PEG 600, ethanediol, 1,2-propanediol, 1,3-propanediol, 1,3-butanediol, 1,4-butanediol, and glycerin) with deionized water at room temperature (25±2°C). TPGS was premixed with Tweens, PEGs or polyols as surfactant mixtures (S_{mix}) at fixed weight ratios (K_m) of 4/1, 2/1, 1/1, 1/2, and 1/4. For each K_m value, the ratios of Captex 300/S_{mix} were set at 9/1, 8/2, 7/3, 6/4, 5/5, 4/6, 3/7, 2/8, and 1/9. For TPGS or TPGS containing mixtures that are solid at room temperature premelting at the appropriate temperature was necessary before weighting or mixing. Total amount of 1 g of Captex 300/S_{mix} was accurately weighed into screw-capped glass tubes with tight closures. Samples were vortexed for sufficient time to attain equilibrium and then progressively diluted with water and mixed using a vortexer for a short time period to accelerate equilibrium. After mixing, the mixture was stood for several hours at room temperature to accomplish the equilibrium. The equilibrated samples were then centrifuged at 4000 rpm (7000×g) for 10 min and assessed for their macroscopically appearance. Centrifugation can be useful to speed up any separation if it occurs. If the mixtures became inhomogeneous and/or had solid precipitates, heating the mixtures to liquid state and vortexed to homogeneity before subsequently water titration was necessary.

The systems were checked for visual clarity and fluidity. The microemulsion domain was determined by visual observation for fluid, optically isotropic, and transparent appearance. No attempt was made to recognize the microemulsion structures between o/w, w/o, or bicontinuous type microemulsions. But owing to the continuity between the water-poor and the water-rich regions, it may be predicted that the microemulsion structure will vary greatly, but progressively, as the composition varies over such a wide range. The clear domain that did not show a change in meniscus after tilting to an angle of 90° was classified as gel. The liquid crystalline phase was detected by using polarized light microscopy. No attempts were made to identify in detail other regions of the phase diagram that has been described only in terms of their visual appearance and stability. Other domains were appearance of turbidity or phase separation after centrifugation.

3. Results and discussion

Fig. 1 represents a phase diagram of H_2O/Captex 300/TPGS system. The apices of the phase diagram

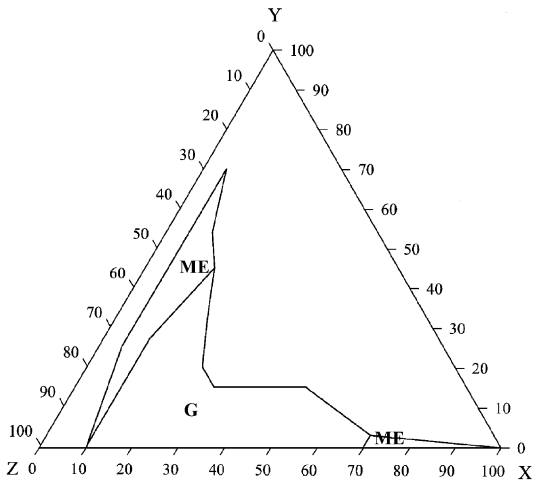

Fig. 1. Phase diagram of H_2O (X)/Captex 300 (Y)/TPGS (Z) system. G: transparent gel; ME: microemulsion.

are oil (Captex 300), water and surfactant mixtures (S_{mix}). Each vertex of the triangle represents 100% (w/w) of the respective component. The clear, isotropic, transparent, and low viscosity microemulsion areas are presented in the phase diagrams as ME areas. The gel area (G) indicates the clear and high viscosity region that is attributed to be lamellar, hexagonal, or cubic phases. The rest of the region on the phase diagram represents the turbid or conventional macroemulsions based on visual identification. The phase diagram reveals fluid–gel–fluid transition with water dilution. For low water content, the type of microemulsion is w/o. As water content increase, the system became ordered gel form. This result is caused by water molecular adsorbed or intercalated between the hydrophilic polyoxyethylene (POE) chains of TPGS via hydrogen bonding which resulted in less mobile and regular gel structure. As water content further increase, the gel structure became fluid, and o/w microemulsion was formed. The phase diagram reveals that when TPGS was used as sole surfactant, it is not capable of producing isotropic solutions of water and oil over a wide range of the compositions of H_2O/Captex 300/TPGS system. On the other hand, gel covers most regions from water content 10% to 70%. Outside the microemulsion region, particularly for compositions close to the oil–water binary (X–Y) axis, there is insufficient surfactant to facilitate the formation of a single microemulsion phase. Other additives may need to increase the mobility of TPGS for production of a large area of microemulsion.

The pseudo-ternary phase diagrams of systems containing H_2O/Captex 300/TPGS/Tweens with various K_m were displayed in Figs. 2–5. Fig. 2 was the phase diagram of H_2O/Captex 300/TPGS/Tween 20 systems. As the K_m decreased, the microemulsion region slightly increased and then decreased and was shifted towards the TPGS/Tween 20 corner. While the gel region shrank as the K_m decreased, and then disappeared as the K_m at 1/4. Fig. 3 was a similar phase diagram obtained using Tween 40 as adjuvant surfactant, but the isotropic regions, either microemulsion or gel, were slightly larger than Tween 20. Fig. 4 was the phase diagrams of H_2O/Captex 300/TPGS/Tween 60 systems. Unlike Tween 20 and Tween 40 containing systems, at low water and Tween 60 content systems (K_m=4/1 and 2/1), gel structure was the predominant. In addition, the gel region was decreased as the K_m decreased, but microemulsion region was increased. It was not found out the isotropic regions in system without TPGS when using Tween 60 as a sole surfactant. For H_2O/Captex 300/TPGS/Tween 80 systems (Fig. 5), gel region also cover most area and microemulsion region was larger than other Tween systems. From these phase diagrams, the influence of relative TPGS/Tween concentrations on the microemulsion isotropic region could be evidently seen. All systems, regardless of the adjuvant surfactant used, were capable of producing an isotropic phase. The extension of microemulsion phase and the presence and extension of the gel phase were found to be dependent on the surfactant mixture. The types of Tweens as well as the relative concentrations of TPGS to Tweens were seen to have a pronounced effect on the region of existence of the microemulsions. Comparison between the isotropic regions for the Tween system revealed that as the relative concentration of Tweens increase, the isotropic region decrease in size. This decrease was towards the S_{mix}–water axis (i.e., away from the Captex 300 apex) and indicated that as the relative concentration of Tweens increased, the maximum amount of oil solubilized decreased. The gel region decreased in size with the increase of Tween weight ratio.

Fig. 6 was the phase diagrams of H_2O/Captex 300/TPGS/PEG 400 system. A decrease in the area of the gel region was noted with an increase in the PEG 400 content of the system. Microemulsion region was first increased and then decreased as K_m decreased. Fig. 7 was the phase diagrams of H_2O/Captex 300/TPGS/PEG 600 systems with different K_m. The phase behavior was similar to PEG 400, but it was not possible to detect microemulsion regions in systems without TPGS.

It has reported that alkandiols have similar properties to aliphatic alcohols, but less toxic and thereby may be suitable substitutes for use in the formulation of microemulsion [20]. Figs. 8–13 showed the phase diagrams of H_2O/Captex 300/TPGS systems using polyols (diols and glycerin) as cosurfactants. Microemulsion systems manufactured using ethanediol as cosurfactant were shown in Fig. 8. In this case, the fluid–gel–fluid transition was seen with increasing water content at K_m of 4/1, while the region at K_m of 2/1 was initially gel-like and attained a fluid nature at

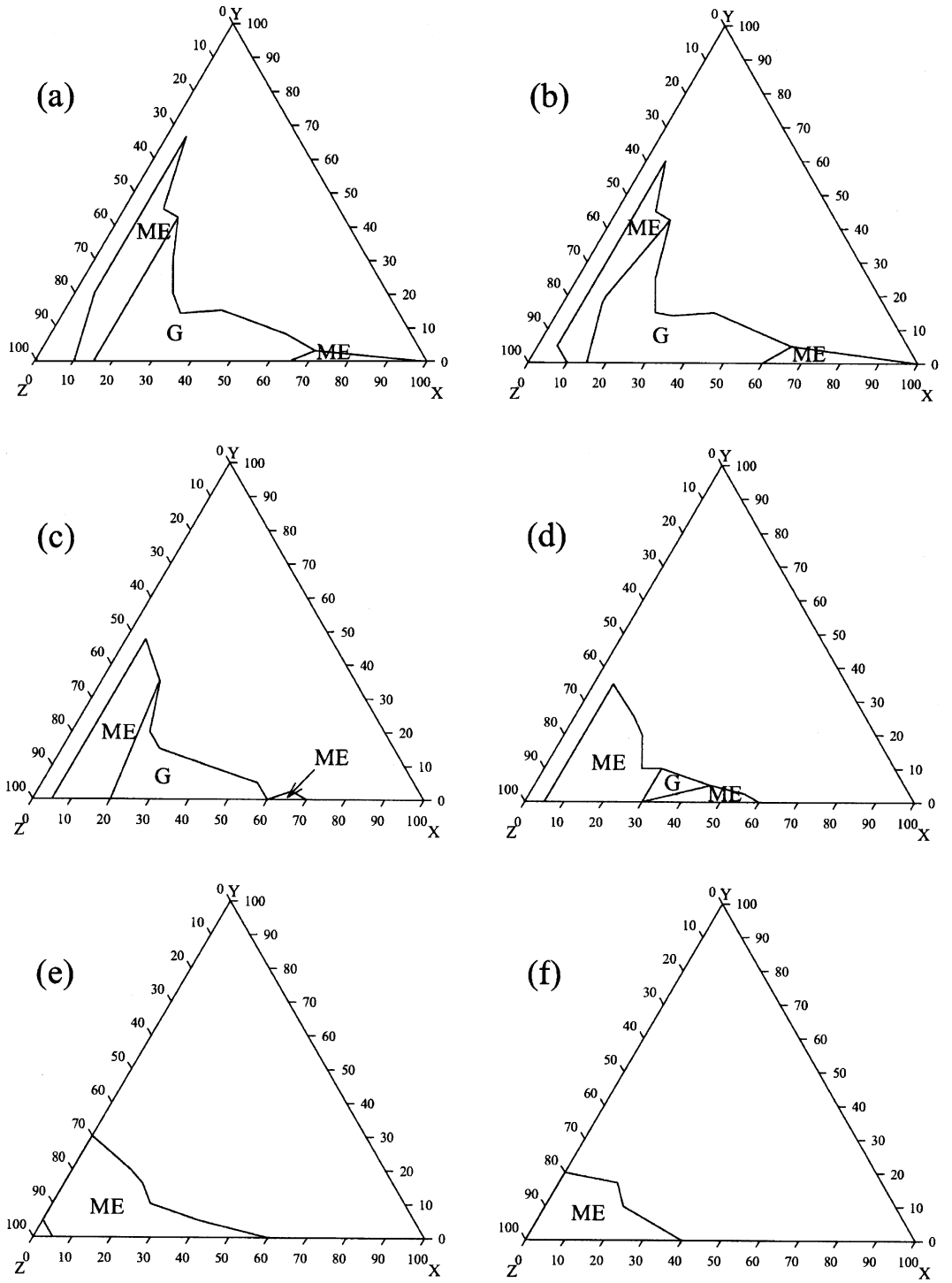

Fig. 2. Phase diagrams of H_2O/Captex 300/TPGS/Tween 20 systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/Tween 20=(a) 4/1, (b) 2/1, (c) 1/1, (d) 1/2, (e) 1/4, and (f) 0/1. G: transparent gel; ME: microemulsion.

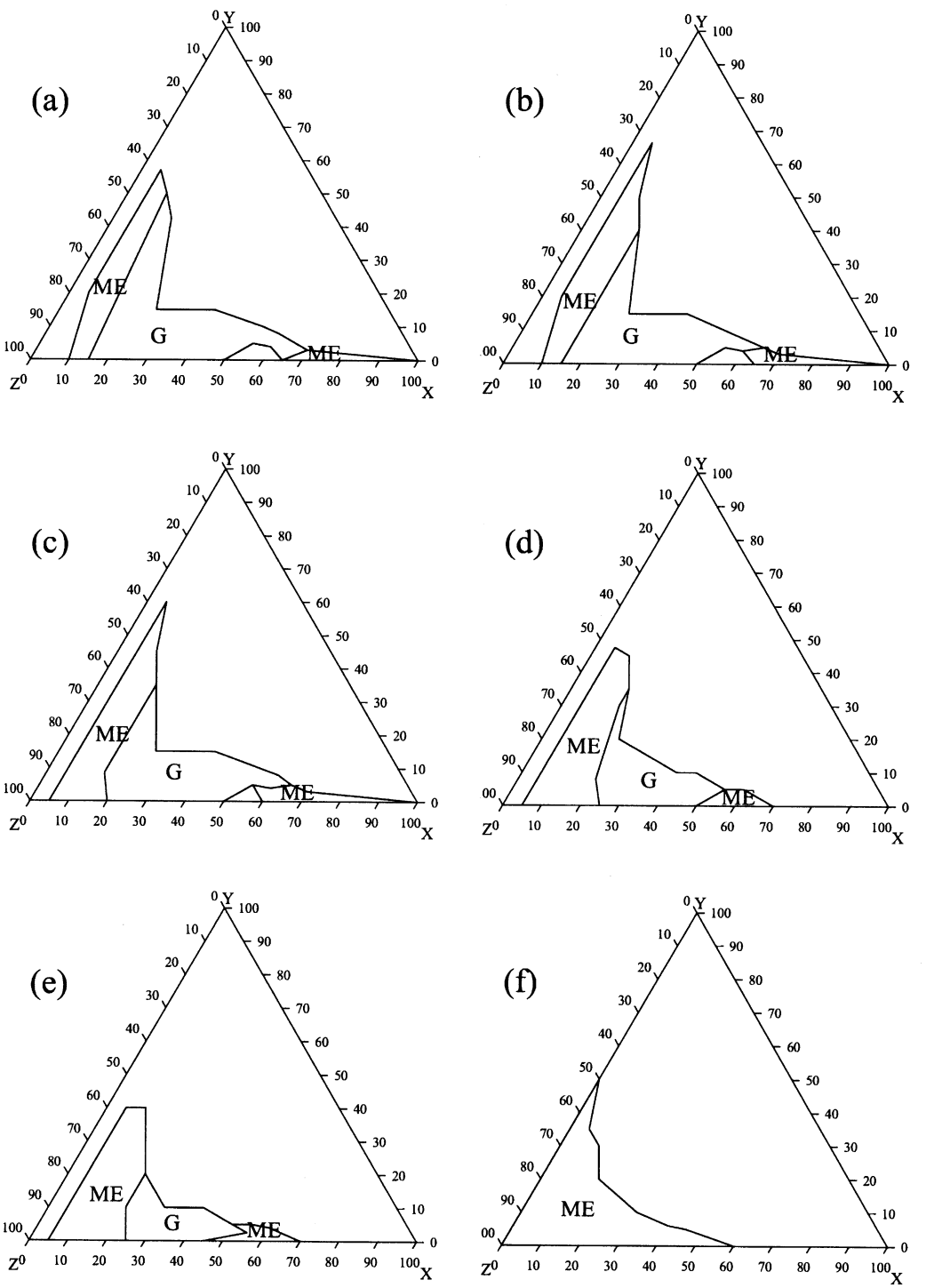

Fig. 3. Phase diagrams of H_2O/Captex 300/TPGS/Tween 40 systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/Tween 40=(a) 4/1, (b) 2/1, (c) 1/1, (d) 1/2, (e) 1/4, and (f) 0/1. G: transparent gel; ME: microemulsion.

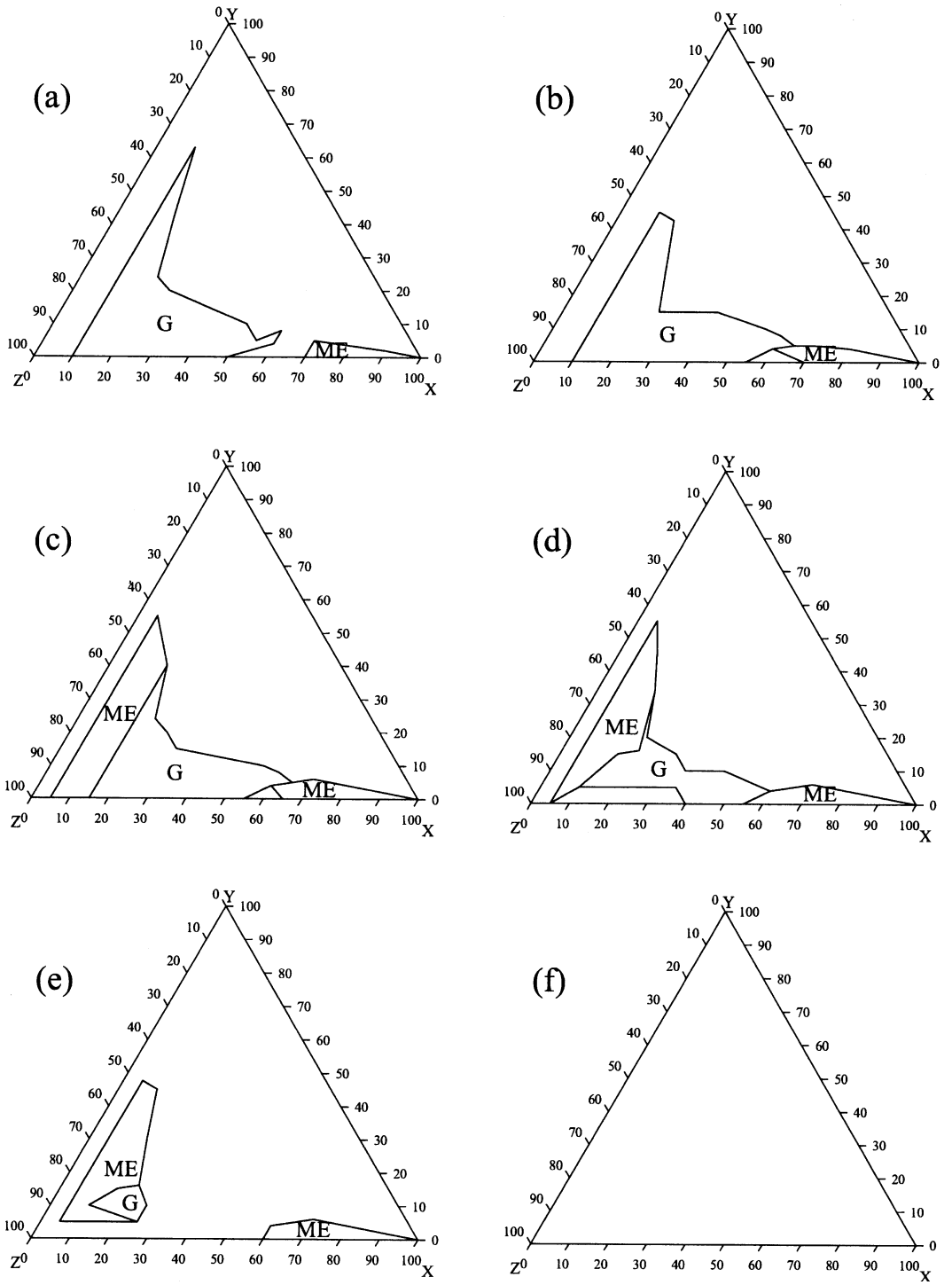

Fig. 4. Phase diagrams of H_2O/Captex 300/TPGS/Tween 60 systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/Tween 60=(a) 4/1, (b) 2/1, (c) 1/1, (d) 1/2, (e) 1/4, and (f) 0/1. G: transparent gel; ME: microemulsion.

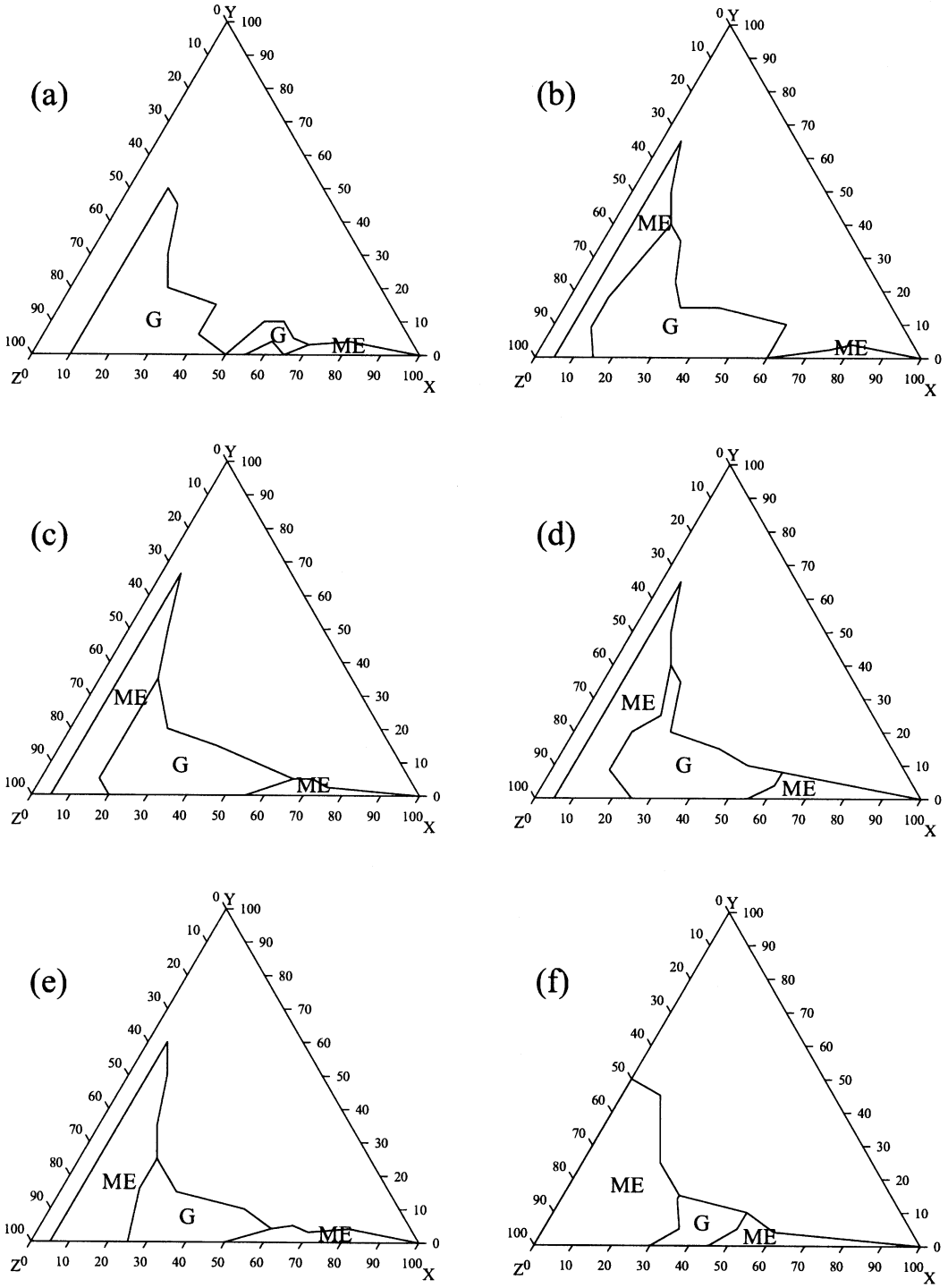

Fig. 5. Phase diagrams of H_2O/Captex 300/TPGS/Tween 80 systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/Tween 80=(a) 4/1, (b) 2/1, (c) 1/1, (d) 1/2, (e) 1/4, and (f) 0/1. G: transparent gel; ME: microemulsion.

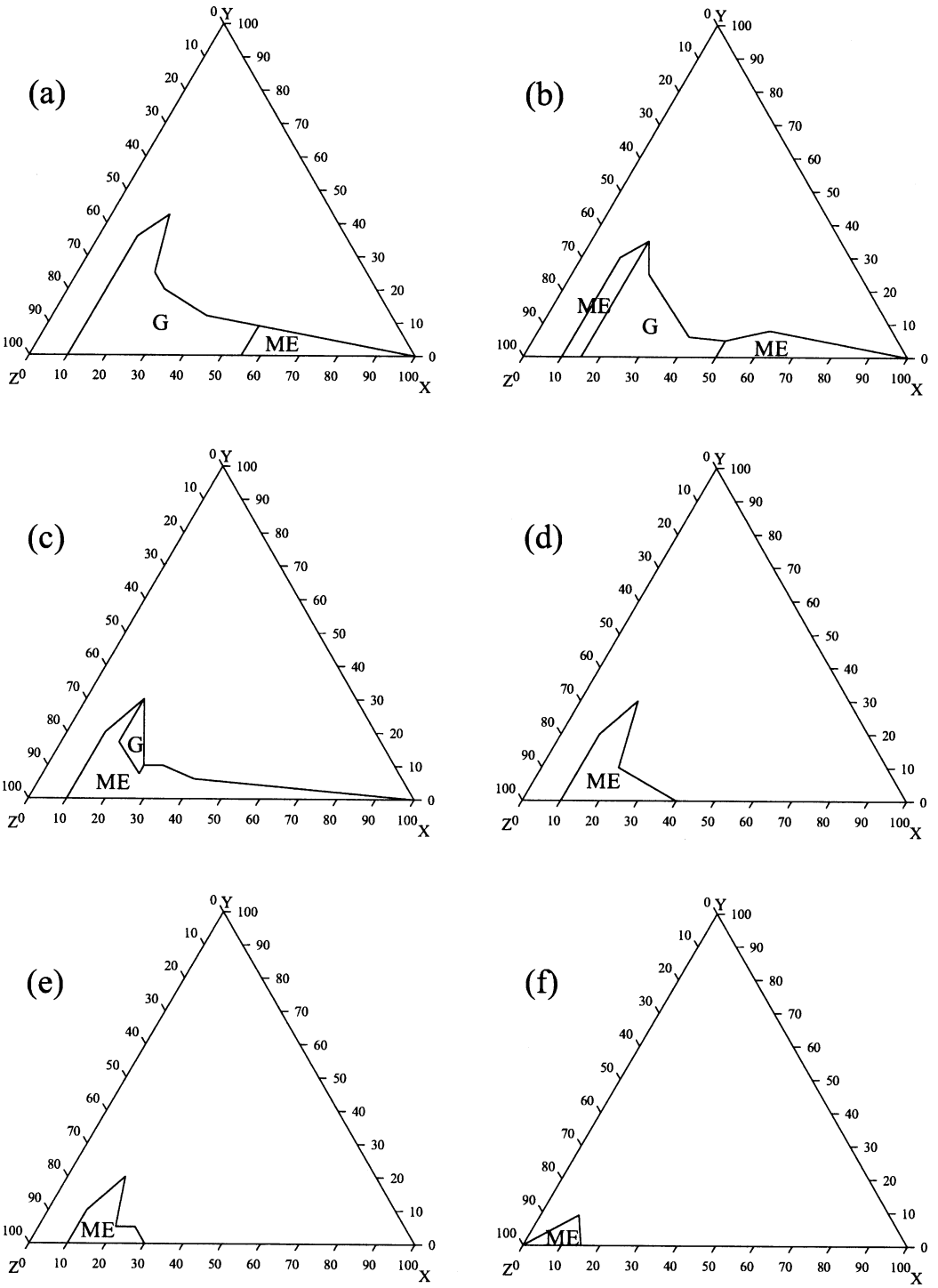

Fig. 6. Phase diagrams of H_2O/Captex 300/TPGS/PEG 400 systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/PEG 400=(a) 4/1, (b) 2/1, (c) 1/1, (d) 1/2, (e) 1/4, and (f) 0/1. G: transparent gel; ME: microemulsion.

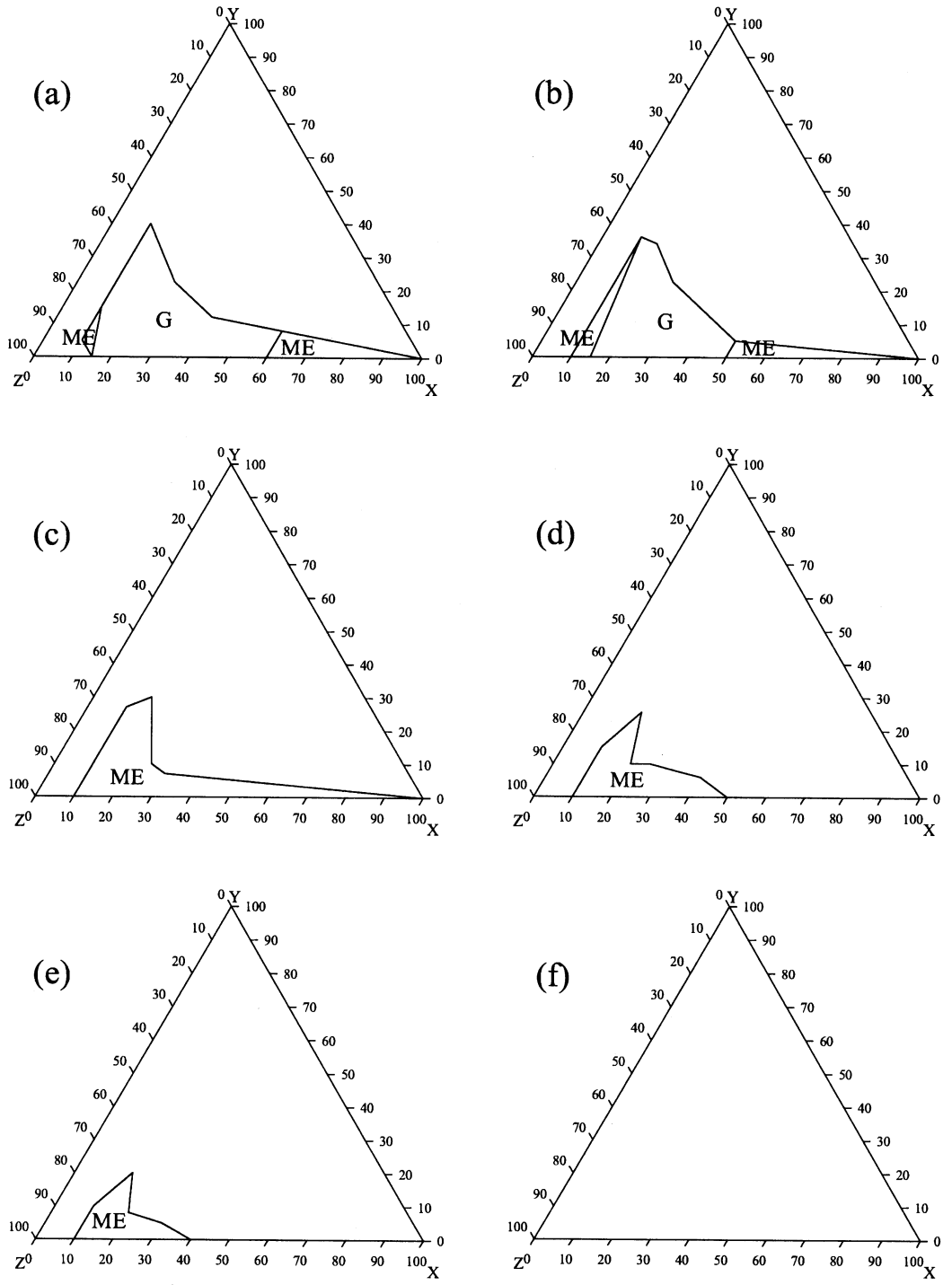

Fig. 7. Phase diagrams of H_2O/Captex 300/TPGS/PEG 600 systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/PEG 600=(a) 4/1, (b) 2/1, (c) 1/1, (d) 1/2, (e) 1/4, and (f) 0/1. G: transparent gel; ME: microemulsion.

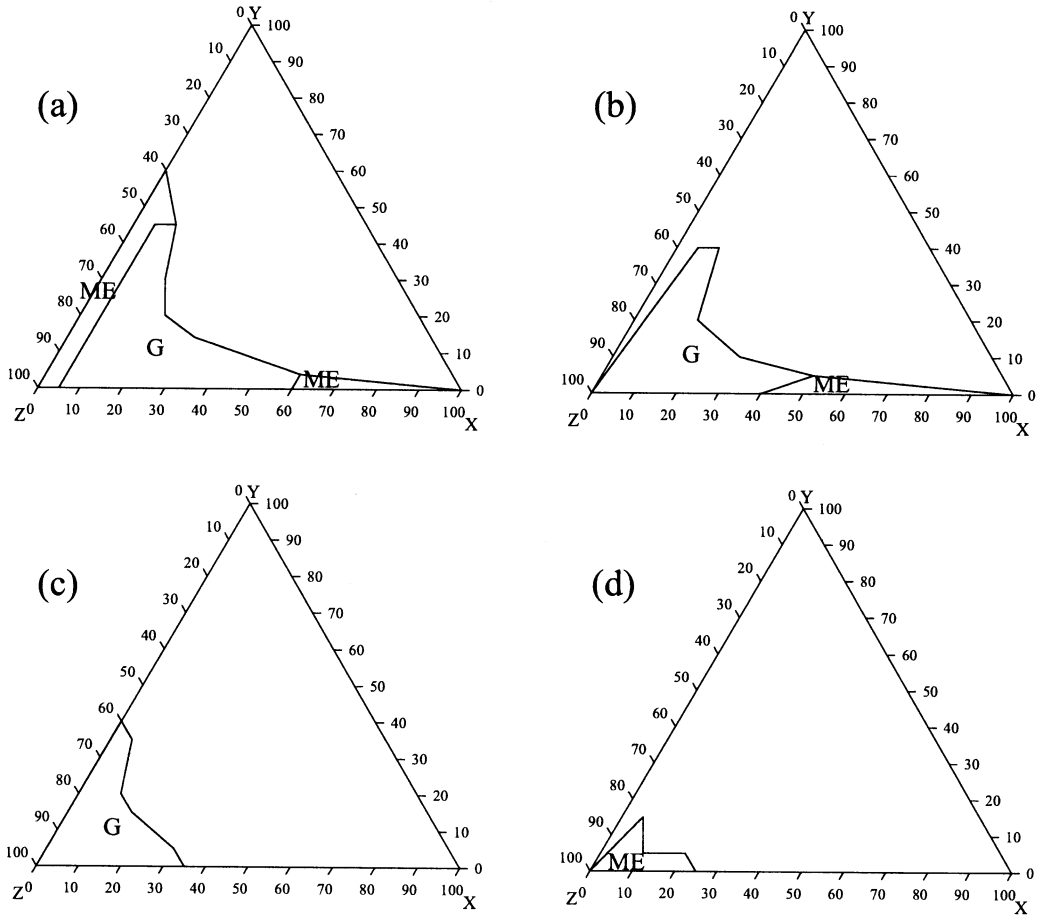

Fig. 8. Phase diagrams of H_2O/Captex 300/TPGS/ethanediol systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/ethanediol=(a) 4/1, (b) 2/1, (c) 1/1, and (d) 1/2. G: transparent gel; ME: microemulsion.

about 40% water content. At K_m of 1/1, only gel region occurred at water content less than 35%. The microemulsion region at K_m of 1/2 was again entirely fluid in nature. System containing TPGS/ethanediol with K_m of 1/4 does not solubilize Captex 300 at any composition. Microemulsions manufactured using 1,2-propanediol as the cosurfactant showed a similar fluid–gel–fluid transition at K_m of 4/1 and the region was decreased when the K_m decreased (Fig. 9). The gel state disappeared when K_m reached 1/2. At K_m of 1/4 and 0/1, the microemulsion or gel region was not observed. Using 1,3-propanediol as cosurfactant, phase diagram in Fig. 10 showed that the phase behavior was similar to 1,2-propanediol as cosurfactant. Fig. 11 was phase diagram of H_2O/Captex 300/TPGS/1,3-butanediol systems, in which the gel and microemulsion regions were decreased as the K_m decreased. At the K_m of 1/4 and 0/1, there was no isotropic region. Fig. 12 was the phase diagrams using 1,4-butanediol as cosurfactant. Basically, the phase behaviors of the systems were similar to 1,3-butanediol, but at K_m of 1/2, a liquid crystalline region occurred at low water content. Fig. 13 was the pseudo-ternary phase diagrams of H_2O/Captex 300/TPGS/glycerin system. When glycerin was used as the cosurfactant, at the K_m of 4/1, the system at low water content, 5–10%, was microemulsion and as the water content increased, the system became gel-like and finally turned back to fluid. At the K_m of 2/1 and 1/1, the systems at low water content were gel-like in nature; as the water content increased the microemulsions became fluid systems. While at the K_m of

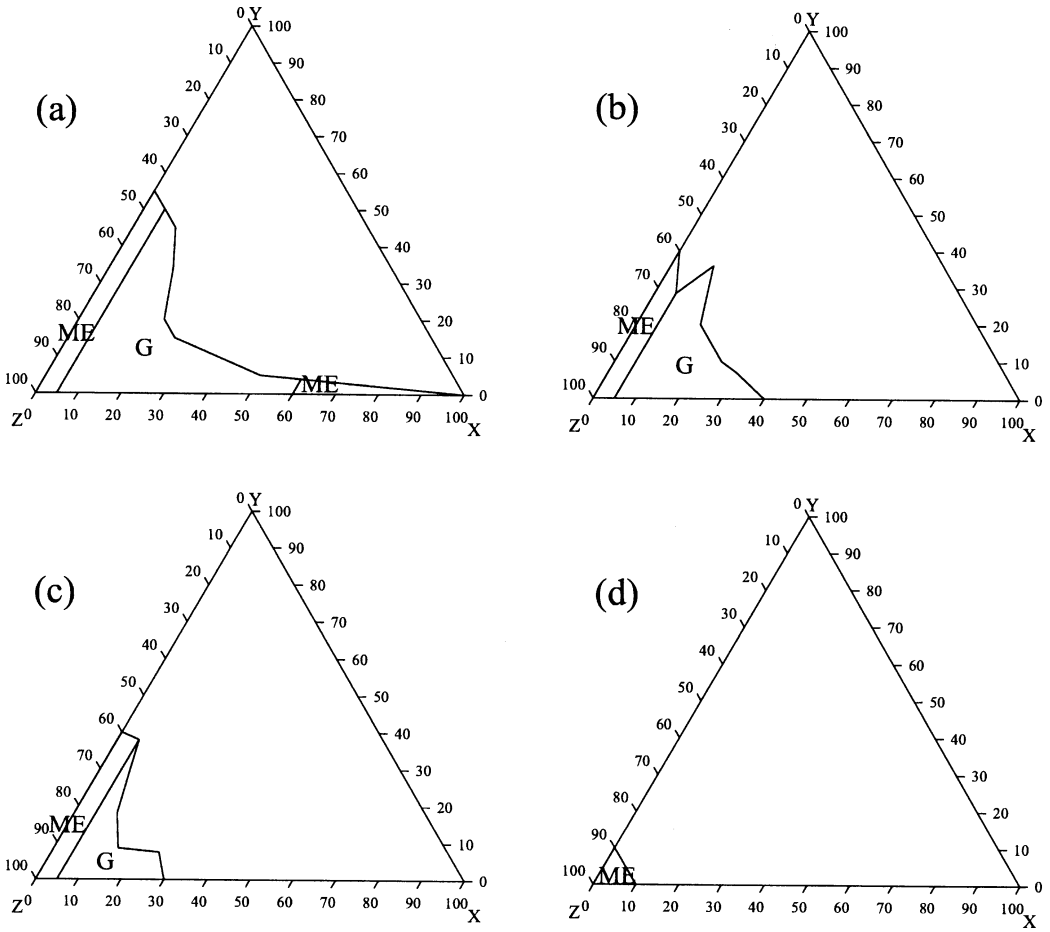

Fig. 9. Phase diagrams of H_2O/Captex 300/TPGS/1,2-propanediol systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/1,2-propanediol=(a) 4/1, (b) 2/1, (c) 1/1, and (d) 1/2. G: transparent gel; ME: microemulsion.

1/2 and 1/4, the microemulsion region was composed of entirely fluid systems. Glycerin does not solubilize any Captex 300. From these phase diagrams (Figs. 8–13), the types of polyols were seen to have a slight effect on the region of existence of the microemulsions. Comparison between the isotropic regions for the polyols system reveals that as the relative concentration of polyols increase, the isotropic region (microemulsion and gel phase) decrease in size. This decrease is towards the S_{mix}–water axis (i.e., away from the Captex 300 apex) and indicates that as the relative concentration of polyols increase, the maximum amount of oil solubilized decreases. The gel region decreased in size with the increase of polyols weight ratio. All polyols do not solubilize Captex 300 without using TPGS as surfactant.

The rationale behind the choice of components and their influence on the phase behavior and microstructure of the microemulsion is best understood by referring to the flexible surface model, in which the microstructure was described in terms of the properties of the surfactant film separating the water and oil domains [21]. One parameter for this film is the spontaneous mean curvature H_0, which is defined as "$H_0=0.5\cdot(c_1+c_2)$", where c_1 and c_2 are the principal curvatures of the surfactant film. H_0 expresses the natural tendency of the monolayer to bend away from a flat geometry and it is, by definition, positive if it tends to enclose the oil and negative if it tends to include the water. H_0 depends on the nature of the surfactant and also on the composition of the aqueous and oil phases it separates. For example, H_0 is positive

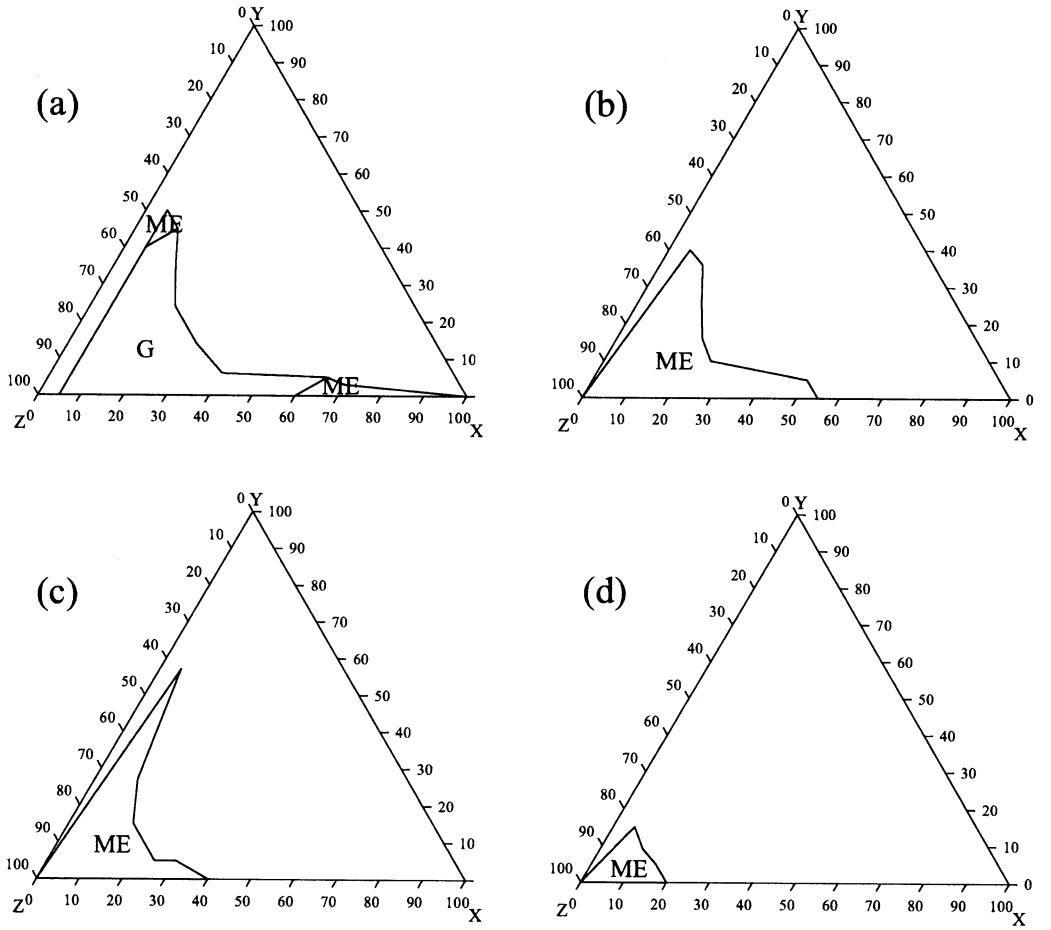

Fig. 10. Phase diagrams of H_2O/Captex 300/TPGS/1,3-propanediol systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/1,3-propanediol=(a) 4/1, (b) 2/1, (c) 1/1, and (d) 1/2. G: transparent gel; ME: microemulsion.

for surfactants with a large polar head group and a small nonpolar tail group and decreases with oil–water interface by the surfactant and/or cosurfactant. This caused a reduction in the oil–water interfacial tension to very low values. It has been reported that a very low interfacial tension ($\gamma_i < 10^{-3}$) is a prerequisite for the formation of microemulsions. The absorption of surfactant to the interfacial area causes a two-dimensional spreading pressure (π) that depresses the interfacial tension in accordance with the equation "$\gamma_i = \gamma_{o/w} - \pi$", in which $\gamma_{o/w}$ is the oil/water interfacial tension after the chemical potential of the surfactant in each phase has been equalized by partitioning. When large amounts of surfactant and/or cosurfactant are adsorbed to form the interface, the spreading pressure (π) may become larger than $\gamma_{o/w}$. Thus, a negative interfacial tension results and energy is available to increase the interfacial area, effectively reducing droplet size. This negative interfacial tension produced by the mixing of the components is a transient phenomenon, and at equilibrium it becomes zero or a very small positive value.

In this study, TPGS, used as the main surfactant for emulsification of Captex 300 and water, has a large hydrophobic tocopheryl group and a long hydrophilic PEG 1000 chain. In the H_2O/Captex 300/TPGS system, most water was adsorbed to PEG chains of TPGS and constructed a regular and rigid network via hydrogen bonding. Thus, the gel phase includes most area of phase diagram. As the system with other

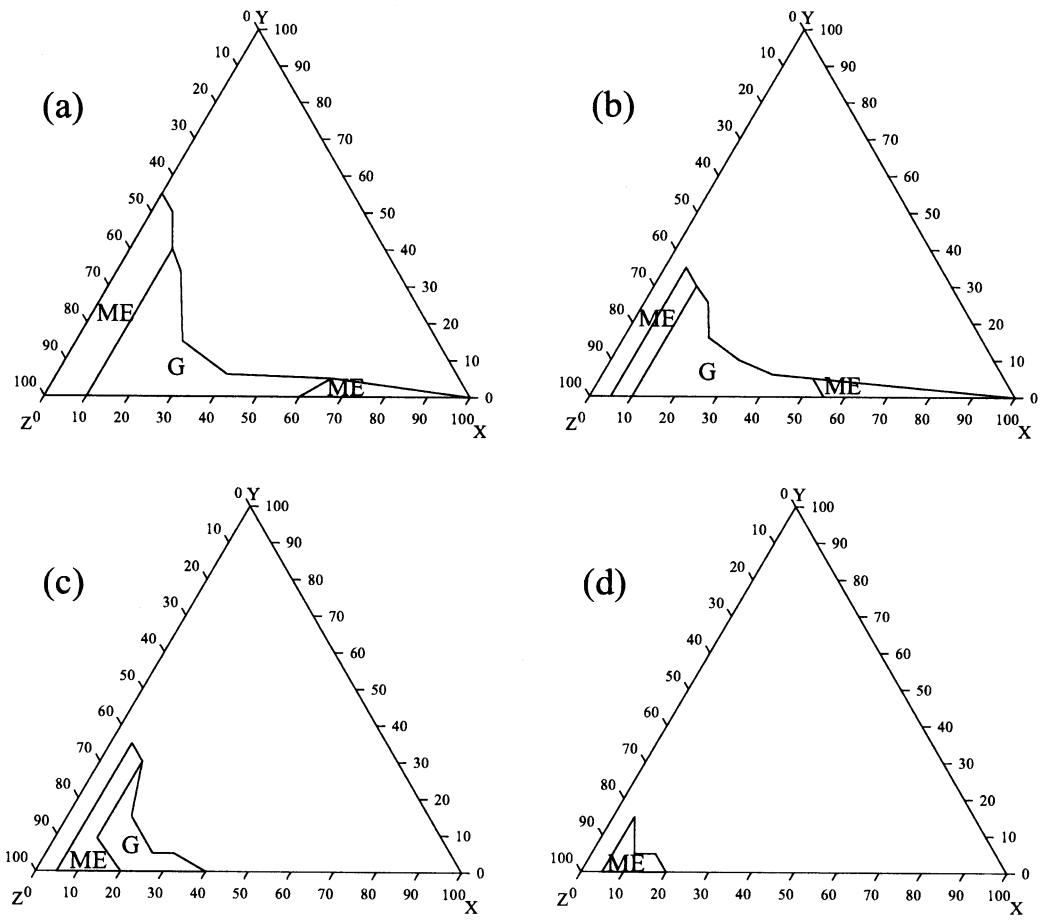

Fig. 11. Phase diagrams of H_2O/Captex 300/TPGS/1,3-butanediol systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/1,3-butanediol=(a) 4/1, (b) 2/1, (c) 1/1, and (d) 1/2. G: transparent gel; ME: microemulsion.

additives such as polysorbates, PEGs or polyols, the curvature and packing of surfactant film may be influenced. No matter what additives (polysorbates, PEGs or polyols) were used, at high K_m, the most isotropic region was still a rigid gel structure. As these additives concentration increased (K_m decreased), the systems became fluid. This transition can be explained in two ways. First, it may be due to the relative viscosity of TPGS, since TPGS is much more viscous than any of the additives used, however, this does not account for the initial fluid stage in some cases. Another possible explanation is that there occurs a transition in the nature and shape of the internal phase. The number and size of the alkyl chain of the nonpolar group increase. Decreasing the polarity of the polar phase by adding a cosolvent decreases H_0, and any penetration by the nonpolar phase in the hydrocarbon tails of the surfactant also decreases H_0. For a bicontinuous microemulsion, H_0 is close to zero.

The analysis of film curvature for surfactant associations leading to microemulsion formation could further be explained by the concept of critical packing parameter (CPP), which was defined as: "CPP=v/la", where v is the hydrophobic group volume of the surfactant, l is the critical hydrophobic group length of the surfactant chain, and a is the cross-sectional area of the hydrophilic head group of the surfactant. The o/w structures are favored if the effective polar part is more bulky than the hydrophobic part (CPP<1), and the interface curves spontaneously toward water (positive curvature; H_0>0). While for the w/o structure, the interface

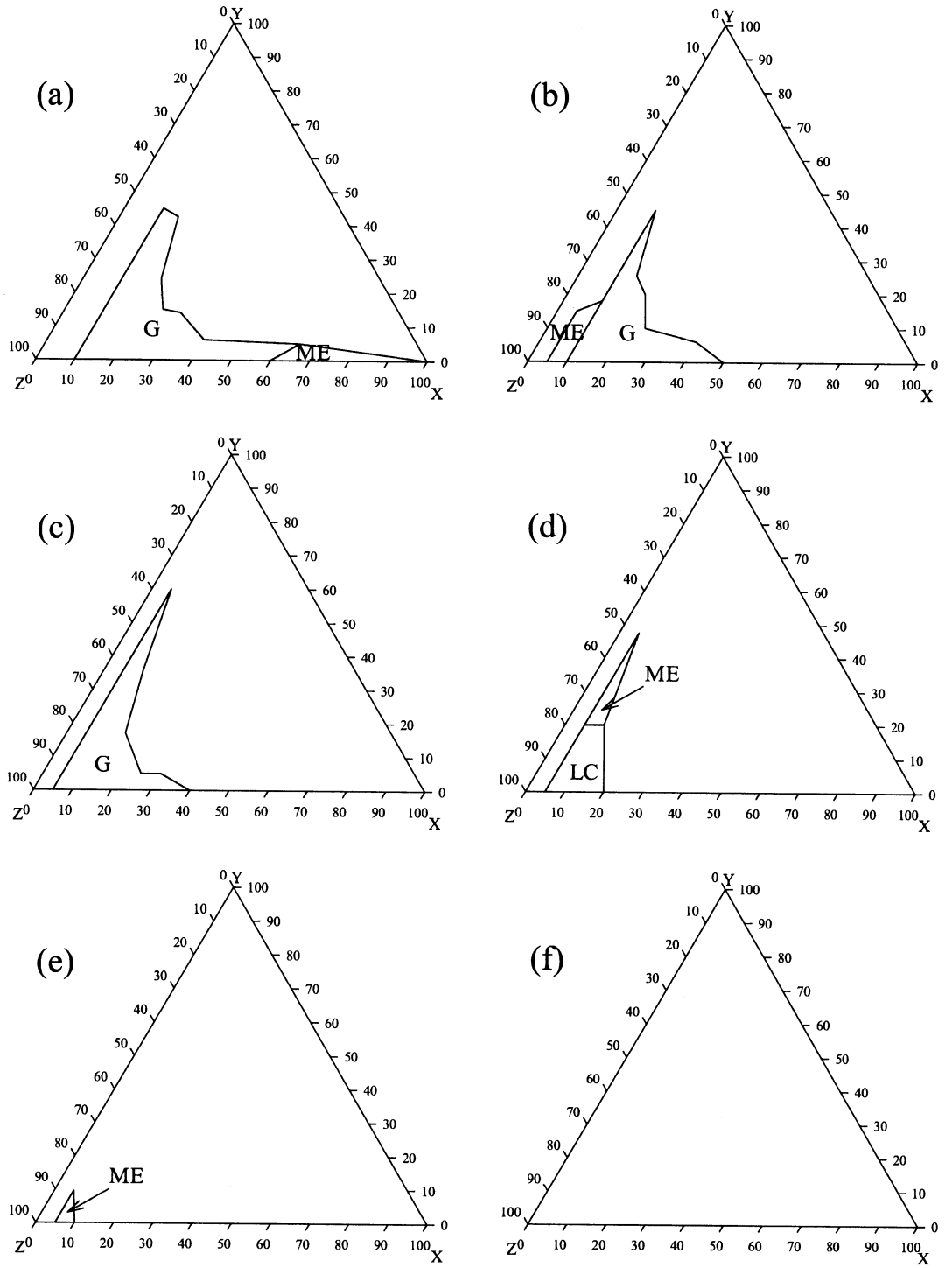

Fig. 12. Phase diagrams of H_2O/Captex 300/TPGS/1,4-butanediol systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/1,4-butanediol=(a) 4/1, (b) 2/1, (c) 1/1, (d) 1/2, (e) 1/4, and (f) 0/1. G: transparent gel; ME: microemulsion; LC: liquid crystal.

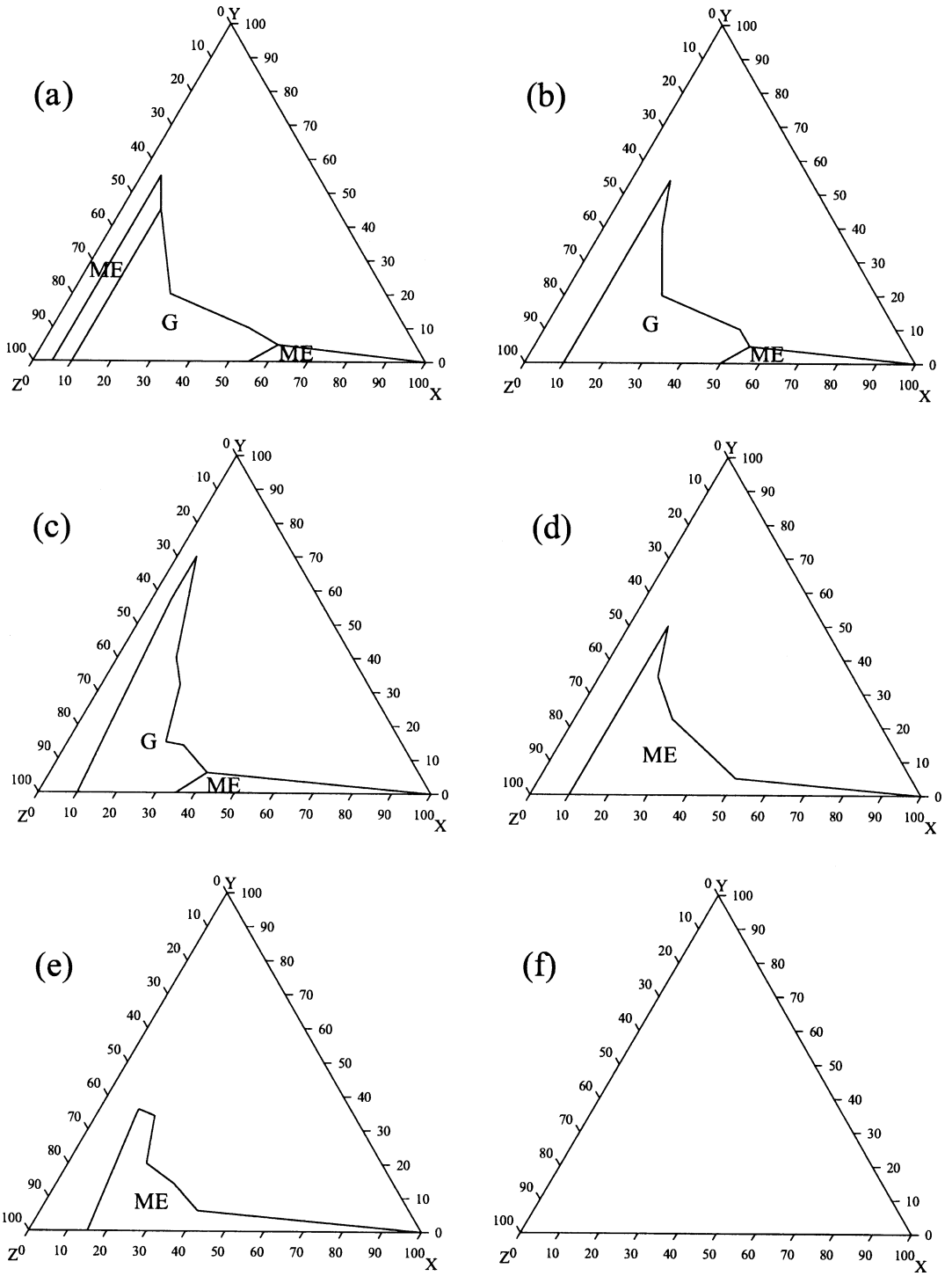

Fig. 13. Phase diagrams of H_2O/Captex 300/TPGS/glycerin systems. *X*: H_2O; *Y*: Captex 300; *Z*: TPGS/glycerin=(a) 4/1, (b) 2/1, (c) 1/1, (d) 1/2, (e) 1/4, and (f) 0/1. G: transparent gel; ME: microemulsion.

curve is in the opposite direction (CPP>1), and the interface curves spontaneously toward to oil (negative curvature; H_0<0). At zero curvature (CPP ≈ 1), either bicontinuous or lamellar structures may form according to the rigidity of the film [22]. The curvature is also influenced by the elasticity of the surfactant film. In general, an elastic surfactant film favors the formation of a microemulsion, whereas a lamellar phase is formed with a more rigid or stiff film. The elasticity of the film depends on the molecular structure of the surfactant and can be reduced by the addition of cosolvents such as short-chain alcohols. The elasticity is also affected by any penetration by the nonpolar phase in the hydrocarbon tails of the surfactant.

Another important parameter governed the surfactant film formation and curvature bending is the interfacial tension between oil and water interface. The spontaneous formation of microemulsion droplets was considered to be due to the formation of a complex film at the systems at low water content are of the water-in-oil type with a spherical internal phase. As the water content is increased, the interfacial film expands and finally collapses to form cylindrical and then laminar structures, which account for the gel-like nature. As the water content is further increased, water continuous systems with spherical internal phase are formed again and exhibit low viscosity.

Polysorbates are probably the most widely used, commercially inexpensive, and readily available pharmaceutical grade surfactants. They are nonionic surfactants with a sorbitan backbone and four bulky polyoxyethylene head groups, one of which is esterified with fatty acids. The formula, molecular weight, HLB, and viscosity of polysorbates used in this study were listed in Table 1 [23]. Since polysorbates are surfactants, they may increase the interfacial fluidity by penetrating into the TPGS surfactant film and consequently creating a disordered film due to the void space among surfactant molecules. From the phase diagrams of Figs. 2–5, the ester chain of fatty acids showed different packing behaviors. The region of gel phase was increased with the esterified fatty acid chains. Tween 80 (polyoxyethylene 20 sorbitan monooleate), which is an ester of the unsaturated C_{18} fatty acid, oleic acid, is more effective in forming a microemulsion than Tween 60 (polyoxyethylene 20 sorbitan monostearate), which is an ester of the saturated C_{18} fatty acid, stearic acid, reflecting differences in the molecular packing at the oil/water interface.

By partitioning between aqueous and oil phases, PEGs can also modify the solvent properties of these phases, i.e., making an oil phase relatively more hydrophilic or an aqueous phase relatively more hydrophobic. PEGs are perhaps to prevent formation of rigid structures such as gels, liquid crystals, precipitates, etc., and to lower the viscosity of the system. These solvents like water form hydrogen bonds have relatively high dielectric constants and are immiscible with hydrocarbon solvents. Critical micelle concentrations are higher in polar nonaqueous solvents than in water. When these solvents were used as water substitutes, their resulting penetration into the surfactant interface leads to smaller or no liquid crystal phase regions. Hence, these PEGs perturb the long-range ordered packing of the TPGS surfactant.

Polyols are highly soluble in water, thus they are expected to partition mainly into the aqueous phase and partially in the polar parts of the surfactant layer. The presence of polyols in the interfacial region causes a reduction in the rigidity of the condensed TPGS film, allowing the curvature necessary for droplet formation. The distribution of the polyols between the interface and the aqueous continuous phase depends on its hydrophilicity. Adsorption of surfactant causes the interfacial film to condense while addition of the cosurfactant would cause that film to expand. Another reason is if the tails of polyols intercalate between TPGS, a high two-dimensional

Table 1
Empirical formula, molecular weight, HLB and viscosity of selected polysorbates

Polysorbates	Chemical name	Formula	Molecular weight	HLB	Viscosity (mPa s)
Tween 20	polyoxyethylene 20 sorbitan monolaurate	$C_{58}H_{114}O_{26}$	1128	16.7	400
Tween 40	polyoxyethylene 20 sorbitan monopalmitate	$C_{62}H_{122}O_{26}$	1284	15.6	500
Tween 60	polyoxyethylene 20 sorbitan monostearate	$C_{64}H_{126}O_{26}$	1312	14.9	600
Tween 80	polyoxyethylene 20 sorbitan monoleate	$C_{64}H_{124}O_{26}$	1310	15.0	425

pressure (π) can be developed that further depresses the interfacial tension (γ_i) close to zero to form a microemulsion. As a result, the addition of short-chain polyols as cosurfactants is able to reduce interfacial free energy and tension by their incorporation into the interfacial layer. This kind of cosurfactant also modifies the HLB value of the surfactant to an optimal value suitable for microemulsion formulation. Polyols can act in the interface to reduce the tendency of surfactants to form highly rigid films, thus allowing the interfacial film to take up the different curvatures required to form balanced microemulsions. Therefore, inclusion of these polyols as cosurfactants is essential to promote interfacial fluidity for the formation of a microemulsion. However, short chain polyols (C_2–C_4) acted very differently in formation of the phase diagrams. Actually, the effectiveness of polyols as cosurfactants is also determined by the extent of their distribution in the interface. The distribution of polyols between the aqueous phase, the oil phase, and the interface is dependent on their partition coefficients. The more hydrophilic polyols would be expected to distribute mainly between the aqueous and the interfacial layers, whereas the hydrophobic polyols would be expected to distribute primarily between the oil and the interfacial layer.

To produce microemulsions, it is necessary to reduce the CPP either by using cosolvent or cosurfactant. This alters the CPP either by making the aqueous phase less hydrophilic and/or by incorporating it into the interfacial film. TPGS has a long hydrophilic PEG chain; short chain polyols enable them to interact with TPGS films at the interface thereby affecting their packing, which in turn can influence the curvature of the interface and interfacial energy. In addition, some polyols may interact with PEG chains of TPGS reducing the hydrogen bonding and resulted in destroying the highly rigid films of TPGS and increase the fluidity of the interfacial surfactant layer, thus giving the interfacial film sufficient flexibility to take up the different curvatures required to form microemulsions. The amphiphilic nature of low molecular weight cosurfactants also enable them to distribute between the aqueous and oil phase thereby altering the chemical composition and hence the relative hydrophilicity and lipophilicity. The role of the cosurfactant cannot be entirely reconciled to its effect on packing. A highly flexible film is required to form small droplets. The bending of an interface requires work against both interfacial tension and the bending stress of the interface.

By partitioning between aqueous and oil phases, polyols can modify the solvent properties of these phases, i.e., making an oil phase relatively more hydrophilic or an aqueous phase relatively more hydrophobic. The most basic function of polyols is perhaps to prevent formation of rigid structures such as gels, liquid crystals, precipitates, etc., and to lower the viscosity of the system. These solvents like water form hydrogen bonds, have relatively high dielectric constants, and are immiscible with hydrocarbon solvents. Critical micelle concentrations are higher in polar nonaqueous solvents than in water. When these solvents were used as water substitutes, their resulting penetration into the surfactant interface leads to smaller or no liquid crystal phase regions. Hence, these short chain polyols perturb the long-range ordered packing of the TPGS surfactant. Polyols increase both the hydrophobic volume and the area per head group of TPGS molecules at the interface and thus, affect the spontaneous curvature of the surfactant molecules. It is also thought that alcohols are capable of swelling the chain volume allowing substantial oil uptake.

4. Conclusion

The existence of isotropic microemulsion regions in the quaternary systems composed of H_2O/Captex 300/TPGS and Tweens, PEGs, or polyols were characterized. Stable and transparent microemulsion and gel regions were identified. Pseudo-ternary phase diagrams showed that the adjuvant surfactants cosolvent and cosurfactants and the K_m value might affect the shape and the extent of gel and microemulsion regions. The region of gel phase was increased with the esterified fatty acid chains. Tween 80 (polyoxyethylene 20 sorbitan monooleate), which is an ester of the unsaturated C_{18} fatty acid, oleic acid, is more effective in forming a microemulsion than Tween 60 (polyoxyethylene 20 sorbitan monostearate), which is an ester of the saturated C_{18} fatty acid, stearic acid, reflecting differences in the molecular packing at the oil/water interface. Critical micelle concentrations of TPGS are higher in polar nonaqueous solvents than in

water. When these solvents were used as water substitutes, their resulting penetration into the surfactant interface leads to smaller or no liquid crystal phase regions. Hence, these PEGs perturb the long-range ordered packing of the TPGS surfactant. Polyols can act in the interface to reduce the tendency of surfactants to form highly rigid films, thus allowing the interfacial film to take up the different curvatures required to form balanced microemulsions. Therefore, inclusion of these polyols as cosurfactants is essential to promote interfacial fluidity for the formation of a microemulsion. The microemulsion may be suitable for peptide, protein or poorly water-soluble drugs and the gels may act as a controlled release system. Both forms of delivery system are currently under evaluation.

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