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Studies on microemulsions using Brij 96 as surfactant and glycerin, ethylene glycol and propylene glycol as cosurfactants

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Summary

The existence of microemulsion regions was investigated in quaternary systems composed of Brij 96/cosurfactant/mineral oil/water by constructing phase diagrams. The cosurfactants used were glycerin, ethylene glycol and propylene glycol, all of which are polyhydroxy compounds used widely in the pharmaceutical industry. Light scattering data was used to determine the diameter of the internal phase as a function of the surfactant:cosurfactant ratio at a constant internal phase/oil ratio. Results suggest that the surfactant:cosurfactant ratio is an important parameter in determining the size of the internal phase of these microemulsion systems.

Introduction

The design and development of new drug delivery systems with a view to enhance the efficacy of existing drugs is an ongoing process in pharmaceutical research. A lot of recent dosage form development activity has focused on the development of microemulsions as drug delivery systems.

Dispersion of oil and water are commonly employed in the pharmaceutical industry. These dispersions can be classified in 3 major categories: microemulsions, micellar solutions and the common macroemulsions. Of these, the latter are characterized by their milky white appearance and propensity to separate into their two original liquid phases upon standing. Microemulsions and micellar solutions do not appear white; they are translucent or transparent to the eye and they do not separate. While neither microemulsions nor micellar solutions have been characterized sufficiently to make possible a clear-cut definition between the two, generally microemulsions are accepted as having droplet diameters between 1 and 100 nm.

Microemulsions are expected to have a variety of uses in oral and transdermal delivery. Along with the usual advantages of improved drug stability and availability afforded by surfactant solubilization, a microemulsion system has the added advantage of a very small disperse phase diameter and thermodynamic stability. Microemulsions can be used to prepare oral dosage forms of drugs whose bioavailability is hindered due to its hydrophobic nature and low aqueous solubility. They

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can also be used to deliver a combination of drugs of varying lipophilicity in an aesthetically appealing dosage form.

Surfactant solubilization has been demonstrated to have a significant effect on transdermal availability. The presence of surfactant alone has been shown to decrease transdermal flux (Dalvi and Zatz, 1981), however the addition of propylene glycol to a surfactant solubilized system causes an increase in the transdermal flux (Sarpotdar and Zatz, 1986). Since microemulsions are quaternary systems with a surfactant and an alcohol as its constituents, they may have a significant impact on transdermal delivery.

In order to make these systems pharmaceutically and biologically more useful, it is necessary to explore the feasibility of formulating microemulsions using commercially available and pharmaceutically acceptable components. The early scientific treatment of these systems was developed mainly by Schulman and co-workers using low-angle X-ray diffraction (Schulman and Riley, 1943), light-scattering (Schulman and Friend, 1949), NMR spectroscopy (Shah and Hamlin, Jr., 1971), and viscosity measurements. Other investigators have also used conductivity and polarographic (Mackay and Agarwal, 1978) measurements to characterize such systems. It was the purpose of this investigation to examine the areas of existence of transparent systems in 4 component systems comprised of Brij 96® (a commercially available surfactant), mineral oil, water and a variety of cosurfactants i.e. ethylene glycol, propylene glycol and glycerin.

Materials and Methods

The experimental procedure consisted of 3 different parts: (1) the preparation of the microemulsions, (2) visual observations and the preparation of the phase diagrams and (3) the measurement of the size of the disperse phase using light scattering.

Materials

Brij 96® [Polyoxyethylene (10) oleyl ether] and ethylene glycol were received from Sigma Chemical Company, St. Louis, MO. Glycerin and propylene glycol were received from J.T. Baker Company, Phillipsburg, NJ. Light mineral oil (liquid paraffin) was received from Fisher Scientific, Fair Lawn, NJ. All chemicals were used as received.

Microemulsion preparation

The microemulsions were prepared by heating a mixture of the surfactant and cosurfactant at 90 °C in a water bath. For each of the cosurfactants a mixture of the cosurfactant with the Brij 96 in fixed weight ratios was prepared. The Brij 96 : cosurfactant weight ratios used were 9 : 1, 3 : 1, 1 : 1 and 1 : 3. Each of these mixtures was allowed to stand in a water bath at 90 °C for 5 min and then stirred using a magnetic stirrer at high speed. The Brij 96 and cosurfactant mixtures were then allowed to cool to room temperature. Aliquots of each of the mixtures were then mixed with mineral oil to give (Brij 96 + cosurfactant) : mineral oil weight ratios of 9 : 1, 8 : 2, 7 : 3, 6 : 4, 5 : 5, 4 : 6, 3 : 7, 2 : 8 and 1 : 9. These mixtures were vigorously mixed using a magnetic stirrer until a homogeneous dispersion was obtained. Approximately 1–2 g of the Brij 96 + cosurfactant + mineral oil mixture was diluted with water at 90 °C to obtain the desired disperse phase concentration, where the dispersed phase consisted of the Brij 96, the cosurfactant and the mineral oil. The amount of water added was varied to give water concentrations in the range of 0–95% by weight at 10% intervals. 5% intervals were used near the boundaries of the gel and fluid regions.

The systems were allowed to cool to room temperature and stored for 24 h before further observations were made.

Visual observation and preparation of phase diagrams

The systems were observed for visual clarity and flow. Those which did not show a change in the meniscus after tilting to an angle of 90° were classified as gels. The phase diagram was obtained by the method of Treguier et al. (1975). The physical state of the microemulsion was marked on a pseudo-three-component phase diagram with one axis representing water, one representing mineral oil and the third representing a mixture of surfactant and cosurfactant at fixed weight ratios. The samples were marked as being optically clear or turbid and as fluids or gels. The fluid areas were chosen for light scattering studies. A cut-and-weigh method was used to determine the percentage of the total area of the phase diagram covered by the isotropic systems.

Light scattering studies

The light scattering measurements were conducted using a light scattering monophotometer, (model 6000, C.N. Wood Co., Newtown, PA). The ratio of intensity of scattered light of wavelength 546 nm, at 90 ° to the intensity of transmitted light at 0 ° was determined and used to calculate the turbidity. The refractive indices of the microemulsions were measured at 25 ° C using an Abbe refractometer (Bausch and Lomb Optical Co, Rochester, NY).

Results and Discussion

Figure 1 shows the isotropic regions obtained by using glycerin as a cosurfactant at various Brij 96 : glycerin weight ratios. Figure 2 is a similar phase diagram obtained using ethylene glycol as cosurfactant while Fig. 3 shows the isotropic regions obtained using propylene glycol as cosurfactant. The type of cosurfactant as well as the relative concentrations of the surfactant and the cosurfactant are seen to have a pronounced effect on the region of existence of the microemulsions. Table 1 lists the percentage of the total region of a pseudo-three-component region covered by microemulsions prepared using the three cosurfactants at various surfactant : cosurfactant weight ratios.

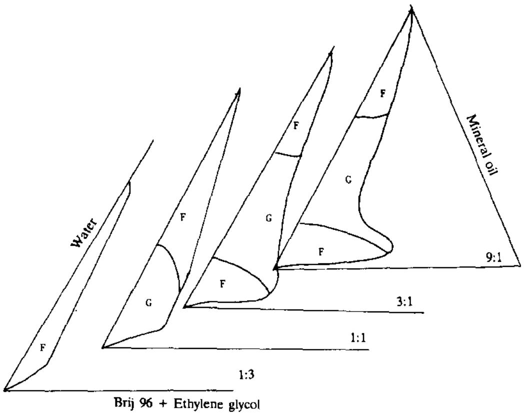

Fig. 2. Pseudo-three-component phase diagrams for a Brij 96/ethylene glycol/mineral oil/water system at various Brij 96 : ethylene glycol weight ratios. F = fluid, G = gel.

Comparison between the isotropic regions for the cosurfactant systems reveals that as the relative concentration of the cosurfactant increases, the microemulsion region decreases in size. This decrease is towards the emulsifier–water axis (i.e., away from the mineral oil apex) and indicates that as the relative concentration of the cosurfactant

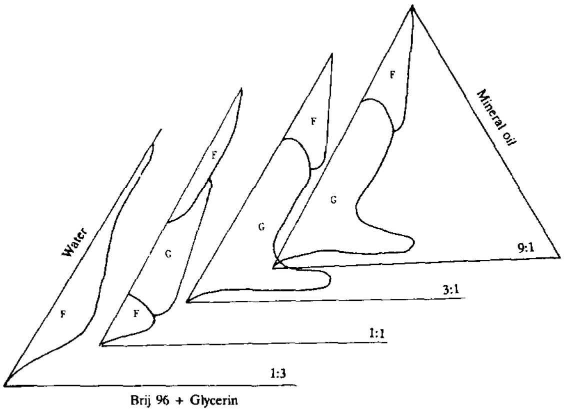

Fig. 1. Pseudo-three-component phase diagrams for a Brij 96/glycerin/mineral oil/water system at various Brij 96 : glycerin weight ratios. F = fluid, G = gel.

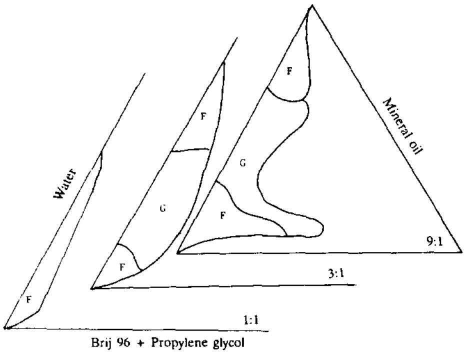

Fig. 3. Pseudo-three-component phase diagrams for a Brij 96/propylene glycol/mineral oil/water system at various Brij 96 : propylene glycol weight ratios. F = fluid, G = gel.

TABLE 1

Microemulsion region of a pseudo-three-component phase diagram

Cosurfactant	Brij 96 : cosurfactant weight ratio	% Isotropic region	% Isotropic gel region	% Isotropic fluid region
Glycerin	9 : 1	33.73	27.43	6.30
	3 : 1	32.18	25.99	6.17
	1 : 1	18.38	10.34	8.04
	1 : 3	12.27	-	12.27
Ethylene glycol	9 : 1	28.16	15.78	12.38
	3 : 1	23.70	15.87	7.83
	1 : 1	17.72	10.06	7.66
	1 : 3	9.90	-	9.90
Propylene glycol	9 : 1	31.52	17.95	14.47
	3 : 1	23.90	15.45	8.45
	1 : 1	8.14	6.59	1.59

increases the maximum amount of oil solubilized decreases. Table 2 lists the maximum oil solubilized by the various systems studied. The effect of the surfactant : cosurfactant weight ratio may be explained by the opposing effects of the surfactant and the cosurfactant on the interfacial film. Addition of surfactant causes the interfacial film to condense while addition of the cosurfactant would cause that film to expand. A similar effect has been noted by Osipow (1963) for oil/water solutions of Tween 60, Span 80, mineral oil, 2-ethyl-1,3-hexanediol and water.

TABLE 2

Maximum oil solubilization by microemulsion systems

Cosurfactant	Brij 96 : cosurfactant weight ratio	Maximum amount of oil solubilized (%, w/w)
Glycerin	9 : 1	47
	3 : 1	45
	1 : 1	17
	1 : 3	16
Ethylene glycol	9 : 1	38
	3 : 1	28
	1 : 1	17
	1 : 3	10
Propylene glycol	9 : 1	48
	3 : 1	21
	1 : 1	9

Comparison between the phase diagrams for glycerin at surfactant : cosurfactant weight ratios of 9 : 1 and 3 : 1 reveals that the microemulsion region for the lower surfactant : cosurfactant weight ratio is slightly greater between water content of 25% to 40% than the corresponding region at the higher surfactant : cosurfactant weight ratio. A similar observation can be made for the systems manufactured using propylene glycol as the cosurfactant.

It is seen that for a surfactant : cosurfactant weight ratio of 9 : 1 the isotropic region for glycerin and propylene glycol is nearly equal and extends to a maximum oil content of 47%, while the region for ethylene glycol is much smaller and extends to a maximum oil content of 39%. At a Brij 96 : glycerin weight ratio of 9 : 1 and an emulsifier (surfactant + cosurfactant) : oil ratio of 3 : 2, microemulsion formation is observed between 5%–15% water content and 45–55% water content. The region in between, i.e. from 15–45% water content, is not isotropic. A similar region is observed when propylene glycol is used as the cosurfactant. The higher water content microemulsions were not observed when ethylene glycol was used as the cosurfactant.

Comparing the phase diagrams at a surfactant : cosurfactant weight ratio of 3 : 1, it is seen that the isotropic region is much larger when glycerin is used as the cosurfactant. Also, the maximum amount of oil solubilized is 40% for glycerin, 28% for ethylene glycol and 22% for propylene glycol. Comparing the phase diagrams at a surfactant : cosurfactant weight ratio of 1 : 1, it is seen that the isotropic regions for systems in which glycerin and ethylene glycol were used as the cosurfactant are now comparable, with a maximum oil solubilization of around 17% in both cases. The microemulsion region for ethylene glycol however is much smaller, extending to only about 8% maximum oil content. This region also shows a maximum water content of about 75% beyond which microemulsions were not observed.

This upper limit on water content was not seen in any of the other systems.

In all the systems an increase in the mineral oil content led to a shift of the isotropic region towards the surfactant apex which suggested that excess surfactant molecules were required to cover an expanded hydrophobic core and pointed towards the water continuous nature of the systems.

When glycerin was used as the cosurfactant, at the higher surfactant : cosurfactant ratios of 9 : 1 and 3 : 1, the microemulsion systems at low water content were gel-like in nature; as the water content was increased the microemulsions became fluid systems. At the lower surfactant : cosurfactant weight ratio of 3 : 1 the microemulsion systems at low water content were fluid in nature. As the water content was increased, microemulsions became gel-like and finally turned back to fluid. At the surfactant : cosurfactant weight ratio of 1 : 3 the microemulsion region was composed of entirely fluid systems.

Microemulsion systems manufactured using ethylene glycol as cosurfactant are shown in Fig. 2. Unlike the systems obtained using glycerin, in this case the fluid-gel-fluid transition is seen with increasing water content at surfactant : cosurfactant weight ratios of 9 : 1 and 3 : 1, while the region at a ratio of 1 : 1 was initially gel-like and attained a fluid nature at about 50% water content. The microemulsion region at a 1 : 3 ratio was again entirely fluid in nature.

Microemulsions manufactured using propylene glycol as the cosurfactant showed a similar fluid-gel-fluid transition at a surfactant : cosurfactant ratio of 9 : 1 and 3 : 1 by weight, while the region at a ratio of 1 : 1 was initially gel-like and then fluid at higher water content. It is noteworthy that a microemulsion region was not observed at a surfactant : cosurfactant weight ratio of 3 : 1 when propylene glycol was used as the cosurfactant.

Looking at the phase diagrams along a line that represents increasing cosurfactant concentrations, it is seen that at a constant oil : water weight ratio and a low water content, the systems obtained by using glycerin are gel-like at low glycerin concentrations and become fluid as the glycerin content is increased. Similarly, systems in which either ethylene glycol or propylene glycol are used as the cosurfactant, at low water and cosurfactant content microemulsions are fluid in nature; as the cosurfactant concentration is increased the microemulsions become gel like. However, as the cosurfactant concentration is further increased, these systems again attain a fluid nature. This transition can be explained in two ways. First it may be due to the relative viscosity of the surfactant and cosurfactant, since Brij 96 is much more viscous than any of the cosurfactants used, however, this does not account for the initial fluid stage. Another possible explanation is that there occurs a transition in the nature and shape of the internal phase. As proposed by Shah et al. (1972) such 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.

The refractive index of the microemulsion systems was found to decrease in a linear manner upon dilution with water. This enabled the calculation of dn/dc, the increment in refractive index with concentration directly from a plot of refractive index vs. concentration.

The concentration of the microemulsions was calculated as follows (Hermansky and MacKay, 1980). It was assumed that the scattering species was made of microdroplets composed of all the oil, surfactant and cosurfactant but no water. Hence the concentration in g/ml of the scatterer is given by $c = \rho\phi$, where ρ is the density of the microemulsion and ϕ is its phase volume. $\phi = 1 - wg$ where w is the weight fraction of water and g is the specific gravity of the microemulsion.

The turbidity of the systems as indicated by the ratio of intensity of light scattered at 90° (D_s) to the intensity of light transmitted (D_w) was measured and used to calculate the diameter of the disperse phase. The turbidity, τ, is calculated as $\tau = Kn^2D_s/D_w$, where K is a collection of instrument constants. This enables the calculation of a weight average molecular weight using Debye's equation (Debye, 1947),

$$M = (\tau - \tau_0)/Hc$$

where H is a proportionality constant of the system given by

$$H = 32\pi^3 n^2 (dn/dc)^2 / 3\lambda^4 N_0,$$

where N_0 = Avogadro's number, n = refractive index, and dn/dc = increment in refractive index with concentration.

Debye's equation was derived for dilute solutions in which the scatterer concentration rarely exceeded 0.01 g/ml. Subsequently, the scatterer particles could move independently of each other. In the microemulsion systems measured, the internal phase concentration varied from 0.05–0.70 g/ml in most cases. As a result there is destructive interference of the scattered light from the adjacent particles or 'droplets' which results in a net decrease in the intensity of scattered light. Since the turbidity is directly proportional to the intensity of scattered light, there is a net decrease in the turbidity which manifests itself as a decrease in the effective particle diameter. Thus it is seen that the diameter obtained using Debye's equation will be substantially smaller than the actual diameter of the internal phase and will increase as the system is continually diluted with the continuous phase.

Some sort of extrapolation to infinite dilution, where the scattering particles can move independently of each other, was necessary. The method proposed by Schulman and Friend (1949) was adopted. The basic underlying assumption is that the droplet diameter does not vary upon dilution with the continuous phase over the range of stable existence of the microemulsion. The actual diameter of the internal phase was then obtained by constructing a plot of Log(effective diameter, nm) vs. concentration of the scattering species, and extrapolation to zero concentration. Figure 4 shows a plot for the quaternary system composed of Brij 96/glycerin/mineral oil/water. The extrapolated values for the internal phase diameter, d_0, obtained for the systems studied are in Table 3. A marked increase in the internal phase diameter is seen following an increase in the oil : surfactant ratio.

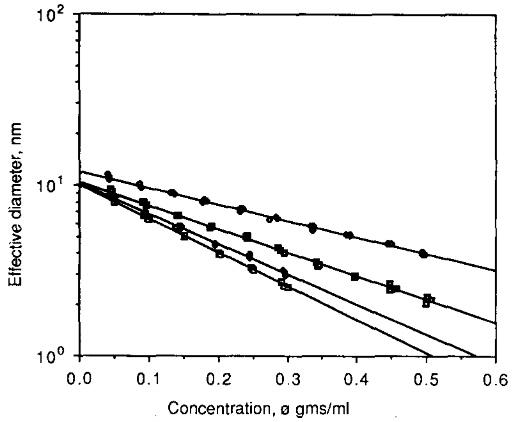

Fig. 4. Plot of Log(effective diameter, nm) vs. concentration of the internal phase (ϕ) for a Brij 96/glycerin/mineral oil/water system at various Brij 96 : glycerin weight ratios. Brij 96 : glycerin ratios: □ 9 : 1, ◆ 3 : 1, ■ 1 : 1 and ▲ 1 : 3.

A noticeable feature of the light scattering results is the dependence of the internal diameter on the relative concentrations of the surfactant and the cosurfactant. Initially, the diameter was found to decrease when the surfactant : cosurfactant weight ratio is increased until a limiting diameter, which did not change upon increasing the ratio, was attained. The decrease in the internal phase diameter can be attributed to the solubilization of oil within a larger number of surfactant micelles, which are consequently swollen to a lesser extent.

TABLE 3

Limiting diameter (d_0) of microemulsion systems

Cosurfactant	Brij 96 : co-surfactant weight ratio	Limiting diameter (d_0, nm)	Slope of plot of Deff vs. ϕ
Glycerin	9 : 1	9.98	−1.9670
	3 : 1	10.24	−1.7683
	1 : 1	10.35	−1.3658
	1 : 3	12.06	−0.9639
Ethylene glycol	9 : 1	9.06	−1.5873
	3 : 1	9.77	−1.6071
	1 : 1	10.82	−1.2577
	1 : 3	12.93	−0.7317
Propylene glycol	9 : 1	10.39	−1.8761
	3 : 1	10.33	−1.8414
	1 : 1	12.71	−1.2486

The failure of the microemulsions to form in the absence of the cosurfactant demonstrates the necessity of a minimum quantity of cosurfactant for microemulsion formation.

It is seen that at a surfactant : cosurfactant weight ratio of 9 : 1 and 3 : 1 there is no appreciable difference in the internal phase diameter. At a ratio of 1 : 1 glycerin and ethylene glycol systems have comparable diameters while the systems with propylene glycol have a much larger diameter. At a ratio of 1 : 3 glycerin and ethylene glycol systems are again comparable in diameter.

Conclusion

The existence of isotropic microemulsion regions in the quaternary systems composed of Brij 96/cosurfactant/mineral oil/water, using glycerin, ethylene glycol or propylene glycol as the cosurfactant has been demonstrated. The microemulsions at low water content were of a gel like consistency, while those at high water content were fluid in nature. The effect of the surfactant : cosurfactant ratio on the internal diameter was studied at a fixed internal phase/oil ratio of 0.1. The diameter of the internal phase was found to decrease as the surfactant : cosurfactant ratio increased.

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