

Study of Phase Behavior of Poly(ethylene glycol)–Polysorbate 80 and Poly(ethylene glycol)–Polysorbate 80–Water Mixtures

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ABSTRACT: Mixtures of poly(ethylene glycols) (PEGs) with polysorbate 80 are often used to dissolve poorly water-soluble drugs in dosage forms, where polysorbate 80 helps either in enhancing dispersion or in inhibiting precipitation of drugs once the solution is mixed with water. Binary phase diagrams of polysorbate 80 with several low molecular weight PEGs and a ternary phase diagram of polysorbate 80 with PEG 400 and water are presented. Two phases were observed in the binary mixtures when the concentration of PEG 200, PEG 300, PEG 400, or PEG 600 was >55%(w/w). The miscibility of the binary mixtures increases with an increase in temperature; the upper consolute temperatures of PEG 200–polysorbate 80, PEG 300–polysorbate 80, PEG 400–polysorbate 80, and PEG 600–polysorbate 80 mixtures were 100, 85, 75, and 40 °C, respectively. The upper consolute temperature of PEG 1000–polysorbate 80 could not be determined because the melting temperature of the mixtures is –40 °C and the consolute temperature appeared to be less than this temperature. The decrease in upper consolute temperature with an increase in PEG molecular weight indicated a greater miscibility of the two components. In the ternary system, phase separation of polysorbate 80 was observed when the concentration of PEG 400 was >50–60 % (w/w), possibly because of the high exclusion volume of PEG 400. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association *J Pharm Sci* 89:946–950, 2000

Keywords: poly(ethylene glycol); polysorbate 80; phase diagram; solubility; dosage form; phase separation; consolute temperature

INTRODUCTION

Poly(ethylene glycols) (PEGs) enjoy wide application in pharmaceutical dosage forms because of their high solubilization capacities for poorly water-soluble drugs and a relatively low toxicity. Depending on their molecular weights (MWs), they exist either as liquid or solid at room temperature. Liquid forms of PEG are commonly used as solvents or cosolvents for drugs in preclinical and

clinical studies.¹ PEG 400, which exists as a liquid, is one of the most commonly used vehicles in soft gelatin capsules.^{2–4} The solid forms of PEG, with MWs ranging from 1000 to 8000, are used as vehicles for solid dispersions or solid solutions of poorly water-soluble drugs.⁵

A potential problem with the use of PEG as a solvent is the precipitation of drug (phase separation and aggregation) on dilution with water.⁶ Such a situation could have an adverse impact on the dissolution of drugs in aqueous media and, consequently, the desired bioavailability enhancement might not be possible.⁷ The aggregation of drugs after phase separation can be minimized if a surfactant is used as a neat vehicle or as a mixture with another vehicle. Because of the surface activity of such a vehicle, any drug sepa-

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rating out of solution in an aqueous medium can disperse or emulsify as fine particles or fine oily globules.⁶ The resulting increase in surface area of drugs is conducive to high dissolution rates and bioavailability. Most of the surface-active vehicles are, however, relatively more toxic than PEG and can be ingested only in limited amounts. Also, some of the commonly used surfactants, such as polysorbate 80 and polysorbate 20, are highly viscous and difficult to use as neat solvents for drug solutions. Many investigators took advantage of both the high solubilization capacity of PEG and the dispersing capability of a surface-active vehicle by mixing the two together.⁸⁻¹⁰ PEG-polysorbate 80 mixtures were used to increase dissolution rates of drugs from solid dispersions^{11, 12} and formulations for air-jet nebulization,¹³ and for intramuscular injection of drugs.¹⁴

Despite the advantages of PEG-surfactant mixed vehicles in dosage forms, no systematic study on the miscibility and the phase behavior of PEG with commonly used surfactants has been reported in the literature. We report here the phase behavior of mixtures of a commonly used surfactant, polysorbate 80, with five relatively low MW PEGs (PEG 200, PEG 300, PEG 400, PEG 600, and PEG 1000). The PEGs were selected such that their MWs are within a narrow range, but their melting points range from -60 to +40 °C, indicating a great difference in their physical properties. With further increase in MW, the difference in physical properties is limited; for example, the difference in melting points between PEG 1000 and PEG 8000 is only 23 °C. In addition to PEG and polysorbate 80 mixtures, the phase behavior of their ternary mixtures with water was also studied, using PEG 400 as a representative PEG. This study is important because such ternary mixtures can be used as vehicles for dosage forms. Also, the ternary mixtures with water are produced in the gastrointestinal tract after oral ingestion of a PEG-polysorbate 80 mixture.

EXPERIMENTAL SECTION

Materials

Polysorbate 80, PEG 200, PEG 400, and PEG 600 were obtained from Sigma Chemical Company, St. Louis, MO; PEG 300 was obtained from J. T. Baker, Phillipsburg, NJ; PEG 1000 was obtained from Union Carbide Chemicals and Plastics Company, Inc., Danbury, CT; and methylene blue

was obtained from E. M. Industries, Inc., Gibbstown, NJ.

PEG-Polysorbate 80 Mixtures

PEG 200, PEG 300, and PEG 400 are liquid at room temperature (22 ± 2 °C). Mixtures with polysorbate 80 were prepared in 20-mL scintillation vials where the total weight of each mixture was kept at ~10 g. All the vials were vortexed for ~5 min to allow the two liquids to dissolve or disperse well into each other. A drop of each sample was placed on a glass slide and a few crystals of methylene blue were added. A cover slip was placed on the sample and rotated gently to distribute the dye evenly in the sample. Preliminary experiments showed that the presence of dye did not interfere with the phase behavior of the mixtures. The sample was examined under a microscope with 250x magnification. In the case of a sample showing globules of polysorbate 80 within PEG (two phases), the slide was heated slowly until the two phases dissolved into each other. Care was taken to ensure that the two phases mixed well during heating. For this purpose, a rough estimate of a consolute temperature was first obtained by heating the sample at 5 °C/min. For a more accurate determination, a second sample was heated at a rate of 5 °C/min to a temperature ~20 °C below the previous rough estimate. At this point, the hot stage cover was opened and the cover slip over the specimen was gently rotated to mix the two phases. Following such a mixing, the temperature was allowed to equilibrate for ~1 min, and the temperature ramp was then resumed at a rate of 1 °C/min. The mixing was continued at every 2 °C rise in temperature until the globules could no longer be observed. This temperature was defined as the consolute temperature. From multiple experiments for certain mixtures, it was established that any variation in the observed consolute temperatures was within ± 3 °C. Mixtures of PEG 600 and PEG 1000 with polysorbate 80 were studied similarly except that the initial equilibration was carried out at 25 and 50 °C, respectively.

PEG 400-Polysorbate 80-Water Mixtures

PEG 400-water, PEG 400-polysorbate 80, and polysorbate 80-water binary mixtures (~10g each) were prepared in 20-mL scintillation vials and were vortexed for ~5 min for thorough mixing. These mixtures were examined visually and

under the microscope for any phase separation as already described. The third phase was then added to each mixture in increments of 0.1 to 1 g each. The ternary mixtures were then vortexed again before visual and microscopic examination.

RESULTS

PEGs are neutral polyethers with repeating oxyethylene ($-\text{CH}_2\text{CH}_2\text{O}-$) $_n$ groups that have chains ending in hydroxyl groups. The average value of n is 4.1 for PEG 200, 6.4 for PEG 300, 8.7 for PEG 400, 13.2 for PEG 600, and 22.3 for PEG 1000.¹⁵ Polysorbate 80 (Figure 1) is a nonionic surfactant with a sorbitan backbone and four polyoxyethylene groups, one of which is esterified with oleic acid. Despite structural similarities because of the presence of oxyethylene groups in both PEG and polysorbate 80, some PEGs were not completely miscible with polysorbate 80. The details of such observations are given next.

PEG–Polysorbate 80 Mixtures

Figure 2 shows the phase diagrams of binary mixtures of polysorbate 80 with PEG 200, PEG 300, PEG 400, and PEG 600. At room temperature ($\sim 22^\circ\text{C}$), polysorbate 80 was completely miscible when its concentration in binary mixtures with PEG 200, PEG 300, or PEG 400 was $>45\%$ (w/w). At lower concentrations of polysorbate 80, globules of the surfactant were observed, indicating the presence of two phases. Polysorbate 80 was also completely miscible with PEG 200, PEG 300, and PEG 400 at 22°C when its concentration was $<2\%$ (w/w). It was miscible with PEG 600 outside of the concentration range 7–35% (w/w) at 25°C . In all of the binary mixtures just mentioned, the region of partial miscibility narrowed with an increase in temperature. The upper consolute temperatures of polysorbate 80 with PEG 200, PEG

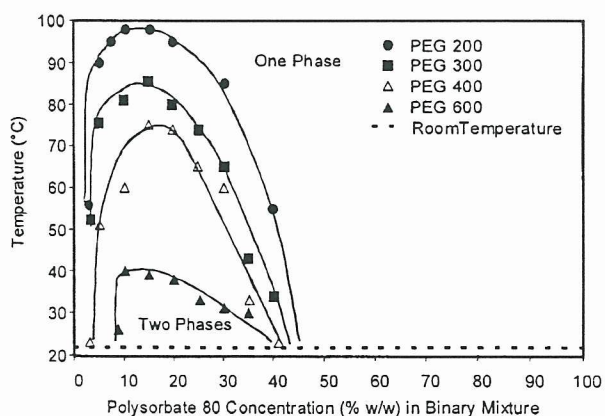


Figure 2. Binary phase diagrams for PEG and polysorbate 80. The separated phase present as globules in the two-phase system was polysorbate 80-rich. The horizontal broken line at 22°C represents the room temperature.

300, PEG 400, and PEG 600 were 100, 85, 75, and 40°C , respectively. PEG 1000 and polysorbate 80 are miscible in all proportions at 50°C . This result was not unexpected because the upper consolute temperature of PEG 600 with polysorbate 80 is only 40°C and, following the trend, the upper consolute temperature of PEG 1000 with polysorbate 80 could be even lower.

PEG 400–Polysorbate 80–Water Mixtures

The phase diagram of the mixtures of PEG 400, polysorbate 80, and water at room temperature ($22 \pm 2^\circ\text{C}$) is shown in Figure 3. The vertices of the triangle represent 100% (w/w) of the respective components. Because PEG 400 and polysorbate 80 are individually miscible with water, the binary PEG 400–water and polysorbate 80–water mixtures yield clear solutions. However, when the respective third component was added to each of the two sets of binary mixtures, two phases were observed in certain regions of the phase diagram. Globules of polysorbate 80 separated out as the second phase. As shown in Figure 2, the PEG 400 and polysorbate 80 form a two-phase mixture at room temperature for PEG 400 concentrations $>55\%$ (w/w). The phase boundary in Figure 3 is between the PEG 400 concentration of 50 and 60% (w/w), which is essentially the same as that in the binary mixture (Figure 2). Polysorbate 80 formed a separate phase when the concentration of PEG 400 exceeded this level. Thus, looking at the phase diagram in another way, although polysorbate 80 and water are miscible in all propor-

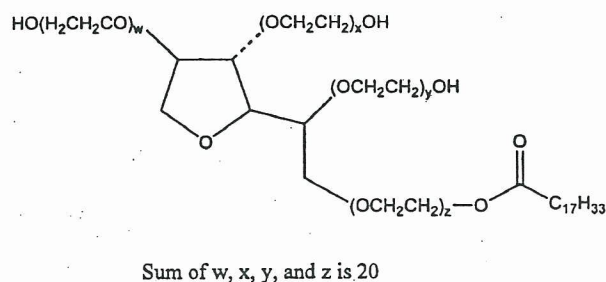


Figure 1. Chemical structure of polysorbate 80.

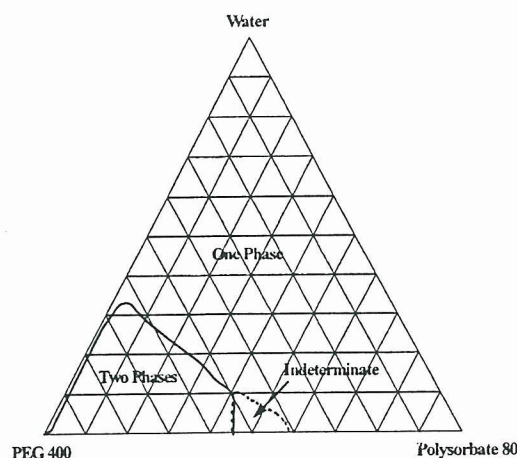


Figure 3. Ternary phase diagram for PEG 400-polysorbate 80-water at 24 ± 2 °C. The separated phase present as globules in the two-phase system was polysorbate 80-rich. Vertices represent 100% (w/w) of the indicated component. The three sides represent the corresponding binary compositions.

tions, the presence of PEG 400 as the third component makes them less miscible.

DISCUSSION

As reported by Harris,¹⁶ PEG exhibits unusual solubility patterns, and the effect of chemical structure on its solubility behavior is not fully understood. For example, PEG, which is chemically poly(ethylene oxide), is soluble with water, whereas the closely related poly(methylene oxide) and poly(propylene oxide) are water insoluble. Although PEG is soluble in methylene chloride and many other organic solvents, it is insoluble in ethyl ether and ethylene chloride, which are molecules that closely resemble its structure. Another interesting property of PEG reported by Harris¹⁶ is that it has a high exclusion volume in aqueous solutions. As a result, PEG displaces other polymers from water solutions and forms two phases when its concentration is high. This property of PEG is evident from the ternary diagram presented in Figure 3, where all the inhomogeneity lies in the region in which the PEG concentration is high (>50–60% w/w). Another observation that reiterates the unusual solubility behavior of the PEG is its only partial miscibility with polysorbate 80 despite significant structural similarity. At room temperature, the partial immiscibility of low MW PEGs with polysorbate 80

indicates that there may not be a good interaction between the polyethylene oxide chains of the two compounds. They become miscible at a high temperature, possibly because of a change in the orientation of PEG chains.¹⁷ Like other polymers and proteins, the immiscibility of polysorbate 80 (seen in Figure 3) at a high PEG concentration appears to be due to the high exclusion volume of PEG.

It is evident from the lowering of upper consolute temperature that the miscibility of PEG with polysorbate 80 increases with an increase in its MW (Figure 2). It is possible that the molecular orientation of PEG changes with an increase in its MW. The inference that the high MW PEGs may be miscible with polysorbate 80 is in agreement with the finding of Morris et al.¹⁸ who observed that polysorbate 80 was miscible with the molten forms of the higher MW PEGs (MW, 1000–8000) in the temperature range 40–70 °C. They also observed that when a high MW PEG mixture with polysorbate 80 was cooled to room temperature, polysorbate 80 was possibly excluded to the amorphous region of PEG because the crystalline region of solid PEG remained practically unchanged. This result could be because of the immiscibility between the two components in the solid state.

The objective of the present study was to determine phase boundaries of various mixtures to facilitate dosage form design. No attempt was made to determine concentrations of individual components in different phases when phase separation occurs. Whether various mixtures in the phase diagrams (Figures 2 and 3) exist as a solution, micellar dispersion or microemulsion was also not established. This subject will be the focus of a future study.

Although mixtures of PEG and polysorbate 80 are attractive vehicles for pharmaceutical dosage forms to increase solubility, dissolution rate, and bioavailability of poorly water-soluble drugs, the results of the present study show that their miscibility must be carefully evaluated during formulation development. This type of evaluation is especially important for low MW PEGs (MW, 200–600).

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