The solubility of 17 β-oestradiol in aqueous polyethylene glycol 400

M. J. GROVES*, B. BASSETT AND V. SHETH

Pharmaceutical Development Department, G. D. Searle & Co., Skokie, IL 60077, USA

The solubility of 17 β-oestradiol (E_2) in aqueous solutions of polyethylene glycol (PEG) 400 has been measured at 35 °C. Up to 80% w/w PEG the solubility data conform to a log linear equation $\ln S = \ln S_w + f\sigma$ where S is the E_2 concentration in the water/cosolvent mixture, S_w is E_2 solubility in water, f is the weight fraction of PEG 400 and σ is a parameter representing the solubilizing power of the cosolvent for the drug. Above 80% PEG the relationship becomes less convincing, with significant deviation from anticipated values. Reasons for these aberrations are discussed. It is suggested that conformational changes may be induced in the PEG by the addition of small quantities of water. Deviations noted for the melting point, viscosity and density data of PEG 400–water solutions may also confirm this suggestion.

Polyethylene glycols (PEGs) are ubiquitous pharmaceutical solvents or cosolvents having low toxicity and often a high solvent capacity for materials with poor water solubility.

During an investigation of the solubility of 17 β-oestradiol (E_2) in aqueous mixtures of PEG 400 it became apparent that the solubility of the drug conformed to the log linear equation introduced by Yalkowsky et al (1972) in the form

$$\ln S = \ln S_w + f\sigma \qquad (1)$$

where S = solute solubility in the solvent consisting of f volume fractions of cosolvent in water, S_w is the water solubility and σ is a parameter representing the solubilizing power of the cosolvent for the drug. Equation 1 is only applicable to systems where the polarity of the drug is significantly lower than that of either of the solvents in the binary mixture. Although basically an empirical observation, Martin et al (1982) have recently provided a rationalization based on Hildebrand solubility parameters (Hildebrand et al 1978).

Closer examination of our data suggested less convincing linearity at levels of PEG 400 in excess of 80% w/w. Accordingly, other properties of aqueous PEG 400 solutions were evaluated in more detail in order to obtain some insight into the observed anomalies.

MATERIALS AND METHODS
Materials
17 β-Oestradiol (E_2), lot 42F-0756, Sigma Chemicals Co., St Louis, Missouri 63178, USA. Polyethylene

glycol 400 (PEG 400) lots 737343 and 74901, J. T. Baker Chemical Company, Phillipsburg, New Jersey 08865, USA, used as received after drying over molecular sieve. Water—distilled. Solutions of PEG in water were made by weight.

Methods
Solubility method. To avoid supersaturation, excess solid E_2 was shaken with the appropriate solvent solution at 35 °C (±0·5) in a rocking thermostated water bath (Precision Scientific Model 50 Shaker Bath) in sealed stoppered glass tubes for 48 h. Preliminary experiments demonstrated rapid equilibration within the first 12 h; the additional time was regarded as a safety factor. The temperature of the water bath was checked at appropriate intervals using a precalibrated digital electronic thermometer reading to 0·1 °C. Solid was separated from the solution by rapid filtration through preheated glass fibre filter pads (Whitman GF/B, nominal pore diameter 1 μm) held in a Millipore stainless steel Swinnex filter unit. Care was taken to avoid contact of the solutions with plastic surfaces, following the observations by Hahnel (1971) and Batra (1975) of the adsorption of steroids, including E_2, onto plastic and cellulose membrane filters. Each data point was obtained from the average of three replicate solubility determinations. Concentrations of E_2 (weight/volume) were measured spectrophotometrically after appropriate dilution with methanol at a wavelength of 281nm using a Hewlett Packard Model 8450A spectrophotometer. Samples from the same solutions were independently assayed by an hplc (detector set at 280 nm) in a method developed by Sheth et al (1984). The two sets of data were

* Correspondence and present address: Pharmaceutics Department, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612, USA.

similar: slope of the correlation curve = 1·005, r = 0·9999, n = 3 at each level by each method.

Viscosities of aqueous solutions of PEG 400 were measured at 35·0 ± 0·1 °C using a Ferranti-Shirley cone-plate viscometer fitted with a 7·0 cm cone. The speed of rotation was varied from 0–1000–0 rev min⁻¹ over 2 min using the instrument automatic mode. The rheograms were carefully examined for evidence of non-Newtonian flow behaviour. However, this was not seen and viscosities reported are those measured at the maximum shear rate.

Densities of the same solutions were measured at 35 °C using a Mettler-Paar Model DMA 60/602 Digital densitometer (Kratky et al 1973).

Differential scanning calorimetry (DSC) of aqueous solutions of PEG 400 was carried out using a DuPont 1090 Thermal Analyzer, scanning at a rate of 2 °C min⁻¹ in the interactive mode.

FIG. 2. E_2 solubility data obtained on two lots of polyethylene glycol 400 over the range 90–100% w/w PEG 400 showing the negative deviation from the line of best fit 92–98% and positive deviation above 99% PEG. % Lot 737343. X Lot 749401. Continuous line is statistical line of best fit, Lot 737343, 0–100% w/w PEG (Fig. 1).

RESULTS

Solubility data are shown in Fig. 1. It will be noted that there is good linearity (r better than 0·99) for data points up to 80% w/w PEG 400. Beyond this point some deviation from the line of best fit obtained at the lower levels became evident. This was particularly pronounced at PEG levels close to 100%. The experiment was repeated with a different lot of PEG, to much the same conclusion, Fig. 2.

The work of Huttenrauch & Fricke (1981a, b) suggested that anomalous solution behaviour of PEG for griseofulvin may be attributed to structural changes in the PEG. DSC examination of aqueous PEG solutions demonstrated anomalous behaviour, Fig. 3, but not over the upper concentration ranges. Accordingly, viscosities and densities of aqueous PEG solutions were also measured at 35 °C, Fig. 3.
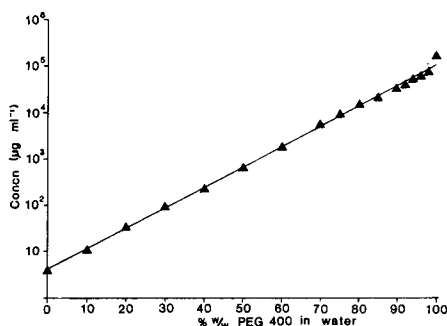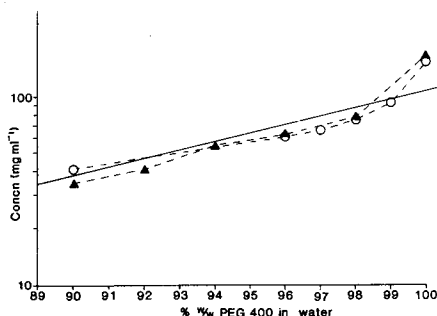

FIG. 1. The solubility of β-oestradiol in aqueous polyethylene glycol 400. Data taken from the uv analyses for PEG 400, lot 737343. r = 0·9986 (all data points), ln S = ln S_w + fσ, S_w = 4 μg cm⁻³, σ = 0·102 where S = solubility of E_2 in water–cosolvent mixture, f is the weight fraction of PEG 400 and S_w is the saturated aqueous solubility.

DISCUSSION

The solubility data shown in Fig. 1 appeared to conform to the log linear equation 1, with an estimate of σ = 0·10, here a weight fraction, and S_w = 1·47 × 10⁻⁵ mol dm⁻³ at 35 °C. Experimental values for the saturated aqeuous solubility were 1·46 × 10⁻⁵ mol dm⁻³ (3·99 μg cm⁻³) by the hplc assay method and 1·45 × 10⁻⁵ mol dm⁻³ by the uv method. These may be compared with literature values of 2·06 × 10⁻⁵ mol dm⁻³ (Lundberg 1979) obtained at 35 °C by a radiolabel method and 1·43 × 10⁻⁵ mol dm⁻³ at 25 °C by Hurwitz & Lui (1977) by a spectrophotometric procedure.

However, when equation 1 was used to estimate the 17 β-oestradiol solubility in anhydrous polyethylene glycol numerically, a discrepancy became evident. Will et al (1980) obtained a lower value (at a higher temperature) than our extrapolated value of 123 mg cm⁻³, itself considerably lower than the experimental measurement of 167 mg cm⁻³.

Closer examination of the uv data shown in Fig. 1 suggested that there was deviation from linearity at PEG 400 concentrations in excess of 80% w/w.

The same effect was seen with a second lot of PEG, Fig. 2. This was manifested as a negative departure from the line of best fit (obtained over the 0–100% PEG data range) between approximately 92 and 98% PEG, followed by a marked positive deviation between 98 and 100%.

The most dramatic change in properties of aqueous PEG 400 solutions was found by DSC when measuring the melting point, Fig. 3. This shows a rapid drop as either water is added to PEG or PEG added to water. However, the two curves do not meet and experimentally the temperature of 60 and
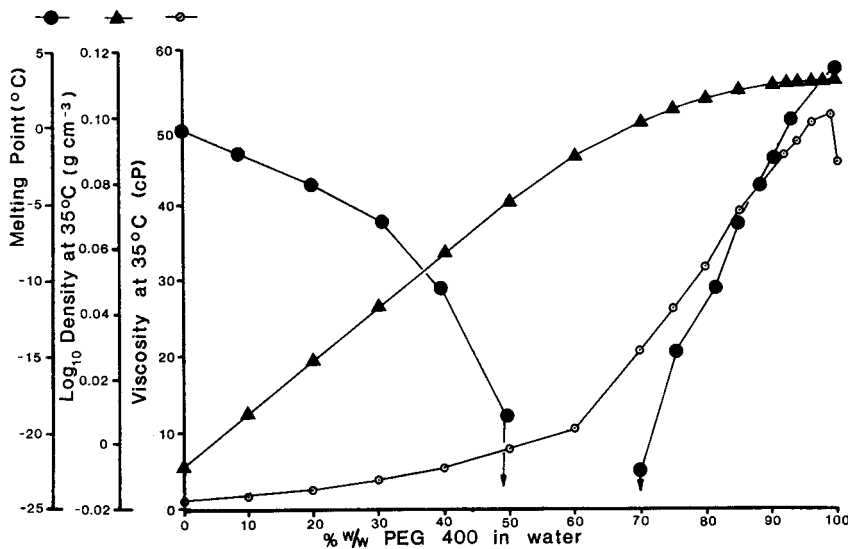
FIG. 3. Physical properties of aqueous PEG 400 solutions. DSC melting point (°C) —●—, Density (g cm⁻³) at 35 °C —●—, Viscosity (P) at 35 °C —○—.

70% w/w PEG 400 solutions in water were lowered to −70 °C without freezing.

This curve, similar to a family of curves drawn for PEGs of different molecular weight (Powell 1976), suggests that two molecular conformational regimes exist. In the first regime the freezing point is depressed proportionally as single molecular species are increased in number. Eventually a point is reached where the solvent-solution interactions are increased as the concentration of glycol is increased and all the water molecules are bound. These interactions result in structural changes such as progressive helix formation. The net effect is an increase in freezing point with concentration in the second regime. For example, Tilcock & Fisher (1982) suggest that all water in the system is bound at PEG 400 concentrations in excess of 58% w/w, consistent with our experimental observations at 60% w/w PEG 400 and above, Fig. 3.

It is clear that the PEG-water bonding does not affect the PEG solubility of β-oestradiol, Fig. 1. Thus, solvent–solvent interaction is not involved and the solute–solvent interaction observed at the highest PEG concentrations requires another explanation.

Huttenrauch & Fricke (1981a, b) have drawn attention to the structural changes induced in polyethylene glycols by the addition of small quantities of water. Using X-ray and infrared measurements, previous authors (Davison 1955; Miyazawa et al 1961, 1962; Price & Kilb 1962) noted a tendency for polyethylene glycols of molecular weight 4000 and higher to form crumpled helix structures in the solid state. Huttenrauch & Fricke (1981b) suggested that the polymer molecules also exist in the anhydrous PEG 400 liquid as the linear or, so-called, 'zig-zag' form. The addition of small quantities (<5%) of water was considered to induce helix formation in the system, thereby increasing the viscosity. The same effect was noted with semi-solid higher molecular weight polyethylene glycols, manifested as a change in the flow curve.

An interaction or structure development in the system was suggested as the solution densities and viscosities changed over the range 80–100% PEG, Fig. 3. Tilcock & Fisher (1982) demonstrated from DSC and density measurements over the range 5–40% w/w aqueous PEG 400 that 1·8 molecules of water are bound per monomer unit. These authors found a linear regression line for density of 0·998 + 1·75 × 10⁻³x, where x is the polymer concentration, % w/w, measurements being taken at room temperature (18–22 °C). This may be compared to the linear regression obtained from Fig. 3 over the range 0–60% PEG of 0·993 + 1·63 × 10⁻³x at a closely controlled temperature of 35 °C.

Our data may be explained if E_2 is more soluble in the zig-zag form of PEG 40 than it is in the helix

structure. On addition of the small quantities of water necessary to induce helix formation in the polymer, the solubility of the E_2 is depressed. Finally, as the helix structure is diluted out by further addition of water, the solubility curve becomes more consistent with Hildebrand solubility curve predictions, equation 1, for binary water-cosolvent systems. Since PEG 400 is hygroscopic, differences between our data and those of Will et al (1980) are readily explained if small quantities of water were inadvertently present in the latters' starting materials.

REFERENCES

Batra, S. (1975) J. Pharm. Pharmacol. 27: 777–778

Davison, W. H. T. (1955) J. Chem. Soc. II: 2431; 3270–3274

Hahnel, R. (1971) J. Steroid. Biochem. 2: 61–62

Hildebrand, J. H., Prausnitz, J. M., Scott, R. L. (1978) in: the Solubility of Non-Electrolytes. 3rd edn, Dover, New York

Hurwitz, A. R., Liu, St., T. (1977) J. Pharm. Sci. 66 (5): 624–627

Huttenrauch, R., Fricke, S. (1981a) Pharmazie 36: 575–576

Huttenrauch, R., Fricke, S. (1981b) Act. Pharm. Technol. 27 (2): 93–98

Kratky, O., Leopold, H., Stabinger, H. (1973) in: Enzyme Structure, Methods in Enzymology. Academic Press, New York, pp 48–63

Lundberg, B. (1979) Act. Pharm. Suec. 16: 151–159

Martin, A., Wu, P. L., Adjei, A., Lundstrom, R. E., Elworthy, P. H. (1982) J. Pharm. Sci. 71 (8): 849–856

Miyazawa, T. (1961) J. Chem. Phys. 35 (2): 693–713

Miyazawa, T., Fukushima, K., Yoshiko, I. (1962) Ibid. 37 (12): 2764–2776

Powell, A. M. (1976) in: Davison, R. L. (ed.) Handbook of Water-Soluble Gums and Resins. McGraw, New York. p 18

Price, F. P., Kilb, R. W. (1962) J. Polymer Sci. 57: 395–403

Sheth, V., Kosobud, T., Mikulec, R., Dugar, S. (1984) J. Pharm. Sci., in the press

Tilcock, C. P. S., Fisher, D. (1982) Biochem. Biophys. Act. 688: 645–652

Will, P. C., Cortright, R. N., Hopfer, U. (1980) J. Pharm. Sci. 69 (6): 747–749

Yalkowsky, S. H., Flynn, G. L., Amidon, G. L. (1972) Ibid. 61 (6): 983–984