

A NOTE ON THE SOLUBILITY OF PROGESTERONE
IN AQUEOUS POLYETHYLENE GLYCOL 400

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ABSTRACT

The solubility curve of progesterone in aqueous polyethylene glycol (PEG) 400 at ambient room temperature ($\sim 25^{\circ}\text{C}$) is bimodal, a break occurring at approximately 60% w/w PEG.

It is speculated that the presence of unbound water in the PEG 400/water system depresses the solubility of progesterone in PEG 400 disproportionately.

INTRODUCTION

Progesterone (pregn-4-ene-3,zo-dione) is a progestational hormone used to control habitual abortion. In recent years it has been widely prescribed in human medicine for the treatment of post-menopausal syndrome.

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At present no commercial product is available and the drug is usually supplied as extemporaneously prepared vaginal suppositories using polyethylene glycol or coco butter bases. Reports of variable clinical response are occasionally encountered although these are mainly anecdotal. However, as part of a systematic investigation of factors possibly influencing bioavailability the solubility of progesterone in a liquid polyethylene glycol was measured.

MATERIALS AND METHODS

Progesterone Sigma, St. Louis, Missouri, lot number 13F-0838.

Polyethylene glycol (PEG) 400, Union Carbide Carbowax 400¹. Laboratory grade, lot number 764824, dried over molecular sieve.

Water glass distilled.

Solutions of progesterone were made by weight in aqueous dilutions of PEG 400 also prepared by weight.

Solubility Method. Excess progesterone was added to the appropriate solvent system in glass tubes, covered with aluminum foil and capped prior to shaking for 24 hours at ambient room temperature ($\sim 25^{\circ}\text{C}$). Contact with plastic surfaces was avoided to prevent absorption of progesterone, as reported by others^{1,2,3}.

The tubes were centrifuged and the supernatant liquid analyzed by reference to standard solutions using a Cary Model 118 spectrophotometer at 246 nm.

Each measurement is the mean of duplicate determinations.

RESULTS

The solubility curve is shown in Fig. 1 and is clearly bimodal with an intersection at approximately 60% w/w PEG 400. Assuming two solubility curves, A and B, the Yalkowsky⁴ equation parameters ($\log s = \log s_w + fC$) are $S_{WA} = 12.0$, $f_A = 0.056$ and $S_{WB} = 0.70$, $f_B = 0.10$ where S_{WA} and S_{WB} are the appropriate estimated solubilities in water and f_A and f_B the corresponding cosolvent solubilizing functions, with S being the solubility of progesterone in $C_g 100 g^{-1}$ PEG 400 in water.

DISCUSSION

The estimated water solubility S_{WA} of $12 g g^{-1}$ is in reasonable agreement with the literature value of $15.2 \mu g mL^{-1}$,¹ suggesting that the first part of the curve is due to solubility of progesterone in water containing PEG 400. The inflection point is in close agreement with the region of the water PEG 400 system where there is no longer any free water³, confirmed by others⁵. The change of cosolvent solubilizing function from 0.06 to 0.10 suggests an appreciably higher solubility of progesterone in PEG 400 that is suppressed by addition of water. As soon as free water appears in the system the solubilizing capacity is lowered even further.

Transfer of drug from delivery system (vaginal suppositories) to the physiological absorption site

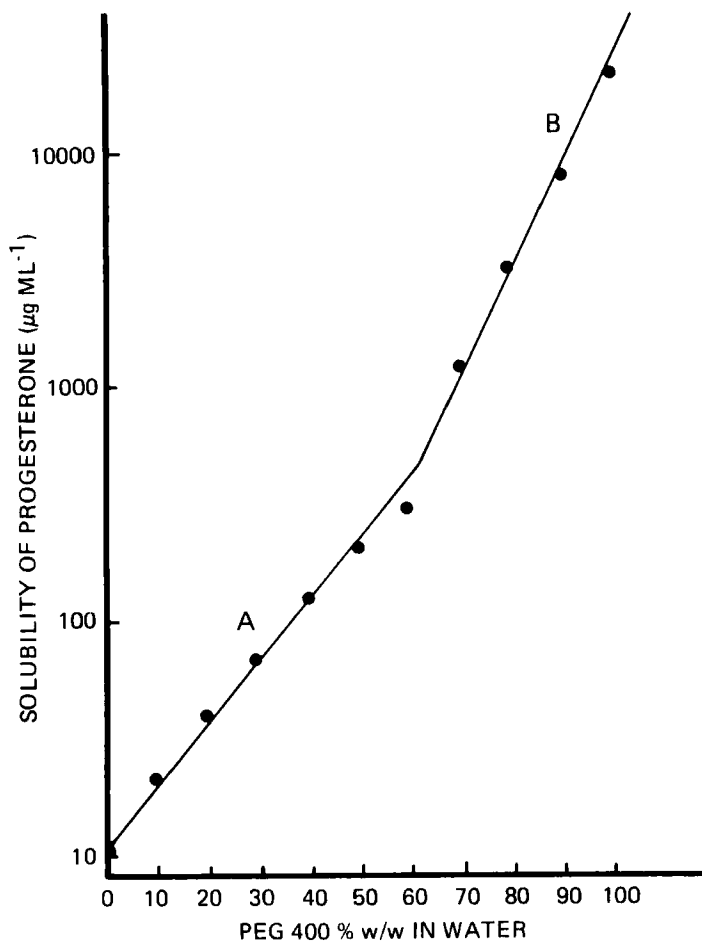


FIGURE 1

The solubility of progesterone in aqueous PEG 400 solutions at ambient room temperature (25°C).

Region A (0-60% PEG 400)

$$\ln S = \ln 11.957 + 0.0565 C$$

correlation = 0.997

Region B (60-100% PEG 400)

$$\ln S = \ln 0.704 + 0.1043 C$$

correlation = 0.997

where

S = solubility of progesterone in Cg/100 g PEG 400 in water

in the vagina will be a function of the solubility gradient between water, aqueous PEG and PEG alone. This present investigation might indicate that enhanced bioavailability could be anticipated from polyethylene glycol bases when compared to oleagineous bases. This requires further investigation.

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