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Solubilization of Steroids by Multiple co-Solvent Systems

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The aqueous solubility of steroids was exponentially increased following the addition of a co-solvent. A theoretical equation was derived to describe the relationship between the amount of drug solubilized and the volume fraction of co-solvent incorporated. Both single and multiple co-solvent systems followed the derived relationship.

Introduction

In the practice of pharmaceutical formulation, the challenge of improving the solubility of many poorly soluble drugs, *e.g.*, steroids, in solution dosage forms is common. To solve such problems, scientists often incorporate one or more co-solvents with distilled water to overcome the poor aqueous solubility.

Ethanol, propylene glycol, and several members of the polyethylene glycol polymer series, *e.g.*, polyethylene glycol 400, represent the limited number of co-solvents that are both useful and generally acceptable in the formulation of aqueous liquids[2]. In addition, Spiegal and Noseworthy[3] in their review of nonaqueous solvents used in parenteral products, also suggested a number of co-solvents, such as 2,2-dimethyl-1,3-dioxolane-4-methanol (Solketal), dimethylacetamide, glycerol formal, glycofurol, N-(β-hydroxyethyl)-lactamide, and ethyl lactate.

There have been several reports dealing with the systematic investigation of drug solubility and solvent composition.[2,4–7] Observations to date indicate that the solubility of many drugs and druglike substances in binary aqueous systems is enhanced exponentially by the addition of a co-solvent.[4]

Past experiences in our laboratories with solution dosage formulation indicated that the semilogarithmic relationship of drug solubility to co-solvent composition was followed not only in binary aqueous systems containing a single co-solvent, but also in the systems containing 2 or more different co-solvents. In this paper, the authors will report their observations on the dependency of steroid solubility on the concentration of single, binary, and/or ternary co-solvents, and will present a theoretical analysis on the semilogarithmic relationship of drug solubility to co-solvent concentration.

Experimental

Materials——SC-9376, SC-4640, SC-11800, and SC-25152 (Fig. 1) (Searle Laboratories, Skokie, Illinois), propylene glycol, polyethylene glycol 400, 2,2-dimethyl-1,3-dioxolane-4-methanol, and N,N-dimethylacetamide (Matheson Coleman Bell Co., Norwood, Ohio) and 95% ethanol for medical use were utilized as obtained.

1) Location: *Skokie, Illinois 60076, U.S.A.*
2) L. Lachman, H.A. Lieberman, and J.L. Kanig, "The Theory and Practice of Industrial Pharmacy," Lea & Febiger, Philadelphia, 1970, Chapter 15.
3) A.J. Spiegel and M.M. Noseworthy, *J. Pharm. Sci.*, **52**, 917 (1963).
4) S.H. Yalkowsky, G.L. Flynn, and G.L. Amidon, *J. Pharm. Sci.*, **61**, 983 (1972).
5) A.N. Parnta and S.A. Irani, *J. Pharm. Sci.*, **54**, 1334 (1965).
6) W.G. Gorman and G.D. Hall, *J. Pharm. Sci.*, **53**, 1017 (1964).
7) K.S. Lin, J. Anschel, and C.J. Swartz, *Bull. Parenteral Drug Assoc.*, **25**, 40 (1971).

Parenteral quality distilled water was prepared and used for the preparation of 0—80% co-solvent–water combinations. Absolute methanol (spectroquality, J.T. Baker Chemical, Cleveland, Ohio) was employed for the dilution of filtered drug solutions to an appropriate concentration for spectrophotometric measurement.

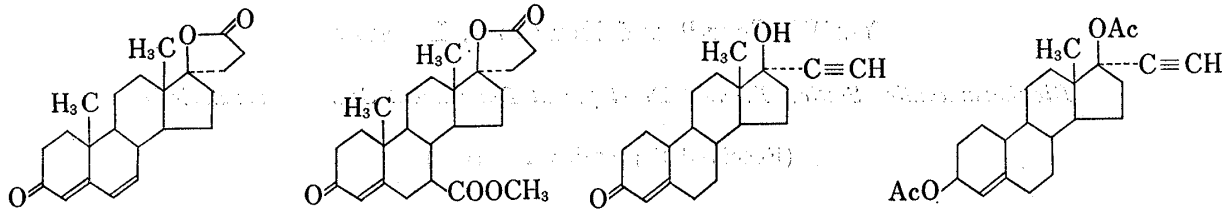

Fig. 1. Molecular Structures of the Steroids investigated

Determination of Drug Solubility——The methodology reported earlier[8] was adopted here with minor modifications to avoid the possible hydrolysis of SC-9376 and SC-25152 after 48-hour equilibration at 37°. Excess drug solid was equilibrated with 10 ml of a co-solvent–water combination at 37° for 2 hours with constant shaking. After cooling to room temperature, the over-saturated drug solution was quickly filtered through a filter holder (millipore) containing a glass fiber membrane (Reeve Angel). The filtered drug solution was diluted 10 to 4000 times with methanol to an appropriate drug concentration and then read spectrophotometrically. The magnitude of the absorbance at the λ max was used to calculate the amount of a drug solubilized in a given solvent system. The filtered solution of ethynodiol diacetate (SC-11800) was subjected to acidic hydrolysis[8] before dilution.

Results and Discussions

In nonideal solutions,[9] the solubility of a drug (C_w) in pure water system is defined by

$$\log C_w = -\frac{\Delta S_W}{2.303RT}(T_m - T) + \log \gamma_w \tag{1}$$

Also, the solubilities of this drug (C_A, C_B, or C_X) in pure systems of co-solvent A, B, or X, may be defined in the same way:

$$\log C_A = -\frac{\Delta S_A}{2.303RT}(T_m - T) + \log \gamma_A \tag{2}$$

$$\log C_B = -\frac{\Delta S_B}{2.303RT}(T_m - T) + \log \gamma_B \tag{3}$$

$$\log C_X = -\frac{\Delta S_X}{2.303RT}(T_m - T) + \log \gamma_X \tag{4}$$

where ΔS_w, ΔS_A, ΔS_B, and ΔS_X are the entropies of the drug species in the pure solvent systems and γ_w, γ_A, γ_B, and γ_X are the corresponding activity coefficients; T_m is the drug melting point; and T is the temperature of the system investigated.

In a nonideal multiple solvent system containing f_A fraction of co-solvent A, f_B fraction of co-solvent B, f_X fraction of co-solvent X, and $[1-(f_A+f_B+f_X)]$ fraction of water, the apparent solubility ($C_{A,B,X}$) of the same drug species may be expressed as

$$\log C_{A,B,X} = f_w \log C_w + f_A \log C_A + f_B \log C_B + f_X \log C_X \tag{5a}$$

$$= \log C_w + f_A(\log C_A - \log C_w) + f_B(\log C_B - \log C_w) + f_X(\log C_X - \log C_w) \tag{5b}$$

8) Y.W. Chien, H.J. Lambert, and D.E. Grant, *J. Pharm. Sci.*, 63, 365 (1974).
9) A.N. Martin, "Physical Pharmacy," Lea & Febiger, Philadelphia, 1960, Chapter 14.

since

$$\log C_A - \log C_w = \frac{(T_m - T)}{2.303RT}(\Delta S_w - \Delta S_A) + \log \frac{\gamma_A}{\gamma_w} \quad (6)$$

$$\log C_B - \log C_w = \frac{(T_m - T)}{2.303RT}(\Delta S_w - \Delta S_B) + \log \frac{\gamma_B}{\gamma_w} \quad (7)$$

$$\log C_X - \log C_w = \frac{(T_m - T)}{2.303RT}(\Delta S_w - \Delta S_X) + \log \frac{\gamma_X}{\gamma_w} \quad (8)$$

Substituting Eqs. (6), (7), and (8) into (5-b) gives

$$\log C_{A,B,X} = \log C_w + \varepsilon_A f_A + \varepsilon_B f_B + \varepsilon_X f_X \quad (9)$$

where the slopes (ε_A, ε_B, and ε_X) of the semilogarithmic relationship between the drug solubility ($C_{A,B,X}$) and the composition of co-solvent (f_A, f_B, and f_X) are defined by:

$$\varepsilon_A = \frac{(T_m - T)}{2.303RT}(\Delta S_w - \Delta S_A) + \log \frac{\gamma_A}{\gamma_w} \quad (10)$$

$$\varepsilon_B = \frac{(T_m - T)}{2.303RT}(\Delta S_w - \Delta S_B) + \log \frac{\gamma_B}{\gamma_w} \quad (11)$$

$$\varepsilon_X = \frac{(T_m - T)}{2.303RT}(\Delta S_w - \Delta S_X) + \log \frac{\gamma_X}{\gamma_w} \quad (12)$$

Eqs. (10) to (12) point out that the magnitudes of the slopes (ε_A, ε_B, and ε_X) are determined by the difference in entropies, ($\Delta S_w - \Delta S_A$), ($\Delta S_w - \Delta S_B$), and ($\Delta S_w - \Delta S_X$), respectively, the ratio of the activity coefficients (γ_A/γ_w, γ_B/γ_w and γ_X/γ_w and the difference between the melting point temperature (T_m) and the temperature of the system studied (T).

Eq. (9) indicates that the solubility of a drug species in a given multiple co-solvent system ($C_{A,B,X}$,) is exponentially related to the volume fractions of co-solvents (A, B, and X) added. In the case of a ternary system containing a fixed (f_A) of co-solvent A and a varying fraction (f_X) of co-solvent X, Eq. (9) may be simplified. Since $f_B=0$, the apparent drug solubility ($C_{A,X}$) in such a ternary system is:

$$\log C_{A,X} = \log C_w + \varepsilon_A f_A + \varepsilon_X f_X \quad (13)$$

When using a binary system, (only one co-solvent), Eq. (13) may be further simplified to

$$\log C_X = \log C_w + \varepsilon_X f_X \quad (14)$$

An equation similar to Eq. (14) was reported previously by Yalkowsky, *et al.*[4] to describe the solubility of alkyl *p*-aminobenzoates in propylene glycol–water systems.

The experimental evidence for the dependence of drug solubility upon co-solvent composition in a binary system (Eq. 14) is demonstrated in Fig. 2, where the solubility of poorly soluble steroids, *e.g.*, progestins (SC-11800 and SC-4640) as well as anti-mineralcorticoid drugs (SC-9376 and SC-25152), is exponentially enhanced as the volume fraction of polyethylene glycol 400 co-solvent increases. The molecular structures of the four synthetic steroids investigated were shown earlier in Fig. 1.

Eq. (14) was also followed in binary systems containing either ethanol, propylene glycol, solketal (2,2-dimethyl-1,3-dioxolane-4-methanol), or dimethylacetamide. For example, the solubilization of canrenone by ethanol, propylene glycol, and PEG 400 is illustrated in Fig. 3. A common ordinate intercept, which was equivalent to the actual aqueous solubility (C_w) of canrenone (8.1×10^{-5}M) measured independently, was obtained. The relative efficiency on the solubilization of canrenone by these five co-solvents is tabulated in Table I in order of solubilizing efficiency. Ethanol is the most effective solubilizer and polyethylene glycol 400 is least effective.

The validity of Eq. (13) in a ternary system containing a fixed (f_A) volume fraction of co-solvent A and a varying fraction (f_X) of co-solvent X is demonstrated by the data in Fig. 4. In this experiment, the incorporation of a fixed concentration (19 or 28.5% v/v) of ethanol

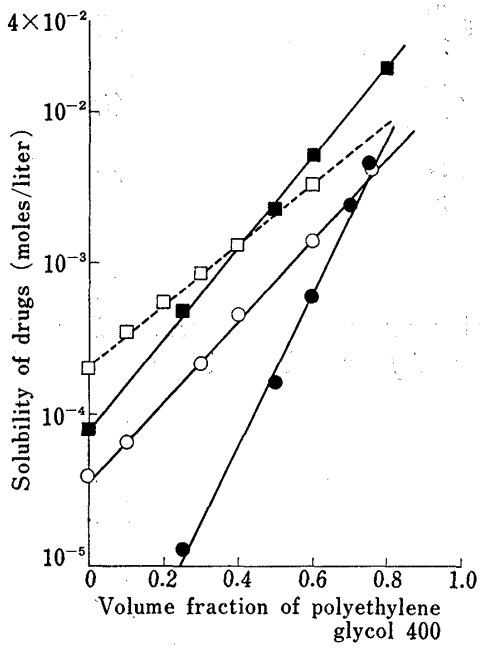

Fig. 2. Solubilization of Some Synthetic Steroids by the Addition of Polyethylene Glycol

keys: ● SC-11800, ○ SC-4640, ■ SC-9376, and □ SC-25152

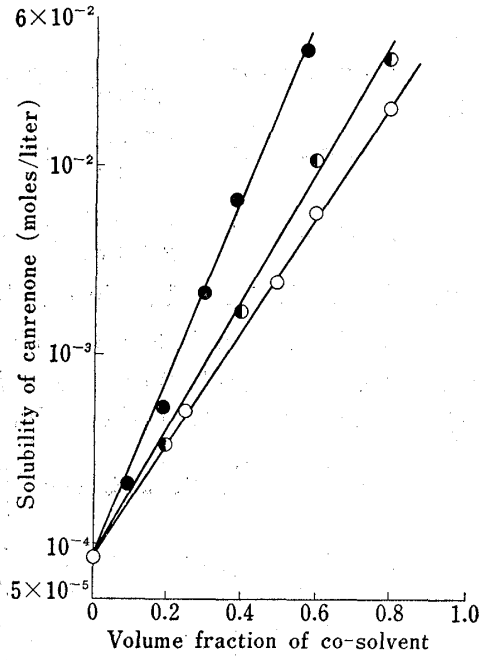

Fig. 3. Semilogarithmic Relationship between the Concentration of Canrenone (moles/liter) solubilized and the Volume Fraction of a Single co-Solvent

A common intercept at 8.1×10^{-5}M was observed.
keys: ○ ethanol, ◑ propylene glycol, and ● polyethylene glycol 400

Table I. The Solubilization of Canrenone by the Binary Systems Containing a Single co-Solvent and Water

Solubilizers	ε_X[a)]
Ethanol	4.75
Solketal	3.97
Propylene glycol	3.42
Dimethylacetamide	3.21
Polyethylene glycol 400	2.93

a) ε_X is the slope of the log C_X *vs.* f_X profiles as defined in Eq. (14).

substantially enhanced the magnitude of the intercept (from log C_w to log $C_w+\varepsilon_A f_A$) (compare Eqs. 14 with 13); but, the linear relationship of log $C_{A,X}$ to f_X was still followed and the magnitude of the slope (ε_X) stayed about the same (ε_X=3.34 to 3.43).

When a fixed concentration of a third co-solvent, *e.g.*, solketal (20% v/v) or dimethylacetamide (20% v/v) was incorporated into mixtures of ethanol–propylene glycol–water, the solubility of canrenone was enhanced. The linearity of log $C_{A,B,X}$ to the volume fraction of propylene glycol (as expected from Eq. (9)) was still observed. Following the addition of 20% v/v of either dimethylacetamide or solketal (Fig 5) the intercept (at zero concentration of propylene glycol) was significantly increased from log $C_w+\varepsilon_A f_A$ (Eq. 13) to log $C_w+\varepsilon_A f_A+\varepsilon_B f_B$ (Eq. 9). The effect of addition of a third solubilizer on the magnitude of both the intercept (log $C_w+\varepsilon_A f_A+\varepsilon_B f_B$) and the slope ($\varepsilon_X$) of the log $C_{A,B,X}$ *vs.* f_w profiles are found in Table II. Along with the increase in the intercept, the slopes were slightly minimized due to the addition of a third co-solvent. This may be due to the change in the entropy and activity coefficient of the resultant solution. The predictive value of Eq. (9) is demonstrated in Table III.

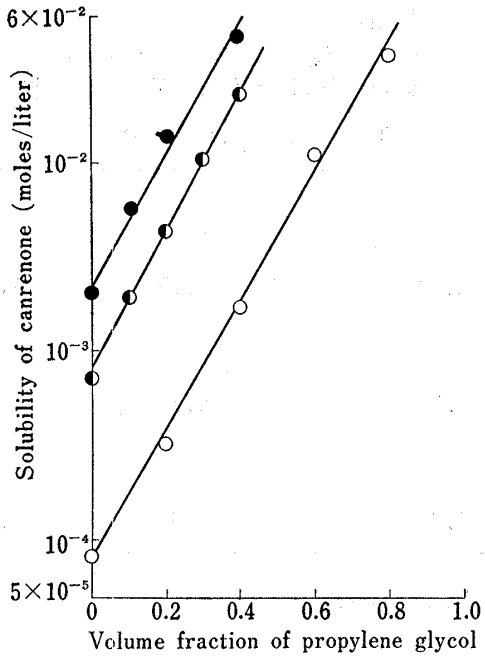

Fig. 4. Semilogarithmic Relationship between the Concentration (moles/liter) of Canrenone solubilized and the Volume Fraction of Propylene Glycol in a Two co-Solvent Aqueous System

keys: ○ propylene glycol alone, ◐ plus 19% v/v of ethanol, and ● plus 28.5% v/v of ethanol

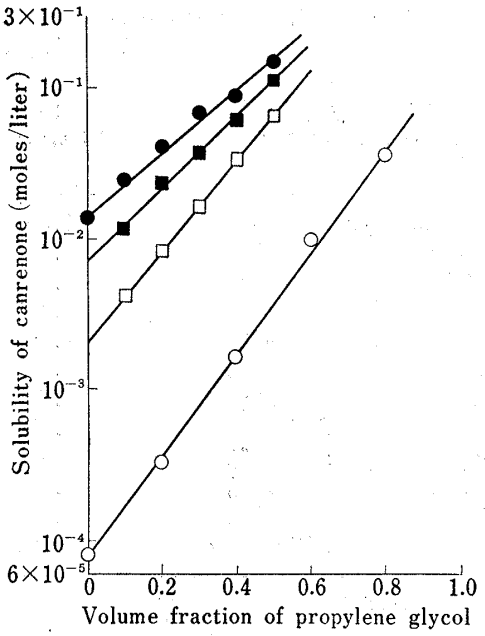

Fig. 5. Semilogarithmic Relationship between the Concentration of Canrenone (moles/liter) solubilized and the Volume Fraction of Propylene Glycol in a Three co-Solvent Aqueous System

keys: ○ propylene glycol alone, □ plus 9.5% ethanol and 20% dimethylacetamide, ■ plus 19% ethanol and 20% dimethylacetamide, and ● plus 19% ethanol and 20% solketal

TABLE II. Effect of the Addition of Third co-Solvent on the Intercept and Slope Values of log $C_{A,B,X}$ *vs.* f_X Profiles (Eq. 9)

co-Solvent combinations			Intercept	Slope
# 1	# 2	# 3	($M \times 10^3$)	
Propylene glycol	—	—	0.081	3.42
Propylene glycol	19.0% ethanol	—	0.80	3.43
Propylene glycol	9.5% ethanol	20% DMA	2.06	3.00
Propylene glycol	19.0% ethanol	20% DMA	7.00	2.39
Propylene glycol	19.0% ethanol	20% solketal	13.80	2.08

The product of the slope (ε) (obtained from the solubilization of canrenone with individual co-solvents) and the volume fraction (f's) used was employed to estimate the expected canrenone solubility in multi-co-solvent systems. The agreement of the observed solubility with that calculated is good. The small deviation of the observed solubility from the estimated value (low ratio, *ca.* 0.76) may be due to the slight decline in slope (Table II) observed after the incorporation of a third co-solvent.

The use of multiple co-solvent combinations to enhance steroid solubility is an improvement over solubilization with a high volume fraction of a single co-solvent. For example, 55% ethanol, or 77% propylene glycol, or 87% polyethylene glycol 400 was required in order to effectively solubilize 3.25×10^{-2}M of canrenone in aqueous solution. The use of high co-solvent concentrations may unfavorably affect the desired viscosity, and the esthetic acceptability of the resultant formulations. On the other hand, this drug concentration (3.25×10^{-2}M) was achieved with a multiple co-solvent system containing either 9.5% ethanol–20% dimethylacetamide–40% propylene glycol or 19% ethanol–20% solketal–18% propylene glycol. In

Table III. Agreement between Calculated and Observed Canrenone Solubility in Multiple co-Solvent Systems

Multiple co-Solvent systems[a]		log $C_{A,B,X}$[b]	Canrenone solubility ($M \times 10^2$)		Ratio[c]
			Calculated[d]	Observed	
Propylene glycol	40%	1.368			
Ethanol	9.5%	0.451			
DMA[e]	20%	0.642			
SUM		2.461	2.89	3.25	1.12
Propylene glycol	40%	1.368			
Ethanol	19%	0.903			
DMA[e]	20%	0.642			
SUM		2.913	8.18	6.25	0.76
Propylene glycol	40%	1.368			
Ethanol	19%	0.903			
Solketal	20%	0.794			
SUM		3.065	11.61	9.61	0.83

a) Q.S. of distilled water is added to make 100%
b) calculated from Table I by multiplying the slope (ε) with volume fraction (f) for each co-solvent used
c) ratio of observed solubility over calculated value
d) antilogarithmic of log $C_{A,B,X}$
e) dimethylacetamide

practice, any number of combinations may be blended depending on specific formulation requirements and the physico-chemical properties of the drug. Finally, the use of a multiple co-solvent system may prevent the occurence of undesirable toxicity which may result from the use of a high volume fraction of a single co-solvent.

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