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Solubilization of poorly soluble compounds using 2-pyrrolidone

Parijat Jain *, Samuel H. Yalkowsky

Department of Pharmacy Practice and Science, College of Pharmacy, The University of Arizona, 1703 E. Mabel St., Tucson AZ 85721, USA

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Abstract

The solubilization of nine poorly soluble compounds in aqueous solution by 2-pyrrolidone has been studied. Solubility enhancement as high as 500-fold is achieved using 20% 2-pyrrolidone. A comparison shows that 2-pyrrolidone is a better solubilizer than glycerin, propylene glycol, polyethylene glycol 400 or ethanol. The observed solubilization curves are deconvoluted into components representing complexation and cosolvency. A clear linear relationship exists between the cosolvency solubilization power (σ) of 2-pyrrolidone and the partition coefficient ($\log K_{ow}$) of the drug ($R^2 = 0.96$) extending over three orders of magnitude. The stability constants for the formation of 1:1 complex ($K_{1:1}$) involving 2-pyrrolidone and the drugs have been calculated. A weaker correlation ($R^2 = 0.74$) is observed between the complexation constants and the partition coefficients of respective drugs. This study indicates that 2-pyrrolidone, like NMP, can act as a complexant at low concentrations and as a cosolvent at high concentrations and that both these properties are affected by the partition coefficient of the solute.
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Keywords: 2-Pyrrolidone; Solubilization; Cosolvency; Complexation

1. Introduction

Poor aqueous solubility is a common concern in the pharmaceutical sciences, especially in screening studies of new chemical entities and formulation research (Bittner and Mountfield, 2002a,b). Several techniques have been established for enhancing the equilibrium solubility of non-polar drugs in aqueous vehicles (Myrdal and Yalkowsky, 2002). Cosolvency or solvent blending and complexation are two frequently used methods for the stated purpose.

1.1. Cosolvency

Cosolvency utilizes a water-miscible liquid known as a 'cosolvent' to disrupt the self-association of water. This leads to a reduction of its ability to squeeze out non-polar hydrophobic compounds, and consequently to the enhancement of the solubility of non-polar solutes.

Although several models have been proposed for the prediction of cosolvent solubilization of non-polar drugs (Yalkowsky and Roseman, 1981; Machatha and Yalkowsky, 2005), the log-linear model, still remains to be the most useful, simple and accurate (Yalkowsky and Rubino, 1985, 1987; Li and Yalkowsky, 1994). Furthermore, its application requires little or no experimental data. The basic assumptions of the log-linear model are: the cosolvent/water mixture is ideal; the logarithm of the molar solubility of a solute in a cosolvent/water mixture is a linear combination of the logarithms of its molar solubilities in the pure component solvents; and the solute is not altered by changes in the solvent. It describes an exponential increase in non-polar drug solubility with a linear increase in cosolvent concentration, as described by:

$$S_{mix} = S_w 10^{\sigma f} \quad (1)$$

or

$$\log S_{mix} = \log S_w + \sigma f \quad (2)$$

where S_{mix} and S_w are the total solute solubilities in the cosolvent/water mixture and in water, respectively; σ the cosolvent solubilization power for the particular cosolvent-solute system, and f is the volume fraction of the cosolvent in the aqueous mixture.

Also, the linear relationship of σ with the octanol-water partition coefficient (Valvani et al., 1981) is given by the following

* Corresponding author. Tel.: +1 520 626 4309; fax: +1 520 626 4063.
E-mail address: jainp@pharmacy.arizona.edu (P. Jain).

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equation:

$$\sigma = s \log K_{ow} + t \quad (3)$$

where $\log K_{ow}$ is the octanol-water partition coefficient of the solute of interest. The s and t values are constant and unique for each individual cosolvent (Millard et al., 2002).

1.2. Complexation

Complexation, on the other hand, is the non-covalent stoichiometric association of two or more molecules into a distinct well-defined structural entity. A complex formed from n molecules of solute D and m molecules of complexing agent (or ligand) L is designated as D_nL_m. The equilibrium constant for the formation of the complex is

$$K_{m:n} = \frac{[D_nL_m]}{[D]_n[L]_m} \quad (4)$$

where $[D_nL_m]$ and $[D]$ are the concentrations of complex and free solute, respectively, and where $[L]$ is the equilibrium concentration of free or uncomplexed ligand. For a 1:1 complex the stability constant for complexation is given as

$$K_{1:1} = \frac{[DL]}{[D][L]} \quad (5)$$

The total concentration of ligand added to the solution is given by

$$[L_t] = [L] + [DL] \quad (6)$$

A general equation for solubilization by a complexing ligand may be given by

$$S_{mix} = S_w + \tau[L_t] \quad (7)$$

where S_w is the aqueous solubility of the pure solute and τ is the slope of the plot of S_{mix} versus the total ligand concentration $[L_t]$. Eq. (7) describes the total solubility of a solute and its complex as a linear function of the concentration of complexing agent. Mathematically, τ could be calculated using the following equation

$$\tau = \frac{K_{1:1}S_w}{1 + K_{1:1}S_w} \quad (8)$$

Note that if $K_{1:1}S_w$ is large, the value of τ approaches unity.

Eq. (8) can be rearranged to obtain the value of the 1:1 complexation constant as,

$$K_{1:1} = \frac{\tau}{(1-\tau)S_w} \quad (9)$$

1.3. Cosolvency and complexation

Sanghvi (2006) has proposed a new model wherein a solubilizer could have both cosolvent and complexant properties. Assuming that both, cosolvation and complexation are independent of each other and a 1:1 complex is being formed between the drug and 2-pyrrolidone, the total solubility (S_{mix}) of a solute in the solvent mix could be given by,

$$S_{mix} = S_w + S_{cosolvency} + S_{complexation} \quad (10)$$

where $S_{cosolvency}$ and $S_{complexation}$ are the contribution of the solubilizer to the total solubility by cosolvency and complexation, respectively. S_{mix} in Eq. (1) is the sum of the intrinsic solubility and solubility due to cosolvency, and may be expressed by

$$S_{mix} = S_w + S_{cosolvency} = S_w 10^{\sigma f} \quad (11)$$

or

$$S_{cosolvency} = S_w 10^{\sigma f} - S_w \quad (12)$$

$[L_t]$ in Eq. (7) can be expressed in terms of volume fraction f (assuming that the total volume, pre and post mixing, is constant) by multiplying f by the molarity of 2-pyrrolidone (13.18 moles/l). Thus, Eq. (10) may be written as,

$$S_{mix} = S_w 10^{\sigma f} + \tau(f 13.18) \quad (13)$$

1.4. 2-Pyrrolidone

2-Pyrrolidone (2-P) is an organic, colorless, readily biodegradable, water-miscible liquid with solubilizing properties. It has a partition coefficient ($\log K_{ow}$) of −0.71, a melting point of 25.5 °C and a boiling point of 245 °C. The chemical structure of 2-pyrrolidone is depicted in Fig. 1.

2-Pyrrolidone lacks mutagenic or genotoxic activity. It has a high oral LD_{50} of 5000 mg/(kg-body weight) in rats, a low aquatic hazard, a low developmental toxicity and no reproductive toxicity (EPA website: http://www.epa.gov/oppt/chemrtk/pubs/summaries/2pyrroli/c14223rt.pdf).

Although 2-pyrrolidone has a potentially hydrolysable amide group, amides are considered resistant to hydrolysis in a pH range of 1.0–8.0, and require prolonged heating in strong base or acid to accomplish hydrolysis (Volhardt, 1987). These observations suggest that 2-pyrrolidone could be used safely as a solubilizer or a solvent, environmentally as well as pharmaceutically. As far as we know, 2-pyrrolidone has not yet been used in any of the pharmaceutically marketed preparations as a solubilizer.

The purpose of this study was to understand the solubilization of a set of poorly soluble drugs by 2-pyrrolidone and then to compare it with other traditional and pharmaceutically accepted, cosolvents like ethanol, propylene glycol, polyethylene glycol 400 and glycerin.

2. Materials

2-Pyrrolidone was provided by BASF (West Ledgewood, NJ). Phenobarbitone, griseofulvin, phenytoin, ketoprofen, estrone were purchased from Sigma (St. Louis, MO) and carbendazim from Aldrich (Milwaukee, WI). XK-469 and NSC-639829, a benzoylphenyl urea (BPU) derivative were obtained from National Cancer Institue (Bethesda, MD) and

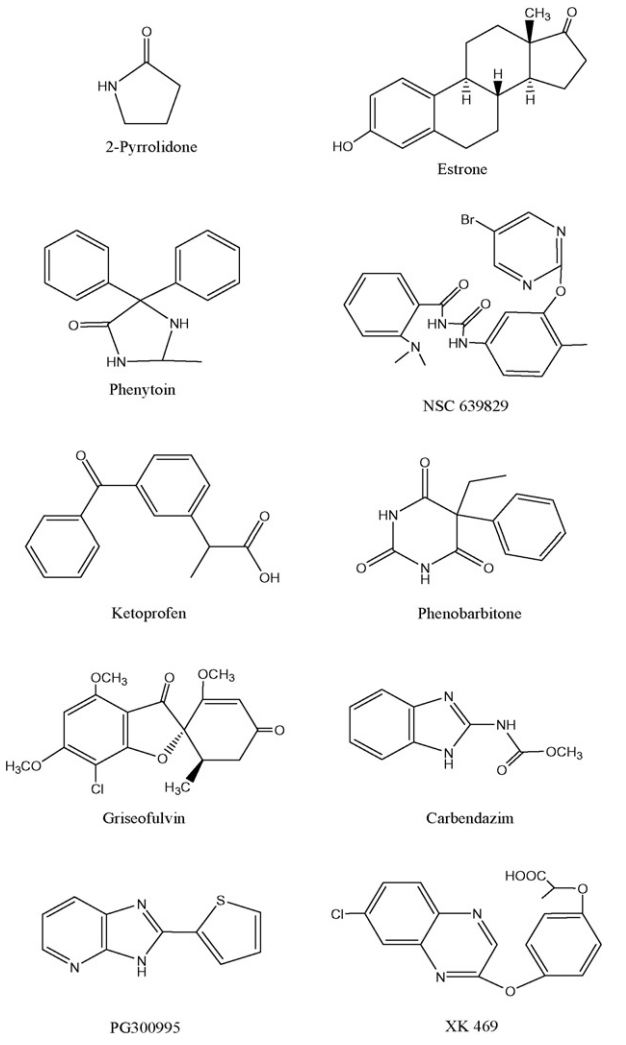

Fig. 1. Chemical structure of the solubilizer and the drugs used in the study.

PG300995 from Proctor & Gamble (Cincinnati, OH). All other chemicals were of reagent or HPLC grade and used without further purification as purchased from Aldrich (Milwaukee, WI) or VWR. Millipore water was used throughout the study.

3. Methods

A set of nine structurally diverse drugs (carbendazim, ketoprofen, phenobarbital, phenytoin, PG300995, XK469, NSC 639829, estrone and griseofulvin) with intrinsic solubilities ranging from 1.48E−07 M to 5.41E−03 M, was chosen. The solubilities of the compounds were determined for 0, 2.5, 5.0, 10.0, 20.0 and 40.0% of 2-pyrrolidone in aqueous buffer solution (for weak electrolytes) or water (for non-electrolytes) using phase solubility analysis (Higuchi and Connors, 1965).

In case of weak electrolytes, the pH of the buffers was maintained at least 2 units from their respective pK_a so as to ensure that greater than 99% unionized form was present. Excess solute was added directly into duplicate 4 ml screw capped vials containing the cosolvent-water/buffer mixture. The vials were then end-over-end rotated at room temperature (25 °C) at a constant speed of 8 rpm on a Labquake rotator (Barnstead International, model no. 415110, Dubuque, IA). Equilibrium was assumed to be reached after subsequent measurements (at least 24 h apart) gave a constant pH. The solution was filtered through 0.45 μm disposable Millipore PTFE membrane filters before analysis by Agilent 1100 Series HPLC (G1315B DAD, Chemstations Software). HPLC assays are presented in Table 1.

Solubilization curves were plotted for each drug using log (S_{mix}/S_w) versus f (Eq. (2)) using Microsoft Excel 2002. The individual solubilization powers (σ values) and the τ values for all the nine drugs were obtained from the deconvolution of their respective solubilization curves using WinCurve Fit V1.1.8 (2002). The log K_{ow} values were obtained from ClogP® for Windows V4.0 and ACDLabs 7.0. The σ values were then plotted against the log K_{ow} values, to obtain the s and t values for 2-pyrrolidone using Eq. (3). The ratio of the solubility at 0.2 cosolvent fraction ($S_{0.2}$) and the intrinsic solubility (S_w) was used as a basis to compare the solubilization efficiency of 2-pyrrolidone for drugs with varying partition coefficients. The complexation constants ($K_{1:1}$) for various drugs with 2-pyrrolidone, were obtained using Eq. (9).

4. Results and discussion

Fig. 2 shows the solubilization curves for XK469 and Griseofulvin. All the drugs follow the same pattern,

Table 1
HPLC assays for the drugs under study

Drug	Column length × i.d.	Mobile phase (proportion)	Inj. vol. (μl)	Detection λ (nm)	Ret. time (min)
Phenobarbital	Lichosorb RP18 150 mm × 4.6 mm	0.01% TFA:ACN (75:25)	20	210	5.7
Carbendazim	Agilent C-18 150 mm × 4.6 mm	DSPB pH 3.2:ACN (40:60)	20	280	4.0
Griseofulvin	Zorbax C-8 150 mm × 4.6 mm	Water:MeOH (46:54)	20	295	8.2
Phenytoin	PinnacleODS 150 mm × 4.6 mm	0.01% AA:MeOH (50:50)	50	258	4.1
PG-300995	PinnacleODS 250 mm × 4.6 mm	0.1% TFA:ACN (82:18)	20	254	4.9
Ketoprofen	Zorbax C-8 150 mm × 4.6 mm	PB pH 5.1:ACN (60:40)	10	260	5.0
Estrone	Zorbax C-8 250 mm × 4.6 mm	Water:ACN (40:60)	20	282	5.5
XK-469	DiscoveryC-18 150 mm × 4.6 mm	0.1% TFA pH 2:ACN (45:55)	10	245	6.5
NSC 639829	Lichosorb RP18 250 mm × 4.6 mm	Water:MeOH (20:80)	20	254	7.7

i.d.: internal diameter; inj. vol.: injection volume; ret. time: retention time; λ: wavelength; AA: acetic acid; ACN: acetonitrile; DSPB: disodium phosphate buffer; MeOH: methanol; PA: phosphoric acid; PB: phosphate buffer; TFA: triflouroacetic acid. Flow rate for all the drugs except phenobarbitone (2.0 ml/min) was 1.0 ml/min.

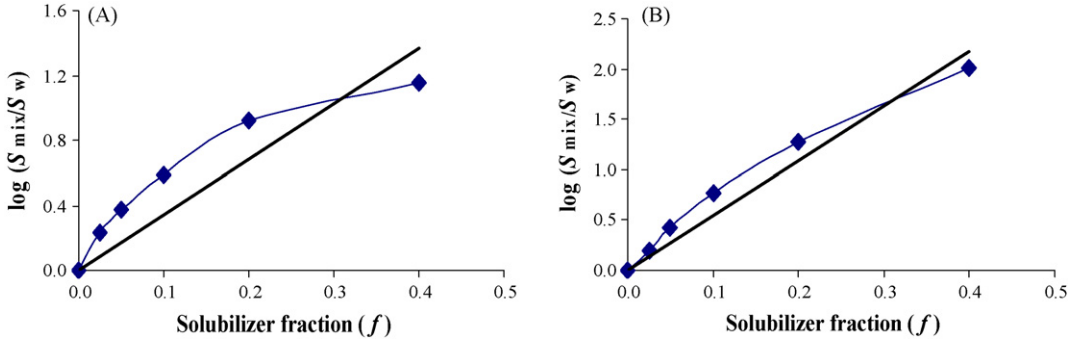

Fig. 2. (A) Solubility curve of XK469 at pH 1.0. (B) Solubility curve of Griseofulvin at neutral pH. S_{mix} is the solubility of the drug in the cosolvent-buffer mixture and S_w is the intrinsic solubility.

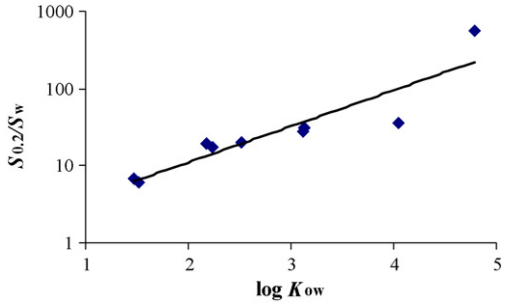

Fig. 3. Semi-log plot of $S_{0.2}/S_w$ vs. log partition coefficient for various drugs using 2-pyrrolidone as solubilizer.

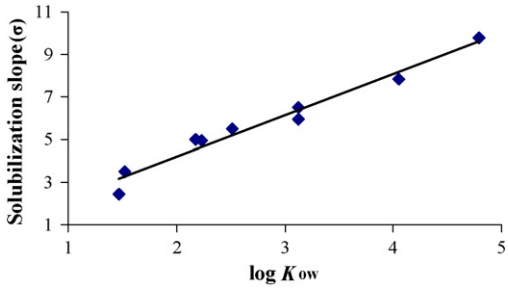

Fig. 4. Cosolvent solubilization power (σ) vs. log partition coefficient for poorly soluble drugs.

with a slight positive deviation at the lower solubilizer concentrations.

The ratios of solubility at 20% solubilizer and intrinsic solubility ($S_{0.2}/S_w$) for various drugs are shown in Table 2. Solubility enhancement as high as 500-fold is achieved. A semi-log plot of $S_{0.2}/S_w$ versus $\log K_{ow}$ (Fig. 3) shows a proportional increase in the solubilization of drugs ($R^2 = 0.84$), supporting the observation that cosolvents increase the solubility of non-polar compounds by reducing the polarity of the aqueous environment.

A drug solubilized only by cosolvation would give a linear relationship for log (S_{mix}/S_w) versus f as per the log-linear model. Hence, a slight curve (with positive deviation) in Fig. 2 indicates the involvement of some other phenomena. Sanghvi (2006) proposed that complexation (in addition to cosolvation) plays a role at lower concentrations of *N*-methyl pyrrolidone (NMP). We propose that this is also the case for 2-pyrrolidone.

To confirm our speculation the solubility curves were deconvoluted using WinCurve Fit V1.1.8, into two components viz. solubilization power (σ) and (τ). The stability constant for the formation of 1:1 complex ($K_{1:1}$) involving 2-pyrrolidone and the respective drugs, was calculated using Eq. (9). The values of σ, τ and $K_{1:1}$ are reported in Table 2.

The relationship between cosolvent solubilization power (σ) for the 2-pyrrolidone and $\log K_{ow}$ depicted in Fig. 4, has an R^2 of 0.96. The linear relationship between σ and $\log K_{ow}$ extending over more than three orders of magnitude indicates that the

Table 2
Values for pK_a, $\log K_{ow}$, $S_{0.2}/S_w$, σ, τ and $K_{1:1}$ for various drugs

Drugs	pK_a		$\log K_{ow}$	$S_{0.2}/S_w$	σ	τ	$K_{1:1}$
	Values	Reference					
Phenobarbital	7.4[a]; 11.2[a]	Kasim et al. (2004)	1.47	6.9	2.42	5.66E−03	1.05
Carbendazim	4.5; 10.8[a]	Ni et al. (2002)	1.52	6.1	3.51	2.45E−05	0.96
Griseofulvin	–	–	2.18	19.1	5.01	4.00E−05	1.77
PG300995	3.7[b]	Ran et al. (2005)	2.23	17.4	4.94	3.43E−04	2.24
Phenytoin	8.3[a]	Kasim et al. (2004)	2.52	20.0	5.48	8.70E−05	1.08
Ketoprofen	4.8[a]	Shenga et al. (2006)	3.12	28.1	6.52	2.26E−04	0.91
Estrone	10.8[a]	Hurwitz and Liu (1977)	3.13	31.2	5.94	7.88E−06	2.68
XK469	2.7[a]	He et al. (2005)	4.05	35.5	7.86	2.05E−06	10.1
NSC 639829	5.0[b]	Jain et al. (2001)	4.79	553.0	9.76	3.71E−06	25.0

[a] Acidic pK_a.
[b] Basic pK_a.

Table 3
Comparison of log K_{ow}, s and t values for various cosolvents along with n (the number of individual compounds in regression), and R^2 (correlation values)

Cosolvents[a]	log K_{ow}	s	t	n	R^2
Glycerin	−1.96	0.35	0.26	22	0.82
Propylene glycol	−0.92	0.77	0.58	84	0.94
Polyethylene glycol 400	−0.88	0.74	1.26	25	0.84
2-Pyrrolidone	−0.71	1.94	0.33	9	0.96
Ethanol	−0.31	0.93	0.40	120	0.96

[a] All values except 2-pyrrolidone were taken from Millard et al. (2002).

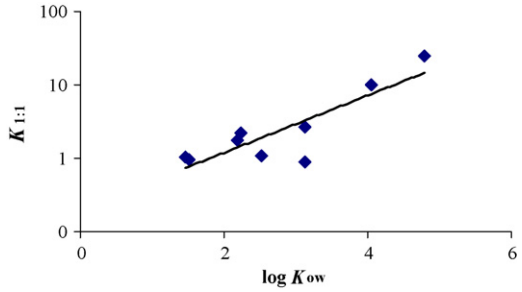

Fig. 5. Complexation constant ($K_{1:1}$) vs. log partition coefficient for poorly soluble drugs.

more hydrophobic the solute, the more it will be solubilized by cosolvent addition. This confirms the predictive ability of the log-linear model (Valvani et al., 1981).

As mentioned earlier, each solvent has constant and unique, s and t values. Millard et al. (2002) reported the s and t values of ethanol, propylene glycol, polyethylene glycol 400 and glycerin. Table 3 shows that the s value of 2-pyrrolidone is at least twice as large as other commonly used cosolvents. This is an interesting observation since the partition coefficient of 2-pyrrolidone is close to that of polyethylene glycol 400. No trend was observed in the t values.

2-Pyrrolidone has a planar hydrophobic region, which leads to a possibility of stacking complexation or overlap of planar non-polar regions. The relationship between stability constant for 1:1 complexation ($K_{1:1}$) and log K_{ow} for the 2-pyrrolidone depicted in Fig. 5, has an R^2 of 0.74. Our results support the proposition that the complex stability is proportional to the hydrophobicity or the partition coefficient (Kenley et al., 1986; Kostenbauder and Higuchi, 1956; Gans and Higuchi, 1957). But hydrophobicity in itself is not a sole indicator of stacking complexation. Stacking is also affected by aromaticity and molecular geometry. This is likely responsible for the greater scatter in Fig. 5 as compared to Fig. 4.

5. Conclusion

2-Pyrrolidone, like NMP, can act as a complexant at low concentrations and as a cosolvent at high concentrations. It is a better cosolvent than the commonly used pharmaceutical cosolvents. Solubilization as high as 500-fold can be achieved using 2-pyrrolidone. Also, both the complexation and cosolvation properties of 2-pyrrolidone are affected by the log K_{ow} of the solute.

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