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Solubilization of monovalent weak electrolytes by micellization or complexation

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Abstract

In order to prepare a liquid formulation for a weak electrolyte, micellization or complexation is often applied with the solution pH controlled to have some of the drug molecules ionized. The efficiency of the micellization is evaluated by either the micellar solubilization capacities, κ_u, and κ_i or the micellar partition coefficients, K_u^m and K_i^m, for the unionized and ionized drug species. Similarly, the efficiency of complexation is evaluated by either the complex solubilization capacities, τ_u and τ_i or the drug–ligand binding constants, $K_u^{1:1}$ and $K_i^{1:1}$. In this study, the experimental values of these descriptors were generated for seven ionizable drugs. The relationships of the logarithms of each descriptor to the logarithm of the octanol-water partition coefficient of the unionized drug ($\log P_u$) and ionized drug species ($\log P_i$) were evaluated. Although κ and τ cannot be predicted, this study shows that K^m and $K^{1:1}$ are dependent on $\log P$ for both the unionized and ionized drug species. Thus, the total drug solubility for a weak electrolyte solubilized by micellization or complexation can be predicted at any pH.

1. Introduction

More than one-third of drugs in the United States Pharmacopoeia are poorly water-soluble or water insoluble and most of them are weak acids or weak bases (Pace et al., 1999; Sweetana and Akers, 1996; Liu and Sadrzadeh, 2000). In order to prepare a liquid dosage formulation for these drugs, a solubilization technique is usually applied. The most commonly used techniques are pH adjustment, cosolvency, micellization, and complexation. For a drug with a p*K*a at the range of 2–8, cosolvency, micellization, or complexation can be applied with the solution pH controlled to have some of the drug molecules ionized. This increases solubilization efficiency and minimizes the need for excipients because the total dissolved drug is contributed from the solubilized unionized and ionized drug species. This paper is aimed at the prediction of the efficiency of micellization and complexation on the solubilization of both the neutral and charged species of weak electrolytes. Thus, the optimum formulation with minimum excipient concentration can be chosen for early drug development to save time and cost before the effort is put into laboratory work.

2. Background

2.1. Micellization

Micellization solubilizes poorly water-soluble compounds by incorporating them into the interior of micelles, which are formed when the surfactant concentration in an aqueous medium is greater than its critical micellar concentration, CMC. A general linear solubilization curve is observed above the CMC. Since most surfactants in the pharmaceutical industry have very small CMC values, the CMC effect is usually not observed in the solubilization curves and the micellar surfactant concentration can be approximated by the total surfactant concentration. The solubilization curve can be described by the following equation:

$$S_{tot} = S_w + \kappa(C_{surf} - CMC) = S_w + \kappa C_{mic} \approx S_w + \kappa C_{surf} \quad (1)$$

where S_{tot} = total drug solubility; κ = surfactant solubilization capacity; C_{surf} = surfactant concentration; CMC = critical micellar concentration; C_{mic} = micellar surfactant concentration.

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The descriptor, κ, is the surfactant solubilization capacity, which is the slope of the solubilization curve and its unit depends on the units of drug solubility and surfactant concentration. This descriptor measures the ability of a surfactant to solubilize a drug. As this technique can be viewed as the partitioning of the drug between the pseudo-micelle phase and the aqueous phase, the micellar partition coefficient, K^{m}, is the other descriptor to evaluate this technique. K^{m} is defined as the ratio of the drug concentration in the micelle phase to its concentration in the aqueous phase:

$$K^{m} = \frac{S_m}{S_w} \tag{2}$$

where S_m = drug solubility in pseudo-micelle phase; S_w = drug solubility in aqueous phase.

This unitless descriptor measures the ability of micelles to extract drug from water. In other words, K^{m} measures the ratio of the affinity of the solute to the micelles to its affinity to water. The use of the micellar partition coefficient descriptor assumes that all of the drug in excess of the aqueous solubility is in the micelle phase:

$$S_m = \kappa C_{surf} \tag{3}$$

Note that in order to obtain a meaningful value of K^{m}, the units of S_m and S_w have to be the same. When the drug solubility is expressed in unit of mg/mL and the surfactant concentration is expressed as percentage, the value of K^{m} can be calculated from the slope of the solubilization curve and the water solubility of the drug by the following equation (He et al., 2006):

$$K^{m} = 100 \times \frac{\kappa}{S_w} \tag{4}$$

The total drug solubility can be expressed by the micellar partition coefficient after inserting the rearranged Eq. (4) into Eq. (1):

$$S_{tot} = S_w + 0.01 K^{m} S_w C_{surf} \tag{5}$$

When a weak monovalent electrolyte is solubilized by surfactant with the solution pH controlled to have some of the molecules ionized, the total dissolved drug is the summation of the dissolved unionized drug and the dissolved ionized drug (Li et al., 1999a,b; Jinno et al., 2000):

$$S_{tot} = S_u + \kappa_u C_{surf} + S_i + \kappa_i C_{surf} \tag{6}$$

$$S_{tot} = S_u + K_u^{m} S_u C_{surf} + S_i + K_i^{m} S_i C_{surf} \tag{7}$$

Micelles in aqueous medium solubilize ionized drug in the same manner as they solubilize unionized drug. The solubilization capacity of the ionized drug species, κ_i, is dependent on S_i, which is dependent on solution pH. On the other hand, the micellar partition coefficient for the ionized species, K_i^{m}, is an intrinsic descriptor for the ionized drug species as it is pH independent. Once K_u^{m} and K_i^{m} are known, drug solubility by any percentage of surfactant at any pH can be estimated with the help of the Henderson–Hasselbach equation to estimate S_i at that specific pH for monovalent acidic and basic drugs:

$$S_i = S_u \times 10^{(pH - pKa)} \tag{8}$$

$$S_i = S_u \times 10^{(pKa - pH)} \tag{9}$$

2.2. Complexation

The most widely applied complexation technique in pharmaceutics is inclusion complexation, which is based on the non-covalent interaction of the non-polar region of drug with the non-polar region of the complexation ligand cavity. This inclusion increases the solution stability as it minimizes contact the drug with water. The solubilization curve of a drug by a complexation agent is usually linear. The slope of the solubilization curve is called the complexation solubilization capacity, denoted as τ. The total drug solubility with the respect of the ligand concentration, C_L, can be expressed as:

$$S_{tot} = S_w + \tau C_L \tag{10}$$

Again, the slope of the solubilization curve, τ, evaluates the ability of a ligand to solubilize a drug. Alternatively, the drug–ligand binding constant, K, can be used to evaluate the affinity between the drug and the ligand because the complex is in equilibrium with both the free ligand and the free drug in the aqueous medium. In the solution of a poorly water-soluble drug, most ligand remains as free ligand. Thus, the free ligand concentration can be approximated as the total ligand concentration (Li et al., 1998). In most cases, only a 1:1 complex is formed, the solubilization curve can be expressed by the following equation:

$$S_{tot} = S_w + K^{1:1} S_w C_{L,free} \approx S_w + K^{1:1} S_w C_L \tag{11}$$

Comparing Eqs. (10) and (11), the value of $K^{1:1}$ can be calculated from the solubilization curve slope divided by the drug water solubility:

$$K^{1:1} = \frac{\tau}{S_w} \tag{12}$$

Note that a unit conversion factor is needed in this equation if the drug concentration and the ligand concentration are not expressed with the same units in the solubilization curve. For convenience, it is traditional to calculate a binding constant with drug and ligand in molar concentrations. Therefore, $K^{1:1}$ usually has unit of M^{-1}.

Like micellization, complexation ligand can solubilize both unionized and ionized drug species when solution pH is controlled so that some of weak electrolyte molecules are charged. The total dissolved drug can be expressed by (Tinwalla et al., 1993; Johnson et al., 1994; Okimoto et al., 1996; Li et al., 1998):

$$S_{tot} = S_u + \tau_u C_L + S_i + \tau_i C_L \tag{13}$$

$$S_{tot} = S_u + K_u^{1:1} S_u C_L + S_i + K_i^{1:1} S_i C_L \tag{14}$$

While the solubilization capacity of the ionized drug species, τ_i, is dependent on solution pH, the binding constant of the ionized drug with the ligand, $K_i^{1:1}$, is independent of pH. A drug solubility can be estimated at any pH after obtaining $K_u^{1:1}$ and $K_i^{1:1}$.

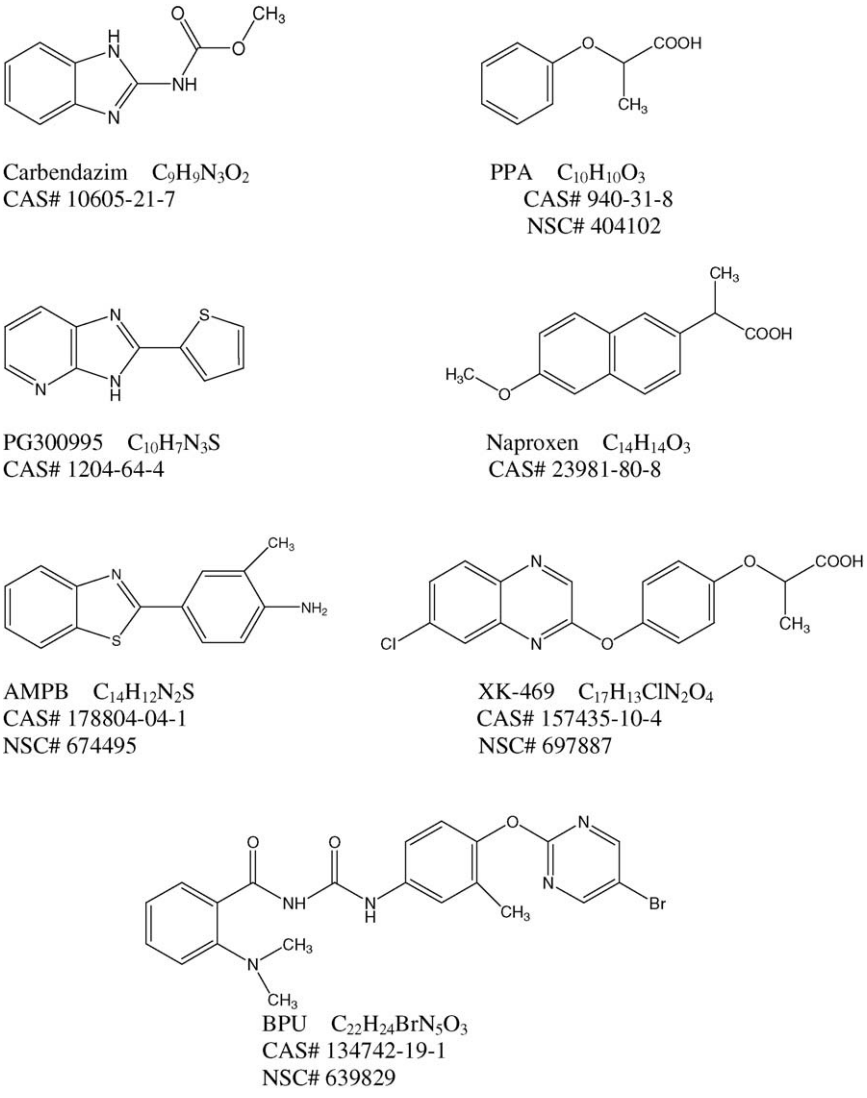

Fig. 1. Structures of these seven drugs.

2.3. Data set

The descriptors for the unionized species and ionized species by micellization or complexation are generated from experimental data for seven ionizable drugs, which have been studied in this laboratory. These compounds are AMPB (4-(2-benzothiazolyl)-2-methyl-benzenamine); BPU (*N*-[[[4-[(5-bromo-2-pyrimidinyl)oxy]-3-methylphenyl]amino]carbonyl]-2-(dimethylamino)-benzamide); carbendazim (2-(carbomethoxyamino)-benzimidazole); naproxen (2-(6-methoxy-2-naphthalenyl)propionic acid); PPA (2-phenoxy-propanoic acid); PG 300995 (2-(2-thienyl)-1H-imidazo[4,5-b]pyridine); XK-469 (2-[4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy]-propanoic acid). The structures for these compounds are shown in Fig. 1.

3. Materials and methods

3.1. Materials

AMPB, XK-469, and BPU were received from the National Cancer Institute (Rockville, MD). Carbendazim and PG 300995 were donated by the Procter and Gamble Company (Cincinnati, OH). PPA, naproxen and Tween 80 (polysorbate 80) were purchased from Sigma, (Milwaukee, WI). HPβCD (hydroxypropyl-β-cyclodextrin, Trappsol®) was purchased from Cyclodextrin Technologies Development Inc., (Gainesville, FL). SBEβCD (sulfobutyl ether-β-cyclodextrin, Captisol®) was a gift from CyDex Inc., (Lenexa, KS). HPβCD has an average molecular weight of 1390 and an average degree of substitution of 4.4. SBEβCD has an average molecular weight of 2160 and an average degree of substitution of 7. All other chemicals were of reagent or HPLC grade and purchased from Aldrich (Milwaukee, WI). All chemicals were used as received without further purification and the water was double-deionized.

3.2. Methods

The solubilities of these seven drugs were measured in controlled pH aqueous solutions, containing various concentrations of Tween 80, HPβCD, or SBEβCD up to 20%. The experimental details are described by El-Sayed et al. (2000), Jain et al. (2001),

Peterson (2001), Ni et al. (2002), Ran et al. (2005), and He et al. (2006). In brief, excess drug was added to the testing solution and the sample vials were rotated to reach the equilibrium solubility, they were then filtered and the drug concentration in filtrate was analyzed by HPLC.

The log P values for the unionized and ionized drug species, log P_u and log P_i, were calculated from the ACD/Labs™ software (Advanced Chemistry Development Inc., Toronto, ON, Canada).

4. Results and discussion

All seven drugs displayed solubilization cures similar to those illustrated in Fig. 2. The κ_u, τ_u, κ_i, and τ_i values for the studied drugs in Tween 80, HPβCD, and SBEβCD were obtained from the solubilization curves using Eqs. (1), (6), (10) and (13). These values are listed in Tables 1a and 1b. The logarithms of these values with the respect to the log P_u and log P_i are plotted and no simple relationship between log P and log κ for Tween 80 (Fig. 3(a)) or between log P and log τ for the cyclodextrins were observed.

On the other hand, Alvarez-Núñez and Yalkowsky (2000) reported a linear correlation of log K^m with log P for non-electrolytes. The regression of their dataset (symbol of ×) in Fig. 3(b) is expressed by:

$$\log K^m = 0.9201 \log P + 0.0690 \quad (15)$$

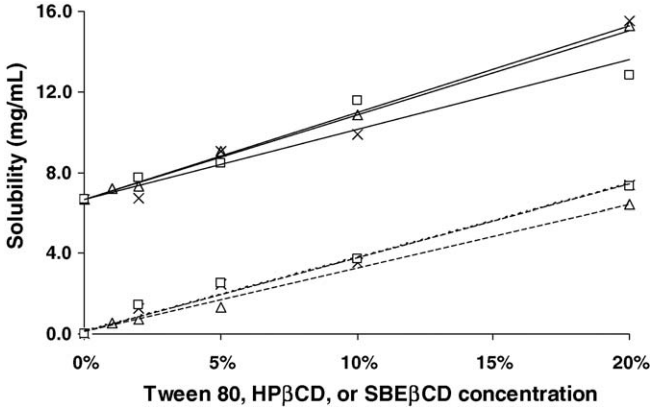

Fig. 2. Solubilization curves of naproxen by Tween 80 (△), HPbCD (×), or SBEbCD (□). Unionized condition (pH 2.0, - - -), ionized condition (pH 7.0, —).

Table 1a
Solubilization capacity (κ_u) for Tween 80 and (τ_u) for HPβCD, and SBEβCD

Compound	log P_u	Tween 80, κ_u (experimental)	HPβCD, τ_u (experimental)	SBEβCD, τ_u (experimental)
Carbendazim	1.5	0.005	0.002	0.002
PPA	1.7	0.99	0.87	0.62
PG300995	2.2	0.034	0.019	0.033
Naproxen	3.0	0.332	0.368	0.385
AMPB	4.0	0.041	0.013	0.019
XK-469	4.1	0.026	0.007	0.007
BPU	4.3	0.091	0.034	0.038

Table 1b
Solubilization capacity (κ_i) for Tween 80 and (τ_i) for HPβCD and SBEβCD

Compound	log P_i	Tween 80, κ_i (experimental)	HPβCD, τ_i (experimental)	SBEβCD, τ_i (experimental)
PPA	−2.1	−0.050	−0.140	−0.710
Carbendazim	−1.0	0.000	0.035	0.088
Naproxen	−0.8	0.102	0.103	−0.070
PG300995	−0.3	0.033	0.144	0.411
XK-469	0.3	0.033	0.111	0.091
BPU	0.8	0.045	0.599	1.752
AMPB	1.5	0.072	0.233	0.422

From the Tween 80 solubilization curves, the values of micellar partition coefficient were obtained for the unionized and ionized drug species using Eqs. (5) and (7). These values are listed in Tables 2a and 2b. The logarithms of K_u^m and K_i^m with the respect to log P_u and log P_i are plotted in Fig. 3(b) as the solid squares and solid triangles, respectively, along with the regression of Eq. (15) as the solid line. These symbols are in good agreement with the correlation of log K^m with log P for non-electrolytes. The K_u^m and K_i^m values, estimated values by Eq. (15), are also listed in Tables 2a and 2b. Evidently, the values of both K_u^m and K_i^m can be reasonably estimated from log P_u and log P_i based on the correlation of log K with log P. However, the deviation of

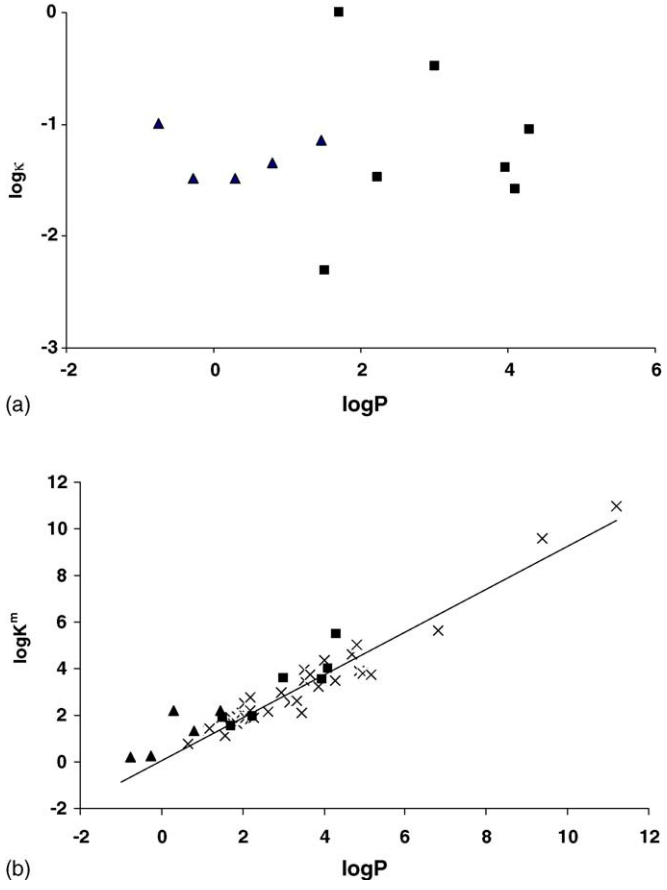

Fig. 3. Solubilization descriptors of Tween 80 vs. drug log P: (a) log κ; (b) log K^m. Unionized drug species in this study (■), ionized drug species in this study (▲), data reported by Alvarez-Nunez and Yalkowsky (×).

Table 2a
Micellar partition coefficient (K_u^m) of Tween 80, and binding constant ($K_u^{1:1}$, M^{-1}) of HPβCD and SBEβCD

Compound	log P_u	Tween 80		HPβCD, $K_u^{1:1}$ (experimental)	SBEβCD, $K_u^{1:1}$ (experimental)
		K_u^m (experimental)	K_u^m (calculated)		
Carbendazim	1.5	81	29	47	74
PPA	1.7	35	2075	157	245
PG300995	2.2	93	132	73	205
Naproxen	3.0	3682	675	7282	14402
AMPB	4.0	3393	5181	1572	3469
XK-469	4.1	9489	10381	1886	5543
BPU	4.3	301945	49997	159374	278474

Table 2b
Micellar partition coefficient (K_i^m) of Tween 80, and binding constant ($K_i^{1:1}$, M^{-1}) of HPβCD and SBEβCD

Compound	log P_i	Tween 80		HPβCD, $K_i^{1:1}$ (experimental)	SBEβCD, $K_i^{1:1}$ (experimental)
		K_i^m (experimental)	K_i^m (calculated)		
PPA	−2.1	−0.1	0.01	−1	−2
Carbendazim	−1.0	−0.01	0.1	9	14
Naproxen	−0.8	2	0.2	−2	−2
PG300995	−0.3	2	1	33	52
XK-469	0.3	169	2	660	1021
BPU	0.8	21	6	1160	1802
AMPB	1.5	164	26	1374	2135

K_u^m or K_i^m from the correlation can occur because micelles are structured entities and the structure of the compound can affect its partitioning.

Using a complexation ligand, HPβCD or SBEβCD, the drug–ligand complex binding constants of the unionized and ionized drugs, $K_u^{1:1}$ and $K_i^{1:1}$, were obtained from the solubilization curves using Eqs. (11) and (14). These values are listed in Tables 2a and 2b. The log $K_u^{1:1}$ with respect to log P_u and log $K_i^{1:1}$ with respect to log P_i are plotted in Figs. 4 and 5. The following regressions were obtained as the solid lines in the graphs:

$$\text{HP}\beta\text{CD}: \quad \log K^{1:1} = 0.4977 \log P + 1.8148 \tag{16}$$

$$\text{SBE}\beta\text{CD}: \quad \log K^{1:1} = 0.5365 \log P + 2.0047 \tag{17}$$

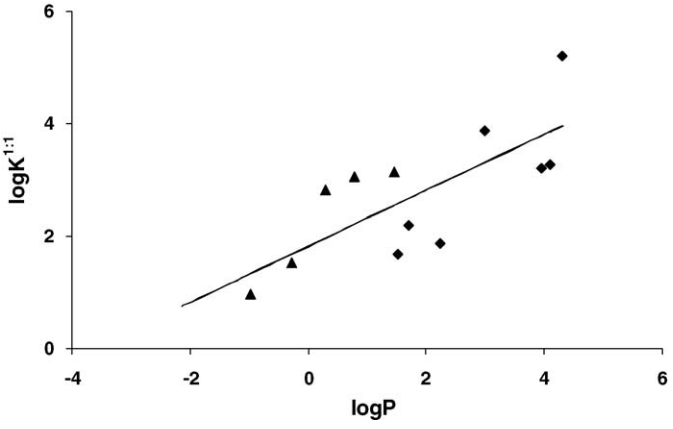

Fig. 4. log $K^{1:1}$ of HPβCD vs. drug log P: unionized drug species in this study (■), ionized drug species in this study (▲).

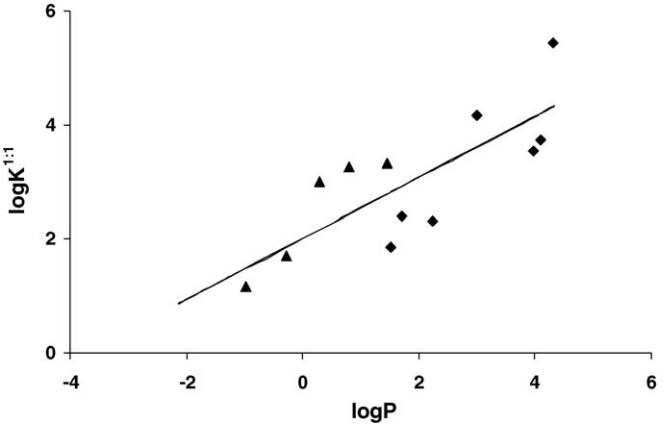

Fig. 5. log $K^{1:1}$ of SBEβCD vs. drug log P: unionized drug species in this study (■), ionized drug species in this study (▲).

These correlations were observed because the polarity of the solute is the driving force for the complex. However, the correlations of log $K^{1:1}$ with log P for these two complexation agents in Figs. 4 and 5 are weaker than the correlation of log K^m with log P for Tween 80 in Fig. 3(b). This is likely due to the fact that each drug fit differently into the rigid 6–6.5 Å cyclodextrin cavity.

5. Conclusions

Micellization or complexation with pH adjustment can be very efficient to solubilize a weak electrolyte as shown in the solubilization curves of Fig. 2. Despite the fact that the solubilization capacities of micellization and complexation, κ and τ, cannot be predicted from structure because they are only

partially dependent upon drug polarity, the micellar partition coefficient of micellization, K^{m}, and the binding constants of complexation, $K^{1:1}$, can be predicted. This study shows that not only K_u^m and $K_u^{1:1}$ are dependent on polarity of the uncharged drug species, $\log P_u$, the descriptors for the charged counterparts, $K_i^{1:1}$ and $K_i^{1:1}$, are also dependent on the polarity of the ionized species, $\log P_i$ (Figs. 3(b), 4, and 5). Thus, the total drug solubility for a weak electrolyte solubilized by micellization or complexation at any pH can be predicted. Therefore, an efficient formulation can be selected before the effort is put into lab to save time and cost.

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