Independence of the Product of Solubility and Distribution Coefficient of pH

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Purpose. The relationship between the pH, solubility, and partition coefficient was investigated to show that the product of intrinsic values of solubility and partition coefficient is equal to the product of total values of solubility and distribution coefficient at different pH.
Methods. The pH distribution profiles were obtained from the literature and the pH solubility profiles were obtained from the literature or calculated from their intrinsic solubility and pK_a.
Results. The pH solubility and pH distribution coefficient profiles of 25 compounds were investigated to show that the product of intrinsic solubility (S_w) and intrinsic octanol-water partition coefficient (K_{ow}) is equal to the product of total solubility of a partially ionized solute (S_T) and its octanol-buffer distribution coefficient (K_D) at any pH where ion pair formation and salt precipitation are not present.
Conclusions. The fact that $S_w \cdot K_{ow}$ can be used instead of $S_T \cdot K_D$ to model the absorption of partially ionized drugs in the gastrointestinal tract has important biopharmaceutical implications.

KEY WORDS: pH; solubility; octanol-water partition coefficient; octanol-buffer distribution coefficient; absorption potential.

INTRODUCTION

The product of the total aqueous solubility at pH 6.8, $S_T^{6.8}$, and its octanol-buffer distribution coefficient at pH 6.8, $K_D^{6.8}$, has been proposed to be related to the rate of absorption of a drug from the gastrointestinal tract (1,2); in fact, this product divided by the dose has been termed the absorption parameter (1,2). Dressman *et al.* (1) introduced the fraction of drug nonionized (F_{non}) at pH 6.5 in the absorption potential (AP) term for predicting the fraction absorbed of a passive transported drug with the following equation:

$$\mathrm{AP} = \log\left[\frac{S_w K_{ow} F_{non}}{\frac{D}{V}}\right] \tag{1}$$

where D is the dose administered and V is the volume of the gut lumen fluids.

Balon *et al.* (2) modified the numerator by using the product of $S_T^{6.8}$ and $K_D^{6.8}$ instead of the product of $S_w \cdot K_{ow}$ and F_{non} for predicting the absorption potential of a passively transported, shown as follows:

$$\mathrm{AP} = \log\left[\frac{S_T^{6.8} K_D^{6.8}}{\frac{D}{V}}\right] \tag{2}$$

Because D and V are not properties of the drug, the product of $S_T \cdot K_D$ at pH 6.8 is a useful measure of the potential of a drug to be efficiently absorbed upon oral administration.

Unfortunately, it is frequently difficult to obtain reliable solubilities and partition coefficients at a particular pH. Also the pH of the gastrointestinal tract is not constant but increases as it is traversed (1). Furthermore, dissolution is dependent upon the microscopic pH at the particle surface rather than the pH of the bulk phase, and the distribution at the gut wall is more relevant than that in the bulk of the lumen.

It is well known that both the total solubility and octanol-buffer partition coefficient are dependent on pH. However, it is less well known that the product of S_T and K_D at any pH is equal to the product of the intrinsic properties, S_w and K_{ow}, i.e.,

$$S_w \cdot K_{ow} = S_T \cdot K_D \tag{3}$$

where S_w is the intrinsic water solubility and K_{ow} is the intrinsic octanol-water partition coefficient. Although this result may be expected under certain conditions, its wide pH range of applicability has not been demonstrated.

In this article, experimental and calculated pH solubility and experimental pH distribution coefficient profiles obtained from the literature for 25 compounds comprising acids, bases, and ampholytes are used to show that the product of S_w and K_{ow} equals the product of S_T and K_D over a wide pH range, provided that the counterion concentration is low enough so that both salt precipitation and ion pair formation are not significant. Thus, the solubility and partition coefficient of the unionized species ($S_w \cdot K_{ow}$) can be used instead of this value at a specified pH ($S_T \cdot K_D$) to model the absorption of weak electrolyte drugs in gastrointestinal tract (3). Sanghvi *et al.* (3) showed that modified absorption potential (MAP), which is defined by the following

$$\mathrm{MAP} = \log\left[\frac{S_w K_{ow}}{\frac{D}{V}}\right], \tag{4}$$

is a better predictor of the passive absorption of drugs than either of the two APs described above.

THEORETICAL

Alteration of the solution pH is the most commonly used method to solubilize weak electrolytes in aqueous media. Because the solubilization curves of weak bases are mirror images of those for weak acids, only the latter will be discussed in detail.

According to the Henderson-Hasselbalch equation, the total aqueous solubility, S_T, of a weakly acidic solute is dependent upon the solution pH, shown as follows:

$$S_T = S_w\,(1 + 10^{(\mathrm{pH}-\mathrm{pK_a})}) \tag{5}$$

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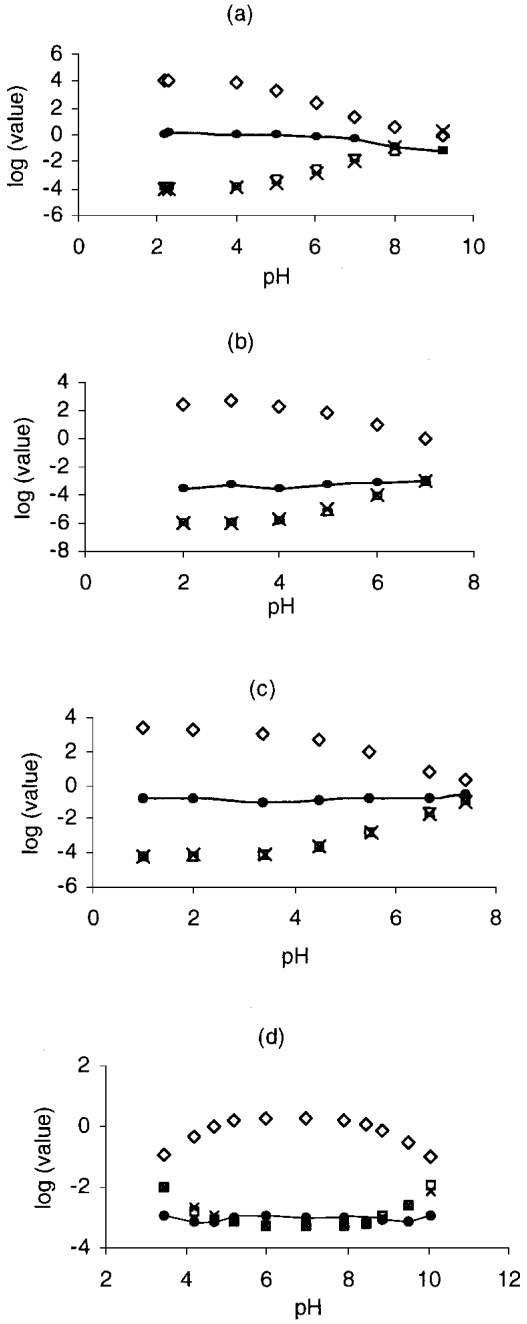

Fig. 1. Plot of log S_T, log K_D, and log (S_TK_D) vs. pH for (a) ibuprofen; (b) meloxicam; (c) naproxen; and (d) pelrinone hydrochloride.

Alteration of the solution pH also changes the distribution coefficient, K_D, for the weak electrolyte. Although the partition coefficient and the distribution coefficient are defined in terms of the concentration ratio at infinite dilution, Yalkowsky (4) has shown that they can be reasonably well approximated by the solubility ratio. Thus, the partition coefficient of a weak acid in the octanol-water system can be approximated by the following

$$K_{OW} = \frac{S_w^{oct}}{S_w} \tag{6}$$

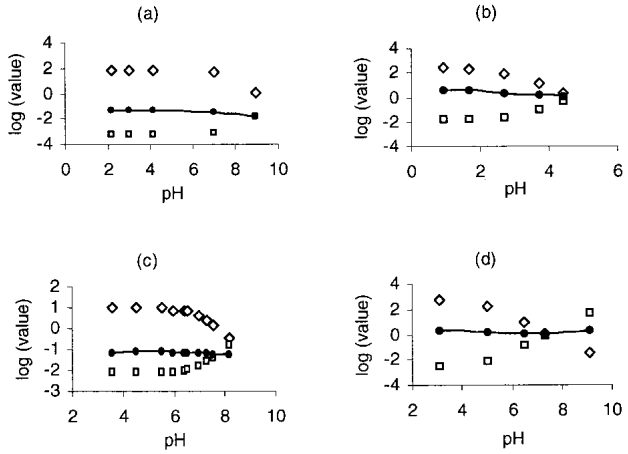

Fig. 2. Plot of log S_T, log K_D, and log (S_TK_D) vs. pH for four acids: (a) methylphenobarbital; (b) salicylic acid; (c) oxolinic acid; and (d) 5-phenylvaleric acid.

where S_w^{oct} is the solubility of the unionized weak acid in octanol. Similarly, the distribution coefficient of weak acid in the octanol-buffer system can be estimated by the following:

$$K_D = \frac{S_T^{oct}}{S_T} \tag{7}$$

where S_T^{oct} is the total solubility in octanol. If we assume the solubility of the ionized form of the drug in octanol is close to zero, then the following is true:

$$S_T^{oct} \approx S_w^{oct}. \tag{8}$$

Combining Eqs. (6) through (8) gives Eq. (3), QED. This indicates that the product of the total solubility, S_T, and the distribution coefficient, K_D, is constant and equal to the product of the intrinsic solubility, S_w, and the intrinsic partition coefficient, K_{ow}. In other words, pH does not affect $S_T \cdot K_D$ because for every increase in total solubility, there is a proportionate decrease in the distribution coefficient.

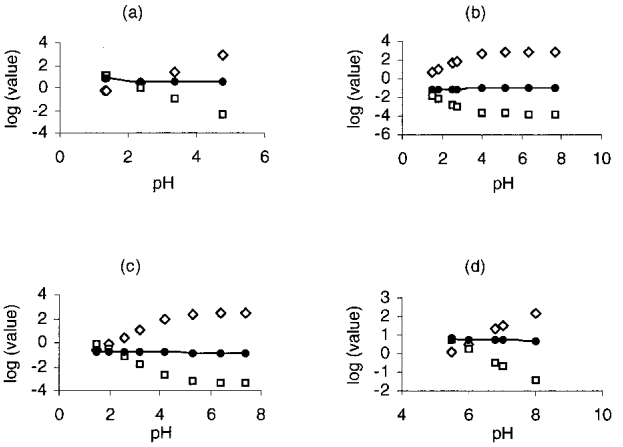

Fig. 3. Plot of log S_T, log K_D, and log (S_TK_D) vs. pH for four bases: (a) medazepam; (b) diazepam; (c) chlordiazepoxide; and (d) lignocaine.

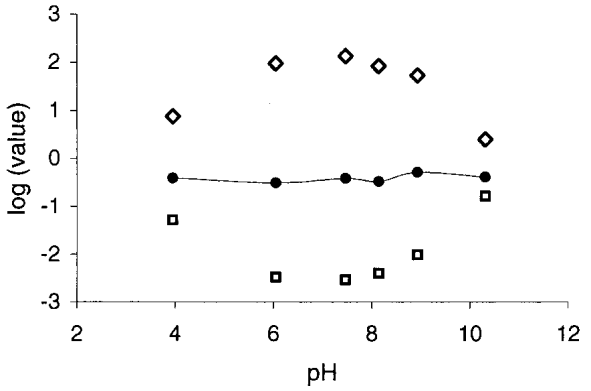

Fig. 4. Plot of log S_T, log K_D, and log ($S_T K_D$) vs. pH for an ampholyte, 5-hydroxyquinoline.

COLLECTION OF DATA

Experimental pH distribution coefficient data were obtained from the literature for 25 compounds. Experimental pH solubility data were obtained from the literature for four compounds. For compounds having only reported pH distribution coefficient profiles, the pH solubility profiles were calculated by the Henderson and Hasselbach equation from their experimental intrinsic solubility and pK_a value. The experimental intrinsic solubility was obtained from the AQUASOL dATAbASE (5), and the pK_a values were obtained from *Handbook of Physical Properties of Organic Chemicals* (6), *Beilstein Commander* (7), or the *Merck Index* (8).

RESULTS AND DISCUSSION

Figure 1 shows the dependence of log S_T-exp. (squares), log K_D (diamonds), and log ($S_T \cdot K_D$) (dots) upon pH for ibuprofen, meloxicam, naproxen, and pelrinone hydrochloride using experimental pH solubility and pH distribution coefficient profiles. The pH solubility profile calculated from the experimental intrinsic solubility and the experimental pK_a is also shown in the Fig. 1 as log S_T-cal. (X). The agreement between the calculated and experimental solubility is obvious.

As can be seen from the flat line in the Fig. 1, pH has no significant effect on the product of S_T and K_D, as expected from Eq. (3). The effect of pH on the log S_T, log K_D, and log ($S_T \cdot K_D$) for four acids (methylphenobarbital, salicylic acid, oxolinic acid, and 5-phenylvaleric acid) and four bases (medazepam, diazepam, chlordiazepoxide, and lignocain) can be seen from Figs. 2 and 3, respectively. In addition, Fig. 4 shows the independence of log ($S_T \cdot K_D$) of pH holds for the ampholyte, 5-hydroxyquinoline. Figures 2 through 4 are plotted using experimental pH distribution coefficient profiles and calculated pH solubility profiles.

The constancy of the dots in the figures further confirms that the product of S_T and K_D is equal to the product of S_W and K_{ow} over a wide pH range. It also confirms that Eq. (8) is a reasonable assumption.

Table I lists the relevant physicochemical properties of the 13 compounds described above along with the data for 12 additional compounds. Table II shows the difference between log ($S_w \cdot K_{ow}$) and log ($S_T \cdot K_D$) for all 25 compounds at two different pH values, one above pK_a, the other below pK_a. The absolute average error (AAE) associated with using $S_w \cdot K_{ow}$ instead of $S_T \cdot K_D$ is only 0.116 log units. The small error confirms the applicability of Eq. (3).

In this article, we have not considered either the effect of the solubility product (K_{sp}) or the effect of the ion pair partitioning on pH. Each of these effects can influence the product of S_T and K_D. Interestingly, exceeding the solubility product will cause S_T to be lower than the calculated value and ion

Table I. Physicochemical Properties of 25 Compounds

Name	pK_a	logK_{ow}	logS_w	log($S_w \cdot K_{ow}$)	Ref.
Ibuprofen	4.91	3.97	–3.992	–0.022	9
Meloxicam	4.08	3.01	–5.978	–2.968	10
Naproxen	4.15	3.18	–4.161	–0.981	11,12
Pelrinone hydrochloride	4.71, 8.94	0.29	–3.286	–2.998	13
Methylphenolbarbital	7.65	1.84	–3.215	–1.375	14
Salicylic acid	3.00	2.26	–1.790	0.470	14
Oxolinic acid	6.90	0.68	–2.105	–1.425	15
5-Phenylvaleric acid	4.90	2.94	–2.466	0.474	16
Medazepam	6.20	4.41	–3.755	0.655	14
Diazepam	3.40	2.82	–3.755	–0.935	14
Chlordiazepoxide	4.80	2.44	–3.390	–0.950	14
Lignocaine	8.01	2.44	–1.757	0.683	9
5-Hydroxyquinoline	5.18, 8.60	1.85	–2.542	–0.692	16
Phenylbutazone	4.50	3.16	–3.812	–0.652	14
Phenytoin	8.33	2.47	–3.897	–1.427	14
Acetylsalicylic acid	3.50	1.19	–1.593	–0.403	14
Phenobarbital	7.30	1.47	–2.321	–0.851	14
Mefenamic acid	4.20	5.12	–4.082	1.038	12
Diclofenac	4.15	4.51	–5.128	–0.618	12
Indomethacin	4.50	4.27	–5.582	–1.312	12
Oxyphenbutazone	4.70	2.72	–3.733	–1.013	12
Chloropromazine	9.30	5.41	–5.097	0.313	12
Aminophenazone	5.00	1.00	–0.629	0.371	14
Ketoprofen	4.45	3.12	–3.698	–0.578	12
Pindolol	8.80	1.75	–3.638	–1.888	17

Table II. Comparison of the Product of $S_T \cdot K_D$ and $S_w \cdot K_{ow}$ at Two Different pH Values

Name	pH-pK_a	$\log(S_T \cdot K_D)$	$\log(S_w \cdot K_{ow})$	Difference
Ibuprofen	–2.20	0.069	–0.022	0.091
	1.10	–0.218	–0.022	–0.196
Meloxicam	–1.08	–3.286	–2.968	–0.318
	2.92	–3.051	–2.968	–0.083
Naproxen	–0.75	–1.039	–0.981	–0.058
	2.55	–0.819	–0.981	0.162
Pelrinone hydrochloride	–1.25	–2.941	–2.998	0.057
	1.12	–2.960	–2.998	0.038
Methylphenolbarbital	–4.62	–1.373	–1.375	0.002
	–0.69	–1.465	–1.375	–0.090
Salicylic acid	0.70	0.161	0.470	–0.309
	–1.33	0.531	0.470	0.061
Oxolinic acid	–2.40	–1.113	–1.425	0.312
	1.30	–1.242	–1.425	0.183
5-Phenylvaleric acid	–1.90	0.275	0.474	–0.199
	4.22	0.321	0.474	–0.153
Medazepam	–3.82	0.543	0.655	–0.112
Diazepam	2.90	–0.948	–0.935	–0.013
	–1.57	–1.107	–0.935	–0.172
Chlordiazepoxide	2.59	–0.955	–0.950	–0.005
	–2.23	–0.736	–0.950	0.214
Lignocaine	–2.01	0.763	0.683	0.080
5-Hydroxyquinoline	–1.28	–0.406	–0.692	0.286
	1.71	–0.389	–0.692	0.303
Phenylbutazone	1.14	–0.436	–0.652	0.216
	–1.94	–0.525	–0.652	0.127
Phenytoin	2.19	–1.492	–1.427	–0.065
	–2.11	–1.601	–1.427	–0.174
Acetylsalicylic acid	1.30	–0.181	–0.403	0.222
	–1.36	–0.392	–0.403	0.011
Phenobarbital	1.25	–0.918	–0.851	–0.067
	–2.90	–0.910	–0.851	–0.059
Mefenamic acid	3.20	1.119	1.038	0.081
	–2.20	1.041	1.038	0.003
Diclofenac	3.25	–0.658	–0.618	–0.040
	–1.15	–0.698	–0.618	–0.080
Indomethacin	3.70	–1.372	–1.312	–0.060
	–2.50	–1.310	–1.312	0.002
Oxyphenbutazone	2.70	–0.872	–1.013	0.141
	–2.70	–1.012	–1.013	0.001
Chloropromazine	–2.70	0.394	0.313	0.081
Aminophenazone	–1.87	0.421	0.371	0.050
	1.91	0.328	0.371	–0.043
Ketoprofen	–2.25	–0.575	–0.578	0.003
	2.95	–0.746	–0.578	–0.168
Pindolol	–3.20	–1.788	–1.888	0.100
	1.40	–1.901	–1.888	–0.013
AAE				0.116

pair formation will cause K_D to be higher than the calculated value. Because both of these effects will occur at high counterion concentration, there is a tendency for them to cancel one another to maintain a relatively constant product.

The use of $S_w \cdot K_{ow}$ instead of $S_T \cdot K_D$ provides an additional advantage for the prediction of intestinal absorption. Because the former does not require knowledge of the pK_a of the solute, it is not subject to errors in its measurement or estimation. Furthermore, it eliminates the need to account for the nonconstancy of the pH of either the gastrointestinal tract or the microenvironment of the dissolving drug.

CONCLUSIONS

A total of 25 compounds, which included acids, bases, and ampholytes having pK_a values that range between 3 and 10, were investigated in this work. The product of the intrinsic solubility and the octanol-water partition coefficient, $S_w \cdot K_{ow}$, is equal to the product of the total solubility and the octanol-buffer distribution coefficient, $S_T \cdot K_D$, at any pH where ion pair partitioning and salt precipitation are not significant. This equality described by Eq. (3) enables the more accurate determination of S_T and K_D from the more easily

measured and calculated S_w and K_{ow}. Furthermore, because of the independence of $S_T \cdot K_D$ of pH, it is not necessary to consider either the pK_a of the drug or the pH of the gastrointestinal tract to predict the passive absorption of orally administrated drugs. This supports the use of the MAP of Sanghvi *et al.* (3) over other absorption parameters that use distribution coefficients.

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