

## Estimation of the Aqueous Solubility of Some Acetanilide Derivatives from Octanol-Water Partition Coefficients and Entropies of Fusion

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**SUMMARY.** Some semi empirical equations developed by Yalkowsky *et al.* were used to estimate the aqueous solubility ( $S_W$ ), of acetaminophen, phenacetin, and acetanilide, using experimental octanol-water partition coefficients ( $P_C$ ), entropies of fusion ( $\Delta S_f$ ), and melting points ( $t_m$ ). The calculated solubilities were compared with those experimentally determined. In almost all cases for acetanilide and phenacetin a good agreement was found, while this is not valid for acetaminophen.

**RESUMEN.** "Estimación de la Solubilidad Acuosa de Derivados de la Acetanilida a Partir de Coeficientes de Reparto Octanol-Agua y Entropías de Fusión". Se utilizaron algunas ecuaciones empíricas desarrolladas por Yalkowsky *et al.* para la estimación de la solubilidad en medios acuosos ( $S_W$ ), del acetaminofén, la fenacetina y la acetanilida, utilizando valores experimentales de coeficiente de reparto ( $P_C$ ) y, de temperaturas ( $t_m$ ) y entropías de fusión ( $\Delta S_f$ ). Las solubilidades calculadas fueron comparadas con las determinadas experimentalmente, encontrando buena concordancia para la acetanilida y la fenacetina en la mayoría de los casos, mientras que para el acetaminofén ningún modelo ofrece resultados confiables.

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### INTRODUCTION

The importance of the aqueous solubility in the dissolution and transport of drugs, and in general, in all pharmaceutical sciences is very well documented in literature <sup>1</sup>. For these reasons several methods for the estimation and prediction of solubilities have been developed. These methods arise from equations that involve other physicochemical properties of solutes such as molar volumes, partition coefficients and melting temperatures, chromatographic retention parameters, as well as other methods that include calculated molecular properties such as molecular surface area, molecular volume, and molecular connectivity. At present there are other approaches that involve neural network models, Monte Carlo simulations, and semi empirical quantum mechanical methods which make use of properties such as dipole moments, charge distribution, geometric param-

eters, and some extended linear solvation relationships (LSER). Also some applications of the thermodynamics of mobile disorder and the extended regular solutions theory can be used <sup>2,3</sup>.

As to the methods that include other experimental physicochemical properties of solutes, the earlier investigations were performed by Hansch *et al.* <sup>4</sup>, who developed a basic relationship [Eq 1] between the molar aqueous solubility ( $S_W$ ), and the octanol-water partition coefficient ( $P_C$ ), for 156 liquid substances.

$$\log S_W = -1.339 \log P_C + 0.978 \quad [1]$$

Since almost every pharmaceutical interesting compound is solid in nature, Yalkowsky & Valvani <sup>1</sup> have extended Eq [1] including terms relative to the melting of the solute (considering the classical model of solution process as melting of the solute and its further mixing with the

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solvent <sup>5,6</sup>). They also demonstrated that the entropy of melting ( $\Delta S_f$ ), may be calculated <sup>7</sup>. Consequently they have established the relationship shown in Eq [2] <sup>8</sup>.

$$\log S_W = - 1.00 \log P_C - 1.11 \Delta S_f (t_m - 25) / 1364 + 0.54 \quad [2]$$

The previous relationship was developed by means of multiple linear regression analysis of experimental values of  $S_W$ , calculated values of  $P_C$ , experimental values of  $\Delta S_f$  (in entropy units: cal-mol<sup>-1</sup> K<sup>-1</sup>), and melting temperature ( $t_m$ ), in °C, from 167 compounds. For rigid molecules, these authors propose a constant value of  $\Delta S_f$  of 56.5 J-mol<sup>-1</sup> K<sup>-1</sup> (Walden's rule), and by means of regression analysis of  $S_W$ , calculate  $P_C$ , and  $t_m$  for 155 compounds, Yalkowsky and Valvani established Eq [3].

$$\log S_W = - 1.05 \log P_C - 0.012 t_m + 0.87 \quad [3]$$

Equations [2] and [3] have been widely used for estimation of the aqueous solubility of some important pharmaceutical compounds such as barbiturate derivatives with good results <sup>9</sup>. Nevertheless in the case of sulfonamides and guanine derivatives these equations do not give good results <sup>2,10</sup>.

More recently, by means of a more complete thermodynamic analysis and by using data from a set of 580 pharmaceutically, environmentally, and industrially relevant compounds, Jain & Yalkowsky <sup>11</sup> have extended Eq [3] to obtain Eq [4].

$$\log S_W = - 1.031 \log P_C - 0.0102 t_m + 0.679 \quad [4]$$

Equation [4] has been so-called as GSE (General Solubility Equation). In some recent investigations carried by Yalkowsky *et al.* GSE has been challenged in front to other more complicated models used for the estimation of aqueous solubility, by determining the solubility of several compounds, and founding good results for GSE in those compared studies <sup>12,13</sup>.

The aim of this paper is to evaluate the validity of Yalkowsky-Valvani and Jain-Yalkowsky equations for the estimation of the aqueous solubility of acetanilide, acetaminophen, and phenacetin (structurally related compounds); this study is analogous to those made for guanine derivatives and sulfonamides, which have been presented in literature <sup>2,10</sup>.

## MATERIALS AND METHODS

In this study the following materials were used: acetanilide S.R. Merck (ACN); acetaminophen USP <sup>14</sup> QAC (ACP); Phenacetin A.R. BDF (PNC); octanol extra pure (ROH) Merck; distilled water (W) conductivity < 2 μS, Laboratory of Pharmaceutics UNC; alcohol USP <sup>14</sup> ELC; potassium chloride A.R. Merck; sodium mono and dihydrogen phosphates A.R. Merck; Millipore Corp. Swinnex<sup>®</sup>-13 filter units.

### Solubility determinations

Nearly 500 mg of each compound studied (an excess of substance) were added to 20 mL of each solvent in glass flasks. The mixtures were then stirred in a Wrist Action Burrel model 75 mechanical shaker for 1 h. Samples were allowed to stand in a Magni Whirl Blue M. Electric Company water bath kept at 25.0 ± 0.1 °C for 72 h. After this time the supernatant solutions were filtered to ensure that the solutions were particulate matter free before sampling. The solution concentrations were determined by measuring UV absorbances after appropriate dilution and interpolation from previously constructed calibration curves for each compound in a Hewlett Packard 8452A spectrophotometer, with diode array. All solubility experiments were repeated at least three times. The density of the saturated solutions was determined by using a DMA 45 Anton Paar digital density meter according to a previously reported procedure to facilitate the conversion of the concentration scales between molarity and mole fraction <sup>15</sup>.

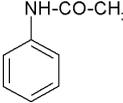
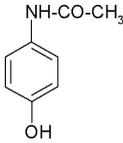
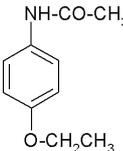
### Partitioning studies

Both solvents were mutually saturated before performing the experiments. Solutions of well known concentration, about 1 · 10<sup>-4</sup> mol-L<sup>-1</sup> of each compound, were prepared in aqueous buffer solutions adjusted to pH 7.4 at ionic strength of 0.15 mol-L<sup>-1</sup>. Then 5.0 mL of octanol were added to 20.0 mL of the aqueous compound solution in glass flasks. The mixtures were then stirred in a Wrist Action Burrel model 75 mechanical shaker for one hour. Samples were allowed to stand in a Magni Whirl Blue M. Electric Company water bath kept at 25.0 ± 0.1 °C at least for 48 h. After this time the aqueous phases were isolated and the concentrations of drug were determined by measuring the UV absorbances as previously described. The partition coefficients were calculated by mass balance. All the partitioning experiments were repeated at least three times.

## RESULTS AND DISCUSSION

The molecular structures of the studied compounds, their abbreviations, and some of their physicochemical properties are summarized in Table 1<sup>16-18</sup>. The maximum wavelength values are in good agreement with those of literature<sup>17</sup>. The partitioning and the solubility of com-

pounds in water were determined at pH 7.4 (physiological value of blood). This pH value was regulated by phosphate buffer having 0.01 in  $\beta$  capacity, using pKa values corrected to  $\mu = 0.15 \text{ mol-L}^{-1}$  (GIT value<sup>19</sup>) by means of Debye-Hückel equation<sup>18</sup>.

| Compound      | Abbreviation | Molecular Structure   | Molar mass / g-mol <sup>-1</sup> | pK <sub>a</sub> | $\lambda_{\text{max}}$ / nm <sup>(a)</sup> |
|---------------|--------------|---|----------------------------------|-----------------|--|
| Acetanilide   | ACN          |    | 135.16                           | 0.61            | 240<br>246                                 |
| Acetaminophen | ACP          |    | 151.16                           | 9.92            | 242<br>250                                 |
| Phenacetin    | PNC          |  | 179.21                           | 2.2             | 242<br>250                                 |

**Table 1.** Some physicochemical properties of the compounds studied<sup>16-18</sup>. (a) First value in water at pH 7.4 and second in alcohol USP.

Table 2 summarizes the melting point, enthalpy and entropy of fusion of the evaluated compounds which were reported previously in the literature<sup>20,21</sup>. It may be seen that all the entropies of fusion differ from  $56.5 \text{ J-mol}^{-1} \text{ K}^{-1}$ , value proposed by Yalkowsky & Valvani for rigid molecules according to Walden's rule. This behavior may be attributed to the thermal analy-

sis method used, since the values presented in Table 2 were obtained by differential scanning calorimetry (DSC), that is, a quantitative method, while Yalkowsky and Valvani used differential thermal analysis (DTA), which is considered a semiquantitative method. The former method is more appropriate for the determination of specific and molar enthalpies of fusion<sup>22</sup>.

| Compound | $t_m$ / °C | $\Delta H_f$ / kJ-mol <sup>-1</sup> | $\Delta S_f$ / J-mol <sup>-1</sup> K <sup>-1</sup> |
|----------|------------|-------------------------------------|--|
| ACN      | 114.3      | 20.30                               | 52.43  |
| ACP      | 169.5      | 27.71                               | 62.60  |
| PNC      | 134.5      | 30.72                               | 75.38  |

**Table 2.** Properties of melting of the compounds studied<sup>20,21</sup>.

Table 3 summarizes the experimental octanol-water partition coefficients, the experimental solubilities in water and octanol in molarity ( $S_W$  and  $S_{ROH}$ ) and mole fraction ( $X_W$  and  $X_{ROH}$ )

[the respective corrected standard deviations were calculated according to Dean and Dixon<sup>23</sup>], as well as the ideal solubilities ( $X^i_2$ ) calculated by means of Eq [5]<sup>6</sup>.

| Compound | $P_C$           | Solubility           |                    |                       |           |         |
|----------|-----------------|----------------------|--------------------|-----------------------|-----------|---------|
|          |                 | $S_W$                | $S_{ROH}$          | $X_W$                 | $X_{ROH}$ | $X_2^i$ |
| ACN      | 13.60<br>(0.07) | 0.0445<br>(0.0015)   | 0.6008<br>(0.0011) | $8.067 \cdot 10^{-4}$ | 0.09281   | 0.1521  |
| ACP      | 2.73<br>(0.09)  | 0.1019<br>(0.0015)   | 0.1351<br>(0.0007) | $1.858 \cdot 10^{-3}$ | 0.02126   | 0.02602 |
| PNC      | 30.3<br>(0.4)   | 0.00518<br>(0.00004) | 0.1196<br>(0.0021) | $9.313 \cdot 10^{-5}$ | 0.01895   | 0.03582 |

**Table 3.** Partition coefficient, experimental solubilities in water and octanol, and ideal solubilities at 25.0 °C. (Values in parentheses are corrected standard deviations <sup>23</sup>).

| Compound | Activity coefficients |                         |                         |                |
|----------|-----------------------|-------------------------|-------------------------|----------------|
|          | $\gamma_W$            | $\gamma_{W(ROH)}^{(a)}$ | $\gamma_{ROH(W)}^{(a)}$ | $\gamma_{ROH}$ |
| ACN      | 188.6                 | 204.3                   | 1.219                   | 1.639          |
| ACP      | 14.00                 | 14.98                   | 0.973                   | 1.224          |
| PNC      | 384.6                 | 355.7                   | 1.842                   | 1.890          |

**Table 4.** Activity coefficients of solutes in water and octanol, and the mutually saturated solvents at 25.0 °C. <sup>(a)</sup> W(ROH) is octanol-saturated water and ROH(W) is water-saturated octanol.

| Compound | $\log P_C$ | $\log S_W$ | Calculated $\log S_W$ |        |        | Deviation (as $\Delta \log S_W$ ) <sup>(a)</sup> |       |        |
|----------|------------|------------|-----------------------|--------|--------|--|-------|--------|
|          |            |            | Eq 2                  | Eq 3   | Eq 4   | Eq 2   | Eq 3  | Eq 4   |
| ACN      | 1.134      | -1.352     | -1.504                | -1.692 | -1.656 | 0.152  | 0.340 | 0.304  |
| ACP      | 0.436      | -0.992     | -1.656                | -1.622 | -1.500 | 0.664  | 0.630 | 0.508  |
| PNC      | 1.481      | -2.286     | -2.546                | -2.300 | -2.220 | 0.261  | 0.014 | -0.066 |

**Table 5.** Octanol-water partition coefficient, experimental and calculated aqueous solubilities as decimal logarithms and the respective deviations at 25.0 °C. <sup>(a)</sup> Calculated as  $\log S_{W(exp)} - \log S_{W(calc)}$ .

The  $P_C$  values decrease in the order PNC > ACN > ACP, while the aqueous solubilities decrease as ACP > ACN > PNC, and the organic solubilities decrease as ACN > ACP > PNC, and finally, the ideal solubilities decrease in the order ACN > PNC > ACP.

$$\ln X_2^i = -\Delta H_f(T_m - T) / (R T_m T) \quad [5]$$

On the other hand, in Table 4 the respective activity coefficients in water ( $\gamma_w$ ) and octanol ( $\gamma_{ROH}$ ) calculated from real and ideal solubilities by means of Eq [6] <sup>6</sup> are presented.

$$\gamma_2 = X_2^i / X_2 \quad [6]$$

The logarithms of the experimental aqueous solubility and partitioning values for the compounds at 25.0 °C, and the solubilities calculated by Eqs [2]-[4] are presented in Table 5. The differences between experimental and calculated values are also presented, as  $\log S_{W(exp)} - \log S_{W(calc)}$ .

Deviations lower than 0.30 log units are found when Eqs [2]-[4] are used except for ACP. This shows that for the analysis of these compounds it is valid to use a constant value for the entropy of fusion (56.5 J·mol<sup>-1</sup> K<sup>-1</sup>), which is lower than those obtained for all studied compounds except for ACN.

The good agreement between the experi-

mental  $S_W$  and the values calculated by Eqs [2]-[4] in a first approach may be explained if it is assumed that the solutes show ideal behavior in the organic medium, that is, the activity coefficients in octanol  $\gamma_{ROH}$  are unity such as it has been explained by Yalkowsky & Valvani <sup>8</sup> [according to these authors  $P_C = \gamma_W / \gamma_{ROH}$ , but assuming that if the molar cohesive energy interactions are similar in drug and in octanol, then  $\gamma_{ROH}$  is near to unity, hence,  $\log \gamma_{ROH}$  is near to zero, therefore  $\log \gamma_W \approx \log P_C$  <sup>8</sup>], which is almost valid for the compounds studied (Table 3). The previous reasoning do not explain the high deviation for ACP because the respective  $\gamma_W$  and  $\gamma_{ROH}$  values are the smallest among all the compounds studied here, that is, ACP shows the most ideal behavior in water and octanol.

If a difference lower than 0.30 log units is considered as valid for the estimation of  $S_W$  such as it has been made for similar calculations of drugs in theoretical chemistry <sup>10,24</sup>, then only the aqueous solubility of PNC calculated by Eqs [2]-[4] are valid, in special [3] and [4], as well as  $S_W$  for ACN calculated by Eqs [2] and [4]. In all other cases, the evaluated equations do not give a reasonable estimation of this physicochemical property. Since a difference of 0.30 log units indicates a limit between twice and half the values of solubility in the non-logarithmic scale, then these equations are not valid for quantitative estimations in the case of ACP.

In addition to the assumption that  $\gamma_{ROH} \approx 1$ , Yalkowsky & Valvani assume that the effect of the partial miscibility between octanol and wa-

ter on the activity coefficients is not significant upon phenomena such as solubility and partitioning <sup>8</sup>, which is not valid in the case of solutes such as guanine derivatives or sulfonamides (e.g. semipolar compounds). For those solutes the activity coefficients are different in pure solvents than in those mutually saturated <sup>6,25,26</sup>, while, these properties are not significantly different for the compounds studied in this investigation (Table 4), then, the partial miscibility apparently is not very significant on solubility and partitioning behavior <sup>27</sup>.

## CONCLUSIONS

From the previous analysis it may be concluded that the Yalkowsky-Valvani and Jain-Yalkowsky equations give good results for the estimation of aqueous solubility of acetanilide and phenacetin but need more refinement for give reasonable estimations of the aqueous solubility of the acetaminophen. In addition, according to the behavior of ACP, also it may conclude that the physicochemical aspects related to solubility of organic compounds such as several drugs in aqueous media, are more complex than those described by the parameters used in the developing of these predictive models.

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