

COMMENTARY ON “MEASUREMENT AND CORRELATION OF THE SOLUBILITY OF
TELMISARTAN (FORM A) IN NINE DIFFERENT SOLVENTS FROM 277.85 TO 338.35 K”

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Abstract

Several errors and shortcomings in the paper by Liu and coworkers [Journal of Solution Chemistry, **45** (2016) 932-946] concerning the calculation of Abraham model solution descriptors of telmisartan are discussed. The authors' calculated solute descriptors give an unreasonable value for the water-to-1-octanol partition coefficient of telmisartan, which is eight orders of magnitude smaller than values predicted by other methods. The correct computation methodology for determining solute descriptors from experimental solubility data is presented.

KEYWORDS AND PHRASES:

Abraham model solute descriptors; solubility of telmisartan; organic solvents; partition coefficients

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In a recent paper appearing in This Journal [1] Liu and coworkers reported the solubility of telmisartan (form A) in nine different organic solvents in the temperature range from 277.88 K to 338.35 K. The solubilities were measured using a laser monitoring method that detected the temperature at which the last added portion of solute did not dissolve. The authors described the temperature dependence of the measured mole fraction solubilities, x_1 , in each individual organic solvent in terms of both the Apelblat equation:

$$\ln x_1 = A_A + B_A/T + C_A \ln (T) \quad (1)$$

and λh equation:

$$x_1 = \frac{1}{(1/\lambda)\{\exp[\lambda h (\frac{1}{T} - \frac{1}{T_m})] - 1\} + 1} \quad (2)$$

where T and T_m correspond to the system temperature and melting point temperature of telmisartan, respectively. The empirical model curve-fit constants are denoted as A_A , B_A , C_A , λ and h in Eqns. 1 and 2.

As part of the study the authors used the Abraham model

$$\log_{10} P = c_p + e_p \cdot \mathbf{E} + s_p \cdot \mathbf{S} + a_p \cdot \mathbf{A} + b_p \cdot \mathbf{B} + v_p \cdot \mathbf{V} \quad (3)$$

to calculate the solute's excess molar refraction descriptor (**E**), dipolarity/polarizability descriptor (**S**), hydrogen-bond acidity and basicity descriptors (**A** and **B**), and McGowan characteristic volume (**V**). The calculated numerical values, **E** = 0.71; **S** = 1.35; **A** = -0.16; **B** = 1.33; and **V** = 1.27, were obtained by fitting the data at about 298 K. The Abraham model, Eqn. 3, correlates the logarithm of the water-to-solvent partition coefficient, $\log_{10} P$, which can be estimated as the logarithm of the solute's molar solubility in the organic solvent divided by the solute's aqueous

molar solubility. No reference was given in the paper [1] for the source of the aqueous molar solubility, and the authors did not state how the $\log_{10} P$ values were obtained.

The purpose of the present communication is to point out several errors in the authors' curve-fitting results and several shortcomings in the solute descriptor computations. First, the Apelblat model equation coefficients that Liu and coworkers report in Table 4 of their paper are not consistent with the Apelblat model. If one simply substitutes the numerical values from Table into Eqn. 1 above one obtains $10^3 x_1$, rather than x_1 . The back-calculated mole fraction solubilities differ from the experimental values by a factor of 1000. Readers should be aware of this problem when using the tabulated equation coefficients to calculate mole fraction solubilities at other temperatures.

Second, the calculation methodology for obtaining the Abraham model solute descriptors is seriously flawed. The McGowan characteristic volume should not be treated as a curve-fit parameter, but rather calculated from the molecular structure, atomic sizes and number of bonds as described elsewhere [2]. Correctly calculated, the McGowan volume for telmisartan is $V = 3.9785$. The E solute descriptor can be estimated by the PharmaAlgorithm software [3], which is based on molecular structure considerations using fragment group values [4,5], or calculated using a measured value (liquid solute) or an estimated value (solid solute) for the solute's refractive index. The refractive index of solid solutes can be estimated using the (free) ACD software [6]. The value of E that we calculate is $E = 4.61$. This leaves us with three solute descriptors (S , A and B) to be calculated from the measured experimental solubility data. In the present case, the aqueous molar solubility of telmisartan is unknown, which leaves us with a fourth value to be calculated.

Liu and coworkers measured the solubility of telmisartan in nine different organic solvents; however, not all of the experimental data is useable in terms of calculating the Abraham descriptors since the solute is capable of dimerization. Carboxylic acids are known to dimerize in alkane and aromatic hydrocarbon solutes, and in other nonpolar solvents. The numerical values of the solute descriptors of monomeric carboxylic acids are different than the numerical values of dimeric carboxylic acids. One must select solubility data for solvents in which telmisartan is expected to exist almost entirely in monomeric form. Solubility data in dichloromethane, trichloromethane, benzene and toluene is eliminated from consideration because of dimerization concerns. This leaves us with solubility data in methanol, ethanol, 2-propanol, propanone and ethyl acetate for use in the solute descriptor calculations. We have three solute descriptors and an unknown aqueous solubility to be calculated from five experimental $\log_{10} P$ equations - one equation for each of the five different solvents in which telmisartan exists predominantly in monomeric form.

It is possible to double the number of equations by converting all the $\log_{10} P$ values into $\log_{10} K$ values through Eq. 4, where K_w is the gas-to-water partition coefficient (unit-less if concentrations in the gas phase and the aqueous phase are both in mol/L)

$$\log_{10} P = \log_{10} K - \log_{10} K_w \quad (4)$$

$$\log_{10} K = c_k + e_k \cdot \mathbf{E} + s_k \cdot \mathbf{S} + a_k \cdot \mathbf{A} + b_k \cdot \mathbf{B} + l_k \cdot \mathbf{L} \quad (5)$$

Then if, say, five $\log_{10} P$ values are available, five more equations in $\log_{10} K$ can be used, and two more equations in $\log_{10} K_w$ are also available

$$\log_{10} K_w = -0.994 + 0.577 \mathbf{E} + 2.549 \mathbf{S} + 3.813 \mathbf{A} + 4.841 \mathbf{B} - 0.869 \mathbf{V} \quad (6)$$

$$\log_{10} K_w = -1.271 + 0.822 \mathbf{E} + 2.743 \mathbf{S} + 3.904 \mathbf{A} + 4.814 \mathbf{B} - 0.213 \mathbf{L} \quad (7)$$

$\log_{10} K_w$ will normally have to be found by trial-and-error, so that two extra descriptors (\mathbf{L} and $\log_{10} K_w$) have to be determined. However, starting with five $\log P$ values, no less than ten

equations will be available to calculate the four missing descriptors (**S**, **A**, **B**, and **L**), the aqueous molar solubility of telmisartan (C_w) and $\log_{10} K_w$. This method has been applied extensively to the solubility of solids by Acree, Abraham and coworkers [7-10]

We have compiled in Table 1 the numerical values of the $\log_{10} P$ and $\log_{10} K$ equation coefficients for methanol, ethanol, 2-propanol, acetone and ethyl acetate. Preliminary regression analysis showed that the methanol data were outliers. The two data points were removed from the analysis. The ten remaining equations were solved simultaneously using Microsoft Solver software to yield numerical values of: **E** = 4.610; **S** = 3.651; **A** = 0.565; **B** = 2.130; **V** = 3.9785; **L** = 23.155; $\log_{10} C_w$ = -9.436; and $\log_{10} K_w$ = 20.021 with the overall standard error being SE = 0.048 \log_{10} units. As an informational note, the calculated Absolv descriptors are [11]: **E** = 4.61, **S** = 3.56, **A** = 0.57, **B** = 1.59, **V** = 3.9785, and **L** = 21.58 in reasonably good agreement with the values that we have calculated.

The solute descriptors that were reported by Liu and coworkers are totally unrealistic and are not consistent with the molecular structure of telmisartan. A very simple way of checking any set of descriptors is to calculate $\log_{10} P$ for the water-wet octanol system by combining the descriptor set with the equation for water- (wet) octanol partition coefficients (Table 1). The descriptors of Liu and coworkers yield a value of -0.70, our descriptors yield 6.64, and calculated values of $\log_{10} P$ are 7.29 (BioLoom),¹² 7.73 (ACD),^{6,13} 6.04 (ChemAxon),¹³ 6.95 (Absolv)¹¹ and 8.42 (EPI).¹⁴ Our value is within the range of the various calculated values, whilst the Liu and coworkers value¹ is out by some 8 log units.

We urge workers who are interested in our method to study a number of published reviews.¹⁵⁻¹⁸ That of Clarke and Mallon¹⁸ is particularly detailed.

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Table 1. $\log_{10} P$ and $\log_{10} K$ Equation Coefficients for the Solvents Considered in the Present
Commentary

Partition System	c	e	s	a	b	l	v
Gas -water/298	-0.994	0.577	2.549	3.813	4.841	0.000	-0.869
Water-methanol	0.276	0.334	-0.714	0.243	-3.320	0.000	3.549
Water-ethanol	0.222	0.471	-1.035	0.326	-3.596	0.000	3.857
Water-2-propanol	0.099	0.344	-1.049	0.406	-3.827	0.000	4.033
Water-ethyl acetate	0.328	0.369	-0.446	-0.700	-4.904	0.000	4.150
Water-propanone	0.313	0.312	-0.121	-0.608	-4.753	0.000	3.942
Water-wet octanol	0.088	0.562	-1.054	0.034	-3.460	0.000	3.814
Gas-water/298	-1.271	0.822	2.743	3.904	4.814	-0.213	0.000
Gas-methanol	-0.039	-0.338	1.317	3.826	1.396	0.773	0.000
Gas-ethanol	0.017	-0.232	0.867	3.894	1.192	0.846	0.000
Gas-2-propanol	-0.048	-0.324	0.713	4.036	1.055	0.884	0.000
Gas-ethyl acetate	0.182	-0.352	1.316	2.891	0.000	0.916	0.000
Gas-propanone	0.127	-0.387	1.733	3.060	0.000	0.866	0.000