Journal of Pharmaceutical Sciences xxx (2016) 1–4

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Calculating the Solubilities of Drugs and Drug-Like Compounds in Octanol

Doaa Alantary*, Samuel Yalkowsky

Department of Pharmaceutics, College of Pharmacy, University of Arizona, Tucson, Arizona 85721

ARTICLE INFO

Article history:
Received 16 December 2015
Revised 26 January 2016
Accepted 2 February 2016

Keywords:
permeability
solubility
QSPR
structure-property relationship (SPR)
physicochemical properties

ABSTRACT

A modification of the Van't Hoff equation is used to predict the solubility of organic compounds in dry octanol. The new equation describes a linear relationship between the logarithm of the solubility of a solute in octanol to its melting temperature. More than 620 experimentally measured octanol solubilities, collected from the literature, are used to validate the equation without using any regression or fitting. The average absolute error of the prediction is 0.66 log units.

Introduction

Determining the solubilities of chemicals in octanol has many applications in the pharmaceutical and environmental sciences. Solubility in octanol is an indicator of how easily a drug will permeate the biological membranes, how strongly it will bind to its receptor, and how long it will remain in the body. Furthermore, it is a good indicator of its solubility in natural lipids.[5] The European Economic Council and the Organization for Economic Co-operation and Development recommend examining the solubilities of chemicals in fat to assess their environmental risks.[41]

In spite of its importance, only limited information on solubility of organic compounds in octanol, or animal fat, is available in the literature. The purpose of this study is to generate a simple equation for the rapid and reasonable estimation of the solubility of nonelectrolytes in octanol, which is commonly used as a surrogate for animal lipids.

Brief Background

The mole fraction solubility of nonelectrolytes in octanol (X^C_{oct}) is related to the liquid or hypothetical supercooled liquid solubility of the solute in octanol (X^L_{oct}) and the relationship between the solubility of a crystalline compound and that of a liquid as described by the Clausius-Clapyron equation, that is:

$$\log X^C_{oct} = \log X^L_{oct} - \frac{\Delta H_m \cdot (T_m - T)}{2.303 \cdot \mathrm{R} \cdot T_m \cdot T} \quad (1)$$

where R is the gas constant (8.314 J/K.mol), T is the temperature in Kelvin, ΔH_m is the enthalpy of melting of the solute, and T_m is its absolute melting point.

Liquid Term

The product of the solute molar volume (V_u) and the solubility parameter difference between octanol δ_{oct} and the solute δ_s can be used to calculate the activity coefficient using the Scatchard-Hildebrand equation:

$$\log X^L_{oct} = \frac{V_u \cdot (\delta_{oct} - \delta_u)^2 \cdot \phi^2_{oct}}{2.303 \cdot R \cdot T} \quad (2)$$

where ϕ_{oct} is the volume fraction of octanol.

This article contains supplementary material available from the authors by request or via the Internet at http://dx.doi.org/10.1016/j.xphs.2016.02.002.

* *Correspondence to:* Doaa Alantary (Telephone: +1-520-838-4336; Fax: +1-520-626-4063).
E-mail address: alantary@pharmacy.arizona.edu (D. Alantary).

http://dx.doi.org/10.1016/j.xphs.2016.02.002
0022-3549/

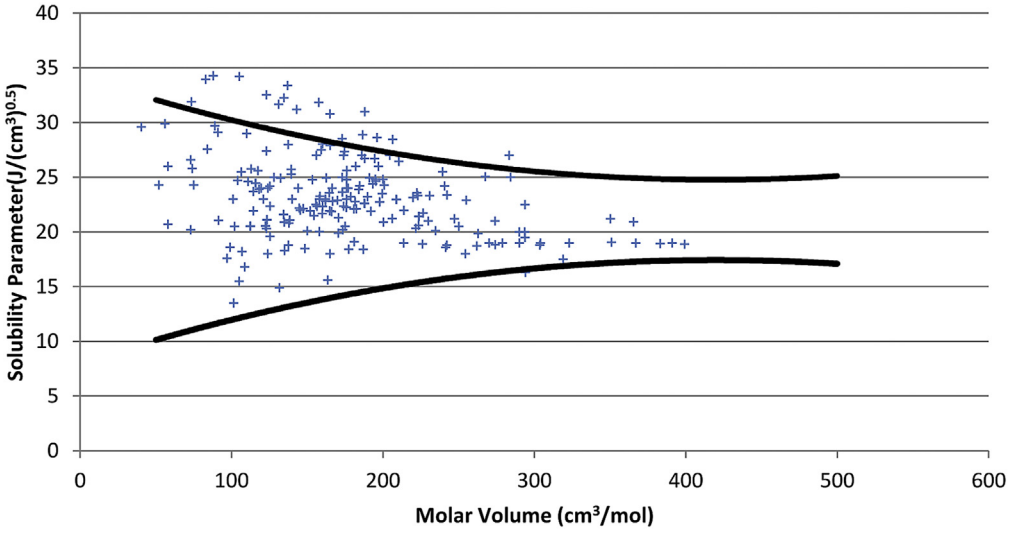

Figure 1. Theoretical relationship between molar volume and the solubility parameter range that would produce complete miscibility (solid curves). The points represent solubility parameters of 216 environmental compounds from Admire and Yalkowsky[4] and Barton.[8]

Sepassi and Yalkowsky[62] assumed that complete miscibility can be characterized by a value of 0.5 for both the mole fraction of solute and the volume fraction of octanol. A solute with a molar volume similar to that of octanol will be completely miscible with octanol if

$$\log 0.5 = \frac{V_u \cdot (\delta_{oct} - \delta_u)^2 \cdot 0.5^2}{5700} \tag{3}$$

Rearranging gives

$$|\delta_{oct} - \delta_u| \leq 6.6 \tag{4}$$

Therefore, a solute with a molar volume equal to that of octanol (159 cm^3/mol) will be miscible with octanol if its solubility parameter (δ_u) differs from the solubility parameter of octanol (21.1 J/$[cm^3]^{0.5}$) by <6.6 units. The solubility parameters required for complete miscibility with octanol as a function of molar volume are illustrated in Figure 1.

Because most environmental and pharmaceutical compounds have molar volumes within a factor of 2 from that of octanol, and solubility parameters between 15 and 28 $(J/cm^3)^{0.5}$, their liquid forms are miscible with octanol, that is, a mole fraction solubility of

$$X_{oct}^L = 0.5 \tag{5}$$

Crystal Term

Using Equation 2 and replacing $(\Delta H_m/T_m)$ with ΔS_m in Equation 1 gives the solubility of a crystalline solute in octanol X_{oct}^C as

$$\log X_{oct}^C = \log X_{oct}^L - \frac{\Delta S_m (T_m - T)}{2.303 \cdot R \cdot T} \tag{6}$$

Coincidentally, if $X_{oct}^L = 0.5$ then $S_{oct}^L = 3.15\ mol/L$ and $\log S_{oct}^L = 0.5$. Therefore, converting the mole fraction solubility to molar solubility (S_{oct}) at ambient temperature gives:

$$\log S_{oct}^C = 0.5 - \frac{\Delta S_m \cdot (T_m - 298)}{5700} \tag{7}$$

According to Walden's rule, the entropy of melting of most organic compounds can be approximated by a constant value of 56.5 J/mol.K. This further simplifies the equation to

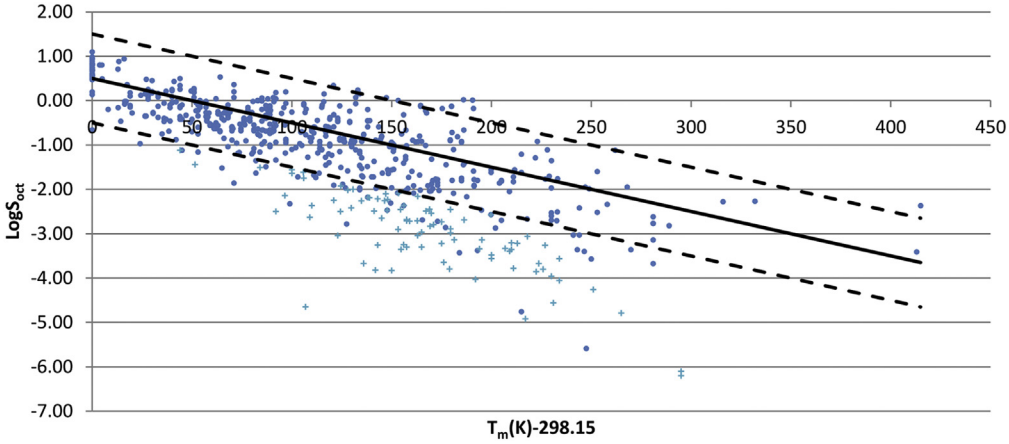

Figure 2. The figure shows the experimental solute molar solubilities obtained from the literature,[2-71] of the studied compounds as a function of their melting points in Kelvin (●). Sulfonamides, pigments, and guanosine derivatives (+).