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Editorial

Hansen Solubility Parameters: A Tool for Solvent Selection in Drugs

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Hildebrand[1] defined the solubility parameter as measures the contribution to the solubility of the cohesive energy density. Then, Hildebrand solubility parameter is calculated from the square root of the cohesive energy density, which is a characteristic of the intermolecular interactions in a compound. Subsequently, total solubility parameter of Hildebrand (δ_T^2) was divided into the contribution of several partial parameters, so that they can be applied to polar systems. Several authors have proposed dividing the total solubility parameter into partial solubility parameters. Nevertheless, perhaps it was Hansen in 1967[2] who achieved a more exact approximation for the calculation of partial solubility parameters (Eq. 1).

$$\delta_T^2 = \frac{\Delta E}{V} = \frac{\Delta E_d}{V} + \frac{\Delta E_p}{V} + \frac{\Delta E_h}{V} \quad \text{Eq. (1)}$$

where, ΔE, is the vaporization energy of the compound; ΔE_d, is the molar cohesive energy of dispersion; ΔE_p, is the molar polar cohesive energy; ΔE_h is the molar cohesive energy of hydrogen bonds and V is the molar volume of the compound, obtained using the group contribution method of Fedors.[3]

Later on, Bustamante *et al.*[4] related the dependent variable ln X_2 with the dispersion (δ_d), dipole (δ_p) and hydrogen bond (δ_h) parameters. Equation 2 summarizes this three-parameter model:

$$\ln X_2 = C_0 + C_1\delta^2_d + C_2\delta_d + C_3\delta^2_p + C_4\delta_p + C_5\delta^2_h + C_6\delta_h \quad \text{Eq. (2)}$$

ln X_2 is experimental solubility of each drug in several individual solvents, and $C_{0\text{-}6}$ are regression coefficients that are obtained by regression analysis. The partial solubility parameters are calculated using $C_{0\text{-}6}$ obtained with the following expressions,[4] $\delta_d = -(C_2/2C_1)$; $\delta_p = -(C_4/2C_3)$ and $\delta_h = -(C_6/2C_5)$.

To calculate with Eq. 2 the partial and total solubility parameters of drugs, a wide battery of pure solvents belonging to different chemical families is used,[5-11] on the other hand, the experimental calculation of the total solubility parameters could be carried out with aqueous or non-aqueous solvent mixtures.[12]

The Hansen Space is a three-dimensional parameter that allows the coordination between the Hildebrand solubility parameters and ΔE; it is expressed as the ratio between the energy of each component and the molar volume. Each compound will possess a unique coordination. The closer two molecules are in Hansen's space, the greater the chance of dissolving into each other.[13] The distance parameter could be calculated with the Eq. 3.

$$(\text{Ra})^2 = 4\,(\delta^2_d - \delta_d)^2 + (\delta^2_p - \delta_p)^2 + (\delta^2_h - \delta_h)^2 \quad \text{Eq. (3)}$$

To give a more practical use to the equation 3, the radius of interaction, or the radius of the sphere R0, is defined for two compounds to know if their partial solubility parameters are within the dissolution range. The partial solubility parameters are located in the centre of the sphere, and a new parameter number, RED (relative energy difference) is defined. Giving a simple analogy for solubility in relativity terms, and following that RED = Ra/R0, it follows that, if RED < 1, the two materials will dissolve; if RED = 1, the materials partially dissolve; and if RED >1, two materials do not dissolve.

However, the three-parameter model has limitations, Hansen's partial solubility parameters cannot be used to predict the solubility of complex molecules, or with high molecular weight, and these parameters are hardly applicable to electrolyte solutions. To solve it, Karger *et al.*[14] considered the partial parameter of hydrogen bonding as the product of the acidic (δ_a) and basic (δ_b) partial parameters, depending on their ability to accept or donate protons (Eq. 4).

$$\delta^2_T = \delta^2_d + \delta^2_p + 2\delta_a\delta_b \quad \text{Eq. (4)}$$

Once more Bustamante *et al.*[15] related the logarithm of the mole fraction solubility, ln X_2, against the four-partial

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solubility parameters as follows. This dependent variable assumes no significant changes of the thermodynamic activity (α) of the drug from one to another solvent from the model of Martin *et al.*,[16] $\ln \alpha_2/U$.

U is calculated using the expression $V_2\emptyset_1^2/RT$ and it considers the formation of cavities in the solvent and solute-solvent interactions, and α_2 is the activity of the solute, defined as the ratio of the ideal (X_2^i) to the experimental (X_2) mole fraction solubility. Eq. 5 summarizes four-parameter model:

$$\ln X_2 = C_0 + C_1\delta^2_d + C_2\delta_d + C_3\delta^2_p + C_4\delta_p + C_5\delta_a + C_6\delta_b + C_7\delta_a\delta_b \quad \text{Eq. (5)}$$

In the same way, based on the regression coefficients, the particulate solubility parameters can be calculated in the form, $\delta_d = -(C_2/2C_1)$; $\delta_p = -(C_4/2C_3)$; $\delta_a = -(C_6/C_7)$ and $\delta_b = -(C_5/C_7)$.

The values of dispersion parameter vary in the range of values 16-19 $MPa^{1/2}$ because it is the interval where most of the values of the parameters of pure solvents are included. An accepted explanation is that it is a parameter that represents the London dispersion forces, which is an interaction for both polar and nonpolar molecules. Therefore, the rest of the parameters are the most useful to determine the behaviour of drugs, in relation to their solubility, affinity with excipients, diffusion or absorption through biological membranes.

Author Contributions

The manuscript was written by MAP and FM, and approving the final version for submitting in journal.

Conflict of Interest

The authors report no conflicts of interest.

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