



Hansen solubility parameters: A quick review in pharmaceutical aspect

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ABSTRACT

This review is spotlighting the Hansen solubility parameters theory throughout seven decades of continuous development, especially in pharmaceutical field. Many applications in both pharmaceutical industry and administration are found, and the door of research is wide opened.

Keywords: Hansen Solubility Parameters, Cohesion energy density, formulation, interaction, pharmaceutics.

INTRODUCTION

In early 1950s, Hildebrand reported that both physical and chemical bonds in any material e.g., Van der Waals interactions, covalent bonds, hydrogen bonds, ionic bonds., etc., are a calculative value; the sufficient energy needed to overcome all these forces and allow a molecule (or an atom) to be pulled away from the whole assembly is called *cohesion energy*[1]. By dividing this value by molar volume we get the *cohesion energy density* or *Solubility parameter* (δ). When two materials have the same or relatively close solubility parameters, it means they are miscible in each other [2]. This theory was developed then by Hansen, in 1967, when he divided the cohesion energy to 3 components: physical, polar and hydrogen forces which are all contributed in molecular structure. This idea was the core of Hansen Solubility Parameters theory (HSPs)[3]. This division has broadened all possible application to include chemical industries in addition to pharmaceutical field; a thorough understanding of the cohesive energies in pharmaceutical ingredients permits prediction of their behavior under different conditions, like heating, milling, exposure to light or other manufacturing processes, besides how their behavior would be inside the human body. In addition, cohesive energy rules the physicochemical properties of the material (e.g. melting point, solubility) and any changes occur to the cohesive energy will definitely reflect on the material properties[2], [3].

Through literatures, many ways to express the concept of cohesive energy by means of numbers are been used, the most common way is the *solubility parameter* δ concept. δ is the square root of *cohesion energy density* of a material, as it was developed by Hildebrand *et al.* [4] based on regular solution theory. They said that the heat of mixing two materials together is given as:

$$\Delta H = V_T \left(\sqrt{\Delta E_{V1}/V_{m1}} - \sqrt{\Delta E_{V2}/V_{m2}} \right)^2 \cdot \phi_1 \cdot \phi_2 \quad (1)$$

ΔH is the heat of mixing, V_T is the total volume, ΔE_V is the energy of vaporization, V_m is the molar volume, ϕ is the volume fraction, and 1 and 2 stands for the solute and solvent. Hildebrand *et al* named the energy of vaporization per unit volume as the *cohesion energy density*(CED).

$$\delta = (CED)^{0.5} = (\Delta E/V)^{0.5}$$

Where V is the molar volume [1].

Hansen assumed that total cohesion energy is the sum of dispersion E_D , polar E_p , and hydrogen bond energy E_H [3].

$$E_T = E_D + E_p + E_H$$

And by dividing both sides of the equation by molar volume V , we will have the total Hansen solubility parameter or Hildebrand solubility parameter δ_T :

$$\delta_T^2 = \delta_D^2 + \delta_p^2 + \delta_H^2$$

If δ_T of both solute and solvent are alike, this will allow predicting solubility according to equation (1). The common used units for δ in literatures are $(J/m^3)^{0.5}$, $MPa^{0.5}$ or $(cal/cm^3)^{0.5}$, where one $(cal/cm^3)^{0.5}$ is equivalent to 2.0421 $MPa^{0.5}$ or $(J/m^3)^{0.5}$ [2]. This concept has modified the traditional rule “like dissolves like” to be “like seeks like”, to comprise surfaces that don’t usually dissolve [3].

δ calculation methods were varied between practical and theoretical ones [2] according to either direct/ indirect measuring of intrinsic properties of material as evaporation temperature, viscosity, solubility in predetermined solvents, etc., or counting on theoretical calculative methods that depend on additive contribution of each chemical group in the whole molecular energy [1].

1. HSP and Pharmaceuticals:

Predetermination of HSPs value of each pharmaceutical component in a formula will definitely save both time and cost in industrial process[5]. In literature, many researchers have discussed the ability to predict substance characters via its HSPs[2]; melting point is a good example because it reflects the energy that hold the whole matter [6]. Dielectric constant also correlated with δT [7]. In addition to predict ingredient’s solubility in solvents [8] and with another excipients i.e., interaction or incompatibility [9].

Industrial process has an important effect on pharmaceutical formulation, and HSP calculation for substances before and after process can give a clue on what happened to intrinsic properties for each substance, especially using Inverse Gas Chromatography technique (IGC) [10], [11].

Cohesion and adhesion properties are one example of powder interaction, and it is a crucial step in any industrial process because it affects mixing quality, subsequently the drug distribution in the dosage form or the colorant distribution in the coating step [12]. Besides, many articles have applied HSPs in developing biocompatible polymers in order to get longer action or good drug targeting [13].

Wetting stage is a result of solid – liquid interaction, so HSPs will put the conditions to select the best solvent/mixture of solvents to dissolve or wet a material[14].

2. Troubles associated with applying HSPs theory

This theory doesn’t consider entropy of amorphous solids, but it focuses on surface energy in general [2]. Besides it is based on normal solutions and any changes on normal solutions conditions will affect the results[4]. And all the methods used to determine a substance HSPs values will give approximate numbers that differ from one method to other according to the property it measures.[10], [15].

CONCLUSION

Since Hansen had developed Hildebrand solubility parameter in 1967, almost all science fields benefited from its application including pharmaceutical industry. The future is so promising and the door is wide opened for extended research.

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