(Review Article)

# Theoretical consideration of solubility by Hildebrand solubility approach

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## Abstract

Pharmaceutical field is widely focusing on solubility parameter models to select solvent or non-solvent that can enhance solvency of drug. Solubility Parameter is very useful concept in understanding the mechanism of solvent and solvency behavior with their applications in pharmaceuticals to open the door of research having focus on theoretical considerations of solubility. Hildebrand and Hansen Solubility Parameter are frequently used to identify solvents.

**Keywords:** Solubility; Solvation; Hildebrand Solubility Parameter; Hansen solubility parameter

## 1. Introduction

Currently solubility study is on the peak point of formulation scientist and the basic reason is existence of nearly 70% drug in class II of BCS classification [1]. Solubility Parameter is very useful concept in understanding the mechanism of solvent. Hildebrand is the first one to coin the term solubility parameter [2,3]. The Solubility Parameter is a numerical figure which gives solvency behavior of specific solvent [4].

Various Solubility Parameter like Hildebrand Solubility, Hansen Solubility, Fedors, Van Krevelen are in use to depict the solvency behavior of solvent [5]. The Solubility Parameter, which expresses the cohesion between like molecules, is obtained from heat of vaporization, internal pressure, surface tension and other properties as expressed by Hildebrand and Scott [6]. Coating's pharmaceutical, cosmetics foodstuffs are produced as multi- component chemical mixture and Hildebrand solubility Parameter and Hansen solubility parameter plays vital role to meet environmental shelf life and product quality specifications of these compounds [7].

The solubility of drug is very important for pharmaceutical industry. Solubility means ability of solute to dissolve in a solvent especially water [8]. According IUPAC solubility is defined as ratio of designated solute in solvent [9]. Solubility plays major role in the manufacture of liquids orals as well as in the manufacturing of parenteral formulations, also it is important to obtain desired concentration of drug in systemic circulation for getting pharmacological response. The solubility of drugs in gastrointestinal fluids is an important step for absorption of drugs. Thus, solubility phenomenon is important in pharmacy [10,11,12].

## 2. Solution as a system

A solution is a special type of homogeneous mixture composed of two or more substance. A Solvent is a substance that dissolves a solute resulting in a solution. The substance dissolved is called as the solute [13,14,15,16]. Solvents plays vital role like applying coatings, removing stains or adhesive. Choice of solvent mainly depend on factors such as

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evaporation rate, viscosity, environmental condition, health condition. And it is executed by the rule "like dissolves like" [17,18,19].

## 2.1. Ideal Solution

The gas phase shows thermodynamic properties equivalent to the mixture of ideal gas [20]. The concept of the Ideal solutions describes limiting behavior of solution in similar way that the ideal gas explains the gases limiting behavior [21]. Ideal solution is equivalent to the perfect gases, but intermolecular attraction is not present in perfect gases [22]. In simple language ideal solution is a solution that for which each entity executes Raoult's law [23,24,25]. In Ideal solution solubility of solute does not depend on nature of solvent. There is no change in volume when components are mixed during mixture. The solute –solvent interactions are same as that of solute –solute and solvent- solvent interactions [26,27,28].

## 2.2. Non-Ideal Solution

The Non-Ideal solution does not fallow Raoult's Law. This solution can occur when intermolecular forces between dissimilar molecules are greater than those between similar molecules and intermolecular forces between solute or solvent molecules are less strong than between molecules of similar (of the same type) molecules [29].

## 3. Solubility Parameter

Solubility Parameter is an intrinsic physicochemical property of substance. It expresses the cohesive forces between like molecules [30]. The simple definition of solubility parameter is as "a systematic description of the miscibility behavior of solvents" [31]. It is a square root of the cohesive energy density in which numerical value indicates the solvency behavior of a specific solvent and the represented by a delta ($\delta$) [32]. It provides straightforward method of comparing and predicting cohesive and adhesive properties of materials [33]. It is useful for polymer, predicting the swelling of elastomers by solvents, determining solvent pressure in devolatilization and predicting polymer-binary, polymer-polymer solvent equilibrium, permeation rates of solvent, also, it is useful for characterizing the surface of fibers, pigments, fillers [34,35,36,37].

In case of polymer, Hildebrand Parameter cannot obtain from heat of vaporization because of their no volatility [38,39,40]. Therefore, it is obtained using atomic contribution group method or direct correlation method [41,42,43].

Indirect methods namely consist of solvency testing, osmotic pressure, swelling values and specific volume [44]. Refractive index, H-bonding parameter, dielectric constant, surface tension these are the Correlation method [45]. Van Krevelen and Hoftyzer (VKH) method also used to determine the polymer and solvent volume. They are also known as atomic group contribution method [46,47]. Partial solubility of polymer can be calculated from VKH with the help of molar volume and molar attractions [48].

## 4. Hildebrand solubility parameter

Hildebrand solubility Parameter provides numerical value of the degree of interactions between materials [49,50,51]. It is a good sign of solubility mainly for non-polar material such as polymers. The entity of this method is Cohesive Energy Density [52].

Hildebrand Solubility is defined as "square root of Cohesive Energy Density" [53].

$$\delta = \sqrt{\frac{\Delta Hv - RT}{Vm}}$$

Were,

Hv is the Heat of Vaporization

Vm is the Molar volume

RT is the Ideal gas

Hildebrand Solubility is most widely applicable among all the systems which include Hildebrand number, hydrogen bonding value, fractional parameter and Hansen parameter [54]. Also, it is presented in the form of two- or three-dimensional graph and a triangular graph known as a Teas graph. The Hildebrand Solubility Parameter is one of the oldest measures of solvent polarity. "Higher value of solubility parameter indicates greater solvent polarity" [55,56,57].

Hildebrand Solubility Parameter was first introduced by Joel H. Hildebrand and Scott (1936) in the article "The Solubility of Non-electrolytes" [58]. The numerical value that indicates relative solvency behavior of a specific solvent is known as Solubility Parameter. The said numerical value is derived from Cohesive Energy Density of the substance [59].

Heat of vaporization governs the basis for cohesive energy density [60,61]. The interdependence of solubility parameter on cohesive energy density and of cohesive energy density on heat of vaporization is clarified from relationship between heat of vaporization, Van der Waals force and solubility [62].

### 4.1. Heat of vaporization

Vaporization is a transitional phase, in which transition of molecules proceeds from a liquid/solid to a gaseous form [63]. Molecule on a surface is usually the first to undergo a phase change. Heat of Vaporization means amount of heat required to evaporate a liquid [64]. Direct conversion of solid to vapor is called as sublimation whereas the formation of vapor bubble within liquid is called as boiling [65].

There are two types of vaporization namely evaporation and boiling [66]. When liquid is heated to its boiling point, energy is added which separate the liquid into the gas and temperature increases. Added energy is used to break the bonds and separate the molecule of the liquid. Once all the bonds are broken into there is no use of further addition of heat [67].
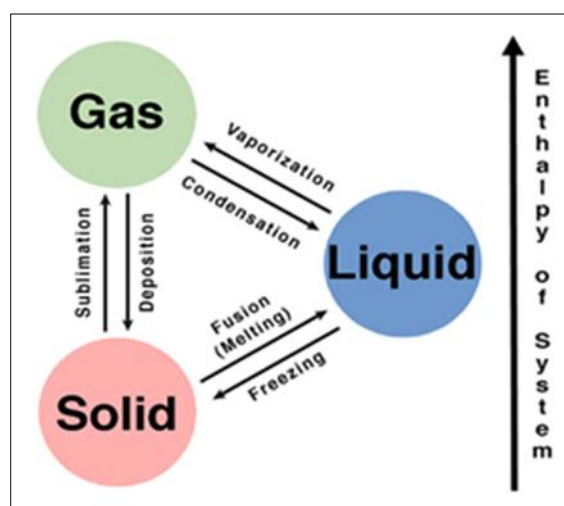


**Figure 1** Enthalpy of System

If we measure the amount of energy, it gives amount of Van der Waals force that molecule of liquid carries together. The temperature at which liquid boils is not that much important in contrast of the amount of heat required for separation of the molecule [68]. Here, temperature at which liquid begins to boils is not essential, but the amount of heat required to separate the molecules plays important role [69]. A liquid having low boiling point required large amount of energy to vaporize, while liquid with high boiling point may vaporized rapidly, or vice versa [70].

Vaporization is an Endothermic process, hence $H_{vap} > 0$ [71].

$$H_{Vapor} - H_{liquid} = H_{vap}$$

Where,

$H_{vap}$ is the change in enthalpy

H $_{vapor}$ is the enthalpy of the gas state of compound

H $_{liquid}$ is the enthalpy of the liquid state of compound

## 4.2. Cohesive energy density

Cohesive Energy Density is defined as energy needed to expel a molecule from its adjacent neighbors [72].

Cohesive Energy Density = $\frac{\Delta E}{V}$

Also, from heat of vaporization

$$C = \frac{\Delta Hv - RT}{Vm}$$

Where,

C is the cohesive energy density

H is the heat of vaporization

R is the gas constant

T is the temperature

Vm is the molar volume

In other quarters, the cohesive energy density is a numerical value that indicates the heat of vaporization in calories per cubic centimeter and it is related to the degree of Van der Waals forces [73].

Cohesive Energy density method are used to determine the group of pressure and temperature equilibrated structure it gives condensed phase properties, consisting Hildebrand and Hansen solubility behavior of polymer and solvent [74].

## 4.3. Molecular attraction

Intermolecular force creates interaction between molecules which contained force of attraction or repulsion [75]. This force acts in middle of molecules and atoms or ions. In a solution, the solvent molecules reduce this intermolecular adhesiveness in the solute and find their path between and around the molecule of solute. At the same time solvent molecules must be separated from each other by the molecules of solute. This can be done when attractions between molecules of both components are similar. If attraction is different, it results immiscibility [76,77].

## 4.4. Van der Waals force

Van der Waals Force defined as weak, short range electrostatic attractive force, present in between uncharged molecule and it is obtained from the interaction of transit or permanent electric dipole moments [78,79,80]. Sticky forces between molecules are called as Van der Waals force. Van der Waals forces occur due to electromagnetic interactions between molecules. It is a total Van der Waals force which is reflected in the simplest solubility value [81,82].

Examples of Van der Waals force are hydrogen bonding, dispersion forces and dipole-dipole interactions [83,84].

## 4.5. Solvent Spectrum

Solvent spectrum is obtained by ranking solvents according to solubility parameter, with solvents occupying positions near to other solvents of comparable strength [85,86].

## 4.6. Solvent Mixture

It is an important parameter of Hildebrand solvent spectrum that the Hildebrand value of a solvent mixture can be determined by averaging the Hildebrand values of the individual solvents by volume [87,88]. For example, two parts of Toluene + one part of Acetone

$$(18.3 \times 2/3 + 19.7 \times 1/3) = 18.7$$

18.7 is the Hildebrand value which is same as chloroform

## 4.7. Triangular Graph

In triangular graph instead of two axes there are three axes oriented at 60°, and instead of three dimensions in space, the triangular graph is flat. On a triangular graph the zero point of any one scale is an upper limit of another one [89].



**Figure 2** Triangular Graph

## 4.8. Teas Graph



**Figure 3** Teas Graph

The teas graph is known as a ternary fractional parameter solubility diagram. The teas graph is depended on the hypothetical presumption that all the component has the same Hildebrand value [90]. According this hypothesis the solubility behavior is determined, not by variation in total Hildebrand value, but the relative amount of three components forces (hydrogen bonding, dipole –dipole force and dispersion force [91].

## 5. Hansen Solubility Parameter

Determination of Hildebrand solubility parameter faces difficulty in case of substance with high boiling point. Hansen gives an extension of Hildebrand Solubility Method to determine relative miscibility of polar and hydrogen bonding system [92].

Based on the interaction between solute and solvent Charles M. Hansen distributes this Hildebrand solubility parameter into three components: Polar, Dispersion, and Hydrogen bonding thus, named as 3-D model or 3D solubility parameter [93,94].

Dispersion force, Dipole-Dipole Force and Hydrogen Bonding are the three-dimensional solubility parameter [95,96].

It is given as,

$$E = Ed + Ep + Eh$$

The sum of the energy from dispersion (d), dipole-dipole(p), and hydrogen bonding (h) forces between molecules gives total Cohesive energy density(E) Dividing it by the molar volume gives the square of the total Hansen solubility parameter as the sum of the squares of the Hansen $\delta d$, $\delta p$ and $\delta h$ [97].

$$\frac{E}{V} = \frac{E_d}{V} + \frac{E_p}{v} + \frac{E_h}{V}$$

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$$

Where $\delta_d$, the energy from dispersion forces between molecules. $\delta_p$, the energy from dipole –dipole force between molecules. $\delta_h$, the energy from hydrogen bonds in between molecules. $\delta$ value can be easily determined from heat of vaporization [98].

Hansen solubility parameter was first used in polymer and paint industry, now days it is also used in various industries like drug, cosmetic, oligomers. But results are not satisfactory in the case of polymer. There are two reasons, one is thermodynamic consideration and other is different functional group of drugs or cosmetic [99].

### 5.1. Disperation Force

The Dispersion force is the intermolecular force and impermanent attractive force that comes into existence when the electrons in two neighboring atoms occupies such a position that they form particular atoms which obtained from temporary dipoles [100,101]. Sometimes this attraction also called as London Dispersion force [102,103].

It is present in molecule, whether they are polar or non-polar. Larger molecules indicate stronger dispersion force than lighter molecule. This force is stronger between polarized molecules and weaker between the molecules that are not easily polarized [104].

### 5.2. Dipole-Dipole force

The positive end of one polar molecule is attracted towards negative end of another polar molecule with particular attractive forces known as Dipole-dipole force. They have vitality that range from 5kJ to 20kJ per mole [105]. It also called as Polar Forces. The polarity of molecule is related to its atomic composition its size and geometry [106]. Water and alcohol are strongly polar hexane is non polar and toluene is slightly polar. "Polar molecules organize themselves head to tail that means positive to negative and thus escalate in intermolecular attraction" [107].

### 5.3. Hydrogen Bonding

In hydrogen bonding electromagnetic attraction present between polar molecules in which hydrogen is attached to a larger atom, like carbon, oxygen or nitrogen. It is an attraction between the positive and negative poles of charged atoms [108].

## 5.4. Three-Dimensional Hansen Space

In three-dimensional Hansen space Dispersion force, Dipole-Dipole force and Hydrogen bonding can be treated as co-ordinates and closer molecules are more likely dissolved into each other. Interaction Radius ($R_0$) is used to determine the parameter of two molecules within range [109].

Solubility distance (Ra), which can be calculated for molecule combination (polymer-solvent combination), gives the region between solute and solvent in Hansen space. Once the polymer is clinched, then the distance between polymer and solvent can be calculated in Hansen Polymer are as fallow [110,111].

$$(R_a)^2 = \sqrt{4(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2}$$

Dividing Solubility distance ($R_a$) by the Interaction Radius ($R_0$) gives Relative Energy Difference, which explain togetherness of polymer and solvent9 [112].

$$RED = \frac{R_a}{R_o}$$

Condition: If the RED value will be less than 1 then solute and solvent are fully compatible to each other, estimated to be soluble. If the RED value 0, then there is no any difference between solvent and polymer or solute and the polymer is predicted as soluble. If the RED value is higher than the 1 it shows lower affinities between solute and solvent. And if the RED is nearer to 1, this condition is called as Boundary condition [113].
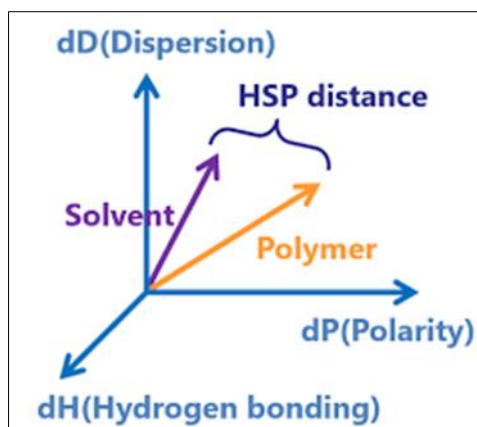


**Figure 4** Three-Dimensional Hansen space

## 5.5. Hildebrand Solubility and Solvation Process

Solvation is the process of transferring a solute from some fixed point in an ideal gas phase, into a fixed point in the liquid [114]. It is the requirement of the solvation process that change in the Gibbs energy of the process be negative or zero. Solvation process will be thermodynamically selected only if the Gibbs energy of the solution is lessened, as compared to the Gibbs energy of solvent and solid or liquid or gas [115]. For the solvation process the Gibbs energy change splits into entropic components and enthalpic components [116,117].

$$\Delta G_M = \Delta H_M - T\Delta S_M$$

$G_M$ is Gibb's energy of mixing, $H_M$, is Enthalpy of mixing, $S_M$ is Entropy of mixing. T is Temperature. Enthalpy of mixing can be expressed by, [118,119]

$$\Delta H_M = V_{mix}\left[\left(\frac{\Delta E_1^V}{V_1}\right)^{1/2} - \left(\frac{\Delta E_2^V}{V_2}\right)^{1/2}\right]^2 \emptyset_1 \emptyset_2$$

Where,

$V_{mix}$ is the volume of mixture. $E^V1$ is Vaporization energy of entity I, $EV_2$ is vaporization of energy of entity II, $V_1$ is molar volume of entity I, $V_2$ is molar volume of entity II. $\emptyset_1$ is volume fraction of entity I, $\emptyset_2$ is volume fraction entity II [120].

## 6. Extended Hildebrand Solubility Approach

The Extended Hildebrand Solubility is modified version of the Scatchhard Hildebrand Equation. This parameter is used to calculate salvation of polar and non-polar solvents ranging from non-polar hydrocarbons to highly polar solvents like alcohols, glycols, water. It is applied to liquid - liquid systems [121,122].

## 7. Units

Hildebrand Values are shown in both, common form and newer form. In common form which is derived from cohesive energy densities (calories/cc) and a newer form means standard international units (SI) is derived from cohesive pressure. The SI unit for indicating pressure is Pascal and SI unit for indicating Hildebrand solubility parameter is Mega-Pascal [123,124]

SI Parameters are twice the value of standard parameters

$\delta/cal^{1/2} cm^{-3/2} = 0.48888 \times \delta/MPa^{1/2}$

$\delta/MPa^{1/2} = 2.0455 \times \delta/cal^{1/2} cm^{-3/2}$

## 8. Standard Hildebrand values of solvent [125]

**Table 1** Standard Hildebrand values of solvent

| Solvent | $\Delta[cal^{1/2} cm^{-3/2}]$ | $\Delta[MPa^{1/2}]$ (SI unit) |
|---|---|---|
| Diethyl ether | 7.62 | 15.4 |
| Cyclohexane | 8.18 | 16.8 |
| Carbon tetrachloride | 8.65 | 18.0 |
| Ethyl acetate | 9.1 | 18.2 |
| Toluene | 8.91 | 18.3 |
| Benzene | 9.15 | 18.7 |
| Chloroform | 9.21 | 18.7 |
| Dichloromethane | 9.93 | 20.2 |
| Acetone | 9.77 | 19.9 |
| Ethylene dichloride | 9.76 | 20.2 |
| Ethanol | 12.92 | 26.2 |
| Dimethyl sulphoxide | 12.93 | 26.4 |
| Methyl alcohol | 14.28 | 29.7 |
| Propylene glycol | 14.80 | 30.7 |
| Ethylene glycol | 16.30 | 34.9 |
| Glycerol | 21.10 | 36.2 |
| Water | 23.5 | 48.0 |

## 9. Advantages of Hildebrand Solubility Approach [126,127]

- It gives simple predictions of phase equilibrium based on single parameter.
- It is also used in predicting solubility and swelling of polymers by solvents.
- It is useful for solvent and additives selection in formulation.
- Hildebrand solubility parameter of the solute is equivalent to Hildebrand Solubility Parameter of solvent.

## 10. Limitations of Hildebrand Solubility Approach [128]

- Important limitation of Hildebrand Solubility Parameter is that it is applied only to associated solutions (like dissolve like) or positive deviation from Raoult's Law.
- It is not applied to negative deviation from Raoult's Law which affect solvation or formation of electron donor acceptor complexes.
- It does not consider any specific interaction between molecules; therefore, three-dimensional Hansen solubility parameter are more practical in case of polymerization system.
- The Hildebrand solubility parameters will vary with temperature.

## 11. Applications of Hildebrand Solubility Approach [129]

- It can be applied in analytical chemistry, plasticizers, electrochemical sensors and catalysis.
- Extended Hildebrand Solubility Approach is used to determine the solubility of drug in binary solvents.
- It determines the maximum solubility in binary solvents like methanol-water. Solubility parameter, density, molar volumes were calculated and solubility was expressed in mole fraction.
- It is used to determine the solubility parameters of ionic liquids and Ionic-Liquid solvent mixtures from Intrinsic Viscosity.
- This study provides basic information on the solubility parameter of Ionic Liquids and mixture of Ionic liquid and solvents at different composition
- In molecular Dynamic with application to Electronic Nose Polymer Sensors.
- It is used in stable chemical formulation development.
- It is used by the industry for the determination of the permeation rate, mechanical properties and chemical resistance of polymer.
- It is used in the study and control of solvent –polymer behavior.

## 12. Conclusion

The numerical estimation of the degree of interaction between various materials signifies their solubility behavior. More closely the values, more likely solvation can take place. Thus the relative solvency behavior of a specific solvent can be a model to guide solvent selection.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest.

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