PDA Journal
of Pharmaceutical Science and Technology

Solubility Concepts and Their Applications to the Formulation of Pharmaceutical Systems: Part I. Theoretical Foundations

Gordon L. Flynn

PDA J Pharm Sci and Tech **1984**, *38* 202-209

Solubility Concepts and Their Applications to the Formulation of Pharmaceutical Systems

Part I. Theoretical Foundations

GORDON L. FLYNN

The University of Michigan, College of Pharmacy, Ann Arbor, Michigan

I. Solubility Fundamentals

The subject of solubility is of fundamental importance to the student and formulating scientist as everyday decisions concerning the design and use of dosage forms are affected by the ease and extent to which drugs and excipients dissolve. The study of solubility also puts the student and formulating scientist in touch with a practical subject whose understanding draws deeply from the thermodynamic wellspring and which provides, through pragmatic example, a working feel for the intermolecular interactions which is the basis of all physical behavior. No other subject of comparable utility serves so admirably as an exercise in the study of these thermodynamic and intermolecular spheres and for this reason alone solubility theory should be profoundly interesting to the scientifically minded.

A. Solubility and Drug System Performance: The solubility of a chemical is more often than not a determining factor of its ultimate usefulness as a drug or as an excipient or even for other purposes. A drug's solution behavior relative to its dose may dictate the type of physical system most appropriate for administration of the drug. A drug's aqueous solubility may also influence the choice of administration route and even the administration technique via that route. For example, certain poorly water soluble drugs such as diazepam and phenytoin are formulated for parenteral purposes in semiaqueous solutions containing high percentages of water miscible organic solvents. Such systems must be given exclusively by vein and also at very slow rates of injection. To do otherwise results in precipitation within the injection site, even including precipitation in the vein's fast flowing stream. In the latter instance blockage of small blood vessels downstream of the injection point occurs, with the possibility of serious untoward effects like phlebitis. There are also situations where limited solubility may be advantageous. Insolubility in water, for instance, offers the pharmaceutical scientist a ready means of prolonging drug release as is done with depotinjectables.

Some of the ways solubilities of drugs influence formulation and, more specifically, the elementary processes governing a drug's biologic availability and interactivity should be considered. A schematic representation of the fate of an administered drug is provided in Figure 1. Generally, drug dissolution and other mass transfer processes involving drug passage through actual membranes and drug binding to biological receptors are all involved. Under certain circumstances any of these processes may be rate limited by the solubility of the involved drug.

The rate of solution of a drug administered as a solid mass (tablet, capsule or even an injected depot) is determined by its *effective* state of subdivision; by mixing in the physiologic mileau, which determines the local biological hydrodynamics; and by the prevailing degree of saturation of the drug in the physiologic fluids. Equation 1 describes the dissolution reaction in terms of the amount of substance, dM, dissolving in a small increment of time, dt (1):

$$\frac{dM}{dt} = BA\,(C_s - C_b) \qquad \text{(Eq. 1)}$$

Here B is a mass transfer coefficient or dissolution rate coefficient, A is the *effective* surface area, C_s is the drug's solubility and also its concentration at the interface of the solid surface with the dissolving medium, and C_b is the bulk phase concentration. The mixing action of local fluid flow over the solid's surface is the primary factor determining the dissolution rate coefficient, and the more forceful the shearing action is, the larger the value of B. Therefore, vigorous stirring accelerates solution rates. However, hydrodynamics and therefore the dissolution coefficient normally cannot be controlled *in vivo*. The effective state of subdivision of a solid and the nature of the solid surface determine the *effective* surface area for the dissolution reaction. Reducing particle size increases the actual surface area but, if the particles remain aggregated, they may dissolve as slowly as a single large mass. Thus dispersibility of particulates as well as size reduction must receive a great deal of developmental attention, especially for drugs which

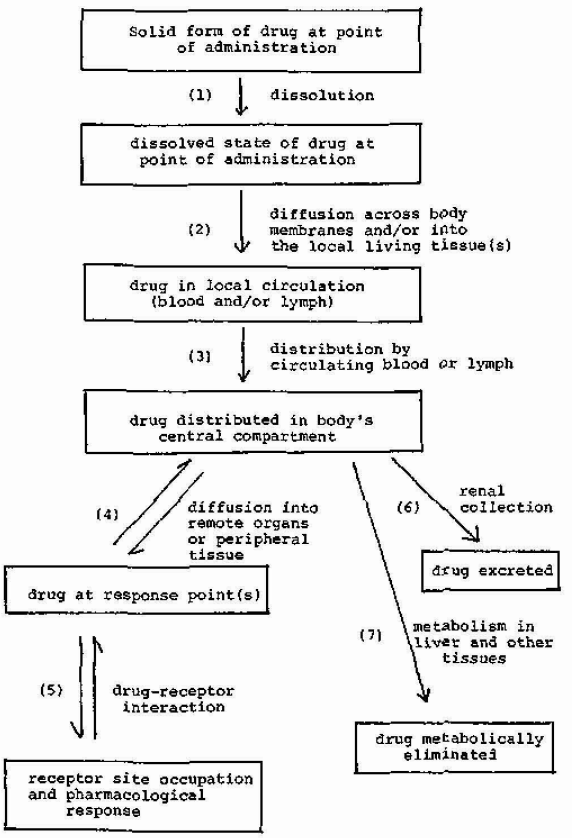

Figure 1

have solubility related absorption problems by the oral route. The ultimate limit on the rate of solution, however, is the solubility itself. From drug to drug it exhibits the widest extremes in its values of all the dissolution rate determining parameters. For a specified drug it also sets the upper limit on the concentration differential $(C_s - C_b)$. Sometimes the solubility of a given drug can be manipulated through physical methods such as the preparation of high free energy polymorphic and solvate crystalline forms. On other occasions solubility may be chemically tailored as done through prodrug approaches. Since solubility is the main factor differentiating compounds with regard to dissolution abilities, it has an enormous impact on the selection of a drug candidate from the many congeners available to be developed and marketed.

In the absorption, distribution, metabolism and elimination scheme outlined in Figure 1, the second indicated step is absorption. In very general descriptive terms this involves diffusion from a region of external application to another region inside of a tissue where the drug either is active (local effect) or where it gains entrance to the circulatory system. No matter whether a discrete membrane is involved or not, there is a thickness of tissue which acts as a barrier to diffusion. Once the drug has gained entrance to the downstream side of the barrier, the rate of the mass transfer process can be described by (2):

$$\frac{dM}{dt} = PA\,(C_o - C_i) \qquad \text{(Eq. 2)}$$

This equation has the same form as the dissolution equation but now dM/dt is the amount of the drug penetrating the barrier in an instant of time. A is the area of the application or the area of the membrane involved and P is another mass transfer coefficient termed the permeability coefficient. The value of P is determined by the ease of diffusion of the drug in the various phases of the membrane and by the thickness of the membrane, factors set apart from solubility, but it is also in part determined by distribution coefficients between the application and the membrane's phases, which can be viewed as relative solubilities. The bracket term, $(C_o - C_i)$, is the difference in concentration of the permeant on opposite sides of the barrier and is often simply represented by ΔC. In many cases C_i represents the systemic concentration of the drug and, as such, is generally negligibly small. Regardless, barring supersaturation, ΔC's magnitude is at its maximum when C_o, the concentration of the drug at the point of application, represents a saturated state:

$$\Delta C_{max} = (C_s - C_i) \qquad \text{(Eq. 3)}$$

In this manner solubility directly sets an upper limit on absorption rates.

Even the occupation of a set of biological receptors can be directly related to the saturated state of a solution, although this is normally not the case. Usually a drug's action is remote from the site of administration, in which case solubility only figures remotely in the eliciting of a response. There are, however, some exceptional instances where the active sites are more or less directly accessed. For example, the taste buds of the oral cavity are bathed by the fluids of orally administered liquids. If binding of the solutes in such preparations to the taste response provoking sites on the taste buds follows Langmuir's sorption isotherm, then the concentration dependency for this receptor interaction may be stated as:

$$F = \frac{QC}{1 + QC} \qquad \text{(Eq. 4)}$$

where F is the fraction of sites occupied, Q is a constant describing the microscopic binding equilibrium between sites and surrounding medium, and C is concentration in the medium. Up to a point, the higher the concentration, the greater the fractional coverage of the receptors and, in turn, the greater the response. It is possible for essentially full coverage and maximal response to be obtained at a solution concentration less than saturation depending on the magnitudes of Q and C. However, when the product of QC falls well short of unity all the way to the drug's solubility, then the maximum site coverage and associated response occurs at the saturated solution condition in the aqueous environment of the receptor. Normally, as a drug is modified chemically and made more hydrophobic, the magnitude of the binding constant, Q, is increased. However, solubility in an aqueous medium as found in the oral environment is invariably affected in the opposite direction. With some irregularity, aqueous solubilities of homologs tend to be suppressed to an even greater extent than receptor

site binding constants are increased. Thus the product, $(Q C_s)_n$, tends to smaller and smaller values as the chain length (hydrophobicity), n, lengthens. Because of this it is possible to make long alkyl chain derivatives with little or no tendency to evoke a taste response. What, in effect, happens is that the solid-solution equilibrium is driven down to a concentration below the threshold for a response. By such methods, noxiously bitter drugs like chloroamphenicol and clindamycin have been made reasonably palatable as palmitate esters, extending their use to pediatric patients.

To this point the solubility concerns considered are those governing the behavior of drugs during or after their administration. Earlier problems facing a formulator center around the initial preparation of solutions of drugs suitable for administration. Limited solubility is especially troublesome when injectable solutions are desired. Problems here begin with the fact that some drugs are plainly poorly soluble no matter the solvent. When severe toxicological constraints on solvent choice are taken into account, which limits physiologically tolerable solvents to water and a few water miscible organics where injectibles are concerned, the task of solution preparation becomes formidable. Compounding the complexity, drugs represent a diversity of chemical types. Strong electrolyte salts, weak electrolytes and non-electrolytes of widely ranging polarity are all well represented in the drug armamentarium. Each of these solute types must be approached differently in terms of solubilization. For each type general techniques of solubilization have become established mostly through years of formulating experience. The physical phenomena underlying these approaches are only now becoming well understood. Application of these concepts offers the formulator swifter resolution of solubility related problems.

B. General Thermodynamics Considerations: In its context in this review, solubility refers specifically to the solution equilibrium between a solute, generally a solid in a defined state of crystallinity, and a solvent. This defines the saturated solution condition. It should be kept in mind that a solute or solvent can technically by any state of matter. Only those cases where liquid or solid solutes are dissolved in liquid solvents are to be considered here.

Intermolecular forces within the pure solid solute (or within the solute rich liquid phase where liquid in liquid solubility is concerned) and within the solution phase determine the position of the solubility equilibrium; an understanding of these is necessary to interpret solubility. Since it involves an equilibrium, the process of forming a saturated solution can also be treated with full thermodynamic rigor. A description of the thermodynamic events, interpreted in so far as possible in terms of intermolecular interactions, presently provides the most insightful approach to characterizing solution phenomena.

The second law of thermodynamics provides necessary and sufficient criteria for judging whether or not a system is at equilibrium. In its most general form the second law states that the universe naturally tends towards its most random state. This means that interacting systems, chemical or otherwise, overall become increasingly disordered in the course of their spontaneous change. Equilibrium within a system is achieved when the maximum possible disorder for a system and its surroundings is attained. For an isolated system, literally one without contact with its surroundings, equilibrium is attained when the system's disorder itself reaches its attainable maximum. Entropy is the quantitative measure of the disorder and the second law of thermodynamics can be rephrased to say that in a spontaneously occurring process or reaction the entropy of the universe increases. This is an unconditional statement! The universe includes a system, which is that part of the objective world isolated for thermodynamic study, and the surroundings, which in pragmatic terms includes that part of the rest of the objective world capable of influencing events in the system. Thus, in an irreversible, spontaneous process:

$$\Delta S_{\text{universe}} = \Delta S_{\text{system}} + \Delta S_{\text{surroundings}} > 0 \quad \text{(Eq. 5)}$$

While overall entropy increases during spontaneous change there is no net change in the entropy of the universe for systems in equilibrium, including the continuous equilibrium of the reversible process.

It is usually possible to evaluate changes in the magnitudes of critical thermodynamic variables (state functions) within a system under study. It is not a straightforward matter, however, to characterize concurrent thermodynamic events in the surroundings. For this reason derivative restatements of Eq. 5 were developed long ago which place the criteria for non-equilibrium and equilibrium strictly in terms of measurements within the system. The most familiar and useful of these are the criteria based on Gibbs free energy. The Gibbs criteria may only be applied to constant pressure, isothermal processes in closed systems which involve no work but the work of expansion or compression of the system, so-called PV work. These boundary conditions are the prevailing conditions for most laboratory investigations as experiments are most often carried out in the open and at atmospheric pressure, at ambient or experimentally fixed temperature, and with conservation of a system's mass (if not actually in a closed system).

A system's Gibbs free energy decreases during spontaneous change providing the stated boundary conditions of temperature, pressure and work are met. Gibbs free energy is given the symbol G. It follows for a process under consideration that $[\Delta G]_{T,P,\text{ only PV work}} < 0$ indicates a spontaneous, irreversible process while $[\Delta G]_{T,P,\text{ only PV work}} \leqq 0$ indicates either a state of equilibrium or a process which can only be affected through the expenditure of work (by definition a process which cannot proceed spontaneously). At constant temperature and pressure the Gibbs free energy change between final and initial states of a system, $G_{II} - G_I = \Delta G$, is related to changes in the system's enthalpy (heat content) and entropy through:

$$\Delta G = \Delta H - T\Delta S \quad \text{(Eq. 6)}$$

The enthalpy change, $H_{II} - H_I = \Delta H$, is the quantity of heat absorbed or evolved by the system during the process to maintain its isothermal condition; that is, $\Delta H = q_p$ for the constant pressure process. By convention, heat absorbed by a system is positive heat. The terms, ΔS (or, more formally, $S_{II} - S_I$) and T, in Eq. 6 are the entropy change and absolute temperature, respectively.

Since $\Delta G < 0$ characterizes spontaneous change in a system,[1] processes continue until the Gibbs free energy reaches its minimum value, at which time the system is in equilibrium within itself and with its surroundings. The greater the difference in Gibbs free energy between the system's prevailing state and its final equilibrium state (the larger the possible ΔG for a process), the further a system is from equilibrium and therefore the greater is the ultimate extent of reaction. According to Eq. 6, negative values of ΔH and positive values of ΔS increase the negative magnitude of ΔG and therefore favor reaction. A negative value of ΔH is synonymous with an exothermic reaction, consistent with the general observation that reactions which "heat up" are spontaneous. Absorption of thermal energy (positive ΔH) and increased system order (negative ΔS) are in the direction of limiting or forbidding self driven change. These generalities apply to all processes, chemical and physical.

During any reaction a system goes from some initial state to some final state. Thus the solution reaction can be written as:

$$\underset{\text{Initial State}}{\text{Solute} + \text{Solvent}} = \underset{\text{Final State}}{\text{Solution}} \quad \text{(Eq. 7)}$$

Once the solute and solvent "reactants" are placed in contact, the solution process commences spontaneously and continues until there is either total solution or until the capacity of the solvent to take up the solute is exhausted, that is, until a saturated solution is obtained. Either way, the Gibbs free energy change for the solution process may be generally described by:

$$\Delta G = \Sigma G_i \text{ (Products)} - \Sigma G_i \text{ (Reactants)} \quad \text{(Eq. 8)}$$

In the case of a solid-solution equilibrium where there is unreacted solute, the excess, undissolved solid appears as both reactant and product and its contribution to the free energy change cancels. Therefore, it need not be considered explicitly. With this proviso it follows that:

$$\Delta G_{\text{solution process}} = G_{\text{solution}} - (G_{\text{solute}} + G_{\text{solvent}}) \quad \text{(Eq. 9)}$$

where G_{solute} refers only to that amount of solute which has actually dissolved. In terms of enthalpy and entropy the equation becomes:

$$\Delta G_{\text{solution process}} = H_{\text{solution}} - (H_{\text{solute}} + H_{\text{solvent}}) - T[S_{\text{solution}} - (S_{\text{solute}} + S_{\text{solvent}})] \quad \text{(Eq. 10)}$$

It remains to select thermodynamic reference states for the solute and solvent. For liquid solutes and solvents the pure liquid state is an especially convenient choice, and the effective concentrations (thermodynamic activities) of liquid components are taken as the ratios of their existing vapor pressures to their neat liquid vapor pressures. The standard state usually chosen for solid solutes is the melted solid cooled without crystallization to the temperature of the experiment, the so-called super-cooled liquid state. This choice of solid reference state allows the solution phase's formation to be treated simply as the mixing of two liquids. Fusion and cooling of the solid to form the super-cooled melt is then dealt with separately and additively, which is perfectly acceptable thermodynamically. The free energy change accompanying the formation of a solution from a solid, non-electrolyte solute and solvent is:

$$\Delta G_{\text{solution process}} = H_{\text{solution}} - (H_{\text{SCL}} - \Delta H'_f + H_{\text{solvent}}) - T[S_{\text{solution}} - (S_{\text{SCL}} - \Delta S'_f + S_{\text{solvent}})] \quad \text{(Eq. 11)}$$

Here the subscript SCL refers to the super-cooled liquid state and the subscript f refers to fusion. In this equation the fusion terms are written with a superscript as technically, they include, in addition to the actual enthalpy and entropy of fusion, changes in enthalpy and entropy accompanying the hypothetically separable heating of the solid solute to its melting point and cooling the formed melt to the experimental temperature. A last technicality is that, when more than one solution phase participates in the final equilibrium, as with mutually saturated liquids, the changes in the system's free energy, enthalpy and entropy represent the summed changes in both distinct phases.

C. Intermolecular Forces: As mentioned earlier, some knowledge of intermolecular forces, which are outlined in Table I, is also helpful in coming to grips with solubility phenomena. All chemical and physical change except that involving subatomic particles is the consequence of a rearrangement of the chemical bonds holding atoms together as molecules and the "physical bonds" causing molecules to associate. During reactions some bonds are broken and some new ones are formed, with change in the internal energy of a system, all of which is commensurate with a rearrangement of the participating atoms and/or molecules. At *constant pressure* the change in internal energy, ΔE, plus the energy gain or loss associated with the expansion or contraction of the system, a part of the PV-energy of a system, yields the enthalpy change, ΔH. The net gain or loss of atomic or molecular order is the microscopic basis of the entropy change, ΔS.

Almost all solubility phenomena rest on the changing association of matter through "physical bonds" or, more properly, intermolecular forces. It is only when there is ionization that any form of what we normally regard as chemical bonding, specifically the energy to separate ions of unlike charge, becomes a factor. Among other things,

TABLE I: Intermolecular Forces

A.	*Van der Waals Forces*
	1. London Dispersion Interaction
	2. Debye Interaction
	3. Keesom Force of Dipole-Dipole Bonding
B.	*Hydrogen Bonding*
C.	*Ionic Interactions*
	1. Ion-Ion Bonding
	2. Ion-Dipole Bonding
	3. Ion-Induced Dipole Interaction
D.	*Repulsive Forces*

[1] A closed system, constant temperature and contrast pressure and only PV work are assumed in the remainder of the text and the reader should not lose sight of these necessary boundary conditions.

intermolecular forces are responsible for the condensed states of most matter (metals and salts excepted). Like other interactive forces in nature, they are electrostatic in origin, but they are far weaker in individual bond strength than are the strong covalent and ionic bonds which link atoms in the molecular and ionic assemblies which exist at ordinary temperatures. The summation of all intermolecular forces holding matter in a condensed form yields the cohesive energy (or, more formally, the internal energy of cohesion) of that matter. This is readily experimentally estimated for pure constituents from the internal energies of vaporization (neat liquids) or sublimation (solids) as there is usually negligible net attractiveness in the formed gaseous states. Therefore, the net energy change solely represents that of molecular separation. Cohesive energy on a per unit volume basis is referred to as the cohesive energy density. When interactions between different materials are being considered, cohesion is used to describe the interactions within the pure phases (between like molecules) while adhesion describes the interspecies attractiveness.

Of all the possible purely physical interactions, London's dispersion force and hydrogen bonding are of the greatest importance in solubility and solubilization, at least in so far as nonelectrolytes are concerned. When charged atoms or molecules are considered, ion-dipole interactions are also a principal solubility determining factor. A listing of the types of intermolecular forces is presented in Table I. There are three distinct categories, van der Waals forces, hydrogen bonding and ionic interactions. A complete description of these forces is outside of the scope of this review but there is reason to discuss aspects of the subject in at least a little detail in order to correct a few widely held misconceptions.

Van der Waals forces include three distinguishable modes of interaction, namely the London's dispersion force, the Debye force and the Keesom force. The first of these, the London dispersion force (or the force sometimes referred to as the induced dipole-induced interaction) is the most ubiquitous form of physical association of matter. It is generated through the coordination of the electronic motions of the countless atoms comprising a finite system. The electron motions of an atom are most correlated with those of its nearest neighbors and the induction time frame from atom to atom is measurable in terms of the time frame of electronic oscillations, $\sim 10^{-14}$ seconds. The electron motions become less and less synchronized as the distance between atoms of reference in a condensed phase is increased and ultimately the interaction passes from attraction to repulsion (retardation). Since the interaction between specific atoms decays rapidly with distance, neighboring atom interactions predominate and the net effect is attraction. The correlation length, or distance over which the electronic fields are at least partially in phase and attractive is related to the optical density of the material in question. In nonoptically dense media such as water and the myriad organic liquids of the chemistry lab, correlation lengths are measured in *tens of centimeters!* Also of great consequence, the electronic motions underlying the London force instantaneously accommodate to what are, in relative terms, slow translational movements of molecules which cause them to reorient in space. Thus, this force is independent of intermolecular juxtaposition. As a result, the London force is relatively temperature insensitive.

A great misconception about London's attractiveness is the belief that the net attractiveness is exceedingly short ranged. This is true for two isolated atoms considered as the sole interactants. But in a condensed phase the proper summation of the interactions of all atoms over all other atoms, which involves multiple integrals, yields a net attractiveness with long range character approaching that found between ions! A second misconception about London's attractivenes is that it is relatively weak. Again, this is true if the focus is an isolated pair of atoms. But in summation over all atoms in a finite system the net attractiveness is hardly insignificant. Since there is no preferred molecular orientation to this force, its contribution to the cohesive energy per unit volume of semi-polar and polar substances is, with few exceptions, far greater than that of co-existing Debye and Keesom forces, which on a single bond basis may appear far stronger. This is readily seen in Tables II and III. In Table II dispersion forces are roughly 20% of the association energy of water despite its hydrogen bonding networks. In Table III acetone with its strong dipole is seen to have but twice the cohesive energy density of alkanes of comparable molecular weight. Butyl chloride's cohesive energy density is only marginally greater than hexane's. When hydrogen bonding is possible, however, cohesive energy densities jump to high levels as seen in the alkanols, polyols and water.

The Debye force involves the perturbation of the electronic structure of an atom or molecule by the permanent dipole of a neighboring molecule, the so-called dipole-induced dipole interaction. The net strength of this interaction depends on the strength of the dipole and the polarizability of the induced molecule. This force is found when there are dipolar molecular species present but it generally makes a minor contribution to cohesiveness. It is never repulsive; it is not considered an orientating force.

The Keesom force arises as the result of interactions of two fixed dipoles. In order for the individual interaction to be attractive the positive and negative centers of the two participating molecules have to be favorably oriented. The strength of interaction depends on the dipole movements of the molecules and their relative positions in space. It takes a strong dipole–dipole bond to overcome the translation energies of molecules so that in most condensed phases of dipolar substances there is extensive cancellation of attractiveness by pairs of molecules which have attained unfavorable orientation as the consequence of thermally induced motions. Because of the orientational requirement, Keesom forces are highly temperature sensitive.

Hydrogen bonding is a unique interaction in which a proton covalently attached to one electronegative center is shared with a second electronegative center. The bond is regarded as partly covalent and partly simple electrostatic. The strength of the individual bond depends on the electronegativities of the centers sharing the proton and can be as much as 6–7 Kcal/mole for bonds involving oxygen and nitrogen atoms. Fluorine is mentioned widely in hydrogen bonding discussions as another electronegative atom of

TABLE II

Substance	Force Contribution: Dispersion	Induction	H-bonding and Orientation	Ion–Ion	Total Internal Energy of Association K_{cal} @ 25 °C
H_2O	2.15	0.46	8.69	~	11.30
HCl	4.02	0.24	0.79	~	5.05
HI	6.18	0.027	0.006	~	6.21
NaCl	~3.0	~	~	180	183.0
C_6H_{14}	6.96	~	~	~	6.96

Table III: Cohesive Energies of Selected Organic Liquids

Class and Substance	Normal Boiling Point (°C)	Molecular Weight	Solubility Parameter $(cal/cm^3)^{1/2}$	Cohesive Energy Density (cal/cm^3)	Liquid Density (gm/cm^3)	Molar Volume, $\bar{V}$ (cm^3)	Molar Cohesive Energy, $\Delta\xi$ (cal/mole)
HYDROCARBONS:							
Propane	−42.1	44.1	5.77	33.3	0.493	89.5	2,980
n-Butane	−0.5	58.1	6.59	43.4	0.573	101.4	4,400
n-Pentane	36.1	72.2	7.02	49.3	0.622	116.1	5,960
n-Hexane	68.7	86.2	7.27	52.9	0.655	131.6	6,960
n-Heptane	102.4	100.2	7.50	56.3	0.679	147.6	8,310
n-Octane	123	114.2	7.54	56.9	0.699	163.4	9,300
n-Nonane	148.8	128.3	7.64	58.4	0.714	179.7	10,490
n-Decane	172.5	142.3	7.74	59.9	0.727	195.7	11,730
ALCOHOLS:							
Methanol	64.5	32.04	14.50	210.3	0.787	40.7	8,560
Ethanol	78.3	46.07	12.78	163.3	0.785	58.7	9,580
n-Propanol	97.2	60.1	12.18	148.4	0.799	75.2	11,160
iso-Propanol	82.5	60.1	11.44	190.9	0.781	77.0	10,070
n-Butanol	117.7	74.12	11.60	135	0.806	92.0	12,420
iso-Butanol	99.5	74.12	11.08	123	0.802	92.4	11,370
n-Pentanol	138.0	88.15	11.12	123.7	0.811	108.7	13,440
n-Hexanol	157.0	102.18	10.77	116.0	0.815	125.3	14,540
n-Heptanol	176.2	116.20	10.50	110.3	0.819	141.9	15,650
n-Octanol	195.2	130.23	10.30	106.1	0.822	158.4	16,810
n-Nonanol	213.5	144.26	10.13	102.6	0.825	175.0	17,950
n-Decanol	229.8	158.29	10.03	100.6	0.826	191.5	19,270
n-Undecanol	244.4	172.31	9.85	97.0	0.828	208.0	20,180
n-Dodecanol	259.6	186.34	9.78	95.7	0.830	224.6	21,480
GLYCOLS, DIOLS, POLYOLS:							
Ethylene glycol	197.6	62.07	17.05	290.7	1.110	55.9	16,270
Propylene glycol	187.3	76.1	14.99	224.7	1.033	73.7	16,550
1,3 Propane diol	214.9	76.1	16.11	259.5	1.050	72.5	18,810
Glycerol	290.1	92.09	17.69	312.9	1.259	73.2	22,710
1,3 Butane diol	207.0	90.12	13.76	189	1.004	89.8	16,970
OTHER MISCELLANEOUS SOLVENTS:							
Benzene	80.1	78.11	9.16	83.9	0.874	89.4	7,500
Ether	34.7	74.12	7.53	56.7	0.708	104.7	5,940
Acetone	56.1	58.11	9.62	92.5	0.785	74.0	6,840
Butyraldehyde	74.8	72.11	9.09	82.6	0.797	90.5	7,480
Butylchloride	78.4	92.57	8.37	70.1	0.881	105.1	7,370
Chloroform	62.1	119.4	9.16	83.9	1.480	80.7	6,770
Carbon tetrachloride	76.5	153.8	8.55	73.1	1.585	97.0	8,090
Water	100.2	18.02	23.53	553.7	0.9971	18.07	10,010

consequence. While it allows strong hydrogen bonding networks in hydrogen fluoride, one should take note that the organic fluorine atom (fluorine attached to a carbon atom) is essentially devoid of hydrogen bonding ability and thus is a liability with respect to aqueous solubility. Carboxylic acids, on the other hand, are capable of interacting exceedingly strongly through a pair of H-bonds and they form relatively stable dimers in organic media through hydrogen bonding. In water and alcohols and glycols structuring related to hydrogen bonding has a more fleeting nature but it is nevertheless highly significant within the time scale of molecular events. Therefore, such solvents exist in an ordered state relative to apolar solvents. In water and the other mentioned polar solvents hydrogen bonding is the major contributor to the internal energy of cohesion but not so much so that the net London's force is made insignificant. Because hydrogen bonding involves precise posturing of its molecular participants, it is a highly temperature sensitive interaction and it rapidly decays as temperature is raised.

The ion–ion interaction is a strong and long range force. It is the dominant association force in high melting salt crystals, in which capacity it is a "chemical bond." Yet, unlike covalent bonding, the energy of ion to ion interaction figures directly into solubility as the energy for dissociation of a salt into ions is an integral part of the energetics of the overall solution process. To reflect this, eq. 11 can be rewritten:

$$\Delta G_{\substack{\text{solution}\\ \text{process}\\ -\text{salt}}} = H_{\text{solution}} - (H_{\text{SCL}} - \Delta H_f' - \Delta H_{\text{ionization}} + H_{\text{solvent}}) - T[S_{\text{solution}} - (S_{\text{SCL}} - \Delta S_f' - \Delta S_{\text{ionization}} + S_{\text{solvent}})] \quad \text{(Eq. 12)}$$

More will be said of ionization energy later. For the moment it should be noted that ion–ion attractiveness can also be important in the solubility behavior of weak organic electrolytes. This is so even though large organic ions tend to crystallize in molecular rather than ionic assemblies and despite the fact that other forms of solute-solvent association are always involved. Once the salt unit has dissociated into ions in a solvent, however, ion–ion attractiveness is but a secondary factor determining the position of the solubility equilibrium. That is to say, ionic strength effects on ionic activities modulate the position of equilibrium somewhat but it is the strength of the formed ions' interactions with surrounding solvent molecules which determines whether there is an appreciable amount of salt dissolved or not.

Of the possible ion–solvent interactions, the ion–dipole interaction is the overwhelmingly important one. Without extensive, strong ion–dipole bonding, inorganic salts are simply not soluble. An inorganic ion is a monopole and, for atomic ionic species, the charge on the ion is centered. An ion's interaction with a neighboring dipole depends on its charge and on the dipole moment and orientation of the dipole. Calculations indicate the individual interaction of a dipole with favorable orientation close to the ion's surface can be of the same order as a strong hydrogen bond, ~5 kcal/mole. The size of the ion is also a factor as it limits the closeness of approach of the nearest dipoles. Thus ions from the latter part of the periodic table with multiple electronic shells shielding the center of charge have less strength of ion–dipole interaction than small ions of the same charge, and taking all factors into account, their salts tend to be less soluble. The interaction is orientational with respect to the dipolar partner in the bond and it is relatively long range. Of great importance, an ion interacts with many dipoles at the same time in much the same way as a magnet can attract and fix into position myriad iron filings. Hydrated ions, as an example, are surrounded by a thick envelope of water molecules fixed, albeit transiently, in place by ionic association. This structure is further stabilized by a hydrogen bonding network between the water molecules. Amongst other resulting behaviors, ions diffuse in water with effective radii far greater than attributable to the naked ions themselves. As the sum of the multiple associations, a large favorable enthalpy accompanies the solvation of ions in dipolar media and it is only because of this that inorganic salts have measurable solubilities. In other words, ion–dipole bonding is the only phenomenon in the energetic scheme associated with the solution of a salt which is capable of offsetting the enormously unfavorable energies associated with fusion of the inorganic salt to a melt and dissociation of the salt units to form discrete ions.

Thermodynamic considerations of ion–dipole bonding must also account for negative entropy due to ordering of the dipoles in this interaction. Here water, which based on experience is a good solvent for salts, has an advantage relative to most other solvents with strong dipoles. It is a highly structured liquid to begin with and new order associated with the formation of the ion's hydration shell represents a fractional increase in the overall solvent order in the system. Chloroform, which has a dipole of comparable strength to water's, exists in an essentially totally random molecular organization. Therefore, the solvation of ions would create a great deal of new order in chloroform. This is a subtle and often forgotten factor highly unfavorable to the solution of salts in organic solvents.

An ion is capable of inducing a temporary dipole in a nearby molecule. The ion-induced dipole interaction is dependent on the charge of the ion and the polarizability of the associated electrically neutral species. It is a weak interaction and therefore apolar solvents are essentially non-solvents for salts. This completes the list of important intermolecular attractive interactions.

It might be noted that there is no mention of hydrophobic bonding in either Table I or the text. This is because there is no such thing as a hydrophobic bond, although there are complex phenomena associated with the solution behavior of a hydrophobic substance in water which involve the self-association of water molecular at the molecular interface with the solute. These complex phenomena have been popularized as "hydrophobic bonding." The unique phenomena and their solubility manifestations will be discussed later when nonideality within aqueous media is considered. It is only important to realize here that "hydrophobic bonding" is merely the result of a complex interplay of the real intermolecular forces just described.

Finally, the same strong forces of repulsion which keep the atoms within molecules from collapsing into one another

limit the closeness of approach of different molecules. Repulsion associated with the Pauli exclusion principle is thus the counterbalance providing for an energy minimum for the condensed state.

These descriptions of the modes of intermolecular association together with consideration of the interactions found in various media allow an interesting definition of the nebulous idea of polarity. Molecules without ionic character are classified as being non-polar, semi-polar, and polar. Yet, if one asks a group of scientists what is meant by being "polar," one will get many disparate answer. Some will say polar molecules have strong dipoles, thereby placing polarity in terms of dipole moments. Water, ethanol and chloroform have nearly the same dipole moment and by this index would be comparatively polar, a conclusion hardly in keeping with actual behavior.

Others will suggest polarity relates to the polarizability of molecules, an equally unsatisfying index if broadly applied. Some will point out that polarity should be placed in terms of partition coefficients. This works well and may be the most universally acceptable measure. Based on the discussion here polarity could also be couched in terms of cohesive energy densities (or their square roots which are called solubility parameters).

More importantly and irrespective of the scale, we see from this discussion that polarity, whatever it is, is connected with different abilities of the molecules under question to interact with themselves and with other molecules. Apolar substances such as hexane and carbon tetrachloride only interact within themselves through dispersion forces and with other matter through dispersion forces and possibly weak induced forces. Low molecular weight apolar substances, if they are liquids at all, vaporize at relatively low temperatures. Cohesive energy densities (cohesive energies per unit volume) of much less than 100 cal/cm^3 are typical, as seen in Table III, column 5.

Semipolar substances such as ether, chloroform, acetone and the various alkanols contain permanent dipoles. However, they are of themselves either incapable of hydrogen bonding or their hydrogen bonding tends to be weak or limited in extent so that hydrogen bonding energy is but a small fraction of the net energy of interaction. Thus, they differ from apolar substances in that they have significant dipolar interactions and possibly limited hydrogen bonding *in addition to the London dispersion forces.* They are slightly higher boiling and more easily solidified. Cohesive energy densities of semipolar liquid are larger than found for totally apolar substances, directly reflecting these additional modes of self association (Table III, column 5).

Polar substances are represented either by materials capable of forming extensive hydrogen bonding networks (i.e., water, propylene glycol, methanol, sucrose, etc.) or, like dimethyl sulfoxide and dimethyl formamide, they have unusually strong dipolar interactions. As in the case of formamide, they may exhibit both. Liquid polar substances tend to be viscid and very high boiling for their molecular weights. Many polar substances are solid at room temperature and are often found to have high melting points due to strong intracrystalline bonding. The net cohesiveness of polar substances is made up of dispersion forces (significant), dipolar forces (modest) and hydrogen bonding (usually the greatest contributor to cohesion) and other interactions of marginal significance. The additional strong intermolecular forces contributing to cohesiveness raises cohesive energy densities to very high levels (Table III, column 5).

These considerations form the basis for interpreting solubility patterns of organic compounds in water and the myriad organic solvents of the chemistry laboratory. Specifically, the enthalpy and entropy associated with the solution of a particular compound in a particular solvent provide strong clues to the underlying events. Coupled with understanding of how the molecules in question can molecularly associate and given that hypothesized molecular behaviors must be internally consistent with the thermodynamics, a good picture usually forms of the solubility event all the way to the molecular level. These features of solubility will be emphasized in the remaining parts of this review which will deal with quantitative solubility theories and solubilization techniques and examples.

General References

Hoy, K. L., "New values of the solubility parameters from vapor pressure data," *J. Paint Technology*, **42**, 76 (1970).

Kurpp, H., "Particle adhesion theory and experiment," *Advan. Colloid. Interface Sci.*, **1**, 111 (1967).

Israelachvili, J. N., and Ninham, B. W., "Intermolecular forces—the long and the short of it," *J. Colloid. Interface Sci.*, **58**, 14 (1977).

Mahan, B. H., *Elementary Chemical Thermodynamics*, W. A. Benjamin, Inc., Menlo Park, CA, 1963.

Lewis, G. N., and Randall, M., as revised by Pitzer, K. S., and Brewer, L., *Thermodynamics, 2nd Ed.*, McGraw Hill Book Co., New York, NY 1961.

PDA Journal
of Pharmaceutical Science and Technology