Pharmaceutical Dosage Forms:

Parenteral Medications

Third Edition

Volume 1: Formulation and Packaging

Edited by
Sandeep Nema
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6 Drug solubility and solubilization

Ching-Chiang Su, Lan Xiao, and Michael Hageman

SOLUBILITY AND PARENTERAL PRODUCTS

This chapter provides a practical description of the physical phenomena leading to molecular level solubilization or dispersion of solutes (drugs) in a way that should enable the formulator to make informed decisions regarding formulation strategies for parenteral delivery. Solubility is discussed from the perspective of a thermodynamically defined equilibrium requiring several energetic steps in going from solute in a condensed phase to a solute in solution. Discussions will include the nonequilibrium state of supersaturation while focusing on the fit-for-purpose definition of solubility targeting parenteral drug delivery. The definition of solubility can relate to the solubility of any physical state of matter in another, or even in a similar state (miscibility), but this chapter will focus on solubility of a solid state in a liquid media, resulting in a solution mixture, which is of primary pharmaceutical importance for parenteral drug delivery (1).

Thermodynamic solubility can be described as the condition where the chemical potential of solute (μ_{solute}) in solution is in equilibrium with, and equal to, the chemical potential of the solute in its respective solid phase (μ_{solid}) under consideration (2). At a constant temperature and pressure, this equilibrium defines the saturated solution with respect to the designated solid phase and respective media. Any perturbation in the solute phase or solvent phase can result in a temporary metastable state of either supersaturation ($\mu_{solute} > \mu_{solid}$) or subsaturation ($\mu_{solute} < \mu_{solid}$), where the chemical potentials differ and the system will spontaneously attempt to reestablish equilibrium. Any effort to intentionally alter solubility will require a modification in the chemical potentials of either the solute solid state or the solute in solution.

To better understand strategies to modify solubility, three key energetic drivers for the solubilization process should be considered (2). The first step is the necessary energy input to overcome the intermolecular interactions of the solute in its respective condensed state (Fig. 1). The second step is the energy input necessary to overcome solvent-solvent interactions and create a cavity in the solvent which accommodates the solute. The unfavorable energy input to this point is then countered with the energy release occurring upon collapse of the solvent cavity around the solute and ensuing intermolecular interactions between solute and solvent.

Alterations in the solvent can influence both solvent-solvent interactions and subsequent solvent-solute interactions. This is the basis for many of the cosolvent strategies used for solubilization, wherein the μ_{solute} is decreased shifting the equilibrium toward increased amounts of drug in solution. Solubilization through changes in the solid form of a drug (amphorous, polymorphs, etc.) leads to increases in the μ_{solid}, which also shifts the equilibrium, but also runs the risk of conversion to a more thermodynamically stable and less soluble solid form with time. Solubilization obtained through alterations in the solute's molecular structure has the potential to significantly alter solubility by impacting specific solvent—solute interactions or solute—solute interactions. This is probably the preferred strategy for enhancing solubility, but such molecular modifications are difficult to introduce once the drug development process on an entity has been initiated. Hence, molecular design modifications are best instituted through interactions with medicinal chemists in the discovery organization prior to drug candidate selection.

One of the most commonly used strategies to provide apparent increases in solubility, or total drug in solution, is to create alternative equilibria for the drug or solute to reside in. While these equilibria enhance the total amount of drug in solution, the μ_{solute} remains equivalent to that of the solid phase, that is, the intrinsic solubility is not altered but instead the μ_{solute} residing in some additional equilibrium is reduced through specific interations or altered solvation. Creation of alternative equilibria to "sequester" drug provides the basis for solubilization strategies, such as micellar partitioning, chemical ionization, complexation, and partitioning into emulsions.

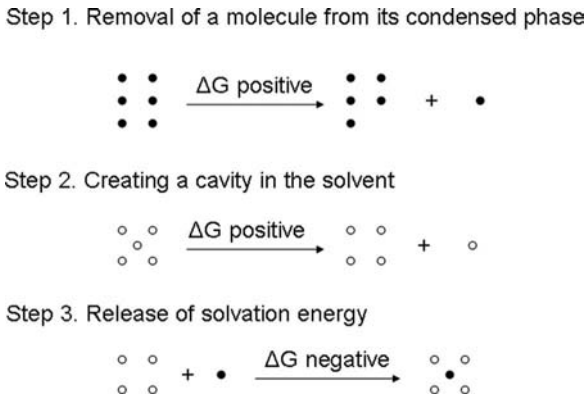

Figure 1 An illustration of the three steps needed for drug solubility.

In the simplest of terms, the solubility of a solute in a given solvent system, as defined by amount of drug dissolved, seems easily determined, but reliable, reproducible and meaningful numbers can be difficult to obtain. The more common methods are best described as "fit for use," wherein the solid phase of interest is incubated in solvent and the total amount of solute present in solution is measured. The method of solid-phase separation is critical and really defines the utility of the apparent solubility obtained. Typically, either filtration or centrifugation is used with subsequent assay of filtrate (filtration) or supernatant (centrifugation). Details of separation can be particularly important when colloid scale dispersions exist. Furthermore, as solubilities begin to drop below 1 μg/mL, issues of nonspecific adsorption to surfaces (filter, container), coupled with analytical detection limitations can result in highly variable values across labs.

Factors such as temperature, energy input and the nature of both the solid phase and the solvent can significantly impact how rapidly equilibrium is obtained. Approaching equilibrium from both a state of supersaturation and subsaturation taking measurements as a function of time is probably the best approach. At equilibrium both should approach similar values. When solubilities are >1 μg/mL, 24-hour incubation will generally approach 90% to 95% of equilibrium value, assuming particle sizes are small (3).

IMPLICATIONS OF SOLUBILITY FOR PARENTERALS

A common challenge in development of drugs intended for parenteral administration is the solubilization of a poorly soluble active ingredient (4). For intravenous (intravascular) injection, solubility of the active ingredient in the plasma needs to be below saturation upon dilution to prevent precipitation or formation of phlebitis. Injection of a drug into an extravascular site may establish a depot depending on the type of formulation administered. Drug absorption from a depot by passive diffusion and partitioning is dependent on drug solubility. Only the fraction of drug in solution is available for absorption. A critical difference between the pH of the administered drug solution and the physiological pH at the injection site (and/or solubility of the drug in a cosolvent vehicle and in physiological tissue fluid) can cause an unpredicted decrease in absorption due to precipitation of the drug at the injection site. Phenytoin is formulated as a sodium salt in a pH 12 solution of 40% propylene glycol, 10% alcohol and water for injection. When injected into muscle tissue, the large difference in pH and simultaneous dilution of propylene glycol with tissue fluids cause conversion of the sodium salt to less soluble free acid and precipitation at the injection site. Amphotericin B has a low aqueous solubility of 0.1 mg/mL at pH 2 or pH 11. However, Amphotericin B is highly soluble in liposomal intercalation and becomes an integral part of the lipid-bilayer membrane. These liposomal products permit administration by IV infusion. Another commonly studied low solubility drug is paclitaxel with an aqueous solubility of 0.1 μg/mL. Wheelar et al. manufactured an emulsion and liposome blend using corn oil, cholesterol and egg phosphotidylcholine containing 5 mg/mL of paclitaxel, a 50,000-fold increase in solubility (5).

PROPERTIES OF THE SOLVENT

A popular aphorism used for predicting solubility is "*like dissolves like*" (6). This statement indicates that a solute will dissolve best in a solvent that has a similar polarity to itself. This view is rather simplistic, since it ignores many solvent-solute interactions, but it is a useful rule of thumb. Strongly polar compounds like sugars or ionic compounds like inorganic salts dissolve only in very polar solvents like water, while strongly nonpolar compounds like oils or waxes dissolve only in very nonpolar organic solvents like hexane. The dielectric constant, solubility parameter and interfacial/surface tension are among the most common polarity indices used for solvent blending to improve solubility.

Generally, the dielectric constant of the solvent provides a rough measure of a solvent's polarity. It is the electric permittivity ratio of solvent to vacuum. It measures the solvent's ability to reduce the strength of the electric field surrounding a charged particle immersed in it. This reduction is then compared with the field strength of the charged particle in a vacuum. In general, polar solvents have higher dielectric constant values than nonpolar molecules. Solvents with a dielectric constant of less than 15 are generally considered nonpolar (7). The dielectric constants of some commonly used solvents and cosolvents in parenteral products are listed in (Table 1).

Gorman and Hall (10) studied the solubility of methyl salicylate in isopropanol-water mixtures, and obtained a linear relationship between log mole fraction of the methyl salicylate and the dielectric constant of the mixed solvent.

For a solution to occur, both solute and solvent molecules must overcome their own intermolecular attraction forces, so called van der Waals forces, and find their way between and around each other. This is accomplished best when the attractions between the molecules of both components are similar. The solubility parameters are defined to express the cohesion between like molecules. It is a numerical value that indicates the relative solvency behavior of a specific solvent and can be calculated from heats of vaporization, internal pressures, surface tensions, and other properties, as described by Hildebrand and Scott (11). The heat of vaporization in conjunction with the molar volume of the species, when available at the desired temperature, probably affords the best means for calculating the solubility parameter. It can be expressed as equation (1).

$$\delta = \left(\frac{\Delta H_v - RT}{V_l}\right)^{1/2} \tag{1}$$

where ΔH_v is the heat of vaporization and V_l is the molar volume of the liquid compound at the desired temperature, R is the gas constant, and T is the desired absolute temperature. Hildebrand and Scott include solubility parameters for a number of compounds in their book. A table of solubility parameters has also been compiled by Hansen and Beerbower (12), wherein the authors introduced partial solubility parameters δ_D, δ_p, and δ_H. The parameter δ_D accounts for nonpolar effects, δ_p for polar effects, and δ_H to express the hydrogen bonding

Table 1 Dielectric Constant, Solubility Parameter, and Surface Tension of Common Solvents and Cosolvents

Solvent	Dielectric constant	Solubility parameter $(cal/cm^3)^{1/2}$	Surface tension 20°C (dyne/cm)
Water	78.5	23.4	72.8
Ethanol	24.3	12.7	22.4
Propylene glycol	32	14.8	38.0
Glycerin	43	16.5	64.3
PEG 300 or 400	35	9.9	43.5 (PEG 200)
Benzyl alcohol	13	12.1	40.7
Dimethyl sulphoxide (DMSO)	47	12.0	43.5
N,N-dimethylacetamide (DMA)	38	10.8	36.7
N,N-dimethylformamide (DMF)	37	12.1	39.1
N-methyl-2-pyrrolidone (NMP)	32	23.0	40.8

Source: From Refs. 8 and 9.

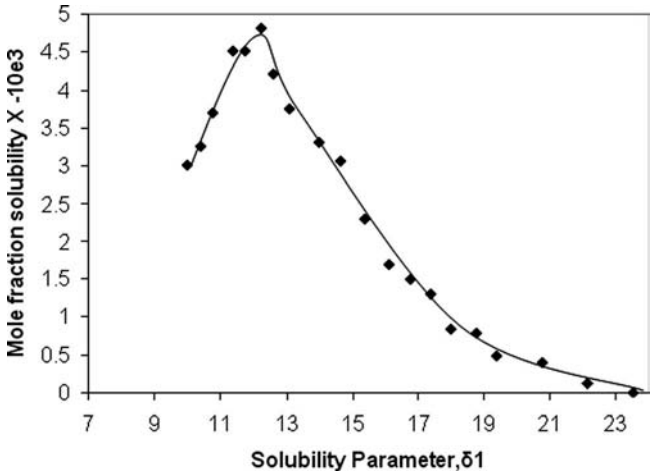

Figure 2 Solubility of trimethoprim in dioxane-water mixture of varying solubility parameter. *Source*: From Ref. 14.

nature of the solvent molecules. The sum of the squares of the partial parameters gives the total cohesive energy density $\delta^2_{(\text{total})}$ [eq. (2)]. Kesselring et al. have determined both total and partial solubility parameters using gas-liquid chromatography (13).

$$\delta^2_{(\text{total})} = \delta^2_{\text{D}} + \delta^2_{\text{P}} + \delta^2_{\text{H}} \tag{2}$$

The more alike are the δ values of two components, the greater is the mutual solubility, miscibility, of the pair. For example, the δ value of phenanthrene is 9.8; it would be expected to be more soluble in carbon disulfide with a δ value of 10 than in normal hexane with a δ value of 7.3. Conversely, δ of a drug can be estimated from measured solubility as a function of solvent solubility parameter (14) (Fig. 2).

Interfacial/surface tension is another solvent property caused by the attraction between the liquid's molecules by various intermolecular forces. It is a measure of the work required to create a cavity of unit area of surface from molecules in the bulk, hence relating to cavity formation for solutes. Polar solvent generally has higher surface tension than nonpolar solvent. Some surface tension and interfacial tension (against water) at 20°C are listed in Table 1 (15).

PROPERTIES OF THE SOLUTE

Drug molecules contain different structures and functional groups. The collective contributions from each functional group make the macroscopic physicochemical properties of the drug, which are a reflection of inter- or intramolecular interactions. For example, the stronger the attractions between molecules or ions, the more difficult it is to separate the molecules, therefore, the higher the melting point and poorer the solubility. The intra- or intermolecular forces are dictated by intrinsic molecular properties, such as polarizability, electronic factors, topology and steric factors, lipophilicity, hydrogen bonding, surface areas, volumes and connectivity, etc.

Molecular Properties

Polarizability and Electronic Factors

Polarizability is a characteristic property of the particular molecule. It is defined as the ease with which an ion or molecule can be polarized by any external forces. From electromagnetic theory, there is a relationship between polarizability α_{p} and dielectric constant ε of a molecule, where n is the number of molecules per unit volume [eq. (3)].

$$\frac{\varepsilon - 1}{\varepsilon + 2} = \frac{4}{3}\pi \cdot n \cdot \alpha_{\text{p}} \tag{3}$$

When a molecule cannot be represented by a single Lewis structure, that is, using an integral number of covalent bonds between two atoms, but rather has properties in some sense

intermediate to these, resonance structures are then employed to approximate the true electronic structure. Because of confusion with the physical meaning of the word resonance, as no elements actually appear to be resonating, it has been suggested that the term resonance be abandoned in favor of delocalization and delocalization energies (16).

An electric dipole is a separation of positive and negative charges. It can be characterized by dipole moment, μ, which is equal to the product of charge on the atoms and the distance between the two atoms bounded with each other. Many molecules have such dipole moments because of nonuniform distributions of positive and negative charges on the various atoms. Such is the case with polar compounds like hydroxide (OH^-), where electron density is shared unequally between atoms. Dipole moment is the polarity measurement of a polar covalent bond. The higher the polarity of a molecule the greater the dipole moment and the value can be calculated through the comparison of dielectric constant and the refractive index of the solutions.

Some drugs are known to form a charge-transfer complex with certain solvents. A charge-transfer complex (or CT complex, electron-donor-acceptor-complex) is a chemical association of two or more molecules, or of different parts of one very large molecule, in which the attraction between the molecules (or parts) is created by an electronic transition into an excited electronic state, such that a fraction of electronic charge is transferred between the molecules. The resulting electrostatic attraction provides a stabilizing force for the molecular complex. The association does not constitute a strong covalent bond and is subject to significant temperature, concentration, and host (e.g., solvent) dependencies and occurs in a chemical equilibrium with the independent donor (D) and acceptor (A) molecules.

The great majority of drugs contain ionizable groups; most are basic, some are acidic. The ionization constant (K_a) indicates a compound's propensity to ionize. It is a function of the acidity or basicity of group(s) in the molecule. Because of the many orders of magnitude spanned by K_a values, a logarithmic measure of the constant is more commonly used in practice, wherein the pK_a is equal to $-\log_{10} K_a$. The equilbria for acids [eqs. (4) and (5)] and for bases [eqs. (6) and (7)] are described as follows:

$$HA = H^+ + A^- \tag{4}$$

$$pK_a = -\log([H^+] \cdot [A^-]/[HA]) \tag{5}$$

$$HB^+ = H^+ + B \tag{6}$$

$$pK_a = -\log([H^+] \cdot [B]/[HB^+]) \tag{7}$$

Rearranging the pK_a equations give the well-known Henderson-Hasselbalch equations for both weak acid (HA) and weak base (B) and the ability to calculate the percentage of ionized species at any particular pH [eqs. (8) and (9)].

$$pH = pK_a + \log[A^-]/[HA] \tag{8}$$

$$pH = pK_a + \log([B]/[BH^+]) \tag{9}$$

When the pH is two units either side of the pK_a, then the drug will be almost completely ionized (BH^+, A^-) or unionized (B, HA). The solution pH and the pK_a are important because the charged form of a drug is more soluble than the neutral form. To have any realistic chance of significant pH-solubility manipulation for a parenteral, the pK_a for a base must be greater than 3 and for an acid less than 11.

Lipophilicity

Lipophilicty is the tendency of a compound to partition into a nonpolar lipid matrix versus an aqueous matrix. Lipophilicity is readily calculated, thanks to the work of Hansch and Leo (17).

It is a rapid and effective tool for initial compound property assessment. One traditional approach for assessing lipophilicity is to partition the compound between immiscible nonpolar and polar liquid phases. Traditionally, octanol is the nonpolar phase and aqueous buffer as the polar phase with the partition value, log*P* defined below [eq. (10)]. Log*P* is measured at a pH of the buffer where all of the compound molecules are in the neutral form.

$$\text{Log}\,P = \log \frac{[C_{\text{nonpolar}}]}{[C_{\text{polar}}]} \tag{10}$$

Hydrogen Bonding

The assumption that the solubility of a solute in a given solvent is related simply to the bulk properties of the pure components, that is, "like dissolves like," was originally intended strictly for systems involving only London dispersion forces. For quite polar solution components, the specific intermolecular interactions, such as hydrogen bonding, when they occur, are often the dominant factors in determining solubility (18).

A hydrogen bond is a special type of attractive interaction that exists between an electronegative atom and a hydrogen atom covalently bonded to another electronegative atom. Usually the electronegative atom is oxygen, nitrogen, or fluorine, which has a partial negative charge and is the hydrogen bond acceptor. The hydrogen then has the partial positive charge and is the hydrogen bond donor. The typical hydrogen bond is stronger than van der Waals forces, but weaker than covalent or ionic bonds and can occur intermolecularly, or intramolecularly. When hydrogen bonding between solute and solvent is possible, solubility is greater than expected for compounds of similar polarity that cannot form hydrogen bonds. Hansen and Beerbower (12) have introduced hydrogen bond partial solubility parameter, δ_H, to account for the nonideality effect from hydrogen bonding on total solubility (see above).

Topology and Steric Factors

It is believed that the variations in the magnitude of solubility of different solutes in water are caused by their dissimilar chemical structures and much attention has been paid to quantitative structure activity relationship (QSAR) studies of modeling the relationship between chemical structure and solubility of organic compounds. Molecular topology as one of the structure indices has been used widely to study the solubility of compound in different models (18,19).

Molecular topology is the mathematical description of molecular structure allowing a unique and easy characterization of molecules by means of invariants, called topological indices, which are the molecular descriptors to correlate with the experimental properties. Different from the conventional physicochemical descriptors, topological indices (TIs) allow the use of the QSAR relations to design new compounds from scratch. This is possible because, contrary to the physical parameters, the algebraic descriptors are not indirectly related to structure but they are a mathematical depiction of the structure itself.

Besides the chemical structure of the molecules, the spatial arrangement of their functional groups can play a significant role in compound solubility when it influences the degree of interaction between solute and solvent. For example, two isomers can exhibit very different solubilities in the same solvent (20). The influence of the location of the functional groups is referred to here as the steric effect. For strongly interactive solvents like water, the steric effect is particularly severe and sometimes dominating when it hinders or promotes hydrogen bonding interaction. On the other hand, structural alterations that are not in the vicinity of an interacting functional group and do not alter the functionality of the group, have little influence on solubility.

Surface Areas, Volumes, Connectivity

Theoretically, the dissolution process of a crystalline solid can be carried out in four hypothetical steps: (1) melting of the crystalline solute, (2) separation of a solute molecule from the molten bulk, (3) creation of a cavity in the solvent for accommodation of a solute, and (4) placement of the solute molecule into the cavity created. The energy required for these

processes can be characterized using the enthalpy of melting, the cohesive energy of the solute and solvents, and the adhesive energy at the interface, which are directly proportional to the interfacial area. Hence, solubility can be related to the molecular surface area of a solute.

The solubility in water of aliphatic compounds has been successively related to molecular surface area by Amidon and associates (21,22). They investigated the aqueous solubility of hydrocarbons, alcohols, esters, ketones, esters, and carboxylic acids. Excluding olefins, a linear relationship was found between log (solubility) and total surface area with 158 compounds that they investigated. Similarly, molar volume of the solute is another property impacting solubility. It is related to molecular weight and affects the size of the cavity that must be formed in the solvent to solubilize the molecule.

Molecular connectivity is a measure of extent of molecular branching and normally used as a connectivity index. The connectivity index, easily computed, based on the degree of connectedness at each vertex in the molecular skeleton, is shown to give highly significant correlations with water solubility of branched, cyclic, and straight-chain alcohols and hydrocarbons as well as boiling points of alcohols (23). These correlations are superior to those based on well-founded theory relating to solvent cavity surface area.

Macroscopic Properties

The melting point or freezing point of a pure crystalline solid is strictly defined as the temperature at which the pure liquid and solid exist in equilibrium. The heat absorbed when a gram of a solid melts, or the heat liberated when it freezes, is known as the latent heat of fusion. The heat added during the melting process does not bring about a change in temperature until the entire solid has disappeared, since this heat is converted into the potential energy of the molecules that have escaped from the solid into the liquid state.

The heat of fusion may be considered as the heat required to increase the interatomic or intermolecular distances in crystals, thus allowing melting to occur. Heat of fusion is dictated by crystal packing. A crystal that is packed by weak forces generally has a low heat of fusion and a low melting point, whereas one packed together with strong forces has a high heat of fusion and a high melting point.

Solubility, as discussed earlier, is strongly influenced by intermolecular forces, similar to melting point. This similarity was demonstrated by Guttman and Higuchi, who studied the melting points and solubilities of xanthines. When the side chain at 7 position changed from H (theophylline) to propyl (7-propyltheophylline), the melting point decreased from 270 to 100°C, while solubility in water at 30°C increased from 0.045 to 1.04 mol/L. An empirical equation was derived by Yalkowsky and Banerjee (24) to estimate solubility on the basis of the lipophilicity and melting point [eq. (11)].

$$\mathrm{Log}S = 0.8 - \log P_{\mathrm{ow}} - 0.01(\mathrm{MP} - 25) \tag{11}$$

Here S is solubility, $\log P_{\mathrm{ow}}$ is the octanol/water partition coefficient (a measure of lipophilicity), and MP is the melting point (a measure of crystal packing).

Polymorphs exist when two crystals have the same chemical composition but different unit cell dimensions and crystal packing. Compounds that crystallize as polymorphs generally have different physical and chemical properties, including different melting points, x-ray diffraction patterns, and solubilities. Generally, the most stable polymorph has the highest melting point and lowest solubility; other polymorphs are metastable and convert. A consideration of the data in the literature indicates that improvements in solubility of metastable crystal forms can be expected to be as high as twofold (25).

When the crystal lattice contains solvents that induce polymorphic changes, they are called solvates. If the solvent is water, these pseudo-polymorphs are called hydrates. These hydrates and solvates are easily confused with true polymorphism and lead to the term pseudo-polymorphism. The solvates may be discriminated by DSC/TGA, where an additional endotherm due to the solvent will be apparent in DSC provided the heating rate is slow, and weight loss at similar temperature is observed in TGA.

Hydrate formation generally leads to a lower solubility since the preexistence of water in the crystal lattice reduces the energy available for solvation. For example, glutethimide

anhydrate has melting point 83°C and solubility 0.42mg/mL, but its hydrate has melting point 68°C but solubility only 0.26mg/mL. However, solvates tend to have higher solubility than the neat form because of the weakening of the crystal lattice by the organic solvent. For example, succinylsulphathiazole neat has a solubility of 0.39mg/mL, and its pentanol solvate has solubility of 0.80mg/mL (26).

Amorphous solids may be considered as supercooled liquids in which the molecules are arranged in a random manner somewhat as in the liquid state and do not have melting points. Amorphous solids are in a high energy state relative to their respective crystalline solids, therefore, leading to differences in dissolution rate, chemical reaction rate and mechanical properties. Amorphous solids also have a higher solubility than their crystal form. The solubility advantage compared with the most stable crystalline counterpart was predicted to be from 10 to 1600 fold, as shown by Hancock and Parks (25). However, the experimental solubility advantage was usually considerably less than this, because determining solubility for amorphous materials under true equilibrium conditions is difficult because of the tendency for such materials to crystallize upon exposure to small quantities of solvents.

When particles are in the submicron range, a small increase in the saturation solubility is expected as described by the Freundlich–Ostwald equation [eq. (12)] (27,28).

$$\frac{RT}{V_m}\ln\frac{S}{S_0}=\frac{2\gamma}{r} \tag{12}$$

where S is the saturation solubility of nanosized particle, S_0 is saturation solubility of an infinitely large crystal, γ is the crystal-medium interfacial tension, r is the particle radius, V_m is the molar volume, R is a gas constant, and T is the temperature. Assuming a molecular weight of 500, density of 1 gm/mL, and a value of 60 to 70 mN/m for the crystal-water interfacial tension, the above equation would predict a 62% to 76% increase in solubility at a particle size of 100 nm.

IONIZATION AND THE SOLUBILITY PROFILE

The total solubility of a compound at a particular pH is the sum of the "intrinsic solubility" of the neutral species in solution plus the solubility of the charged species. For a weak base, when the aqueous medium at a given pH is saturated with free base, the total solubility at that pH may be expressed as described [eq. (13)]. The typical solubility profile of a weak base when $\mathrm{pH} > \mathrm{pH}_{max}$ is shown in (Fig. 3).

$$S_{base}(\mathrm{pH} > \mathrm{pH}_{max}) = [\mathrm{B}]_s + [\mathrm{BH}^+] = [\mathrm{B}]_s\left(1+\frac{[\mathrm{H_3O^+}]}{K_a}\right) \tag{13}$$

When there are counterions present in the solution, at low enough pH, the entire free base will be converted into salt form, and the salt is the solid form. In this case, the equilibrium solubility at a particular pH may be expressed by equation (14).

$$S_{base}(\mathrm{pH} < \mathrm{pH}_{max}) = [\mathrm{B}] + [\mathrm{BH}^+]_s = [\mathrm{BH}^+]_s\left(1+\frac{K_a}{[\mathrm{H_3O^+}]}\right) \tag{14}$$

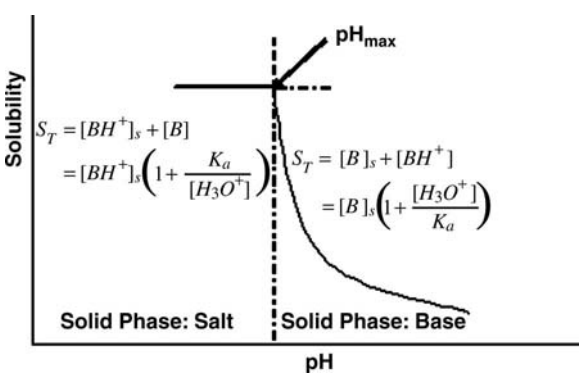

Figure 3 Schematic representation of the pH-solubility profile of a weakly basic compound.

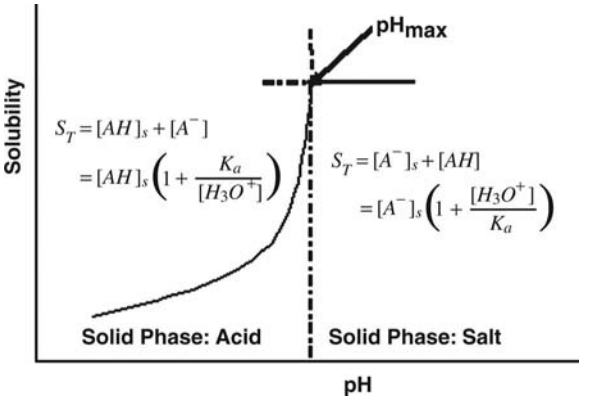

Figure 4 Schematic representation of the pH-solubility profile of a weakly acidic compound.

When these two independent curves in solubility pH profile intersect, the point is called pH_{max} as shown in the Figure 3. Similarly, the pH-solubility profile for a weak acid is also shown (Fig. 4).

Zwitterions refer to compounds with oppositely charged groups, but carry a total net charge of 0 and is thus electrically neutral. Solubility of zwitterions at certain pH is the combination of the contributions from all the charge groups. For compounds with two ionizable groups, solubility can be expressed by the following equation [eq. (15)].

$$S = S_0(1 + 10^{pK_{a1} - pH} + 10^{pH - pK_{a2}}) \tag{15}$$

It depends on its ionization constants, pH and intrinsic solubility, S_0, which is defined as the solubility of the neutral form of the compound. The solubility profile is U-shape characteristic for zwitterionic compounds.

For weak electrolyte drugs, salt formation is a common approach to improve solubility. Acids form salts with basic drugs and bases form salts with acidic drugs (29). For the salt of a basic drug, the dissolution equilibrium can be described as equation (16).

$$(BH^+X^-)_{solid} \leftrightarrow [BH^+]_s + [X^-] \tag{16}$$

Where $[BH^+]_s$ is the salt solubility and $[X^-]$ is the counterion concentration. The apparent solubility product K_{sp} can be derived as equation (17).

$$K_{sp} = [BH^+]_s[X^-] \tag{17}$$

In the absence of excess counterion, $[BH^+]_s = [X^-]$, solubility is the square root of K_{sp}. Under such conditions, drug solubility does not change with pH, as indicated in the figures above. On the other hand, if a significant amount of counterions exit in the formulation, decrease in solubility may be observed according to equation (18).

$$[BH^+]_s = K_{sp}/[X^-] \tag{18}$$

SOLUBILITY PREDICTION

A number of approaches to solubility prediction have been developed over the years and continue to be used (30). Recently many successful attempts were made for predicting aqueous solubility of compounds, but it is still a challenge to identify a single method that is best at predicting aqueous solubility (31). The first hurdle in the prediction of aqueous solubility is the estimation of melting point or enthalpy of sublimation (32). In addition, it is difficult to predict the solubility of a complex drug candidate on the basis of the presence or absence of certain functional groups. Conformational effects in solution may play a role in solubility and cannot be accounted for by a simple summation of contributing groups.

Because of the complexity involved in developing the prediction models, most models were completed using nonelectrolytes.

The prediction of aqueous solubility tends to use three approaches: methods correlating experimentally determined melting points and log$P$, correlations based on group contributions, and correlations with physicochemical and quantum chemical descriptors calculated from the molecular structure [quantitative structure property relationship (QSPR) approaches] (1).

Methods using melting point and log$P$ are best exemplified by the general solubility equation (GSE) model (33). The GSE model is based on the fact that the aqueous solubility of a nonelectrolyte solute depends on its crystallinity and its polarity, wherein the melting point and the octanol-water partition coefficient act as good surrogate measures, respectfully. For compounds with melting points $< 25^{\circ}$C, the melting point is taken to be 25°C. Ran, Yalkowsky and coworkers (34) revised equation 11 to equation (19).

$$\mathrm{Log}S = 0.5 - \log P_{\mathrm{ow}} - 0.01(\mathrm{MP} - 25) \tag{19}$$

The theoretical treatment of this solubility prediction method is presented in more details elsewhere (1). With this prediction model, the absolute average error ranged from 0.5 to 1 log molar solubility unit for drug-like compounds (35).

The aqueous functional group activity coefficients (AQUAFAC) model is based on group contribution values, which are based on experimental aqueous solubilities (36). In this model, the molar aqueous solubility can be calculated using equation (20).

$$\mathrm{Log}S = 1.74 - \log \gamma_{\mathrm{w}} - \frac{\Delta S_{\mathrm{m}}(T_{\mathrm{m}} - T)}{2.303RT} \tag{20}$$

Where, γ_{w} is the aqueous activity coefficient of a compound, which is obtained from the AQUAFAC model. ΔS_{m} is the entropy of melting, T_{m} is the melting point, and T is the ambient temperature, both in Kelvin, R is the gas constant.

Using QSPR models, aqueous solubility is controlled predominantly by solute molecular size and shape, by its polar nature and hydrogen bonding capabilities. In addition, hydrophobicity, flexibility, electron distribution and charge have been found to play important roles in prediction (37). Many molecular property desciptors are now available computationally. Aqueous solubility has been modeled by correlating measured solubilities with one or more physicochemical and/or structure properties. Most methods use linear methods such as multiple linear regression (PLS) or nonlinear methods such as artificial neural networks (ANN). In general, nonlinear methods appear to provide better predictions (38). The root mean squared errors for models based on QSPR tends to range from approximately 0.7 log units to 1 log units. Recently, the effect of crystal packing on solubility has been added into the computational model (39).

Jain et al. applied two methods to compare aqueous solubility estimation of 1642 organic nonelctrolyte compounds ranging from 10^{-13} to 10^{0} in experimental molar solubility (33). The average absolute errors in the solubility prediction are 0.543 log units for AQUAFAC and 0.576 log units for the GSE. About 88.0% of the AQUAFAC solubilities and 83.0% of the GSE molar solubilities are predicted within one log unit of the observed values. The marginally better accuracy of AQUAFAC is assumed to be due to the fact that it utilizes fitted-parameters for many structural fragments and is based on experimental solubility data. The AQUAFAC also includes reasonable estimate of the role of crystallinity in determining solubility. The GSE on the other hand is a simpler, nonregression based equation, which uses two parameters (MP and logK_{ow}) for solubility prediction. The major assumption in the GSE is that octanol is an ideal solvent for all the solutes. This may not be true for strongly hydrogen bonding compounds, and consequently might result in larger error for such compounds.

With some computational packages it is now possible to make predictions on aqueous solubility that are as good as experimental measurements ($\pm$0.5 log unit) for many compounds. However, all of the commercial programs were trained on selected organic chemicals and the predictive ability for drug-like compounds is still a challenge. When the commercial software programs do not yield good results for internal compounds, it may be necessary to evaluate various QSAR models and develop an in-house model (30).

SOLUBILIZATION AND "ENHANCED SOLUBILITY"

Modifications to the Solid State

Salt formation is probably the most common way to increase both the solubility and dissolution rate of ionizable drugs (29). The solid form, clearly distinct from the free acid or base solid form, provides significant enhancement in solubility through the provision of alternative equilibria, thus driving the total solubility (intrinsic + ionized) up significantly. This alternative equilibria results in a more readily solvated ionized form in hydrolytic solvents. As discussed earlier, the saturation solubility of the salt will be defined in conjunction with the Ksp, resulting pH and relative pK_a of the drug. As shown earlier (Figs. 3 and 4), changes in the pH or media composition can alter the solubility through common ion effects, or if the pH deviates well away from the pK_a, can actually result in precipitation of the free acid or base solid.

Selection of the counterion can actually be used to control the solubility by varying the Ksp. As pointed out by Anderson and Conradi (40), the impact of hydrogen bonding within the conjugate species can play a role in the Ksp and ends up also being translated into effects on the melting point of the salt. Common ion effects are manifested through the relationship defined by the Ksp. The solubility of the hydrochloride salt of the zwitterionic molecule lomefloxacin is a good example where excess chloride ion, as in admixtures with normal saline, can impact the solubility of the salt (41) (Fig. 5).

It is important to recognize that with any salt, the resulting pH of the media will be paramount in avoiding precipitation of the free base or acid. The strong acid conjugate salt of a weakly basic drug will end up driving the pH of the solution acidic, and conversely for strong base conjugate of weakly acidic drug. Care must be taken when such salts are dissolved into buffered systems where supersaturated solutions of the free base or acid may occur and have the propensity to precipitate with time. In such cases, a full understanding of the solubility versus pH curve is critical when using salts to provide improved solubility.

Cocrystals, similar to salts, provide a means to generate a crystalline form of the drug. While these solid phases can provide increased dissolution rates there has been minimal use of cocrystals to facilitate parenteral drug delivery. The properties and description of cocrystals has been discussed at length in a recent review (42).

The use of high energy amorphous solids can often result in temporary increases in solubility, but with a propensity to generate more stable crystalline forms. In parenteral

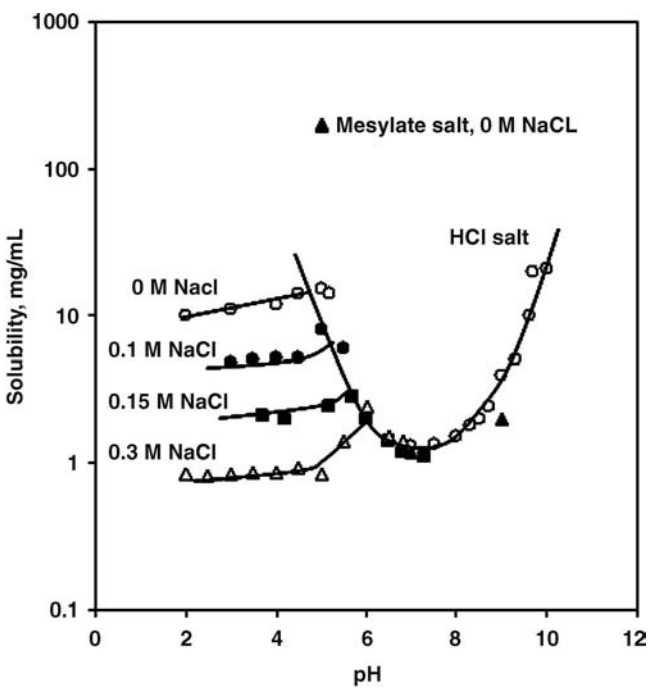

Figure 5 Effect of pH and NaCl concentration on the solubility of the zwitterionic quinolone lomefloxacin. *Source*: From Ref. 41.

products, the importance of metastable solids can many times play a role with lyophilized products upon reconstitution. The process of lyophilization often results in higher energy polymorphs or amorphous solids which allow for a very rapid dissolution and reconstitution back to the solution state. A thorough understanding of the dynamic nature of the lyophilized solid forms and the more stable crystalline forms which may exist is critical, whether they are hydrates, solvates, or polymorphs. The intentional use of such high energy states to increase solubility is limited because of its unpredictable behavior.

The best way to adjust solid form and impact solubility is via molecular modification, either as an analog or through formation of a prodrug. While these must be considered new chemical entities, they can provide a broad range of possible properties. Analog strategies are often focused on attempts to either decrease the lipophilicity and/or introduce hydrogen bonding groups which can enhance solvation in more hydrophilic media. In either case, especially with introduction of hydrogen bonding groups, increased interactions in the solid phase and its melt can actually increase as well, thus offsetting any gains afforded by increases in solvation. When possible, the introduction of ionizable groups can provide great solubility advantages (43).

In those cases where the perservation of the pharmacophore or desired biopharmaceutical properties does not permit molecular modifications leading to a more soluble molecule, a prodrug strategy can be invoked, overcoming immediate solubility limitations, yet when appropriately triggered, can release the active parent of interest (44).

Modifications to the Solution Phase

The use of cosolvents as was discussed earlier, has the ability to alter the dielectric constant of the solvent, influence the energy required to overcome hydrogen bonding forces in aqueous media and reduce the amount of energy necessary to create a cavity sufficient to accommodate the solute. Furthermore, these changes in solvent can greatly alter the degree of solvation of the solute once molecularly dispersed in the solvent. Soubility enhancement by addition of cosolvent is very typically log linear with respect to the cosolvent (Fig. 6). The degree of solubilization is dependent on both the lipophilicty, or log*P*, of the drug and type of cosolvent (45) (Fig. 6). Cosolvency and solubilization have been discussed by Rubino (46).

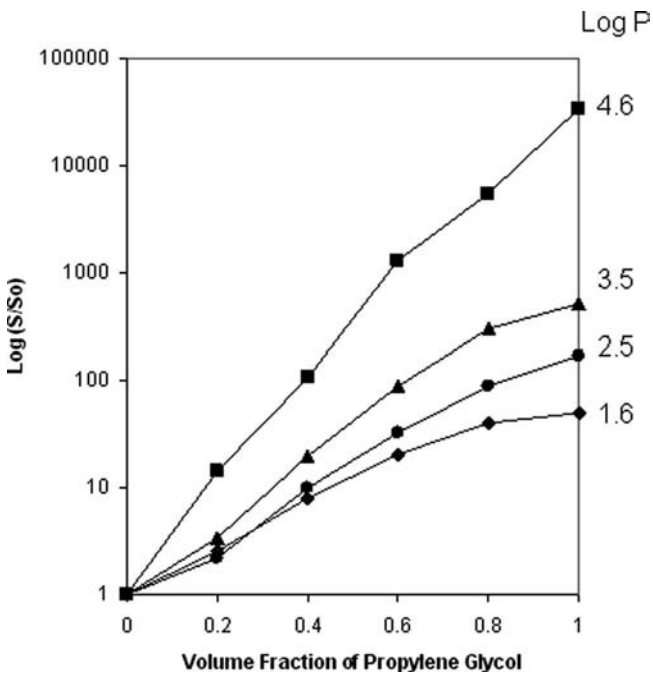

Figure 6 Propylene glycol solubilization of hydrocortisone esters. *Source*: From Ref. 45.

Modification due to Alternative Equilibria for Solute

An excellent overview of various methods to provide alternative equilibria for solubilization was presented by Yalkowsky (1). The rational selection of a solubilizing agent should be based on the structure of the drug to be solubilized and on the degree of solubilization needed to obtain the desired dose. The generation of alternative equilibria for the drug to exist in is one of the most commonly used methods to provide enhancements in the overall "apparent solubility" of the drug in solution. This strategy includes the use of ionization equilibria (discussed above in conjunction with salts), complexation equilibria, partitioning into surfactant micelles, partitioning into emulsion systems, and liposomal type systems.

Complexation and Association

Strategies of complexation include the use of chelating agents, organic molecular associations and inclusion complexes. The most common formulation strategies using complexation are centered around the use of cyclodextrins, with more emphasis generally placed on derivatized cyclodextrins because of their greater solubility and improved in vivo safety margin. Typically only those drugs with an aromatic ring or a nonpolar side chain are solubilized by cyclodextrin complexation (4). If complexation alone is insufficient, then a combination of complexation and pH modification or/and cosolvent may be used (47).

Complexation is an equilibrium process and the binding constant (or stability constant) for the formation of a 1:1 complex is given by equation (21).

$$\kappa_{1:1} = \frac{[\mathrm{Drug}]_{\mathrm{complex}}}{[\mathrm{Drug}]_{\mathrm{free}}[\mathrm{Ligand}]_{\mathrm{free}}} \tag{21}$$

$[\mathrm{Drug}]_{\mathrm{free}}$, $[\mathrm{Ligand}]_{\mathrm{free}}$ and $[\mathrm{Drug}]_{\mathrm{complex}}$ (m molecules of drug, n molecules of ligand) are the equilibrium molar concentrations of the free drug, the ligand and the drug in the complex form, respectively. Often, it is impossible to separate the individual binding constants and the apparent binding constant (κ_{app}) is used [eq. (22)].

$$\kappa_{\mathrm{appm:n}} = \frac{[\mathrm{Drug_m Ligand_n}]_{\mathrm{complex}}}{[\mathrm{Drug}]^{\mathrm{m}}[\mathrm{Ligand}]^{\mathrm{n}}} \tag{22}$$

The total solubility of the drug in the presence of ligand is the sum of the intrinsic solubility of the drug in the absence of the ligand and the solubility of the drug in the ligand(s) [eqs. (23) and (24)].

$$[\mathrm{Drug}]_{\mathrm{total}} = [\mathrm{Drug}]_{\mathrm{intrinsic}} + \tau[\mathrm{Ligand}]_{\mathrm{total}} \tag{23}$$

$$\tau = \frac{\mathrm{m}\kappa_{\mathrm{appm:n}}[\mathrm{Drug}]^{\mathrm{m}}_{\mathrm{intrinsic}}}{1 + \kappa_{\mathrm{appm:n}}[\mathrm{Drug}]^{\mathrm{m}}_{\mathrm{intrinsic}}} \tag{24}$$

A plot of $[\mathrm{Drug}]_{\mathrm{total}}$ versus $[\mathrm{Ligand}]_{\mathrm{total}}$ gives an intercept of $[\mathrm{Drug}]_{\mathrm{intrinsic}}$ and a slope τ. According to the above equation, the total solubility of a drug undergoing complexation is a linear function of the ligand concentration. The intercept of this line is equal to the solubility of the free drug and its slope is given by τ. Rearrangement of the equation allowed the calculation of the apparent binding constant, $\kappa_{\mathrm{appm:n}}$ [eq. (25)].

$$\kappa_{\mathrm{appm:n}} = \frac{\tau}{\mathrm{m}[\mathrm{Drug}]^{\mathrm{m}}_{\mathrm{intrinsic}} - \tau[\mathrm{Drug}]^{\mathrm{m}}_{\mathrm{intrinsic}}} \tag{25}$$

The value of κ is a measure of the strength of the drug-ligand interactions and is dependent on the properties of the drug and the ligand molecules. For a particular ligand, the size, shape, aromaticity and the nonpolarity of the drug molecule play important roles in determining this strength. The properties of the solubilizing medium, such as temperature and polarity also influence the strength of these interactions (48–50).

Complexation of lomefloxacin with five metal ions (Al^{3+}, Ca^{2+}, Mg^{2+}, Bi^{3+}, and Fe^{3+}) was found to increase solubility of lomefloxacin (50). The stoichiometrics of the various complexes were different. In the presence of 0.25 M Ca^{2+} ion, solubility of lomefloxacin was raised by two to threefold at pH 5, while 0.25 M Al^{3+} increased the solubility by nearly 30 fold. The stability constants were determined from the solubility, which ranged from 11.2 for L:Ca^{2+} complexes to 2.34×10^{10} for L:Al^{3+} complexes. The authors concluded that the higher order of stability for lomefloxacin-Al ion complex was related to the higher charge density of the metal ion.

Hydrotropic agents (hydrotropes) have been used to increase the water solubility of poorly soluble drugs, and in many cases, the water solubility has increased by orders of magnitude (51). Several hydrotropic agents such as urea, caffeine and other xanthine derivatives, tryptophan, sodium benzoate, PABA-HCl, Procaine-HCl and nicotinamides have been identified. Solubilization diagram for riboflavine exhibits a positive deviation from linearity, which implies a greater solubilizing power at higher concentrations of PABA-HCl and is characteristics of hydrotropic solubilization (52). In the study to increase the solubility of paclitaxel, 5.95 M of *N*,*N*-doethylnicotinamide was found to raise the solubility by 1700 fold (from 0.30 μg/mL to 512 mg/mL or 0.6 M). The authors indicated that an effective hydrotropic agent should be highly water soluble while maintaining a hydrophobic segment (51). Almost all highly effective hydrotropic agents have a pyridine or a benzene ring in their structure.

Complexation of a drug molecule with a ligand molecule reduces the exposure of former's hydrophobic region to water resulting in an increase in its solubility. The practical and phenomenological implications of phase-solubility analysis were developed by Higuchi and Connors in their pioneering work published in 1965 (53). On the basis of the shape of the generated phase-solubility relationships, several types of behaviors can be identified (Fig. 7). The two major types are A and B. Only A-type of profile will be discussed in this Chapter.

In an A-type system, the apparent solubility of the substrate increases as a function of CD concentration. In A_L subtype, the solubility is increased linearly as a function of solubilizing concentration. A_P system indicates an isotherm wherein the curve deviates in a positive direction from linearity and the A_N system indicates a negative deviation from linearity. The equations related to complexation with cyclodextrin were presented in the previous section except that the ligand is replaced with cyclodextrin.

The use of CDs to enhance solubilization of a poorly soluble drug is often preferred to organic solvents (54). As a solution is administered, both the drug and CD concentration are reduced in a linear manner making precipitation is less likely. Drug release from parenteral administration of CD complexes is thought to be associated with complete and almost instantaneous dissociation via the dilution of the complex (49). For strongly bound drugs, or for those cases where dilution is minimal, contributions from competitive displacement by endogenous materials, drug binding to plasma and tissue components, uptake of the drug by tissue not available to the complex or CD, and CD elimination may also be important (55). In ophthalmic applications where the possibility for dilution is more limited, factors associated with partitioning and secondary equilibria may be the main mechanisms for drug release.

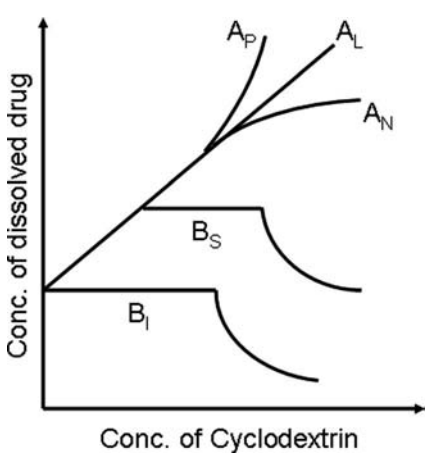

Figure 7 Graphical representation of A- and B-type phase-solubility profiles with applicable subtypes (A_P, A_L, A_N, and B_S, B_I). *Source*: From Ref. 53.

Inclusion complexation is restricted to drugs that have a hydrophobic region that can be inserted into a cavity that has the fixed dimensions. For α-, β-, and γ-cyclodextrins, the cross section of the solute protrusion must be less than 6, 8, and 10 Å, respectively. The αCD can preferentially accommodate aliphatic chains, and the βCD accommodates aromatic rings most efficiently. Fused ring or branched compounds can often best accommodate in the larger γCD cavity. Modified cyclodextrins are very water soluble and form moderately nonviscous solutions (1). Because of the large molecular weight and relatively high cost of cyclodextrins, their use is generally limited to solutes for which a low molar solubility is desired.

Cyclodextrins are cyclic oligosacchrides derived from starch containing six (αCD), seven (βCD), eight (γCD), nine (δCD), ten (εCD) or more (α-1,4)-linked α-D-glucopyranose units (54). In addition to increase the aqueous solubility of poorly water-soluble drugs and stability, CDs can be used to reduce or prevent irritation and prevent drug-drug interactions (56). The central cavity of the CD molecule carries lipophilic characteristic (57). In aqueous solution, the hydroxy groups form hydrogen bonds with the surrounding water molecules resulting in a hydration shell around the dissolved CD molecule (54). In general, the natural cyclodextrins exhibited less than 10-fold improvement in the solubility of compound.

The rates of formation and dissociation of drug:CD complexes are very close to diffusion rate-controlled with drug: CD complexes continuously being formed and broken apart (55). The equilibrium constants were reported to have a mean value of 130, 490 and 350 M^{-1} for αCD, βCD and γCD (58). A marketed parenteral solution, Caverject Dual® (alprostadil IV solution), contains αCD in which αCD is mainly excreted unchanged in the urine after IV injection and it has a higher solubility of 145 mg/mL at 25°C in water (59). βCD is limited in its parenteral application by its low aqueous solubility of 18.5 mg/mL at 25°C and adverse nephrotoxicity.

The natural CDs and their complexes are of limited aqueous solubility. Substitution of the hydrogen bond-forming hydroxyl groups results in improvement in their aqueous solubility. Modified CD include the hydroxypropyl derivatives of βCD (HPβCD) and γCD (HPγCD), the randomly methylated βCD (RMβCD) and sulfobutylether βCD (SBEβCD) (54). The modified cyclodextrin has been reported to increase solubility of progesterone by 3600 fold in with 300 mM of HPβCD (60). HPβCD and SBEβCD are considered nontoxic at low to moderate i.v. doses (54). HPβCD and SBEβCD are much more water soluble than natural βCD and have been used in several parenteral products, including Itraconazole (Sporanox) and Voriconazole (Vfend®, containing 16%w/v SBEβCD). After i.v. injection, HPβCD is almost exclusively eliminated through the kidneys. HPγCD has been incorporated in an eye drop solution and a parenteral diagnostic product.

Cyclodextrins can be used in combination with pH adjustment for synergistic drug solubility enhancement, according to the following equation [eq. (26)].

$$[\mathrm{Drug}]_{\mathrm{total}} = [\mathrm{Drug_u}] + [\mathrm{Drug_i}] + [\mathrm{Drug_u CD}] + [\mathrm{Drug_i CD}] \tag{26}$$

Where $[\mathrm{Drug_u CD}]$ is unionized drug-cyclodextrin complex, and $[\mathrm{Drug_i CD}]$ is ionized drug-cyclodextrin complex. The synergistic effect is generated because of the ionized drug-ligand complex $[\mathrm{Drug_i CD}]$, which is absent in situations where pH adjustment or cyclodextrin is used alone (61). The interactions of charged and uncharged drugs with neutral (HPβCD) and anionically charged (SBEβCD) modified β-cyclodextrins have been studied (62). The authors found the binding constants for the neutral forms of the drugs to be greater with SBEβCD than with HPβCD. For the anionic drugs, the binding constants between SBEβCD and HPβCD were similar, while the binding constants for the cationic agents with SBEβCD were superior to those of HPβCD. Therefore, a clear charge effect on complexation, attraction in the case of cationic drugs and perhaps inhibition in the case of anionic drugs, was seen with the SBEβCD.

Micellar

If a drug is not solubilized by aqueous pH-modification, cosolvents, complexation, or combinations of these, surfactants are often used. The formulations are usually concentrated drug solutions in water-miscible organic solvent(s) that are diluted prior to intravenous administration (4). Water-miscible surfactant molecules contain both hydrophilic and

hydrophobic portions which self-associate to form micelles once the surfactant monomer concentration reaches the critical micelle concentration (CMC). Surfactants in parenterals can increase drug solubility through micellization, improve drug wetting, prevent drug precipitation upon injection, improve the stability of a drug in solution, modulate drug release or to prevent aggregation due to liquid/air or liquid/solid interfacial interactions (63).

A simple equation illustrates the principle of surfactant induced micellization and its impact on drug dissolution is as follows [eq. (27)].

$$[\text{Drug}]_{\text{total}} = [\text{Drug}]_{\text{aqueous}}(1 + \kappa[\text{Surfactant}]_{\text{m}}) \tag{27}$$

Where $[\text{Drug}]_{\text{total}}$ is the total solubility, $[\text{Drug}]_{\text{aqueous}}$ is the drug aqueous solubility, κ is a distribution coefficient, $[\text{Surfactant}]_{\text{m}}$ is the difference between the surfactant concentration and the CMC. The total drug in solution increases linearly with the linear increase in surfactant concentration once the surfactant concentration exceeds the CMC. While the linear response limits the degree of solubilization, it minimizes the potential for supersaturation or precipitation upon dilution.

The surfactants commonly used for intravenous infusion formulation include cremophor EL, cremophor RH60, and polysorbate 80. The solubilizing solvent is typically a mixture of surfactant and solvent(s) such as cremophor EL/ethanol/propylene glycol. The upper limit of surfactant administered in vivo is 10% for the cremophor EL and up to 25% polysorbate 80 for IV infusion. Cremophor EL is known to have significant side effects such as hypersensitivity reactions and liver damage (64).

Polysorbate 80 is a nonionic surfactant commonly used in parenteral formulations. Chlordiazepoxide (Librium™) comprises 4% of polysorbate 80 along with 20% propylene glycol and is injected undiluted intramuscularly. Quite often the surfactant containing formulation is diluted prior to intravenous administration to reduce toxicity. For example, amidarone hydrochloride has a water solubility of 0.7 mg/mL, is solubilized to 50 mg/mL in Cordarone™ by a combination of 10% polysorbate 80 and pH adjustment to 4.1. It is administered by intravenous infusion after a 25-fold dilution with dextrose 5%. Solutol HS-15 is a newer nonionic surfactant for parenteral formulation. Solutol HS-15 is used up to 50% to solubilize Propanidid, 7% to solubilize Vitamin K_1. Solutol HS-15 has also been used in preclinical formulations to prepare supersaturated injectable formulations of water-insoluble molecules (65).

Emulsions

Highly lipophilic, low melting point drugs can be quite soluble in oils and formulated for intravenous administration by employing an oil-in-water emulsion stabilized by surfactants in interfacial phases. A recent review by Strickley provides an excellent summary of excipients used in commercially available lipid-based formulations (4). Emulsions typically contain 10% to 20% oil and 2% glycerol for isotonicity, 1% phospholipid surfactant (e.g., lecithin), at pH 7 to 8 and an oil-soluble drug partitioned into the oil phase. The surfactant is applied to provide an energy barrier to agglomeration of the emulsion droplets. Lipid-based systems can exist in a wide variety of microstructures depending on the components used and their concentration, such as w/o or o/w emulsion and microemulsions, micelles, reverse micelles, bicontinuous phases, or mesomorphous pases (66). The solubilization capacity and drug release rate of the active molecules are related to the microstructure. Understanding solubility in lipid mixture is complicated by the fact that these systems are strongly affected by their interfacial nature, the nature of the oil, surfactant, cosurfactant, the size of the droplet and the preferred location of the drug within the system (67). The unique structural organization of the microemulsion results in additional domains which may increase their solubilization capacity as compared with nonstructured solutions containing the same fraction of components.

A marketed emulsion in the United States, Diprivan®, in which propofol, a water-insoluble compound is solubilized to 10 mg/mL in an emulsion composed of 10% soybean oil, is administered by IV bolus or IN infusion (4). There are other commercial emulsions in Europe and Japan, including diazepam, PGE1, dexamethasone palmitate and flurbiprofen.

Emulsions are being prepared with an energy input, such as ultrasonication, homogenization, or high-speed stirring and are thermodynamically unstable because of high

interfacial energy. Stabilization hinges on the ability to reduce interfacial tension, forming an interfacial film barrier to kinetically impede coalescence of droplets. There are four types of stabilizing agents: inorganic electrolytes, surfactants, macromolecules and solid particles. Detailed discussion is available elsewhere (68).

Microemulsions are a thermodynamically stable isotropically clear dispersion composed of a polar solvent, an oil, a surfactant, and a cosurfactant. The potential to form self-emulsifying drug delivery systems was evaluated by Pouton in 1985 (69). Recently, development of injectable microemlsuions has received considerable attention for IV delivery of drugs because of its potential to increase solubility (e.g., solubility of felodipine was increased by 10,000 fold in the microemulsion), reduce toxicity and hypersensitivity, reduce pain upon injection, as a long circulating formulation for drug targeting, and as a depot for IM delivery of drugs (70–72).

Microemulsions offer many advantages compared with macroemulsions: smaller particles (often <100 nm), require less energy to process and have higher physical stability (73). Microemulsions generally have very low interfacial tension at the water-oil interface, and form a highly fluid interfacial surfactant film. Because of the numerous small droplets, the surface area to volume ratio of microemulsions are very high and it forms easily because of the low surface tension, typically due to high levels of surface active species.

Most drugs that can be formulated in emulsions are generally liquids or low melting solids that have high octanol-water partition coefficients (74). In the Diprivan emulsion, Propofol has a high solubility in vegetable oil (>0 mg/mL), a low melting point of 18°C, and a large octanol-water partition coefficient (log$P$ 3.83 in pH 6–8.5). Drugs with moderate to high melting point often cannot be formulated as emulsions because of the high lattice energy and low solubility in oil. High melting drugs possess some degree of polarity (i.e., presence of permanent dipoles and ability to form hydrogen bond), and these strong intermolecular forces cannot be readily overcome by the weak dispersion forces operating between solute and oil. Malcolmson studied the effect of oil on the solubility of testosterone propionate in nonionic o/w microemulsions and reported that larger molecular volume oils such as triglycerides miglyol 812 significantly increased the solubility of the compound over the corresponding micellar solution (75).

Predicting the solubility in lipid emulsions may be quite complicated because of the interfacial nature of the systems and the distribution of the drug in the continuous or dispersed phase and sometimes preferred location at the surfactant interface (67). If the drug preferentially resides at the interface in microemulsions, the creation of a larger interfacial area upon mixing the components may result in higher solubility. Testard studied the solubilization of a lipophilic molecule, lindane, in a microemulsion with a nonioinc surfactant. They found the solubility of lindane increased in the microemulsion region compared with the bulk oil; it was attributed to the incorporation of lindane in the surfactant interface (76). Addition of an amphiphilic block copolymer to medium chain surfactants has been shown to favorably alter the interfacial structure and significantly boost the solubilization capacity of microemulsions (77).

Surfactants are added to emulsion systems to reduce interfacial tension, reduce initial droplet size and size distribution, draw a liquid fill between droplets in areas where film thinning may have occurred, impart steric stabilization and in the case of charged surfactants give rise to charge distribution. The presence of surfactant and cosurfactant could make microemulsion supersolvents for drugs relatively insoluble in both aqueous and hydrophobic solvents (78). Using mixed oils and/or mixed surfactants in microemulsion may offer significant advantages over using pure single component materials (79). Prediction of absolute solubility in lipid vehicles is difficult since it requires similar knowledge as needed for aqueous solubility prediction, but also knowledge of the drug's specific interactions between the solute and formulation components, including an understanding of the lipid microstructure (67).

Liposome

Liposome formulations can be used as a means to solubilize some drugs for intravenous administration, to improve pharmacokinetics, enhance efficacy, and reduce toxicity (4). Liposomes are closed spherical vesicles composed of one or more bilayers of amphipathic lipid molecules enclosing one or more aqueous core compartments (80). Moderately hydrophobic

drugs can be solubilized by liposomes if the drug becomes encapsulated or intercalated within the liposome. Hydrophobic drugs can also be solubilized by liposomes as an integral part of the lipid bilayer. Water-soluble drugs reside within the aqueous inner core and are released as the liposome erodes in vivo or by leakage. A typical liposome formulation contains water with phopholipid at ~5 to 20 mg/mL, an isotonicifier, a pH 5 to 8 buffer, and potentially cholesterol.

Liposomes are injectd either by IV infusion or intrathecally. Upon IV administration, most conventional liposomes are easily taken up by the reticuloendothelial system (RES, in the body. There are several liposome formulations on the market. Amphotericin B, a compound with low aqueous solubility of ~0.1 mg/mL at pH 2 (anion) or pH 11 (cation), is solubilized to 5 mg/mL by liposomal intercaltion and becomes an integral part of the lipid bilayer (81). The amphotericin B liposomal products are being administered by IV infusion and have a longer in vivo half-life. Upon formulation in liposomes, paclitaxel, a low solubility drug (< 2 μg/mL), has been reported to achieve a solubility of 3.39 mg/mL in a liposomal formulation of polyethylene glycol 400, soybean phosphatidylcholine (PC) and cholesterol (82). Liposomes can be classified on the basis of liposome size or lamellarity as multilamellar large vesicles (MLVs), small unilamellar vesicles (SUVs), and large unilamellar vesicles (LUVs).

The lipids normally used are the unsaturated PC, phosphatidic acid (PA), phosphatidylglycerol (PG), and the saturated lipids L-a-dimyristoylphosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC), dipalmitoyl phosphatidic acid (DPPA), and L-a-dimyristoylphosphatidylglycerol (DMPG). ABELCET® is an example of MLV consists of amphotericin B complexed with DMPC and DMPG in a 1/0.7/03 molar ratio. The complex assumes a flattened, ribbon-like mutilamellar structure with a particle size ranging from 1600 to 11,000 nm. Upon administration, ABELCET exhibits large volume of distribution, high clearance from blood and long terminal elimination half-life.

Large unilamellar liposomes (LUV) refer to vesicles > 100 nm in diameter bounded to single bilayer membrane. LUV provides higher encapsulation of water-soluble drugs, economy of lipids and reproducible drug release rates; however, these LUV liposomes are difficult to produce. Small unilamellar liposomes (SUV) are formed by dispersing multilamellar vesicles into water using sonication, extrusion through filters of various pore sizes, or homogenization to form optically clear suspensions. AmBisome® is an example of closed fluid-filled unilamellar bilayer liposomes made of a single phospholipid bilayer with amphotericin B intercalated within the membrane at drug:lipid molecular ratio 1:9, and particle size 45 to 80 nm. Upon injection, AmBisome exhibits smaller volume of distribution than the multilamellar ABELCET. Several excellent reviews on liposome technology and its application have been published (83,84).

Combined Solubilization Strategies

Various methods have been reported to enhance solubility of poorly soluble compounds by utilizing a combination of more than one of the solubilization techniques (54,85,86).

Combined use of pH with surfactants was reported to significantly increase drug solubility. The total solubility of a weak electrolyte undergoing ionization and micellization can be accounting for the free unionized drug D_u, free ionized drug D_i, micellized unionized drug D_uM, and micellized ionized drug D_iM as equation (28).

$$[\text{Drug}]_{\text{total}} = [\text{Drug}_u] + [\text{Drug}_i] + K_u[\text{Drug}_u][\text{M}] + K_i[\text{Drug}_i][\text{M}] \tag{28}$$

where K_u and K_i are the micellar equilibrium constants for the unionized and ionized drug, respectively. This equation is valid for surfactants that are either neutral or completely ionized in the pH range studied. Li discussed this approach using polysorbate 20 on flavopiridol, a weakly basic compound with an apparent pK_a of 5.69 and a low intrinsic solubility of 0.025 mg/mL for its zwitterionic form (87). The solubility of flavopiridol in 10% polysorbate 20 solution at pH 4.3 (27.3 mM) is much higher than that could be expected by increasing the total solubility through appropriate pH adjustment from pH 8.4 and solubilization of the unionized drug in the micelles (3.3 mM). The authors pointed out that high solubility of the ionized drug in the micelles is the source of synergism for solubility enhancement in the

pH-surfactant solutions. Furthermore, this formulation does not precipitate upon dilution with isotonic Sorensen's phosphate buffer.

Combination usage of pH control and cosolvent has been reported to increase solubility of flavopiridol (87). Since solubility of the unionized form is pH independent, the authors concluded the higher total solubility at low pH is attributed to the solubilization of the ionized species by the cosolvent. The pH related solubilization produced by cosolvent can be described by equation (29).

$$[\mathrm{Drug}]_{\mathrm{total}} = [\mathrm{Drug_u}]10^{\sigma_{\mathrm{u}} f} + [\mathrm{Drug_u}]10^{(\mathrm{p}K_{\mathrm{a}} - \mathrm{pH})}10^{\sigma_{\mathrm{i}} f} \tag{29}$$

Where f is the volume fraction of cosolvent, σ_{u} and σ_{i} are the solubilizing powers of the cosolvent for the unionized and the ionized species, respectively.

Redenti reported that hydroxylcarboxylic acids (such as citric acid, lactic acid, malic acid, tartaric acid), or bases (such as tromethamine, diethanolamine, triethanolamine) can be used in drug-cyclodextrin solutions to enhance drug solubility by several orders of magnitude through formation of a "multicomponent complex" while that of cyclodextrin can be enahanced more than10 fold (54). The synergistic effect was rationalized due to the specific interaction of the hydroxyl acid groups with the hydrogen bond system of the host and/or the modification of the hydrogen bond network of the surrounding water molecules. Astemizole, upon βCD multicomponent complexation with tartaric acid, achieved 27,600-fold enhancement of solubility. The resulting amorphous complex dissolved rapidly and generated supersaturation that remains stable for several days.

Loftsson reported that addition of small percentage of hydrophilic polymers in cyclodextrin-based formulation can further enhance drug solubility (88). With the addition of 0.25% polyvinylpyrrolidone, the solubility of a number of compounds was increased from 12% to 129% in a 10% (w/v) HPβCD vehicle. The authors suggested that the polymer increased the stability constants of the drug-cyclodextrin complexes because of increased negative enthalpy change together with an increased negative entropy change.

Pitha reported that gradual addition of ethanol decreased and eventually abolished the formation of inclusion complexes of testosterone with HPβCD in aqueous solutions (89) (Fig. 8). Initially, at ethanol concentration <30%, the solvent acted as a competing for the cavity of HPβCD and reduced the solubility of testosterone; at higher ethanol concentrations

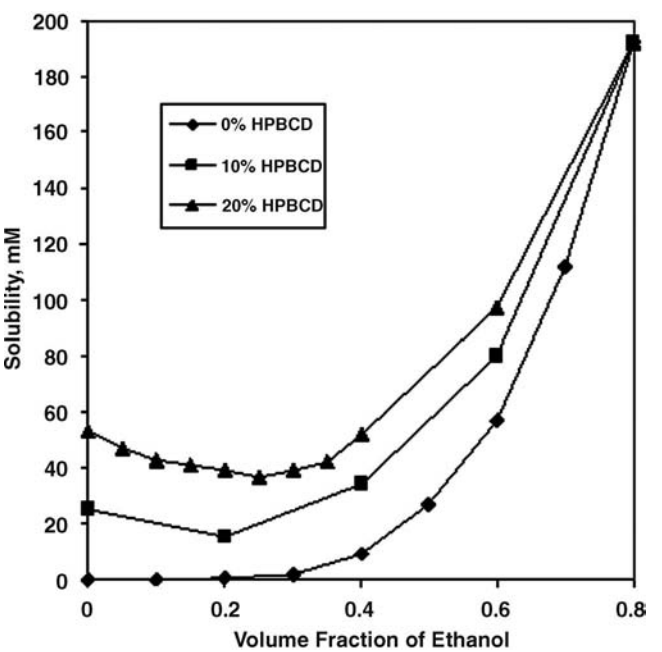

Figure 8 Effect of ethanol on solubilization of testosterone into aqueous solution containing hydroxyl-β-cyclodextrin. *Source*: From Ref. 89.

the solubility of testosterone started to rise, in which the dissolution primarily occurred through nonspecific solvent effects.

The effect of pH variation on complexation and solubilization of naproxen (a weak acid with pK_a 4.2) with natural βCD and various neutral, cationic and anionic βCD derivatives, and hydrophilic polymers has been investigated (86). The authors found the presence of 0.1% PVP increased the solubility of naproxen in the presence of 25 mM HPβCD complex by approximately 30%, at pH 1.1 and 6.5. This integrated strategy of pH control and polymer addition to the CD complexing medium allows a smaller quantity of CD be used to solubilize a given amount of drug.

Propylene glycol, PEG, ethanol, cremophor EL, cremophor RH60, and polysorbate 80 are water-miscible solvents and surfactants in commercially available injectable formulations. These solvents and surfactants are used in combination with each other, usually as a concentrate for dilution just prior to IV injection (4). In general, the cosolvent increases the CMC of the surfactant and increases solubility of the drug. Paclitaxel, a water-insoluble compound (aqueous solubility of 0.1 μg/mL), is solubilized in Taxol® to 6 mg/mL (i.e., 60,000-fold aqueous solubility) with 51% cremophor EL and 49% ethanol, and is diluted 5 to 20 fold with dextrose 5% or lactated Ringer's prior to administration. The final dosing formulation of Taxol is a micellar dispersion (90). The combination of cremophor EL and ethanol has also been used to solubilize teniposide, valrubicin, tacrolimus and cyclosporin.

Trace amount of polymer may decrease the precipitation rate (91), stabilize micelles and other type of aggregates in aqueous solutions and increase the solubility of the compounds by about twofold (92). Water-soluble polymers not only solubilize βCD and its complexes, but they are also able to enhance formation of complexes between drugs and βCD (54). Quarternary complexs of drug, cyclodextrin, polymer and tartaric acid have been reported to further enhance drug solubility (93). However, contrary results have been reported that formation of polymer/cyclodextrin complexes reduced the ability of the cyclodextrin to solubilize drug through complexation (54).

SUMMARY

The decisions regarding solubilization strategy often reside in the intrinsic solubility of the drug, solubilization capacity of the particular strategy, dose of drug to be delivered, infusion time, and potential safety concerns with the excipients, all coupled with the therapeutic area and unmet need. Technologies such as cosolvency and pH modification (indirectly salts) are often favored because of their very high capacity for solubilization. They typically result in exponential increases in solubility and can be very valuable for very low intrinsic solubility drugs (i.e., less than 10 mcg/mL), leading to apparent solubilities in excess of 50 mg/mL. However, given the exponential nature of solubilization and linear nature of subsequent dilution on administration, they are much more prone to precipitation upon dilution. Other approaches (micellar, complexation, emulsions, liposomes) often have lower capacity, but tend to solubilize in a more linear proportionality to concentration of solubilizer, thus being much less prone to precipitation upon dilution. These more linear alternative equilibrium type approaches are not likely to provide solubilization in excess of 20 mg/mL, often much less.

The risk in any sort of solubilization strategy is the propensity for precipitation upon administration and dilution into biological media. The presence of proteins and lipoproteins upon dilution can often facilitate supersaturation and allow for the time necessary to get further dilution and distribution in vivo. In essence, they often provide alternative equilibria for drug solubilization in vivo. The use of in vitro methods (94) and in vivo methods (95) to explore propensity for precipitation can often be very useful.

Solubility, coupled with dose and therapeutic indication, often define the ability to adequately deliver a drug parenterally. While the thermodynamic solubility ultimately dictates the actual chemical potential of the drug in solution under specified conditions, the total "solubilized drug" probably becomes the more relevant descriptor for drug delivery in parenteral systems. Efforts to solubilize drugs are highly dependent on altering either the conditions of the solvent system, creating alternative equilibria for the drug to reside in, changing the macroscopic solid form of the solute, or actually changing the solute at the molecular level (i.e., creating a new chemical entity). These alterations can increase the

escaping tendency from the solid state, facilitate the cavity formation in the solvent necessary for solute insertion, enhance the level of interactions between the solute and solvent, or simply provide an alternative state in which the molecule can reside. As will be discussed elsewhere in this book, the ultimate success of these strategies resides in the ability to deliver the molecule of interest to the in vivo milieu without deleterious results of precipitation upon administration.

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