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SOLUBILITY AND DISSOLUTION OF DRUG PRODUCT: A REVIEW

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Introduction

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration, for example, parenteral.

Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. In this article, solubility and dissolution will be discussed.

Solubility and Dissolution

Solubility

The saturation solubility of a substance can be defined as the amount of that substance in a solution, under given conditions (temperature, pressure, etc.), that is at chemical equilibrium with an excess of the undissolved substance (i.e. the solid phase)[1]. Solubility is thus a chemical equilibrium between the solid and dissolved states of a compound at saturation.

An unsaturated solution is a solution containing the dissolved solute in a concentration less than a saturated solution. A supersaturated solution is a solution that contains more of the dissolved solute than normal for a given temperature.

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The solvation process of a solid into a liquid is a three-step process[2]. The first step is the separation of the solute molecule from its crystal lattice. This step requires a work that is dependent on the intermolecular forces of the solute (i.e. the solute affinity for itself) within the lattice. The second step involves the separation of the solvent molecules and the creation of a cavity in the solvent to accommodate a solute molecule. Here again, intermolecular forces of the solvent are very important. The third step is the placement of the separated solute molecule within the created cavity and we must here consider the importance of the solute-solvent intermolecular forces, i.e. how strongly the molecule associates with the solvent. Compound and solvent entropy also play a role in the regulation of this multi-step operation; having a positive and a negative influence, respectively[3].

Factors influencing solubility

Drug characteristics

Drug characteristics such as molecular size, structure and polarity are factors governing intrinsic solubility. Solutes (and solvents) can be broadly classified as polar (hydrophilic) and non-polar (lipophilic). The polarity can be measured as the dielectric constant or the dipole moment of a molecule. A dipole moment is defined as a nonuniform distribution of negative and positive charges amongst the various atoms of the molecule. Molecules with a permanent dipole moment are said to be polar. The polarity of a molecule is thus related to its atomic composition, its geometry, and its size. Generally polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in nonpolar solvents (“like dissolves like” rule of thumb). Dipole-dipole interactions (e.g. hydrogen bonding as water is the encountered solvent in vivo) are responsible for the dissolution of many pharmaceutical drugs; the solubility of the low molecular weight organic acids, alcohols, amides, amines, esters, ketones and sugars in polar solvents is a result of dipole-dipole interactions. Structurally, as the number of polar groups (hydroxyl groups, carboxylic groups, amine groups, etc.) increases on a molecule, water solubility is enhanced as more solute-solvent interactions are made possible. Nevertheless, it has to be noted that strong inter and/or intramolecular bonds may possibly be a cause of poor water solubility[4]. Concerning molecular size, generally, the larger the molecule (i.e. the higher its molecular weight) the less soluble the substance will be. For example, within alkanes, molecular size is the primary determinant of their solubility in water, and increasing molecular size results in a decrease in water solubility mainly due to the increased free energy penalty for cavity formation in water[5].

Temperature and pressure

During the dissolution of a solid into a liquid, a change in the physical state of the solid takes place. Energy (e.g. in the form of heat) is necessary to break the intermolecular bonds in the solid and heat is given off during the formation of the new solute/solvent bonds (solvation). The first phenomenon is always endothermic and the second is always exothermic. The resulting enthalpy of this two-step phenomenon will determine if the overall dissolution is exothermic or endothermic. If the heat given off in the solvation process is greater than the heat required to break apart the solid, the net dissolving reaction produces heat and the dissolution is called exothermic. In contrary, if the heat given off in the dissolving reaction is less than the heat required to break apart the solid, the net dissolving reaction requires heat and dissolution is then called endothermic. The solubility of solutes is thus highly dependent on temperature. In the first case (i.e.

exothermic dissolution), an external increase of temperature will inhibit the dissolution of the solid as an excess of heat is already being produced and a lower solubility will be achieved if temperature is increased. In the second case, on the contrary, an external increase of temperature will facilitate the dissolution of the solid and a higher solubility will be achieved if temperature is increased. Endothermic dissolution is the most generally encountered phenomenon for organic drugs and thus, an increase in temperature will result in increased drug solubility.

Unlike gases (Henry's law – increase in pressure yielding an increase in solubility), liquids and solids exhibit practically no change of solubility with modifications in pressure; the latter physical forms being barely compressible.

pKa and GIT pH profile

The solubility of weak acids and weak bases is highly dependent on their acid-dissociation (or acid-ionization) constant (Ka) and the pH of the medium they are placed in. Ka is the equilibrium constant for the reaction in which a weak acid is in equilibrium with its conjugate base in aqueous solution and it indicates the extent of dissociation of hydrogen ions from an acid. The higher the Ka value (or the lower the pKa value – $pKa = -\log_{10} Ka$), the stronger the acid.

The intrinsic solubility of a compound is defined as the solubility of the compound in its free acid or base form and shall thus be evaluated at pH values more than one unit below the pKa for weak acids and more than one unit above the pKa for weak bases[6]. At pH values exceeding pH = pKa +1 for weak acids and for pH values below pH = pKa – 1 for weak bases, there is a linear relationship between the logarithm of the solubility and the pH untill the limiting solubility of the ionized specie is reached.

Considering these aspects, in vivo GIT pH profile is of high relevance when considering weak acids and weak bases as their solubility and thus their dissolution will be either greater in the intestinal fluids than in the stomach or greater in the stomach than in intestinal fluids, respectively. The fasted and fed state conditions also need to be taken into account as they are both characterized by different stomachal pH, implying a resulting different behavior of these kind of compounds. Furthermore, for poorly water-soluble weak bases, if rapid and complete dissolution occurs in the stomach, the possibility of reprecipitation following stomach exiting shall be considered[7].

Crystalline state - polymorphism

Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. Because these different crystalline forms will differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physicochemical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, hygroscopicity, vapor pressure, solubility, dissolution rate, chemical stability, as well as other thermodynamic and kinetic properties[8]. A crystal can be viewed as a solid in which the molecules are packed in a regularly ordered, indefinitely repeating pattern extending in all three spatial dimensions. In crystals the repeated structural units are called unit cells. Unit cells are defined by various parameters including the length of the cell edges and the angles between them, and are arranged in a specific order that describes the crystal. Crystalline solids can exist in the form of monocrystals or polycrystals. Monocrystals are crystalline solids in which the crystal lattice of the entire sample is continuous and unbroken to the edges of the sample. Polycrystals are crystalline solids where the regular

pattern of arrangements is interrupted by crystal defects and are materials made up of numerous smaller crystals (called crystallites) that have an equivalent type of structure as monocrystals. Crystalline drugs are generally polycrystals (monocrystals are not easily found or obtained). The most common crystalline forms in which a drug substance can be found are polymorphs and solvates (or pseudopolymorphs).

By definition, crystalline polymorphs have identical chemical composition but possess different crystal structures. The differences in crystal structure allow, due to differences in energy states, for differences in physicochemical characteristics, notably in solubility (the lowest energy state polymorph being generally characterized by the lowest solubility). Polymorphs are classified, based on their differences in thermodynamic properties and their ability to transform reversibly one to another, as enantiotropes or monotropes; a reversible transformation between polymorphs being possible at a definite transition temperature below the melting point in the first case[9].

Solvates are crystalline solids that include solvent molecules into their crystalline lattice. Depending on the type of solvent used, the physicochemical properties of the substance will be modified. Solvates of drugs show, presumably by weakening of the crystal lattice, increased solubility characteristics[10]. Based on the thermodynamic theory of solubility of solvates however, the rule applying to solubility behaviour is that solid solvates are always less soluble in the solvent forming the solvate than the original solid[11]. Solvates formed from other solvents however, if the solvent is water-miscible, are more soluble in water than the corresponding non-solvated form[12]. Hydrates (i.e. solvates where the incorporated solvent is water) are thus less soluble in water.

When no long-range order, as described for crystalline solids, can be found within the organization of the molecules of a specific substance, the substance is called amorphous. The amorphous state is characterized by an even greater energy state than some polymorphs (metastable polymorphs) and is much more thermodynamically unstable. The amorphous state of a compound can be obtained by various techniques such as rapid melting/cooling or precipitation techniques.

Since lattice energies of physical forms (amorphous, polymorphs or solvates) are responsible for the difference in solubility, the largest difference in solubility is observed between amorphous and crystalline materials[12]. In fact, when considering polymorphs, the solubility ratio between polymorphs is rarely found to be above 5. In the review from Pudipeddi and coworkers[13]**,** out of 50 drugs investigated (comprising 81 polymorph comparisons), the solubility ratio never exceeded 5 (except for 1 compound). Similar conclusions could be made for solvates. However for amorphous drugs the solubility ratio can be increased up to several hundred times when compared to the stable crystalline drug[12].

The use of metastable polymorphic forms and solvates, and to a greater extent of amorphous forms, is frequently relied upon when considering solubility/dissolution formulation enhancement technologies for poorly water-soluble drugs. However, the biggest problem associated with the use of the metastable polymorphs and amorphous forms is the risk of conversion of the higher energy, more soluble form into the crystalline form with the lowest energy state, characterized by a lower solubility. Without any stabilization strategy behind their utilization, their marketing possibility is limited due to the possible conversions during both manufacturing and storage. The importance of the crystalline state (polymorphs, solvates, amorphous) in pharmaceuticals cannot thus be overlooked. It is important that crystalline forms of drug substances used in solid dosage forms be characterized, and the appropriate forms selected to ensure that the product performance with respect to manufacturability, stability, and of course desired properties (e.g. solubility/dissolution/bioavailability) remain unchanged[13].

Surfactants

Surfactants, both in vitro and in vivo, significantly influence the solubility of a poorly water-soluble drug substance by enhancing its solubilization. Surfactants also interfere with the interfacial transport of solute from the crystal to the bulk solution (enhanced wetting characteristics – Young's equation)[14]. Solubilization, in this case, can be defined as "the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent, by the introduction of one or more amphiphilic component(s)"[6]. The solubility enhancement properties of surfactants are the result of the dual nature of the surfactant molecules, i.e. possession of distinct hydrophobic and hydrophilic regions which allow them to orient at polar/non polar interfaces[15]. In the absence of such interface or above a concentration known as the critical micelle concentration (CMC), surfactants self-associate to form micelles or other aggregates (depending on the surfactant concentration), where their hydrophobic regionsare separated from aqueous contact by their hydrophilic regions; this creating an hydrophobic environment (hydrophobic core) suitable for the solubilization of many hydrophobic compounds[16]. The solubility of an hydrophobic poorly water-soluble drug will thus see its aqueous solubility increase above the CMC of the surfactant used for solubility enhancement.

In vivo, in the small intestine, drug solubility can be enhanced by amphiphilic bile components such as bile salts, lecithin and monooleins; for some reported poorly water-soluble compounds, increases in solubility of up to a hundred-fold upon addition of physiological concentrations of bile salts to aqueous media have been reported[6]. In vivo solubility of a drug compound, at least for lipophilic drugs, is in fact generally greater than its referred in vitro aqueous solubility[17].

Particle size

Drug particle size can also have an influence on saturation solubility; the size dependency, however, coming into effect only for particles having a size below approximately 1 μm[18]. The increase in the saturation solubility with respect to diminution of particle size is explained by the Ostwald-Freundlich equation.

$$C_S = C_\infty \, e^{\frac{2\gamma M}{R T \rho r}}$$

……Eq-1

Cs: Solubility (mg/ml)
C∞: Solubility of infinite radius particles
γ: Interfacial tension between drug particles and the solubilizing fluids
M: Molecular weight
R: Ideal gas constant
T: Absolute temperature
ρ: Density of the solid
r: Radius of the particles

The Ostwald-Freundlich equation is the equation used to explain crystal growth in a dispersed system. Any particle system dispersed in a medium and having a certain degree of solubility in it is thermodynamically unstable due to its large interface area. One way of decreasing the high interfacial energy associated with this large interfacial area is through particle growth, and the mechanism most likely to achieve this reduction is called the

Ostwald ripening[19]. This Ostwald ripening is due to the solubility difference between smaller and larger particles, i.e. enhanced solubility for smaller particles.

It has been reported that an increase in γ can take place during sample processing (i.e. particle size reduction operations such as high pressure homogenization in our case). The energy introduced during such process might lead to an increase in γ and thus to an increase in saturation solubility[20]. Converting microparticles into nanoparticles might also lead to the formation of defects in the original crystals. These crystal defects, including dislocations, influence the crystal lattice energy and give rise to increased surface energy and thus to an increased saturation solubility[21]. Another reported possible explanation is the change in radius curvature of the particles, meaning that the packing density of the surfactants at the surface is no longer optimal and is less dense due to the changed geometrics, resulting in an increased surface tension at the interface with the nanoparticles[22].

Dissolution

Dissolution of a solid dispersed in a liquid takes place in two stages: the first stage is an interfacial interaction between the solid and the liquid phase leading to the formation of solute molecules from the solid phase, and the second is the transport of these molecules from the interface into the bulk medium under the influence of diffusion[23]. The dissolution process is described by the Noyes-Whitney equation:

$$dm / dt = \frac{D \; x \; A}{h} (S - C_b)$$

……Eq-2

D: Diffusion coefficient of the solute
A: Effective surface area of the dispersed solid (surface area of the particles exposed to the solvent)
h: Diffusion boundary layer thickness
S: Saturation solubility (i.e. the equilibrium solubility)
C_b: Concentration of the solute in the bulk medium at time "t"

The diffusion coefficient D being defined by the Stockes – Einstein equation:

$$D = \frac{R \; T}{6 \; \pi \; \eta \; \; r \; N}$$

……Eq-3

D: Diffusion coefficient of the solute ($m^2 \; s^{-1}$)
R: Ideal gas constant
T: Temperature (Kelvin)
η: Viscosity of the dissolution medium
R: Molecular radius of the solute
N: Avogadro's number.

The Noyes-Whitney equation is a model that assumes that (1) the drug is dissolved uniformly from all surfaces of the particles, that (2) the particles are spherical, that (3) the thickness of the diffusion boundary layer is constantand that (4) the thickness of the diffusion boundary layer and the saturation solubility are independent of particle size[24]. Figure 1.1 illustrates the relationship of the terms of the Noyes – Whitney Equation.

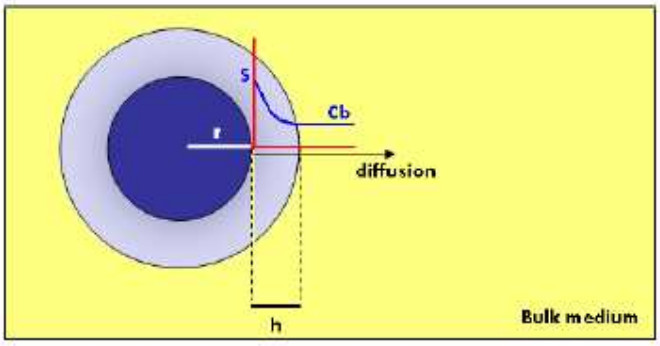

Figure 1 Schematic representation including the parameters of the Noyes – Whitney equation.

Factors influencing dissolution rate

According to the Noyes-Whitney equation, there are many ways to enhance the dissolution rate of drug compounds. Table 1.1 summarizes the physicochemical characteristics and the in vitro-in vivo factors influencing the terms of the Noyes-Whitney equation.

Table 1 Factors influencing dissolution rate[25]. Temperature, also having an influence on drug dissolution, is not mentioned in this table.

Parameter	**Physicochemical characteristic**	**Physiological variable - in vivo factor**	**In vitro factor**
A	Particle size	Presence of surfactants	Presence of surfactants
h		GIT motility	Stirring rate System hydrodynamics
D	Molecular size	Viscosity of gastrointestinal fluids	Viscosity of medium
S	Hydrophilicity Crystalline state	pH Surfactants	pH Surfactants
C_b		Volume of gastrointestinal fluids	Volume of medium

Conclusion

Factors of solubility and dissolution are almost same. To modify the dissolution of a substance, modification of factor(s) affecting solubility is/are required. Moreover, physiological factors should consider to modify dissolution of a substance/ drug product.

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