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Solubility: it's not just for physical chemists

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Solubility data are used to make crucial decisions from the earliest stages of drug discovery throughout the development process, but often the decision-maker is far removed, in terms of both organization and scientific background, from the scientist who generates the data. Here we provide a reference point for consumers of solubility who are presented with increasingly sophisticated strategies to measure sooner, faster or more accurately. We discuss the fundamental forces that govern solubility, the role of physical–chemical parameters such as pH and pK_a, and the principles involved in different solubility measurements. Our ultimate goal is to enable a decision-maker, when presented with solubility data, to have in hand the tools to evaluate not just the magnitude but also the context and appropriateness of those measurements to the drug in question.

Introduction

The aqueous solubility of a drug substance is an important physicochemical parameter that has a significant role in various physical and biological processes. Solubility is central to *in vitro* screening assays, because poor solubility leads to problems with reproducibility and unreliable results. If a drug precipitates in either the source plate or the screening well before reaching its cellular target, the target will be exposed to a lower concentration of free drug than was intended in the experimental design and could yield a response that is diminished, undetectable or independent of the input concentration. Thus, this problem of physical chemistry can appear as a biological problem. *In vivo*, inadequate solubility of the desired dose results in incomplete absorption of orally administered drugs. In addition, low solubility of compounds also contributes to extended timelines, owing to the heroic measures required to produce dosage forms that consistently deliver the desired quantities of drug at the site of absorption [1].

Throughout the various phases of discovery and development, solubility information serves a wide range of needs. In the early stages, solubility is used to characterize compounds belonging to a chemical series and to determine whether these compounds are soluble enough for structure–activity relationship screens. As compounds advance past structure–activity relationship screens, solubility data are used to assess absorption, distribution, metabolism and elimination parameters and to develop formulations for safety screens, pre-clinical and early clinical use. This review takes the reader through a discussion on the fundamentals of solubility from the molecular level, returning a property often dismissed as a formulation parameter, to its proper place in the pantheon of physical chemistry.

What is solubility?

According to the simplest definition, the thermodynamic solubility of a compound in a solvent is the maximum amount of the most stable crystalline form of the compound that can remain in solution in a given volume of the solvent at a given temperature and pressure under equilibrium conditions. This equilibrium balances the energy of solvent and solute interacting with themselves against the energy of solvent and solute interacting with each other [2–4] (Figure 1).

Thermodynamic equilibrium will always seek the overall lowest energy state of the system; thus, only the 'real' equilibrium solubility reflects the balance of forces between the solution and the most stable, lowest energy crystalline form of the solid. The less solid-state energy stabilization that has to be overcome, the more molecules that can be accommodated in the solution state before the energy required to break a molecule out of its crystal lattice

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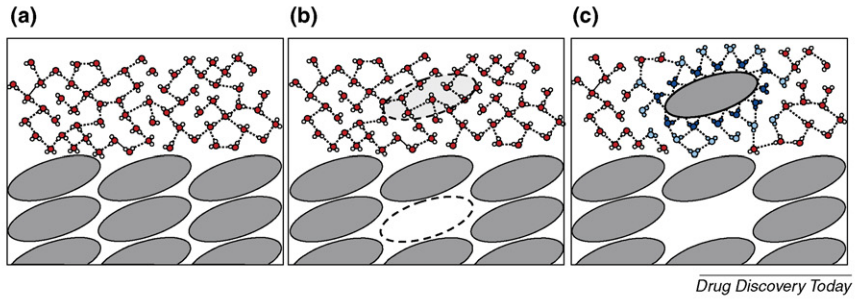

FIGURE 1

The intermolecular forces that determine thermodynamic solubility. (a) Solvent and solute are segregated, each interacts primarily with other molecules of the same type. **(b)** To move a solute molecule into solution, the interactions among solute molecules in the crystal (lattice energy) and among solvent molecules in the space required to accommodate the solute (cavitation energy) must be broken. The system entropy increases slightly because the ordered network of hydrogen bonds among solvent molecules has been disrupted. **(c)** Once the solute molecule is surrounded by solvent, new stabilizing interactions between the solute and solvent are formed (solvation energy), as indicated by the dark blue molecules. The system entropy increases owing to the mingling of solute and solvent (entropy of mixing), but also decreases locally owing to the new short-range order introduced by the presence of the solute, as indicated by the light blue molecules.

overwhelms the energy returned from solute–solvent interactions and the increase in system entropy. Thus, the most stable crystal form will also have the lowest solubility.

Although solubility experiments that begin with a metastable solid form might measure a higher apparent solubility, given enough time the limiting solubility of the most stable form will eventually dominate (Figure 2). This phenomenon has considerable pharmaceutical importance, as vividly illustrated by Abbott's antiviral drug Ritonavir: the slow precipitation of a new stable polymorph of Ritonavir from dosing solutions demanded an emergency reformulation to ensure consistent drug release characteristics [5].

Solubility of ionizable compounds

Most pharmaceutical compounds are weakly ionizable acids or bases, or combinations of these two ionization types. The solubility

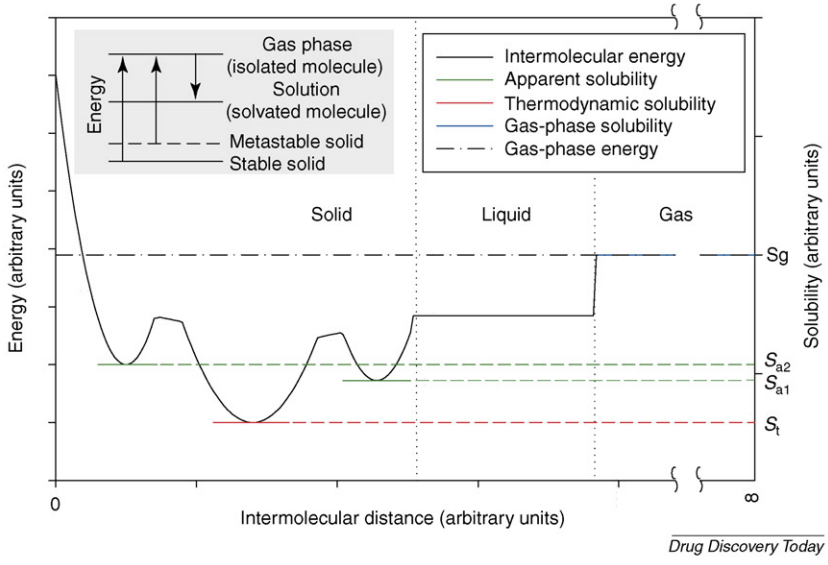

FIGURE 2

Relationship between energy and solubility. Solid forms are found in energy minima, representing the favorable intermolecular interactions that hold molecules together in a crystal form. The deepest trough represents the lowest energy crystal form, giving rise the lowest (thermodynamic) solubility, S_t. Other minima represent metastable solid forms, which have differing degrees of intermolecular energy stabilization that yield different apparent solubilities, S_{a1} and S_{a2}. These metastable forms, if provided with activation energy, will eventually convert to the lowest energy form and yield thermodynamic solubility. In the absence of intermolecular interactions (gas phase), the solubility reflects only the interaction between solute and solvent, shown as S_g. The inset provides another view of the relationship between energy and solubility: whereas the isolated molecule and solvated molecule have fixed energies, different solid states provide different energy barriers that must be overcome to achieve dissolution.