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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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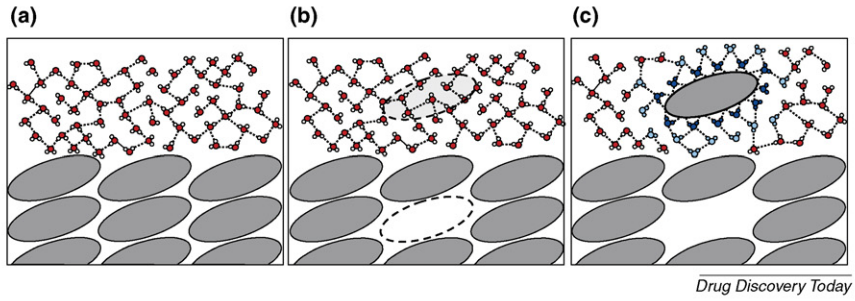

FIGURE 1

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

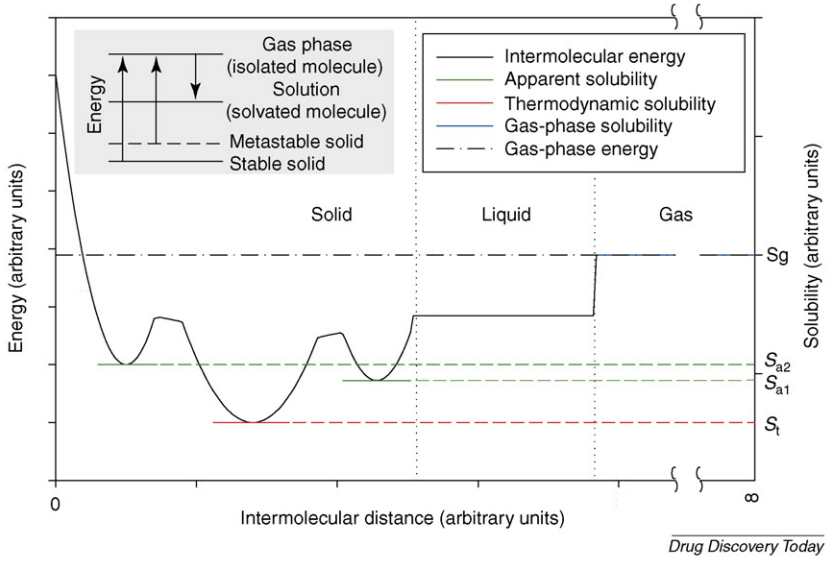

FIGURE 2

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.

of non-ionizable compounds is a single value that reflects a simple balance between the molar free energy of the solid drug and that of the drug interacting with a polar aqueous solvent; for an ionizable drug, however, the ionizability of both the drug and the solvent must be considered. Because the extent of drug ionization changes with the extent of solvent ionization (i.e. the pH), the solid-state to solution-state equilibrium of the drug will also change with pH [6]; thus, the measured solubility has to be viewed in the context of the pH of the solution at equilibrium and the pK_a values of the compound [7,8].

Solubility profile

If we were to measure the solubility of a weakly basic compound in a range of aqueous solutions at different pH values, the solubility profile would look similar to the one shown in Figure 3 (and the profile for a weakly acidic compound would resemble the mirror image). The pH–solubility relationship of ionizable compounds is based on the Henderson–Hasselbach relationship, which relates the solubility of the completely 'unionized' compound (S_o, intrinsic solubility) to both the solubility measured at a given pH (S) and the pK_a of the compound.

The Henderson–Hasselbach equation takes slightly different forms for acidic and basic compounds, which can be written as:

$$S = S_o\left[1 + 10^{(pK_a - pH)}\right] \text{for a monobasic compound}$$

$$S = S_o\left[1 + 10^{(pH - pK_a)}\right] \text{for a monoacidic compound}$$

Thus, it can be seen that the solubility of an acid increases with pH at pH values greater than the pK_a. For bases, the solubility value increases with decreasing pH at pH values less than pK_a. The strengths and limitations of the Henderson–Hasselbach equation are discussed at length elsewhere [9–12].

pH-dependent regions of solubility

It is clear from the above equations that pH has an enormous effect on the solubility of ionizable compounds. In general, the pH–solubility profile can be divided into four different regions according to the physical interactions that dominate (Figure 3).

(i) The intrinsic solubility region (pH > 7 in Figure 3). This region is defined as the pH range in which the compound is completely unionized in solution and has the lowest solubility. In this pH range, any compound that precipitates from solution will precipitate as the unionized free form, regardless of the initial salt form.

(ii) The ionizing portion of the curve and the region of the steepest slope. This region begins around the pK_a value (~pH 4–5.5 in Figure 3). At the pK_a, there are equal concentrations of ionized and unionized forms of the compound in solution. Every pH unit change on either side of the pK_a will give a tenfold change in the amount of ionized drug in solution. Precipitate formed in this pH range can be in either the free form or the salt form, depending on the strength of the solid-state interactions. Figure 3 shows the pH–solubility profile for a base with a single pK_a. The ionized portion of the curve is more complex for compounds with multiple ionization sites.

(iii) pH_{max}. This region corresponds to the pH that yields maximum solubility of the compound (~pH 4 in Figure 3), where the ionizing portion of the curve meets the salt plateau on the pH–solubility profile. At this point, the equilibrium solid state will be a salt: that is, completely ionized drug associated with an oppositely charged counter-ion through coulombic interactions.

(iv) The salt plateau (pH > 4 in Figure 3). In this pH range, the salt solubility of the compound prevails. The solubility of the compound is almost constant: its value is dependent on the

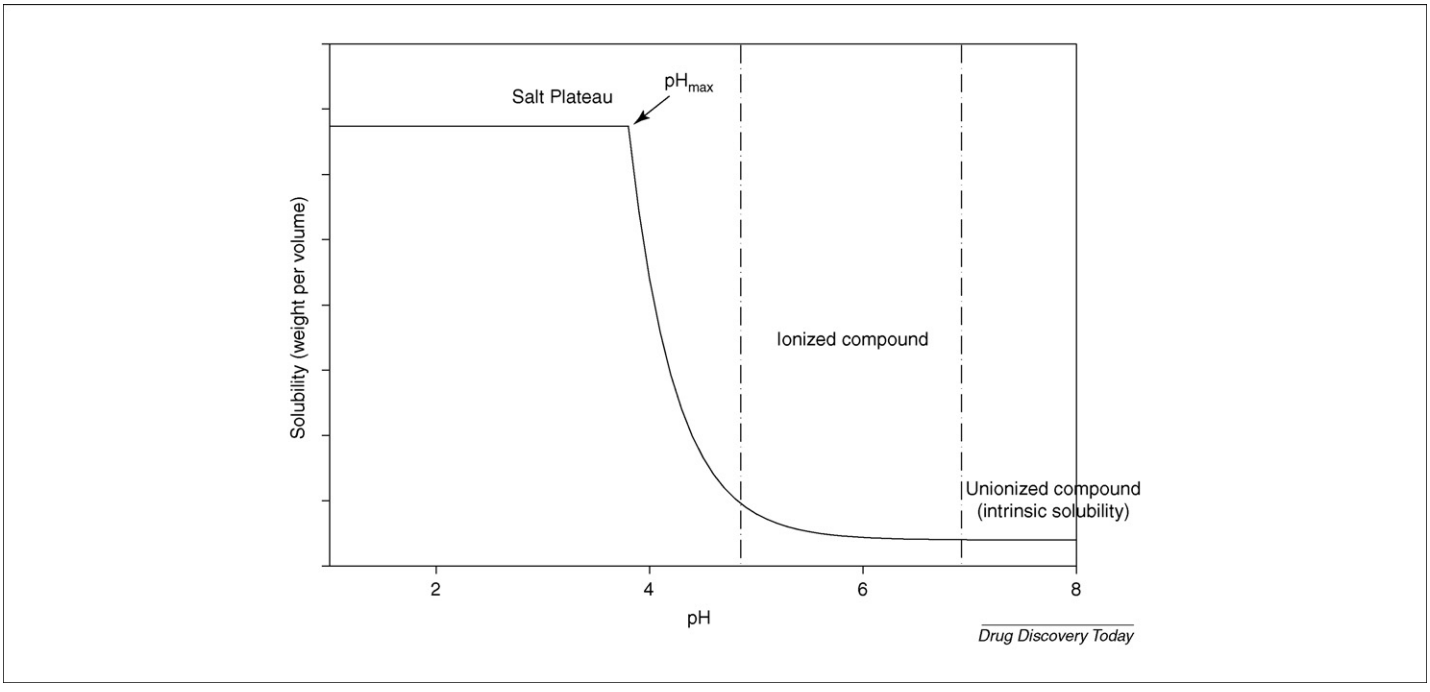

FIGURE 3

pH–solubility profile for a compound with a single, basic pK_a value of 5. The four regions of pH-dependent solubility – salt plateau, pH_{max}, ionized compound and unionized compound – are discussed in Figure 4.

strength of solid-state interactions with the counterion forming the salt and is given by the solubility product, Ksp, which is defined as the product of the concentrations of ion and counterion in solution:

$$drug \cdot salt \xleftrightarrow{dissolution} drug\ ion + salt\ counterion$$

$$K_{sp} = [drug\ ion][salt\ counterion]$$

$$S = \sqrt{K_{sp}}$$

The K_{sp} value for a given salt of a compound is a constant value. Therefore, the drug concentration in saturated solutions is a function of the counterion concentration. As the counterion concentration in solution increases, the dissolved drug concentration decreases to maintain the K_{sp}. This is an important concept, especially for hydrochloride salts of poorly soluble compounds, because the active drug concentration that can be achieved is a function of the chloride concentration in the solvent or the gastrointestinal tract on oral dosing [13–15].

Equations describing the concentrations of ionized and unionized species and salt in solution as a function of pH are described elsewhere [12,16,17].

Increasing the solubility of ionizable compounds

Having examined the shape of the pH–solubility profile for ionizable compounds, it is worth discussing the ways that this profile can be used to engineer solubility improvements for ionizable compounds.

Special case of apparent solubility: salts

Pharmaceutical salts pose a special case of apparent solubility that has important implications for drug discovery and development [17–19]. Salts are formed when a compound that is ionized in solution forms a strong ionic interaction with an oppositely charged counterion and maintains that interaction through crystallization. The resulting solid comprises charged drug molecules and their associated oppositely charged counterions.

The essential characteristic of salts that makes them so attractive in pharmaceutical applications is that the coulombic attraction between the drug molecule and counterion changes the potential energy landscape of the solid state and leads to stronger interactions between the charged active pharmaceutical ingredient and polar aqueous solvents. This can result in enhanced dissolution rates and higher apparent solubility on physiologically relevant timescales, resulting in more effective drug delivery *in vivo*.

Caution must be applied when discussing salt solubilities: the ionizable drug molecule that facilitates salt formation complicates the discussion of solubility, as mentioned in the previous section. Because salts have such a crucial role in pharmaceutical drug delivery, it is important to understand how the choice of counterion for a salt affects solubility.

Optimizing factors that affect solubility

Following the example of Bogardus and Blackwood [20], a simple relationship can be developed among pH_{max}, pK_a, intrinsic solubility and salt solubility that can be applied to a specific salt of any monoprotic compound:

$$pH_{max} = pK_a + \log\left(\frac{S_o}{\sqrt{K_{sp}}}\right)$$

K_{sp}, it must be recalled, is related to the constant solubility achieved on the salt plateau and depends on the identity of the salt. Because S_o and pK_a depend on the properties of the drug, not on those of the counterion, this equation can be used to describe the pH at which maximum solubility is achieved. It can also rationalize the improvements in solubility that can be achieved through physical and chemical manipulation of the drug molecule.

First, simply by increasing the strength of the pK_a, the whole pH–solubility curve can be shifted (Figure 4a). This is useful for pharmaceutical compounds because it can be used to ensure that the region of maximum solubility corresponds to the physiologically relevant pH range, or that the solubility of a solution formulation is governed by the desired solid form (free form or salt).

Second, increases in the intrinsic solubility of the unionized molecule might lead to increases in solubility across the whole pH–solubility profile (Figure 4b). Although this is an attractive possibility, it can be difficult to achieve because the factors governing intrinsic solubility (e.g. stability of the solid state or strength of intermolecular interactions) can be difficult to predict and to alter systematically.

Last, a higher K_{sp} value signifies increased solubility along the salt plateau and at pH_{max}, but it will not change the shape or position of the rest of the pH–solubility curve (Figure 4c). Nonetheless, raising K_{sp} is perhaps the most valuable scheme for enhancing the solubility of pharmaceutical molecules because, unlike changes in S_o or pK_a, it does not require alterations to molecular structure that could adversely affect pharmaceutical activity.

Although it can be both simple and fruitful to enhance solubility by exploiting K_{sp}, unfortunately the opposite effect can also be achieved if ionized molecules in solution encounter counterions with which they form a less soluble salt. Similarly, excess counterions can drive the drug out of solution through the common ion effect [4,15,21].

Measuring solubility

Having established the fundamental basis of solubility, some hardy souls might feel the desire to measure it. Measuring thermodynamic solubility is not a task for the faint hearted because, although simple in principle (add excess solid to the solvent of choice, stir the system for an infinite amount of time, and then measure the concentration of the resulting solution), the practical aspects of this process can be daunting. Because few researches have the patience to stir their solutions for an infinite amount of time to ensure equilibrium has been reached between the solution and the most stable crystalline form, some enabling conventions have been developed [22].

First, starting the experiment with crystalline material of high purity gives the best chance that the solubility measured after a more reasonable incubation period (several hours to several days) will be the true equilibrium solubility. There is still a risk that this foreshortened incubation will not be sufficient for metastable crystal forms to convert to the most stable form, and that the measured concentration will represent the apparent solubility of a different crystal form. This risk must be taken into consideration

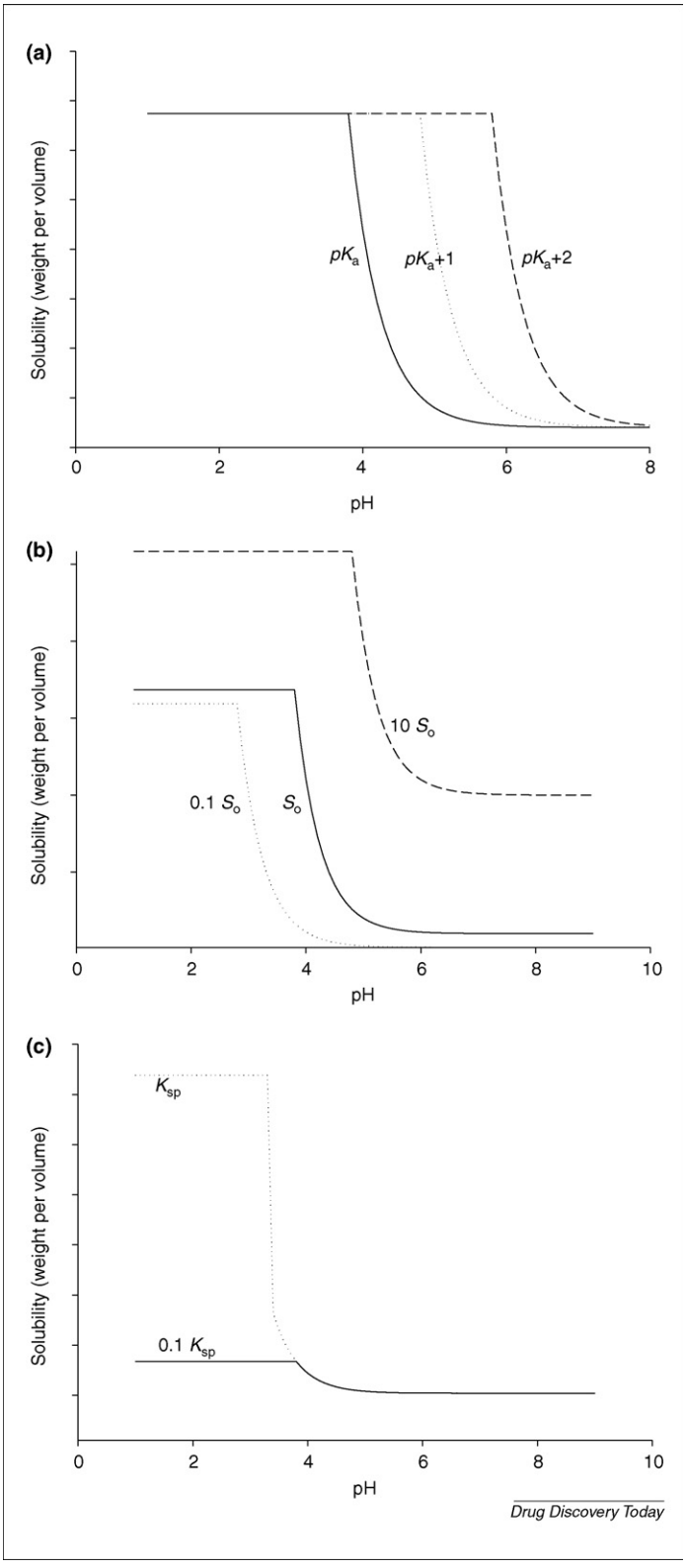

FIGURE 4

Strategies to increase solubility in the physiological pH range by altering physical chemical properties. (a) By strengthening the pK_a of a weak base by 1 or 2 pH units, the whole pH–solubility curve can be shifted so that the region of maximum solubility (salt plateau and pH_{max}) overlaps with the physiologically relevant pH range. **(b)** Increased intrinsic solubility (S_o) can lead to increased solubility at every pH, although the solubility product (K_{sp}) or common ion effects can effectively limit solubility at the salt plateau. **(c)** Effect of enhanced salt solubility (increased K_{sp}) on the pH–solubility profile. Reproduced, with permission, from Ref. [29].

when running a solubility experiment with material that is not known to be the most stable crystalline form.

Furthermore, the prudent analyst will measure not only the equilibrium concentration of drug, but also the pH of the resulting solution and the pK_a of the molecule. Consider the following experiment: the solubility of an ionizable molecule is measured in water. The measured concentration at equilibrium is 1.5 mg/ml. Is this solubility sufficient to deliver an intravenous solution of 2.0 mg/ml at pH 7.4? Without knowing the pH of the final solution and the pK_a of the molecule, this question is impossible to answer. Care must be taken to consider solubility always in the context of pH and pK_a.

Similarly, if the measured solubility falls on the steep portion of the pH–solubility profile, small changes to the pH can have a marked effect on the solubility. To maintain a drug concentration of 2.0 mg/ml in an intravenous solution at pH 7.4, the formulator has to ensure that the pH–solubility profile has sufficient margins with respect to the pH and the desired concentration in solution to prevent the compound from precipitating.

Even when measuring pH–solubility profiles, experimental details must be considered with care. Buffers of various types are commonly used in measurements of solubility as a function of pH. Because buffers can contain a cocktail of different ions, it is important to characterize the solid in equilibrium with the solution at the end of the experiment. Precipitation of insoluble salts can give erroneously low solubility values (HCl salts are notorious) [15], as can the common ion effect [21]. Nonetheless, with care, thermodynamic solubility measurements are an absolutely crucial part of physical characterization and have far-reaching implications for drug delivery and formulation.

In practice, the stable crystalline form of the compound is not available in sufficient purity during the discovery phases and the labor-intensive thermodynamic solubility measurement is not commonly made. The amount of compound required to measure a thermodynamic solubility measurement depends on the volume of solvent used to make the saturated solution and the solubility of the compound in that solvent. Recent reports for miniaturized systems list compound requirements ranging from ~100 μg per measurement for poorly soluble compounds [23] to 3–10 mg for pharmaceutically relevant compounds [24]. Although thermodynamic solubility provides invaluable information, the requirements of both solid purified compound and time (with a maximum throughput of 200 compounds per week) make even the most advanced automated systems unsuited to screening solubility during early lead discovery.

Early stage solubility information is nonetheless crucial to discovery teams seeking to explore structure–solubility relationships for their lead series or looking to troubleshoot biological assays for compounds of questionable solubility. Among the challenges facing early stage solubility testing are the sheer numbers of compounds being assessed at that stage, the scarcity of compound, and the questionable purity and crystallinity of the earliest discovery lots. All of these challenges have been partially met in a

high-throughput kinetic measurement of anti-solvent precipitation commonly misnamed 'kinetic solubility' [25–28].

Kinetic solubility is a misnomer, not because it is not kinetic, but because it measures a precipitation rate rather than a solubility. Kinetic solubility methods are designed to facilitate high-throughput (>600 compounds per week) measurements, using submilligram quantities of compound, in a manner that closely mimics the actual solubilization process used in biological laboratories. Typically, the compound is dissolved in dimethyl sulfoxide (because it is a strong organic solvent) to make a stock solution of known concentration. This stock is added gradually to the aqueous solvent of interest until the anti-solvent properties of the water drive the compound out of solution. The resulting precipitation is detected optically, and the kinetic solubility is defined as the point at which the aqueous component can no longer solvate the drug.

Solubility results obtained from kinetic measurements might not match the thermodynamic solubility results perfectly; therefore, caution must be exercised such that the data from the kinetic solubility measurements are used only for their intended application. It is not uncommon for discovery teams to use kinetic solubility data to assess structure–solubility relationships and pre-clinical formulation activities, but this application carries a significant risk. Kinetic solubility is determined on compounds that often have not been purified to a high degree or crystallized. The impurities and amorphous content in the material used in kinetic solubility measurements sometimes lead to a measured kinetic solubility that is higher than the true solubility by inhibiting precipitation from the aqueous medium. Because kinetic solubility experiments begin with the drug in solution, there is a significant risk of achieving supersaturation of the aqueous solvent through precipitation of an amorphous or metastable crystalline form. This supersaturation can lead to a measured value that is significantly higher than the thermodynamic solubility, masking a solubility problem that will become apparent as soon as the compound is crystallized.

Owing to the nature of kinetic solubility measurements, there is no time for equilibration of the compound in the aqueous solvent of measurement. Because the compounds tested are in dimethyl sulfoxide solutions, the energy required to break the crystal lattice is not factored into the solubility measurements. We therefore stress that kinetic solubility data are intended only to assess feasibility for biological assays. In fact, it is not uncommon to divide compounds into low-, medium- and high-solubility bins, depending on their kinetic solubility values, in order to reduce the importance placed on the actual numbers obtained. Rank ordering of compounds according to solubility on the basis of kinetic data can be done only if prior a comparison of the kinetic and thermodynamic solubilities of the compounds shows that these parameters have rank agreement.

Conclusion

Solubility determination plays an essential role in all phases of drug discovery and development. The key to success is, as always, to use appropriate data in an appropriate setting. For an ionizable compound, solubility without reference to pH and pK_a is meaningless. For both ionizable and non-ionizable compounds, the specific solid state of the compound is central to determination of the solubility.

Although thermodynamic solubility is the most theoretically and experimentally rigorous parameter, it is neither practical nor useful to measure it in the earliest discovery stages when purity, physical form and compound supply are all in question. At this stage, kinetic solubility measurements facilitate the rapid binning of large numbers of compounds for which little material is available. Kinetic and thermodynamic solubility measurements are not interchangeable: they rely on fundamentally different physical properties to assess solid-state and solvation interactions and thus should be approached and interpreted with both caution and a detailed understanding of their strengths and limitations.

References

1 Chen, X.Q. and Venkatesh, S. (2004) Miniature device for aqueous and non-aqueous solubility measurements during drug discovery. *Pharm. Res.* 21, 1758–1761

2 Jain, N. and Yalkowsky, S.H. (2001) Estimation of the aqueous solubility I: application to organic nonelectrolytes. *J. Pharm. Sci.* 90, 234–252

3 Yalkowsky, S.H. and Valvani, S.C. (1980) Solubility and partitioning I: solubility of nonelectrolytes in water. *J. Pharm. Sci.* 69, 912–922

4 Martin, A.N. (1993) *Physical Pharmacy*. Lea and Febiger

5 Bauer, J. *et al.* (2001) Ritonavir: an extraordinary example of conformational polymorphism. *Pharm. Res.* 18, 859–866

6 Wang, Z. *et al.* (2002) Solubility of E2050 at various pH: a case in which apparent solubility is affected by the amount of excess solid. *J. Pharm. Sci.* 91, 1445–1455

7 Avdeef, A. *et al.* (1998) pH–metric logP 10. Determination of liposomal membrane–water partition coefficients of ionizable drugs. *Pharm. Res.* 15, 209–215

8 Li, P. *et al.* (1999) Solubilization of ionized and un-ionized flavopiridol by ethanol and polysorbate 20. *J. Pharm. Sci.* 88, 507–509

9 Surakitbanharn, Y. *et al.* (1995) Self-association of dexverapamil in aqueous solution. *J. Pharm. Sci.* 84, 720–723

10 Ledwidge, M.T. and Corrigan, O.I. (1998) Effects of surface active characteristics and solid state forms on the pH solubility profiles of drug–salt systems. *Int. J. Pharm.* 174, 187–200

11 Bergstrom, C.A. *et al.* (2004) Accuracy of calculated pH-dependent aqueous drug solubility. *Eur. J. Pharm. Sci.* 22, 387–398

12 Chowhan, Z.T. (1978) pH–solubility profiles or organic carboxylic acids and their salts. *J. Pharm. Sci.* 67, 1257–1260

13 Li, S. *et al.* (2005) Effect of chloride ion on dissolution of different salt forms of haloperidol, a model basic drug. *J. Pharm. Sci.* 94, 2224–2231

14 Wagner, D. *et al.* (2003) Different dissolution media lead to different crystal structures of talinolol with impact on its dissolution and solubility. *Drug Dev. Ind. Pharm.* 29, 891–902

15 Serajuddin, A.T.M. and Mufson, D. (1985) pH–solubility profiles of organic bases and their hydrochloride salts. *Pharm. Res.* 2, 65–68

16 Kramer, S.F. and Flynn, G.L. (1972) Solubility of organic hydrochlorides. *J. Pharm. Sci.* 61, 1896–1904

17 Streng, W.H. *et al.* (1984) General treatment of pH–solubility profiles of weak acids and bases and the effects of different acids on the solubility of a weak base. *J. Pharm. Sci.* 73, 1679–1684

18 Hendriksen, B.A. *et al.* (2003) The composite solubility versus pH profile and its role in intestinal absorption prediction. *AAPS PharmSci* 5, E4

19 Berge, S.M. *et al.* (1977) Pharmaceutical salts. *J. Pharm. Sci.* 66, 1–19

20 Bogardus, J.B. and Blackwood, R.K., Jr (1979) Solubility of doxycycline in aqueous solution. *J. Pharm. Sci.* 68, 188–194

21 Serajuddin, A.T. *et al.* (1987) Common ion effect on solubility and dissolution rate of the sodium salt of an organic acid. *J. Pharm. Pharmacol.* 39, 587–591

22 Avdeef, A. (2001) Physicochemical profiling (solubility, permeability and charge state). *Curr. Top. Med. Chem.* 1, 277–351

23 Glomme, A. *et al.* (2005) Comparison of a miniaturized shake-flask solubility method with automated potentiometric acid/base titrations and calculated solubilities. *J. Pharm. Sci.* 94, 1–16
24 Bhattachar, S.N. *et al.* (2006) Evaluation of the chemiluminescent nitrogen detector for solubility determinations to support drug discovery. *J. Pharm. Biomed. Anal.* 41, 152–157
25 Avdeef, A. (2003) *Absorption and Drug Development Solubility, Permeability, and Charge State*. John Wiley & Sons
26 Dehring, K.A. *et al.* (2004) Automated robotic liquid handling/laser-based nephelometry system for high throughput measurement of kinetic aqueous solubility. *J. Pharm. Biomed. Anal.* 36, 447–456
27 Chen, T.M. *et al.* (2002) Evaluation of a method for high throughput solubility determination using a multi-wavelength UV plate reader. *Comb. Chem. High Throughput Screen.* 5, 575–581
28 Lipinski, C.A. *et al.* (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 46, 3–26
29 Pudipeddi, M. *et al.* (2002) Solubility and dissolution of weak acids, bases and salts. In *Handbook of Pharmaceutical Salts – Properties, Selection and Use* (Stahl, P.H. and Wermuth, C.G., eds), pp. 19–39, Wiley-VCH

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