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# Solubility Concerns: API and Excipient Solutions

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James Mitchell
David Elder, Ph.D.

- GlaxoSmithKline Pharmaceuticals

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## Introduction

Lipinski's influential paper on strategies to assess solubility and permeability of drug candidates was published nearly two decades ago1. The 'Rule of 5' demonstrated that exposure was negatively impacted if the calculated LogP (cLogP) was >5, if molecular weight (MW) was >500, when there are >5 H-bond donors or >10 H-bond acceptors. 'Drug-likeness' crucially focuses on potency and physicochemical attributes and has been extensively utilized across the pharmaceutical industry to try and minimize the high attrition rates (>90%). Regrettably, combinatorial and high throughput chemistry (HTS) strategies favor leads with higher cLogP, higher MW, and commensurately lower aqueous solubilities[1].

Hence, the best drug discovery strategies appear to be a balance between trying to optimize hydrophilicity-driven biopharmaceutics properties and hydrophobicity-driven potency properties[2,3]. As a consequence, optimizing potency without assessing the impact on physicochemical properties yields sub-optimal ADMET (absorption, distribution, metabolism, excretion and toxicity) properties and lowers the likelihood of clinical success[4]. Sub-optimal physicochemical properties can often be addressed using sophisticated formulation approaches[5,6], but the intrinsic deficiencies of these properties can often impact on the progression of drug candidates.

The solubility of any molecule is a function of the free energy of the solid and of the molecule in the solution state. Whereas, the free energy of the solid is an intrinsic property of that material, the free energy of the solution state is dependent on the solvent and the concentration of the solute in the solvent. At the equilibrium solubility, the free energy of the solid equals that of the solution[7].

## Enhancement of Solubility by Modifying the Solid-State Properties

Therefore the solubility of the drug substance can be increased by modifying its free energy by chemical (salt, cocrystal, polymorph) or physical (amorphous, size reduction) means.

### Chemical Approaches

Salt and cocrystal formation are the most commonly used approaches to enhance solubility and dissolution rates of drugs with low aqueous solubility[8]. Selection of an appropriate salt can significantly increase the drug's solubility (often $>10^3$ fold)[9,10]. Cocrystals have a more limited affect on solubility; the enhancement is similar to that seen between

different polymorphs, i.e. up to 5 fold[11]. However, the most appropriate counterion does not always equate to selecting the salt/cocrystal with the highest aqueous solubility, but rather it is a balance between the optimal solubility and the best physicochemical properties[8]. Korn and Balbach[12] indicated that over 50% of the salt screens performed at Sanofi-Aventis over the last 10-years were conducted to address inadequate solubility of the free acid/base. The majority of salts (86%) demonstrated good aqueous solubility, but these solubility improvements were 'often counterbalanced by partly unexpected physicochemical issues, which were not identified for the free base/ acid itself'. They indicated that the good aqueous solubility and high melting points often resulted in increased hygroscopicity, often resulting in deliquescence, phase transformations and formation of amorphous material. These issues were a significant impediment towards progression of these salts.

### Physical Approaches

Particle size reduction (milling, micronization, nano-milling) and surface area modification techniques can increase absorption by increasing the surface area and the dissolution rate -but rarely the solubility rate[13]. This approach can be described using the Noyes- Whitney equation:

$$\frac{dm}{dt} = \frac{DA_s(C_s - C)}{L} = kA_s(C_s - C)$$

*Where m is the undissolved solids mass, t the time, L the diffusional boundary layer, D the diffusion coefficient, k the intrinsic dissolution constant, As the surface area of the dissolving solid, C the concentration of solute in solution, and Cs the equilibrium solubility.*

Micronized drugs can often exhibit poor flow properties[14]. Gouthami et al.[15] engineered cilostazol crystals that had similar dissolution profiles to micronized material but which showed good handling properties. Spray drying can also produce engineered particles that are micronized-sized, i.e. $d_{50}$ 2-3 µm particles (or smaller), with narrow particle size distributions and which show increased dissolution rates versus traditional size reduction techniques.

Size reduction can be particularly successful when using nano-sized particles in a drug product. For example, decreasing the particle size of a 5µm particle to 50nm will only increase the surface energy by about 50%. The true benefit is achieved by the significant increase in surface area[16]. Nano-spray dried nimesulide exhibited reduced particle size and partial crystalinity with an associated increase in intrinsic dissolution rate[17]. However, increasing the dissolution rate is only relevant if it is the rate limiting process in the absorption of the drug from the gastrointestinal system. If absorption is solubility or permeability limited, further reduction in drug substance particle size will have no effect on the absorption rate of the drug in vivo. Amorphous forms can significantly enhance solubility (not just dissolution rate), often by $>10^3$ fold[18]. Unfortunately, amorphous forms tend to rapidly crystallize (metastable state) and they also show decreased chemical stability. Amorphous spray dried dispersions of tenoxicam, showed enhanced solubility relative to crystalline tenoxicam, while also exhibiting suitable physical properties and appropriate chemical stability for ongoing development[19]. However, modification of the solid-state is only viable if there is no phase change during the reaction, i.e. the solid-state form must remain the same. This can of course be quite challenging, particularly for amorphous materials.

## Enhancement of Solubility by Modifying the Solution-State Properties

A more controlled approach to enhancing solubility is to decrease the chemical potential of the solute in solution by selection of appropriate solubilizing excipient(s)[7]. Oral solution formulations are typically developed for pediatric or

geriatric use. Increased solubility can be achieved using several different excipient/formulation strategies.

## Using Buffer Systems to Optimize Solubility

Modification of the formulation pH is the simplest and most common approach to increasing the solubility of poorly soluble drugs[20]. Solubility enhancements of several orders of magnitude (≥$10^3$) can be readily achieved by modifying, then controlling the formulation pH (using buffer systems), at values of >3 pH units away from the respective pKa[7]. Typically, strong acids/bases, e.g. HCl or NaOH, will be used for making large changes in formulation pH and buffer systems will be used to control the pH at the designated value. Citrates, acetates, phosphates, glycine and TRIS (tris(hydroxymethyl)aminomethane) are commonly used buffer systems[20,21]. It should be understood that the pH of maximal solubility isn't always the pH of optimal stability and selection of the optimal formulation pH can involve 'trade-offs' between solubility and stability.

## Use of Co-Solvents to Optimize Solubility

Co-solvents are water miscible solvents that facilitate aqueous solubility. The most commonly used co-solvents are glycerine, propylene glycol, polyethylene glycol 400 and ethanol. Typically, solubility increases in a logarithmic fashion with increasing fraction of the co-solvent. However, there may be physicochemical, regulatory or safety considerations that constrain the absolute amount of the co-solvent within the formulation, particularly for pediatric use[7,20,21]. The EMA has recently published useful background information on propylene glycol and ethanol[22,23].

## Use of Surfactants

Drugs with high lipophilicity can have poor wetting properties and solubilization can be facilitated by surfactants. In addition, they can solubilize poorly soluble drug molecules by micelle formation or by acting as co-solvents[24,25]. Non-ionic surfactants are widely used and some typical examples are polysorbate 20 and 80, sorbitan monooleate 80, polyoxyl 40 stearate, solutol HS-15, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, d-α-tocopherol polyethylene glycol 1000 succinate and various polyglycol glycerides[7,21]. The latter class of surfactants, are useful in preparing lipid based formulations that can significantly enhance solubility and thereby oral bioavailability using the various 'self-emulsifying' systems, e.g. SEDDS (self-emulsifying drug delivery systems)[24-26]. Microemulsions, which are thermodynamically clear dispersions, can also be used to solubilize hydrophobic APIs[7,21].

## Use of Complexing Agents

Complexation between a solute and a complexing agent can enhance the API's aqueous solubility. The complexation reaction is dependent on relative size of the solute and the complexing agent, charge and lipophilicity. Complexing agents form non-covalent inclusion complexes with the hydrophobic API, with the API or the most non-polar fraction of the API 'included' within the complexation agent. In contrast to cosolvents, this has the advantage compared to other approaches that after dilution, a 1:1 complex will not precipitate. Complexation agents are typically pharmacologically inert and readily dissociate in the system or gastro-intestinal tracts[27].

Cyclodextrins (CDs) are common complexation agents[28]. They are α-(1-4) linked oligosaccharides comprising of α-D-glucanpyranose sub-units and they form a relatively hydrophilic outer surface (facilitating aqueous solubility), with a relatively hydrophobic inner surface which can accommodate the hydrophobic API. There are three types of cyclodextrins (α, β and γ), which are comprised of 6, 7 or 8 sub-units, and which form cavities with diameters of 5.0±0.3, 6.25±0.25 and 7.9±0.4Å, respectively[28]. The β form is the most commonly used,but covalent modifications

(hydroxypropyl- (HPβCD) or sulfobutylether-β-cyclodextrin (SBEβCD)) can dramatically enhance the aqueous solubility[28]. For example, 400mg/ml solubility with itraconazole (<5µg/ml solubility in water) is achievable[27]. Common development themes for using cyclodextrins are low CD:drug ratios (<2:1), low dose (<100mg), low drug solubility (<1mg/ml), medium drug hydrophobicity (cLogP>2.5) and moderate binding constants (<5000$M^{-1}$)[29]

### Use of Adsorbants

Adsorption of drugs onto the surfaces of selected excipients can lead to enhancement in the surface area of those drugs, thereby improving wetting and increasing the rate and extent of drug release. The adsorption capacity and available surface area of the excipients determine the total amount of drug adsorption[27]. For example, silica aerogels can increase the dissolution rates of certain poorly soluble drugs, e.g. ketoprofen and griseofulvin[30].

## Interface Between API Optimization Strategy and the Formulation Strategy

In oral drug development, the API optimization strategy and the formulation strategy can often diverge from one another[8]. In many cases the early-development strategy is focused on optimizing the drug substance solubility (and thus the bioavailability), irrespective of whether this is the best API form for longer term development needs[31]. Korn and Balbach[12] reflected that the use of bio-enhanced formulation strategies might be a more appropriate alternative to salt formation.

Elder et al.[8] indicated that 'The formulation strategies for poorly soluble compounds, e.g. size reduction via wet-bead milling or development of an amorphous stabilized dosage form using lyophilization, spray drying or hot melt granulation are better served by using the free acid/ base version of the drug, which are less prone to disproportionation.' They highlighted that many organizations were delaying 'version/ form optimization until after clinical efficacy has been demonstrated to mitigate against the very high attrition rate in early development'. The authors[8] reflected however that, the selection of the appropriate solid-state form is critical for both primary and secondary processing[32]. Therefore this activity should be initiated to allow sufficient time without introducing an unacceptably high risk to the subsequent clinical program.

## Conclusion

Various strategies are open to the development scientist to address the intrinsically poor aqueous solubility of modern drug substances. This can be achieved by modifying the free energy of the drug substance in the solid-state (salt, cocrystal, polymorph) or by using physical (size reduction, amorphous) approaches. A complimentary strategy is modifying the free energy of the drug substance in solution, which can be achieved as part of formulation optimization. Common strategies include pH optimization using buffers, direct enhancement of solubility using co-solvents/surfactants/adsorbants and lastly, complexation, whereby the solubility is improved by formation of an inclusion complex that can be readily dissociated prior to absorption. Oftentimes these solubility enhancement strategies are embraced without due regard as to whether the drug substance and drug product approaches are truly compatible. This disconnect between the two strategies is often exacerbated by attrition drivers, i.e. in many cases the early-development strategy is focused on optimizing solubility (and thereby bioavailability), irrespective of whether this is the optimal API form or drug product formulation for longer term development needs. In reality the best approach will recognize the need for "fit for purpose" approaches during early development, whilst ensuring that there is subsequently an adequate assessment and alignment of the API and drug product strategies to ensure optimal properties (biopharmaceutical, physicochemical and stability) going forward.

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