Using Absorption Prediction Tools to Optimize Formulation Strategy at the Preclinical Stage

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Achieving efficient GI absorption remains a critical hurdle in early development of orally dosed drugs, but new predictive methods can reduce the risk of failure and help identify optimal formulation strategies.

Oral dosing is often the simplest way for patients to take their medication, and it also remains the most popular choice for drug developers. Indeed, nearly half of the drugs approved in 2020—24 out of 53—were formulated as tablets, capsules, or solutions (FIGURE 1).[1]

But this route of delivery can also create daunting challenges in terms of ensuring that the active ingredient can effectively be absorbed into the bloodstream from the digestive tract. Drug makers must reckon with two key considerations in their efforts to optimize drug absorption. The first is solubility, which reflects the extent to which the drug can be dissolved in aqueous solution, and the second is permeability, which is a measure of how readily the drug can pass through gastrointestinal membranes.

Figure 1: Oral solid dosage forms remain robust.

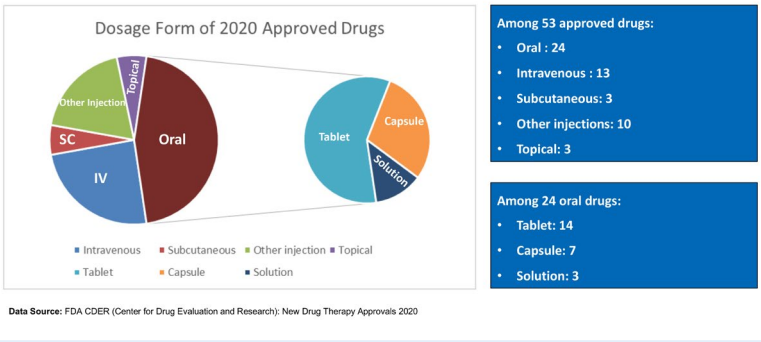


Figure 2: Solubility remains a challenge.

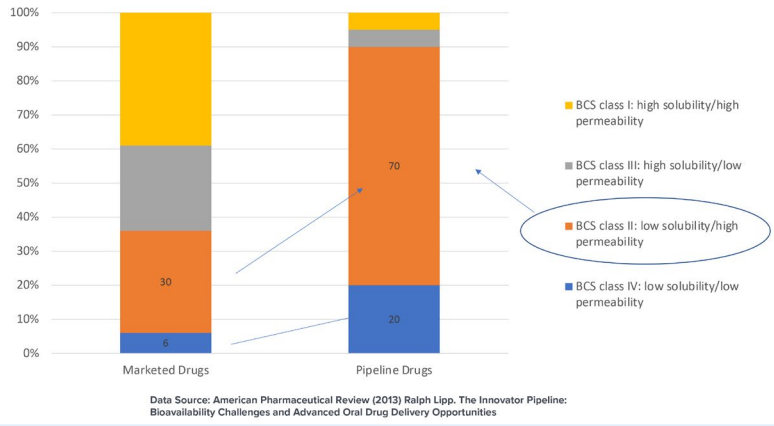
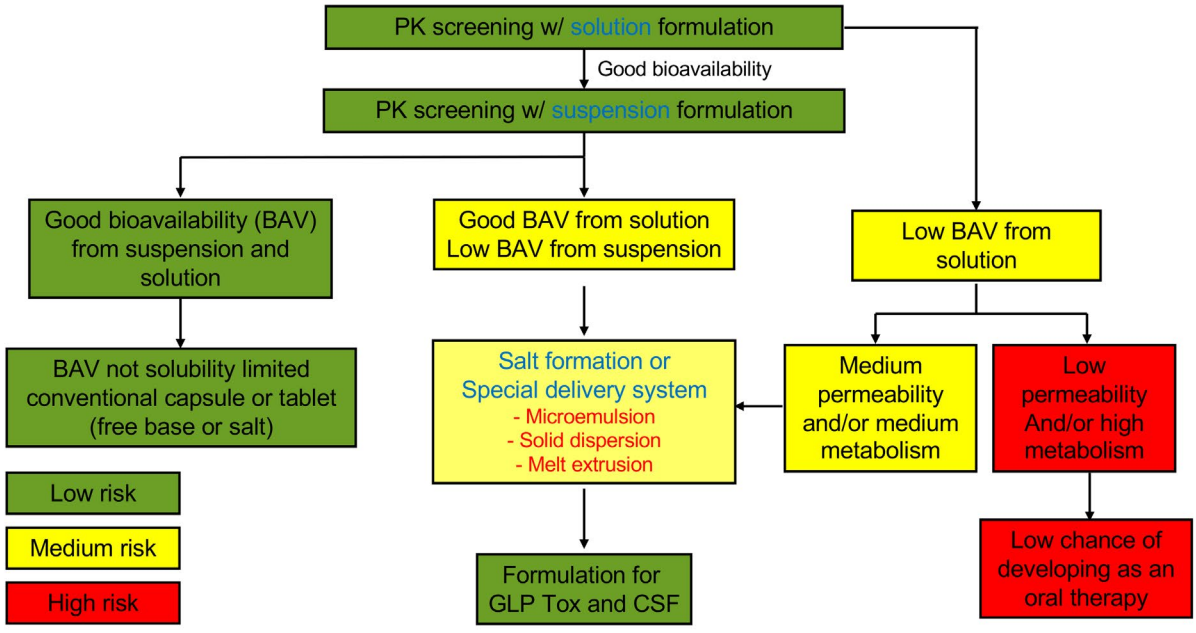


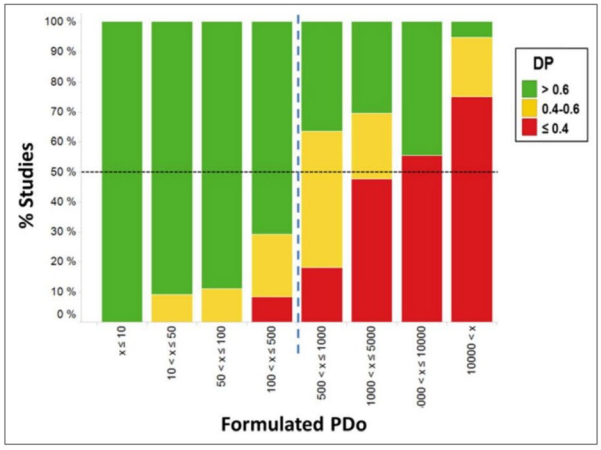
Figure 3: Formulation approach decision tree.



Solubility issues in particular can easily derail an otherwise promising drug candidate. A 2013 analysis found that 90% of drugs in the pipeline fall into the low-solubility categories of the Biopharmaceutical Classification System (BCS).[2] Nonetheless, only 36% of drugs on the market fall into these categories, indicating considerable attrition for these compounds during clinical development (FIGURE 2). Consequently, there is a critical need to evaluate and optimize the solubility of drug candidates early in the development process.

In the early 2000s, Novartis implemented a system for performing a "developability assessment," which entailed the interrogation

Figure 4: Use preclinical dose number (PDo) to help select formulation strategy.



Preclinical dose number (PDo)

$$= \frac{\text{oral dose(mg/kg)}}{\text{compound solubility in biorelevant media(mg/ml)}}$$

- PDo: >1000, higher probability of under-proportionality (AUC-Dose proportionality < 0.6)
- PDo: <1000, higher probability of proportionality (AUC-Dose proportionality > 0.6)

- Quickly estimates risk of non-linearity in preclinical species based on solubility in biorelevant media.
- The PDo tool can save time & resource in avoiding "over-formulation", as well as reduce animal experiments.

Data Source: W.Peter Wuelfing. et.al., *Mol. Pharmaceutics*, 2015, 12, 1031−1039

of four key features of new molecules. The first relates to whether the compound can be produced in a stable, crystalline form that is also soluble. The second question is whether linear dose-dependent drug exposure can be achieved in at least one rodent and one non-rodent animal model. Third, can the compound be produced as a formulation that is suitable for use in toxicology and clinical testing? The final challenge is whether a mitigation strategy can be identified if the compound is unstable. By devising experiments to test these questions, one can meaningfully reduce the odds of attrition due to unforeseen solubility issues.

One can also make use of a decision tree to assess the risk of failure for a drug development program in this context (FIGURE 3). This process begins with the pharmacokinetic (PK) evaluation of the drug's bioavailability when prepared as a solution, and then—if it achieves robust bioavailability in that first test—as a suspension. A drug that passes both tests has low risk in terms of solubility, whereas a drug that shows poor bioavailability as a solution is unlikely to succeed—particularly if that compound also exhibits poor permeability and/or is subject to a high rate of metabolism. If a drug performs well as a solution but poorly as a suspension, drug makers may have opportunities to boost solubility. For example, it may be possible to develop salts with improved solubility, or to turn to alternative formulation systems based on hot melt extrusion, solid dispersion, or the production of microemulsions.

PREDICTING AND OPTIMIZING SOLUBILITY

Pharmaceutical chemists now have access to a range of different prediction tools that can guide the formulation process to achieve optimal solubility for a given compound. *In vitro* dissolution testing has been a mainstay for evaluating oral drug solubility for decades, but improved versions of this testing approach are necessary to deal with contemporary drug development programs. This is partly because modern screening strategies are commonly

performed in non-aqueous media, favoring the selection of lipophilic compounds.[3] Furthermore, additional lipophilic chemical groups are sometimes added to compounds to tune their target-binding properties.

These characteristics have heightened the need for improved formulation strategies as well as more reliable *in vitro* dissolution testing regimens to evaluate the resulting products. Novel methods based on multi-compartment dissolution systems may offer a superior alternative to a traditional basket- or paddle-type apparatus. Such methods can better model the diverse range of processes—including disintegration, dissolution, super-saturation, precipitation, and absorption—that a drug may undergo during its transit through the gastrointestinal tract.

In one recent demonstration of this approach, a team at WuXi STA evaluated three different formulations of the antifungal agent itraconazole with a Pion MicroFLUX multi-chamber dissolution apparatus. This device employs pairs of chambers separated by a lipid-coated membrane, where users can control the pressure and agitation applied to the chambers. Based on this evaluation, it became clear that an amorphous solid dispersion (ASD) formulation achieved far superior absorption relative to a crystalline suspension or nanosuspension of the same drug.

Preclinical dose number calculations are another useful tool for guiding formulation decisions. This is a metric describing the number of intestinal volumes of FaSSIF—a standard *in vitro* dissolution medium—required to solubilize an entire dose of a given compound.[4] When the preclinical dose number is less than 1,000 (**FIGURE 4**), standard formulation strategies will most likely be sufficient to achieve good drug exposure *in vivo*, but a higher number indicates the need for a more sophisticated approach. For example, WuXi STA scientists recently tested one compound for which the preclinical dose number of the free form was 1,805 in a rat model. But when they worked with a salt suspension of the same compound, the number dropped to 446—within the acceptable range for in vivo absorption. The team obtained the same outcome in a dog model as well, supporting further development of the salt-based formulation.

The BCS is a standard tool for characterizing drug absorption, which employs a four-quadrant matrix that classifies compounds in terms of their solubility and permeability. In 2010, GSK scientists James Butler and Jennifer Dressman described a revised tool known as the developability classification system (DCS), which can offer further guidance as to how to proceed with a compound that exhibits sub-optimal absorption properties.[5]

In this framework, BCS class II compounds—which have good permeability but poor solubility—are further subdivided as being "dissolution rate limited" (class IIa) or “solubility limited” (class IIb). Both categories represent moderate risk for drug developers, but also provide opportunities for improved formulation. For compounds that fall into DCS IIa, reduction of drug particle size might lead to better dissolution properties, whereas

Figure 5: Implication of DCS for formulation selection.

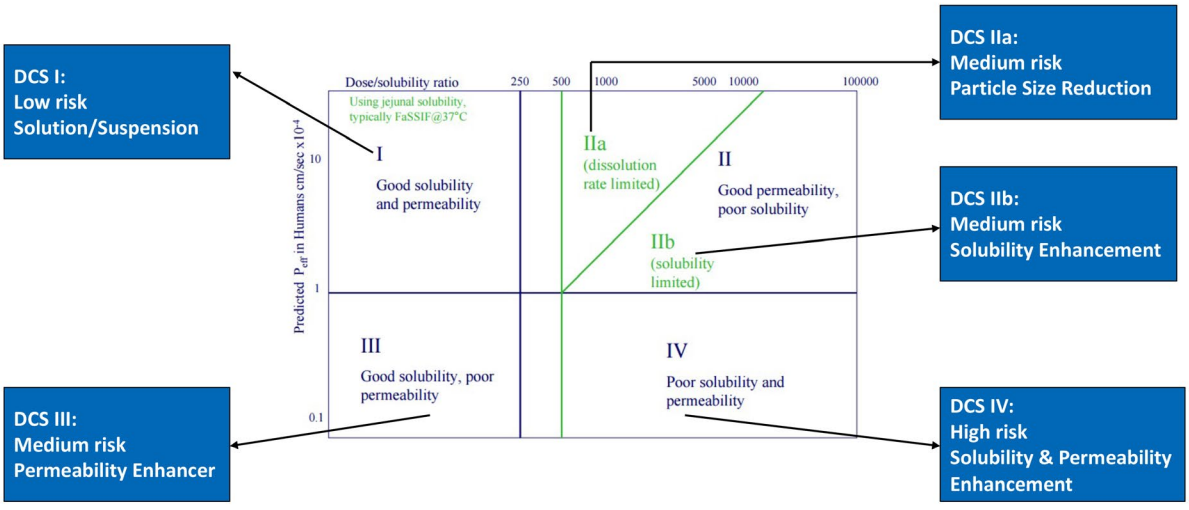
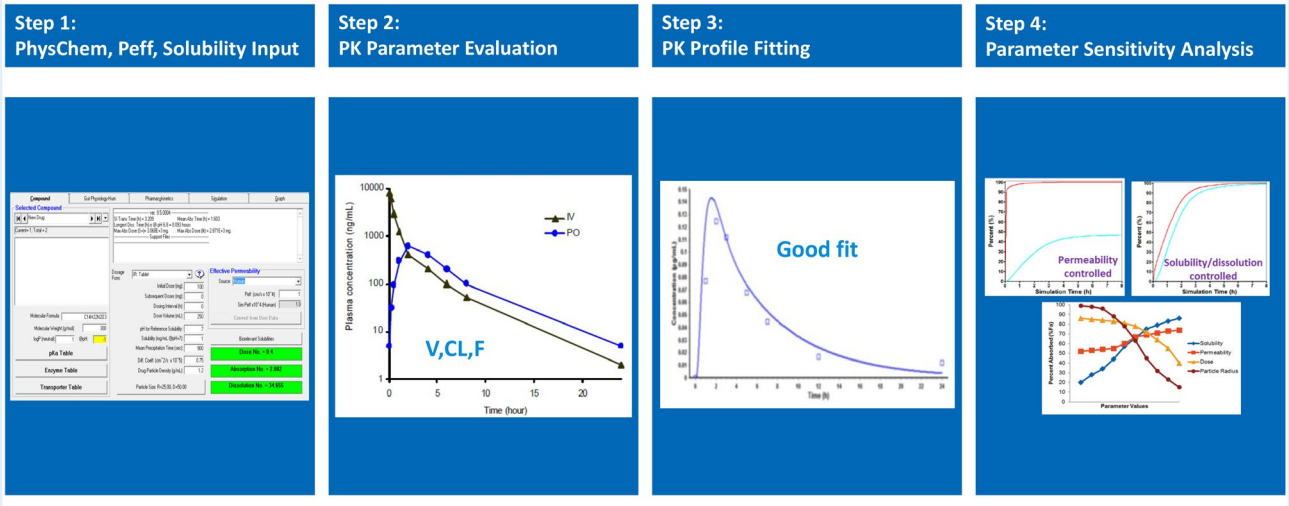


Figure 6: Implication of GastroPlus for formulation selection.



DCS IIb molecules would benefit from careful investigation of formulations that offer superior solubility (FIGURE 5).

Finally, WuXi STA scientists are now making routine use of the GastroPlus software, which models gastrointestinal absorption and helps identify the best formulation and dosing strategy to achieve the desired drug exposure for both toxicological studies and clinical testing. Modeling is typically a four-step process (FIGURE 6). First, users input the physicochemical properties of their compound, including solubility and effective permeability, followed by oral and intravenous PK parameters. After performing multiple simulation runs, one can identify the conditions under which the

modeled PK profile most closely matches the observed data. If the predicted values of key metrics such as C_{max} and area under the curve (AUC) are within a two-fold range of the experimentally measured numbers, the resulting model should be robust. Parameter sensitivity analysis (PSA) can also be applied as a final step to identify drug properties such as particle size or dissolution that are likely to be critical in determining *in vivo* exposure.

In one recent test of GastroPlus, WuXi STA researchers assessed two different batches of a pharmaceutical compound with high permeability and moderate solubility. These varied in particle size, with a 50-µm batch for initial characterization of the compound and a 200-µm batch for toxicological testing. During their modeling analysis, the team performed PSA to determine the impact of this parameter, and found that drug absorption drops dramatically for particles larger than 25 µm.

Based on this result, the project team performed a micronization process to further reduce the size of the drug particles used for toxicological analysis. In another demonstration of GastroPlus, WuXi STA researchers devised an improved formulation for a DCS 4 compound, which exhibits poor solubility and permeability and would generally be considered a high-risk drug program. But computational modeling revealed that an ASD formulation for this compound could prevent it from precipitating out in the GI tract and thereby boost absorption by three-fold, making this formulation viable for further development.

INTEGRATED MANUFACTURING AND DEVELOPMENT

Collectively, these prediction tools give drug developers the capability to rapidly assess a compound's absorption and bioavailability and determine whether an alternative formulation approach might improve the likelihood of success for a potentially risky program. WuXi STA employs these and other strategies as part of its end-to-end service for pharmaceutical industry clients, guiding the optimization and production of molecules for preclinical development and testing. Within 8–12 weeks, WuXi STA can perform an extensive preformulation assessment from just a few grams of active pharmaceutical ingredient (API), allowing clients to move quickly toward IND filing. This efficiency is achieved by performing all *in vitro, in vivo,* and *in silico* studies on the same site. For more challenging compounds, the company can devise and implement formulation strategies that improve drug absorption.

In parallel, the company can rapidly generate clinical-grade API for first-in-human studies as part of its "fast to clinical supply" (F2CS) service. F2CS scientists can develop a phase 1-ready formulation for an API in less than eight weeks, and have that GMP-grade formulation manufactured, packaged, and released within another month or two. In 2020 alone, the F2CS team has delivered more than 1,200 batches of clinical trial materials.

WuXi STA offers a world-class, end-to-end chemistry, manufacturing, and controls (CMC) platform that can save clients time and money, reduce the risk associated with a

new drug program, and add efficiency by bringing every step of the drug substance and drug product development and manufacturing under one roof.

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