Strategies for API Solubility and Bioavailability Enhancement

SELECTING TECHNOLOGIES AND EXCIPIENTS

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Low aqueous solubility is a major problem encountered during the formulation development of drug molecules. A drug that is not able to dissolve in a patient's gastrointestinal tract is unable to be systemically absorbed and, as a result, carries a higher risk of failure during development.[1] Therefore, with about 70 to 90 percent of the drugs in development falling in the two low-solubility classes of the Biopharmaceutical Classification System (BCS),[2] it is critical that formulation scientists use the most appropriate solubility enhancement technology and formulation strategies to improve the bioavailability of poorly soluble drugs.

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Traditional methods for completing these tasks are time consuming and labor intensive, and they often rely on either trial-and-error testing or just using the excipient and technology that have been the most reliable in the past. Instead, as one company found, the use of computational modeling in drug product development can simplify decision making and mitigate uncertainties, giving your product the best chance of survival in an increasingly competitive market.

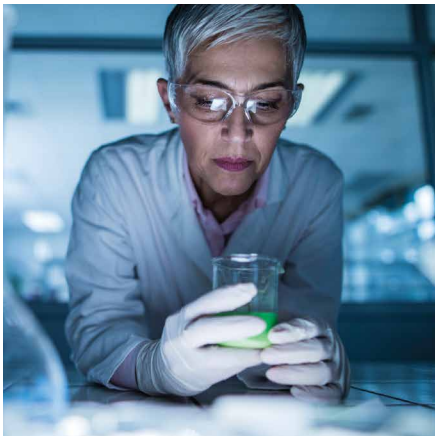
Addressing solubility challenges in a changing market

The landscape of today's industry looks far different than it did only a decade ago. Innovation in drug development is creating exciting new possibilities in patient care. Improvements in synthetic chemistry and high-throughput screening have opened up the small molecule chemical space, leading to novel compounds with the desirable potency. However, they also come with greater solubility challenges. In addition, medicinal chemists targeting less "druggable" entities must use lipophilic compounds to capture potency, also resulting in decreased solubility.[3] These obstacles, in combination with the typical attrition rates during drug product development and clinical trials, make it incredibly difficult to advance a new chemical entity (NCE) to a commercially marketed product.

The onus falls on formulation scientists to make sure they design a robust formulation that provides adequate bioavailability, stability, and manufacturability. This requires them to have proper knowledge about drug substance properties, how they interact, and any potential issues the scientist may face during formulation development. If the compound falls in BCS Class II or IV, the formulation scientist must select a solubilization approach to improve oral absorption and bioavailability. A variety of options can include[4]:

- **Spray drying** – codissolving drug and polymeric excipients to form a mutually compatible organic solvent. The solution is then sprayed through a nozzle to form solid particles that can be collected into a dry powder.
- **Hot melt extrusion** – using a thermal fusion process to form amorphous solid dispersions
- **Coated beads** – dissolving the API and a suitable polymer in organic solvents and spraying onto a substrate, depositing a layer of amorphous drug/polymer
- **Lipid-based formulations** – using lipids to solubilize and deliver the drug compound
- **Size reduction** – using either a "top down" or "bottom up" approach to reduce particle size, which expands the surface area to mass ratio, thereby increasing the dissolution rate of the API
- **Amorphous** – dissolving a crystalline API in a suitable organic solvent and then spray drying

- **Cocrystals** – using crystalline structures comprised of the API and a coformer to improve the physical properties of the API (yielding better dissolution and stability characteristics)
- **Complexes** – forming an inclusion complex using the API and companion molecule, preserving the integrity of the API



Historically, formulators have navigated this landscape through trial and error. This process is not only resource intensive and time consuming but can also lead to unnecessary delays in product development timelines. In one specific case, a customer came to Thermo Fisher Scientific after they had tested nearly 50 formulations for one compound across five different technologies without success. We readily found an appropriate solution for improving the bioavailability of this poorly soluble drug and quickly progressed it to successful human clinical studies using our Patheon Quadrant 2® approach.

Patheon Quadrant 2®: A structure-based approach to solubility exnhancement

The empirical process of selecting excipients and solubility technology is similar to a ball bouncing around in a maze. It will hit many dead ends before it finally finds its way out. In drug development, though, each dead end equates to more time and money being invested and ultimately wasted. The customer seeking our help had already lost a considerable amount of resources with its own internal testing, so time was of the essence.

A team of experts created a unique approach to selecting the most appropriate solubility enhancement technology and excipients for a customer's molecule without using extensive and unnecessary testing. This tool, known as Quadrant 2®, uses a proprietary computer algorithm to select the most effective solubility enhancement for a compound as well as which excipients should be used for formulation and process development. By doing so, Quadrant 2® reduces formulation development timelines significantly. Its algorithms have been validated to a high degree of predictive accuracy.

The Quadrant 2® algorithm requires the following information:

- an API's chemical structure
- an API's physico-chemical properties, such as the melting point

The technology selection output displays like a traffic light: green indicates the technologies that have the highest probability of effectively enhancing solubility and bioavailability; yellow implies a discussion and possibly additional evaluation are needed; and red implies there is a low probably of the technology working as needed.

When excipients are required for solubility enhancement, the next step is to figure out the formulation. The algorithm, based on decades of expertise from a team of formulation scientists and computational chemists, looks at how the drug and potential excipients interact at a molecular level and ranks which excipient and drug

loading option have the most favorable interactions with the API. It uses a complementary series of analyses involving quantum mechanical modeling, molecular dynamic simulations, and statistical modeling to identify the top five to six excipients that would have the best chance of working as amorphous dispersions.

For the above-mentioned compound, spray drying came out as one of the lead approaches to improving bioavailability. After screening a broad range of excipients, Quadrant 2® selected five candidate polymer excipients, which were then tested in animal models. The dispersions made by the five different polymers had higher bioavailability compared to the crystalline drug. Further experimentation narrowed the lead excipient and resulted in the lead candidate selection for progression to human clinical studies. The subsequent work involved process development and scale-up for manufacturing tablets containing the spray-dried amorphous dispersion intermediate.

The feasibility formulation work based on the Quadrant 2® excipient selection process was conducted on a lab-bench scale spray dryer. This process was successfully scaled up to the 10+ kg pilot scale spray dryer at the Thermo Fisher Scientific Early Development site located in Bend, OR. The scale-up of the spray-drying process was conducted by invoking fundamental thermodynamic models developed internally at Thermo Fisher as well as applying Quality by Design (QbD)-based Design of Experiments (DOE) principles to establish the process design space. Additionally, a robust tablet dosage form was also developed based on a formulation strategy that optimized the attributes of performance, manufacturability, and stability of the drug product. This approach led to a successful phase outcome for the customer.

In the end, Thermo Fisher was able to use a targeted experimental plan to provide the customer with a more effective and strategic plan and on-time delivery for the business and patient needs. Thermo Fisher Scientific also has a commercial spray drying site in Florence, SC, where customers now have access to an end-to-end solution for products with solubility and bioavailability challenges.

Conclusion

Obstacles that can slow the progress of a drug in a clinical pathway not only raise the costs and pressures of drug development, but they also can delay the delivery of drugs to patients in need. We have developed a rational computational and formulation strategy based on a drug molecule's physico-chemical properties. This approach bypasses conventional trial-and-error methods for solubility challenges and excipient selection. With this approach you can eliminate unnecessary testing, improve the efficacy of your formulation, and increase your overall speed to market.

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