AN INTERVIEW WITH...

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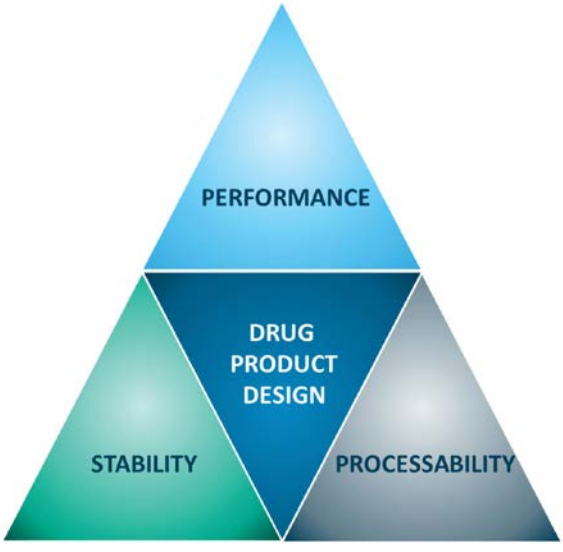
Navigating Formulation Development

Key Questions for Pharmaceutical R&D Leaders

The journey of transforming a drug candidate into an optimal drug product requires a strategic and informed approach. This article answers key questions, drawn from recent insights into formulation development and drug product design, that research and development management, and executives in the pharmaceutical industry should consider.

What fundamental principles support successful formulation development in today's small molecule landscape?

Successful formulation development and drug product design are the result of a technology-agnostic approach based on a fundamental understanding of Active Pharmaceutical Ingredient (API) properties, a well-defined yet flexible Target Product Profile (TPP), and a viewpoint for scalability and commercial relevance. In the current environment, many complex, low solubility, or low permeability drug candidates are viable oral New Chemical Entities (NCEs) thanks to modern drug delivery tools. Medicinal chemists can focus on optimizing molecular properties for safety and efficacy, relying on formulation and delivery technologies to enable oral bioavailability.



How critical is the Target Product Profile (TPP) in guiding technology selection for oral absorption enhancement?

Defining the TPP early is critical as it establishes key product attributes that directly inform technology selection. Understanding the target population (e.g., adults, pediatrics, geriatrics) is also important to address, as specific patient needs like flexible dosing or ease of swallowing can dictate technology choices. The dose range, even if preliminary, significantly impacts technology selection and if enabled technology is necessary. These steps can ensure proper drug delivery technology selection right from the start and avoid later stage reformulation.

How do API classification systems like BCS and DCS contribute to dosage form design?

API classification systems, specifically the Biopharmaceutics Classification System (BCS) and the Developability Classification System (DCS), are valuable tools for predicting a drug's absorption and bioavailability, thereby informing dosage form design. BCS and DCS both categorize drugs based on solubility and permeability. The BCS is commonly leveraged to guide regulatory requirements for demonstrating bioequivalency and the DCS is used to guide formulation development. The DCS classification system can be overlaid with a technology selection map to further guide the development of enabled formulations.

What are the key considerations when selecting a technology to enhance the oral absorption of solubility-limited molecules?

While there may be multiple technologies that achieve the necessary enhancement, the simplest approach to meet the TPP should be considered. For solubility-limited molecules, technology selection is guided by measured solubility relative to dose and permeability, which often correlates with molecular weight and LogP. The lipophilicity of the molecule (LogP) is also an important factor in identifying the most suitable formulation technology to maximize bio-performance. Additionally, the API form (e.g., polymorphs or salt forms) can significantly alter solubility and thus the dose number,

impacting technology selection. The dose itself also plays a crucial role; lower doses might be adequately addressed by particle size reduction, while higher doses may require more sophisticated enabled intermediates.

How can bio-performance modeling refine formulation strategy and design space?

While API classification provides strategic guidance, evaluating bio-performance and predicting the fraction absorbed (Fa) as a function of key parameters further refines the formulation strategy and design space. Estimates of Fa, based on API properties, solubility, and human physiology, can be used to compare different API forms, formulations, and highlight potential food effects. These predictions assume absorption is not limited by kinetic solubility or diffusion and that when considering amorphous forms, that solubility enhancement sustains throughout GI transit.

What insights can fraction absorbed (Fa) predictions based on dose and particle size provide?

Predicting Fa as a function of dose and particle size can offer valuable insights into formulation development. This assessment can help us understand when particle size should be considered an enabling design feature or the extent to which it needs to be controlled for a given technology. While these estimates are based on dissolution rates calculated from API properties (assuming spherical particles) and illustrate trends rather than absolute values, they provide crucial guidance.

What factors beyond bio-performance influence the final selection of an enabling technology?

While enabling bio-performance is paramount, the final technology selection may also be driven by considerations around manufacturability and stability. It is not uncommon for more than one technology to be appropriate for enhancing bio-performance, and the ultimate choice may hinge on the feasibility and robustness of the manufacturing process or the long-term stability of the formulated product.

Serán employs a wide range of pharmaceutical manufacturing operations, including spray drying, hot melt extrusion, dry and wet granulation, nano-milling and micronization, fluid bed processing, solid dosage forms (tablets, capsules, and OPCs), and many other enabling approaches to deliver their clients' NCEs to patients.

The Serán team has decades of experience in drug product design, process engineering, and scale-up activities including product launches and commercial manufacturing. To learn more about Serán, connect with them at www.seranbio.com