ADDRESSING ONGOING AND NEW BIOAVAILABILITY CHALLENGES

Here, Stephanie Emory, PhD, Associate Director of Pharmaceutical Development at Metrics Contract Services, explores the pros and cons of various technologies for enhancing solubility and bioavailability for oral drug formulations. Further, Dr Emory draws on her experience as a reviewer at the US FDA to discuss how developers can view the FDA as a partner to aid success when leveraging innovative approaches.

As drug discovery continues to rely heavily on high-throughput screening techniques to identify drug candidates based on receptor binding affinity, it is increasingly common that potential candidates suffer from low solubility and bioavailability. In turn, the challenge of dealing with this issue is faced by an ever-growing number of projects.

It is reported that the majority of new chemical entities (NCEs) currently in development have bioavailability challenges due to low solubility, low permeability or both. While low permeability is a more complex problem to solve, there is an increasing number of technological solutions to address the two main culprits of low solubility: high crystalline lattice energy and greater lipophilicity.

Enhanced dissolution, solubility and bioavailability of poorly soluble APIs can be achieved using a variety of approaches. For oral solid dosage forms, which continue to be the most desirable finished dosage forms, common approaches include solubilisers, micro/nanoparticles, salts, co-crystals and amorphous solids dispersions (ASDs).

SOLUBILISERS

Simple approaches to mild solubility limitations include co-mixing of solubilisers or self-emulsifying excipient systems into traditional solid oral dosage formulations or dissolving the API in a liquid-filled capsule formulation. These techniques can be effective for some APIs, particularly those that are highly lipophilic, and the time and cost required to determine their effectiveness is relatively low. This technique is often combined with particle size reduction to further enhance solubilisation. However, for more significant solubility challenges, these approaches often fall short of achieving sufficient increases in bioavailability and, for liquid-filled capsules, can present additional stability challenges for APIs that are unstable in solution.

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MICRO/NANOPARTICLES

Particle size reduction technologies are now routinely used to increase bioavailability in poorly soluble drugs. The principle is relatively simple; reducing particle size increases the relative surface area and consequently the rate of solvation. Overall, the degree of crystallinity is significantly reduced and, particularly at the nano-scale, an increase in apparent solubility results in faster and more complete dissolution.

While traditional milling and homogenisation techniques are widely available for particle size reduction, these high-energy processes are not ideal for heat-sensitive APIs. An array of alternative, lower-energy techniques are becoming increasingly common, using both top-down (cryo-milling) and bottom-up (nanocrystals) approaches. While bottom-up techniques typically result in a smaller and more uniform particle size distribution compared with top-down methods, they require appreciable

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solubility in appropriate solvents, which limits their use for extremely insoluble compounds.

AMORPHOUS SOLID DISPERSIONS

Creating ASDs offers better dissolution profiles and enhanced bioavailability by completely eliminating the crystal structure, making this technique ideal for APIs where high lattice energy is the main reason for low solubility. High lipophilicity can also be addressed by choosing a more hydrophobic carrier.

Both spray drying and hot melt extrusion (HME) can be used to produce ASDs. Several factors come into play when deciding whether to progress with an ASD and which technology to use. These include performance, projected dose, stability and manufacturability. When choosing which technology to employ for optimising the ASD's performance, two key factors should be considered: the physicochemical properties of the API and the phase of development, which influences the amount of API available for formulation development.

Important physicochemical properties for creating an ASD include the solubility of the API in a solvent suitable for spray drying, as this is crucial to ensuring a readily scalable and viable process. HME is sometimes preferable as it does not rely on solvents. The heat and shear forces exerted during HME can be critical for overcoming really tough solubility challenges but pose significant barriers for heat-sensitive APIs.

In early-stage or discovery-support activities, API availability is limited, which often makes spray drying the preferable approach because its feasibility can be determined with much less API than with HME. For APIs that are amenable to HME, which is typically identified after proof-of-concept clinical studies, an initial spray-drying process can sometimes be converted to HME where necessary.

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ASDs present several challenges to downstream formulation. Poor flow is a particular concern, especially for spray-dried dispersions. Dry granulation is often employed to improve flow, although this also reduces compressibility, creating challenges for tablet compression. Due to the ratio of polymer to drug required to create a stable ASD, additional excipients must be included judiciously to produce a reasonably-sized finished dosage form. Ideally this is balanced by an increase in bioavailability, which allows for a lower dose, although this is not always the case. Given the increased focus on patient-centricity and compliance in today's drug delivery industry, size and swallowability are imperative considerations, and excipient use must be finely balanced.

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ASDs are subject to what is commonly referred to as the "spring and parachute" effect; in the gastrointestinal (GI) tract, compared with pure crystalline API, ASDs exhibit more rapid and complete dissolution (the "spring") resulting in a metastable supersaturated solution of API which, if not maintained or slowed by crystallisation inhibitors (the "parachute"), can result in precipitation of the API to its most thermodynamically stable (i.e. low solubility) form, reducing or even eliminating any increase in bioavailability using an ASD enabled in the first place. While polymers used for ASDs often have additive effects, such as crystallisation inhibition or influence on the polymorph formed during re-crystallisation, their use levels and the need for additional crystallisation inhibitors should be examined during formulation optimisation to maximise both *in vivo* performance and stability to fully capture the benefits of ASDs.

SALTS

Salt formation and selection is one of the most frequently used approaches to increase the bioavailability of poorly soluble ionisable APIs. However, while solubility is increased, permeability may be negatively impacted, as passive diffusion across the GI membrane is significantly reduced when the drug is in its charged form. This affects the location and extent of absorption *in vivo* as the changing pH along the GI tract creates "windows" where more of the drug molecule is in its neutral form and can be more easily absorbed. In addition to effects on permeability, the *in vivo* dissolution of some salts, especially hydrochloride salts, can be limited by the common ion effect of chloride in the GI tract. The overall benefit of salt formation depends on the balance of its impact on solubility and permeability.

CO-CRYSTALS

Unlike salt formation, co-crystal technology can be applied to non-ionisable APIs. Co-crystallisation is a more contemporary approach to improving bioavailability that involves co-precipitation of an API with a soluble co-former, using non-covalent

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intermolecular forces (primarily hydrogen bonds) between the two compounds to form a single-phase crystalline material with a lower lattice energy and higher apparent solubility compared with pure crystalline API.

Improvement of physicochemical properties, such as solubility, dissolution rate, stability and melting point, makes co-crystals an attractive option for poorly soluble APIs. However, it is important to note that co-crystals are more stable than ASDs but suffer the same "spring and parachute" phenomenon without the additive effects on crystallisation inhibition afforded by many ASD polymers. Therefore, additional formulation development is needed to optimise *in vivo* performance.

There is also evidence that co-crystals can impact membrane permeability, although this is not yet fully understood, and both positive and negative effects have been observed. Further, the potential for co-crystals to interrupt cellular integrity has raised concerns about their toxicity, as well as the physiological effects on the GI tract exerted by some co-formers leading to changes in absorption.

FDA AS A "PARTNER"

With the pharma industry continuing to churn out increasingly complex and challenging molecules, novel formulation and processing strategies continually emerge to support these efforts. With limited official guidance available for these new technologies, developers are often hesitant to fully embrace them for fear of significant regulatory hurdles.

The US FDA's response in recent years has been to publicise its intent to make regulatory decisions based on scientific reasoning rather than stoic adherence to guidelines that are often not fully applicable to newer technologies. Evidence of this can be seen in the FDA's Emerging Technology Program, which invites drug sponsors to meet with the agency to proactively explore new technologies and discuss potential issues before these novel processes and formulations are included in new drug applications (NDAs). Ultimately, the FDA's mission is to advance new therapies to market that are safe and effective.

Regardless of whether well-established or innovative approaches are employed, sponsors would be wise to communicate and be transparent during their investigational new drug (IND) and pre-NDA phases, openly discussing challenges and potential solutions. This allows the agency to fully understand and provide guidance well before the NDA review clock starts.

Addressing issues ahead of time helps ensure a smoother and more favourable review process, whereas downplaying significant challenges rather than addressing them directly is a high-risk strategy. A major amendment or complete response letter can lead to significant delays in approval and loss of first-to-market advantages.

CONCLUSION

With so many options for bioavailability enhancement currently available, developers who invest in thorough API characterisation are well-poised to swiftly overcome these challenges by identifying the technologies best suited to their product. Conversely, when API characterisation is limited, exploring multiple pathways in parallel can save considerable time.

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Although relying on new technology and complex formulation carries inherent risks to the drug development cost and timeline, careful development strategies and transparent collaboration with regulators is the best strategy to avoid delays in getting new therapies on the market.

ABOUT THE COMPANY

Metric Contract Services, founded in 1994, now a division of Mayne Pharma, is an oral solid dosage form CDMO providing formulation development, analytical testing and commercial manufacturing services to support drug development from concept to global commercialisation.

ABOUT THE AUTHOR

Stephanie Emory is Associate Director of Pharmaceutical Development at Metrics Contract Services. Dr Emory has 12 years of pharmaceutical industry experience and a strong background in product development, specifically in the field of bioavailability enhancement of small molecule formulations. She joined Metrics from the FDA where she reviewed the CMC/Drug Product portions of INDs, NDAs and industry meeting packages for CDER's Office of Pharmaceutical Quality. Prior to the FDA, she spent seven years at UPM Pharmaceuticals, a then Baltimore-based CDMO, serving as both technical lead and project manager for the development of pre-clinical through Phase III clinical supplies. She has experience with a wide range of solid oral dosage forms and manufacturing processes, including solubility-enhancing formulations, as well as scale-up, tech transfer and process validation activities. Dr Emory holds a Bachelor of Science in Pharmaceutical Sciences and a doctorate in Industrial & Physical Pharmacy from Purdue University (West Lafayette, IN, US).