Bioavailability Enhancement: The Key To Unlocking The Potential Of Drug Development Pipelines

After a series of scientific breakthroughs the pharmaceutical industry is edging closer to developing treatments for many devastating diseases. But the newfound optimism is offset by a big, common barrier: bioavailability. With as much as 95% of the drug development pipeline suffering from low solubility or permeability, the conversion of cutting-edge science into life-saving treatments is wholly reliant on the advancement and application of bioavailability-enhancement techniques.

Bioavailability is a long-standing problem for drug developers. At the start of the 1990s, adverse pharmacokinetic and bioavailability characteristics accounted for 40% of clinical-stage pipeline failures. Over the next 10 years, drug developers got much better at spotting drugs with these traits during preclinical research — culminating in bioavailability being a causal factor in less than 10% of failures by 2000 — but the underlying challenge of turning poorly soluble active ingredients into viable therapeutics never went away.

The challenge is now greater than ever. Some estimates suggest around 90% of pipeline candidates are categorized as poorly soluble under the Biopharmaceutical Classification System (BCS), with a further 5% presenting bioavailability challenges because of their low permeability. Just one-third of approved drugs are classed as poorly soluble. The growing prevalence of pipeline products with poor bioavailability has intensified demand for technologies and methods that can overcome these traits, as well as for companies that understand how and when they should be applied.

In this paper we look at the process CoreRx goes through when given an active ingredient with low bioavailability and four approaches that may be applied to increase the amount of the therapeutic that enters systemic circulation.

Brian McMillan, M.S.Pharm.
VP Product Development
CoreRx

The Process: How To Decide Which Approach To Take

The process of turning a low bioavailability drug into a viable therapy begins by looking at the physical properties of the active ingredient. Data on thermal properties, particle size distribution, morphology, and other factors can yield insights into which method will deliver the best results. CoreRx then runs various analyses evaluating chemical properties of the substance including assay, related compounds, intrinsic dissolution in various media, and molecular stability. The third critical piece of information is the targeted level of bioavailability. If animal studies have shown that a threefold rise in bioavailability is needed, the team will focus on both physical and chemical methods that can achieve this goal.

Once the team understands the active's characteristics, it chooses bioavailability enhancement techniques from one of three broad categories: physical, chemical, and complexation. Physical modifications include micronization,

solid state dispersion, and creation of nanoparticles. If the team decides a chemical modification would work better, a change in pH, use of a buffer, or different salt form of the molecule might be considered with the client. In other instances, CoreRx uses complexation — a growing approach that combines the molecule with other agents such as cyclodextrins or hydrophobic materials — which can have a dramatic effect on both solubility and bioenhancement.

Many clients want the same thing: a high-energy amorphous state of their molecule. The challenge is working out the most effective, efficient way to achieve this goal. A skilled team will know which approach to use and have proprietary technologies that deliver the best possible outcome.

Spray Drying: Creating Solid Dispersions To Boost Bioavailability

Solid state dispersions (SSD) are one answer to the question of how to create high-energy amorphous molecules. Spray drying entails creating a suspension or solution — consisting of the active, a polymer, and, in some cases, surfactants — and atomizing it to create droplets. As the droplets dry, they form amorphous, solid particles. The resulting state lacks a crystal lattice and therefore has greater thermodynamic solubility. Bioavailability is further enhanced by the fine particles that form in spray drying. These particles offer a greater surface area, which boosts kinetic dissolution.

The shift in state from crystalline to amorphous makes spray drying particularly well-suited to actives with high crystal lattice energy. Solubility is the other key criteria for evaluating whether spray drying is the most appropriate approach. For the right compound, spray drying is a highly-effective way of creating a high-energy amorphous state without needing large quantities of the active pharmaceutical ingredient (API) for initial R&D trials.

Hot-Melt Extrusion: Enhancing Bioavailability Without Solvents

Formulators use hot-melt extrusion (HME) to achieve similar results to spray drying, but each approach is better suited to particular situations. HME entails melting, mixing, extruding, and pelletizing the active ingredient and a polymer. The use of heat dictates which ingredients can undergo HME. If the active melts — or can be dissolved by shear stress — at a temperature that neither degrades it nor the polymer, HME may be suitable. CoreRx also looks at the ingredient's solubility in the chosen polymer to assess whether the resulting mixture will be sufficiently stable.

When an ingredient meets these criteria, HME is a good choice. The development of an HME process may require more of the API for initial trials versus spray drying — making it potentially less suitable for early-stage research — but the lack of solvents and compact nature of the equipment means it offers advantages as the drug nears approval. Using HME frees the manufacturer from the cost of buying — and then trying to recover — the solvent, while also lessening the potential for regulatory health and safety concerns. Complications that stem from

using solvents have encouraged firms to look for alternatives.

Nanomilling: Reducing Particle Size To Permeate Cell Membranes

Nanomilling is an alternative route to the small particles that enable spray drying to enhance bioavailability. The end goal of nanomilling is to create tiny particles — the resulting nanocrystals typically measure 200 to 500 nm — that have a faster dissolution rate than the original ingredient. A variety of technologies can achieve this goal, with media milling being the approach behind many of the first wave of approved nanocrystal drugs. Many companies utilize NETZSCH mills for this wet grinding process to create nanoparticles and enhance the bioavailability of clients' APIs.

The technique is best suited to starting materials with high melting points and molecular weights, as well as ingredients that are poorly soluble. Once the processing technique has reduced the particle size, CoreRx uses stabilizers to prevent coagulation. Formulators use a variety of materials for this task, with nonionic and ionic surfactants, as well as polymers, all proving to be effective stabilizers. In many cases, the selection of the stabilizing agent is the key decision. The technology to reduce particle size is widely available, but the expertise needed to prevent aggregation is rarer.

Complexation: Broadening The Range Of Possible Actives

For some actives, none of the above mentioned bioavailability-enhancement techniques are suitable or effective. In the past, drug developers might cease research into such molecules, but complexation has given formulators a new way to boost bioavailability. The technique involves numerous methods, including use of cyclodextrins.

These molecules are cyclic oligosaccharides which exhibit a hydrophilic exterior and hydrophobic interior, enabling them to form complexes with APIs. Cyclodextrins are non-toxic and are also used in solid oral dosages to enhance taste, solubility, and permeability. The class is also suitable for enabling enhanced ophthalmic delivery of contemporary dosage forms.

Other possibilities are complexation with various hydrophobic materials such as phospholipids. These systems utilize complexation of the API with the hydrophobic material using a solvent system. The dosage form is then covered with an enteric coating, enabling the API to pass the rigors and low pH of the stomach and enter the intestines where it can be bio-absorbed.

CoreRx has used complexation with materials such as cyclodextrins and phospholipids to dramatically enhance the bioavailability of molecules, with five to tenfold increases seen in animal studies. Complexation can turn an active that passes right through the gastrointestinal tract without being absorbed into a candidate with an acceptable bioavailability profile. This increases the pool of molecules from which drug developers can choose. APIs that were previously written off because of low bioavailability are now becoming viable

alternatives as solid oral dosage forms versus, for example, parenteral delivery.

Vendor Selection: Picking A Partner To Enhance Bioavailability

The bioenhancement-availability techniques discussed in this paper — and particularly the proprietary ways in which the best formulators improve the core methods — mean the dominance of poorly-soluble molecules in drug development pipelines is a manageable problem. Drug development service providers have the technology and expertise to help any company with a low-bioavailability active to formulate a product with an acceptable dissolution and absorption profile. Discovering an active has poor bioavailability is no longer the unfavorable outcome it once was.

For drug developers, the challenge now is selecting a vendor that offers more than just basic SSD or HME. The best service providers can develop proprietary technologies and methods for their clients and have knowledge of how and when to use them. This elevates the effectiveness of these techniques. Such partners can turn bioavailability problems with the potential to slow development into manageable challenges that can be overcome quickly with cost-effective alternatives.

CoreRx, Inc.
14205 Myerlake Circle
Clearwater, FL 33760 USA
(727) 259-6950
corerxpharma.com

core Rx