Lonza
Pharma & Biotech

Executive Summary: Technology Selection To Enhance Bioavailability

INTRODUCTION

Bioavailability challenges are among the toughest problems faced by today's formulators. Most of the prospective drugs in pharmaceutical pipelines today have low solubility, which means the active therapeutic ingredients can't be absorbed when patients take them orally. In many cases, this low bioavailability can mean promising medicines are abandoned because no technology can be identified that delivers the required therapeutic dose conveniently.

To solve this critical problem—which industry experts estimate affects as many as 7 in 10 of the compounds in pharmaceutical pipelines today—numerous approaches have been developed. These include the use of salts, cocrystals, amorphous solid dispersions, and nano- or microcrystals manufactured with a variety of technologies—spray drying, particle-size reduction, hot-melt extrusion (HME), cyclodextrin complexation, and lipid-based technologies. These approaches may enable development of low-solubility compounds, bringing new medicines to market or reformulating existing products to improve performance, extending the product lifecycle.

However, the wide array of these enabling technologies spawns another dilemma for formulators: how to choose the optimum technology from among this sea of choices. What factors need to be considered and how can the selection process be streamlined so the development of promising compounds is not delayed?

At Lonza, we've studied technology selection in depth and developed a science-based process to guide development of low-solubility compounds to improve bioavailability. Our approach recognizes several important facts.

- Given the diversity of compounds in pipelines today, all needs cannot be addressed by a single technology.
- The chances of success are higher if the technology is matched to compound properties and the target product profile.
- In some cases, more than one technology can be used successfully to increase bioavailability. In such a case, the desired product profile and desired dosage form—tablets versus capsules, for instance—may be the deciding factor.

In this paper, we summarize the Lonza technology selection process, which is efficient and effective. We review the key physicochemical and biological obstacles to drug absorption from oral dosage forms and then discuss how our process takes these factors into account. We then describe the tools that we have developed through a thorough investigation of key technologies and our experience with hundreds of bioavailability enhancement products.

OBSTACLES TO BIOAVAILABILITY

There are two main types of obstacles to bioavailability of oral drug products: (1) physicochemical obstacles and (2) biological obstacles.

Physicochemical Obstacles

The first category of obstacles encompass the physical and chemical characteristics of the compound to be delivered. For compounds with low bioavailability, two factors are usually in play: (1) they do not dissolve well in water and/or (2) they dissolve too slowly. The first factor—low solubility—limits the maximum drug concentration that can be achieved in the small intestine, where most drug absorption from oral dosage forms takes place. The second factor—slow dissolution rate—is almost always associated with low solubility, but can be compounded by small drug surface area and/or slow diffusion rates into the gastrointestinal (GI) tract. A slow dissolution rate may limit drug absorption, particularly when the solubility of the drug form is so low that the drug concentration must be maintained near its maximum solubility limit so that enough drug can be absorbed during the limited time the drug transits the GI tract.

Low drug solubility is common among drugs that fall in Class II or Class IV of the Biopharmaceutical Classification System (BCS). Common characteristics of these compounds include

- a high crystal lattice energy, which generally increases as the melting temperature (Tm) of the compound increases—so-called "high-melting" compounds;
- a low energy of aqueous solvation, which decreases as the Log P value of the compound (i.e., its lipophilicity) increases—so-called "grease-ball" compounds;
- a combination of both factors—so-called "brick-dust" compounds.

To overcome these obstacles, we must find enabling technologies that reduce the drug lattice energy, increase the available drug surface area, or increase the energy of solvation.

Example technologies are shown in Figure 1, which roughly matches potential solubility/dissolution obstacles to formulation technologies. For instance, where a compound's low solubility stems from a high crystal lattice energy, the solution will likely rely on a technology that reduces solid-state interactions, such as solid dispersions. Compounds with limited affinity for aqueous solvents would benefit most from technologies that enrich the GI environment with exogenous solvents such as lipid-based formulations. Some technologies—such as cocrystals and salts—provide the benefits of both solid-state and solubilization approaches. As an example, introducing a counterion would change the solid-state energy (by changing the molecular packing in the crystal) and the solvation energy (by changing the nature of the local solvent [e.g., pH in the case of adding a salt counterion] or by changing the drug form. Alternatively, solid dispersions that are created using amphiphilic polymers such as hydroxypropyl methylcellulose acetate succinate (HPMCAS) or nonionic surfactants may improve solvation, while predissolving a drug within a lipid-based formulation may eliminate solid-state obstacles.

Biological Obstacles

In some cases, extensive formulation work may be undertaken to improve a drug's physicochemical properties only for intrinsic biological processes to prove the limiting factor in the drug's bioavailability. These biological obstacles may include

- efflux of absorbed drug back into the intestinal lumen),
- presystemic drug metabolism in the intestine), and
- extensive hepatic first-pass drug metabolism.

Significantly, enabling technologies exist that may reduce the impact of these biological obstacles, particularly by reducing efflux and metabolism in the intestine.

TECHNOLOGY SELECTION TO ENHANCE BIOAVAILABILITY

Taking into account the barriers described above and the company's extensive experience overcoming bioavailability challenges for many different types of compounds, Lonza has developed an efficient technology selection process that is anchored on four main data sources. As illustrated in Figure 2, they are (1) compound characteristics, (2) product needs, (3) absorption models, and (4) technology maps. As discussed below, consideration of each component is required for selection of the optimal enabling technology.

This ensures that informed decisions are made for each new compound and associated target product profile early in the development process, eliminating waste of time, money, and valuable active ingredient. Ensuring that a particular technology is well matched to a drug compound enables easier feasibility assessment, better performance in vivo of early concept formulations, and ultimate success in reaching the target product profile. In other words, it helps avoid future stumbling blocks, ensuring that the technology selected will be suitable throughout the development, scale-up, and commercialization process.

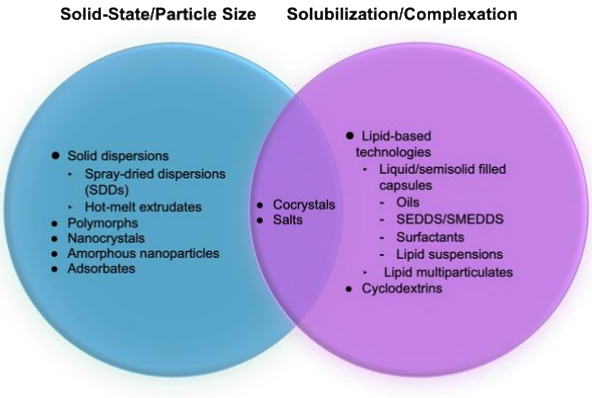

Figure 1. *Main mechanism of enabling technologies to increase drug solubility or dissolution rate*

Defining Compound Properties

A key starting point in identifying the optimal bioavailability enhancement technology is defining the physicochemical and biological properties of the active compound. This knowledge is essential in probing the reasons behind poor bioavailability, as described above, so solutions can be tailored to address root causes. In-depth knowledge of active compound characteristics is also important since it is essential in evaluating the feasibility

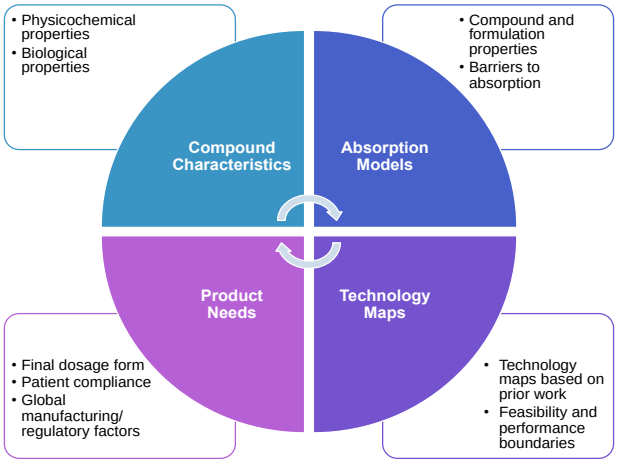

Figure 2. *Inputs to technology selection process*

and scale-up potential of candidate technologies. Dialog with clients and exchange of information is essential, as is access to in silico tools that may be used to predict how certain compound properties (e.g., Log P and solubility) are expected to affect performance.

Defining Product Needs

An important part of Lonza's technology selection process is working with clients to define the product needs of the final dosage form, including target dose, preferred dosage form and size, frequency of administration, specific storage and/or packaging requirements, excipient acceptance, and potential intellectual property rights. This knowledge reduce the risk of pursuing technologies that would later be deemed unsuitable. These discussions are critical to technology selection, as well as preclinical and early clinical development, since they may affect critical elements of ultimate success, such as compliance. Within Lonza, such discussions are greatly supported by our experience developing formulations in the North America, Europe, and Asia, taking into account the significant variations in regulatory requirements and patient preferences around the globe.

Using Absorption Models

Absorption models—physiologically based pharmacokinetic (PBPK) models—are used to evaluate hypotheses about barriers to absorption, understand existing in vivo data for a formulation of interest, and establish a framework for predicting in vivo performance with existing in vitro data. These models may also be useful for predicting specific attributes of enabling formulations (e.g., amorphous solid dispersions, lipid-based formulations) such as drug speciation and how undissolved species—nanocolloids or bile-salt micelles—may contribute to absorption.

In our experience, the best approach to using absorption modelling in formulation development is through hypothesis testing and understanding parameter sensitivity (i.e., critical bioperformance attributes). This involves careful consideration of assumptions (e.g., can a physical interpretation be provided to support assumptions?) and the in vitro data incorporated into the model, reducing reliance on "curve fitting" and performing multiple iterations to understand different in vivo scenarios that may ultimately impact performance.

Using Technology Maps

The final input in the technology selection process is the use of conceptual technology maps, which are based on in-depth analysis of data from our past projects, centering on how key physicochemical drug properties impact oral absorption. This

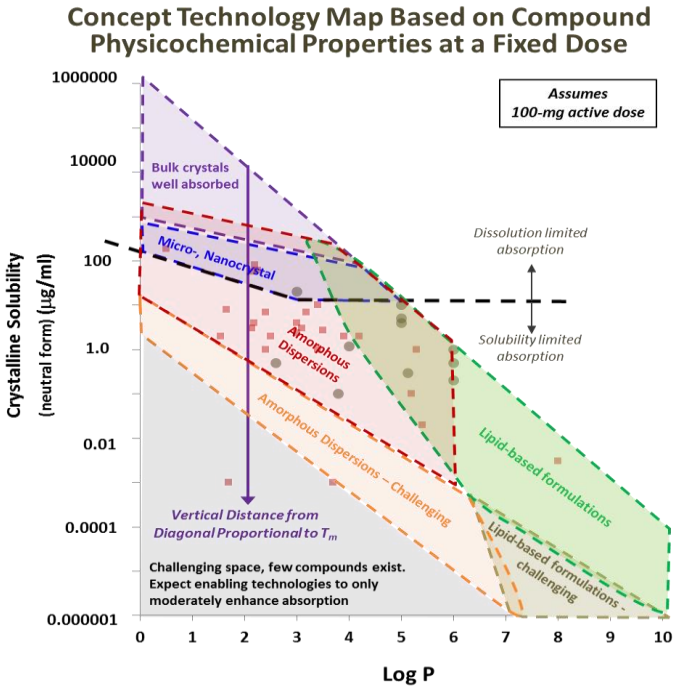

Figure 3. *Technology map showing crystalline solubility as a function of Log P for a variety of compounds previously developed into SDDs (squares) or lipid formulations (circles) at Lonza with an overlay that shows the optimal space(s) for nanocrystal, amorphous (including SDDs and HME formulations) and lipid-based technologies at a fixed 100-mg dose (per dosage unit)*

effort is grounded in Lonza's extensive experience with a wide range of technologies and on extensive speciation work with numerous formulation types. For instance, for spray-dried dispersions, we have evaluated more than 5,000 compounds in vitro, more than 1,500 compounds in preclinical studies, and more than 300 compounds in clinical studies.

Figure 3 shows an example of a technology map, which is a based on extensive data mining from development work with thousands of product development programs. This map plots the solubility of active compounds' crystalline drug form in aqueous media as a function of Log P (lipophilicity). The map shows the relationship between compound properties and "regions" in which different enabling technologies are a good fit for the compound's physicochemical properties. Data points in this graph denote just a few of the compounds that have been successfully developed in recent years.

Decreasing aqueous solubility at a constant Log P value is driven primarily by an increase in the overall solid-state interactions and is directly proportional to the Tm of the active compound. In the upper region of this map, crystalline solubility is high enough that bioavailability is sufficient when simple, nonenabling formulations are used. However, as Log P increases and/or Tm increases, solubility decreases, creating the need for enabling technologies that increase dissolution

rate to maintain good in vivo performance. As solubility decreases further (i.e., below 10 to 100 µg/ml, depending on the Log P of the compound), solubility reaches the point at which absorption is inadequate even if high dissolution rates are achieved. At these low solubilities, technologies are needed that improve drug concentration in the GI lumen above the drug's equilibrium solubility and/or drug transport across the unstirred water layer via submicron colloids. The map shows which technology sources are applicable for the combination of solubility and Log P. In some cases, technology regions overlap, allowing the formulator a choice of technology.

Lonza's absorption models and technology maps are continuously updated and refined through data and experience gained through an ever-expanding project pipeline with new chemical entities (NCEs) and existing compounds. We continue to invest in our fundamental understanding and are currently performing a deeper scientific analysis of all our development projects to establish better relationships between drug properties and development success using SDD, HME, nanocrystal, and lipid-based technologies.

CONCLUSIONS

Lonza and the legacy companies it has acquired have been at the forefront of amorphous dispersion, nanocrystal, and lipid-based formulation development, expanding these technologies' application and range in overcoming the physicochemical and biological barriers to bioavailability.

The fundamental understanding derived from this collective investment across the key enabling technologies has resulted in the science-based technology selection process described here, which has demonstrated benefits in minimizing the complexity, time, and cost of the drug development process.

Lonza's approach to technology selection relies on (1) compound properties, which are often already available (or otherwise measurable in silico); and (2) an in-depth understanding of the technology constraints in relation to product needs.

Our approach offers a sharp contrast to more empirical approaches that focus on "screening" various technologies. These approaches are time-consuming and may require a substantial amount of compound to effectively evaluate several technology paths. Empirical screening's biggest risk, however, is that a compound fails to perform across all technologies (i.e., the compound is considered "undeliverable"). In many cases, this failure may stem from a lack of appropriate formulation design/manufacture, rather than fundamental technology ineffectiveness. Lonza believes that the best enabling technology for a particular drug can be predicted using our science-based process, heading off these difficulties.

Our scientific understanding of the key bioavailability enhancement technologies, based on extensive development work, intellectual property, scale-up, and manufacturing experience has been integrated into a full design, development, and commercial manufacturing offering for pharmaceutical clients who face bioavailability challenges with new or existing compounds. This collective capability and infrastructure further reduces development time, risk, and complexity by giving pharmaceutical clients the option of dealing with a single partner at all stages of the drug development process.

About Lonza

At Lonza, we combine technological innovation with world class manufacturing and process excellence. Together, these enable our customers to deliver their discoveries in the healthcare, preservation, and protection sectors.

We are a preferred global partner to the pharmaceutical, biotech, and specialty ingredients markets. We work to prevent illness and promote a healthier world by enabling our customers to deliver innovative medicines that help treat or even cure a wide range of diseases.

Founded in 1897 in the Swiss Alps, Lonza today operates in 120 sites and offices in more than 35 countries. With approximately 15,500 full-time employees, we are built from high-performing teams and of individual employees who make a meaningful difference to our own business, as well as the communities in which we operate. Find out more at https://pharma.lonza.com/.