# Drug Development® & Delivery

March 2020 Vol 20 No 2 www.drug-dev.com


# Bioavailability & Solubility: Understand Your Molecule!

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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# Special Feature

## Improving Bioavailability & Solubility: Understand Your Molecule

By: Cindy H. Dubin, Contributor

Given that a large number of drugs fail to reach the market due to poor solubility and bioavailability, the industry is seeking various methods to mitigate this challenge while many choose to re-formulate existing product candidates. Either way, the demand for novel bioavailability and solubility enhancement methods has grown significantly. To cater to this increasing demand, several contract manufacturers and technology developers have emerged.

This annual *Drug Development & Delivery* magazine report asked several of those providers about how they are solving bioavailability and solubility challenges for their pharma clients. A commonality is how they are formulating to the specific molecule and not taking a one-size-fits-all approach. This includes assessing the compound's physical and chemical properties, evaluating the drug and its intended target site, and recognizing the drug's uptake. In addition to formulation strategies, technologies such as hot melt extrusion (HME), spray drying, and complexation continue to be among the techniques providers offer, and bioavailability-enhancement approaches such as particle size reduction, solid dispersion, and lipid-based approaches show promise for small molecules, according to Roots Analysis.[1]

"In my opinion, the greatest advancements in solubility enhancement are related to the democratization of solutions," says Márcio Temtem, PhD, Site Manager, R&D Services, Hovione. "Scientists have a broad tool box to tackle a variety of problems, from the basic salt screening, cyclodextrins, and milling, to the more complex amorphous solid dispersions. The particular case of amorphous solid dispersions and the developments that occur in manufacturing processes has been key for the success and approval of many New Chemical Entities."

### Ascendia Pharmaceuticals: Tailored Formulation Rapidly Transitions Compounds from Preclinical to Clinic

A tailored formulation strategy has been found to be the most successful in addressing small-molecule solubility and bioavailability challenges. Different formulation technologies that tailor each compound's unique properties are warranted to ensure a successful

**Evonik's MemFis™ tool identifies the most miscible combinations and selects the right solubility parameters for the polymer and drug target.**

outcome of the animal toxicity and human clinical trials for each compound.

"A specialty one-stop-shop CDMO that offers tailored formulation solutions will ensure a rapid, successful transition of compounds from preclinical to the clinic," says Jim Huang, PhD, Founder and CEO of Ascendia Pharmaceuticals. "A formulation partner that understands rational design of dosage forms based on compound properties, possesses different technologies to address varied compound challenges, and offers flexibility in terms of time and deliverables, will be an ideal partner."

To illustrate his point, he explains how one client worked with another CDMO without success to explore human formulation using a single technology. This particularly pharma client wanted to develop a human formulation for an insoluble small molecule and supply GMP CTM for human clinical trials within 4-5 months. This compound was classified as BCS II (low solubility and high permeability), which has no pKa, logP of ~5.6 and a melting point of ~130°C. Its aqueous solubility is extremely low, <0.2 microgram/mL. As a result, its crystalline form's bioavailability in animal models is <4% and a significant food effect is observed.

"It was desirable to obtain a human formulation that has an enhanced bioavailability and a reduced food effect," says Dr. Huang.

Based on the assessment of the compound properties and a tight timeline, Ascendia's three most promising technologies for insoluble compounds – NanoSol (nanoparticles), Emulsol (nanoemulsion), and AmorSol (amorphous nano) – were simultaneously utilized for formulation screening and *in vitro* assessment. Three prototype formulations (one from each technology) were developed and tested in animal models within three months of project initiation that resulted in a 3-, 5-, and 10-fold enhancement in bioavailability that were respectively achieved with NanoSol, AmorSol, and EmulSol technologies, says Dr. Huang.

## Ashland: Focused on Solid Dispersions & Complexation

Ashland's focus is on two technologies that utilize excipients for improving bioavailability and solubility: solid dispersions, both hot melt extrusion and spray drying; and complexation. Ashland offers three types of excipient chemistries and a variety of grades to improve the bioavailability and solubility of drug product formulations. These chemistries can be found in the inert ingredient list of approved pharmaceutical products. Copovidone, sold by Ashland under the brand name Plasdone S630, is an ingredient in several antiviral formulations for treating HIV and Hepatitis. Ashland claims it is the largest-volume excipient used in HME to improve bioavailability and solubility. "Ashland recently launched an improved grade that may significantly decrease HME and continuous processing manufacturing costs due to its improved processability," says Dean Ross, Global Business Manager, Pharmaceutical Specialties, Ashland.

For solid dispersion technologies, Ashland markets three grades of hydroxypropyl methyl cellulose acetate succinate (HPMC-AS), which is an effective excipient for improving bioavailability and solubility, and currently listed as an inert ingredient in many commercial pharmaceutical products produced by both spray drying and HME, says Mr. Ross. One study conducted at Ashland demonstrated the importance of evaluating all three grades of HPMC-AS (LG, MG, HG) in a proof-of-concept study to determine which grade provides the best possible increase in solubility. Each grade differs by acetate and succinoyl content and these differences impact solubility depending on the nature of the API being evaluated. "It's an important point because many formulators do not initially consider the differences and may evaluate one grade only," says Mr. Ross.

A second proven strategy for improving bioavailability and solubility is to complex the poorly soluble API with a cyclodextrin. These carbohydrate compounds have a bucket-like structure that encapsulates all or a portion of the lypophilic structure, leaving the hydrophilic component exposed and leading to improved solubility. "The great thing about cyclodextrins is their versatility in a variety of drug delivery systems, including oral solid dosage, oral liquid dosage, and parenteral systems (ophthalmic, IV, SC)," says Mr. Ross.

To support formulators, Ashland has six global R&D centers outfitted with spray driers or extruders to assist with proof-of-concept and/or process development. Mr. Ross says: "Recently, Ashland completed the development of a predictive solubilization model that can speed up development time by analyzing API characteristics with excipients to identify the most likely combination that will lead to improved solubility."

## BASF Pharma Solutions: A Four-Tiered Approach to Poorly Water-Soluble Drugs

Dr. Nitin Swarnakar, Scientist III, Global Technical Marketing, BASF Pharma Solutions, says that successful products can be developed by careful evaluation of disease, drug, destiny (target site), and dosage form. Based on this approach, the formulator will know the class of drug and delivery route to determine suitable strategies that increase the bioavailability and solubility of a

Scientists at BASF Pharma Solutions evaluate drug, disease, target site, and dosage form to determine a successful strategy aimed at increasing bioavailability and solubility.

poorly water-soluble drug.

For instance, a parenteral formulation typically requires liquid solubilizers or other nanotechnology-based technologies that can improve solubility and bioavailability to the target site. "Specifically, Paclitaxel may be solubilized successfully in Kolliphor® ELP or encapsulated in a PEGylated liposomal," he says. "For the oral route, Amorphous Solid Dispersion (ASD) and Lipid-based Drug Delivery System (LBBDS) have been shown to be effective technologies for poorly water-soluble drugs, yet require special functional excipients such as Kollidon® VA64, Soluplus®, Kolliphor RH 40, Kolliphor EL, and Kollisolv® MCT 70 to be effective." He adds that the conventional approach of converting immediate-release to modified-release dosage forms can also increase the solubility and bioavailability of molecules.

One BASF solubilization project involved a poorly water-soluble and highly permeable drug. Dr. Swarnakar says the solubility of the drug was increased by selecting a suitable surfactant (based on the hydrophilic and lipophilic balance (HLB) value) and its respective concentration in the formulation. During *in vitro* and *in vivo* correlation, it was concluded that higher concentration of surfactant in the formulation demonstrated good solubilization, but negatively affected the flux of drug across the biological membrane leading to poor bioavailability. Therefore, a minimum required concentration of surfactant was recommended to overcome the drug problem.

## BioDuro: A Strategy for Rapid Formulation Development with Minimal Material Use

Even though organic solvents are toxic and incompatible for clinical use, researchers often do preclinical studies in solvents, such as Dimethyl Sulfoxide, and wait until late in the development process to solve the bioavailability/solubility problem of drug formulation. The ability to address solubility challenges early saves costs, saves time, and rescues potentially life-saving compounds.

To improve a drug's kinetic solubility, amorphous dispersions (amorphous API in a polymer matrix) are commonly used. "Determining the right polymer to keep the API in a shelf-stable, non-crystalline form is traditionally a lengthy evaluation process that requires gram quantities of API," says Ruchit Trivedi, PhD, Associate Director, BioDuro. "BioDuro has developed a streamlined approach, called Solution Engine, to help our clients find the best formulation quickly – as early as lead optimization – with minimal material use. "We utilize small-scale studies that test multiple polymer matrices in parallel and only require milligram quantities of API. In evaluating candidate amorphous dispersions, we collaborate with in-house DMPK scientists to rapidly verify bioavailability in animal studies. We then scale up the best formulations for spray dry dispersions or HMEs. This approach can solve the most difficult solubility challenges, and typically shortens formulation development time for Phase 1 clinical supplies from 6 to 9 months to only 4 months."

One BioDuro client had an oral antibacterial drug candidate with the goal to develop an immediate-release tablet for Phase 1 clinical trials. This particular compound was extremely hydrophobic and formed a strong crystal structure that was hard to dissolve even in organic solvents, which Dr. Trivedi says is rare. "BioDuro used Solution Engine, its proprietary technique for solving API bioavailability/solubility issues, to identify the best solubilization technology and the optimal formulation to scale-up and produce clinical materials," he says.

"We started with micro-evaporation studies to efficiently determine the polymer matrix that best enhances solubility," he explains. "This innovative small-scale screen requires only milligrams of API, and allows parallel evaluation of multiple approaches, including different excipients, proportions, and concentrations. We characterized kinetic solubility of the micro-evaporative dispersions *in vitro* using non-sink dissolution in simulated intestinal fluid as an indicator of opportunity for intestinal drug absorption. Quickly coordinating *in vivo* pharmacokinetic studies gave insights to bioavailability of the candidate API formu-

lations. We found that micro-evaporative dispersions are a good predictor for spray-dried dispersion, and leveraged these results for downstream development of the right formulation. We scaled it up for larger animal toxicology studies and successfully manufactured tablets for Phase 1 clinical trials BioDuro moved forward successfully and expeditiously with this small-molecule API as a viable clinical candidate and it's now in the clinic."

## Catalent: Different Approaches are Critical to the Success of Small Molecules

It is important to realize that the premise of a one-size-fits-all approach to improve oral bioavailability and solubility challenges is flawed because it assumes that all small molecules behave in the same way, believes William Wei Lim Chin, PhD, Manager, Global Scientific Affairs, Catalent. To successfully formulate a small molecule, the question of whether the molecule is dissolution-rate limited or solubility-limited for it to become systematically bioavailable must be addressed. To answer this question, the total dose, the solubility in biorelevant media, and the human intestinal permeability of the molecule should be known.

"The determination of these three critical parameters forms the basis for the Developability Classification System (DCS)," he says. "Catalent takes the approach that particle-size reduction technologies or formation of high-energy crystal forms would be the preferred choice of technology for DCS IIa molecules, whereas solid amorphous dispersions or lipid-based formulations would be recommended for DCS IIb molecules. For DCS III molecules that have permeability challenges, formulation with permeation-enhancing excipients would be recommended."

In cases where bioavailability is caused by pre-systemic metabolism, Dr. Chin advises that it is important to recognize that formulation approaches may not necessarily overcome intrinsic metabolic effects, although it has been documented that formulation methods that leverage high solubility, at high doses, may saturate certain metabolic enzymes and thus improve the bioavailability of the drug.

At the structural modification level, a prodrug approach is also typically used to mitigate high first-pass metabolism. Prodrugs can be used for injectable products to improve the solubility and stability of the solution formulation. Catalent previously worked with a client that was developing a prodrug as an orphan drug for a rare disease. The prodrug was only partially successful in increasing the solubility and bioavailability of the parent compound to the desired level for clinical studies, Dr. Chin explains.

"By understanding the limitation of this prodrug, Catalent's formulation experts successfully screened three formulation technologies and provided four formulation prototypes, in only 12 weeks, through a parallel technology screening platform," he says. "In three of the four prototypes, the bioavailability of the molecule was enhanced substantially. Based on the assessment of physical and chemical properties, processability, and DCS classification, a co-micronized formulation was identified as the best prototype to bring forward in the clinic. The implication of this was significant to the pharma company as it was able to progress to the next clinical milestone."

## Croda Inc.: Understand the Nature of Every Molecule

Small-molecule pharma is a complex balance between optimizing characteristics of the drug and optimizing the components of the final formulation. "Small doesn't necessarily correlate to straightforward and every molecule is slightly different, so the first step to ensuring drug success is to understand the nature of the molecule, advises Arsalan Khan, Technical Marketing Coordinator, Croda Inc. "This isn't just understanding the basic chemistry behind it, but also understanding its mechanism of breakdown, the way it behaves in different temperature and pH conditions, and in what sorts of environments the molecule's uptake is most enhanced."

The next step is determining what is in the formulation. Mr. Khan says this involves selecting the appropriate ingredient, and if it will be used as a solubilizer, a delivery agent, a stabilizer, or anything else. This is key to ensuring that the drug remains solubilized and stable.

Impurity profile also plays a key role, as various impurities can cause the drug to break down or destabilize the formulation. This means the drug and excipients in the formulation must be free of various oxidative impurities, he explains.

Additionally, a focus needs to be put on the actual uptake of the drug. "There are a host of options to maximize drug uptake, but the key here, again, is to understand its core mechanism and look at the best option," says Mr. Khan. "Consider the effect of decreasing particle size of the active, using a delivery-enhancing ingredient, or encapsulating into a multi-component micro- or nanoparticle that can improve drug absorption through the various cell membranes that the drug will encounter upon administration, whether that be the skin, gut lining, or blood-brain barrier."

Supply chain should also be held to a paramount importance throughout the development process. "From the formulator's per-

spective, it's important to work with your suppliers to look at all options available that will make preclinical development either very straightforward or very difficult," says Mr. Khan. "The decision of choosing one or multiple suppliers is another serious consideration. This can be tricky because while it makes sense to consolidate to one partner for the sake of convenience and ease of tracking, it also poses a risk for the same reason. Additionally, one supplier may not necessarily provide every ingredient or may not have expertise on every material that is needed. In that case, expectations need to be maintained."

With that in mind, Mr. Khan says all partners must be in agreement when proceeding on formulation and development, including preclinical development, ingredient selection, processing, analytical characterization and testing, and trial protocols.

## Evonik: Stabilized ASDs Can Result in Higher Bioavailability

In order to make any active bioavailable, keep in mind that attaining some level of aqueous solubility is essential, and that insoluble compounds have virtually no bioavailability. On the other hand, high solubility is not always a guarantee of achieving high bioavailability, as this will depend upon the inherent permeability of the drug. The physical modification of small molecules, such as through particle engineering, salt, and polymorph screening, have proven to be largely ineffective in enhancing the solubility of poorly soluble actives, says Dr. Firouz Asgarzadeh, Director of Technical Marketing, Evonik Health Care.

"We have found that stabilized amorphous solid dispersions (ASDs) are the most effective and commonly used method of solubility enhancement that can result in higher bioavailability, especially when permeability is not the limiting factor," he says. "ASD formulations are typically either prepared from active and polymer solutions in organic solvents using film casting, precipitation, or spray-drying technologies, or from polymer-drug high temperature mixtures cooled down to room temperature, or below, using co-melting, differential scanning calorimetry or hot-melt extrusion."

To identify the most miscible combinations and select the right solubility parameters for the polymer and drug target, Evonik utilizes the Melt Extrusion Modeling and Formulation Information System (MemFisTM) tool. "We've found that the most reliable combinations are then screened using spray drying and/or hot-melt extrusion," says Dr. Asgarzadeh. "Because MemFis includes all pharmaceutical polymers, including EUDRAGIT®, Cellulosic, Povidones, and others, these screening studies can identify the best formulations to optimize solubility enhancement outcomes."

Dr. Asgarzadeh explains how one client previously developed an ASD with only a slight increase in solubility for its poorly soluble active. Limited screening was conducted using two pre-selected polymers with no consideration for polymer drug physical bond interactions and miscibility. "By using MemFis, we were able to screen all pharmaceutical polymers and identify attractive new combinations that were not included in the original development program," he says. "The client measured the solubility of these new ASDs *in vitro*, and identified significantly improved solubility outcomes. This led to a change of direction in upcoming animal studies and the selection of a superior product for further clinical studies."

Additionally, Dr. Asgarzadeh says that ASD and other solubility-enhancement technologies can be incorporated in pharmaceutical 3D printing substrate powders and filaments during the printing process.

## Gattefossé Corp., USA: The Advantages of LBDDS vs. Polymeric ASD

"Lipid-based drug delivery systems (LBDDS) are among the most effective approaches to development and delivery of poorly soluble, poorly absorbed actives," says Jasmine Musakhanian, Scientific and Marketing Director, Gattefossé Corp., USA. "This discipline takes into account drug solubilization/dissolution in the dose, dissolution behavior in relevant media, and the biopharmaceutical role of the excipients (formulation), which impact the *in vivo* performance of the dosage form."

The biopharmaceutics of LBDDS involves digestion, permeation at the enterocytes, and the path of absorption (hepatic vs. lymphatic). When assembled appropriately, LBDDS offer safety, biocompatibility, low intra/inter subject variability, and speedy path to market, she adds. "A lipid formulation developed in the early preclinical phase can be carried to late-stage human clinical stages with little or no modification, shaving 1.5 to 3 years off the development timelines." LBDDS offer several advantages over polymer-based amorphous solid dispersion (ASD) technologies, she says. Table 1 shows % PK variability and food effect associated with drugs formulated with LBDDS are significantly lower than those with polymeric ASD.

To address the unique challenges of a drug, Ms. Musakhanian says that Gattefossé applies a systematic approach to the selection of the excipient(s) followed by the

**TABLE 1**

| Drug Product | Technology | PK (%) Variability | Food Effect |
|---|---|---|---|
| Paricalcitol | LBDD | <30 | No significant effect |
| Enzalutamide | LBDD | <30 | No significant effect |
| Isotretinoin | LBDD | <30 | 1.5-fold increase |
| Dutasteride | LBDD | <30 | No significant effect |
| Norethindrone acetate /ethinyl estradiol | LBDD | ? | No significant effect |
| Nintedanib* | LBDD-MCT | 30-70 | 20 % increase* |
| Ivacaftor | Spray Drying | 30-50 | 2.5 to 4-fold increase with food |
| Etravirine | Spray Drying | 40-60 | 1.5-fold increase with food |
| Itraconazole | Melt Extrusion | 44-66 | 2-fold increase with food |
| Vemarafenib | Co-precipitation | >66 | 5-fold increase AUC with food |
| Ledipasvir/sofosbuvir | Spray Drying | ? | 2-fold increase AUC |
| Lopinavir/ritonavir | Melt Extrusion | ? | Can be taken with/without food |

**Comparing PK variability and food effect: lipid-based drug delivery systems vs. amorphous solid dispersions (Gattefossé).**

assembly of the drug delivery system. "This includes sophisticated solubility screening in liquid and solid excipients, evaluating compatibility/stability of two or more components in the system within days of preparation, and assessing the formulation performance (lipolysis testing) in biorelevant media to predict the impact of digestion on drug dissolution *in vivo*," she says.

For high-LogP/highly lipophilic actives, for example, she recommends screening of Gattefossé glycerides like Maisine®, Peceol®, Labrafac®, or Labrafil®. For API that are poorly soluble in both hydrophilic and lipophilic media, she proposes self-emulsifying lipid formulations (SELF), commonly known as SEDDS, SMEDDS, or SNEDDS. Gattefossé excipients for SELF include Plurol®, Labrasol®, Labrafil, and Gelucire® series. "Combined, the SELF act as a carrier for the solubilized/suspended drug active in the dosage, but then form fine dispersions in the aqueous media of the gut, maintaining drug solubility *in vivo* to accommodate absorption."

## HERMES PHARMA: User-Friendly Dosage Forms Are Well-Suited to Small Molecules

User-friendly dosage forms – such as effervescent tablets, chewable tablets, orally disintegrating granules (ODGs) and instant (hot) drinks – are ideally suited to improving the bioavailability and solubility of small molecules. All these dosage forms are already dissolved or dispersed when administered, and so can result in a faster onset of action, says Dr. Martin Koeberle, Head of Analytical Development & Stability Testing, HERMES PHARMA.

As user-friendly dosage forms are not swallowed whole, relatively large amounts of API(s) and excipients can be incorporated in a single dose (sometimes as much as 5g). "Compared with conventional tablets and capsules, this affords more freedom to fine-tune the quantities of excipients for optimization of pH and solubility," he says.

User-friendly dosage forms may be worth considering when the target patient population takes numerous tablets per day, which can lead to altered disintegration and dissolution characteristics. Likewise, if patients take medication for acid reflux, and therefore have an increased stomach pH, the solubility of tablets can be affected. "User-friendly dosage forms eliminate problems associated with disintegration and dissolution as the API is already dispersed when it is swallowed," he says.

3D-printing brings exciting possibilities for pharmaceutical manufacturing, particularly in user-friendly dosage forms. Dr. Koeberle explains that user-friendly dosage forms, such as orally disintegrating granules, sometimes require a very narrow particle size distribution. With 3D-printing, particle size distribution can be adjusted and controlled very precisely. For difficult APIs with narrow therapeutic or small absorption window, 3D-printing may be the solution because almost any geometric shape, which determines dissolution, is possible. In addition, it may be easier to achieve certain dissolution characteristics, such as pulsatile release. However, like in other industries, 3D-printing is best suited to short-run and bespoke manufacturing – such as for personalized medicine and clinical trials – rather than larger-scale manufacture.

Relying on computer-aided formulation development is challenging because evaluating the functionality of any formulation is a complex process, he says. "Aside from physico-chemical properties, the morphological characteristics of API and excipients need to be considered, including how these may change during manufacture."

Drug developers also need to explore the impact of scaling effects and how impurities in the APIs and constituents may affect the formulation's functionality. "Nevertheless, research into computer-aided formulations is a worthwhile en-

deavor since it will help us better understand certain aspects of a formulation's functionality and interactions," says Dr. Koeberle. "It would not replace, but could reduce, the amount of trial and error required by starting from a stronger, more informed position."

## Idifarma: Spray Drying Turned Injectable Drug into Oral Dosage Form

Idifarma is an independent, privately-owned pharmaceutical CDMO specializing in highly potent drugs. Throughout its experience in improving bioavailability and solubility in small molecules, Idifarma has used different strategies, such as surfactants, reducing particle size in low-solubility active ingredients — excipients that increase the solubility of the APIs — amorphizing active ingredients through the use of spray drying technology, and working with solid dispersions by choosing suitable polymers to increase solubility.

"One of the great successes achieved by Idifarma has been with solid dispersions and using spray drying technology," says Iñaki Bueno, Formulation and Manufacturing Manager at Idifarma. "We were able to develop a product that can be administered in oral solid dosage form, which due to its low bioavailability, was only formulated in injectables. The change in the form of administration is an advantage for the patient and results in better compliance with the dosage schedule."

Prodrugs are also a strategy aimed at improving bioavailability of oncological BCS class III, IV products that usually have been formulated as injectable, and with this strategy have been formulated by oral dosages and once they achieve the system circulation are metabolized by the organism in an active compound. "This strategy is mainly used for innovative products that achieve higher solubility in aqueous media and higher permeability throughout biological membranes to improve the solubility and bioavailability of active ingredients, which Idifarma has used on several occasions," he says.

## Lonza: Two Technologies for a Range of Molecules

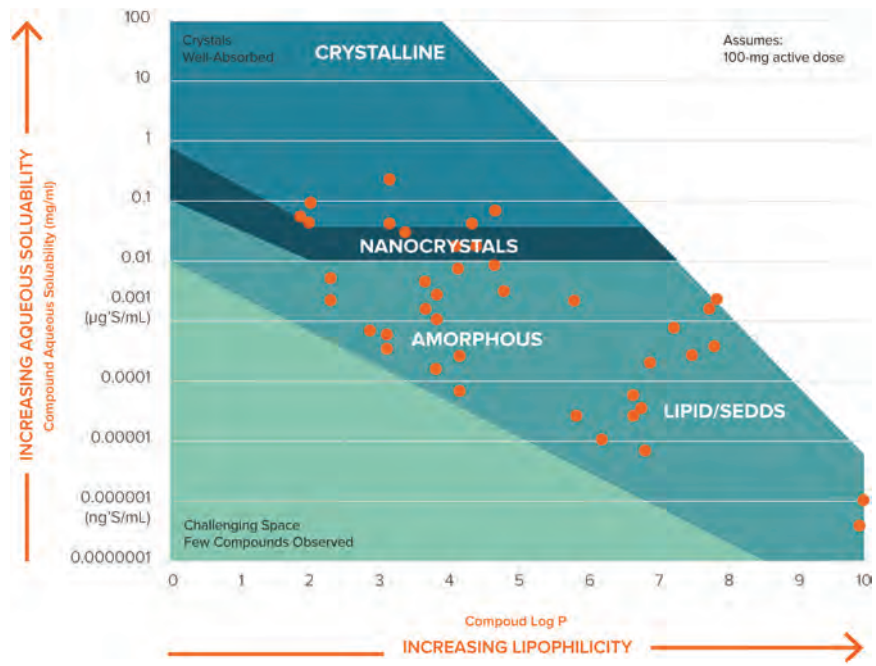
Two bioavailability- and solubility-enhancing technologies found successful and used in many marketed drug products are amorphous solid dispersions (ASD) and lipid-based formulations (LBF). But bioavailability enhancement is not one-size-fits-all. "ASD and LBF technologies are appropriate in different scenarios and with different molecules, depending on a range of physicochemical properties," says David Lyon, PhD, Senior Fellow, Research, Lonza.

An ASD formulation renders compounds amorphous and high energy, resulting in supersaturation of the molecules once they are in the GI tract. Typical approaches for developing an ASD incorporate hot-melt extrusion or spray-drying technology. "ASDs are solid forms, which allows for molecules to be readily developed into conventional dosage forms such as tablets, which are typically preferred in most drug development programs," he says.

LBFs center on getting a bioavailability-challenged compound to dissolve in a lipid. This technology is most appropriate for lipophilic compounds with a lower melting point. Dr. Lyon says the end result tends to be amenable to soft-gel and liquid-filled hard capsule dosage forms.

Lonza's SimpliFiH™ Solutions is an integrated first-in-human service specifically designed to accelerate bioavailability-challenged molecules to Phase I and on to commercialization. This service offering leverages Lonza's experience across multiple enabling technologies and processing techniques for ASD and LBF, as well as par-

**TABLE 2**




**Lonza uses a concept technology guidance map based on compound physicochemical properties at a fixed dose to help select the most appropriate bioavailability-enhancing technology for a given compound.**

ticle size reduction.

Dr. Lyon shares two examples based on ASD in which Lonza teams worked with customers to enhance bioavailability and move drug products through the development process toward patients. First, a customer was developing a protease inhibitor for HIV treatment. In its crystalline form, the molecule's bioavailability was extremely low, at around 1%. "After we worked to reformulate the molecule in an ASD form, we were able to achieve a high-loading tablet – 400mg/tablet – with close to 95-100% bioavailability," he explains.

Second, Lonza helped formulate a compound for a cardiovascular indication. The original form of the API was an oil, with a logP of 9.5-10 and solubility of about 1 nanogram/mL. He says: "After formulating the compound as an ASD with some processing additives, we achieved a stable formulation with a dose-linear exposure up to 2 grams active in humans (60-70% bioavailability) that we could produce in tablet form."

## Lubrizol Life Science Health: Nanomilling Enhances Dissolution Rates

Manipulating particle size/morphology is a proving successful in improving solubility. Reducing particle size, most commonly through nanomilling, increases specific surface area, leading to enhanced dissolution rate. "Lubrizol Life Science (LLS) Health has found nanomilling to be an effective, scalable, and reproducible process," says Robert W. Lee, PhD, President, CDMO Division, LLS Health. "We are the only CDMO capable of performing nanomilling under aseptic conditions and can take our clients into commercial production. Traditional milling equipment is not set up for aseptic processing, but LLS Health's SteriMill™ was specifically designed for this purpose."

**LLS Health's SteriMill™ was designed for aseptic processing.**

Lubrizol's proprietary SteriMill technology employs high energy media milling (nanomilling) to reduce particle size and increase the dissolution rate of poorly water-soluble APIs. The technology uses Lubrizol-developed equipment that enables aseptic production of nanosuspensions from R&D through commercial scale.

One LLS Health client was seeking to match the pharmacokinetic profile of a rectally administered gel, containing a DEA-schedule IV API, with a nasal spray formulation. "We were able to formulate the poorly water-soluble API (aqueous solubility of 50µg /mL), along with a proprietary permeation enhancer in a solution formulation with equivalent bioavailability when dosed intranasally," explains Dr. Lee.

LLS Health has also used computer modeling to predict the flux of an API out of a non-bioerodible drug eluting device. "With knowledge of the API's solubility in the polymer and its molecular diffusivity, the elution rate of the API can be accurately calculated," he explains. "LLS Health also has models to predict stability of electrostatically-stabilized colloidal suspensions as a function of ionic strength. As long as the technologies expedite the drug development process and provide a better outcome, they are useful and warrant consideration."

## Metrics Contract Services: Two Projects Illustrate Experience with Amorphous Material

To improve solubility and bioavailability of API, Metrics Contract Services offers clients the ability to manufacture spray-dried material or to micronize the API through jet milling. The resulting material will be formulated as a capsule or a tablet. "These technologies fit well within our scientists' skill sets as they have a keen understanding of amorphous material and nanoparticles," says Brad Gold, PhD, Vice President, Pharmaceutical Development, Metrics Contract Services.

This experience was put to the test when one of Metrics' clients had a clinical candidate that demonstrated variable pharmacokinetic data using a Phase I formulation of API in a commercially available one-size-fits-all aqueous vehicle with sweetener, suspending agent, and preser-

vative. Metrics scientists reformulated the Phase I formulation to simply incorporate the API in a dispersant consisting of a low molecular weight amphiphilic solvent, says Dr. Gold. "The dispersed API then was added to the client's original off-the-shelf vehicle to provide a well-dispersed final product. The new formulation not only provided increased bioavailability, it also removed variability previously observed in *in vivo* performance."

In another example, a poorly water-soluble and highly permeable molecule (BCS class IV) was provided by a client for reformulation. Initial Phase I studies on a simple capsule (API and lactose anhydrous) formulation showed poor oral bioavailability. Several solubility enhancement approaches — such as particle size reduction, inclusion complex (using HP B-CD), surfactant (sodium lauryl sulfate with dry granulation process, polysorbate 80 with wet granulation process), hot melt granulation, hot melt extrusion — were evaluated to improve solubility. Hot melt extrusion with copovidone as carrier and sorbitan monolaurate as surfactant/plasticizer showed improved dissolution in water, 0.1 N HCl, and pH 4.5 buffer, explains Dr. Gold. Batches with different levels of polymer and surfactant were manufactured to identify the optimum ratio of drug, polymer, and surfactant. Clinical trial material batches were manufactured for Phase I study using the optimized formulation.

Formulation methods such as micronization, amorphous solid dispersion, nanocrystals, and nanoparticle — all of which Metrics offers — are commonly used for solubility enhancement. Dr. Gold says that although these approaches have shown positive results for many drugs, there are some APIs that need further formulation to increase solubility. ◆

## Reference


1. Bioavailability Enhancement Technologies and Services Market, 2020-2030, Roots Analysis, https://www.rootsanalysis.com/reports/view_document/bioavailability-enhancement-technologies-and-services/198.html.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