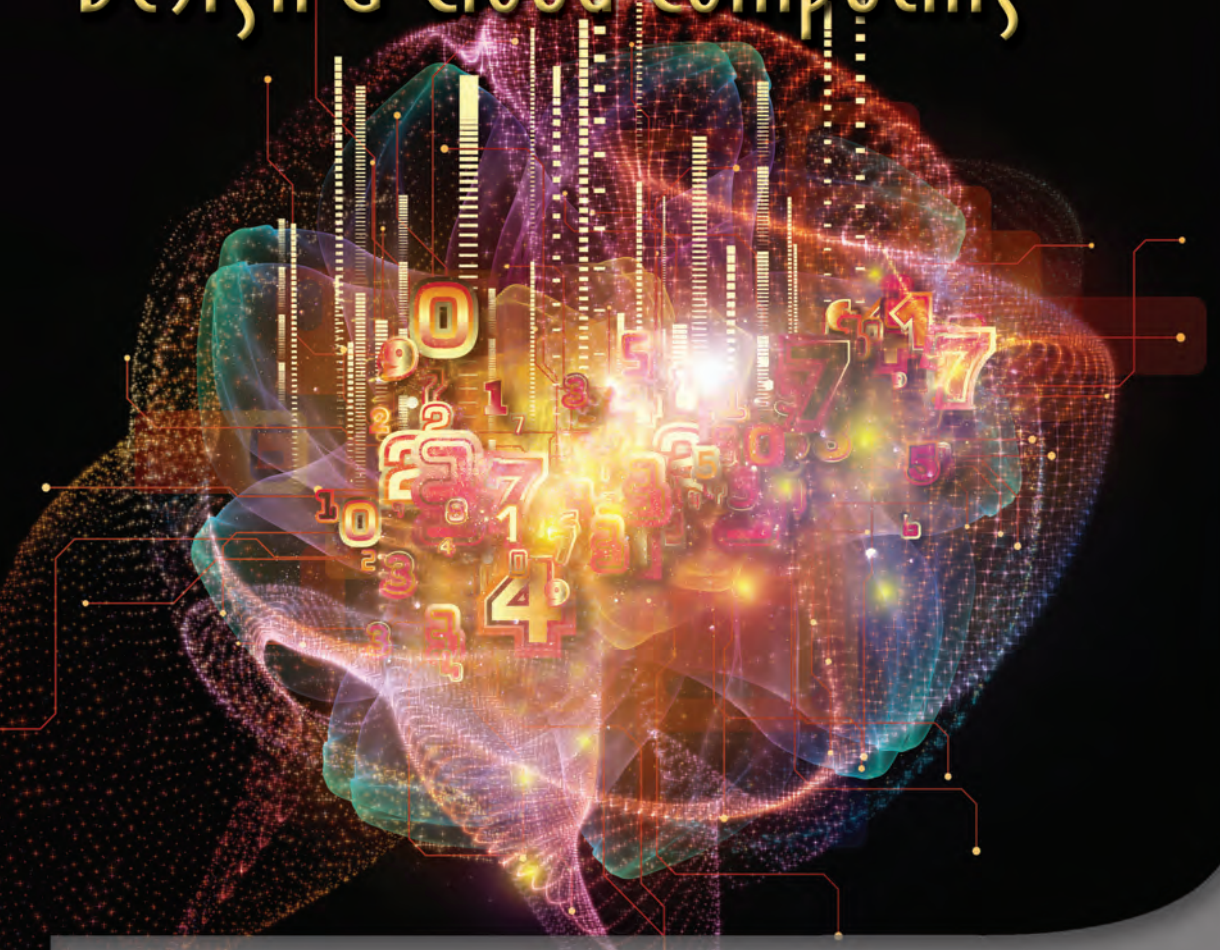
Drug Development & Delivery

March 2016 Vol 16 No 2

www.drug-dev.com

Quantum Molecular Design & Cloud Computing



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Special Feature

Advancements in Drug Delivery Technologies Tackle Solubility & Bioavailability Challenges

By: Cindy H. Dubin, Contributor

Capsugel's commercial manufacturing facility features three commercial-scale spray dryers. Pictured here is the tank room showing a 2500L solution tank using 500L IBCs and pillar lift.

The emerging trends in the combinatorial chemistry and drug design have led to the development of drug candidates with poor water solubility. Issues associated with poor solubility can lead to low bioavailability, resulting in suboptimal drug delivery. About 40% of drugs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble. With the advent of various insoluble drug delivery technologies, the challenge to formulate poorly water-soluble drugs can be achieved. In fact, numerous drugs associated with poor solubility and low bioavailabilities have been formulated into successful drug products, and several marketed drugs have been reformulated to improve efficacy, safety, and patient compliance. In order to gain marketing exclusivity and patent protection for such products, revitalization of poorly soluble drugs using insoluble drug delivery technologies have been successfully adopted by many pharmaceutical companies.[1]

In this annual special feature, *Drug Development & Delivery* spoke with several innovator companies to learn more about the latest advances in drug delivery to address the ever-present challenging issues of solubility and bioavailability today.

BASF—Excipients & Solubilizers Achieve Desired Solubility/Bioavailability

As the number of poorly soluble compounds continues to rise in drug discoveries, so is the interest in the pharma industry to adopt new strategies to overcome these challenges. Such strategies go beyond the traditional or conventional formulation approaches such as micro-milling or micronization, pH adjustment/salt formation, pro-drug, or complexation, and include the non-conventional innovative solid dispersion and self-emulsifying liquid dispersion technologies. "Such technologies are aimed at transforming the crystalline and high melting insoluble hydrophobic compounds to solid or liquid dispersions in pharmaceutically accepted polymers and solubilizers to achieve the desired solubility and bioavailability," says Shaukat Ali, PhD, Technical Support Manager, BASF Corporation, Pharma Ingredients & Services.

BASF offers a range of polymeric excipients and solubilizers with the desired properties compatible to formulation (and non-conventional formulation) technologies. "BASF's polymeric excipients used in solid oral dosages and surfactants/solubilizers used in liquid oral dosages could overcome the solubility challenges by maintaining the drug in supersaturation without nucleation or crystallization for an extended period," says Dr. Ali. "Highly functional excipients are versatile and can be used, and preferably switched, to meet the technological needs to yield the desired performances of a particular dosage."

Enablers such as Kollidon® VA64, Soluplus®, Kollidon®, and Kollicoat®, among others, are used in amorphous dispersion technologies, including hot-melt extrusion, spray drying, Kinetisol®, co-precipitation and/or electospraying/electrospinning. Other excipients, such as lipid-based solubilizers and surfactants, such as Kolliphor® RH40, EL, HS15, TPGS, P407, P188, PS80, are also used in the development of self-emulsifying/micro-emulsifying drug delivery systems (SEDDS/SMEDDS). "Compatibility of these excipients contributes to greater stability of APIs, and hence the development of a robust formulation," says Dr. Ali.

BASF offers a high throughput screening (SoluHTS) tool to identify excipients in the early stages of formulation development. Other approaches, such as film casting, also help expedite compound screening in a range of polymers/solubilizers, which helps identify and establish the maximum solubility or miscibility of molecules in polymers and solubilizers. "Such understanding is important for selecting an appropriate formulation technology and the excipients for an individual drug candidate," says Dr. Ali. "The SoluHTS technique provides the opportunity for formulators to rapidly

screen multiple molecules and helps establish and identify the excipients suited for the appropriate technologies involving either amorphous solid dispersions or lipid-based self-emulsifying dispersions."

Capsugel—Breadth & Depth of Technologies for Product Design to Commerical Manufacture

"As an industry, we tend to oversimplify our situation by referencing statistics about a majority of compounds in development having 'poor solubility.' The reality is, more often than not, these molecules also have additional challenges such as permeability, stability, metabolism, regional absorption, or food/pH sensitivity," comments Dan Dobry, Vice President, Bend Research, a division of Capsugel Dosage Form Solutions. "The key questions are rarely as simple as 'What's it soluble in?' or 'Can I make it amorphous?' or 'Is it physically stable?' These days, that is a low bar to set."

Capsugel Dosage Form Solutions is investing in core technologies and infrastructure that address specific industry trends, such as the growing number of highly potent compounds that are in the pipeline, partially driven by continued investments in oncology; a focus on niche areas, such as orphan drugs and pediatric applications; the 505(b)(2) regulatory pathway as an increasingly utilized route for changes in formulation, form, route of administration, and combination products, among other factors; and virtual and specialty companies, which have limited internal development and manufacturing capability, making up a larger percentage of the pharmaceutical product pipeline.

In response to these trends, Mr. Dobry points out that Capsugel Dosage Form Solutions has invested in an array of bioavailability enhancing and modified-release technologies to achieve breadth and depth, from product design to commercial manufacture of finished dosage forms. For example, Capsugel has ensured integrated product development capability from design to commercial manufacture for spray-dried dispersions (SDD), recently completing construction of a new pharmaceutical SDD commercial manufacturing facility in Bend, OR. The company has expanded its capacity and capabilities in lipid-based formulation development and manufacturing. Investments in the company's Edinburgh, Scotland facility (Encap Drug Delivery) will help increase liquid- and semi-solid-fill hard capsule manufacturing capacity, as well as add an SDD formulation and development capability. All of these investments include high containment capabilities as a critical component, says Mr. Dobry.

"Capsugel Dosage Form Solutions has also acquired Xcelience and Powdersize to further enhance our clinical trial and commercial manufacturing capability across a range of solid oral dosage forms, and the addition of clinical trial services inclusive of primary and secondary packaging," he says. "Furthermore, adding micronization and nano-milling to our toolkit allows us to support more clients at the earliest stages of product development."

Capsugel Dosage Form Solutions' technologies, including amorphous dispersions, lipid/liquid solubilized dosage forms, and micronization/particle size reduction are complemented by modified release options, and multiparticulate approaches based on fluid bed, extrusion/spheronization, mini-tablet and melt-spray-congeal processing. "We believe that our breadth in technology is critical to meeting client target product profiles and commercial objectives," says Mr. Dobry.

Gattefossé—Lipid Excipients Enhance Delivery of Challenging Molecules

Insufficient or unpredictable oral absorption is associated with poor solubility, slow dissolution and inadequate intestinal permeability. Often presented together in a single drug entity, these multiple challenges associated with an increasing number of drug entities can only be addressed by unique excipients and enabling technologies. Among the approaches that enable oral absorption of difficult molecules, lipid-based formulation strategies stand out

for their unique abilities such as concurrently addressing the physical, chemical, and biopharmaceutical challenges of a given drug. Capitalizing on lipid formulation technologies is further facilitated by significant advances in analytical, characterization, and predictive tools for successful application of lipid excipients in enhancing oral delivery of challenging molecules.

Gattefossé specializes in lipid excipients and related drug delivery technologies that aim to improve oral bioavailability. "Lipid excipients are unique because they play significant roles in the drug delivery system," says Jasmine Musakhanian, Scientific and Marketing Director at Gattefossé USA. "Depending on their physico-chemical properties, lipid excipients may influence *in vivo* processes such as biliary secretion, be subject of digestive enzymes, influence absorption barriers by for example opening of epithelial tight junctions, contribute to drug supersaturation, and even influence the route of absorption.

To simplify formulation decisions that can help minimize attrition rates and shorten the drug development path, Gattefossé created guidance documents for preclinical as well as late development stages. These documents use evaluation methods to arrive at key decisions based on API solubility in individual excipients, solubility of API in mixtures, miscibility of excipients at the desired concentrations, needed concentration of the excipient(s) to achieve the targeted dose, ability of the eventual formulation to disperse in aqueous media and more importantly to maintain API solubilization *in vivo*, and the biopharmaceutical role of the excipient(s) and their potential impact on drug absorption.

LATITUDE's PG Depot™ is a proprietary parenteral drug delivery platform for the sustained release of small molecules, peptides, and proteins over 1-7 days.

LATITUDE Pharmaceuticals, Inc.—Proprietary Platforms Establish New Intellectual Property

Experts consider approximately 90% of new chemical entities to have an aqueous solubility of less than 1 microgram per mL. LATITUDE utilizes extensive experience and proprietary technologies to solve issues of insolubility, instability, poor absorption, vein irritation, large/bulky doses, lack of IP protection, and other formulation challenges over a range of dosage forms. "LATITUDE develops its own proprietary drug formulation technologies and makes these available to its clients to improve efficacy, safety, and overall therapeutic value, and establish new intellectual property for their drug compounds," says Andrew Chen, PhD, RPh, President, LATITUDE. "In addition, LATITUDE applies its own technologies to develop improved formulations of existing drugs for out-licensing as accelerated approval 505(b)(2) NDA candidates."

Two such LATITUDE formulation platforms are Nano-E™ and PG Depot™. The Nanoemulsion Drug Delivery System (Nano-E) is a liquid formulation drug delivery platform for highly insoluble small molecule, peptide, and protein drugs. Nano-E technology is the 505(b)(2)-enabling formulation behind two NDA-stage compounds that LATITUDE has developed for its clients. One specialty pharma client needed a topical formulation to substitute for a currently marketed solvent-based topical product known to cause dry

Employees at Metrics Contract Services inspect sample taken from a processing line.

skin and eczema. LATITUDE developed an equivalent and stable solvent-free aqueous formulation using the proprietary Nano-E technology platform. The aqueous formulation was evaluated for efficacy with *in-vivo* animal models and subsequently in humans.

The Phospholipid Gel (PG) Depot technology is a versatile parenteral drug delivery platform for applications requiring the sustained release of small molecules, peptides, and proteins over 1-7 days. A pharma company requested LATITUDE develop an improved formulation for its peptide drug that was currently injected up to twice daily to control blood glucose in adults with Type 2 diabetes. To reduce the frequency of required injections, LATITUDE incorporated the peptide into its PG Depot to create a new sustained-release formulation that reduced the injection frequency to only once per week. "Reducing the injection frequency created a paradigm shift in the dosing frequency and a potential key competitive advantage over drugs in this category," explains Dr. Chen. PK studies in a diabetic rat model confirmed the no-burst, peakless, ear zero-order, and sustained-release kinetics for this peptide from the PG Depot.

Metrics Contract Services—Spray Drying & Micronization Accelerate Development

Nanoparticulate formulations can increase bioavailability in multiple ways. Due to the high surface area-to-volume ratio associated with decreased particle size, nanocrystals of poorly dissolving APIs can provide faster drug absorption and higher bioavailability by increasing the API's dissolution rate. Amorphous nanoparticle dispersions also can increase the absorption rate of drug due to the same enhancement in surface area and dissolution described above while simultaneously stabilizing the amorphous state of the API and its higher solubility. Still other forms of nanoparticles can achieve high drug loading of poorly soluble compounds (e.g. polymeric micelles and liposomes) by providing a suspending vehicle capable of transporting their drug payload across the permeable intestinal wall. On the other hand, localization to the permeable tissue may forego the need for the API to reach a higher bulk solubility in the intestinal fluid. This can be accomplished by the incorporation of adhesive excipients into the nanoparticle's composition.

To help improve solubility and bioavailability, Metrics Contract Services offers clients the ability to manufacture spray-dried material or to micronize the API received through jet milling. "Both of these technologies work well within our business model because the resulting material still will be formulated as a capsule or a tablet," says Michael DeHart, PhD, Senior Formulation Scientist at Metrics Contract Services.

In addition to technologies, Dr. DeHart says communication is the best way to accelerate the development of these challenging compounds. "It helps to know if the client has already performed some preliminary solubility studies, any kind of simple animal PK studies, or even what the critical quality attributes are (e.g., modified release, specific delivery in the small intestine). This allows us to move the project forward without having to redo, or in some cases relearn, information that may already be known."

Kyle Fugit, PhD, Formulation Developmental Scientist at Metrics, shares a case study that best

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exemplifies how technology and communication worked together to address a client's challenge. "The client brought us a pro-drug that was susceptible to acid degradation and general hydrolysis. This meant that the drug had to be protected from stomach acid. In addition, the exposure time to the intestinal fluid of the small intestine had to be minimal. We took a combination approach to this type of drug delivery. First, we knew that an enteric coat was essential to provide acid protection. Second, we incorporated mucoadhesive polymers into the core tablet to help the tablet adhere to the walls of the small intestine. This allowed the pro-drug to permeate across the small intestine where it was then hydrolyzed to the active drug. Despite the daunting challenge of preventing hydrolysis throughout transit in the stomach and small intestine, animal studies confirmed that we were able to provide bioavailability of the molecule of interest."

Particle Sciences, Inc.—An API's Characteristics Determine the Best Approach to Improving Solubility

Solubility is one of the key physicochemical parameters a formulator needs to understand and manipulate in order to develop viable formulations. APIs are often sparingly water-soluble with a majority of New Chemical Entities belonging to the BCS Class II. "Particle Sciences, Inc. (PSI) sees its share of BCS II and IV molecules. In fact, 90% of its client's small molecules fall into these two classifications," says Robert W. Lee, PhD, Vice President, Pharmaceutical Development Services, PSI. PSI offers a number of solubilization approaches ranging from *in silico* design to nanoparticulate suspensions to solid solutions and lipid-based systems such as LyoCells® (PSI's proprietary reverse cubic and hexagonal phase nanoparticulate delivery system). For long-term delivery, PSIs drug-eluting device may also be a solution.

"It's really a question of to which technology do the API's characteristics drive one towards," states Mark Mitchnick, MD, CEO of PSI. For instance, a heat-stable, highly potent compound with a positive log P naturally drives towards hot-melt extrusion. A relatively labile molecule with good lipid solubility would warrant looking at LyoCells, says Dr. Mitchnick. Note that a classic BCS II molecule should always be evaluated for its amenability to nanoparticulate suspensions, either crystalline or stabilized amorphous.

Both gentlemen agree that a well-informed formulation effort starts with preformulation data, including extensive solubility and excipient compatibility data. PSI uses DOSE™, a proprietary solubility evaluation approach based on Hansen Solubility Parameters. "This data helps guide our selection of excipients and matrix components in the case of emulsions, solid lipid nanoparticles, polymeric micro/nanoparticles, and solid solution approaches," explains Dr. Lee. "Based on the physicochemical characteristics of the API, we assess which drug delivery approaches will

provide the biological performance and match the desired target product profile."

In all of these approaches, the excipients play a key role–whether to assist in stabilization, complexation, targeting or modifying biodistribution–and provide a pharmaceutically more acceptable or elegant dosage form.

PSI has assembled a range of technologies aimed at getting past the common bioavailability barriers of highly potent or DEA-controlled substances, to translate them from the benchtop into the clinic. And, with the acquisition of PSI by Lubrizol, clients have access to an end-to-end solution starting from polymers, through formulation development, and into commercial manufacturing on a global scale, says Dr. Lee.

"A methodical approach to increasing bioavailability through the manipulation of solubility and related addressable parameters is the path to success, especially for BCS IV molecules," says Dr. Mitchnick. "Keeping in mind that bioavailability is a multifactorial property, combining approaches in a disciplined development program is the way to go for these types of molecules. There are only a handful of unique drug delivery approaches–particle size reduction, amorphous forms, permeation enhancers, etc., but each has a different flavor and one size does not fit all. Having access to a full array of approaches ensures that the best products are developed." ◆

Reference

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