Issue: March 2015, **Posted Date:** 3/3/2015

SPECIAL FEATURE - Bioavailability & Solubility: A Demand for Enhanced Technologies & Materials is Spurring Innovation

Poor bioavailability is a major reason for compounds to fail in preclinical development. Due to the complex nature of a multitude of existing as well as newly discovered active ingredients, solubility and bioavailability problems are inherent in the pharmaceutical industry causing major delays in drug development. Fortuitously, several novel technologies can now be deployed to address solubility and bioavailability issues. These include solid dispersion, hot melt extrusion, nanotechnology, lipids-based approaches, micronization, and advances in solubilization platforms.

A new report identifies 30 poorly soluble drugs with low bioavailability recently launched in the US that represent a huge business opportunity for specialty pharmaceutical, drug delivery, as well as generic companies using these technologies.1 In fact, the authors of the report believe that poorly soluble and poorly permeable drugs are valued at $145 billion. Thus, demand for novel technologies and materials to improve solubility and permeability of drugs is only going to rapidly increase over time.

In addition to technological advancements, excipients continue to play a key role in bioavailability and solubility. The industry is building relationships with CROs/CMOs and excipients manufacturers to expedite excipient selection and identify the desired technologies to shorten the overall development timeline, explains Shaukat Ali, Technical Support Manager at BASF. Furthermore, rising expectations from regulatory agencies to meet the desired safety profile of dosage formulations forces industry to take the necessary steps and take the appropriate measures to mitigate toxicity and alleviate the side effects of drug candidates. As a consequence, the excipient manufacturers are in the midst of assessing their portfolios, and designing, developing, and launching new and innovative ingredients to meet the solubility and bioavailability challenges.

This report will highlight some of the ways that CROs and CMOs are overcoming issues of poor solubility and bioavailability—from matching APIs to formulations to choosing the best excipients.

AgerePharmaceuticals, Inc.— Analyzing Best-FitTechnology

There are numerous technologies and approaches available to overcome poor solubility, but this

wasn't always the case. The number of solubilization service providers has grown significantly from six in the 1970s to approximately 75 today.2 The emerging preponderance of BCS Type II/IV molecules combined with the advances in solubilization platforms – and the specialized expertise required to fully exploit them – makes it economically viable, and even essential to engage external experts in solubility at the earliest stages of development. Agere specializes in amorphous solid dispersions, which is growing in popularity with now 35% of companies in this solubilization service segment offering this technology.

Agere offers clients full-service from formulation through cGMP. Its solubilization formulation platform, Quadrant 2™, is used to analyze the best-fit technology for each API and client business objectives, and then to explore a range of excipient candidates and enhancing additives as required for an optimal formulation, explains Casey Jones, Vice President Corporate Development, Agere. The platform performs rigorous modeling of the drug and polymer molecular properties and analyses to obtain a fundamental understanding of drug-polymer interactions. Included are an assessment of the single crystal structure, full-scale molecular modeling, and advanced thermodynamic analyses.

An example of results using Agere's Quadrant 2 platform is evidenced in a Phase I pharmacokinetic (PK) study of relative bioavailability, comparing a client's prior formulation with one enhanced by Agere. The process started by identifying and modeling five lead amorphous dispersion polymer candidates, and then selecting the top two to progress as amorphous dispersion formulations. After formulation optimization and solid dosage form development, clinical trial materials (CTM) were manufactured and dosed in a Phase I human clinical study. The PK data from the study showed substantial improvement in exposure levels with the amorphous solid dispersion formulation that delivered a 9-fold improvement in Cmax, and a 5-fold increase in AUC.

Ashland—UnderstandingSolid-Dispersion Technology

Over the last decade, Ashland has made significant investments in the understanding and development of solid-dispersion technology, believing the technology has tremendous potential to increase bioavailability and absorption for active pharmaceutical ingredients (API) with poor solubility. Although the technology requires some specialized manufacturing equipment, early development can be accomplished relatively quickly and at a reasonable cost.

A key component of a solid dispersion is the polymer system. Some scientists will choose a carrier that has limited or no history of use in solid-dispersion technology. Still others will select known polymer systems, but make the mistake of limiting their evaluation to one type or what seems to be the most popular at the time, explains Dean Ross, Sr. Business Manager, Solubilization. Over the years, Ashland has developed and characterized hundreds of solid-dispersion prototype APIs. In more than 90% of the studies, a prototype with good stability and increased solubility was achieved. "We have learned that no one polymer system is a solution for all APIs," says Mr. Ross.

Mr. Ross points out that Ashland can provide know-how and expertise to support R&D programs focused on improving solubility. Ashland can help with advice and guidance on polymer selection and if a facility is needed to outsource solid-dispersion studies. It all starts with feasibility or proof-of-concept studies to determine if solid-dispersion technology is the right approach for increasing API solubility. Initial studies can be conducted with small amounts of API (~10 g) for development of several formulations to select an effective combination of drug and dispersant system. The study can then be expanded to a comprehensive set of experiments to optimize the drug load and dispersant system. Once the optimum formulation is selected, Ashland's scientists can continue the drug development program by providing scale-up, process development, final dosage form development, and non-GMP manufacturing services for animal toxicology or

additional studies.

As an example, a pharmaceutical innovator approached Ashland with a poorly soluble API, for which an exceptionally large dosage was required to achieve therapeutic benefits. The company planned clinical trials within the next three months, and requested Ashland's scientists to design a program that included development of a solid-dispersion formulation; a film-coated modified-release tablet formulation, and a scaled-up manufacturing process for spray drying, tableting, and coating. The resulting tablet formulation had significantly better drug solubility and bioavailability with excellent shelf stability. "Most important, the dosage was reduced from 18 capsules per day to two tablets," Mr. Ross says.

BASF—Excipients & Polymers Enhance Solubility

More than 70% of new chemical entities (NCEs) are poorly soluble and the drug industry is at a crossroad to find the desired solutions by identifying the appropriate formulation technologies for those molecules. Those solubility challenges stem from inherent highly crystalline (melting temperature), lipophilicity, and/or hydrophobicity of drug candidates. The conventional formulation approaches of micronization/milling, pH modification/salt formation, and/or pro-drug approaches, all bode well for designing and developing low-dose drugs, but for those requiring medium to high doses the choices of using physical modifications of NCEs are often limited. Therefore, the nonconventional formulations technologies such as amorphous solid dispersions (ASD) and lipid-based self-emulsifying drug delivery systems (SEDDS) have been the subject of continued interest to overcome these challenges to design better and smarter pills that improve solubility and enhance bioavailability and meet the requirements of regulatory agencies for patient compliance.

BASF Pharma marketing platforms include solubilization, instant and modified release, skin delivery, and soft gels technologies to meet formulation challenges. Each of the market platforms covers a range of high functional excipients for multifunction applications in solid and/or liquid dosage formulation development. For instance, BASF's expertise in hot melt extrusion and a range of polymers, such as Kollidon® VA64, Soluplus®, Kollidon® (12PF, 17PF, 25, 30 and 90F), Kollidon® SR, Kollicoat® IR, Kollicoat® MAE100P, and others, provide boundless opportunities to find the desired solutions for drug candidates being pursued either in the early or late stage of development process, explains Shaukat Ali, PhD, Technical Support Manager at BASF. In addition, with a wide solubilizers portfolio ranging from low molecular weight polyethylene glycols (PEGs) to surfactant-based solubilizers such as Kolliphor® grades possessing an array of hydrophilic lipophilic balance (HLB) values, offer the additional choices to formulators working with insoluble drug candidates.

Recent trends in poorly soluble drug candidates will continue to rise. BASF is addressing these challenges in solubilization by offering a broad product portfolio to meet industry needs. "Building partnerships and working closely with drug manufacturers, CROs and CMOs and equipment manufacturers, BASF will design and introduce new and innovative polymers and ingredients to address the solubility and bioavailability and other areas of formulation development," says Dr. Ali.

Gattefossé—DrugDevelopment Options With the End in Mind

Bioavailability is the rate and extent to which the active drug molecule reaches the systemic circulation or a specific site of action. Attaining the right dose at the desired rate however is a daunting challenge for drug delivery scientists. Currently, a vast majority of molecules out of drug discovery have poor solubility/dissolution properties. Further complicating the task are the biological barriers to absorption like poor intestinal permeability often coupled with pre-systemic degradation found with a significant percentage of new APIs.

Among the possible solutions, and of increasing interest to scientists, are lipid-based drug delivery (LBDD) systems that help solubilize/disperse the drug molecule, notably in the gut milieu by micellization, thus preventing the active drug from falling out of solution; ameliorate the drug affinity for the aqueous monolayer; and crossing the intestinal wall due to enhanced membrane fluidity. Additionally, certain classes of lipid excipients can improve drug permeability by inhibiting/saturating the enterocyte-based transporters; or may increase bioavailability by promoting lymphatic absorption of highly lipophilic drugs that would otherwise be eliminated presystemically.

Achieving adequate bioavailability may be challenging but remains the ultimate goal of every therapy. “Our company recognizes the importance of expanding the drug development toolbox by providing new products and new approaches much needed for the development of new and effective dosage forms,” says Jasmine Musakhanian, Scientific & Marketing Director, Pharmaceutical Division of Gattefossé USA.

“Lipid excipients and LBDD systems are core specialties of Gattefossé. “As such, we provide guidance documents for excipient selection and formulation design for preclinical as well as late development stages,” she continues. “To meet the bioavailability challenge, we have worked hard developing new excipients. This has meant extensive investments in creation and characterization; conducting safety studies; guaranteeing quality and consistency of supply; and seeing that the new products have global regulatory acceptance. In the past decade, Gattefossé was responsible for more than 25 new excipient monographs.”

MetricsContract Services—Optimizing Formulations for Site-Specific Delivery Improves Bioavailability

Many new drugs have either poor bioavailability or solubility and are in limited quantity. Some of the quickest and easiest ways of trying to improve solubility is to change the physical properties of the drug molecule itself. This would include reducing particle size by various forms of milling. Milling can be performed on a limited quantity of API and is a continuous process that is easily scalable.

Another way of improving solubility is to make a salt form of the drug to utilize ionizable groups. Generally, manufacturing a salt form of a drug is performed during the API synthesis and not at the formulation stage. From a formulation perspective, a scientist can change the crystalline drug molecule to an amorphous form. This can be achieved using spray drying or hot melt extrusion — techniques common to solid oral dosage forms.

Metrics offers several formulation approaches to increase solubility or bioavailability. “For drugs formulated as a solution, we optimize the pH of the solution to maximize ionization of the drug molecule. We also can incorporate other excipients — such as surfactants, alcohols, etc. — to help increase solubility,” explains Michael DeHart, PhD, Developmental Scientist II at Metrics Contract Services. “In the case of solid oral dosage, we can micronize the drug molecule to increase the surface area of the drug to help solubility.”

Metrics also has the ability to generate amorphous material via spray drying. Spray dried material is generally amorphous in material that has significantly higher solubility when compared to the crystalline form. Both micronization and spray drying allows the powder to be further processed into a capsule or tablet — two dosage forms that Metrics manufactures on a regular basis.

“The pharma industry is always looking for ways to improve the solubility or bioavailability of a drug molecule. Conventional methods, such as micronization, spray drying and hot melt extrusion, are used on a regular basis. However, something that seems to be common in the

work being performed at Metrics is optimizing a formulation to provide site-specific drug delivery, or modified-release profiles, to increase bioavailability," says Dr. DeHart. One of the most common methods is enterically coating multi-particulates, or tablets, to optimize drug delivery in the small intestine. In the small intestine, the pH helps deliver molecules that are susceptible to acid degradation or may have increased solubility in slightly basic conditions.

Nanocopoeia—Nano-Enabled Particle Design

Pharmaceutical companies continually search for better, faster, scalable ways to improve drug performance. Common problems include poor solubility, low bioavailability, impractical dosage regimens, and need for alternatives to injection. Nanoformulation is an emerging tool for addressing these challenges, but only a limited number of processes for producing nanoparticle formulations have been scaled for commercial production needs. The ability to get a BCS class II or IV compound into a solubilizable form is what guides most decisions to use solubilization technologies, explains Robert Hoerr MD, PhD, Co-Founder, CSO, Nanocopoeia.

Nanocopoeia is a therapeutic particle engineering company providing nano-enabled particle design, services, and equipment to the pharmaceutical industry. Specific to ElectroNanospray™ (ENS) nanoformulation, the most important API considerations are solubility in organic solvents, the need to reduce or eliminate problematic excipients, and the desire to protect, stabilize, and/or control the release of the API at the point of delivery.

Nanocopoeia's ENS process creates complex, homogeneous nanoparticles in a single processing step. First, by using electrospray in a stable cone-jet mode, ENS provides exquisite control over particle size (from a few nanometers to micrometers) and composition at ambient conditions. "Second, our patented D-series co-axial spray nozzle allows us to create complex composite nanoscale particles from a range of compounds, boosting throughput 30-60x vs. single-capillary nozzle ES processes," says Dr. Hoerr.

Because ENS is a non-destructive process, particles' chemical or biological properties can be preserved without degradation from heat or mechanical stresses. Thus, ENS can provide the enhanced drug solubility pharmaceutical manufacturers seek by producing consistently sized nanoparticles and enabling scale-up ES capabilities.

"Nanocopoeia is targeting commercial activity in drug discovery and development as a formulation resource for industry and academic researchers," says Jane Nichols, Director of Business Development, Nanocopoeia. "Nanocopoeia can work with those researchers to create an efficient and effective way to leverage existing libraries of compounds with known solubility issues but potentially great commercial potential. A particular advantage of the ElectroNanospray process is the ability to work with very small quantities of expensive research grade materials that the compounding pharmacists can make of these materials. A further advantage of ENS-produced drug nano-formulations is our ability to rapidly turnaround fully characterized material for preclinical testing."

Particle Sciences—An Array of Services for Successful Execution

Bioavailability is the ultimate determinant of efficacy for any therapeutic, and solubility along with permeability, are the drivers of bioavailability. Both solubility and permeability are inherent properties of a given molecule and can't be altered. However, permeation can be maximized by high local concentrations of drugs and the rate of solubilization is critical for it is the kinetics that dictate local concentration, explains Robert W. Lee, PhD, Particle Sciences (PSI). Therefore, solubility rate is one of the key physicochemical parameters a formulator needs to manipulate to develop viable formulations.

Active Pharmaceutical Ingredients (APIs) of interest are often sparingly water-soluble with a majority of New Chemical Entities (NCEs) belonging to the BCS Class II. “At PSI, we have a number of solubilization approaches ranging from *in silico* design to nanoparticles to solid solutions to lipid-based systems, such as LyoCells® (PSI proprietary reverse cubic and hexagonal phase nanoparticulate delivery system),” says Dr. Mark Mitchnick of PSI. “For long-term delivery, our drug-eluting device work is frequently the solution.”

A well-informed formulation effort starts with preformulation data, including extensive solubility 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,” says Dr. Lee. “Based on the physicochemical characteristics of the API, we assess what drug delivery approaches will provide the biological performance and match the desired target product profile.”

PSI has assembled a range of technologies aimed at getting past the common bioavailability barriers. “Key to our clients’ success is PSI’s ability to work with their molecules, even if highly potent or DEA controlled substances and importantly, to quickly bring them into the clinic with our cGMP production of both sterile and non-sterile products,” says Dr. Mitchnick.

Dr. Lee adds: “It is becoming increasingly accepted that bioavailability can be impacted in a predictable way. If one studies the currently available, scalable technologies, it is clear that there have been only incremental technical advances, but the real improvements have come from better execution. There are only a handful of unique drug delivery approaches – particle size reduction, amorphous forms, permeation enhancers – but each has different flavors. It is in excellent execution and having access to a full array of approaches that the best products are developed.”

Solubest Ltd.—Increasing Solubility & Drug Absorption

Most molecular interactions within the body occur in solution or colloid, but around 50% of known pharmaceutical and natural bioactive compounds, as well as drug candidates under discovery, have poor aqueous solubility properties and/or poor permeability. Such low solubility in body fluids is translated to inadequate bioavailability and, thereby, insufficient bio-performance.

Most known drug delivery systems that aim to improve bioperformance essentially interfere with this basic physico-chemical parameter. Solubest lets clients leverage its proprietary particle engineering R&D and drug development expertise to overcome formulation challenges of hydrophobic, poor permeable, instable bioactive ingredients for multiple applications.

In addition to its leading technology, Solumer™, Solubest offers a diverse array of drug delivery approaches tailored to client needs. The proprietary solid dispersion of liphophilic APIs in polymer matrix is produced by a spray drying technique. Once in the body, Solumer solid-dispersions disintegrate into colloids, increasing drug solubility and bio-absorption. “It’s important to note that particle size minimization is not the only parameter that enhances solubility,” points out Dr. Galia Temtsin Krayz, Solubest COO and Vice President, R&D. There are additional essential Solumer characteristics that result in the enhanced prolonged super-saturation in relevant biological fluids. These include physico-chemical characteristics where the solubilized drug homogeneously disperses in disordered crystalline form that is interwoven into dual polymer matrix; thermodynamic features, such as depressed melting temperature and enthalpy of fusion; and surface-to-volume characteristics, the spontaneous formation of nanocolloidal dispersions upon contact with aqueous media.

Solumer technology has been used to generate a new solubilized formulation of natural

antioxidant resveratrol with improved solubility. Solu-Resveratrol needs 4-5 times less dose to get the same bioavailability as not improved resveratrol products.

Xcelience—BalancingSolubility & Bioavailability

The pharmacokinetics of an active pharmaceutical ingredient can be a laborious scientific endeavor in the early stages of drug product development. As these newly synthesized compounds show significant advantage or promise in animal models, many pharmaceutical companies look toward preformulation to provide the foundation of the program's design space. Many contract pharmaceutical development companies (CDMOs) are challenged with high level details of getting as much of the API into a single dosage form, physically and chemically stable, tolerable for human ingestion, all in an expedient timeframe by using a limited amount of material at a low cost. Thus, any specific measures on to gain scientific confidence on how the API will likely "behave" when orally administered becomes critical at an early stage. The API solubility profile and how solubility can be improved usually leads the charge.

Combinatorial chemistry and high throughput screening techniques are used in drug research for their efficiency that compares favorably with rational drug design. However, oral activity of these compounds is dependent on the ability to dissolve in the GI fluids for absorption "At Xcelience, we understand the delicate balance of solubility as it relates to bioavailability versus the need to keep it simple for early phase development without compromising quality," says Parag Ved, PhD, Team Leader, Formulation Development, Xcelience. "We use a systematic approach towards improving solubility starting with the conventional pH solubility profile. For instance, a simple titration experiment with a dispersion of the drug at desired concentration and the use of GRAS excipients such as citric acid or sodium bicarbonate can be performed to visually confirm solubility."

The same acid or base can be incorporated in the formulation at the desired concentration to assist with the dissolution. Certain compounds may show preferentially higher solubility in presence of a specific buffer system in solution at a given pH as compared to other salts under the same condition. "We also have the ability to measure pH solubility with the aid of instrumentation," says Mark Cappucci, Team Leader, Preformulation & Formulation Development, Xcelience. "The use of automated systems at Xcelience can help determine the kinetic, equilibrium and intrinsic solubility using significantly lower amounts of API as compared to the conventional titration methods."

Cyclodextrins are cyclic oligosaccharides consisting of 6, 7, 8 or more glucopyranose units linked by α- (1,4) bonds that have been used at Xcelience to formulate orally active formulations of poorly soluble compounds. "These provide a micro heterogeneous environment that is hydrophilic outside and dissolve in water, and a hydrophobic cavity that can form inclusion complex with compounds to keep them solubilized," explains Dr. Ved.

"It is a never-ending battle of solubility versus bioavailability; enhancements to increase a poorly soluble compound sometimes lead to a decrease in the compound's ability to reach the intended target area," says Mr. Cappucci. "At Xcelience we understand the concerns and utilize several approaches, whether chemical or physical to drive the compound into a successful life cycle that includes a commercial product."

References

1. Technology Catalysts International, Poorly Soluble and Poorly Permeable Drugs, Seventh Edition, 2014.
2. Agere Pharmaceuticals, Inc. analysis, January 2015.

Related Taxonomy

- **Cover Story**

Popularity:
This record has been viewed **41** times.

Comments:

Be the first to leave a comment.

Leave your comment

CAPTCHA Validation

Code:

Name:

Email:

Publish Comment