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AN INTERVIEW WITH...

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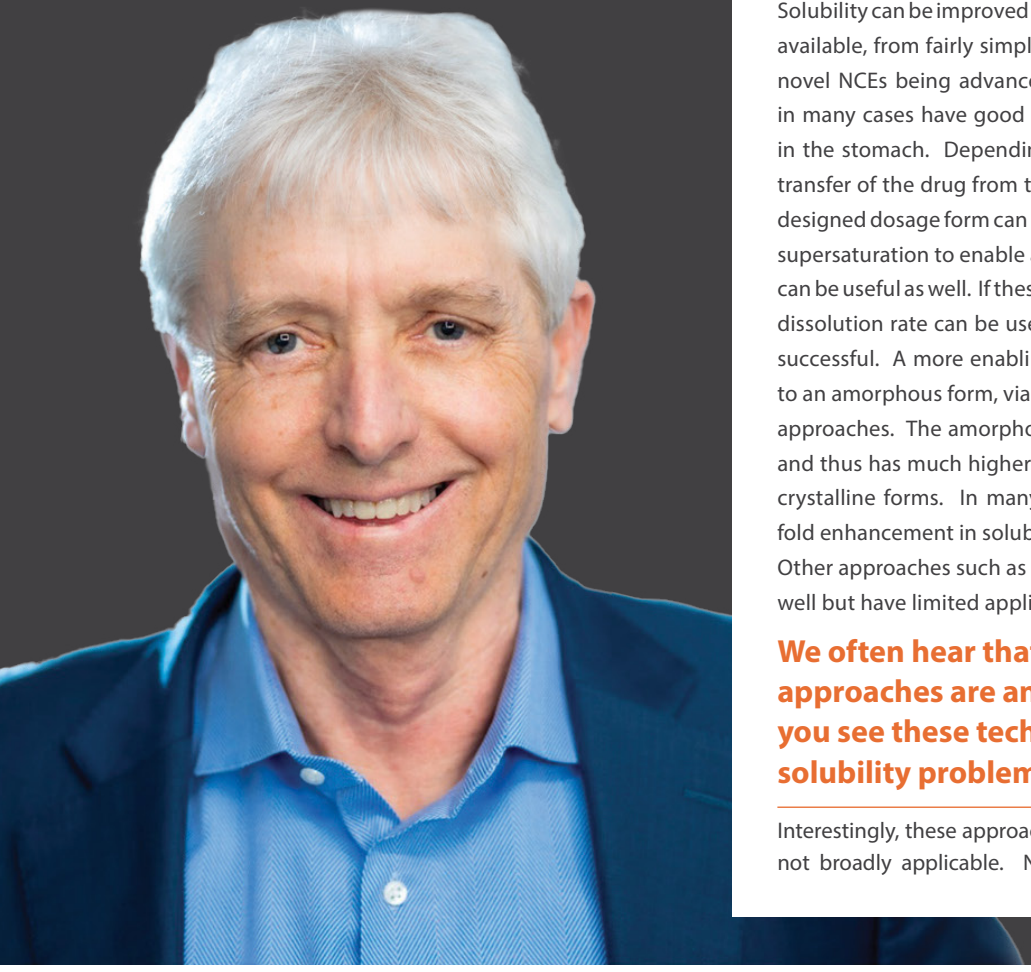
Turning Complex Molecules into Medicines:

Leveraging advanced formulation technologies to enable solubility and permeability



Medicines are becoming more complex, leading to significant barriers to achieving acceptable pharmacokinetics for oral delivery, what are the tools to solve these challenges?

The industry has many tools available to deliver medicines, although there is certainly still significant unmet need. There are essentially three main barriers to achieving high oral bioavailability, and hence achieving acceptable pharmacokinetics: solubility, permeability, and first-pass metabolism. We have good tools for overcoming solubility, a few marginal tools for overcoming permeability, and almost none for overcoming metabolism. In many cases, just increasing solubility can mitigate issues with permeability (due to increase in the driving force across the intestinal membrane) and metabolism (by saturating enzymes responsible for metabolism).

Solubility challenges continue to be a significant issue for drug development. What approaches do you consider enabling to solve these challenges?

Solubility can be improved in most cases. There are a range of approaches available, from fairly simple to more complex ones. For example, most novel NCEs being advanced from discovery are weak bases, and thus in many cases have good solubility in the low-pH gastric environment in the stomach. Depending on how rapidly the solubility drops upon transfer of the drug from the stomach to the small intestine, a properly designed dosage form can be successful in providing sufficient sustained supersaturation to enable absorption. Engineering the proper salt form can be useful as well. If these approaches are insufficient, then enhancing dissolution rate can be useful, but typically only rarely is this approach successful. A more enabling approach is to convert the crystalline API to an amorphous form, via spray drying, melt extrusion, or precipitation approaches. The amorphous form has significantly higher free energy, and thus has much higher solubility in the small intestine compared to crystalline forms. In many cases, amorphous forms can lead to a 10-fold enhancement in solubility or more, and thus can be quite enabling. Other approaches such as lipid systems and co-crystals can be useful as well but have limited applicability.

We often hear that nanotechnology or lipid approaches are an enabling approach, how do you see these technologies as solutions to the solubility problem?

Interestingly, these approaches seem to garner a lot of attention, but are not broadly applicable. Nanoparticulate approaches do not enhance

solubility unless the particles are in the 10-nm diameter range, which is exceedingly difficult to achieve. Most approaches to produce nanoparticles result in diameters of a few 100-nm. The main benefit of nanoparticles is a significant enhancement in dissolution rate relative to typical crystalline API (which tend to fall in the 1–100-micron diameter range). So, they don't really enhance solubility. However, in some cases, for hydrophobic API, dissolution rates can be quite slow, so this approach can lead to enhanced absorption as long as the solubility of the crystalline drug is not too low. Typically, nanoparticle approaches work for APIs with crystalline solubilities > 10 ug/mL. Lipid systems are useful for classes of APIs which are lipophilic, and in these cases can be the method of choice. Most modern active molecules targeting novel biological targets are only slightly lipophilic, so this approach is somewhat niche.

Spray dried dispersions appear to be the preferred approach to enhancing solubility in the GI tract, can you give us an overview of how this works and the limitations of this approach?

Spray Dried Dispersions, stable amorphous formulations of an API, are by far the preferred approach to overcoming solubility limited absorption in the GI tract. Typically, the API and a polymer are combined in an organic solvent as a solution, and then spray dried to form 5-50 um sized particles. These particles, which are a combination of an amphiphilic polymer and the API, are physically stable and have dissolution properties that lead to substantial increases in bioavailability relative to crystalline API alone. There really are no other formulation approaches that can broadly achieve performance, stability, and manufacturability goals needed for insoluble small molecules. The technology is very scalable and well established. There are over 45 spray dried products on the market and 100's in development today. While it is truly an amazing technology, it isn't easy to develop or scale for those who don't have the experience. It is critical that clients choose a CDMO with extensive particle engineering experience and proven processes to deliver successful spray-dried products. Our estimates are that as much as 80% of insoluble compounds that require an enabled approach should use spray drying as the preferred approach. There are certainly other approaches, such as twin-screw melt-extrusion that can produce amorphous materials, but this approach is only applicable to 10-20% of the APIs that our clients have today.

In addition to solubility, permeability in the GI tract is a major challenge. Could you outline the existing approaches to improving permeability?

Permeability limited absorption is becoming a major barrier for many novel molecules that are being developed. Specifically, molecules are becoming much more complex structurally in order to enable sufficient interaction with novel targets. For example, protein degraders and molecular glues are clearly a promising class of compounds for treating a broad range of diseases, but these molecules are generally large (800-1500 MW) and thus have significantly reduced passive permeability across the epithelium in the small intestine. Another class of compounds, peptides, are also generally large and have very poor permeability. Unfortunately, there aren't a lot of tools that we can use to improve permeability. There are generally two main approaches that are practical: increasing solubility to increase the flux across the membrane, and using excipients that modify the lipid bilayer or tight junction between epithelial cells to allow for increased transport. We have used both successfully, but in general, these formulation approaches are still far from ideal in terms of enhancement in bioavailability. It takes a very comprehensive approach to formulation and the dosage form to truly have an impact here, and we have ongoing research to explore other approaches that appear promising.

Going back to complexity, and given the challenges of permeability for oral delivery of peptides and other larger molecules, what other approaches do you see that might make an impact?

Given the complexity of molecules that we see and the significant limitations in existing formulation technologies, it is clear we need "outside the box" approaches to obtaining acceptable PK. There are some novel approaches that utilize nanoparticles to at least maximize drug at the surface of the epithelium that may help, and certainly for peptides, it is critical to protect the peptide from the enzymatic degradation that occurs in the GI tract. So, designing a dosage form that transits through the gut to deliver the peptide to the right location to maximize absorption and minimize degradation is key. It's more than just enterically coating your tablet, one needs to design the form to transit, protect, and dissolve at the right location. Also, we are developing injectables (SQ and IM) that are simple to deliver and patient friendly that should be considered when developing and drug that has significant permeability issues.

For compounds that are complex and can't be given orally, what needs do you see that are unmet and how would you address these needs?

Advanced injectable formulations and devices are likely to be adopted more and more as a viable approach. If we are limited to a few percent

bioavailability, then we will likely need to develop an injectable formulation. Key to success, however, is that we must consider ease of use and compliance, in other words, the patient experience. Given the success of GLP-1s, and the broad range of potential benefits to patients, these therapies are likely to become very broadly accepted. We will need to make delivery systems simple and robust to expand to other targets.

We have all been hearing about the success of GLP-1 and related therapies. These peptides are good examples of how medicines have become increasingly complex. While there are oral versions, they have vanishingly low bioavailability. What are the options available to improve their delivery?

Certainly, the success of GLP-1 peptides is beyond expectation. While there are oral formulations of these peptides, the bioavailability is generally a few percent or less. Obviously, this isn't ideal, and thus there is great need for improved formulations that would enable increased oral bioavailability. Some approaches being explored include novel lipids that may improve permeability, but these are not likely to have a dramatic effect. There are some interesting peptide designs, such as circular constructs that are also showing promise. More likely, an optimization of chemistry, formulation, solid dosage form, and process is required to maximize oral absorption of peptides.

For injectables, what are some of the challenges that you see and how might we overcome them from a drug delivery standpoint?

There are some really exciting opportunities for parenteral delivery for both small and large molecules. Some examples are high concentration suspensions of antibodies to convert from IV delivery to SQ. We are working on a spray drying approach to particle design that really looks promising. These delivery challenges require substantial particle design and formulation optimization to be successful, as well as integration with the delivery device. The neat thing about this technology is that it is applicable to any drug modality (protein, peptide, small molecule) that needs a very high dose in a small dosing volume and requiring the use of suspensions. I also think that oral permeability is such a daunting challenge that we will see more innovative patient friendly SQ dosing systems be developed as well.

The IRA has put a lot of pressure on small molecules, and there is a debate over how investment could be impacted in this space, what are your thoughts here?

I think small molecules are here to stay since in many cases, for example for intra-cellular targets and crossing the blood-brain barrier, small molecules are in most cases the only practical approach for achieving desired PK. I do think that in the short term the IRA will cause a shift in investment in small molecules, but for the reasons I just stated, I don't think it will have a lasting impact.

Given the need for rapid development because of the 9-year exclusivity for small molecules, how can the industry advance drugs more rapidly to patients?

This is a good question. We are taking this very seriously and have an approach we think could be beneficial. Essentially, assuming the 9-year window remains, we need to develop medicines much faster. Thinking about the whole drug development process is required to do this, including design and implementation of clinical trials, patient selection, target selection etc., but also, we think that CMC can be performed much faster as well. Our approach simply put is to provide a commercially viable formulation and analytical path forward for first in human studies. This avoids time consuming efforts that require bio-equivalency studies and reformulation and enables collection of data that supports QBD from the very beginning of CMC activities.

Dr. Smithey *is the President, CEO and Co-founder of Serán BioScience. Over his 30-year career, he has led multiple research and development projects in a broad range of therapeutic areas. His work has led to the successful development of several novel medicines, including Tucatinib (Tukysa®) for the treatment of metastatic breast cancer. Dr. Smithey has extensive experience building entrepreneurial organizations that embrace a strong science and engineering approach to solving unmet need in drug development and biotechnology. Previously, Dr. Smithey led a team at Bend Research (now Lonza®) directed at research and development of novel pharmaceutical technologies, including the industry leading spray-dried dispersion technology that is broadly in use today. Subsequently, Dr. Smithey co-founded Agere Pharmaceuticals, a specialty CDMO, which was acquired by Patheon in 2015. He is an inventor in over 50 patent and patent applications in numerous technology and therapeutic areas. Dr. Smithey obtained a Ph.D. in Quantum Information and Optical Physics from the University of Oregon.*