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PHARMACEUTICS / MANUFACTURING

CLIENT-CENTRIC CDMO

WINNING STRATEGIES FOR ORAL DOSAGE FORM DEVELOPMENT **AND MANUFACTURING**

By Dave Miller, Ph.D., AustinPx

Oral solid dose (OSD) formulation development must adhere to common considerations, such as project timelines, facilitating CDMO/client transparency and overcoming regulatory challenges. However, development's difficulty often is compounded by numerous factors such as API supply constraints, challenging physiochemical properties, poor bioavailability, and/or constrained safe handling requirements, to name just a few. Therefore, successful pharmaceutical formulation hinges on front-loaded risk identification and mitigation.

Failure to identify a compound's red flags — bioavailability, stability, processability, etc. — early in development often manifests as program delays or failures. These setbacks can be avoided through complete molecular characterization, which can de-risk development and accelerate entry into human studies while also increasing the probability of clinical success.

Nonetheless, many sponsor companies, depending on how their molecule was discovered, focus heavily on molecule toxicology and pharmacology. They may forego complete characterization of the molecule to instead solely prioritize speed to clinic. But developing an oral therapeutic that is stable, bioavailable, and manufacturable can be quite complex. Accordingly, every formulation plan should benefit from a thorough pre-formulation package and an expert partner who can create a development plan and advise the sponsor on various risks and recommended solutions, enabling the latter to make data-informed decisions.

Seek simplicity out of complexity

All sponsors want a stable, manufacturable, bioavailable dosage form with as little complexity as possible. Ostensibly, this would comprise powder within a capsule. However, if the pre-formulation data suggests that dosage form will be problematic, the project is likely to step up in tiers of complexity.

Consider a molecule with no bioavailability that must be converted into a supersaturating delivery system. For example, a molecular dispersion or a self-emulsifying lipid system must be generated to achieve the desired bioavailability. So, upward movement in complexity is directly related to the molecule itself and its performance.

Additionally, the pre-formulation data set should be considered together with the target product profile: the indication, anticipated dose, and patient population. How does that align with the molecule's absorption,

distribution, metabolism, elimination data, etc.? Those information sources inform the formulation plan, which hopefully supports a simple dosage form. In reality, though, simple molecules and simple dosage forms are fairly rare in 2024 as sponsors push the boundaries of the chemical space in search of potential new drugs that better serve specific patient populations.

Fortunately, there exists extensive historical information, either in the literature or internal company knowledge, that provides insight and guidance into common problems and allows for risk mitigation early in development. Still, the modern pharmaceutical industry is relying more on in silico-based drug discovery, leading to more complex molecules than ever before and, by extension, problems that are somewhat new and nuanced. A CDMO partner must possess deep, relevant experience to supplement that textbook understanding, enabling it to identify those more nuanced issues and to skillfully inform the client of its options moving forward.

AustinPx, as a former sponsor company, is uniquely equipped and staffed to fill this role because we see molecules from a sponsor company's perspective. During its time as a sponsor, AustinPx authored 13 regulatory filings, executing its own clinical trials on six different assets. That in-the-trenches experience is equally powerful and difficult to quantify: it is not a direct project deliverable, but it is an intangible that positively impacts the entirety of our operations.

Can AustinPX handle highly potent compounds?

As a startup company, AustinPx often worked with highly potent APIs (HPAPIs), so the company had to build the infrastructure for toxicology assessment as well as write categorizing and handling SOPs, establish engineering controls, and become adept in surrogate monitoring. Our infrastructure and its engineering controls were built from scratch, and our equipment trains have been validated/qualified for use in very high potency compounds, e.g., occupational exposure band (OEB) 5.

After refining its HPAPI practices with the help of outside experts, AustinPx established HPAPI expertise in-house and purchased equipment to facilitate surrogate monitoring. This allowed us to test more equipment, faster, and to qualify the containment systems and engineering controls as being effective at controlling exposure levels.

HPAPIs were essential to our operation as a sponsor, to developing drug products and manufacturing clinical supplies. So, as a CDMO, AustinPx strives to educate and equip our whole staff to understand the importance of toxicology assessment and the band system, general HPAPI risks, and the required safety/handling procedures and personal protective equipment.

How does AustinPx overcome poor molecule bioavailability?

AustinPx's origin is based around KinetiSol,[1] which is becoming the world's premier technology for amorphous solid dispersions (ASDs), an increasingly important element of bioavailability enhancement (BAE). Consequently, since the company's inception in 2012, we have developed extensive BAE capabilities, including pre-formulation strategies that guide development, drug property-centric formulation design, solid-state characterization, chemical analysis, and biopharmaceutical performance evaluation — which includes state-of-the-art in-vitro and in-silico tools as well as expertise in designing comparative in-vivo studies.

AustinPx has all the equipment and expertise needed to apply various formulation strategies to any poorly soluble compound, including particle size reduction, lipid-based formulations, spray drying, hot-melt extrusion, co-precipitation, and, of course, KinetiSol. Again, assessing BAE for a given molecule begins by thoroughly characterizing the compound, in tandem with reviewing its ADME properties and the target product profile. This foundation of understanding allows our scientists to prioritize the investigation of formulation strategies toward streamlining development and mitigating development risks.

Notably, insoluble molecules require more than a standard pre-formulation package. More time is necessary to understand the solubility and how it precipitates from supersaturated solution, etc., so AustinPx developed unique in-house testing approaches. The testing looks at drug substance amorphous solubility in various types of biorelevant media, and in the presence of pre-dissolved polymers and excipients capable of further improving solubility and/or delaying precipitation. Additionally, AustinPx examines different types of transmembrane permeation studies in the presence of excipients, and speciation in the presence of polymers, seeking data on how those variables affect flux and permeability.

Guided by these data, a formulation development strategy is generated, and various BAE formulation technologies and compositions are rapidly evaluated by applying API-sparing, small-scale screening tools. The various prototypes that emerge from screening are then thoroughly characterized and scrutinized for performance, stability, and early assessments of manufacturability.

At this point, lead approaches emerge, and following client consultation and agreement, efforts to fully develop and optimize those leads begin with an eye toward rapid transfer to clinical trial material manufacturing. By this process, AustinPx has streamlined and optimized comprehensive evaluation, development, and manufacturing of BAE formulations, enabling faster entry into clinical development and increasing odds of success.

Oral solid dose development demands appropriate tools and information

The amount of pre-formulation data necessary to fully understand a molecule and to begin preparing a viable development path can catch sponsor companies off guard. It is not that the requirements are overwhelmingly extensive, expensive, or time-consuming — full molecule characterization is fairly standard — but the importance of data and the criticality of context within that package cannot be overstated. It is both a short- and long-term development map for your OSD formulation.

The pharmaceutical scientists at AustinPx are drug product development experts with sponsor experience under the same roof, and their training and skill level confirm the fact. This high-touch, high-science approach is unique to AustinPx, allowing us to remain an agile boutique CDMO with deep focus and expertise in OSD development.

Finally, in KinetiSol, AustinPx offers a value-adding tool that is unmatched in the market. KinetiSol offers the broadest design space of any amorphous solid dispersion technology. However, while legacy technologies are limited in the types of molecules they can be applied to, KinetiSol can be applied to nearly any molecule. Related, developing more complex delivery systems specific to certain molecules inherently involves novel IP. This is refreshing and valuable in a formulation technology patent landscape so crowded that there is little to no opportunity for new IP with old technologies. Thus, AustinPx seeks to develop strong drug product patents that will protect client assets for longer durations.

Our ultimate goal is to help clients fast-track a compound into the clinic while avoiding early oversights that can disrupt development downstream. Investing what amounts to minimal time and cost into thorough molecular characterization, as well as utilizing predictive tools to fully understand a compound's risks and inform phase-appropriate development via routinized and rapid protocols, speeds progress toward first-in-human (FIH) studies while substantially de-risking downstream development. To learn more, contact the author and visit https://www.austinpx.com.

Resources

- *AustinPx Facility Tour & Capacity Update (youtube.com)*
- *Why KinetiSol® is Disrupting Spray Drying: Dave Miller, Ph.D., AustinPx (youtube.com)*

About The Author

Dave Miller, Ph.D., is Chief Scientific Officer (CSO) for AustinPx, a role that takes advantage of his more than two decades of pharmaceutical development experience. Dr. Miller has spent his career investigating ways to improve the bioavailability of poorly soluble molecules and as CSO he leads AustinPx's pharmaceutics and analytical development teams, as well as oversees the application of KinetiSol™ technology.

Dr. Miller formerly served as Vice President of Research and Development at DisperSol Technologies and as Senior Principal Scientist at Hoffmann-La Roche. He is a co-inventor on numerous granted and pending patents worldwide, including the pharmaceutical applications of the KinetiSol technology and continues to be a key innovative driver for application and expansion of the platform. Dr. Miller has published more than 40 research articles in peer-reviewed journals, authored eight book chapters, and is co-editor of the First, Second, and Third Editions of *Formulating Poorly Water-Soluble Drugs*.[2] He holds a B.S. in chemical engineering and a Ph.D. in pharmaceutics from the University of Texas at Austin.

About AustinPx

AustinPx Pharmaceutics and Manufacturing is a contract development and manufacturing organization (CDMO) providing analytical and formulation development services and cGMP manufacturing for small molecule drugs. They specialize in phase-appropriate development strategies, speed to clinic and market strategies, and bioavailability enhancement of poorly soluble molecules — including the next-generation amorphous dispersion platform, KinetiSol™ technology.

References

1. Brough, Chris. "Less Mess, Less Stress, Best Expressed: A Superior Alternative To Spray Drying." Austin Pharmaceuticals, Outsourced Pharma, July 16, 2024. https://www.outsourcedpharma.com/doc/less-mess-less-stress-best-expressed-a-superior-alternative-to-spray-drying-0001 Accessed Sept. 4, 2024.

2. Williams III, Robert O.; Davis Jr., Daniel A.; Miller, Dave A. "Formulating Poorly Water-Soluble Drugs." 3rd ed., Springer, 2022.