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PUSHING THE BOUNDARIES OF DRUG DEVELOPMENT: **IS LIPINSKI'S RULE OF FIVE STILL RELEVANT?**

By Dave Miller, Ph.D., AustinPx Pharmaceutics and Manufacturing

Christopher Lipinski's Rule of Five (Ro5) has been used for nearly three decades to evaluate whether a compound possesses the chemical and physical properties to potentially be an orally active drug in humans. But have modern molecules and technologies rendered Lipinski's guidelines irrelevant?

The pharmaceutical industry has shifted away from irrational drug discovery, wherein researchers try to replicate a known pharmacological effect by extracting a drug substance from natural sources and attempting to purify or modify it. Instead, drug developers have increasingly embraced rational drug discovery, driven by greater understanding of the human genome and disease pathways, as well as advancements in molecular and microbiology.

These leaps enabled drug developers to target specific sites with greater efficacy. Additionally, high throughput combinatorial chemistry and robotics advanced, leading to the creation of vast libraries of novel molecules that were screened against those known targets. This departure from naturally derived compounds expanded the chemical space and began a trend toward compounds with diminished drug-like properties.

AI tools and machine learning have now prompted the next shift in drug discovery, enabling researchers to build compounds in-silico, without the constraints of the physical realm. Docking experiments establishing the binding efficiency of these novel molecules to the target site are also conducted in-silico. Molecules emerging from this paradigm are deviating even further from the historical context of drug-like properties.

Additionally, numerous modern drugs violate multiple Ro5 elements, yet developers were able to find a development pathway, often using amorphous solid dispersion approaches. Conversely, some molecules adhere to every element of the Ro5, but their properties are not conducive to development: they may be insoluble in all solvents, aqueous and otherwise, and/or they exhibit ultra-high melting temperatures. But what does this mean in terms of risk and opportunity for developers?

An industry growing beyond Lipinski

As noted above, many Ro5 violators have been enabled by amorphous solid dispersion (ASD) formulation approaches. Spray dried dispersions (SDDs) and hot-melt extrusion (HME) have largely met that need, but gaps exist in that coverage. Even some Ro5 satisfiers have properties that would preclude development and commercialization.

The unprecedented challenge of developing these molecules requires an ambitious mindset and innovative — but proven — tools to overcome it.

Drug candidate screening during discovery is too often based on antiquated perspectives about drugability, which limits the discovery chemistry space to areas where molecular descriptors and predicted properties suggest adequate developability. Discovery chemists may trust that following the Ro5 will yield easily developable drugs, but the Ro5 focuses on properties like hydrogen bond donors, hydrogen bond acceptors, and molecular weight — structural attributes that do not require synthesizing the compound to gauge or understand.

This leads to scenarios where discovery chemists modify the best drug candidate to impart better drug-like properties, but at the expense of target-binding efficiency and specificity. In effect, they are compromising the relationship between the molecule's chemical structure and its biological activity (its structure-activity relationship, or SAR) to achieve a "more developable" drug. For example, applying such filters early in discovery would have precluded the creation of drugs like ritonavir and venetoclax, which violate the Ro5 but still made it to patients.

Once a compound is physically produced and its properties can be measured, researchers can start collecting pre-formulation data on the lead compound and its backups. Even if the lead compound seems hopelessly insoluble in aqueous media and poorly soluble in organic solvents, discovery chemists are familiar with formulation approaches to address that. Numerous modern molecules are optimized for binding efficiency and, as a result, they bind to the target site well. But their properties make enabled formulation production beyond the bench or preclinical scale difficult. For example, using SDDs, the amount of solvent that must be evaporated to produce a minor amount of solids is tremendous and impractical.

In response, the drug developer may begin to compromise, switching to backup compounds that don't bind as efficiently. The new compound lacks the same level of specificity, so it is hitting off-target sites, necessitating a larger dose and diminishing the safety profile. Clinical risks to safety and efficacy increase substantially when binding efficiency and specificity are compromised to improve drug-like properties.

In fact, many compounds that satisfy the Ro5, like vemurafenib and regorafenib, have solubility and thermal properties that preclude development by current commercial processes. Only a supersaturating drug delivery system will suffice to achieve adequate bioavailability. But the compound's properties also preclude the use of traditional supersaturating formulation approaches. These "brick dust" compounds are often shelved or modified based on an assumption that viable bioavailability enhancement (BAE) technology, serving early phase discovery through commercial production, does not exist.

Still, some companies proceed with brick dust compounds because the molecule shows promising efficacy. They progress through Phases 1 and 2 with a formulation and a process that are not commercially viable. Commercial drug product and process issues are kicked down the road, to be solved later in development, or the developer counts on an acquiring company to figure out those details.

However, this strategy places drug quality, safety, and efficacy at risk, since it often necessitates formulation and process changes at a later stage of clinical development, when the impact on timelines and costs is likely to be most severe. Delaying commercial DP and process issues also introduces risk that any potential acquiring company will view the CMC risk as unacceptable or see the risk as sufficient to justify reducing the acquisition price. For these reasons and more, a technology has been created that drives drug discovery beyond the Ro5.

KinetiSol breaks the rules

KinetiSol was once considered a last-resort large-scale formulation technology option only after lipid formulations, SDDs, and HME fail to generate a bioavailable formulation and/or a scalable process. The KinetiSol process accommodates high-temperature

melters without issue and solvent solubility is irrelevant to the process. Compared to other technologies, KinetiSol formulations typically result in superior bioavailability, smoother planning and execution of manufacturing, and a significantly reduced environmental impact.

Just as important, KinetiSol can be applied during discovery stages, when API supply is limited, to assess candidate developability by an ASD approach. Then, KinetiSol can be carried through all stages of clinical development to commercialization. More than 20 drug products have advanced through the clinic using KinetiSol, two of which are approaching Phase 3. One asset has progressed to registration scale in preparation for a regulatory filing. That means the KinetiSol process has been validated, on equipment trains in AustinPx's facility and partner facilities, more than 20 times.

Consider, too, that SDDs and HME both require moving to new equipment to execute commercial production. KinetiSol uses the same equipment from the clinical scale through commercial manufacturing. The only difference in production is the operation duration necessary to satisfy commercial demand. KinetiSol is more robust, simpler, more efficient, and more ecologically friendly. In short, it is a lower-risk option relative to other technologies, and thus is no longer regarded as a last-resort option.

Bioavailability is the key ingredient

In light of KinetiSol's capability and the inapplicability of Lipinski's Ro5 to modern molecule development, the industry must reevaluate its approaches to discovery screening and development candidate nomination, as well as its philosophy. A viable path — end-to-end, from preclinical studies and clinical trials to commercialization — has proven to work for compounds with "undevelopable" properties, from poor lipid and organic solvent solubility to thermal instability.

Drug developers now can select compounds for development based largely on SAR, rather than balancing activity against drug-like properties.

AustinPx leverages a full suite of pre-formulation and formulation tools, plus unique development insights, to direct our clients toward understanding their compounds' developability. We also possess the tools and expertise to apply precise molecule development and manufacturing strategies from preclinical to commercialization.

By vetting KinetiSol alongside lipid formulations, spray drying and HME early in drug development, we ensure that candidates highly optimized for target binding and specificity are not shelved, or modified, to meet solubility requirements at the expense of therapeutic potential. KinetiSol as a unique formulation tool differentiates AustinPx, but it is neither a preference nor a last resort. The majority of the work in characterizing these molecules, and then characterizing and developing the delivery system, is agnostic.

Everything upstream and downstream of KinetiSol is common to all solubility enhancing technologies. All the pre-formulation data gathered is the same. Most enablement also requires a delivery system that allows the drug to exceed its equilibrium solubility — a supersaturating drug delivery system. Each involves making a crystalline drug non-crystalline and then putting it into an excipient system that prevents recrystallization and promotes prolonged supersaturation in aqueous environments. This determination is common across all technologies. It all comes down to which formulation will best combine target bioavailability with scalability.

AustinPx is a leading expert in bioavailability enhancement techniques, including all upstream and downstream elements of amorphous solid dispersions, lipid formulations, particle size reduction, and other strategies to improve dissolution and bioavailability. We operate at the cutting edge of what current science believes is possible, writing new rules as we break new ground. To learn more, contact the author and visit https://www.austinpx.com.

Resources

- *Dave Miller: Pioneer in Pharmaceutical Innovation (insightscare.com)*
- *Pharma Matters Q&A: AustinPx | Contract Pharma*
- *AustinPx Facility Tour & Capacity Update (youtube.com)*
- *Why KinetiSol® is Disrupting Spray Drying: Dave Miller, PhD, 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 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*.[1] 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. We 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. Williams III, Robert O.; Davis Jr., Daniel A.; Miller, Dave A. "Formulating Poorly Water-Soluble Drugs." 3rd ed., Springer, 2022.