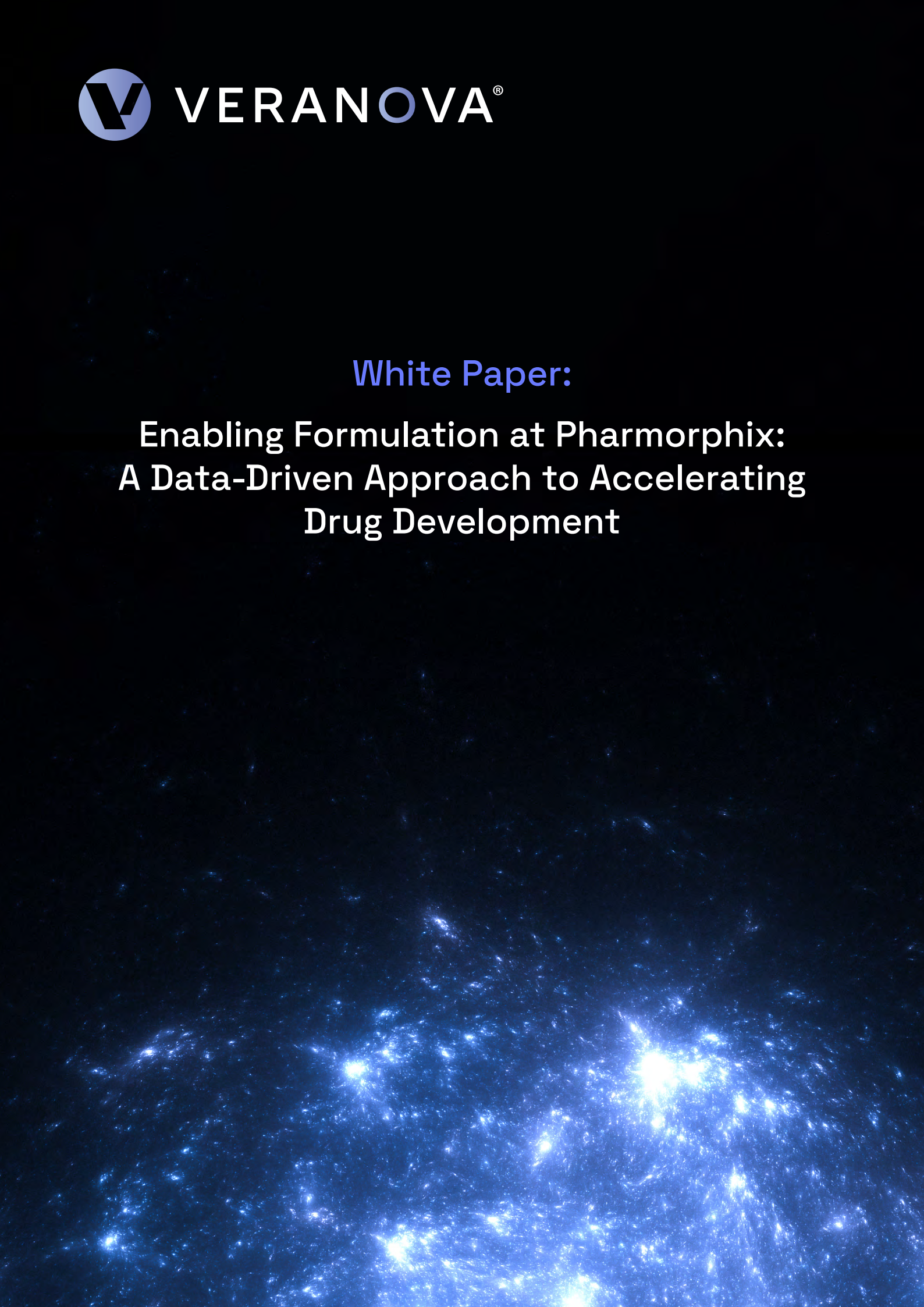
VERANOVA®

White Paper:

Enabling Formulation at Pharmorphix: A Data-Driven Approach to Accelerating Drug Development



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Olana Couzins is an Associate Director in the Pharmorphix team, Veranova's Centre of Excellence for Solid Form and Particle Engineering (SFPE).

After studying Forensic Science at the University of Lincoln and undertaking a bio-business internship program, Olana held an R&D position within GSK's Analytical Research and Development team. Since joining Veranova in 2010, Olana has led various projects and managed teams providing key analytical support for SFPE projects, specifically focusing on physicochemical profiling. Olana initially joined as an Analytical Scientist, undertaking core analytical services for SFPE projects. Over the years Olana has progressively assumed more senior roles to the present day where she is an Associate Director for the Analytical Services team providing key support to all SFPE projects as well as standalone support to clients in this area.

During Olana's tenure, both the size and capabilities of the Pharmorphix Analytical Services team have expanded considerably to offer clients greater phase-appropriate analytical support. This includes the addition of Veranova's physicochemical characterization suite and its enabling formulation offerings.

How Veranova can work with you

- Comprehensive Data-Driven Insights – By providing in-depth solid-state characterization and formulation analysis we can guide your drug development decisions from the earliest stages.
- Tailored Formulation Strategies – Whether addressing solubility challenges, stability concerns, or bioavailability issues, Veranova offers customized formulation pathways, including salt screening, amorphous solid dispersions, and nanosuspensions.
- Seamless Integration Across Development Stages – By keeping formulation and solid-state characterization in-house, Veranova ensures smooth knowledge transfer and efficient progression from candidate selection to clinical formulation.
- Accelerated Development Timelines – With a streamlined approach that reduces the need for repeat studies, Veranova helps you move from lab-scale testing to GMP-ready formulations faster and more effectively.

To find out more visit **veranova.com** or email **info@veranova.com**

Abstract

Selecting the right formulation pathway is crucial to ensuring the success of a pharmaceutical compound from early-stage development through to clinical trials. Under our Pharmorphix brand, Veranova offers an Enabling Formulation service designed to maximize the probability of success by providing data-driven insights that inform formulation decisions from the earliest stages.

This white paper explores how Veranova's integrated approach—from pre-candidate selection to advanced development strategies—enables the identification of optimal drug formulations, enhances bioavailability, and accelerates timelines.

Contents

Early Candidate Selection: Laying the Groundwork for Success

The Enabling Formulation offering at Pharmorphix is designed to select a phase-appropriate formulation route with the highest probability of success, based on a deep understanding of a material's solid form and physicochemical properties, the desired outcome, and the target administration route.

Supplied materials can be characterized, screened for optimal solid forms, and suitable pre-clinical prototype formulations developed, while continuously comparing the performance of newly identified forms and formulations. Running these studies in-house and in parallel results in agile and effective formulation development suitable right up to GMP tox.

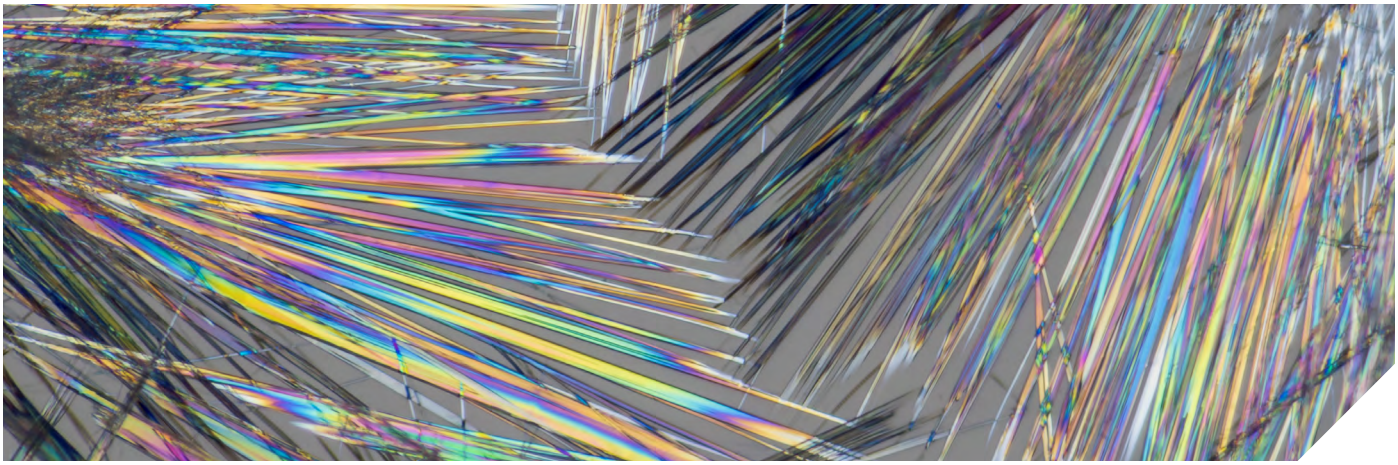
The Pre-Candidate Selection Package

To aid candidate selection and identify early potential formulation routes, Veranova's Pre-Candidate Selection package, is designed to either eliminate or accelerate candidates early on based on inherent molecular properties, and provide an informative data-led approach to select the most effective, compound-specific formulation strategies. With as little as 150 mg of material per compound, we expedite the selection of candidates and suitable formulation pathways, ensuring cost-effective screening while minimizing the risk of failure at later stages of development.

Using this streamlined approach for screening enables multiple candidates to be evaluated before they have been eliminated, while also avoiding unnecessary investment in candidates that may fail at later stages. An example of the types of analysis recommended for the Pre-Candidate Selection package is outlined below.

Pre-Candidate Selection Package			
Structure	**Analysis**	**Method**	**Material (≤ mg)**
Phase 1	Crystallinity Assessment	XRPD	5
	Particle Shape & Size	Microscopy	5
	Thermal Behavior	DSC, TGA, (+ mDSC to obtain Tg for amorphous materials)	5
	Initial Generic Purity Assessment	HPLC	5
	Stability Testing under accelerated conditions	Physical and Chemical stability by HPLC purity and XRPD	20
Phase 2	pKa Measurement to determine propensity for salt formation	Potentiometry/UV	5
	Lipophilicity	LogP by potentiometry/ Shake-Flask LogD	5
	Solubility Profiling in simulated fluids	HPLC	35
	Comparison of performance	Free Powder Dissolution/ Intrinsic Dissolution Rate	60
Total Material Consumption			**145**

Table 1: Pre-Candidate Selection example work package



The Pre-Candidate Selection package is a precursor to subsequent more in-depth studies for selected lead candidates. By understanding these properties, informed decisions can then be made on a suitable Enabling Formulation pathway. The flow diagram below showcases the essential compound properties, driving Veranova's decision process for early formulation development:

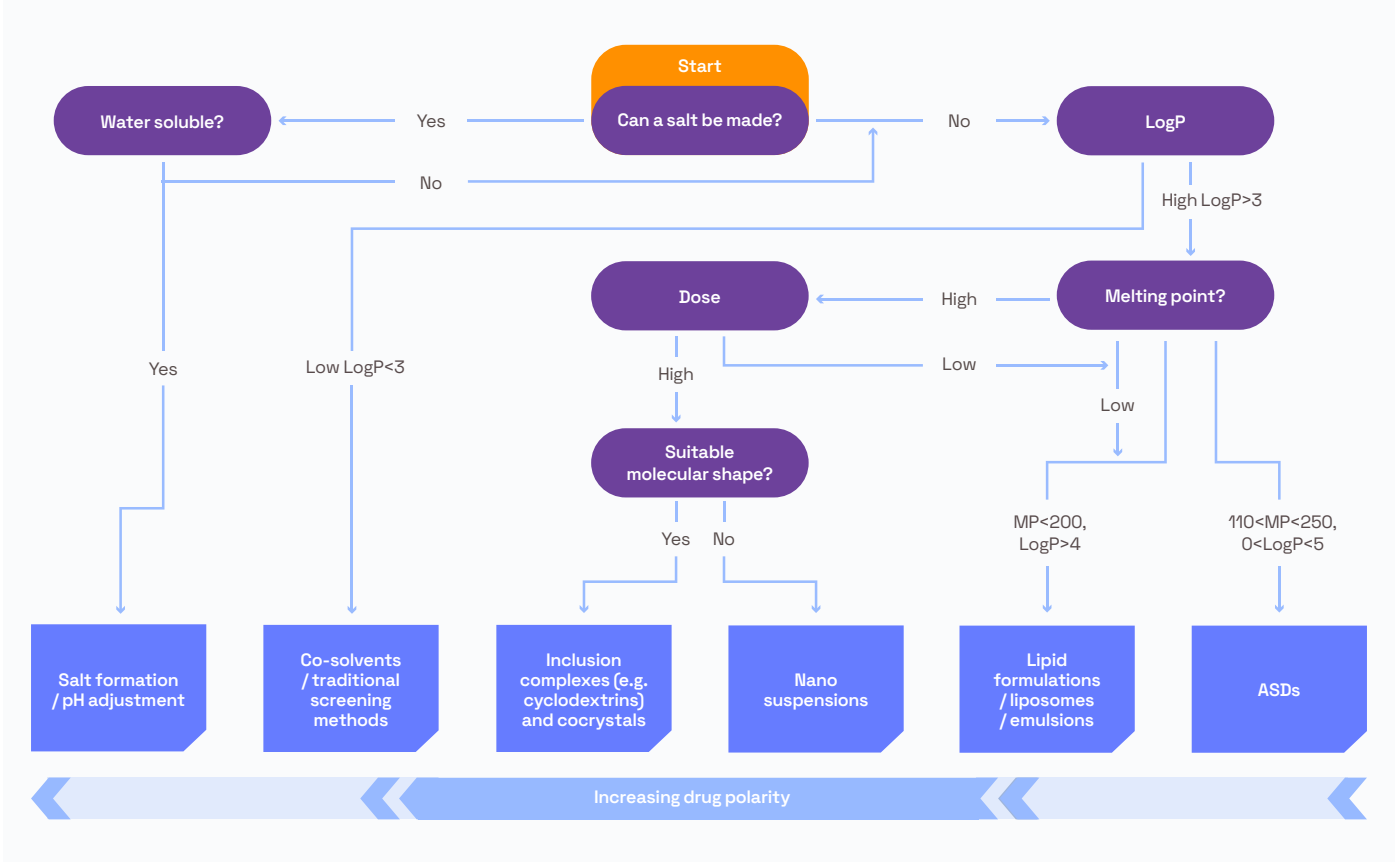


Figure 1: Guidance workflow for enabling formulation pathway at Veranova

If early data collected via the Pre-Candidate Selection package indicates the compound is non-polar and highly lipophilic, the propensity for amorphization can also be evaluated. This is achieved by conducting a focused solvent screen, followed by attempts to generate amorphous material via fast evaporation, coprecipitation and freeze drying.

Solid-State Characterization and Formulation Pathway Selection

Understanding a compound's ionization potential and solubility profile is essential for enhancing and selecting appropriate formulation strategies. If a compound is ionizable, salt formation may enhance bioavailability. Measuring pKa values in-house enables rapid assessment of this potential, while also determining whether co-crystal formation may be a viable alternative.

Salt formation and pH manipulation are typical methods for enhancing solubility. With the broader Pharmorphix screening offering available in-house, this is something that can be done at both a small and large scale, either sequentially or in parallel to exploring other formulation methods. The dissolution profile of salts and cocrystals of pyrimethanil illustrates the advantages of these approaches:

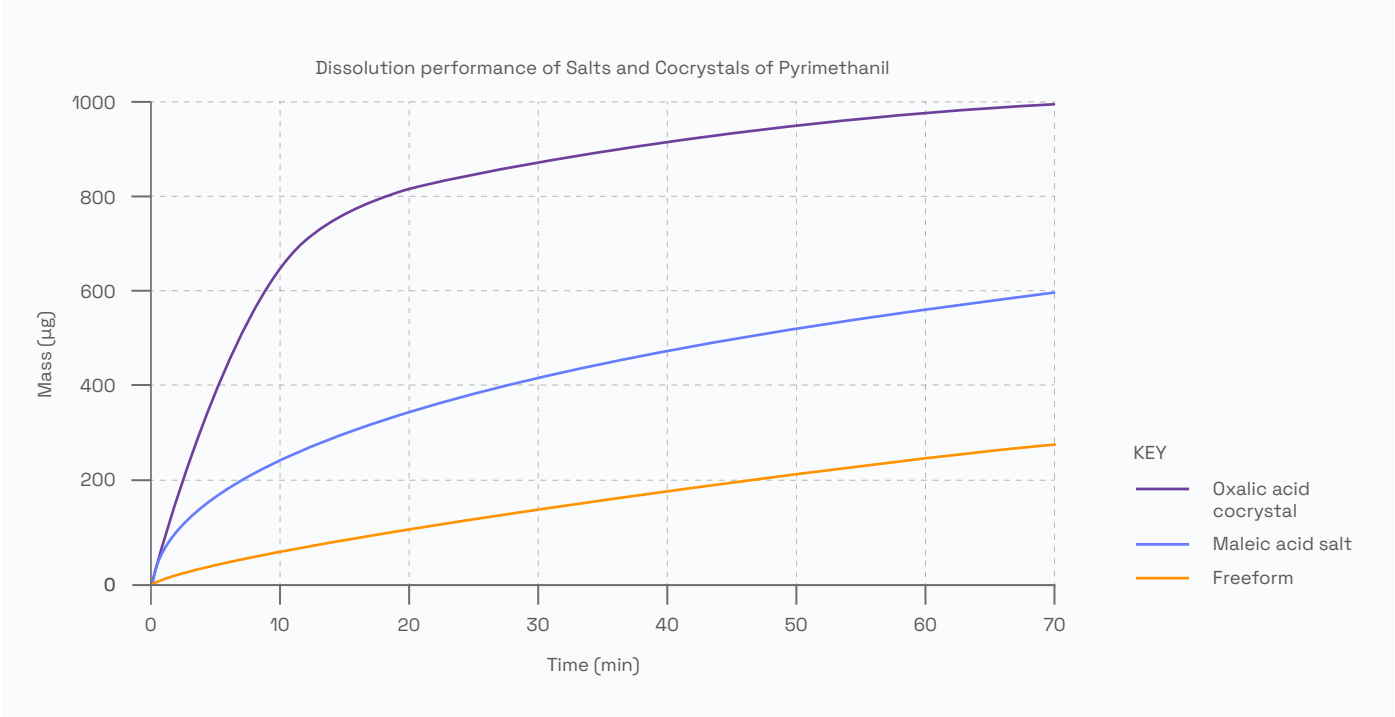


Figure 2: A comparison of the performance of salt and cocrystal forms of Pyrimethanil

Excipient Screening

If salt formation is not a feasible approach, alternative strategies for improving solubility can be considered, including excipient screening and compatibility assessment, as well as the incorporation of co-solvents.

The selection of excipients can be tailored based on the intended route of administration, dosage form, and target species, utilizing the in-house Veranova excipient database in conjunction with publicly available resources such as the FDA's Inactive Ingredient Guide (IIG) list[1].

Maintaining up-to-date internal resources with the latest information is essential for selecting an appropriate range of excipients with relevant properties for screening. Additionally, screening against established, well-characterized excipient lists provided by clients facilitates early-stage assessments for potential incompatibilities. A focused example of a preliminary screening is presented below for a compound with aqueous solubility < 0.1 mg/mL, intended for topical administration:

[1] Inactive Ingredients Database Download | FDA

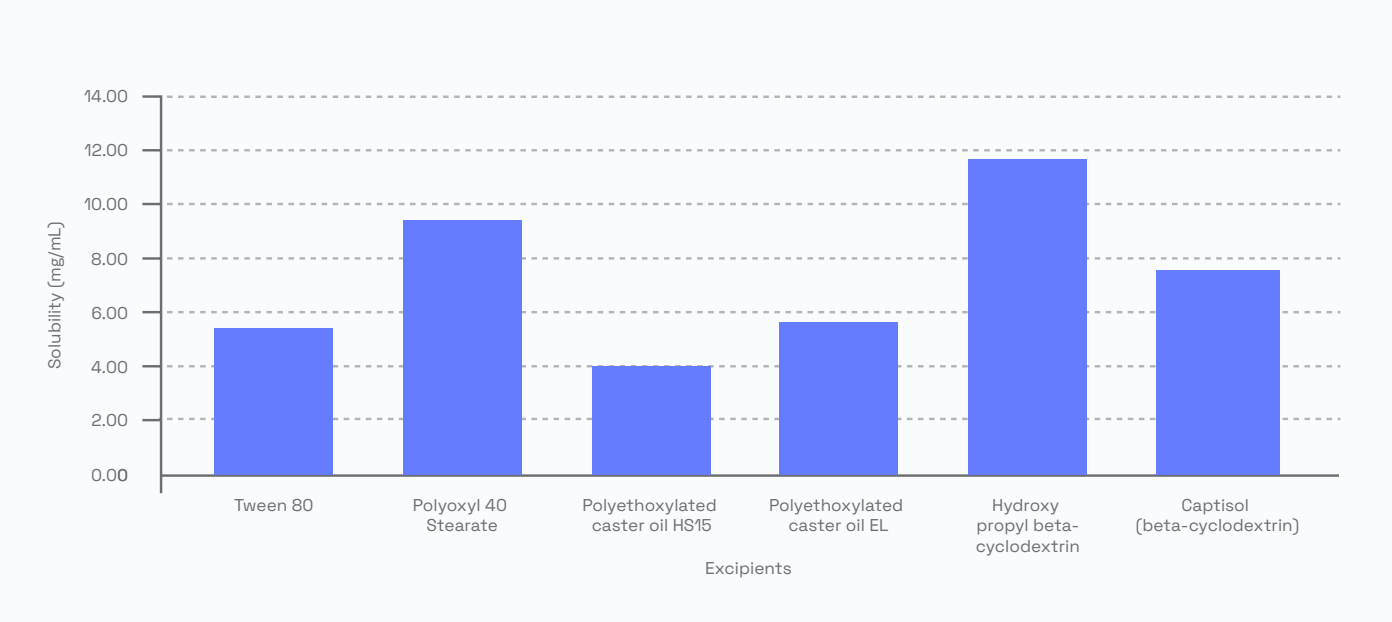
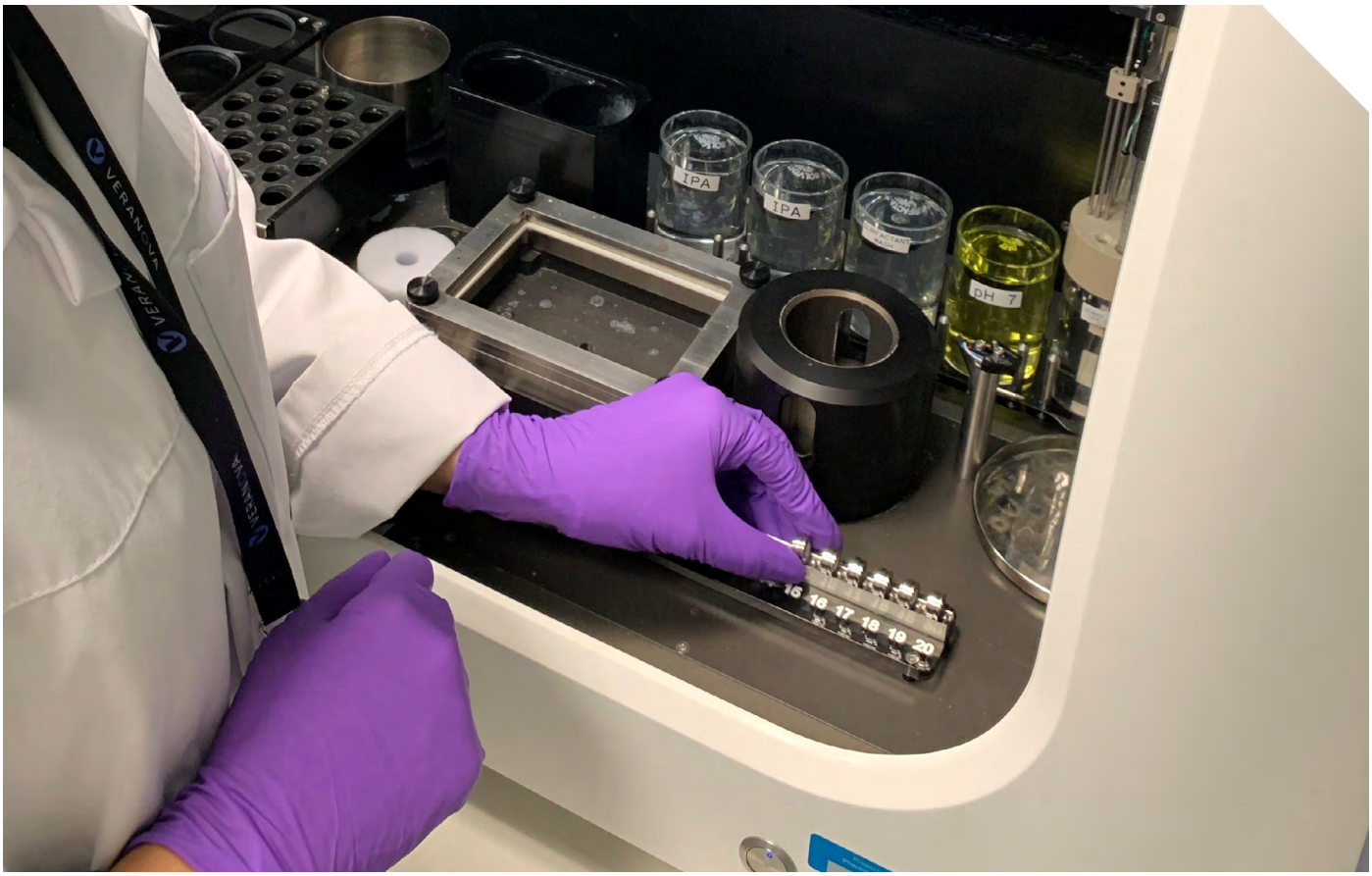


Figure 3: Focused excipient screen to improve aqueous solubility for an API intended for topical administration

While excipient screening and the use of co-solvents are invaluable in enhancing solubility and stability, certain compounds may require more advanced and complex strategies to ensure successful development and commercialization.

Advanced Formulation Strategies

Advanced formulation approaches, such as amorphous solid dispersions (ASDs), nanosuspensions, and lipid-based systems, are increasingly utilized in marketed pharmaceutical products. Early-stage evaluations are crucial, particularly for hydrophobic molecules, which often present formulation challenges when conventional approaches prove inadequate[2].



[2] Amorphous Solid Dispersions (ASDs): The Influence of Material Properties, Manufacturing Processes and Analytical Technologies in Drug Product Development - PubMed

Milling and Micronization

Milling and micronization provide several advantages, including enhanced uniformity and consistency of particle size distribution, improved flowability and compressibility characteristics during manufacturing, and increased surface area, which positively influences dissolution rate and bioavailability. The application of 'top-down' techniques for particle size reduction can be further extended into the sub-micron range through nano milling. This advanced process enables the production of nanosuspensions, which are increasingly being adopted in the pharmaceutical industry due to their significant impact on drug performance.

By reducing particle size to the nanometer scale, nano milling enhances solubility, dissolution rate, and bioavailability, ultimately improving therapeutic efficacy. The benefits of this approach can be observed in the comparative analysis of micronized versus nano-milled Piroxicam, as demonstrated below:

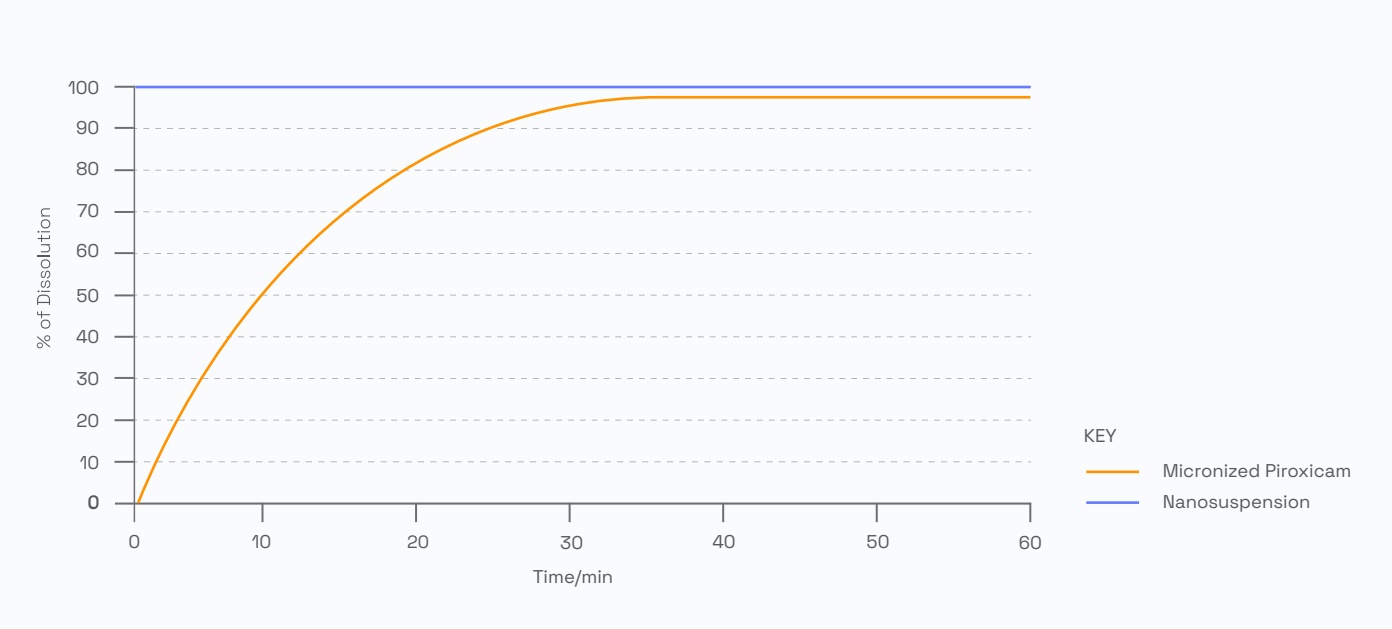


Figure 4: Dissolution performance of micronized vs nano-milled Piroxicam

Nanomilling

Nanomilling, like conventional milling, offers the advantage of requiring minimal excipients to enhance performance. Only small quantities of polymers and surfactants are needed to prevent particle agglomeration, which is particularly beneficial in applications where excipient load must be minimized. This is especially relevant for conditions such as ulcerative colitis, where certain excipients can trigger inflammation, making simplified formulations preferable. By reducing the need for additional components, nanomilling facilitates the development of more biocompatible and well-tolerated drug formulations. A standard framework for conducting a nanosuspension study is outlined below.

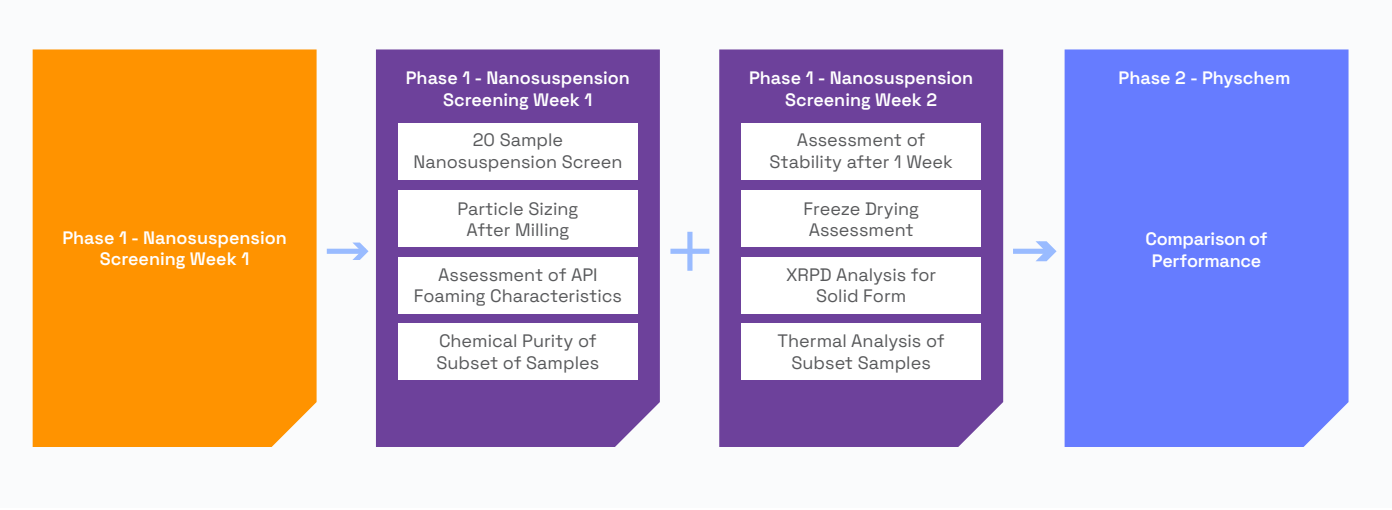


Figure 5: Flow diagram for a Veranova nanosuspension screen and preparation

Amorphous Solid Dispersions

In the last 25 years, another key technology to enhance bioavailability is amorphous solid dispersions (ASDs). Drugs formulated as ASD accounted for approximately 30% of the marketed products that require solubility enhancement between 2000 to 2020 and are still growing in popularity[3]. As depicted below, the main aim of ASD formulation is to disperse the API throughout a polymer matrix to produce a stable amorphous state with improved solubility.

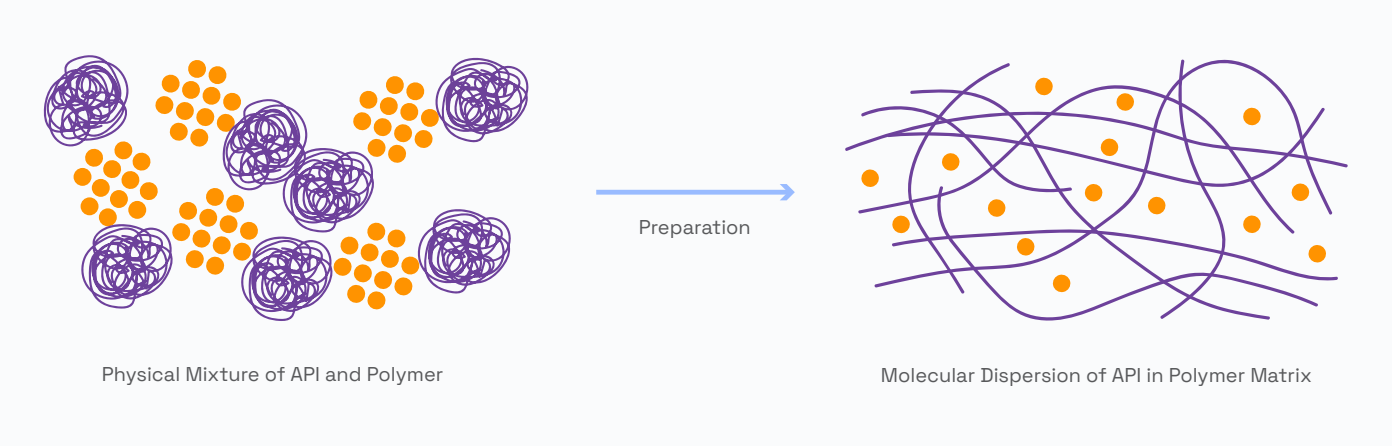


Figure 6: Representation of a physical mixture vs molecular dispersion

[3] Amorphous Solid Dispersions (ASDs): The Influence of Material Properties, Manufacturing Processes and Analytical Technologies in Drug Product Development - PubMed

Supersaturation studies are integral throughout the screening phase, as ASDs from the list of FDA approved polymers often induce a state of supersaturation. These studies can help to narrow down the number of polymers from a wide list of possibilities. The selection of a suitable ASD in drug development involves a comprehensive analysis of its physical and chemical properties.

Our in-depth solid-state characterization, specifically XRPD, DSC, FTIR, and Microscopy can provide insight into whether or not an amorphous dispersion has been formed with a studied polymer. Using our online high throughput dissolution platform, essential information is gathered to narrow down the number of possible ASD to evaluate.

Different approaches are screened to prepare amorphous dispersions on a small scale, including spray-drying and co-precipitation. Veranova can support ASD scale-up using these two techniques for pre-clinical and early clinical phases.

A broad overview of a typical ASD screen is shown below:

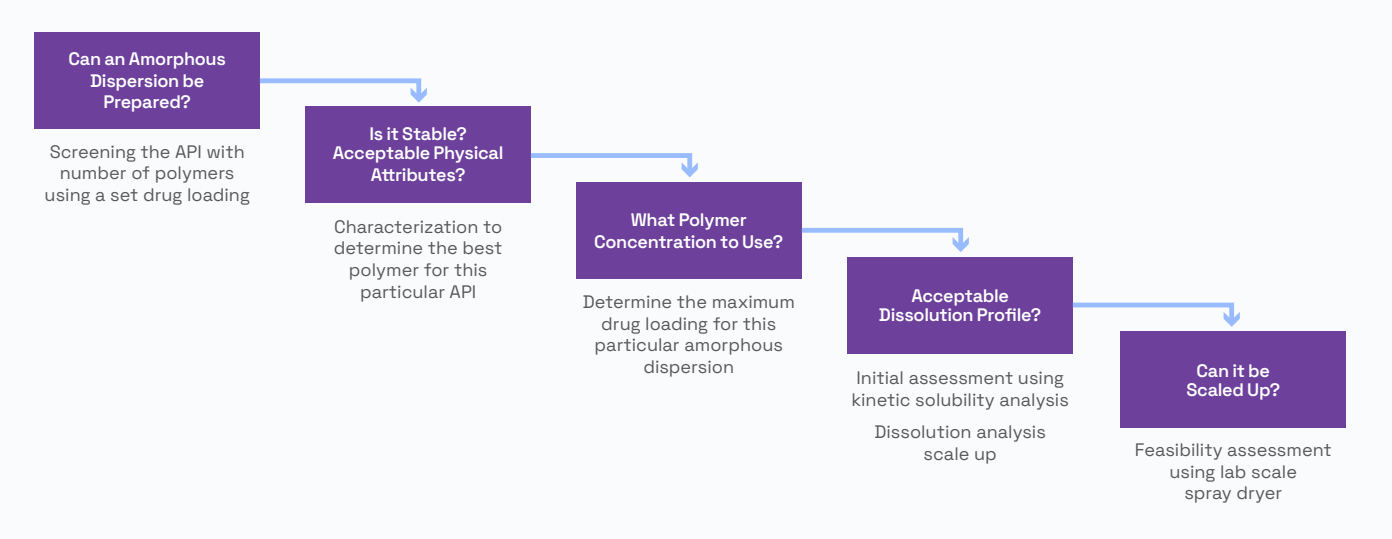


Figure 7: Outline of a typical Veranova ASD screen

Lipid-based formulations

Lipid-based formulations can solubilize hydrophobic drugs, improving their absorption from the gastrointestinal tract. This is achieved by increasing the drug's solubility in the gastrointestinal fluids and by facilitating drug transport across the intestinal mucosa.

Additionally, lipids can protect drugs from degradation in the gastrointestinal environment, such as enzymatic breakdown or chemical hydrolysis which can improve therapeutic efficacy.

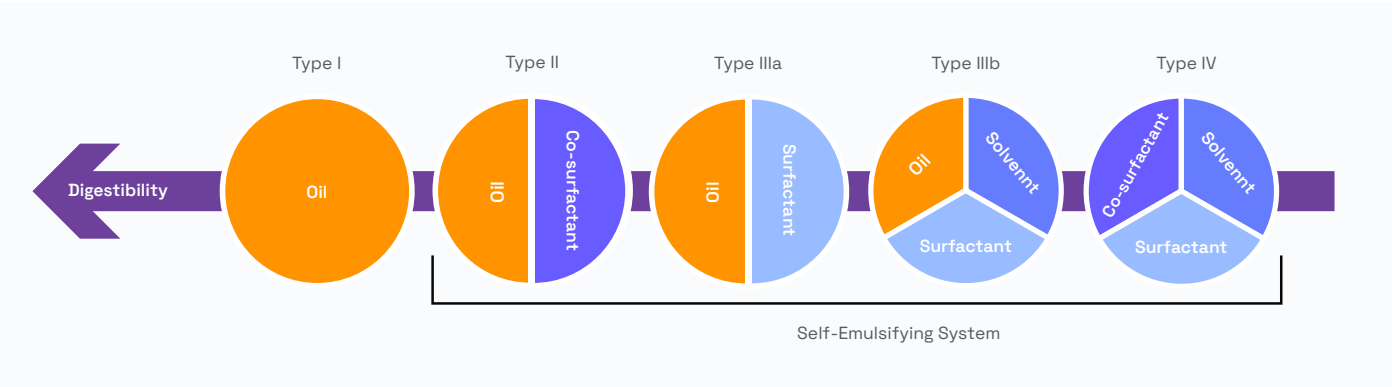


Figure 8: Type I to Type IV SEDDS

Pharmorphix has developed a high throughput screen to rapidly select suitable lipid-based formulations. This approach considers the physchem properties of the molecule, and the HLB (Hydrophillic Lipophillic balance), a critical parameter in lipid-based systems which can help to determine the compatibility and functionality of excipients in a formulation.

The best formulations with enhanced solubility and stability can then be prepared for pharmacokinetic studies.

Integrated Development Approach: From Solid Form to Final Formulation

As with any of these approaches, having the relevant tools and characterization techniques available is pivotal for comparing the performance and ultimately the success of any developed formulations. Using the combined expertise available, a compound can be synthesized, a lead candidate and optimal solid form selected via screening, and prototype formulations developed within the same facility.

Further, by keeping all formulation and solid-state characterization activities in-house, Veranova ensures seamless knowledge transfer across development phases. This continuity enables:

- Rapid adaptation of formulations in response to new solid forms
- Reduced need for repeat studies, saving time and cost
- Streamlined transition from lab-scale to GMP tox formulation

The added benefit of keeping supplier continuity also results in proactive and reactive adjustments throughout the development process. New forms may be identified and fed into existing formulation programs to evaluate compatibility and potentially save time, effort and cost by minimizing repeat studies. Once optimized, the synthesis of selected forms can then be optimized through crystallization development[4] to refine parameters for scale up on a lab scale up to 100 L scale, for proof of concept, before going into manufacturing on a large scale with a licensed vendor and perform a tech transfer.

[4] Harris, J. White paper: Crystallization process development. Veranova, 2023. https://veranova.com/wp-content/uploads/2022/11/Veranova-Crystallization-Process-Development-WP.pdf

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Conclusion

Veranova's Enabling Formulation services via our Pharmorphix brand provide a comprehensive, data-driven approach to drug formulation, from pre-candidate selection through to advanced formulation techniques. By leveraging expertise in solid-state characterization, excipient screening, and cutting-edge formulation strategies, Veranova helps pharmaceutical developers reduce risk, accelerate timelines, and maximize the probability of clinical success.

To learn more, visit

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