Symeres

Making Molecules Matter. Together.

SOLID STATE

Optimizing Solid-State Properties and Enhancing API Bioavailability through Physicochemical Prediction

Solid-State Chemistry – from Molecule to Medicine

EDWIN ARET

Solid-state chemistry research is a key part of the evaluation of whether a molecule is a "druggable" compound, by selecting the optimal form based on physicochemical and biopharmaceutical properties and manufacturability. To be suitable as a medicine, the candidate molecule should show sufficient solubility, dissolution, and bioavailability, as well as good stability – both chemical and physical (see Figure 1). These properties will lead to a developability program, to minimize the timelines and manage risks.

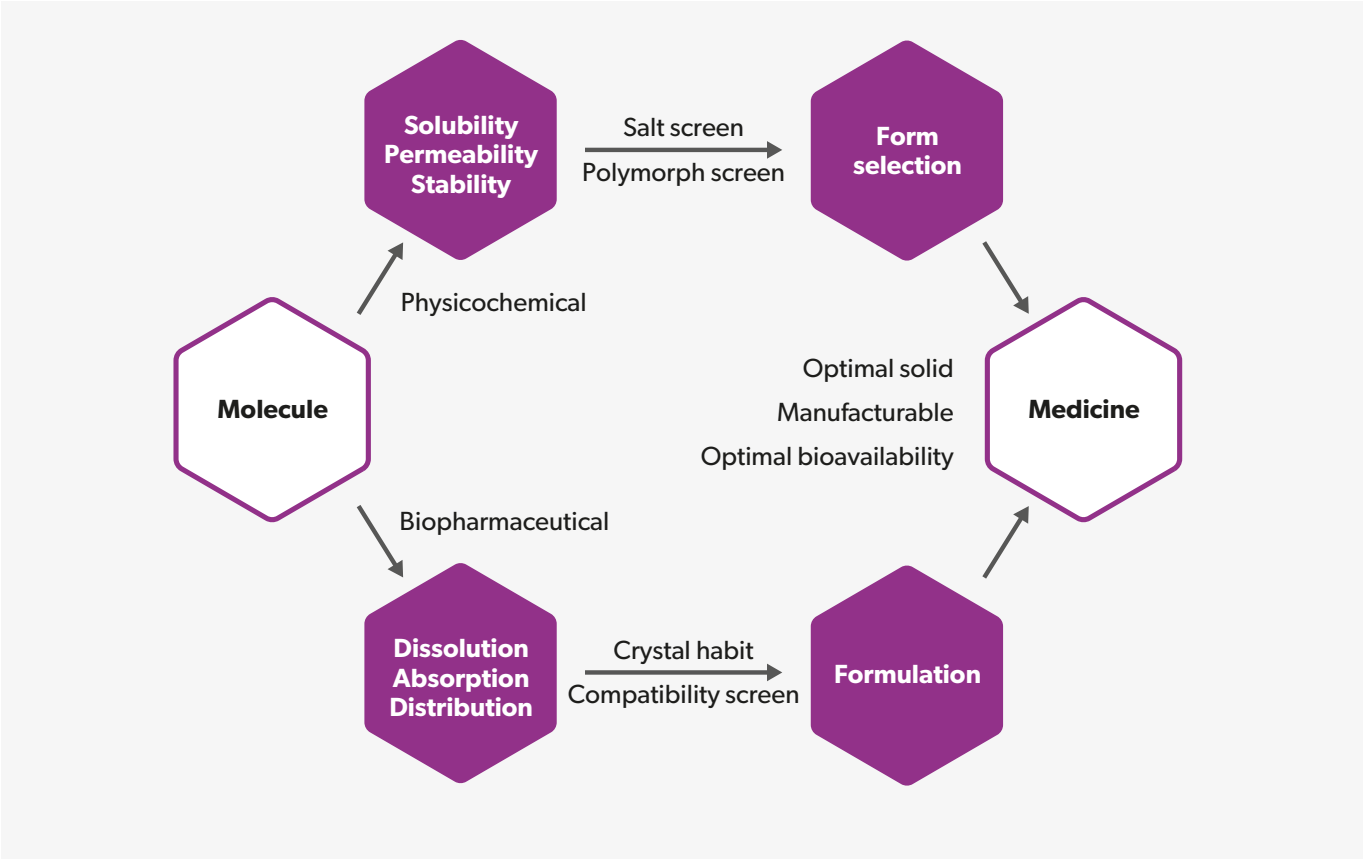

Figure 1. Solid-state chemistry: development route from molecule to medicine

The initial physicochemical and biopharmaceutical performance indicates what development plan is required to move the molecule forward towards a medicine. Reproducibility at scale, time, material costs, and environmental effects help visualize the formulation processability of the candidate molecule. The biopharmaceutics classification scheme (BCS) can be used as a developability risk assessment. The solubility, dissolution rate, and stability can be improved by solid-state and formulation research, to move towards BCS class I. In the case of insufficient permeability or poor first-pass behavior, another molecule or prodrug may be the more optimal choice in lead compound optimization.

Prediction

In drug development, physicochemical properties are the initial criteria to select the preferred form and successfully develop a molecule into a medicine. As well as metabolic liabilities, bioavailability issues can be due to limited solubility, poor dissolution rate, or low permeability, with each requiring a different approach. It would be beneficial to know these properties at the start of your development plan. Since in the preclinical phase one generally has only a small quantity of compound available, we recommend an in silico prediction as the first step of solid-state research. Calculations based on the molecular structure are therefore used to predict if the compound may have liabilities for oral administration, based on Lipinski's "Rule of Five," or if another route of administration may be required. This information, together with the calculated lipophilicity, pK_a, aqueous solubility, and passive absorption, is used to classify the compound according to the BCS, a prediction that provides a blueprint for the development strategy and maps out possible risks without using any material (Figure 2).

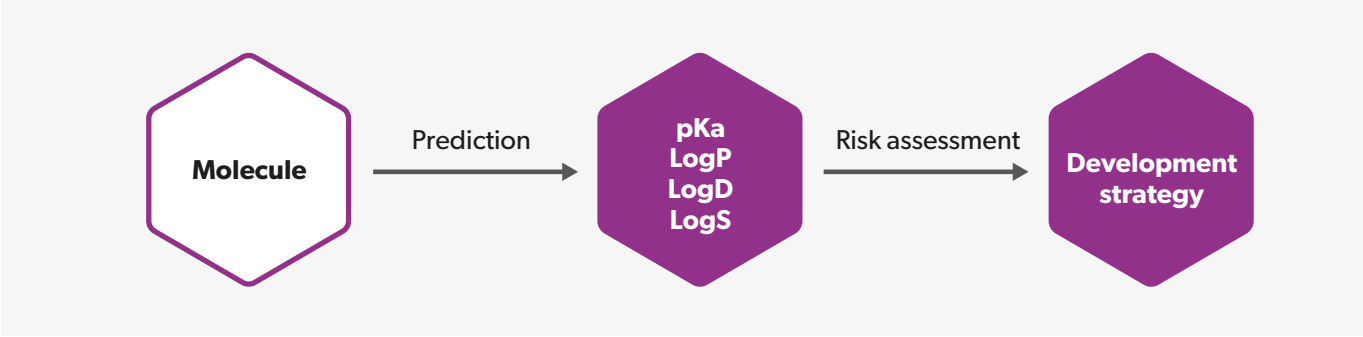

Figure 2. Prenomination phase: in silico prediction of properties of the molecule and developability program

Characterization

Once the molecule has been synthesized and isolated, complete physicochemical and morphological characterization should be performed on the obtained R&D batch. The predicted values are measured for confirmation and comparison. Using only a very limited amount of material, we can determine the properties and provide a detailed and tailored form-selection plan, as well as determine the parameters for screening and follow-up studies.

The main technique we use for the identification of the crystalline compound is XRPD (see Figure 3 for an example of XRPD results). Since time is of the essence, we use a Bruker AXS D8 Discover A25 diffractometer with four 96-well plate positions (see Figure 4) for high-throughput for fast measurements on all solids in a screening and high resolution for the characterization of each unique form.

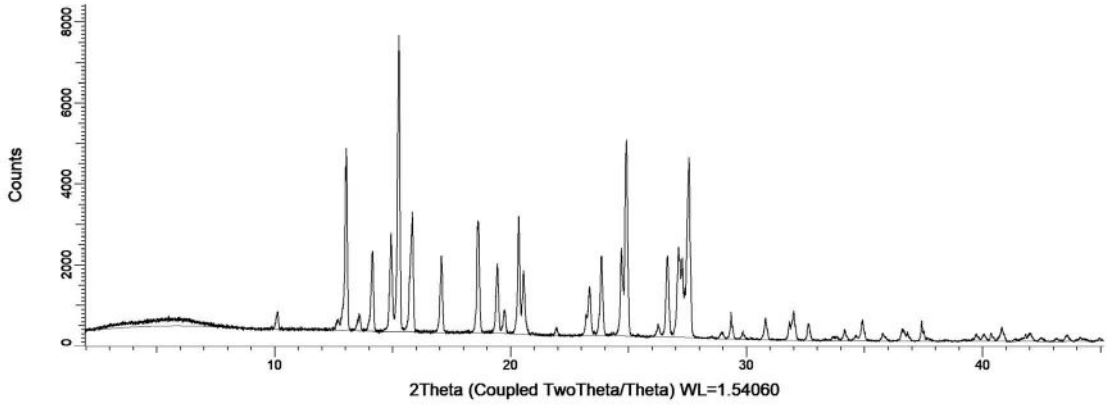

Figure 3. Screening-quality XRPD diffractogram of carbamazepine

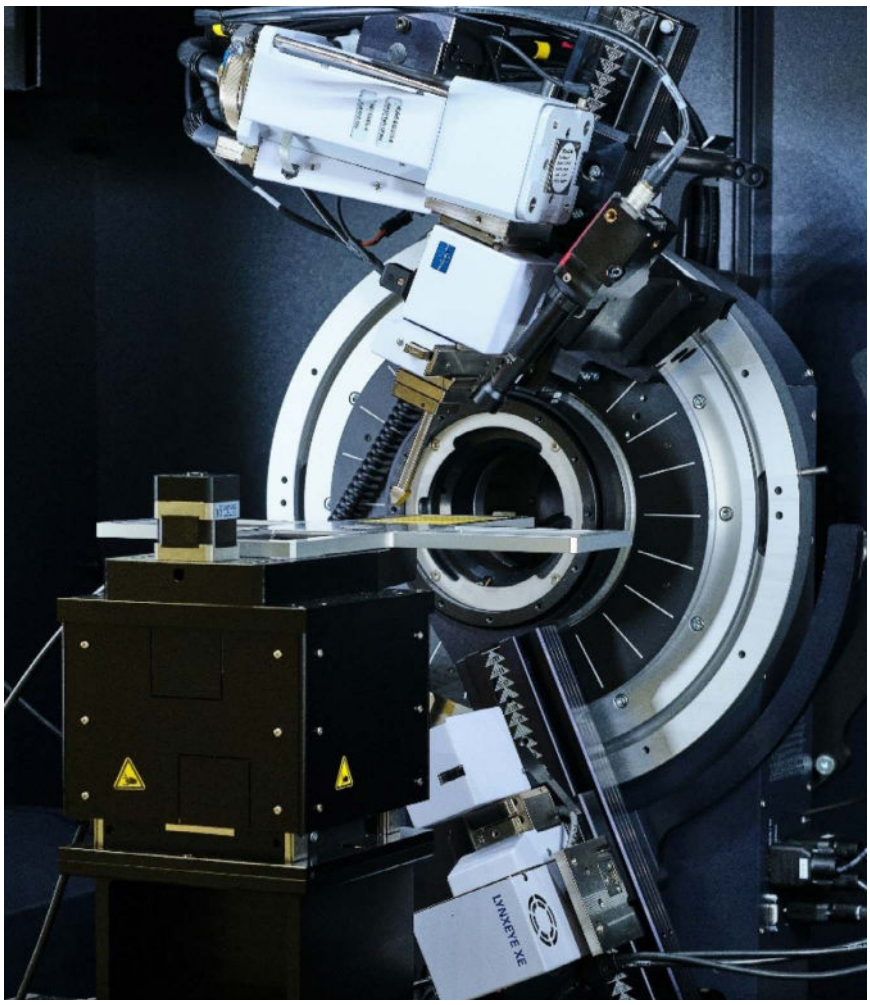

Figure 4. Photograph of a high-throughput XRPD instrument

Form-selection screen

The main reason for salt screening is to obtain improved aqueous solubility or purification. Oral solid, injectable, and inhaled dosage forms each have their own preferred counterions and restrictions. Thanks to our combination of high-throughput automation, crystallization, and formulation experts, solid-state research provides a broad overview of the accessible salts and can be conclusive about the pharmaceutically preferred candidates.

All compounds show polymorphic behavior. The number of polymorphs that can be identified depends on the mutual stability and diversity of the study. During form screening, being aware of the interconversion of the polymorphic forms can be important for developing a robust process, since, if the selected form is not the most stable polymorph, it will convert over time. A change of salt or polymorphic form at a later stage of development requires additional research and is consequently very costly and time-consuming.

Based on the development phase, there are different approaches to form-selection screening:

- Identify the thermodynamic landscape, resulting in the most stable form to move forward.
- Diversity, resulting in many solid forms for patent application.
- Robustness, confirmation of producibility, and stability of the selected form.

Our unique, automated crystallization and analytics platform replaces repetitive handling and allows complete control of the experimental conditions, using a minimum amount of material and time (see Figure 5). Principle component analysis (PCA) for solvent selection specific to crystallization, combined with prediction software, smart design of experiments, and multiple analyses on only milligrams of material, allows excellent opportunities to shorten the critical decision path. A cluster analysis of the morphological properties quickly provides an overview of the polymorphic landscape, the selection of the most suitable form, and the conditions under which to reproducibly manufacture this selected form.

Figure 5. Photographs of the high-throughput screening platform

A reproducible scale-up of the identified forms found in the screening is one of the most difficult challenges of crystallization. Our broad screens provide information on how to produce sufficient material for further characterization and to determine how the different polymorphs relate and possibly interconvert into each other. This allows a conclusive selection of the most suitable form, or the recommendation to continue with a cocrystal screening or stabilizing amorphous solid dispersion study.

Each development phase has its own selection criteria to move the compound forward in development. The optimization of scale-up conditions towards kilogram manufacturing often requires a design of experiments study or a seeding protocol to define the safe ranges of crystallization.

Phase	Properties	Technique
Well plate screening	Crystalline form	High-throughput XRPD, Raman
	Crystallinity	High-resolution XRPD, optical microscopy
	Composition	TGA, (u)HPLC, NMR
150 mg confirmation	Crystal structure	Single-crystal XRD, electron diffraction
	Thermal properties	DSC, TG-IR
	Hygroscopicity	DVS
1 g scale-up	Stability	Climate-chamber storage at different humidities and temperatures
	Solubility	(u)HPLC, in pH-range buffers, biorelevant fluids, formulations
	Permeability	PAMPA (Passive transport)
25 g demo run	Crystallization	FBRM reactor probes, PVM
	Crystal habit	PSD, (tapped) density, true density, surface roughness, porosity, flowability
	Filtration, drying	NIR, micronize

Table 1. Overview of stepwise form-selection studies

Suitable candidates are initially selected based on crystallinity, anhydrous nature, and sufficient aqueous solubility. Hygroscopicity and stability at different relative humidities determine the selection of preferred candidates and restrictions in handling or storage conditions. Particle engineering optimizes the size and shape of the crystals, for flowability and mixability of the solid. The selection of the thermodynamically most stable polymorph will finalize the form-selection study (see Figure 6).

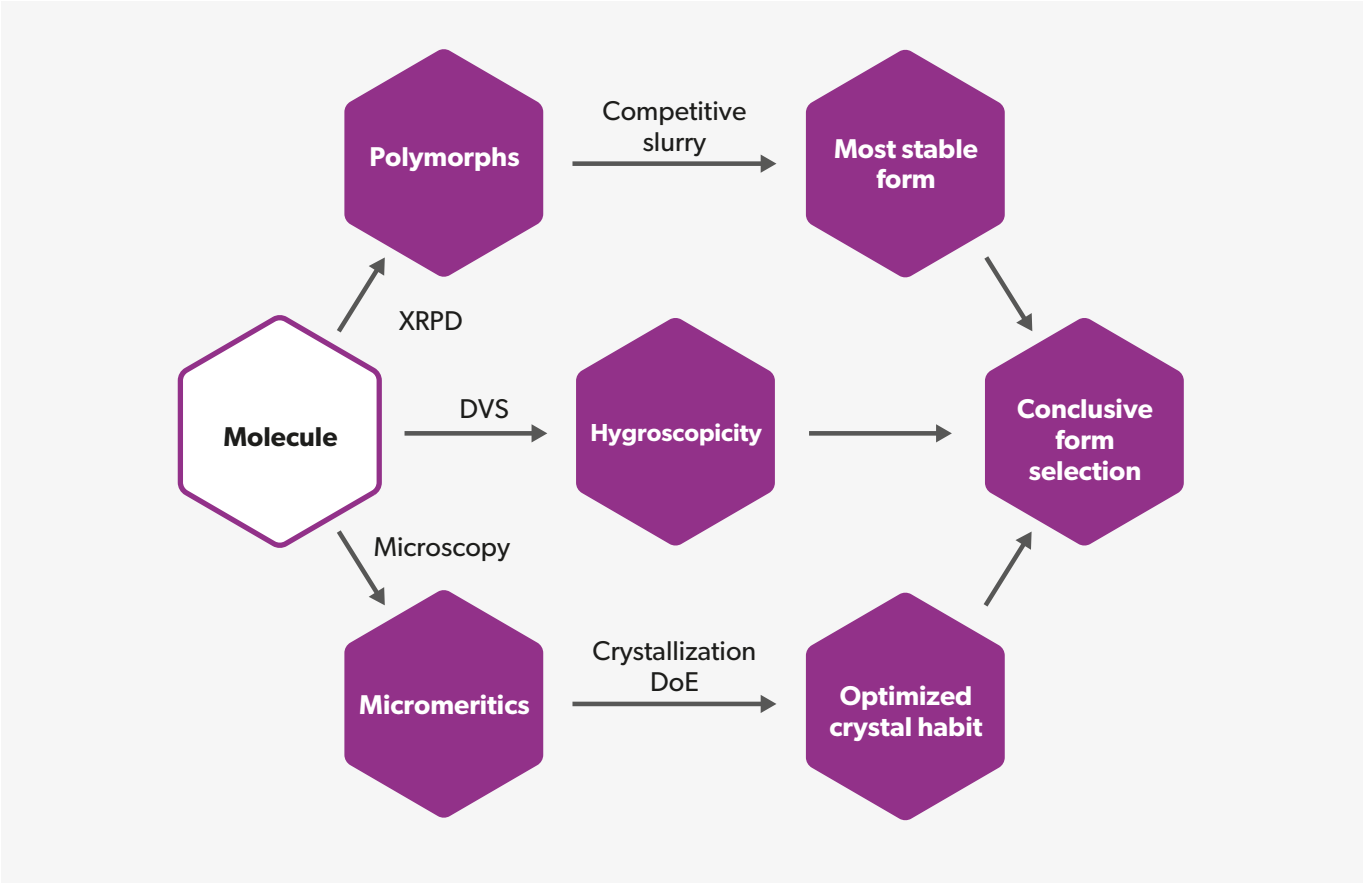

Figure 6. Form-selection diagram

Once the preferred polymorph and crystal habit have been selected, the study continues with excipient compatibility and dissolution-rate determination. The excipient properties can further improve the functional performance of your selected form, specifically for the intended dosage form. Accelerated stress conditions will show stability as a solid and in solution and provide data required for further formulation. The (intrinsic) dissolution rate in buffer solutions and simulated fluids provides additional confirmation that this molecule is a "druggable" compound.

For further inquiries or collaboration opportunities,
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