Solid-State Chemistry

Crystallographic, Solid-State Chemistry
and Pre-formulation Study
in Pharmaceutical Development

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Overview of crystal engineering in pharmaceutical development

Crystal engineering is a fast-growing discipline, developing technologies to control the structure and functional properties of solids [1]. In the pharmaceutical industry, crystal engineering technology covers crystallography, solid-state chemistry, structure prediction, crystallization process, particle engineering, etc. [2]

1. Crystallographic study

The properties of materials is highly related to their molecular arrangement. Different crystal forms will affect critical properties, such as solubility, stability, bioavailability, subsequent formulations, particle engineering, and production processes. Therefore, crystallographic study is a vital part of drug development [3-5].

2. Solid-state chemistry study and application

The purpose of solid-state chemistry research is to study the essential characteristics of active pharmaceutical ingredients (APIs) in the early screening process, including solubility, hygroscopicity, melting point, and chemical/physical stability. These properties are significant because they affect processing, therapeutic efficacy, toxicity, and bioavailability. Solid-state chemistry has significant influence on drug delivery characteristic as summarized in TABLE 1 [6-8]:

TABLE 1 Relationship between drug and solid-state chemistry properties

Solid-state properties	**Effect on drug substance and/or drug product**
Structural	
Crystallinity (existence of amorphous and semi-crystalline forms)	Physical and chemical stability
Polymorphs	% RH profile (hygroscopicity), dissolution rate
Solvates (hydrates)	Solubility profile and dissolution rate
Salts	All aspects of processing
Dimensional	
Particle size distribution	Processing behavior: bulk density, agglomeration,

	flow, compaction
Particle morphology	Particle permeability (i.e. particle adsorption)
Particle surface structure	Bioavailability (drug absorption)
	Consistency and uniformity of the dosage form
Chemical	
Organic and inorganic impurities, residual solvent and decomposition products	Toxicity
Chiral forms and chiral separation	Chemical, physical and enantiomeric stability
Mechanical	
Brittle/ductile transitions, fracture stress, indentation hardness, stress/strain relaxation	Milling and tableting behavior
Electrical	
Electrostatic charge distribution	Agglomeration and flow properties

Although the crystalline form is generally preferred because of enhanced stability provided by its more thermodynamically stable form, it is sometimes advantageous to develop an amorphous form in the pharmaceutical industry. Moreover, salt formation, co-crystal, and co-amorphous are also standard delivery options [9]:

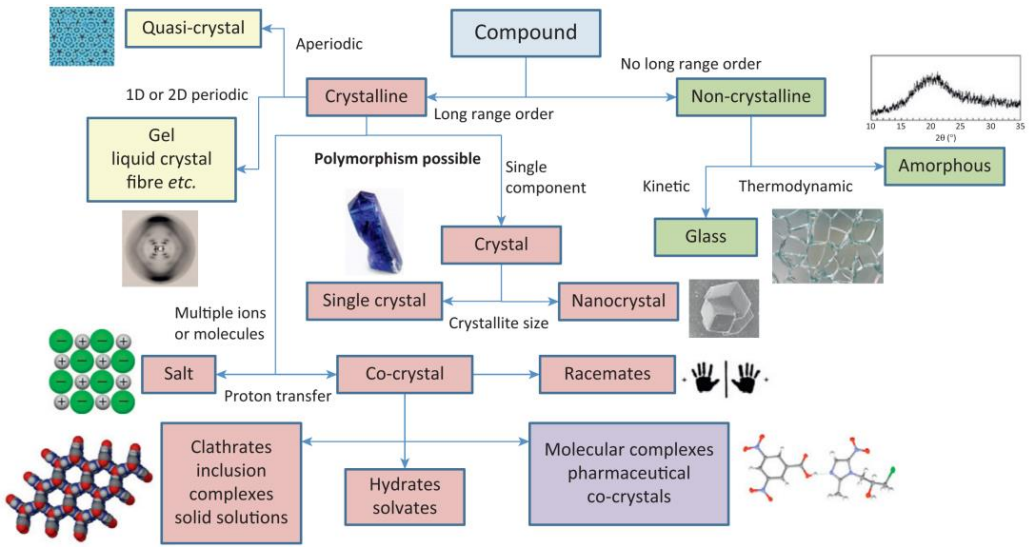


FIGURE 1 Solid-state forms of molecule [9]

Solid form development aims to find and select the solid with the optimal characteristics for the intended use to reduce clinical development risk.

3. Pre-formulation study

Pre-formulation is defined as a stage of development during which the drug substance's physicochemical properties are characterized and established [10-12]. The characterization involves screening for various crystal forms, characterizing their properties, and establishing thermodynamic stability of various solid forms, leading to the selection of an optimal form for formulation development, quality control, and finished product manufacturing. Various solid properties to be evaluated during the pre-formulation study are listed below [13, 14].

TABLE 2 Properties evaluated during the pre-formulation study

Property	Assay Techniques
Solubility: Aqueous and Nonaqueous	HPLC
pKa	UV or potentiometric titration
logP	UV/HPLC
Hygroscopicity	DVS
Stability: Hydrolysis, Photolysis and Oxidation	HPLC and storage conditions chamber
Melting point, Enthalpy of fusion	DSC
Physical forms (polymorphs, or amorphous)	DSC, XPRD, microscopy
Particle size, distribution, morphology, habit	Microscopy, PSD, BET surface study
Density: Bulk, tapped and true	Tapped densitometer
Flow property	Angle of repose
Compressibility	Carr's Index and Hausner's ratio
Excipient compatibility	DSC, FTIR, HPLC
Solution Stability	XRPD, HPLC, NMR
Crystallinity	DVS, DSC, XPRD

In addition, pre-formulation work is to study properties of a compound under extreme conditions where new crystal forms may appear, further reducing the risk of drug development.

4. Applications of solid-state studies in the pharmaceutical industry

4.1 Crystallographic study

- Single crystal growth and molecular structure analysis.
- Research on physical and chemical properties of crystals.
- Prediction of polymorph forms, etc.

4.2 Solid-state chemistry research

- Polymorph screening and study, including hydrates and solvent compounds.
- Salt, co-crystal screening and study.
- Amorphous and co-amorphous screening and study, etc.

4.3 Pre-formulation study

The significant areas of pre-formulation research are as follows:

- Bulk characterization crystallinity and polymorphism. Hygroscopicity, particle size, bulk density, powder flow properties, etc.
- Solubility analysis. Ionization constant-pKa, pH solubility profile, thermal effects, solubilization, partition coefficient, dissolution, etc.
- Stability analysis. Solution stability, pH rate profile, solid-state stability, bulk stability, compatibility, etc.

Challenges in solid-state chemistry study

The study of solid-state chemistry has an impact on virtually all phases of pharmaceutical development. It is estimated that more than 60% of new drug molecules display poor aqueous solubility due to increased size and lipophilicity [15], demanding extensive solid state study by exploring new solid-state forms to modulate properties without changing the pharmacological nature in limited time. Identification of a right form that has optimum performance can sometimes play a vital role in the success of a drug development program. Solid state study can be very challenging due to the complexity of solid forms (crystal, amorphous, salt, co-crystal, co-amorphous), unpredictability of forms existed for a particular molecule, and stability of forms.

- Cultivating high-quality single crystals of suitable size for analysis can be very challenging in some cases. Crystallization experiments usually take several weeks or longer, but the obtained crystals may not meet the requirements for satisfactory structure analysis. Tedious and repeated trials might be dragging on for quite some time without a guarantee of successful crystal growth [5].

- Discovering all possible forms, especially the stable forms suitable for development can be challenging. Polymorphism is prevalent in APIs, especially for small organic molecules. It is not uncommon to encounter a new form during development that is more stable than the form being developed. Crystal form is easily affected by one or more variables: solvent, temperature, impurities, operating parameters, solvent residues, etc. In the solid-state chemistry research stage, identifying as many potential polymorphic compounds as possible can improve development efficiency and provide wider patent space, although the work is complex and challenging [16].

- Achieving a balance between time, risk, and cost is the key for solid-state chemistry research. Because of high cost for drug development and limited patent protection time,

pharmaceutical companies are eager to shorten drug development time. In the solid-state chemistry research phase, our mission is to do detailed and precise research to reduce the risk, save time, and control cost of commercial manufacturing process.

What makes PharmaBlock unique?

The crystallization team at PharmaBlock has multidisciplinary backgrounds such as industrial crystallization, crystallography, pharmaceutical engineering, synthetic chemistry, chemical engineering, etc. The core members have rich experience in the pharmaceutical industry and have successfully delivered over 300 projects to top international pharmaceutical companies. PharmaBlock can provide customized crystallography, solid-state chemistry research, and pre-formulation services:

- **Single crystal culture and structure analysis**

In the solid-state chemistry research phase, our mission is to do detailed and precise research to reduce risk, save time, and control cost of commercial manufacturing process, such as spatial lattice, molecular conformation, absolute configuration, and bonding mode in the crystal structure.

The difficulty in determining molecular structure of a key impurity caused project delay in the case below. After multiple synthetic steps with expensive raw materials, the impurity was obtained but its quality was not good enough for growing single crystal samples with conventional methods. By using sublimation crystallization and controlling the vapor deposition rate instead of conventional crystallization methods, we obtained high-quality single-crystal samples and identified structure of the impurity.

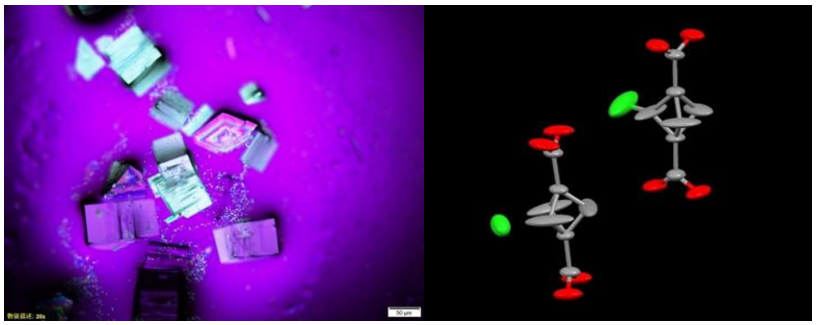
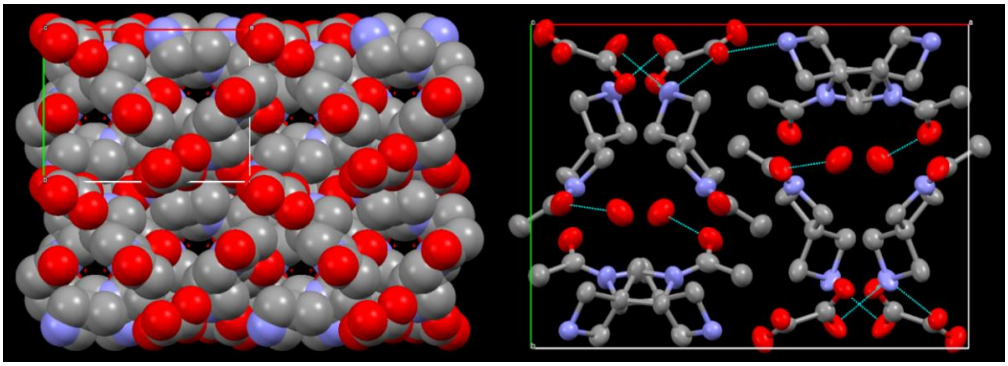


FIGURE 2 Single crystal cultured and molecule structure

- **Crystallographic study and quality standard establishment**

The compound in the following case absorbs water quickly when exposed to air, and the ratio of water/compound is variable, making it difficult to determine the water state in the crystal and establish product delivery quality standard. Various special procedures such as water vapor diffusion, water/organic solvent liquid diffusion were used to prepare the hydrate single crystals successfully. Crystallographic studies have shown that water molecules are filled in one-dimensional channels. The crystalline solid can quickly adsorb water molecules due to hydrogen bonding between water molecules and the compound in the form of channel hydrates. Unlike conventional channel hydrates, this compound forms nonstoichiometric channel solvates, where the solvent molecules occupy channels formed within the solute

lattice and can freely diffuse out when the relative water vapor pressure was reduced, resulting in an unfixed stoichiometry of the water.



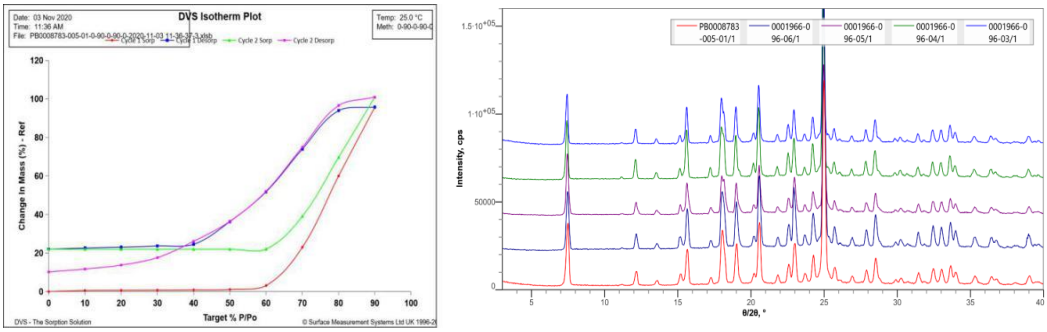


FIGURE 3 Molecule structure and DVS, XPD study

➢ **One-stop research from crystallography, solid-state chemistry to IND filing**

PharmaBlock has a large number of building blocks and provides complete CDMO services so that pharmaceutical crystal engineering research can be carried out at different stages, providing customers with tailor-made services to achieve a deep understanding of critical quality attributes and reducing project risks. For example, in the following case, we provide customers with one-stop solutions, including crystallographic research, solid-state chemistry, pre-formulation R&D and CMC regulatory filing support.

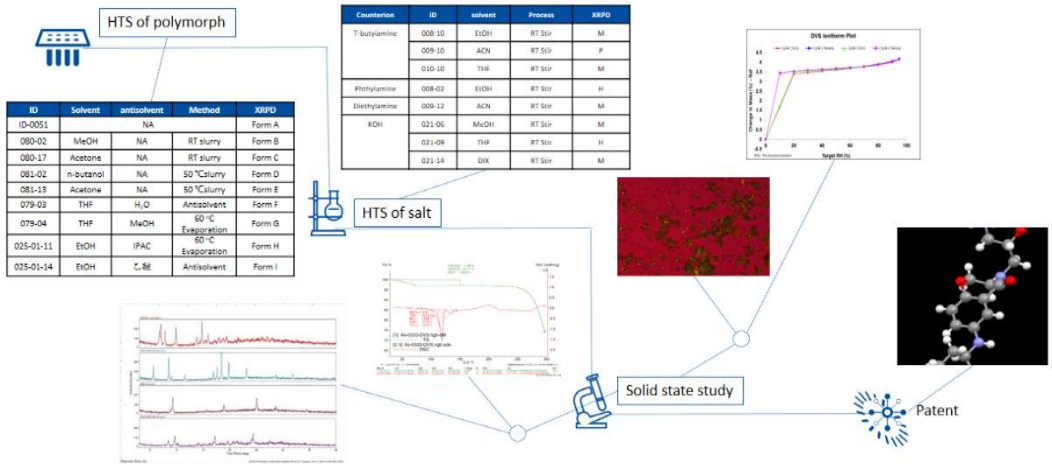


FIGURE 4 one-stop study solution service at early stage study

In addition to rich experience in crystallographic, solid-state chemistry, and pre-formulation research, PharmaBlock is also equipped with state-of-the-art and fully functional instruments and equipment, enabling us to deal with the challenges of solid type selection and improve the efficiency of early-stage research and development. The major instruments and equipment involved are listed in the appendix.

A glimpse into the future

Improving the efficiency and accuracy of solid-state chemistry and crystallography research will significantly shorten the drug development cycle and reduce costs. After years of research and development, crystallographic theory can predict the relationship between a compound's structure and its physical and chemical properties in a reasonable and orderly manner.

PharmaBlock is looking forward to improving its ability to predict multiple crystal forms by applying molecular and process simulation computing technology. Our team is using PAT technology combining with thermodynamics, optics, and other cutting-edge technologies to enhance our development capabilities.

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Appendix

Major instruments and equipment in pharmaceutical crystal engineering department:

Equipment	Detail
Solid state chemistry	
X-ray powder diffractometer (XRPD)	Rigaku (Minflex 600), Rigaku (Smartlab SE)
Single crystal X-ray diffractometer (SXPD)	Rigaku (XtaLAB mini™ II)
DSC	TA (DSC2500)
TGA	TA (TGA550)
Dynamic vapor adsorption meter	SMS (DVS Adventure)
Particle size distribution	Malvern (Mastersize 2000)
Particle morphology	Particle permeability (i.e. particle adsorption)
Polarized light microscope	Olympus (BX53M)
On-line hot stage	Instec (TP102G)
General analytical	HPLC, GC, KF, etc.
PAT instrument	
FBRM	Mettlor (ParticleTrack G400)
On-line Raman	Mettlor (ReactRaman)
High throughput screening tools	
Single crystal culture	Liquid-liquid, gas-liquid diffusion; high-throughput incubation device; hydrothermal, sublimation, deep-cooling equipment, etc.
HTS polymorph and salt tool	36 wells, 48 wells with temperature controller
General analytical	LC, GC, MS, NMR, KF, PH automatic titrator, viscometer, density meter, etc.
Pre-formulation research	
Milling	Jet milling, ball milling, high-pressure homogenizer, wet milling.
Spray dryer	Yamato, ADL311 (1.3L/h); QFN-8000N ,1.5/L.
Other instruments	Freeze-drying, IDR, stability box, Laboratory presser, airtight glove box, precision temperature controller, etc.

About Author

Dr. Yufeng Wei

Senior Director
10+ years' experience in solid-state chemistry and crystallization technology
Served at Novartis (China), National Industrial Crystallization Engineering Technology Center and Proton

Contact Us

PharmaBlock Sciences (Nanjing), Inc.
Tel: +86-400 025 5188
Email: sales@pharmablock.com

PharmaBlock (USA), Inc.
Tel (PA): 1-877 878 5226
Tel (CA): 1-267 649 7271
Email: salesusa@pharmablock.com

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