PharmaBlock

Technical Research Whitepaper

Crystallization Process R&D in Pharmaceutical Development

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Crystallization plays an essential role in the pharmaceutical industry. It is widely used in purification of intermediates and APIs, and is generally a critical operation unit in solid-state control of APIs. Control of crystallization process is to obtain tailored crystal form, size, and shape. Crystal form of API is crucial as it can impact downstream operations such as filtration, drying, and milling, as well as physical and chemical properties such as dissolution rate and solubility [1].

Since process R&D usually depends on experience or time-consuming screening experiments, deep mechanistic insight into the nature of crystallization is seldom adequate. Numerous factors influence crystallization process, and development of a robust process usually requires an in-depth study and control of the following parameters [2]:

- Crystallographic, physical and thermal properties of a crystal.
- Solubility and solubility map.
- Phase equilibrium and phase diagram study.
- Nucleation control.
- Crystal growth control.
- Polymorph study.
- Impurity study.
- Engineering study.

Pharmaceutical manufacturing process usually includes a series of crystallization processes to achieve the following targets:

- Improve the crystallinity and decrease crystal defects.
- Purify product.
- Improve yield.
- Control solid form, morphology, and particle size
- Improve process reliability and operability.

Challenges for crystallization process development:

A good crystallization process should be standardized, reproducible, and scalable. Control of purity, particle properties, and overall quality have to be achieved through crystallization development:

1. Development of scalable crystallization process.

A crystallization process that can be scaled-up is critical for pharmaceutical manufacturing. Crystallization is influenced by various factors. Batch-to-batch consistency throughout all phases of drug development is challenging and must be achieved to ensure quality, efficacy and safety of patients..

2. In-line, on-line process analytical technology development and application.

In 2019, FDA published its Quality Continuous Manufacturing Guidance, putting a higher demand for PAT implementation (process analytical technology) [3]. It is challenging to apply PAT to continuous manufacturing, taking over the empirical model by scientific model.

3. Crystallization mechanisms and predictive tools.

The discovery of polymorph, solvate, hydrate, and the stabilization of non-stable phases are still performed without strategies and profound knowledge. The prediction of the effects of impurities, additives, solvent, etc. is still inaccurate.

What makes PharmaBlock unique?

A multidisciplinary team has been built up over the years at PharmaBlock to develop robust and scalable crystallization processes for clients. With a unique combination of science, engineering, equipment and industrial perspective expertise, the experienced scientists from the team design, develop and manufacture with various types of innovative crystallization processes as show cased in the following:

1. Solution crystallization

Figure 1 One of the crystallizers in cleanroom

Typically, evaporation, cooling, and anti-solvents precipitation are classified into solution crystallization. Equipped with crystallizers ranging from milliliters to 6300 liters, PharmaBlock team can develop various types of solution crystallization process. Full-functional clean rooms have been built to ensure crystallization production under GMP.

In this case, the start material exists in the solution as Form A, and the target monohydrate is named Form C. It has been found that a di-hydrate Form B is unavoidable when obtaining the target Form C, and Form B can be transformed to Form C during the process. However, if the transform rate from B to C is too fast, it tends to become amorphous. Solution pH, ionic strength, water activity, and temperature are all influencing factors. A reliable crystallization

process with controlled polymorph, good crystallinity, purity, and yield has been successfully developed.

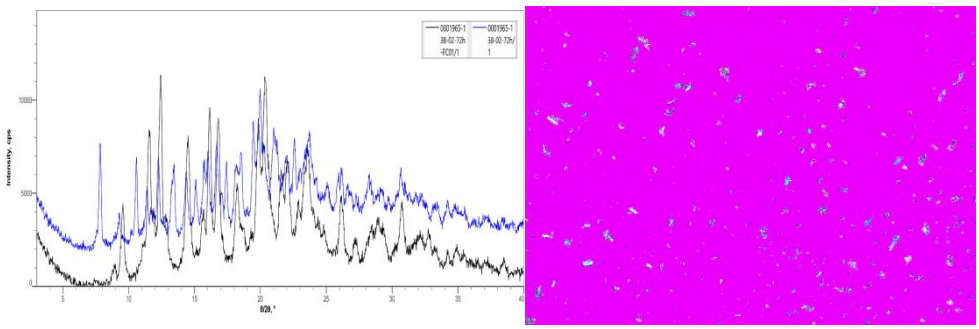

Figure 2 XRPD patterns of Form B and Form C, PLM of the final product

2. Sublimation crystallization

The crystallization of a solid substance induced from a supersaturated vapor is generally known as sublimation.

In this case, all attempts at crystallization from various solvents yielded oil. A sublimation crystallization process and crystallizer were employed to obtain crystal products with more than 99.9% purity and higher than 80% yield.

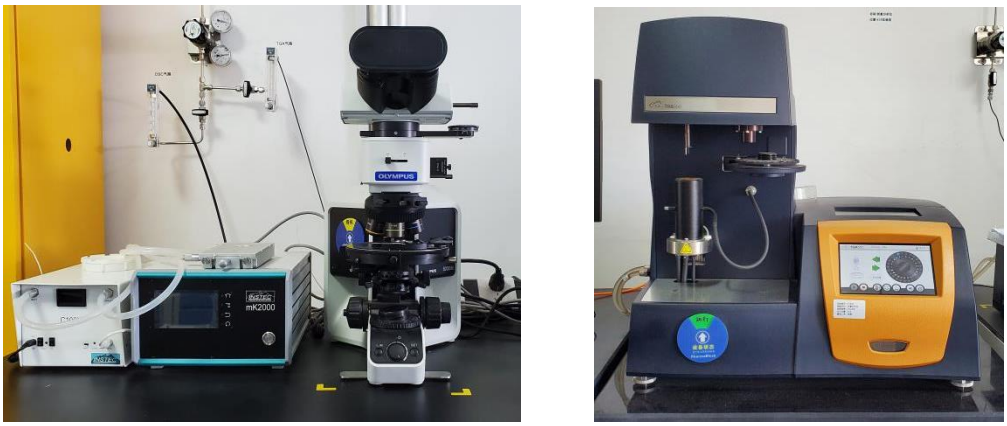

Figure 3 PLM with hot stage and DSC used for sublimation property study.

Figure 4 Sublimation crystallization experiment and manufacturing facility.

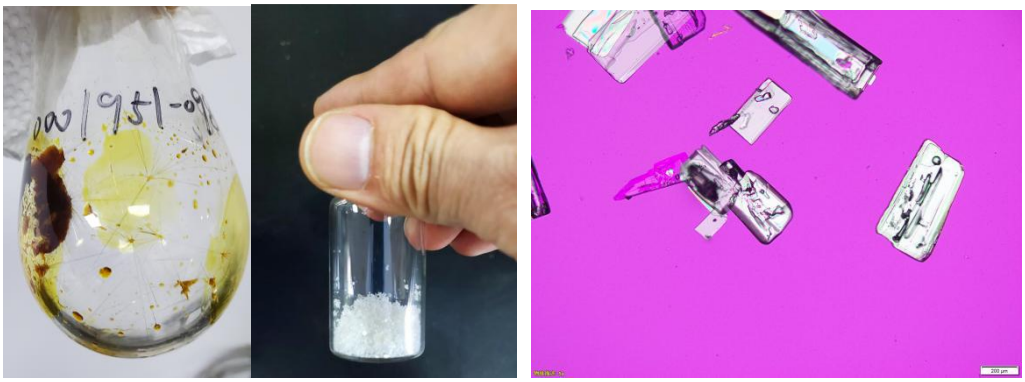

Figure 5 Sublimation crystallization product

3. Melting crystallization

In this case, the phase diagram demonstrates that product and impurity crystals can in principle be obtained over a range of temperatures and concentrations as indicated by the corresponding freezing point curve. Our team developed a melting crystallization with higher than 99.9% purity.

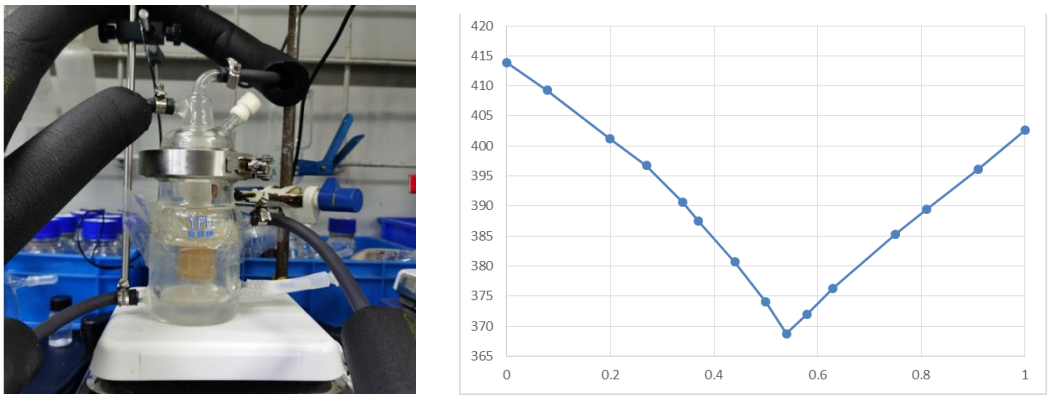

Figure 6 Melting crystallization experiment facility and phase diagrams.

4. Continuous Crystallization

For pharmaceutical applications, two main categories of applicable crystallizers are often used to achieve continuous manufacturing [4], multiple stages mixed suspension mixed product removal (MSMPR) and plug flow reactors. Both types of crystallizers have been built up in our lab. For example, a three-stage MSMPR crystallizer continuously produces drug crystals with very narrow size distributions.

Figure 7 A three-stage MSMPR crystallizer.

5. Continuous Crystallization for nanocrystals

Particle size reduction can enhance dissolution of poorly water-soluble drugs. Nanosuspension has successfully shown its impact on formulation design, patent life, and therapeutic efficacy [5, 6]. In this case, a plug flow crystallizer was built up to produce an API nanosuspension. By adjusting the solution concentration, solvent, pressure, and flow rate, the product particle size could be adjusted from nanometers to micrometers. The product can remain dispersible in aqueous solutions for long periods of time.

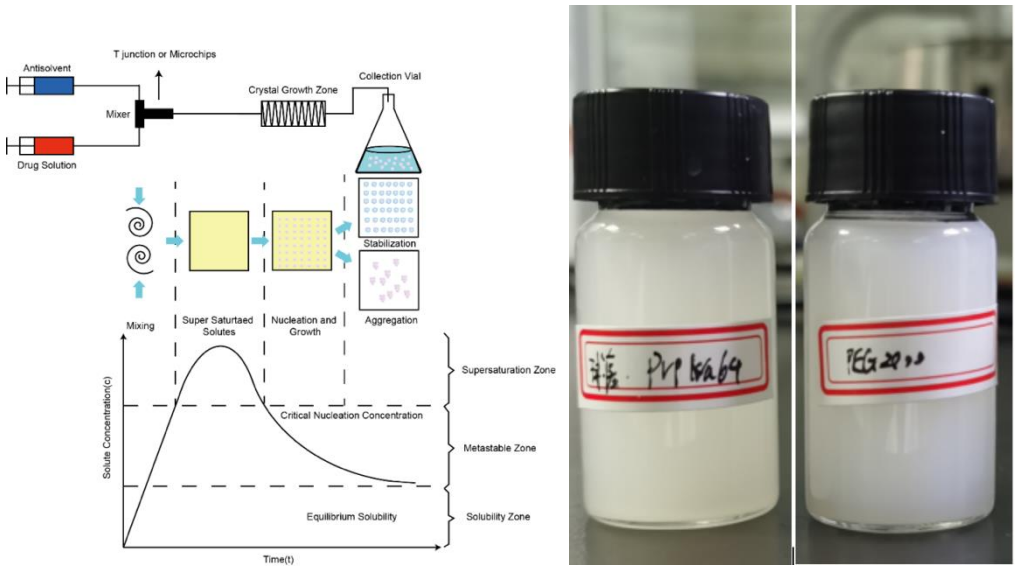

Figure 8 Nanosuspension production of two APIs using a plug flow crystallizer.

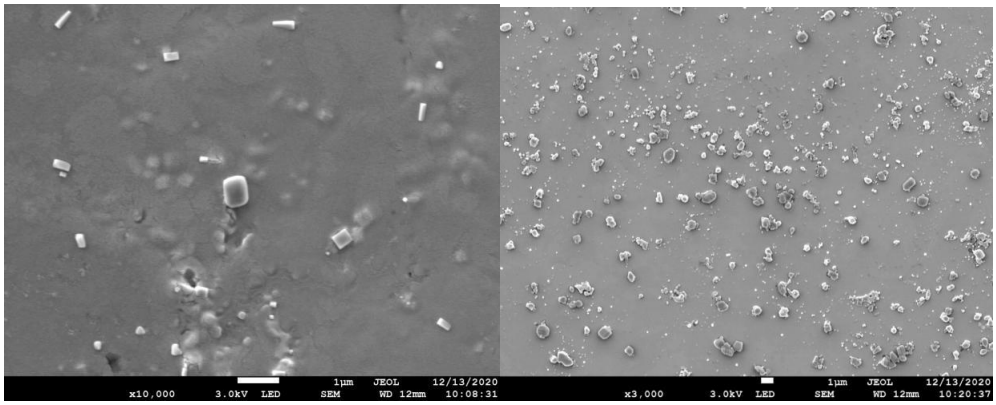

Figure 9 SEM test results of nanometer and micrometer nanosuspension.

6. On-line PAT technology development

The FBRM has been used in coordination with PVM and Raman spectroscopy to investigate and monitor the polymorphic transformation of a compound in solution. The compound has two enantiotropic forms, the application of PAT technology allows effective monitoring of the mutual transformation of crystalline structures and the adoption of control measures.

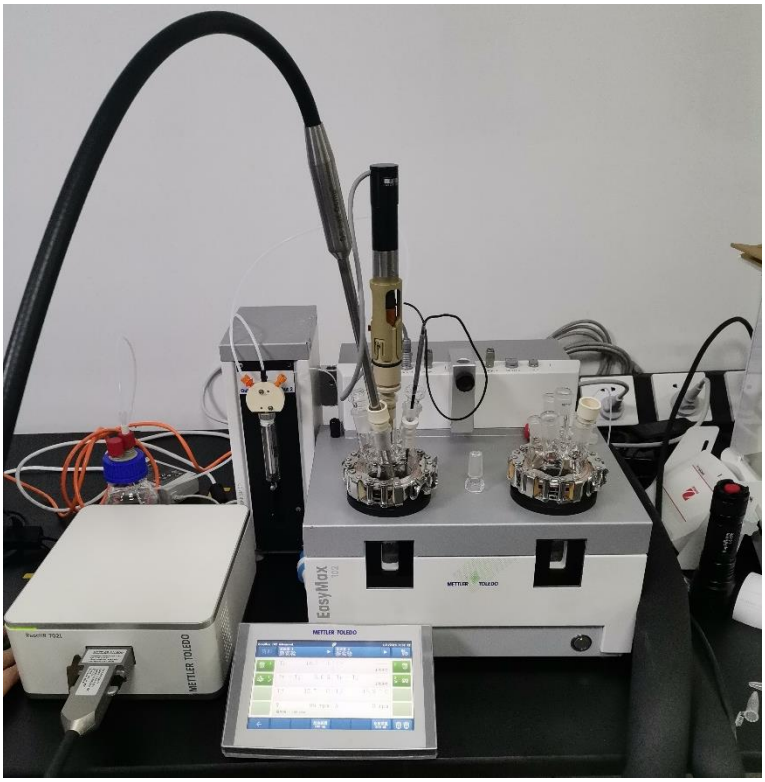

Figure 10 FBRM and On-line Raman PAT instruments.

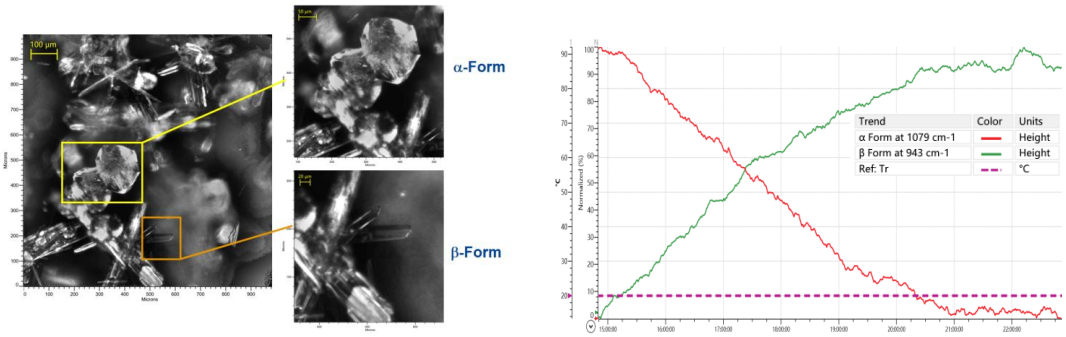

Figure 11 The monitor result of crystalline forms transformation.

Apart from the rich experience in crystallization process development, PharmaBlock is equipped with full-functional, state-of-the-art instruments and equipment, which enable us to tackle the challenging seamless crystallization process and ensure efficient and economic technology transfer at the scale-up stage. The major involved instruments are listed in the appendix section.

A glimpse into the future

A reliable and robust crystallization process is significant to scale-up and tech transfer as it guarantees projects to go well without time-consuming fixes. PharmaBlock employs computer simulation modeling technology and process simulation calculation technology (such as CFD, gPROMS) to simulate and optimize crystallization process, and to make judgment on process parameter ranges in advance, rendering the scale-up manufacturing process more reliable and efficient.

With help of PharmaBlock's extensive industrial crystallization engineering experience, our team is developing continuous crystallization processes for some projects. At the same time, innovative crystallization equipment are also designed in-house. PharmaBlock is exploring application of high throughput instrumentation, nano-crystallization technology, ultra-fine powder technology, continuous crystallization, etc. to manufacturing process.

References

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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.
Crystallization equipment	
FBRM	Mettlor (ParticleTrack G400)
Cooling, antislovent crystallizer	10ml-6300L (glass, stainless steel, hastelloy, halar)
Evaporation crystallizer	10ml-6300L (glass, stainless steel, hastelloy, halar)
Sublimation crystallizer	50L
Melting crystallizer	Kilogram
sonocrystallization	Kilogram
Continuous Crystallizer	Kilogram
Crystallization conditions HTS	4 Set with temperature control
On-line Raman	Mettlor (ReactRaman)

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