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Crystal Pharmatech

Solid State, Crystallization, and CMC Control for Drug Development – A Crystal Pharmatech Case Study Series

From early developability to late-stage specifications—polymorph/salt-cocrystal strategy, SCXRD/MicroED solutions, solvent & pathway design, drug-product form control, ASD crystalline-form limits, PROTAC readiness, and crystal-form IP support.

Solid State Characterization: Techniques, Standards, and Verified Data—An Integrated Lens for CMC Development

Solid state characterization is foundational to API development because crystal form—and its evolution under stress—governs solubility/dissolution (exposure), stability (chemical and phase), and manufacturability (flow, compression, electrostatics). Defensible phase identification and boundaries (e.g., XRPD, DSC/TGA, PLM, DVS, PSD) provide the evidence base for CMC specifications and control strategy under ICH expectations. Done proactively, solid state work de-risks scale-up and storage, strengthens filings and IP, and prevents costly late-stage surprises.

X-Ray Powder Diffraction (XRPD)

XRPD Modes	Key Features
Reflection geometry	Short run time, low sample demand, and low cost; Addresses most polymorph-testing needs
Transmission geometry	For temperature- or humidity-sensitive samples; Allows direct tablet sectioning with minimal prep artifacts; Reduces/evaluates preferred-orientation effects
Variable temperature / variable humidity (VT/VH)	Controlled T/RH during measurement to track phase changes under different environmental conditions
Qualitative / quantitative analysis	Form identification in drug products; Qualitative and quantitative phase analysis for APIs and finished dosage forms

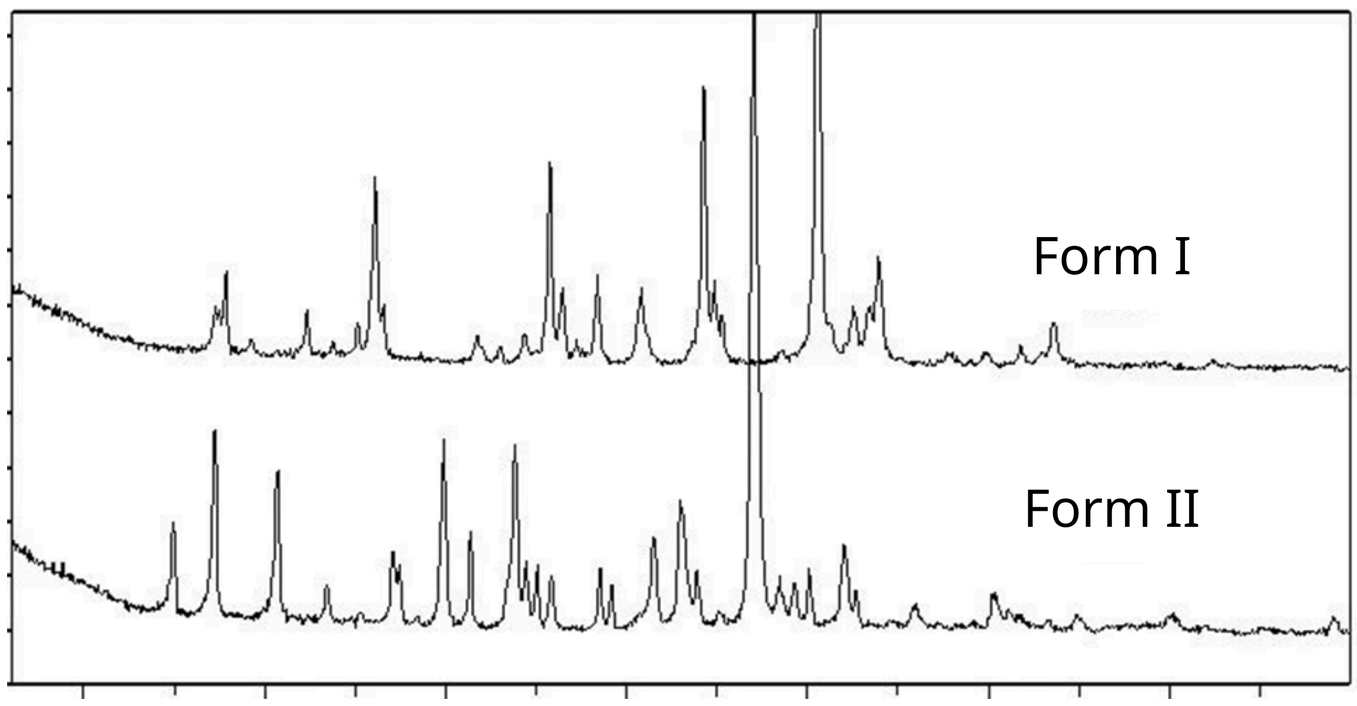


Figure 2

Dynamic Vapor Sorption (DVS)

DVS measures mass change with microgram sensitivity under precisely controlled temperature and relative humidity. By programming sorption–desorption steps, it rapidly generates isotherms and kinetic profiles with minimal material and high automation.

These data guide solid-form decisions across development: selecting the preferred form, defining storage/handling conditions, identifying critical RH and deliquescence, and mapping stability windows and interconversion risks for anhydrates, hydrates/solvates, and amorphous states.

Polarized Light Microscopy (PLM)

PLM enables direct visualization of particle morphology, size, and agglomeration; birefringence further evidences crystallinity and crystal habit. With a hot-stage attachment, crystals can be monitored in real time during temperature ramps to detect melting, desolvation/hydration, and polymorphic transitions. Correlating PLM micrographs with DSC/TGA traces strengthens the interpretation of thermal events and phase changes, using only minute sample amounts.

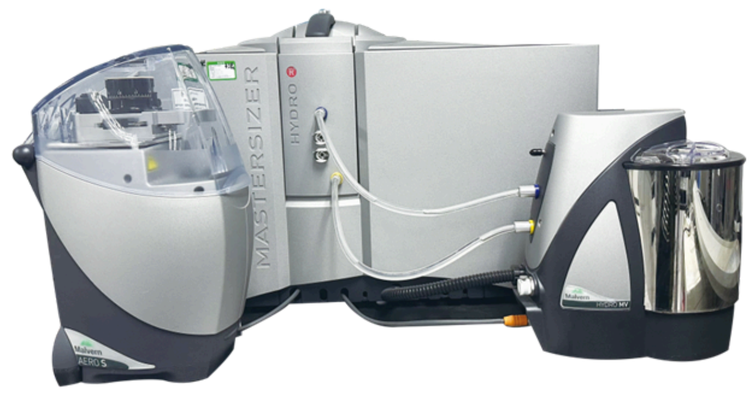
Particle size distribution (PSD)

Particle size distribution (PSD) describes the proportion of particles within defined size ranges as measured by a specified method. Owing to its speed, ease of use, and low material requirement, laser diffraction is a widely adopted technique for PSD measurement.

According to the dispersion medium, PSD testing can be divided into wet testing (liquid medium) and dry testing (gas medium). The appropriate PSD method should be selected based on the sample's physicochemical properties.

DVS

PLM



PSD

Case Study 3: PSD + PLM Combination

PSD can be coupled with complementary techniques to characterize particle attributes. In combination with PLM, micrographs provide direct visualization of approximate morphology, particle size, and the presence of agglomeration, thereby contextualizing PSD data. In the example shown, PLM reveals pronounced agglomeration; consistent with the PSD results, the apparent size decreases after ultrasonication due to disruption of agglomerates. The post-ultrasonication PSD therefore more accurately reflects the sample's true state.

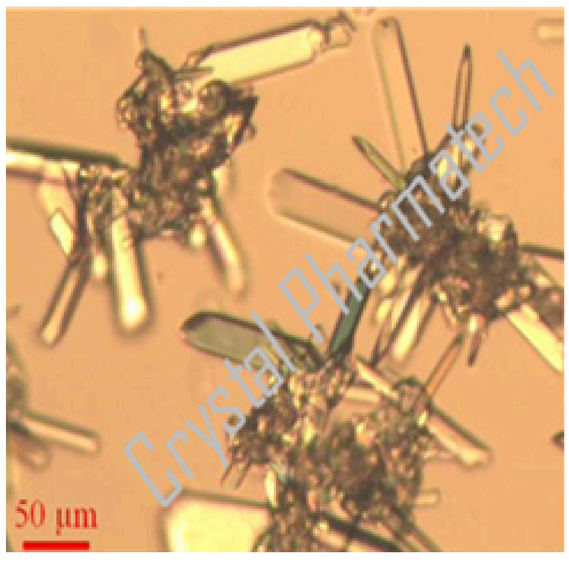


Figure 3

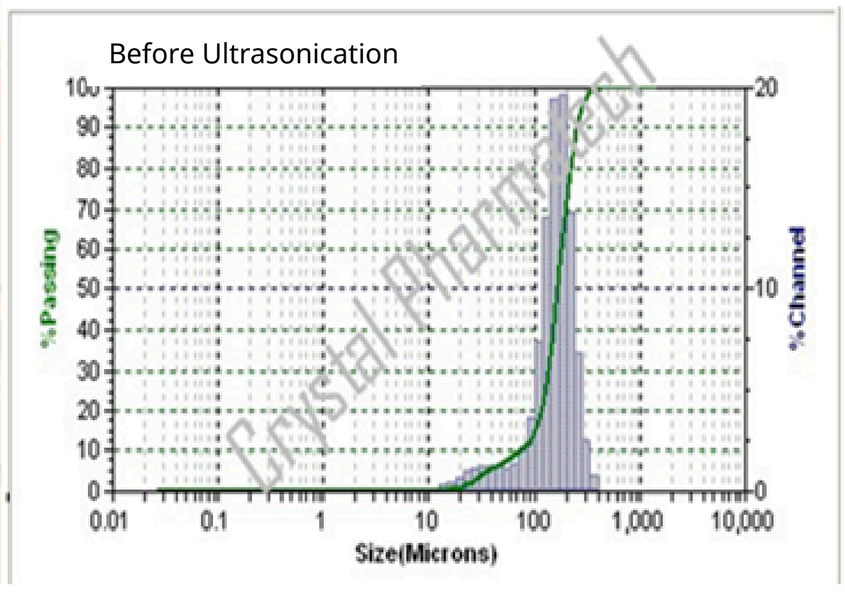


Figure 4

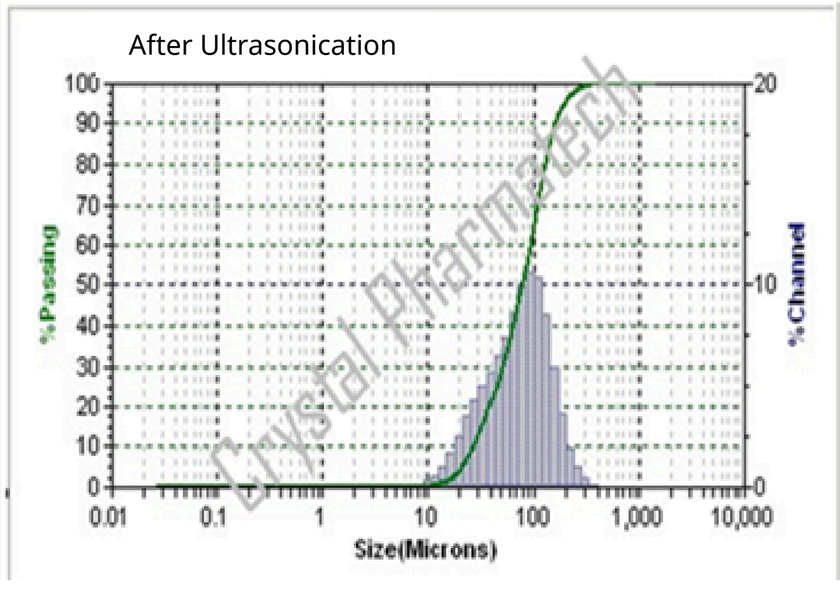


Figure 5

Case Study 4: Combining DVS with Variable-Humidity XRPD

For humidity-sensitive polymorphs, transferring a sample to ambient conditions for XRPD may induce form changes, making potential metastable forms difficult to capture. In such cases, variable-humidity XRPD can be used to collect in-situ diffractograms at different relative

humidities to capture potential forms.

Together with DVS data (see Fig. 6), clear mass increases are observed when RH rises from 50% to 60% and from 90% to 95%, indicating a likelihood of phase transformation. In this project, variable-humidity XRPD was applied to collect patterns at each RH condition and a new polymorph was identified.

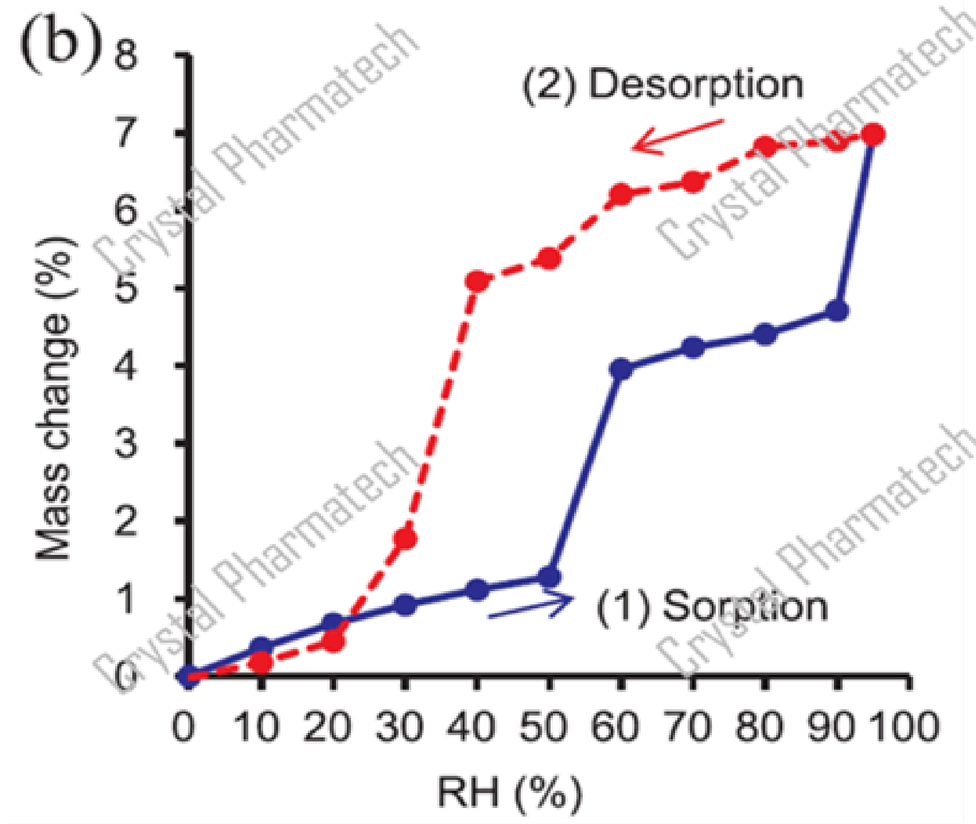


Figure 6

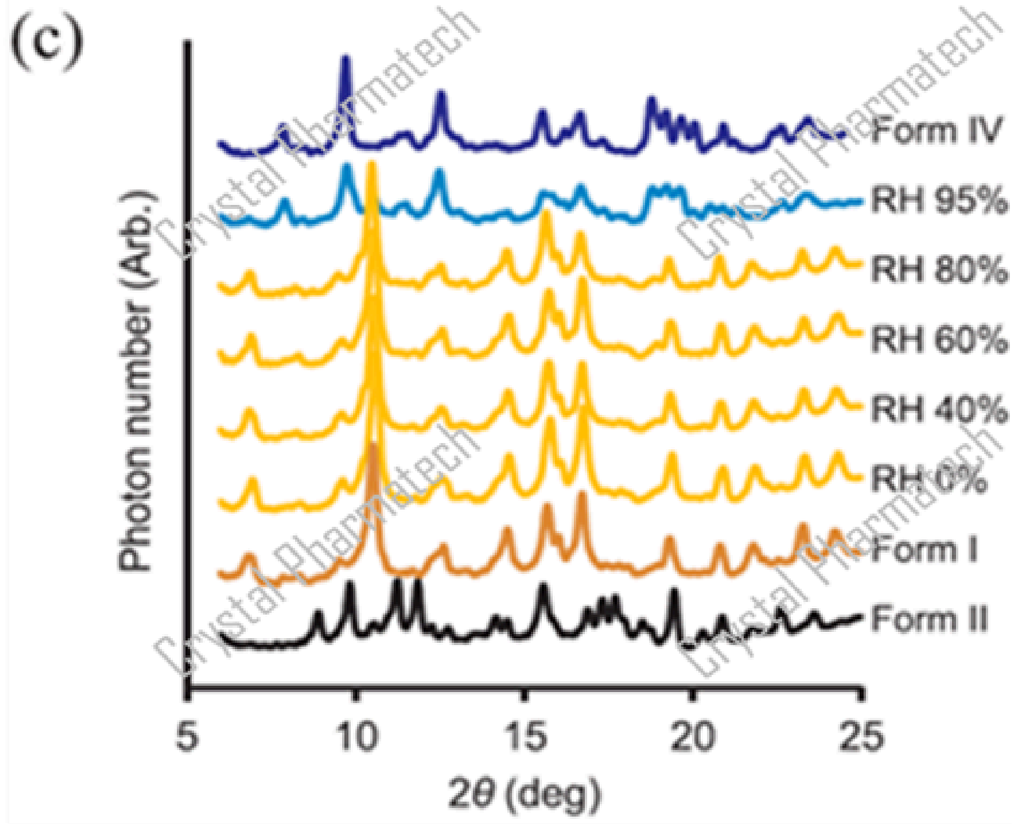


Figure 7

About Crystal Pharmatech

Crystal Pharmatech, founded in 2010, is a global contract research organization with approximately 300 employees and four R&D centers in New Jersey (USA), San Francisco (USA), Toronto (Canada), and Suzhou (China). Collectively, these sites provide integrated support for pharmaceutical and biotechnology companies worldwide. Our capabilities span three specialized platforms: in small molecules, we offer API solid state research and crystallization, preformulation, formulation development, and GMP manufacturing and supply; under Crystal Bio Solutions, we deliver bioanalytical and biomarker testing, biologics CMC analytics, and clinical pharmacology; and through Crystal NAX (Nucleic Acid Excellence), we provide end-to-end solutions for nucleic acid therapeutics, from early research through clinical development.