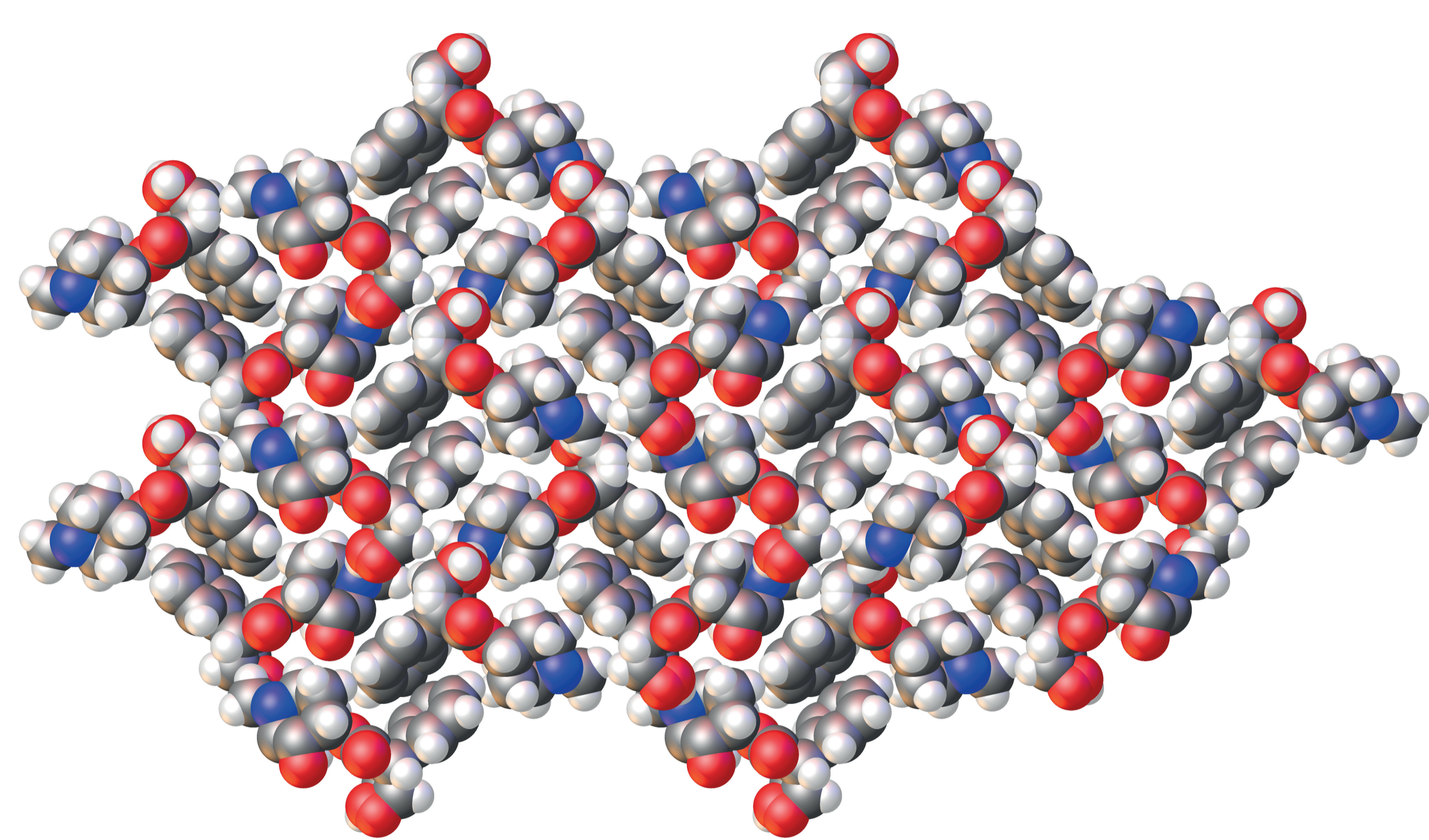


# Locating and understanding hydrated forms of an API

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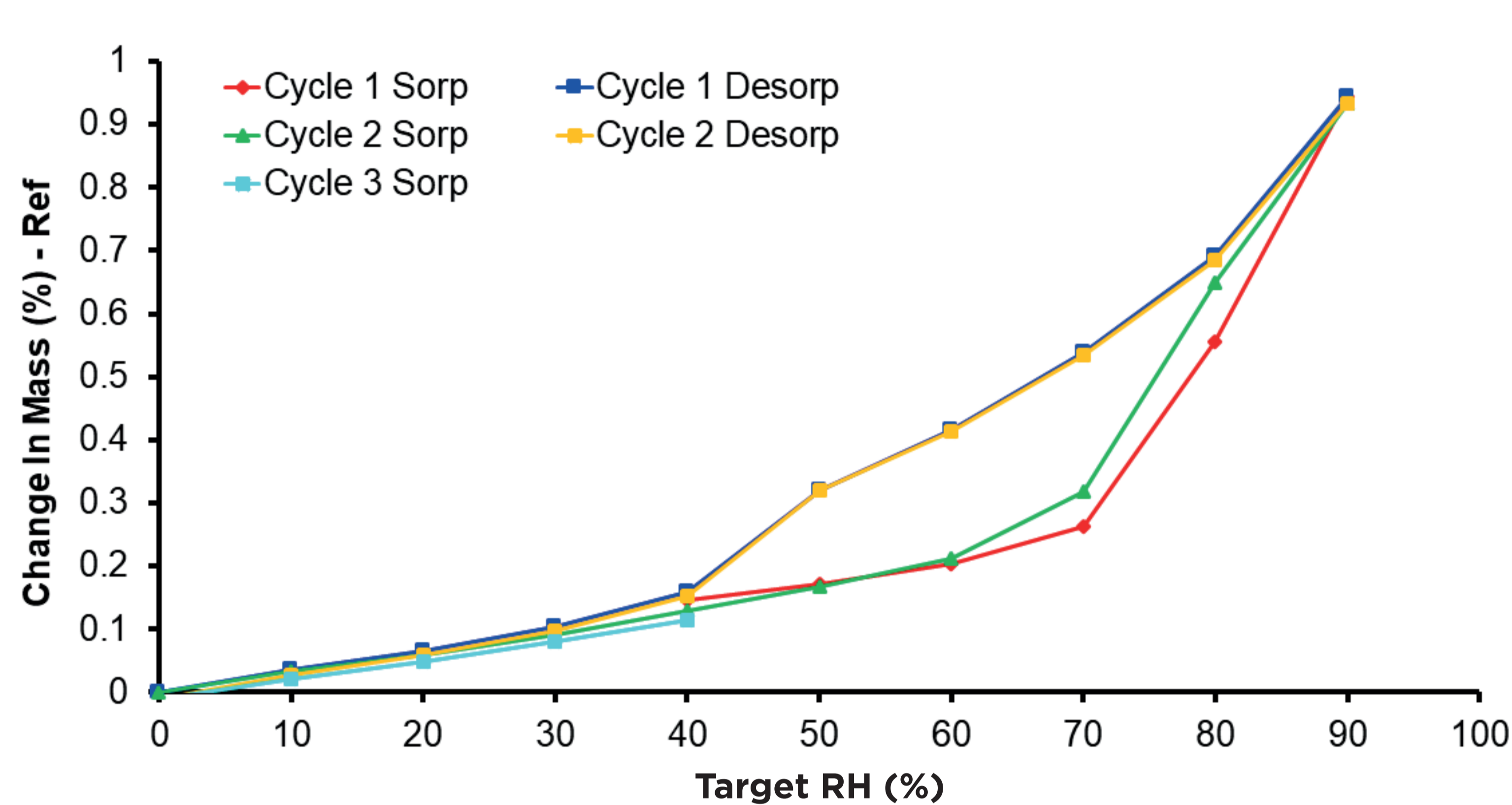
Facile hydrate formation can drastically alter the processability, stability and aqueous solubility of a given API. Cambrex Edinburgh was able to fully characterize and develop a reliable method for avoiding the hemi-hydrated form of an API that was uncovered during a polymorph screening project.



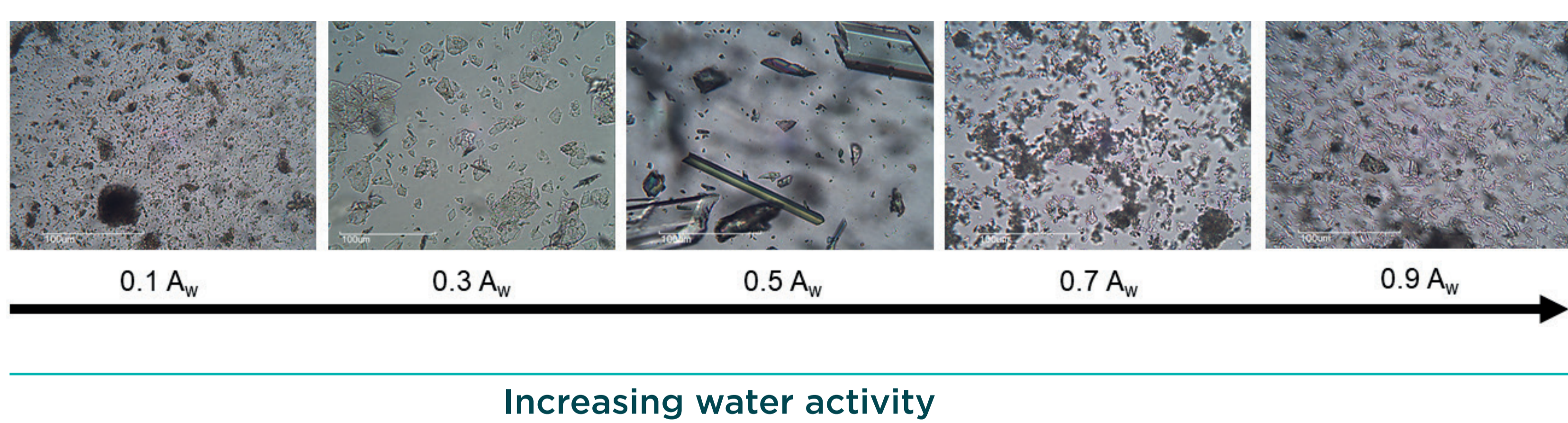
View along unit cell axis a of the API

Upon arrival, the single-crystal structure of the preferred polymorphic form, Form 1, was determined wherein the structure was found to be close-packed with normal density ( $1.3 \text{ g}\cdot\text{cm}^{-3}$ ) and no solvent/water accessible voids. Similarly, thermal-gravimetric analysis (TGA) confirmed the anhydrous, non-solvated nature of the form while analysis by dynamic vapor sorption (DVS) at  $25^\circ\text{C}$ , showed minor hysteresis with a maximum mass uptake of 0.95 wt.% at 90 %RH, confirming its status as a developable form.

DVS Isotherm Plot - Form 1



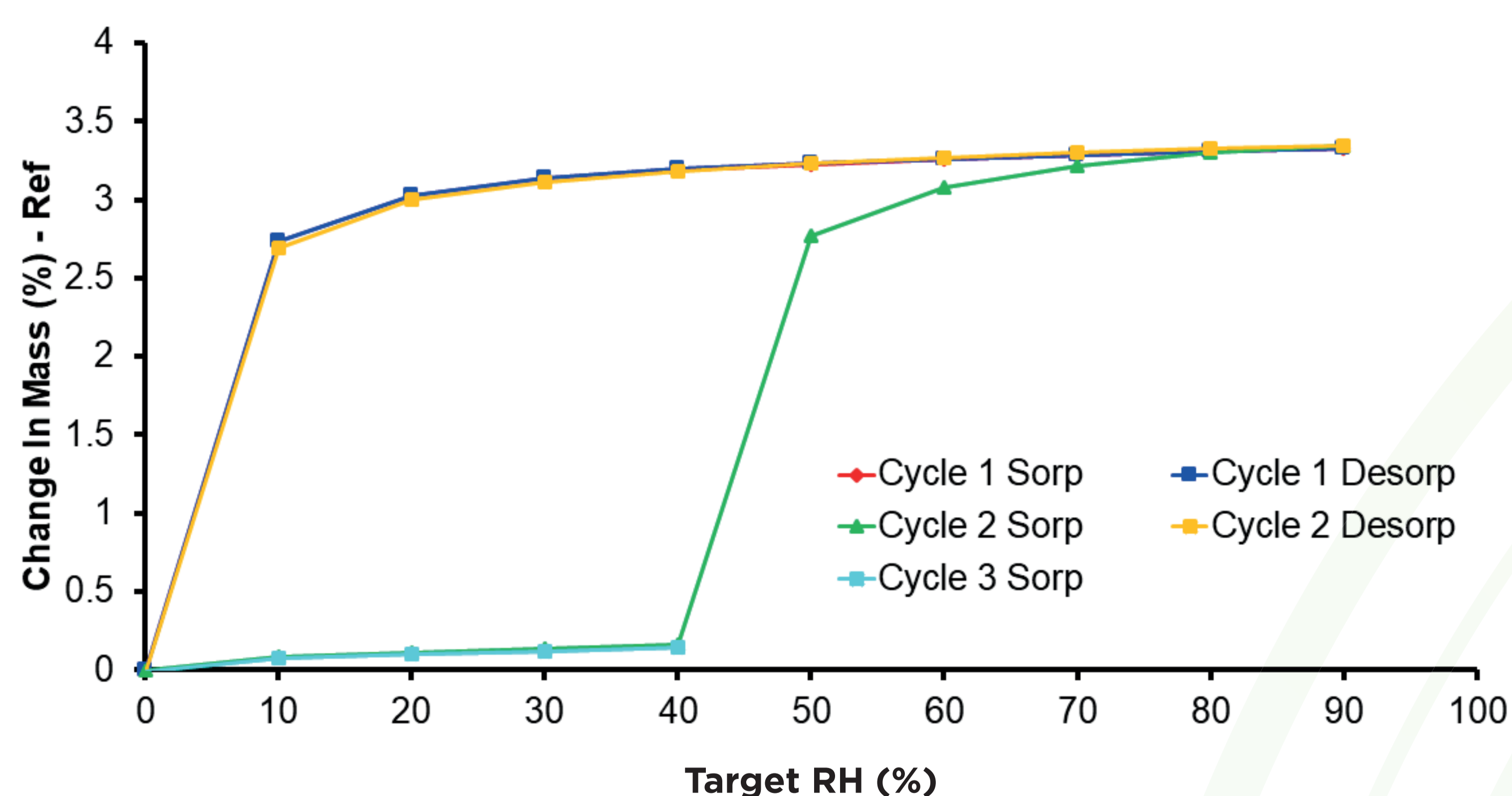
During further screening, it became apparent that the changes in water activity could promote morphological changes in the API. When slurried in systems of varying water activity ( $A_w$ ), the morphology changed from an irregular morphology at  $0.1 A_w$  to a plate-like morphology at  $0.3 A_w$  and finally, to a rod-like morphology at  $0.9 A_w$ . Curiously, at  $0.5 A_w$ , a mixed morphology was obtained, comprising of both plates and rods, indicating competing growth kinetics that could be exploited to maximize processability and filterability of the API at a later date. Further investigation into the solid form recovered at high water activity ( $0.9 A_w$ ) by X-ray powder diffraction (XRPD) showed that this was a novel form, herein denoted as Form 2, and found to be hemi-hydrated when characterized by TGA and Karl Fisher (KF) titration.



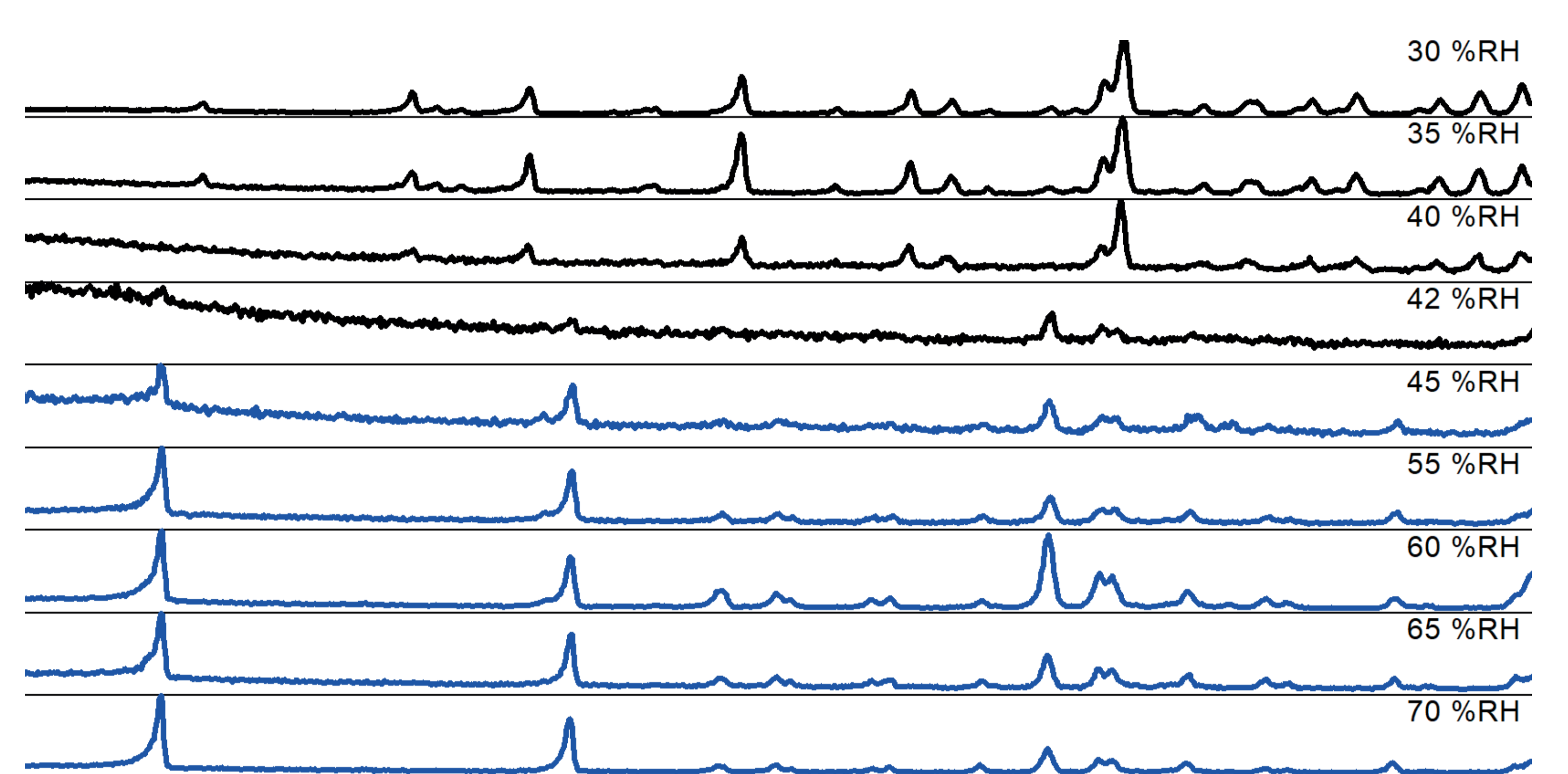
Increasing water activity

In order to properly de-risk the novel hemi-hydrated Form 2, a suitable sample was characterized by DVS which showed that the input Form 2 was stable between 10 and 90 %RH, but de-hydrated rapidly below 10 %RH, forming a novel anhydrous species, Form 3. When the relative humidity at  $25^\circ\text{C}$  was cycled back to 40 %RH, Form 3 prevailed, but rapidly re-hydrated when cycled to 50 %RH. These observations highlighted significant risk with development of the hemi-hydrated species for two reasons; i) the structure of the hemi-hydrated form collapsed on de-hydration, forming a novel form; ii) upon re-hydration, Form 3 collapsed and became amorphous prior to re-crystallizing to Form 2.

DVS Isotherm Plot - Form 2

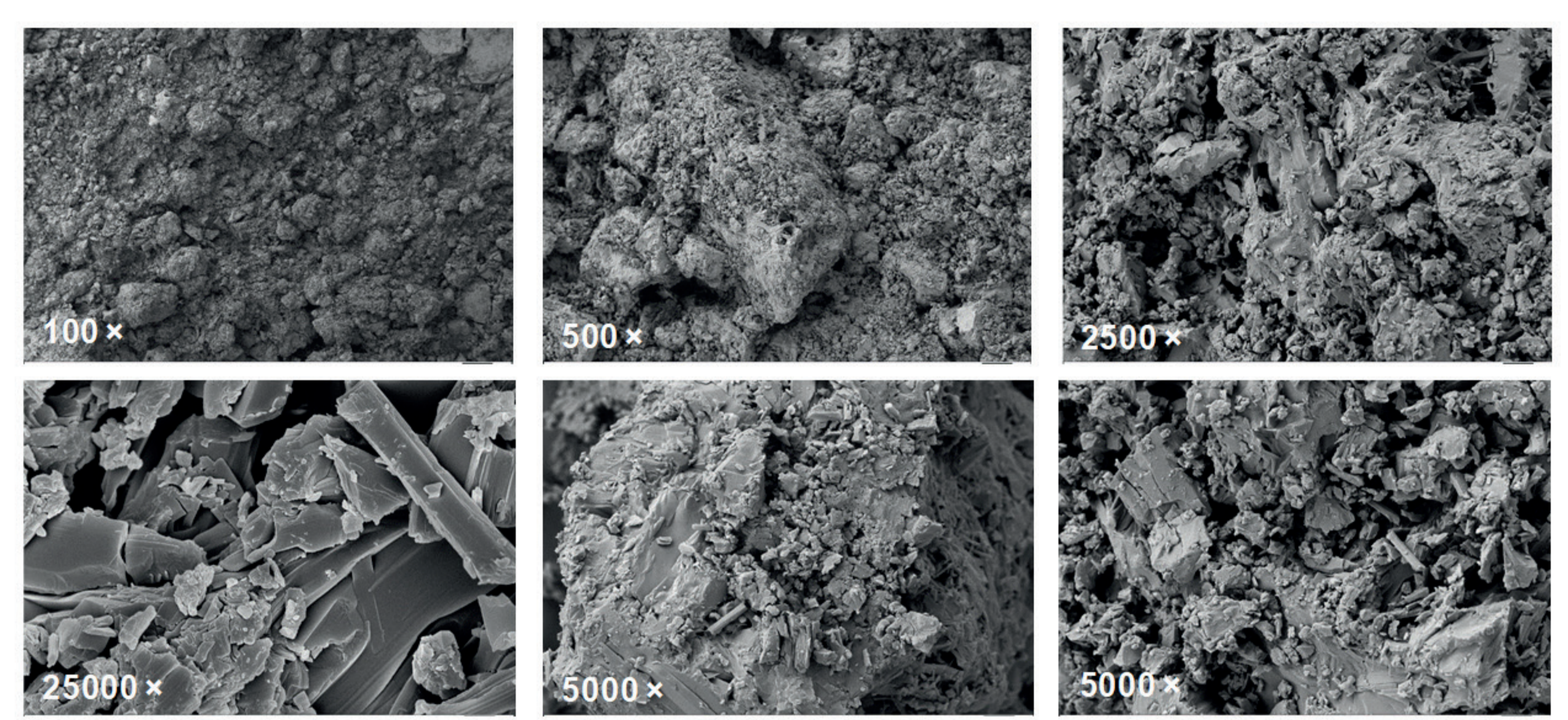


Based on the evidence it was clear that the anhydrous Form 1 was the most desirable form for further development. However, to understand the conditions under which Form 1 would prevail, competitive slurry experiments were performed on Form 1 (anhydrous), Form 2 (hemi-hydrate) and Form 3 (anhydrous) in process relevant media. These experiments clearly showed Form 1 to be the preferred, thermodynamic form under anhydrous conditions for further development.

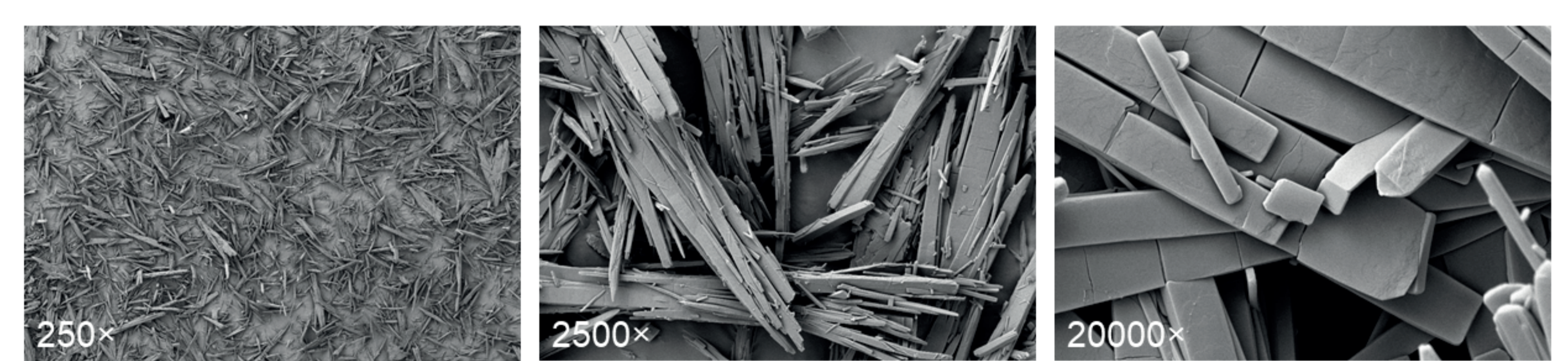


Variable Humidity X-ray Powder Diffraction  $2\theta$  Diffractograms (Black: Form 1; Blue: Form 2)

Despite being the thermodynamic form, a key downside for the development of Form 1 was found to be its poor particle morphology. During the screening studies, however, morphological differences were noticed due to competing crystal growth kinetics in systems containing varying water activity. Using the NRTL equation and measured water activity, a detailed hydration map was investigated across multiple organic solvents where it was found that the morphology of Form 1 was greatly improved using small volume aliquots of water in ICH class 3 solvents (e.g.  $0.5 A_w = 95\% \text{ 2-propanol} : 5\% \text{ water, v/v}$ ) to minimize the risk of hemi-hydrate formation. This vast improvement in particle morphology was exemplified by scanning electron microscopy (SEM).



Scanning Electron Microscopic (SEM) Images of Form 1 (Prior to Morphology Development)



Scanning Electron Microscopic (SEM) Images of Form 1 (After Morphology Development)

The significant increase in particle size coincided with an increase in crystallinity and improvement in material handling properties, specifically with respect to flowability and bulk density. Once the preferred Form 1 was isolated with improved particle morphology, the crystallization development teams at Cambrex Edinburgh were able to carry the compound forward to further investigate the precipitation step by thoroughly investigating the metastable zone and understanding the critical process parameters (CPPs) of the isolation step directly from solution using a design of experiments (DoE) approach.

De-risking the solid form landscape of an API early in development is of utmost importance to ensure success as a viable drug candidate. By controlling the solid-state properties of the API, downstream processing and manufacture will benefit from predictable stability, solubility and bioavailability minimizing development timelines and cost. The above study exemplified the risk that hidden hydrates may pose to process development, but when the solid form landscape is thoroughly investigated and stringently controlled, significant advantages in particle control may be realized.

## How can we help you advance?

Speak with the experts at Cambrex to find out how they are equipped with expertise and tools to locate and understand the most developable solid form of your API.

For further information, please contact Head of Screening Services [jonathan.loughrey@cambrex.com](mailto:jonathan.loughrey@cambrex.com) at our Edinburgh facility