Crystallization

Polymorph and pseudo-polymorph transition

in-process monitoring of habit change

- **Improve purity by ensuring total polymorphic form conversion**
- **Enhance process robustness by monitoring crystallization processes in real time**
- **Characterize the impact of process parameters on transformation kinetics to speed up development time and reduce batch cycle time**

Lasentec® FBRM® and PVM® technologies are directly installed in a LabMax® automated lab reactor for in-process measurement of the crystal product.

Abstract

This application note outlines how FBRM® and PVM® may be implemented at the laboratory scale to monitor polymorphic and pseudo-polymorphic transitions accompanied by a change in crystal habit. Carbamazepine in water was chosen as a simple model system as it rapidly transforms from the anhydrous form to a dihydrate when slurried in water at room temperature.

PVM® images show a distinct change in morphology from the blocks of the anhydrous form to the needles of the dihydrate. FBRM® trends show the onset and end of the transformation process and quantify the kinetics of the transformation. Raman was used to confirm the change in form.

The method outlined here shows how the FBRM® - PVM® combination is a powerful tool for quickly and easily characterizing polymorphic and pseudo-polymorphic transitions in the case where there is a change in habit. Further work may be done to study the impact of process parameters, such as temperature, agitation and concentration on the kinetics of the transformation process in order to affect rapid and efficient scale-up.

Introduction: hydration of CBZ

5g of CBZ was added to 100g of water in a glass lined, temperature controlled vessel. The temperature was set at 35°C and the agitation was set at 275 rpm. The transformation scheme for CBZ is shown in Figure 1. The process of interest was the hydration of CBZ from the anhydrous form to the dihydrate.

The transformation process was studied using Lasentec® FBRM®, Lasentec® PVM® and Raman. Lasentec® FBRM® (Focused Beam Reflectance Measurement) is a probe-based, in-process tool that measures changes in the dimensions, shape and number of crystals in a slurry in real-time. Lasentec® PVM® (Particle Video Microscope) is a probe-based video microscope that provides images of the crystals as they actually exist in process at full process concentration.

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In-process monitoring of habit change
during polymorph and pseudo-polymorph transition

Results and discussion

Figure 2 shows the FBRM® trend for the transformation process. Interpretation of this data is facilitated by studying PVM® images at key point in the process. Stage 1 is identified as the initial charge of the CBZ crystals. As CBZ is charged to the reactor FBRM® trends increases for all size ranges indicating that particles are being measured. After a short time the coarse population statistic (#/s 100-1000 microns) increases and the fine population statistic (#/s 1-30 microns) decreases. This indicates that the CBZ crystals are aggregating, a phenomenon that is confirmed by studying the corresponding PVM® image that shows small aggregated crystals soon after addition (Figure 3). Since CBZ is essentially insoluble in water it is presumed that the CBZ aggregates so as to minimize its surface area relative to the aqueous phase. After a certain period there is a decrease in coarse counts and an increase in fine counts. This corresponds to the onset of the pseudo-polymorphic transition. The coarse population statistic decreases as the block-like crystals disappear and the fine counts increase as needles are formed. In this case fine counts increase due to the measurement of small needle widths by the FBRM®. PVM® images confirm the appearance of needles in the slurry (Figure 4).

Figure 1
Transformation scheme for CBZ

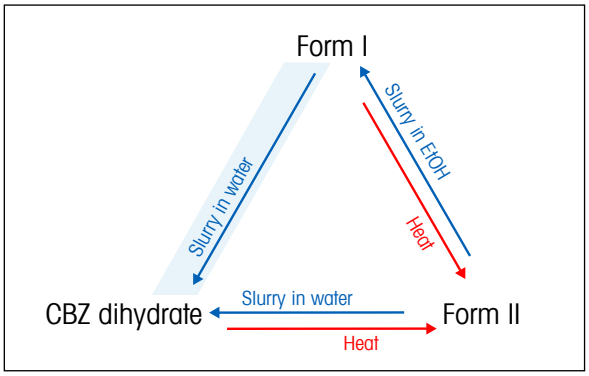


Figure 2
FBRM® trends illustrating the pseudo-polymorphic transition of CBZ

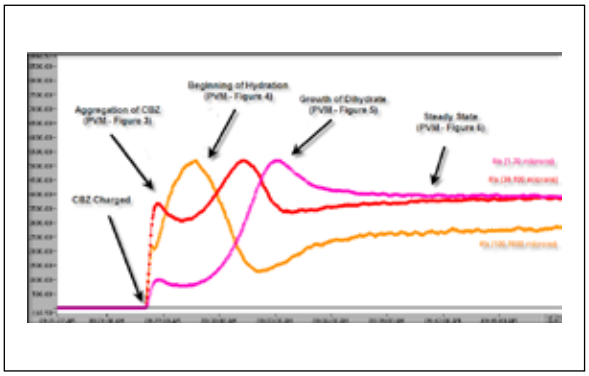


Figure 3
Loosely bound aggregates soon after charging

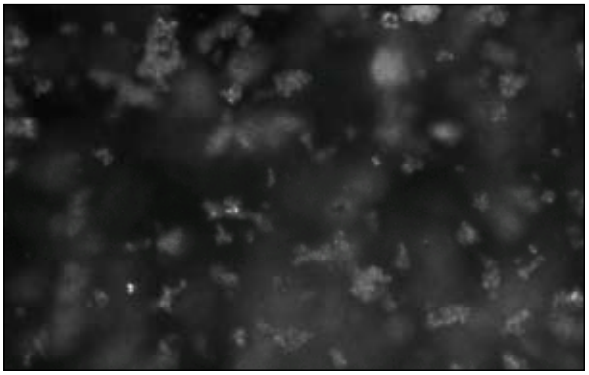
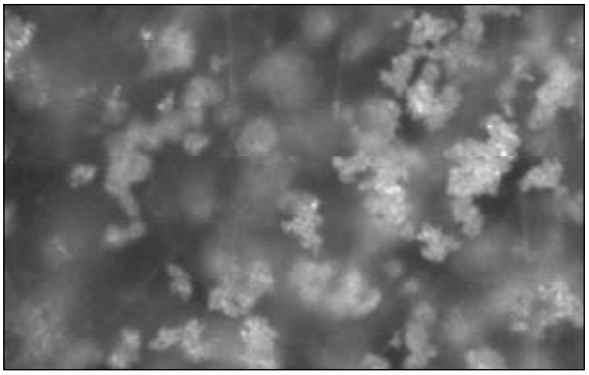


Figure 4
Beginning of Hydration process. Thin needles visible



In-process monitoring of habit change
during polymorph and pseudo-polymorph transition

Over time the coarse counts increase and fine counts decrease as these needles grow into larger size ranges. Once again PVM® images confirm this (Figure 5) The endpoint of the transformation process can be seen when the FBRM® statistics flat-line, indicating that there is no further change in the size, number or morphology of the crystals. PVM® images (Figure 6) shows that the needles have grown and that there are no more anhydrous crystals.

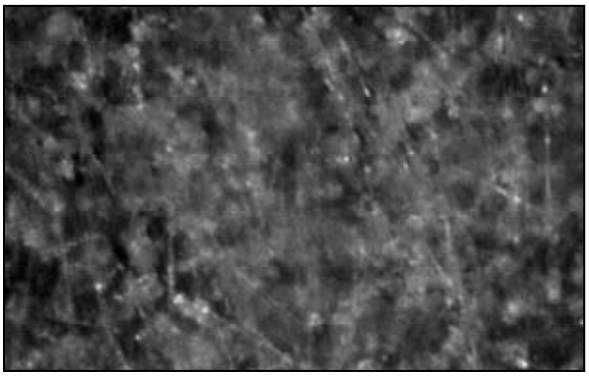


Figure 5
Hydration of anhydrous block-like crystals to dihydrate needles

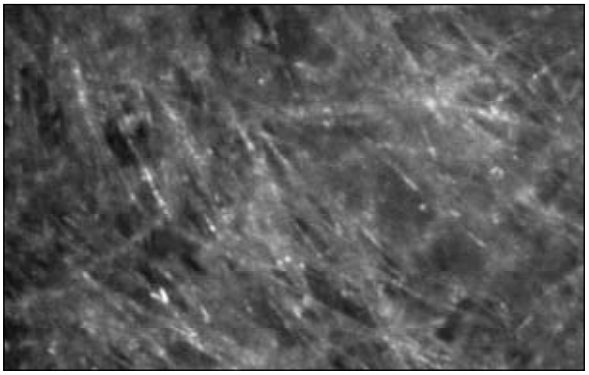


Figure 6
Growth of dihydrate and steady state

References

[1] Application of *in situ* FBRM® and ATR-FTIR to the Monitoring of the Polymorphic Transformation of D-Mannitol, O'Sullivan & Glennon, (2005), Organic Process research and Development, 9, 6, 884-889

[2] Polymorphism of Active Pharmaceutical Ingredients, Karpinski, (2006), Chemical Engineering Technology, 29, 2, 233-237

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