

Control of Crystal Modification and Crystal Shape by Control of Solid-Solid Transitions during Crystallisation and Drying: Two Industrial Case Studies

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SUPPORTING INFORMATION

Additional DSC and XPRD traces for the product KAAD:

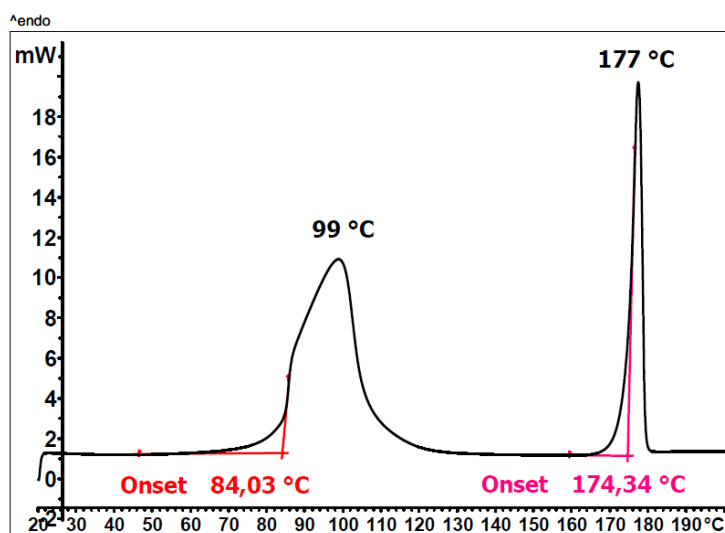


Figure 1. DSC curve of the KAAD monohydrate form M (5K/min). Associated loss of mass: 7,5%.

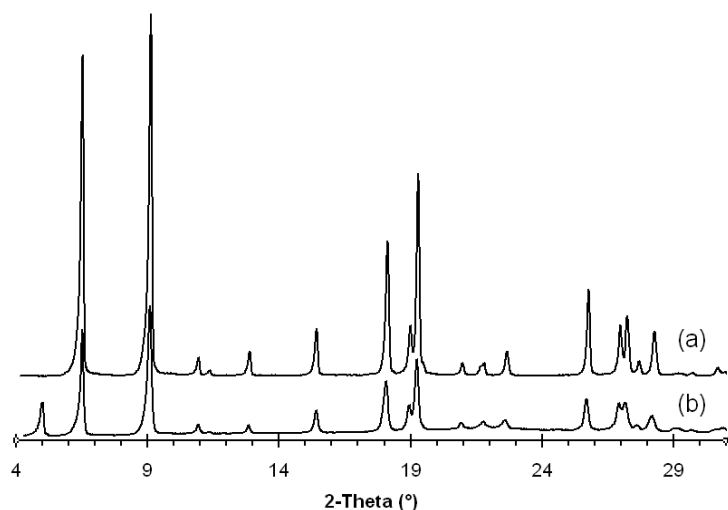


Figure 2. XRPD pattern of a sample of KAAD filtered at 55 °C during the crystallization process, and immediately prepared on the XRPD holder pre-warmed to 55/60 °C and measured *ca* 5 minutes later (b). A residual peak of the LT phase is detected at 4.9° (2 theta) at the beginning of the measurement, but the rest of the pattern corresponds to the reference XRPD pattern of the monohydrate (a).

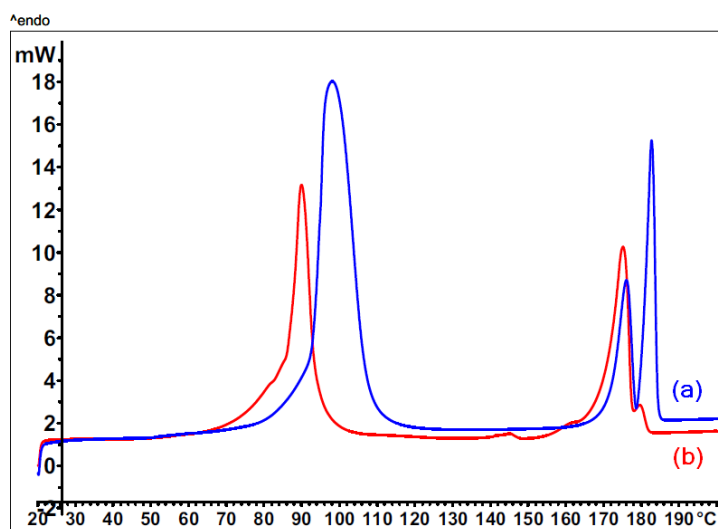


Figure 3. DSC curves of two different samples of KAAD M' phase (5 K/min). The respective associated losses of mass are 5,5% (a) and 12% (b).

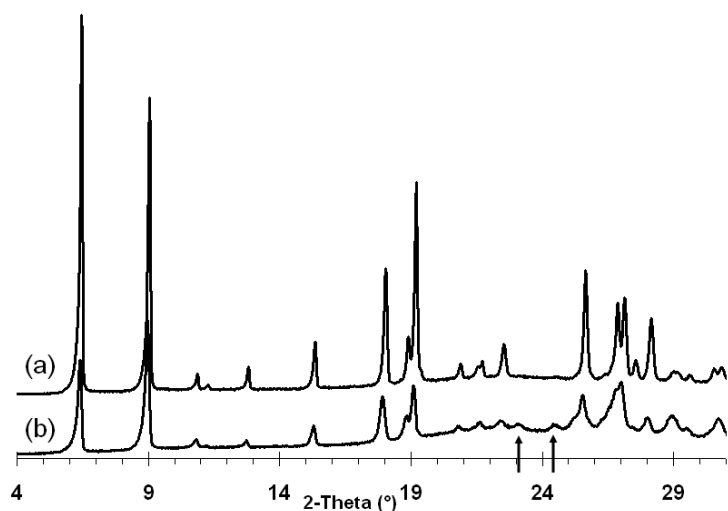


Figure 4. XRPD patterns of the solid phase before (b) and after (a) the exothermic effect observed during the stir period at the end of crystallization of KAAD. The crystallinity is improved (higher intensities, smaller peak width at half maximum, less background) and the 2 small peaks between 23° and 24,5° have disappeared.

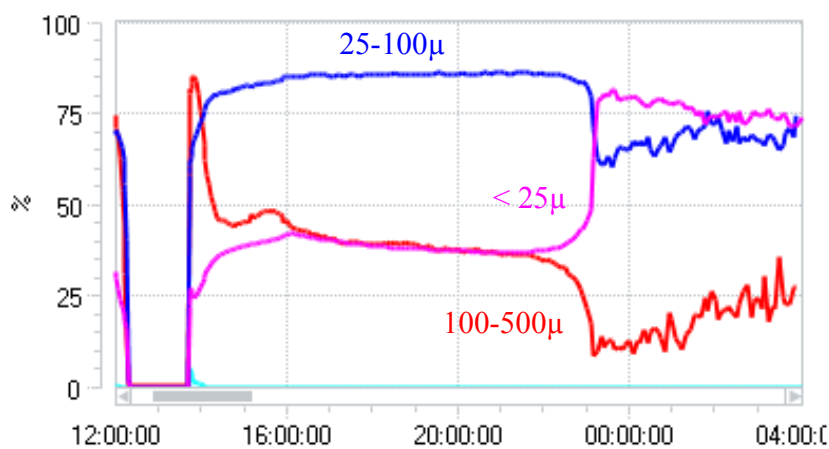


Figure 5. FBRM measurement during the crystallization of KAAD (from 13h to 16h) and the following stir period of time (16h to more than 4h): trend curves of the chord length distribution of the solid particles in suspension. The very small chords (< 25µ) suddenly increase, between 22h and 23h, at the expense of the larger ones (25-500µ). This sudden change of particle size fits exactly the exothermic effect observed on the temperature recordings.

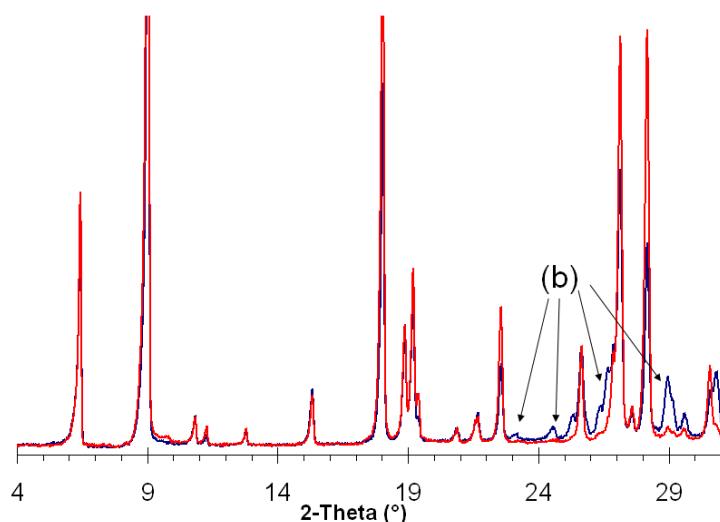


Figure 6. XRPD patterns of KAAD crystals obtained with the modified crystallization conditions in production and at lab. The lab product (b) displays the two peaks between 23° and 25°. No amorphous background is observed (see Figure 7).

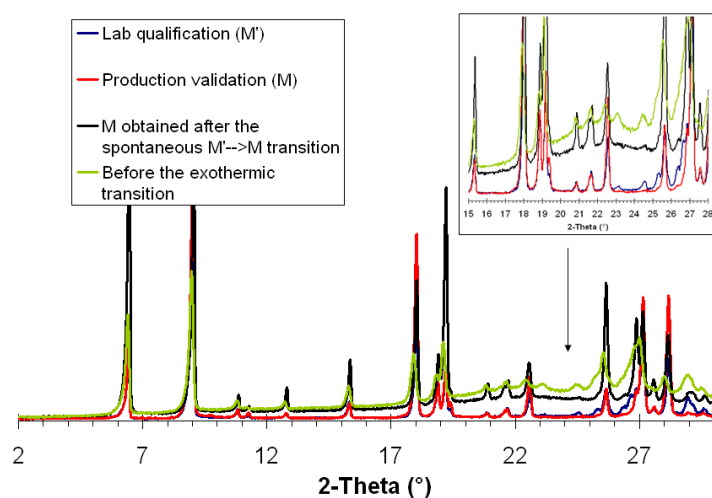


Figure 7. The two XRPD patterns of figure 6 (modified crystallization applied in production (red) and in the laboratory (blue)) are compared with those obtained with the old crystallization process, before (green) and after (black) the exothermic transition after crystallization, *i.e.* with the two diagrams of Figure 4. There is no amorphous background with the new process, but the representative tiny peaks of M' are still observed in the laboratory samples.

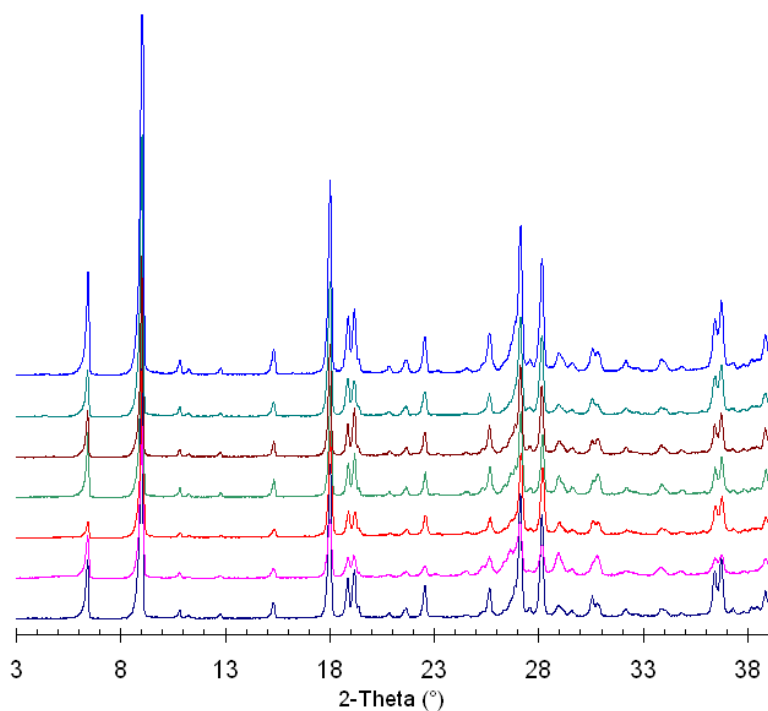


Figure 8. XRPD patterns of the 7 products obtained at laboratory scale (prime batch & 6 times recycling of the mother liquors) with the modified crystallisation conditions. The small peak at 24,5° can be observed.

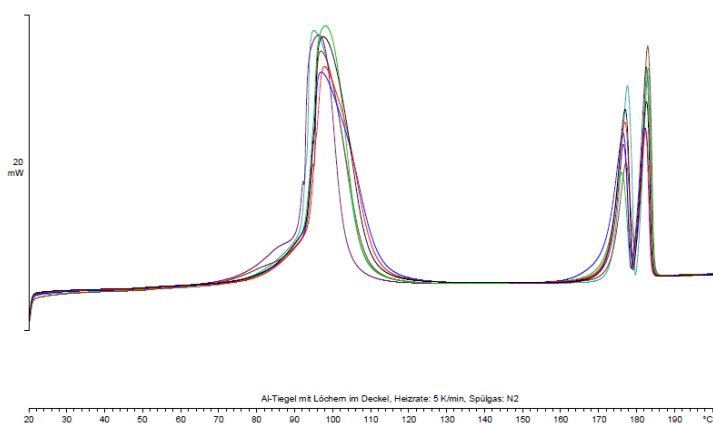


Figure 9. Superimposed DSC curves of the 7 products obtained at laboratory scale (prime batch & 6 times recycling of the mother liquors). As expected based on the XRPD patterns, which all display the two tiny peaks at 23-25° (2 theta), they also all display a double melting peak representative of the M' form.

Additional DSC and XPRD traces and drying curves for the product CASAD:

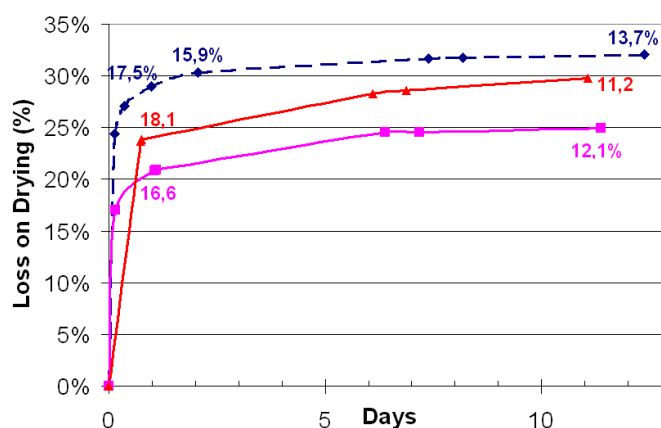


Figure 10. Drying curves of rhombic crystals of CASAD in open air. The values indicated on the curves are the calculated weigh of residual moisture, based on the KF measurement performed at the final point of these drying experiments. (It is assumed that water was the only residual solvent in the crystals at the end of the drying). As the filter cakes were all washed with pure acetone, the amount of water in the residual free moisture is likely to be low. Consequently, it is likely that residual free moisture is completely evaporated within the first 1 or 2 days, and that these ca 16% of residual solvent remaining in the product at the beginning of the very slow drying regime after 2 days consists in solvation /hydration molecules in the crystal structure(s).

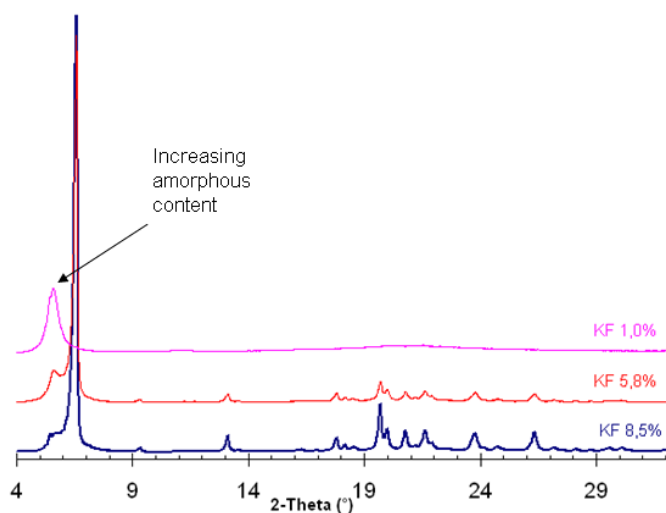


Figure 11. XRPD patterns of H3 samples containing varying water contents. The decreasing water contents are due to increasing amounts of the amorphous form

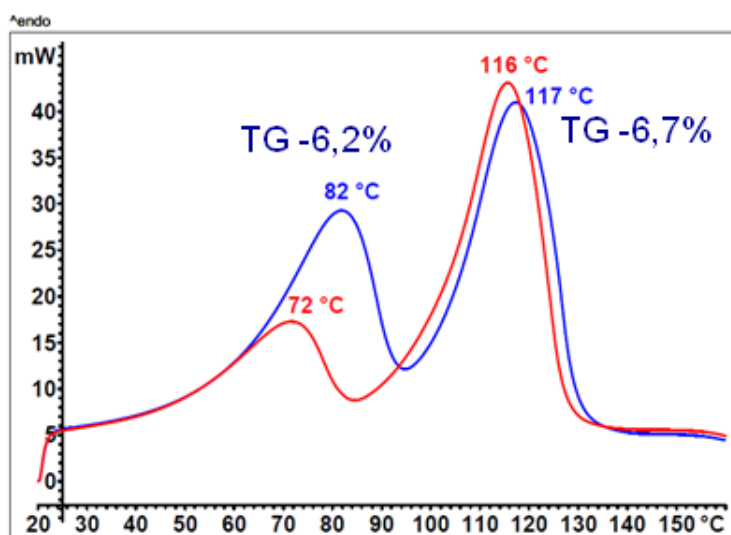


Figure 12. DSC Curves of two samples of CASAD form H3, dried in the open air (10K/min, holes in the cap of the crucible). The corresponding losses of mass measured by TG are indicated on the chart.

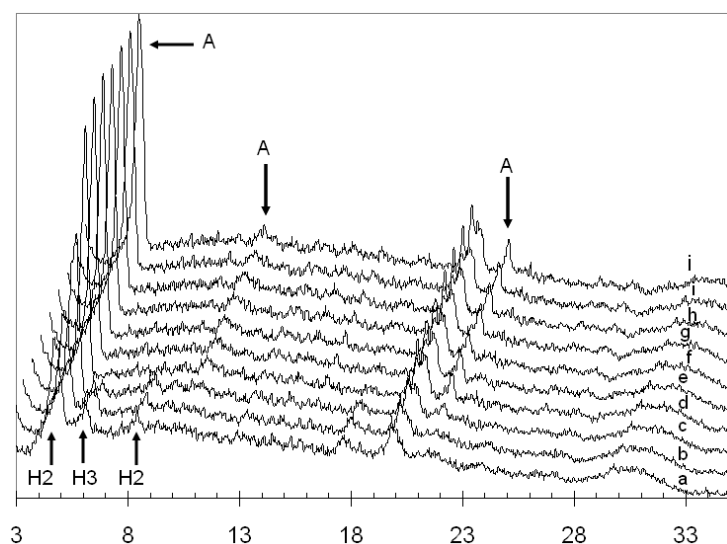


Figure 13. TR-XRPD of the 10% water sample of CASAD form H3 (heating rate 5°C/min, temperature holding time: 30 min, measurement time: 30 min. From a to j: 21°C, 50°C, 60°C, 70°C, 80°C, 90°C, 60°C, 50°C, 40°C, 27°C. The characteristic peaks of A are observed from 60°C. A is the only form at 70°C.

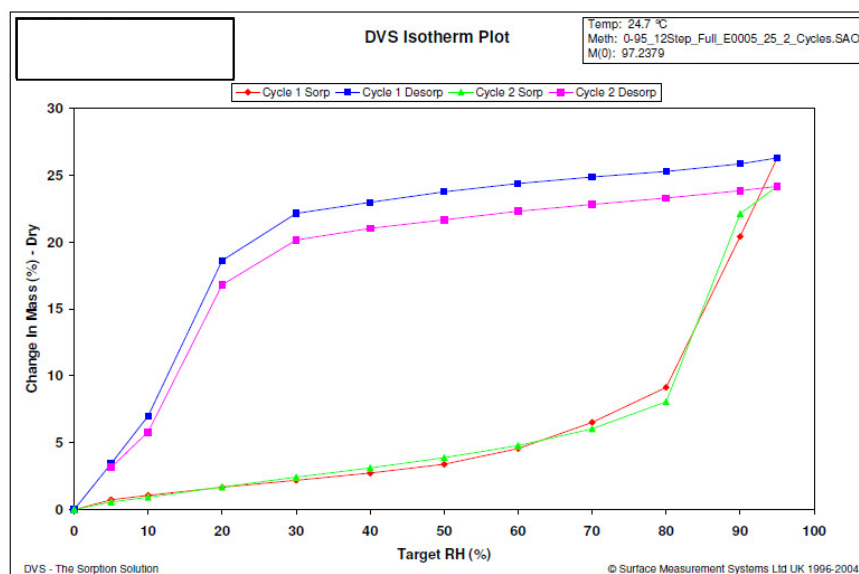


Figure14. DVS analysis at 25 °C of an amorphous sample of CASAD showing reversible adsorption of up to 25% water