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Assessment of the nature of disorder and its effect on recrystallization tendency in a hydrate-anhydrate system

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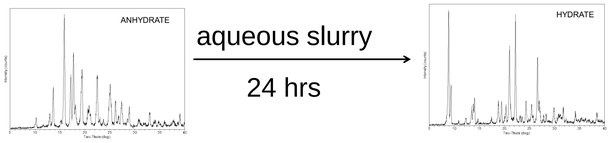
BACKGROUND

- Investigational compound GENE, is characterized as anhydrate. Anhydrate converts to trihydrate in aqueous slurry.



- Hydrate dehydrates to form a “dehydrated hydrate/DH” which is X-ray amorphous. DH crystallizes to anhydrate at ≥192°C.

OBJECTIVE

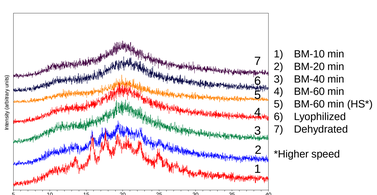
- Investigate the nature of disorder/local order in a “disordered phase” generated through different routes
- Understand effects of disorder/ “existing order” on recrystallization tendency and nature of resulting phase

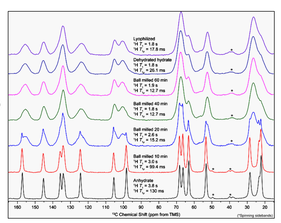
METHODS

- Lattice disorder was induced by ball milling, lyophilization and dehydration
- Characterization: DSC, TGA, XRPD, SSNMR, Water sorption, computational analysis

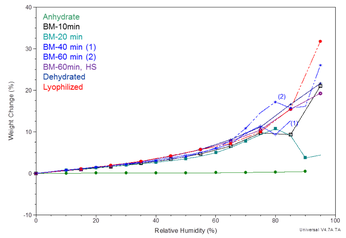
RESULTS

Disordered phases



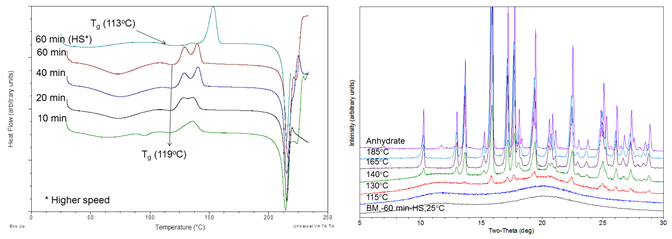


Overlaid patterns (XRPD, left) and spectra (SSNMR, right)



Water sorption (0-95% RH, 25°C)

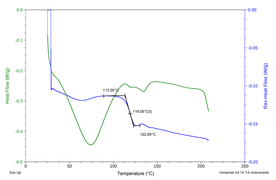
Ball Milled



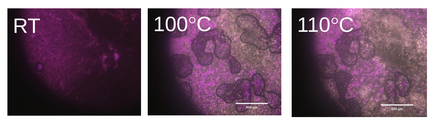
DSC traces (left) of BM samples. Crystallization exotherms overlap with T_g except for the sample ball milled for 60 min, (higher speed/HS)

VTXRPD (right) of the BM-60 min (HS) sample. Crystallization to anhydrate starts at 125°C

Lyophilized

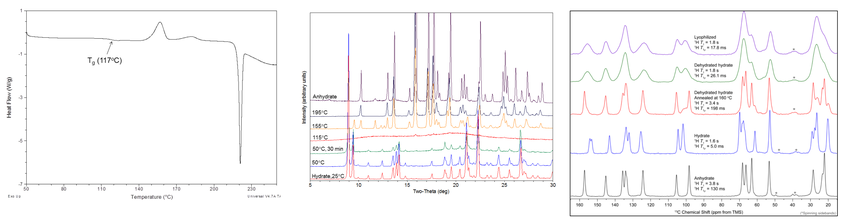


T_g at 119°C



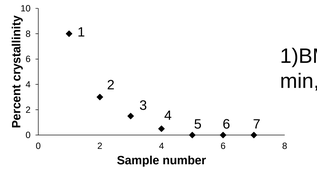
Crystallization observed at 100°C (hot stage microscopy)

Dehydrated (DH)



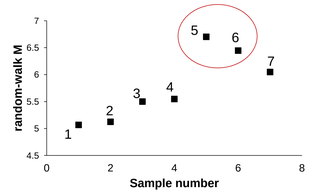
DSC (left) shows 2 crystallization exotherms for DH.VTXRPD (center) and SSNMR (right) reveal an “intermediate” phase at 155-160°C(1st DSC exotherm) which rearranges to form the anhydrate at 195°C

Computational analysis

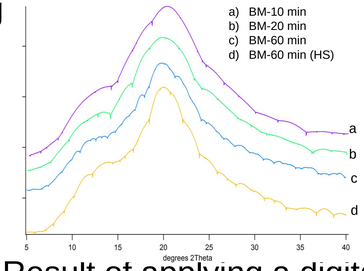


1)BM-10 min, 2) BM-20 min, 3) BM-40 min, 4) BM-60 min, 5) BM-60 min (HS), 6) DH, 7) lyophilized

Sample %crystallinity determined from digital filtering



The change in the random-walk variable M resulting from random-walk direct analysis. The increase in the value of M corresponds to the sharper primary halo profile and increased local order.



Result of applying a digital low pass filter to raw data. Diffuse scattering profile is changing under increase milling time, with the BM-60 min (HS) sample having the narrower diffuse halos.

SUMMARY

1) Two crystallization endotherms observed in dehydrated and BM samples (≥ 20 min milling)
2) Increase in milling time leads to greater local order. Highest degree of local order observed in ball milled (60 min, HF) and dehydrated samples.
3) Since nature of local order influences propensity of crystallization and the resulting crystalline phase, the delayed onset of crystallization in these samples with greater local order suggests presence of a lattice order unlike that in the known crystalline phases

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Triclinic Labs
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