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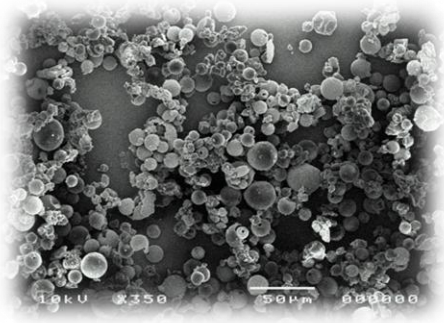
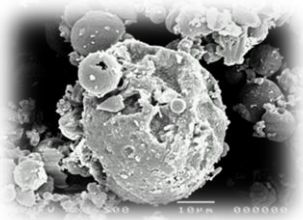
Mannitol Polymorphism as a function of particle size

The effect of Ethanol





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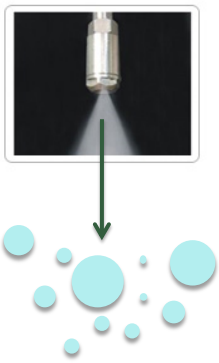
Spray dryer produces particle sizes with a wide distribution



- Various solid state composition
- Depends on the spray dry conditions (i.e temperature, humidity)

Polymorphism

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Aims

Assess if polymorphic change follows the trend linked to the particle size distribution that is normally obtained during spray dry process.

To investigate the effect of ethanol on drying kinectics, which then affect the crystal growth and drying behavior of polymorphs .

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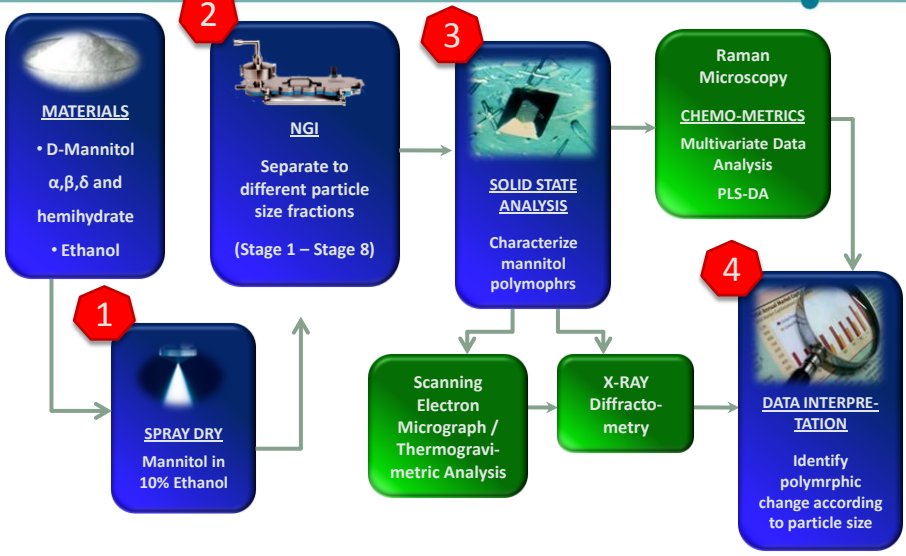
Methods



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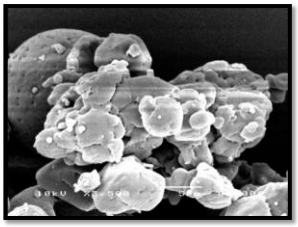
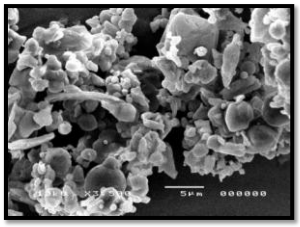
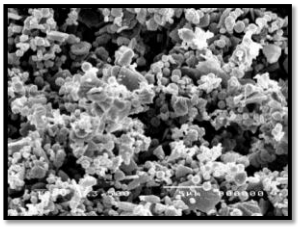
Results – SEM / TGA



Stage 1
10.9 ± 3.4 µm



Stage 4
2.7 ± 1.7 µm



Stage 7,8
1.0 ± 0.4 µm

TGA - No detectable weight loss

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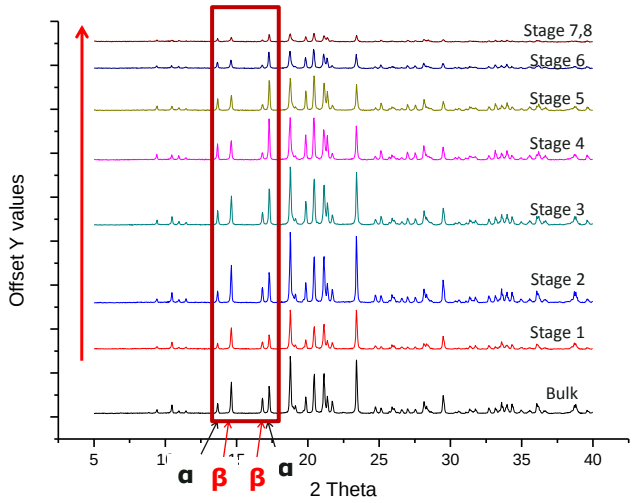
Results - XRD



- All samples contain α and β-mannitol.
- Comparing the ratio of two polymorphs at indicated positions, α contents increase relatively at smaller particle size.

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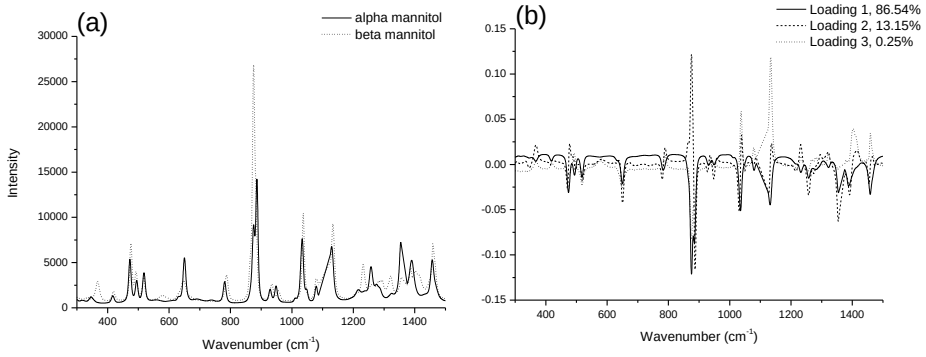
Results – Raman Microscopy



- 3 principal components
- 100% specificity and sensitivity
- 0% misclassification rate

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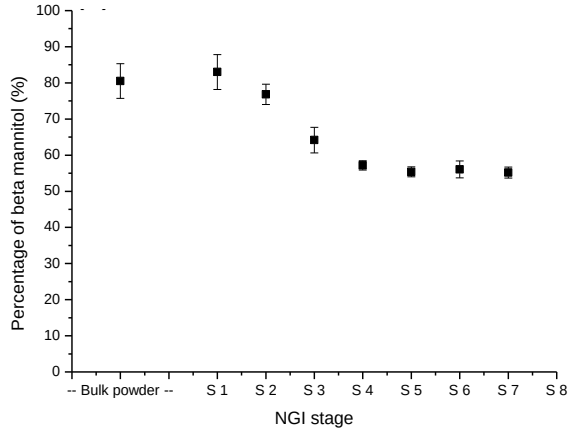
Results – Raman Microscopy



- Content of β-mannitol decreased from NGI Stage 1 to 8

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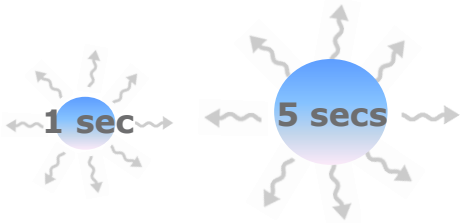
Different drying rates for droplets with various sizes



- Smaller droplets are likely to dry faster than larger droplets
- Ostwald rules of stages
  – more meta-stable α-mannitol in small particles
- Moisture as 'lubricant' for stable crystal arrangement
  – more stable β-mannitol in large particles

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Conclusions

- Ethanol increases drying rate of mannitol in the spray drying system, leading to the presence of meta-stable α-mannitol in addition to stable β-mannitol.
- Polymorphic form of mannitol changes according to particle size from spray drying process.