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MONITORING SOLID-STATE TRANSFORMATIONS IN THEOPHYLLINE-LACTOSE GRANULES DURING DRYING IN MINIATURIZED FLUID-BED

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 HDR 2008



OUTLINE

- Introduction
- Equipment and process
- Results and conclusions
- Future studies



INTRODUCTION

- Process induced transformations may cause changes in API → possible solid-state changes that may affect the therapeutic efficacy
- Important to monitor the process and define the critical steps in manufacturing

pressure

 heat

 humidity

MILLING

 ↓


 GRANULATION

 ↓

 DRYING

 ↓

 TABLETTING



Theophylline anhydrate (stable) TPA

GRANULATION IN PLANETARY MIXER WITH LACTOSE MONOHYDRATE AND WATER

Theophylline monohydrate TPM

DRYING IN FLUID BED

TP META

 Theophylline anhydrate (metastable)

 Theophylline anhydrate (stable)



DRYING IN MMFP



DRYING PROCESS IN MMFP

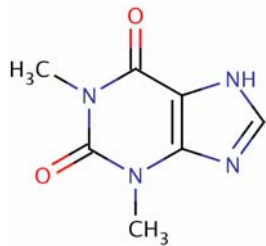
- Granules
 - Theophylline monohydrate, lactose monohydrate and water
- Batch size 7 g
- Air flow rate $300 \cdot 10^{-4} \text{ kg s}^{-1}$
- Inlet air temperature
 - $55 \text{ }^\circ\text{C}$ (328 K)
- Monitoring with Raman spectroscopy



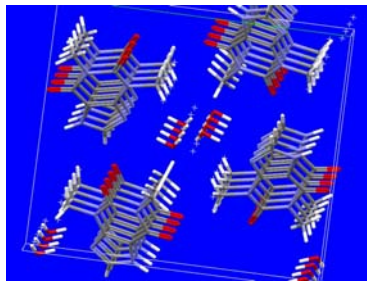
Aaltonen *et al.* Chem Eng Sci 62 (2007)



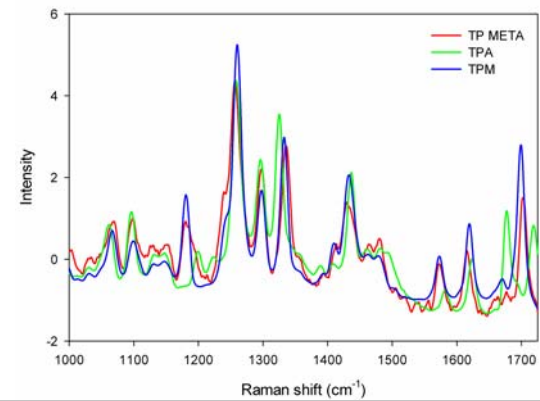
THEOPHYLLINE

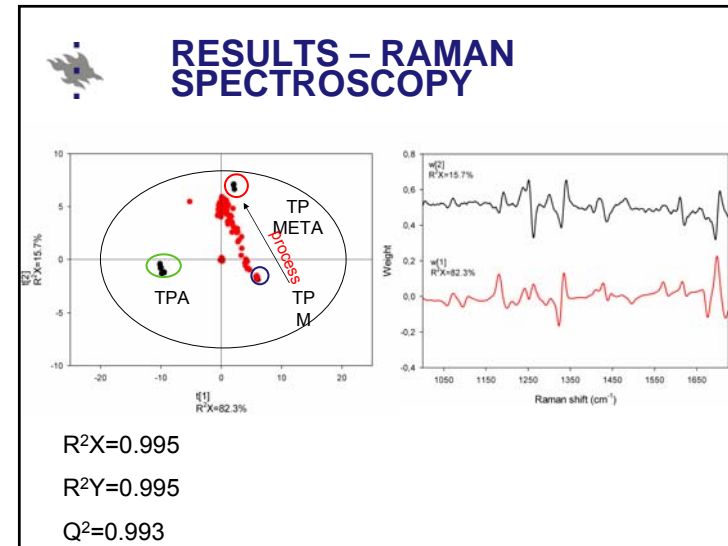
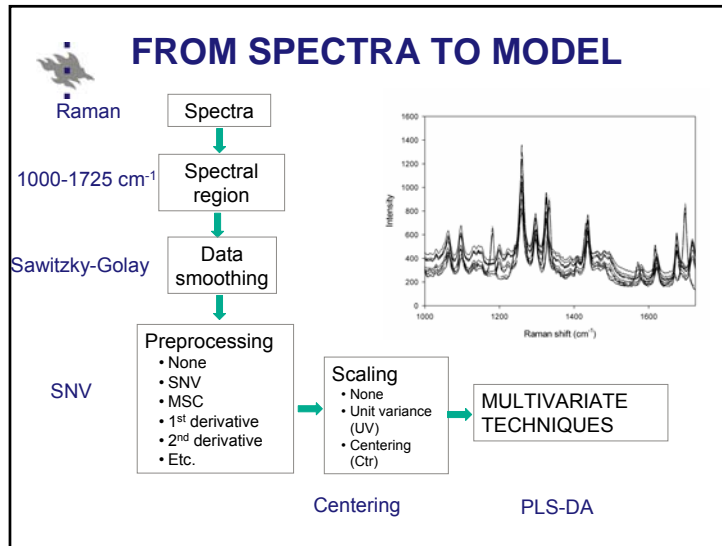


Lattice channel hydrate



THEOPHYLLINE – DIFFERENT FORMS





- ## CONCLUSIONS
- Raman spectroscopy is a good method to monitor solid-state changes during fluid bed drying
 - not sensitive to water
 - gives information about the molecular packing
 - fast, non-destructive
 - possibility for *in-line* measurements
 - Raman spectroscopy combined with multivariate techniques increases the understanding of solid state conversion of theophylline during fluid bed drying process

- ## FUTURE STUDIES
- New Raman probe with larger spot size → larger sample size, more relevant data
 - NIR spectroscopy
 - Preliminary experiments have shown that it is challenging to distinguish between different forms
 - Hyphenated Raman and NIR spectra analysis combined with process data (pressure drop over the bed, granule temperature etc.) → drying and solid state change simultaneously



ACKNOWLEDGEMENTS

- Dr. Karin Kogermann, University of Helsinki, Finland, University of Tartu, Estonia
- M.Sc (Pharm.) Marja Savolainen, University of Helsinki, Finland
- Dr. Clare Strachan, CDR, University of Helsinki, University of Otago, New Zealand
- Professor Anne Juppo, University of Helsinki, Finland

- Docent, Chief Pharmacist Eetu Räsänen, South-Carelian Hospital Pharmacy, Finland
- Laboratory assistant Jenni Honkaselkä

**THANK YOU FOR
YOUR ATTENTION!**