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Improved insight into the dissolution behavior of amorphous drugs by *in situ* solid-state analysis

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Outline

- Introduction
- Case study
 - Dissolution testing of amorphous carbamazepine
 - Monitoring solid-state transformations (PLS-DA)
 - Quantifying solid-state transformations (PLS)
- Conclusions


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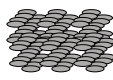
Introduction

Solid-state forms


- Solids can exist in crystalline (anhydrates, hydrates, solvates, cocrystals) and amorphous forms
- Amorphous state differs from the crystalline state
 - No long-range molecular order
 - Different physical, chemical and mechanical properties
 - E.g. melting point, solubility, compressibility, stability



Polymorph I




Polymorph II



Amorphous

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Amorphous state

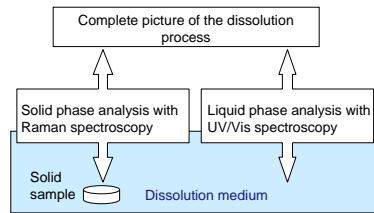
- The number of poorly water soluble drugs is constantly increasing
- Due to the higher solubility amorphous state provides a possibility to increase the dissolution rate of poorly water soluble drugs
- Stability creates problems
 - The solubility advantage is lost if the amorphous form transforms into the crystalline form during dissolution

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Aims of the study

- To use *in situ* Raman spectroscopy to gain understanding of the solid-state changes that might occur during the dissolution testing of amorphous model drug
- To combine Raman spectroscopy with multivariate analysis to improve the interpretation of the spectroscopic data

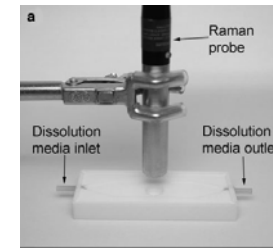
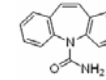


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Materials and methods

- Materials
 - Carbamazepine (CBZ)
 - Polymorph I
 - Polymorph III
 - Dihydrate
 - Amorphous
- Methods
 - Dissolution in phosphate buffer pH 7,2
 - UV-Vis spectroscopy
 - Solid-state analysis
 - *In situ* Raman spectroscopy
 - Monitoring (PLS-DA)
 - Quantification (PLS)
 - Quaternary mixture design (12 mixtures in triplicate)
 - XRPD



Aaltonen *et al.*, 2006, J. Pharm. Sci., 95(12)

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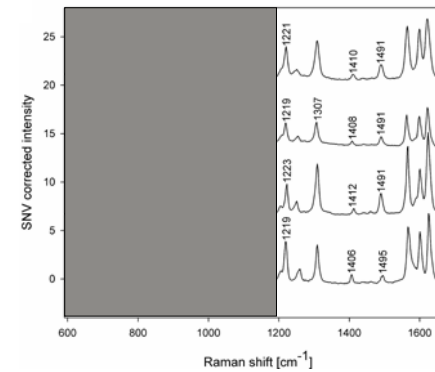
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Results

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Raman spectra of Carbamazepine (CBZ)

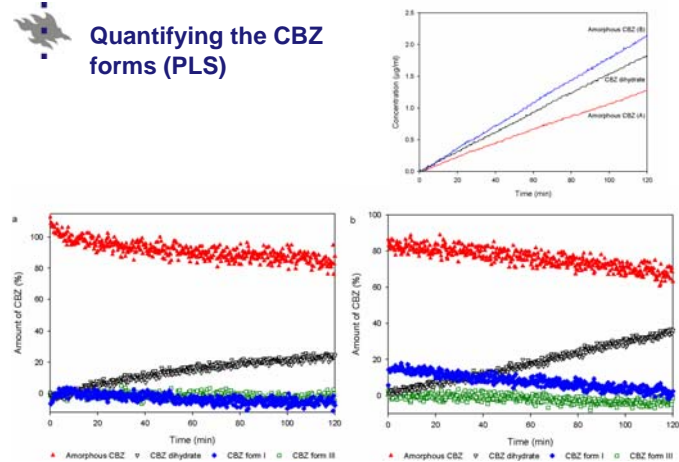


Kogermann *et al.*, 2007, J. Pharm. Sci., 96(7)

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Quantifying the CBZ forms (PLS)



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Conclusions

- The advantage of the higher dissolution rate from the amorphous material might be lost if the drug converts to a crystalline form during the dissolution.
 - The dissolution rate will gradually change to that of the crystalline form.
- Analysis of the dissolved drug concentration is not always enough to explain the phenomena that occur during dissolution.
- Solid-state analysis using Raman spectroscopy combined with multivariate methods can be used to gain information about the solid-state transformations that might occur during dissolution.

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