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Applying MCR-ALS analysis of FT-Raman data for the monitoring of crystal form behaviour of Piroxicam in various solvents and temperatures

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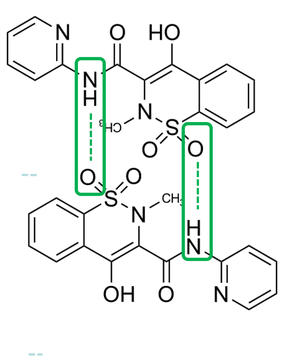
INTRODUCTION

In this work, MCR-ALS analysis were used to monitor the crystal behavior of Piroxicam, in water/ethanol mixtures, using a FT-Raman. Previous studies showed that Piroxicam did change form into a hydrate when water was present. Since form 1 is known to transform into form 2 in ethanol solution it is possible that the transformation is from the less stable form 1 into the more stable form 2 before the monohydrate is formed.
By using a Raman probe, continues measurements could be performed and by analyzing with a MCR-ALS model, the percentage of different forms could be determined. Experiments were run at 37, 40, 60 and 80°C in 70 mol% ethanol/water, 99.9 wt% ethanol and pure water. All data were collected using a Bruker FT MultiRAM with a 1064 nm Nd:YAG laser and a R361 RamProbe with immersion tube RT101-25. Both PLS Toolbox and MCR-ALS command line tool were used for data import, preprocessing and analysis.

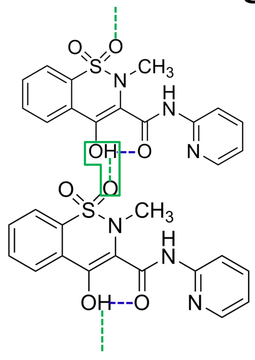
By using MCR-ALS it was not necessary to obtain standard spectra for the different forms, and also it was possible to determine the number of chemical components ie. Forms present in an experiment. This made it possible to reconstruct spectra of pure species as well as determine the relative concentrations of the different forms. Since pure spectra were available it was also possible to do a comparison. This showed only a change in overall intensity and with lower noise levels in reconstructed signals.
During the work, the laser burned out and had to be replaced, this led to a tenfold decrease in signal intensity, however this demonstrated that MCR-ALS can be a very robust method since predictions still matched those of previous experiments.

RESULTS

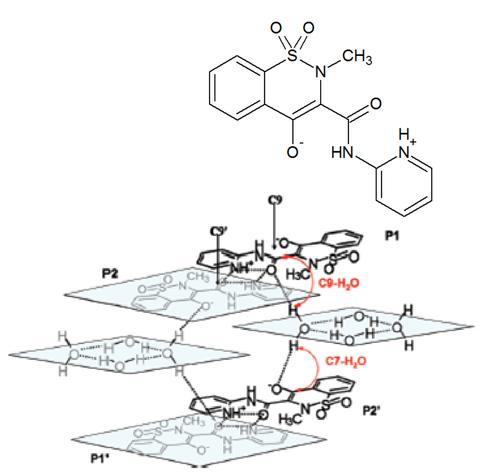
Forms and bonding behaviour



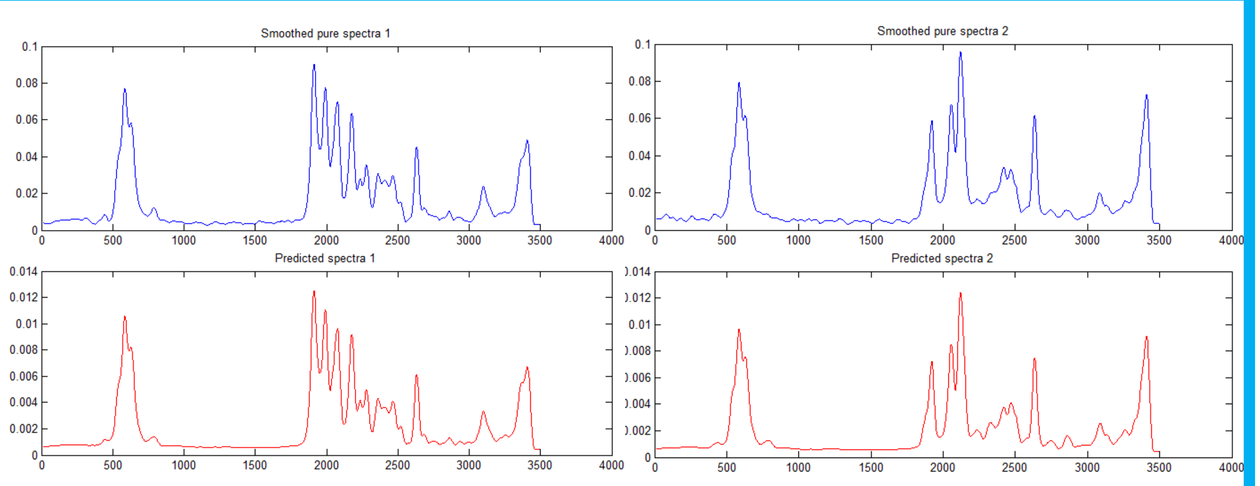
Form 1 - Cubic form
Less stable

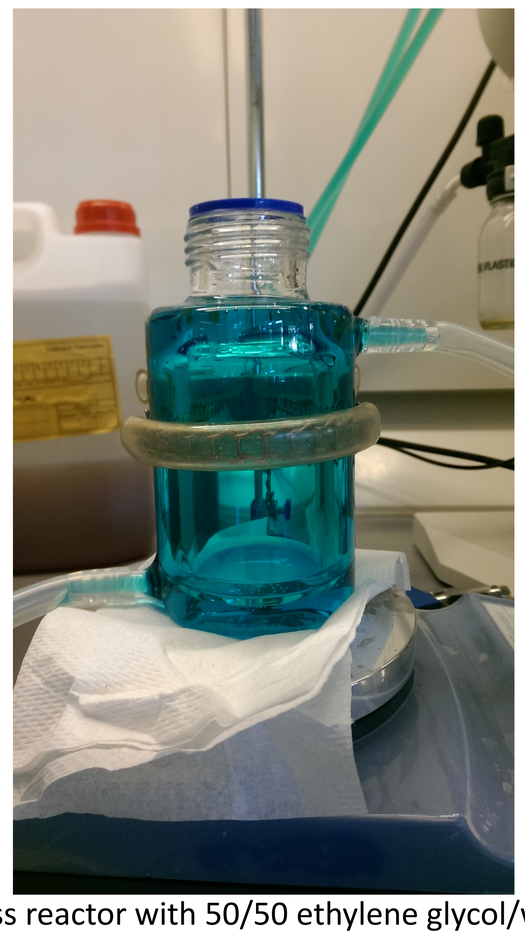


Form 2 -Needle form
More stable



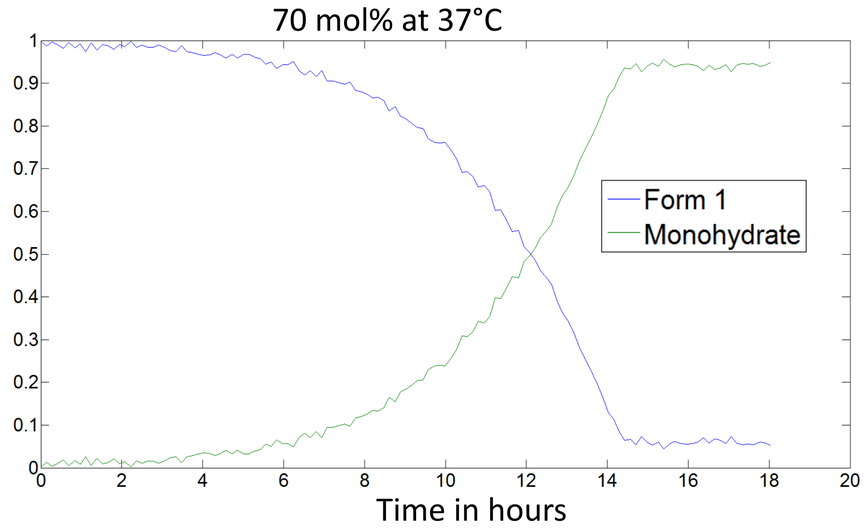
Zwitterionic form in the monohydrate

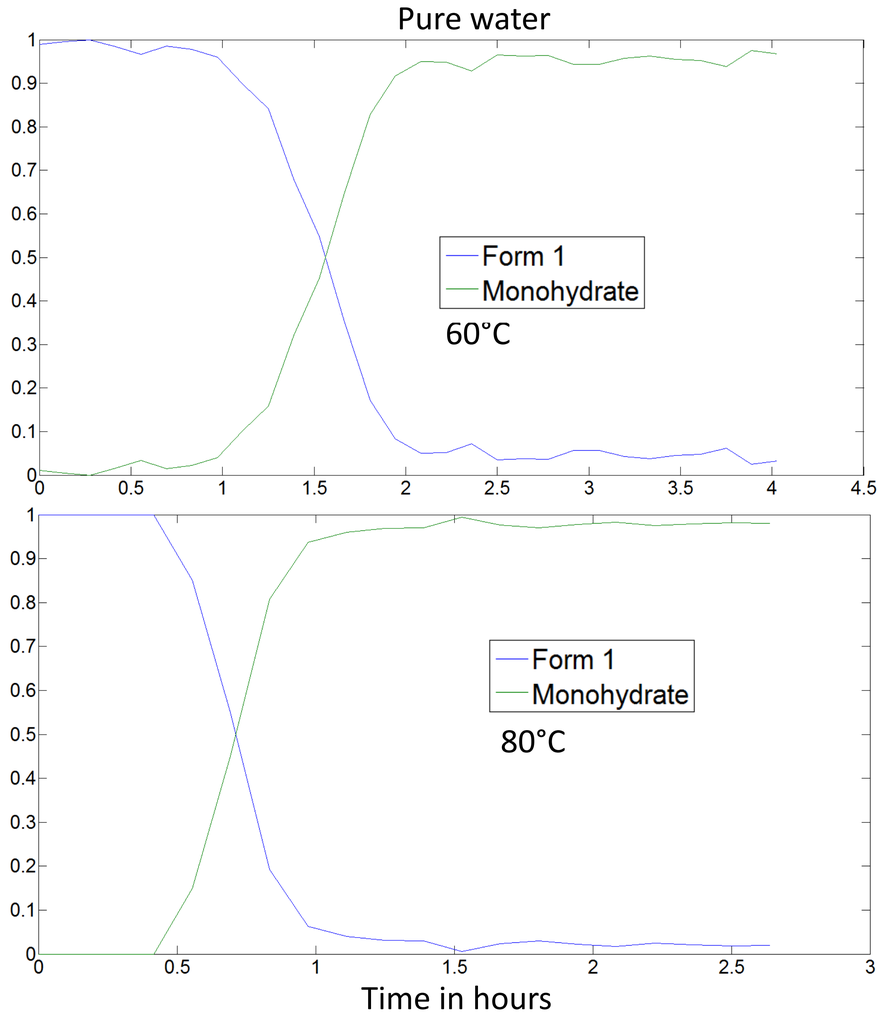




Glass reactor with 50/50 ethylene glycol/water cooling

Raman probe and immersion tube





MCR-ALS results

Solvent	T [deg cel]	N comp	LoF in PCA [%]	LoF in exp [%]	Intercept [Hours]
70 mol% EtOH	37	2	1.6722	3.862	12.08
70 mol% EtOH	60	2	3.0269	5.1492	29.81
99.9% EtOH	40	1	-	-	-
99.9% EtOH	40	1	-	-	-
99.9% EtOH	60	2	5.5514	6.3458	24.49
water	60	2	3.4554	7.1543	1.52
water	80	2	6.378	7.9167	0.695
water	80	2	2.64	5.4593	0.5556
water	80	2	3.0625	7.4389	0.5561

CONCLUSIONS

- In the solvent containing 70 mol% and 100 mol% of water, piroxicam form I transformed to the monohydrate, no intermediate form (form II) was found during the phase transformation.
- In the 99.9% ethanol solvent, experiments at 60°C showed a transformation from form 1 to form 2 after more than 24 hours. At lower temperatures no change was found after 48 hours.
- MCR-ALS made it possible to determine the time before piroxicam started to change form and the rate of change.
- MCR-ALS was found to be able to cope with a tenfold intensity drop while still being able to reconstruct spectra and predict relative concentrations.
- The transformation rate was found to be dependent on temperature and solvent composition.