

Online Monitoring of Dissolved and Crystalline Polymorphic Phases via Raman Spectroscopy and PLS-Based Soft Sensor

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MOTIVATION

Real-time quantification of **dissolved** species and **crystalline polymorphs** remains a major challenge in pharmaceutical crystallization. As polymorphs differ in properties that affect drug performance, robust monitoring is essential. **Automated platforms** integrating advanced sensors, PAT, and intelligent control enable improved observation of crystallization behaviour and support early design-space screening. This work demonstrates an online approach for measuring dissolved and polymorphic composition and linking operating conditions to polymorph outcomes.

RAMAN SPECTROSCOPY

- Used to distinguish polymorphs.
- Ideal for real-time, online analysis.
- Compatible with several common solvents.

PARTIAL LEAST SQUARES (PLS) REGRESSION

- Utilizes entire Raman spectrum.
- Manages spectral overlap.
- Reduces data dimensionality, retains trends.

OBJECTIVES

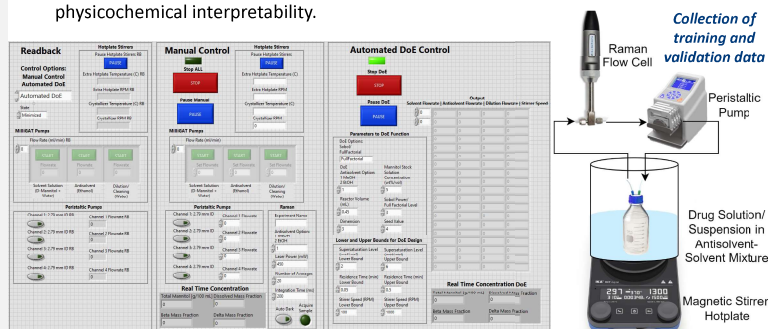
- Develop an accurate and robust multivariate PLS model able to distinguish and quantify dissolved and suspended polymorphic crystal forms.
- Implement the developed models for real-time monitoring of continuous-flow crystallization processes.

MATERIALS AND METHODS

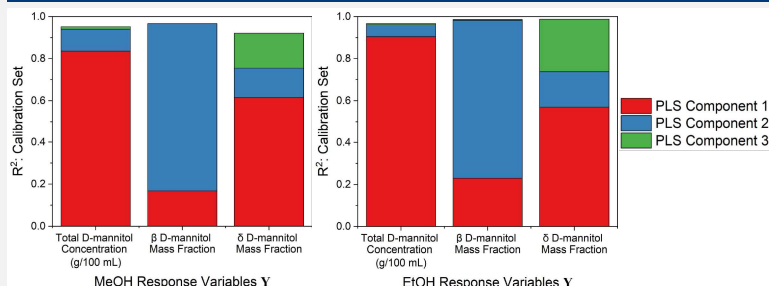
- Automated platform to control all equipment was developed on LabVIEW.
- D-mannitol has three forms: α , β and δ . In this work, the β and δ forms were used.

SOLVENT **ANTISOLVENT** **DRUG** **TEMPERATURE** **ANTISOLVENT-SOLVENT RATIO**
1) Methanol β D-mannitol
2) Ethanol Water δ D-mannitol 25 °C 3.25 g/g

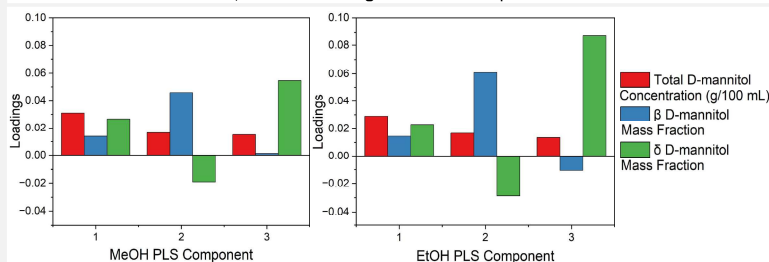
- Calibration:** D-mannitol samples were prepared across known dissolved and suspended concentrations. Raman spectra were split into training and validation sets for PLS modelling with PyPhi^[1].
- Preprocessing:** Baseline correction, smoothing, normalization, and subtraction of antisolvent-solvent backgrounds isolated D-mannitol signals.
- Design & Modelling:** A full factorial calibration with latin hypercube validation ensured broad coverage, and PLS components were selected based on physicochemical interpretability.



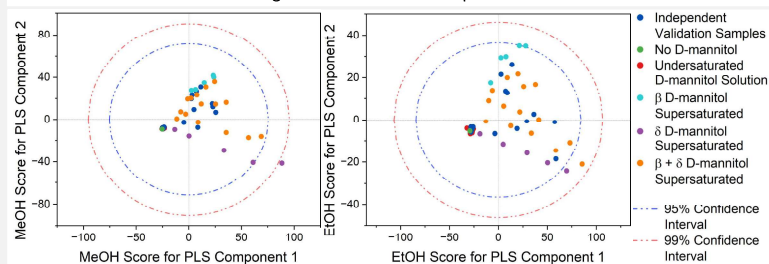
RESULTS AND DISCUSSION



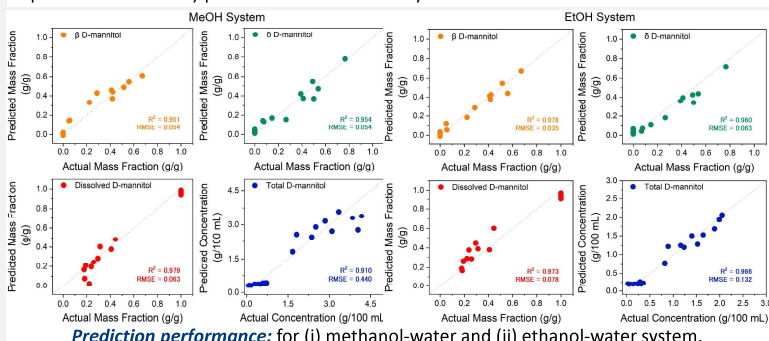
R^2_Y per variable: proportion of variance in each response variable explained by the PLS model, calculated using calibration-set predictions.



Y-loadings for PLS components: contribution of each response variable to PLS components, reflecting correlations in the response matrix.



PLS scores: projection of samples onto the first two PLS components, used to assess class separation and identify potential outliers in the crystallization data.



Prediction performance: for (i) methanol-water and (ii) ethanol-water system.

CONCLUSIONS AND FUTURE WORK

ACHIEVEMENTS

- Developed a **Raman-based soft sensor** capable of real-time, inline quantification of total concentration and polymorphic composition during antisolvent crystallization.
- Created a **LabVIEW-based automated platform** for experimental equipment, capable of running list of experiments and giving real-time dissolved concentration and polymorphic composition.

FUTURE WORK

- Examine how initial solvent concentration, stirrer speed, residence time and other operational parameters impact the **formation of specific polymorphs** using LabVIEW-based automated platform.
- Possible further development of the automated platform to achieve **closed-loop** design space screening.

REFERENCES

- [1] S. G. Munoz, Pyphi v3.0, <https://github.com/salvadorgarciamunoz/pyphi/releases/tag/v3.0>, 2023.