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Application of multivariate curve resolution to *in situ* THz - Raman spectroscopy of amorphous solid dispersions in pharmaceutical products

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Objectives

- To investigate the solubility limit and changes in polymorphic form of mefenamic acid (MFA) in a matrix of sorbitol and Soluplus® with THz-Raman spectroscopy
- To define the concentration ratio of amorphous and crystalline states

Introduction

Off-line techniques such as differential scanning calorimetry (DSC) can be used to characterize solidified extrudates from a hot-melt extrusion (HME) process. However, off-line measurements are not representative of the melt mixture in the HME barrel. THz-Raman spectroscopy can be used to monitor solid dispersions of the melt mixture *in situ*. To avoid needing off-line reference measurements, calibration-free methods for spectral analysis are advantageous. Multivariate curve resolution (MCR) is a calibration-free method of resolving mixture spectra into pure component contributions using an iterative optimization within a set of constraints. The outputs are pure component spectra and concentration profiles for each component.

Materials and methods

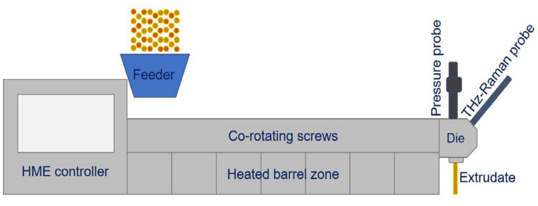

Figure 1 Schematic of extruder coupled with THz-Raman probe*

- Mixtures of 10 – 50% (w/w) MFA, sorbitol (Parteck® SI 150), and polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft copolymer (Soluplus®) were extruded at different temperatures.
- Figure 1 shows the experimental setup used to collect *in situ* THz-Raman spectra to determine the crystalline content of solid dispersions of the melt mixture.

*Adapted from Bordos, E., Islam, M. T., Florence, A. J., Halbert, G. W., & Robertson, J. (2019). *Molecular Pharmaceutics, 16*(10), 4361-4371.

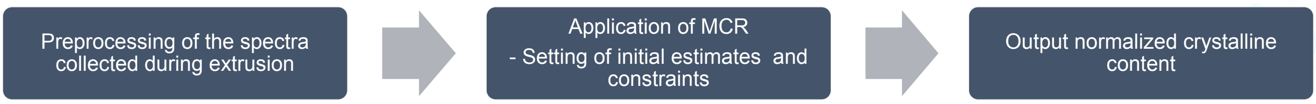

Figure 2 Schematic of data processing

Results and discussion

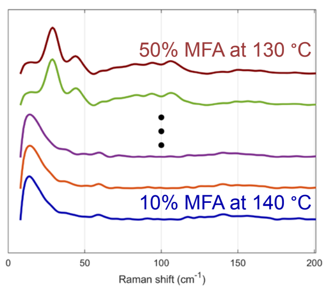

Figure 3 Selected THz Raman spectra acquired for 10 – 50% (w/w) MFA mixtures, which were extruded at different temperatures.

- Figure 3 shows selected spectra from the 75 HME experiments performed.
- Spectra collected for 10% MFA at 140 °C and 50% MFA at 130 °C illustrate those obtained from melts that are amorphous and crystalline, respectively.
- The appearance of characteristic peaks at 29 and 44 cm^{-1} indicates the presence of crystalline MFA.
- The data matrix comprising 75 THz Raman spectra was analysed using MCR:
  - Initial estimates: none.
  - Constraints: non-negativity (spectra and concentration) and closure (concentration).

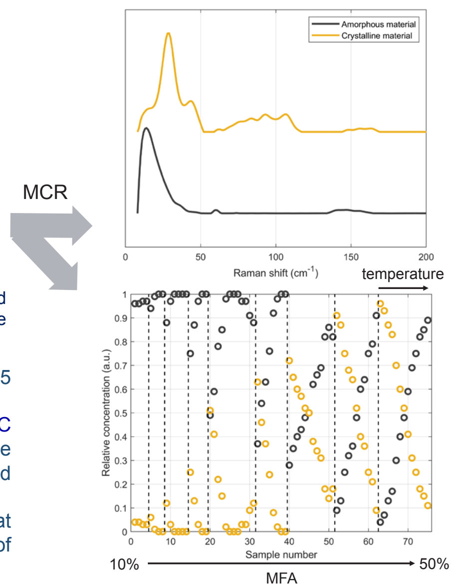

Figure 4 (top) Pure component spectra and (bottom) concentration profiles obtained from MCR. The 9 sections in the lower plot show the effect of extrusion temperature at the 9 different MFA concentrations.

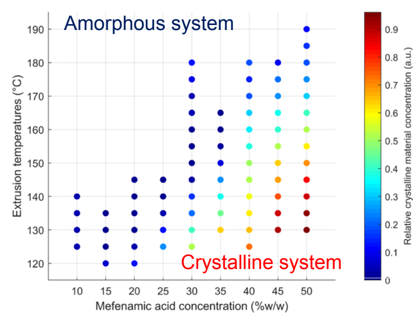

Figure 5 The crystalline content (normalised to 50% MFA at 130 °C) of each mixture as a function of MFA concentration and extrusion temperature

- Figure 4 (top) shows the pure component spectra obtained, which correspond to MFA in the amorphous (grey) and crystalline (yellow) states.
- The relative concentrations of amorphous and crystalline MFA obtained at different temperatures and concentrations of MFA are shown in the lower plot in Figure 4.
- Figure 5 shows the crystalline content of each mixture normalised to the 50% MFA mixture extruded at 130 °C.
- The most crystalline samples were obtained at high MFA concentrations and low extrusion temperatures.

Conclusions and future work

- MCR can be used to successfully resolve the THz-Raman spectra of melt mixtures into contributions arising from 2 different molecular arrangements of MFA along with the corresponding relative concentration profiles.
- This information will be useful in the development and monitoring of extrusion processes, where changes in processing conditions affect molecular arrangement.

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