Project 7: ***Crystal Transformations and Crystallisation Methodologies***	Author: **Weiyi Su**
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	Institute: University College Dublin

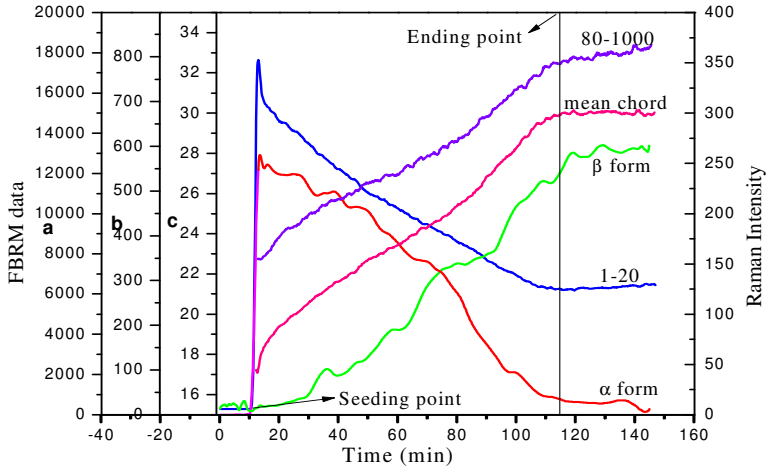
Title: Polymorphic transformation monitoring and the influence of operating parameters

Principal Focus: Raman Spectroscopy was applied to identify different polymorphs of D-mannitol, and the difference of the spectra was distinct with the obvious characteristic peaks of each form [1]. To *in-situ* monitor the polymorphic transformation of D-mannitol, Raman Spectroscopy, FBRM and PVM were used to track the transformation process from the metastable α form to the stable β form. The effect of different parameters, such as temperature, solvent and seed mass on transformation time were investigated in order to get a clear profile of the transformation mechanism.

Transformation Experimental:

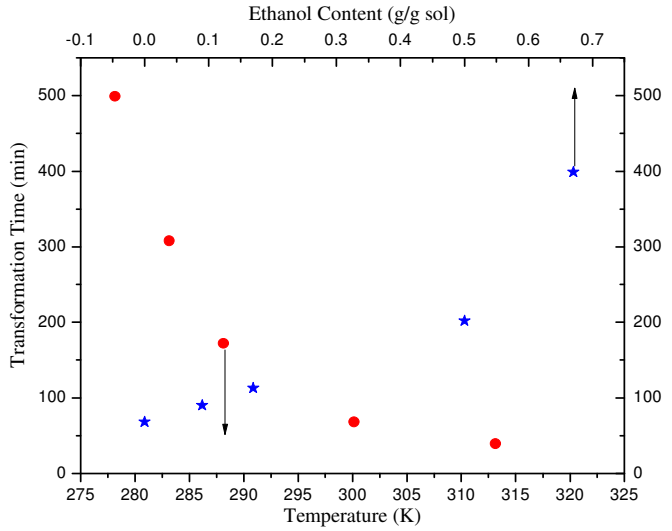
1. Prepare a saturated solution with respect to β mannitol in a 100 mL Mettler-Toledo EasyMax system.
2. Put 4 g α mannitol which is obtained in the lab to the solution to initiate the transformation.
3. Start the *in-situ* tools (Raman Spectroscopy, FBRM and PVM) to monitor the changes of characteristic peak height, crystal size and morphology.

Note: The characteristic peak of α mannitol was chosen at 1355 cm-1, while the peak 1365 cm-1 was used to denote β form.



a---axis for 1-20 (counts/sec, No Wt); b---axis for 80-1000 (counts/sec, No Wt); c---axis for Mean Chord Length (No Wt).

Figure 1: FBRM data and Raman intensity change during the polymorphic transformation.



Parameters Influence Experimental:

1. Get saturated solution of β mannitol in different conditions. (While changing solvents, temperature maintains at 27 °C. All the experiments proceed in water when research the influence from temperature.)
2. Add 4 g α mannitol seeds to the saturated solution, and introduce the *in-situ* Raman Spectroscopy to measure the transformation time.

Note: The transformation time is defined as the difference between seeding and ending point.

Figure 2: Effect of temperature and solvent composition on transformation time

Discussion: Experiments conducted with FBRM, PVM and Raman spectroscopy have shown how these in situ techniques can track changes in particle dimension, morphology, and crystal structure. From Figure 1, the dissolution of metastable form and crystallization of stable form are obvious, which are the two main steps so solution-mediated transformation mechanism. And the transformation time reflected by FBRM and Raman is consistent. The operating temperature and solvent composition had a dramatic impact on the transformation time of the polymorphs according to Figure 2. In addition, the seed mass of α mannitol also has effect on the transformation time.

Future Work: As polymorphs may have different functionalities and physical properties, such as bioavailability, solubility and stability [2], it is essential to investigate the appropriate conditions for each polymorph and the probability of transition between them. In order to investigate the transformation kinetics from α to β form of mannitol quantitatively, a useful model will be established for the dissolution and crystallization process. Some necessary parameters, such as the solubility of the metastable form of mannitol, as well as the rate of nucleation and growth of the stable form of mannitol should be obtained first for the modelling work.

[1] Geoff G.Z.Z.; Devalina L.; Eric A. S. *Phase transformation considerations during process development and manufacture of solid oral dosage forms*, Advanced Drug Delivery Review, 2004, **56**: p.371-390