Electronic Supporting Information for 'Stabilisation of Metastable Polymorphs: The Case of Paracetamol Form III'

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DSC-Raman Experiments

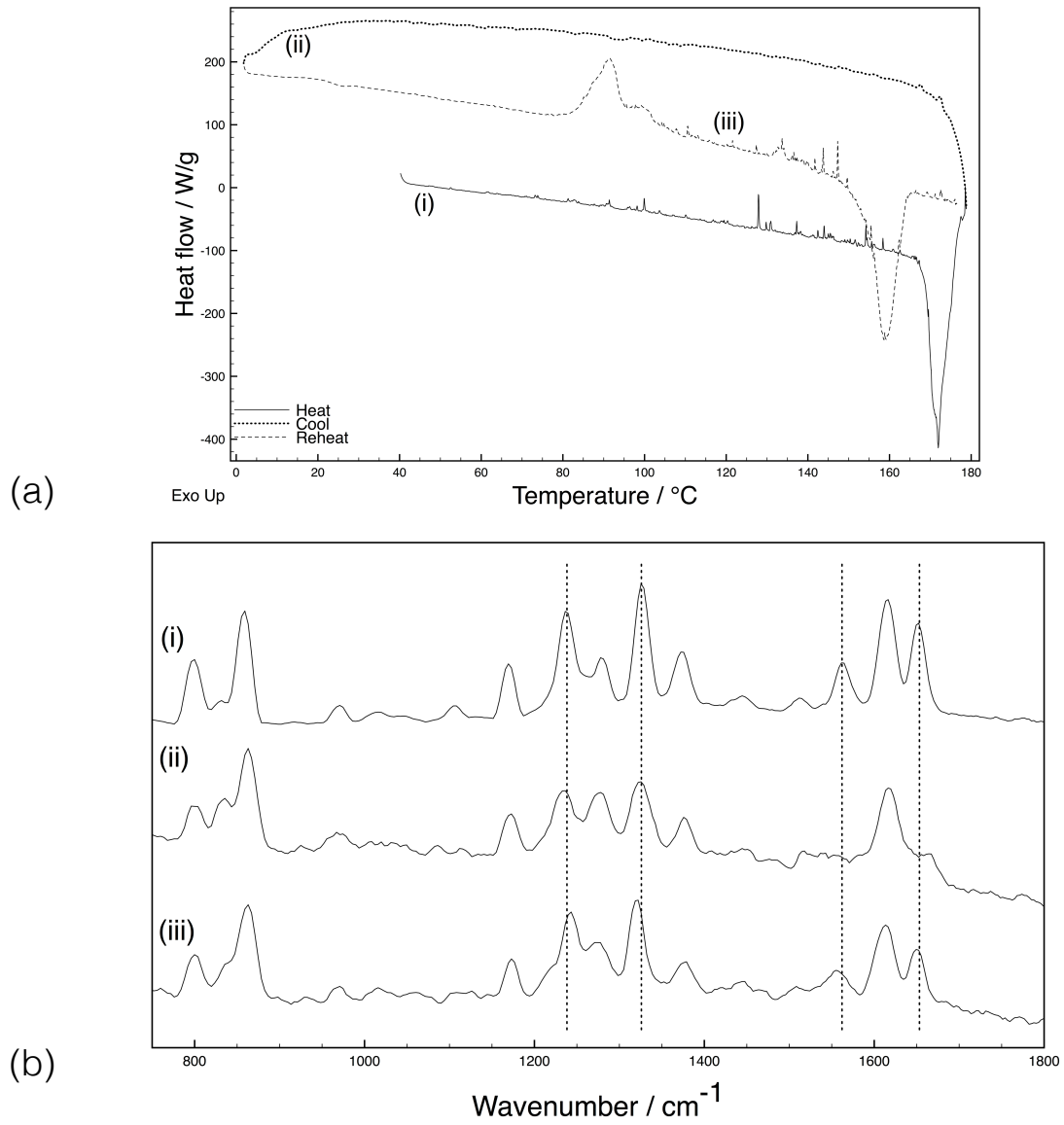

Figure S1. (a) DSC and (b) Raman spectra recorded at (i) 30°C before heating, (ii) 30°C after quench cooling and (iii) 130°C after reheating for a 10% HPMC containing sample of paracetamol (annotated with key spectral shifts observed from I to III).

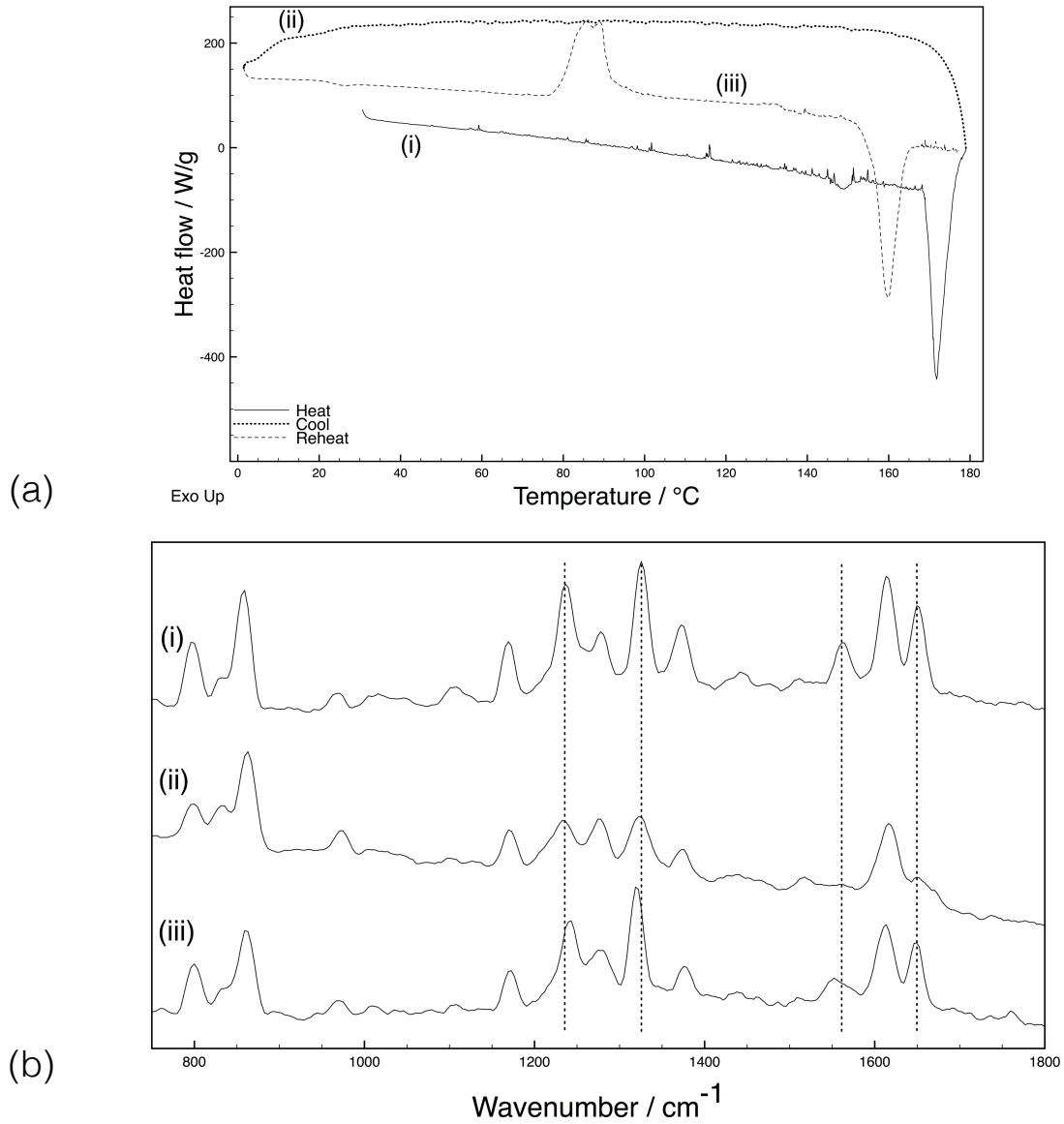

Figure S2. (a) DSC and (b) Raman spectra recorded at (i) 30°C before heating, (ii) 30°C after quench cooling and (iii) 130°C after reheating for a 10% lactose containing sample of paracetamol (annotated with key spectral shifts observed from I to III).

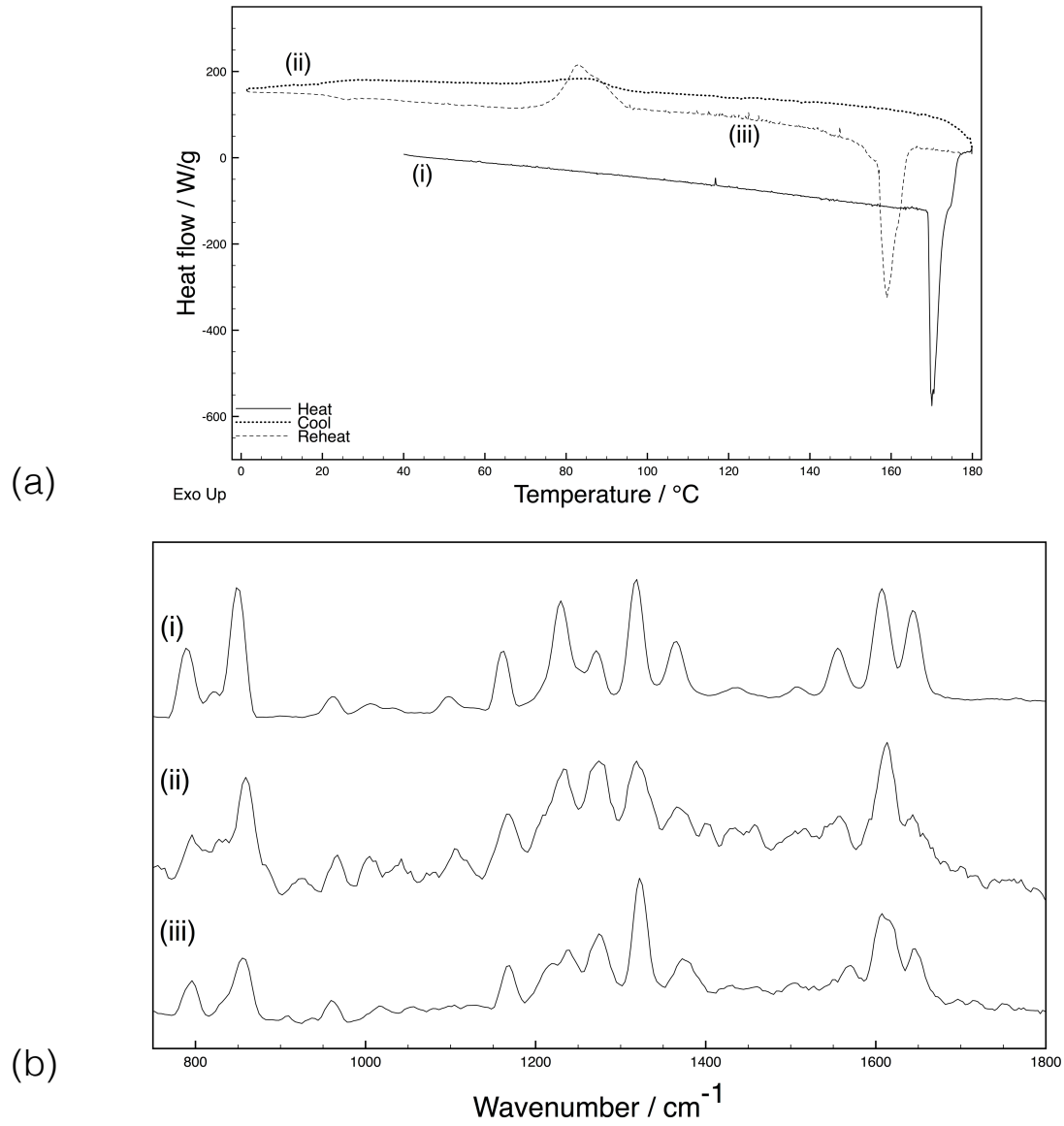

Figure S3. (a) DSC and (b) Raman spectra recorded at (i) 30°C before heating, (ii) 30°C after quench cooling and (iii) 130°C after reheating for an excipient-free sample of paracetamol.

DSC—XRD Experiments

X-ray powder diffraction data were analysed by the Rietveld method implemented within the GSAS suite of programs.

Backgrounds were fitted using a 6-term shifted Chebychev polynomial of the first kind. Lattice parameters and a zero point were refined. A single Gaussian peak shape parameter was refined. In cases where more than one phase was present, the peak shapes for each phase were constrained to be the same. Where more than one phase was present, the phase fraction was refined.

The models used came from the CCDC. The atom positions were not refined. Atom displacement parameters, U_{iso} were set to be 0.15 $Å^2$ in each phase

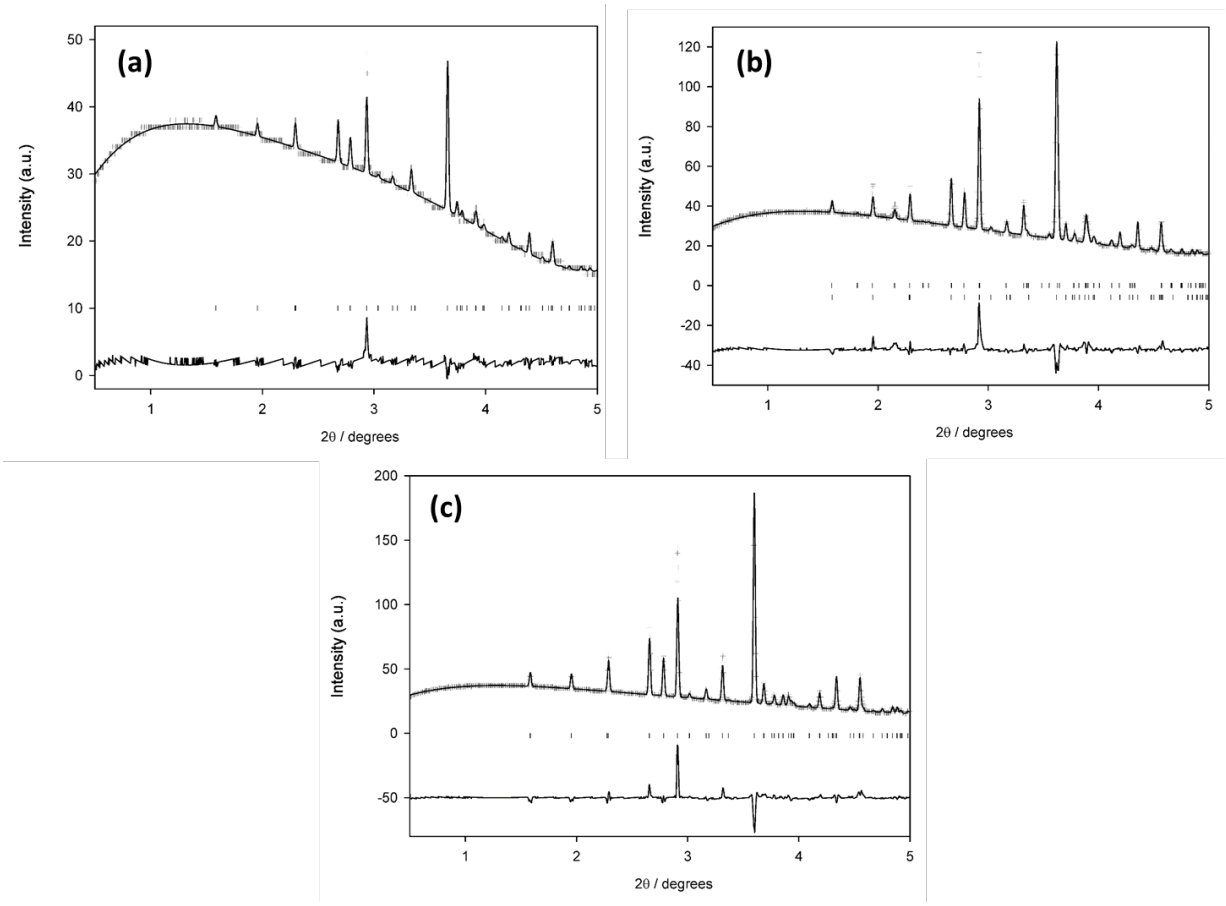

Figure S4: Rietveld refinements of *in-situ* XRD data collected at (a) 40, (b) 110 and (c) 140°C.

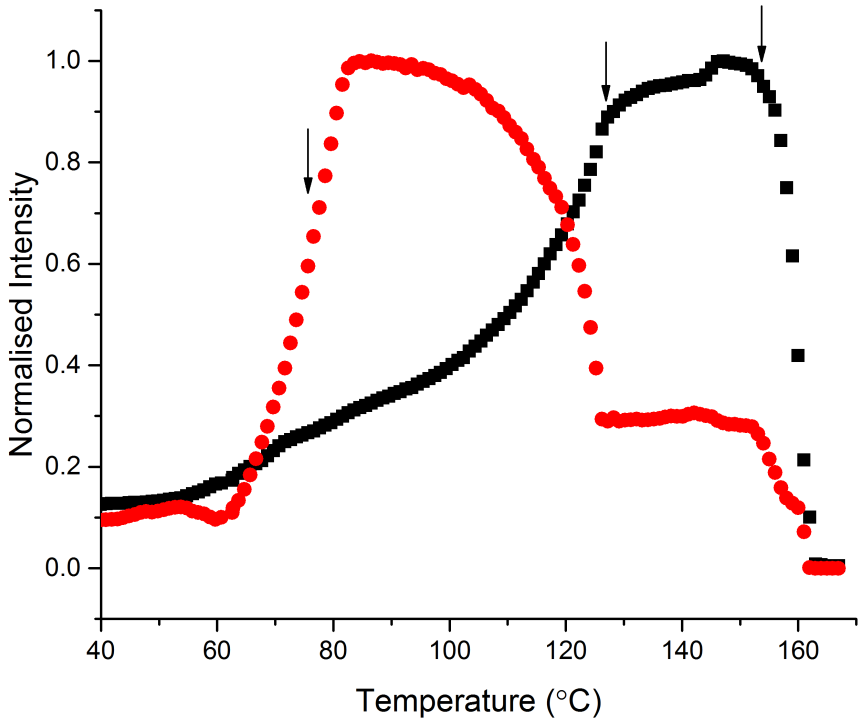

Figure S5: The normalised integrated area under the diffraction patterns for form II (black) and III (red) as a function of temperature. The arrows denote the onset temperatures of each of the three DSC events in Figure 2b.

Table S1: The refined parameters from the Rietveld analyses depicted in Figure S4.

Temperature	**40°C**	**110°C**		**140°C**
No of phases present	1	2		3
Polymorph	II	II	III	II
Space group	Pcab	Pcab	$Pca2_1$	Pcab
a / Å	7.409(2)	7.4885(13)	11.857(5)	7.5283(11)
b / Å	11.815(5)	11.822(3)	8.556(7)	11.842(2)
c / Å	17.122(9)	17.095(6)	14.920(3)	17.110(4)
α / °	90	90	90	90
β / °	90	90	90	90
γ / °	90	90	90	90
Phase fraction / %	100	69.9(9)	30.1(9)	100
CSD reference structure	HXACAN32	HXACAN32	HXACAN29	HXACAN32
R_{wp} / %	0.0182	0.0413		0.0540
R_p /%)	0.0127	0.0243		0.0280

Morphology Prediction

The morphologies for paracetamol form I and III were simulated using the BFDH and attachment energy methodologies. Attachment energies were calculated using the COMPASSII force field with force field assigned charges and Dreiding force field with point charges fitted to the electron density calculated at the hybrid DFT/MP2 level (mPW2PLYP/def2-TZVPPD). The molecular geometries were extracted from the known crystal structures and the hydrogen positions optimised. The crystal geometries and unit cell parameters (HXACAN30 (form I), HXACAN29 (form III)) were optimised in each force field.

In all cases the same set of binding faces were predicted with shifts in the relative sizes. It is clear that the (002) face dominates the plate like morphology of form III (Figure 1), while form I has a blockier structure.

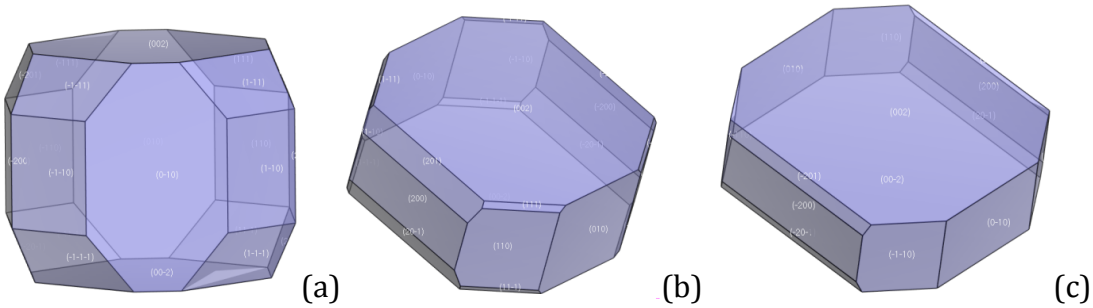

Figure S5. Comparison of the predicted morphologies for PCM form III using (a) BFDH model and the attachment energies model using (b) COMPASSII force field and (c) Dreiding force field.

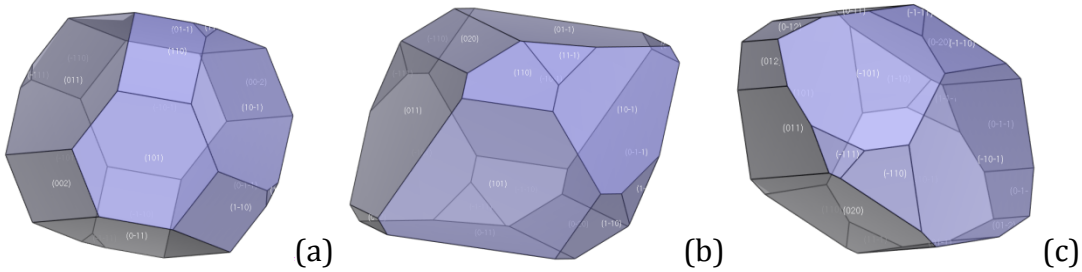

Figure S6. Comparison of the predicted morphologies for PCM form I using (a) BFDH model and the attachment energies model using (b) COMPASSII force field and (c) Dreiding force field.