Supplementary Information

Controlled production of the elusive metastable form II of paracetamol: a fully scalable multicomponent templating approach in a cooling environment

Lauren R. Agnew a,b, Dyanne L. Cruickshank a,c, Thomas McGlone d and Chick C. Wilson a,b,*

a Department of Chemistry, University of Bath, Bath, BA2 7AY, U.K; b EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC), University of Bath, Bath, BA2 7AY, U.K.; c Department of Chemistry, University of Cape Town, Cape Town, Rondebosh 7701, South Africa; d EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC) c/o Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Technology Innovation Centre, 99 George Street, Glasgow, G1 1RD, U.K.

Experimental

PC, 4-BrBA, 4-ClBA and 4-FBA were all purchased from Sigma Aldrich Chemie Gmbh (Steinheim, Germany). Metacetamol (3'-hydroxyacetanilide) was purchased from TCI Ltd. All were used without further purification. Laboratory grade solvents purchased from Sigma Aldrich were used for all crystallisations.

Powder X-ray diffraction (PXRD). PXRD patterns were collected in flat plate mode on a Bruker D8 Advance equipped with monochromated Cu-Kα radiation (λ = 1.54056 Å) in reflection geometry at 298 K.

Differential Scanning Calorimetry (DSC). Differential scanning calorimetry studies were carried out using a Thermal Advantage Q20 DSC from TA Instruments, equipped with Thermal Advantage Cooling System 90 and operated with a dry nitrogen purge gas at a flow rate of 18 cm³ min⁻¹. The samples were placed in sealed Tzero aluminium pans and a heating rate of 5 K min⁻¹ was used. Data were collected using the software Advantage for Qseries (Ver. 5.40 software © 2001-2011 TA Instruments-Waters LLC).

Solubility Measurements. Solubility measurements were carried out in a 60:40 Water:IPA solvent system using a Crystal16 parallel crystalliser from Technobis using turbidity probes on 1mL samples. Vials were subjected to a heat/cool cycle from 20 °C to 75 °C and back again using a heating rate of 0.5 °C min⁻¹ and bottom stirring at 800 rpm using standard magnetic stirrer bars. Data were analysed using CrystalClear software version 1.0.1.614 supplied by Technobis.
Figure S1. Solubility curves of the templating co-formers (a) 4-bromobenzoic acid, (b) 4-chlorobenzoic acid, (c) 4-fluorobenzoic acid
Figure S2. PXRD pattern showing the match of the bulk sample to that calculated from single crystal data.

Figure S3. DSC pattern showing a phase transition between 130-140 °C.
Figure S4: PXRD patterns showing the stability of the form II samples produced over a period of 9 months.