Electronic Supplementary Material (ESI) for CrystEngComm.

Supporting Information

Surface functionalization in combination with confinement for crystallization from undersaturated solutions

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Materials:

Diphenhydramine hydrochloride (DPH) was purchased from BeanTown Chemical (>99.0%). Aspirin (ASA) and nicotinamide (NIC) were purchased from Sigma Life Science (USP grade, Lot #MKBQ8444V and ≥99.5%, Lot #BCBF9698V, respectively). Solvents were purchased at ACS grade or higher purity from Fisher Scientific (Waltham, MA, USA).

Instrumentation and conditions for analysis:

XRPD:

XRPD was performed in a capillary setup using a PANalytical X'Pert PRO (Almelo, the Netherlands) diffractometer at 45 kV with an anode current of 40 mA. The instrument has a PW3050/60 standard resolution goniometer and a PW3373/10 Cu LFF DK241245 X-ray tube.

Samples were loaded in capillary tubes (see later section) and aligned on a goniometer capillary holder in stage capillary spinner mode with a focused point incident beam using a Cu Si focusing mirror. Settings on the incident beam path included: soller slit 0.04 rad, mask fixed 10 mm, programmable divergence slit and fixed ½° anti-scatter slit. Settings on the diffracted beam path include: soller slit 0.04 rad and 1/8°anti-scatter slit. The scan was set as a continuous scan: 2θ angle between 2° and 90°, step size .0167113° and a time per step of 15.240 seconds.

The saturation solubilities of aspirin, nicotinamide, and diphenhydramine hydrochloride in isopropyl alcohol were found by stirring a slurry of the API in solvent at 25°C for several days, filtering the solution, and performing gravimetric analysis. These experiments were repeated in triplicate. The saturation solubility of diphenhydramine hydrochloride in isopropyl alcohol was found to be 38.0 mg/mL and an undersaturated solution of 30.0 mg/mL was prepared. The saturation solubility of aspirin in isopropyl alcohol was determined to be 90.0 mg/mL. An undersaturated solution of 75.0 mg/mL was prepared. Finally, the saturation solubility of nicotinamide in isopropyl alcohol was found to be 46.5 mg/mL and a solution of 40.0 mg/mL was prepared.

Glass capillary tubes were purchased from Hampton Research (Aliso Viejo, CA). The tubes were made of glass #50, with a 1.0 mm OD, wall thickness of 0.01 mm and length of 80 mm. The capillary tubes were packed with Zorbax® or CPG material by scooping powder into the tip, placing the capillary in a larger diameter glass pipette, and tapping to allow gravity to act on the powder to settle. Once packed, the tubes were suctioned at the open end with a 1-mL plastic syringe, using a small piece of rubber tubing to adapt the fit. The filled capillary was then immediately dipped into the undersaturated API solutions to allow the solution to fill the tube. Molten wax was used to plug the end of the capillary, and the tip was then heated in a Bunsen burner flame to seal. Additional capillaries were filled with the API solution and dry commercial API alone.

To check the hypothesis that there exists a critical minimum undersaturation below which the Zorbax ® cannot induce crystallization, solutions of successively decreasing concentrations were tested with the capillary method. The results validate the hypothesis and are shown in Figure S.1 to Figure S.3.

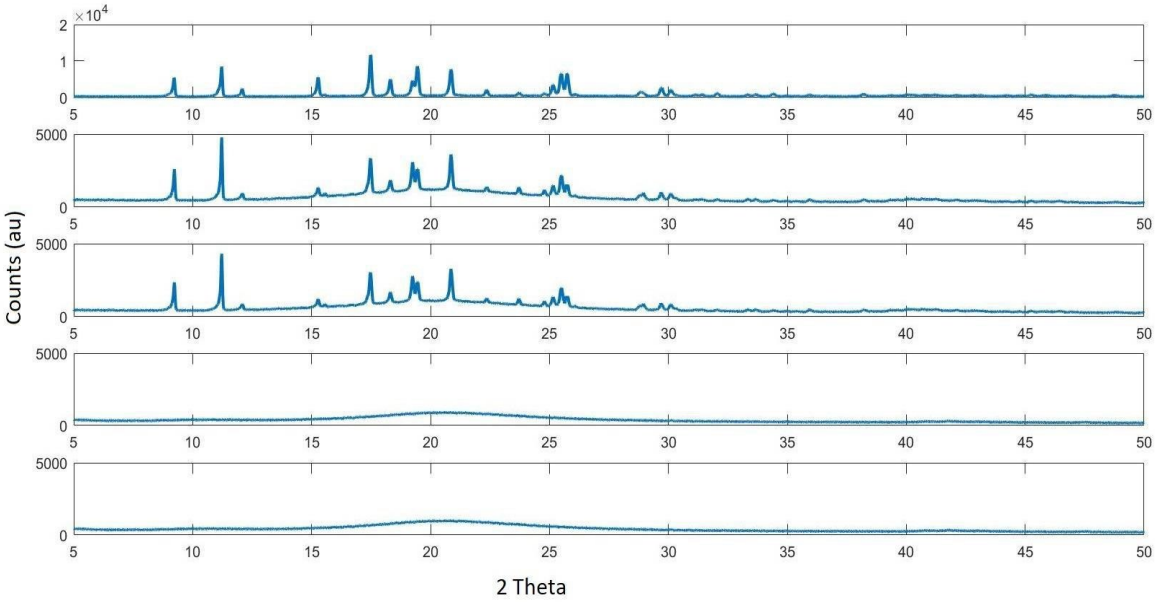

Figure S.1 Diphenhydramine system XRPD scan. From top to bottom: commercial API, 30 mg/mL, 27 mg/mL, 25 mg/mL and 23 mg/mL

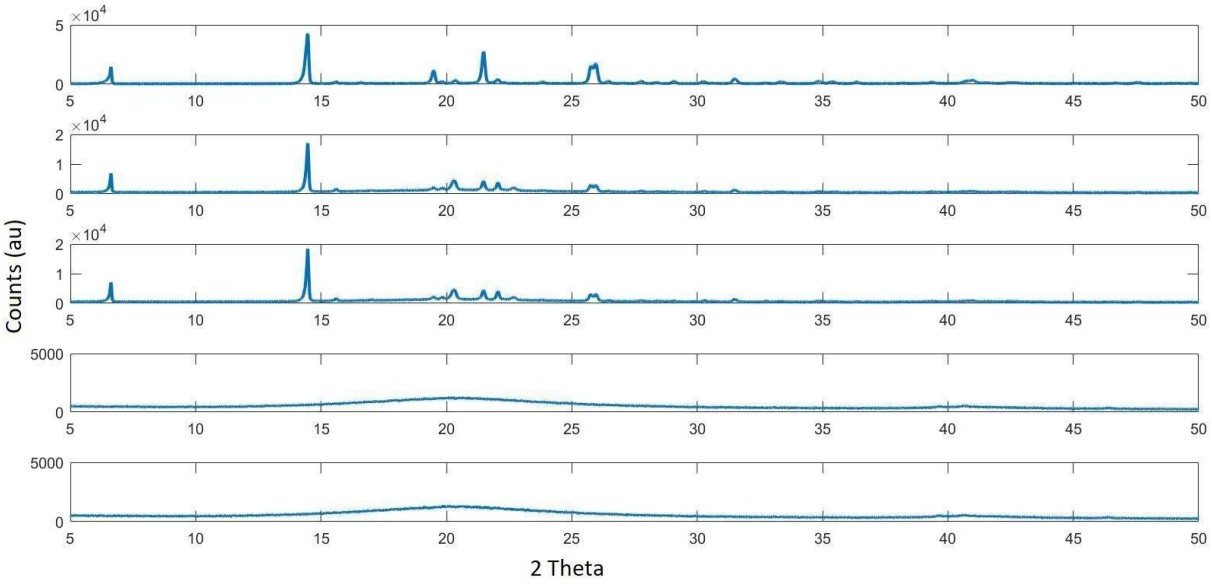

Figure S.2 Aspirin system XRPD scan. From top to bottom: commercial API, 75 mg/mL, 70 mg/mL, 65 mg/mL and 60 mg/mL

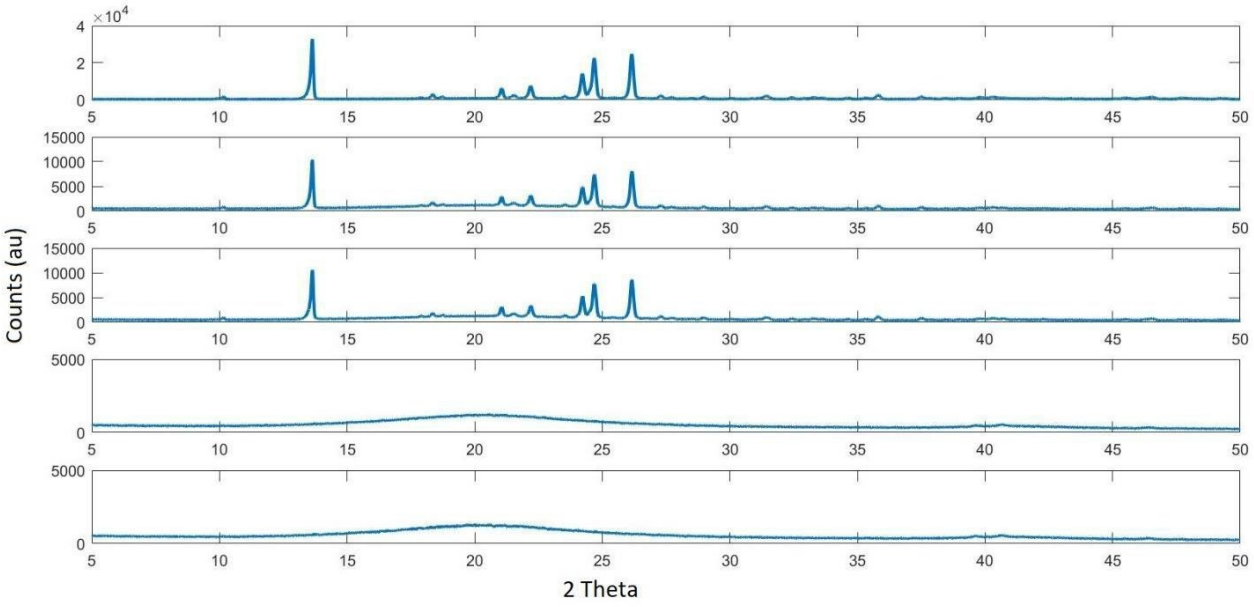

Figure S.3 Nicotinamide system XRPD scan. From top to bottom: commercial API, 40 mg/mL, 35 mg/mL, 30 mg/mL and 25 mg/mL

TGA:

Thermogravimetric analysis (TGA) was performed on a Q500 instrument from TA instruments (Newcastle, DE, USA) connected with a nitrogen gas cylinder to maintain a flow rate of 25 mL/min to maintain an inert gas environment in the sample chamber. Between 5 and 10 mg of sample were loaded on platinum sample pans from TA Instruments. The samples were allowed to equilibrate at 30 °C and then heated at 10 °C/min to 600 °C.

The extent of functionalization on the commercial Zorbax® matrix was studied using TGA. The weight as a function of temperature for one run is shown in Figure *S.*4. The mass loss corresponds to the C8 functionalization. The average mass loss is 12.23% of the functionalized matrix, which translates to the C8 groups amounting to 139.4 mg/g silica matrix. The commercial literature states that the groups are n-octyldimethylsilane (having a molecular weight of 172.4 g/mol) and the nominal surface area of the matrix is 160-180 m^2/g. Thus, the density of groups can be calculated to be $2.86x10^{18}$ groups/m^2 pore surface area corresponding to about 5µmole/m^2. This value can be used for comparison of functionalization efficiency with any functionalization performed in-house in the future.

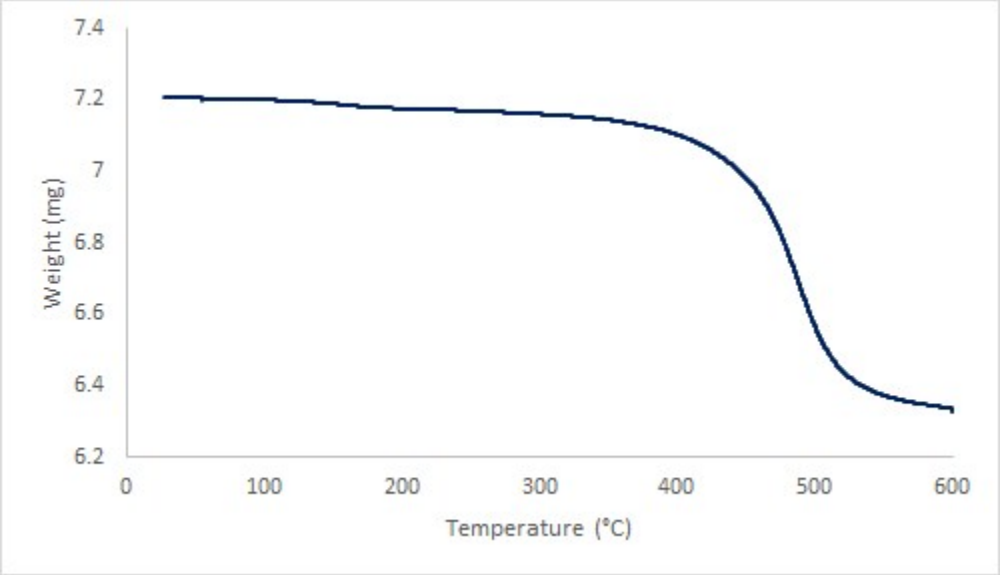

Figure S.4 DSC scan for functionalized Zorbax showing mass loss as a function of temperature

DSC:

A Q2000 instrument from TA instruments was used for the differential scanning calorimetry (DSC) analysis. Inert atmosphere environment was maintained in the sample chamber using a nitrogen gas cylinder set to a flow rate of 50 mL/min. An extra refrigerated cooling system (RCS 40, TA Instruments) was used to widen the available temperature range to between −40 and 400 °C. Tzero® pans and lids were used with ~5 mg of sample. A heating rate of 10 °C/min was applied and the samples were scanned from −20 to 200°C.

The relationship between a crystal of characteristic dimension d and its melting point temperature $T_m(d)$ is dictated by a modified Gibbs-Thompson relationship (from Dwyer et. al.; reference 1 in the main manuscript) given by

$$T_m - T_m(d) = \frac{4\left(\gamma_{solid-substrate} - \gamma_{liquid-substrate}\right)MT_m}{d\Delta H_{fus}\rho_{solid}}$$

Where Tm is the bulk melting point temperature, M is the molecular mass, ρ_{solid} is the density of the solid bulk crystals, ΔH_{fus} is its molar enthalpy of fusion and $\gamma_{solid\text{-}substrate}$ and $\gamma_{liquid\text{-}substrate}$ are the surface free energies of the interface between the substrate and the solid and the liquid phases respectively.

Dwyer et. al. have shown a linear relationship between $T_m(d)$ and 1/d for fenofibrate whereby the decrease in the surface free energies (in the numerator) with crystal size is offset by the decrease in the enthalpy of fusion (in the denominator). Based on their results, the scale of melting point depression, seen in the current work, is consistent with crystal dimensions in the nanometer scale (recall that the average pore size of the Zorbax® matrix is 7 nm).

HPLC:

An Agilent 1100 instrument equipped with a UV diode array detector was used for high performance liquid chromatography (HPLC) analysis of the post-crystallization mother liquor. The assay methods were obtained from US Pharmacopeia version 40 and are listed below:

Diphenhydramine hydrochloride: The column was Ascentis® ES-Cyano column (Sigma-Aldrich) of dimensions 150 mm x 4.6 mm i.d. packed with 5 um particles of 12 nm pore size. An isocratic method with a mobile phase of 50:50:0.5 by volume of acetonitrile, water and trimethylamine adjusted with glacial acetic acid to a pH of 6.5 at a flow rate of 1mL/min was used. The detection wavelength was set to 254 nm.

Aspirin: The column was YMC-Pack ODS-A column (YMC America Inc.) of dimensions 150 mm x 4.6 mm i.d. packed with 3 um particles of 12 nm pore size. An isocratic method with a mobile phase of 69:28:3 by volume of water, methanol and glacial acetic acid at a flow rate of 1mL/min was used. The detection wavelength was set to 280 nm.

Nicotinamide: The column was YMC-Pack ODS-A column (YMC America Inc.) of dimensions 150 mm x 4.6 mm i.d. packed with 3 um particles of 12 nm pore size. An isocratic method with a mobile phase of 20:20:60 by volume of methanol, acetonitrile and water at a flow rate of 1mL/min was used. The detection wavelength was set to 230 nm.