Supporting Information

In situ nanoscale visualization of solvent effects on molecular crystal surfaces

Mikkel Herzberg[a], Anders S. Larsen[a], Tue Hassenkam[b], Anders Ø. Madsen[a] and Jukka Rantanen*[a]

[a] Department of Pharmacy, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark.
[b] Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen, Denmark

Materials and methods

Crystallization: Paracetamol ≥99.0 % (Sigma-Aldrich, Germany) was crystallized in three different water-ethanol mixtures. In 0 % v/v ethanol, 20 % v/v ethanol and 40 % v/v ethanol. To ensure that a degree of supersaturation of two was used in all three mixtures, the solubility of paracetamol as a function of ethanol fraction was estimated using the Jouyban-Acree model[1]. Paracetamol concentrations of 29.80 mg/mL, 61.20 mg/mL and 129.20 mg/mL was prepared by dissolving paracetamol in water-ethanol mixtures containing 0 %, 20 % and 40 % v/v ethanol heated to 50 °C. They were then left at room temperature and crystals began to form. A couple of crystals were removed from each solution for XPRD measurements.

Atomic force microscopy: A paracetamol crystal was removed from the 0 % ethanol (water) solution and dried at room temperature. It was then glued to a glass slice with epoxy (DANALIM), which has previously been shown to be very resistant to different solvents during AFM measurements[2]. The glass slice was mounted on the goniometer of a single crystal diffractometer and the crystal faces were indexed. The glass slice was inserted in a liquid cell in an Asylum Research MFP-3D AFM. Saturated paracetamol solution from the 0 % ethanol solution was added to the liquid cell until the crystal and the cantilever was fully immersed. Olympus Research Biolevers with a spring constant of approximately 15 N/nm were used for the experiments. They were coated using a previously described procedure[2], where the tips were placed in 5.5 M 1-undecanethiol solution resulting in a uniform coating of hydrophobic -CH_3 terminated molecules. The force distance was set to 500 nm and the frequency to 1 Hz resulting in an approach velocity of 1 um/s. The sample rate was kept at 12.500 to ensure a sufficient amount of data points in the force curves. A force limit of 500 pN was used. An optical image of an AFM cantilever over the (-1 -1 0) surface of a paracetamol crystal is shown in Figure S1. The image was focused on the paracetamol surface, which was placed on a glass substrate seen in the bottom right corner. The AFM cantilever in the cantilever holder is shown to left and is approximately 100 μm above the surface. The bright light is the laser, which was positioned directly on the cantilever. The position of the tip was chosen by trying different spots until one with an even surface structure was found. The offset in the instrument covers 90 x 90 μm so the 5 different spots were chosen within this area to prevent upsetting the alignment.

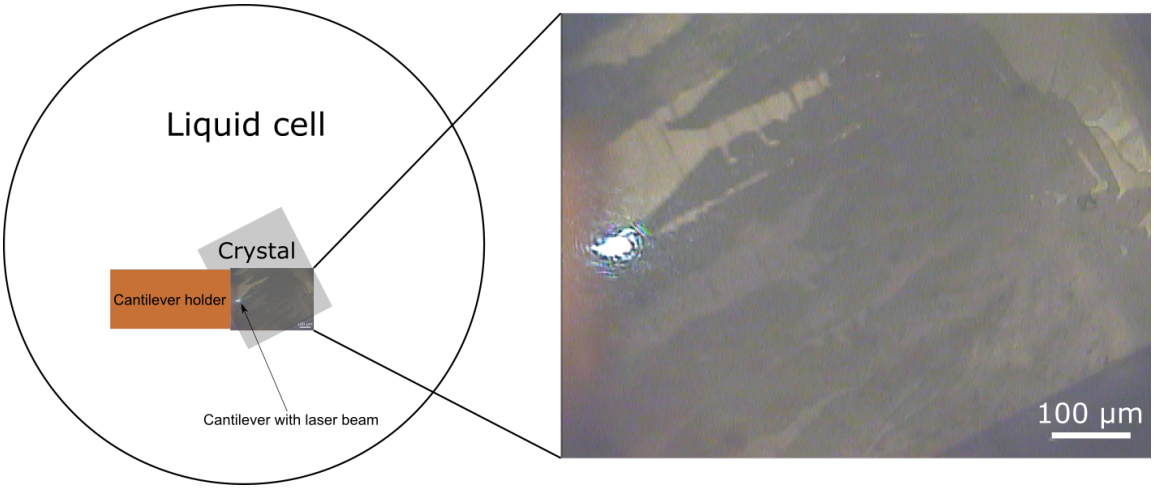

Figure S1: A schematic of the liquid cell arrangement (left) shows the cantilever placement on the crystal. An optical image (right) of the tip placement on the crystal surface is shown with a scale bar.

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A total of 5 force maps, each consisting of 20 x 20 force curves as shown in Figure S2, was obtained over 5 x 5 um. The indentation and adhesion force were extracted from each force curve as shown. They were at least 15 μm apart. The solvent liquid was then changed by exchanging 2 mL of the liquid with 2 mL from the saturated 20 % ethanol solution. This was done three times so 96.5 % had been exchanged in total. In this way, the same paracetamol crystal was measured in 0 %, 20 %, 40 % and 0 % ethanol solutions.

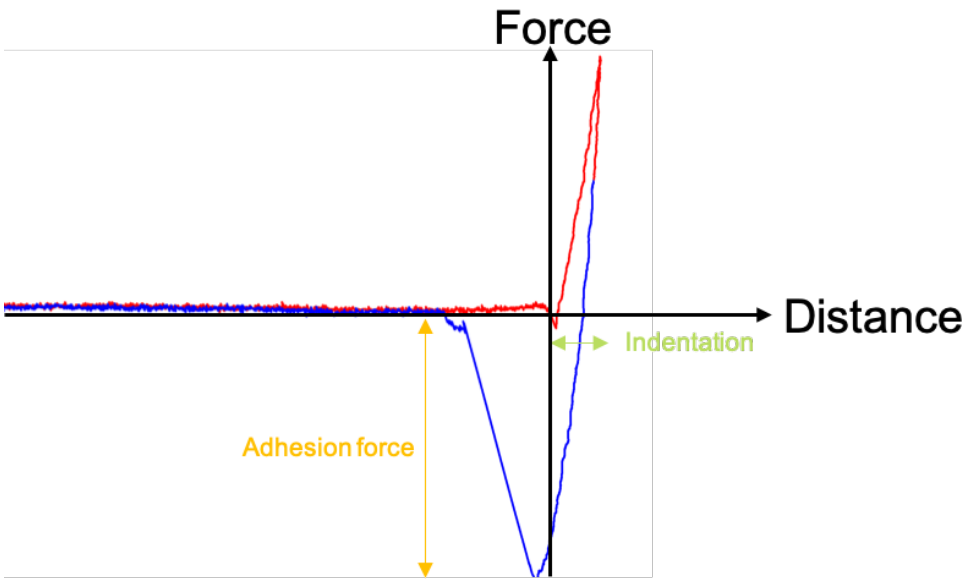

Figure S2: Example force-distance curve obtained on paracetamol exposed to a water-ethanol mixture. The indentation is the distance the tip travels into the surface before reaching the force limit, while adhesion force is the force required to retract the tip.

Molecular dynamics simulations: The simulation box was made from 8 x 5 x 5 unit cells of the paracetamol crystal with total crystal dimensions of 5.3 nm by 5.8 nm by 5.9 nm with 150 nm of free space for the solvent at the (-1 -1 0) surface. Water-ethanol solvent mixtures with 0 %, 20 % and 40 % v/v ethanol were inserted into the free space of the simulation box and paracetamol molecules were added corresponding to concentrations of 29.80 mg/mL, 61.20 mg/mL and 129.20 mg/mL respectively. The CHARMM and CGenFF force field[3] was used for paracetamol, with CGenFF containing parameters explicitly parametrized for paracetamol. The system was equilibrated at 300 K with GROMACS 5.1.4[4] using a semiisotropic barostat with a production run of 600 ns. Coulomb interactions were calculated with Particle mesh Ewald (PME) and Van der Waals forces were calculated with a cutoff of 1.2 nm, which is standard in the CHARMM force field.

X-ray Powder diffraction: X-ray Powder diffraction (XRPD) measurements were performed using an X'Pert PRO diffractometer (PANalytical, Netherlands) using Cu Kα radiation. An angular increment of 0.04/s and a count time of 2s was used and the acceleration voltage and current were set to 45kV and 40mA. A crystal of roughly 2 mm on each side from each sample was ground and placed on aluminium sample holders. All measurements were taken from 5° to 35° 2θ with a step size of 0.05°/s and were performed in triplicate. Results were exported as text files and analysed in Matlab 2018b.

Single-crystal X-ray Diffraction: The paracetamol crystals were face indexed using the Apex3 program (Bruker AXS Inc., Madison, WI) while glued to a glass slice fitting in the AFM liquid cell. This was done on a Bruker D8 Quest (WI, USA) using microfocused Cu Kα radiation at room temperature. The indexing was based on the determination of unit cell and orientation matrix using about 500 reflections collected in three sweeps, each spanning 15 degrees of rotation, collecting 30 frames (0.5 degrees per frame), 10 seconds per degree.

Estimation of diffusion layer

The Noyes Whitney equation[5] is a well-established description of the dissolution rate of particles

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$$\frac{dC_b}{dt} = \frac{D_m A_S}{V_b \delta}[C_S - C_b(t)],$$

where C_b is the bulk concentration, C_s is the surface concentration, D_m is the diffusion coefficient, A_s is the surface area, V_b is the container volume and δ is the diffusion layer thickness defined as

$$\delta(t) \equiv \frac{C_S - C_b}{-\left(\frac{\partial C}{\partial r}\right)_{r \to R}},$$

where r is the container diameter and R is the particle diameter. In this way, the diffusion layer is not a physical entity, but a description of the concentration gradient close to the surface. Literature values are available for the rate constant *k* defined as

$$k = \frac{D_m A_S}{V_b \delta},$$

and the diffusion constant for a similar system. The rate constant k, has been measured to 0.026[6] while the diffusion constant D_m has been measured to 1.24 x 10^{-9} m^2/s[7], both in water. By estimating the surface area A_s to 24 x 10^{-6} m^2 and the container volume to 2 x 10^{-4} m^3, the diffusion layer thickness is approximately 6 nm.

Molecular dynamics simulations

The molecular dynamics (MD) simulations shown in Figure 4 are cropped to better visualize the solid-solution interface. A full simulation box is shown for the system with 40 % ethanol in Figure 4c with a scale bar to show the dimensions of the simulated systems. All the simulations had the same size. A video of the simulation can be found at: https://www.youtube.com/watch?v=jlv1KSs06jk. Ethanol molecules are not shown in the video.

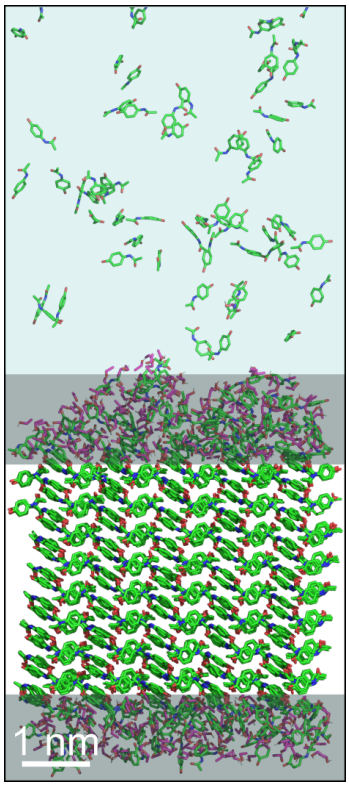

Figure S3: Molecular dynamics (MD) simulation showing the (-1 -1 0) surface of paracetamol (green) exposed to 40 % ethanol (pink). A *dynamic heterogenous disordered surface* (*DHDS*) layer is present in the solid-solution interface. Stable crystal surface layer indicated with white, DHDS with grey and liquid phase with blue background.

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The fractional mass density of the paracetamol molecules in DHDS layer has been calculated by finding the paracetamol molecules within 1.5 nm of the crystal surface. As can be seen in Figure S4 the fractional mass density rises steadily during in the simulation until it reaches a plateau at the end. This indicates that the simulation has reached an equilibrium and that the DHDS differs from the solution.

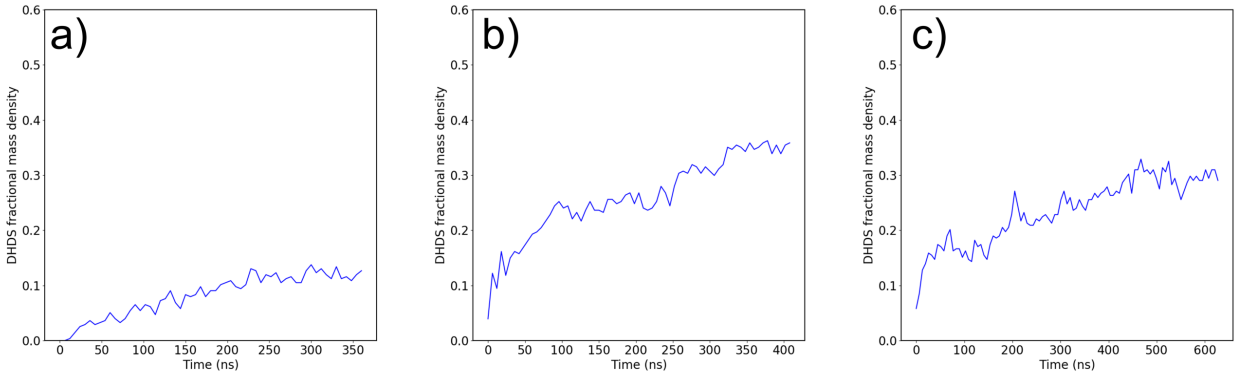

Figure S4: Fractional mass density of the top 1.5 nm in the MD simulations for a) pure water, b) 20 % ethanol and c) 40 % ethanol. The density of crystalline paracetamol is 1.293 g/cm^3.

Optical microscopy image of paracetamol crystal

We show an optical microscopy image of a paracetamol crystal grown in 0 % ethanol. Crystals grown in 20 % and 40 % ethanol were identical. The dimensions of the crystals were approximately 2 x 3 mm.

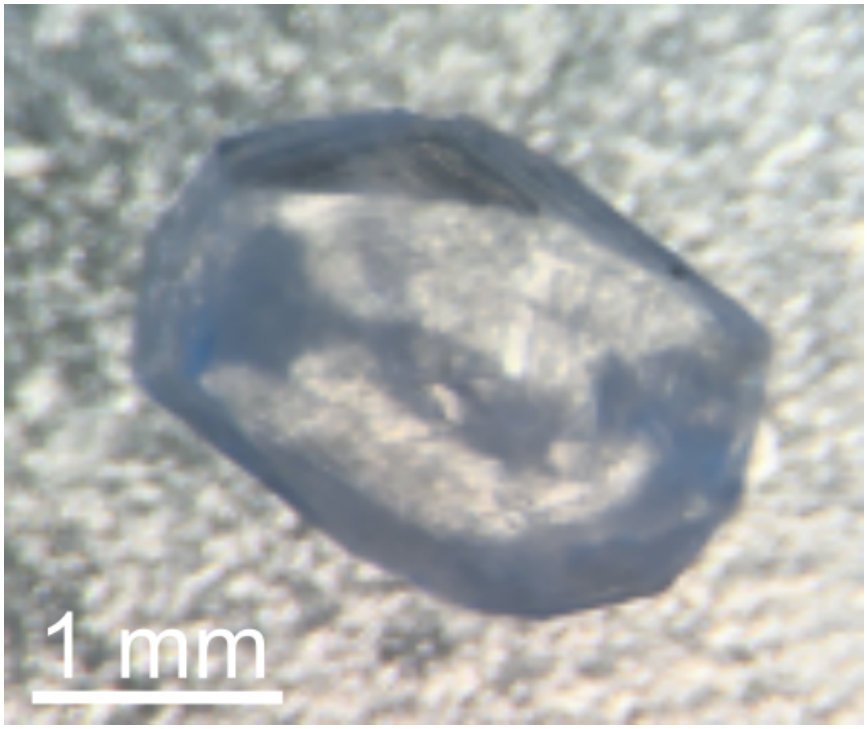

Figure S5: Optical microscopy image of a paracetamol crystal.

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Scanning electron microscopy images

Scanning electron microscopy images were obtained for paracetamol crystals grown in 0 %, 20 % and 40 % water-ethanol mixtures. It is difficult to draw conclusions based on the results as the variability in each image is quite large. All AFM images were obtained in areas with no significant microscale surface features or roughness.

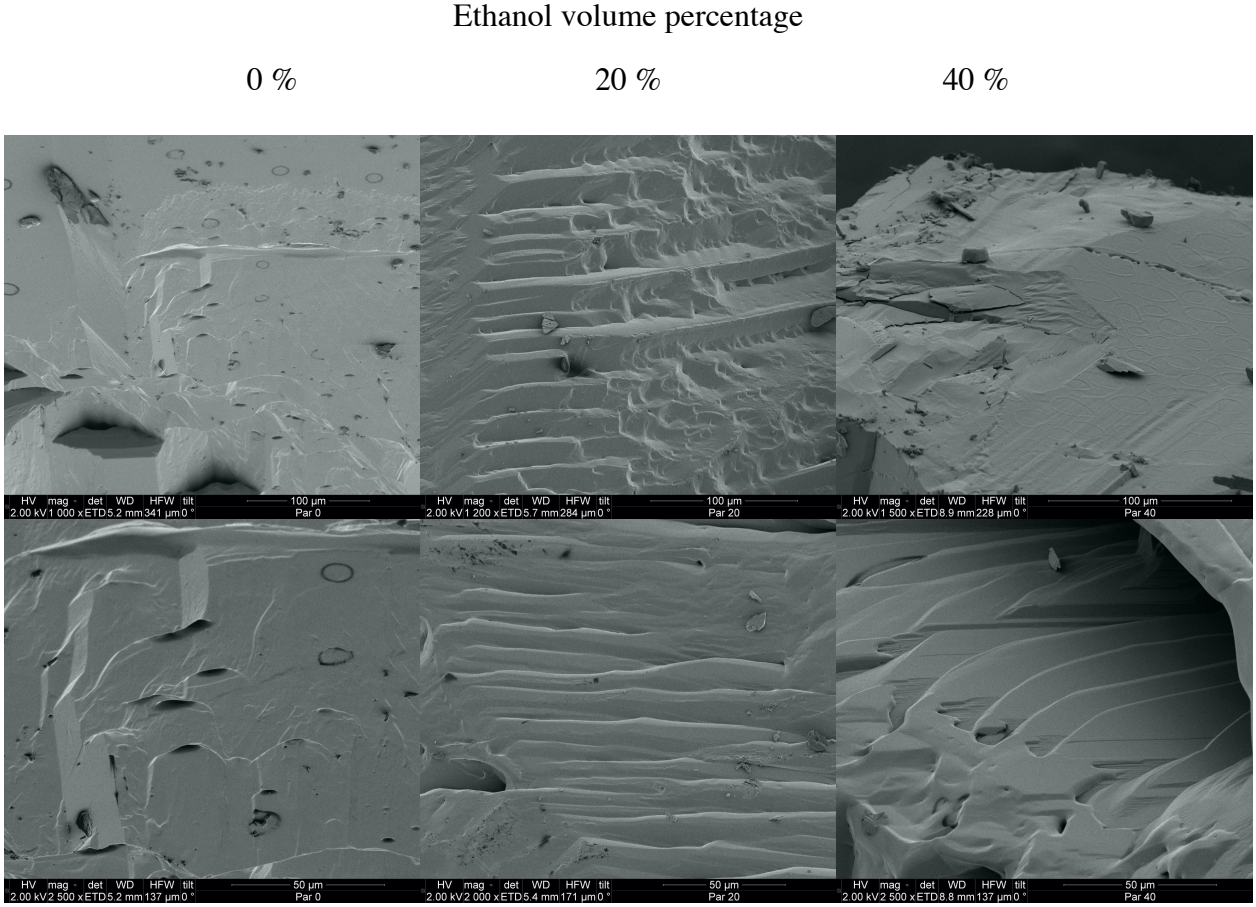

Figure S6: Scanning electron microscopy images of dry paracetamol crystals grown in 0 %, 20 % and 40 % water-ethanol mixture. Top row is 1500 x magnification and bottom row is 2500 x.

AFM images on dry surfaces

AFM images were obtained to investigate the topography of the crystal surfaces after drying. Three images were collected in different places and a representative for each sample is shown. Surface features that could disturb force maps were not observed, but there were domains with varying roughness on surfaces that had been exposed to ethanol.

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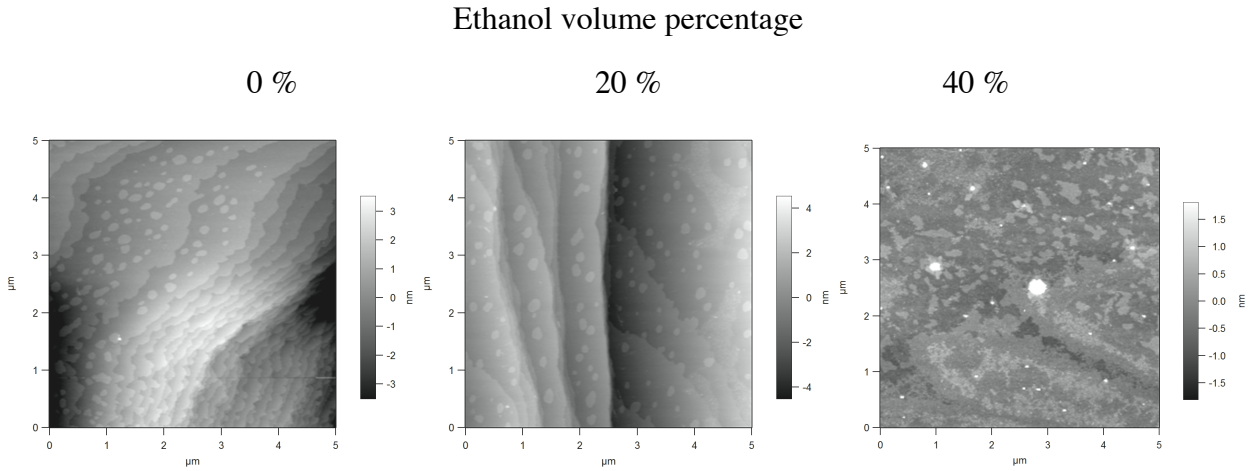

Figure S7: Representative AFM images of dry paracetamol crystals grown in 0 %, 20 % and 40 % water-ethanol mixture. Domains with varying roughness were present on surfaces that had been exposed to ethanol.

References

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