Morphological Diversity of Caffeine on Surfaces: Needles and Hexagons

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Adnan Sarfraz,† Anne Simo,‡ Robert Fenger,‡ Wolfgang Christen,‡ Klaus Rademann,*,† Ulrich Panne,†‡ and Franziska Emmerling*‡

†BAM Federal Institute for Materials Research and Testing, Richard-Willstätter-Strasse 11, 12489 Berlin, Germany
‡Institut für Chemie, Humboldt-Universität zu Berlin, Brook-Taylor-Strasse 2, 12489 Berlin, Germany

ABSTRACT: A systematic crystal morphology study on the pharmaceutical model compound caffeine has been conducted on different surfaces: silicon, silver, soda lime glass, and silver subsurface ion-exchanged soda-lime silicate (SIMO) glasses. The morphology of the solid caffeine deposits has been investigated using environmental scanning electron microscopy (ESEM), atomic force microscopy (AFM), and X-ray diffraction (XRD). Needle-shaped caffeine crystals have been observed by drop-casting and also by applying the rapid expansion of supercritical solutions (RESS) technique using supercritical carbon dioxide. The aspect ratio of the crystalline needles typically vary between 10 and 100, but have been observed as large as 500. The XRD data of the RESS products indicate unambiguously the presence of the thermodynamically most stable polymorph of caffeine known as the β-form. Under defined conditions we observe a unique, surface-mediated morphology for caffeine crystals with nearly perfect hexagonal shape. The relative fraction of the hexagons was seen to strongly increase especially when SIMO glasses were used. These hexagons have a distinct upper size limit depending on the solvent and substrate being used. The size distribution analysis of the hexagons yielded an average perimeter of typically 10 μm. The mechanism of the formation process of this new hexagonal motif is explained in terms of the spinodal dewetting of the thin film of caffeine solution on the surface.

1. INTRODUCTION

Crystallization, i.e., nucleation and growth, of a crystal morphology depends decisively on kinetic and thermodynamic parameters. The most important parameters for the control of crystal morphology are the supersaturation ratio, crystal growth rate, temperature, concentration as a function of time, and chemical potential of the solvent molecule in the gas phase.1,2 Interestingly enough, the crystal structure of caffeine has been solved just in 2007.3,4 Caffeine exists as two crystallographic forms, the high temperature disordered α-form and the room temperature β-form. Upon crystallization from an aqueous solution, the monohydrated form is produced, which converts to the anhydrous β-form at room temperature.5,6 Throughout the history of caffeine research, it has been observed in most cases, that caffeine crystallizes in the form of elongated needles with high aspect ratio.

The interest in studying crystallization and cocrystallization of caffeine stems from its enormous importance for the pharmaceutical industry.1,2 A recent work discusses the details regarding the crystallization of caffeine on different surfaces and the formation of polymorphs with a novel microfocus beam technique coupled to an ultrasonic levitator.1,2 Moreover, the formation of caffeine tubules have been reported to be strongly related to the choice of the solvent.1,2 The suggested mechanism behind the formation of tubules is diffusion limited growth. Moreover,
in situ AFM has also been used to study the kinetics of the transition between the two modifications of caffeine. It has been shown that the interconversion between these two modifications occurs on a time scale of 100 h. The transition between the different polymorphs of caffeine can not only be controlled using temperature, but also by the choice of solvent.

To investigate the morphological diversity, one possibility is to avoid any surface. In this context, the use of an acoustic levitator provides a contactless crystallization of a suspended droplet in air. In these experiments the remaining surface is only the interface between solvent and air. A valuable alternative is the rapid expansion of supercritical solutions (RESS). RESS can be utilized for technical applications ranging from micronization of particles to spray drying as well as for analytical applications based on the transfer of nonvolatile molecules into the gas phase. The expansion conditions provide control over size and morphology of the final product. In addition, control over the crystal polymorph seems feasible.

The objective of this work is to explore the crystal structure and morphology of caffeine deposits on different surfaces in relation to the various polymorphs and solvatomorphs that are known for caffeine. Here, we report on the properties of a unique morphology of caffeine in the form of a hexagon. This novel morphology was recently also reported by Eddleston et al.

2. EXPERIMENTAL SECTION

2.1. Materials. Caffeine (anhydrous 99%) was obtained from Fluka GmbH and used without further treatment. The surfaces involved are pure silicon (111) (Leibniz Institut für Kristallzüchtung (IKZ), Berlin, Germany), soda lime silicate glasses (Carl Roth GmbH + Co., Karlsruhe, Germany) and also silver subsurface ion-exchanged soda-lime silicate (SIMO) glass surfaces. Dichloromethane, AgNO3 and NaNO3 were purchased from Carl Roth GmbH + Co., Karlsruhe, Germany. Carbon dioxide (99.99%) and H2 (99.999%) was obtained from Air Co., Karlsruhe, Germany.

2.2. Methods. Rapid expansion of supercritical solutions (RESS) was carried out in a high pressure cell built from stainless steel parts (see Figure 1). A band heater was used to regulate the temperature of the high pressure cell. Caffeine was placed inside the cell and carbon dioxide was added at the required pressure. All RESS depositions were carried out at a pressure between 80 and 90 bar at a temperature of 313 K. Using the needle valves (V1 and V2), the flow of the supercritical solution was regulated to deposit the crystallized caffeine onto a soda lime silicate glass slide. The distance between the surface and the valve (V1) was kept regulated to deposit the crystallized caffeine onto a soda lime silicate glass slide. The distance between the surface and the valve (V1) was kept at 773 K.

Figure 1. Schematic diagram of the RESS apparatus.

Figure 2. ESEM images of (a) caffeine powder and (b) RESS deposits of caffeine from CO2 on soda lime silicate glasses.

3. RESULTS AND DISCUSSION

3.1. Rapid Expansion of Supercritical Solutions of Caffeine. Caffeine was deposited onto a soda lime silicate glass surface using the RESS process. Figure 2 depicts the ESEM images of caffeine powder and RESS deposits of caffeine obtained using CO2 as solvent. The crystals obtained using RESS exhibit a needle habit with high aspect ratios manifesting the very strong propensity of caffeine to adapt this morphology. The images for the RESS deposits show that the length of the...
needles ranges from about 10 to 30 μm. The ability of caffeine to form needles similar to the ones reported here, using CO₂ as solvent has also been reported previously. It should also be noted here that the details of the morphology of the particles produced using RESS strongly depend on the conditions of the expansion.

The crystallographic structure of caffeine deposits produced using RESS was also recorded and is reported here along with the unit cell in Figure 3. Comparison of the X-ray diffraction pattern of the RESS deposit with the theoretically calculated room-temperature β-modification reveals that after RESS expansion, the crystallographic structure of caffeine remains unchanged.

3.2. Drop-Casting. The drop-casting method was applied on a number of surfaces such as soda lime silicate glasses, silicon, silver, and SIMO glasses. Figure 4 displays the ESEM images of aqueous caffeine solution drop-casted onto a soda lime silicate glass surface. These images show once again the strong tendency of caffeine to form long elongated needles.

Drop-casting of caffeine in dichloromethane produced, apart from the needles, a novel hexagonal motif. A similar hexagonal morphology of caffeine has also been reported previously by Eddleston et al. using different solvents. Interestingly, the relative fraction of this hexagonal motif is highly dependent on the properties of the surfaces used for crystallization and is discussed in detail below. The hexagonal crystals were observed on pure silicon, silver surfaces, soda lime silicate, and SIMO glasses. Upon evaporation of the drop from the silicon surface, the boundary of the deposits mainly consisted of thick caffeine needles, whereas in the middle of the deposit, a large area primarily composed of the hexagon structures was observed, as depicted in Figure 5.

Atomic force microscopy was used to illustrate in detail the morphology of a single hexagon and is shown in Figure 6. The line scan exhibits sharply defined walls with the middle of the hexagon being hollow; the height of the hexagon is ~8 μm.

The size distribution of the hexagons was determined for a selected sample of caffeine deposited on a SIMO glass using a
drop of caffeine solution in dichloromethane. The graph was evaluated using an area of deposit (0.88 mm²) which primarily contained hexagons (compare Figure 5). The statistical calculation was done by analyzing ESEM images with the software ImageJ.32 Particles with sizes less than 5 μm were ignored due to limits of the image resolution. Figure 7 indicates that the average perimeter of the hexagons is about 10 μm and hexagons larger than 30 μm are extremely rare, which leads to the hypothesis that an upper size limit for the hexagons exists.

3.3. Surface-Mediated Formation of Hexagons. In the deposits formed using RESS primarily needles were found and no hexagons were observed. Moreover, previous studies involving crystallization of caffeine in an ultrasonic levitator also did not lead to the formation of this morphology.16 This indicates that the surface as a nucleation substrate plays an important role in the formation of this particular morphology. We systematically investigated the morphology of caffeine on different surfaces to understand the underlying phenomenon controlling the formation of these hexagons. The properties of the surface that showed the strongest influence were identified as roughness and polarity, usually summarized in a single parameter, the wettability, which correlates with the contact angle θc of the sessile drop.3,4 We selected different surfaces to cover a wide range of different contact angles which are reported in Table 1.

A quantitative study was undertaken to calculate the relative area fraction of hexagons and needles on these surfaces. Caffeine in DCM solution was deposited via drop-casting at room temperature and an area of 3.64 mm² was used for the calculations. The area fraction given in Figure 8 was calculated by using ESEM images. The area of hexagons in relation to the total area (3.64 mm²) of the sample that was evaluated, was averaged over 10 single electron microscope images. These images were analyzed using the software ImageJ.32 The results of four different surfaces are displayed in Figure 8. We observed that the relative fraction of hexagons increases in the following order: soda-lime silicate glass slides, silicon, silver and silver subsurface ion-exchanged soda-lime silicate glasses (SIMO). At the same time the relative fraction of needles decreases (Figure 8). Hence, the contact angle and the relative fraction of hexagons produced on a particular surface correlate, i.e., at higher contact angles the relative fraction of hexagons increases.

3.4. Mechanism of Hexagon Formation. On the basis of the experimental results on different surfaces, a mechanism is proposed for the formation of needles and hexagons and is presented schematically in Figure 9a /C0g. The mechanism takes into consideration the crystallization mechanism proposed by Deegan et al.33 Initially, a drop is placed on a surface (a), which exhibits a certain contact angle. The contact line recedes because of the evaporation of the solvent. At this scale (b) the flow direction of the solute is almost parallel to the surface. After initial nucleation, this leads to a very efficient transport of material to the perimeter of the drop. As can be seen in the photograph (e) the receding contact line leads to the preferential formation of needles. After most of the solvent has evaporated, the central area of the drop contains a highly concentrated thin layer of the solution. At this stage, spinodal dewetting leads to the formation of small micrometer sized droplets of the solution (f), which also explains the upper limit of the observed size distributions of the hexagons. At the micrometer scale (g) the material transport direction is almost perpendicular to the surface and leads to the
formation of the stable hexagonal morphology with less material present in the middle of the hexagon. The mechanism is strongly supported by the observed AFM image in Figure 6. The ESEM image (h) reveals the formation of needles at the boundary with a large area in the middle which is dominated by hexagons.

The proposed mechanism provides an understanding for the dependence of the contact angle/dewetting on the amount of hexagons produced. A high contact angle will lead to more efficient breakup of the film and thus more microdroplets producing hexagons.

4. CONCLUDING REMARKS

A study of the morphological diversity of caffeine was carried out on selected surfaces using the RESS method and drop-casting. Different experimental techniques such as ESEM, AFM, and X-ray diffraction were used to gain insight into the parameters governing the crystallization process. The RESS process leads to the formation of the thermodynamically stable crystalline β-form of caffeine. This primarily leads to acicular structures and agglomerates.

Furthermore, we observed that caffeine also has a very strong propensity to form needles with large aspect ratios when crystalized from solutions onto surfaces. The aspect ratio of the needles ranges between 10 and 100. However, a novel morphology, as previously observed by Eddleston et al., was reproducibly identified on specific surfaces. The novel morphology consists of highly symmetric hexagons which by definition have an aspect ratio of one. The size distribution of these hexagons has been quantified. For the system chosen (solution of caffeine in DCM drop-casted on a SIMO glass), there exists an upper size limit for this morphology, which is around 30 μm.

The formation of hexagonal motif is strongly dependent on the interactions between the solvent, solute, and surface. This fact is supported by the absence of the hexagonal morphology in the RESS deposits. From the surfaces studied, SIMO glasses generated the highest yield of hexagons. Moreover, hexagons on silicon surface were also found with a high relative fraction. Only a very small fraction of hexagons appear on untreated soda lime silicate glasses.

The experimental observations were used to propose a mechanism for the formation of hexagons. The mechanism is based on the spinodal dewetting of the solution film on the surface. The spatial distribution of the hexagons is controlled by the breakup of the highly saturated evaporating droplet into smaller supersaturated microdroplets.

The formation of the hexagonal morphology of caffeine deserves further research, especially regarding the interrelation between the hexagons and needles. The most interesting property to be studied is the crystal structure of these hexagons, in order to verify the assignment given by Eddleston et al. This is a challenging task because of the small size of the hexagons. It would lead to results indicating a surface induced crystal structure as well as illustrate the relation between morphology and the modification of the crystal on surfaces. Moreover, the dependence of this morphology on a wide variety of parameters needs to be studied to elucidate the role of the surface, solvent, and temperature in the formation of hexagons.

ASSOCIATED CONTENT

Supporting Information. Raman spectrum of pure caffeine compared to the spectrum obtained from hexagons (PDF). This material is available free of charge via the Internet at http://pubs.acs.org/.
AUTHOR INFORMATION

Corresponding Author
*E-mail: klaus.rademann@chemie.hu-berlin.de (K.R.); franziska.emmerling@bam.de (F.E.).

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