Bulk and Surface-Stabilized Structures of Paracetamol Revisited by Raman Confocal Microscopy

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Supporting Information

ABSTRACT: We revisit the polymorphism of paracetamol by means of a micro-Raman technique, which has proved to be a powerful tool for structure recognition. Distinct lattice phonon spectra clearly identified the pure phases. Confocality enabled us to detect phase mixing between form II and either I or III on a micrometric scale in the same crystallite. Following the most recent findings on surface-mediated structures, we also investigated spin-coated films grown on glass, gold, and polystyrene substrates, confirming the selectivity of these surfaces for the metastable form III, which shows an unprecedented stability over a time span of several months. A mechanism of its transformation to phase II, via a partially ordered intermediate state, is suggested by polarized Raman measurements.

1. INTRODUCTION

Among the various areas where polymorphism plays a relevant role, pharmaceutics is certainly the one with the highest impact because of its strategic role in pharmaceutical companies and in the manufacturing processes for drug development.1−4 In fact, polymorphism has a considerable influence on solid-state properties, leading to modifications of the biopharmaceutical behavior of a drug. Hence, it is necessary to optimize the methods which promote new routes for a fast and non-destructive crystal structure recognition.

Raman spectroscopy is now recognized as one of the most performing analytical tools for molecular and solid-form identification. The present work aims to investigate, by means of confocal Raman microscopy, the polymorphism of paracetamol, N-(4-hydroxyphenyl)acetamide (Scheme 1), a common active pharmaceutical ingredient (API). We have focused our spectroscopic study on the low wavenumber region, typically from 10 to 150 cm−1, whose active modes, called lattice phonons, represent the vibrations of the crystal lattice and, probing the intermolecular interactions, are very sensitive to even minor modifications in crystal packing. This approach enables an efficient and in situ phase characterization,5 with the possibility of obtaining a topography of the physical purity of the sample by the detection of a Raman map.6

For paracetamol, some of the points mentioned above have been recently addressed by Nanubolu and Burley7,8 in the search for transient forms of this system. The purpose here is to revisit its nonsolvated forms and to get further hints on their phase mixing and growth behavior. In particular, contrary to previous findings, we obtained form III by sublimation, though with the concomitant presence of form II. In addition, experiments of growth on substrates have been performed by spin coating solutions of paracetamol on glass, gold, and polystyrene, in light of the recent findings by Ehmann and Werzer.9 Besides confirming the selectivity of these surfaces for the metastable form III, we show its unprecedented stability over a time span of several months. The transformation of form III to II has been studied spectroscopically, showing that this change starts on the surface with (001) layers of form II, which subsequently propagate into the bulk via a partially ordered intermediate state.

2. RESULTS AND DISCUSSION

The monoclinic form I,10 present in the commercial powder, is the most thermodynamically stable polymorph and is the one available on the market. Form II11 is a metastable phase, which...
turns into form I at an ambient temperature. It has distinct processing advantages over form I, as it undergoes a plastic deformation upon compaction, thus allowing for direct compression into tablets, which would result in time and material saving when processed.\textsuperscript{12} Interestingly, it is also slightly more soluble than form I. Finally, the metastable form III\textsuperscript{13} is also known. Information on the relative thermodynamic stability of the three forms and on the phase transformation routes between them is provided by differential scanning calorimetry (DSC) and thermal X-ray diffraction (XRD) measurements given in the Supporting Information (Figures S1–S5). All crystal structures have been resolved by single-crystal XRD, and those used in the present work are listed in Table 1.

### 2.1. Lattice Phonon Raman Spectra: Forms I, II, and III.

Form I was obtained by crystallization from ethanol and methanol as well as by sublimation and physical vapor transport (PVT) methods, whereas form II was grown by slow cooling of the melt at 190 °C. Following consolidated procedures,\textsuperscript{6} the lattice phonon spectra of the corresponding physically pure polymorphs have been recorded as references and are shown in Figure 1.

![Figure 1. Lattice phonon Raman spectra of forms I and II of paracetamol.](image)

The growth of form III, the formerly elusive polymorph of paracetamol,\textsuperscript{3,15} is more challenging. Although it seems clear\textsuperscript{16,17} that this polymorph can be obtained by a thermal cycle after amorphization, a slight change of the experimental conditions as well as employing covered or uncovered conditions\textsuperscript{17} is sufficient to produce the other forms in the same crystallization process. An exhaustive review of these methods is reported in the literature. We indeed obtained form III by slowly heating the amorphous phase up to 85 °C\textsuperscript{18} and letting the whole sample cool down overnight. As suggested in ref 17, though disputed in ref 18, in our case, the use of a coverslip on the sample was crucial to selectively produce the desired phase. The appearance of a new phonon profile in the Raman spectrum (violet trace in Figure 2a) demonstrated the growth of the expected form III.\textsuperscript{17}

Quite interestingly, during the thermal treatment, we could spot the nucleation of the new phase at the center of the topmost layer of the amorphous sample (see arrow in Figure 2b). From here, the slow crystallization of form III started at 85 °C, triggering the transformation of the entire sample, which was completed overnight after returning to an ambient temperature (Figure 2c, d).

On the contrary, the amorphous sample kept at room temperature, that is, not subjected to the heating cycle, after 3 weeks displayed a mixing of forms II and III (vide infra). Notably, the Raman spectra of the polymorphs are clearly distinct in the region of the lattice phonons, thus allowing for a quick polymorph identification, whereas only slight differences in the energy interval of the intramolecular vibrations are observed, confirming the unmodified molecular identity in all phases, as shown in Figure S6. Lattice phonon Raman spectra patterns strongly depend on sample orientation as displayed in Figure S7, in which the spectra recorded in different points of the sample of Figure 2 are given, and all peaks reported in the literature\textsuperscript{8} for form III can be found.

Further information was gathered by exploiting the confocality of the Raman spectrometer, which enabled us to probe the phase homogeneity of crystal domains at different sample depths.\textsuperscript{19} This was achieved by focusing the laser light with microscope objectives having different numerical apertures (NAs). Typical values of the theoretical penetration depths vary from 7.5 μm (100×) to 25 μm (50×), 150 μm (20×), 450 μm (10×), and about 900 μm (6.3×), although the actual values may be considerably lower, depending on the sample conditions. The spectra of Figure 3 are recorded on a sample in which crystallization occurs starting from an amorphous phase. They qualitatively account for the gradual decrease of the crystallinity on going from the surface (form III + II, 50× and 100×) to inside the bulk (amorphous, 6.3×), as a valuable demonstration of the mechanism of surface crystallization proposed by Wu.\textsuperscript{20}

### 2.2. Phase Mixing.

The three known pure phases of paracetamol were also found to display extensive phase mixing, which could be analyzed by Raman mapping.\textsuperscript{19} Phase mixing is a common occurrence in polymorphism, with crystal phases that may coexist on a micrometric scale as different domains in the same crystal lattice, affecting the physical purity of the sample.\textsuperscript{6,8,19,21} In paracetamol, this mixing is selective because the same crystallite, a valuable demonstration of the mechanism of surface crystallization proposed by Wu.\textsuperscript{20}

| Form | a (Å) | b (Å) | c (Å) | β (deg) | V (Å³) | Crystal system | Space group | Z |
|------|-------|-------|-------|--------|--------|---------------|-------------|----|
| I\textsuperscript{14} | 7.10  | 9.21  | 11.60 | 97.84  | 750.39 | monoclinic    | P2\textsubscript{1}/c | 4  |
| II\textsuperscript{12} | 17.17 | 11.78 | 7.21  | 90     | 1458.02| orthorhombic  | P\textsuperscript{bc}a | 8  |
| III\textsuperscript{13} | 11.84 | 8.56  | 14.82 | 97.84  | 1501.41| orthorhombic  | P\textsuperscript{ca}2\textsubscript{1} | 8  |

## Table 1. Structural Parameters under Ambient Conditions of the Currently Known Polymorphs of Paracetamol
nucleation center of form III, triggered from the amorphous phase. The map results are particularly useful, demonstrating that the technique can provide a powerful and immediate visual representation of the amount of form III, which, by heating and with time, spontaneously transforms to form II.

A final interesting point to remark is the attainment of form III by sublimation, although with the concomitant presence of form II, a result not previously reported in the literature (Figure S10).

2.3. Growth on Substrates: Surface-Induced Polymorphs on Glass. Few layers of a given organic material on a suitable substrate can show molecular organizations different from those found in the bulk phase. Typical examples can be found among organic semiconductors such as pentacene and thiophene derivatives. These structures are often referred to as surface-induced polymorphs (SIPs).

The same approach has been applied to pharmaceutical compounds, successfully probing that films grown on substrates may selectively stabilize a particular crystal phase. In particular, paracetamol was studied as a model API system to show that the metastable form III could be selectively stabilized in spin-coated films on silica substrates subjected to thermal treatment.

In this work, spin-coated samples of paracetamol were prepared on glass substrates by following the protocol given in the literature with 1 wt % solutions of either ethanol or tetrahydrofuran (THF) but without any subsequent heating. From both solutions, completely amorphous samples were consistently obtained, which, over time, crystallized with different kinetics and crystal morphologies. In detail, the samples from ethanol crystallized in 1 day, whereas the THF ones could be analyzed just after 1 h and form III was found to grow over large areas of the film. Its stability as well as its spontaneous transformation to II was followed spectroscopically, detecting a progressive rise of the phonon peak at about 122 cm⁻¹, as shown by the arrow of Figure 5, which is the characteristic signature of form II in the film spectra, as extensively discussed in the next section. The example given in Figure 5 refers to a sample obtained by depositing 200 μL of THF solution, crystallized as form III from the amorphous phase and whose process of transformation under ambient conditions is presented in the next section.
conditions to form II was so slow that it was not fully completed even in a time span of months. This exceptional persistence in time of the metastable form III on glass represents an unprecedented record of stability. This result, besides its spectroscopic evidence, has also been confirmed by a specular XRD diffraction pattern of paracetamol on glass, as shown in Figure S11, where only a single peak has been observed. Here, the conclusion is twofold. First, the peak position corresponds to paracetamol in its form III; second, the presence of one peak only is the typical situation of a sample strongly textured, where the crystal preferably contacts the surface with one exclusive orientation, that is, the (001) plane, like samples on silicon. In (001) texturing, the molecules lie flat on the surface, so that the molecular contact area with the underlying substrate is maximized.

Finally, we should point out that the surface-mediated arrangement so obtained is not a new polymorph, as strictly speaking a SIP would be, but rather a metastable form with an unexpected stability in time. Therefore, we would rather call it a surface-stabilized polymorph.

2.4. Transformation from Form III to II. Raman spectroscopy is not only capable of efficiently following the time evolution of form III to form II in paracetamol films but also yields interesting hints about the different route taken by this transformation in the films with respect to the bulk material.

When a smaller amount of THF solution (150 μL, 1 wt %) is deposited on the glass substrate, the film crystallizes to form III and rapidly switches to form II after only 10 min at room temperature. Therefore, the rate of transformation depends on the quantity of material deposited on the substrate: the smaller the amount of material, the faster the process. The reason for this may be that the rate of the variation in the concentration and the level of supersaturation change drastically, especially when using a fast evaporating solvent such as THF. This might result in the formation of a distinct amorphous phase or even of nuclei, which favors the formation of form II. However, as seen in the left panel of Figure 6, we do not detect the direct transformation of form III, but rather a change of its spectral features, which move to a poorly defined profile with basically only one intense band located at 122 cm⁻¹. By comparison with the bulk crystal spectra (blue trace of the same figure), even though at the very same wavenumber, there exists a correspondence with one of the most intense Raman-active phonons of form II, we do notice that all other phonon bands are either fading or completely washed away. The full spectrum of form II finally develops only at a later stage. Therefore, we are inclined to consider the poorly defined pattern indicated by an arrow in the figure as the signature of an intermediate state, which acts as a precursor of form II before completely transforming into it.
To explain the nature of such an intermediate state is not straightforward, as it requires the knowledge of phonon response for each direction of the single crystal and then the transfer of this information to the film grown on the substrate. From a spectroscopic point of view, this implies measuring polarized Raman spectra, in which a mutual orientation between crystal axes and polarization of the exciting laser field is selected, so that a specific correspondence of each phonon band to its symmetry can be determined. Details on the machinery of this procedure go beyond the aim of this paper and can be found in a dedicated book.30 We recall that the polarized Raman spectra of paracetamol can be found in the literature,31 but no data are available in the strategic lattice phonon region.

Polarized phonon spectra of a single crystal of form II are shown in Figure 6 (right panel), the caption of which schematically clarifies the geometry of the experiment. The orientation of the single crystal under investigation must be known to extract useful information from the data. Following experimental reports12,29 and computational predictions,32 the needlelike single crystals lie on the (001) or ab plane, which is also the crystal orientation parallel to the molecular layers9,12,33,34 with a growth direction along a, that is, the direction of elongation of paracetamol molecules.37 With this in mind, we can label all spectra following Porto’s notation, that is, we can identify the matrix element (ij) of the polarizability tensor responsible for the Raman scattering in each specific experimental configuration,30,33 as marked in the figure.

Relating oriented single-crystal polarized phonons to the film spectral features is now achievable. The spectrum of the intermediate state, with the peak at 122 cm⁻¹, corresponds almost exactly to that indicated as (bb) in the single-crystal polarized spectra. It looks as though the presumably random molecular arrangement in the film of paracetamol molecules on top of the substrate behaved as an ordered, organized structure when probed by exciting and collecting light, both polarized parallel to the b-axis. However, the film is far from being a system comparable to a single crystal. Thus, the correspondence between the two spectra must indicate that identical profiles arise from altogether different physical conditions.

To explain this correspondence, precise information is needed on how paracetamol crystal domains organize on a substrate. Ehmann and Werzer9 report that the form II structure grows with the (001) plane parallel to the silica surface. The same orientation is found on glass, as seen in the previous section. Peterson et al.36 suggest that there is only short-range order along the a-axis, which is also the slow growth direction in the calculated morphology.32 It is plausible that this situation along a is maintained in the early stages of form III transformation to the intermediate state, precursor of form II, implying, because of this disorder, a loss of phonon phase correlation along a. Consequently, for all spectral features whose intensity depends on the polarizability matrix elements containing the a-axis, the phase matching between the incoming polarized light and the corresponding phonon mode fails. Accordingly, only those phonons marked as (bb) in Figure 6 do survive. This nicely explains why a specific polarized spectrum of the single crystal appears coincident with that of the partially disordered intermediate state of the film. In other words, the film spectrum is reminiscent of that of the polarized crystal, but the underlying physical meaning is different. We believe that the intermediate state can be described as a partially ordered structure originating on the surface and made of (001) layers of form II, which subsequently propagate into the bulk in a process similar to the so-called surface crystallization, whose mechanism proposed by Wu20 has been so convincingly demonstrated by the data in Figure 4.

2.5. Growth on Gold and Polystyrene. Spin-coated films were also prepared on gold and polystyrene substrates from THF solutions of the same concentration used for the depositions on glass. Films on gold undergo a strong dewetting, so that only 100 μL of solution could be deposited. Even in this case, form III appears to be dominant in the lattice phonon spectra, even after warming the sample above 100 °C. Only during the cooling process, the transformation to form II was observed (Figure S12).

In the case of films on polystyrene, the identification of form III as the one obtained by deposition was performed by specular XRD reflectivity only (Figure S13).

It is once more interesting to remark that by exploiting the complementary Raman and XRD techniques to comply with phase recognition, we could overcome the technical problems for which it was not always possible to perform both structural...
3. CONCLUSIONS

In this work, we have studied the polymorphism of the model API system, paracetamol, by employing phase recognition lattice phonon Raman microscopy. The unique relationship between the phonon pattern (lattice dynamics) and its corresponding XRD pattern (lattice structure) makes Raman microscopy a powerful tool to complement information on different crystal structures. After characterizing the three pure forms of paracetamol, we have also analyzed their mixing as different domains in the same crystallite. The confocality of the micro-Raman technique allowed us to search for polymorphs in the crystal region under investigation down to a spatial resolution below 1 μm. We were thus able to discriminate the presence of different structures as a function of the depth within the sample by a valuable tool, which has demonstrated the mechanism of surface crystallization of the metastable form III as proposed by Wu.

An important task of this work has been the characterization of crystal forms of paracetamol in spin-coated films deposited on different substrates, aiming to stabilize metastable phases as reported by Ehmann and Werzer. Not only did we confirm the high selectivity of Si/SiO₂ substrates in the growth of form III but also succeeded to have it on glass, gold, and polystyrene surfaces, finding a surprising stability in a time scale of months.

Scheme 2 summarizes the outcome of drop-casting and spin-coating depositions of 1 wt % THF solutions on glass, gold, silicon, and polystyrene.

Notably, the measurements of accurate polarized spectra of phonon modes have clarified the mechanism underlying the transformation from form III to II. This occurs via an intermediate state consisting of a partially disordered layered structure building up on top of the film of form III grown on the glass surface. In the second step, the fully ordered structure of the bulk is eventually reached.

In conclusion, micro-Raman spectroscopy has confirmed to be a sound technique to monitor crystal structures in the time scale of seconds, also scanning them for physical impurities. The method can be applied both to bulk crystals and thin films, offering a number of useful applications in pharmaceutical science.

4. EXPERIMENTAL SECTION

4.1. Sample Preparation and Crystal Growth. Crystals of paracetamol (Sigma-Aldrich, purity 98%) were grown from solutions of methanol and ethanol, from the melt, by sublimation in a glass tube and by PVT. Various polymorphs were obtained, as specifically described in the Results and Discussion section. Films on glass, gold, and polystyrene surfaces were deposited by spin coating THF and ethanol solutions, following the protocol described in the literature.

4.2. Raman Spectra. Lattice phonon spectra were obtained with a Horiba Jobin Yvon T64000 Raman spectrometer by placing the sample on the optical stage of an Olympus BX40 microscope, with a number of objectives of different NAs. Confocality allowed us to achieve a spatial resolution below 1 μm and a theoretical field depth ranging from about 7 to 900 μm. The wavenumber region spanned was typically 10−150 cm⁻¹ to detect the lattice modes. The excitation wavelength was from an ion krypton laser tuned at 647.1 nm. The incoming power was reduced by neutral filters whose optical density was selected each time to prevent sample damage, the actual power focused on the sample being anyway less than 1 mW. Molecular identity was checked by simultaneously detecting the intramolecular vibrations of the skeletal modes of paracetamol. More details are available in the study by Brillante et al.

4.3. DSC. DSC measurements of the paracetamol samples were performed using a DSC 204 F1 Phoenix calorimeter (Netzsch, Selb, Germany). In the standard crucibles, a quantity of about 8 mg of paracetamol was included. The measurements were performed under an inert nitrogen atmosphere to prevent potential oxidation.

4.4. XRD. XRD experiments were performed using an Empyrean reflectometer from PANalytical (Netherlands). The radiation was provided by a copper sealed tube and a parallel beam mirror. The beam is further defined by various slits prior entering the three-dimensional pixel solid-state detector in one-dimensional mode. For the heating of the sample, a DHS-900 (Anton-Paar GmbH, Graz, Austria) system was used. This heating device directly allowed thin-film samples to be measured at highly accurate temperatures. To prevent sample degradation due to oxygen, a dome made from PEEK was used, which was constantly flushed with helium.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01246.
glass; lattice phonon Raman spectra of a paracetamol film obtained by spin coating on gold; and specular XRD diffraction pattern of paracetamol on polystyrene (PDF)

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Notes

The authors declare no competing financial interest.

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