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Understanding the Effect of a Solvent on the Crystal Habit

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ABSTRACT: The extreme polar morphology that has been observed for crystals of the stable form of a steroid is explained by a molecular dynamics simulations approach. The habit modification is caused by surface−solvent interactions, which affect the growth rate of the polar faces differently. The same effect was observed for the metastable polymorphic form. Depending on the solvent, the nature of the difference is mainly caused by the hydrogen bond interactions or the electrostatic part of the interactions.

Introduction

Pharmaceutical compounds are mostly produced in crystalline form obtained from solution, and the challenge of producing a formulation that has the desired properties involves hard work, time, and money. An important issue concerning drug products is the bioavailability because that has to be well characterized and has to be reproducible for any active substance in a pharmaceutical product. Many factors influence the bioavailability. One of these is the dissolution rate that depends on the crystal size, but also on its shape: a rule of thumb is that the faster a crystal orientation grows, the faster it dissolves. If the crystal is grown in a different solvent than the one in which it will be dissolved, the resulting differences in growth rate may be exploited. Furthermore, crystal shape is an important factor in handling product streams during manufacturing. Therefore, a lot of work in the area of crystal engineering has been devoted to control the crystal habit.

The crystal habit results from the relative growth rates of its surfaces in different directions.[1] Therefore, preferential growth or inhibition of different crystal faces changes the shape of the crystal. Here we discuss a polar morphology, a crystal habit that lacks inversion symmetry that can be the result of the interaction between the crystal surfaces and the solvent or impurities. One approach to control the solution−surface interactions involves the control of the crystal morphology with tailormade additives.[2] This approach uses the concept of molecular recognition at the interfaces;[3] the crystal favors selective adsorption of the additive at specific crystal faces, resulting in growth inhibition for these faces. According to this model also the solvent molecules can be considered as "tailormade" additives. Strong solvent−surface interactions should inhibit the growth of the corresponding faces as the solute molecules are hampered in reaching the surface. In case of solvent molecules that interact differently at opposite faces, the habit will be polar. To understand the mechanism behind this solvent−surface interaction, we performed molecular dynamics (MD) simulations keeping track of the principal components of the interactions. This study showed that depending on the solvent the electrostatic surface−solvent interactions can be responsible for the resulting polar habit and that, in contrast with common ideas, hydrogen bonding then plays a minor role. We used in both our experiments and in the MD simulations two different solvents: one that forms hydrogen bonds on both opposite surfaces, and one that does so only for one of the surfaces. The results from the MD simulations are in good agreement with the experimental results and confirm that the relevant solvent−surface interactions are not limited to hydrogen bonding.

Experimental Observation of the Polar Morphology

The steroid that we have studied, abbreviated here as 7αMNa, is used as an active ingredient in medicines for hormone replacement therapy. Two polymorphs are known (see Figure 1): form I, a monoclinic $P2_1$ structure, and form II, a triclinic $P1$ structure,[4,5] which are enantiotropically related.[6] The crystal morphologies of both polymorphs are highly dependent on the solvent and growth conditions. The steroid has two conformations labeled X and Y. The triclinic form consists of only conformers X; the monoclinic form has both conformers in the asymmetric unit. The A ring of the steroid flips from a $2\alpha3\beta$ half chair configuration for conformer X into the $2\beta3\alpha$ half chair conformation for conformer Y.

The experiments were performed in-situ using a thermostated growth cell,[7] and the growth of the crystals as well as the polymorphic modifications were observed with a Zeiss Axioplan 2 polarization microscope. The solutions were filtrated using Rezist 30/0.2 PTFE syringe filters of 0.2 μm pore size, although the complete elimination of foreign particles is not possible.

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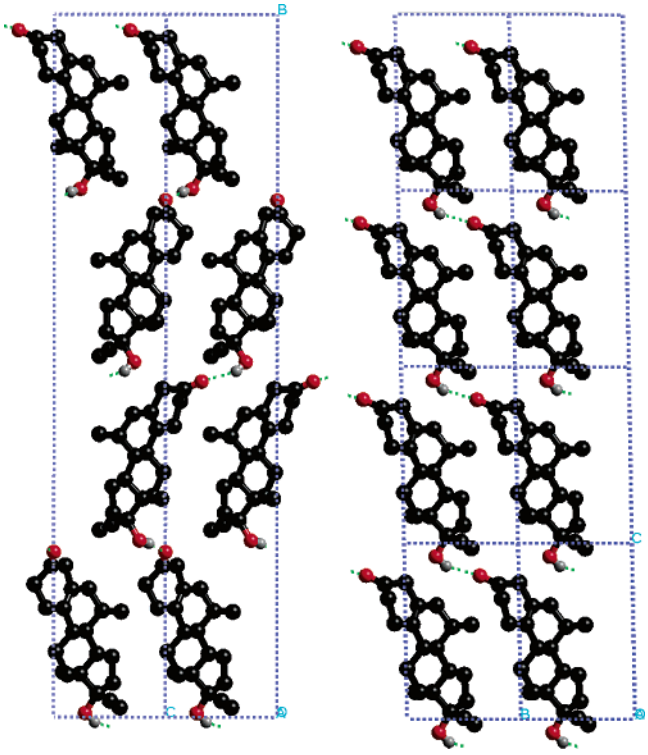

Figure 1. The crystal structures of 7αMNa. Left: two unit cells of form I; right: eight unit cells of form II. Note the similarity in the layered structure of both forms.

Nevertheless, we expect the latter to have a larger influence on the nucleation mechanism than on the growth.

Early experiments showed that the crystals of form I grown from acetone solutions have a platelike morphology with large {010} faces as determined by goniometric measurements (Figure 2a) and are in good agreement with the theoretical prediction (Figure 2b).[8] However, the crystals grown from alcohols such as methanol and ethanol for both polymorphs have an unusual polar habit indicative of a difference in growth rates between the (010) and (0$\bar{1}$0) faces (Figure 2c). The two forms could be easily distinguished by determining their optical extinction directions using polarization microscopy. The polar morphology has to be caused by surface−solvent interactions, which affect the growth of the specific faces. To understand the mechanism of the surface−solvent interactions, first single-crystal X-ray diffraction was performed while keeping track of the orientation of the crystal morphology. For both polymorphs, the orientation of the molecules is such that the large (0$\bar{1}$0) faces are terminated by the hydroxyl groups of the molecules, whereas the small (010) faces contain the carbonyl groups (see Figure 2d). The (0$\bar{1}$0) surface also contains the ethynyl groups, but these have only weak interactions as compared to the hydroxyls. Thus, for the crystals grown from alcohol solutions the solvent molecules appear to block the (0$\bar{1}$0) hydroxyl side. Given these observations, we expected for the crystals grown from acetone solution a polar morphology similar to that of the crystals grown in alcohols because in this case there is only a possibility of hydrogen bonding on the (0$\bar{1}$0) hydroxyl side of the crystals. Further experiments using silane-treated glass, to prevent the crystals to nucleate on the {010} faces,

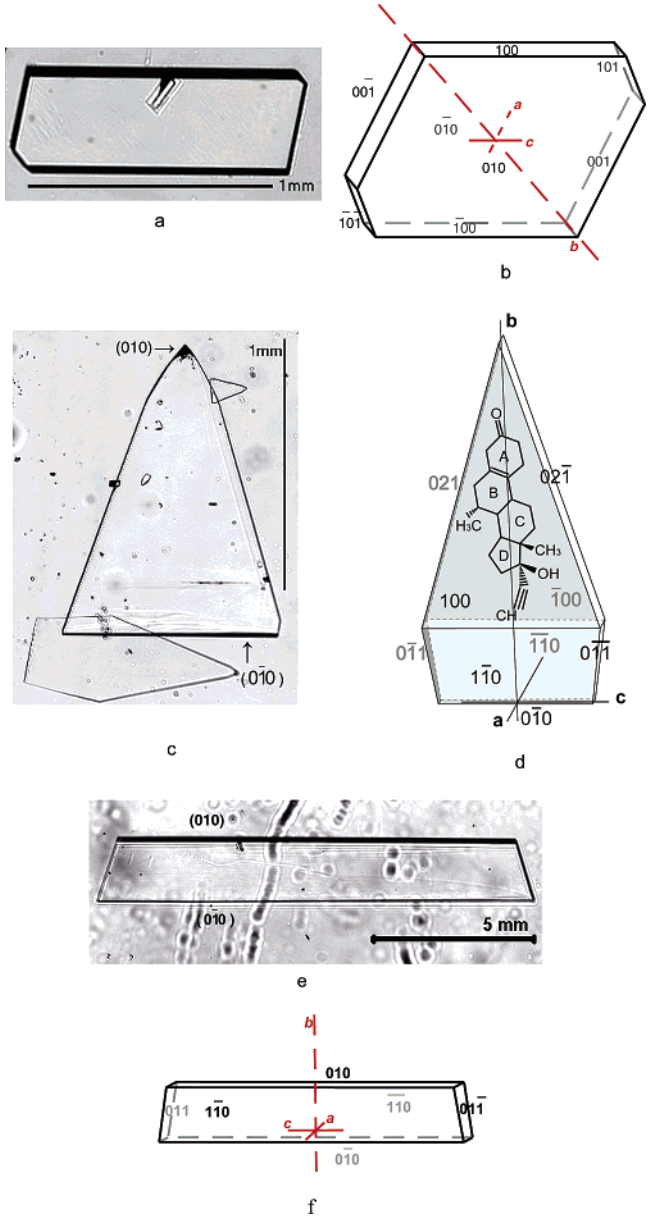

Figure 2. (a) The stable polymorph I in acetone; in a nonsilanized cell it grows with the {010} faces on the bottom of the growth cell. (b) Predicted morphology of form I;[8] the indices are in correspondence with the grown crystal (panel a) as measured by optical goniometry. (c) Polar crystals of form I grown in a methanol solution. The morphology of crystals grown from ethanol/water (80/20%) solutions is similar; also polar crystals of form II show this habit. (d) Indexed morphology of panel c. The orientation of the molecule in the crystal is indicated. (e) Crystal of polymorph I grown in acetone solution in a cell with silane-treated walls resulting in a crystal lying on a {110} face. (f) Indexed crystal of panel e.

showed that the crystals grown from acetone solution indeed also have a polar morphology, although less pronounced (Figure 2e,f). In both solutions, the (0$\bar{1}$0) faces are preferentially blocked as compared to the (010) faces. Considering the fact that methanol should block both (010) and (0$\bar{1}$0) surfaces equally but gives rise to a more pronounced polar habit instead, and the acetone should block just the hydroxyl (0$\bar{1}$0) side but is found to block the (010) and (0$\bar{1}$0) surfaces almost equally, it is clear that the nature of the surface−solvent interactions is not limited to hydrogen-bond interactions.

Molecular Dynamics Simulations

We performed MD simulations to explain the highly polar habit of the crystals grown from methanol solutions as compared to the less polar crystals obtained from acetone. The MD simulations were performed on the (010) and (0$\bar{1}$0) faces of polymorph I in contact with methanol or acetone using the Cerius^2 package.[9] The crystal surface was created using the $P2_1$ structure from the CSD[4] after energy minimization while preserving the symmetry. For the (010) face, the atoms in the two steroid rings closest to the surface, i.e., the A and B rings of the steroid including the carbonyl group (Figure 2d) were allowed to move, while the remaining part of the steroid was fixed. During the simulation runs for the (0$\bar{1}$0) face a similar approach was used for the C and D rings and the attached groups. Then, 80 solvent molecules were placed near the surface at random positions. Molecular mechanics was used to minimize the energy of the solvent layer in the solvent box to obtain the starting position of the solvent molecules for the MD simulations. All energy calculations were done using the Dreiding-2.21 force field[10] with a "spline" cutoff distance of 10−12 Å for both Coulomb and van der Waals interactions and using Gasteiger atomic charges. The simulations were performed at a constant temperature (300 K) and constant number of molecules for both surfaces, keeping the surface lattice parameters fixed. For equilibration, 250 ps dynamics was used, followed by 100 ps dynamics for further analysis. The various energy contributions to the interaction between the solvent and the surface were monitored every 0.5 ps, by calculating the energies and subtracting those from the values obtained after moving the solvent molecules 100 Å away from the surface. This will leave all interactions unchanged, except those between surface and solvent molecules, which will become zero, thus allowing for the calculation of the solvent−surface interaction.

Figure 3 shows snapshots of the (010) and (0$\bar{1}$0) interfaces of the simulations using acetone as the solvent. The simulations with acetone as solvent show hydrogen bond formation (dashed yellow lines) on the (0$\bar{1}$0) hydroxyl side, as expected. On the carbonyl (010) side the acetone molecules prefer to be oriented with the oxygen atoms pointing in the direction of the surface, the molecules forming a dense layer at the surface. The simulations with methanol as solvent revealed that the solvent molecules have a much stronger interaction with the (0$\bar{1}$0) hydroxyl side of the crystal as compared to the (010) carbonyl side. We analyzed the results looking at the three contributions to the energy of the total surface−solvent interactions present in the Dreiding force field: the van der Waals energy, the Coulomb energy, and the hydrogen bond energy. To take into account the effect associated with the formation of hydrogen bonds, the Dreiding force field has a separate energy term of maximally 11 kJ/mol, depending on the donor−acceptor geometry. The three contributions to the energy as well as the total energy were averaged for each of the four MD runs and are summarized in Figure 4. Since a larger interaction energy is interpreted as to correspond to a more slowly growing face, a large value means a large face.

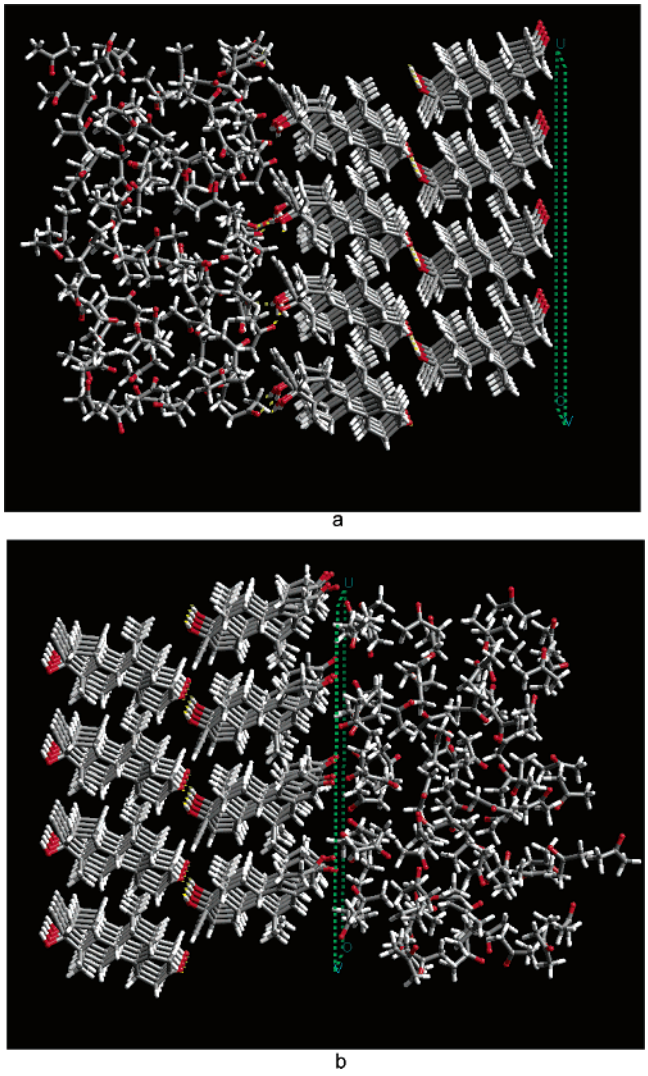

Figure 3. Snapshot of the MD simulations on the {010} faces of polymorph I using a box of 32 steroid molecules, arranged in two layers of 4 × 4 molecules. The box dimensions were 26 × 26 (surface) × 21 (depth) Å. (a) Snapshot of MD simulations for acetone on the (0$\bar{1}$0) surface. The (short) yellow dashed lines indicate the hydrogen bonds, and the green square indicates the crystal surface. (b) Snapshot of MD simulations for acetone on the (010) surface.

Discussion and Conclusion

The experiments clearly show a relatively larger blocking effect for acetone. Looking at the total energy histograms of Figure 4 the MD simulations indeed show that the difference in blocking of the opposite {010} faces by the solvent is stronger for methanol than for acetone. We can, however, draw no conclusion based on the simulations about the absolute blocking effect comparing these solvents. For that it would be necessary to perform a similar study for the other faces to explain the overall morphology. The paper focuses on the {010} faces because from a structural point of view these two faces show the polar nature of the polymorph to the largest extent, as a result of the hydroxyl and carbonyl groups present at these faces.

For the MD simulations with acetone as the solvent, the calculated total interaction energy between the solvent and the steroid for the (010) surface was smaller than that of the (0$\bar{1}$0) surface ($E_t^{Ac}(010) < E_t^{Ac}(0\bar{1}0)$).

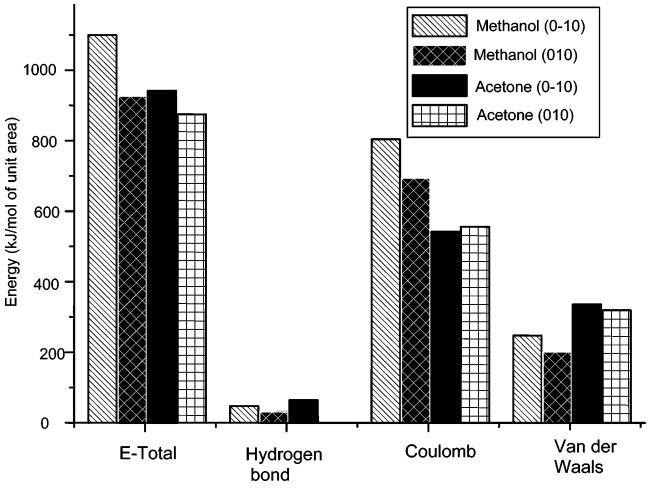

Figure 4. Histogram of the various energy contributions for both {010} faces using methanol and acetone as solvents.

This difference is even larger in the simulations with methanol as the solvent ($E_t^{Me}(010) \ll E_t^{Me}(0\bar{1}0)$) (see Figure 4). This difference explains the highly polar morphology of the crystals grown from methanol solutions, ($0\bar{1}0$) being preferentially blocked over the (010) face. These differences explain also the more pronounced polar morphology of the crystals grown in alcohols as compared to those obtained from acetone solutions (Figure 2c,e). The fact that in acetone the crystals become more platelike could be because for the crystals grown from methanol the side faces are blocked more effectively than for the acetone grown crystals. This will be the subject of future research.

Compared to the total interaction energy, the hydrogen bond contributions are small in all cases. In the case of methanol, the differences between the growth rates of the (010) and ($0\bar{1}0$) faces is principally caused by the Coulomb energy, followed by the van der Waals contribution. In the case of acetone, however, the calculated electrostatic energy for the (010) carbonyl surface is slightly larger than that of the ($0\bar{1}0$) hydroxyl surface (Figure 4), but the difference is canceled by the difference in the van der Waals energy. The hydrogen bond energy in case of acetone has the largest effect for the polar morphology.

The surface configurations of the (010) and ($0\bar{1}0$) faces of form II are very similar to those of form I (see Figure 1).[8] Thus, even though MD simulations were only performed for form I, the calculated interaction will be similar. This is in agreement with the experiments as the polar character of the morphology turns out to be independent of the polymorphic form.

In conclusion, we have studied the experimental polar habit modification in methanol and acetone solutions using MD simulations. We have found that not only hydrogen bonds but also electrostatic and van der Waals interactions between surface and solvent have to be taken into account to explain the polar morphology.

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