Hydrogen bonding interactions between adsorbed polymer molecules and crystal surface of acetaminophen

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Abstract

The objective of this work was to investigate whether or not the hydrogen bonding interaction between polymer and crystal surface can be detected by the etching pattern changes in the presence of polymers. The (010) face of acetaminophen single crystal was used as a model solid surface. The etching patterns on the (010) face of acetaminophen crystal by water are in the directions of \(a\)- and \(c\)-axes, which are the same as the directions of the dominant attachment energies on the (010) face. In the presence of polymer, the hydrogen bonding interactions between adsorbed polymer and crystal surface can affect surface diffusion of acetaminophen molecules and change the etching patterns in the direction of \(a\)-axis, i.e., the direction of one hydrogen bond chain. Studies with 2-hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and poly(vinyl alcohol) (PVA) showed that polymers, which can form hydrogen bonds with acetaminophen crystal surface, can change etching patterns in the direction of \(a\)-axis. Study with Dextran suggested that if a polymer cannot form hydrogen bonds with crystal surface due to steric repulsion, it will not change the etching pattern in the direction of \(a\)-axis. Studies with poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG) further confirmed that only if a polymer can form hydrogen bonds with acetaminophen on crystal surface, the etching patterns in the direction of \(a\)-axis will be affected. The study results suggest that in the presence of polymers, the etching pattern change in the direction of hydrogen bond chain, the \(a\)-axis of acetaminophen crystals, can be used to indicate the existence of the hydrogen bonding interactions between adsorbed polymers and acetaminophen crystal surface.

Keywords: Etching pattern; Crystal surface; Polymer; Adsorption; Hydrogen bond

1. Introduction

Hydrogen bonding interactions and their interplay with other adsorption forces play important roles for the adsorption of macromolecules onto various solid surfaces, for example, the adsorption of bacteria and proteins onto various solid surface [1–11]. Chapman et al. [2] reported that removing hydrogen bond donor groups from polymer surface by acylation may help to resist the attachment of proteins and bacteria. To survive low temperature, many fish, insects and plants have evolved various antifreeze proteins (AFP) that can adsorb onto ice from solution and affect ice growth, possibly through formation of van der Waals interactions and hydrogen bonding interactions between AFP and ice [3,5,6]. Better understanding of the interactions between macromolecules and solid surface in the molecular level is essential in many aspects of life science. Researches on the interaction between polymers, the much simple macromolecule as compared to proteins, and solid surface will shed a light on the mechanisms of macromolecule adsorption on crystal surface.

In pharmaceutical industry, polymers have long been utilized in inhibiting crystallization from supersaturated solutions during the dissolution process, and achieving higher bioavailability [12–15]. Even though many studies have been done about the inhibition on crystal growth by polymers, the mechanism is still poorly understood on the mole-
cular level [13,16–20]. It was proposed that hydrogen bonding interaction between polymers and crystals could be one of the key players. However, no evidences were provided. Understanding of the interactions between polymers and crystal surface in the molecular level will make it possible to design polymeric additives to inhibit crystallization more efficiently.

Many methods have been developed and used in studying polymer adsorption on solid surface, such as solid-state NMR, FTIR (Fourier transform infrared), Raman, UV, electron spin resonance (ESR), photon correlation spectroscopy (PCS), microcalorimetry and surface plasmon resonance (SPR) [4,7,10,11,21–24]. However, all those methods can only detect the change in the adsorbed polymer molecules themselves, no direct information could be obtained on how the solid surface is involved during adsorption on molecular level. A novel technology which could provide insight into the interaction between polymer and crystal surface on molecular level is very well desirable.

The etching pits have been used as a tool for studying the crystal structure, as well as the effects of crystal structure and solvents on crystal dissolution [25–32]. The etching pattern could be influenced not only by the crystal structure but also by the specific interactions between crystal molecules and solvent molecules. Our previous papers have shown that the formation of etching patterns is guided by the attachment energies on the corresponding crystal face [26,33,34]. Solvent molecules may adsorb onto a crystal surface, interrupt the original interaction network within the crystal structure, and cause etching pattern differences in different solvents. For example, 1,2-dichloroethane can adsorb onto the acetaminophen crystal surface more strongly in the direction of the $a$-axis than in the direction of the $c$-axis, causing the slit-like etching pattern and the needle-shape crystal morphology for acetaminophen [26,34]. Li et al. [35] observed that acetanilide and 4-methyl acetanilide, ‘tailor-made’ additives for acetaminophen, can adsorb onto crystal surfaces, diffuse and occupy crystal lattices, interrupt the original crystal interaction network, and change the etching patterns of acetaminophen crystal surface. In this paper, we were able to examine how crystal surface interacts with polymer on molecular level by analyzing the etching pattern change observed by atomic force microscopy (AFM).

The (010) face of monoclinic form acetaminophen has been used as a model solid surface in our study, and the molecular structure of acetaminophen is shown in Fig. 1A. There are two hydrogen bond chains in acetaminophen crystal, and both are on the (010) face. One of the hydrogen bond chains is in the direction of $a$-axis by forming $\text{N-H} \cdots \text{O-H}$, and the other one is in the direction between $a$- and $c$-axes by forming $\text{C-O} \cdots \text{H-O}$. The two strongest attachment energies related to the (010) face of acetaminophen are along $a$- and $c$-axes, which are not exactly the same as the directions of the hydrogen bond chains, as shown in Fig. 2. The acetaminophen structure displayed by Cerius$^2$ shows that there is a much stronger steric repulsion in the direction between $a$-axis and $c$-axis than in the direction of $a$-axis; therefore, the second strongest attachment energy is not in the direction of the hydrogen bond chain but rather in the direction of $c$-axis. The etching patterns of acetaminophen (010) face by water are in the directions of $a$- and $c$-axes; i.e., follow the directions of the dominant attachment energies related to the (010) face [26,27]. In this paper, we will provide data to prove the hypothesis that the etching pattern in the direction of hydrogen bond chain, i.e., $a$-axis, will change if there is hydrogen bonding interaction between the polymer and the crystal surface. As a result, we propose that the change of etching patterns in the direction of hydrogen bond chain can be used to indicate the existence of hydrogen bonding interactions between polymer and crystal surface.
2. Experimental section

Acetaminophen (U.S.P.) was purchased from Amend Drug & Chemical Company (Irvington, NJ). HPMC of four different MW, namely METHOCEL E4M, K3-LV, K4M, K100-LV, were obtained from Dow Chemical Company (Midland, MI). PVA of four different MW: 15,000, 47,000, 72,000, and 195,000, were purchased from Fluka Chemical Company (Milwaukee, WI). Dextran with MW 39,200 was obtained from Sigma Chemical Company (St. Louis, MO).

All the following chemicals were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI): PEG of five different MW: 200, 400, 1000, 3400, and 10,000; poly(ethylene oxide) (PEO) of two different MW: 100,000 and 1,000,000; PPG of three different MW: 425, 1000, and 4000; HEC with average MW ca. 90,000; HPC of two different MW ca. 80,000 and 1,000,000.

After acetaminophen single crystals were prepared, the (010) face of acetaminophen was acquired by cleaving single acetaminophen crystals, and confirmed by X-ray powder diffraction [33]. Before executing partial dissolution on the (010) face of acetaminophen, the $a$- and $c$-axes were identified. For most aqueous polymer solutions, the time of partial dissolution was generally 60 s. For those polymer solutions with high viscosity like pure PEG, PPG and high concentration of HPMC(E4M), time could be longer up to 120 s. After partial dissolution, the surfaces of acetaminophen single crystals were examined with an AFM, and the images in the following sections were in the deflection mode unless otherwise specified [33].

The crystal structure information of acetaminophen was retrieved from Cambridge Structural Database (HXACAN-01) with the following parameters: $P_{2_1}/a$, $a = 12.93$ Å, $b = 9.4$ Å, $c = 7.10$ Å, $\beta = 115.9^\circ$ [36]. Based on the information, Cerius$^2$ 4.2 (Molecular Simulation, Inc., San Diego, CA) has been used to build acetaminophen crystal, and do necessary calculation as well as provide visual observation of the three-dimensional structure of the acetaminophen crystal shown in Fig. 1B.

3. Model

Acetaminophen crystal has two hydrogen bond chains, both on the (010) face as shown in Fig. 2. One hydrogen bond chain is in the direction of $a$-axis, which is also the direction of the strongest attachment energy [33]. Another hydrogen bond chain is in the direction between $a$-axis and $c$-axis, different from the direction of the second strongest attachment energy; thus, no etching pattern in this direction. Because all the hydrogen bonding donor and receptor atoms of acetaminophen are involved in the two hydrogen bond chains on the (010) face, forming hydrogen bonding between polymer and acetaminophen requires breaking of the original hydrogen bond chain between acetaminophen molecules. At kink and step sites, polymer may be able to form hydrogen bond with acetaminophen as well.

For those polymers that have hydrogen bonding interactions with crystal surface, a model has been proposed to illustrate the theoretical effects of the hydrogen bonding interactions on the etching pattern formation. In the simplified system as shown in Fig. 3, one small square represents one crystal molecule. There are only two dominant attachment energies in the directions of X- and Y-axes, and one hydrogen bond chain is in the direction of Y-axis. Assuming the adsorbed polymer can form hydrogen bond with crystal molecule, the possible solubilization effects can be ignored. Assuming sites X2, Y2, and 0 are not occupied, if one polymer molecule adsorbs onto crystal surface at site X2, it may form hydrogen bond with either of the two neighboring molecules of site X2 in the Y direction; if it occupies site Y2, it can only form hydrogen bond with the molecule at site Y1.

Fig. 2. Discrepancy between the directions of hydrogen bond chains and the directions of the dominant attachment energies on the (010) face of acetaminophen crystal. The dotted lines represent the directions of the hydrogen bond chains; the $a$-axis and $c$-axis are the directions of two dominant attachment energies on the (010) face.

Fig. 3. Simplified crystal surface in polymer adsorption assuming the attachment energy in the direction of Y-axis is stronger than in the direction of X-axis. The dotted lines in the direction of Y-axis represent the hydrogen bond.
Therefore, the adsorbed polymer molecule has higher probability to form a hydrogen bond with neighboring molecule if occupying site X2. As analyzed before [33], in the absence of polymer, a surface diffusion crystal molecule will prefer occupying site X2 to Y2. However, in the presence of polymer which can form hydrogen bond with neighboring acetaminophen on crystal surface, the hydrogen bond in the Y direction has to be broken before a surface diffusion crystal molecule can occupy site X2. Then, it will be difficult for a surface diffusion crystal molecule to incorporate into the lattice at site X2.

The adsorbed polymer can also affect the detachment of a crystal molecule from the lattice on the crystal surface. In the absence of polymer, molecules at sites Y2 and Y3 require less energy than X2 and X3 to detach from the lattice if site 0 is not occupied. However, in the presence of polymer, more energy may be needed to detach Y2 or Y3 since molecule at Y2 or Y3 may form a hydrogen bond with the polymer from site 0, but the energy required to detach X2 and X3 remains unchanged.

The effects of adsorbed polymer on incorporation and detachment processes suggest that the etching patterns in the direction of hydrogen bond chain will be affected much more obviously than in other directions. The etching pattern formation is no longer totally under the guidance of the intramolecular interactions network. On the (010) face of acetaminophen crystal, if the adsorbed polymer can form hydrogen bonding interactions with acetaminophen, the etching patterns in the direction of a-axis should be affected much more than in c-axis. It is worthwhile to mention here that for different polymers, the effects of hydrogen bonding interactions between adsorbed polymer and crystal surface may be different, which can be affected by many factors, such as molecular weight, steric repulsion and chain rigidity, etc. The effects of those factors will be further addressed in another paper.

4. Results

The approach employed in this study: first, the effects of cellulose derivatives, HEC, HPC, and HPMC, on the etching pattern were compared with that of Dextran. Secondly, effects of PVA were studied because it is prone to form hydrogen bonding with crystal surface of acetaminophen. Thirdly, to further confirm the correlation between the etching pattern change and hydrogen bonding interaction, PEG and PPG were studied.

4.1. Etching pattern by water

The etching patterns of the acetaminophen (010) face by water have been well studied [26,27], and can be used as a control. Fig. 4 shows the representative etching patterns of the acetaminophen (010) face by water. The etching patterns look regular; i.e., there are two kinds of ledges in all etching images: one parallel to a-axis, and the other parallel to c-axis. Even though water may form hydrogen bonds with

Fig. 4. AFM images of the acetaminophen (010) face etched by water. The scan sizes were 60 × 60 µm² for A and D, 20 × 20 µm² for B and E, and 5 × 5 µm² for C and F. B and C were zoom-in scannings of image A site, and E and F were zoom-in scannings of image D site. The a- and c-axes were marked on images A and D.
acetaminophen on crystal surface, the highly dynamic exchange property of the hydrogen bond between water and acetaminophen does not make it significant enough to deviate the etching patterns from the directions of the two dominant attachment energies on the (010) face.

4.2. Etching pattern changes by HEC, HPC, and HPMC

The backbone of HEC, HPC, and HPMC, whose molecular structures are shown in Fig. 5, is cellulose that is composed of glucose residues joined by $\beta$-1,4 linkage [37]. The most important modification groups are (CH$_2$CHO)$_n$H for HEC, [CH$_2$CH(CH$_3$)O]$_n$H for HPC, as well as CH$_3$ and CH$_2$CH(OH)CH$_3$ for HPMC. The straight backbone of cellulose should not produce significant steric repulsion when the side groups form hydrogen bonds with acetaminophen crystal surface. Whether or not the three polymers can affect the etching patterns on the (010) face of acetaminophen, especially the etching pattern in the direction of $a$-axis, has been systematically studied.

The study shows that the etching patterns in the direction of $c$-axis have not been affected in the presence of HEC, HPC and HPMC, but the etching patterns in the direction of $a$-axis have been significantly affected. Fig. 6 shows the etching patterns of acetaminophen (010) face by different concentrations of HPC(80K) aqueous solutions. The etching patterns at high concentrations, such as 10 and 1 mg/ml, clearly elongate in the direction of $c$-axis, and they have no expansion in the direction of $a$-axis. At low concentration like 10 $\mu$g/ml, the etching patterns become the same as the etching patterns by water. At the transitional concentration 100 $\mu$g/ml, the etching patterns still follow the $c$-axis clearly. However, there appear clear bars in the direction of $a$-axis, which means that around 100 $\mu$g/ml, the surface diffusion in the direction of $a$-axis is still affected by adsorbed HPC but not completely. HPC(1000K) has also been used to check its effects on the etching patterns of acetaminophen, and the same phenomena have been observed. Overall, the etching pattern change by HPC strongly supports the idea that...
HPC can form hydrogen bonds with acetaminophen along \(a\)-axis, and affect the surface diffusion of acetaminophen along \(a\)-axis.

In the presence of HPMC, the etching patterns in the direction of \(a\)-axis have been similarly affected as in the presence of HPC; i.e., the etching patterns in the direction of \(a\)-axis become invisible. In the presence of HEC, the etching patterns in the direction of \(a\)-axis have also been significantly affected, but there is still certain expansion in the direction of \(a\)-axis, visible even in 10 mg/ml HEC aqueous solutions. All the etching patterns have been further checked with their height profiles, which are consistent with their deflection images.

4.3. Etching pattern change by Dextran

The backbone of Dextran, whose molecular structure is shown in Fig. 5, is linked by connecting the hydroxyl groups at site 6, i.e., the one connected to the methylene group and at site 1, i.e., \(\alpha\)-1,6 linkage \([37]\). The \(\alpha\)-1,6 linkage of Dextran causes two linked glucose groups not in a line, but in the form of an arc in which the ring of the second glucose is at the same side of the second hydroxyl group of the first glucose. The bulky backbone may make it difficult for the two oxygen atoms in its backbone to form hydrogen bonds with acetaminophen. However, nearly all the linkages of Dextran are \(\alpha\)-1,6, which means that the hydroxyl group at site 6, i.e., the one connected to the methylene group, has been involved in backbone formation \([37]\).

Therefore, the remaining hydroxyl groups that may be involved in forming the hydrogen bonds with acetaminophen are located in the inner side of the polymer chain arcs. On the one hand, the hydroxyl groups in Dextran are located in the inner side of polymer chain arcs; on the other hand, they are directly connected to glucose rings and are not far away from the glucose rings. All these factors determine that the hydroxyl groups in Dextran are difficult to form hydrogen bonds with acetaminophen on crystal surface, thus the adsorbed Dextran cannot affect the surface diffusion of acetaminophen molecules through the hydrogen bonding interactions.

Fig. 7 shows the etching patterns of the acetaminophen (010) face in the 10 mg/ml Dextran(39.2K) aqueous solution. The etching patterns follow both \(a\)-axis and \(c\)-axis very well, and are exactly the same as the etching patterns by water. 100 and 1 mg/ml of Dextran solutions have also been used to check their effects on the etching pattern formation, and the etching patterns are still the same. The etching patterns by Dextran strongly support the idea that Dextran cannot form hydrogen bonds with acetaminophen on the crystal surface, which is consistent with the three-dimensional structural analysis of Dextran.

4.4. Etching pattern change by PVA

PVA has a hydroxyl group at the side chain position, and there should have been no strong steric repulsion for the hydroxyl group to form hydrogen bond with acetaminophen molecule on crystal surface. The PVA aqueous solutions of five different MW have been used in the etching pattern study, and all have produced similar etching patterns. Fig. 8 shows the etching patterns of the acetaminophen (010) face in different concentrations of PVA(15K) solutions. At high concentrations, like 25 and 1 mg/ml, the etching patterns follow \(c\)-axis well, but deviate somewhat from \(a\)-axis. At low concentration, like 1 \(\mu\)g/ml, the etching patterns are the same as the etching patterns by water; i.e., follow \(a\)- and \(c\)-axes well. At 25 \(\mu\)g/ml, the etching patterns differ from the etching patterns in both high and low concentrations of PVA solutions, and can be considered as the transitional etching patterns. It is possible that PVA can form hydrogen bonds with acetaminophen in the direction of \(a\)-axis and cause surface diffusion unstable in the direction of \(a\)-axis. Even though the ledges close to \(a\)-axis look perpendicular to \(c\)-axis in Fig. 8, the ledges close to \(a\)-axis are not consistent on different images. The etching pattern change in the pres-
ence of PVA shows that PVA may have formed hydrogen bonds with acetaminophen on crystal surface, and affected the etching patterns in the direction of $a$-axis, even though the effects are not as significant as for HPC.

### 4.5. Etching pattern by PEG and PPG

The purpose of comparing PEG and PPG is to further confirm that only if one polymer can form hydrogen bonds with acetaminophen on crystal surface, the etching patterns in the direction of $a$-axis will be affected. As shown in Fig. 9, PEG and PPG have similar molecular structures except that PPG has one methyl group as side group in each sub-unit. For PEG, except two hydroxyl groups at the end of PEG chain, all other oxygen atoms locate within the PEG backbone. Without bulky side groups, there are no obvious steric effects preventing the oxygen atoms in PEG backbone from forming hydrogen bond with acetaminophen on crystal surface. However, the methyl group of PPG may make the oxygen atom in the backbone of PPG difficult to form a hydrogen bond with acetaminophen. However, for PPG with low molecular weight, the effects of the hydroxyl groups at the two ends of PPG molecules cannot be ignored.

Both PEG(200) and PEG(400) exist in liquid state at room temperature, so they can be used directly to perform etching studies without influence from solvents. As shown in Fig. 10, the etching patterns of the acetaminophen (010) face by pure PEG(200) look like circles, i.e., not related with the directionality of the dominant attachment energies. Pure PEG(400) also produces similar etching patterns with no specific direction preference on the (010) face of acetaminophen.

The height profiles of all the etching patterns in the presence of polymers have been checked to make sure that the observed patterns are real etching patterns on crystal surface, rather than the adsorbed polymer molecules. Fig. 11 shows the height profiles of acetaminophen etching patterns in the presence of PEG. The height profiles indicate the layer-by-layer crystal dissolution characteristic, similar to the profiles observed in acetaminophen, $\alpha$-glycine and aspirin [33,34]. This suggests that those patterns are not due to the adsorbed polymer molecules.

Fig. 12 shows the etching patterns of acetaminophen (010) face by PEG(1000) aqueous solutions in different concentrations. At high concentrations, such as 12.5 and 1 mg/ml, the etching patterns are the same as the etching patterns by pure PEG(200); i.e., circular shape. When PEG(1000) solution is diluted to 25 µg/ml, the etching patterns show clear ledges in the directions of $a$- and $c$-axes; i.e., the same as the etching patterns by water. Even though there is still a trace of circular shape patterns at 25 µg/ml, PEG does not play a significant role in etching pattern formation at such low concentration. The aqueous solutions of PEG(200), PEG(400), PEG(3400), PEG(10,000),
Fig. 10. AFM images of the acetaminophen (010) face etched by pure PEG(200). The scan sizes were 60 × 60 µm² for A, 20 × 20 µm² for B, and 5 × 5 µm² for C. B and C were zoom-in scannings of image A site. The α- and c-axes were marked on image A.

Fig. 11. Height profiles of acetaminophen etching patterns in the presence of PEG. The top profile was from the left height image which was the etching patterns in pure PEG(200); the bottom profile was from the right height image which was the etching patterns in the 1 mg/ml PEG(1000) aqueous solution.

PEO(100K), and PEO(1000K) have also been used in the etching pattern study, and all have produced similar results.

The etching patterns of the acetaminophen (010) face by pure PPG(425) and PPG(1000), as shown in Fig. 13, are totally different from those by PEG. For the etching patterns by PPG(425), two ledges exactly follow c-axis. As to the other two ledges, they follow α-axis in zoom-in image in Fig. 13C, but are not stable at larger scale images A and B. It is possible that the hydroxyl groups at the ends of PPG(425) form hydrogen bonds with acetaminophen in the direction of α-axis, and the hydrogen bonding interactions disrupt the surface diffusion of acetaminophen in the direction of α-axis to a limited degree. As to PPG(1000), Figs. 13D and 13E show that the etching patterns follow both the directions of α- and c-axes very well, and the effects of the two terminal hydroxyl groups can be disregarded. The effects of PPG(4000) on the etching pattern formation are similar to the effects of PPG(1000).

5. Discussion

Acetaminophen can provide both hydrogen bond donor and acceptor. The crystal structure of acetaminophen monoclinic crystal in Fig. 1 shows that equal numbers of the two ends of the acetaminophen molecules, i.e., OH group and NHCOCH₃ group, can appear on the crystal surface at the same time no matter which mirror-symmetric (010) face is used in experiment. Whether or not the adsorbed molecules can form hydrogen bonds is mainly determined by the structures of adsorbed molecules.

In the presence of some polymers, the etching patterns of acetaminophen (010) face become significantly different from the etching patterns by water. The question is how the specific adsorption of polymers on the crystal surface affects the etching pattern formation. In the process of etching pattern formation, there are three important steps: surface diffusion, attachment to one specific site on crystal surface, detachment from the surface. In the presence of polymer layer, the transfer of solvent and acetaminophen molecules may be affected, but the formation of etching patterns should not be significantly affected. As analyzed in Section 3, hydrogen bonding interactions between adsorbed polymers and crystal surface may specifically affect the etching patterns in the direction of hydrogen bonding interactions.

Forming hydrogen bonds between polymer and acetaminophen is also important in dragging polymer chains closer to the crystal surface, and make van der Waals interactions stronger. Generally, if polymer has no structure sim-
Fig. 12. AFM images of the acetaminophen (010) face etched by PEG(1000) aqueous solutions. The scan sizes were 60 × 60 µm² for A, D, and G; 20 × 20 µm² for B, E, and H; and 5 × 5 µm² for C, F, and I. B and C were zoom-in scannings of image A site, E and F were zoom-in scannings of image D site, and H and I were zoom-in scannings of image G site. The a- and c-axes were marked on images A, D, and G. The polymer concentration for A, B, and C was 12.5 mg/ml; for D, E, and F was 1 mg/ml; and for G, H, and I was 25 µg/ml.

iliarity to acetaminophen, van der Waals interaction between polymer and crystal surface has no direction preference, and its effect on the etching pattern formation will not have direction preference, i.e., the etching patterns in the directions of both a-axis and c-axis will be affected. However, because hydrogen bonding interactions have direction preference, if polymers can have hydrogen bonding interactions with crystal surface, their effects on the etching pattern formation can be specifically in the direction of a-axis rather than c-axis.

5.1. Effects of HEC, HPC, and HPMC as well as PVA on surface diffusion

In the formation of hydrogen bonds between acetaminophen on crystal surface and adsorbed polymer in the direction of a-axis, steric factors play a very important role. In the direction of another hydrogen bond chain, between a- and c-axes, no matter whether or not polymer can form hydrogen bond with acetaminophen, the etching patterns will not be significantly affected because there is no dominant attachment energy in this direction, i.e., no visible etching pattern in this direction.

For HPMC, HPC, HEC, and PVA, even though all can form hydrogen bonds with the (010) face of acetaminophen crystal and affect the etching patterns in the direction of a-axis, their effects are not the same and follow approximately the order of HPMC ≈ HPC > HEC ≫ PVA. Our research showed that several factors are important in determining the effects of adsorbed polymers on the etching pattern formation, such as polymer chain rigidity, mobility of the side group, which will be further addressed in another paper. The etching pattern changes in the presence of HPMC, HPC, HEC, and PVA support our hypothesis that etching pattern change can be used to study the hydrogen
bonding interactions between adsorbed polymer and solid surface.

5.2. Effects of Dextran and PPG on surface diffusion

The etching patterns of the acetaminophen (010) face in the presence of Dextran were not affected, i.e., the same as the etching patterns by pure water. This suggests that different from HPC, HPMC, HEC, and PVA, Dextran does not have effective hydrogen bonding interactions with the crystal surface; thus, it cannot affect the etching patterns in the direction of a-axis. The consistence between the etching pattern observation and the structural analysis of Dextran further supports our hypothesis that the etching pattern change can be used to study the existence of hydrogen bonding interactions between adsorbed polymer and solid surface.

The molecular structure of PPG determines that its backbone can hardly form hydrogen bonds with the (010) face of acetaminophen. Because the backbone cannot form hydrogen bonds with crystal surface, the PPG backbone of train part will not be as close to surface as the PEG backbone of train part. Therefore, the surface diffusion of acetaminophen should be mainly under the guidance of the supramolecular interaction network of the crystal, and the etching patterns follow the directions of main attachment energies, i.e., a- and c-axes. However, the two hydroxyl groups at two ends of PPG chain may be able to form hydrogen bonds with crystal surface. When the average MW of PPG increases from 400 to 1000 or 4000, the relative contribution of the two terminal hydroxyl groups on the surface diffusion and etching pattern formation decreases. Therefore, the etching patterns by PPG(400) still have a certain variation of etching patterns in the direction of a-axis, but the etching patterns by PPG(1000) or PPG(4000) have stable etching patterns in the direction of a-axis. Overall, the etching patterns by PPG also support the hypothesis that the etching pattern study can be used to indicate the existence of hydrogen bonding interactions between adsorbed polymer and crystal surface.

5.3. Effects of PEG on surface diffusion

As expected, PEG changes the etching pattern in the direction of a-axis, the hydrogen bonding chain. The etching patterns of the acetaminophen (010) face by both pure PEG and PEG aqueous solutions are circular in shape. If there are only van der Waals interactions between PEG and solid surface, the etching patterns by PEG should be similar to the etching patterns by PPG; however, they are completely different. If PEG has formed hydrogen bonds with the crystal surface of acetaminophen, the hydrogen bonds which involve oxygen atoms on the PEG backbone may have brought the PEG chain closer to the crystal surface. Compared with other polymers, PEG has no bulky side group, which is also an important factor in determining that the train part of adsorbed PEG molecules could be closer to the crystal surface than in other polymers with large side chain components. The distance between an adsorbed PEG chain and the crystal surface determines whether acetaminophen molecules diffuse through the adsorbed PEG chains or not.
Because of high flexibility, PEG chains can cover large area of the crystal surface, limiting the surface diffusion of acetaminophen molecules. In the presence of PEG, acetaminophen molecules can only diffuse and incorporate into lattices on the crystal surface not covered by the train part of PEG molecules. However, due to the surface diffusion of adsorbed PEG molecules, those uncovered areas keep changing. Sukhishvili et al. [38] measured the diffusion coefficient of adsorbed PEG at a solid–liquid interface, which supports the idea that adsorbed PEG may diffuse on acetaminophen crystal surface. Of course, the surface diffusion of acetaminophen within those small areas uncovered by PEG is still under the guidance of intramolecular interaction network. Even though for limited time at those uncovered areas, the surface diffusion is guided by crystal structure, the overall effects regarding surface diffusion will not have any direction preference due to the PEG adsorption. The etching patterns in the presence of PEG have no direction preference, and form circular shape patterns; i.e., the patterns may be controlled mainly by the PEG chain diffusing on the crystal surface, which can be considered thermal motion of PEG chain that has no specific direction preference.

6. Conclusions

Among the polymers tested in this study, all polymers that can form hydrogen bonding with the acetaminophen surface, i.e., HEC, HPC, HPMC, PVA, and PEG, change the etching pattern in the direction of α-axis. HEC, HPC, HPMC, and PVA do not affect the etching patterns in the direction of c-axis. However, PEG is an exception. It not only affects the etching patterns in the direction of α-axis as expected from its hydrogen bonding formation ability, but also changes the etching pattern in the direction of c-axis possibly because the train part of adsorbed PEG molecules is closely attached to the crystal surface in the absence of bulky side group, and thus interrupts the free diffusion of acetaminophen molecules. The polymers whose structure indicates significant steric repulsion which prevents the formation of hydrogen bonds between the polymer and the crystal surface, Dextran and PPG, do not change the etching pattern in the direction of α-axis. Etching pattern study on the effects of polymers on the (010) face of acetaminophen crystals in the direction of α-axis suggests that the etching pattern change in the presence of polymers can be used to indicate the existence of the hydrogen bonding interactions between adsorbed polymer and acetaminophen crystal surface.

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