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Research Paper

Synergic Effects of Polymeric Additives on Dissolution and Crystallization of Acetaminophen

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Purpose. To study how polymeric additives interact with the crystal surface of acetaminophen, and why they have different effects on drug crystallization and dissolution.
Methods. The effects of different polymers on the etching patterns, crystallization and intrinsic dissolution rate (IDR) of acetaminophen have been studied.
Results. Some polymers have shown clear consistency in their effects on the etching patterns, crystallization and IDR of acetaminophen. For example, hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP), not only changed the etching patterns of the acetaminophen (010) face, but also inhibited acetaminophen crystallization significantly. Some polymers, like 2-hydroxyethyl cellulose (HEC), poly(vinyl alcohol) (PVA) and poly(ethylene glycol) (PEG) only had limited effects on the IDR and etching patterns, and no significant inhibitory effects on crystallization.
Conclusions. Even though some polymeric additives have no structural similarity to acetaminophen, they still can affect dissolution and crystallization of acetaminophen due to the synergic effects of their neighboring subunits during surface adsorption. The effects of polymeric additives on crystallization and dissolution of acetaminophen are affected not only by the specific interactions between adsorbed polymer molecules and crystal surface, but also by the mobility of the functional groups involved in the specific interactions.

KEY WORDS: crystallization; dissolution; etching pattern; mobility of functional groups; surface adsorption.

INTRODUCTION

To understand the effects of polymeric additives on crystallization and dissolution of crystal drugs is very important for selecting proper polymer excipients in formulation development, especially for stabilizing amorphous drug or supersaturated solution. Many steps are involved in crystallization and dissolution processes of crystals; however, not all steps are significantly affected by the adsorbed polymers. In crystallization, among the seven steps of crystal growth distinguished by Mullin (1), the adsorbed polymer layer may affect solute bulk diffusion as well as surface diffusion. In dissolution, there exist similar steps as in crystallization, such as detachment from the lattice, solvation of crystal molecules, surface diffusion, bulk diffusion through both the adsorption layer and the diffusion boundary layer (2–4). It is possible that the adsorbed polymer may play a similar role in both crystallization and dissolution processes.

A dynamic adsorption model has been proposed to explore why different polymers have different effects on crystallization and dissolution of drug crystals. In the model, it was proposed that to influence both crystallization and dissolution, on one hand, polymers should be able to form specific interactions with crystal surface; on the other hand, the mobility of the functional groups involved in the specific interactions between adsorbed polymers and crystal surface should be relatively low. Even though there is no structural similarity, many polymers have been used in solid dispersions and lyophilized amorphous mixtures for various drugs, and in some cases, the hydrogen bonding interactions between drug and polymer are very important (5,6). Strong interactions between polymers and drugs in aqueous solutions are important, but it may not be enough to inhibit crystallization from the supersaturated solutions (7).

The effects of polymeric additives on the etching patterns may give some information about the interactions between adsorbed polymer molecules and crystal surface. Acetaminophen was chosen as the model compound, and its cleaved (010) face of monoclinic crystal form was used in etching study, i.e. very briefly dissolve crystal surface, by different additives (8–10). In the direction of *a*-axis of the (010) face, there exists one hydrogen bond chain, as well as the strongest attachment energies which determine the etching pattern in this direction. As shown in Fig. 1, our

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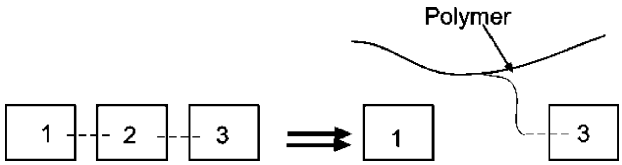

Fig. 1. Polymer forms a hydrogen bond with acetaminophen on crystal surface. The *dotted lines* represent hydrogen bonds.

previous study showed that some polymers like HPMC may have hydrogen-bonding interactions with acetaminophen in the direction of *a*-axis on the (010) face; thus, disrupt the surface diffusion of acetaminophen in the direction of *a*-axis and change the etching patterns (8).

Bliznakow *et al.* (11) proposed a simple model for the growth rate on a crystal surface in the presence of reversible adsorption of impurity on kinks.

$$V_{imp} = V_0(1-\theta_k) + V_{imp,\infty}\theta_k \tag{1}$$

θ_k is the fraction of kinks occupied by impurities, V_{imp}, V_0 and $V_{imp,\infty}$ are the face growth rate in the presence of impurity, in the absence of impurity and in the complete coverage of kinks by impurity, respectively. The growth rate related to steps and ledges can be similarly expressed as kinks. The model assumes that the adsorbed impurity must be detached before a growth unit can be incorporated into the lattice on the specific site.

However, the model proposed by Bliznakow *et al.* (11) has a serious problem when dealing with polymeric additives. One polymer molecule can interact with a crystal surface at many sites through its multiple subunits. Due to the synergic effects of polymer subunits, after the interaction with one site is broken, it is possible that polymer can re-form interaction at the site after a short interval. For small molecule, after it leaves one site, the probability for the molecule to adsorb at the original site should be very low. To certain degree, the polymer adsorption can be considered as partially irreversible depending on polymer properties.

Cabrera and Vermileya (12) proposed that when additive adsorption is irreversible on the crystal surface, the adsorbed units become the stumbling blocks for the advancement of the steps. The advancing step may divide at those sites and continue crystal growth between two neighboring adsorption sites with a radius of curvature *r*. The growth rate will be slower than that in the absence of adsorbed additives. When *r* is smaller than the critical value r_c, the crystal growth step will be stopped on the crystal face. Fig. 2 shows the

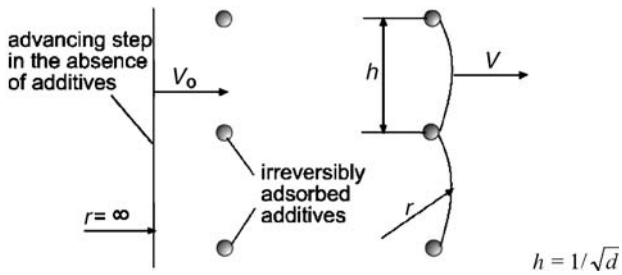

Fig. 2. The crystal growth step in the presence of irreversibly adsorbed additives. V_o or V is the rate of crystal growth in the absence or presence of irreversibly adsorbed additives.

crystal growth step in the presence of irreversibly adsorbed additives. The actual crystal growth rate can be expressed by the following equation:

$$\frac{V}{V_0} = \left(1 - 2r_c\sqrt{d}\right)^{1/2} \tag{2}$$

V is the actual crystal growth speed on the surface in the presence of adsorbed additives, V_0 is the speed in the absence of additives, and d is the average density of adsorbed impurities as shown on Fig. 2. The critical radius of curvature r_c can be expressed by the following equation:

$$r_c = \frac{\gamma_{CL} V_m}{kT\upsilon \ln S} \tag{3}$$

where γ_{CL} is the interfacial tension between crystal and solution, V_m is the molar volume of the crystal molecule, ν is number of ions; i.e., 1 for most organic compounds, and S is the supersaturation ratio.

This study was conducted to clarify the most critical factors in determining the effects of different polymeric additives on crystallization and dissolution of acetaminophen. The basic approaches employed were to investigate the effects of polymeric additives on the etching patterns of the (010) face, intrinsic dissolution rate (IDR), induction time and crystal growth rate of acetaminophen crystal. Even though the nucleation process is not the same as the crystal growth process, since the crystal nuclei have the same crystal structure as the grown crystals, the additives may have, to a certain level, similar effects on both nucleation and crystal growth (13); therefore, the effects of polymeric additives on crystallization may have consistent effects on different steps of crystallization. In order to distinguish the contribution of different factors, the effects of polymers on acetaminophen solubility and solution viscosity were also investigated. In this study, the polymers have been selected based on the following criteria: (1) Same backbone but different side chains, such as HEC, HPC and HPMC; (2) Backbones with different flexibility, such as PVA and HPMC; (3) Commonly used polymers, such as PEG and PVP.

Both the crystal structure and the polymer properties such as chain rigidity as well as the mobility of the functional groups involved in the specific interactions between polymers and crystal surface were analyzed to better understand their effects on crystallization and dissolution of acetaminophen crystal. Using the molecular dynamics simulation, Kramarenko (14) showed that the adsorption of polymer chains can be affected by many factors, such as chain length, adsorption energy, and chain rigidity. The average adsorption degree of the chain characterizes the relative number of chain monomers in the adsorbed state, i.e., a fraction of monomers belong to the trains of polymer chains. Their research showed that when the adsorption energy increases, the average adsorption degree also increases. If the adsorption energy is very low, the average adsorption degree will increase when the chain length decreases. For most adsorption energy, the chain length does not affect the average adsorption degree. As chain rigidity increases, the average adsorption degree also increases. However, if the adsorption energy is very low, the effects of chain rigidity on the average adsorption degree are not significant.

As a control, because the subunits of polymeric additives have no structural similarity as acetaminophen, some small molecules that have no structural similarity have been studied as well. However, it was worthwhile to note that many small molecule additives, like 4-methylacetanilide, that have structural similarity with acetaminophen can affect the crystallization and etching patterns of acetaminophen crystal by incorporating into crystal lattices of acetaminophen (15–17).

EXPERIMENTAL SECTION

Materials

Acetaminophen (U.S.P.) was purchased from Amend Drug & Chemical Company (Irvington, NJ). Three different molecular weight grades of polyvinylpyrrolidone (PVP), namely K16–18, average M.W. 8,000; K30, average M.W. 58,000; K85–95, average M.W. 1,300,000 were purchased from Acros Organics (New Jersey, USA). Four different molecular weight grades of HPMC, namely METHOCEL E4M, K3–LV, K4M, K100–LV, were obtained from Dow Chemical Company (Midland, MI). Sucrose (AR) was purchased from Mallinckrodt Baker, Inc. (Paris, KY). Four different molecular weight grades of PVA corresponding to the molecular weights of 15,000, 47,000, 72,000 and 195,000 were purchased from Fluka Chemical Company (Milwaukee, WI). Dextran with average molecular weight of 39,200 was obtained from Sigma Chemical Company (St. Louis, MO).

All the following chemicals were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI): Five different molecular weight grades of PEG with average molecular weights of 200, 400, 1000, 3400 and 10,000; Two different molecular weight grades of poly(ethylene oxide) (PEO) with average molecular weights of 100,000 and 1,000,000; HEC with average M_v ca. 90,000; Two different molecular weight grades of HPC with average M_w ca. 80,000 and 1,000,000; Anhydrous α-D-Glucose (96% purity); 2-Pyrrolidinone and 1-Vinyl-2-pyrrolidinone.

Acetaminophen Solubility Determination

To determine acetaminophen solubility in different additive solutions at 25.0°C, acetaminophen suspension samples were prepared. The vials containing suspensions were shaken in water bath for more than 24 h, and the saturated solutions were obtained by filtering the suspension samples through 0.45 μm Nalgene syringe filters. The filtered solutions were diluted and measured at 244 nm by a DU Series 600 Spectrophotometer (Beckman Instrument, Inc., Fullerton, CA) (18), and the concentrations were calculated based on the acetaminophen standard curve of UV absorbance and acetaminophen concentration. In the absence of acetaminophen, none of those polymer and small molecule aqueous solutions had absorbance at 244 nm.

Intrinsic Dissolution Rate of Acetaminophen Crystals

The intrinsic dissolution rate (IDR) test for drug was executed in a Wood's apparatus (2,19). The intrinsic dissolution rate is the dissolution rate for pure compounds with constant surface area under sink condition. Generally, the dissolution process was finished until 10% compound dissolved; then acetaminophen only reached less than 0.2% saturated acetaminophen concentration at experiment temperature. 200 to 300 mg acetaminophen were weighed to compress into tablet with two tons force (i.e., 4,400 lbs) for 60 s, and the tablet surface was 0.5 cm^2. 900 ml degassed medium set at 37.3°C was used for the dissolution test, and the rotation speed was set at 50 rpm. Plotting the cumulative amount of acetaminophen per area (mg/cm^2) versus time (min) gave a straight line with R^2 value more than 0.99, and the slope of the straight line was the IDR of acetaminophen in the measured solution.

Viscosity Measurements

The viscosities of all polymer solutions were measured using Cannon-Manning Semi-Micro Viscometer (Cannon Instrument Co., State College, PA) at 25.0°C in one external jacketed flask. The kinematic viscosity was calculated by multiplying efflux time with the viscometer constant. Because the concentrations of nearly all polymer aqueous solutions were lower than 10 mg/ml, the liquid density was approximated as 1.0 g/ml.

$$\text{kinematic viscosity}\left(mm^2/s\right) = \text{time(s)} \times \text{viscometer constant}\left(mm^2/s^2\right) \quad (4)$$

$$\text{viscosity (mPa s)} = \text{kinetic viscosity}\left(mm^2/s\right) \times \text{liquid density(g/ml)} \quad (5)$$

Crystallization of Acetaminophen

In checking the induction time in different polymer solutions, the acetaminophen supersaturation ratio was chosen as 0.5. Based on its solubility at 25°C, for most solutions, 5.44 g of acetaminophen raw materials were dissolved in 250 ml flask by heating. The supersaturated solutions were filtered through 0.2 μm filter membrane into 400 ml new pre-heated beakers. The beakers were covered with film and left at room temperature. The induction time was recorded when observing visible crystal. The experiments for all polymer solutions were executed at the same time, and repeated three or more times.

In addition to the crystallization conditions for observing induction time, seed crystals were added in checking crystal growth rate. The crystal growth rate was roughly estimated by checking how long it took for acetaminophen crystals to have significantly visible growth in different additive solutions.

Observation of Etching Patterns

After single acetaminophen crystals were prepared, the acetaminophen (010) face was acquired by cleaving single acetaminophen crystal and confirmed by X-ray powder diffraction (20). After one confirmed single crystal was mounted onto one AFM sample disk, the *a*-axis and *c*-axis directions were determined by observing the crystal two-dimension morphology. The partial dissolution tests were done at room temper-

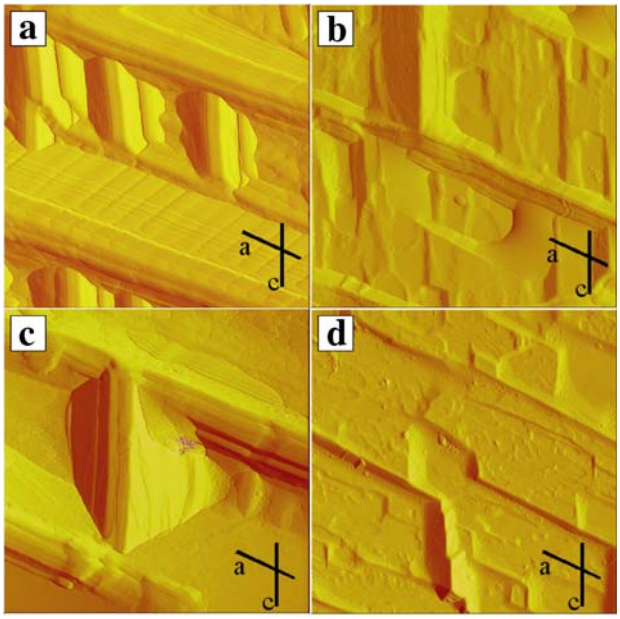

Fig. 3. AFM images of the acetaminophen (010) face etched by **a** water as well as 100 mg/ml **b** glucose, **c** sucrose and **d** 2-pyrrolidinone aqueous solutions. The *a* and *c* axes were marked on corresponding images. All scan sizes were 5×5 μm.

ature, and the time varied from 10 s to 2 min based on the solubility of acetaminophen in the solution as well as the actual depth of etching pattern which was face related. After a pre-determined time, the crystal surface was cleaned and dried before scanning with an AFM (NanoScope Multi-Mode AFM, Digital Instruments, Inc., Santa Barbara, CA) in contact mode at room temperature using a J-type piezo-scanner. The images in the following sections were in the deflection mode unless otherwise specified.

RESULTS AND DISCUSSION

Effects of Small Molecules on Etching Pattern and Crystallization

Some small molecules, including sucrose, glucose and 2-pyrrolidinone, that have no structural similarity as acetaminophen, were studied to show that even though they may have interactions with crystal surface, they cannot create observable effects on the crystallization and etching patterns of acetaminophen crystal. When adsorbed at crystal surface, the major difference between small molecules and polymer additives is that there exist synergic effects between polymer units, but no between small molecules.

Fig. 3a shows that there were two kinds of ledges in the etching patterns of the acetaminophen (010) face by water: one parallel to the *a*-axis, and the other parallel to the *c*-axis, i.e. the directions of the two strongest attachment energies related to the acetaminophen (010) face. Fig. 3b and c show that 100 mg/ml glucose and sucrose did not affect the etching patterns on the (010) face of acetaminophen. Even though 2-pyrrolidinone can increase the solubility of acetaminophen significantly, the etching patterns in 100 mg/ml 2-pyrrolidinone aqueous solutions still have clear ledges in the directions of *a*-axis and *c*-axis, i.e., the same as the etching patterns by water. It has been observed that even at much higher concentrations than the effective concentrations of 4-methylacetanilide in which the etching patterns of the acetaminophen (010) face in aqueous solutions have been affected (21), these small molecules that have no structural similarity to acetaminophen could not affect the etching patterns of the acetaminophen (010) face.

Furthermore, these small molecule additives did not inhibit nucleation or crystal growth of acetaminophen either. Crystallization of acetaminophen in those solutions was observed to be the same as in water, and had no visible crystal morphology change either. However, it is not suitable to conclude that there were no interactions between acetaminophen and small molecules. For example, the aqueous solubility of acetaminophen was slightly lower in high concentration solutions of glucose or sucrose, but it was higher in an aqueous solution of 2-pyrrolidinone which has both hydrophobic and hydrophilic segments (22,23). Based on the proposed dynamic adsorption model, those small molecules may have interactions with crystal surface, but the interactions are very dynamic and cannot induce visible effects on etching patterns and crystallization.

Effects of Polymeric Additives on Etching Patterns

The etching pattern change in the presence of polymeric additives was used in checking whether or not there existed specific interactions between adsorbed polymer molecules and crystal surface of acetaminophen (8,24). Fig. 4 shows the exemplary etching patterns in the presence of Dextran, HEC, HPC and HPMC. Due to its structural property, Dextran can hardly form hydrogen bonding interactions with acetamino-

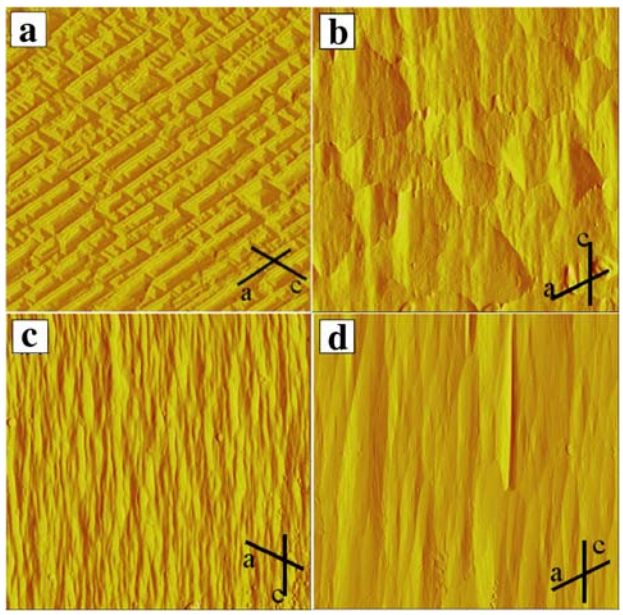

Fig. 4. AFM images of the acetaminophen (010) face etched by **a** 10 mg/ml Dextran (52.9 K), **b** 10 mg/ml HEC(90 K), **c** 10 mg/ml HPC(80 K) and **d** 1 mg/ml HPMC(E4M) aqueous solutions. The *a* and *c* axes were marked on corresponding images. All scan sizes were 20×20 μm.

phen on crystal surface, and could not induce visible etching pattern change as shown in Fig. 4a (8). Even though HEC, HPC and HPMC have the same cellulose backbone, a straight long chain, the side chains which involve in hydrogen bonding interactions are different. By comparing Fig. 4b, c and d, it is easy to see that the etching patterns in the direction of *a*-axis disappeared in the HPC and HPMC solutions, but still partially remained in the HEC solution. The modification groups that could involve in hydrogen bonding interactions are $(CH_2CHO)_mH$ for HEC, $[CH_2CH(CH_3)O]_mH$ for HPC , and $CH_2CH(OH)CH_3$ for HPMC. The side chains of HEC are much longer than those of HPC and HPMC, and make the functional groups of HEC have high mobility than HPC and HPMC, which may cause the effects of HEC on the etching patterns in the direction of *a*-axis not as significant as HPC and HPMC. By comparing the effects of HEC, HPC and HPMC, we can see that the mobility of the functional groups involved in the specific surface interactions plays a critical role in their effects on crystal dissolution and crystallization.

Fig. 5 shows the exemplary etching patterns in the presence of PVA, PEG and PVP. Fig. 5a shows in 25 mg/ml PVA (15 K) solution, the etching patterns followed the *c*-axis well, but slightly deviated from the *a*-axis, which suggested there existed hydrogen bonding interactions between PVA and crystal surface, however the hydrogen bonding interactions were not very strong (25). Fig. 5b shows the etching patterns of the (010) face of acetaminophen in 12.5 mg/ml PEG(1000) aqueous solution. The etching patterns of the acetaminophen (010) face by both pure PEG and PEG aqueous solutions were circular shape, no specific preference of directions, which may be due to that the PEG backbones have been brought very close to crystal surface by the oxygen atoms on the PEG backbone which involved in the hydrogen bonding interactions (8). Fig. 5c shows the etching patterns of the acetaminophen (010) face by 1 mg/ml PVP(K30). The etching patterns have two ledges that follow the *a*-axis well, but other two ledges do not follow the *c*-axis and are nearly perpendicular to the *a*-axis. The solubility of acetaminophen in PVP solutions of high concentrations is higher than that in water, which implies that PVP has strong interaction with acetaminophen through hydrophobic interaction (24). Our previous study suggested that PVP formed direction-specific van der Waals interactions with crystal surface in the direction of *c*-axis (24).

Effects of Polymeric Additives on IDR

Etching patterns were formed by dissolving crystal surface in short time by different solutions, and were determined by not only the supramolecular interactions within crystal itself, but also the interactions between adsorbed additives and crystal surface (8,20,24,26). It would be very interesting to check whether the dissolution pattern change in micro-level can be observed in its intrinsic dissolution rate (IDR), i.e. macro-level, and whether there is clear consistency between them. Besides, considering the effects of viscosity on diffusion to bulk medium during dissolution process, the solution viscosity has been taken into consideration in the study. The viscosity values of different polymer solutions are listed in Table I.

As a control, the IDR of acetaminophen in water without polymeric additives was measured to be 0.86 mg/($cm^2 \times$min). Fig. 6 shows the relationship between polymer concentration and acetaminophen IDR for PVP (K30), HPMC (E4M), Dextran (39.2 K), PEG (400) and PVA (15 K). The viscosity of 100 μg/ml Dextran (39.2 K) was the same as water; and at 100 μg/ml or higher concentration of Dextran (39.2 K) solutions, the IDR of acetaminophen in Dextran solutions were only slightly slower than that in water. As mentioned in "Experimental Section", the IDR of acetaminophen in measured solutions was the slope of the straight lines based on measured data, and all the R^2 values were 0.999 or larger.

The acetaminophen IDR in 1 μg/ml HPMC (E4M) was obviously slower than that in the absence of polymers, but the viscosity of 1 μg/ml HPMC (E4M) was the same as the viscosity of water. In the diluted 100 μg/ml PVA (15 K) and PEG (400) solutions, the acetaminophen IDR was also obviously slower than that in water even though their viscosity was the same as water viscosity. In diluted PVP (K30) solutions, similar results have been observed as well. However, at high concentrations, both PEG (400) and PVP (K30) could increase the acetaminophen IDR, and was checked due to the increased solubility of acetaminophen by PEG (400) and PVP (K30) at high concentrations.

Overall, in concentrated polymer solutions, both the solution viscosity and the effects of polymeric additives on acetaminophen solubility will affect the acetaminophen IDR. However, when polymer solutions were diluted to the level in which the solution viscosity became the same as water, and

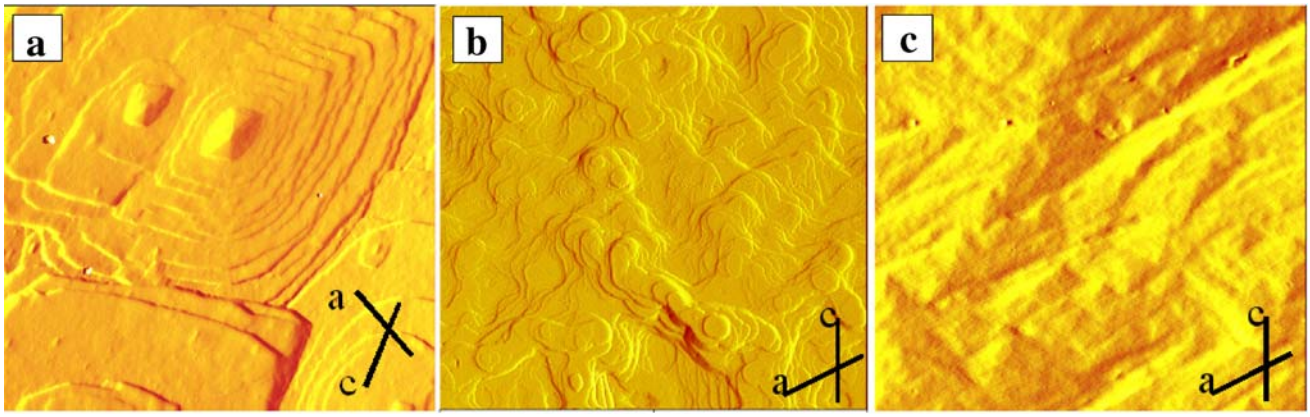

Fig. 5. AFM images of the acetaminophen (010) face etched by **a** 25 mg/ml PVA(15 K), **b** 12.5 mg/ml PEG(1000) and **c** 1 mg/ml PVP(K30). The *a* and *c* axes were marked on corresponding images. All scan sizes were 20×20 μm.

Table I. Viscosity Values of Different Polymer Solution[a]

Concentration	PVP (K30)	HPMC (E4M)	Dextran (39.2 K)	PEG (400)	PVA (15 K)
1.00×10^{-1}			4.01		
5.00×10^{-2}	2.45			1.21	
1.00×10^{-2}	1.22	719	1.36	1.03	1.42
1.00×10^{-3}	1.00	3.06	1.02	1.00	1.10
1.00×10^{-4}		1.14	1.00		1.00
1.00×10^{-5}		1.14			
1.00×10^{-6}		1.00			

The unit of polymer concentration is g/ml, and the unit for viscosity is mPa·s.
[a] Measured water viscosity is 1.00.

polymers had no effects on the acetaminophen solubility, the effects of polymeric additives on acetaminophen IDR may be attributed to the adsorbed polymer which could form specific interactions with crystal surface. Our previous study clearly showed that in those diluted solutions, the etching patterns of the acetaminophen (010) face could still be affected by those polymers like PEG, PVA, HPMC and PVP. Furthermore, among those polymers, PVP and HPMC could slow down the IDR much more than PEG and PVA, and the observations may be due to the lower mobility of those functional groups of HPMC and PVP involved in specific interactions with crystal surface.

Effects of Polymeric Additives on Crystallization

Because polymeric additives may interact with crystal surface similarly during both crystallization and dissolution processes, whether or not the effects of polymeric additives on crystallization are consistent with their effects on dissolution have been checked. Since the induction time was recorded when the crystal(s) was visible, the induction time actually included both nucleation time and certain crystal growth time. It was observed that in 100 μg/ml HPC (80 K), HPMC (E4M) and PVP (K30) solutions, the induction time of acetaminophen were much longer than in 100 μg/ml HEC (90 K) and Dextran (39.2 K) as well as 1 mg/ml PVA (15 K) and PEG (400). Viscosity study showed that the viscosities of all these solutions were the same as or close to the viscosity of water. Diluted solutions, such as 10 μg/ml PVP (K30), 0.1 mg/ml HPMC (E4M) and 1 mg/ml HPC (80 K) which had viscosities nearly the same as water viscosity, could inhibit crystal growth much more significantly than some concentrated polymer solutions with higher viscosities such as 10 mg/ml PVA (15 K) and 10 mg/ml HEC (90 K). Dextran (39.2 K) could not inhibit crystal growth even at 10 mg/ml, at which the viscosity was 1.36 mPa·s at 25°C. Therefore, the difference in inhibiting acetaminophen nucleation and crystal growth may be due to other factors rather than the viscosity of polymer solutions.

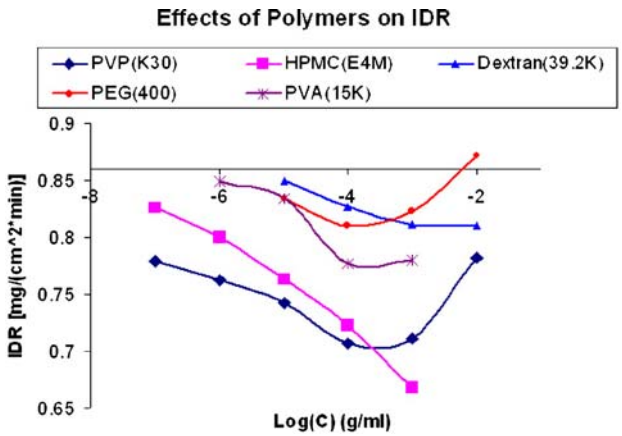

Fig. 6. The effects of polymers on the acetaminophen IDR.

In the crystal growth study, it was found that the relative strength of polymeric additives in inhibiting crystal growth can be ranked as: PVP (K30) > HPMC (E4M)> HPC (80 K) > HEC (90 K), Dextran (39.2 K), PEG (400), PVA (15 K), and small molecule additives. Even though PVA, PEG and HEC have caused the etching pattern change, they could not exert obvious inhibition on crystal growth of acetaminophen, which may due to the high mobility of their functional groups involved in hydrogen bonding interactions with crystal surface. The longer side chain of HPC compared with HPMC may cause the functional groups of HPC have higher mobility than those of HPMC, thus less effective in inhibiting acetaminophen crystallization than HPMC. Among all the polymeric additives studied, PVP shows the strongest inhibitory effect on acetaminophen crystal growth, which may be due to both its strong interactions with crystal surface and low mobility of its functional groups involved in the specific van der Waals interactions (24).

Mobility of Functional Groups

Polymeric additives with different structural properties exhibited different effects on crystallization and dissolution, which may be related to the properties of their backbones as well as the functional group of the side chains. Mobility of the functional groups of polymeric additives used in this study has been analyzed to check whether there exists any relationship between the mobility and the effects on crystallization and dissolution. The rigidity of a polymer chain is determined by both the bond angle and the torsion angle that characterizes the hindered rotation about the backbone due to steric effects (27). The square of the chain's end-to-end distance is:

$$\langle r^2 \rangle = nl^2 \frac{(1-\cos\theta)(1+\cos\langle\phi\rangle)}{(1+\cos\theta)(1-\cos\langle\phi\rangle)} \qquad (6)$$

where $<r^2>$ is the mean square end-to-end distance, n is the number of monomers, l is the length of monomer, θ is the bond angle, and ϕ is the average torsion angle.

Kramarenko (14) showed that the adsorption of polymer chains can be affected by many factors, such as chain length, adsorption energy, and chain rigidity. For most adsorption energy, the chain length does not affect the average adsorption degree. Their research showed that when the adsorption energy or chain rigidity increases, the average adsorption degree also increases. When the side chain of a polymer is not long, the mobility of functional groups in side chain that involved in the hydrogen bonding interactions between polymer and crystal surface is mainly controlled by the rigidity of polymer backbone. If the side chain is long, the flexibility of the side chain also contributes to the mobility of functional groups.

For polymers used in this study, since the bonds in the glucose ring of HPMC are in fixed conformation, and only the COC bonds between two glucose rings can rotate, the overall effects of the bond angle of HPMC are much lower than those in PEG, PVA and PVP. Since the torsion angle is mainly determined by the steric effects, the torsion angles for different polymers are in the rank of PEG > PVA > PVP > HPMC. Torsional angles cannot define polymer mobility exactly, but it can give rough estimation about the relative polymer mobility. Overall, the rigidities of polymer chains are in the rank of HPMC> PVP > PVA > PEG. This is consistent with the observations that HPMC and PVP can affect both dissolution and crystallization much more significantly than PVA and PEG. Furthermore, with longer the side chain, the mobility of the functional groups located in the side chains should have higher mobility. The contribution of side chains determined that among the three cellulose derivatives, the mobility of functional groups can be ranked as HEC > HPC > HPMC, which is consistent with their effects on dissolution and crystallization of acetaminophen.

Dynamic Exchange of Hydrogen Bonds

Those small molecule additives, such as sucrose and glucose in this study which have no structural similarity as acetaminophen and cannot incorporate into the crystal lattice like those "tailor-made" additives, have no significant effects on etching patterns, nucleation, growth and morphology of acetaminophen. The adsorption and desorption processes of those small molecules are very dynamic. When a hydrogen bond between one small molecule and crystal surface is broken, the small molecule may diffuse away from the original site and be unable to form a hydrogen bond with crystal surface at the original location.

For adsorbed polymers, the trains and the loops are in dynamic exchange process, which means the hydrogen bond formed between polymer and acetaminophen on the crystal surface may not always stay at one position. Note that water can also form hydrogen bonds with polymer molecules and acetaminophen molecules. At one instance, one hydrogen bond between acetaminophen and polymer molecule exists; at the next instance, the hydrogen bond may be broken, and the contributors of the hydrogen bond may form hydrogen bonds with water. However, for polymeric additives, the movement of each subunit is restricted by the neighboring subunits and cannot freely diffuse away from the original site. Therefore, the subunit may form a hydrogen bond with the original acetaminophen again or nearby acetaminophen at the following instance as shown in Fig. 7. In the presence of interactions between polymer and crystal surface, either crystal growth or dissolution will be halted at the location of interactions. Polymers that have only non-specific van der Waals interactions with crystal surface can still adsorb onto the crystal surface; however, studies using polymers, such as dextran and poly(propylene glycol) (PPG) (8), showed that those polymers cannot exert significant effects on acetaminophen dissolution or crystallization. Therefore, only those polymers that can form specific interactions, such as hydrogen bonds or direction-specific van der Waals interactions with crystal surface can exert significant effects on acetaminophen dissolution or crystallization.

Analysis on the Effects of Polymers on Crystallization and Dissolution

In crystallization, the surface diffusing molecules generally incorporate into the kink or step sites, and the different attachment energy in different directions will cause direction preference in the crystal growth. Previous study also showed that dissolution process has direction preference like crystallization process (3,20,26). Generally, the distance between two neighboring subunits in contact with the crystal surface should be very small, especially compared to the distance between two neighboring adsorbed small molecule additives at low concentration, and may be even smaller than the

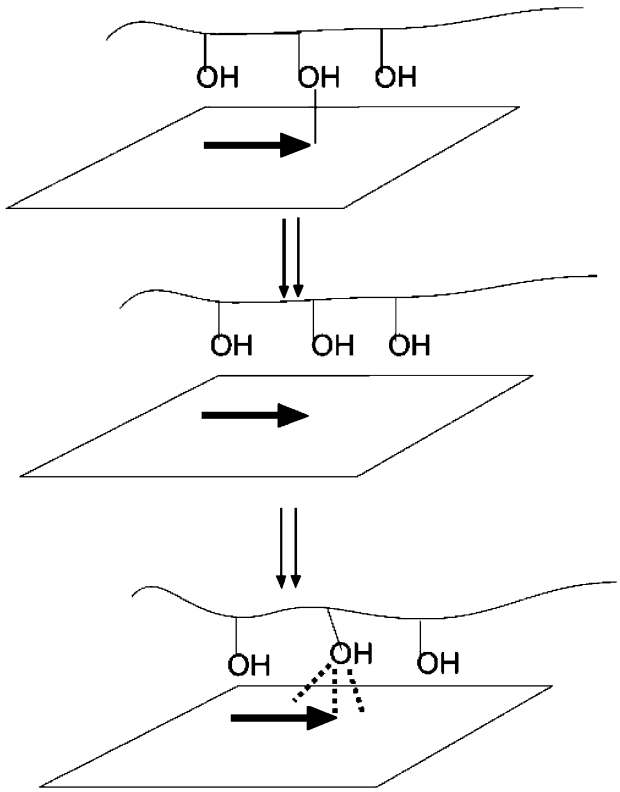

Fig. 7. Illustration of the dynamic adsorption model. The *thick arrow* represents the direction of either crystal growth or dissolution.

critical value r_c (12). Therefore, the adsorbed polymer may stop the crystallization or dissolution process represented by the big arrow at the hydrogen bond position shown in Fig. 7, and the polymer hydrogen bond has to be broken before the crystal growth can proceed in the arrow direction.

Considering the dynamic property of the hydrogen bonding interactions between one subunit and crystal surface, after the hydrogen bond was broken, whether or not the subunit will form hydrogen bond with the original crystal location is determined by the mobility of the subunit as long as the polymer was still adsorbed onto crystal surface. If the mobility of the subunit involving in hydrogen bonding interactions is high, it is highly possible that the subunit may form hydrogen bond with crystal surface at other location; thus, crystal growth or dissolution process can proceed over the position originally blocked. If the mobility of the subunit is low, it is highly possible that the subunit may form hydrogen bond with crystal surface at the original location; thus, crystal growth or dissolution process has to wait another hydrogen bond formation and breakage cycle. Besides, the interval between two hydrogen bond formations may be longer with high mobile subunit, and the longer interval will also help crystallization and dissolution process to move ahead. Overall, the study suggested that those polymers with functional groups of less mobility will affect crystallization and dissolution processes more than those polymers with highly mobile functional groups.

It may be due to the high flexibility of the functional groups that PVA, PEG and HEC do not have obvious effects on crystallization of acetaminophen. The high mobility of PVA and PEG come from their flexible backbones, and HEC from its flexible long side chains. The different effects of HEC, HPC and HPMC on etching patterns and crystallization of acetaminophen may be also due to the different mobility of the functional groups involved in the hydrogen bonding interactions between polymer and crystal surface. Lack of specific interactions between Dextran and crystal surface of acetaminophen may determine why Dextran did not have visible effects on etching patterns and crystallization of acetaminophen. In the pharmaceutical industry, HPMC derivatives (HPMC, HPMC-AS and HPMC-P) and PVP are generally used as potential crystallization inhibitors more commonly than most polymeric excipients, which is consistent with the dynamic adsorption model by taking the relative low mobility of the functional groups of HPMC derivatives and PVP into consideration. Of course, those polymers still need specific interactions, like hydrogen bonding interactions or direction-specific van der Waals interactions, with crystal surface of specific drugs in order to exert significant effects.

Dominant Effects of Polymeric Additives on Crystallization and Dissolution

Since adsorbed polymers may affect several steps in both crystallization and dissolution processes, it is worthwhile to discuss the effects of polymeric additives on those steps.

1. Do the polymers inhibit the bulk diffusion through the diffusion boundary layer?

The crystallization experiments show that the viscosity of polymer solutions might play a certain role in inhibiting crystal growth, for example, high concentration of PVP, HPC and HPMC with higher viscosity did inhibit acetaminophen crystal growth much more efficiently than lower concentration PVP, HPC and HPMC. However, the viscosity of polymer solutions does not have dominant effect in inhibiting crystal growth. For example, 0.1 mg/ml HPMC (E4M) could inhibit crystal growth much more significantly than 10 mg/ml PVA (15 K), but 10 mg/ml PVA solution had higher viscosity than 0.1 mg/ml HPMC (E4M). Similar observations were found in the dissolution processes as well. For example, the IDR of acetaminophen in 0.1 mg/ml HPMC (E4M) was obviously lower than in 10 mg/ml Dextran (39.2 K), but the viscosity of 10 mg/ml Dextran (39.2 K) was higher than that of 0.1 mg/ml HPMC (E4M). Therefore, the effects of polymers on diffusion through the boundary diffusion layer is not the main factor inhibiting crystallization and dissolution of acetaminophen, even though diffusion plays an important role in crystallization and dissolution.

2. Do polymers inhibit bulk diffusion through the adsorption layer?

The effective hydrodynamic radii (8), diffusion coefficients (28) and molecular weights of PVP (K30) and Dextran (39.2 K) are similar; however, PVP (K30) affected crystallization and dissolution of acetaminophen much more significantly than Dextran (39.2 K). This might due to the fact that PVP can increase acetaminophen solubility in water, it may have certain interactions with acetaminophen in solution. Although PEG can also increase acetaminophen solubility, the effects of PEG on crystallization and dissolution are not as obvious as PVP. Therefore, the diffusion through the adsorption layer may have certain effects on crystallization and dissolution, but may not be the main factor in affecting crystallization and dissolution.

3. Can acetaminophen molecules still diffuse on the crystal surface in the presence of the adsorbed polymers?

Li *et al.* (3) reported that surface diffusion is very important in etching pattern formation. On one hand, the existence of the polymers on the crystal surface may increase the surface diffusion time; on the other hand, the adsorbed polymers may be obstacles to surface diffusion of acetaminophen. The etching pattern study shows that in the presence of some polymers, the etching patterns of the acetaminophen (010) face have been significantly changed. Therefore, surface diffusion should still exist for acetaminophen in the presence of adsorbed polymers.

4. Do the interactions between polymer and acetaminophen affect the incorporation or detachment of acetaminophen from the lattice?

The etching pattern study suggests that some polymers can form hydrogen bonds with acetaminophen. Therefore, if acetaminophen needs to incorporate into or detach from the lattice site at which a polymer has formed hydrogen bond(s) with acetaminophen, the process will certainly be affected.

Overall, among various effects of polymeric additives, the effects on surface diffusion as well as incorporation into or detachment from crystal lattice play an important role in crystallization and dissolution of acetaminophen.

CONCLUSIONS

For those small molecules without structural similarity, there were no obvious effects on etching patterns, crystal nucleation or growth. But due to synergic effects between subunits of polymeric additives, many polymeric additives without structural similarity to acetaminophen still can effectively affect the etching patterns, IDR and crystallization of acetaminophen as long as they can form specific interactions like hydrogen bonding interactions with crystal surface. The effects of polymeric additives on acetaminophen crystallization were consistent with their effects on the etching patterns of the acetaminophen (010) face.

For those polymers that have specific interactions with crystal surface, there still exists significant difference among polymers. For adsorbed polymer, the specific interaction like hydrogen-bonding interactions between polymer and crystal surface are in dynamic exchange process. The lower mobility of the functional groups of those polymers involved in the specific interactions, the stronger effects those polymers have on crystallization and dissolution of acetaminophen. The mobility is determined not only by the polymer backbone, but also affected by the flexibility of side chains if those functional groups are located in the side chains.

Based on the dynamic adsorption model, the different effects of PVA and HPMC on crystallization and dissolution are mainly due to the difference in their chain rigidity even though both of them can form hydrogen bonds with acetaminophen on a crystal surface. For HEC, HPC and HPMC, even though they have same backbone, their different side chains cause the mobility of the functional groups to be significantly different, the rigidity of the side chains are ranked as HPMC > HPC > HEC. HEC cannot totally inhibit the etching pattern in the direction of *a*-axis, but HPC and HPMC can. The observed inhibitory effects on crystallization are ranked as HPMC > HPC > HEC, which is consistent with the rigidity of their functional groups involved in the hydrogen bonding interactions between polymer and crystal surface. For PEG, even though it affects the etching patterns significantly, it cannot significantly affect IDR and crystallization of acetaminophen due to its high flexibility. To effectively affect the crystallization, etching patterns and dissolution, the adsorbed polymers need to have specific interactions with crystal surface, as well as low mobility of the functional group(s) involved in the interactions.

Different from many polymers studied, PVP have van der Waals interactions rather than hydrogen bonding interactions with acetaminophen on the (010) face (24). The relative low flexibility of PVP chain compared with PVA and PEG as well as its direction-specific strong van der Waals interactions with crystal surface of acetaminophen may help to understand why PVP can significantly decrease the IDR and crystallization of acetaminophen.

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