# Study on the Interactions between Polyvinylpyrrolidone (PVP) and Acetaminophen Crystals: Partial Dissolution Pattern Change

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*Received 21 December 2004; revised 20 March 2005; accepted 29 March 2005*

*Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20383*

**ABSTRACT:** The objective of the study was to investigate the interactions between polyvinylpyrrolidone (PVP) and acetaminophen crystal especially on crystal surface. The effects of PVP on the etching pattern change of the acetaminophen (010) face, solubility enhancement as well as the intrinsic dissolution rate (IDR) of acetaminophen crystals have been studied. The etching patterns of the acetaminophen (010) face in the presence of PVP have stable ledges in the direction of *a*-axis, but deviate from *c*-axis, which shows that the dissolution on the (010) face has been affected by the adsorbed PVP especially in the direction of *c*-axis through van der Waals interactions rather than hydrogen bonding interactions. Even though PVP(K30) can enhance the solubility of acetaminophen in concentration higher than 1 mg/mL, the IDR of acetaminophen in diluted PVP solutions was lower than in water. Because the viscosity of those diluted PVP(K30) solutions were the same as water viscosity, the lowered IDR of acetaminophen cannot be explained simply by the viscosity effects of PVP solutions. Overall, the study suggests that the PVP molecules adsorbed on the surface of acetaminophen crystals play an important role in etching pattern change as well as the intrinsic dissolution rate change.
 J Pharm Sci 94:2166–2174, 2005
**Keywords:** crystals; dissolution; interaction; polymers; solubility; surface chemistry; viscosity; sorption

## INTRODUCTION

Even though polymeric additives may not have similar structures as crystal molecules, they can significantly affect crystallization process.[1] Polymers have been used in solid dispersion and lyophilized drug products, and in some cases, the hydrogen bonds between drug and polymer plays an important role in formulation development.[2,3] Since PVP, shown in Figure 1, is one of the most commonly used excipients in pharmaceutical industry, it is of practical interest to understand how it interacts with crystal surface during dissolution and crystallization of drug crystals. PVP can inhibit the crystallization of acetaminophen, decrease its crystallinity, and enhance the dissolution rate and/or the compressibility of acetaminophen crystals,[4,5] as well as increase the aqueous solubility of acetaminophen.[6] In addition to functioning as an anti-plasticizer, PVP can stabilize amorphous indomethacin through hydrogen bonding interactions.[3] However, besides the hydrogen bonding interactions, van der Waals interactions may exist between PVP and acetaminophen crystals. Studies on the interaction between polymeric additives and crystals at molecular level are needed to better understand the effects of polymeric additives on crystal dissolution and crystallization.

Etching patterns are formed by partial dissolution of crystal surfaces, and have been widely studied to understand crystal structure, as well as the effects of crystal structures and solvents on

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Journal of Pharmaceutical Sciences, Vol. 94, 2166–2174 (2005)

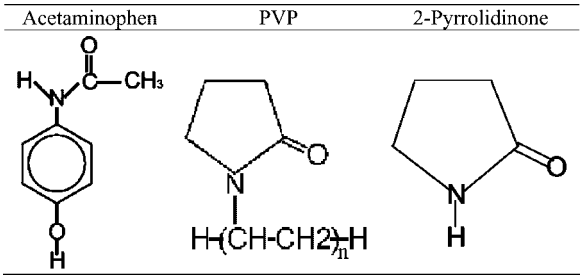


**Figure 1.** Molecular structures of acetaminophen, polyvinylpyrrolidone (PVP), and 2-pyrrolidinone.

crystal dissolution.[7–11] The etching patterns may be influenced by not only crystal structure but also specific interactions between crystal molecules and additive molecules. As to the shape of etching patterns, Li et al.[8] reported that surface diffusion plays an important role in etching pattern formation. Our previous research has shown that the solubilizing ability of different solvents as well as solvent adsorption in specific direction can also affect etching pattern formation.[12,13] The effects of "tailor-made" additives have been widely studied on the etching pattern change.[14] For example, acetanilide and 4-methyl acetanilide have been used as additives for acetaminophen, and the results support the idea that additive molecules can adsorb onto crystal surfaces, diffuse into and occupy crystal lattices, resulting in interruption of the original crystal interaction network and the change of the etching patterns. Even though PVP has no structure similarity with acetaminophen and cannot incorporate into crystal lattices, if PVP can affect the etching patterns of crystal surface, it may help to explore the interactions between PVP and crystal surface.

Acetaminophen, shown in Figure 1, has been chosen as the model compound. The crystal structure information of acetaminophen was retrieved from Cambridge Structural Database (HXACAN01) with the following parameters: $P_{2/1a}$; a = 12.93Å, b = 9.4Å; c = 7.10Å; β = 115.9°.[15] The single crystals collected in the research were in monoclinic form rather than the unstable orthorhombic form,[15,16] and they can be cleaved to create smooth (010) face. Even though the (010) face is not one exposed face of acetaminophen crystals crystallized from water, it has been used as a model surface for partial dissolution study. There are two hydrogen bond chains in acetaminophen crystal, both on the (010) face. Figure 2[17] shows that one of the hydrogen bond chains is in the direction of *a*-axis by forming N–H. . .O–H, and the other is in the direction between *a*-axis and *c*-axis by forming

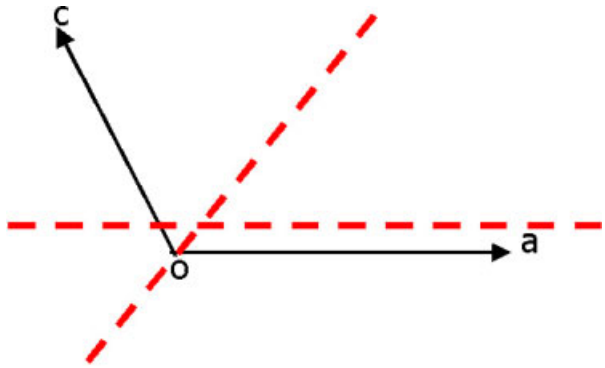


**Figure 2.** Relationship between the directions of hydrogen bond chains and the directions of the dominant attachment energies on the acetaminophen (010) face. The dotted lines represent the directions of the hydrogen bond chains; the *a*-axis and *c*-axis are the directions of the dominant attachment energies on the (010) face.

C–O. . .H–O. The two strongest attachment energies related to the (010) face of acetaminophen are in the directions of *a*-axis and *c*-axis, which are not exactly the same as the directions of the hydrogen bond chains. The attachment energy in the direction of *a*-axis is mainly attributed to hydrogen bonding interactions, and in the direction of *c*-axis is attributed to van der Waals interactions. Under the guidance of supramolecular interactions, the etching patterns of acetaminophen (010) face elongate in the directions of *a*- and *c*-axes in water.[8] If polymeric additives can interact with acetaminophen in the direction of *a*-axis (through Hydrogen bonding interactions) or *c*-axis (through van der Waals interactions), the etching patterns may be affected correspondingly on the (010) face.

The effects of PVP on acetaminophen crystals have also been studied by checking the intrinsic dissolution rate (IDR) of acetaminophen in different PVP solutions. The IDR test was executed in a Wood's apparatus[18,19] by keeping the flat surface constant for those compressed tablets exposed to a dissolution medium. The IDR was measured under sink conditions by measuring only the dissolution rate during the early phase of dissolution. IDR can be described by the Noyes-Nernst equation:

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{hV}$$

where $dC/dt$ is the dissolution rate, $A$ is the surface area of the dissolving tablet, $D$ is the diffusion coefficient, $C_s$ is the drug concentration in the diffusion layer, $C$ is the drug concentration in the bulky medium, $h$ is the diffusion layer thickness,

and $V$ is the volume of the dissolution medium. Because only less than 10% of the tablet was dissolved for the actual measurements of IDR, $C_s$ can be considered as the saturation solubility, and $C$ can be considered as zero.

While historically optical microscopy has been the primary tool for studying crystal growth, atomic force microscopy (AFM) represents a new generation of nano-scale surface characterization methods. Using AFM, Kuznetsov et al.[20] has recorded the incorporation, on the nanometer scale, of molecules to growth steps of macromolecular crystals grown from solution. AFM is generally operated in either the traditional contact mode or the Tapping Mode, and in the current research, contact mode is the most commonly used one. AFM has been shown to be a very useful tool in providing high-resolution three-dimensional images of etched pits.[7,10,21]

## MATERIALS AND METHODS

Acetaminophen (USP) was purchased from Amend Drug & Chemical Company (Irvington, NJ). Three grades of PVP, K16- 18, MW 8,000; K30, MW 58,000; K85-95, MW 1,300,000 were purchased from Acros Organics (Morris Plains, NJ). 2-pyrrolidinone was purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI).

### Partial Dissolution

After the single crystals of acetaminophen were prepared, the (010) face of acetaminophen was obtained by cleaving single acetaminophen crystals, and confirmed by X-ray diffraction.[12] The directions of $a$- and $c$-axes were identified by comparing the observed crystal face with the simulated theoretical crystal morphology. The partial dissolution tests on the (010) face of acetaminophen were conducted at room temperature for 40–90 s. The single crystals for partial dissolution tests were already attached onto an AFM disk before executing an X-ray diffraction. After a pre-determined time, the disk was taken from the solution, and the remaining solution was removed from the crystal surface with filter paper. Finally, the sample was air-dried before executing AFM observation. After partial dissolution, the surfaces of acetaminophen single crystals were examined with an AFM, and the collected images shown in the following sections were in the deflection mode unless otherwise specified.

### Solubility Measurement

At 244 nm, in the absence of acetaminophen, the PVP and 2-pyrrolidinone aqueous solutions have no absorbance. At 25°C, an excess amount of acetaminophen powder (about 150 mg) was added to 5 mL solutions. After at least 24 h under stirring, the saturated solutions were obtained by filtering the suspension samples through 0.45 μm Nalgene syringe filters. The acetaminophen solubility in different concentrations and different grade PVP aqueous solutions as well as in 2-pyrrolidinone solutions were measured at 244 nm by a DU Series 600 Spectrophotometer (Beckman Instrument, Inc., Fullerton, CA), and calculated based on the standard absorbance curve of acetaminophen.[12,22]

### Intrinsic Dissolution Rate of Acetaminophen Crystals

The intrinsic dissolution rate (IDR) is the dissolution rate for pure compounds with constant surface area under sink condition. In these experiments, only the dissolution data obtained from the beginning up to 10% acetaminophen was dissolved has been used to generate IDRs. When 10% acetaminophen was dissolved, the acetaminophen concentration in the vessel was less than 0.2% of the solubility of acetaminophen. Tablets were prepared by compressing 200–300 mg acetaminophen with two tons force (i.e., 4400 pounds) for 60 s. The surface area of tablets was 0.5 $cm^2$. The dissolution conditions were: 37.3°C, 50 rpm and 900 mL degassed medium. At the time points 2, 5, 10, 15, 20, 30, and 45 min, 2 mL solutions were sampled from the middle or lower position of the medium and filtered with a 0.45 μm Nalgene filter. The cumulative amount of acetaminophen from each unit area was acquired by dividing the cumulative amount of dissolved acetaminophen by the tablet surface area (0.5 $cm^2$). 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 Measurement

The viscosities of PVP aqueous 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 jacketed flask was connected to a Brinkmann controllable water bath, and water was circulated through the jacketed layer to control the temperature. The kinematic viscosity was calculated by multiplying efflux time with the viscometer constant. The viscosity in mPa · s can be obtained by multiplying the kinematic viscosity ($mm^2/s$) with liquid density (g/mL). Because the concentrations of PVP solutions were lower than 10 mg/mL, the liquid density was approximated as 1.0 g/mL; i.e., the value of viscosity was the same as the value of kinematic viscosity.

$$\text{Kinematic viscosity}\,(mm^2/s) = \text{time(s)} \times \text{viscometer constant}\,(mm^2/s^2)$$

$$\text{viscosity}\,(mPa \cdot s) = \text{kinematic viscosity}\,(mm^2/s) \times \text{liquid density}\,(g/mL)$$

## RESULTS AND DISCUSSION

The overall approach was to first obtain the effects of PVP on the etching patterns of the acetaminophen (010) face. Secondly, the solubility of acetaminophen crystals in PVP solutions were measured. Thirdly, the effects of PVP on the IDR of acetaminophen have been studied. By comparing the effects of PVP on partial dissolution, solubility and IDR of acetaminophen crystals, the interactions between PVP and acetaminophen on crystal surface have been explored together with molecular structural analysis of acetaminophen crystals and PVP.

### Effects of PVP on Etching Pattern

The etching patterns of acetaminophen (010) face in water have been studied previously,[8,9] and can be used as a control. Shown in Figure 3 are the representative etching patterns of (010) face by water in two acetaminophen crystals. The etching patterns look regular, and the directions of the two ledges are the same as the direction of *a*- and *c*-axes, the directions of the strongest attachment energies on the (010) face. The dominant interaction along *a*-axis is hydrogen bonding interaction because one of the hydrogen bond chains exists in

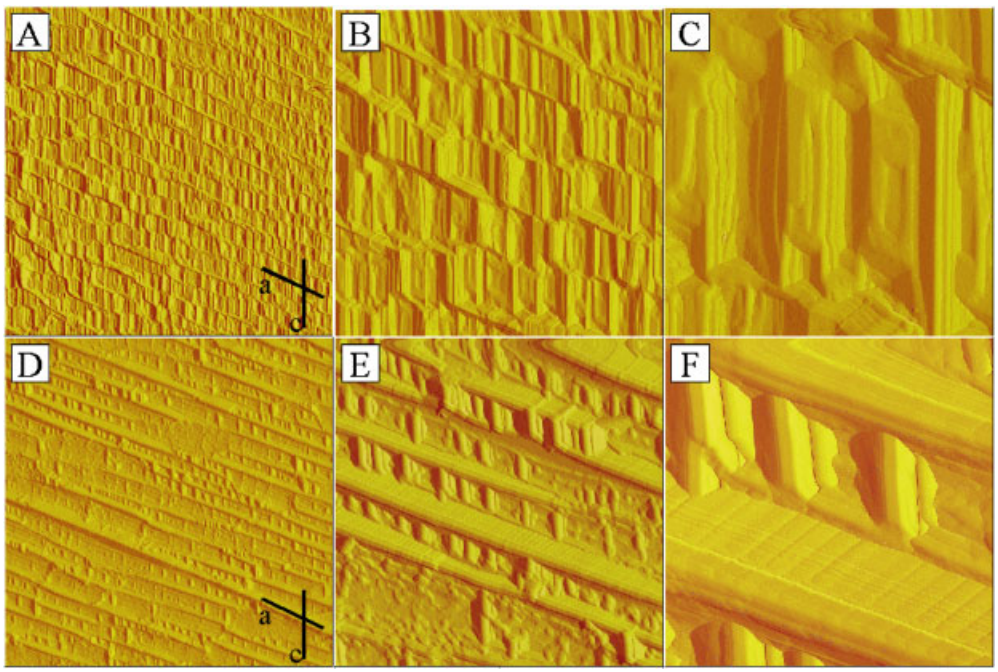


**Figure 3.** Atomic force microscopy (AFM) images of the acetaminophen (010) face etched by water. The scan sizes were $60 \times 60$ $\mu m^2$ for (A) and (D), $20 \times 20$ $\mu m^2$ for (B) and (E) and $5 \times 5$ $\mu m^2$ for (C) and (F). (B) and (C) were zoom-in scanning of image (A) site, and (E) and (F) were zoom-in scanning of image (D) site. *a*- and *c*-axes were marked on images (A) and (D).

this direction, and along *c*-axis is van der Waals interaction. If PVP can interact strongly with acetaminophen in the direction of either *a*- or *c*-axis, the etching patterns in the corresponding direction may be affected. Thus, the effects of PVP on the etching patterns of the acetaminophen (010) face can be used to study the interactions between PVP and acetaminophen crystal surface.

Figure 4 shows the etching patterns of the acetaminophen (010) face in different concentrations of PVP(K30) aqueous solutions. The directions of etching patterns have been approximately illustrated using dotted lines in images C, F, and I of Figure 4. In 10 μg/mL PVP(K30) solution, the etching patterns are the same as the etching patterns by water, i.e., following the directions of *a*- and *c*-axes. In concentrated PVP(K30) solutions, such as 1 mg/mL and 100 μg/mL, one ledge of the etching patterns still follows the direction of *a*-axis, but the other ledge does not follow the direction of *c*-axis anymore, but becomes nearly perpendicular to the direction of *a*-axis. PVP(K16–18) and PVP(K85–95) have similar effects on the etching patterns of the acetaminophen (010) face as PVP(K30), and the only difference is the minimal concentrations needed to affect the etching patterns.

Previous research shows[23] that when polymeric additives have strong hydrogen bonding interactions with acetaminophen, the etching patterns in

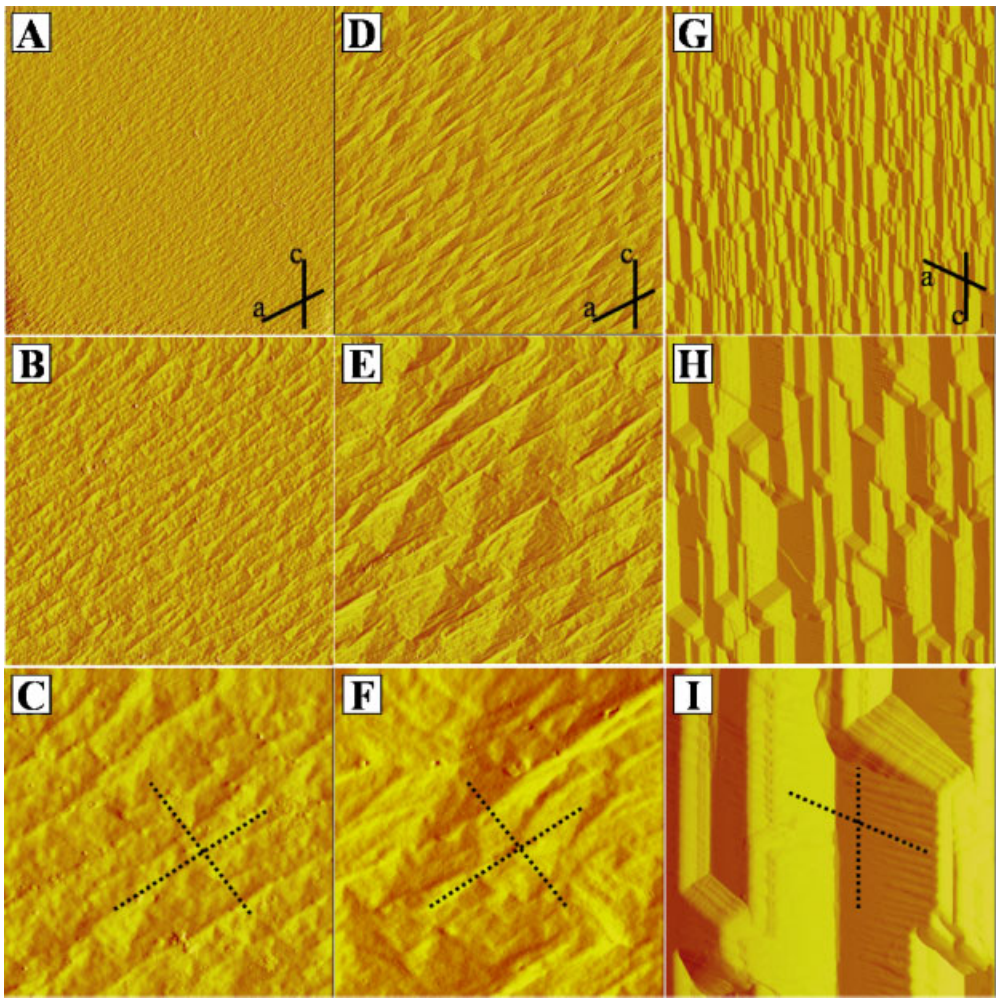


**Figure 4.** AFM images of the acetaminophen (010) face etched by PVP(K30) aqueous solutions. The PVP concentrations were 1 mg/mL for (A), (B), and (C); 100 μg/mL for (D), (E), and (F); and 10 μg/mL for (G), (H), and (I). The scan sizes were $60 \times 60\ \mu m^2$ for (A), (D), and (G), $20 \times 20\ \mu m^2$ for (B), (E), and (H), as well as $5 \times 5\ \mu m^2$ for (C), (F), and (I). The second and third row images were zoom-in scanning of the corresponding first row images in the same column. *a*- and *c*-axes were marked on images (A), (D), and (G).

the direction of $a$-axis will be affected. PVP has no effects on the etching patterns on the (010) face in the direction of $a$-axis, which suggests that there is no significant hydrogen bonding interaction between PVP and acetaminophen crystal surface. In the presence of PVP, the change of etching patterns in the direction of $c$-axis suggests that there exists interaction between PVP and acetaminophen in the direction of $c$-axis. Because there is no hydrogen bond chain in the direction of $c$-axis, the interaction between PVP and acetaminophen crystal surface can only be van der Waals interactions. The molecular structure of PVP also shows that the oxygen and nitrogen atoms of PVP can hardly form hydrogen bonds with acetaminophen on the (010) face due to the steric repulsion of the PVP structure.

### Effects of PVP on Solubility of Acetaminophen

The solubilities of acetaminophen in different concentrations of PVP and 2-pyrrolidinone aqueous solutions have been measured to study the interactions between PVP and acetaminophen. Figure 5 shows that when the concentration of PVP(K30) is higher than 10 mg/mL, acetaminophen solubility increases as PVP concentration increases. When PVP(K30) concentration is no more than 1 mg/mL, the solubility of acetaminophen in PVP(K30) solutions is the same as in pure water. The structure of 2-pyrrolidinone, shown in Figure 1, is the same as subunit of PVP except the vinyl group. Figure 5 also shows that the effects of 2-pyrrolidinone on the solubility of acetaminophen is similar to the effects of PVP.

Solubility of acetaminophen crystals is an indication of equilibrium between acetaminophen molecules in solution and on crystal surface, thus solubility can be affected by affecting the free energy of acetaminophen molecules both in solution and on crystal surface. In solution, because both PVP and 2-pyrrolidinone has both hydrophobic and hydrophilic parts, it is possible that both PVP and 2-pyrrolidinone may have strong interactions with acetaminophen through forming some weak complexations via hydrophobic parts and increases the acetaminophen solubility.

On crystal surface, the partial dissolution study suggests that PVP affects the dissolution process in the direction of $c$-axis on the (010) face through van der Waals interactions between PVP and acetaminophen crystal surface. It is worthwhile to note that in the 100 mg/mL 2-pyrrolidinone, the etching patterns of acetaminophen (010) face is nearly the same as the etching patterns by water, i.e., has no observed effects in the direction of $c$-axis. At 1 mg/mL and 100 μg/mL, PVP can affect the etching patterns of acetaminophen crystals, but cannot obviously enhance the solubility of acetaminophen. The adsorbed PVP molecules can still play an important role in the dissolution process at very low concentration. However, by comparing the effects of PVP and 2-pyrrolidinone on the etching patterns and solubility of acetaminophen crystals, it may conclude that the solubility of acetaminophen is affected mainly through the interactions in solution rather than on crystal surface.

### Effects of PVP on Intrinsic Dissolution Rate of Acetaminophen

The IDR of acetaminophen in water has been measured to be $0.86 \pm 0.04$ mg/(cm$^2$ × min). Figure 6 clearly shows that the acetaminophen IDR in even 0.1 μg/mL PVP(K30) is still lower

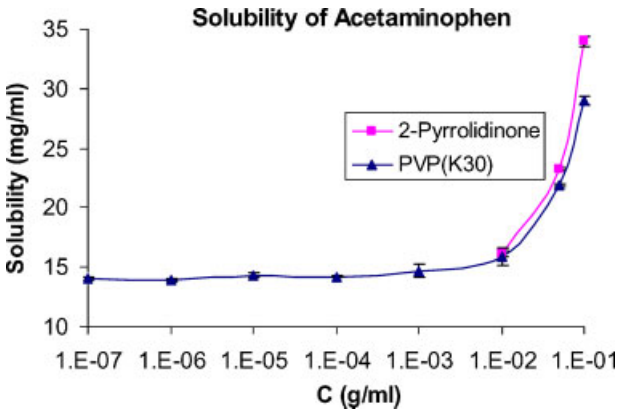


**Figure 5.** Acetaminophen solubility in PVP(K30) and 2-pyrrolidinone aqueous solutions.

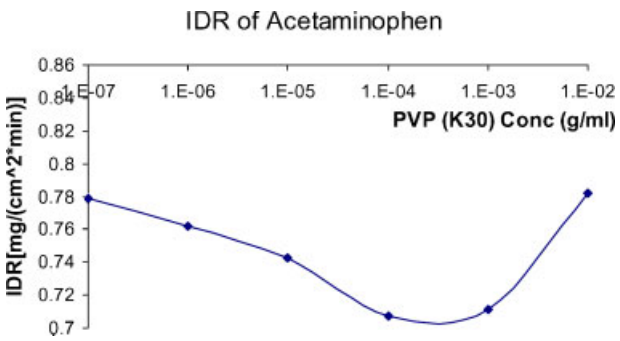


**Figure 6.** Intrinsic dissolution rate (IDR) of acetaminophen in PVP(K30) aqueous solutions.

than in water. When the PVP concentration is lower than about 1 mg/mL, as the concentration of PVP increases, the IDR gradually decreases. However, the IDR of acetaminophen in 10 mg/mL PVP(K30) is higher than in 1 mg/mL PVP(K30), which may be due to the higher acetaminophen solubility in PVP(K30) solutions of high concentration. To exclude the contribution of viscosity to acetaminophen IDR in PVP(K30) solutions of very low concentration, the viscosity of PVP(K30) solutions have been measured, as shown in Figure 7. As PVP(K30) concentration decreases to 100 μg/mL, the viscosity of PVP(K30) solutions become the same as water viscosity (0.89 mPa · s) at 25°C. Overall, in those diluted PVP(K30) solutions the lowered acetaminophen IDR cannot be simply explained by viscosity, and it is highly possible that the adsorption of PVP(K30) causes the IDR of acetaminophen to decrease.

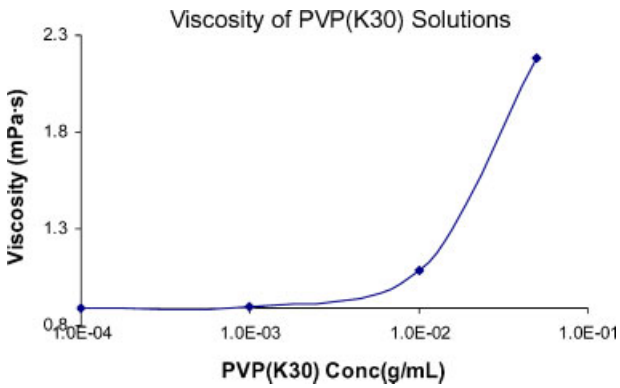


**Figure 7.** Viscosity of PVP(K30) aqueous solutions.

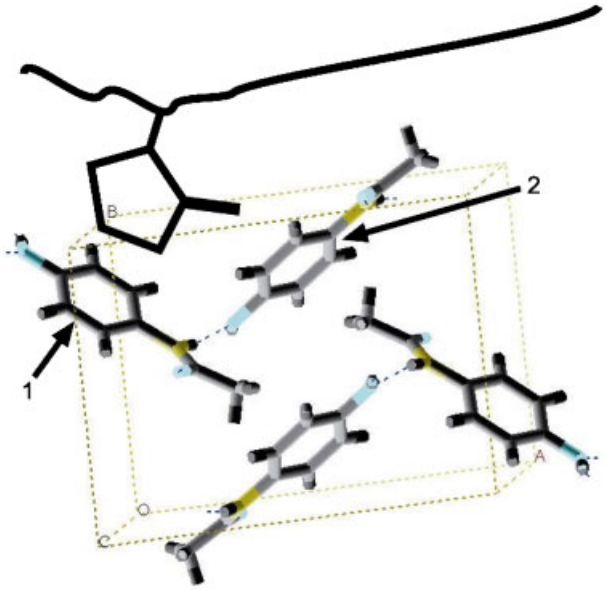


**Figure 8.** The possible three-dimensional relationship of the PVP subunit with acetaminophen crystals.

### Interactions between PVP and Acetaminophen Crystal Surface

The molecular structure of PVP in Figure 1 shows that the oxygen and nitrogen atoms of PVP can hardly form hydrogen bonds with the crystal surface of acetaminophen due to the steric repulsion of the PVP structure. The solubility of acetaminophen in PVP solutions of high concentration is higher than in water, which implies that PVP has strong interaction with acetaminophen through hydrophobic interaction (i.e., van der Waals interactions). For van der Waals interactions, the closer the two molecules, the stronger the interactions. The molecular structures of acetaminophen and PVP suggest that if the phenyl ring of acetaminophen can be parallel to the pyrrolidone ring of PVP, the distance from the geometrical mass center of acetaminophen to that of PVP subunit will be the shortest as shown in Figure 8. The crystal structure determines that for one unit cell, there are two acetaminophen molecules close to the surface. Among them, the phenyl group of molecule 1 points to the crystal surface, and the phenyl group of molecule 2 points away from the crystal surface. Therefore, it is highly possible that molecule 1 plays a more important role in intermolecular interaction between crystal surface and adsorbed PVP than molecule 2.

The parameters of acetaminophen monoclinic form crystal are: a = 12.93Å, b = 9.4Å, c = 7.10Å.[15] Thus, on the (010) face, the distance between molecules 1 in neighboring unit cells in the direction of *a*-axis is 12.93Å, and in the direction of *c*-axis is only 7.10Å. The higher density of acetaminophen in the direction of *c*-axis compared to *a*-axis suggests that PVP has stronger van der Waals interaction with acetaminophen in the direction of *c*-axis than *a*-axis. Because there are no strong hydrogen bonding interactions between PVP and acetaminophen crystal surface, it should be the van der Waals interactions that contribute to the interactions between adsorbed PVP and crystal surface of acetaminophen. Therefore, the adsorption of PVP may have much greater effects on the surface diffusion in the direction of *c*-axis than *a*-axis, which caused the etching patterns to deviate from the direction of *c*-axis but still follow the direction of *a*-axis.

## CONCLUSIONS

The etching patterns of the acetaminophen (010) face in the presence of PVP have stable ledges in the direction of *a*-axis, but deviate from the direction of *c*-axis. The attachment energy of acetaminophen crystals in the direction of *c*-axis is only contributed by van der Waals interactions; the adsorption of PVP may have stronger effects on surface diffusion in the direction of *c*-axis and causes the etching patterns to deviate from the direction of *c*-axis. The etching pattern change on the (010) face of acetaminophen crystals suggest that PVP has van der Waals interactions, rather than hydrogen bonding interactions, with acetaminophen crystal surface especially in the direction of *c*-axis. The structural analysis of acetaminophen crystal and PVP also shows that the van der Waals interactions between PVP and acetaminophen are stronger in the direction of *c*-axis than *a*-axis on the (010) face.

When the concentration of PVP(K30) is higher than 1 mg/mL, PVP(K30) can not only enhance the solubility of acetaminophen, but also improve the IDR of acetaminophen crystals. However, in diluted PVP(K30) solutions, the IDR is obviously lower than in pure water even though the solubility of acetaminophen is the same as in water. The lowered IDR of acetaminophen crystals cannot be simply explained by the viscosity effects of PVP solutions. Because when the concentration of PVP(K30) is lower than 100 μg/mL, the viscosity of PVP(K30) solutions becomes the same as water. The partial dissolution study (etching patterns) shows that in 1 mg/mL and 100 μg/mL, the adsorbed PVP on crystal surface can obviously affect the dissolution process in the direction of *c*-axis on the (010) face. The consistency between the etching pattern change and the lowered IDR of acetaminophen in diluted PVP solutions strongly suggests that the adsorption of PVP causes the lowered IDR of acetaminophen crystals in diluted PVP solutions.

## ACKNOWLEDGMENTS

Financial support from the NSF/Industrial/University Cooperative Research Center for Pharmaceutical Processing at Purdue University is gratefully acknowledged. Dr. Qinghong Lu helped to proofread the text.

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