Understanding Crystal Cleavability and Physical Properties of Crystal Surfaces Using \textit{in Silico} Simulation

Toshiaki Hatanaka,$^a$ Yasuo Yoshishashi,$^b$ Katsuhide Terada,$^c$ and Etsuo Yonemochi$^{*d}$

$^a$Tsumura Co., Ltd.; 3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300–1192, Japan: $^b$Faculty of Pharmaceutical Sciences, Toho University; 2–2–1 Miyama, Funabashi, Chiba 274–8510, Japan: $^c$Faculty of Pharmacy, Takasaki University of Health and Welfare; 60 Nakaarai-machi, Takasaki, Gunma 370–0033: and $^d$School of Pharmacy and Pharmaceutical Sciences, Hoshi University; 2–4–41 Ebara, Shinagawa-ku, Tokyo 142–8501, Japan.

Received September 8, 2020; accepted November 29, 2020

In the drug formulation process, compound dissolution rate and wettability may be improved by grinding. However, there is no method to understand the effects of the wettability of the crystal facets of the ground product. Here, acetylsalicylic acid (ASA) was used to evaluate the changes in crystal morphology and dissolution rate by jet milling using powder X-ray diffraction and \textit{in silico} simulation. Several cleavage facets were observed in cube crystals, and the (0 0 2) facet was observed in plate crystals. Furthermore, the dissolution rate of the ground samples per unit area decreased with the cleavage of the (1 0 0) and (0 0 2) facets. The polar surface energy of the ground sample decreased with increasing grinding pressure. The simulation results showed that the absolute attachment energy of the (1 0 0) and (0 0 2) facets was lower than that of the other crystal facets. Moreover, atoms with low polarity were present on the crystal surface of (0 0 2). The wettability and dissolution rate of the (0 0 2) facet were worse than those of the (1 0 0) facet. It was suggested that the dissolution rate of the ground sample was affected by the wettability of the crystal facet caused by the cleavage. The cleavability and wettability may be understood by simulation.

\textbf{Key words} \hspace{0.5cm} acetylsalicylic acid; cleavage; crystal facet; wettability; \textit{in silico} simulation

Introduction

Pharmaceuticals are administered with various delivery systems; tablets account for most oral solid drugs. Reasons for the widespread use of tablets include low cost and simple manufacture, convenience of administration, reproducibility of dissolution profile, and high stability. There are several manufacturing strategies for tablets, including the direct compression method in which a tablet is produced by mixing the active pharmaceutical ingredients (APIs) with an additive and compressing it. Direct pressing was the simplest and most efficient tablet-preparation method, owing to the following advantages: minimal manufacturing steps, low cost, easily available manufacturing apparatus, and simple prescription design.\textsuperscript{11}

However, formulations that include APIs that have poor flowability or compressibility may be difficult to form by direct pressing. For example, acetaminophen (APAP) is an API with poor flowability and compressibility. It exhibits substantial elastic deformation during compression and is prone to capping at low doses.\textsuperscript{2,3} In the development of such an API, we try to optimize a formulation conducive to tableting and dissolution by adding a binder, a fluidizing agent, and a disintegrant. For the purpose of obtaining tablets by direct compression method, the flowability of the formulation containing APAP can be improved by adding microcrystalline cellulose.\textsuperscript{4} In addition, because ibuprofen has a needle-like particle shape, it has poor flowability. However, it has been shown that by reducing the particle size, the effect of particle shape on flowability can be reduced.\textsuperscript{5} When celecoxib was crystallized into a spherical shape using polyvinylpyrrolidone (PVP), improvements in flowability and compressibility were observed due to an increase in particle size and uniform shape. Also, due to the crystallization using hydrophilic PVP, the dissolution rate was improved compared to pure celecoxib.\textsuperscript{6} In other words, the physicochemical properties of the API directly affect the physical properties of the final product and the difficulty of formulation of the drug.

As described above, there are two approaches for solving challenges associated with the direct compression method: formulation development and manufacturing method development. For the direct compression method, formulation development such as adding additives to the mixed powder containing API is aimed at improving the water conductivity into the tablets, and improvement of the dissolution rate of API itself is not promoted.\textsuperscript{7} It is very effective to change the physical properties of API to the optimal physical properties for the direct compression method, rather than mixing a large amount of additives that is characteristic in formulation design, and it is also effective for cost reduction.\textsuperscript{8} Therefore, research on physicochemical properties of API has become a trend in drug formulation development in recent years.\textsuperscript{9}

As a method of changing the physicochemical properties of API, there is grinding into fine particles.\textsuperscript{9} Micronization through grinding is very simple; it is possible to select a pulverizing device according to the target particle size and the physical properties of the API. Various types of grinders are used in the actual formulation process. Grinding devices can be roughly classified into two types according to the grinding mechanism. Specifically, one type includes devices such as pin or hammer mills that give a shearing force to grind a sample, and another type includes jet mills that collide particles with each other in a high-speed air stream and grinds by impact force. The jet mill can control the grinding efficiency by changing the compressed air. Furthermore, since fresh compressed air is constantly supplied, it is also effective for...
pulverizing heat-sensitive substances.\(^\text{11}\)

Grinding is known to increase the specific surface area by reducing the particle size, and thereby increase the dissolution rate. In addition, as wettability affects the dissolution rate, the molecular arrangement and wettability of crystal facets after grinding are important factors in improving the dissolution rate. Here, it has been reported that, in improving the solubility by grinding, the physicochemical properties of the crystal facets produced by grinding affect the physicochemical properties of the ground sample. For example, in the case of ibuprofen, particle size and the surface free energy of the powder are different due to the different grinding pressure when using a jet mill. Further, it was shown that the dissolution rate of the ground sample was higher than that before the grinding. It is reported that this is because the grinding increased the exposure of the highly polar crystal facets.\(^\text{12}\)

Polymorphs and crystal habits are factors that affect the physicochemical properties of APIs. For example, a study of polymorphs using tibolone reported that the elution rate differs among polymorphs.\(^\text{13}\) In addition, a study of crystal habit using ticagrelor reported that this is because the grinding increased the exposure of specific crystal facets.\(^\text{14}\) These findings suggest that the difference in molecular arrangement on the crystal surface affects the dissolution characteristics of APIs.

These findings regarding the effect of the molecular arrangement of the crystal plane on the wettability and dissolution of the powder suggest that the wettability of the crystal facet after grinding is important for improving the dissolution property. The grinding of crystal habit in which the characteristic crystal facets are anisotropically grown can affect the abundance ratio of specific crystal facets.\(^\text{15}\) Therefore, the grinding process aimed at improving the dissolution rate requires an understanding of the physical properties of the anisotropically grown crystal facets.

Acetylsalicylic acid (ASA) has several crystalline polymorphs, and the crystalline structures of two of them have been reported.\(^\text{15,16}\) Crystals of Form I can be obtained by evaporating a 0.6–0.7 M concentration acetoniite solution at 22–25°C, while Form II crystals can also be obtained by subcooling a 0.6–0.7M acetoniite solution to 0°C following a 7-d incubation period in a water bath at 35–40°C.\(^\text{17}\) In addition, Form I is a stable form and Form II is a metastable form; dissolution rates differ between polymorphs.\(^\text{18}\)

ASA is also known to have a crystal habit, such as cube crystals and plate crystals. Cube crystals are obtained by recrystallization from ethanol, while plate crystals can be recrystallized from a mixture of ethanol and water. In addition, it has been shown that different crystal habits affect crystals’ dissolution since the relative abundance ratio of the crystal facets varies based on appearance morphology.\(^\text{20,21}\)

When grinding API, such as ASA, with polymorphism and crystal habit, selection of crystal properties is critical to determine whether the physical properties post grinding are improved. However, a study has related changes in crystal morphology (cleavage), caused by grinding, to the dissolution property.\(^\text{22}\) Cleavage means that the crystal facets are sliced along the crystal facets and can be caused by grinding.

Therefore, in this study, we used computational science to investigate the influence of grinding on crystal morphological changes and physical properties of crystal facets by in silico simulation, which has been actively investigated in recent years.\(^\text{23}\)

### Experimental

#### Materials

ASA (Wako Special Grade; 99.5 ± %; Wako Pure Chemical Corporation, Osaka, Japan) was the API. Ethanol (99.5% (w/v); guaranteed reagent; Wako Pure Chemical Corporation) and purified water were the solvents used for recrystallization. Purified water, formamide (guaranteed reagent; Wako Pure Chemical Corporation), ethylene glycol (guaranteed reagent; Wako Pure Chemical Corporation), and diiodomethane (guaranteed reagent; Wako Pure Chemical Corporation) were used to measure the contact angles. Decane (Reference material; Tokyo Chemical Industry Co., Ltd. (TCI), Tokyo, Japan), nonane (Reference material; TCI), octane (Reference material; TCI), and heptane (Reference material; TCI) were used to measure the surface free energy (SFE) as non-polar probes. Ethanol (infinity pure; Wako Pure Chemical Corporation), chloroform (infinity pure; Wako Pure Chemical Corporation) and acetoniite (infinity pure; Wako Pure Chemical Corporation) were used to measure SFE as polar probes.

#### Recrystallized and Ground Sample Preparation

**Preparation of Different Crystal Habits**

By stirring at 65°C, 10 g of ASA was completely dissolved in 100 mL of ethanol. Thereafter, the solution was slowly cooled to 20–25°C, and the recrystallized crystals were termed cube crystals. Meanwhile, by stirring at 65°C, 10 g of ASA was completely dissolved in 100 mL of ethanol, to which 100 mL of distilled water was added at 25°C, and the solution was allowed to cool to 20 to 25°C. The recrystallized crystal was termed plate crystal.

**Preparation of Single Crystal**

Several cube crystals were added as a seed to a solution prepared by dissolving 10 g ASA in 100 mL ethanol at 20–25°C. The solution was then allowed to stand at 20–25°C for 2 d to obtain a single ASA crystal. The grown crystal was removed and placed the same ethanol concentration. This process was repeated thrice.

**Preparation of Ground Sample**

The cube and plate crystals were ground in a jet mill (Spiral Jet Mill 50AS; Hosokawa Micron Corp., Hirakata, Japan). The sample input was 5 g from the sample inlet. The nozzle diameter was 0.9 mm. The input speed was 60 g min\(^{-1}\), and grinding was conducted at pressures of 0.11, 0.13, 0.15, and 0.18 MPa. Further, by controlling the air for grinding the sample, the progress of grinding can be adjusted. In order to confirm the morphological change of crystals due to grinding, the grinding pressure usually used is about 1 MPa, but in this study, the...
grinding pressure was lower than usual. With normal grinding pressure, cleavage on specific crystal facets is not recognized and cracks occur on various crystal facets. Therefore, the important grinding conditions in this experiment are the grinding pressure and the sample feeding speed. The pressure was set to 0.11–0.18 MPa and the sample feeding rate was set to 60 g min\(^{-1}\) as conditions for the crystal to be cleaved well. The experiment started with the lowest grinding pressure of 0.11 MPa in the adjustable range of the device. The ground sample was discharged from the ground sample outlet (Fig. 1).

**Evaluation of the Physical Properties of the Recrystallized and Ground Samples**

**Average Particle Size Measurement**

The average particle size was determined by scanning electron microscopy (SEM; VE-7800; Keyence, Osaka, Japan) with an SEM image analysis software (Mac-view v. 4; Mounitech Co., Ltd., Tokyo, Japan). To calculate the average particle diameter of the crystal, 300 particles were randomly selected from the SEM images, and the average particle diameter was determined by image processing software. Software analysis was performed based on the size of the extracted particles, and the Heywood diameter and particle size distribution were calculated.

**Specific Surface Area Measurement**

The specific surface area was measured using a Bunauer–Emett–Teller (BET) type fully automatic specific surface area automatic device (Macscorb HM-1268; Moutech Co., Ltd., Tokyo, Japan). The measurement sample used about 1 g. After filling the sample tube with the sample, deaeration treatment was performed at 40 °C for 30 min as a pretreatment. Nitrogen gas with three different partial concentrations (30.62, 19.84, 9.66%) was used as a probe, and pure nitrogen was used as a carrier gas. The measurement was conducted with \( n = 3 \) ground samples. The measurement time was set to 5 min.

**X-Ray Diffraction (XRD) Measurement**

The crystal forms of the recrystallized and ground samples were assessed based on powder XRD measurements (D8 DISCOVER with GADDS; Bruker, Billerica, MA, U.S.A.). Measurements were made in a 2\(\theta\) range of 5–30°. The diffraction peaks for facets (1 0 0) and (0 0 2) were 2\(\theta\) = 7.8° and 2\(\theta\) = 15.6°, respectively. The measurement was conducted using 20 mg. The measurement was conducted with \( n = 3 \) recrystallized and ground samples.

**Melting Point Measurement**

Melting points were measured with Thermogravimetry-Differential Thermal Analysis (TG-DTA) (Thermo Plus; Rigaku Co., Tokyo, Japan) to confirm the crystal polymorph identity. For melting point measurement, 10 mg sample was placed in an aluminum pan under nitrogen atmosphere and temperature increment of 5 °C min\(^{-1}\). The measurement was conducted with \( n = 3 \) recrystallized samples.

**Dissolution Tests on Ground Samples and Single Crystal**

The dissolution tests were conducted by the paddle method. The rotational speed of the paddle (DT-610; JASCO International Co., Ltd., Tokyo, Japan) was set to 50 rpm. Nine-hundred milliliters of phosphate buffer solution (pH 6.8) at 37 °C was the test solution. Dissolution tests were performed using 50 mg of ground samples. The dissolution test was performed under sink conditions. The measurement was conducted with \( n = 3 \) ground samples. The concentration of the eluted sample solution was measured by UV and visible spectrophotometry (V-530 spectrophotometer; JASCO International Co., Ltd.) at \( \lambda = 265 \) nm.

**Surface Free Energy (SFE) Measurement for Ground Samples by Inverse Gas Chromatography (IGC)**

With reference to several papers on the IGC analysis technique,\(^{24–26}\) the interaction with polar and non-polar probes and SFE were measured using IGC to evaluate the wettability of ground samples (IGC, Surface Measurement Systems Ltd., London, U.K.). A silanized glass column having an inner diameter of 4 mm and a length of 30 cm was used. Silane-treated glass wool was packed on one side and 0.1 g of the sample was put on the other side. The column was tapped for 5 min until the density of the sample in the column was constant. After the tapping was completed, the glass column was capped with silanized glass wool. The analysis was repeated 3 times. Helium was used as carrier gas. Column conditions were set at a temperature of 30 °C and gas flow of 10 mL/min. Methane was injected as reference gas at a concentration of 0.03 p/p 0 (where \( p \) is the partial pressure and \( p 0 \) is the vapor pressure), and several non-polar probes (\( n \)-alkanes) and several polar probes were injected under the same conditions. Decane, nonane, octane and heptane were selected as non-polar probes, and ethanol, chloroform and acetonitrile as polar probes. Based on the net retention time obtained from the measurement by methane and each probe, the dispersive SFE (\( e p \)) and specific free energy of adsorptions (\( \Delta G _{ads} \)) were calculated according to the Schelzu method. In addition, the polar surface energy (\( e p \)) was calculated based on the theory of Good-Van Oss using the \( \Delta G _{ads} \) of chloroform (Lewis acid) and acetonitrile (Lewis base) as a pair of acid and basic monopolar probes, and by using the acid and basic surface tension component of liquid chloroform (\( e l \)) and ethyl acetate (\( e l \)) on the Della Volpe scale.\(^{27,28}\)

**Prediction and Evaluation of Changes in the Surface Physical Properties**

**Estimation of Cleavage Facet by Powder X-Ray Diffraction (PXRD)**

The crystal forms changes of ground samples were assessed based on PXRD measurements (RINT 2200 V/PC, RAD type; Rigaku). Measurements were made in a 2\(\theta\) range of 5–30°. The diffraction peaks for facets (1 0 0) and (0 0 2) were 2\(\theta\) = 7.8° and 2\(\theta\) = 15.6°, respectively. The measurement sample was 50 mg. The measurement was conducted with \( n = 3 \) ground samples. In the usual measurement, the crystal orientation is taken into consideration at the time of measurement, and the powder is ground. However, in this measurement, if the crystal morphology changes due to grinding, the change in the cleavage facet cannot be evaluated correctly. Therefore, we did not crush the ground sample. The ground sample is considered to be unaffected or small due to the specific orientation because the particle size is small and the particles are arranged in various directions on the measuring...
plate. The ground sample of creatine anhydrate was similar to the XRD pattern of the unground sample. The peak intensity of PXRD is affected by the stacking of crystal plane molecules in the crystal. Therefore, when the molecules on the crystal plane are peeled off by cleavage, the number of stacked crystal planes and the peak intensity are reduced.\(^{29}\) It is also shown that the XRD peak of the ground sample is lower than that of the unground sample. In other words, it is reported that the XRD peak of the ground sample is lower than the XRD pattern of the unground sample. The peak intensity was calculated. The peak area of each surface was normalized to the integrated area of all peaks taken as 100%, the peak area ratio was calculated. The obtained peak area ratio was used for evaluation of the change (cleavage) of the crystal form (Fig. S1).

Calculation of Attachment Energy

The crystal morphology was predicted using Material Studio (ver. 4.4, Dassault Systems BIOVIA), an application for modeling and simulating atoms and molecules. For the simulation, we used refined ASA crystal structure data obtained using the ConQuest from the Cambridge Crystal Structure Database (CSD-System) (Table 1, CCDC Deposition Number; 1101020, Database Identifier; ACSALA). First, the crystal structure of ASA was optimized through molecular calculations with the force field COMPASS using the module FORCITE. Next, the crystal structure was predicted using the module MORPHOLOGY and the force field COMPASS. The attachment energy (\(E_{\text{att}}\)) of each crystal facet was obtained from the prediction of the crystal structure. The foregoing simulation generated molecular attachment energy (\(E_{\text{att}}\)) data and supported the prediction of a theoretically stable crystal morphology assuming that the crystal facet growth rate was proportional to \(E_{\text{att}}\).

Physical Property Evaluation of Cleaved Surface Using Single Crystal

Contact Angle Measurement of Single Crystal by the Liquid Drop Method

The contact angle of the facet of a single crystal was measured by the liquid drop method using a DropMaster300 (Kyowa Electronic Instruments Co., Ltd., Tokyo, Japan) and wettability was also evaluated. The measurement was conducted five times, and the average value was used for calculation. The surface tensions (\(\gamma_s^p, \gamma_s^d\)) of the solvents are listed in Table 2. The Owens, Wendt, Rabel, and Kaelble (OWRK) method was used to obtain the SFE of each crystal facet.

Based on the contact angle data in Table 3, the polar component and hydrophobic interaction component of the SFE were calculated using the surface tension data in Table 2 and the equation IV in Supplementary 1. \(\gamma_s^p\) indicates the polar component of the SFE of the solid. Further, \(\gamma_s^d\) indicates a dispersion component of the SFE of the solid. Therefore, it can be said that the larger the \(\gamma_s^p\) in \(\gamma_s^\text{tot}\), the higher the wettability to water. Also, it can be said that the larger the \(\gamma_s^d\) in \(\gamma_s^\text{tot}\), the lower the wettability to water.

Dissolution Rate Measurement from Crystal Facet Using Single Crystal

A dissolution test was conducted using single crystals to establish the differences in the dissolution rate among the crystal facets. In the test, the crystal facets that were not the targets were coated with paraffin to prevent them from contacting the test solution or eluting during measurement (Figs. S2 and S3).

Results and Discussion

Confirmation of Crystal Habit Crystals that were re-crystallized from different solvents had different morphologies. The crystal obtained by recrystallization with ethanol solution presented a polyhedral appearance. This crystal was called cube. The crystal obtained by recrystallization with a mixture of ethanol and water appeared thin and elongated. This crystal was called plate (Fig. 2).

The PXRD indicated that there was no significant difference between the diffraction patterns of the cube and plate crystals. However, the characteristic diffraction peaks of the cube and plate crystals were facets (1 0 0) and (0 0 2), respectively. The position of the (0 0 2) peak was different between the PXRD patterns of forms I and II obtained from the database. The peak marked with a star was not observed in form I but was characteristic of form II. Moreover, it was absent in the cube and plate crystals (Fig. 3).

ASA has two polymorphs, a stable form I and a metastable form II. The melting point of form I is reported to be 143.91 °C and that of form II is 135.5 °C.\(^{16}\) In addition, from the results of thermal analysis, the melting points of the two samples were in agreement, and the value was form I. These
crystals were found to be of form I. The crystal habit is a crystal in which the same polymorphic crystal has an anisotropic crystal face and the appearance is different. Therefore, the melting points of crystal habits are the same. Therefore, the relationship between the cube crystal and plate crystal was a crystal habit. Here, the obtained crystals are referred to as cube crystals and plate crystals.

Changes in Physical Properties of Ground Sample  The ASA obtained by recrystallization was stable form I. However, due to the heat load during grinding, form I may be transformed into form II. Therefore, grinding was performed using a jet mill, which is good at pulverizing heat-sensitive substances. In addition, in order to confirm the change in crystal morphology due to grinding, grinding was performed intentionally at a pressure lower than that of compressed air normally used. The normal pressure is about 1 MPa, but this study was conducted at 0.11–0.18 MPa.

To establish how the ground sample particle shape and diameter change with increasing grinding pressure, the particles were photographed by SEM and the average particle diameters were determined from the SEM image (Fig. 4). According to the SEM images, when a cube crystal was ground, it retained its shape at grinding pressures ≥0.13 MPa. However, its shape changed into various forms at grinding pressures ≥0.15 MPa. In contrast, when the plate crystals were ground, they broke under a minimum pressure of 0.11 MPa. At pressures >0.13 MPa, plate crystal grinding continued. SEM confirmed that the plate crystals gradually broke and their morphology changed because of the lower grinding pressure compared to that applied to the cube crystals. The results of average particle size (D50) calculated from SEM images are shown (Fig. 5).

The relationship between the change in grinding pressure and the average particle size in the cube crystal was confirmed. Consequently, when the grinding pressure was 0.11 MPa, the average particle size was 330.9 µm. Further, when the grinding pressure was gradually increased to 0.13, 0.15, and 0.18 MPa, the average particle size changed to 321.6, 6.9, and 5.2 µm, respectively; that is, the cube crystal maintained its shape up to 0.13 MPa. However, it was found that at a grinding pressure of 0.15 MPa or higher, the grinding proceeded rapidly, and the average particle size decreased drastically. Moreover, when the particle size distribution was confirmed, no change was observed until the grinding pressure was 0.13 MPa. However, it was shown that the particle size (D50) shifted to the lower side when the grinding pressure was 0.15 MPa or higher. On the other hand, the relationship between the change in the grinding pressure and the average particle size in the plate crystal was confirmed. Consequently, when the grinding pressure was gradually increased to 0.11, 0.13, 0.15, and 0.18 MPa, the average particle size changed to 68.9, 52.9, 19.1, and 2.6 µm, respectively. Confirmation of the particle size distribution showed that the particle size (D50) gradually decreased as the grinding pressure increased.

Next, the specific surface area was measured using a BET type fully automatic specific surface area automatic device. The results are shown in Fig. 6.

In the cube crystal, the surface area was 0.01 µm² when the grinding pressure was 0.11 MPa. When the grinding pressure was gradually increased to 0.13, 0.15, and 0.18 MPa, the surface area changed to 0.01, 0.62, and 0.82 µm², respectively. Similar to the average particle size result, the surface area of the cube crystal did not change significantly up to 0.13 MPa. However, when the grinding pressure was 0.15 MPa or more, the grinding proceeded rapidly, and the surface area increased.

On the other hand, in the plate crystal, when the grinding pressure was gradually increased to 0.11, 0.13, 0.15, and 0.18 MPa, the surface area changed to 0.06, 0.08, 0.22, and 1.67 µm², respectively. That is, similar to the result of the
Fig. 4. SEM Image of Ground Samples
Upper panel, cube; lower panel, plate.

Fig. 5. Effect of Grinding Pressure on the Average Particle Size and Size Distribution of Samples
(A, cube; B, plate.)

Fig. 6. Effect of Grinding Pressure on the Surface Area of the Sample
(A, cube; B, plate.)
average particle size, it was found that the plate crystals were gradually ground, and the surface area increased with an increase in the grinding pressure.

The crystal morphology change, the particle size change, and the average particle size change by SEM images of the samples obtained after grinding differed depending on the difference in crystal habit. Therefore, in order to further confirm the change in crystal form, PXRD was measured. The results are shown in Fig. 7.

PXRD measurement of the ground sample was performed to confirm that the crystals with different morphologies generated by grinding were not polymorphic transitions. PXRD measurements of a cube crystal sample ground in a jet mill are shown in Fig. 7A. According to these measurements, the same diffraction pattern was shown in the samples obtained at any grinding pressure. In other words, the changes of crystal morphologies were considered to indicate the cleavage of form I cube crystals. Therefore, the cleavage facet will be verified as it changes with the crystal morphology that changes due to grinding.

The focal points for the examination of the cube crystal were its characteristic crystal facets (1 0 0) and (0 0 2). For cube crystals, the (1 0 0) facet was evaluated. Figure 7 shows that the peak area gradually decreased with increasing grinding pressure. The change in the area of a particular crystal facet during grinding was evaluated by comparing the area values of all crystal faces in the powder. First, the total sum of integrated values of PXRD peaks in the measurement 2θ range of 5–30° was calculated. Next, the integrated value of the (1 0 0) facet peak was calculated. The peak integral of the (1 0 0) facet was divided by the sum of the integral values of the peaks in the measuring 2θ range of 5–30°. This value was defined as the peak area ratio of the (1 0 0) facets and evaluated as the relative abundance ratio of the crystal facet areas. At both 0.11 MPa and 0.13 MPa grinding pressure, the peak area ratio was 5.0%. On the other hand, when the grinding pressure was raised to 0.15 MPa, the peak area ratio fell to 2.5%. At a grinding pressure of 0.18 MPa, the peak area ratio was only 1.0%.

Similar to the cube crystal, the PXRD diffraction pattern was confirmed for the ground sample of the plate crystal. As a result, the PXRD diffraction measurement results of all the ground samples showed the same diffraction pattern. In other words, even when the plate crystal was ground by the jet mill, it was shown that the change in crystal morphology was not the polymorphic transition but the cleavage of the crystal. Therefore, the cleavage facet that changes with the crystal morphology that changes due to grinding will be verified.

Changes in grinding pressure and peak shape were also confirmed for facets (0 0 2) of the plate crystal (Fig. 7). Plate crystals are plate-shaped and anisotropic in the (0 0 2) facet direction. Therefore, we evaluated changes in the (0 0 2) facet that are likely to have an effect after grinding.

Similar to the comparison of PXRD peak intensities of cube crystals, to determine the association between the changes in grinding pressure and facet (0 0 2), the ratio of the integral facet value (0 0 2) to the total integral PXRD value was calculated. As the facet (0 0 2) peak overlapped with others, the
peaks were separated by fitting them with Gaussian functions. The peak area ratio was at a maximum of 6.8% at a grinding pressure of 0.11 MPa. At 0.13 MPa grinding pressure, the peak area ratio was 6.1%. In contrast, when the grinding pressure was elevated to 0.15 MPa, the peak area ratio declined to 4.3%. At 0.18 MPa grinding pressure, the peak area ratio was only 3.0%.

The above experimental results showed that the change in the peak area ratio of the crystal facet due to grinding was different between cube and plate crystals. A dissolution test was conducted to investigate how the difference in the morphological changes affects the dissolution property. The dissolution profile is shown in Fig. 8.

In the dissolution test of cube and plate crystals, although the grinding progresses and the surface area increases, there is no significant improvement in the dissolution property in any grinding pressure sample compared to the unground sample (Figs. 8A, B). Therefore, the dissolution profile obtained above was corrected by the surface area of each sample, and the concentration of ASA per unit area was calculated. The results are shown in Figs. 8C, D.

In the cube crystals, the dissolution profile converted per unit area showed no difference between the 0.11 and 0.13 MPa samples. However, it was observed that when the grinding

Fig. 8. Dissolution Profile of Samples
(A, dissolution profile of cube; B, dissolution profile of plate; C, dissolution profile per unit area of cube; D, dissolution profile per unit area plate.)

Fig. 9. Effect of Grinding Pressure on $\gamma_p$ of the Ground Samples
(A, cube; B, plate.)
pressure was raised to 0.15 MPa or more, and the grinding of crystals proceeded, the dissolution amount of ASA per unit area decreased. On the other hand, in the plate crystal, it was shown that the dissolution amount of ASA per unit area gradually decreased as the grinding pressure increased.

In the ground sample, although the crystal morphology and the particle size were changed, the dissolution amount of ASA per unit area was not significantly improved. Therefore, the wettability of the ground sample was evaluated using IGC. The results are shown in Fig. 9. For the evaluation of wettability, the ratio of $\gamma$ in $\gamma_{\text{tot}}$ was used.

When the relationship between $\gamma_p$ of ground samples and the grinding pressure was confirmed, the ground sample of cube crystals had a $\gamma_p$ ratio of 14% at a grinding pressure of 0.11 MPa. When the grinding pressure was increased to 0.13, 0.15, and 0.18 MPa, the ratio of $\gamma_p$ was 14, 6, and 4%, respectively. It was found that $\gamma_p$, which represents the polar component of SFE, decreased as the grinding proceeded, and it was shown that the ratio of $\gamma_p$ sharply decreased, especially at 0.15 MPa or higher. The $\gamma_p$ of the ground sample of the plate crystals was 20, 23, 15, and 10% when the grinding pressure was 0.11, 0.13, 0.15, and 0.18 MPa, respectively. Similarly, in the ground sample of the plate crystals, it was confirmed that $\gamma_p$ tends to decrease by an increase in the grinding pressure.

**Prediction and Evaluation of Surface Physical Property Changes**

From the results of the simulation, it was shown that the peak area ratio of the (1 0 0) facet decreased in the cube crystal after grinding. On the other hand, it was shown that the peak area ratio of the (0 0 2) facet decreased in the plate crystal after grinding. From the result of this PXRD, it was predicted that each crystal was cracked on the (1 0 0) facet and the (0 0 2) facet due to the grinding, and the surface was likely to be cleaved. Therefore, in order to predict the cleavage facet, the attachment energy was calculated by in silico simulation. The results are shown in Fig. 10. The absolute value of the attachment energy was used for the discussion.

As a rule, the amount of energy required to break crystal facet bonds decreases with increasing attachment energy ($E_{\text{att}}$). The $E_{\text{att}}$ values of crystal faces (1 0 0) and (0 0 2) were -22 and -41 kJ/mol, respectively. The absolute $E_{\text{att}}$ values on the crystal planes (1 0 0) and (0 0 2) were much lower than those on the other crystal planes. Furthermore, the $E_{\text{att}}$ for facet (1 0 0) was half that of facet (0 0 2). Thus, the molecular bonds of facets (1 0 0) and (0 0 2) are weak compared to those of the other crystal facets and the former are associated with crystal facets that are easy to cleave. Furthermore, the molecular sequence of the cleavage facets (1 0 0) and (0 0 2) were confirmed.

To identify the differences in the physical properties of facets (1 0 0) and (0 0 2) in the single crystal structure, molecular alignments of the crystal facets were simulated in Materials Studio (Fig. 11). There are reports of studies on the affinity for water for the purpose of evaluating solubility. We evaluated the physical properties of the crystal facet using this evaluation method as a reference.

The molecular arrangement of the crystal facets is shown in Fig. 11. Atoms below the white line indicate atoms exposed on the surface of the crystal. The red elements are oxygen and the white elements are hydrogen. Facet (1 0 0) has a carbonyl oxygen emerging from its surface whereas facet (0 0 2) has part of a benzene ring coming out of its surface. The carbonyl oxygen was relatively more polar. Thus, the differences in the surface atoms of facets (1 0 0) and (0 0 2) account for the relative differences in their physicochemical properties.

**Physical Property Evaluation of Cleaved Surface Using Single Crystal**

From the results of the simulation, there is a difference in polarity between the cleavage facets (1 0 0) and (0 0 2) due to the difference in molecular arrangement. Therefore, the relative wettabilities of the crystals by solvents differing in polarity were determined by the contact angle method using single crystal. The contact angles with water were 51.2° and 66.0° for facets (1 0 0) and (0 0 2), respectively (Table 3). The fact that the contact angle of water for facet (1 0 0) was lower than that for facet (0 0 2) shows that the former has a higher affinity for water than the latter. The surface free energies of facets (1 0 0) and (0 0 2) in a single crystal were calculated using these contact angles and the surface free energy of the solvent. $\gamma_s$ and $\gamma_d$ of each crystal were 11.8 mN m$^{-1}$ and 36.3 mN m$^{-1}$, respectively. For facet (0 0 2), $\gamma_s$ and $\gamma_d$ were 6.2 mN m$^{-1}$ and 40.9 mN m$^{-1}$, respectively (Table 4).

Thus, facet (1 0 0) had a higher $\gamma_p^s$ than facet (0 0 2). As $\gamma_p^s$ uses polarity as a wetting index, facet (1 0 0) had high polarity and was easy to wet. This conclusion was consistent with the output of the Materials Studio simulation.

From the molecular arrangement of the cleavage facet by in silico simulation, differences in the affinity to water and polarity were found. Furthermore, the wettability evaluation experiment using the droplet method was in agreement with the result of the in silico simulation.

Next, in order to confirm the influence of the cleaved surface (1 0 0) (0 0 2) on the dissolution property, a dissolution test of a crystal surface using a single crystal was performed. The results are shown in Fig. 12.

Dissolution test was performed from the single crystal facets to create the dissolution profile. The dissolution rate was calculated by dividing the dissolution amount per unit area of ASA single crystal facet by time. This method allows you to compare the dissolution rates of single crystal planes per unit area. The dissolution rates for facets (1 0 0) and (0 0 2) were 8 ($\times 10^{-6}$ g L$^{-1}$ min$^{-1}$ mm$^{-2}$) and 4 ($\times 10^{-6}$ g L$^{-1}$ min$^{-1}$ mm$^{-2}$), respectively. Thus, the dissolution rate of facet (1 0 0) was approximately two times faster than that of facet (0 0 2).

**Effect of Changes in the Physical Properties of Ground Powder on Wettability and Solubility**

Up to this point,
the influence of the difference in grinding pressure on the physical properties of powder has been shown. Furthermore, the effect of the difference in physical properties on different crystal planes has been evaluated. In this section, from the physical property results of the ground sample, the influence of the abundance ratio of the crystal plane on the dissolution property and the relationship between the dissolution property and wettability is discussed in detail. The effect of changes in crystal morphology on dissolution is shown in Fig. 13. The effect of powder wettability on dissolution is shown in Fig. 14.

Table 4. Surface Free Energy of Facets (1 0 0) and (0 0 2)

| Facet     | $\gamma_s^p$ | $\gamma_s^d$ |
|-----------|---------------|---------------|
| (1 0 0)   | 11.8 ± 2.1    | 36.3 ± 1.6    |
| (0 0 2)   | 6.2 ± 1.3     | 40.9 ± 2.0    |

$\gamma_s^p$: Polar component for the surface tension of solid. $\gamma_s^d$: Dispersive component for the surface tension of solid.

The change in the peak area ratio of XRD indicates that the stacking of crystal faces was altered by cleavage. The horizontal axis shows the peak area ratio and the vertical axis shows the dissolution rate per unit area, and the results of samples whose grinding pressure of each crystal is different are shown. The dissolution amount per unit area calculated in Fig. 8 was used as the dissolution rate per unit area of the ground samples (Fig. 13). First, consider the plate crystal. When the peak area ratio of the (0 0 2) facet is 3.0%, the initial dissolution rate per unit area is $0.01 \times 10^{14} \text{gL}^{-1}\text{min}^{-1}\text{m}^{-2}$.
powder), and when the peak area ratio is 4.3%, the initial dissolution rate per unit area is $0.20 \times 10^{-14} \text{g L}^{-1} \text{min}^{-1} \text{m}^{-2}$ powder). Furthermore, it was observed that the higher the peak area ratio of the (0 0 2) facet, the higher the initial dissolution rate per unit area. The results showed that as the grinding pressure increased, the peak area ratio of the (0 0 2) facet decreased, and at the same time, the initial dissolution rate per unit area also decreased.

Next, consider the cube crystal. When the peak area ratio was 1.0 and 2.5%, the dissolution rate was $0.01 \times 10^{-14} \text{g L}^{-1} \text{min}^{-1} \text{m}^{-2}$ powder), and no significant change was observed. Further, when the peak area ratio of the crystal facet (1 0 0) was 5.0%, the initial dissolution rate was $0.45 \times 10^{-14} \text{g L}^{-1} \text{min}^{-1} \text{m}^{-2}$ powder). From this result, even when the peak area ratio of the crystal facet (1 0 0) increased in the range of 1.0 to 2.5%, no change was observed in the initial dissolution rate. However, when the peak area ratio was 5.0%, the initial dissolution rate per unit area was shown to increase sharply. As a result, the peak area ratio and crystal morphology did not change in the range of 0.11 MPa to 0.13 MPa, and the initial dissolution rate was not affected. However, when the grinding pressure was raised to 0.15 MPa or more, the peak area ratio of the (1 0 0) plane decreased sharply, and it is considered that the change in crystal morphology affected the decrease in the initial dissolution rate.

In other words, it was shown that the dissolution characteristics of the crystal facet that appeared on the surface after the grinding affected the dissolution properties after the grinding.

**Effect of Powder Wettability on Dissolution**

Next, the relationship between the wettability ($\gamma^p$) of the ground cube and plate crystals and the dissolution rate per unit area is shown. The ratio of $\gamma^p$ was calculated by dividing $\gamma^p$ by $\gamma^{tot}$. Since $\gamma^p$ represents a polar term in SFE, the larger the ratio, the higher the wettability. As the dissolution rate per unit area of the ground samples, the value calculated from the dissolution amount per unit area in Fig. 8 was used (Fig. 14).

In the ground sample of cube crystals, the dissolution rate per unit area was $0.01 \times 10^{-14} \text{g L}^{-1} \text{min}^{-1} \text{m}^{-2}$ when the $\gamma^p$ ratio was about 4%. When the $\gamma^p$ ratio increased to 14%, the dissolution rate per unit area was high at $0.44 \times 10^{-14} \text{g L}^{-1} \text{min}^{-1} \text{m}^{-2}$. On the other hand, in the ground sample of the plate crystals, the dissolution rate per unit area was $0.01 \times 10^{-14} \text{g L}^{-1} \text{min}^{-1} \text{m}^{-2}$ when the $\gamma^p$ ratio was about 10%. When the $\gamma^p$ ratio increased to 15 and 20%, the disso-
lution rate per unit area tended to increase to 0.20 and 0.50 ($\times 10^{-6}$ g L$^{-1}$ min$^{-1}$ m$^{-2}$), respectively. The results of presented in Figs. 13 and 14 revealed that the crystals would be cleaved by change in the grinding pressure, and that the dissolution rate of the ground sample decreased. Additionally, when the change in the peak area ratio in PXRD was considered, as the grinding pressure changed, the ratio of crystal facets (1 0 0) and (0 0 2) with poor wettability increased, and the dissolution rate of the ground sample decreased. That is, there would be a correlation between the wettability of the crystal facet generated by cleavage and the dissolution rate of the ground sample.

Furthermore, the relationship between the peak area ratio of the crystal facet and the wettability was confirmed. The results are shown in Fig. 15.

**Effect of Abundance Ratio of Crystal Planes in Powder on Wettability**

In the cube crystal, the relationship between the peak area ratio of the (1 0 0) facet and $\gamma^p$ was confirmed. The ratio of $\gamma^p$ was 14% when the peak area ratio of (1 0 0) was 5%. When the peak area of (1 0 0) was 2.5%, the ratio of $\gamma^p$ was 6%. Furthermore, when the peak area of (1 0 0) was 1%, the ratio of $\gamma^p$ was 4%. It was shown that the $\gamma^p$ ratio decreased as the peak area ratio of the (1 0 0) facet decreased. In the plate crystal, the relationship between the peak area ratio of the (0 0 2) facet and $\gamma^p$ was confirmed. When the peak area ratio of the (0 0 2) facet was 6.8%, the $\gamma^p$ ratio was 20%. When the peak area ratio of the (0 0 2) facet was 6.1%, the $\gamma^p$ ratio was 23%. When the peak area ratio of the (0 0 2) facet was 4.3%, the $\gamma^p$ ratio was 15%. When the peak area ratio of the (0 0 2) facet was 3%, the $\gamma^p$ ratio was 10%. It was found that $\gamma^p$ decreased as the peak area ratio of the (0 0 2) facet decreased. In other words, it was suggested that the abundance ratio of the crystal facets changes with the cleavage of the crystal facets, which affects the wettability of the ground sample.

The summary of the results so far is as shown in Fig. 16.

**Discussion of Powder Wettability Change Mechanism Caused by Cleavage in Silico**

The cleaving mechanism was predicted by *in silico* simulation, and the relationship with the experimental results was confirmed. *In silico* simulations revealed that the (1 0 0) and (0 0 2) facets are easier to cleave than other facets due to their lower absolute attachment energies. *In silico* modeling of crystal morphology based on cube and plate morphology has shown that the cleavable crystal faces (1 0 0) and (0 0 2) are more stacking structures. On the (1 0 0) facet, the oxygen atoms of the polar carbonyl group were exposed on the crystal surface. On the (0 0 2) facet, however, the hydrogen atoms of the nonpolar benzene ring were exposed on the crystal surface. From these results, it was suggested that the (0 0 2) facet has a low affinity for water.

A diagram of cleavage in a plate crystal is shown. Cleavage occurred on the (0 0 2) facet in the plate crystal as the grinding pressure increased. The observed decrease in the PXRD peak area ratio suggests that cleavage was promoted by peeling off the (0 0 2) facet stacked in the plate crystal. As cleavage progressed, the surface area of the (0 0 2) facet increased. The (0 0 2) facet had relatively low wettability. Cleavage increased the abundance ratio of the (0 0 2) facet and the wettability of the ground sample decreased. Therefore, the influence of the wettability of the crystal facet on the dissolution property increased with cleavage.

From the results of the studies so far, it is inferred that there may be a correlation between the molecular arrangement of the crystal facet and the polarity.

As a basis for this relationship, the research by Ito *et al.* states as follows. It has been reported from the results of *in silico* simulation that the crystal facet (001) of t-arginine valproic acid crystal has a polar group—a carboxyl group, an amino group, or a guanidino group—and has a high affinity for water. In the previously reported simulation results, a polar carbonyl group was exposed on the (1 0 0) facet of the ASA crystal and a non-polar benzene ring was exposed on the (0 0 2) facet, indicating the different affinity of water molecules for each crystal facet. Indicates that the (1 0 0) facet is higher. Therefore, it has been reported that in the recrystallization of the plate crystal, water molecules are easily adsorbed on the (1 0 0) facet, which inhibits the adsorption of ASA molecules and relatively grows in the (0 0 2) facet direction.

Based on the findings of these studies, it would be considered that the (0 0 2) facet has low polarity and poor wettability because the hydrogen atoms of the benzene ring would be exposed on the surface of the (0 0 2) facet. By grinding, the (0 0 2) facet would be cleaved and the relative abundance ratio of the (0 0 2) facet with poor wettability might increases. Consequently, it would be considered that the wettability of the ground sample and the dissolution rate were reduced.

For the cube crystals, there was no change in crystal morphology at very low grinding pressure. The cube crystal may
have been difficult to cleave. The reason would be that long and thin crystals are easily cleaved, but crystals close to cubes have high strength and may be difficult to cleave. Since it has a three-dimensional structure than plate crystals, we thought that the influence of crushing force could be dispersed. In the PXRD result of the cube crystal, (20–2) at $2\theta = 21.0^\circ$. When the grinding pressure was 0.11 MPa, the peak of (2 0 −2) was observed, but when the grinding pressure was 0.18 MPa, it became very small, indicating that the crystal plane was cracked by grinding. Furthermore, when the molecular arrangement of this crystal plane was confirmed, it was considered that a crystal plane with poor wettability was generated...
because a part of the benzene ring was present on the crystal plane. Therefore, when the pressure was further increased, not only the (1 0 0) and (0 0 2) facets but also other facets were cleaved, and the micronization proceeded rapidly. Grinding might break various crystal facets. It can be inferred that the change in the dissolution rate was due to the fact that the number of crystal planes with low wettability became larger due to the cleavage and was exposed on the surface of the crystal powder. Cleavage altered the wettability and dissolution rate of the ground sample in accordance with the grinding pressure. The observed changes in the physical properties of the ground sample would be influenced by the wettability of the cleaved surface.

The results of cleavage and wettability were consistent with the results of $E_{ad}$ calculations and molecular sequence predictions in silico.

Conclusion

The present study showed that the wettability of the crystal facets cleaved by grinding would influence the dissolution rate of ground samples. In the formulation development of grinding crystals with a habit, it is essential to understand the wettability of the crystal facets. Therefore, it was suggested that the cleavage properties and the wettability of the cleavage facet can be predicted by using in silico simulation to predict the adhesion energy of the cleavage facet, molecular arrangement, and its polarity. In silico simulations can be used to predict changes in crystal shape due to grinding, as well as wettability and dissolution rate after grinding. It also enables you to select the optimal crystal habit and design the grinding process. In addition, it saves drug development time and costs.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Materials

The online version of this article contains supplementary materials. Supplementary 1: Supplement to the formula for obtaining surface tension, Supplementary 2: Figure S1. Image of calculation of peak area, Supplementary 3: Figure S2. Image of dissolution test method using single crystal, Supplementary 4: Figure S3. Image of single crystal used for dissolution test and contact angle measurement.

References

1) McCormick D., Pharm. Technol., 29, 52–62 (2005).
2) Basim P., Haware R. V., Dave R. H., Int. J. Pharm., 569, 118548 (2019).
3) Ghazi N., Liu Z., Bhatt C., Kiang S., Cuitino A., AAPS PharmSciTech, 20, 168 (2019).
4) Capece M., Huang Z., Davé R., J. Pharm. Sci., 106, 1608–1617 (2017).
5) Liu T. X., Marziano L., Bentham A. C., Litster J. D., White E. T., Howes T., Int. J. Pharm., 362, 109–117 (2008).
6) Gupta V. R., Mutalik S., Patel M. M., Jani G. K., Acta Pharm., 57, 173–184 (2007).
7) Markl D., Zeitler J. A., Pharm. Res., 34, 890–917 (2017).
8) Chen L., He Z., Kunnath K. T., Fan S., Wei Y., Ding X., Zheng K., Dave R. N., Int. J. Pharm., 577, 354–365 (2019).
9) Lob Z. H., Samanta A. K., Heng P. W. S., Asian J. Pharm., 10, 255–274 (2015).
10) Fukunaka T., Tom J. W., J. Soc. Powder Technol. Japan, 40, 655–663 (2003).
11) Nakach M., Authelin J. R., Chamayou A., Dodds J., Int. J. Miner. Process., 74, 173–181 (2004).
12) Shariare M. H., Blagden S. N., Matas M., Leusen F. J. J., York P., Int. J. Pharm., 101, 1108–1119 (2012).
13) Bonfilio R., Souza M. C. O., Leal J. S., Viana O. M. M., Doriguetto A. C., Araújo M. B., Brazilian J. Pharm. Sci., 53, 4 (2017).
14) Ren Y., Shen J., Yu K., Phan C. U., Chen G., Liu J., Hu X., Feng J., Crystals, 9, 556 (2019).
15) Kim Y., Machada K., Taga T., Osaki K., Chem. Pharm. Bull., 33, 2641–2647 (1985).
16) Vishweswar P., McMahon J. A., Oliveira M., Peterson M. L., Zaworotko M. J., J. Am. Chem. Soc., 127, 16802–16803 (2005).
17) Chan E. J., Welberry T. R., Heerdegen A. P., Goossens D. J., Acta Crystallogr. B. Struct. Sci. Cryst. Eng. Mater., 66, 606–610 (2010).
18) Varughese S., Kiran M. S. P. N., Solanko K., Bond A. D., Ramamurty U., Desiraju G. R., Chem. Sci., 2, 2236 (2011).
19) Tawashi R., Science, 160, 76 (1968).
20) Hatanaka T., Yoshihashi Y., Ito M., Terada K., Yonemochi E., Yakugaku Zasshi, 140, 913–921 (2020).
21) Hammond R. B., Pencheva K., Roberts K. J., Auffret T., J. Pharm. Sci., 96, 1967–1973 (2007).
22) Hammond R. B., Pencheva K., Ramachandran V., Roberts K. J., Cryst. Growth Des., 7, 1571–1574 (2007).
23) Okky D. P., Furushiri T., Yonemochi E., Terada K., Uekusa H., Cryst. Growth Des., 16, 3577–3581 (2016).
24) Swaminathan V., Cobb J., Saracovav I., Int. J. Pharm., 312, 158–165 (2006).
25) Das S. C., Zhou Q., Morton D. A. V., Larson I., Stewart P. J., Eur. J. Pharm. Sci., 43, 325–333 (2011).
26) Mohammedi-Jam S., Waters K. E., Adv. Colloid Interface Sci., 212, 21–44 (2014).
27) Das S. C., Larso I., Morton D. A. V., Stewart P. J., Langmuir, 27, 521–523 (2011).
28) Kondor A., Quellet C., Dallos A., Langmuir, 27, 1040–1050 (2015).
29) Sakata Y., Shiraishi S., Otsuka M., Adv. Colloid Interface Sci., 16, 92–100 (2005).
30) Mittal A., Malhotra D., Jain P., Kalia A., Shunmugaperumal T., AAPS PharmSciTech, 17, 988–994 (2016).
31) Strukkenberg A. G., Hu C. T., Zu O., Schmidt M. U., Wu W., Tan M., Kahr B., Cryst. Growth Des., 15, 3562–3566 (2017).
32) Modi S. R., Dantuluri A. K. R., Puri Y., Pawar Y. B., Nandekar P., Sangamwar A. T., Perumalla S. R., Sun C. C., Bansal A., Cryst. Growth Des., 13, 2824–2832 (2013).
33) Ito M., Nambu K., Sakon A., Uekusa H., Yonemochi E., Noguchi S., Terada K., J. Pharm. Sci., 106, 859–865 (2017).
34) KRÜSS GmbH, Two-Component Surface Energy Characterization as a Predictor of Wettability and Dispensability; KRÜSS Application Report AR213e: Hamburg, Germany, 2020.