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Factors affecting the apparent solubility of ursodeoxycholic acid in the grinding process

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Abstract

Ursodeoxycholic acid (UDCA) was ground by a vibrating mill. Apparent solubility of the ground sample was determined by Coulter counter method. The samples were characterized by pore size distribution measurement, powder X-ray diffraction (PXRD) measurement, near infra-red (NIR) spectroscopy and contact angle measurement. The dispersive and polar components of surface free energy were calculated from the contact angle data determined by a contact angle analyzer. Surface polarity was calculated from the surface free energy components. The apparent solubility of UDCA was increased by the grinding with vibrating mill, however, the particle size of ground sample was not decreased. An amorphization was observed in the PXRD pattern of the ground sample, and the crystallinity of sample was decreased with increasing the grinding time. During the initial grinding, the dispersive component of surface free energy was decreased, whereas the polar part of surface free energy was increased. The surface polarity of the sample was increased in the same manner. Relationship between the solubility and the factors changing in the grinding process was evaluated. There was a significant correlation between the apparent solubility and the surface polarity and crystallinity of the sample. The NIR spectra confirmed the appearance of –OH group on the sample surface. The apparent solubility increase of the ground sample was closely related to the improvement of the surface polarity and the destruction of crystalline structure.

Keywords: Ursodeoxycholic acid; Solubility; Grinding; Crystallinity; Surface free energy

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1. Introduction

Many attempts have been conducted to obtain a good bioavailability achieved by creating an amorphous product (Chow and Riegelman, 1971). The amorphization of drug in co-grinding process has been recognized as one of the effective way to improve the dissolution behavior (Yamamoto et al., 1974; Nakai et al., 1984). It is well known that the pharmaceutical processing of a solid causes defects in the crystal lattice, which contribute to the disorder (Morita et al., 1984). A grinding process could induce defects in the crystalline network: these defects would improve the compression and dissolution (Pirttimaki et al., 1993).

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The amorphous and crystalline states are two extreme states of solid substances. In an amorphous product, molecules are in an irregular arrangement within the particles. The lack of long-range order that characterizes crystalline state confers on the particles a good compression ability due to the plasticity and isotropy of force transmission through such a structure. However, amorphous states have been known as a high energy state, and their physical and chemical stability is poor (Piyarom et al., 1997).

Because of the complicating features, there are a few reports concerning the evaluation of the grinding mechanism in a molecular order. We have already reported that an amorphous ursodeoxycholic acid (UDCA) was prepared by spray drying, melt-quenching, mixing with porous materials, and grinding. (Yonemochi et al., 1994, 1997; Okonogi et al., 1997; Ueno et al., 1998). There were some differences in physical characteristics among the amorphous UDCAs prepared by different method. The purpose of this report is to study the effect of the factors, e.g. particle size distribution, crystallinity, and surface free energy, on the apparent solubility of UDCA during the grinding process using a vibrating mill, and to clarify the grinding mechanism of the vibrating mill.

2. Materials and methods

2.1. Materials

UDCA was supplied by Dawoong Chemical (Korea). Organic solvents were of analytical reagent grade.

2.2. Preparation of ground samples

Samples of ground UDCA were prepared by grinding using the vibrating mill described previously (Yonemochi et al., 1999a). Jet mill (50AS Spiral Jet mill, Hosokawa Micron Corp., Japan) was used for preparing the reference ground sample. The grinding condition of the reference sample was as follows; the injector nozzle was 0.9 mm, the air pressure was 5.0 kg/cm^2 G, and the feeding rate of sample was 330 g/h. Before experiment, ground sample was sieved using 150 mesh sieve. HPLC assay could not detect any decomposition product in the ground samples.

2.3. Powder X-ray diffraction (PXRD) measurement

The PXRD patterns were measured with Cu Kα radiation using a Rigaku RAD system (Rigaku, Japan). Crystallinity was calculated using Hermans method.

2.4. Particle size distribution measurement

The particle size distributions of intact and ground samples were measured using Mastersizer microplus (Malvern Instruments Ltd., UK) on the basis of particle size analysis by the laser diffraction and scattering method. Water was used for the dispersion solvent and no surfactant was added. When measured, the external ultrasonicator (model: US-300T, Nihonseiki Co., Japan) was used for the dispersion of sample, and the obtained data were reproducible on repeated runs.

2.5. Apparent solubility measurement

Apparent aqueous solubility was measured by the Coulter counter method (Nyström et al., 1985; Nyström and Bisrat, 1986). Coulter counter TA II (Coulter Corp., UK) was used and a sample weight was 40 mg and aperture size was 200 μm.

2.6. Surface energy determination

The liquid penetration rate was measured by capillary method using KRÜSS K121 Processor Tensiometer (KRÜSS GmbH, Germany) at 25 °C. The contact angle was calculated by the Washburn equation using the penetration rate. Hexane, tetrachloromethane, chloroform, dichloromethane, ethanol, *N*,*N*-dimethylformamide, benzylalcohol were used as probe solvents having different polarity. The surface free energy was calculated from following equation using the contact angle between liquid and powder (Owens and Wendt, 1969)

$$\frac{1+\cos\theta}{2}\frac{\gamma_L}{\sqrt{\gamma_L^d}} = \sqrt{\gamma_S^p} \times \sqrt{\frac{\gamma_L^p}{\gamma_L^d}} + \sqrt{\gamma_S^d}$$

where γ_L is a surface free energy of the liquid (mJ/m^2), γ_S is a surface free energy of the solid (mJ/m^2), θ is a contact angle (degree), and the subscriptions, d and p, show the dispersive and polar component of the surface free energy.

2.7. Near infrared spectroscopy

Samples (2 g) of the ground UDCA were placed into flat bottom clear glass containers. The samples were placed on the lens of Rapid Content Analyzer module attached to a NIRSystems 6500 spectrophotometer (FOSS NIRSystems, USA). The NIR instrument recorded the mean spectrum of 32 scans of each sample, over the wavelength region 1100–2500 nm.

3. Results and discussion

3.1. Factors affecting the apparent solubility of ground UDCA

Fig. 1 shows the effect of grinding with the vibrating mill on the apparent solubility of the sample. The apparent solubility of intact UDCA was 186.6 μg/ml. After 15 min grinding, the apparent solubility was 254.2 μg/ml. The apparent solubility of UDCA was increased with increasing the grinding time. Decreasing the particle size and increasing the effective surface area of the ground sample seems to be the reason for the apparent solubility variation. In order to clarify the reason, we have measured the particle size distribution of samples. Fig. 2 shows the change in the particle size distribution of UDCA by grinding. The mean particle size of intact UDCA was 29.6 μm, and the particle size distribution of ground sample of 1 min was clearly changed. The fraction of small particle (less than 10 μm) was significantly increased by grinding. However, the particle size distribution was recovered by 5 min grinding, and the particle size distribution was not changed until grinding time exceeded more than 60 min. On the other hand, the mean particle size of ground sample using a jet mill was 1.7 μm, and the obtained size was much smaller than that of ground sample with the vibrating mill. These data suggested that the re-aggregation of ground particle was occurred during grinding, and the improvement of the apparent solubility was not affected by the particle size of UDCA. Fig. 3 shows the change in the PXRD pattern of UDCA by grinding. It was clearly seen that the peak intensity of ground sample using the vibrating mill was decreased with increasing the grinding time. The

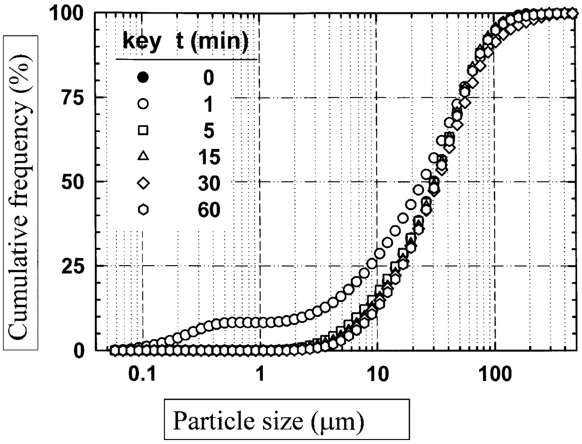

Fig. 2. Change in the particle size distribution of UDCA by grinding using a vibrating mill.

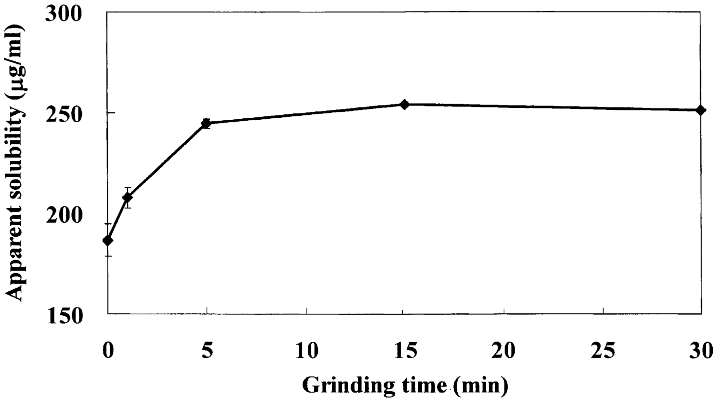

Fig. 1. Effect of grinding using a vibrating mill on the apparent solubility of UDCA.

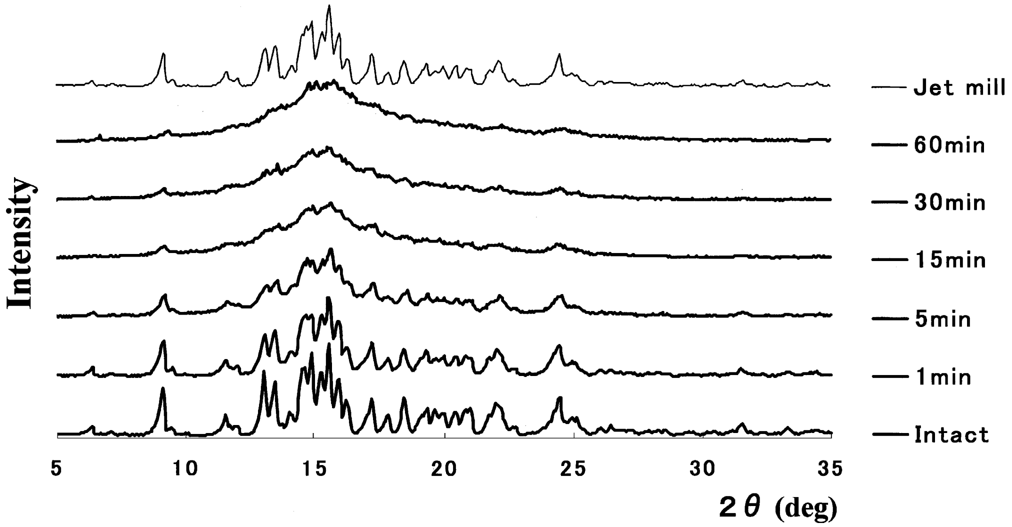

Fig. 3. Change in the PXRD pattern of UDCA by grinding.

crystallinity of intact UDCA was 89% and the sample crystallinity was decreased to 2.7% by grinding for 60 min. On the other hand, the crystallinity of the ground sample using the jet mill was 87%, suggesting that the significant amorphization did not occurred in this sample. We have already reported that the surface nature of clarithromycin was changed by spray drying and grinding, therefore, the surface free energies of ground samples was measured (Yonemochi et al., 1999b). As shown in Fig. 4, during the initial grinding, the disperse component of the surface free energy of sample was decreased, whereas the polar part of the surface free energy was increased. The surface polarity of the sample was increased in the same manner. Fig. 5 shows the effect of the grinding machine on the surface free energy of UDCA. The dispersive component was similar among these samples. The polar component was slightly increased in the ground sample using the jet mill; on the other hand, the polar component of 60 mm ground sample using the

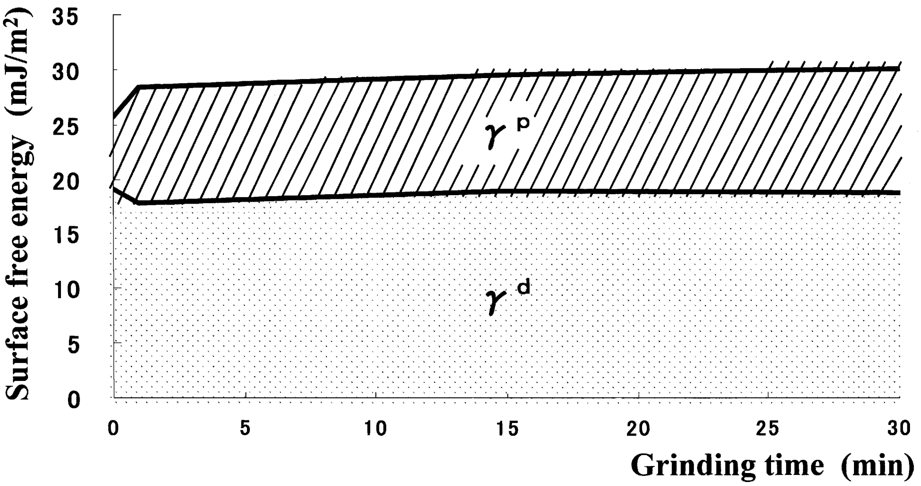

Fig. 4. Relationship between grinding time and surface free energy of the samples.

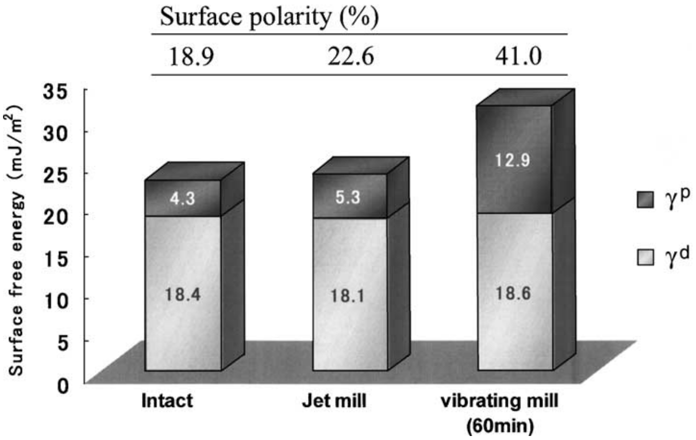

Fig. 5. Effect of grinding machine on the surface free energy of UDCA.

vibrating mill was three times larger than that of intact UDCA. The surface polarity of the 60 min ground sample was twice that of the intact and jet milled samples. It was suggested that the apparent solubility would be affected by the crystallinity and the surface polarity of the samples. Fig. 6 shows the change in the crystallinity and surface polarity of UDCA by grinding. During the initial grinding, the crystallinity was gradually decreased; on the other hand, the surface polarity was increased abruptly. We have evaluated the factors changing in the grinding process, and analyzed the effect of the factors, which were particle size, crystallinity, and surface free energy, on the apparent solubility of UDCA during the grinding process. Fig. 7 shows the relationship between the apparent solubility and crystallinity and surface polarity of ground samples. Both parameters showed a certain correlation against the apparent solubility. The regression coefficient of D_{50} against the apparent solubility were poor compared to the coefficients shown in Fig. 7. These results suggested that the apparent solubility enhancement was closely related to the crystallinity and surface polarity of UDCA.

3.2. The surface character of the ground UDCA

The NIR spectra measured by reflectance mode revealed the information of the molecular state of sample surface. We have measured the NIR spectra of the various samples to evaluated the surface nature

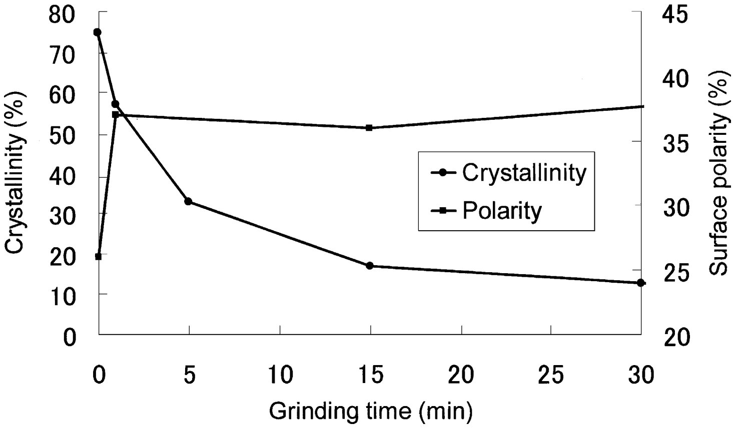

Fig. 6. Change in the crystallinity and surface polarity of UDCA by grinding.

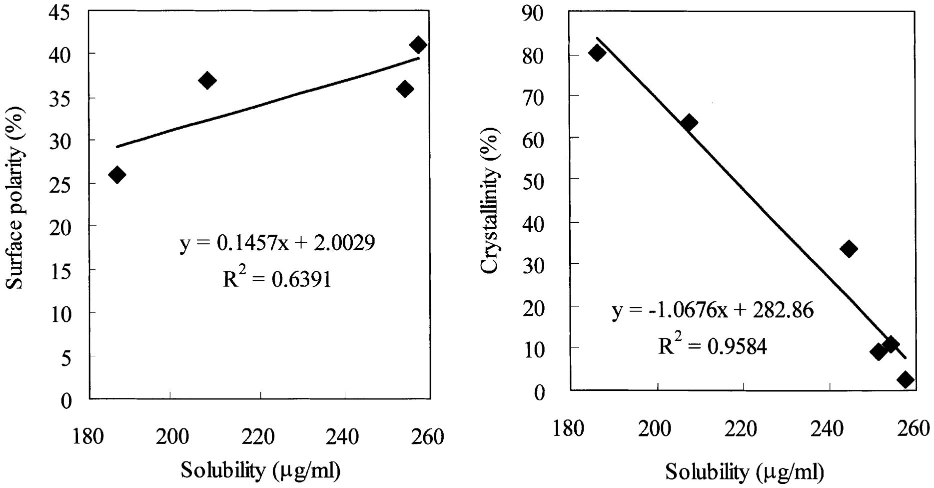

Fig. 7. Relationship between the solubility against the surface polarity and crystallinity of the samples.

of samples. Obtained NIR spectra for these samples are shown in Fig. 8. It can be seen that all the samples have differences around 1450 and 1900 nm. However, no significant spectral difference can be seen in the C–H related peaks that are located around 1200, 1750, and 2300 nm. The intact sample has peak due to the first overtone O–H at 1 450 nm (Shenk et al., 1992; Buckton et al., 1998), and this peak was shifted from 1450 to 1422 nm by grinding using the vibrating mill. This result suggested that the molecular state of sample surface was changed by grinding. Change in the peak intensity around 1900 nm due to the O–H deformation combination band was also observed. From the crystalline structure data of UDCA, there is an inter-molecular hydrogen bond between each UDCA molecule in the unit cell. The spectral difference between these samples in this region (1400–1500 nm) could be related to an alteration of the hydrogen-bonding network in the samples. The second derivative NIR spectra of the samples are shown in Fig. 9. By the second derivative treatment of the raw spectra, a peak of negative displacement in the second derivative spectrum corresponds directly to a positively displaced peak in the original spectrum. Therefore, in the following discussions, the peaks described show negative values. The peak at

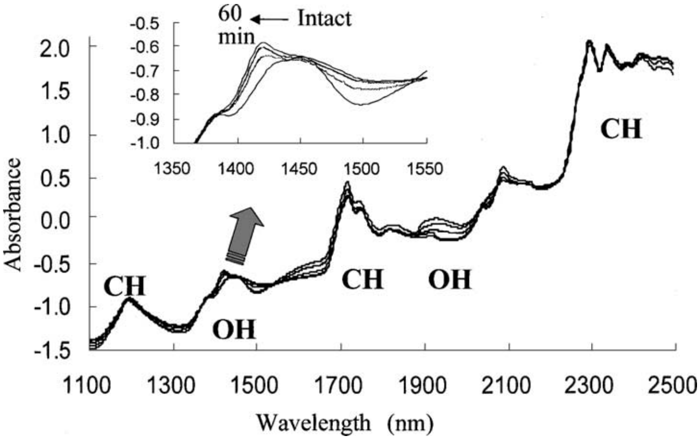

Fig. 8. Change in the NIR spectrum of UDCA by grinding.

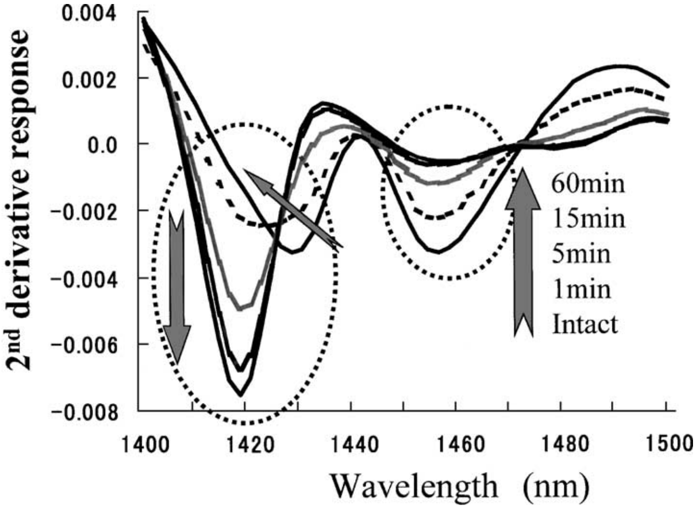

Fig. 9. Change in the second derivative NIR spectrum of UDCA by grinding.

1428 nm due to O–H group was shifted to 1418 nm, and the peak intensity was increased by the grinding. The intensity of the peak at 1460 nm due to the inter-molecular hydrogen bond was also decreased. On the other hand, the ground sample using the jet mill showed the O–H related peak at 1424 and 1460 nm. These results should be a consequence of structural changes during the grinding process. In an amorphous fraction of the samples, UDCA molecules would be in an irregular arrangement, and the spectral change observed at 1420 and 1460 nm that characterized the hydrogen bonding supported the transformation of the molecular conformation. These results confirmed that the O–H groups were appeared in the sample surface during the grinding with the vibration mill and the surface polarity was induced by the destruction of crystalline structure of UDCA.

4. Conclusion

Using a vibrating mill, the apparent solubility of UDCA was improved by grinding. The surface polarity of the sample ground by the vibrating mill was higher compared to the sample ground by the jet mill. The NIR spectra confirmed the appearance of O–H group on the ground sample surface using the vibrating mill. These results suggested that the apparent solubility increase of the ground sample was closely related to the improvement of the surface polarity resulting by the destruction of crystalline structure of UDCA.

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