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Characterization of monoclinic crystals in tablets by pattern-fitting procedure using X-ray powder diffraction data

Shigeo Yamamura*, Yasunori Momose

School of Pharmaceutical Sciences, Toho University, Miyama 2-2-1, Funabashi, Chiba 274-8510, Japan

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Abstract

The purpose of this study is to characterize the monoclinic crystals in tablets by using X-ray powder diffraction data and to evaluate the deformation feature of crystals during compression. The monoclinic crystals of acetaminophen and benzoic acid were used as the samples. The observed X-ray diffraction intensities were fitted to the analytic expression, and the fitting parameters, such as the lattice parameters, the peak-width parameters, the preferred orientation parameter and peak asymmetric parameter were optimized by a non-linear least-squares procedure. The Gauss and March distribution functions were used to correct the preferred orientation of crystallites in the tablet. The March function performed better in correcting the modification of diffraction intensity by preferred orientation of crystallites, suggesting that the crystallites in the tablets had fiber texture with axial orientation. Although a broadening of diffraction peaks was observed in acetaminophen tablets with an increase of compression pressure, little broadening was observed in the benzoic tablets. These results suggest that "acetaminophen is a material consolidating by fragmentation of crystalline particles and benzoic acid is a material consolidating by plastic deformation then occurred rearrangement of molecules during compression". A pattern-fitting procedure is the superior method for characterizing the crystalline drugs of monoclinic crystals in the tablets, as well as orthorhombic isoniazid and mannitol crystals reported in the previous paper.

Keywords: X-ray diffraction; Pattern-fitting; Monoclinic crystals; Preferred orientation; Lattice disorder; Tablet

1. Introduction

In previous reports, we described the pattern-fitting procedure for characterizing orthorhombic isoniazid and mannitol crystals in the tablets using X-ray powder diffraction intensities (Fukuoka et al., 1993a,b). This method is based on Rietveld analysis (Rietveld, 1969) that has been applied to the crystal structure refinement (Kariuki et al., 1999), quantitative analysis (Orlhac et al., 2001) and strain–size evaluation (Pratapa et al., 2001). We applied the pattern-fitting procedure to investigate the crystallographic properties of crystals and/or crystallites in the tablet.

In the present investigation, we developed a computer program of pattern-fitting for characterizing the crystals and/or crystallites of monoclinic acetaminophen and benzoic acid crystals in the tablet using X-ray powder diffraction data. In order to correct the preferred orientation of crystallites in the sample, the performance of the Gauss and the March distribution functions were compared and the feature of preferred orientation of crystallites in the tablets was evaluated from the results. The mechanical properties of acetaminophen and benzoic acid crystals during

* Corresponding author. Tel.: +81-47-472-1350; fax: +81-47-472-1350.
E-mail address: yamamura@phar.toho-u.ac.jp (S. Yamamura).

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compression were investigated from the scattering angle dependency of diffraction peak widths and the molecular arrangement in the crystals.

2. Materials and methods

2.1. Materials

The powders of acetaminophen and benzoic acid (Sigma Chemical Co., St. Louis, MO), passed through a 250 mesh (63 μm) sieve, were used. Sample powders were stored in the desiccator with silica gel until X-ray measurement. The crystal structures of acetaminophen and benzoic acid have been determined: acetaminophen: monoclinic, $P2_1/a$, $a = 12.93$ Å, $b = 9.40$ Å, $c = 7.10$ Å and $\beta = 115.9°$ (Haisa et al., 1976), benzoic acid: monoclinic, $P2_1/c$, $a = 5.510$ Å, $b = 5.157$ Å, $c = 5.157$ Å and $\beta = 97.41°$ (Bruno and Randaccio, 1980). Lists of the crystal structure factors of acetaminophen and benzoic acid crystals were obtained from the International Union of Crystallography.

2.2. Tabletting

Five hundred milligrams of the sample powder was compressed under various pressures for 30 s by the direct compression method. The die available to the sample plate for X-ray diffraction measurement was designed and used (Fukuoka et al., 1993a). Diameter of the tablet was 13 mm and the tablet was placed in the die without ejection during X-ray measurement. X-ray measurement was carried out immediately after the tablet preparation.

2.3. X-ray powder diffraction

The X-ray powder diffraction intensities were measured using a RINT 2500 X-ray diffractometer (Rigaku Co., Japan) and symmetrical reflection geometry was employed. The X-ray source was Cu-Kα radiation with a voltage of 50 kV and a current of 100 mA. The diffracted X-ray beam was monochromated by a bent-type graphite monochromator, and a scintillation counter was used as the detector. Diffraction intensities were measured by a fixed-time step-scanning method in the range of 5–40° (2θ) at an interval of 0.02°. X-ray absorption by the specimen and the contribution of Cu-Kα_2 to the observed diffraction intensity were ignored in the calculation.

2.4. Pattern-fitting

A computer program for pattern-fitting was developed with MATLAB software version 6.12 with optimization and statistics toolboxes (The Math Works Inc., MA, USA). The trust-region reflective Newton method was applied to optimize the fitting parameters (Coleman and Li, 1994, 1996).

In the pattern-fitting procedure, the observed diffraction intensities were fitted to Eq. (1) in order to optimize fitting parameters (Rietveld, 1969; Young, 1993; McCusker et al., 1999).

$$I(2\theta_i) = K\sum_n F_{hkl}^2 m_{hkl} \mathrm{Lp}_{hkl} G(2\theta_{hkl} - 2\theta_i) P_{hkl} + y_\mathrm{b}(2\theta_i) \quad (1)$$

where $I(2\theta_i)$ is the observed intensity at $2\theta_i$, K the normalization constant, n the number of $h\,k\,l$ reflection, F_{hkl} the crystal structure factor of nth $h\,k\,l$ reflection, m the multiplicity factor, Lp the Lorentz-polarization factor, $2\theta_{hkl}$ is the scattering angle of $h\,k\,l$ reflection calculated from the lattice constants and Miller indices as Eq. (2), G the profile function (modified Lorentz function) as Eq. (3), H the full-width at half-maximum (FWHM) as Eq. (4), s the asymmetric parameter as Eq. (5), P the preferred orientation function as Eq. (6a) or (6b), and $y_\mathrm{b}(2\theta_i)$ is the background intensity at $2\theta_i$, defined as fifth order function.

$$\theta = \sin^{-1}\left\{\frac{\lambda}{2}\sqrt{\frac{(h^2/a^2) + (k^2\sin^2\beta/b^2) + (l^2/c^2) - (2hl\cos\beta/ac)}{\sin^2\beta}}\right\} \quad (2)$$

where a, b, c and β are the lattice constants of monoclinic crystals.

$$G = \frac{2sc_\mathrm{ML}^{1/2}}{\pi H(1 + c_\mathrm{ML}(2\theta_{hkl} - 2\theta_i)^2/H^2)^2} \quad (3)$$

$$H^2 = U\tan^2\theta_{hkl} + V\tan\theta_{hkl} + W \quad (4)$$

$$s = 1 - \frac{A\,\mathrm{sign}(2\theta_{hkl} - 2\theta_i)(2\theta_{hkl} - 2\theta_i)^2}{\tan\theta_{hkl}} \quad (5)$$

where s is the function for the correction of the peak asymmetry and c_{ML} is a normalization constant for modified Lorentzian function (Sonneveld and Visser, 1975). U, V and W in Eq. (4) are the peak width parameters (Young, 1993) and A in Eq. (5) is the asymmetric parameter.

$$P_{hkl} = \exp(-\alpha\phi_{hkl}^2) \tag{6a}$$

$$P_{hkl} = \left(\alpha^2 \cos^2 \phi_{hkl} + \frac{\sin^2 \phi_{hkl}}{\alpha}\right)^{-1.5} \tag{6b}$$

Either Eq. (6a) or (6b) was used for the preferred orientation function where α is the preferred orientation parameter indicating the strength of the preferred orientation of crystallites, and ϕ is the acute angle between the preferred orientation plane (normal to preferred orientation axis) and ($h\,k\,l$) plane. The preferred orientation plane was selected when the best fit was achieved by a trial and error approach. When using Eqs. (6a) and (6b), the diffraction intensities were assumed to be modified by the preferred orientation of crystallites according to the Gauss distribution or the March distribution curves (Dollase, 1986) with an angle of ($h\,k\,l$) plane and the selected preferred orientation plane by preferred orientation of crystallites, respectively.

The observed intensities were corrected for Lorentz-polarization factor using θ_{hkl} calculated by Eq. (2). In the present investigation, we assumed that "there are no changes in crystal structure factors of $h\,k\,l$ reflections with compression of crystals, because the shift in diffraction angle was negligibly small".

By the pattern-fitting procedure, crystal lattice parameters (a, b, c and β), FWHM parameters (U, V and W), asymmetric parameter (A), preferred orientation parameter (α) and background parameters were optimized simultaneously in order to minimize the value of sum (Eq. (7)), by least squares procedure. The values of R_{wp} and R_p were used for a criteria of fit, as Eqs. (8) and (9) (McCusker et al., 1999).

$$\text{Sum} = \sum_{i=1}^{N} [w_i (I_{obs}(2\theta_i) - I_{cal}(2\theta_i))^2] \tag{7}$$

$$R_{wp} = \left\{ \frac{\sum_{i=1}^{N} [w_i (I_{obs}(2\theta_i) - I_{cal}(2\theta_i))^2]}{\sum_{i=1}^{N} w_i I_{obs}(2\theta_i)^2} \right\}^{1/2} \tag{8}$$

$$R_p = \frac{\sum_{i=1}^{N} |I_{obs}(2\theta_i) - I_{cal}(2\theta_i)|}{\sum_{i=1}^{N} I_{obs}(2\theta_i)} \tag{9}$$

where N is the data points, w_i the weight of the data ($1/I_{obs}(2\theta_i)$), $I_{obs}(2\theta_i)$, and $I_{cal}(2\theta_i)$ are the observed and calculated intensities at $2\theta_i$, respectively.

The crystal structure factors of acetaminophen and benzoic acid using the simulation are summarized in Tables 1 and 2. The diffraction intensity data of all reflections calculated to be observed between 5 and 40° (2θ) were used in the calculation.

Table 1
Plane indices, crystal structure factors and multiplicity of diffraction peaks of acetaminophen crystal

$h\,k\,l$	F	m	$h\,k\,l$	F	m
1 1 0	−26.8	4	0 3 1	0.6	4
0 0 1	51.5	2	$\bar{1}$ 2 2	12.7	4
2 0 0	−23.1	2	4 1 0	−3.0	4
$\bar{2}$ 0 1	63.9	2	2 3 0	32.2	4
$\bar{1}$ 1 1	−10.1	4	$\bar{2}$ 3 1	−25.0	4
0 1 1	31.5	4	$\bar{4}$ 1 2	35.6	4
2 1 0	−15.7	4	3 1 1	−18.9	4
$\bar{2}$ 1 1	52.0	4	$\bar{3}$ 2 2	5.7	4
0 2 0	17.2	2	1 1 2	7.4	4
1 2 0	−38.0	4	$\bar{4}$ 2 1	−7.8	4
1 1 1	31.4	4	0 2 2	5.9	4
$\bar{1}$ 2 1	−2.9	4	1 3 1	12.1	4
$\bar{3}$ 1 1	24.9	4	$\bar{3}$ 3 1	−14.0	4
0 2 1	−76.5	4	$\bar{5}$ 1 1	47.5	4
2 2 0	−88.2	4	4 2 0	18.8	4
$\bar{2}$ 2 1	19.8	4	$\bar{4}$ 2 2	−7.2	4
2 0 1	43.5	2	3 3 0	51.5	4
3 1 0	6.9	4	3 2 1	−6.3	4
$\bar{2}$ 0 2	−4.5	2	1 2 2	−27.5	4
2 1 1	−6.1	4	2 0 2	−52.8	2
1 2 1	−106.4	4	$\bar{5}$ 1 2	17.0	4
$\bar{2}$ 1 2	−0.6	4	2 3 1	6.3	4
$\bar{1}$ 1 2	43.0	4	$\bar{2}$ 0 3	−8.3	2
$\bar{4}$ 0 1	−3.6	2	0 4 0	7.1	2
0 0 2	36.0	2	$\bar{2}$ 3 2	26.7	4
$\bar{3}$ 2 1	−7.8	4	$\bar{1}$ 3 2	35.2	4
$\bar{3}$ 1 2	−23.5	4	2 1 2	−5.9	4
$\bar{4}$ 1 1	28.7	4	1 4 0	−9.4	4
1 3 0	−7.5	4	4 0 1	−3.5	2
0 1 2	12.9	4	$\bar{2}$ 1 3	−1.2	4
3 2 0	−15.7	4	$\bar{3}$ 1 3	−29.7	4
4 0 0	10.6	2	$\bar{5}$ 2 1	−5.7	4
$\bar{1}$ 3 1	−10.3	4	$\bar{3}$ 3 2	−0.5	4
$\bar{4}$ 0 2	1.1	2	5 1 0	−22.2	4
2 2 1	−28.0	4	5 1 0	5.3	4
$\bar{2}$ 2 2	−7.8	4			

Table 2
Plane indices, crystal structure factors and multiplicity of diffraction peaks of benzoic acid crystal

h k l	*F*	*m*	*h k l*	*F*	*m*
0 0 2	33.2	2	1 1 5	8.8	4
1 0 0	41.2	2	0 0 8	21.4	2
0 0 4	30.6	2	0 1 7	10.6	4
$\bar{1}$ 0 2	82.0	2	$\bar{2}$ 0 4	40.1	2
0 1 1	13.4	4	$\bar{1}$ 0 8	35.8	2
0 1 2	19.7	4	2 0 2	6.1	2
1 0 2	36.6	2	0 2 2	18.0	4
0 1 3	22.2	4	$\bar{1}$ 1 7	7.6	4
$\bar{1}$ 0 4	3.4	2	1 1 6	12.6	4
$\bar{1}$ 1 1	18.4	4	$\bar{2}$ 1 1	18.3	4
1 1 0	10.1	4	0 2 3	19.8	4
0 1 4	73.0	4	$\bar{2}$ 1 2	17.5	4
$\bar{1}$ 1 2	2.6	4	2 1 0	14.6	4
1 1 1	10.5	4	0 1 8	18.3	4
0 0 6	7.8	2	2 1 1	23.5	4
1 0 4	27.2	2	$\bar{2}$ 0 6	8.7	2
$\bar{1}$ 1 3	3.2	4	$\bar{1}$ 2 1	20.3	4
1 1 2	81.8	4	0 2 4	31.5	4
0 1 5	24.9	4	2 0 4	16.0	2
$\bar{1}$ 1 4	8.5	4	1 0 8	19.2	2
$\bar{1}$ 0 6	6.4	2	$\bar{2}$ 1 4	4.8	4
1 1 3	66.6	4	$\bar{1}$ 2 2	9.4	4
$\bar{1}$ 1 5	18.9	4	1 2 1	9.5	4
0 1 6	24.7	4	$\bar{1}$ 1 8	21.0	4
1 1 4	56.2	4	2 1 2	5.8	4
1 0 6	16.9	2	1 1 7	36.0	4
$\bar{2}$ 0 2	18.8	2	$\bar{1}$ 2 3	3.0	4
$\bar{1}$ 1 6	11.6	4	1 2 2	8.8	4
2 0 0	5.1	2			

3. Results

3.1. Pattern-fitting of diffraction patterns of acetaminophen and benzoic acid

Fig. 1 shows the examples of pattern-fitting of observed calculated intensities of acetaminophen tablet (compression pressure: 2250 kg/cm^2) using the March function for the correction of preferred orientation of crystallites. Table 3 summarizes the optimized values with 95% confidential intervals (CI) of fitting parameters. Because the best fitting was achieved when the (0 0 1) plane was used for the preferred orientation plane, the (0 0 1) plane was selected for the preferred orientation plane. The fitting between observed and calculated intensities when using the March function ($R_{wp} = 0.132$, $R_p = 0.030$) was better than when using Gauss function ($R_{wp} = 0.141$, $R_p = 0.030$). From the R_{wp} value, the March function was found to have a better fitting performance than the Gauss function in all tablet samples.

The R_{wp} values were larger than the result of crystal structure analysis using single crystal. It is known that R_{wp} obtained from pattern-fitting using powder diffraction data is strongly dependent on the signal-to-noise ratio of the data (Sonneveld and Visser, 1975). When the background levels are low enough for the Bragg diffraction, R_{wp} is calculated to be larger. Because the background noise was very low in the observed diffraction patterns, the fitting between observed and calculated intensity was considered to be satisfactory and the fitting parameters were optimized significantly, as shown in Fig. 1 and Table 3.

As the 95% confidence interval of each optimized parameter obtained by three independent X-ray measurements was almost closed, the results of the analysis is considered to show the characteristics of the crystals in the tablets.

Fig. 2 shows the observed intensities and calculated intensities of benzoic acid tablet (compression pressure: 2250 kg/cm^2) using the March function for correction of preferred orientation of the crystallites. The (0 0 1) plane was selected for preferred orientation plane by a trial and error approach. This plane is one of the planes with lower interaction energy (Fukuoka et al., 1993c). We reported that when the pattern-fitting was carried out using lower interaction plane in the crystal as the preferred orientation plane, the fit between observed and calculated intensities was found to be better (Fukuoka et al., 1993b).

The fit between the observed and calculated intensities was considered to be satisfactory using either the Gauss function ($R_{wp} = 0.143$, $R_p = 0.030$) or the March function ($R_{wp} = 0.138$, $R_p = 0.030$), and the fitted results from the March function was better than the Gauss function in all tablet samples.

There were no significant changes in crystal lattice parameters (a, b, c and β) with compression pressure in both acetaminophen and benzoic acid samples.

3.2. Preferred orientation of crystallites in acetaminophen and benzoic acid tablets

From the magnitude of optimized preferred orientation parameter (α), the modification of diffraction

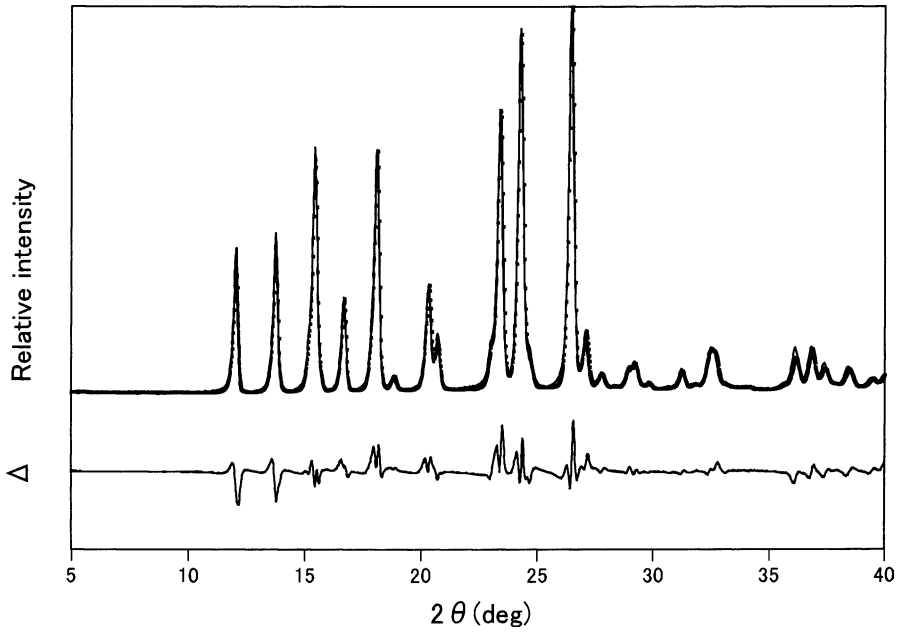

Fig. 1. Observed and calculated X-ray diffraction intensities of acetaminophen tablet using the Gauss function as preferred orientation function. Δ shows the difference between observed and calculated intensities. Compression pressure: 2250 kg/cm^2, $R_{wp} = 0.132$, $R_p = 0.030$.

intensity by preferred orientation of crystallites was investigated. Figs. 3 and 4 show the modification of diffraction intensity by preferred orientation of acetaminophen crystallites estimated by the Gauss and the March functions, respectively.

If the crystallites have no preferred orientation, α should be optimized to be 1 (March function) or to be 0 (Gauss function) and no modification of intensity with ϕ. In the acetaminophen powder, α was optimized to be 0.9882 (March function) and 0.0621 (Gauss function), indicating little preferred orientation. In the tablets samples, the modification of diffraction intensity from crystallites with ϕ were larger rather than powder samples and the modification increased with increasing compression pressure.

Table 3
Result of pattern-fitting of acetaminophen tablet

Fitting parameter	Optimized value	95% CI
a	12.93	12.92–12.93
b	9.412	9.410–9.414
c	7.128	7.127–7.130
β	115.8	115.7–115.8
U	1.235	0.876–1.594
V	−0.2880	−0.4232 to −0.1528
W	0.06056	0.04844–0.07268
K	0.01536	0.01520–0.01551
A	1.048	0.982–1.114
α	1.065	1.057–1.073

Compression pressure: 2250 kg/cm^2.

Figs. 5 and 6 show the modification of diffraction intensity by preferred orientation of benzoic acid crystallites with angle ϕ estimated by the March and the Gauss functions, respectively.

In the powder sample, α was optimized to be 1.0039 (March function) and −0.0244 (Gauss function), indicating little preferred orientation. The diffraction intensities from tablet samples were modified by the preferred orientation of crystallites and the preferred orientation parameter (α) was increased with increasing the compression pressure.

These results indicate that the crystallites of acetaminophen and benzoic acid would be oriented gradually with an increase in compression pressure. The modification profile of diffraction intensity with ϕ was different between the Gauss function and March function at high ϕ values as shown in Figs. 3–6.

In the original report by Rietveld, the preferred orientation of crystallites was corrected by the Gauss function (Rietveld, 1969). However, in order to

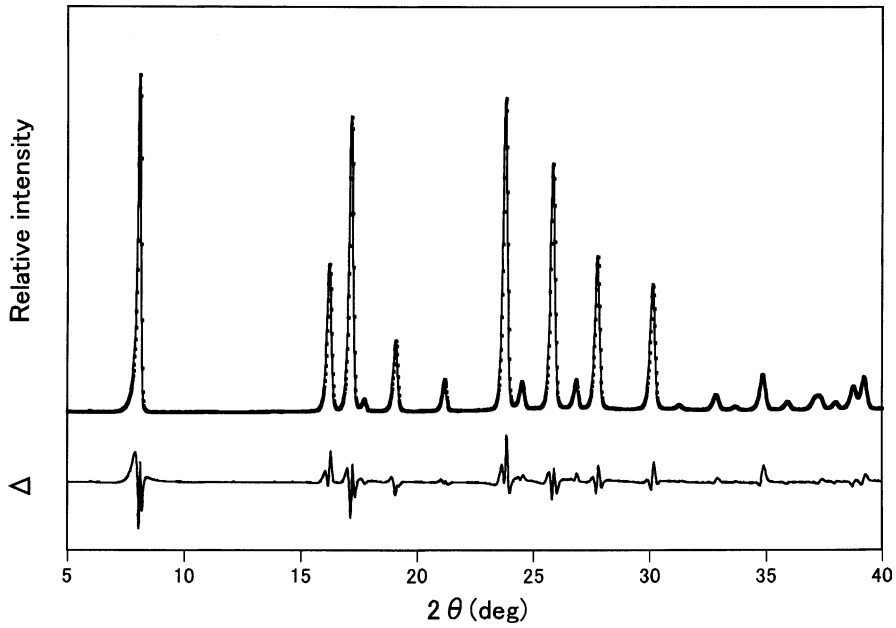

Fig. 2. Observed and calculated X-ray diffraction intensities of benzoic acid tablet using the March function as preferred orientation function. Δ shows the difference between observed and calculated intensities. Compression pressure: 2250 kg/cm^2, $R_{wp} = 0.138$, $R_p = 0.030$.

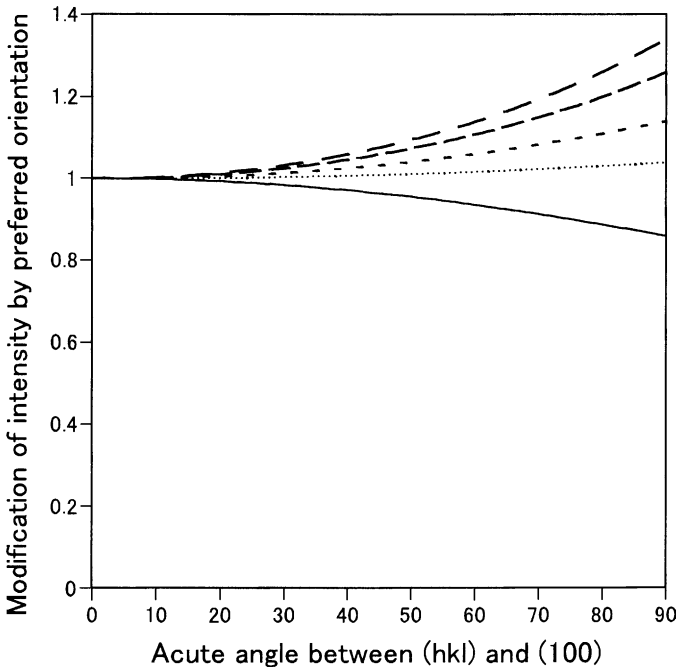

Fig. 3. Modification of diffraction intensities by preferred orientation of crystallites assuming the Gauss distribution of crystallite orientation in acetaminophen tablets: (—), powder ($\alpha = 0.0621$); (· · ·), compression pressure: 375 kg/cm^2 ($\alpha = -0.0158$); (· · ·), compression pressure: 750 kg/cm^2 ($\alpha = -0.0523$); (- - -), compression pressure: 1500 kg/cm^2 ($\alpha = -0.0939$); (— — —), compression pressure: 2250 kg/cm^2 ($\alpha = -0.1192$).

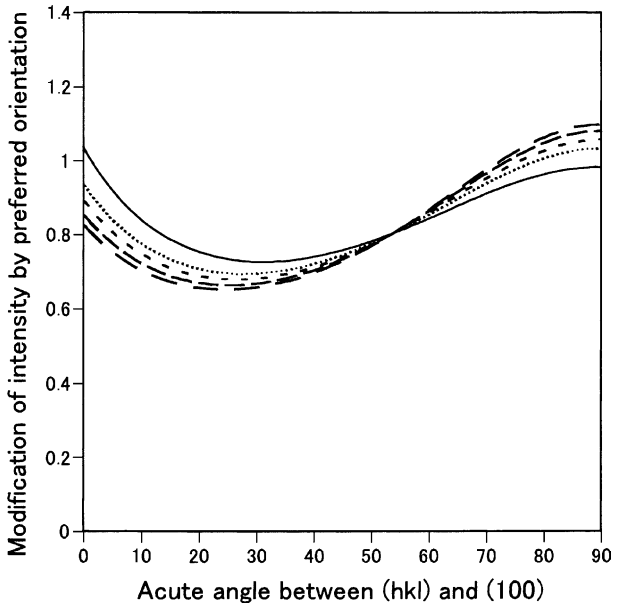

Fig. 4. Modification of diffraction intensities by preferred orientation of crystallites assuming the March distribution of crystallite orientation in acetaminophen tablets: (—), powder ($\alpha = 0.9882$); (· · ·), compression pressure: 375 kg/cm^2 ($\alpha = 1.0225$); (· · ·), compression pressure: 750 kg/cm^2 ($\alpha = 1.0381$); (- - -), compression pressure: 1500 kg/cm^2 ($\alpha = 1.0536$); (— — —), compression pressure: 2250 kg/cm^2 ($\alpha = 1.0651$).

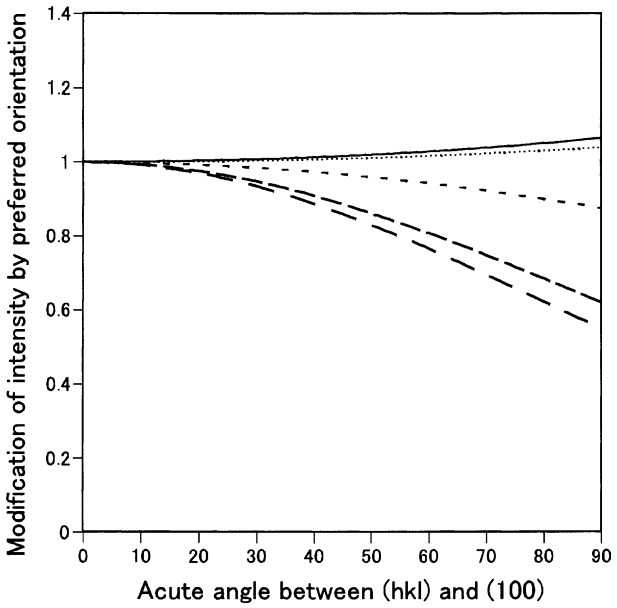

Fig. 5. Modification of diffraction intensities by preferred orientation of crystallites assuming the Gauss distribution of crystallite orientation in benzoic acid tablets: (—), powder ($\alpha = -0.0244$); (· · ·), compression pressure: 375 kg/cm^2 ($\alpha = -0.0158$); (· · ·), compression pressure: 750 kg/cm^2 ($\alpha = 0.0531$); (- - -), compression pressure: 1500 kg/cm^2 ($\alpha = 0.1939$); (— — —), compression pressure: 2250 kg/cm^2 ($\alpha = 0.24326$).

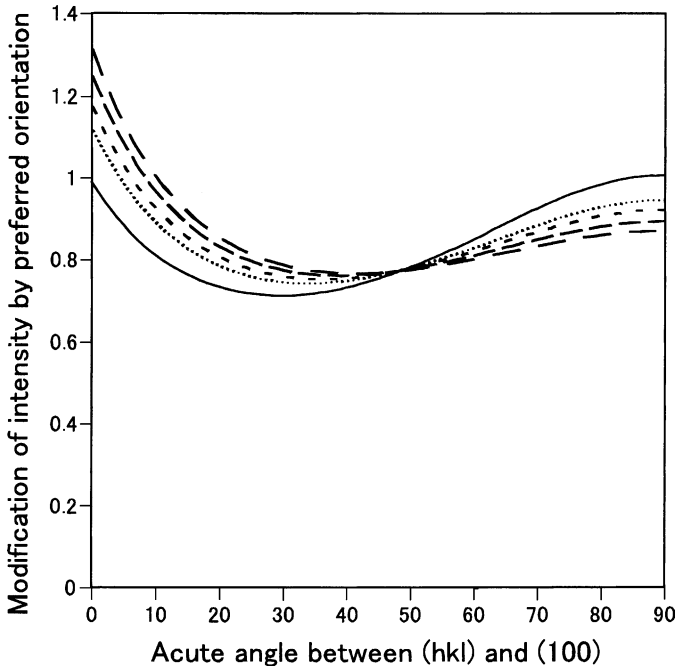

Fig. 6. Modification of diffraction intensities by preferred orientation of crystallites assuming the March distribution of crystallite orientation in benzoic acid tablets: (—), powder ($\alpha = 1.0039$); (· · ·), compression pressure: 375 kg/cm^2 ($\alpha = 0.9624$); (· · ·), compression pressure: 750 kg/cm^2 ($\alpha = 0.9474$); (- - -), compression pressure: 1500 kg/cm^2 ($\alpha = 0.9284$); (— — —), compression pressure: 2250 kg/cm^2 ($\alpha = 0.9126$).

improve the fitting performance, the March function is now widely used in the Rietveld refinements (McCusker et al., 1999). The March function is known to closely approximate the pole-density profile of axially symmetric textures called "fiber texture" (Howard and Kisi, 2000) and describes the pole density profile produced by rigid body rotation of inequant crystallites on axially symmetrical compression or expansion (Dollase, 1986).

Better fits were obtained when the March function was used for the preferred orientation function. These results suggest that the crystallites of acetaminophen and benzoic acid have a fiber texture along the compression axis in the tablet. Acetaminophen molecules link by hydrogen bond with each other and form a plated sheet parallel to *ac* plane in the crystal. The sheet are stacked along *b* axis (Haisa et al., 1976). On the other hand, two benzoic acid molecules bound with hydrogen bond and have coplanar structure in the crystal. The dimmers arranged form stacking structure along $(1\,0\,\bar{2})$ and $(0\,0\,1)$ (Bruno and Randaccio, 1980). These stacking structure would facilitate the movement of molecules along particular direction, and produce a texture structure during compression.

The modification of diffraction intensity by preferred orientation in acetaminophen tablets was smaller than that in benzoic acid tablets. This would result that acetaminophen crystal is brittle and consolidates by fragmentation of the crystals during compression.

There are some limitations on discussion for anisotropic distortion of crystals in the tablet by pattern-fitting procedure. In the symmetrical reflection geometry, the diffraction lines are obtained only from the crystal planes parallel to the upper surface of the tablet. The strength of preferred orientation determined by the pattern-fitting is considered to estimate from the modification of diffraction intensities from the crystal planes parallel to the upper surface of the tablet.

3.3. Change in peak-width with compression pressure

Figs. 7 and 8 show the change in FWHM of the diffraction peaks of acetaminophen and benzoic acid

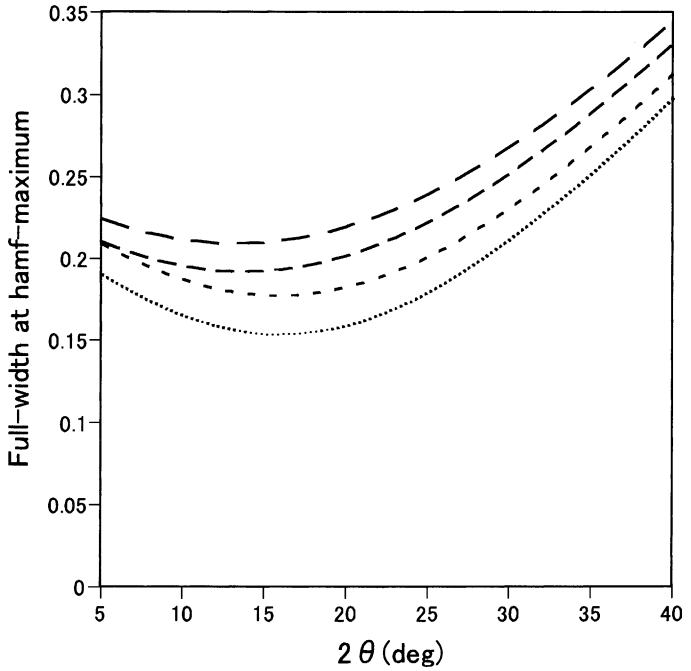

Fig. 7. Change in FWHM of acetaminophen tablets with compression pressure: (···), 375 kg/cm^2; (···), 750 kg/cm^2; (---), 1500 kg/cm^2; (– – –), 2250 kg/cm^2.

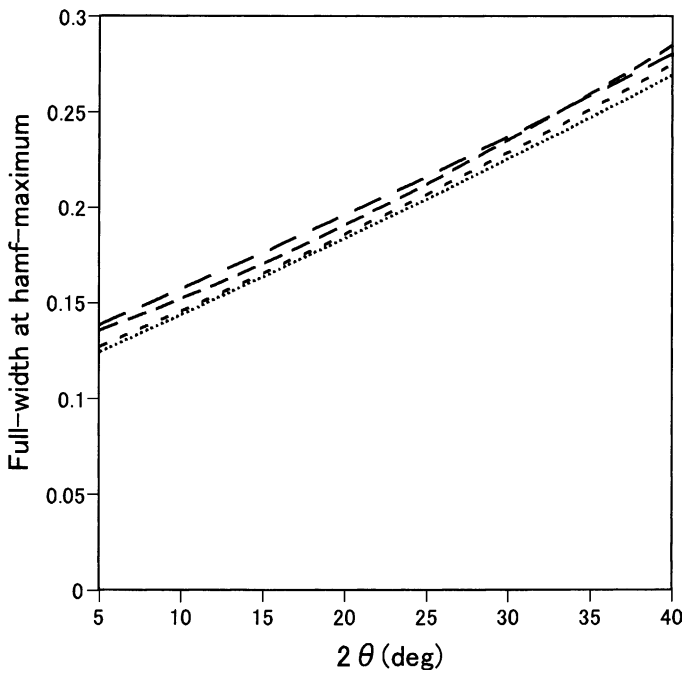

Fig. 8. Change of FWHM of benzoic acid tablets with compression pressure: (···), 375 kg/cm^2; (···), 750 kg/cm^2; (---), 1500 kg/cm^2; (– – –), 2250 kg/cm^2.

tablets with scattering angle, calculated from optimized *U*, *V* and *W*. The FWHM of powder sample were much broader than the tablet samples (data not shown). Since the crystals were packed loosely in the powder sample, the X-ray could penetrate more deeply into the sample than into the compressed sample. The penetration effect causes the peak width to be broad, thus, the peak width of the powder sample was broader than compressed samples.

Although the FWHM of acetaminophen broadened with an increase in compression pressure, the FWHM of benzoic acid scarcely broadened.

In size–strain analysis, a decrease of crystallites and increase of lattice distortion are the causes of a broadening diffraction peak. A decrease of crystallite size is cause the broadening independent of the scattering angle. Also, the lattice strain produced by plastic deformation and other causes results in an increase in peak width with an increase in scattering angle (Buchanan and Miller, 1966; Scardi and Leoni, 1999).

The scattering angle independent broadening of FWHM with compression pressure of acetaminophen suggests that the decrease in the size of the crystallites would occur with compression, but without an increase in lattice strain. Acetaminophen crystal was considered to be brittle and consolidated with fragmentation of crystals during compression without plastic strain.

Little change in FWHM with compression pressure of benzoic acid would indicate that there were a little decrease in crystallite size and no increase in lattice strain with compression. This result suggest that benzoic acid crystals are consolidated with rearrangement of molecules during compression and also show preferred orientation of crystallites in the tablet.

Acetaminophen molecules form hydrogen bond network parallel to *ac* plane in the crystal (Haisa et al., 1976). Because this network would be broken during compression, acetaminophen crystals *would be brittle*. On the other hand, two benzoic acid molecules form strong hydrogen bonds and the dimmers arrange with forming two stacking structure in the crystal (Bruno and Randaccio, 1980). Because of two stacking planes, there would be some space to rearrangement of benzoic acid dimmers during compression. Packing of molecules in the crystal lattice would affect the mechanical properties of the crystals during compression.

4. Conclusion

A pattern-fitting procedure made it possible to characterize the monoclinic crystals in the tablets using X-ray powder diffraction data. In preferred orientation function, the March function showed better performance than the Gauss function for correcting the preferred orientation of crystallites. These results suggest that the crystallites in the tablets have fiber texture with a compression axis. From the analysis of FWHM, acetaminophen and benzoic acid crystals are considered to be a material consolidation by fragmentation of crystals and by plastic deformation with rearrangement of molecules during compression, respectively.

The characteristics of the crystals and/or crystallites in the tablet can be evaluated from the optimized parameters obtained by pattern-fitting using X-ray powder diffraction data. Pattern-fitting is the superior method for characterizing the crystalline drugs in the tablet.

References

Bruno, G., Randaccio, L., 1980. A refinement of the benzoic acid structure at room temperature. Acta Crystallogr. B36, 1711–1712.

Buchanan, D.R., Miller, R.L., 1966. X-ray broadening in isotactic polystyrene. J. Appl. Phys. 37, 4003–4012.

Coleman, T.F., Li, Y., 1994. On the convergence of reflective Newton methods for large-scale nonlinear minimization subject to bounds. Math. Programming 67, 189–224.

Coleman, T.F., Li, Y., 1996. An interior region approach for nonlinear minimization subject to bounds. SIAM J. Optimization 6, 418–445.

Dollase, W.A., 1986. Correction of intensities for preferred orientation in powder diffractometry: application of the March model. J. Appl. Crystallogr. 19, 267–272.

Fukuoka, E., Terada, K., Makita, M., Yamamura, S., 1993a. Preferred orientation of crystallites in tablets. V. Pattern-fitting procedure for the determination of strength of preferred orientation of crystallites. Chem. Pharm. Bull. 41, 1636–1639.

Fukuoka, E., Makita, M., Yamamura, S., 1993b. Pattern fitting procedure for the characterization of crystals and/or crystallites in tablets. Chem. Pharm. Bull. 41, 2166–2171.

Fukuoka, E., Makita, M., Yamamura, S., 1993c. Preferred orientation of crystallites in tablets. IV. Features of the preferred orientation plane. Chem. Pharm. Bull. 41, 1284–1289.

Haisa, M., Kashino, S., Kawai, R., Maeda, H., 1976. The monoclinic form of *p*-hydroxyacetanilide. Acta Crystllogr. B32, 1283–1285.

Howard, C.J., Kisi, E.H., 2000. Preferred orientation in Debye–Scherrer geometry. Interpretation of the March coefficient. J. Appl. Crystallogr. 33, 1434–1435.

Kariuki, B.M., Psallidas, K., Harris, K.D.M., Johnston, R.L., Lancaster, R.W., Staniforth, S.E., Cooper, S.M., 1999. Structure determination of a steroid directly from powder diffraction data. Chem. Commun. (Cambridge) 17, 1677–1678.

McCusker, L.B., Von Dreele, R.B., Cox, D.E., Louer, D., Scardi, P., 1999. Rietveld refinement guidelines. J. Appl. Crystallogr. 32, 36–50.

Orlhac, X., Fillet, C., Deniard, P., Dulac, A.M., Brec, R., 2001. Determination of the crystallized fractions of a largely amorphous multiphase material by the Rietveld method. J. Appl. Crystallogr. 34, 114–118.

Pratapa, A., O'Connor, B., Hunter, B., 2001. A comparative study of single-line and Rietveld strain–size evaluation procedures using MgO ceramics. J. Appl. Crystallogr. 35, 155–162.

Rietveld, H.M., 1969. A profile refinement method for nuclear and magnetic structure. J. Appl. Crystallogr. 2, 65–71.

Scardi, P., Leoni, M., 1999. Fourier modeling of the anisotropic line broadening of X-ray diffraction profiles due to line and plane lattice defects. J. Appl. Crystallogr. 32, 671–682.

Sonneveld, E.J., Visser, J.W., 1975. Automatic collection of powder data from photographs. J. Appl. Crystallogr. 8, 1–7.

Young, R.A., 1993. Introduction to the Rietveld Method in the "Rietveld Method". Oxford University Press, Oxford, pp. 1–38.