

Pattern Fitting Procedure for the Characterization of Crystals and/or Crystallites in Tablets^{1,2)}

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A pattern fitting procedure for the characterization of crystals and/or crystallites in tablets using X-ray powder diffraction data has been described. Observed X-ray diffraction intensities were fitted to the analytic expression, and the fitting parameters, such as the lattice parameters, the peak-width parameters and the preferred orientation parameter(s), were optimized by a non-linear least-squares procedure. Orthorhombic crystals of isoniazid and D-mannitol were used for the samples.

Lattice parameters were found to increase slightly with an increase in compression pressure. In isoniazid, the peak-width broadened with an increase of compression pressure, and a marked broadening at a relatively high scattering angle was observed. It is indicated that both a decrease of the crystallite size and the lattice disorder occurred simultaneously with compression. In D-mannitol, the peak-width broadened with compression and the broadening was independent of the scattering angle. It is indicated that although the crystallite size decreased, the lattice disorder did not increase with compression. The strength of the preferred orientation of the crystallites increased with compression in both crystals.

Keywords pattern fitting; X-ray powder diffraction; tablets; lattice parameter; lattice disorder; preferred orientation

We reported that the crystallites in tablets showed a preferred orientation,^{1a-c)} and the features of the preferred orientation planes were investigated by means of molecular orbital calculations.^{1d)} In the preceding paper,^{1e)} a pattern fitting procedure was presented to evaluate the strength of preferred orientation of crystallites in tablets.

In the present paper, the pattern fitting procedure was applied to characterize the crystals and/or crystallites in tablets. Variations of the lattice parameters of the crystal, the broadening of diffraction peaks and the strength of the preferred orientation with compression were investigated, and compression behaviors of the crystals were discussed.

Experimental

Materials Isoniazid (JP grade, Daiichi Pharmaceuticals Co., Ltd.), D-(+)-mannitol, β form (reagent grade, Nakarai Chemicals Co., Ltd.) and LiF (reagent grade, Wako Pure Chemicals Co., Ltd.) were used without further purification. The powders, passed through a 250 mesh (63 μ m) sieve, were used. Because LiF crystal has no diffraction peak between 5–35° (2 θ), LiF powder was used as an internal standard substance. Mixed powders of the samples and LiF (4:1, w/w) were used for the sample powders. The crystal structure of isoniazid, D-mannitol and LiF have been determined previously (isoniazid,³⁾ D-mannitol⁴⁾ and LiF⁵⁾).

Tableting Five hundred mg of the sample powder was compressed by the direct compression method using the sample plate described in the preceding paper.^{1e)}

X-Ray Diffraction (Powder Method) A Geigerflex RAD type diffractometer (Rigaku Denki Co., Ltd.) was used, and symmetrical-reflection geometry was employed. The X-ray source was CuK α , and the diffracted beam was monochromated using a bent-graphite monochromator. Measurement conditions were the same as described in the preceding paper.^{1e)} Systematic errors, caused by slit width, axial divergence and so on, to the diffraction angle,⁶⁾ were not calibrated. Absorption of X-ray by the specimen, and the contribution of CuK α_2 to the diffraction intensity, were ignored in the calculation.

Pattern Fitting Optimization of the fitting parameters was carried out by the Marquardt and the dumping Gauss-Newton methods using the BASIC program developed in our laboratory.

Results and Discussion

Equations Used in the Pattern Fitting Procedure In the preceding paper,^{1e)} the strength of the preferred orientation of crystallites was evaluated by the pattern fitting procedure.

Usually, Eq. 1 is used for the pattern fitting procedure⁷⁾:

$$y(2\theta) = K \sum_i |F_i|^2 m_i Lp_i G(2\theta - 2\theta_i) P_i + y_b(2\theta) \quad (1)$$

where $y(2\theta)$ is the observed scattering intensity at 2θ , K is the scale factor, F is the crystal structure factor, m is the multiplicity factor, Lp is the Lorentz-polarization factor, P is the preferred orientation function, G is the peak shape function (profile function), θ_i is the Bragg angle of i -th reflection and $y_b(2\theta)$ is the background intensity.

In the Rietveld method,⁷⁾ the crystal structure factors are calculated as a function of the structure parameters, while in the present method they are obtained from the refined crystal structure model.

In the present investigation, the following equations were employed in order to determine the lattice parameters and to analyze the broadening of the diffraction peak.

(1) Lattice parameters were treated as the fitting parameters, and the Bragg angle was calculated from the lattice parameters and the indices of Bragg reflection using Eq. 2⁸⁾:

$$\theta_i = \sin^{-1} (2/\lambda \sqrt{h^2/a^2 + k^2/b^2 + l^2/c^2}) \quad (2)$$

where a , b and c are the lattice parameters and h , k and l are the indices of the Bragg reflection. λ is the wavelength of the X-ray.

(2) Full-width at half-maximum (FWHM) of the diffraction peak was defined as a function of the Bragg angle using Eq. 3^{7,9)}:

$$H_i^2 = U \tan^2 \theta_i + V \tan \theta_i + W \quad (3)$$

where U , V and W are the peak-width parameters (fitting parameters).

(3) The modified Lorentzian function¹⁰⁾ corrected for peak asymmetry was used for the profile function (Eq. 4):

$$G = 2sc_{mi}^{0.5} / [\pi H_i \{1 + c_{mi}(2\theta - 2\theta_i)^2 / H_i^2\}^2] \quad (4)$$

where s is the function for the correction of the peak

asymmetry (Eq. 5).⁷⁾ c_{m1} is a normalization constant for the modified Lorentzian function:

$$s = 1 - A \operatorname{sign}(2\theta - 2\theta_i)(2\theta - 2\theta_i)^2 / \tan \theta_i \quad (5)$$

where A is the asymmetric parameter (fitting parameter).

(4) Equation 6 was used for the preferred orientation function, in which one or more directions were selected for the preferred orientation axis:

$$P = \sum_k \exp(-\alpha_k \phi_{ki}^2) \quad (6)$$

where k is the number of the preferred orientation axis, α is the preferred orientation parameter (fitting parameter), and ϕ is the acute angle between the preferred orientation

TABLE I. Variable Parameters Used in Pattern Fitting Procedure

Parameter	Symbol	Number
Lattice parameters	a, b, c	3
FWHM ^{a)} parameters	U, V, W	3
Asymmetric parameter	A	1
Scale factor	K	1
Preferred orientation parameter	α	1 or 2
Background parameters		6

a) Full-width at half-maximum.

TABLE II. Structural Parameters of Isoniazid Crystal Used in the Pattern Fitting Procedure

$hkl^a)$	$2\theta_{hkl}^b)$	$F^c)$	$m^d)$	$I^e)$	$\phi_{100}^f)$	$\phi_{010}^g)$
110	9.77	6.1	4	0.3	0.92	0.65
200	11.87	28.6	2	3.3	0.00	1.57
210	14.87	24.4	4	4.9	0.58	0.99
020	15.55	48.4	2	9.6	1.57	0.00
120	16.65	52.1	4	22.1	1.21	0.37
310	19.48	28.9	4	6.8	0.41	1.16
220	19.60	15.3	4	1.9	0.92	0.65
320	23.75	5.9	4	0.3	0.72	0.85
400	23.86	34.6	2	4.9	0.00	1.57
101	23.96	31.5	4	8.1	1.32	1.57
130	24.17	6.4	4	0.3	1.32	0.25
011	24.49	0.8	4	0.0	1.57	1.25
410	25.13	33.1	4	8.9	0.32	1.25
111	25.22	57.6	8	54.1	1.33	1.26
201	26.13	68.0	4	37.7	1.10	1.57
230	26.32	14.1	4	1.6	1.10	0.47
211	27.29	78.3	8	100.0	1.12	1.28
021	28.04	7.6	4	0.5	1.57	0.98
420	28.61	30.9	4	7.8	0.58	0.99
121	28.69	25.9	8	10.9	1.36	0.99
301	29.41	38.5	4	12.1	0.91	1.57
330	29.59	12.6	4	1.3	0.92	0.65
311	30.46	24.8	8	10.0	0.94	1.31
221	30.55	7.4	8	0.9	1.17	1.03
510	30.99	2.2	4	0.0	0.26	1.31
040	31.39	0.3	2	0.0	1.57	0.00
140	31.97	35.8	4	10.5	1.38	0.19
031	33.19	2.5	4	0.1	1.57	0.78
321	33.43	6.7	8	0.7	1.00	1.08
401	33.52	20.9	4	3.6	0.77	1.57
240	33.66	9.4	4	0.7	1.21	0.37
430	33.67	7.3	4	0.4	0.78	0.79
131	33.75	8.6	8	1.2	1.39	0.80
520	33.92	20.3	4	3.4	0.48	1.09

a) Diffracting plane indices; b) diffraction angle; c) crystal structure factor; d) multiplicity factor; e) relative intensity ($F^2 \cdot m$); f) angle between reciprocal lattice vector and the normal to the (100) plane in radian; g) angle between reciprocal lattice vector and the normal to the (010) plane in radian.

plane (normal to preferred orientation axis) and i -th (hkl) plane in the crystal.

(5) Background intensities were approximated by the 5th order function of 2θ . The Lorentz factor was calculated using θ_i (Eq. 2), and the polarization effect of an X-ray was corrected using an equation reported previously in literature.¹¹⁾

The variable parameters (fitting parameters) used in the pattern fitting were listed in Table I.

This procedure is similar to the Pawley method,¹²⁾ in which the diffraction intensities were treated as independent parameters and the lattice parameters could be refined by the pattern fitting. In the present method, the diffraction intensities were calculated from the crystal structure factors; therefore, it is possible to evaluate the strength of the preferred orientation of the crystallites from the modification of diffraction intensities^{1e)} as well as to evaluate lattice parameters by the pattern fitting.

Examples of Pattern Fitting The structure parameters of isoniazid and D-mannitol used in the pattern fitting are summarized in Tables II and III. The intensity data of all reflections observed in 5–35° (2θ) were used in the calculation. It was assumed that the crystal system and the

TABLE III. Structural Parameters of D-Mannitol Crystal Used in the Pattern Fitting Procedure

$hkl^a)$	$2\theta_{hkl}^b)$	$F^c)$	$m^d)$	$I^e)$	$\phi_{120}^f)$
020	10.48	20.7	2	2.4	0.77
110	11.47	10.2	4	1.2	0.32
120	14.65	41.4	4	19.2	0.00
011	16.79	38.6	4	16.7	1.34
130	18.80	71.4	4	57.2	0.20
101	18.96	8.9	4	0.9	1.18
021	19.12	20.7	4	4.8	1.17
111	19.68	11.2	8	2.8	0.98
200	20.48	75.4	2	31.9	0.80
040	21.06	24.0	2	3.2	0.77
210	21.16	68.1	4	52.0	0.55
121	21.71	33.6	8	25.3	0.83
031	22.48	9.8	4	1.1	1.04
220	23.06	3.3	4	0.1	0.32
140	23.45	94.4	4	100.0	0.32
131	24.74	28.9	8	18.7	0.73
230	25.94	38.1	4	16.3	0.14
201	26.06	32.8	4	12.1	0.99
041	26.52	5.2	4	0.3	0.96
211	26.60	22.9	8	11.8	0.82
221	28.16	26.5	8	15.8	0.68
150	28.38	41.2	4	19.0	0.40
240	29.54	72.3	4	58.7	0.00
231	30.60	16.6	8	6.2	0.57
310	31.40	33.8	4	12.8	0.63
060	31.82	51.1	2	14.7	0.77
002	32.20	18.6	2	1.9	1.57
012	32.64	8.9	4	0.9	1.45
151	32.71	4.3	8	0.4	0.64
320	32.75	43.2	4	20.9	0.47
160	33.49	27.2	4	8.3	0.46
250	33.65	60.8	4	41.5	0.11
241	33.75	15.3	8	5.3	0.50
102	33.86	52.5	4	30.9	1.36
022	33.95	20.7	4	4.8	1.34
112	34.29	52.5	8	61.9	1.24
330	34.90	9.6	4	1.0	0.32

a) Diffracting plane indices; b) diffraction angle; c) crystal structure factor; d) multiplicity factor; e) relative intensity ($F^2 \cdot m$); f) angle between reciprocal lattice vector and the normal to the (120) plane in radian.

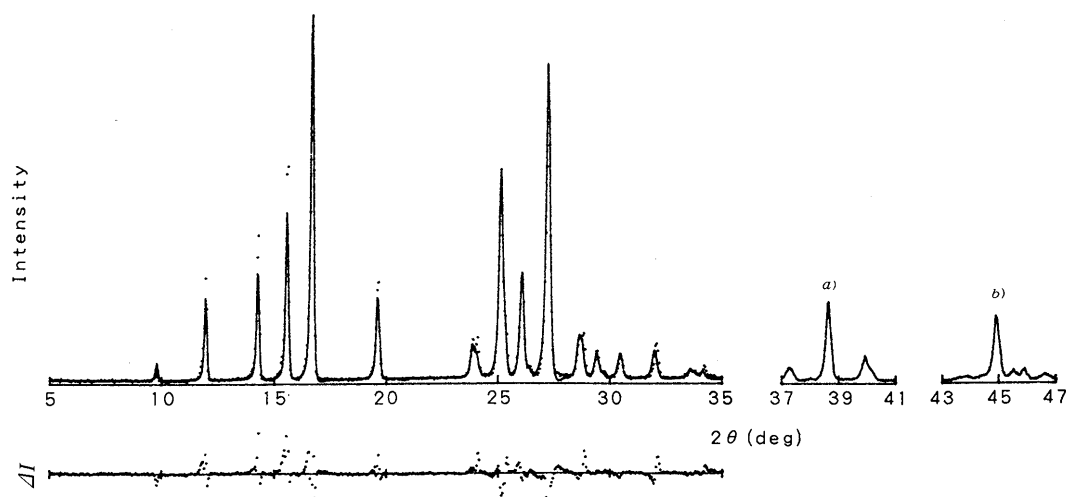


Fig. 1. X-Ray Diffraction Intensities and the Simulation Pattern of an Isoniazid Tablet Compressed under 375 kg/cm². ΔI shows the difference of observed and calculated intensities. *a)* and *b)* indicate the 111 and 002 reflections of LiF, respectively.

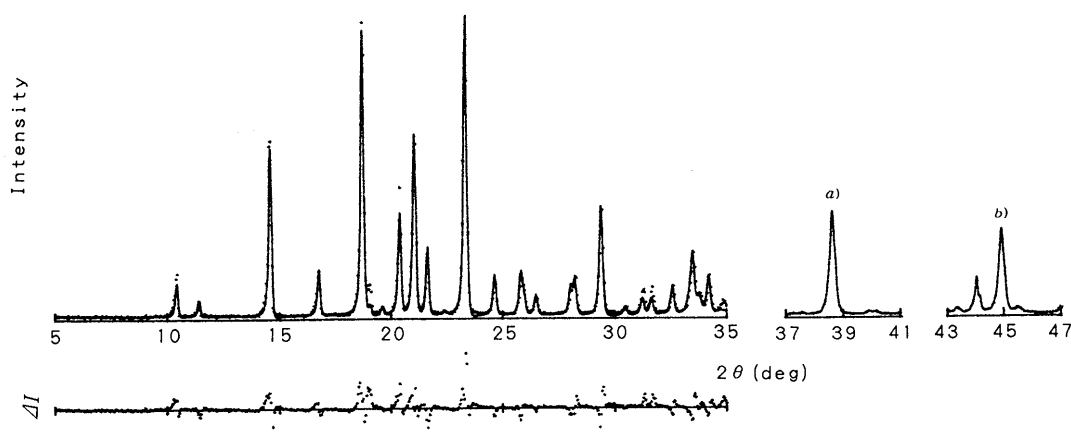


Fig. 2. X-Ray diffraction Intensities and the Simulation Pattern of a D-Mannitol Tablet Compressed under 375 kg/cm². ΔI shows the difference of observed and calculated intensities. *a)* and *b)* indicate the 111 and 002 reflections of LiF, respectively.

magnitude of the crystal structure factors did not change as a result of compression. The (100) and (010) planes of isoniazid, and the (120) plane of D-mannitol were selected as preferred orientation planes. These planes were considered to have relatively low interaction energy in view of the molecular packing in the crystal lattice. When the pattern fitting was carried out using these planes as the preferred orientation planes, the lowest weighted reliability index was produced.^{1e)} Figures 1 and 2 show the X-ray diffraction intensities and the simulation patterns of isoniazid and D-mannitol tablets, respectively. The peaks in the vicinity of $2\theta = 38.6^\circ$ and 45.0° are 111 and 002 reflections of LiF crystals, respectively. Since the LiF crystal is cubic system, the lattice parameter *a* was calculated from the diffraction angle of $2\theta_{111}$ and $2\theta_{002}$ determined by profile fitting using an asymmetric modified Lorentzian function. When only LiF powder was compressed under various pressures, the lattice parameter *a* did not change. So, the deviation of sample face from the focusing condition of the diffractometer was monitored by *a* of the LiF crystal.

Examples of optimized fitting parameters for isoniazid

TABLE IV. Optimized Parameters for Isoniazid Tablet^{a)} Obtained by Pattern Fitting Procedure

Parameter	Optimized value
<i>a</i>	14.800 (3)
<i>b</i>	11.393 (2)
<i>c</i>	3.951 (1)
<i>U</i>	0.86 (20)
<i>V</i>	-0.10 (4)
<i>W</i>	0.014 (3)
<i>A</i>	2.2 (2)
$\alpha(100)^b$	0.49 (3)
$\alpha(010)^c$	0.38 (2)
R_{wp}^d	0.168

^{a)} Compression pressure; 375 kg/cm²; ^{b)} preferred orientation plane is (100); ^{c)} preferred orientation plane is (010); ^{d)} $R_{wp} = [\sum w_i (y_{obs} - y_{cal})^2 / \sum w_i y_{obs}^2]^{1/2}$.

and D-mannitol were summarized in Tables IV and V, respectively. Fitting between observed and calculated intensities was considered to be satisfactory in view of the final R_{wp} values.^{1e)}

TABLE V. Optimized Parameters for D-Mannitol Tablet^{a)} Obtained by Pattern Fitting Procedure

Parameter	Optimized value
<i>a</i>	8.701 (1)
<i>b</i>	16.946 (2)
<i>c</i>	5.571 (2)
<i>U</i>	-0.03 (2)
<i>V</i>	0.12 (6)
<i>W</i>	-0.002 (1)
<i>A</i>	2.4 (2)
$\alpha(120)^b$	1.57 (7)
R_{wp}^c	0.198

a) Compression pressure; 375 kg/cm²; b) preferred orientation plane is (120); c) $R_{wp} = [\sum w_i(y_{obs} - y_{cal})^2 / \sum w_i y_{obs}^2]^{1/2}$

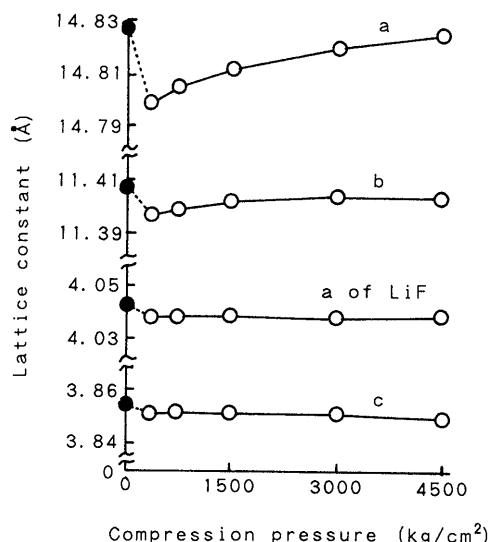


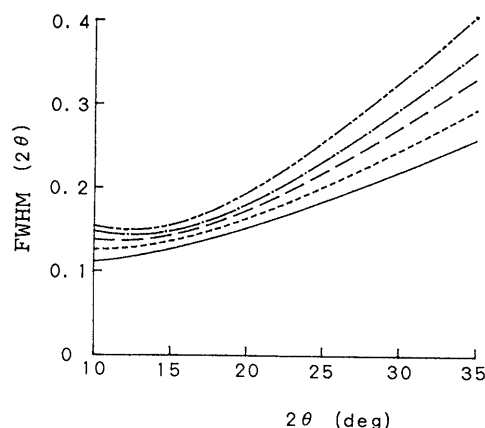
Fig. 3. Variation of Lattice Parameters of Isoniazid Crystals with Compression

Data points indicate the mean values for 3 experiments. Closed symbols represent the data for the powder. *a* of LiF shows the mean value of *a* calculated from $2\theta_{111}$ and $2\theta_{002}$.

Variation of the Optimized Fitting Parameters with Compression Isoniazid: Isoniazid tablets were prepared under various compression pressures, and the X-ray diffraction intensities were measured. The observed diffraction intensities were fitted to Eq. 1 and the fitting parameters were optimized. Figure 3 shows the variations of the lattice parameters with compression pressure. Triplicates agreed at a variance of less than 0.004 from the mean.

The lattice parameters of isoniazid and LiF crystals of a space group: $P2_12_12_1$ and $a=14.915 \text{ Å}$, $b=11.400 \text{ Å}$, $c=3.835 \text{ Å}$.³⁾ The lattice parameters optimized by the pattern fitting were slightly different from the values in the literature.³⁾ One reason could be that the scattering angle was not calibrated for systematic errors of the diffractometer.

The crystal structure of isoniazid had been reported as the powdered specimen were optimized as larger values than those in the compressed specimen. Since the crystals were packed loosely in the powdered specimen, the X-ray could penetrate more deeply into the powdered specimen than into the compressed specimens. The penetration effect shifts the diffraction line to a lower scattering angle,⁶⁾ thus the

Fig. 4. Increase in FWHM with 2θ for Isoniazid Tablets

Compression pressure: —, 375 kg/cm²; ----, 750 kg/cm²; ····, 1500 kg/cm²; — · —, 3000 kg/cm²; — — —, 4500 kg/cm².

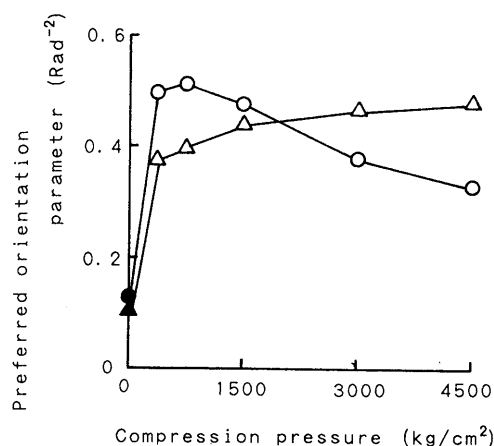


Fig. 5. Variation of Preferred Orientation Parameters of Isoniazid Crystallites in Tablets with Compression Pressure

Preferred orientation plane: ○, (100) plane; △, (010) plane. Closed symbols represent the data for the powders.

lattice parameters of the powdered specimen would be optimized as a larger value than those for the tablets. Because the lattice parameter *a* of LiF crystal did not change with compression pressure, the penetration effect would be negligible for the tablets. As shown in Fig. 3, although the value of *a* of the LiF crystal in a tablet was constant, the lattice parameters *a* and *b* of the isoniazid crystal increased with an increase in compression pressure. This result indicates that there was no apparent change in the lattice parameters of isoniazid crystal with compression. Thus, it was found that the lattice parameters of isoniazid crystals varied gradually with compression.

Figure 4 shows the increase of the FWHM of the diffraction peaks with scattering angles calculated from optimized *U*, *V* and *W* in Eq. 3. The FWHM for the powdered specimen was almost the same as that for the tablet compressed under 375 kg/cm².

The FWHM broadened with an increase in compression pressure, and a marked broadening at a relatively high scattering angle was observed. A broadening of the diffraction peak is affected by both the crystallite size and the lattice disorder.⁶⁾

In paracrystal theory, a crystallite, less than about 1000 Å, is the cause of a broadening of diffraction peaks, and the

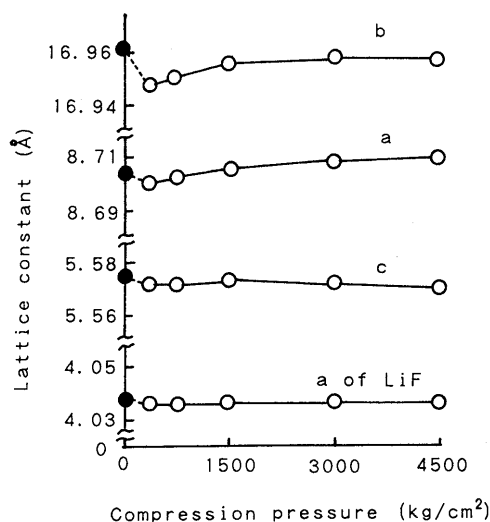


Fig. 6. Variation of Lattice Parameters of D-Mannitol Crystals with Compression

Data points indicate the mean value for 3 experiments. Closed symbols represent the data for the powders. a of LiF showed the mean value of a calculated from $2\theta_{111}$ and $2\theta_{002}$.

broadening is independent of the scattering angle. Also, the lattice disorder results in an increase in peak breadth with an increase in the scattering angle.^{6,13} The change in FWHM with the compression of isoniazid was considered as follows: The increase in the breadth of diffraction peaks at a low scattering angle would indicate a decrease of crystallite size with compression. The marked broadening at a high scattering angle would be due to the disordering of the crystal lattice. Thus, both a decrease in crystallite size and an increase in lattice disorder are considered to occur simultaneously during the compression of isoniazid crystals.

Figure 5 shows the variation of the preferred orientation parameter with an increase in compression pressure. The crystallites in powders showed a slightly preferred orientation, while those in tablets showed a marked preferred orientation. The strength of the preferred orientation varied with compression, *i.e.*, the orientation of the (010) plane increased and that of the (100) plane decreased with an increase in compression pressure.

A marked increase of the lattice parameter a of isoniazid crystals with compression (Fig. 3) may bring about the disorder of molecular arrangement along the [100], and the lattice disorder will cause a decrease in intensity of the 100 reflection. Therefore, the strength of preferred orientation of the (100) plane was considered to decrease with compression.

D-Mannitol: The crystal structure of D-mannitol has been reported as space group: $P2_12_12_1$ and $a=8.672$ Å, $b=16.875$ Å, $c=5.560$ Å.⁴⁾ Figure 6 shows the variation of the lattice parameters with compression. Triplicates agreed at a variance of less than 0.003 from the mean. The lattice parameter a of the LiF crystals did not change, while the parameters a and b of D-mannitol crystals increased slightly with compression. The optimized values for the powdered specimen were larger than those for the compressed specimens for the same reason described before.

Figure 7 shows an increase in FWHM with the scattering angle. The FWHM broadened with compression, in-

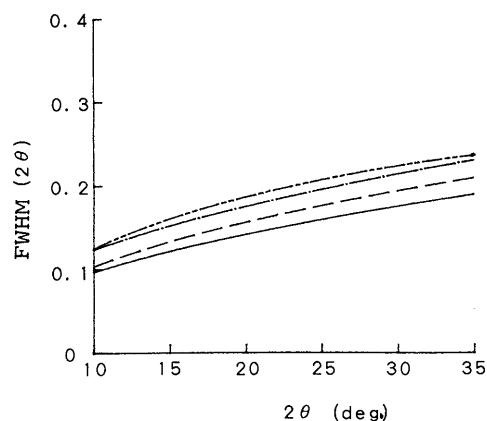


Fig. 7. Increase in FWHM with 2θ for D-Mannitol Tablets

Compression pressure: —, 375 kg/cm²; ---, 750 kg/cm²; ···, 1500 kg/cm²; - · - ·, 4500 kg/cm².

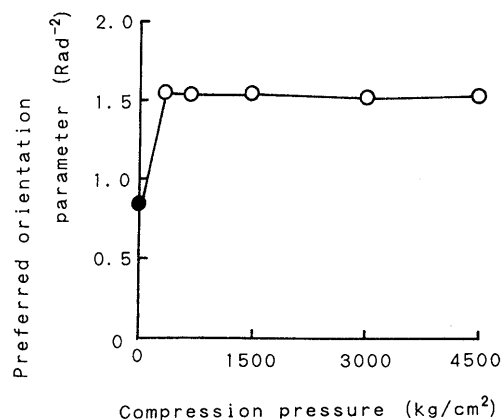


Fig. 8. Variation of Preferred Orientation Parameter of D-Mannitol Crystallites in Tablets with Compression Pressure

Preferred orientation plane: ○, (120) plane. Closed symbol represents the data for the powder.

dependent of the scattering angle. As described before, the broadening of the diffraction peak is caused by a decrease in crystallite size and by an increase of lattice disorder. The peak broadening, independent of scattering angle, would suggest that the crystallite size decreased, while the lattice disorder scarcely occurred as a result of the compression of D-mannitol crystals.

A difference in the scattering angle dependence of the broadening of FWHM between isoniazid and D-mannitol would reflect the characteristics of the crystals. It is considered that D-mannitol crystals would be compressed with elastic deformation and the crystals would be destructed by compression: therefore, the crystallite size would decrease and the lattice disorder would not change as a result of compression. On the other hand, isoniazid crystals might be compressed with elastic deformation accompanied by some plastic deformation: therefore, the crystallite size decreased and the lattice disorder increased as a result of compression.

Figure 8 shows variations in the preferred orientation parameter. The preferred orientation parameter for the tablets was optimized at larger value than that for the powders, and that did not change with compression pressure.

In conclusion, a pattern fitting procedure made it possible

to characterize the crystals and/or crystallites in tablets. In the present investigation, the lattice parameters of the crystals were found to vary with compression. From the analysis of the scattering angle dependence of the broadening of FWHM, the variations in crystallite size and lattice disorder during compression were estimated. The crystallites in tablets showed a preferred orientation, and preferred orientation behavior was found to vary with the preferred orientation plane.

References and Notes

- 1) This report constitutes Part VI of the series entitled "Preferred Orientation of Crystallites in Tablets"; a) Part I: E. Fukuoka, M. Makita, S. Yamamura, *Chem. Pharm. Bull.*, **35**, 1564 (1987); b) Part II: *idem, ibid.*, **39**, 3313 (1991); c) Part III: *idem, ibid.*, **41**, 595 (1993); d) Part IV: *idem, ibid.*, **41**, 1284 (1993); e) Part V: E. Fukuoka, K. Terada, M. Makita, S. Yamamura, *ibid.*, **41**, 1636 (1993).
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