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Preferred Orientation of Crystallites in Tablets. V.[1] Pattern-Fitting Procedure for the Determination of Strength of Preferred Orientation of Crystallites[2]

Eihei FUKUOKA,* Katsuhide TERADA,[3] Midori MAKITA, and Shigeo YAMAMURA

School of Pharmaceutical Sciences, Toho University, 2–2–1 Miyama, Funabashi, Chiba 274, Japan.

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A pattern-fitting procedure was described to determine the strength of preferred orientation of crystallite in tablets using X-ray powder diffraction data. This method is based on the pattern-fitting crystal structure refinement method which also uses powder diffraction data. Observed X-ray scattering intensities were fitted to analytic expression including some fitting parameters, namely peak positions, peak widths, background intensities and preferred orientation. All fitting parameters were optimized by non-linear least-squares procedure. Then the strength of preferred orientation of crystallites was evaluated from the magnitude of preferred orientation parameter.

Aspirin was used for the sample, and though aspirin crystallites showed little preferred orientation in powders, they showed marked preference in tablets. The magnitude of preferred orientation parameter increased with increasing compression pressure of tablet. This indicated that aspirin crystallites showed stronger preferred orientation in tablets prepared under higher compression pressure.

Keywords pattern-fitting; preferred orientation; X-ray powder diffraction; crystallite; tablet; aspirin

In the previous papers,[1a–c] we have been reported that crystallites in tablets showed a preferred orientation. And features of preferred orientation plane were elucidated by means of molecular orbital calculations.[1d]

The strength of preferred orientation of crystallites is considered to vary during compression process, but there is no method for the analysis of strength of preferred orientation of crystallites in tablets.

It is known that the pattern-fitting procedure for crystal structure refinement using powder diffraction data, called as the Rietveld method[4] in which preferred orientation of crystallites in the specimen was corrected using a preferred orientation function. So, we attempted to apply the pattern-fitting procedure in order to evaluate the strength of preferred orientation of crystallites in tablets.

In the present report, the theory and practice of the pattern-fitting procedure to evaluate the strength of preferred orientation of crystallites were investigated.

Theoretical A pattern-fitting procedure using powder diffraction data can be applied to crystal structure analysis and to quantitative phase analysis.[5] This method can be classified into two categories: First, peak positions are considered an independent parameter to resolve individual peaks. Second, peak positions are calculated from lattice constants, so that crystallographic knowledge can be obtained.[6]

Rietveld introduced a method to refine the crystal structure using powder diffraction data.[4] In the Rietveld method, crystal structure is refined by fitting the scattering intensities obtained by a step-scanning measurement to a suitable analytical expression such as Eq. 1,

$$y(2\theta_i)=c\sum_j |F_j|^2 m_j Lp_j P_j G(2\theta_i-2\theta_j)+y_b(2\theta_i) \quad (1)$$

where $y(2\theta_i)$ is the observed scattering intensity at $2\theta_i$, c is the scale factor, j is the number of reflections, F is the crystal structure factor, m is the multiplicity, Lp is the Lorentz-polarization factor, P is the preferred orientation function, G is the peak shape function (profile function), θ_j is the Bragg angle of j-th reflection and y_b is background intensity. In the present investigation, some simplifying treatments were made to evaluate the strength of preferred orientation of crystallites but these did not lead to serious errors, as described below. The parameters, F, m and Lp, are the structure parameters calculated from the crystal structure model. So, when the crystal structure of the sample has been determined, the structure parameters can be calculated from the crystal data. Thus, it is possible to substitute the product, $|F_j|^2 m_j Lp_j$, for the constant, I_j, representing the integral intensity of the j-th reflection. The structure parameters used for aspirin crystal are listed in Table I.[7]

G is the peak shape function normalized in such a way that integral intensity is 1, and is usually defined as a function of the Bragg angle (θ_j) and full-width at half-maximum (H_j). In the original Rietveld method, θ_j is given as a function of the cell parameters and H_j is defined as a function of θ_j,[4,8] but we did not use these relations here. Because some observed diffraction peaks completely overlapped with two or more reflections in aspirin under the measurement conditions used, for example (002, 011, 110, 200) reflections (Table I), θ_j and H_j of individual reflections would not be determined precisely by the pattern-fitting procedure. The position and width of individually observed diffraction peaks were therefore regarded as fitting parameters, and the intensities of the diffraction peaks were considered to be the sum of the intensities of overlapping reflections. Then, Eq. 1 is rewritten as Eq. 2,

$$y(2\theta_i)=c\sum_j \{G(2\theta_i-2\theta_j)\sum_k I_{jk}P_{jk}\}+y_b(2\theta_i) \quad (2)$$

where k is the number of overlapping reflections in the j-th observed diffraction peak and $I_{jk}=|F_{jk}|^2 m_{jk} Lp_{jk}$. The procedure that each peak position is considered an independent parameter is known as the pattern-decomposition method.[6] Usually, profile shape is fixed and the parameters of peak intensity, profile half-width and peak

TABLE I. Parameters for the Determination of Strength of Preferred Orientation of Aspirin Crystallites Used the Pattern-Fitting Procedure

No.	2θ	hkl[a]	Structure factor (F)	m[b]	L. P[c] factor (Lp)	Relative intensity[d] (I)	ϕ (Rad)[e]
1	7.75	100	38.28	2	390.8	34.98	0.00
2	15.60	002	108.04	2	95.0	67.75	1.47
		011	−31.19	4	96.2	11.43	1.52
		110	−26.64	4	96.4	8.36	1.05
		200	−46.09	2	96.0	12.46	0.00
3	16.75	$10\bar{2}$	31.51	2	82.3	4.99	1.19
4	18.10	102	−16.21	2	70.2	1.13	1.03
5	20.60	012	49.77	4	53.7	16.26	1.50
		210	28.41	4	54.1	5.33	0.71
6	21.00	$20\bar{2}$	39.13	2	51.9	4.85	0.84
7	22.60	112	−76.13	4	44.5	31.52	1.14
		211	76.53	4	44.7	31.97	0.76
8	23.15	202	−68.50	2	42.4	12.14	0.74
9	26.90	212	−92.11	4	31.1	32.27	0.88
		$30\bar{2}$	25.86	2	30.9	1.26	0.62
10	28.90	113	21.59	4	26.6	1.52	1.21
		311	39.70	4	26.8	5.16	0.57
11	31.40	022	−22.84	4	22.5	1.43	1.52
		220	−25.35	4	22.5	1.77	1.05
		400	−40.57	2	22.4	2.26	0.00
12	32.60	213	53.74	4	20.7	7.30	0.99
		312	−49.13	4	20.8	6.12	0.69

a) Reflecting plane indices. *b*) Multiplicity. *c*) Lorentz-polarization factor. *d*) Intensity relative to (002, 011, 110, 200) reflections. *e*) Acute angle between the preferred orientation plane and (hkl) plane in radian. Reflections with very small F were neglected in the calculation.

TABLE II. List of 28 Fitting Parameters Using in the Pattern-Fitting Procedure

Parameter	Symbol[a]	Number of parameters
Peak position	$2\theta_j$	12
Peak width	c_{ml}[b]	12
Scale factor	c	1
Background intensity (linear function)		2
Preferred orientation parameter	a	1

a) Symbols used in this report. *b*) See Eq. 11.

position are varied. The form of peak shape function will be discussed later. Background intensities were approximated by the linear function of $2\theta_i$.

Several mathematical forms of the preferred orientation function were reported.[4,9,10] Equation 3,[4] assuming a uniaxial orientation having Gaussian distribution about a preferred orientation axis was used in the present investigation,

$$P_{jk}=\exp(-a\phi_{jk}^2) \tag{3}$$

where a is the preferred orientation parameter showing the strength of preferred orientation of crystallites. ϕ is the acute angle between the preferred orientation plane and the (hkl) plane in the crystal. This preferred orientation function describes a curve with maximum at $\phi=0$ and with minimum at $\phi=\pi/2$, and shows that the diffraction intensity from (hkl) plane with large ϕ decreases by preferred orientation of crystallites. When there is no knowledge of this preferred orientation understood without repeating, the preferred orientation plane has to be selected by trial and error. In general, the preferred orientation axis is selected as normal to the cleavage plane for plate-like crystals and as parallel to the elongation axis for needle-like crystals.[10]

We previously reported[1b] that 100 planes of aspirin have a tendency to orient parallel to the upper surface of a tablet during compression, and that a relative intensity of 100 reflection increased with preferred orientation of crystallites. Thus, the (100) plane, is the cleavage plane,[7] and considered to appropriate for a preferred orientation plane. ϕ used in the calculation are listed in Table I.

Then, the fitting parameters listed in Table II were optimized by minimizing the value M defined as Eq. 4 using non-linear least-squares procedure.

$$M=\sum_{i=1}^{N} w_i\{y_{obs}(2\theta_i)-y_{cal}(2\theta_i)\}^2 \tag{4}$$

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

Experimental

Materials Aspirin (JP grade, Iwaki Pharmaceuticals Co., Ltd.) was used without further purification. Fine powders, having been passed through a 250 mesh (63 μm) sieve were used. Crystallographic data for aspirin were taken from the literature.[7]

Tableting A 300 mg of sample powder was compressed under various pressures by the direct compression method. The die available to the sample plate for X-ray diffraction measurements was designed in our laboratory and used for tableting (Fig. 1). Diameter of the tablet was 1.3 cm. It was assumed that the crystal structure of aspirin was not changed by the compression.

X-Ray Diffraction (Powder Method) Sample tablet fixed in the die was placed with the upper surface of the tablet in line with the front of the sample plate. A Geigerflex RAD type diffractometer (Rigaku Denki Co., Ltd.) was used and symmetrical reflection geometry was employed. X-Ray source was Cu-K_α and the diffracted beam was monochromated using a bent-graphite monochromator. Other conditions were as follows: voltage, 35 kV; current, 10 mA; divergence and scatter slits; 0.5°; receiving slit; 0.15 mm; monochromator slit; 0.45 mm. Scattering intensities were measured by the fixed-time step-scanning method between 5 and 35° (2θ) at intervals of 0.05° (2θ). The counting period was 20 s at each point..

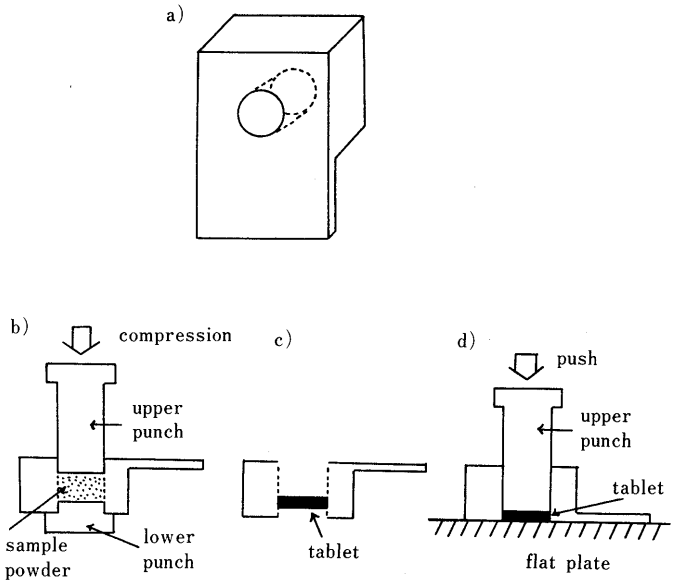

Fig. 1. Schematic Representation of Sample Plate Available to Die for Compression

a) sample plate; b—d) preparation of sample tablet.

Equation 5[11] was used for the Lorentz-polarization factor (Lp),

$$Lp=(1+\cos^2 2\theta_{jk}\cos^2 2\theta_m)/(\sin^2\theta_{jk}\cos\theta_{jk}) \quad (5)$$

where θ_m is the diffraction angle of the monochromator crystal. Absorption of X-ray by the specimen and contribution of Cu-K_{α_2} to diffraction intensity were ignored in the calculation.

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

Results and Discussion

Selection of Peak Shape Function Rietveld used a Gaussian peak shape function for the constant wavelength neutron diffractometry[4]; it is said, however, that Gaussian is inadequate for the analysis using constant wavelength X-ray powder diffraction data.[12] We tested the suitability of three other functions in an effort to improve the overall fit.

(1) The Gaussian function

$$y=y_o\exp[-c_1(2\theta-2\theta_o)^2] \quad (6)$$

(2) The Lorentzian function

$$y=y_o[1+c_2(2\theta-2\theta_o)^2]^{-1} \quad (7)$$

(3) The modified Lorentzian function[13]

$$y=y_o[1+c_3(2\theta-2\theta_o)^2]^{-2} \quad (8)$$

(4) The intermediate Lorentzian function[14]

$$y=y_o[1+c_4(2\theta-2\theta_o)^2]^{-1.5} \quad (9)$$

where c_1, c_2, c_3, and c_4 are parameters relating peak-width, and $2\theta_o$ is a peak position.

The goodness of fit between the observed and calculated intensities was estimated by the weighted reliability index (R_{wp}) defined as Eq. 10,

$$R_{wp}=[\sum_{i=1}^{N} w_i\{y_{obs}(2\theta_i)-y_{cal}(2\theta_i)\}^2/\sum_{i=1}^{N} w_i y_{obs}(2\theta_i)^2]^{1/2} \quad (10)$$

The profiles of 100 and (002, 011, 110, 200) reflections of aspirin powders were simulated using four different peak shape functions, and obtained R_{wp} are summarized in Table III. Since the modified Lorentzian function gives the best fit with the experimental data among the four functions, the normalized modified Lorentzian function[13] (Eq. 11) was used for the peak shape function in the present investigation.

$$y=2\sqrt{c_{ml}}/[\pi\{1+c_{ml}(2\theta_i-2\theta_j)^2\}^2] \quad (11)$$

where c_{ml} is the parameter relating the peak width. A constant $2/\pi$ was incorporated with a scale factor in the calculation.

TABLE III. R_{wp}[a] Values of Curve Fits for the Profiles of 100 and (002, 011, 110, 200) Reflections of Aspirin Powder Using Four Peak Shape Functions

Peak shape function	Reflection(s)	
	100[b,c]	(002, 011, 110, 200)[b,d]
Gaussian function	0.104	0.146
Lorentzian function	0.114	0.180
Modified Lorentzian function	0.073	0.108
Intermediate Lorentzian function	0.089	0.141

a) As defined in Eq. 10. b) Reflecting plane indices. c) Intensity data of 6.5—8.5° (2θ) were used. d) Intensity data of 14.5—16.3° (2θ) were used.

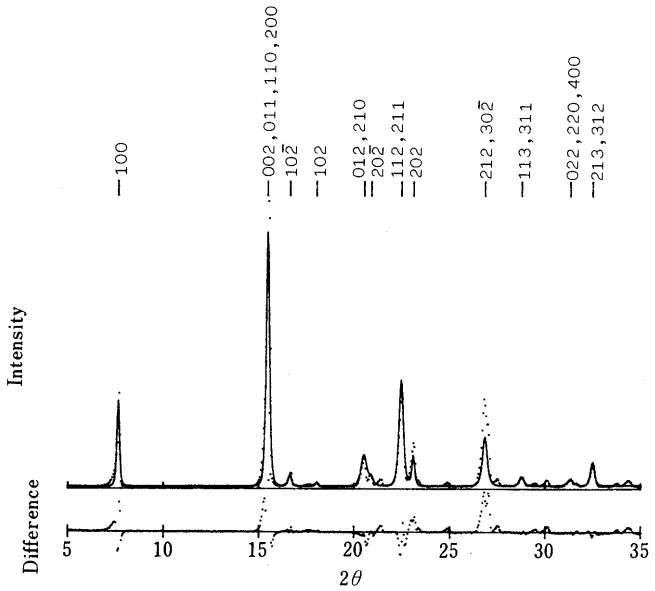

Fig. 2. Observed X-Ray Diffraction Intensities (Dots) and Simulation Pattern (Solid Line) of Aspirin Powder

Bars represent the peak positions. Difference line is that between observed and calculated intensities. Numbers represent the reflecting plane indices.

Preferred Orientation of Aspirin Crystallites in Powder and in Tablet Figures 2 and 3 show the observed X-ray diffraction intensities with simulation pattern of aspirin powder and tablet obtained by the pattern-fitting procedure, respectively. The final weighted reliability index (R_{wp}) was 0.22 (powder) and 0.27 (tablet). Obtained R_{wp} values were larger than that for the typical crystal structure determination using single crystal. It is known that R_{wp} obtained by pattern-fitting procedure is strongly dependent on signal-to-noise ratio of X-ray diffraction data.[13] In other words, if the background level is high relative to

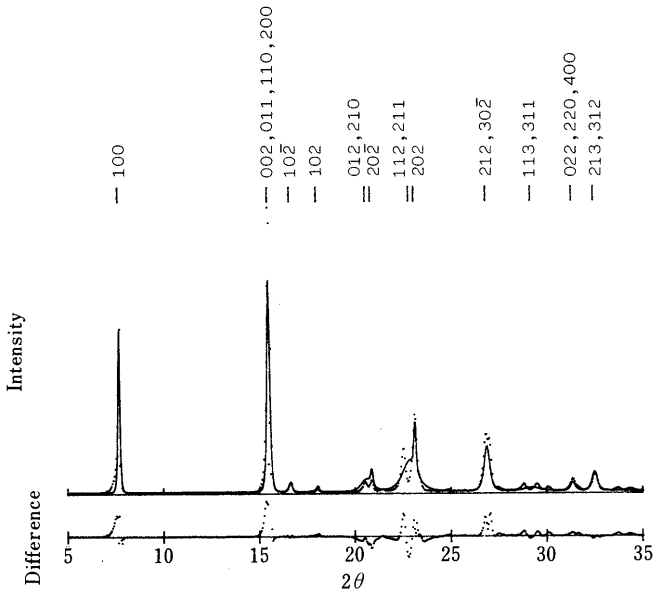

Fig. 3. Observed X-Ray Diffraction Intensities (Dots) and Simulation Pattern (Solid Line) of Aspirin Tablet Compressed under 750 kg/cm^2

Bars represent the peak positions. Difference line is that between observed and calculated intensities. Numbers represent the reflecting plane indices.

peak intensity, then the background intensities themselves will contribute to the denominator but not the numerator of Eq. 10; thereby R_{wp} becomes noticeably low. In the present cases, because background levels were low enough for the intensities of Bragg reflections, although the R_{wp} were relatively large, the fitting of observed and calculated intensities was considered to be satisfactory. The (100) plane was selected as the preferred orientation plane, and when any other plane was selected as such, the final R_{wp} was larger than 0.22 in powder or 0.27 in tablet. The plane giving the lowest R_{wp} should be selected as the preferred orientation plane.

The preferred orientation parameter was optimized as -0.007/Rad^2 for powder and 0.134/Rad^2 for tablet, respectively. When the preferred orientation parameter was refined as a larger value, crystallites in the specimen were considered to show stronger preferred orientation. Aspirin crystallites in powder thus showed a random orientation because the preferred orientation parameter was almost zero, while the crystallites in tablet showed a marked preferred orientation. These results indicate that 100 planes of aspirin crystallites oriented parallel to the upper surface of the tablet by compression, because the (100) plane was selected for the preferred orientation plane in the calculation. Thus, preferred orientation of crystallites could be evaluated by the pattern-fitting procedure.

Variation of Preferred Orientation Parameter with Compression Pressure of Aspirin Tablet X-Ray diffraction intensities from aspirin tablets prepared under various compression pressures were measured, and the preferred orientation parameter was calculated by the pattern-fitting procedure. Figure 4 shows the variation of the parameter with pressure: the magnitude of the former increased gradually with increasing compression pressure. This result indicates that the strength of preferred orientation of crystallites increased gradually during the compression process, and that the 100 planes of aspirin crystallites oriented more strongly in the tablet prepared under higher compression pressure.

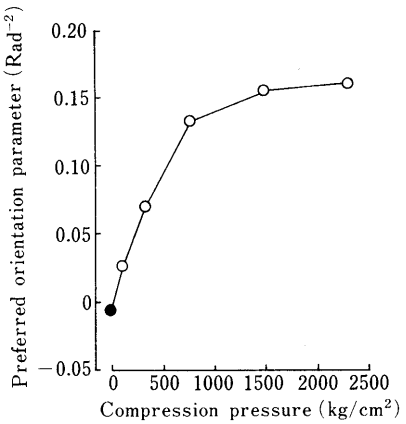

Fig. 4. Variation of Preferred Orientation Parameter with Compression Pressure of Aspirin Tablet

Closed symbol represents the data for aspirin powder.

In conclusion, the strength of preferred orientation of crystallites could be determined by the pattern-fitting procedure. This method is applicable to many other crystalline powders of which the crystal structure has been determined. It was found that aspirin crystallites showed no preferred orientation in powder, while in tablet they did show this. It was also found that aspirin crystallites in tablets prepared under higher compression pressure showed stronger preferred orientation. The pattern-fitting procedure is thus expected to be a useful tool for elucidation of the compression mechanism of crystalline pharmaceuticals.

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