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Quantitative analysis of crystalline pharmaceuticals in tablets by pattern-fitting procedure using X-ray diffraction pattern

Rieko Takehira [a], Yasunori Momose [b], Shigeo Yamamura [a,*]

[a] Faculty of Pharmaceutical Sciences, Josai International University, Gumyo 1, Togane, Chiba 283-8555, Japan
[b] Faculty of Pharmaceutical Sciences, Toho University, Miyama 2-2-1, Funabashi, Chiba 274-8510, Japan

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ABSTRACT

A pattern-fitting procedure using an X-ray diffraction pattern was applied to the quantitative analysis of binary system of crystalline pharmaceuticals in tablets. Orthorhombic crystals of isoniazid (INH) and mannitol (MAN) were used for the analysis. Tablets were prepared under various compression pressures using a direct compression method with various compositions of INH and MAN. Assuming that X-ray diffraction pattern of INH–MAN system consists of diffraction intensities from respective crystals, observed diffraction intensities were fitted to analytic expression based on X-ray diffraction theory and separated into two intensities from INH and MAN crystals by a nonlinear least-squares procedure. After separation, the contents of INH were determined by using the optimized normalization constants for INH and MAN. The correction parameter including all the factors that are beyond experimental control was required for quantitative analysis without calibration curve. The pattern-fitting procedure made it possible to determine crystalline phases in the range of 10–90% (w/w) of the INH contents. Further, certain characteristics of the crystals in the tablets, such as the preferred orientation, size of crystallite, and lattice disorder were determined simultaneously. This method can be adopted to analyze compounds whose crystal structures are known. It is a potentially powerful tool for the quantitative phase analysis and characterization of crystals in tablets and powders using X-ray diffraction patterns.

1. Introduction

The X-ray diffraction method has been widely employed for the identification and quantitative analysis of solid phases (Yamamura and Momose, 2001; Shah et al., 2006; Otsuka et al., 2003; Roberts et al., 2002; Sheikhzadeh et al., 2007). Quantitative phase analysis by X-ray diffraction is based on the assumption that the diffraction intensity is proportional to the amount of the solid phase in the sample. There have been some reports of quantitative phase analysis using an internal or external standard substance, and the reference intensity ratio method is widely used for quantitative X-ray diffraction (Otsuka et al., 2003; Roberts et al., 2002; Sheikhzadeh et al., 2007). In the field of pharmaceutical sciences, X-ray diffraction has been widely employed for quantitative phase analysis, the analysis of the degree of crystallinity (amorphous contents), and determination of polymorphic composition (Dash et al., 2002; Bergese et al., 2003; Cao et al., 2002; Al-Zoubi et al., 2002; Tiwari et al., 2007). In such cases, the solid phase content was determined from the intensities of particular diffraction lines or from the ratio of the diffraction intensities of the crystal and an internal standard substance.

Because almost all drugs consist of organic compounds, their crystallites easily exhibit a preferred orientation when packed in a sample plate for X-ray measurement (Roberts et al., 2002; Yamamura and Momose, 2003). The preferred orientation leads to a modification in the diffraction intensities, which results in a decrease in the accuracy of the quantitative analysis. Therefore, it is crucial to correct for the preferred orientation of the crystallites in drugs when carrying out quantitative phase analysis using X-ray diffraction. However, there have been only a few reports on quantitative phase analysis wherein the preferred orientation of the crystallites in the tablet has been taken into account.

In previous studies, we have described the pattern-fitting procedure for characterizing orthorhombic and monoclinic crystals by using X-ray powder diffraction intensities (Yamamura and Momose, 2001, 2003). This method is based on Rietveld analysis (Rietveld, 1969) and it has been employed for crystal-structure determination and strain-size determination in crystal sciences (Kariuki et al., 1999; Pratapa et al., 2001; Kaduk, 2004).

The pattern-fitting procedure would be potentially capable for quantitative analysis of the crystalline phase taking into account strain-size determination and preferred orientation of crystallites.

* Corresponding author. Tel.: +81 475 53 4637; fax: +81 475 53 4637.
E-mail address: s_yama@jiu.ac.jp (S. Yamamura).

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Table 1
Crystal structure of isoniazid and D-mannitol.

	Isoniazid[a]	D-Mannitol[b]
Formula	$C_6H_7ON_3$	$C_6H_{14}O_6$
Formula weight	137.14	182.17
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	3.842(1)	8.672
b (Å)	11.328(4)	16.875
c (Å)	14.743(5)	5.560
V (Å^3)	641.6(3)	813.7
Z	4	4
μ (Cu-Kα) (cm^{-1})	7.23	11.76
Number of reflections	3031	
R; Rw	0.053; 0.091	
R1	0.035	
Goodness-of-fit	1.34	

[a] From crystal-structure analysis.
[b] From the literature (Berman et al., 1968).

In this study, the pattern-fitting procedure was employed for the quantitative analysis of two orthorhombic crystal systems—isoniazid and D-mannitol without calibration curve. We also investigated changes of preferred orientation and strain-size of crystallites during compression with quantitative analysis.

2. Materials and methods

2.1. Materials

Crystalline powders of isoniazid (INH) and D-mannitol (MAN) (Sigma Chemical Co., St. Louis, MO, USA) were passed through a 250-mesh (63 μm) sieve. Samples of these powders were stored in a desiccator containing silica gel before X-ray measurement.

2.2. Tableting

By using the direct compression method, 500 mg of the sample powder was compressed under various pressures for 30 s. A specially designed die was used in the sample plate for X-ray diffraction measurement (Fukuoka et al., 1993). The diameter of the tablet was 13 mm, and it was placed in the die such that it would not get dislodged during the X-ray measurement. Fixing the tablet in the die was required for accurate analysis, its surface to meet diffraction geometry. The X-ray measurement was carried out immediately after tablet preparation.

2.3. Crystal-structure analysis and crystal-structure factors

The crystal structure of INH was determined by using the RASA system (Rigaku Co., Tokyo, Japan). A summary of the crystal-structure analysis is given in Table 1, and the Oak Ridge thermal ellipsoid plot (ORTEP) of the crystal structure is shown in Fig. 1. For the pattern-fitting procedure, the crystal-structure factors of INH were derived from its refined crystal structure whereas those of MAN were obtained from the literature (Berman et al., 1968).

2.4. Powder X-ray diffraction

The powder X-ray diffraction intensities were measured using a RINT-2500 X-ray diffractometer (Rigaku Co., Tokyo, Japan), and symmetrical reflection geometry was employed. The X-ray source was Cu-Kα radiation at a voltage of 50 kV and current of 100 mA. The diffracted X-ray beam was monochromated by a bent 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 5–35° (2θ) at intervals 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 calculations.

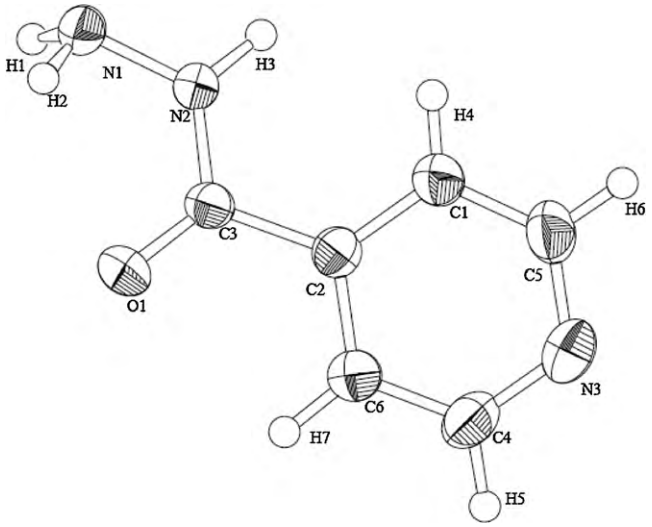

Fig. 1. ORTEP of isoniazid crystal.

2.5. Pattern-fitting

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

The theoretical background of the pattern-fitting procedure for quantitative analysis is briefly described as follows.

The observed X-ray diffraction intensities of one component were expressed as (Yamamura and Momose, 2003; Young, 1993; McCusker et al., 1999):

$$I(2\theta_i)=K\sum_{j=1}^{N}\left\{F^2_{h_j k_j l_j}\cdot m_{h_j k_j l_j}\cdot Lp_{h_j k_j l_j}\cdot G(2\theta_{h_j k_j l_j}-2\theta_i)\cdot P_{h_j k_j l_j}\right\} \quad (1)$$

where $I(2\theta_i)$ is the observed intensity at $2\theta_i$; K, the normalization constant; N, the number of $h\,k\,l$ reflections; F, the crystal-structure factor; m, the multiplicity factor; and Lp, the Lorentz-polarization factor. The profile function G (in this case, a modified Lorentz function (Sonneveld and Visser, 1975)) is given by Eq. (2). The full-width at half-maximum (FWHM) H is given by Eq. (3). The function for the correction in the peak symmetry, s, is given by Eq. (4). The diffraction angles $\theta_{h\,k\,l}$ were calculated from the lattice constants and Miller indices ($h\,k\,l$) of the reflection:

$$G=\frac{2sc_{\mathrm{ML}}^{0.5}}{\pi H\left(1+c_{\mathrm{ML}}(2\theta_{h\,k\,l}-2\theta_i)^2/H^2\right)^2} \quad (2)$$

$$H^2=U\tan^2\theta_{h\,k\,l}+V\tan\theta_{h\,k\,l}+W \quad (3)$$

$$s=\frac{1-S\cdot\mathrm{sign}(2\theta_{h\,k\,l}-2\theta_i)(2\theta_{h\,k\,l}-2\theta_i)^2}{\tan\theta_{h\,k\,l}} \quad (4)$$

In Eq. (2), c_{ML} is a normalization constant for the modified Lorentz function (Sonneveld and Visser, 1975). In Eq. (3), U, V, and W are the peak-width parameters (Young, 1993). In Eq. (4), S is the asymmetric parameter. The preferred orientation function, P, is given by

$$P_{h\,k\,l}=\exp(-\alpha\varphi^2_{h\,k\,l}) \quad (5)$$

where α is a preferred orientation parameter that indicates the strength of the preferred orientation of the crystallites and φ is the acute angle between the preferred-orientation plane (normal to the preferred orientation axis) and the $h\,k\,l$ plane. The preferred-orientation plane was selected once the best fit was achieved by trial and error. For Eq. (5), the diffraction intensities were assumed to be modified by the preferred orientation of the crystallites, according to a Gauss distribution.

In a two-component system (components A and B), the observed patterns consist of the diffraction patterns of the two components and can be written as

$$I(2\theta_i) = K_A I_A(2\theta_i) + (K_B) I_B(2\theta_i) + y_b(2\theta_i) \quad (6)$$

where $K_A I_A$ and $K_B I_B$ are the diffraction intensities of components A and B calculated by Eq. (1), respectively. The background intensity y_b is assumed to be a linear function.

When a reasonable fit of the observed intensities was achieved, not only K_A and K_B, but also the crystal lattice parameters (a, b, and c), FWHM parameters (U, V, and W), and preferred orientation parameter (α) of components A and B were optimized simultaneously.

2.6. Quantitative analysis without calibration curve

In two-component system, the contents of crystalline phases A may be calculated from two normalization constants, K_A and K_B as Eq. (7):

$$x_A = \frac{K_A}{K_A + K_B} \quad (7)$$

However, this may not be a good indicator of the weight fraction of each component. The integrated intensity of X-rays diffracted from a randomly oriented crystalline sample by a diffracted-beam monochromator can be written as (Cullity, 1978):

$$I_{hkl} = \left\{ \left[\frac{I_0 A_0 \lambda^3}{32\pi r} \left(\frac{\mu_0}{4\pi} \right)^2 \frac{e^4}{m^2} \right] \left[\frac{1}{2\mu V^2} \right] \left[|F|^2 m \left(\frac{1+\cos^2 2\theta \cos^2 2\theta_m}{\sin^2 \theta \cos \theta} \right) \exp^{-2M} \right] \right\} \quad (8)$$

where I_0 is the intensity of the incident beam; A_0, the cross-sectional area of the incident beam; λ, the wavelength of the X-ray; r, the radius of the diffractometer circle; e, the charge on an electron; m, the mass of an electron; V, the volume of the unit cell; exp(−2M), the temperature factor; and μ, the linear absorption coefficient. The terms in the first pair of square brackets are dependent only on the instrumental conditions of the X-ray diffractometer. The terms in the third pair of square brackets represent the intensity of one diffraction peak. On the basis of a comparison between Eqs. (1) and (8), K (in Eq. (1)) can be written as

$$K = \frac{K'}{2\mu V^2} \quad K' = \left[\frac{I_0 A \lambda^3}{32\pi r} \left(\frac{\mu_0}{4\pi} \right)^2 \frac{e^4}{m^2} \right] \quad (9)$$

Because K' is a constant that is independent of the sample, the ratio of $2\mu_A V_A^2 K_A$ and $2\mu_B V_B^2 K_B$ should indicate the weight fraction of each component. For example, compoent A is given by

$$X_A = \frac{2\mu_A V_A^2 K_A}{2\mu_A V_A^2 K_A + 2\mu_B V_B^2 K_B} = \frac{\mu_A V_A^2 K_A}{\mu_A V_A^2 K_A + \mu_B V_B^2 K_B} \quad (10)$$

In practice, however, this relation does not always hold true because the preferred orientation, degree of crystallinity, microabsorption, and extinction effects of the real sample would disturb the relation (Cullity, 1978), which in turn would result in some deviation from diffraction theory.

Table 2
Diffraction plane indices, crystal-structure factors and multiplicity factors of isoniazid for pattern-fitting.

h	k	l	F	p	h	k	l	F	p
1	1	0	6.4	4	2	0	1	7.2	4
0	2	0	28.3	2	2	1	1	24.5	8
1	2	0	24.4	4	2	4	0	31.1	4
2	0	0	48.5	2	0	3	1	38.2	4
2	1	0	51.1	4	3	3	0	14.1	4
1	3	0	28.3	4	1	3	1	25.3	8
2	2	0	14	4	2	2	1	8.8	8
0	1	1	32.2	4	4	1	0	34.2	4
2	3	0	4.3	4	2	3	1	5.9	8
0	4	0	32.4	2	0	4	1	20.7	4
3	1	0	7.1	4	3	1	1	8.4	8
1	1	1	55	8	4	2	0	8.4	4
1	4	0	32.3	4	3	4	0	5	4
0	2	1	69.1	4	2	5	0	19.4	4
3	2	0	12	4	1	4	1	11.2	8

In the present report, we have introduced a correction parameter, k, to compensate for the deviation from diffraction theory for real samples:

$$K_A \mu_A V_A^2 = k \times K_B \mu_B V_B^2 \quad (11)$$

The correction parameter k includes all the factors that are beyond experimental control. The value of k was determined by using a pattern-fitting procedure to compare the optimized normalization constants obtained by diffraction pattern of components A and B, respectively:

$$k = \frac{K_A \mu_A V_A^2}{K_B \mu_B V_B^2} \quad (12)$$

Since k can be determined before quantitative analysis, the content of component A, X'_A, can be calculated from K_A and K_B, while k can be obtained from the pattern-fitting procedure, without a calibration curve, as follows:

$$X'_A = \frac{K_A}{K_A + K_B/k} \quad (13)$$

In this procedure, quantitative phase analysis along with a correction for preferred orientation of crystallites can be carried out simultaneously.

3. Results and discussion

3.1. Quantitative phase analysis of INH–MAN system

The crystal-structure factors of INH and MAN using the pattern-fitting simulation are summarized in Tables 2 and 3. All reflections that theoretically occurred in the range of 5–35° (2θ) were used in the simulation. Typical examples of the pattern-fitting of INH, MAN, and isoniazid–MAN (1:1) tablet samples are shown in Figs. 2–4.

Reasonably accurate pattern-fitting between observed and simulated intensities is achieved in the range of 10–90% (w/w) of INH contents.

Figs. 5 and 6 show the plots of INH content (X_{INH} and X'_{INH}, calculated from Eqs. (10) and (13)) against the weight fraction of INH in powders and tablets, respectively. The observed values of X_{INH} were greater than the actual values. This disparity can be explained as follows: the normalization constants were modified because of the differences in the degree of crystallinity and preferred orientation of crystallites of each sample at different diffraction intensities, i.e., the degree of crystallinity of MAN was lower than that of INH, and the strength of the preferred orientation of MAN crystallites was greater than that of INH crystallites. Because lower degree of crystallinity and stronger preferred orientation result in decrease

Table 3
Diffraction plane indices, crystal-structure factor and multiplicity factors of D-mannitol for pattern-fitting.

h	*k*	*l*	*F*	*p*	*h*	*k*	*l*	*F*	*p*
0	2	0	20.7	2	2	1	1	22.9	8
1	1	0	10.2	4	2	2	1	26.5	8
1	2	0	41.4	4	1	5	0	41.2	4
0	1	1	38.6	4	2	4	0	72.3	4
1	3	0	71.4	4	2	3	1	16.6	8
1	0	1	23.6	4	3	1	0	33.8	4
0	2	1	30.8	4	0	6	0	51.1	2
1	1	1	11.2	8	0	0	2	18.6	2
2	0	0	75.4	2	0	1	2	8.9	4
0	4	0	24	2	1	5	1	4.3	8
2	1	0	68.1	4	3	2	0	43.2	4
1	2	1	33.6	8	1	6	0	27.2	4
0	3	1	9.8	4	2	5	0	60.8	4
2	2	0	3.3	4	2	4	1	15.3	8
1	4	0	94.4	4	1	0	2	51.4	4
1	3	1	28.9	4	0	2	2	20.7	4
2	3	0	38.1	4	1	1	2	52.5	8
2	0	1	32.8	4	3	3	0	9.6	4
0	4	1	5.2	4					

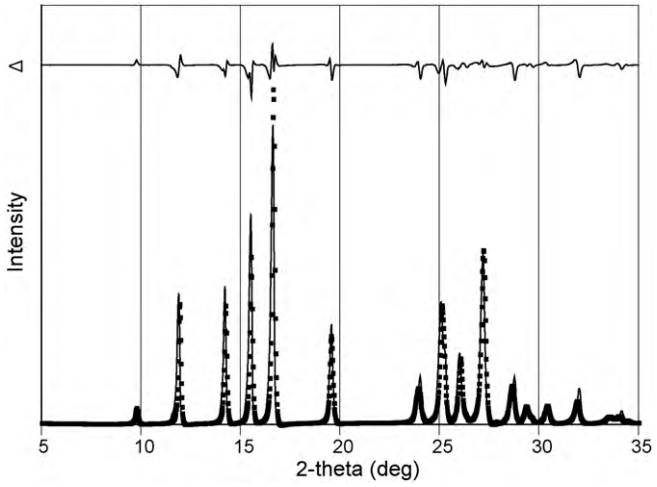

Fig. 2. Observed X-ray diffraction intensities (dots) and calculated pattern (solid line) of isoniazid tablet. Δ is the difference between observed and calculated intensities.

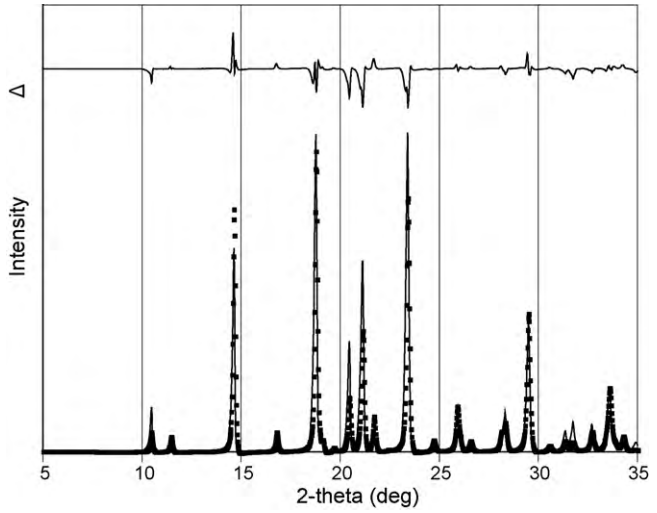

Fig. 3. Observed X-ray diffraction intensities (dots) and calculated pattern (solid line) of D-mannitol tablet. Δ is the difference between observed and calculated intensities.

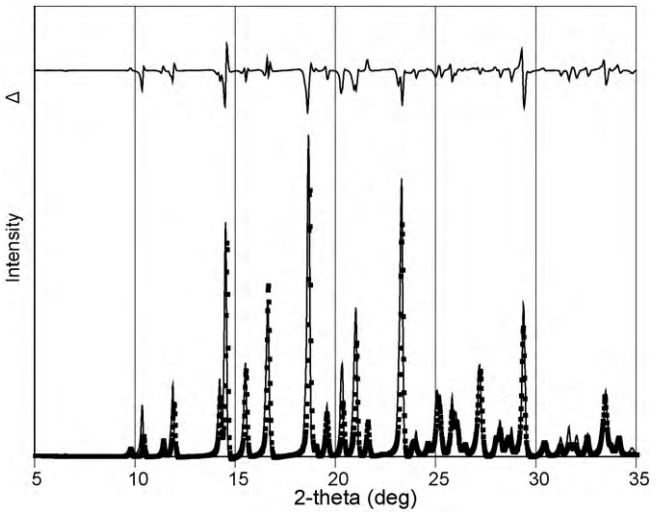

Fig. 4. Observed X-ray diffraction intensities (dots) and calculated pattern (solid line) of isoniazid-D-mannitol (50:50) tablet compressed under 750 kg/cm^2. Δ is the difference between observed and calculated intensities.

of diffraction intensities, a normalization constant of MAN should be optimized such that it is smaller than that of INH. Consequently, X_{INH} was optimized such that its observed values were greater than its actual values. A limited scan range of diffraction data was used for the fit, which might result in errors during the fitting process.

In both powders and tablets, X'_{INH} showed an improved linear relationship with actual INH weight fractions, following correction by Eq. (13).

As shown in Figs. 5 and 6, three independent measurements of powder samples yielded larger standard errors in the mean of X_{INH} and poorer correlation between X'_{INH} and the actual INH weight fraction than those of tablet samples. This result implies that the nonuniformity in the packing of crystals in the sample powders produces some deviation from the theoretical diffraction intensities. On the other hand, three independent measurements of the tablet samples revealed that there was little variation in the obtained

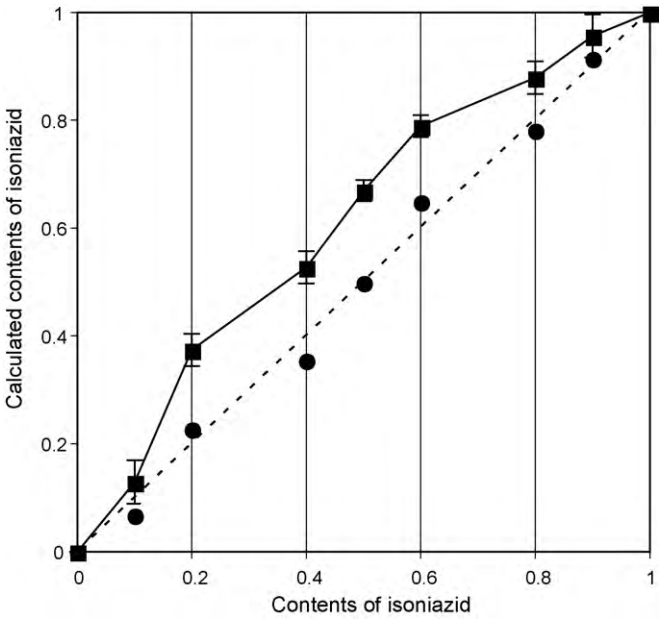

Fig. 5. Relationship between weight fraction and calculated isoniazid content as determined by pattern-fitting in the INH and MAN powder systems. (■) X_{INH}; (●) X'_{INH}. Bars represent the standard error for three experiments. $r = 0.993$.

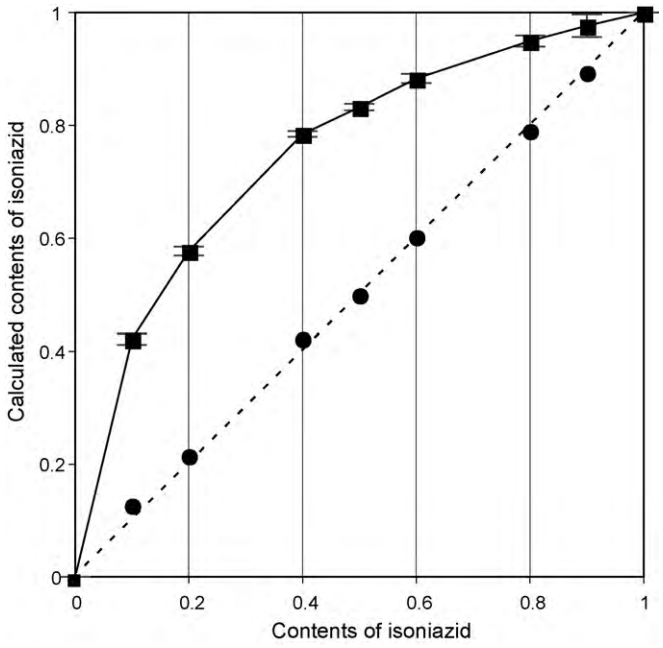

Fig. 6. Relationship between weight fraction and calculated isoniazid content as determined by pattern-fitting in the INH and MAN tablet systems. (■) X_{INH}; (●) X'_{INH}. Bars represent the standard error for three experiments. $r = 0.999$.

values because of the diffraction intensities of the densely packed crystals in the tablet samples were not affected significantly.

In both powder and tablet samples, the relationship between X'_{INH} and INH weight fractions exhibited good linearity (with slope approximately unity), following correction by Eq. (13). These results indicate that the pattern-fitting procedure can be used for the quantitative analysis of crystalline powders and tablets—in the range of 10–90% (w/w)—and without a calibration curve.

3.2. Characterization of INH and MAN crystals by compression

Fig. 7 shows the change in the FWHM of the diffraction peaks of INH and MAN crystals, as calculated from *U*, *V*, and *W*, optimized by the pattern-fitting procedure. The FWHMs of INH and MAN crystals increased with increasing compression pressure, and there was a difference in the scattering-angle dependence of diffraction peak widths of INH and MAN. The FWHM of INH crystals further increased at higher diffraction angles, whereas that of MAN crystals exhibited little dependence on the scattering angles.

The broadening of the diffraction peak is affected by both the crystallite size and the lattice disorder (Klug and Alexander, 1974). In paracrystal theory, the peak broadens with both decrease in crystallite size and increase in lattice distortion. The broadening of diffraction peaks is independent of scattering angles for crystallites smaller than 1000 Å. The lattice disorder contributes to an increase in the peak width with increasing scattering angle (Hosemann and Bagchi, 1962).

The scattering-angle dependence of the FWHM indicates that INH crystals exhibit considerable lattice disorder whereas MAN crystals do not exhibit much lattice disorder. With compression, some broadenings with parallel each other were observed in both INH and MAN. These results indicate that the size of the crystallites decreased with increasing compression pressure because there was no increase in lattice distortion.

These results indicate that both crystals are brittle and reinforced by fragmentation during compression, without an increase in the plastic strain.

Fig. 8 shows the change in the preferred orientation parameters of INH and MAN with compression pressure. The strength of the preferred orientation increased under low compression pressures and increased slightly with increasing compression pressure.

These results indicate that the strength of the preferred orientation of INH and MAN crystals increased in the first stage of compression, presumably accompanied by cleaving along the preferred-orientation planes. Thus, the fragmentation of crystals occurred according to the preferred orientation during the ini-

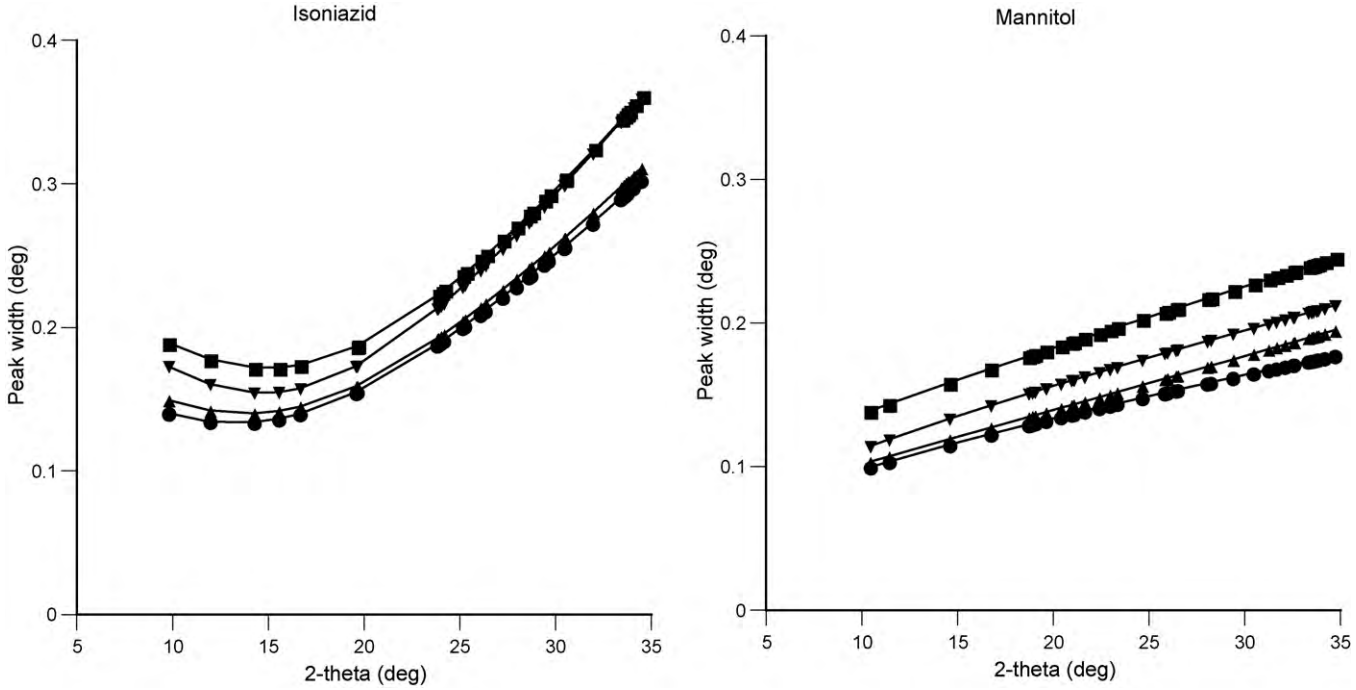

Fig. 7. Change of FWHM of INH and MAN crystals with compression pressure in INH–MAN (1:1, w/w) tablet. Compression pressure: (●) powder sample of INH or MAN alone; (▲) 375 kg/cm^2; (▼) 750 kg/cm^2; (■) 3000 kg/cm^2.

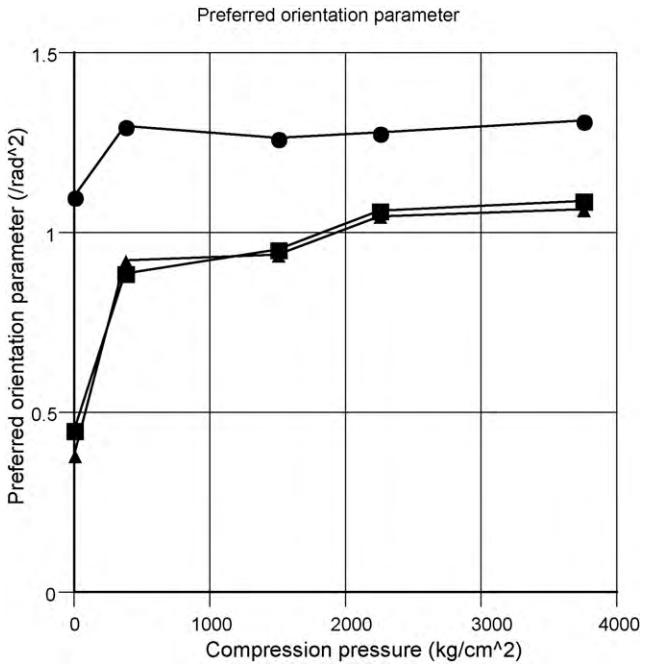

Fig. 8. Change of preferred orientation parameters of INH and MAN with compression pressure. Preferred-orientation plane: (●) (1 2 0) of MAN; (▲) (1 0 0) of INH; (■) (0 1 0) of INH.

tial stage of compression, and then the size of the crystallites decreased during the packing process, under higher compression pressure.

4. Conclusion

A pattern-fitting procedure made it possible to determine the crystalline phase of binary orthorhombic crystal systems of INH and MAN without calibration curve. Calibration free quantitative phase analysis was successfully employed in the range of 10–90% (w/w) of INH and MAN. The range of quantitative analysis may be expanded out of 10–90% by fitting with multiplying particular weights for observed intensities. Theoretically, this procedure can be extended also for three or more component systems. This method has also the advantage that by using it, the crystal characteristics of a particular sample, such as preferred orientation, crystallite size, and lattice disorder, can be simultaneously determined. However, it is necessary to determine the crystal structure of the sample before analysis, which is not a major hurdle because a database of crystal structures has been established and is easily accessible. Therefore, the pattern-fitting method is a potentially powerful tool for the quantitative phase analysis of crystal structures in tablets.

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