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# Quantitative analysis of crystalline pharmaceuticals in powders and tablets by a pattern-fitting procedure using X-ray powder diffraction data

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## Abstract

A pattern-fitting procedure for quantitative analysis of crystalline pharmaceuticals in solid dosage forms using X-ray powder diffraction data is described. This method is based on a procedure for pattern-fitting in crystal structure refinement, and observed X-ray scattering intensities were fitted to analytical expressions including some fitting parameters, i.e. scale factor, peak positions, peak widths and degree of preferred orientation of the crystallites. All fitting parameters were optimized by the non-linear least-squares procedure. Then the weight fraction of each component was determined from the optimized scale factors. In the present study, well-crystallized binary systems, zinc oxide–zinc sulfide (ZnO–ZnS) and salicylic acid–benzoic acid (SA–BA), were used as the samples. In analysis of the ZnO–ZnS system, the weight fraction of ZnO or ZnS could be determined quantitatively in the range of 5–95% in the case of both powders and tablets. In analysis of the SA–BA systems, the weight fraction of SA or BA could be determined quantitatively in the range of 20–80% in the case of both powders and tablets. Quantitative analysis applying this pattern-fitting procedure showed better reproducibility than other X-ray methods based on the linear or integral intensities of particular diffraction peaks. Analysis using this pattern-fitting procedure also has the advantage that the preferred orientation of the crystallites in solid dosage forms can be also determined in the course of quantitative analysis. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* Quantitative analysis; Pattern-fitting; X-ray powder diffraction; Solid dosage forms; Preferred orientation

## 1. Introduction

We have reported that crystallites in tablets showed a preferred orientation and the strength of the preferred orientation varied during compression of powders, as demonstrated by a pattern-fitting procedure (Fukuoka et al., 1993). The pattern-fitting procedure has been applied to crystal structure refinement using powder diffraction data, and this is called the Rietveld method (Rietveld, 1969; Cernik et al., 1991). The pattern-fitting procedure is also a powerful technique for characterizing solid materials (Lurrerotti and Scardi, 1990; Young and Sakthivel, 1988). There

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are some reports on quantitative analysis using the pattern-fitting procedure in the field of material science (Hill and Howard, 1987; Bish and Howard, 1988; Toraya and Tsusaka, 1995). Also, there are some reports on quantitative phase analysis of pharmaceutical mixtures based on the intensities of X-ray diffraction peaks (Tanninen and Yliruusi, 1992; Giron et al., 1990). They determined the weight fraction of components quantitatively by comparing the diffraction intensities with those of another component or an internal standard material. Many organic molecular crystals, as well as many pharmaceutical crystalline powders, are known to show a preferred orientation only when packed in the sample plate for the X-ray measurements. This suggests that the observed diffraction intensities may be modified by the preferred orientation of the crystallites and this would produce some errors in quantitative analysis.

In this study, we have applied a pattern-fitting procedure to quantitative analysis of X-ray powder diffraction data on crystalline pharmaceuticals in powders and tablets. The inorganic and organic systems, zinc oxide–zinc sulfide and salicylic acid–benzoic acid, were used as the samples. Because they are all well-crystallized powders, their X-ray diffraction patterns consist of sharp peaks with Bragg reflections and low background intensities. Therefore, further corrections for background intensity with change in degree of crystallinity would not be necessary in the analysis. So, they are considered to appropriate for the model samples to investigate the applicability of the pattern-fitting procedure for quantitative analysis. Moreover, the preferred orientation of the crystallites was corrected by using a suitable preferred orientation function in the pattern-fitting procedure. Thus both the contents and the preferred orientation of the crystallites in solid dosage forms can be analyzed simultaneously.

## 2. Theoretical

A pattern-fitting procedure using powder diffraction data can be applied to crystal structure analysis, the Rietveld method (Rietveld 1969; Cernik et al., 1991) and quantitative phase analysis (Young and Sakthivel, 1988; Lurrerotti and Scardi, 1990). In the Rietveld method, crystal structure is refined by fitting the observed diffraction intensities to a suitable analytical expression such as Eq. (1):

$$y(2\theta) = c\sum_i |F_i|^2 \cdot \mathrm{Lp}_i \cdot p_i \cdot G(2\theta - 2\theta_i) \cdot PO_i + y_b(2\theta), \tag{1}$$

where $y(2\theta)$ is the observed scattering intensity at $2\theta$, $c$ is the scale factor for normalization of the observed intensity to the electron unit, $i$ is the number of reflections, $F$ is the crystal structure factor, $Lp$ is the Lorentz-polarization factor, $p$ is the multiplicity, $PO$ is the preferred orientation function, $G$ is the peak shape function (profile function), $\theta_i$ is the Bragg angle of the $i$th reflection and $y_b$is the background intensity.

When the crystal structure of the sample has been determined, the integral diffraction intensity of the $hkl$ reflection ($I_{hkl}$)can be replaced by a constant as in Eq. (2) (Cullity, 1978a).

$$I_{hkl} = |F_{hkl}|^2 \cdot m_{hkl} \cdot Lp_{hkl} \tag{2}$$

Furthermore, the observed powder diffraction data in the case of a two-component system can be expressed as Eq. (3), base on Eq. (1) and Eq. (2).

$$y(2\theta) = C\left\{c_1 \sum_i I_i \cdot G\,(2\theta - 2\theta_i) \cdot PO_i + (1 - c_i)\sum_j I_j \cdot G\,(2\theta - 2\theta_j) \cdot PO_j\right\} + y_b(2\theta). \tag{3}$$

Here $C$ is the overall scale factor. The optimized $c_1$ seems to indicate a weight fraction of component 1. However, $c_1$ does not always indicate the weight fraction of component 1. The reasons are as follows. The integrated intensity of X-rays diffracted from a randomly oriented crystalline sample utilizing a diffracted beam monochromator can be written as Eq. (4) (Cullity, 1978b),

$$I_{hkl} = \left\{\left[\frac{I_0 A\lambda^3}{32\pi r}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{e^4}{m^2}\right]\left[\frac{1}{2\mu V^2}\right] \times \left[|F|^2 p\left(\frac{1+\cos^2 2\theta_m}{\sin^2\theta\cos\theta}\right)\mathrm{e}^{-2M}\right]\right\}, \tag{4}$$

where $I_{hkl}$ is the integrated intensity of the *hkl* reflection, $I_0$ is the intensity of the incident beam, $A$ is the cross-sectional area of the incident beam, $\lambda$ is the wavelength of the X-ray, $r$ is the radius of the diffractometer circle, $\theta_m$ is the Bragg angle of 0002 reflection of graphite (monochromator), $e$ is the charge on an electron, $m$ is the mass of an electron, $V$ is the volume of the unit cell, $e^{-2M}$ is the temperature factor and $\mu$ is the linear absorption coefficient. The first, second and third parentheses are dependend upon the instrumental conditions of the X-ray diffractometer, the chemical formula of the sample and the crystal structure of the sample, respectively. Comparing Eq. (1) and Eq. (4), the $c$ optimized by pattern-fitting can be written as Eq. (5)

$$c = \frac{K}{2\mu V^2} \quad K = \left[\frac{I_0 A \lambda^3}{32\pi r}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{e^4}{m^2}\right]. \tag{5}$$

Therefore, $2c\mu V^2$ of samples should become theoretically a constant $K$, depending on only instrumental conditions of the diffractometer. In practice, however, this relation does not always hold because the microabsorption and extinction effects in a mixed powder cannot be corrected on the basis of X-ray diffraction theory (Klug and Alexander, 1974; Cullity, 1978c). Furthermore, the pattern-fitting was carried out using diffraction data measured with a limited diffraction angle. This would produce some deviation from diffraction theory, and $2c\mu V^2$ would not be a constant for all samples.

In the present report, we introduce one more parameter, $k$, adjusting the deviation from the diffraction theory in Eq. (5) for each component as Eq. (6)

$$2c_1\mu_1 V_1^2 = 2(1-c_1)\mu_2 V_2^2 k, \tag{6}$$

where subscript 1 and 2 indicate the relationship to component 1 and 2, respectively. The parameter $k$ is the correction parameter for adjusting the deviation from X-ray diffraction theory between samples, and it is considered to include all other elements that are beyond control experimentally. The parameter $k$ was determined to compare the optimized scale factor of component 1 and 2 by pattern-fitting using the single component system ($k = c_2/c_1$). The $k$ value for powder and tablet samples were each determined. Thus, since $k$ can be determined before quantitative analysis, the content of component 1 can be calculated from $c$ and $k$ can be obtained from the pattern-fitting procedure without a calibration curve as Eq. (7).

$$X_1 = \frac{c_1}{c_1 + (1-c_1)/k}. \tag{7}$$

Use of Eq. (7) would make it possible a quantitative analysis of the crystalline samples by the pattern-fitting procedure, whether the linear absorption coefficients of the samples are closed or not.

## 3. Experimental

### 3.1. Materials

Zinc oxide (ZnO), zinc sulfide (ZnS), salicylic acid (SA) and benzoic acid (BA) (Koso Chemical Co. Ltd., Tokyo, Japan) were used without further purification and powders, having been passed through a 250 mesh (63 μm) sieve, were used. The ZnO–ZnS and SA–BA systems were used in the present investigation. The crystal structure of each of these materials has been determined: ZnO (Abrahams and Bernstein, 1969), ZnS (Reeber and Powell, 1967), SA (Sundaralingam and Jensen, 1965) and BA (Bruno and Randaccio, 1980). A 40 g portion of the two powers in various weight ratios (1, 2, 5, 10, 20, 40, 50, 60, 80, 90, 95, 98 and 99 w/w % of ZnO or SA) was mixed well with a V-type micromixer. Sample powders, 1 g (ZnO–ZnS system) or 0.5 g (SA–BA system), were packed in an aluminum plate.

### 3.2. Tableting

A 500 mg portion of sample powder was compressed under a pressure of 1000 kg/cm$^2$ by the direct compression method. The strength of preferred orientation of aspirin crystallites became constant in the tablet compressed under a pressure of more than 1000 kg/cm$^2$ (Fukuoka et al., 1993). This suggests that the preferred orientation of crystallites in the tablets compressed under

1000 kg/cm$^2$ is not influenced to the reproducibility of the results obtained by the pattern-fitting analysis. The die available for the sample plate for X-ray diffraction measurements was used for tableting (Fukuoka et al., 1993). The diameter of the tablet was 1.3 cm.

### 3.3. X-Ray diffraction (powder method)

A RINT 2500 diffractometer (Rigaku Co. Ltd. Japan) was used and symmetrical-reflection geometry was employed. The X-ray source was Cu–K$\alpha$ and the diffracted beam was monochromated using a bent-graphite monochromator. Other conditions were as follows: voltage, 50 kV; current, 100 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 25–65° ($2\theta$) in the case of the ZnO–ZnS system and 5–35° ($2\theta$) in the case of the SA–BA system at an interval of 0.05° ($2\theta$). The counting period was 2 s at each point. In the diffraction patterns of ZnO–ZnS systems, since double diffraction lines were observed with K$\alpha_1$ and K$\alpha_2$, the contribution by K$\alpha_2$ was removed assuming that the intensity ratio of K$\alpha_1$ and K$\alpha_2$ is 2:1. Polarization for X-ray powder diffraction was corrected using the equation described by Yao and Jinno (1982).

### 3.4. Pattern-fitting

In the present investigation, normalized modified Lorentzian (Eq. (8)) (Sonneveld and Visser, 1975), Gaussian (Eq. (9)) and linear functions were used for the profile function, the preferred orientation function and the background intensity, respectively. These functions have been shown to yield reasonable results in analysis of the preferred orientation of crystallites by pattern-fitting analysis (Fukuoka et al., 1993).

$$G = \frac{2\sqrt{c_{\text{ml}}}}{\pi\,\{1 + c_{\text{ml}}\,(2\theta - 2\theta_0)^2\}^2} \tag{8}$$

$$PO = \exp\,(-a\phi^2). \tag{9}$$

$c_{\text{ml}}$ is the parameter relating to peak width, $a$ is the preferred orientation parameter showing the strength of the preferred orientation of the crystallites and $\phi$ is the acute angle between the preferred orientation plane and ($hkl$) plane of the crystal. Eq. (8) is an expression normalized such that the integral intensity is unity. The preferred orientation plane is usually selected as normal to the cleavage plane for plate-like crystals and as parallel to the elongation axis for needle-like crystals (Sasa and Ueda, 1976). The preferred orientation planes used in the case of materials used in the present study are summarized in Table 1.

All fitting parameters were optimized by minimizing the value of Sum defined as Eq. (10) using the non-linear least squares procedure.

$$\text{Sum} = \sum_{i=1}^{N} w_i\{y_{\text{obs}}(2\theta_i) - y_{\text{cal}}(2\theta_i)\}^2, \tag{10}$$

$N$ is the data points, $w$ is the weight of the data given by $1/y_{\text{obs}}(2\theta_i)$, and $y_{\text{obs}}(2\theta_i)$ and $y_{\text{cal}}(2\theta_i)$ are the observed and calculated diffraction intensities at $2\theta_i$, respectively. The Bragg angle and the peak width parameter for each peak were dealt with as independent parameters in the calculation. A dumping Gauss–Newton algorithm was applied for non-linear least squares calculations. The computer program used for pattern-fitting was developed in our laboratory.

### 3.5. Some crystallographic parameters used in pattern-fitting

Table 2 and Table 3 summarize the intensity data used in the pattern-fitting in the case of ZnO, ZnS, SA and BA. The crystal structure factors of the reflections of ZnO and ZnS crystals were calculated from lattice parameters, atomic positions and atomic scattering factors (Ibers et al., 1973) following X-ray diffraction theory. The crystal structure factors of SA and BA were obtained from the literature (Sundaralingam and Jensen, 1965; Bruno and Randaccio, 1980). The intensity data of the diffraction peaks with an intensity less than 3% of the maximum intensity were neglected in the pattern-fitting calculation because these peaks would have contributed only slightly to the final result and would complicate the optimization by least-squares calculation. The preferred orientation planes for the four samples have to be selected by trial and error (Table 1). We tried to fit the observed intensities using several possible crystal planes as the preferred orientation plane, and the plane which showed best fit to the observed intensity was selected as the preferred orientation plane (Fukuoka et al., 1993).

## 4. Results and discussion

### 4.1. Quantitative analysis of ZnO–ZnS system by pattern-fitting

We first examined the ZnO–ZnS system to elucidate the validity of quantitative analysis by the pattern-fitting procedure. Since they are well-crystallized and fine inorganic materials, the diffraction patterns consist of sharp peaks with low background intensity and they would not show a strong preferred orientation.

Fig. 1 shows a typical example of the result of pattern-fitting in the case of the ZnO–ZnS system. The pattern-fitting was successful in the range of 5–95% ZnO content for both powders and tablets. In the case of samples containing more than 95% or less than 5% ZnO, the optimization criterion was not met, because the parameters for the diffraction peaks of week intensity obtained for samples with a smaller content were difficult to optimize by overall pattern-fitting. No change in the preferred orientation of ZnO or ZnS crystallites was found to occur as a result of tableting.

Fig. 2 and Fig. 3 show the plots of $c_{\mathrm{ZnO}}$ (Eq. (3)) and $X_{\mathrm{ZnO}}$ (Eq. (7)) determined by pattern-fitting against the weight fraction of ZnO in the case of the ZnO–ZnS system for powders and tablets. The standard deviation of optimized $c_{\mathrm{ZnO}}$ for the three different measurements was very small and the reproducibility was satisfactory. Further details will be discussed later. While the plots of $c_{\mathrm{ZnO}}$ against ZnO content (□) did not show a linear relationship, the plots of $X_{\mathrm{ZnO}}$ against ZnO content (○) calculated by means of Eq. (7) showed a good linear relationship. In this range of ZnO content, the slope and correlation coefficient ($r^2$) were 0.989, 0.999 for powders and 0.992, 0.999 for tablets, respectively. The reason that the plots of $c_{\mathrm{ZnO}}$ against ZnO content did not show a linear relationship may be the result of large difference in the linear absorption coefficient between ZnO and ZnS. This indicates that correction for the deviation from X-ray diffraction theory is required for quantitative analysis by the pattern-fitting procedure in a binary system such as powders with a large difference in the absorp-

Table 1
Crystallographic parameters for ZnO, ZnS, salicylic acid (SA) and benzoic acid (BA)[a]

| Crystal system | Hexagonal | | Monoclinic | |
|---|---|---|---|---|
| | ZnO | ZnS | SA | BA |
| Space group | $P6_3$mc | $P6_3$mc | $P2_1$/a | $P2_1$/c |
| $a$ (Å) | 3.249858 | 3.8226 | 11.52 | 5.510 |
| $b$ (Å) | 3.249858 | 3.8226 | 11.21 | 5.157 |
| $c$ (Å) | 5.206619 | 6.2605 | 4.92 | 21.973 |
| $\beta$ | – | – | 90.83 | 97.41 |
| $\rho$ (g/cm$^{-3}$) | 5.6730 | 4.085 | 1.41 | 1.44 |
| $\mu$ (cm$^{-1}$) | 287.68 | 285.01 | 6.201 | 6.815 |
| Preferred orientation plane | (100) | (100) | (210) | (001) |

[a] $\rho$ is the density and $\mu$ is the linear absorption coefficients. $\mu/\rho$ and $\mu$ for each elements were taken from (Macgillan et al., 1968).

Table 2
Crystallographic parameters used in pattern-fitting of the ZnO–ZnS system

| $2\theta$ | *hkl*[a] | *F*[b] | *m*[c] | Lp[d] | *I*[e] | $\varphi$[f] |
|---|---|---|---|---|---|---|
| *ZnO* | | | | | | |
| 31.9 | 100 | 31.08 | 6 | 21.86 | 50.1 | 0.00 |
| 34.5 | 002 | 50.46 | 2 | 18.43 | 37.1 | 90.00 |
| 36.3 | 101 | 35.74 | 12 | 16.49 | 100.0 | 28.39 |
| 47.6[g] | 102 | 22.53 | 12 | 9.16 | 22.1 | 47.23 |
| 56.6 | 110 | 48.89 | 6 | 6.27 | 35.6 | 30.00 |
| 62.9 | 103 | 38.29 | 12 | 5.02 | 34.9 | 58.34 |
| *ZnS* | | | | | | |
| 26.9 | 100 | 38.62 | 6 | 31.01 | 90.9 | 0.00 |
| 28.5 | 002 | 57.04 | 2 | 27.51 | 58.6 | 90.00 |
| 30.6 | 101 | 32.71 | 12 | 23.80 | 100.0 | 27.87 |
| 39.6 | 102 | 25.83 | 12 | 13.64 | 35.7 | 46.60 |
| 47.6 | 110 | 63.50 | 6 | 9.16 | 72.5 | 30.00 |
| 51.8 | 103 | 49.67 | 12 | 7.61 | 73.7 | 57.77 |
| 56.4 | 112 | 44.71 | 12 | 6.32 | 49.7 | 42.34 |

[a] Diffracting plane indices.

[b] Crystal structure factor.

[c] Multiplicity factor.

[d] Lorentz-polarization factor.

[e] Relative intensity.

[f] Angle between (*hkl*) and preferred orientation plane.

[g] Peak observed at 47.6° was considered to be sum of contribution of ZnO and ZnS.

tion coefficients. Thus, quantitative analysis by the pattern-fitting procedure is applicable to binary powders where the crystal structure has been determined, and also our findings indicate that the method is not appropriate for samples containing a small amount, less than 5%, of another component in inorganic materials.

### *4.2. Comparison of the precision and accuracy of quantitative analysis by pattern-fitting with other X-ray diffraction methods*

Fig. 4 shows the results of quantitative analysis by five different X-ray methods for the ZnO–ZnS tablet system. A plot of $X_{\rm ZnO}$ calculated from the results of pattern-fitting showed the best linear relationship with the ZnO content. When the absolute intensities of ZnO are used in the analysis, the plots deviated to below the line corresponding to a 1:1 relationship. Also, when the relative intensities of ZnO and ZnS are used in the analysis, the plots deviated above the line. These results indicate that the pattern-fitting is a good method for quantitative analysis in wide range of content of solid materials, and that the other X-ray methods were not suitable for quantitative analysis without use a calibration curve.

Table 4 summarizes the coefficients of variable for the calculated ZnO content obtained in three different measurements by five different X-ray methods. The coefficient of variable of $X_{\rm ZnO}$ determined by pattern-fitting was the smallest among the five methods, indicating that the pattern-fitting method is superior for quantitative analysis in terms of reproducibility. This would be

Table 3
Crystallographic parameters used in pattern-fitting of the SA–BA system

| $2\theta$ | *hkl*[a] | *F*[b] | *m*[c] | Lp[d] | *I*[e] | $\varphi$[f] |
|---|---|---|---|---|---|---|
| *Salicylic acid* | | | | | | |
| 11 | 110 | 39.8 | 4 | 193.19 | 58.62 | 18.59 |
| 15.4 | 200 | 25.6 | 2 | 98.21 | 6.16 | 27.19 |
| 17.3[g] | 210 | −59.1 | 4 | 77.24 | 51.67 | 0.00 |
| 25.2 | 121 | 105.8 | 4 | 35.11 | 75.28 | 55.51 |
| | 211 | 58.4 | 4 | 35.46 | 23.16 | 45.77 |
| 28.2 | 320 | 35.0 | 4 | 28.23 | 6.62 | 7.2 |
| 28.8 | 221 | 73.0 | 4 | 26.88 | 27.43 | 42.38 |
| 30.8 | 311 | 61.8 | 4 | 23.39 | 17.11 | 37.01 |
| *Benzoic acid* | | | | | | |
| 8.1 | 002 | 33.2 | 2 | 357.21 | 74.8 | 0.00 |
| 16.2 | 004 | 30.6 | 2 | 87.62 | 15.6 | 0.00 |
| | 100 | 41.2 | 2 | 88.17 | 28.4 | 82.59 |
| 17.2[g] | 102 | 82.0 | 2 | 78.33 | 100.0 | 69.41 |
| 19.1 | 012 | 19.7 | 4 | 63.57 | 9.4 | 64.67 |
| | 102 | 36.6 | 2 | 63.25 | 16.1 | 57.55 |
| 23.8 | 014 | 73.0 | 4 | 40.28 | 81.5 | 46.57 |
| 25.8 | 112 | 81.8 | 4 | 33.93 | 86.2 | 66.52 |
| 27.7 | 113 | 66.6 | 4 | 29.20 | 49.2 | 58.73 |
| 30.1 | 016 | 24.7 | 4 | 24.56 | 5.7 | 35.15 |
| | 114 | 56.2 | 4 | 24.56 | 29.5 | 52.04 |

[a] Diffracting plane indices.

[b] Crystal structure factor.

[c] Multiplicity factor.

[d] Lorentz-polarization factor.

[e] Relative intensity.

[f] Angle between (*hkl*) and preferred orientation plane.

[g] Peak observed at 17.3° was considered to be sum of contribution of benzoic acid and salicylic acid.

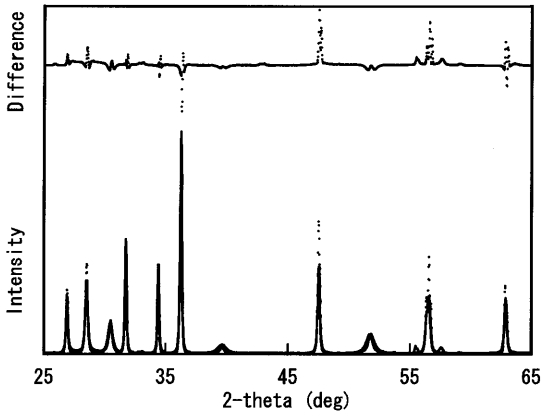

Fig. 1. Observed X-ray diffraction intensities (dots) and calculated profile (solid line) of the ZnO–ZnS (50:50) powder system. The difference between observed and calculated intensities is indicated.

because the results determined by the pattern-fitting procedure are not affected by the weight of the sample packed in the sample plate. These results indicate that quantitative analysis by pattern-fitting yields better results than other X-ray methods, in terms of both accuracy and precision.

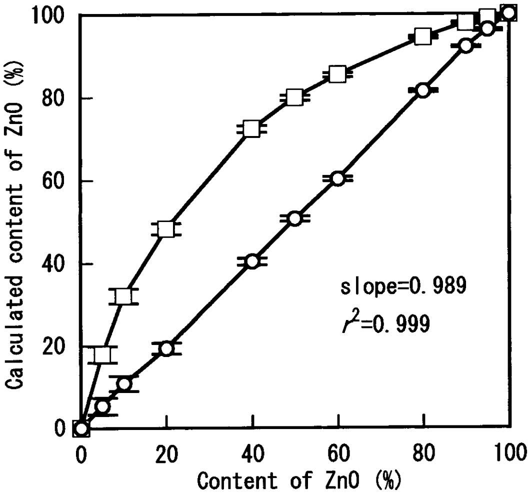

Fig. 2. Relationship between weight fraction and calculated ZnO content as determined by pattern-fitting in the case of the ZnO–ZnS powder system. □, $c_{ZnO}$; ○, $X_{ZnO}$ calculated by means of Eq. (7). Bars represent the standard deviation for three experiments. The slope was 0.989 and $r^2 = 0.999$ as determined by regression analysis.

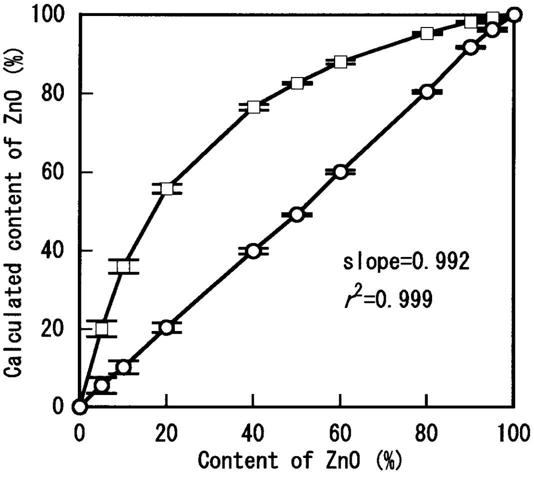

Fig. 3. Relationship between weight fraction and calculated ZnO content as determined by pattern-fitting in the case of the ZnO–ZnS tablet system. □, $c_{ZnO}$; ○, $X_{ZnO}$ calculated by means of Eq. (7). Bars represent the standard deviation for three experiments. The slope was 0.992 and $r^2 = 0.999$ as determined by regression analysis.

### *4.3. Quantitative analysis of the SA–BA system*

Fig. 5 shows a typical example of the results of pattern-fitting in the case of the SA–BA system. The pattern-fitting was successful in the range of 20–80% SA content for both powders and tablets. The range was narrower than that in the case of the ZnO–ZnS system. There were some weak diffraction peaks obtained on analysis of the SA and BA crystals thus the parameters for the weak peaks were difficult to optimize by overall pattern-fitting. This indicates that pattern-fitting was successful only within a narrow range in the case of the SA–BA system.

Fig. 6 and Fig. 7 show the calculated SA content plotted against the SA content for powders and tablets, respectively. Both $c_{SA}$ determined by means of Eq. (3) (□) and $X_{SA}$ calculated by means of Eq. (7) (○) when plotted against SA content showed a good linear relationship. Because the linear absorption coefficient and the volume of the unit cell SA and BA crystals are almost the same, there is little effect upon the correction by means of Eq. (5). In the range of 20–80% SA content, the slope and correlation coefficient ($r^2$) were 1.038, 0.995 for powders and 1.007, 0.995 for tablets, respectively. These results indicate that quantitative analysis by the pattern-fitting procedure is a powerful technique for organic crystalline pharmaceuticals.

Many organic crystalline pharmaceuticals were found to show a preferred orientation in the tablet. Based on the pattern-fitting results, the change in the preferred orientation of the SA and BA crystallites with the content was examined. Fig. 8 shows the change in the preferred orientation parameter of SA and BA crystallites in tablets. The preferred orientation of the SA crystallites was found to increase as the SA content decreased. This result suggests that a smaller content of SA would be lead to a change in preferred orientation during compression because the SA crystallites would have some elastic properties. On the other hand, since the BA crystallites would be compressed with plastic deformation, there was no change in preferred orientation with change of the BA content. This result also indicates that the pattern-fitting procedure is applicable to analysis of the content taking into account the preferred orientation of the organic pharmaceutical crystals.

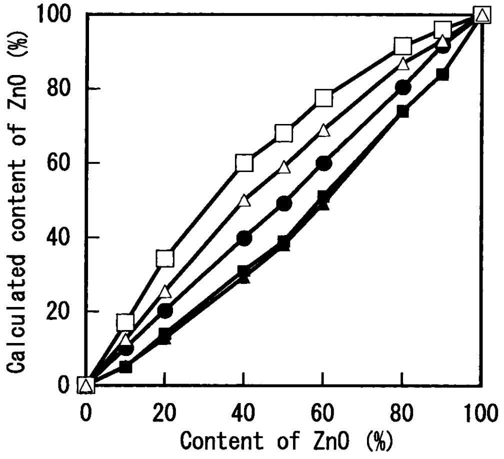

Fig. 4. Results of quantitative analysis of ZnO in the ZnO–ZnS system by five different X-ray methods. ●, plot of $X_{ZnO}$ calculated by means of Eq. (7) (pattern-fitting method), ■, plot of the sum of the line intensity of 100, 002 and 101 reflections of ZnO: $I_{ZnO}/I'_{ZnO} \times 100$, where $I'$ is the integral intensity determined for ZnO powder without ZnS; ▲, plot of the integral intensities of 100, 002 and 101 reflections of ZnO::$I_{ZnO}/I'_{ZnO} \times 100$, where $I'$ is the integral intensity determined for ZnO powder without ZnS; □, plot of the ratio of the line intensities of 100, 002 and 101 reflections of ZnO against the sum of those of ZnO and ZnS; :$I_{ZnO}/(I_{ZnO}+I_{ZnS}) \times 100$; △, plot of the ratio of the integral intensities of 100, 002 and 101 reflections of ZnO against the sum of those of ZnO and ZnS;: $I_{ZnO}/(I_{ZnO}+I_{ZnS}) \times 100$.

Table 4
Coefficient of variance of ZnO contents determined with five different X-ray methods[a]

| Method | c.v. (%) |
|---|---|
| Pattern-fitting method[b] | 0.4 |
| Line intensity method 1[c] | 2.8 |
| Integral intensity method 1[d] | 1.3 |
| Line intensity method 2[e] | 2.3 |
| Integral intensity method 2[f] | 1.1 |

[a] c.v. is determined from three different measurements. Composition: ZnO–ZnS = 50:50 (w/w).

[b] $X_{ZnO}$ calculated by pattern-fitting by means of Eq. (7).

[c] The ZnO content was calculated using the sum of the line intensities of the 100, 002 and 101 reflections of ZnO by $I^{line}_{ZnO}/I^{line'}_{ZnO} \times 100$, where $I^{line}$ is the line intensity of ZnO powder without ZnS.

[d] The ZnO content was calculated using the sum of the integral intensities of the 100, 002 and 101 reflections of ZnO by $I^{int}_{ZnO}/I^{int'}_{ZnO} \times 100$, where $I^{int'}$, is the integral intensity of ZnO powder without ZnS.

[e] The ZnO content was calculated using the ratio of the sum of the line intensities of the 100, 002 and 101 reflections of ZnO and ZnS by $I^{line}_{ZnO}/(I^{line}_{ZnO}+I^{line}_{ZnS}) \times 100$.

[f] The ZnO content was calculated using the ratio of the sum of the integral intensities of the 100, 002 and 101 reflections of ZnO and ZnS by $I^{int}_{ZnO}/(I^{int}_{ZnO}+I^{int}_{ZnS})$.

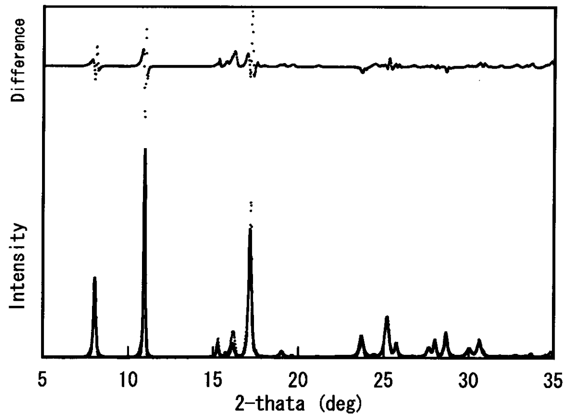

Fig. 5. Observed X-ray diffraction intensities (dots) and calculated profile (solid line) of the SA–BA (50:50) powder system. The difference between observed and calculated intensities is indicated.

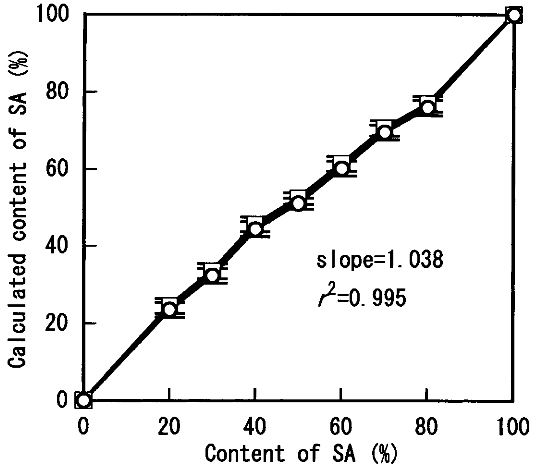

Fig. 6. Plot of SA content calculated from fitting parameters against SA content in the case of the the SA–BA powder system. □, $c_{SA}$; ○, $X_{SA}$ calculated by means of Eq. (7). Bars represent the standard deviation for three experiments. The slope as 1.038 and $r^2 = 0.995$ as determined by regression analysis.

## 5. Conclusion

We have found that the pattern-fitting procedure is a powerful technique for quantitative analysis of well-crystallized inorganic materials and organic pharmaceuticals. Using this method, it is not necessary to use a calibration curve when the diffraction pattern of single component system has been measured. The pattern-fitting procedure was found to be superior to other X-ray methods in terms of both precision and accuracy. The preferred orientation parameters can be optimized during pattern-fitting, indicating that both quantitative analysis and analysis of the preferred orientation in tablets can be performed simultaneously.

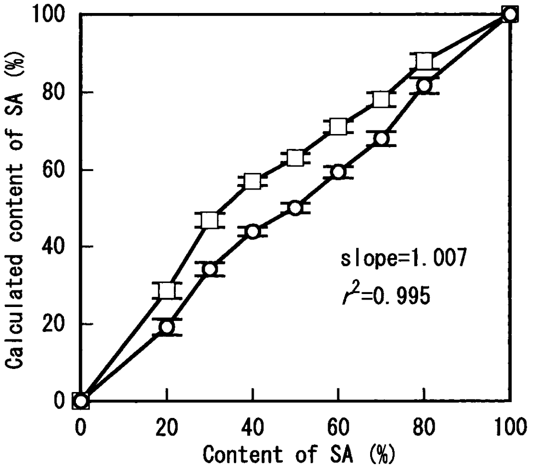

Fig. 7. Plot of SA content calculated from fitting parameters against SA content in the case of the SA–BA tablet system. □, $c_{SA}$; ○, $X_{SA}$ calculated by means of Eq. (7). Bars represent the standard deviation for three experiments. The slope as 1.007 and $r^2 = 0.995$ as determined by regression analysis.

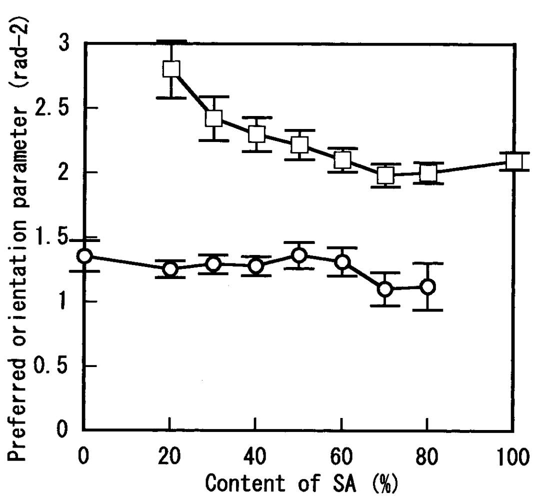

Fig. 8. Change in the preferred orientation parameter for SA and BA with the ratio of their contents. □, SA; ○, BA. Bars represent the standard deviation for three experiments.

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