Preferred Orientation of Crystallites in Tablets. III.[1] Variations of Crystallinity and Crystallite Size of Pharmaceuticals with Compression[2]

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Variation of the degree of crystallinity, lattice-disorder and crystallite size of pharmaceuticals with compression were investigated by X-ray powder diffraction method. The degree of crystallinity and lattice-disorder parameter were determined by Ruland's method. Crystallite size was calculated by Scherrer's equation after correction for the instrumental broadening of the diffraction line. Crystalline powders of aspirin and nicotinic acid were used as samples.

The degree of crystallinity, lattice-disorder and crystallite size of pharmaceuticals varied with compression. In aspirin, the degree of crystallinity and crystallite size calculated from the profile of 100 reflection decreased and lattice-disorder increased with compression. The degree of crystallinity and crystallite size remarkably decreased immediately after compression and then recovered gradually with stress relaxation. In nicotinic acid powder, however, although the degree of crystallinity decreased and lattice-disorder increased with compression, these features did not recover with stress relaxation.

Keywords crystallinity; crystallite size; tablets; X-ray powder diffraction; Ruland's method

X-Ray powder diffraction methods were employed to evaluate the preferred orientation of crystallites in tablets using some crystalline powders (aspirin, salicylic acid, benzoic acid and nicotinic acid).[1] It has been said that crystalline particles are deformed plastically and/or are partially destroyed during compression.[3] Although the dissolution properties of some pharmaceuticals were reportedly affected by the degree of crystallinity,[4] there have been few reports on variation of the degree of crystallinity of pharmaceuticals with compression.

In the present study, the crystalline powders aspirin and nicotinic acid were compressed under various conditions, and the degree of crystallinity (X_{cr}) and lattice-disorder parameter (k) were determined by Ruland's method (an X-ray powder diffraction method). Mean crystallite size (L_{100}) of aspirin in a tablet perpendicular to the 100 plane was calculated by Scherrer's equation,[5] after extracting the pure diffraction profile free of instrumental line broadening. The correlations of preferred orientation tendency and variation of the X_{cr}, k and L_{hkl} are then discussed.

Experimental

Materials Aspirin (JP grade, Iwaki Pharmaceutical Co., Ltd.) and nicotinic acid (reagent grade, Daiichi Pure Chemicals Co., Ltd.) were used without further purification. Fine powders, having been passed through a 250 mesh (63 μm) sieve, were used as sample.

Tableting Two hundred fifty mg of sample powder was compressed using a KBr disc press for infrared spectrophotometry by a direct compression method. Diameter and thickness of each tablet were 1.3 cm and about 1.2 mm, respectively.

X-Ray Diffraction (Powder Method) A Geigerflex RAD type X-ray diffractometer (Rigaku Denki, Co., Ltd.) was used. X-Ray scattering intensities were measured by symmetrical-reflection geometry. Other measurement conditions were the same as described.[1] Control of the goniometer and collection of scattering intensities ($I(s)$ or $I(2\theta)$) were carried out using a HP9816S model 216 computer (Hewlett-Packard Co., Ltd.).

1) X-Ray scattering intensities for the determination of X_{cr} and k were obtained by a fixed-time step-scanning method in the range of 0.04 (integral lower limit) -1.24 in s at an interval of 0.001 (s). s is the magnitude of radial vector in reciprocal space, $s=2\sin\theta/\lambda$. The counting period was 10 s at each point.

2) X-Ray diffraction profiles for the calculation of L perpendicular to 100 reflection of aspirin were obtained by the fixed-time step-scanning method in the range of 6.5—9.0 (2θ) at intervals of 0.02 (2θ). The counting period was 50 s at each point. The profile of 100 reflection from the (100)-face of aspirin crystal, cut out to exhibit 13 mm i.d. of (100)-face from well growth large crystal, was used as a standard profile having no crystallite broadening.

Results and Discussion

Determination of the Degree of Crystallinity and Lattice-Disorder Parameter by Ruland's Method Ruland's method[6] conforms closely to X-ray diffraction theory and yields X_{cr} and k from X-ray scattering intensities by Eq. 1.

$$X_{cr}=\frac{\int_{s_o}^{s_p} s^2 I_c(s)\mathrm{d}s \cdot \int_{s_o}^{s_p} s^2 \bar{f}^2(s)\mathrm{d}s}{\int_{s_o}^{s_p} s^2 I(s)\mathrm{d}s \cdot \int_{s_o}^{s_p} s^2 \bar{f}^2(s) D\mathrm{d}s} \quad (1)$$

where X_{cr} is the degree of crystallinity, s is the magnitude of radial vector in reciprocal space, and s_o and s_p are integral lower and upper limits, respectively. $I(s)$ is the intensity of coherent X-ray scattering from sample at s, $I_c(s)$ is the diffraction intensity from the crystalline regions at s, $\bar{f}^2$ is the weighted mean-square atomic-scattering factor and D is a disorder function which was assumed to be given as Gaussian function (Eq. 2).

$$D=\exp(-ks^2) \quad (2)$$

where k is a lattice-disorder parameter.

Some computerized procedures based on Ruland's method have been reported.[7] In the present study, X_{cr} and k were determined according to the method reported by Nakai *et al.*[7a] BASIC computer program was developed in our laboratory. Coherent and incoherent atomic scattering factors were calculated with analytic approximations.[8,9]

The applicability of Ruland's method to experimental X-ray scattering curves presupposes that the crystallites in the specimen have a random orientation. This means that X_{cr} and k of a compressed specimen may not be determined by Ruland's method because of the probability of preferred orientation of crystallites in the tablet. Observed X-ray scattering patterns of aspirin powders having no preferred

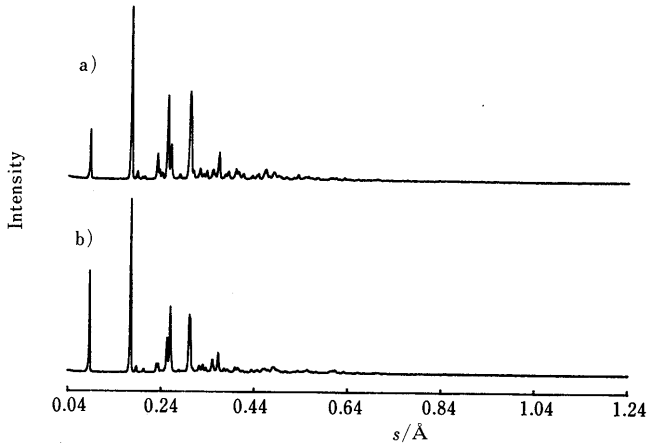

Fig. 1. Normalized X-Ray Scattering Intensities of Aspirin Powder and Tablet

a) powder; b) tablet.

orientation and that of an aspirin tablet having a preferred orientation were normalized to electron units[7a] and are shown in Fig. 1. A preferred orientation of crystallites primarily affected the intensities at relatively low scattering angle in the present cases. In the analysis by Ruland's method, because the scattering intensities were multiplied by s^2, those at low scattering angle would have little influence on the calculated value of X_{cr}; and because the diffraction intensities at low scattering angle were less modified by lattice disorder, they would have little influence on the calculated value of k. Furthermore, the integrated normalized scattering intensities, $\int_{s_o}^{s} s^2 I ds$, of aspirin powder and tablet were almost equal above $s=0.35$. It is therefore considered that if the value above 0.35 was selected as the smallest integral upper limit, preferred orientation of crystallites in a tablet would have little influence on the calculated values of X_{cr} and k. Thus, 0.36, 0.60, 0.80, 1.00 and 1.20 (s) were selected as integral upper limits with reference to the Y-function.[7a] For nicotinic acid, 0.40, 0.60, 0.80, 1.00 and 1.20 (s) were selected as integral upper limits.

Calculation of Crystallite Size It is known that small crystallites of less than about 0.1 μm cause broadening of the X-ray diffraction line.[5] As the X-ray diffraction line profile is affected not only by crystallite size but also by instrumental broadening, the observed diffraction profile, $h(\varepsilon)$, is expressed as the convolution of the instrumental profile, $g(\varepsilon)$, and the pure diffraction profile, $f(\varepsilon)$, as Eq. 3.

$$h(\varepsilon)=\int_{-\infty}^{\infty} g(\eta)f(\varepsilon-\eta)d\eta \tag{3}$$

$$\int_{-\infty}^{\infty} g(\varepsilon)d\varepsilon=1 \tag{4}$$

where ε and η are appropriate angle scales (2θ in the present study). It is necessary to know the pure diffraction profile free of instrumental broadening in precise studies of breadth of the X-ray diffraction line. In this study, the pure diffraction profile $f(\varepsilon)$ was calculated by Ergun's successive convolution method.[10] The procedure was as follows: A $g(\varepsilon)$ is normalized as Eq. 4. A first approximation of f, $f_1(\varepsilon)$, can be obtained by subtracting the convolution products of $g(\varepsilon)$ and $h(\varepsilon)$ from $h(\varepsilon)$ and then adding this difference to $h(\varepsilon)$.

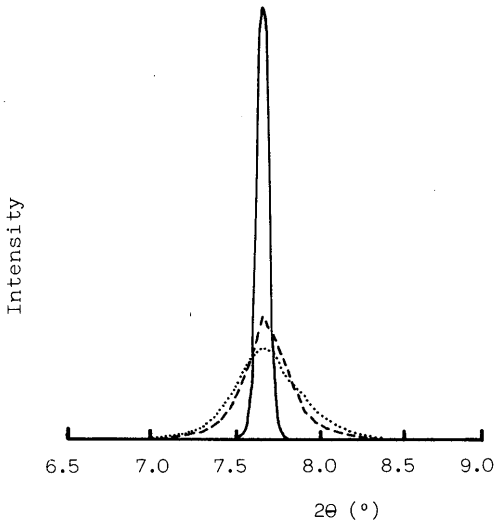

Fig. 2. Profiles of the 100 Reflection of Aspirin

——, single crystal (instrumental profile); – – –, calculated profile free of instrumental broadening; ------, experimentally observed profile.

The second approximation, $f_2(\varepsilon)$, is given by subtracting the convolution products of $g(\varepsilon)$ and $f_1(\varepsilon)$ from $h(\varepsilon)$ and then adding the difference to $f_1(\varepsilon)$. The operation was repeated until a convergence criterion was satisfied, then the pure diffraction profile $f(\varepsilon)$ was obtained. Figure 2 shows the typical profiles of $h(\varepsilon)$, $g(\varepsilon)$ and $f(\varepsilon)$.

Mean crystallite size was calculated by Scherrer's equation[5] (Eq. 5),

$$L_{hkl}=\frac{K\lambda}{B\cos\theta} \tag{5}$$

where L_{hkl} is the mean crystallite size perpendicular to the plane hkl, λ is wavelength of X-ray, B is the integral breadth of pure diffraction profile in radians, θ is a Bragg angle and K is Scherrer constant approximately equal to unity.[5]

The successive convolution and calculation of L_{hkl} were carried out using the BASIC program developed in our laboratory. When the calculation of L_{100} for aspirin powder was repeated 3 times, triplicates deviated less than 10 Å from the mean.

Variation of X_{cr}, k and L_{100} of Aspirin with Compression Aspirin powders were compressed under various pressures for 1 min, and their X_{cr} and k were determined by Ruland's method. Figure 3 shows X_{cr} and k of aspirin tablets plotted against compression pressure. As compression pressure increased, X_{cr} decreased gradually up to about 1500 kg/cm^2 and then slightly increased, while k increased and remained constant. Figure 4 shows L_{100} of aspirin tablet plotted against compression pressure. L_{100} decreased with increase in the pressure up to about 1500 kg/cm^2 and then slightly increased. Decrease in X_{cr} and L_{100} and increase in k with compression are considered to result from disorder of the crystalline region and destruction of crystallites by the strong compression force. The subsequent increase in X_{cr} and L_{100} may be the result of the molecules, made more mobile with destruction of the crystallites rearranging so that they reproduce ordered crystallites in the tablet.

Variation of X_{cr}, k and L_{100} of Aspirin Tablet by Stress Relaxation Aspirin powder was compressed under 1500 kg/cm^2, and kept under the compression for various

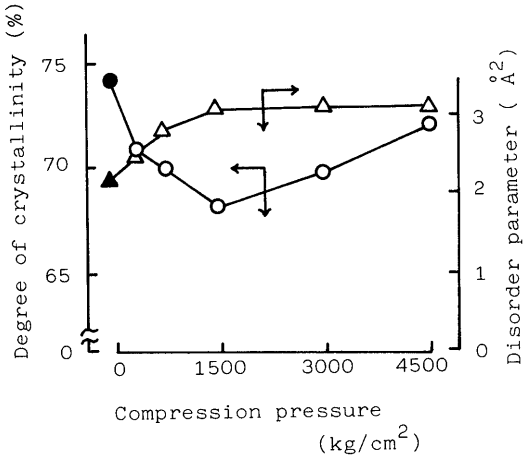

Fig. 3. Variation of X_{cr} and k of Aspirin with Compression

Compression time, 1 min. Closed symbols represent the values for aspirin powder.

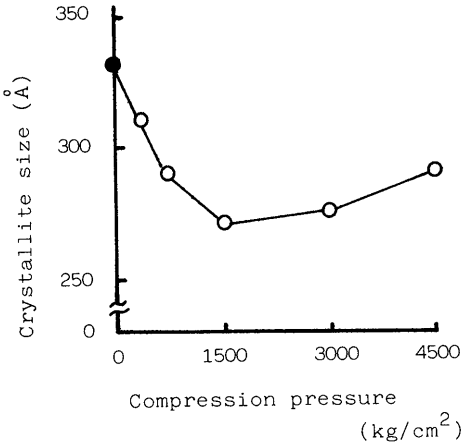

Fig. 4. Variation of Crystallite Size of Aspirin Calculated from the Profile of 100 Reflection with Compression

Compression time, 1 min. Closed symbol represents the value for aspirin powder.

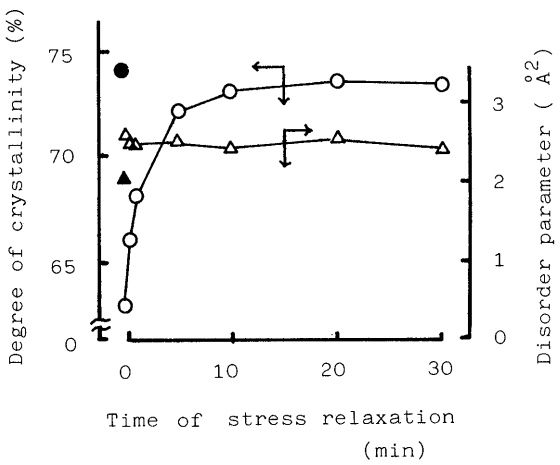

Fig. 5. Variation of X_{cr} and k of Aspirin with Stress Relaxation

Compression pressure, 1500 kg/cm². Closed symbols represent the values for aspirin powder.

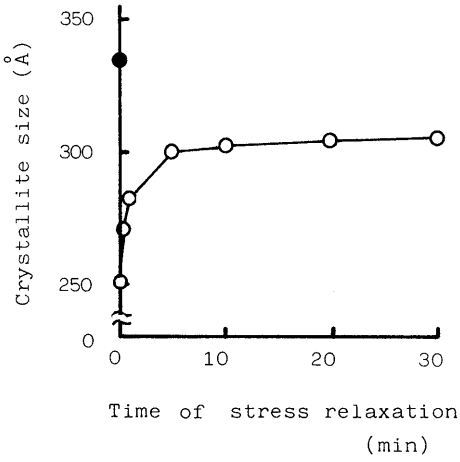

Fig. 6. Variation of Crystallite Size of Aspirin Calculated from the Profile of 100 Reflection with Stress Relaxation

Compression pressure, 1500 kg/cm². Closed symbol represents the value for aspirin powder.

periods of time. The X_{cr}, k and L_{100} of the tablets were determined. Figure 5 shows the variation of X_{cr} and k, and Fig. 6 the variation of L_{100} induced by stress relaxation. X_{cr} and L_{100} decreased remarkably immediately after compression and then increased gradually with stress relaxation, while k increased with compression and did not change with stress relaxation. These results indicate that a part of the crystalline region of aspirin powder was disordered and the crystallites were destroyed immediately after compression; then part of the molecules in the crystallites destroyed by compression may have become arranged with stress relaxation so as to reproduce the crystalline order.

As shown in Figs. 3—6, change in X_{cr} of aspirin tablet with compression was well correlated to that in L_{100}, suggesting that the width of the line profile of a particular diffraction line reflected the degree of crystallinity of sample.

It was reported previously[2b] that the 100 plane of aspirin was a preferred orientation plane having a tendency to orient parallel to the upper surface of the tablet during compression. A shearing movement along the (100) plane occurs easily in aspirin crystal.[11] These results may indicate that a preferred orientation of crystallites in the tablet occurred by the shearing movement of molecules along the (100) plane of aspirin crystals, so that L_{100} markedly decreased immediately after compression. It is further considered that since the molecules moved by compression were rearranged so as to reproduce the crystalline order during continued compression, X_{cr} and L_{100} were restored by stress relaxation. The disorder produced by compression was believed to remain after the tablet was ejected from the die.

Variation of X_{cr} and k of Nicotinic Acid with Compression

Nicotinic acid powder was compressed under various pressures for 1 min, and the X_{cr} and k were determined by Ruland's method. Figures 7 and 8 show X_{cr} and k of nicotinic acid tablet as plotted against compression pressure and against time for stress relaxation, respectively. X_{cr} decreased and k increased by the compression, but there was little change in either as pressure was varied. There was also no change in X_{cr} or k with stress relaxation. These results indicate that a part of the crystalline region of nicotinic acid was disordered or destroyed by the compression. The subsequent arrangement of molecules, however, may not readily occur during compression of stress relaxation, because nicotinic acid crystals presumably do not have

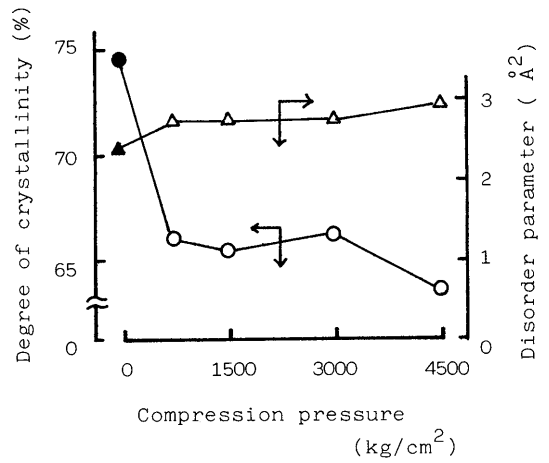

Fig. 7. Variation of X_{cr} and k of Nicotinic Acid with Compression

Compression time, 1 min. Closed symbols represent the values for nicotinic acid powder.

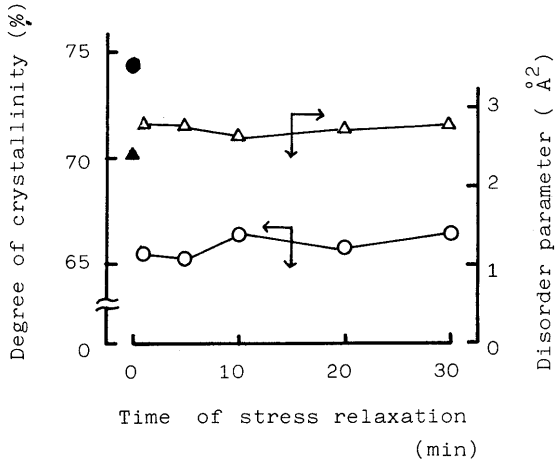

Fig. 8. Variation of X_{cr} and k of Nicotinic Acid by Stress Relaxation

Compression pressure, 1500 kg/cm^2. Closed symbols represent the values for nicotinic acid powder.

a plane showing a shearing movement. Nicotinic acid crystallites may thus have a slight tendency to orient preferentially in a tablet rather than in aspirin.[1b] Because the profile of 002 reflection in nicotinic acid, which corresponds to the preferred orientation plane, overlaps with other profiles, crystallite size (L_{002}) cannot be determined quantitatively.

In conclusion, it was found that the degree of crystallinity, lattice disorder and crystallite size of crystalline pharmaceuticals changed with compression. In aspirin and nicotinic acid, the degree of crystallinity decreased with compression. While the degree of crystallinity of aspirin was restored with stress relaxation, that of nicotinic acid did not change. These results seem to depend on the such properties of a crystal as whether or not it has a plane exhibiting a shearing movement. They suggest that the variation of the degree of crystallinity with stress relaxation may be correlated to a preferred orientation tendency of crystallites in a tablet.

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References and Notes

1) *a*) Part I: E. Fukuoka, M. Makita and S. Yamamura, *Chem. Pharm. Bull.*, **35**, 1564 (1987); *b*) Part II: *idem*, *ibid.*, **39**, 3313 (1991).
2) A part of this work was presented at the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, April 1985.
3) S. T. David and L. L. Augsburger, *J. Pharm. Sci.*, **66**, 155 (1977); R. J. Roberts and R. C. Rowe, *J. Pharm. Pharmacol.*, **38**, 567 (1986).
4) M. Morita, Y. Nakai, E. Fukuoka and S. Nakajima, *Chem. Pharm. Bull.*, **32**, 4076 (1984); D. J. Allen and K. C. Kwan, *J. Pharm. Sci.*, **58**, 1190 (1969); J. W. McGinity, P. Maincent and H. Steinfink, *ibid.*, **73**, 1441 (1984).
5) H. P. Klug and L. E. Alexander, "X-Ray Diffraction Procedures for Polycrystalline and Amorphous Materials," 2nd ed., John Wiley and Sons, New York, 1974.
6) W. Ruland, *Acta Crystallogr.*, **14**, 1180 (1961).
7) *a*) Y. Nakai, E. Fukuoka, S. Nakajima and M. Morita, *Chem. Pharm. Bull.*, **30**, 1811 (1982); *b*) C. G. Vonk, *J. Appl. Crystallogr.*, **6**, 148 (1973).
8) "International Tables for *X*-Ray Crystallography," Vol. IV. Kynoch Press, Birmingham, 1974.
9) G. Palinkas and T. Radnai, *Acta Crystallogr.*, **A32**, 666 (1976).
10) S. Ergun, *J. Appl. Crystallogr.*, **1**, 19 (1968).
11) H. Hess, *Pharm. Technol.*, **2**, 38 (1978).