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Change of the Microstructure of Microcrystalline Cellulose with Grinding and Compression

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Abstract

The microstructure of microcrystalline cellulose was investigated by use of a radial distribution function (RDF) based on the intensity of X-ray scattering data. Changes in the microstructure of the cellulose as a result of grinding and compression were detected by use of the RDF.

The RDF of intact microcrystalline cellulose had peak maxima corresponding to distances of approximately 1·5, 2·6, 5·0, 8·2, 13·3 and 17·0 Å. The first two corresponded to the intramolecular atomic distances; other peaks were attributable to the intermolecular (inter-fibre) atomic distance. Changes in the RDF as a result of grinding indicated that the regular intermolecular atomic arrangement was gradually lost. Compression resulted in formation of long-range (> 20 Å) ordering of the intermolecular (inter-fibre) atomic arrangement.

These results show that RDF analysis is suitable for monitoring changes in the structure of microcrystalline cellulose which occur as a result of grinding and compression.

Many cellulose derivatives are used in the pharmaceutical industry. Microcrystalline cellulose has been widely used as an excipient or binder in pharmaceutical formulations. Nakai et al (1977a, b, c) studied the physicochemical properties of microcrystalline cellulose and discovered anomalous properties of ground mixtures of the material with medicinal products. Moreover, microcrystalline cellulose has been reported to show batch variations influencing its pharmaceutical properties (Soltys et al 1984; Landin et al 1993; Rowe et al 1994) – correlation was found between the extent of crystallinity and other physicochemical properties of the microcrystalline cellulose. On the other hand, the most important parameter affecting the breaking strength of cellulose tablets was reported to be the specific surface area, although no correlation was found between crystallinity and the strength of the tablets (Pesonen & Paronen 1990). This suggests that the extent of crystallinity does not always reflect the pharmaceutical properties of microcrystalline cellulose, other structural parameters also being important.

In this study we have used a radial distribution function (RDF) to characterize the microstructure of microcrystalline cellulose by use of X-ray diffraction intensities. The change in the structure of microcrystalline cellulose as a result of grinding and compression was then determined and the relationship between crystallinity and the microstructure of microcrystalline cellulose was also investigated.

Materials and Methods

Materials

Microcrystalline cellulose (Avicel PH102, Asahi Kasei, Japan) was used after passage through a 250-mesh (63 μm) sieve. Ground samples were prepared using a tungsten carbide ball-mill (Fritsch P-6 grinding apparatus). The tablets were prepared by direct compression using a flat-faced punch 1·30 cm in diameter under a pressure of 441 Mpa. The die available with the sample plate was designed and used for tableting and subsequent X-ray measurements (Fukuoka et al 1993b).

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X-ray diffraction (powder method)

X-ray diffraction intensities were measured with a Rint 2500 X-ray diffractometer (Rigaku, Japan) under ambient conditions (approximately 20°C and 70% relative humidity). The X-ray source was Mo-K_α ($\lambda = 0{\cdot}7108$ Å) for RDF analysis and the Cu-K_α ($\lambda = 1{\cdot}5418$ Å) for determination of crystallinity. The diffracted beam was monochromated by means of a bent-graphite monochromator. Scan ranges in 2θ were 4–136° in steps of 0·5° (RDF) and 3–143° in steps of 0·5° (crystallinity). A fixed-time step-scanning method was employed to obtain the diffractogram, and the fixed time was 2 s at each point. Observed diffraction intensities, I(2θ), were converted into I(s) ($s = 2 \sin\theta/\lambda$). Other conditions were: voltage, 50 kV; current, 100 mA; divergence and scatter slits, 1·0°; receiving slit, 0·15 mm. The sample powder was packed on an aluminium plate (20 × 18 mm) with a square hole.

To calibrate the scattering of X-rays by air and the sample plate for RDF analysis the X-ray scattering intensities from the sample plate without sample powder were measured before measurement of the sample pattern; these values were then subtracted from the intensities of the sample pattern. After corrections for air scattering and polarization of the X-rays (Yao & Jinno 1982), the scattering intensities were normalized in electron units in the usual way, assuming that the intensities at a high scattering angle ($s > 2{\cdot}00$) were not affected by Bragg reflections. Thus the scattering intensities were multiplied by an appropriate constant so that the intensities at a higher scattering angle were equal to the sum of the coherent and incoherent atomic scattering factors. Coherent and incoherent atomic scattering factors were calculated from analytical expressions (Cromer & Waber 1974; Palinkas & Radnai 1976).

Radial distribution function (RDF)

The RDF values were calculated theoretically. The scattering intensities at 2θ, I(2θ), in electron units, scattered by non-

crystalline substances are given by:

$$I(2\theta) = \sum_i \sum_j f_i f_j \sin Sr_{ij}/Sr_{ij} \quad (1)$$

where f_i and f_j are the respective atomic scattering factors of the ith and jth atoms, S is the radial vector in reciprocal space ($=4\pi\sin\theta/\lambda$) and r_{ij} is the vector distance between the ith and jth atoms. In principle, equation 1 makes it possible to calculate the scattering curve corresponding to any atomic arrangement irrespective of whether or not the substance is an amorphous structure. However, this procedure is limited in practice to amorphous and fibrous substances (Alexander 1969).

The RDF is evaluated by comparing the experimental scattering curve with the theoretical functions by application of the Fourier integral theorem. When a substance consists of more than one kind of atom, an RDF in electron units is expressed by equation 2, using the s ($=2\sin\theta/\lambda$) scale (Warren 1969):

$$\sum K_m 4\pi r^2 \rho_m(r) = \sum K_m 4\pi r^2 \rho_0 + 8\pi r \int si(s) \times \exp(-\alpha^2 s^2) \sin(2\pi sr) ds \quad (2)$$

$$i(s) = (I(s)_{normal} - \sum f_m^2 - \sum I_{m,inco})/f_e^2 \quad (3)$$

where K_m is the effective number of electrons of atomic species m defined as the ratio f_m/f_e where f_m and f_e are the atomic scattering factor and the mean electron scattering factor, respectively ($f_e = \sum f_m/\sum Z_m$ where Z_m is the atomic number). ρ_0 is the mean electron density in the specimen and ρ_m is the electron-density distribution function. $\exp(-\alpha^2 s^2)$ is the damping factor (arbitrary temperature factor), $I(s)_{normal}$ is the normalized scattering intensity and I_{inco} is the incoherent atomic scattering factor (Compton scattering factor). Without the dumping factor, we would be giving equal weight to the peaks and dips of the si(s) function in equation 2, although the experimental accuracy is low at large s because of the weak coherent scattering intensity at high scattering angles. Warren (1969) has recommended that α be taken as $\alpha^2 S_{max}{}^2 = 1{\cdot}0$. In the current investigation, because S_{max} ($=4\pi \sin\theta/\lambda$) is approximately 16·4/Å, the value of 0·06 Å^2 was used for α. By Fourier transformation an electron RDF, $\sum K_m 4\pi r^2(\rho_m(r) - \rho_0)$, was calculated from the normalized X-ray scattering intensities. A computer program for the determination of RDF was developed in our laboratory.

Determination of crystallinity

The crystallinity of microcrystalline cellulose was determined by the method of Ruland (1961). The computer program was developed in our laboratory (Fukuoka et al 1993a).

Results and Discussion

RDF of microcrystalline cellulose powder

Fig. 1 shows an RDF of intact microcrystalline cellulose powder. It has peaks corresponding to distances of approximately 1·5, 2·6, 5·0, 8·2, 13·3 and 17·0 Å, indicative of regions of rich electron density. In other words, the peaks and dips in the RDF indicate the presence of regular arrangements at the atomic level. The first two peaks in the RDF are attributable to the vector distances between C–C (approximately 1·54 Å) or C–O (approximately 1·45 Å) and between the second neighbours of C–C–C, C–O–C or O–C–C in the intramolecular atomic pairs.

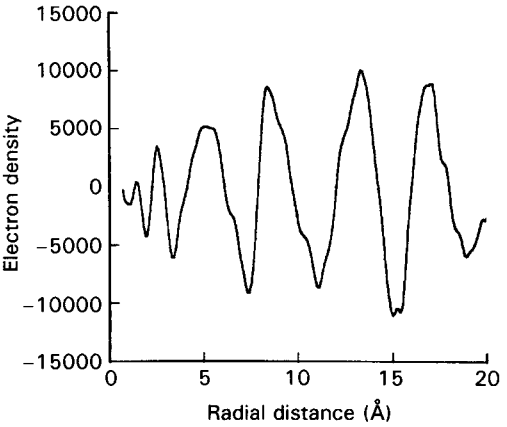

FIG. 1. The radial distribution function of intact microcrystalline cellulose powder.

The crystal structure of cellulose has been reported as a space group: $P2_1$, and a = 8·35 Å, b = 10·3 Å, c = 7·9 Å and $\beta = 84°$ (Meyer & Misch 1937). Table 1 summarizes the intermolecular atomic distances calculated from the crystal structure of cellulose. Peaks corresponding to distances greater than 5·0 Å were attributable to vectors between the intermolecular atomic distance. Intact microcrystalline cellulose was found to have a regular atomic arrangement even beyond 15 Å, suggesting that intact microcrystalline cellulose preserves the regular atomic arrangements at the intermolecular (inter-fibre) level.

Change in the RDF of microcrystalline cellulose with grinding

Figs 2 and 3 show the changes in X-ray diffraction pattern and the RDF of microcrystalline cellulose which result from grinding. X-ray diffraction intensities decreased with grinding; after grinding for 40 h the pattern became a halo. In the RDF

Table 1. Peaks in the RDF and atom-pair vectors corresponding to the peaks calculated from the crystal structure of cellulose.

Peak position	Attributable vectors
1·5	Nearest neighbour of intramolecular atomic distance between C–C and C–O
2·6	Second neighbour of intramolecular atomic distance between C–C–C, C–C–O and O–C–C
5·0	Nearest neighbour of inter-atomic distance between C–C and O–O of the independent glucose units positioned (x,y,z) and (x,y + 0·5,z)*
8·2	Inter-atomic distance between C–C or O–O positioned (x,y,z) and (x,y,z + 1), and (x,y,z) and (x + 1,y,z)
13·3	Inter-atomic distance between C–C and O–O positioned (x,y,z) and (x,y + 1,z + 1), (x,y,z) and (x,y,z) and (x + 1,y + 1,z)
17·0	Inter-atomic distance between C–C and O–O positioned (x,y,z) and (x + 2,y,z), and (x,y,z) and (x,y,z + 2)

*Except for the atom pairs which form hydrogen bonding.

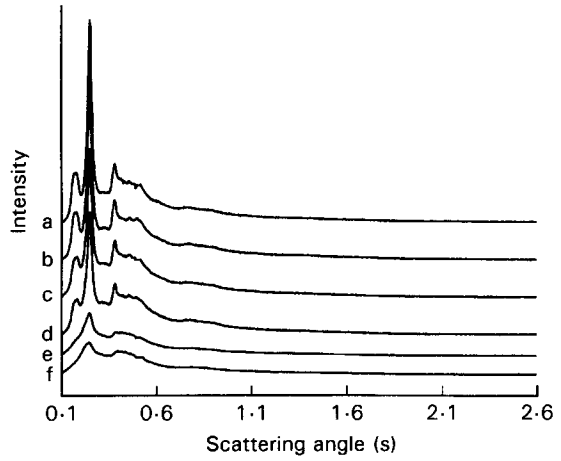

FIG. 2. X-ray diffraction patterns of intact and ground microcrystalline cellulose powders. a. Intact powder, b. powder ground for 1 h, c. powder ground for 2 h, d. powder ground for 4 h, e. powder ground for 10 h, f. powder ground for 40 h.

the peaks attributable to the intramolecular atomic vectors (1·5 and 2·6 Å) did not change in intensity. On the other hand, the peak intensities for the intermolecular atomic arrangements gradually decreased with grinding. After grinding for 10 h the peaks corresponding to distances greater than 7 Å almost disappeared, but the peak at 5 Å still remained in the RDF, because this peak corresponds to the atomic distances between fibres forming hydrogen-bonds. The regular intermolecular atomic arrangements were almost lost after grinding for 4 h. These results indicate that the cellulose fibres in the crystalline region of microcrystalline cellulose were gradually split into individual fibres by grinding and the microcrystalline cellulose finally became amorphous.

Relationship between crystallinity and microstructure

Table 2 summarizes the extent of crystallinity and the disorder parameters of intact and ground microcrystalline cellulose determined by the Ruland method. The extent of crystallinity was defined as the weight fraction of the crystalline part of the specimen whereas the lattice-disorder parameter was defined as the magnitude of paracrystalline lattice distortion in the crystalline region (Ruland 1961). At the initial stage of grinding the extent of crystallinity decreased and the disorder parameter increased slightly. After grinding for 4 h, the disorder parameter then increased with grinding.

Table 2. Extent of crystallinity and disorder parameter of intact and ground microcrystalline cellulose determined by the Ruland method.

Sample	Crystallinity (%)	Disorder parameter (Å^2)
Intact	68	7·2
Ground for 1 h	58	7·4
Ground for 2 h	52	7·5
Ground for 4 h	34	8·3
Ground for 10 h	35	9·7
Ground for 40 h*	32	14·3

*Because the crystalline region was extremely disordered, it is indistinguishable from the structure of the amorphous material.

As shown in Fig. 2, although peaks corresponding to radial distances greater than 7 Å were observed in the RDF after grinding for 4 h, they had almost disappeared after grinding for 10 h. It is suggested that the increase of the lattice-disorder parameter with grinding corresponds with the change in intermolecular atomic arrangement.

In the powder after grinding for 40 h, because the crystalline region was extremely disordered (lattice-disorder parameter 14·3 Å^2), the diffraction peaks from the crystalline region almost disappeared. Consequently, after grinding for 40 h microcrystalline cellulose powder was indistinguishable from amorphous cellulose.

Change in the RDF of microcrystalline cellulose with compression

Fig. 4 shows the RDFs of microcrystalline cellulose powder and tablets. The peaks in the RDF of microcrystalline cellulose powder corresponding to radial distances larger than 20 Å were noisy and not very clear. On the other hand, distinct peaks indicative of intermolecular atomic arrangements larger than 20 Å, were found in the RDF of the microcrystalline

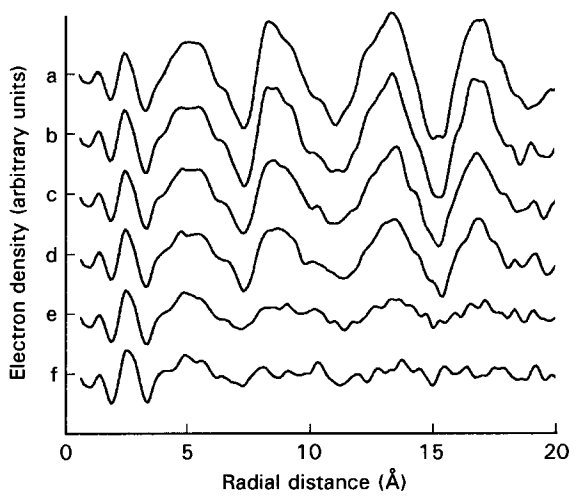

FIG. 3. Changes in the RDF of microcrystalline cellulose with grinding. a. Intact powder, b. powder ground for 1 h, c. powder ground for 2 h, d. powder ground for 4 h, e. powder ground for 10 h, f. powder ground for 40 h.

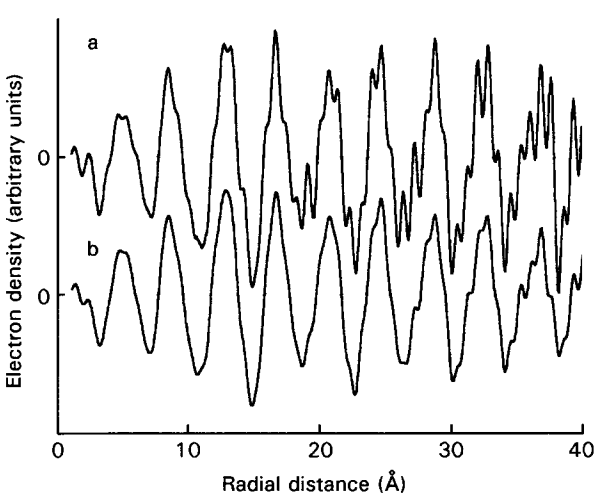

FIG. 4. Atomic radial distribution function of microcrystalline cellulose powder (a) and tablet (b).

cellulose tablet. These results imply the formation of a regular long-range intermolecular atomic arrangement as a result of compression. Microcrystalline cellulose is known to have high compactability. This could be not only because of cohesion between cellulose particles but also because of the production of regular intermolecular (inter-fibre) atomic arrangement as a result of compression.

In conclusion, changes in the microstructure of microcrystalline cellulose were determined by radial distribution analysis. The RDF of microcrystalline cellulose was indicative of a gradual loss of regular intermolecular (inter-fibre) atomic arrangement as a result of grinding. Compression resulted in the formation of long-range ordering as a result of intermolecular (inter-fibre) atomic arrangement.

Although some physicochemical properties of amorphous pharmaceuticals have been reported (Hancock & Zografi 1994; Hendriksen et al 1995), little structural information on amorphous pharmaceuticals is available in the literature. The RDF could be useful for examining the relationship between microstructure and pharmaceutical properties.

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