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Research paper

Effect of compression force on the crystal properties of erythromycin acistrate tablets

Merja Riippi[a,*], Veli-Pekka Tanninen[a], Jouko Yliruusi[b]

[a] *R & D, Orion Corporation, Orion Pharma, Espoo, Finland*
[b] *Pharmaceutical Technology Division, University of Helsinki, Helsinki, Finland*

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Abstract

The crystal properties of compressed and powdered erythromycin acistrate tablets were studied by the X-ray powder diffraction (XRPD) method. Detailed analysis of X-ray powder diffraction line profiles was performed. Diffraction peak intensities and full width at half maximum (FWHM) values of the peaks corresponding to three different crystal lattice directions were determined. Crystallite size was calculated by Scherrer's equation using the data of integral breadth of the peaks. The preferred orientation of the crystallites is also discussed. According to the results, the crystallite size increased on the tablet surface after a small compression force (4 kN) in all crystal lattice directions studied. Even small compression forces caused recrystallization. With higher compression forces (8–18 kN) the crystallite size and the FWHM values remained rather constant. After the compression force of 18 kN the peaks in different crystal lattice directions behaved differently. In the lattice directions of diffraction maxima 2 and 3, the effect was the same with the small (4 kN) and the high compression force (22 kN). Further recrystallization occurred with 22 kN. However, in the crystal lattice direction of diffraction maximum 1 at the compression force of 8 kN the crystallite broke and crystallinity decreased. These were not seen in the powdered tablet samples. It could be concluded that the effect of compression force on the crystal properties of erythromycin acistrate tablets was seen on the tablet surface but not in the powdered tablets. Compression force also affected the preferred orientation of crystallites on the tablet surface and especially in the lattice direction of diffraction maximum 3. This was not seen in the powdered tablets.

Keywords: Crystal properties; Crystallite size; Preferred orientation; Full width at half maximum; Integral breadth; X-ray powder diffraction; Compression force; Tablet; Erythromycin acistrate

1. Introduction

The crystal properties of pharmaceutical powders and compressed tablets may be of great importance due to the possible effects on their stability, processibility and bioavailability. All crystalline solids contain within their lattices defects which can influence their physical and mechanical properties and their processing, as well as the properties of the final dosage form. By understanding the role of the crystal structure in the compressional process it may be possible to predict the features of a tablet formulation and processing [1,2]. Properties like powder flow, compressibility and dissolution rate can vary for different crystal habits of the same drug [1,3]. The effect of compression on the crystal properties of pharmaceuticals has been studied to some extent [4–12,18]. Crystal habit was seen to have a great influence on the compaction behaviour of paracetamol by Garekani et al. [4]. The thin plate-like crystals showed a greater fragmentation compared to polyhedral crystals. Compacts made from thin plate-like crystals exhibited higher elastic recoveries indicating less plastic deformation of crystals during compression [4]. Even the crystal habits of ibuprofen [5] and nitrofurantoin [3] have been modified using alternative crystallization procedures in order to change the morphology and workability of the drugs.

Pirttimäki et al. [6] found that both grinding and compression affect the degree of transformation of anhydrous caffeine and that transition is greater near the surface than in the middle of the tablet. Yamamura et al. [7] investigated also the effect of compression and grinding on the physicochemical properties of the crystalline powders of naproxen and griseofulvin. The strength of the preferred orientation of crystallites in tablets increased and the unit cell parameters were slightly affected by compression. The crystallite size decreased and the lattice distortion increased with grinding [7]. Pintye-Hodi et al. [8] studied sulfaethidol tablets and found that the crystal structure remained unchanged when

* Corresponding author. Orion Corporation, Orion Pharma, R & D, P.O. Box 65, FIN-02101 Espoo, Finland. Tel.: +358-9-429-4158.
E-mail address: merja.riippi@orion.fi (M. Riippi).

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pressing power increased. The preferred orientation of crystallites has been studied also by Fukuoka et al. [9–12]. They found that aspirin crystallites showed no preferred orientation in powder, while in tablets they did, and also that aspirin crystallites in tablets prepared under higher compression pressures showed a stronger preferred orientation.

In our earlier paper [13] we studied the effect of compression pressure on the surface structure of erythromycin acistrate tablets (by non-contacting laser profilometry). Several roughness parameters were determined and the results showed an interesting connection between the roughness of the surface and the friability of the tablets. These results were considered to illustrate the surface properties of the tablets more than their bulk properties [13].

The purpose of this study was to examine the effect of compression force on the crystal properties of erythromycin acistrate tablets. Especially the crystallinity, crystallite size and some estimation of preferred orientation with the aid of the variation of peak intensities were studied. This method can probe about 100 μm of the surface layer. Whether the possible effect will be seen on the surface of the tablets or even inside the tablet (powdered tablet sample) was also examined.

2. Materials and methods

2.1. Materials

The active ingredient used in this study was erythromycin acistrate (stearate salt of acetylerythromycin) [14,15]. It is a white, moderately or highly crystalline and slightly aggregating powder. The mass was dry-granulated and contained about 82% of erythromycin acistrate. Scanning electron micrographs of erythromycin acistrate are shown in Fig. 9a and b. The tablets were compressed using an instrumented eccentric tablet machine (Korsh EK-0, Erweka Apparatebau, Germany) and flat punches with a diameter of 9 mm and an average weight of 200 mg. The compression forces were 4, 8, 12, 18 and 22 kN (corresponding to pressures of 63–346 MPa), and the compression speed was constant (34 rev/min). The instrumented tablet machine enables the evaluation of different compression parameters from the compression of the tablets [16,17]. The tablets were gently ground with a pestle and mortal for X-ray powder diffraction (XRPD) analysis of the powdered sample.

2.2. Methods

2.2.1. Equipment

The crystal properties of the samples were studied by XRPD (Diffractometer D500, Siemens GmbH, Karlsruhe, Germany). A copper target X-ray tube (wavelength 0.1541nm) was operated with a power of 45 kV × 40 mA. The measurements were performed at 2θ range 3–53° with a step size of 0.02° and a measuring time of 1.0 s/step. For X-ray powder diffraction analysis, the sample was mounted by loosely pressing about 500 mg of powder to a specific cylindrical sample stage which had a diameter of 20 mm and a height of about 2 mm. The unpowdered erythromycin acistrate tablets and pure erythromycin acistrate were also studied by XRPD. The tablets were placed to the sample holder so that the diffractograms were always taken from the upper surface of the tablets. Three measurements of the tablets were made, but only the mean value is shown in the figures. The powdered sample represents the mean of three tablets, and only one measurement was done. The statistical error in the evaluation of each peak averaged 5–6%.

2.2.2. Profile fitting

The peak properties were determined using the Bruker AXS Diffrac^{plus} Profile–Profile Fitting program (version 3.0). The lineshape function Split Pearson VII was used in the profile fitting of diffraction peaks (least squares refinement). The fitting function used was

$$y = \left[1 + \left(2^{1/e} - 1\right)x^2\right]^{-e} \quad (1)$$

Estimation of relative crystallinity was made on the basis of the broadening of intensity maxima by measuring the full width at half maximum (FWHM) values. For the estimation, the intensity maxima at 2θ angles 6.0°, 9.4° and 14.0° were used. The degree of crystallinity is inversely proportional to the broadening of the intensity maximum. Reliability of the fit procedure is defined as

$$R = 100\%\sqrt{\frac{\sum W(I_o - I_c)^2}{\sum WI_o^2}} \quad (2)$$

where I_o is observed intensity, I_c is calculated intensity and W is the weighting factor.

The X-ray diffraction profile analysis was carried out for three different peaks positioned at 6.0°, 9.4° and 14.0°. These peaks were relatively well separated from the neighbouring peaks and were considered reasonably good for mathematical analysis. An example of profile fitting is shown in Fig. 3. In peak 2, for instance, there are three slightly overlapping peaks separated by means of the asymmetrical Split Pearson VII function fit to obtain a more precise FWHM value for the peak positioned at 9.4°.

3. Results and discussion

The X-ray diffractograms of upper tablet surfaces and powdered tablets are presented in Figs. 1 and 2. The diffractogram of pure erythromycin acistrate is also included at the bottom of the two figures for comparison. The compression force used and the decrease of the concentration of erythromycin acistrate (about 82%) in the tablets compared to the pure erythromycin acistrate sample (100%) decreased the level of the signals in the diffractogram. However, the most

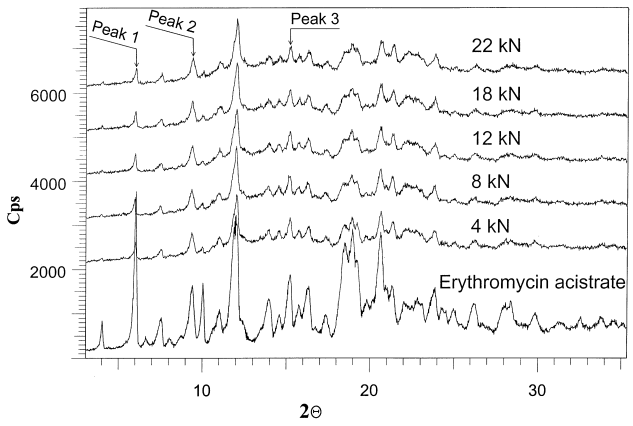

Fig. 1. X-ray diffractograms of tablet surfaces compressed with different compression forces (4, 8, 12, 18 and 22 kN). The active ingredient erythromycin acistrate is shown at the bottom for comparison.

dominating signals in the diffractograms were those of erythromycin acistrate. The main peaks numbered 1–3 (corresponding peak positions at 6.0°, 9.4° and 14.0°) were studied in more detail. The reliability of the fit procedure (observed − calculated) varied from 4 to 9%.

An example of the curve fitting for these three peaks is shown in Fig. 3.

3.1. Peak broadening

Peak broadening was calculated by measuring the full width at half maximum values.

The effects of compression force on the FWHM values of the peaks studied from the tablet surfaces are seen in Fig. 4 and those from the powdered tablet samples in Fig. 5. The zero value represents the data of pure erythromycin acistrate powder.

The three peaks studied describe the crystal lattice ordering of the samples in three different directions. On the surface of the tablets the FWHM values decreased in all these directions when the compression force increased

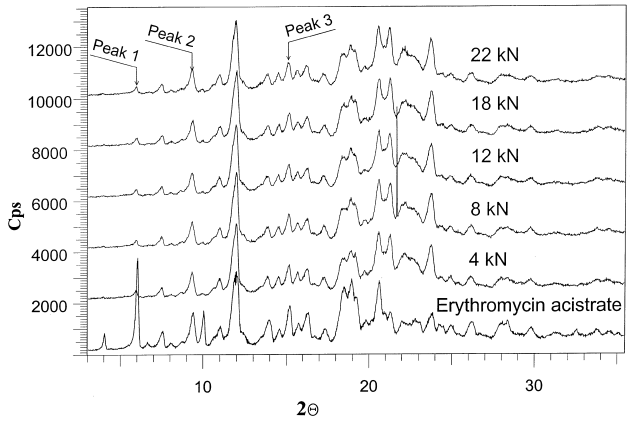

Fig. 2. X-ray diffractograms of powdered tablets compressed with different compression forces (4, 8, 12, 18 and 22 kN). The active ingredient erythromycin acistrate is shown at the bottom for comparison.

(4 kN) and hence recrystallization occurred even with small compression forces (Fig. 4). Compression and heat forced the crystallites closer to each other. Breakages of the crystallites and possible empty spaces between the crystallites were closed and so the lattice ordering increased. After small compression forces (4 and 8 kN) the FWHM values increased slightly in the lattice direction of peaks 2 and 3, but remained rather constant in the lattice direction of peak 1. After the compression force of 18 kN the differences between the different directions increased. In the crystal lattice direction of peaks 2 and 3 the FWHM values decreased, which could be explained by further recrystallization. However, in the crystal lattice direction of peak 1 the FWHM values increased slightly. The crystallites broke and crystallinity decreased. Fukuoka et al. [12] studied isoniazine and D-mannitol and found out that with increasing compression pressure the FWHM values increased and were affected by both the crystallite size and lattice disorder. In our study, the samples of the powdered tablet did not show results similar to those of the tablet surface (Fig. 5). Fig. 5 shows the results of one measurement of three powdered tablets. The grinding of the tablets seemed to hide the effect of compression force on the FWHM values especially in the lattice directions of peaks 2 and 3. The effect of compression force on the FWHM values in the lattice direction of peak 1 differs also from that of the surface. First the FWHM values increased with the small compression force (4 kN), then remained quite constant up to 18 kN and thereafter decreased again with 22 kN. This means that in powdered tablets with small compression forces the crystals break, and recrystallization can be seen only with very high forces.

3.2. Crystallite size

Crystallite size was defined by Scherrer's equation

$$D = \frac{k\lambda}{\beta\cos\theta} \tag{3}$$

where k varies from 0.89 to 1.39, but the assumption of $k = 1.0$ is generally justifiable. λ is X-ray wavelength 0.1541 nm and β is integral breadth [18].

The effect of compression force on the crystallite size is shown in Fig. 6 (tablet surface) and in Fig. 7 (powdered tablet). The results of crystallite size in different crystal lattice directions (corresponding to peaks 1, 2 and 3) supported the results of FWHM (Fig. 4). After a small compression force (4 kN) the crystallite size increased in all three lattice directions. In the lattice directions of peaks 2 and 3 the crystallite size remained rather constant when the compression force increased further (from 4 to 18 kN), but some recrystallization could be seen after 22 kN. However, the crystallite size in the crystal lattice direction of peak 1 increased further when the compression force increased, but after 8 kN the crystallite size decreased. With higher

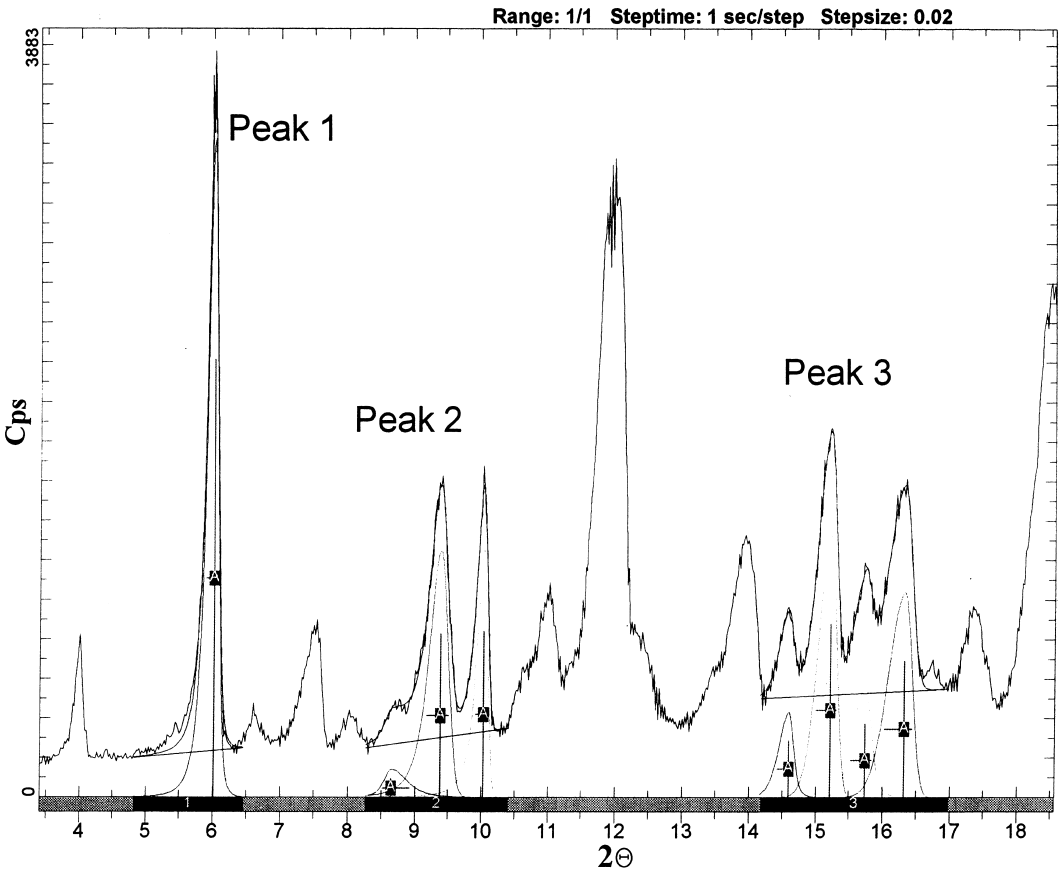

Fig. 3. Profile fittings of three diffraction maxima (peaks) of different lattice directions (average peak positions 6.0, 9.4 and 14.0°).

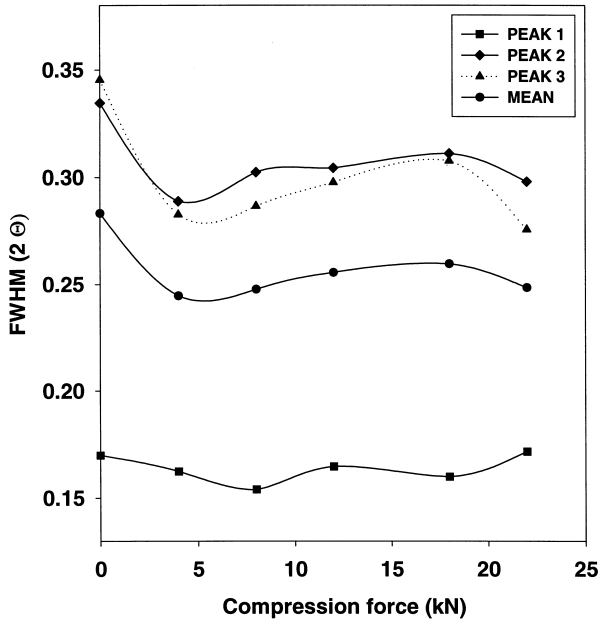

Fig. 4. FWHM from diffraction maxima (peaks) 1, 2 and 3 and mean of three peaks calculated from the surface of the tablets (compressed with different compression forces).

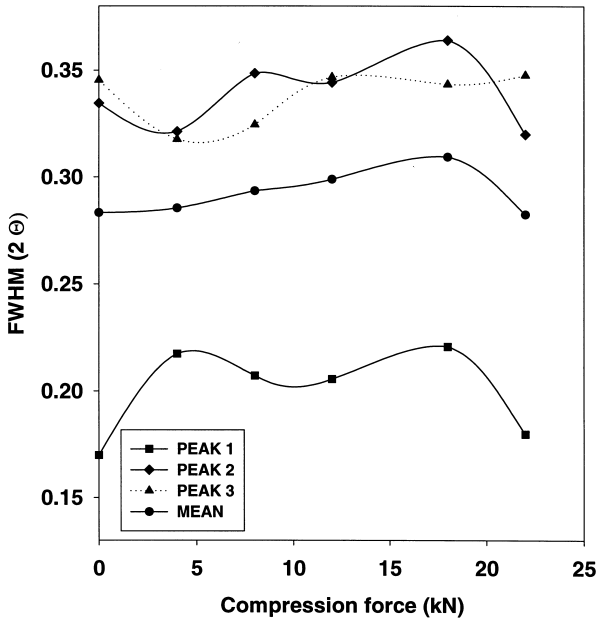

Fig. 5. FWHM from diffraction maxima (peaks) 1, 2 and 3 and mean of three peaks calculated from powdered tablets (compressed with different compression forces).

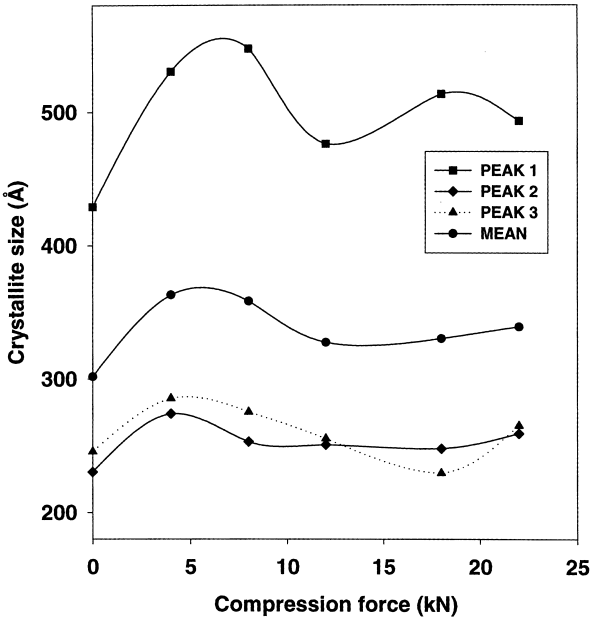

Fig. 6. Crystallite sizes from diffraction maxima (peaks) 1, 2 and 3 and mean of three peaks calculated from the surface of the tablets (compressed with different compression forces).

compression forces some variation was seen in the crystallite size in this crystal lattice direction.

In Fig. 7, the crystallite size of the powdered tablet samples decreased quite significantly in the lattice direction of peak 1 with small compression forces (4 or 8 kN). Higher forces are needed, however, for recrystallization to occur in the powdered tablet samples. The crystallite size results in the lattice direction of peaks 2 and 3 were considered to be rather constant regardless of the compression force used.

Fukuoka et al. [10] reported a remarkable decrease of crystallinity and crystal size after compression of aspirin crystal. Yamamura et al. [7] found that the unit cell parameters of crystals were slightly changed by compression, and with grinding the size of crystallites decreased.

3.3. Preferred orientation of crystals

Preferred orientation or texture can be defined as a condition where the distribution of crystal orientation is non-random [18]. The changes in the intensity of the diffraction maximum can be explained by preferred orientation. The effect of compression force and grinding of the tablets on the preferred orientation have been studied by many authors [6,7,9–12]. Yamamura et al. [7] stated that the strength of preferred orientation of crystallites in tablets increased with increasing compression pressure. El-Said [19] reported that the paracetamol crystals obtained from different solvents exhibited similar X-ray diffraction patters, but different intensities. This attributed to differences in crystal size.

The effect of compression force on the peak intensities on the surface of the erythromycin acistrate tablets is shown in Fig. 8. It was observed that the increase in compression force had a strong effect on the preferred orientation of crystals in tablets and especially in the crystal lattice direction of diffraction maxima 2 and 3. When the compression force increased, the peak intensity decreased, but some variation in the results of preferred orientation was seen in lattice direction 1.

It is possible to assume the preferred orientation of crys-

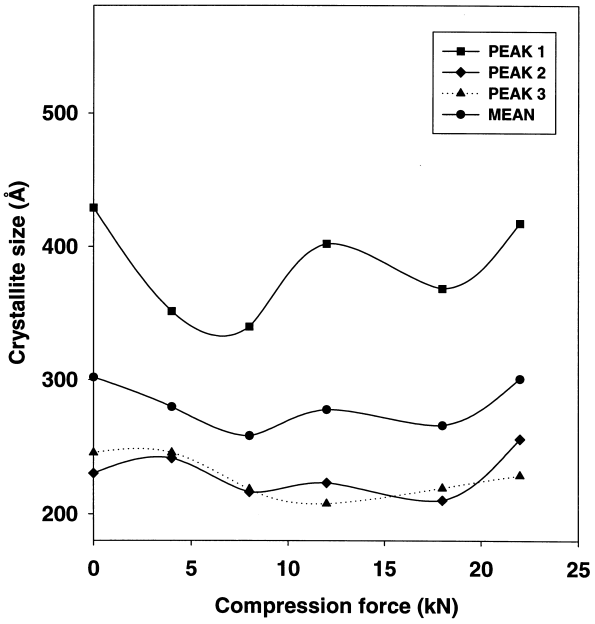

Fig. 7. Crystallite sizes from diffraction maxima (peaks) 1, 2 and 3 and mean of three peaks calculated from powdered tablets (compressed with different compression forces).

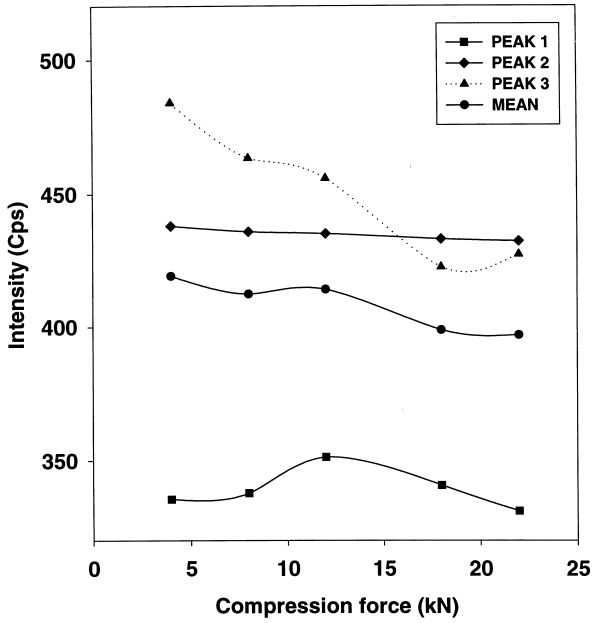

Fig. 8. Intensities of diffraction maxima (peaks) 1, 2 and 3 and mean of three peaks calculated from the surface of the tablets (compressed with different compression forces).

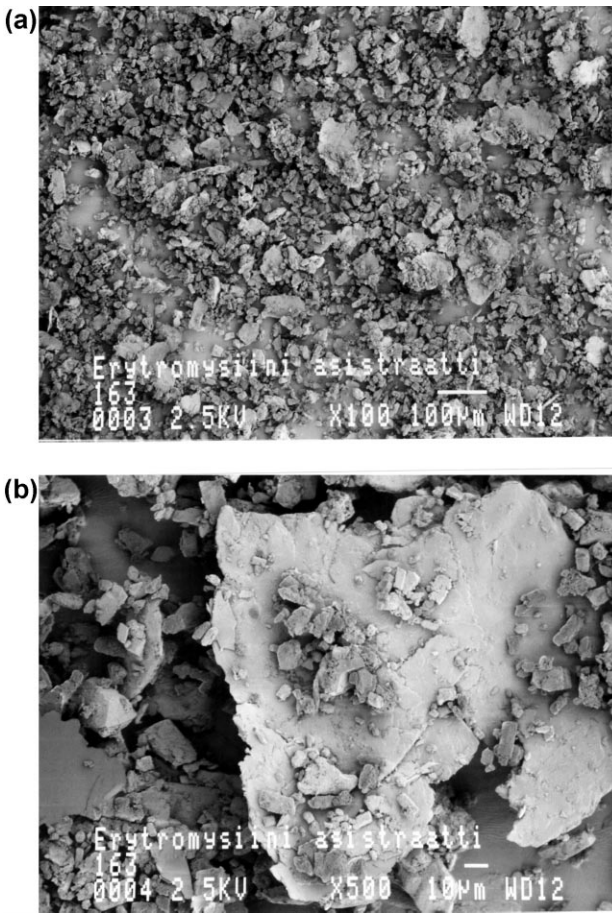

Fig. 9. Scanning electron micrographs of erythromycin acistrate raw material. Bars: (a) 100 μm; (b) 10 μm.

tallites parallel to the surface if the shape of erythromycin acistrate particles is known (Fig. 9a,b). No such effect of compression force on the preferred orientation was seen in the samples of powdered tablets. Fukuoka et al. [10] observed that aspirin crystallites showed no preferred orientation in powder while in tablets they did, and the preferred orientation was stronger in tablets prepared under higher compression pressures. The crystals had a tendency to orient parallel to the upper surface of the tablets during compression [10].

3.4. Scanning electron micrographs

Scanning electron micrographs of the erythromycin acistrate batch used are shown in Fig. 9a,b. It gives a visual impression of the particles, while the XRPD analysis gives information about the substructure of particles, crystals and crystallites. The particles of erythromycin acistrate were relatively well crystallized and had a partly lamellar structure.

4. Conclusion

The effect of compression force on the crystal properties of erythromycin acistrate tablets was seen on the surface of the tablets but not in the powdered tablets. Recrystallization of the active substance was clearly demonstrated on the surface of the tablets. Based on the absorption of X-rays this surface profiling is done mainly from the first 100-μm layer of the tablet surface. Recrystallization appeared as an increase of crystallite size and as a change of their orientation. The size of the crystallites increased on the surface of the tablets with small (4 kN) compression forces in all crystal lattice directions studied. A similar recrystallization effect was seen also with the highest (22 kN) compression force used in two of the crystal lattice directions studied. Within this range the crystal properties were regarded as rather constant.

The preferred orientation of the crystallites affected by compression was strongest in the lattice direction of diffraction maximum 3. The compression force did not affect similarly the preferred orientation of crystallites in the powdered tablets.

XRPD, including software properties like the one applied here, is a rather well standardized method in material research laboratories. The phenomena observed in the crystal properties of erythromycin acistrate tablets by XRPD can be obtained also for any powder formulation or pure substance. The only limitation is that the XRPD-line broadening analysis can be performed for amorphous substances because of their totally diffuse X-ray signal.

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