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Research paper

The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets

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Abstract

The surface roughness of erythromycin acistrate tablets was studied by non-contact laser profilometry. Seven roughness parameters and 3D fractal dimension were examined. The mechanical properties (including crushing strength, friability and disintegration time) were determined, and SEM data were taken from the tablets. According to the results, the crushing strength and the disintegration time of the tablets increased with increasing compression force. At higher compression forces the crushing strength reached a constant level. The friability of the tablets behaved quite unexpectedly and minimum friability was observed at a compression force of 14 kN. Except for fractal dimension, the roughness parameters behaved very much in the same way as the friability of the tablets. The SEM data supported the friability and surface roughness data of the tablets.

Keywords: Non-contact profilometry; Roughness parameters; Compression force; Tablets; Erythromycin acistrate; Crushing strength; Friability; Disintegration time

1. Introduction

Erythromycin acistrate is a prodrug of erythromycin in which an acetyl group is attached to the 2′ position of erythromycin by an ester linkage [1,2]. It is a white, moderately or highly crystallized and slightly aggregating powder. It does not have a distinct melting behaviour; the melting range varies from +45 to +70°C. The specific surface area of erythromycin acistrate samples varies from 1.98 to 2.74 m^2/g. The density is about 1.1 g/cm^3.

The surface roughness of tablets can be expected to be an important parameter, especially when tablet friability or coating of tablets is being evaluated. Also the dissolution of the tablets is very much dependent on the surface characteristics of the tablets. The determination of the roughness parameters by non-contact profilometry is relatively easy. Surface roughness parameters are well standardized and they have been used for a long time, especially in the characterisation of metal surfaces. However, these parameters may have practical importance in tablet surface studies. The parameters offer an alternative to obtaining a comparable numerical value for the surface characteristics. The behaviour and the position of the particles in the tablet bulk cannot be explained by the roughness parameters, but they will give valuable information about the surface of the tablet system. By using this method the whole surface of the tablet can be evaluated.

Fractal dimensions (FD) describe the boundary or the surface structure of materials [3]. The applicability of fractal dimensions of particles has been discussed in pharmaceutical powder technology in a few papers, but the usefulness of FD of tablet surfaces is still quite unknown.

Usually the surface roughness of tablets has been deter-

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mined by stylus instruments [4–6]. These methods are, however, quite laborious, time-consuming and, with measuring by contact, there is a risk that the surface of the tablet is altered or even damaged during the determination.

Recently, Healy et al. [7] used non-contact surface profilometry in a surface texture study of solid dosage forms. The non-contact laser profilometry is an important method for studying the surface texture of different materials. The method has been used traditionally in engineering and material sciences. In pharmaceutical sciences it has been used mainly to investigate skin surfaces, nail dystrophies and dental materials [8–11].

The purpose of this study was to examine the effect of compression force on the mechanical properties, surface roughness and surface fractal dimension of erythromycin acistrate tablets. Whether these results correlate with each other and whether they can be explained by the surface properties or the bulk properties of the tablets are also discussed.

2. Materials and methods

The active ingredient used in this study was erythromycin acistrate (stearate salt of acetylerythromycin). The mass, which contained 82% of erythromycin acistrate, batch 163 (Fermion, Orion Pharma, Finland), 15% of Avicel PH101®, batch 005 (Orion Pharma, Finland) and small amounts of disintegrants: 1% Amberlite IRP 88®, batch 035 (Orion Pharma, Finland) and 0.75% Ac-Di-Sol®, batch 032 (Orion Pharma, Finland) was dry granulated with a roller compactor (Aleksanderwerk WP 50N/75, Germany) [12, 13]. Thereafter 0.75% of magnesium stearate, batch 091 (Orion Pharma, Finland) was added as a lubricant. The tablet mass was mixed for 12 min by Turbula mixer (WAB, Willy A. Bachofen Maschinen Fabrik, Switzerland). 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. The compression speed was constant (34 rev./min). The instrumented tablet machine enables up to forty different compression parameters to be evaluated from the compression of the tablets [14–16].

The weight, crushing strength, thickness and diameter of the tablets were measured ($n = 100$, Erweka Multicheck tablet tester, Erweka GmbH, Heusenstamm, Germany). Other measured responses were friability ($n = 3$, Friabilator, Ernst-Keller, Basel, Switzerland, using 100 revolutions) and disintegration time of the tablets using the method described in Ph. Eur. ($n = 6$, Sotax DT3, Sotax AG CH-4008, Basel, Switzerland).

2.1. Profilometry

The roughness parameters and three-dimensional tablet surface were evaluated by non-contacting laser profilometry (UBM Microfocus Measurement System, UBM Mebtechnik GMbH, Ettlingen, Germany). The profilometer uses infrared light from a semiconductor laser focused on the surface by an objective lens. The light reflected by the object surface is directed by a beam splitter through a prism, and is viewed as a pair of spots on an arrangement of photodiodes. When the objective lens is exactly at its focal distance from the surface, both diodes are illuminated equally. If the distance between the object surface and the objective lens is then altered, the imaged focus point is shifted and the illumination of the photodiodes becomes unequal. This generates a focus error signal by means of a differential amplifier. A control circuit monitors the focus error signal and controls the position of a mobile lens suspended within the sensor so that the focal spot of the beam remains coincident with the surface measured. The changing illumination of the photodiodes can be interpreted as a measurement of surface roughness [17,18].

The upper surface of tablets was measured by scanning an area of 2×2 mm in the centre of the tablets ($n = 3$). The roughness parameters were calculated from the data of 1000 pixels/cm (x-y resolution) and z resolution of 0.1 μm. The image data of 100 pixels per centimeter was transferred to Mathematica program software (Wolfram Research, USA) which was used to draw the 3-dimensional surface plots. In the figures the Z-axis represents μm, while the X- and the Y-axis represent in mm.

2.2. Surface roughness

The roughness parameters measured were Rz, Ra, Rq, Rp, Rpm, Rt and Rtm which have been described in the UBM System Reference Guide [19]. The most commonly

Table 1

Properties of erythromycin acistrate tablets compressed with different compression forces (mean ± SD)

Compression force (kN)	Crushing strength (N)	Weight (mg)	Thickness (mm)	Friability (%)	Disintegration time (s)
4	61 ± 8	209.1 ± 4.3	3.06 ± 0.04	0.88 ± 0.06	27 ± 10
8	91 ± 17	202.9 ± 3.7	2.95 ± 0.03	0.75 ± 0.05	88 ± 31
12	106 ± 10	213.8 ± 4.4	3.04 ± 0.05	0.69 ± 0.04	264 ± 40
18	108 ± 11	208.9 ± 4.0	2.94 ± 0.05	0.73 ± 0.07	467 ± 120
22	108 ± 11	208.7 ± 4.3	2.89 ± 0.06	0.92 ± 05	618 ± 82

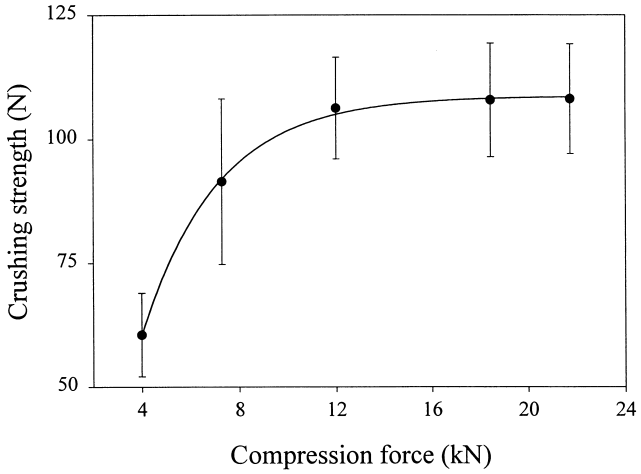

Fig. 1. Effect of compression force on the crushing strength of erythromycin acistrate tablets.

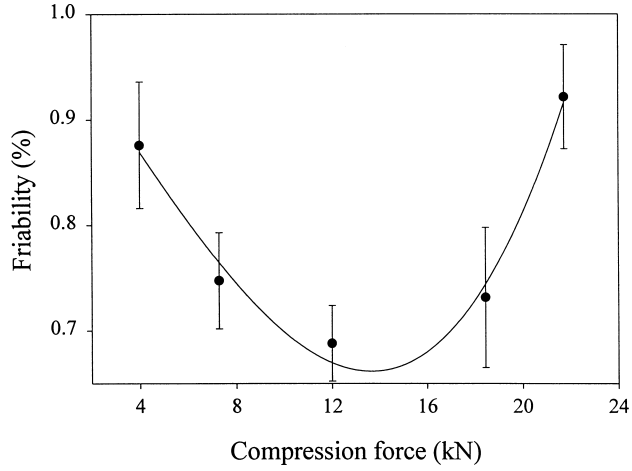

Fig. 2. Effect of compression force on the friability of erythromycin acistrate tablets.

used parameters are the arithmetic average of the absolute values of all points of the profile (Ra) and the root mean square of all points of the profile (Rq). The roughness parameter Rp illustrates the maximum distance between the highest point and the mean line of the profile.

The surface fractal dimension (FD) of the tablets was determined directly by an automatic routine of the profilometer [17,18]. The surface structure of the tablets was studied by a scanning electron microscope (JEOL, JSM-840A Scanning Microscope, Japanese Electron Optics Limited, Japan).

3. Results and discussion

3.1. Weight and thickness

For all the compression forces used the weight variation was under 4.4%. The variation of thickness was minimal as can be seen in Table 1. The results for the diameter of the tablets are not shown because of the calibration failure of the measurement.

Table 2

Curve fittings and coefficients of determination for the dependence of crushing strength, friability, disintegration time and roughness parameter Rp on the compression force

	Curve fitting	R^2
Crushing strength Y_1 (N)	$Y_1 = 175\ [\ 1 - e^{(-0.323\ x)}\ ] - 66.3$	0.999
Friability Y_2 (%)	$Y_2 = 13.2\ e^{(-0.024\ x)} + 0.235\ x - 12.02$	0.941
Disintegration time Y_3 (s)	$Y_3 = 676\ e^{(0.032\ x)} - 748$	0.997
Parameter Rp Y_4	$Y_4 = 76.2\ e^{(-0.0002\ x)} + 0.0018\ x - 10.44$	0.998

Data and curves are shown in Figs. 1–4. x, Compression force (kN) in all curve fittings; R^2, coefficient of determination.

3.2. Crushing strength

The crushing strength of the tablets increased with increasing compression force (Fig. 1). At lower compression forces this increase was exponential but reached a constant level at a compression force of 12 kN. This is quite normal behaviour with tablets. Crushing strength of tablets clearly describes a certain mechanical property of a whole tablet. Crushing strength is obviously a parameter which can be related quite directly to the compression force used. The dependence of the crushing strength on compression force is presented with an experimental equation in Table 2.

3.3. Friability

The friability of the tablets behaved quite unexpectedly (Fig. 2). Within the compression region 4–12 kN the friability of the tablets decreased, but increased with the higher forces. Normally with the tablets, the increase of compression force causes a reduction of friability.

In our work, the friability of the tablets behaves as

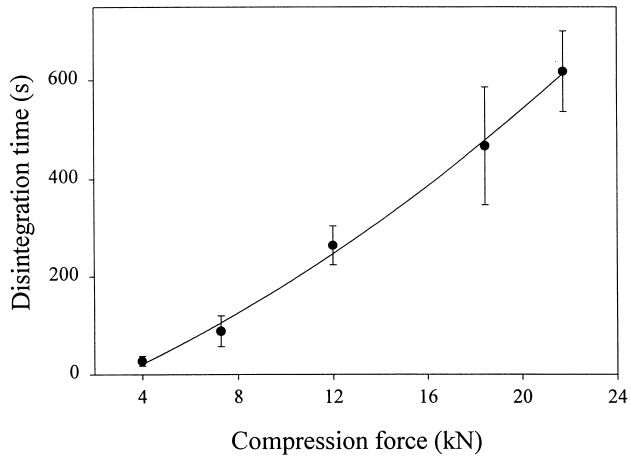

Fig. 3. Effect of compression force on the disintegration time of erythromycin acistrate tablets.

Table 3

Effect of compression force on the roughness parameters and fractal dimension (FD) of erythromycin acistrate tablets (mean ± SD; $n = 3$)

Compression force (kN)	Roughness parameters							Fractal dimension
	Rz	Ra	Rq	Rp	Rpm	Rt	Rtm	FD
4	38.6 ± 5.48	2.03 ± 0.38	2.91 ± 0.67	38.5 ± 6.38	12.4 ± 1.34	52.7 ± 6.43	19.6 ± 1.55	2.39 ± 0.04
8	20.8 ± 4.63	1.01 ± 0.10	1.38 ± 0.11	26.0 ± 16.02	7.02 ± 1.54	34.9 ± 14.6	12.5 ± 1.58	2.50 ± 0.06
12	25.4 ± 3.96	1.24 ± 0.11	1.74 ± 0.22	23.6 ± 9.99	8.12 ± 1.50	35.6 ± 9.66	14.9 ± 1.40	2.50 ± 0.05
18	31.4 ± 3.94	1.20 ± 0.05	1.74 ± 0.25	27.4 ± 3.18	11.8 ± 2.03	40.7 ± 2.79	19.8 ± 2.06	2.47 ± 0.01
22	34.0 ± 2.85	1.25 ± 0.03	1.95 ± 0.10	32.2 ± 9.53	12.5 ± 1.18	46.6 ± 5.96	20.9 ± 1.11	2.47 ± 0.03

expected at lower compression forces. When the compression force increases, the particles deform plastically and the tablets become harder and less friable. At higher compression forces the friability of the tablets seemed to increase again although the crushing strength remained stable. This could be explained by some fragmentation of the system. When the crushing strength was 22 kN, the friability of the tablets was at the same level as at the compression force of 4 kN.

Minimum friability was obtained near the compression force of 14 kN. This is obviously the optimum compression force for this formulation. However, all the friability values were under 1%, which can generally be regarded as desirable. The dependence of friability on the compression force can be explained quite well by a 3rd order polynomial shown in Table 2.

3.4. Disintegration time

The disintegration time of the tablets increased quite linearly within the range of compression force used (Fig. 3). The disintegrants used, croscarmellose sodium (Ac-Di-Sol®) and polacrilin potassium (Amberlite IRP-88®), are commonly used disintegrants in tablet formulations and are reported to be very effective [20]. Croscarmellose sodium (AcDiSol®) is a cross-linked polymer of carboxymethylcellulose sodium and is often used in concentrations of 0.5–5.0%. The material is also hygroscopic [21].

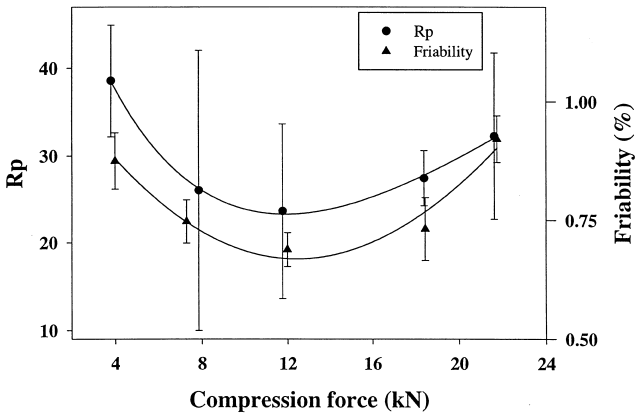

Fig. 4. Behaviour of friability and roughness parameter Rp of erythromycin acistrate tablets as a function of compression force.

Amberlite IRP-88® is a potassium salt of methacrylic acid polymer with divinylbenzene and is typically used in amounts of 2% in tablet formulations [22]. The dependence of disintegration time and compression force can be presented by the 2nd order polynomial.

The disintegration time of tablets mainly describes the bulk properties of tablets. Usually it can be assumed that disintegration of a tablet is a continuous process. Disintegration from a constant surface in a certain tablet is, in a first approximation, quite a constant phenomenon. It is commonly known that the disintegration time of tablets increases with increasing compression force. However, small amounts of disintegrants may affect the disintegration time markedly.

3.5. Surface roughness parameters

The seven roughness parameters (Table 3) behaved very much in the same way as the friability. In each case the lowest roughness parameter values were obtained with the compression force of 8 or 12 kN. The surface fractal dimension seemed to be quite insensitive to the compression force. As the experimental data were quite limited, it is difficult to determine the most valuable roughness parameters. However, it seemed that Rp, Rt and Rtm explained the friability most accurately (Table 3), and the behaviour of parameter Rp was closest to that of the friability (Fig. 4). As described earlier, the roughness parameter Rp illustrates the maximum distance between the highest point and the mean line of the profile and so it seemed most likely that this parameter correlated best with the friability of the tablets. It could be expected that the tablets which have a very coarse surface (Fig. 5a,e) will 'suffer' more during the friability test than the tablets with the smoother surface (Fig. 5b,c,d). The high peaks are likely to break and the surface will get smoother. This could possibly be confirmed by also examining the surface after the friability test.

3.6. Surface profiles and SEM figures

The surface profiles (Fig. 5a–e) and the SEM figures of the tablets (Fig. 6a–d) supported the data shown in Table 3. According to the profilometric Fig. 5, the surface was smoothest in tablets compressed with the compression

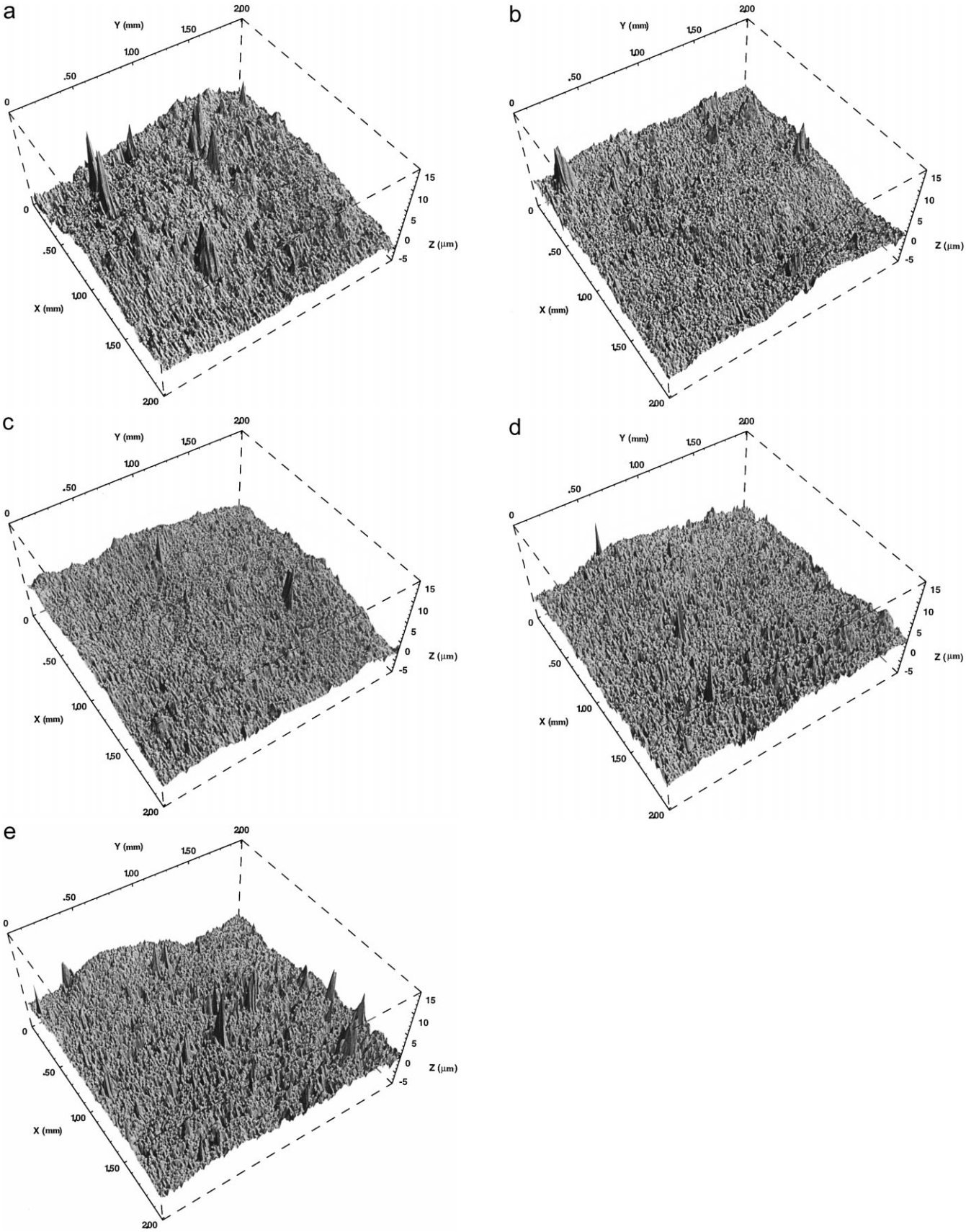

Fig. 5. (a–e) Surface profiles of erythromycin acistrate tablets. The Z axis represents μm, the X and Y axes represent mm. The compression forces are: (a) 4 kN, (b) 8 kN, (c) 12 kN, (d) 18 kN and (e) 22 kN.

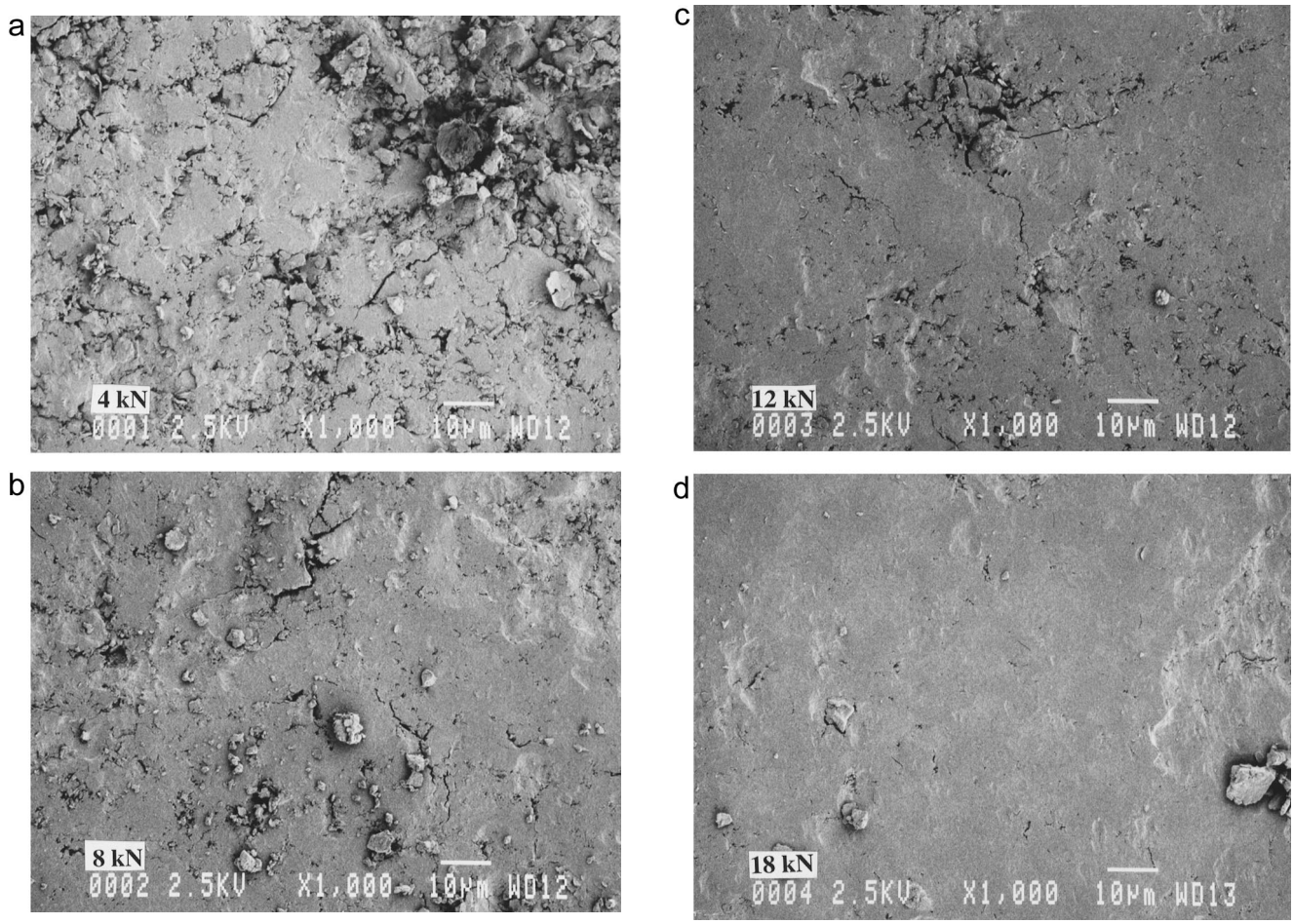

Fig. 6. (a–d). Scanning electron micrographs of erythromycin acistrate tablets. The compression forces are: (a) 4 kN, (b) 8 kN, (c) 12 kN, (d) 18 kN. Scale bars, 10 μm.

force of 8 kN (Fig. 5b), and the roughest tablets were obtained with the lowest compression force of 4 kN (Fig. 5a). The SEM photographs suggested that the smoothest surface was in the tablets compressed using the compression force of 18 kN (Fig. 4d).

These two methods are not similar and it has to be noted that the scales in these figures are different. In Fig. 5a–e the scale of the X and Y axes is in mm while in the SEM figures the bar is only 10 μm. Even the scale of the Z axis (Fig. 5a–e) was increased remarkably. However, these methods seem to illustrate the surface roughness of the tablets quite similarly.

The results of this study, especially the friability and surface parameters and the SEM figures, could be explained by the bulk or surface properties of the tablet system. Crushing strength gives us information about the whole tablet and can be regarded as a bulk property of the tablet system. Also, disintegration time illustrates the whole tablet although disintegration mainly takes place in the surface of the tablet. When disintegration proceeds, the surface of the tablet keeps changing all the time. In the friability test the stress to the tablets is not as great as in crushing strength and so friability is observed mainly on the surface of the tablet. Therefore friablity can be regarded as a surface property of the tablet. The roughness of the tablets measured by profilometry is clearly a surface property of the tablets. The method used in this study can be applied to drawing 3D figures. Also SEM figures illustrate the surface of the tablet.

In an earlier paper Riippi et al. [23] studied the porosity of erythromycin acistrate tablets. Now it seems important to extend the present study using the same tablets in the porosity determinations. Porosity can also be seen as a bulk property of the tablets. It was earlier found that an increase in compression force decreases the total porosity, the surface area of the pores and the number of big pores in the tablets studied. Compression force also affected the crushing strength and the disintegration time in the same way as in this study.

4. Conclusions

The crushing strength of the tablets increased at the lower

compression forces but remained constant at higher forces. The friability of the tablets behaved quite unexpectedly. Minimum friability was obtained at a compression force of about 14 kN, whereas the disintegration time of the tablets increased quite linearly with increasing compression force. Finally, it appeared that the surface roughness parameters behaved very much in the same way as friability, but the surface fractal dimension seemed to be insensitive to the compression force. These roughness parameters seemed to be quite valuable in tablet surface characterization. Inversely, this was not the case for surface fractal dimension. Also, SEM figures were seen to support the friability and surface roughness data.

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