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Influence of dry granulation on compactibility and capping tendency of macrolide antibiotic formulation

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Abstract

The effect of dry granulation (roller compaction and slugging) on compactibility and tablet capping tendency in a formulation with macrolide antibiotic and microcrystalline cellulose (MCC) was investigated. Direct tableting of this formulation revealed a pronounced capping tendency. Both dry granulated systems exhibit better compactibility and significant reductions in capping tendency compared to direct tableting. The capping tendency was also reduced through the use of precompression during direct tableting. The main volume reduction mechanism for macrolide antibiotic is fragmentation; this was confirmed by Heckel analysis, the lubricant sensitivity test, and SEM images. The yield pressure (P_y) of the direct tableting system is lower than the P_y of dry granulated systems, which indicates the lower plasticity of dry granulated systems. These findings do not explain the lower capping tendency of dry granulated systems compared to direct tableting. The main differentiating bonding mechanism is attributed to long distance intermolecular bonds due to the intense amorphization of macrolide antibiotic that occurs during dry granulation. Amorphization leads to a significant increase in surface free energy and consequently stronger long distance bonding between particles, which can withstand elastic relaxation and therefore reduce the capping problem. Solid bridges probably do not make a notable contribution to the mechanical strength of tablets, due to the brittle nature of the particles and the complex molecular structure of macrolide antibiotic.

Keywords: Dry granulation; Capping; Macrolide antibiotic; Tableting; Heckel equation; Compactibility; Particle fragmentation; Amorphization

1. Introduction

Compactibility is the process of volume reduction and bond formation in a powder bed during compression, which produces compacts of a certain mechanical strength. When pressure is applied to a powder bed, particle rearrangement occurs first, followed by particle fragmentation and deformation (plastic and elastic deformation), and bond formation on the contact surfaces (Duberg and Nyström, 1986). Plastic deformation is an irreversible process of particle shape changing that contributes to stronger tablets, while elastic deformation is reversible and leads to elastic recovery of compacts in the decompression phase and the breakage of some previously formed bonds, which results in lower tablet strength and capping problems. In the case of plastically flowing material, the particle shape changes during compression, but the surface area remains nearly unchanged. On the other hand, primary particles of materials that fragment break into smaller parts during compression, leading to an increased surface area and increased number of contact points suitable for bond formation. In both cases plastic deformation occurs at later stages of compression and adequate tablet strength can be obtained. Typical examples of materials with mainly plastic flow include microcrystalline cellulose (MCC), pregelatinized starch, sodium chloride, etc.; typical materials that mainly fragment include dicalcium phosphate dihydrate (Emcompress), crystal lactose, paracetamol, ascorbic acid, etc. (De Boer et al., 1978; Alderborn et al., 1985; Karehill et al., 1990).

The main bonding mechanisms involved in compact formation are: (a) solid bridges, which represent the strongest bonds between particles, (b) intermolecular or long distance forces (van der Waals forces, electrostatic forces, hydrogen bonding), representing weaker attraction forces, and (c) mechanical interlocking, denoting hooking and twisting of irregularly shaped particles (Nyström et al., 1993). The most common dominant bonding mechanisms for pharmaceutical materials are long distance forces, especially van der Waals forces and hydrogen

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bonds in some cases. The prerequisites for solid bridges are a relatively simple molecular structure and plastic deformation (e.g., sodium chloride). The predominant bonding mechanisms of pharmaceutical materials have been studied by many authors (Luangtana-Anan and Fell, 1990; Adolfsson et al., 1997).

In order to form a coherent tablet, bonds on the particle contact surfaces must be strong enough to withstand the elastic component of the material. The final compact strength is dependent on many materials and process attributes. The tensile strength of tablets is generally higher if the particle size is smaller (Shotton and Ganderton, 1961; McKenna and McCafferty, 1982; Nyström et al., 1982). If the material undergoes fragmentation during volume reduction, the particle size and shape will have a minor effect on tablet strength (Alderborn and Nyström, 1982).

Poor compactibility of powders, weak bonds between particles, or extensive elastic relaxation of materials can decrease tablet strength and increase the capping tendency. Capping is a phenomenon whereby extensive elastic relaxation breaks bonds that were formed during compression, leading to laminar breakage of the upper part of the tablet. Capping increases with increasing compression pressure, tableting speed, and tablet thickness, as well as low powder humidity (Ritter and Sucker, 1980). Using precompression before the main compression during tableting can lead to lower capping incidence (Parrott, 1990).

Dry granulation is one of the options used to reduce capping tendency (Eggelkraut-Gottanka et al., 2002). It can be performed using a tablet press or roller compactor for the first compaction, in which primary particles are agglomerated to form slugs or ribbons, which are afterwards treated by milling and sieving. It has been demonstrated that multiple compaction of a material can also lead to changes in compactibility. Lower tensile strength is usually observed, due to a reduction in bonding potential, which is partly spent during the first compression and not completely recovered while breaking the slugs or ribbons (Rocksloh et al., 1999; Bultmann, 2002; Freitag et al., 2004; Soares et al., 2005).

Many methods have been used over the decades to study the volume reduction mechanism and bond formation of pharmaceutical powders. The most frequently used method for studying the powder volume reduction process is the Heckel equation, or the porosity–pressure function, which is based on the assumption that the process of pore reduction during compression follows a first-order kinetic (Heckel, 1961). The parameters concerning compressibility characteristics can be obtained from the porosity–pressure plot. Yield pressure (P_y) is a measure of the plasticity of materials and can be used for relative comparisons between different material compression characteristics. A Heckel plot can be used to study plain materials, but it can also be used to study powder mixtures whose characteristics are usually a combination of plain material characteristics. However, this relation can be also nonlinear when mixing materials with different deformation properties, so the Heckel equation should be used with caution when applied to powder mixtures (Ilkka and Paronen, 1993). It has also been used to study dry granulated materials (Kochhar et al., 1995).

Some limitations to Heckel analysis have also been demonstrated. It is sensitive to even small errors in the experimental conditions and variations in the true density value (Rue and Rees, 1978; York, 1979; Pedersen and Kristensen, 1994; Sonnergaard, 1999). A Heckel plot can also be affected by particle size (Roberts and Rowe, 1987); wet granulated materials can have altered rearrangement and densification behavior compared to the original particles, which can result in difficulties when describing the system by Heckel plot (Wikberg and Alderborn, 1990).

Other methods for studying volume reduction mechanisms have also been described in the literature. Particle fragmentation can be determined using an indirect method by evaluating the system sensitivity to a lubricant addition, which can cause a reduction of intermolecular forces leading to a lower tablet strength. Lubricant covers particle surfaces and thus lowers the free energy of clean surfaces that can form bonds. Because plastically deforming particles do not break during compression, particle surfaces remain contaminated with lubricant, and tablet strength decreases significantly due to the lack of bonding capacity. On the other hand, if a material fragments, the addition of lubricant does not decrease tablet strength, while as a consequence of particle fragmentation many new clean surfaces are formed that are able to form new bonds leading to strong compacts (Ragnarsson and Sjögren, 1985; De Boer et al., 1978). The same mechanism also works in combination with a dry binder (such as MCC), which is added to promote bonding when only weak bonds exist between plain active ingredient particles. The dry binder's bonding function may be reduced because of the new active ingredient surfaces that are formed during compression and come into direct intimate contact (Nyström et al., 1982). It has been suggested that the tablet strength remaining after lubricant contamination can be attributed to solid bridges, as studied with sodium chloride (Nyström et al., 1993).

The volume reduction mechanism can also be studied using scanning electron microscopy (SEM). When there is fragmentation the original particles' integrity is broken, but it can be still observed if the material undergoes plastic deformation (Duberg and Nyström, 1982; De Boer et al., 1978; Karehill et al., 1990). SEM is not recognized as a suitable method for determining the extent of elastic deformation on tablets with a high capping tendency (Ritter and Sucker, 1980).

The solid-state material properties, surface free energy, and structural changes have important influence on powder compression behavior. The existence of polymorphism and the degree of material crystallinity can have a significant impact on the tablet properties. During compaction, mechanical energy can cause surfaces to become disordered and activated, which can cause more intensive bonding (Hüttenrauch, 1988; York, 1983). It has been reported that a more disordered structure of amorphous lactose deforms more plastically than the crystalline form and forms stronger compacts (Sebhatu and Alderborn, 1999).

The powder deformation mechanism and its effect on the tensile strength of a compact are intrinsic properties of the material and can be correlated to its surface free energy. A high surface free energy of the material can be associated with high tablet strength, while it can affect the bonding properties (El Gindy and Samaha, 1983). Inverse gas chromatography (IGC) can be used for detecting material surface free energy changes during pharmaceutical processes, which are often associated with

changes in the degree of crystallinity (Planinsek and Buckton, 2003).

The aim of this study is to investigate the effects of dry granulation (slugging and roller compaction) of macrolide antibiotic formulation on capping tendency where the drug fraction in the formulation is high (75%), and a pronounced capping tendency during direct tableting of the model formulation is observed. The study also aimed to determine the predominant volume reduction mechanism of the formulation studied and the suitability of a Heckel plot to study the capping tendency. Another goal was to examine the mechanism contributing to the significant decrease in capping incidence after dry granulation.

2. Materials and methods

2.1. Materials

Formulation: active ingredient macrolide antibiotic, code: M-112 (supplied by Krka, d.d., Novo mesto, Slovenia), 75% (w/w); microcrystalline cellulose (MCC, Avicel PH 101, FMC, Germany), 15% (w/w). Cation-exchange resin: Amberlite IRP88 (Rohm and Haas, France), 5% (w/w); talc (Luzenac val Chisone SPA, Italy), 4% (w/w); magnesium stearate (Faci SPA, Italy), 1% (w/w).

2.2. Preparation of powder mixtures, dry granulation

Three different powder mixtures with the same qualitative and quantitative composition but different manufacturing routes were made: direct tableting (DIRECT), tableting after dry granulation using a roller compactor to produce ribbons (ROLLER) and using a tableting machine to produce slugs (SLUGGING). All three mixtures were prepared in the amount of 4.0 kg.

(a) *Mixture for direct tableting* (*DIRECT*): all materials except magnesium stearate were mixed in the bin (10 rpm, 10 min). After magnesium stearate was added, additional mixing at 10 rpm for 2 min was performed.
(b) *Mixture with dry granulated material compacted in roller compactor* (*ROLLER*): M-112 75% (w/w), Avicel PH 101 15% (w/w), and talc 2% (w/w) were mixed in the bin at 10 rpm for 10 min. After the addition of 0.5% magnesium stearate, additional mixing was performed at 10 rpm for 2 min. The powder mixture was compacted with a roller compactor (Alexanderwerk WP 200VN, Germany) with rolls 75 mm wide, using the following set parameters: pressure 60 bar (40 kN), roller speed 20 rpm, and gap width 1.6 mm. The ribbons were crushed using an oscillating 1.5 mm sieve. The granules obtained were mixed with Amberlite IRP88 5% (w/w), and the rest of talc and magnesium stearate in the bin at 10 rpm for 2 min.
(c) *Mixture with dry granulated material, slugged* (*SLUGGING*): M-112 75% (w/w), Avicel PH 101 15% (w/w), and talc 2% (w/w) were mixed in the bin at 10 rpm for 10 min; after the addition of 0.5% magnesium stearate, additional mixing was performed at 10 rpm for 2 min. Slugging was performed on a rotary tableting machine (Killian T300/40 IMA, Germany) using curved shape punches (Ø = 13 mm, R = 26 mm), and using the following set parameters: main pressure 82 MPa and tableting speed 26,000 tablets per hour. The slugs were crushed in a mill (Quadro Comil, Canada), with a 1.5 mm sieve opening. The resulting granules were mixed with Amberlite IRP88 5% (w/w), and the rest of talc and magnesium stearate in the bin at 10 rpm for 2 min.
(d) *The two particle size fractions for SLUGGING* were prepared using manual sieving of the SLUGGING mixture into particle fraction <0.125 mm and particle fraction >0.125 mm.

2.3. Particle size distribution

Particle size distribution of plain M-112 and mixtures before tableting the DIRECT, ROLLER, and SLUGGING mixtures was determined with the sieve analyzer (Alpine 200LS-N, Hosokawa, Germany), using the following sieves: 0.045, 0.071, 0.125, 0.500, 0.710, 1.00, and 1.25 mm.

2.4. True density

The true density of the DIRECT, ROLLER, and SLUGGING powder mixtures was determined (n = 3) with a helium picnometer (AccuPyc 1330, Micromeritics, USA).

2.5. Tableting and Heckel analysis

Tableting of the three tablet mixtures (DIRECT, ROLLER, and SLUGGING) was performed on an instrumented eccentric tablet press (Killian SP300, IMA, Germany) using round flat-faced punches (diameter 12 mm). The target tablet mass was 550 mg. The applied upper punch compression pressures were (without precompression) 25, 50, 75, 100, 125, 150, 175, and 200 MPa. The compresssion speed was 30 tablets/min. These tablets were evaluated in order to construct a Heckel plot using the "out-die" method.

For the "in-die" method of Heckel analysis, tablets were compressed at 195 MPa, and force-displacement data were measured for the porosity calculation. The elastic deformation of the punch and punch holder was considered (18.6 μm/kN).

"In-die" and "out-die" Heckel analyses were performed and compared. Data were presented as Heckel plots based on Eq. (1) (Heckel, 1961):

$$\ln\left[\frac{1}{1-D}\right] = kP + A \quad (1)$$

D is relative density, P is applied pressure, k and A are constants. The k constants for the three samples were obtained by linear regression of the plots using the least squares method, and the mean yield pressure P_y was calculated based on the following equation:

$$P_y = \frac{1}{k} \quad (2)$$

The data sets in the range from 25 to 100 MPa in the "out-die" method and from 25 to 60 MPa in the "in-die" method were regarded as linear parts of the Heckel plots.

Additional tableting with precompression of 57 MPa was used only for tableting the DIRECT mixture at main pressures of 150, 175, and 200 MPa in order to study capping incidence.

A main compression of 350 MPa (without precompression) was used only for ROLLER to determine if capping can be triggered in a dry granulated system at such high pressure.

The SLUGGING particle fraction of <0.125 mm and complete particle size distribution of DIRECT were compressed at a compression pressure of 175 MPa. Particle fractions of SLUGGING <0.125 mm and >0.125 mm were compressed at 350 MPa.

2.6. Tablet evaluation

Samples of 10 tablets were evaluated at each compression pressure and the average values were used for the Heckel analysis and compactibility plot. Tablets were stored for 1 h in closed containers before evaluation (22 °C, 45% relative humidity). Tablet mass was determined using a BP 310 S analytical balance (Sartorius AG, Germany). Tablet thickness and diameter were measured using a slide caliper (MIB Messzeuge Gmbh., Germany). Tablets crushing strength was evaluated on a VK 200 (Varian, USA). Radial tensile strength (σ_t) was calculated according to the following equation:

$$\sigma_t = \frac{2F}{\pi DT} \quad (3)$$

F is the crushing force, D is tablet diameter, and T is tablet thickness.

The compactibility slope was determined by linear regression from the plot: tablet tensile strength (MPa) versus tableting pressure (MPa) in the compression interval up to 100 MPa.

2.7. Capping coefficient

The capping coefficient was taken as a measure of capping tendency. Capping was evaluated during the tablet crushing strength test. The tablet was considered to have a capping tendency if the upper part of the tablet completely fell away from the tablet body after breakage during crushing strength testing (Fig. 1a), or if a typical relief (significant indication of step form) appeared on the fractured surface of the tablet (Fig. 1b). The capping coefficient (CC) was calculated based on the following equation:

$$CC = \frac{x_c}{x} \quad (4)$$

x_c is the number of tablets with a capping tendency and x is the number of all measured tablets.

2.8. Lubricant sensitivity test

Tablets of plain M-112 and tablets of M-112 mixed with 2% magnesium stearate (mixing time 10 min) were pressed on an instrumented single punch tablet press (Killian SP300, IMA, Gemany) using round flat-faced punches (12 mm), with compression pressure 50 MPa; tablet mass was 500 mg. Six tablets of each formulation were prepared and tablet mass and crushing strength was measured after 1 h.

2.9. Scanning electron microscopy (SEM)

Powder and tablet samples were imaged with a SEM (Supra 32VP, Zeiss, Germany) with an acceleration voltage of 1.0 kV. Samples were scanned at magnifications of 2000×. The following samples were imaged: (a) plain M-112 (before compression); (b) Avicel PH 101 (before compression); (c) talc (before compression); (d) plain M-112 (after compression); (e) DIRECT—mixture before tableting; (f) ROLLER—dry granulated mixture before tableting; (g) SLUGGING—dry granulated mixture before tableting; (h) DIRECT—tablet fracture surface; (i) ROLLER—tablet fracture surface; (j) SLUGGING—tablet fracture surface. Compression pressure was 100 MPa.

2.10. X-ray powder diffraction (XRD)

X-ray powder diffraction patterns were measured on an X'Pert PRO PW3040/60 (Philips, Netherlands) diffractometer equipped with an X'Celerator detector using Cu Kα radiation (λ = 1.541874 Å). Samples in the Bragg-Brentano geometry were scanned with voltage 45 kV and current 40 mA. Three samples were analyzed: (a) DIRECT—powder mixture before tableting, (b) ROLLER—ribbons (after first compression, before

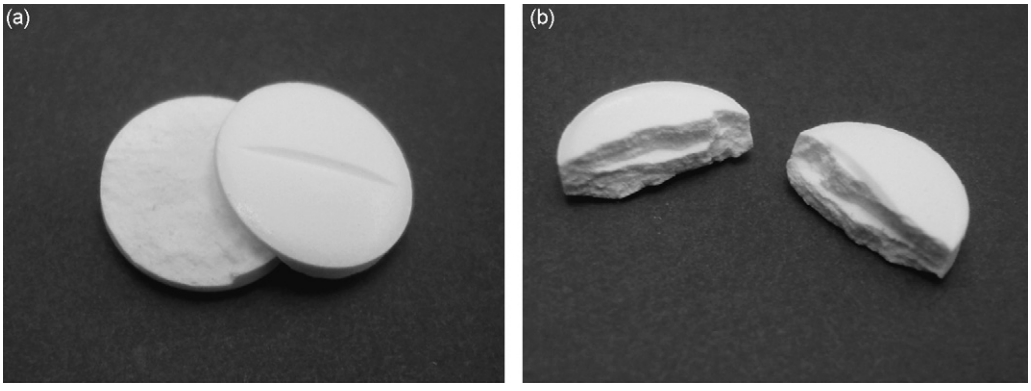


Fig. 1. Tablets with capping tendency: (a) Tablet where the upper part of the tablet has completely fallen away from the tablet body. (b) Tablet with typical relief (significant indication of step form) on the fractured surface of the tablet.

sieving), and (c) ROLLER tablets (tableting compression pressure 125 MPa). The powder mixture and ribbons were analyzed immediately after mixing and compression. The tablets were analyzed 1 year after compression. The samples were stored before analysis in tightly closed plastic containers at 21 °C and 40% relative humidity.

2.11. Differential scanning calorimetry (DSC)

DSC measurements were performed with a DSC822 (Mettler Toledo, Switzerland). The mass of the sample was about 3 mg and the scanning rate was 10 °C/min in a nitrogen atmosphere. The DSC was calibrated with indium at the same heating rate as the samples. Four samples were analyzed: (a) plain M-112 without compression, (b) ROLLER—powder mixture before first compression, (c) ROLLER—compacts (ribbons) after first compression, before sieving, (d) DIRECT—tablets (compression pressure 50 MPa), and (e) DIRECT—tablets (compression pressure 125 MPa).

2.12. Inverse gas chromatography (IGC)

IGC was used to determine the surface free energy of mixtures before tableting using a 6890N (Agilent Technologies, USA) chromatograph. The carrier gas was helium at a gas flow of 10 ml/min, 30 °C. Ethyl acetate and acetone were used as non-polar probes, and chloroform (acid) and tetrahydrofuran (basic) were used as polar probes.

3. Results and discussion

3.1. Particle size distribution of plain active ingredient and powder mixtures (DIRECT, ROLLER, and SLUGGING)

Due to the high weight fraction of M-112 in the tablet formulation, i.e. 75% (w/w), the particle size distribution of DIRECT closely resembles the particle distribution of the plain drug (M-112). Approximately 85% of the particles in DIRECT are <0.071 mm. After dry granulation, primary particles are agglomerated into bigger aggregates (granules) and consequently only 45% of particles in ROLLER and 40% in SLUGGING are <0.071 mm. This shift of particle size distribution towards larger particles is significant in both dry granulated systems. The particle size distribution in dry granulated samples is also much wider in comparison with the distribution of the DIRECT mixture, although a relatively large fraction of very small particles (<0.045 mm) was found in the dry granulated mixtures. This observation can be explained by the high level of secondary particle fragmentation that occurs during sieving of compacts (ribbons and slugs). Comparison of the fractions of particles <0.125 mm in the SLUGGING and ROLLER granulated samples (Fig. 2) showed higher values of fine particles in ROLLER, which was attributed to the presence of residual uncompressed material in the sample. It was assumed that leakage of some material near the rollers could be the reason for this.

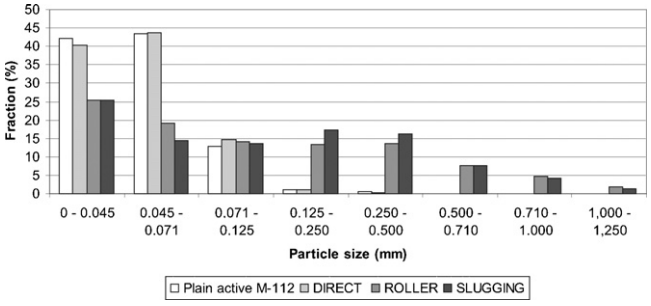


Fig. 2. Particle size distribution of the plain active ingredient M-112 and three powder mixtures (DIRECT, ROLLER, and SLUGGING).

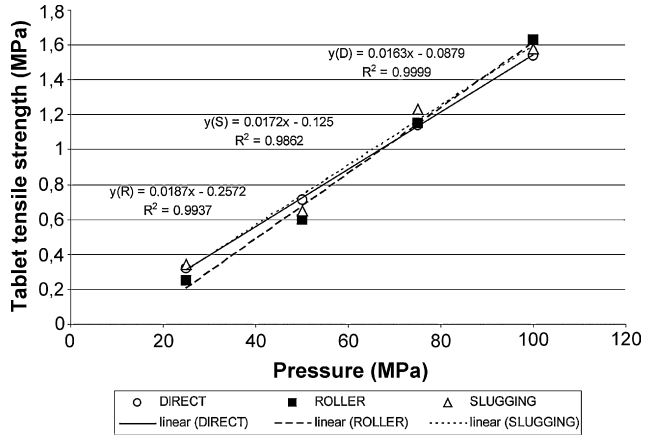


Fig. 3. Tablet tensile strength and compactibility plot.

3.2. Tablet strength and capping tendency

The compactibility slopes obtained in the compression pressure interval 25–100 MPa of both dry granulated systems are higher than those of the direct tableting system (DIRECT: $1.63 \times 10^{-2} \pm 9.60 \times 10^{-4}$; ROLLER: $1.87 \times 10^{-2} \pm 1.10 \times 10^{-3}$; SLUGGING: $1.72 \times 10^{-2} \pm 8.93 \times 10^{-4}$) (Fig. 3). This may indicate that both dry granulated systems are capable of forming stronger compacts than the direct tableting system.

The difference in tablet crushing strength and capping tendency between DIRECT and the ROLLER and SLUGGING dry granulated systems at compression pressures of 100 MPa and higher is presented in Fig. 4. The tablet crushing strength of

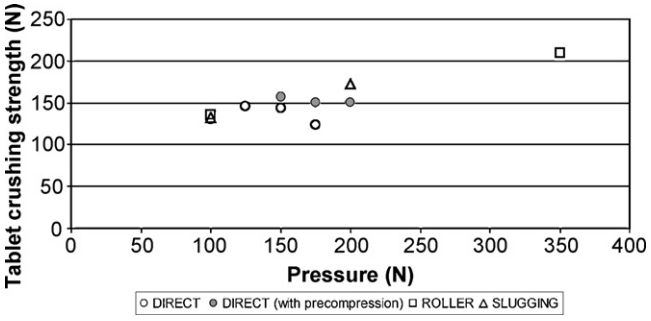


Fig. 4. Tablet crushing strength at higher pressures.

Table 1
Capping coefficient at different compaction pressures

Compaction pressure (MPa)	25	50	75	100	125	150	175	200
DIRECT (no precompression)	0.00	0.00	0.00	0.00	0.00	0.37	0.90	1.00
DIRECT (with precompression 57 MPa)	–	–	–	–	–	0.00	0.20	0.43
ROLLER (no precompression)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SLUGGING (no precompression)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

both dry granulated systems is higher than that of DIRECT at pressures above 100 MPa. Tablets from DIRECT exhibit capping tendencies at pressures as low as 150 MPa, which is also evident from the decrease in tablet crushing strength. The introduction of a precompression phase in the tableting process increased the tablet crushing strength and lowered the capping incidence in the DIRECT formulation. SLUGGING tablets do not exhibit any capping tendencies at a pressure of 200 MPa; capping could not be triggered in ROLLER tablets even at pressures as high as 350 MPa.

The difference in capping tendencies between the three systems is also presented in Table 1. There was considerable capping in DIRECT at a compaction pressure of 150 MPa if no precompression was used. The main compression pressure of 200 MPa caused capping in all DIRECT tablets, while no capping was observed in tablets produced from both dry granulated materials (SLUGGING and ROLLER).

Because of the intensive fragmentation of active ingredient particles during compression, MCC – which is a dry binder in this formulation – cannot help to promote bonding, because new clean surfaces are created on macrolide antibiotic crystals that are not covered with MCC.

The use of precompression during tableting significantly minimizes the capping tendency and increases the tablet tensile strength of tablets produced from DIRECT. Using precompression before the main compression offers the particles more time for rearrangement, fragmentation, and stronger bond formation. Stronger bonds can resist the elastic recovery forces that arise during the decompression phase. Elastic recovery can result in breaking bonds between particles and, consequently, capping.

The reason for the high capping tendency in DIRECT is probably the weak bonding between drug crystals in spite of their high specific surface. The lower capping tendency and higher tablet strength in both dry granulated systems may be the consequence of stronger bonds; this is elaborated in the following sections.

In order to find out if the particle size distribution significantly affects capping, tablets produced from two particle size fractions were compared. The particle size distribution of the SLUGGING fraction smaller than 1.25 mm was considered to be similar to the particle size distribution of DIRECT (the fraction of particles smaller than 0.125 mm in DIRECT is 98.9%). The tablet strength of DIRECT was significantly lower than the strength of tablets produced from a SLUGGING particle fraction smaller than 0.125 mm compressed at the same compaction pressure of 175 MPa (Table 2). The difference is significant when comparing the crushing strength of all tablets made from the DIRECT mixture, as well as when comparing the crushing strength only of DIRECT tablets without capping tendencies.

Two conclusions were drawn from the results shown in Table 2, where the influence of compaction pressure at a constant particle size fraction and the difference of particle size at constant compaction pressure to the crushing strength of tablets produced with the same process (SLUGGING) was studied. As expected, higher compaction pressure during tableting of the same mixture resulted in a higher crushing strength. The results also showed that the smaller particle size of the SLUGGING powder mixture resulted in a higher crushing strength of tablets. No capping tendency was observed in tablets from any SLUGGING size fraction. These results show that particle size can influence tablet strength, but only as a secondary factor—if it is considered within the same formulation system: dry granulated or direct tableting. This again indicates that other factors must be the essential reason for this difference.

3.3. Heckel analysis

The influence of the compression pressure on tablet porosity in all three systems studied (DIRECT, ROLLER and SLUGGING) is shown in Fig. 5. The Heckel plot shapes for all three systems are similar. The pronounced initial curvature of all three Heckel plots is an indicator of intensive particle rearrangement and fragmentation. Particles with a regular shape can rearrange

Table 2
Tablet crushing strength: comparison of DIRECT and two particle size fractions of SLUGGING

	Particle size fraction (mm)	Pressure (MPa)	Tablet crushing strength (N)
DIRECT	Complete[a]	175	123.7[b] (±17.9) 165.8[c] (±6.0)
SLUGGING	<0.125	175	212.8 (±13.6)
SLUGGING	<0.125	350	230.9 (±10.1)
SLUGGING	>0.125	350	200.4 (±12.0)

[a] 98.9% of particles in DIRECT is smaller than 0.125 mm.
[b] All tablets were considered.
[c] Only tablets with no capping tendency were considered.

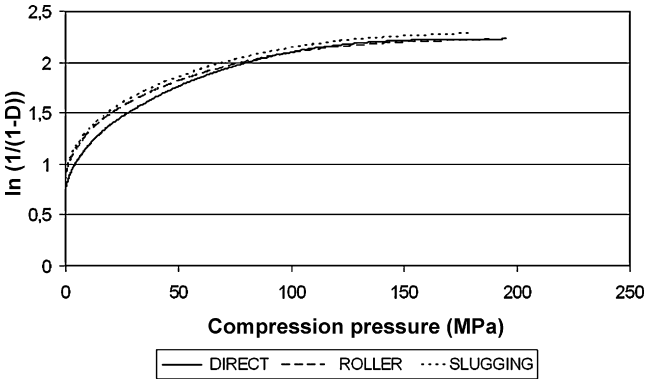


Fig. 5. Heckel plot based on "in-die" method for the three systems: DIRECT, ROLLER, and SLUGGING.

more easily than irregular particles. DIRECT particles, which possess more regular shapes, can rearrange faster than ROLLER and SLUGGING particles, which have more irregular shapes as a consequence of dry granulation.

The slope of the linear part of the plot, which represents a plastic deformation, is not very distinctive among the samples tested, which is typical for materials that fragment easily. Comparison of the results of yield pressure values (P_y) and the shapes of Heckel plots of the formulations studied with the literature data for some excipients with known volume reduction mechanisms (Ilkka and Paronen, 1993; Busignies et al., 2006) demonstrates that, aside from significant fragmentation, some plastic flow during compression can also contribute to the overall reduction mechanism.

Initial particle rearrangement is very intense, especially in the two dry granulated systems, due to their wider particle size distribution compared to DIRECT, which is expressed as bigger curvature in the Heckel plot and higher *A*-value (Table 3). The particle size distributions of the dry granulated systems indicate that there is a relatively high fraction of fine particles among the larger granules, which can slide between larger particles in the rearrangement stage.

P_y of DIRECT is slightly lower than the P_y obtained for both dry granulated systems. Since a lower P_y indicates a greater degree of plastic deformation, the comparison of the three systems shows that DIRECT behaves as a more plastic system than the dry granulated ROLLER and SLUGGING. This finding can be at least partly attributed to the functionality of MCC in the formulation. The MCC in the dry granulated systems was already plastically deformed during dry granulation and could not be further deformed to a significant extent during tableting, as its bonding capacity had already been used. On the other hand, in the DIRECT formulation MCC had its full capacity for plastic deformation.

Dry granulated materials usually express lower compression capability, because some bonds that have been formed between particles during dry granulations are still present after breaking the slugs or ribbons. The bonding potential of granules after dry granulation is lower compared to that of the original particles, which has also been confirmed in other studies (e.g., Bultmann, 2002; Freitag et al., 2004; Soares et al., 2005). These authors reported that tablet tensile strength is usually lower after dry granulation compared to direct tableting, which is not the case in our system.

By comparing the P_y values obtained with the "out-die" and "in-die" methods (Table 3) it is evident that both methods gave comparable results in this study. P_y values in the "in-die" method are usually lower than those in the "out-die" method, due to the fact that, in the "in-die" method, the tablets have not yet exhibited elastic deformation. Our findings are in agreement with the results of some other studies published in the literature (Monedero Perales et al., 1994; Sun and Grant, 2001; Busignies et al., 2006).

No significant differences in Heckel plots among the three systems tested in our study were found that could explain the significant differences in capping tendencies among the tested systems. It can thus be concluded that Heckel analysis cannot be used to predict the capping tendency in studied formulations.

3.4. Lubricant sensitivity test

The results in Table 4 demonstrate that the addition of 2% magnesium stearate to the plain active M-112 does not significantly change the crushing strength of tablets in comparison to tablets produced without magnesium stearate. This was attributed to the fragmentation volume reduction mechanism occurring during compression of M-112. As the weight fraction of the active ingredient M-112 in the formulation is high (75%, w/w), it can also be assumed that fragmentation is the predominant deformation mechanism of the formulation studied. MCC, which is known to deform plastically, is present in a smaller fraction (15%, w/w) in the formulation and obviously does not affect the volume reduction mechanism of the whole formulation to a greater extent. From the results mentioned above it can be concluded that the main volume reduction mechanism of the macrolide antibiotic M-112 is particle fragmentation, and that it belongs to a group of brittle materials. These findings are supported by other published studies, where

Table 3
True density, mean yield pressure (P_y) and intercept (*A*) of Heckel plot based on "out-die" and "in-die" method

System	True density (g/cm^3)	P_y (MPa)	*A*	P_y (MPa)	*A*
		Out-die	Out-die	In-die	In-die
DIRECT	1.2607 ± 0.0021	114	1.08	96	1.28
ROLLER	1.2586 ± 0.0006	126	1.21	113	1.34
SLUGGING	1.2608 ± 0.0012	148	1.22	112	1.36

Table 4
The effect of lubricant on tablet crushing strength

	Tablet mass (g)	Tablet crushing strength (N)
Plain macrolide antibiotic (M-112)	0.5067 ± 0.0039	98.37 ± 5.09
Macrolide antibiotic + 2% Mg stearate	0.5032 ± 0.0020	102.73 ± 1.92

even 0.5% of magnesium stearate mixed for 0.5 min significantly reduced the crushing strength in plastic materials (sodium chloride) and had no effect on brittle materials (Emcompress) that were mixed with lubricant for 1 min (Ragnarsson and Sjögren, 1985).

3.5. Scanning electron microscopy

Fig. 6 shows evident structural changes on particle surfaces after dry granulation and tableting. The macrolide antibiotic studied, M-112, originally appears in the form of plate-like crystals with sharp edges and many smaller particles between bigger ones (Fig. 6a). The crystals have distinct, smooth surfaces, which could be the reason for poor bonding and, consequently, frequent capping.

After compression, the particle size of the active is significantly reduced due to particle fragmentation; the original structure of individual crystals is no longer visible. In addition to particle fragmentation, crystallinity changes can also be observed. Crystal surfaces became more disordered, a feature that can be attributed to partial amorphization (Fig. 6d).

Images of Avicel PH 101 and talc are given as references to enable better explanation of the complete formulation images (Fig. 6b and c).

The original crystalline particles of M-112 and particles of the excipients are evident in photomicrographs of the powder mixture before tableting (Fig. 6e). Some individual fragmented crystals can be still seen in the tablet made with direct compression (Fig. 6h), but they can hardly be distinguished in tablets made from both dry granulated systems (Fig. 6i and j). The original boundaries of particles and their surfaces had mostly disappeared, indicating fragmentation, and amorphization.

The irregular particle shape and rough, disordered surface structure of particles after dry granulation contribute to improved compactibility, stronger bonding with intermolecular forces, and lower capping tendencies of tablets.

3.6. X-ray powder diffraction (XRD)

From the X-ray powder diffraction analysis it is evident that significant crystal structure changes occurred during compression (Fig. 7). The diffraction lines before compression are sharp and high, which indicates a high degree of material crystallinity. After dry granulation, which is the first compression step (ROLLER—ribbons), the lines are significantly lower and broader, and the ordered crystalline structure of the material is extensively destroyed during compression and partially converted to an amorphous phase.

After the second compression (tableting), the percentage of material converted to an amorphous phase increases further, which is evident in the plot (ROLLER—tablets). Since the tablets were analyzed 1 year after compression, it can be assumed that a transformation back to crystalline form does not occur. While there are no new diffraction peaks on the ROLLER plot it can also be concluded that there are no polymorphic transformations during compression in the formulation studied.

3.7. Differential scanning calorimetry (DSC)

The DSC data confirm the transformation from crystalline form to a partially amorphous state (Table 5). The heat of fusion of M-112 is decreased by approx. 20% when it is compressed. This decrease in heat of fusion was attributed to partial amorphization during compression. The results also indicate that higher compression pressures cause a greater change in heat of fusion and amorphization. The presence of glass transition in the DSC curve of compressed materials confirms the partial amorphization of M-112 during compression.

3.8. Surface free energy

There is a significant increase in dispersive surface free energy (γ_S^D) and specific components of free energy in the dry granulated samples (ROLLER and SLUGGING) compared

Table 5
DSC results—the compression effect

	Onset temperature (°C)	Peak temperature (°C)	Heat of fusion (J/g)	Glass transition temperature (°C)
Plain active ingredient M-112—powder	154.12	160.67	50.69	–
ROLLER—powder mixture (before first compression)	154.05	160.67	42.19	–
ROLLER—ribbons (after first compression)	148.48	153.33	34.47	110
DIRECT—tablets (compression pressure 50 MPa)	150.63	158.67	35.42	110
DIRECT—tablets (compression pressure 125 MPa)	149.21	157.00	32.86	110

Table 6
Surface energy of tableting mixtures before tableting: DIRECT, ROLLER, and SLUGGING

System	γ_S^D (mN/m)	$-\Delta G_A^{SP}$ kJ/mol			
		THF (kJ/mol)	Acetone (kJ/mol)	EtAc (kJ/mol)	$CHCl_3$ (kJ/mol)
DIRECT	41.62 (±1.43)	5.09 (±0.96)	9.53 (±0.89)	7.10 (±0.29)	3.40 (±0.80)
ROLLER	47.19 (±0.02)	8.05 (±0.86)	12.87 (±1.44)	11.18 (±1.17)	5.69 (±0.59)
SLUGGING	49.17 (±0.48)	7.45 (±0.60)	11.40 (±1.86)	10.59 (±0.59)	5.89 (±0.74)

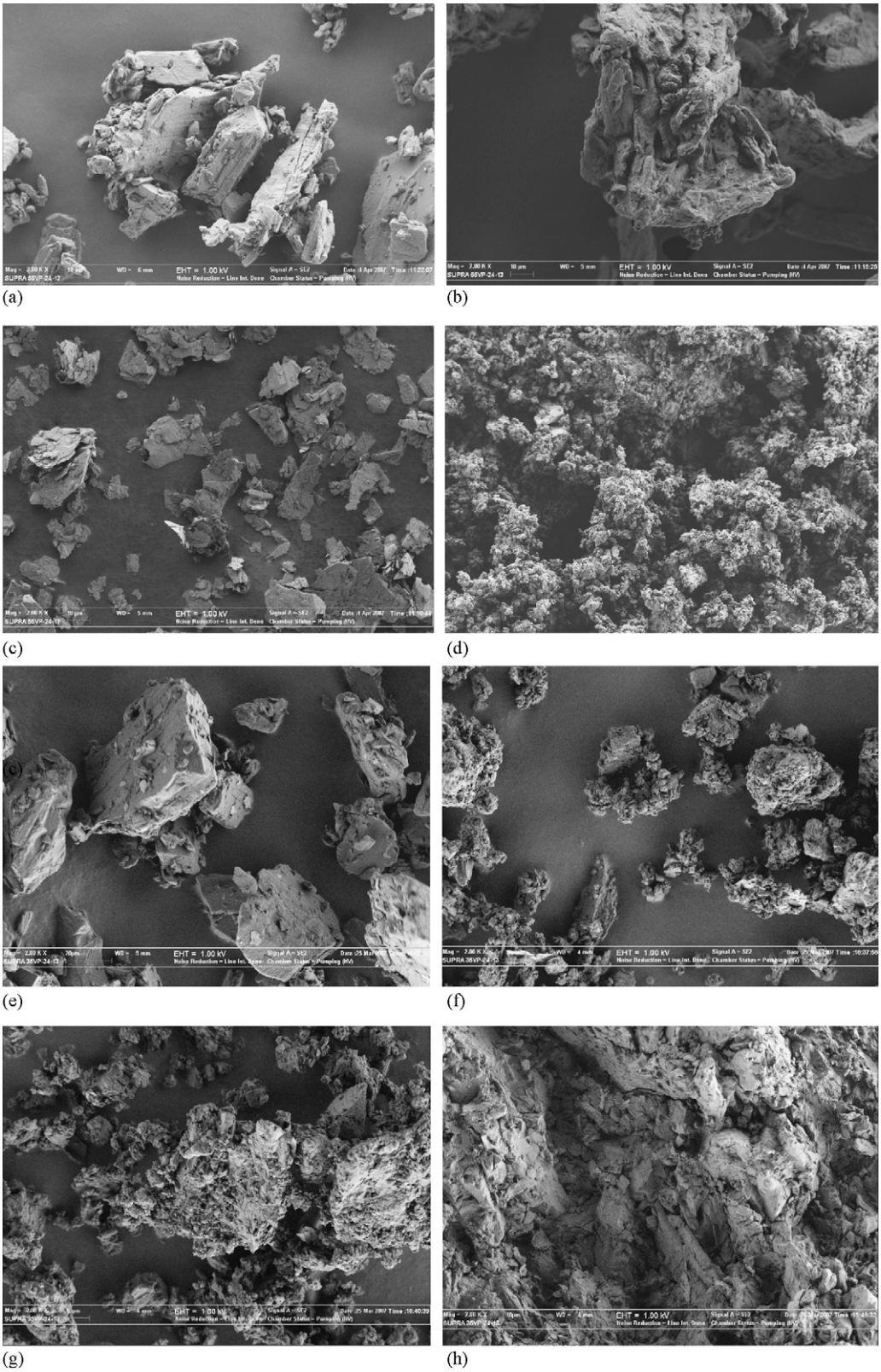
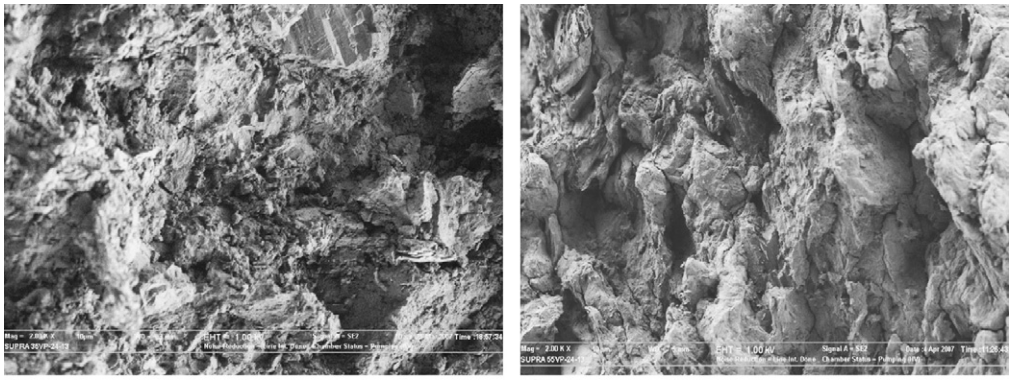


Fig. 6. Scanning electron microscope images: (a) plain macrolide antibiotic (before compression); (b) Avicel PH 101 (before compression); (c) talc (before compression); (d) plain macrolide antibiotic (after compression); (e) DIRECT—mixture before tableting; (f) ROLLER—mixture before tableting; (g) SLUGGING—mixture before tableting; (h) DIRECT—tablet fracture surface; (i) ROLLER—tablet fracture surface; (j) SLUGGING—tablet fracture surface.



(i) (j)

Fig. 6. (*Continued*).

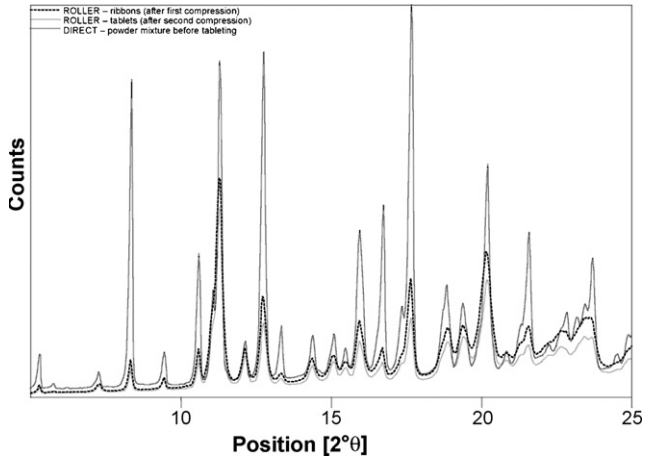


Fig. 7. X-ray powder diffraction: the effect of compression on crystallinity changes.

to the sample not exposed to mechanical stress (DIRECT) (Table 6). This change can be attributed to material amorphization during dry granulation. The greater surface free energy of the tableting mixture enables stronger intermolecular bonds to be formed between particles during tableting, which can lead to lower capping tendencies in tablets made of dry granulated material, while stronger bonds between particles represent a stronger barrier to the energy of elastic relaxation after compression.

4. Conclusions

After dry granulation (roller compaction and slugging) of macrolide antibiotic formulation, the particle size distribution is shifted towards larger particles and the particle size distribution is wider in comparison with the powder mixture before dry granulation.

Particle size alone does not have a significant influence on tablet crushing strength in the model formulation, but the process of dry granulation does. Tablets made from the same particle size fraction of the direct tableting system (DIRECT) exhibit lower crushing strength than tablets from the dry granulated system (SLUGGING) compressed at the same compression pressure.

The compactibility slopes of both dry granulated formulations are significantly higher compared to the direct tableting one. A significant reduction in capping tendency in both dry granulated systems compared to direct tableting was also found. The introduction of a precompression phase in the tableting process reduced the capping tendency in direct tableting.

The predominant volume reduction mechanism of the macrolide antibiotic studied is fragmentation. The complete formulation, which in addition to 75% of macrolide antibiotic also includes 15% of MCC, also demonstrates some plastic behavior. Intensive particle rearrangement takes place at lower compression pressures.

The Heckel plot indicates that both dry granulated systems (SLUGGING and ROLLER) express lower plasticity, as their P_y is higher than the P_y of DIRECT, which appears to be inconsistent with the fact that the dry granulated systems produce stronger tablets. The lower P_y can be partly attributed to partial loss of bonding capacity due to dry granulation, which is also in accordance with other studies. There was no significant difference in the Heckel plot of the dry granulated systems compared to the direct tableting system that would explain the huge difference in capping tendencies. This means that Heckel analysis findings must be taken with caution when applied to dry granulated systems where crystallinity changes can occur.

The dominant type of bonding between particles is probably long distance attractive force. There is unlikely to be a significant occurrence of solid bridges, due to the complex chemical structure of macrolide antibiotic and its intense fragmenting properties.

The model macrolide antibiotic originally appears in crystalline form, which is partially transformed to an amorphous state during compression. This was confirmed with the XRD, DSC, and IGC methods. Both dry granulated systems, which were exposed to higher mechanical stress during granulation compared to the direct tableting system, exhibit higher levels of amorphization and significantly lower capping tendencies of tablets. This finding can be attributed to the fact that materials in amorphous form can accomplish stronger bonding than those in the crystalline form.

This structural change of the model macrolide antibiotic is therefore the crucial factor that can explain the huge difference in capping tendencies between direct tableting and tableting after dry granulation.

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