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Investigation of compressibility and compactibility parameters of roller compacted Theophylline and its binary mixtures

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ABSTRACT

Roller compaction is a dry granulation method which results in tablets with inferior tensile strength comparing to direct compaction. The effect of roller compaction on compressibility and compactibility of tablets prepared from Theophylline anhydrate powder, Theophylline anhydrate fine powder and Theophylline monohydrate was investigated by measuring tensile strength of tablets as well as calculating compressibility and compactibility parameters by Leuenberger equation. The tablets under the same conditions were prepared by direct compaction and roller compaction. The binary mixtures of Theophylline anhydrate powder, Theophylline anhydrate fine powder, Theophylline monohydrate and microcrystalline cellulose were prepared in order to determine the optimal ratio of active material and excipients which delivers a sufficient mechanical strength of tablets. Tensile strength of MCC tablets and compactibility parameters calculated by Leuenberger equation after roller compaction was significantly decreased, while THAP, THAFP and THMO tablets showed only a minor reduction in compactibility and compressibility. Adding MCC to a mixture with Theophylline showed that the right choice and ratio of excipients can enable a sufficient mechanical strength of the tablets after roller compaction.

1. Introduction

In the pharmaceutical industry, roller compaction is frequently used to improve the handling properties of powders especially where the active ingredients are not stable in presence of moisture and high temperature or cause difficulties owing to sticking so wet granulation or direct compaction is not possible (Jeon et al., 2010; Farber et al., 2008; Bindhumadhavan et al., 2005). Besides the many advantages of roller compaction it is often reported in the literature that the tensile strength of tablets produced by roller compaction decreased when compared with direct compression (Malkowska and Khan, 1983; Herting and Kleinebudde, 2007). This phenomenon of reduced tabletability of powders after dry granulation is termed "loss of reworkability" or "loss of tabletability" and has been explained to be due to the limited binding potential which was partially consumed in the first compression step as a result of increasing particle size and decreasing specific surface area of the material. Materials with plastic deformation properties are particularly sensitive to loss of tabletability, while on the other hand, if granules undergo extensive fracture under pressure, the effect of granule size enlargement on tabletability of granules prepared by roller compaction should be diminished (Wu and Sun, 2007). This can be explained by the fact that fracture of particles significantly reduces the original particles size thereby minimizing or even eliminating any difference in the original particle size of the material. The loss of tabletability after roller compaction is an example of how the process can affect performance of formulations (Sun and Himmelspach, 2006).

Tablets produced in the pharmaceutical industry commonly consist of more than one component. The mechanical strength of tablets depends on formulation as well as on the processing parameters. Although the same process parameters are used, the strength of tablets compressed from binary mixtures often cannot be predicted from the compaction properties of the individual materials. This phenomenon may be due to interaction between materials, which may occur during the compaction process (Van Veen et al., 2000). Many workers have reported on the use of powder mixtures because they may exhibit significantly better properties than the individual components.

It is often reported in the literature that different polymorphs/pseudopolymorphs of the same material can exhibit differences in compactibility and compressibility (Sehic et al.,

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2010). It is also known that they can behave differently regarding compactibility and loss of tabletability during roller compaction.

In a recent study by these authors (Hadžović et al., 2010) it was demonstrated that the compressibility and the compactibility of Theophylline anhydrate and Theophylline monohydrate as well as of their binary mixtures with microcrystalline cellulose (MCC) was altered in different ways by roller compaction. The authors also reported that the disintegration and the dissolution behavior of tablets was significantly improved when tablets were compressed from roller-compacted powders and powder mixtures.

The aim of this study was to evaluate the effect of roller compaction on the tensile strength of tablets made from Theophylline of different sizes and polymorphic/pseudopolymorphic forms by means of parameters which quantitatively describe the changes in compactibility on one hand and in compressibility on the other. For this purpose the Leuenberger model is used which correlates the tensile strength of tablets to the compatibility parameter, σ_{Tmax} and the compressibility parameter γ.

It was previously mentioned that materials which exhibit different type of deformation under compression may affect the tablet strength in different ways. Therefore the further aim of the present study is to determine the impact of microcrystalline cellulose (MCC) on the tensile strength of tablets of binary mixtures of MCC with Theophylline anhydrate and Theophylline monohydrate in order to improve the properties of Theophylline tablets obtained by roller compaction and at the same time to find the best ratio of the powders in the mixture which will give tablets with the highest tablet strength.

2. Materials and methods

2.1. Materials

Two pseudo polymorphic forms of Theophylline were used, Theophylline anhydrate and Theophylline monohydrate (THMO). Theophylline anhydrate was used in two different particle sizes, Theophylline anhydrate powder (THAP) and Theophylline anhydrate fine powder (THAFP). All three materials were purchased from BASF ChemTrade GmbH, Germany. Microcrystalline cellulose (Avicel PH101) was purchased from FMC BioPolymer, USA.

2.2. Preparation of binary mixtures

Mixtures of THAP, THAFP and THMO and 0, 30, 50, 70, 90, and 100% (w/w) of Microcrystalline cellulose were prepared by mixing the powders for 20 min in a Turbula® mixer type T2C (Willy Bachofen AG, Basel, Switzerland). No lubricant was used for the binary mixtures and individual materials.

2.3. Roller compaction and granulation

Roller compaction of all starting materials and their binary mixtures was carried out in the Fitzpatrick IR220 Chilsonator® (Fitzpatrick, Elmhurst, USA), equipped with smooth rolls, under standardized conditions (horizontal screw speed HSV 22 rpm, vertical screw speed FSV 200 rpm, roll speed 3 rpm, pressure 20 bar).

THAP was chosen as a model drug for roller compaction under the following conditions: horizontal screw speed (HSV) 25 rpm, vertical screw speed (FSV) 200 rpm, roll speed 3 rpm and pressure 30 bar. After roller compaction the ribbons were subsequently milled using a L1A Lab Scale FitzMill® (Fitzpatrick, Elmhurst, USA) equipped with 1.3 mm bar rotor, rasping screen for minimizing fines, and set at a speed of 600 rpm.

2.4. Tablet production

Tablets were prepared under the same conditions by both direct compaction and following roller compaction.

Tablets (round, flat, 11 mm diameter, 400 mg weight) consisting of the original and granulated materials as well as from the mixtures were prepared by filling manually pre-weighed material into the die of the Zwick® material tester 1478 (Zwick® GmbH, Ulm, Germany). For each powder system three tablets were compressed at different pressure levels of 10.5, 21.05, 31.50, 42.1, 63.15, 84.21, 105.26 and 126. 32 MPa (1, 2, 3, 4, 6, 8, 10 and 12 kN).

After compaction the tablets were stored for 48 h in a closed chamber maintained at relative humidity of 42–44%.

2.5. Characterization of powders and tablets

2.5.1. Scanning electron microscopy and particle size analysis

Images of the powders were taken using an ESEM Philips XL 30 at a voltage of 10 kV after sputtering with gold.

Particle size and particle size distribution were measured by laser diffraction (Malvern Mastersizer 2000, Scirocco 2000). For all samples dry measurement method was employed using air pressure for dispersing the particles. According to the material properties different pressures were used: Theophylline anhydrate powder 0.5 bar, Theophylline anhydrate fine powder 2.0 bar, Theophylline monohydrate 2.0 bar and Cellulose microcrystalline 2.0 bar. Each sample was measured in triplicate.

2.5.2. Differential Scanning Calorimetry (DSC)

DSC measurements of THAP, THAFP and THMO powder were performed (Pyris Diamond 1, Perkin Elmer, Switzerland) in order to characterize and examine the polymorphic forms of the materials.

Approximately 4 mg of the sample were weighed into 30 μl aluminum pan with hole and heated in the DSC from 30 °C to 300 °C. Heating rate was set to 10 °C/min under nitrogen purge. Measurements were performed in triplicate.

2.5.3. Tensile strength

Dimensions of the flat-faced tablets were measured as follows: weight (Balance-AT 460 Delat Range, Mettler Toledo), thickness (Digital caliper) and crushing strength (Tablet Tester 8M, Dr. Schleuniger, Pharmatron Inc, Manchester).

Breaking force was converted into tensile strength according to Newton (Fell and Newton, 1970) (Eq. (1)):

$$\sigma = \frac{2F}{\pi dh} \quad (1)$$

where σ – radial tensile strength [N/cm]; F – maximal force [N]; d – tablet diameter [cm].

2.5.4. Leuenberger equation

Compressibility, the ability of the material to decrease in volume under pressure, is only indirect measure of its ability to form tablets. However in practice it is more important that compression produces a compact of adequate strength, what can be defined as compactibility of the material. The physical model of powder compression proposed by Leuenberger (1982) connects the compressibility and compactibility. Interrelation between these two characteristics can be expressed with Eq. (2).

$$\sigma_t = \sigma_{Tmax}(1 - e^{\gamma\sigma\rho}) \quad (2)$$

where σ_t – radial crushing strength at certain pressure (MPa); σ_{Tmax} – maximum crushing strength (MPa); γ – compression susceptibility (MPa^{-1}); ρ – relative density.

The equation can be used for a single substance as well as for powder or granules mixtures. The parameter σ_{Tmax} can be used to

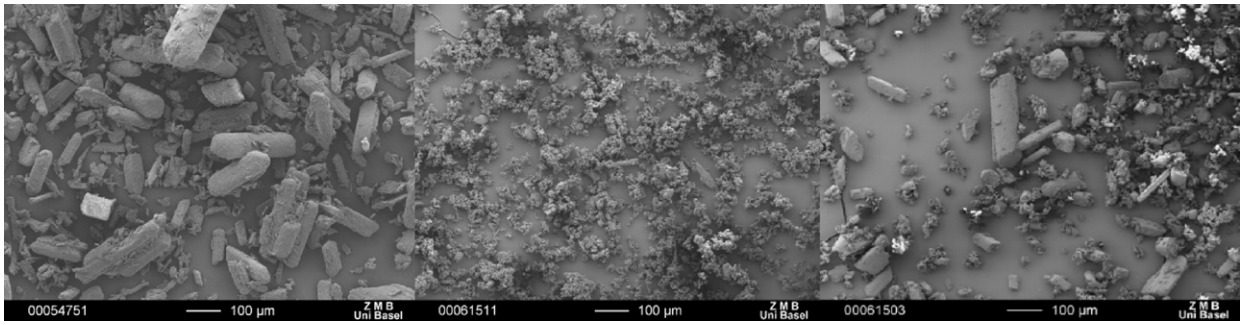

Fig. 1. SEM images of THAP, THAFP, THMO (magnification 100×).

quantify compactibility and the parameter γ to quantify compressibility (Leuenberger, 1982).

2.6. Statistical analysis

ANOVA single-factor analysis (0.05) was applied in order to detect statistical differences in the characteristics of the tablets produced by direct compaction and by roller compaction at pressures of 20 and 30 bar. Differences in results are considered as statistically significant in the case of $p < 0.05$.

3. Results and discussions

3.1. Scanning electron microscopy and particle size distribution

Images (see Fig. 1) of THAP, THAFP and THMO showed that the particles have elongated shapes and that the particles of THAFP were agglomerated. Agglomeration of the particles can have an impact on the specific surface area and thus on the behavior of the powder during tableting process. Even after sieving of the material it was impossible to separate the particles of THAFP.

THAP exhibited the largest particles (90% < 386.06 μm), followed by MCC (90% < 135.92 μm), THMO (90% < 107.94 μm) and THAFP (90% < 38.08 μm).

3.2. Differential Scanning Calorimetry (DSC)

In order to check the influence of roller compaction and milling on the structure and polymorphism of Theophylline, DSC measurement of pure powders (THAP, THAFP and THMO), ribbons, granules and tablets were performed. According to the European Pharmacopoeia the melting point of Theophylline is 270–274 °C. Suzuki et al. (1989) prepared separately two polymorphic forms of Theophylline (form II and form I) and examined their thermo-chemical properties. They illustrated by DSC measurements that form II had a melting point at 273.4 ± 1.0 °C and form I at 269.1 ± 0.4 °C. Phadnis and Suryanarayanan (1997) showed that the stable form II had a melting point of 271 °C. THAP and THAFP used in this study showed the same endothermic event at temperature 271 °C (see Table 1) which is due to the melting point of the materials. Ribbons obtained by roller compaction at pressure of 30 bar had the same melting point as ribbons produced at 20 bar which led to the conclusion that increasing the pressure of compaction did not affect the polymorphic form of THAP.

THMO showed first endothermic broad peak around 60–80 °C due to dehydration and transition of hydrate to anhydrate and a second endothermic sharp peak due to melting of the anhydrate at 271–272 °C. Suzuki et al. (1989) showed that a dehydration of Theophylline monohydrate to anhydrate is at 71 °C and further melting of the stable anhydrate form is at 273 °C. After compression ribbons were milled and granulate was used to produce tablets of 12% of porosity (4.5 kN). Results presented in Table 1 showed that all mentioned processes did not change polymorphic forms of THAP, THAFP and THMO.

3.3. Tensile strength

Due to the fact that THAFP (90% less than 38.08 μm) had smaller particle size than THAP (90% less than 386.09 μm) the tensile strength of tablets produced from THAFP should be higher than the tensile strength of THAP tablets. Because of its smaller particle size, THAFP exhibited higher specific surface area which is a criterion for increased particle bonding in tablets. Surprisingly however the THAFP tablets did not show significantly higher mechanical strength compared to the tablets prepared from THAP, except at very low compression pressure (see Fig. 5). Tensile strength of THAFP at compression force of 1 kN and 12 kN (the lowest and the highest compression pressures) was 34.2 ± 6.7 N/cm^2 and 233.4 ± 4.5 N/cm^2 respectively, and for THAP 19.2 ± 1.6 N/cm^2 and 260.2 ± 14.4 N/cm^2 respectively (Fig. 2).

Table 1
Results of DSC measurement (melting point and enthalpy) for THAP, THAFP and THMO – pure materials, ribbons, granules and tablets.

	Transition of hydrate to anhydrate ± SD (°C)	Enthalpy ± SD (J/g)	Melting point ± SD (°C)	Enthalpy ± SD (J/g)
THAP powder	–	–	271.05 ± 0.56	157.25 ± 3.20
THAP ribbon 20 bar	–	–	272.01 ± 0.21	152.13 ± 2.20
THAP ribbon 30 bar	–	–	271.19 ± 0.09	153.83 ± 1.22
THAP granules	–	–	271.95 ± 0.36	153.83 ± 3.38
THAP tablets	–	–	271.77 ± 0.16	156.01 ± 6.51
THAFP powder	–	–	271.33 ± 0.23	162.87 ± 3.41
THAFP ribbon 20 bar	–	–	271.06 ± 0.10	160.21 ± 1.50
THAFP granules	–	–	271.10 ± 0.11	161.76 ± 6.30
THAFP tablets	–	–	271.41 ± 0.20	154.67 ± 3.23
THMO powder	72.90 ± 2.23	186.09 ± 14.63	271.86 ± 0.24	149.40 ± 1.81
THMO ribbon 20 bar	75.19 ± 1.03	165.99 ± 10.36	271.61 ± 0.25	146.92 ± 6.48
THMO granules	76.04 ± 0.70	170.27 ± 4.31	271.66 ± 0.23	147.03 ± 006
THMO tablets	73.37 ± 0.37	164.02 ± 3.23	270.62 ± 0.14	140.52 ± 2.46

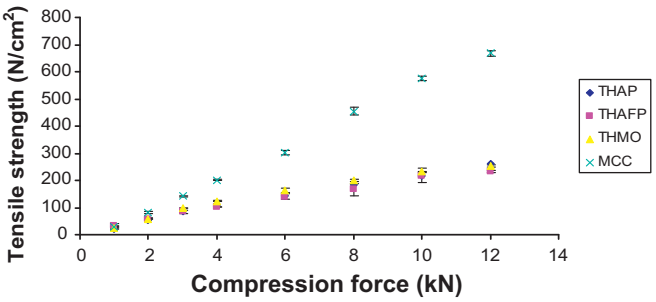

Fig. 2. Tensile strength of THAP, THAFP, THMO and MCC – powder.

In the research of Herting and Kleinebudde (2007), it was reported that decreasing the particle size of Theophylline and MCC results in stronger tablets and even if tablets are produced by roller compaction, tensile strength is still dependent of the particle sizes of the original materials. This was explained by more available binding points due to the larger surface area. As it was previously shown that THAFP used in this study was agglomerated, the differences in the obtained results can thus be clarified. THMO powder formed tablets with higher tensile strength than THAP and THAFP. The highest tensile strength value can be a result of high moisture content of hydrate what can improve compressibility and compactibility. Results obtained at compression force of 12 kN could be explained by the possibility that at high compression force THMO dehydrated and lost its tabletability. DSC results showed that THMO in tablets with 12% porosity (4.5 kN) did not lose water, but it is assumed that it is possible that at very high pressure (12 kN) it might undergo dehydration.

The tensile strength of tablets prepared by direct compression (powder) and following roller compaction (granules) is plotted against the compression force in Figs. 3–6 for THAP, THAFP, THMO and MCC, respectively. A linear dependence of tensile strength in relation to compression force can be observed.

The tensile strength of tablets produced from THAP powder at compression force 12 kN was 260.6 ± 7.1 N/cm^2, from THAP granules (20 bar) was 237.8 ± 6.7 N/cm^2, from THAP granules (30 bar) was 227.9 ± 9.4 N/cm^2. From these results it can be seen that roller compaction decreased the tensile strength of tablets, especially at higher roller compaction pressure (30 bar). The difference in the tensile strength of the tablets produced by direct compaction and by roller compaction was even more noticeable in the case of MCC: the tensile strength of tablets produced at compression force of 12 kN was 672.0 ± 10.6 N/cm^2, while the tensile strength of tablets produced by roller compaction at pressure of 20 bar was 367.1 ± 3.2 N/cm^2, and at pressure of 30 bar was 331.8 ± 10.8 N/cm^2.

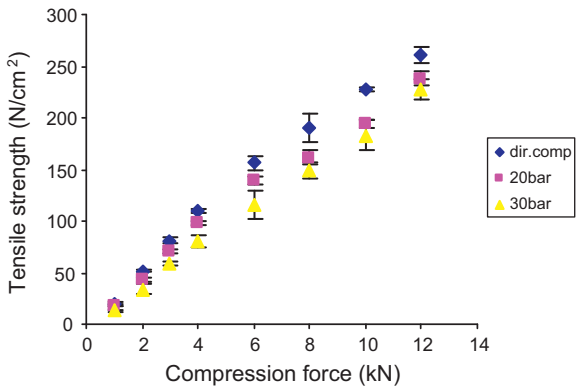

Fig. 3. Tensile strength – THAP 100%.

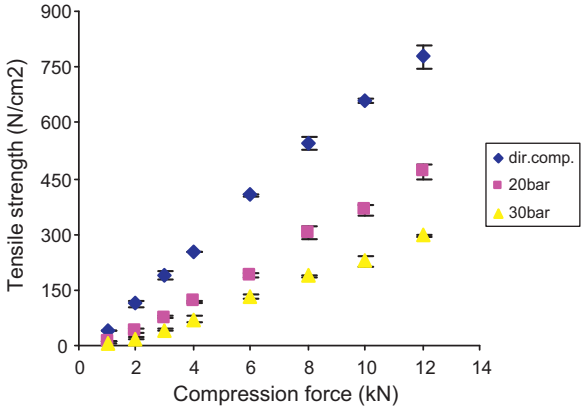

Fig. 4. Tensile strength – MCC 100%.

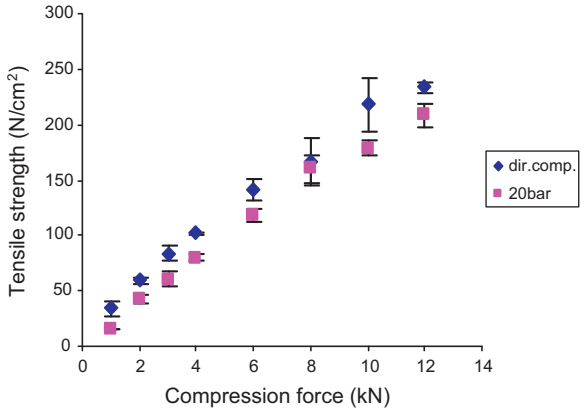

Fig. 5. Tensile strength – THAFP 100%.

The tensile strength of tablets prepared from THAFP powder at compression force of 12 kN was 233.4 ± 4.5 N/cm^2, for THAFP granules (20 bar) was 208.4 N/cm^2.

Tablets produced from THMO powder showed tensile strength of 254.25 ± 4.02 N/cm^2 and tablets produced from THMO granules (20 bar) had tensile strength of 242.55 ± 10.47 N/cm^2 at compression force of 12 kN.

The plots of tensile strength vs. compression force of tablets of all binary mixtures (100%, 70%, 50%, 30% and 10% of THAP, THAFP, THMO and MCC) produced by direct compaction and roller compaction are not presented here, but exhibited analogous behavior (see Hadžović, 2008). The ratio of THAP and MCC in the mixtures

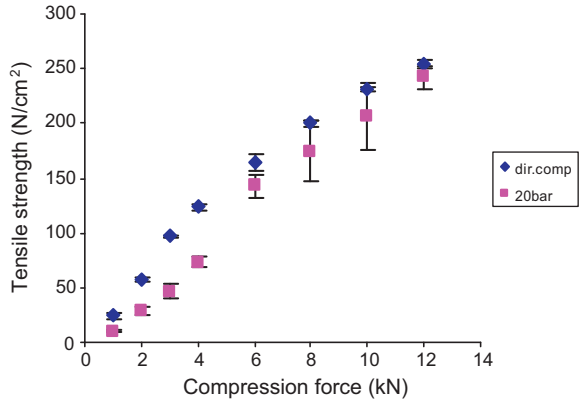

Fig. 6. Tensile strength – THMO 100%.

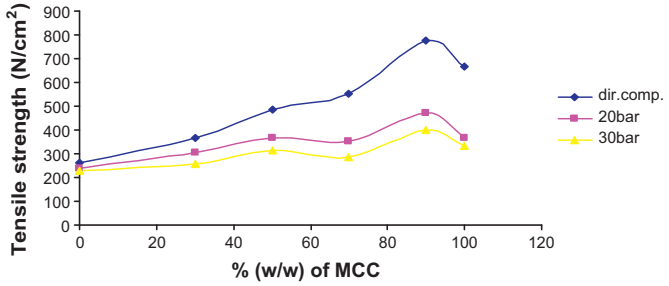

Fig. 7. The effect of MCC mass (w/w) on radial tensile strength for THAP/MCC mixtures.

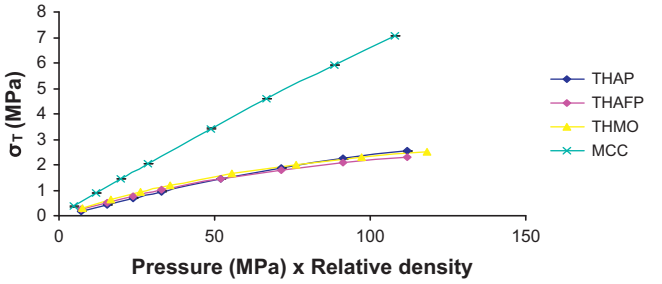

Fig. 8. Tensile strength of THAP, THAFP, THMO and MCC according to Leuenberger equation.

affects the changes of tensile strength in the way that increasing of MCC in the mixtures led to the increasing in tensile strength values.

Fig. 7 shows the effect of different concentrations of THAP and MCC in the mixture on tablet tensile strength (direct compaction, roller compaction at pressure of 20 and 30 bar) compressed at compression force 12 kN. It can be seen from Fig. 7 that the tensile strength of tablets compressed from 100% MCC was higher than tensile strength of tablets containing 100% THAP. According to this result and the fact that after roller compaction tensile strength of THAP was not decreased significantly, it could be hypothesized that THAP consolidated more by fragmentation than by plastic deformation. Furthermore, the strength of the tablets produced from the mixture was not a simple function of strength of individual components. As the result of tensile strength of MCC was higher than tensile strength of THAP, it was expected that tensile strength of the binary mixtures are between the individual materials. However, the strengths of the mixtures were different than predicted.

It is interesting to note that the mixture of THAP 10% + MCC 90% produced tablets with higher tensile strength than the individual materials. This phenomenon that tensile strength of tablets produced from the powder mixture is higher than the strength of tablets produced from the individual components is characteristic of mixtures of two materials which consolidate by different mechanisms. Garr and Rubinstein (1991) examined the tabletability of MCC and dicalcium phosphate hydrate mixtures in direct compaction and after slugging. They found that the tablets with the highest strength were produced within the range of 66–99% MCC and 10–33% dicalcium phosphate hydrate. It is well known that MCC shows plastic deformation and dicalcium phosphate hydrate brittle behavior under pressure. Results obtained in this study showed the same trend, because the mixture with the best tablets was in this range. Fig. 7 showed the effect of different concentration of THAP and MCC in the mixture on tablet tensile strength (direct compaction, roller compaction at pressure of 20 and 30 bar).

Roller compaction decreased slightly the mechanical strength of tablets produced from THAP, THAFP and THMO, however this was not statistically significant ($p > 0.05$). Comparing this reduction in tablet strength with MCC tablets, it could be observed that Theophylline showed different behavior when it was exposed to pressure. Due to the observation that materials with different properties under compression showed different results, it is essential to find an optimum composition of the formulation. Well designed tablet formulation produced by roller compaction should maintain a good balance between plasticity and fragmentation. As it is shown in this study, MCC in the binary mixtures was responsible for the mechanical strength of the tablets being a very plastic material. Observing the properties of the tablets produced from THAP, THAFP and THMO, they could be considered as materials which partly fragmentized during compaction. In the combination with MCC, their function was to minimize the effect of particles enlargement occurring during roller compaction.

3.4. Leuenberger equation

In a previous study conducted in our laboratories (Hadžović et al., 2010) different mathematical equations were applied in order to characterize the compressibility of THAP, THAFP, THMO and MCC powders and granules obtained by roller compaction. The results obtained in the quoted study as well as the results obtained for the tensile strength of tablets in this study could not satisfactorily characterize the materials. In order to find a better model for the tensile strength, the Leuenberger equation was applied (Eq. (2)). For this model the radial tensile strength σ_t at certain forming pressure σ_c was plotted against the product of the compression pressure and the relative density of the tablets. In Eq. (2) the parameter σ_{Tmax} is the theoretically maximal possible tensile strength for a compact whose porosity is equal to zero and the parameter γ termed compression susceptibility is a specific constant which describes compressibility. Materials with low σ_{Tmax} show relatively poor compactibility, and even if high compression pressure is applied this value cannot be exceeded. A high γ value on the other hand means that the maximal tensile strength could be achieved at low compression pressure (Leuenberger, 1982).

Fig. 8 shows that THAP, THAFP and THMO would reach the plateau of the maximal tensile strength at lower compression pressures than MCC, which means that higher compression pressure should be applied to reach maximal tensile strength for MCC. This can be confirmed by the results in Table 2. According to the results of σ_{Tmax}, MCC is the most compactable material with extremely high maximal tensile strength of 29.9 ± 1.8 MPa. On the other hand THAP, THAFP and THMO exhibited maximal tensile strength of 3.1 ± 0.2 MPa, 3.9 ± 0.6 and 3.2 ± 0.1 MPa respectively. It is seen from Fig. 2 that MCC showed the highest tensile strength σ which is in agreement with these results.

According to the pressure susceptibility parameter γ, THAP, THAFP and THMO will reach maximal tensile strength much faster than MCC. This could also be observed in Fig. 8. The γ values for THAP, THAFP, THMO and MCC were $8.9 \pm 0.0 \times 10^{-3}$ MPa^{-1}, $11.7 \pm 0.3 \times 10^{-3}$ MPa^{-1}, and $12.7 \pm 0.0 \times 10^{-3}$ MPa^{-1} and

Table 2
The compression susceptibility parameter $\gamma \times 10^{-3}$ (MPa)$^{-1}$, and the maximum tensile strength σ_{Tmax} (MPa) of THAP, THAFP, THMO and MCC – direct compression and roller compaction.

$n = 3 \pm$ SD	$\gamma \times 10^{-3}$ [MPa^{-1}]	σ_{Tmax} [MPa]	R^2
THAP powder	8.91 ± 0.1	3.22 ± 0.1	0.999
THAP 20 bar	7.82 ± 0.1	3.94 ± 0.0	0.999
THAP 30 bar	8.25 ± 0.2	2.80 ± 0.1	0.998
THAFP powder	11.78 ± 0.0	3.97 ± 0.1	0.999
THAFP 20 bar	7.33 ± 0.3	3.74 ± 0.1	0.998
THMO powder	12.79 ± 0.0	3.25 ± 0.0	0.999
THMO 20 bar	11.37 ± 0.4	2.11 ± 0.0	0.997
MCC powder	2.45 ± 0.0	29.99 ± 1.8	0.998
MCC 20 bar	5.90 ± 0.2	7.52 ± 0.1	0.999

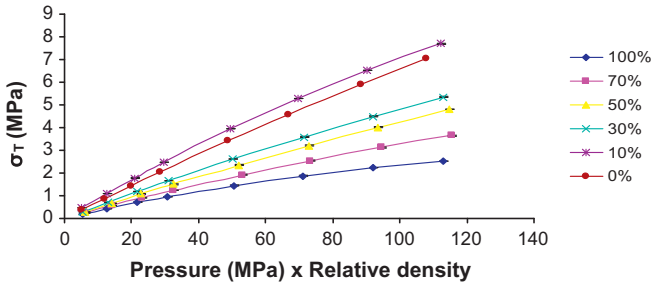

Fig. 9. Tensile strength of THAP and MCC binary mixtures according to Leuenberger equation.

$2.5 \pm 0.0 \times 10^{-3}$ MPa^{-1} respectively, means that at very similar compression pressure will reach the same maximal tensile strength.

All the binary mixtures showed maximum tensile strength and pressure susceptibility values between the values of these parameters for pure THAP, THAFP, THMO and MCC.

Fig. 9 shows the Leuenberger plots of the individual components as well as the binary mixtures of THAP and MCC. It can be seen that though pure MCC had a higher maximal tensile strength than most of the binary mixtures, the THAP 10% + MCC 90% mixture exhibited even higher tensile strength σ_T in the pressure range between 10.2–120.6 MPa. This indicates that MCC could reach a higher tensile strength (29.9 ± 1.8 MPa) when compacts with zero porosity are produced, but the mixture Theophylline 10% + MCC 90%, having high pressure susceptibility value, can reach the maximal tensile strength at lower compression pressure.

If higher compression pressure were used for this experiment the point could have been manifested when the maximal tensile strength was reached. However, even with the pressure range used in Fig. 9 it could be observed that the mixture of THAP10% + MCC 90% will reach the maximum tensile strength before MCC because the MCC plot is more linear and it needs higher pressures to reach the plateau.

It should be noted that the results obtained for THAFP, THMO and their binary mixtures with MCC (not presented here) showed analogous behavior to that of the THAP:MCC mixtures (Hadžović, 2008).

As example of materials with good and poor compression properties, acetyl salicylic acid and paracetamol were chosen from the literature (Orelli, 2005). The maximum tensile strength and pressure susceptibility of acetyl salicylic acid were 2.4 MPa and 7.5×10^{-3} MPa^{-1} and those of paracetamol were 0.4 MPa and 3.5×10^{-3} MPa^{-1}. According to these results the values of σ_{Tmax} and γ shown in Table 2 indicate that all examined materials in this study are supposed to be used in direct compression.

Results of σ_{Tmax} and γ showed that roller compaction did not change significantly the compressibility and compactibility of THAP. These results are in agreement with the results obtained by Heckel and modified Heckel equations as reported previously (Hadžović et al., 2010) as well as with the tensile strength measurements (see Fig. 2).

Contrary to THAP, the compressibility and compactibility parameters of MCC were changed after roller compaction. Maximal tensile strength and pressure susceptibility of MCC tablets produced by direct compression were 29.9 ± 1.8 MPa and $2.4 \pm 0.0 \times 10^{-3}$ MPa^{-1}, while the same parameters of tablets produced by roller compaction were $7.5 \pm$ MPa and 5.9×10^{-3} MPa^{-1} indicating that the maximal tensile strength which the compact could reach when it has zero porosity was largely decreased. At the same time, according to the fact that the pressure susceptibility was increased, maximal tensile strength could be achieved at lower compression pressures.

Radial tensile strength of THAP, THAFP, THMO and MCC tablets (direct compaction and roller compaction) plotted against the product of compression pressure and relative density of the compacts showed that compacts produced from powder by direct compaction showed a higher crushing strength at certain pressure than tablets prepared from the granules (Hadžović, 2008). The differences in crushing strength are more remarkable in the case of MCC than THAP, THAFP and THMO.

It should be noted that in order to fit the Leuenberger plot for the binary mixtures, higher pressures would be required to reach the plateau for tensile strength. As the calculation of the maximal tensile strength and pressure susceptibility parameters was done by nonlinear regression, lack of data at such pressures would have led to inaccurate results and for this reason results for tablets produced from the binary mixtures by roller compaction were not presented.

4. Conclusions

THAP, THAFP and THMO used in this study exhibited their stable polymorphic form. DSC measurements of compacts (roller compaction) granules (milling) and tablets (tableting) showed that after processing of the materials the melting point was not affected by roller compaction. Tensile strength values indicated that the most compactable material is MCC followed by THMO, THAP and THAFP. After roller compaction the tensile strength of THAP, THAFP and THMO tablets was not significantly decreased, but MCC tablets produced by roller compaction showed much lower tensile strength. As the amount of MCC in the binary mixtures was increased differences in tensile strength of tablets prepared by direct compaction and roller compaction became more prominent. Reduction of the tensile strength after roller compaction is a typical property of the plastic material and therefore MCC could be ranked as more plastic than THAP, THAFP and THMO.

Using the Leuenberger model it was shown that THAP, THAFP and THMO were more compressible, whereas MCC was the most compactable material.

The results of this study showed that the selection of the right excipients in combination with the drug plays a major role in the mechanical properties of a formulation.

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