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Roller compaction of different pseudopolymorphic forms of Theophylline: Effect on compressibility and tablet properties

Ervina Hadžović[a,b,1], Gabriele Betz[a,*], Šeherzada Hadžidedić[b], Silvia Kocova El-Arini[c], Hans Leuenberger[a,d,1]

[a] Industrial Pharmacy Lab, Department of Pharmaceutical Sciences, University of Basel, Klingelbergstr. 50, 4056 Basel, Switzerland
[b] Bosnalijek d.d., Development Department, Jukićeva 53, 71000 Sarajevo, Bosnia and Herzegovina
[c] National Research Centre, Tahrir Street, Cairo – Dokki, Egypt
[d] Ifiip GmbH, Institute for Innovation in Industrial Pharmacy, Birsigstr. 79, P.O. Box, CH-4011 Basel, Switzerland

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ABSTRACT

The effect of roller compaction on disintegration time, dissolution rate and compressibility of tablets prepared from Theophylline anhydrate powder, Theophylline anhydrate fine powder and Theophylline monohydrate was studied. In addition, the influence of adding microcrystalline cellulose, a commonly used excipient, in mixtures with these materials was investigated. Theophylline anhydrate powder was used as a model drug to investigate the influence of different compaction pressures on the tablet properties. Tablets with same porosity were prepared by direct compaction and by roller compaction/re-compaction. Compressibility was characterized by Heckel and modified Heckel equations. Due to the property of polymorphic materials to change their form during milling and compression, X-ray diffraction analysis of Theophylline anhydrate powder, Theophylline anhydrate fine powder and Theophylline monohydrate powders and granules was carried out. After roller compaction the disintegration time and the dissolution rate of the tablets were significantly improved. Compressibility of Theophylline anhydrate powder and Theophylline anhydrate fine powder was decreased, while Theophylline monohydrate showed higher compressibility after roller compaction. Microcrystalline cellulose affected compressibility of Theophylline anhydrate powder, Theophylline anhydrate fine powder and Theophylline monohydrate whereby the binary mixtures showed higher compressibility than the individual materials. X-ray diffraction analyses confirmed that there were no polymorphic/pseudopolymorphic changes after roller compaction.

1. Introduction

Direct compaction in pharmaceutical tablet manufacturing requires a very good flowability and compressibility of the particulate starting materials. Those parameters become even more critical if the formulation contains a large amount of active substance. To overcome these problems, several alternatives have been used in the past, in particular wet and dry granulation methods. Roller compaction is a very attractive technology in the pharmaceutical industry to densify materials in order to improve their flow properties, content uniformity and prevent particle segregation (Xiarong et al., 2007; Teng et al., 2009). This method allows granulation of materials sensitive to moisture, which is a significant advantage in comparison to wet granulation. Another advantage is that it does not require a drying stage and therefore it is suitable for compounds that either have a low melting point or degrade rapidly upon heating (Bindhumadhavan et al., 2005). Roller compaction is a continuous dry compaction process in which uniformly mixed powders are compressed between two counter rotating rolls to form compacts which are subsequently broken into granules (Guigon and Simon, 2003; Yehia, 2007). It also can be described as a particle-bonding process where the bonds within the granules are subsequently formed through particle rearrangement, deformation, fragmentation, and bonding (Miller, 1997). In the literature it is often shown that after roller compaction a material tend to loose mechanical strength named as loss of reworkability (Kleinebudde, 2004; Herting and Kleinebudde, 2007). This phenomenon is dependent on the deformation behavior of the materials exposed to roller compaction. Plastic deformable materials are particularly sensitive because of the limiting binding potential which may be consumed in the first compression step by increasing particle size and decreasing specific surface area (Malkowska and Khan, 1983; Herting and Kleinebudde, 2007). However, materials, which undergo fragmen-

* Corresponding author. Tel.: +41 61 381 07 20; fax: +41 61 381 04 30.
E-mail address: gabriele.betz@unibas.ch (G. Betz).
[1] Tel.: +41 61 267 15 01, fax: +41 61 267 15 16.

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tation under pressure showed less or even no loss of reworkability after roller compaction. To diminish or even eliminate loss of reworkability the crucial moment in the development of a robust formulation is the application of systematic quality by design. If excipients with adequate properties, regarding the active material, are chosen it is possible to keep mechanical strength of the tablets constant. In pharmaceutical formulation design it is still not possible to predict the behavior of binary or more complex particulate mixtures under pressure even if the properties of the starting materials are known, e.g. the properties of the pure active substance and of the excipients. Therefore each pharmaceutical formulation is tailor made for a certain active substance and its dose.

Manufacturing processes such as milling, granulation, drying, and compaction can induce phase transformations of metastable drugs (Suihko et al., 2001). During roller compaction disruption of crystal lattice and change in polymorphic or/and pseudo polymorphic forms of the material can take place. Polymorphic transitions may occur as a result of applied pressure during roller compaction or due to double compaction after tabletting. Even if the physical form of the material is carefully selected for the manufacture of a certain dosage form, the processing conditions may change the final solid state of the drug (Debnath and Suryanarayanan, 2004).

Herting and Kleinebudde (2007) investigated the influence of changing the particle size in the binary starting mixture of microcrystalline cellulose (MCC) and Theophylline anhydrate on the flowability of granules. However, influence of direct compaction and roller compaction on the properties of the final pharmaceutical compacts, such as disintegration time and dissolution rate, was not yet investigated and therefore was one focus of the present study. In the present work we also question if a possible change of the polymorphic or/and pseudo polymorphic form occurs during processing (roller compaction and tablet compaction) of Theophylline anhydrate and Theophylline monohydrate. Microcrystalline cellulose (AVICEL PH101) known for its excellent compression characteristics was used as excipient in binary mixtures with Theophylline anhydrate and Theophylline monohydrate in order to study its effect on roller compaction and re-compaction behavior of the drugs in comparison to direct compaction. We hypothesize that the different amounts of MCC together with various Theophylline forms will have an influence on the compressibility and compactibility properties of the powder mixtures and granules and therefore on the characteristics of the final tablets. Heckel and modified Heckel analyses are applied to study the effect of applied pressure on the relative density of compacts and characterize the various powder materials including the active drugs. Finally the most compressible mixtures according to the two equations will be identified and suggested as immediate release dosage forms for Theophylline including the process.

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 Theophylline anhydrate powder, Theophylline anhydrate fine powder and Theophylline monohydrate 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

In order to study the influence of roller compaction on tablet properties, tablets were prepared from the same materials and under the same conditions by both roller compaction/re-compaction and direct compaction.

For determination of disintegration time and dissolution rate, tablets (round, flat, 10 mm diameter and 350 mg weight) with a constant porosity of 12 ± 0, 5% were prepared using a compaction simulator Presster™ (Metropolitan Computing Corporation). The Korsch 329 rotating press with 29 press stations was simulated. The gap, thereby compression force, was adjusted in order to get tablet thickness suitable for porosity of 12%. Tabletting speed was kept constant at 5 rpm. The process was controlled using Presster® software version 3.8.4. (MCC, New Jersey, USA).

Tablets (round, flat, 11 mm diameter, 400 mg weight), for the determination of compressibility (applying Heckel and modified Heckel equations), were prepared from the original and granulated materials as well as from the mixtures using Zwick® material tester 1478 (Zwick® GmbH, Ulm, Germany) by filling manually preweighed material into the die. For each powder system three tablets were compressed at different pressure levels in the pressure range 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).

The porosity of tablets prepared from the single component ε (%) was calculated from the tablet weight m (g), volume of tablets V_t (cm^3) and the true density ρ_t (g/cm^3) of the used material (Eq. (1)):

$$\varepsilon = \left(1 - \frac{m}{V_t \cdot \rho_t}\right) \times 100 \quad (1)$$

The porosity of the tablets prepared from the binary mixtures of the materials was calculated according to Eq. (2):

$$\varepsilon = \frac{v_t - (v_a + v_b)}{v_t} \times 100 \quad (2)$$

where ε is tablet porosity (%), v_t is tablet volume (cm^3), v_a is volume of fraction a of the binary mixture (cm^3) and v_b is volume of fraction b of the binary mixture (cm^3).

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

2.5. Characterization of powders, granules and tablets

2.5.1. Scanning electron microscopy and particle size analysis

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

Particle size and particle size distribution in volume for all samples were measured by laser diffraction (Malvern Mastersizer 2000, Scirocco 2000). For all samples dry measurement method was employed. An adequate amount of each powder was introduced with a dispersion by air pressure. 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.

The size distribution of the granules was evaluated by sieve analysis. The analysis was performed using 50 g granules, sieved on a sieve shaker (Sieve analyzer – Schieritz and Hauenstein AG, Retsch) for 10 min at level 45, using 90, 125, 180, 250, 355, 500, 710 and 1000 μm sieves. The results were expressed as median particle size.

2.5.2. Density of powders

True density of the powders was measured in triplicate with AccuPyc 1330 V2.02 (Micromeritics Instrument Corporation, Norcross, USA). A known weight of the samples was placed into the sample cell. Helium was used as a measuring gas and values were expressed as the mean of five parallel measurements.

2.5.3. Specific surface area

Specific surface area was determined by multipoint (5 point) BET method using surface area and pore analyzer (Quantachrome NOVA 2000 E, Florida, USA). Accurately weighed samples were degassed under vacuum at room temperature for 24 h, and measurements were made using nitrogen as adsorbate and helium as a carrier gas.

2.5.4. X-ray diffractometry

The samples of powders and granules were exposed to Cu-Kα radiation (45 kV × 40 mA) in a wide angle X-ray diffractometer (Model D 5005, Siemens). The instrument was operated in a step scan mode and in increment of 0.01° 2θ. The angular range was 5–40° 2θ and counts were accumulated for 10 s at each step.

2.5.5. Disintegration time

The average disintegration time of 6 tablets prepared by direct compaction and roller compaction was determined in 900 ml water at 37 °C (Sotax DT2 Automated Detection, Sotax, Switzerland).

2.5.6. Dissolution rate

Measurement of dissolution rate was performed in the USP paddle type II apparatus (Sotax AT 7, Sotax, Switzerland) at 37 °C and 50 rpm. The dissolution studies were carried out for 240 min in 900 ml of distilled water, as dissolution medium. First half an hour aliquots of 5 ml were removed every 5 min, for the rest of the dissolution time, every 10 min. All samples were replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution drug content was determined by UV spectrophotometry at 272 nm.

2.5.7. Compressibility and compactibility of the materials

The compressional behavior of the unprocessed and roller compacted and milled materials were evaluated using Heckel equation (Eq. (3)) and modified Heckel equation (Eq. (4)):

$$\ln\left(\frac{1}{1-\rho}\right) = K \times P + A \tag{3}$$

where ρ is the relative density of the powder compact at pressure P, constant K is the slope and constant A is the intercept of the linear part from the Heckel plot. The reciprocal value of K is a material dependent constant Py, known as yield pressure, which is inversely connected to the ability of the material to deform plastically under pressure (Zhang et al., 2003; Odeku, 2007). The analysis was performed with "out of die" data, 48 h after tablet production. Due to the fact that Heckel equation shows linearity only in a region of high pressures, Leuenberger developed a modified Heckel equation (Kuentz and Leuenberger, 1999) suitable for the low pressure range. This equation takes into consideration the relation between pressure susceptibility and relative density of the material.

$$P = \frac{1}{C}\left[\rho_c - \rho - (1-\rho_c)\,\ln\left(\frac{1-\rho}{1-\rho_c}\right)\right] \tag{4}$$

where P is compression pressure (MPa), ρ is relative density, ρ_c is critical relative density and C is a constant which corresponds to the constant K in the Heckel equation. The critical relative density is a point where powder beds for the first time show mechanical rigidity.

2.5.8. 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 discussion

3.1. Scanning electron microscopy and particle size distribution

The shape of Theophylline particles was generally elongated, with differences in particle size distribution (see Fig. 1). The particle size distributions of drugs and excipients have a direct effect on the mixing process and on the possible segregation during the mixing process, on the flowability of the materials, tablet formation and finally on the bioavailability of the active drug.

THAP showed the biggest particles (90% < 386.06 μm), followed by MCC (90% < 135.92 μm), THMO (90% < 107.94 μm) and THAFP (90% < 38.08 μm), consecutively (see Table 1). In Fig. 1 it can be seen that particles of THAFP formed agglomerates which can have impact on the powder behavior during tabletting and finally on the tablet characteristics. Even after sieving it was impossible to separate THAFP particles.

Sieve analysis showed that median particle size of the granules produced from the pure materials by roller compaction increased with decreasing particle size of the starting materials (see Table 2). This fact is related to a larger specific surface area available for bonding during the process. Adding MCC (30%) in combination with Theophylline, particle size of granules obtained by roller compaction of the mixture was smaller than particle size of granules obtained from pure Theophylline. We assume that this was caused by different type of binding during compaction between MCC and Theophylline particles than type of binding which occurs between particles of only one material in this case Theophylline. Further decreasing of amount of Theophylline in the binary mixtures led to an increase in particle size of the obtained granules. The increase of compaction force during the roller compaction of THAP from 20 to 30 bar showed that median particle size of the granules was increased. Herting and Kleinebudde (2008) showed that MCC compacted with different compaction forces had higher median particle size with the increase of compaction force. This is explained by the fact that ribbons with lower porosity gave a higher particle size distribution after milling. With decreasing amounts of Theophylline in the binary mixtures an increase in particle size of the granules (see Table 2) was observed, what is in agreement with the research of Herting and Kleinebudde (2007).

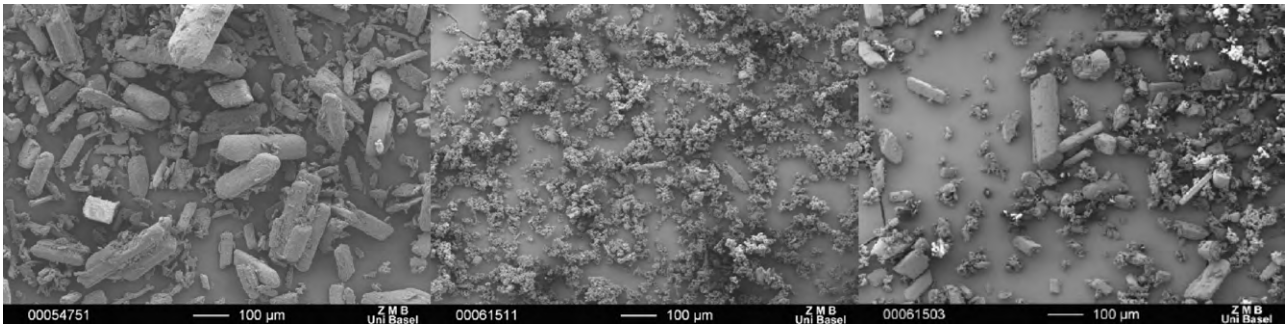

Fig. 1. SEM images of THAP, THAFP, THMO (magnification 100×).

Table 1
Powder characterization: particle size distribution, true density and specific surface area.

Material	Particle size distribution $n = 3$, ±S.D. (μm)	True density $n = 3$, ±S.D. (g/cm^3)	Specific surface area $n = 3$, ±S.D. (m^2/g)
THAP	$d(0.1) < 40.97$ $d(0.5) < 144.73$ $d(0.9) < 386.06$	1.466 ± 0.00	0.781 ± 0.04
THAFP	$d(0.1) < 2.65$ $d(0.5) < 7.71$ $d(0.9) < 38.08$	1.470 ± 0.00	1.426 ± 0.03
THMO	$d(0.1) < 5.85$ $d(0.5) < 27.73$ $d(0.9) < 107.74$	1.475 ± 0.00	1.444 ± 0.03
MCC	$d(0.1) < 20.03$ $d(0.5) < 58.81$ $d(0.9) < 135.92$	1.589 ± 0.00	1.285 ± 0.05

3.2. Density of the powders

The true density results of THAP, THAFP and THMO are presented in Table 1. True density can be used for characterization of the materials regarding polymorphic forms (Suihko et al., 2001). The values for the true density of THAP and THAFP comply with the true density of Theophylline anhydrate polymorphic form II (stable at room temperature) and those of THMO with the true density of Theophylline monohydrate according to literature data (Suihko et al., 2001; Suzuki et al., 1989).

3.3. Specific surface area

As the specific surface area corresponds with particle size, THAFP, having the smallest particle size, should exhibit the highest value for the specific surface area. However due to its very small size (see Table 1) the particles agglomerated during the sample preparation for the measurement of specific surface area and this led to incorrect values. This is illustrated in Table 1, where it can be seen that THAFP and THMO exhibited similar specific surface areas despite the difference in particle size distribution. The lowest value was obtained for THAP, 0.781 m^2/g, which is in agreement with literature according to greater particle size distribution.

3.4. X-ray diffractometry

X-ray diffraction patterns of powders and granules were significantly different for monohydrate and anhydrous form and in agreement with those presented in the literature (Airaksinen et al., 2004). The pure powder and granules of THAP and THAFP, produced by roller compaction at 20 and 30 bar, showed characteristic peaks for Theophylline anhydrate form II which is stable at room temperature.

The patterns of THAP (unprocessed powder, granules obtained at 20 bar and granules obtained at 30 bar) shown in Fig. 2 were in agreement with the results presented in the literature (Airaksinen et al., 2004). Characteristic peaks corresponded to peaks of stable anhydrous Theophylline form II at 7.2°, 12.6° and 14.5° 2θ. Phadnis and Suryanarayanan (1997) described anhydrous metastable form of Theophylline with different X-ray diffraction patterns, with characteristics peaks at 9.4°, 11.3°, 12.4°, 13.5° and 15.4° 2θ.

In Fig. 2 it can be observed that the diffraction patterns of THAP granules (obtained at 20 and 30 bar) were not changed in comparison to THAP powder meaning that roller compaction did not have any influence on the polymorphic form. Therefore THAP was considered to be stable during processing.

THAFP exhibits stable anhydrous form II as well, which was confirmed by its diffraction pattern presented in Fig. 3. It showed the same characteristic peaks like THAP at 7.2°, 12.6° and 14.5° 2θ.

Table 2
Median particle size distribution of granules: binary mixture of THAP, THAFP, THMO and MCC.

Theoph. % (w/w)	THAP 20 bar (μm)	THAP 30 bar (μm)	THAFP 20 bar (μm)	THMO 20 bar (μm)
0	512.23	660.33	512.23	512.23
10	488.17	608.82	591.45	556.02
30	445.15	626.23	571.86	539.65
50	411.44	530.73	543.42	510.12
70	385.62	506.32	500.06	457.69
100	450.90	470.72	557.69	555.56

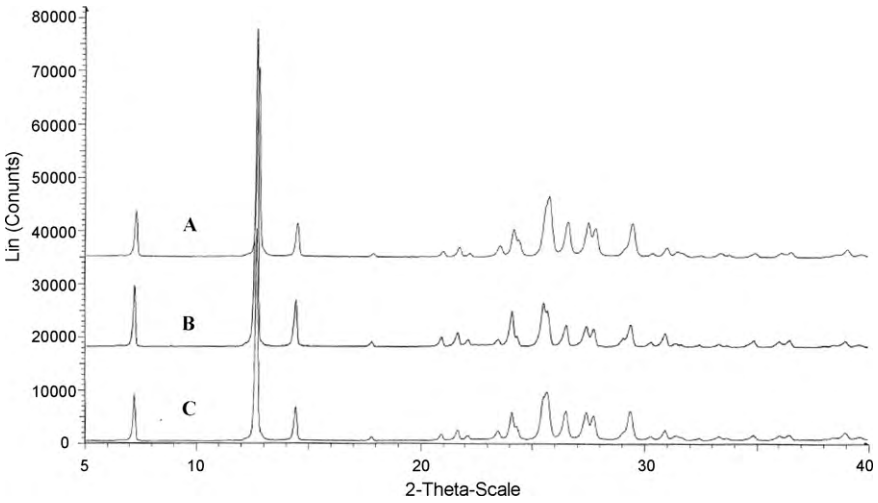

Fig. 2. X-ray diffraction patterns of THAP (upper), granules produced at pressure of 20 bar (middle) and granules produced at 30 bar (lower).

After roller compaction diffraction pattern was unchanged indicating that roller compaction had no influence on the polymorphic form of THAFP.

The X-ray diffraction pattern of THMO was in agreement with results previous presented in the literature for the monohydrate form of Theophylline (Airaksinen et al., 2004) with peaks at 8.8, 11.5, 13.3 and 14.7 2θ (see Fig. 4). Phadnis and Suryanarayanan (1997) show that X-ray powder pattern in a function of temperature leads to dehydration of monohydrate and formation of metastable and stable form of anhydrate, respectively. Since roller compaction is a process where, due to friction of the material and the roll surface, temperature increase can occur, this phenomenon may be present during processing resulting in formation of regions containing the metastable form. However, as confirmed in Fig. 4 roller compaction and milling did not affect the monohydrate quality.

3.5. Disintegration time

Disintegration of pharmaceutical tablets is still an important issue for fast release of the active drug from a solid dosage formulation. In many cases fast disintegration time is the first step of reaching high bioavailability of drugs and therefore disintegration time of tablets are commonly improved by addition of disintegrants (Leuenberger, 1982). Disintegration time of THAP, THAFP and THMO tablets produced by direct compaction or roller compaction at pressures of 20 and 30 bar was very slow in all cases because Theophylline has poor disintegration properties. Due to the good disintegration properties of MCC, adding certain amount of MCC improved the disintegration time of Theophylline tablets. The lower disintegration times can be found in the range between 20% (w/w) and 70% (w/w) of MCC in tablets. These findings can be related to percolation theory (Leuenberger, 1999), i.e. to the fact, that within this range both the active substance and MCC are percolating the tablet system. It is important to realize, that MCC lost the functionality as a disintegrant at higher concentrations (e.g. $\geq$70%, w/w), i.e. above the second percolation threshold, which has to be expected around this value. For such high concentrations MCC dominated completely the system by isolating the active ingredient. Table 3 shows that the critical amount of MCC needed to improve disintegration time significantly, was determined to be 20% (w/w) independent of the method of preparation (i.e. whether direct compaction or roller compaction was used). In a previous work of our research group (Krausbauer et al., 2008) geometrical description of heterogeneous ensembles like pharmaceutical formulations for solid dosage forms were taken into account in order to calculate the percolation thresholds of such disordered particulate systems. Geometrical phase transitions are independent of chemical properties of the components and percolation theory is

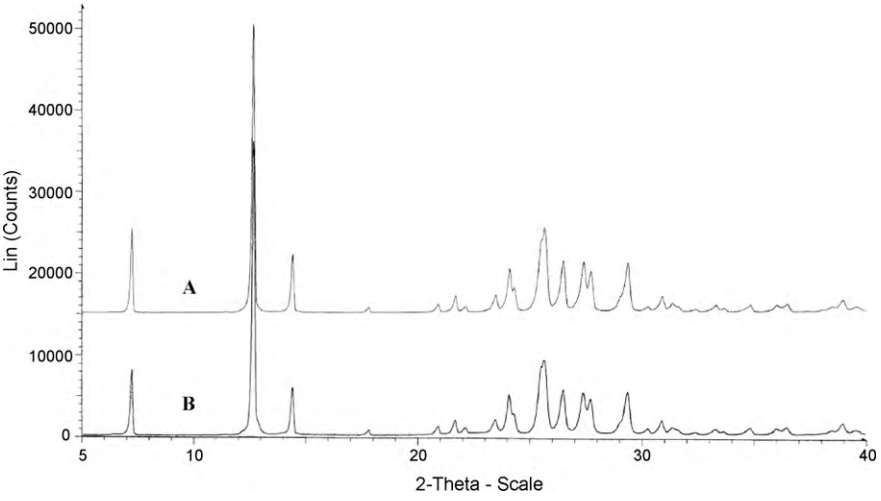

Fig. 3. X-ray diffraction patterns of THAFP (upper), granules produced at pressure of 20 bar (lower).

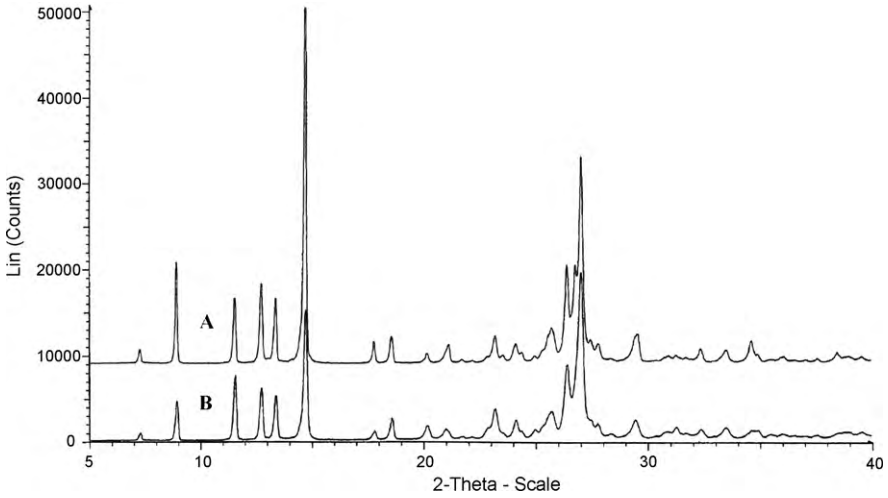

Fig. 4. X-ray diffraction patterns of THMO (upper), granules produced at pressure of 20 bar (lower).

Table 3
Experimentally determined values of disintegration time of binary mixtures of THAP/MCC, THAFP/MCC and THMO/MCC for tablets produced by direct compaction and roller compaction.

Theoph. % (w/w)	THAP direct comp (min)	THAP 20 bar (min)	THAP 30 bar (min)	THAFP direct comp (min)	THAFP 20 bar (min)	THMO direct comp (min)	THMO 20 bar (min)
0	11.64 ± 0.57	1.42 ± 0.09	0.32 ± 0.03	11.64 ± 0.57	1.42 ± 0.09	11.64 ± 0.57	1.42 ± 0.09
10	11.07 ± 4.34	0.58 ± 0.31	0.23 ± 0.02	4.96 ± 0.50	0.37 ± 0.09	5.43 ± 0.34	1.05 ± 0.25
30	5.41 ± 3.45	0.39 ± 0.06	0.20 ± 0.01	2.01 ± 0.30	0.25 ± 0.03	3.29 ± 0.59	0.62 ± 0.07
50	0.49 ± 0.29	0.26 ± 0.03	0.18 ± 0.01	1.12 ± 0.56	0.22 ± 0.03	3.09 ± 1.30	0.59 ± 0.10
70	0.30 ± 0.06	0.22 ± 0.08	0.13 ± 0.01	1.14 ± 0.03	0.18 ± 0.03	2.88 ± 2.29	0.34 ± 0.77
80	0.19 ± 0.01	0.14 ± 0.06	0.11 ± 0.02	0.97 ± 0.73	0.16 ± 0.13	1.34 ± 0.87	0.20 ± 0.02
90	48.98 ± 4.26	42.78 ± 3.74	35.25 ± 5.62	57.25 ± 9.05	41.31 ± 2.31	48.22 ± 6.13	47.00 ± 11.3
100	89.47 ± 16.4	71.47 ± 3.25	58.70 ± 15.6	95.56 ± 5.24	87.04 ± 5.57	87.63 ± 6.37	75.52 ± 6.37

the most suitable tool to predict and simulate these transitions. Thus, the important points are to know which binary mixtures (formulations) show the minimum of the disintegration time meaning to determine the percolation threshold and further to know the behavior of the system in the vicinity of the threshold.

Mixtures of different ratios of MCC and Theophylline (THAP, THAFP and THMO) exhibited reduced disintegration times, but the differences which were obtained by increasing the amount of MCC from 20 to 70% were not significant. If disintegration time of tablets produced by direct compaction and roller compaction are compared it was obvious that in the case of roller compaction disintegration time was faster (Table 3). Tablets produced by roller compaction had granulation as an intermediate step, which means that tablets were made from granules and subsequently led to a faster disintegration into granules and/or other subunits. In parallel, tablets were produced by direct compaction form the starting powders and these tablets did not disintegrate at all. They were dissolving gradually, what was significantly slower than in the case of the tablets produced by roller compaction.

Increasing the content of Theophylline in the binary mixtures with MCC decreased the differences in disintegration time of tablets prepared by direct compaction and roller compaction. In the case of THAP, increasing the compaction pressure during roller compaction from 20 to 30 bar slightly improved disintegration, but this was not significant as it was in the case of direct compaction.

3.6. Dissolution rate

Dissolution rate is influenced by particle size due to the fact that small particles have high surface area exposed to the solvent, allowing a greater number of particles to dissolve more rapidly (Bisrat and Nyström, 1988; Lauwo, 1985). According to this phenomenon the dissolution rate of THAFP tablets produced by direct compaction was higher than the dissolution rate of THAP. However taking into account the very fine particle size of THAFP, the dissolution rate was not influenced proportionally by particle size (see Fig. 5). Montel et al. (1983) reported that Theophylline with very small particle size had lower dissolution rate than the one with larger particle size. This was proven with microscopy studies which showed the presence of agglomerates in the tablet when using smallest particle size of Theophylline. In general, agglomerated particles are undesirable because they reduce the surface area leading to slower dissolution rate (Randall, 1995). SEM images (Fig. 1) showed that particles of THAFP were agglomerated and this phenomenon had influenced the dissolution rate of THAFP. During dissolution process Theophylline anhydrate undergoes transformation to monohydrate almost immediately after the tablets are

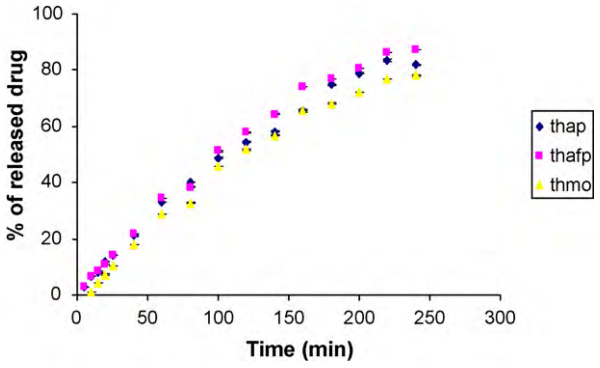

Fig. 5. Dissolution rate of THAP, THAFP and THMO.

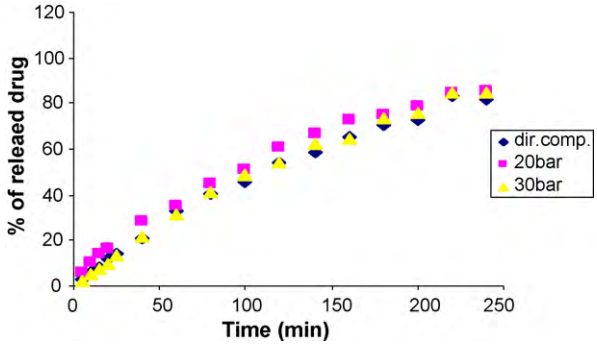

Fig. 6. Dissolution rate – THAP 100%.

exposed to water (Aaltonen, 2007; Shesky et al., 2000). In Fig. 5 it can be noticed that dissolution rate of THMO tablets was slightly lower than dissolution rate of THAP and THAFP, even according to Aaltonen (2007), anhydrate was transformed to monohydrate during the whole dissolution process. These differences could be explained by variations in particle shape and specific surface area of THMO and monohydrate which was obtained by monohydrate crystal growth on the initially anhydrous surface–needle like surface (Aaltonen, 2007; Shesky et al., 2000). Dissolution rates 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 were determined but as illustration only the results obtained for tablets produced from 100% of Theophylline and binary mixture of 50% Theophylline and 50% of MCC are presented here. The remaining mixtures exhibited analogous behavior (Hadzovic, 2008). Roller compaction improved significantly the dissolution rate of tablets, exception were tablets prepared from 100% Theophylline (see Figs. 6, 8 and 10). Theophylline tablets had very slow disintegration time and analogous to that dissolution rate was very slow. Tablets containing MCC disintegrated very fast (see Table 3) allowing fast release of Theophylline from the tablets. Increasing content of MCC in the binary mixtures increased the dissolution rate of Theophylline. This phenomenon can be explained by disintegration property of MCC. In the case of tablets made from the pure Theophylline there was no disintegration observed, they were gradually dissolving and it took some time for the drug to be released from the tablets. Although, MCC improved dissolution rate of tablets in general, this was more significant in the case of tablets produced by roller compaction (see Figs. 7, 9 and 11) since they were disintegrating very fast into granules and/or other subunits allowing fast release of the drug. Increasing the compaction pressure from 20 to 30 bar improved the dissolution rate but these differences were not significant (see Fig. 7).

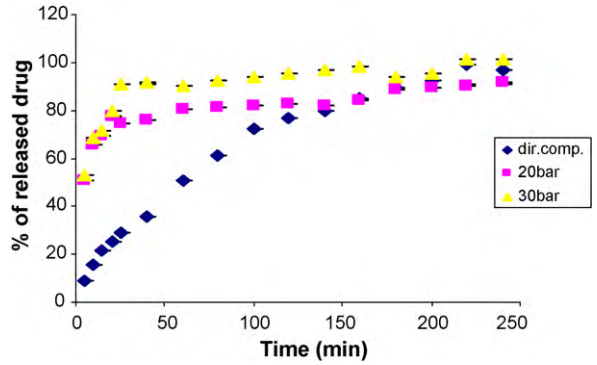

Fig. 7. Dissolution rate – THAP 50% + MCC 50%.

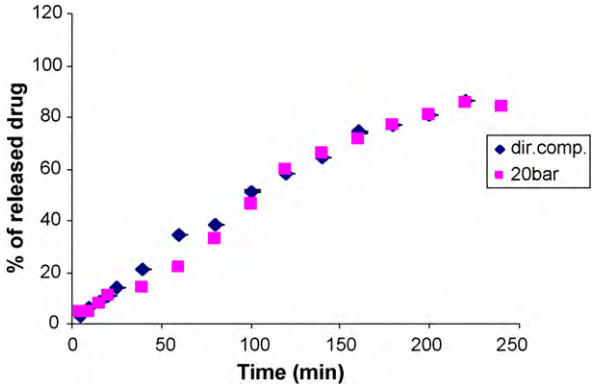

Fig. 8. Dissolution rate – THAFP 100%.

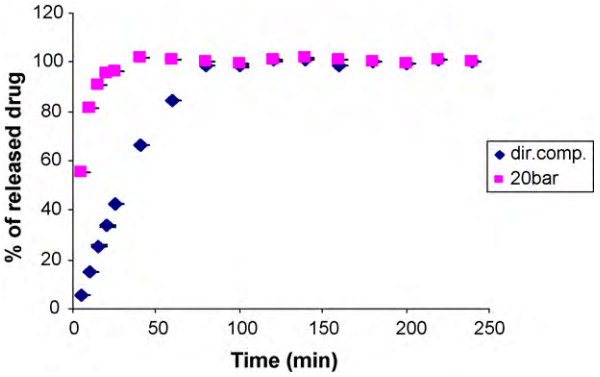

Fig. 9. Dissolution rate – THAFP 50% + MCC 50%.

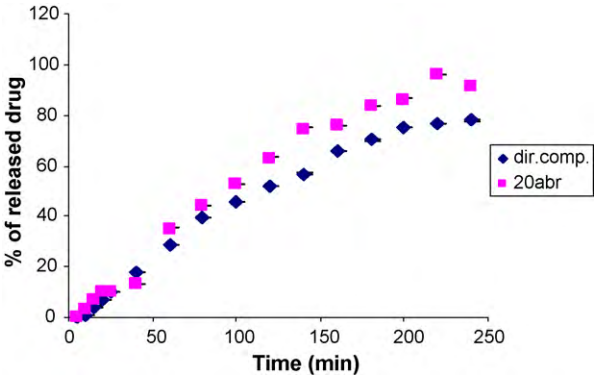

Fig. 10. Dissolution rate – THMO 100%.

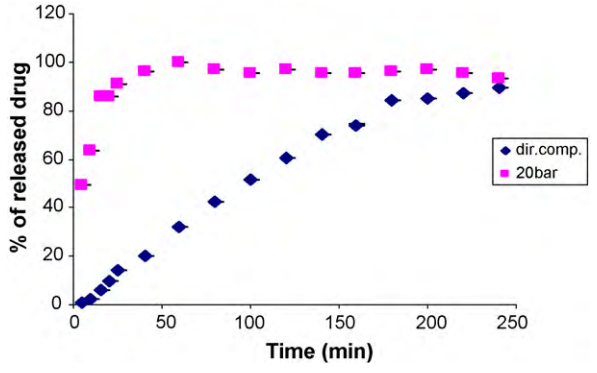

Fig. 11. Dissolution rate – THMO 50% + MCC 50%.

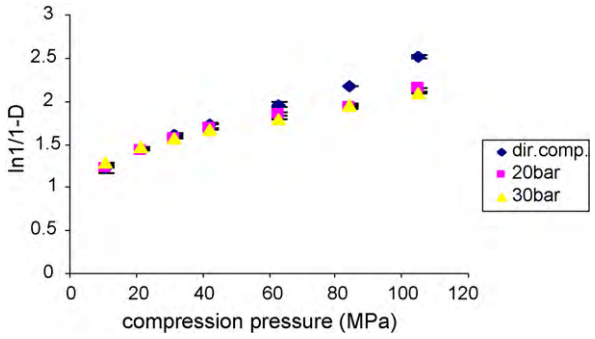

Fig. 12. Heckel plot – THAP 100%.

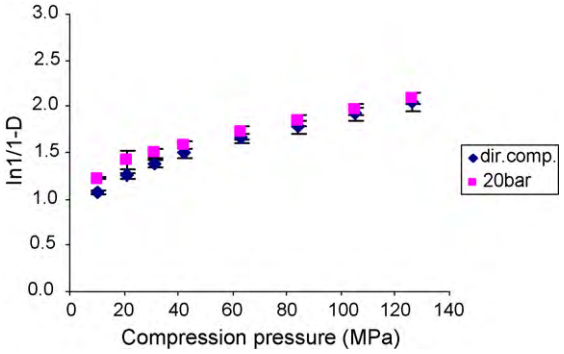

Fig. 14. Heckel plot – THAFP 100%.

3.7. Heckel and modified Heckel equation

During tabletting, the bed density or porosity of powder changes as a function of applied compaction force (Jain, 1999). Heckel and modified Heckel analyses were performed to study the effect of applied pressure on the relative density of compacts of powders and granules during compaction. This was done in order to study the influence of roller compaction and tabletting (double compaction) on densification and deformation properties of THAP, THAFP, THMO and their binary mixtures with MCC. Figs. 12, 14 and 16 show that all plots have a curvature in the region of low pressures, 10.5–31.5 MPa, which is caused by the fragmentation and rearrangement of the agglomerates. The curve was followed by a linear portion at pressures higher than 42.1 MPa. This was even more pronounced if lower compression forces and more points in this region were used. Suihko et al. (2001) studied properties of the tablets produced from different Theophylline forms. Stable and metastable form of Theophylline anhydrate and Theophylline monohydrate is studied and the research concluded that under compression all modifications of Theophylline deform primarily by plastic flow. The results from the present study showed that Theophylline at low compaction range underwent fragmentation, followed by plastic flow, which occurred at higher compaction pressures (Figs. 13, 15 and 17).

As mentioned earlier, the parameters K and Py calculated from the Heckel equation (see Eq. (3)) are measures of the materials' ability to deform plastically. THAP and THAFP showed that after roller compaction compressibility and at the same time plasticity of the materials were decreased. This could be noticed from the parameters obtained by Heckel and modified Heckel equations (see Table 4). A decrease in the constants K and C and at the same time increase in Py and ρ_{rc} led to this conclusion. Herting and Kleinebudde (2008) investigated the effect of roller compaction on different types of MCC and observed that after mechanical pretreat-

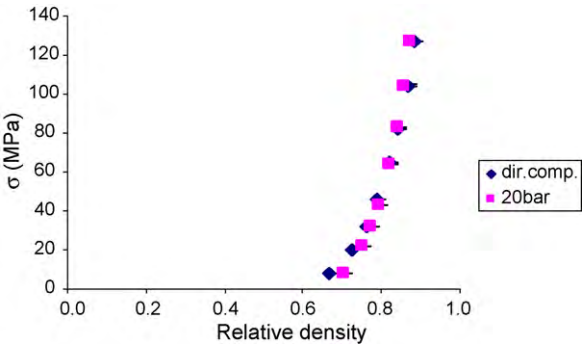

Fig. 15. . Modified Heckel plot – THAFP 100%.

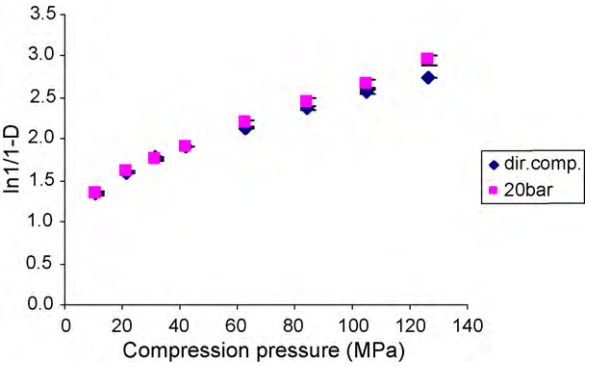

Fig. 16. Heckel plot – THMO 100%.

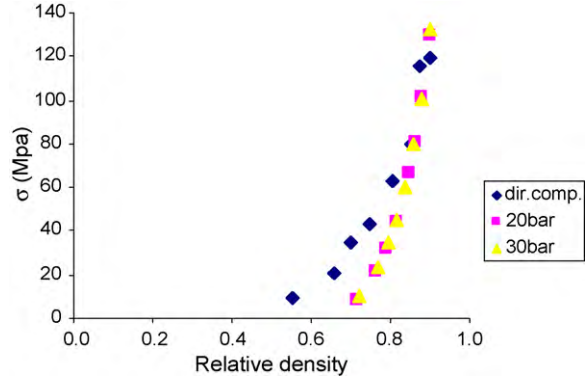

Fig. 13. Modified Heckel plot – THAP 100%.

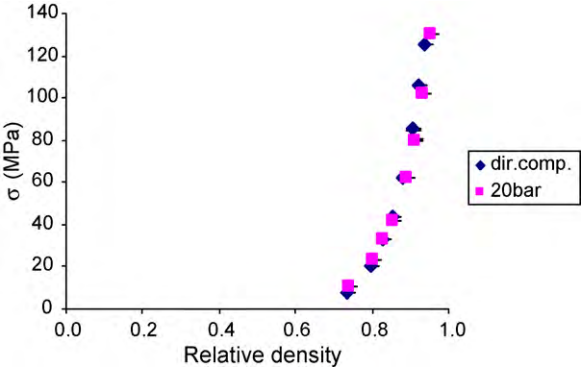

Fig. 17. Modified Heckel plot – THMO 100%.

Table 4
Heckel and modified Heckel parameters for characterization of the compression behavior of THAP, THAFP and THMO.

	K, $n = 3$, ±S.D. (10^{-3} MPa)	Py, $n = 3$, ±S.D. (MPa)	R^2	C, $n = 3$, ±S.D. (10^{-3} MPa)	ρ_{rc}, $n = 3$, ±S.D.	R^2
THAP dir. comp	10.66 ± 0.12	94.05 ± 1.35	0.967	3.64 ± 0.01	0.54 ± 0.00	0.995
THAP 20 bar	7.33 ± 0.15	136.39 ± 2.82	0.998	1.88 ± 0.05	0.61 ± 0.01	0.998
THAP 30 bar	6.96 ± 0.28	143.70 ± 5.81	0.996	1.74 ± 0.20	0.61 ± 0.00	0.997
THAFP dir. comp	6.16 ± 0.25	162.17 ± 1.52	0.996	2.10 ± 0.01	0.55 ± 0.00	0.999
THAFP 20 bar	5.69 ± 0.30	167.88 ± 8.46	0.998	1.27 ± 0.03	0.62 ± 0.00	0.998
THMO dir. comp	10.76 ± 0.20	92.89 ± 1.78	0.996	2.80 ± 0.07	0.64 ± 0.00	0.999
THMO 20 bar	12.20 ± 0.88	82.26 ± 6.20	0.992	3.94 ± 0.45	0.57 ± 0.02	0.998

ment the resistance of the material toward plastic deformation is increased. In contrast to the two previous mentioned materials and results obtained in the research of Herting and Kleinebudde (2008), THMO showed in the present work more plastic behavior under pressure after roller compaction calculated by Heckel and modified Heckel equation (see Table 4). The binary mixtures of Theophylline (THAP, THAFP and THMO) and MCC behaved in the same way as the pure materials, this means at low pressure range there was no linearity because of fragmentation and rearrangement of the particles followed by the linear part of the plot at high pressure range. According to the Heckel equation the most compressible mixture was the binary mixture of THAP 30% + MCC 70%, followed by the mixtures of THAP 10% + MCC 90%, THAP 50% + MCC 50% and THAP 70% + MCC 30%. In addition to the Heckel equation, which observes only the linear part of the plot, the modified Heckel equation, which takes the entire pressure range into account, highest compressibility parameter C and lowest value for the critical relative density ρ_{rc} was seen in the binary mixture of THAP 10% + MCC 90%, followed by mixtures of THAP 30% + MCC 70%, THAP 50% + MCC 50% and THAP 70% + MCC 30%. The same results were obtained with tablets made from granules produced by roller compaction at compaction pressure of 20 and 30 bar. Analogous to THAP, the binary mixtures of THAFP and THMO with MCC showed the same results. Even though THMO was more compressible and more plastic after roller compaction, the binary mixtures of this material with MCC showed the reversed behavior. From these results it can be observed that properties of tablets compressed from binary mixtures can often not be predicted from the compaction properties of the individual starting materials. Reasons for this phenomenon can be found in interactions between materials which may occur during the compaction process (van Veen et al., 2000).

All results showed that goodness of fit was always better for modified Heckel equation independent of whether powder or granules were analyzed. According to these results it appears that the Heckel equation has limitations to characterize powder materials. Due to the powder behavior to undergo compression by fragmentation first which is followed by plastic deformation, and the fact that Heckel equation considers only the linear part of the plot, it can be concluded that the material can be better characterized using the modified Heckel equation (Hadzovic, 2008). The weakness of the Heckel plots is among other things related to the fact, that only the linear part of the plot is evaluated. In this context it is important to realize, that it is often difficult to identify clearly the range of linearity.

4. Conclusions

THAP, THAFP and THMO used in this study were present in stable polymorphic forms during all processing steps. X-ray measurements of powders and granules, obtained by roller compaction, showed that after processing of the materials polymorphic forms were not changed. Regardless of the production method (direct compaction or roller compaction), tablets of pure THAP, THAFP and THMO had a very slow disintegration time. Adding MCC to the pharmaceutical tablet formulation decreased the disintegration time and could be further improved by including the step of roller compaction. As it was previously mentioned, MCC improved disintegration of tablets and in the same time faster release of the drug was achieved. Tablets produced by roller compaction had extremely higher dissolution rate than tablets produced under the same conditions by direct compaction. Measurement of disintegration time and dissolution rate of tablets with constant porosity, prepared by direct compaction and roller compaction, showed that roller compaction is a method of choice for immediate release dosage forms containing Theophylline.

Compressibility of THAP and THAFP was decreased after roller compaction and with further increasing of compaction pressure (from 20 to 30 bar) compressibility of only THAP was further decreased. In contrast to these two materials THMO granules produced by roller compaction showed higher compressibility than THMO powder. MCC, known as very compressible material combined with THAP, THAFP and THMO significantly affected the properties of the used active materials. The whole range of the binary mixtures showed more plastic behavior under pressure than both individual materials (either powder or granules). Observing the properties of tablets produced from THAP, THAFP and THMO, it can be concluded that they can be considered as materials undergoing partial fragmentation during compaction at low pressures and then it is followed by plastic deformation at higher compaction pressures.

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