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Comparison of Compression and Material Properties of Differently Shaped and Sized Paracetamols †

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Abstract

Paracetamol is well-known API (active pharmaceutical ingredient) for its bad flow and compression abilities. To improve the compressibility, a high amount of excipient is commonly mixed with paracetamol to create better compressible material. Conversely, we used modified crystallization procedures to prepare plate, irregular and spherical particles from original raw paracetamol to prepare directly compressible API. To expand our screening, several sizes of each shape were prepared and material properties analyzed, mainly the flow and compression abilities, and significant variation of the properties presented; from very poor properties of raw paracetamol to excellent properties of spherical crystals which exhibited ability to be directly compressed without excipient. The analysis also showed very small effect of the size modification on tablet compression and material behavior as the main contribution had the shape alteration and compression force.

Keywords: API, shape modification, particle, properties, compression

1. Introduction

Crystal habit, polymorphism, size and other properties can be modified by the variation of crystallization conditions such as the presence of impurities, ultrasonic frequency, type of solvent and cooling rate (Jordens et al., 2014; Lacmann, 1998). Different crystal habit of a particular drug possesses different in the specific surface and free surface energy. Therefore, they may exhibit different physico-mechanical properties, powder flow and compressibility, which are of pharmaceutical interest (El-Zhry El-Yafi and El-Zein, 2015; Huettenrauch and Moeller, 1983; Marshall and York, 1991; York, 1983).

Attempts to change the crystal habit and the workability of drugs using alternative crystallization procedures of drugs has been published; for example ibuprofen (Gordon and Amin, 1984), hexamethylmelamine (Gonda, 1985), nitrofurantoin (Marshall and York, 1989) and paracetamol (Ó'Ciardhá et al., 2011). Although, more general influence of several different shapes and sizes of a single API on flowability and compressibility has not yet been presented.

Several shapes and sizes of paracetamol crystals (Form I) were prepared; and their material properties and compressibility compared. We varied the already published different methods of paracetamol crystallization to prepare plates (Garekani et al., 1999), irregular (Kaialy et al., 2014) and spherical (Garekani et al., 2000) paracetamol. Some particle sizes of the described procedures could not have been reproduced; thus, some of the methods were redesigned as described.

2. Materials and methods

Different shapes were prepared from raw paracetamol (Anqiu Lu'an Pharmaceutical Co. Ltd, Anqui, Shandong province, China), which was consisted of very small needle-shaped and mainly of irregular particles (**Fig. 3**). This active pharmaceutical ingredient (API) is a widely used over-the-counter analgesic and antipyretic (Aghababian, 2010; Ahmad, 2010). Other used solutions and solids of this work were obtained from Sigma-Aldrich (Sigma-Aldrich Co., Prague, Czech Republic).

2.1 Crystallization procedures

The addition of a second substance, usually a liquid diluent, which reduces the solubility of the solute in the solvent, is one of the common methods of crystallization and it is known as salting-out. The diluent must be misci-

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be with the crystallization solvent and the solute should be relatively insoluble in it. The preparation of different shapes of paracetamol was driven by the change of the solvent, temperature or usage of additives. The additive inhibited the crystal growth in some directions and produced unusual shapes of the crystal habit. The change of the stirring speed provided different particle size distribution of prepared paracetamols. In every case, the precipitated crystals were collected by filtration using a Büchner funnel under vacuum with no agitation. They were dried for 24 h and stored in tightly closed jars. One size of the original supplied raw paracetamol, two sizes of spheres, three sizes of plates and three sizes of irregulars were prepared (in amount of 30 g) and used for next experiments. Polymorphic purity of prepared samples was tested.

2.1.1 Plates

Paracetamol (50 g) was dissolved in ethanol p.a. (120 ml) at 65 °C. The solution was poured into cooled distilled water (500 ml, 3 °C) with stirring speed 100 rpm to obtain big plates, or 200 rpm to obtain medium plates of paracetamol. After the cooling of the mixture to 25 °C, products were filtered and dried in an oven (80 °C, 24 h). Higher stirring did not produce smaller plates, but irregular shaped particles. To produce smaller plates, the procedure was modified. If methanol was used as a solvent, the procedure led to small plates. Paracetamol (50 g) was dissolved in methanol p.a. (170 ml) at 40 °C. The solution was poured into cooled distilled water (500 ml, 3 °C) with stirring speed 600 rpm. The product was filtered and dried as described.

2.1.2 Irregulars

Paracetamol (50 g) was dissolved in the solution of ethanol p.a. (120 ml) and distilled water (500 ml) at 65 °C. The solution was placed into ice bath and slowly cooled to 25 °C with stirring speed 100 rpm to obtain big irregulars, or 300 rpm to obtain medium irregulars, or 1200 rpm for small irregulars of paracetamol. Products were filtered and dried in an oven (80 °C, 24 h).

2.1.3 Spheres

Paracetamol (50 g) was dissolved in ethanol p.a. (120 ml) at 65 °C. The solution was poured into cooled distilled water (500 ml, 3 °C). The water contained PVP 40000. The stirring speed was set to 200 rpm to obtain medium spheres, or 300 rpm to obtain small spheres of paracetamol. After the cooling of the mixture to 25 °C, products were filtered and dried in an oven (55 °C, 24 h). The big sized particles were not prepared. Although reduction of the stirring speed led to bigger particles, they were contaminated by different shape of particles, mainly irregular and columnar particles.

Table 1 Flow properties and angle of repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	> 66

2.1.4 Bulk volume and tapped volume of powders

Paracetamol (20 g) was placed into a measuring cylinder (250 ml) which was mounted into Sotax TD2 Tap density tester (Sotax Pharmaceutical Testing s.r.o., Prague, Czech Republic) and the apparent volume of the material noted. The machine did 1250 taps and the volume was noted again after tapping. The experiments were in the keeping with European Pharmacopoeia (European Medicines Agency, 2006a).

2.1.5 Angle of repose

Paracetamol (20 g) was placed into a funnel of Pharmatest PTG S-3XY(Pharma test AG, Hainburg, Germany) and depleted, with the secondary stirring of 20 rpm, through a release flap (15 mm) into a measurement plate and the angle of repose from the created powder cone was measured by a detector. The classification system of the powder flowability from European Pharmacopoeia is shown in **Table 1** (European Medicines Agency, 2006b).

2.2 Analysis of particle size and shape

A small amount of paracetamol was fixed on aluminum stubs using the double sided conductive adhesive carbon tapes and sputtered with platinum for 240 s (Sputter SC7640; Quorum Technologies Ltd, Ashford, United Kingdom) and observed with a scanning electron microscope Mira/Tescan LM (Tescan a.s., Brno-Kohoutovice, Czech Republic). Particle size distribution (PSD) was analyzed with image analyse software NIS Elements and *d*-values [lower decil *d*(0.1), median *d*(0.5) and upper decil *d*(0.9)] of particle size distributions were obtained (Šimek et al., 2015).

2.3 DSC analysis

All prepared products was tested of polymorphic purity of paracetamol with differential scanning calorimeter (DSC Pyris 1, Perkin Elmer, Waltham, Massachusetts, USA) was used to determine the solid-state nature of dif-

Table 2 Melting points of paracetamol forms

Form	T_m/°C
I	168,6 ± 0,2
II	156,4 ± 0,2

ferent paracetamols. An accurate weight of each paracetamol powder (4–8 mg) was placed in 40 µL aluminium DSC pan, sealed non-hermetically and heated (range 30–200 °C) at a heating ramp rate of 10 °C/min under a nitrogen gas (50 L/min). Before each measurement, the sample was allowed to equilibrate for 5 min at 30 °C. Melting points of known paracetamol forms are shown in **Table 2** (Di Martino et al., 1996).

2.4 Tablet compression

Each of prepared materials was formulated into tablets. Tablets contained only paracetamol (200 mg); no excipient was used. The die wall was cleaned with acetone and prelubricated with 4 % w/w magnesium stearate in acetone before each compression. The compression was carried out using Style one Classic compactor (Medel Pharm Beynost, France) with 7 mm flat faced punches. Ten tablets were produces at compression forces of 5, 10, 15 and 25 kN. Three speeds of compression were used: 25 percent of max speed (87.5 mm/s), 50 percent of max speed (175 mm/s) and 75 percent of max speed (262.5 mm/s). During the compression, punch separation and applied mean force were monitored with Analis software v.2 (Medel Pharm Beynost, France).

2.5 Analyses of compression data

Both force and displacement data from the upper and lower punches were collected from Analis v.2 software during a compression cycle and data were processed to the Heckel equation (Eq. (1)) (Heckel, 1961a, b).

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

A typical Heckel plot of Eq. (1) is illustrated in **Fig. 1.** Parameter D is the relative density of tablet (the ratio of tablet density to true density of powder) at applied pressure P. k is the slope of the straight line portion of the Heckel plot and the reciprocal of k is the mean yield pressure (Garekani et al., 1999). Since the tablet dimensions were measured in the die, it is referred to as apparent mean yield pressure. The total densification of the powder bed due to die filling and particle rearrangement, D_a, was obtained from the intercept of the linear portion of this plot, A, using Eq. (2).

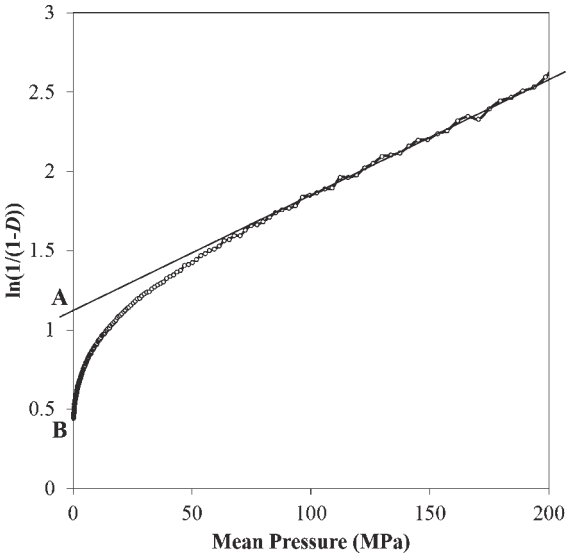

Fig. 1 Heckel plot for paracetamol (Irregular, small) obtained at a compression speed 25 percent and compression force 25 kN.

$$D_a = 1 - e^{-A} \tag{2}$$

From B, the place where the Heckel plot intercepts the ln (1/1-D) axis (**Fig. 1**), the density of powder at zero pressure, D_0, is obtained (Eq. (3)). D_0 can be defined as the densification due to die filling or to initial powder packing.

$$D_0 = 1 - e^{-B} \tag{3}$$

2.6 Measurement of elastic and plastic energy, elastic recovery

For our system in which both punches were mobile, the punch separation was plotted against the mean compression force (Garekani et al., 1999; Gibson, 2009). The area under this curve is the work done or energy. The work done of compression (plastic energy) and expansion work of compression (elastic energy) were calculated using the data collected from Analis v.2 software.

Fig. 2 illustrates a typical force-punch separation. Point A represents the minimal force and maximal punch separation at the beginning of compression. Point B represents the peak force at minimal punch separation, C shows the minimum punch separation and D represents the punch separation after decompression when the force is zero, giving the tablet thickness. The total compression energy is represented by area ABC, and the decompression energy or elastic energy is equal to area under curve CBD. The difference between area ABC and CBD determines the plastic energy (the area under curve ABD).

To calculate the elastic recovery of each tablet in the die we used Eq. (4) (Armstrong and Haines-Nutt, 1972).

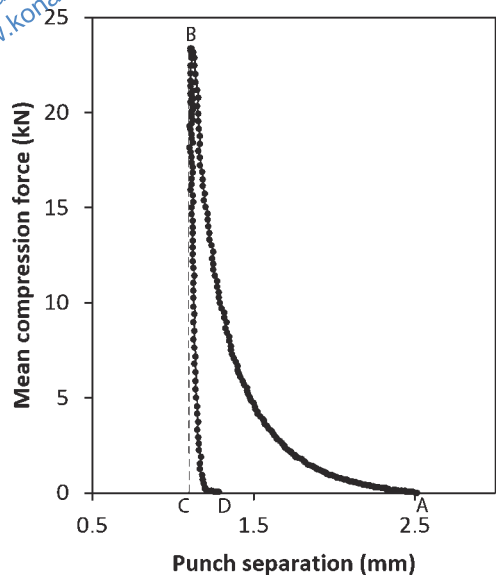

Fig. 2 Force-punch separation plot for paracetamol (Irregular, small) obtained at a compression speed 25 percent and compression force 25 kN.

$$\% \text{ Elastic recovery} = [(H - H_C) / H_C] \times 100, \quad (4)$$

where H_c and H are the thickness of tablet under maximum pressure and after the compression force was removed, respectively (Garekani et al., 1999).

3. Results and discussion

Under the conditions, described in the methodology section, we prepared several samples of paracetamol with different shape (**Fig. 3**). At the first sign, the properties of the materials were mainly relevant to the shape of the crystals and less appropriate to the crystal size.

Particles size distributions of prepared samples, described with *d*-values, are presented in **Table 3.** Samples of different sizes of each shape were labelled big, medium, or small according to the *d*-values. The particle size distribution of raw paracetamol was in good keeping with the medium class; and two prepared samples of spherical paracetamols were in keeping with medium and small class.

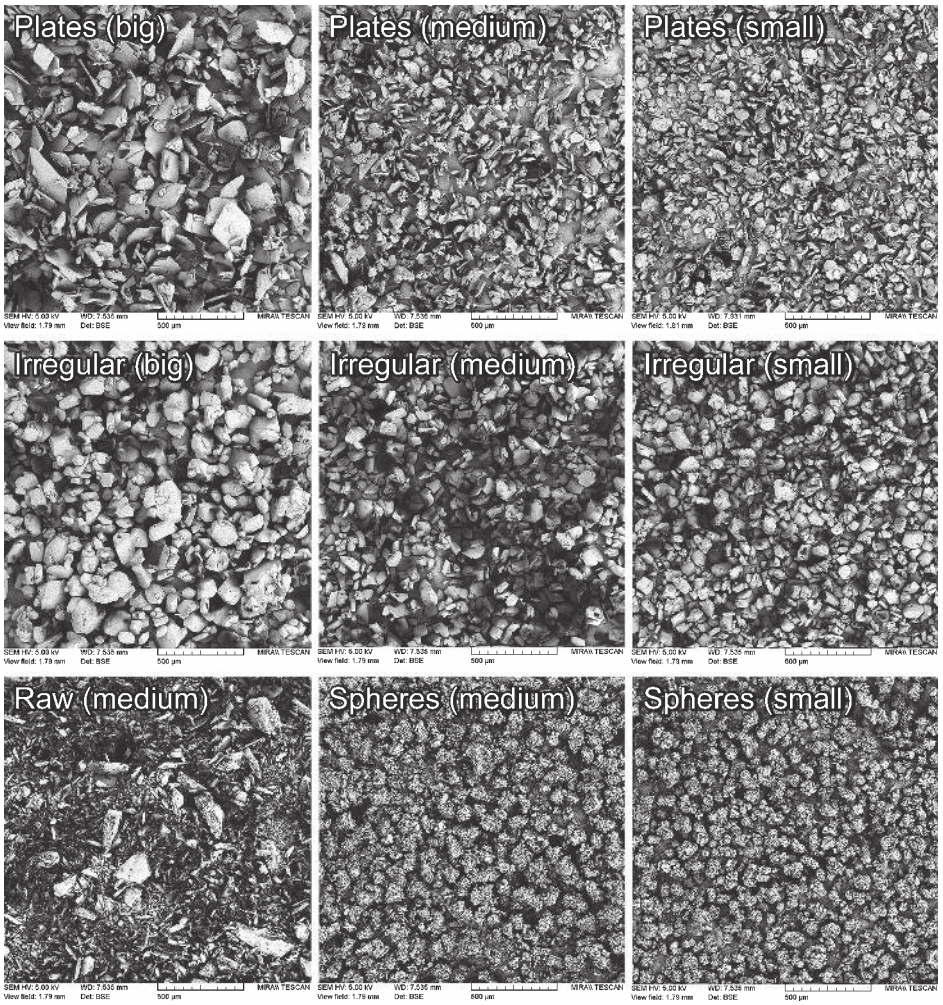

Fig. 3 SEM micrographs of prepared paracetamols and raw paracetamol.

Table 3 Overview of *d*-values of all prepared paracetamols

Shape	*d*(0.1) [μm]	*d*(0.5) [μm]	*d*(0.9) [μm]
Raw (medium)	17	40	100
Plates (big)	51	113	203
Plates (medium)	37	67	105
Plates (small)	19	40	61
Irregular (big)	51	102	222
Irregular (medium)	44	91	159
Irregular (small)	10	25	57
Spheres (medium)	26	56	103
Spheres (small)	23	39	62

DSC scans of the paracetamols showed only the melting endotherm of paracetamol Form I. No events such as phase transformation or hydration were seen during the crystallization process.

3.1 Bulk volume and tapped volume of powders

The difference between untapped and tapped volume is in the rearrangement of the particles in the bulk of material. The rearrangement mainly consisted of two main events. The first is the movement of the small and very small particles into the space between big particles. It means that samples with a wider PSD, e.g. raw paracetamol, more tended to change the bulk volume according to tapping than paracetamol with a narrow PSD. The second event relates to a crystal shape and orientation of the particles due to the crystal shape. For example, plates can be settled in the bulk in two preferred position—perpendicularly or parallel. Perpendicular position tend to a big inter-particle space, therefore, the volume of material bulk significantly increases. Tapping of plates caused the reorganization of the particles to the parallel position and a significant reduction of the inter-particle space and the overall volume of the bulk were significantly reduced even after several taps. The product was not so dense in comparison to other crystal shapes because the plate particles were not locked together. Conversely, irregular particles and spheres exhibited small change after tapping as the starting position of the particles was very tight due to the very good flow of the particles and very good natural rearrangement, more significant for irregular particles.

The effect of the different sizes of particles was slightly observed for all types of shape. In all cases, smaller particles tended to smaller bulk volume and smaller tapped volume. But overall, the effect of size was very small and negligible.

3.2 Angle of repose

Wide PSD and irregularly-needled shape of raw paracetamol created big contact areas between the particles, thus, the spill of the raw paracetamol was minimal and material was practically only stacked. Even the flow must have been supported by secondary stirring to deplete the material from the funnel to the measurement plate. Similar to the measurement of the bulk and tapped volumes, size variation minimally affected the angle of repose and the main difference was based on the different shape of paracetamol crystals. Plates created big contact areas and, when they run from the funnel to the measurements plates, adhesion forces held particles together, the spread of the particles on the measurement plate was low and the created angle of repose was high. Irregular and spherical

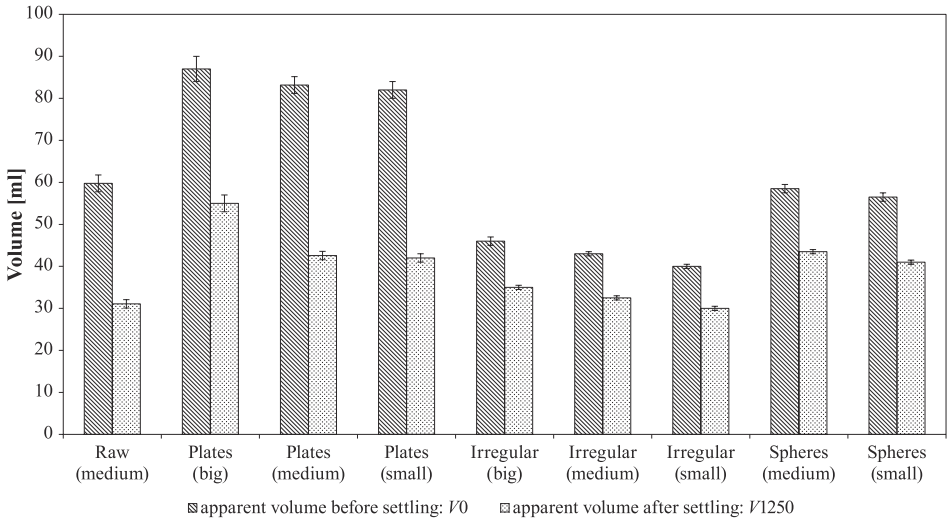

Fig. 4 Bulk volume before the tapping started (*V*0) and tapped volume after 1250 taps (*V*1250) of different shapes of paracetamol crystals with different PSD.

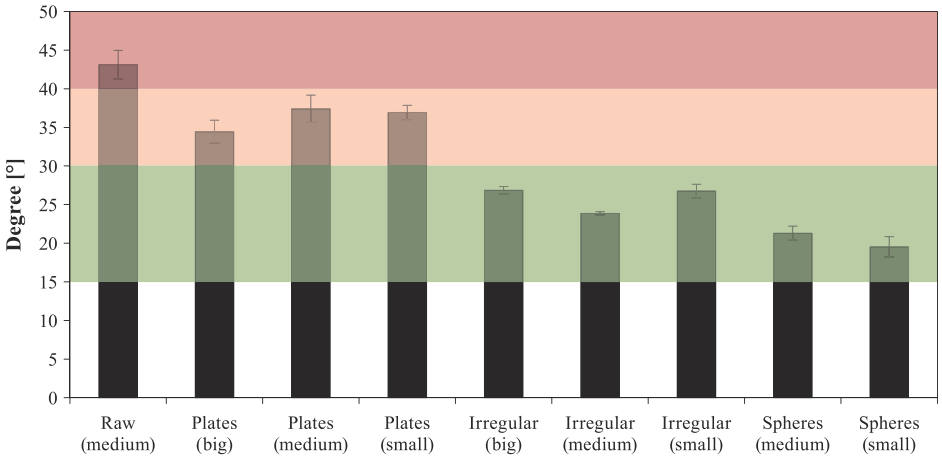

Fig. 5 Angle of repose of different shapes of paracetamol crystals with different PSD.

particles exhibited a free flow into the measurement plate and the angle of repose was very small. The smallest angles of repose were measured for spherical particles and they were even smaller than the values stated in the classification system of the powder flowability (**Table 1**) of European Pharmacopoeia (European Medicines Agency, 2006b).

3.3 Compression properties of paracetamols

Compression of raw, irregular or plate-like crystals of paracetamol produced very weak compacts which had no measureable strength, but they had a high tendency to cap and laminate at all compression forces used. Conversely, spherical crystals produced very strong compacts under the same conditions with no tendency to cap. The strength of these tablets oscillated from 42 N (at compression force 5 kN) to 90 N (at compression force 25 kN).

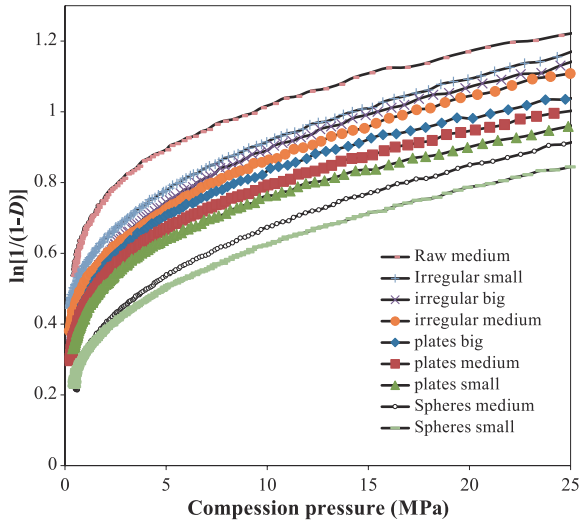

Fig. 6 Heckel plots of different shapes and sizes of paracetamols obtained at compression speed 25 percent.

Crystal shape was the main distributive parameter and size was the minor distributive parameter of the Heckel plots of paracetamols (**Fig. 6**). Irregular and raw paracetamols (irregular particles with a wide PSD) exhibited higher change of densities for given applied pressure than plate-like and spherical paracetamols (**Table 4**). Therefore, the greatest degree of densification during compression was seen for irregular particles, including also raw paracetamol.

Increased frictional and cohesive forces between thin plate-like crystals, due to their large and flat surface, restricted particle sliding and thus reduced densification rate. Additional fragmentation, easier packing or rearrangement occurred at lower pressure. The differentials of D_a-D_0 (**Table 4**) also indicated that densification due to die filling and particle rearrangement for the irregular crystals was higher than for plate-like or spherical crystals. Spherical crystals exhibited very good flowability (**Fig. 5**), thus, the die was filled very tight according to the good natural particle rearrangement.

The particle size effect was identical for all paracetamols. Bigger particles tended more to rearrangement at the beginning of compression than smaller particles of the same shape, as illustrated in higher values of the differential D_a-D_0 for bigger particles (**Table 4**). It was the most probably caused by higher amount of inter-particle space between bigger than smaller particles. The effect of different particle sizes and shapes was reduced when compression force and speed were increased.

3.4 Elastic recovery and tablet capping analysis

Generally, elastic recovery of tablets most depended on both the shape of particles and compression force; which influenced the total area of permanent bonds created between crystals when compressed. The effect of the force and shape on the elastic recovery of in-die tablets indi-

Table 4 The values D_a-D_0 derived from the Heckel plots of compressed paracetamols

	Irregular			Plates			Raw	Spheres	
	(big)	(med.)	(small)	(big)	(med.)	(small)	(med.)	(med.)	(small)
25 % speed									
5 kN	0.50	0.47	0.41	0.43	0.42	0.36	0.48	0.36	0.35
10 kN	0.44	0.42	0.40	0.42	0.40	0.36	0.44	0.35	0.33
15 kN	0.44	0.41	0.39	0.40	0.39	0.35	0.39	0.34	0.30
20 kN	0.41	0.40	0.36	0.38	0.38	0.34	0.39	0.32	0.30
25 kN	0.38	0.38	0.34	0.37	0.36	0.32	0.39	0.31	0.30
50 % speed									
5 kN	0.42	0.38	0.37	0.41	0.37	0.35	0.40	0.36	0.34
10 kN	0.41	0.38	0.36	0.37	0.36	0.34	0.39	0.32	0.31
15 kN	0.40	0.37	0.36	0.37	0.36	0.32	0.38	0.31	0.30
20 kN	0.39	0.36	0.36	0.36	0.35	0.32	0.37	0.30	0.30
25 kN	0.37	0.31	0.33	0.35	0.34	0.29	0.37	0.30	0.29
75 % speed									
5 kN	0.42	0.38	0.37	0.38	0.36	0.32	0.39	0.34	0.33
10 kN	0.41	0.36	0.35	0.37	0.36	0.32	0.38	0.32	0.30
15 kN	0.41	0.36	0.34	0.36	0.36	0.31	0.37	0.31	0.29
20 kN	0.40	0.32	0.34	0.35	0.33	0.31	0.37	0.30	0.28
25 kN	0.36	0.29	0.33	0.34	0.31	0.27	0.37	0.29	0.28

cated that tablets made from spherical crystals exhibited the lowest elastic recoveries (**Table 5**). Spheres (spherulites) probably fragmented and they created very strong bonds between particles, which were originally very close to each other before compression; due to small bulk volume (**Fig. 4**) and very good powder flow (**Fig. 5**). Irregular particles, which are the most similar in shape to spheres, exhibited different compression behaviour, as irregular particles were single crystals, not made from many small crystals like spherulites of paracetamol, thus the attraction of fragmentation was reduced. Raw paracetamol highly tended to rearrangement of the small particles into the inter-particle space between the big particles when compressed due to high heterogeneity of particle sizes (see in **Fig. 3**); therefore, a lot of the permanent bonds were created. But the heterogeneous distribution of the bonds created in the tablet led to high tendency of capping.

Capping was observed in case of raw, irregular and plates. The degree of capping corresponded with the trend of elastic recovery. Apart from the spheres, the lowest elastic recovery (5.9 %—irregular, small, 5 kN, 25 % speed) led to capping chance up to 86 percent; and the highest elastic recovery (22.4 %—plates, small, 25 kN, 75 % speed) led to 100 percent chance of capping. Spheres exhibited no sign of capping. Besides the theory of higher fragmentation of the polycrystalline spherules, the most reasonable explanation of this significantly different behaviour may be attributed to the residuals of PVP remaining on the face of the crystals after crystallization. The amount of residual PVP was under detectable limit of DSC analysis; and functioned as particle glue.

The size effect was also observed. Conversely to the effect of particle rearrangement, the effect was not identical for all the shapes. Except the plate-like particles, bigger particles led to higher elastic recovery of tablets. Abnormal behaviour of plates may be assigned to high content of air in the powder bulk (**Fig. 4**).

Lower compression speed probably allowed better reorganization of the crystals at the beginning of compression; therefore, the elastic recovery was higher when higher compression speed applied. Insufficient time to rearrangement the compressed particles caused weaker bonds between particles, thus, tablets more expanded after compression. Moreover, combination of highest compression speeds and highest compression forces caused insufficient time for particle rearrangement which resulted in abnormalities from the trend observed at lower force and speed.

Table 5 Effect of compression force and speed on the elastic recovery of in-die tablets made from all paracetamols

	Irregular			Plates			Raw	Spheres	
	(big) [%]	(med.) [%]	(small) [%]	(big) [%]	(med.) [%]	(small) [%]	(med.) [%]	(med.) [%]	(small) [%]
25 % speed									
5 kN	8.1	7.8	5.9	9.5	9.6	10.2	8.1	4.2	3.5
10 kN	10.5	10.3	7.8	11.6	11.7	13.7	10.4	4.6	4.3
15 kN	14.1	11.7	10.1	11.9	14.0	14.1	10.9	6.5	5.3
20 kN	15.5	12.8	10.9	13.4	14.1	15.2	11.1	6.9	6.1
25 kN	15.1	13.7	11.9	17.1	17.4	19.8	11.7	7.4	6.2
50 % speed									
5 kN	9.5	8.4	7.9	13.0	14.1	14.6	10.9	4.3	4.2
10 kN	11.9	11.8	9.4	15.5	16.3	17.7	11.9	5.2	5.0
15 kN	14.7	13.2	11.4	18.0	18.1	18.4	12.7	6.9	6.1
20 kN	13.4	12.9	12.8	19.2	19.4	19.5	12.9	8.3	7.8
25 kN	11.5	11.6	11.7	18.9	19.5	19.9	13.2	9.4	8.1
75 % speed									
5 kN	10.5	9.4	9.1	14.2	15.1	15.7	11.8	5.5	4.7
10 kN	11.3	11.2	10.1	16.2	16.4	16.9	12.6	6.2	5.7
15 kN	10.7	11.9	10.8	18.5	19.4	20.6	13.1	8.6	6.3
20 kN	10.7	10.9	10.8	19.8	20.8	21.3	13.2	9.2	8.1
25 kN	10.1	10.1	10.0	20.1	22.2	22.4	13.4	9.8	8.3

4. Conclusion

Paracetamol is an active pharmaceutical ingredient known for its bad compression properties. Modified crystallization of paracetamol by a combination of solvents, stirring speed, cooling rate and additives caused a marked modification of the crystal habit and material properties; however, no polymorphic transformation was induced. Raw paracetamol had a wide PSD of irregular particles which caused poor flowability and a high difference of bulk and tapped densities. These properties predetermined this material to be badly compressible, whereas modified crystallization led to the preparation of spherical paracetamol which exhibited precisely opposite behavior.

The comparison of material properties shows that the particles shape, compression force and speed are the main parameters which influenced the compression and quality of prepared tables as well as the material properties. Conversely, different particle size had relatively small influence, which was more reduced with increased compression speed and force.

The most plastic material was the spherical paracetamol. The spherulites, the polycrystalline particles of paracetamol, probably tended to a significant fragmentation of particles, thus, strong bonds and significantly larger contact area were made between fragmented particles; and probably a non-detectable residuals of PVP after crystallization remained on the surface of particles and functioned as a particle glue. The elastic recovery of tablet, which were made from spherical paracetamol, was very low (from 3.5 to 9.8 percent) and we concluded it was responsible for no capping of these tablets. Other used shapes exhibited high elastic recovery and high probability of the visible capping of produced tablets (at least 86 percent) at all used conditions. The main difference was caused by the shape of the particles and less by the compression speed and force. The particles size had the smaller influence on this property.

Based on the experimental data, crystal manipulation via particle engineering is an efficient tool in producing crystals with optimal physico-mechanical properties to affect the compression behavior of API crystals. This approach might be of interest to those persons who are developing and optimizing the formulation process of poorly compressible APIs. Our further step is to assess the exact fragmentation of different shapes and size of paracetamol by our hot-stage methodology and compare the results with the presented evaluation.

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In 1972 graduated in chemistry at the Faculty of Science, Charles University in Prague. In 1985 the transition from the Faculty of Science to the University of Chemistry and Technology, Prague (UCT). Positions : Head of the Department of Solid State Chemistry of the UCT , Vice-dean of the Faculty of Chemical Technology of the UCT and Vice-Rector for Science and Research of the UCT. Editor in Chief of the Chemicke Listy journal (1986–2012). Research : Crystallography of coordination, inorganic and small organic compounds , recently application of X-ray diffraction methods in pharmaceutical research , development, production and control. Study of solid pharmaceutical phases: polymorphs, hydrates, cocrystals. Solid dosage forms.