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ORIGINAL ARTICLE

Study of radial die-wall pressure changes during pharmaceutical powder compaction

Sameh Abdel-Hamid and Gabriele Betz

Department of Pharmaceutical Sciences, Industrial Pharmacy Research Group, University of Basel, Basel, Switzerland

Abstract

Context: In tablet manufacturing, less attention is paid to the measurement of die-wall pressure than to force–displacement diagrams. *Objective*: Therefore, the aim of this study was to investigate radial stress change during pharmaceutical compaction. *Materials and Methods*: The Presster^{TM}, a tablet-press replicator was used to characterize compaction behavior of microcrystalline cellulose (viscoelastic), calcium hydrogen phosphate dihydrate (brittle), direct compressible mannitol (plastic), pre-gelatinized starch (plastic/elastic), and spray dried lactose monohydrate (plastic/brittle) by measuring radial die-wall pressure; therefore powders were compacted at different (pre) compaction pressures as well as different speeds. Residual die-wall pressure (RDP) and maximum die-wall pressure (MDP) were measured. Various tablet physical properties were correlated to radial die-wall pressure. *Results and Discussion*: With increasing compaction pressure, RDP and MDP ($P < 0.0001$) increased for all materials, with increasing precompaction RDP decreased for plastic materials ($P < 0.05$), whereas with increasing speed MDP decreased for all materials ($P < 0.05$). During decompression, microcrystalline cellulose and pre-gelatinized starch showed higher axial relaxation, whereas mannitol and lactose showed higher radial relaxation, calcium hydrogen phosphate showed high axial and radial relaxations. Plastic and brittle materials showed increased tendencies for friction because of high radial relaxation. *Conclusion*: Die-wall monitoring is suggested as a valuable tool for characterizing compaction behavior of materials and detecting friction phenomena in the early stage of development.

Key words: Capping, compaction simulation, die-wall instrumentation, friction, (pre)compaction pressure, radial die-wall pressure, speed

Introduction

Understanding the behavior of particles during each stage of powder compaction is very important. Parameters used to assess the compaction behavior of powders include Heckel analysis[1], stress relaxation[2], and elastic recovery[3]. Heckel equation[4,5] has been the most frequently used method to characterize powder compaction behavior. However, this equation has some drawbacks like the curvature at low pressures because of particle rearrangement and the exponential curvature at high pressures because of elastic deformation as well as high error probability at relative density higher than 0.95[6]. Powder behavior under very low compaction pressures was described by a modified Heckel equation[7], which investigates the conversion of particles into a solid compact. However, most of these approaches do not consider the radial stress transmission and powder–die-wall friction where the latter is mainly responsible for density inhomogeneity within the compact[8–11]. This can lead to a nonuniform stress distribution which may result in problems like capping and lamination on decompression[12]. Radial versus axial pressure cycles introduced by Long[13] can give an idea about the different deformation behaviors of materials such as Mohr body, brittle fracture, plastic deformation, and a perfect elastic body[14–17]. However, it is rare in reality to find such cycles typically, as most powders are anisotropic and nonhomogeneous in density during compaction[18].

The complexity of compaction process specially with using high-speed tablet presses necessitates the use of robust monitoring tools during the process. The use of an instrumented compaction simulator in the early stage

Address for correspondence: Gabriele Betz, Department of Pharmaceutical Sciences, Industrial Pharmacy Research Group, University of Basel, Mülhauser Street 51, CH-4056 Basel, Switzerland. Tel: +41 61 3810 720, Fax: +41 61 3810 430. E-mail: gabriele.betz@unibas.ch

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of development has a significant benefit for product development process.

The Presster™ is a linear mechanical replicator for rotary tablet machines designed by Metropolitan Computing Corporation MCC™ to match compression force and dwell time as well as to mimic the punch displacement profile of any press. It is a high-speed, single-station, tablet-press simulator with standard tooling (IPT B, D-type). It is also a powerhouse computer for compressibility profiles, Heckel and Picker plots, lubricant studies, and others. Figure 1 shows a compression waveform displayed by Presster™ software with peak pressure, peak offset time, decompression time, dwell time, contact time, upper and lower displacement curves, and radial die-wall (RDW) pressure. The Presster™ instrumentation includes linear variable differential transformers (LVDTS) for upper and lower punch displacement as well as strain gauges for (pre)-compression, ejection, take-off forces, and RDW pressure. The Presster™ RDW transducer is a solid die with a cutout that creates two sensing elements of a uniform section area on the opposite sides of the die opening along its entire height (Figure 2). Two pairs of tension–compression strain gauges are positioned in such a way that the tablet compaction on Presster™ always takes place between them. The upper pair covers the area of upper punch penetration (4 mm from the die's top), the second pair is placed 6 mm below. The recommended maximum tablet thickness for RDW pressure measurements is 4.5 mm. The voltage output of the transducer is proportional to the radial force transmitted to the die-wall.

The recent quality-by-design initiative by the Food and Drug Administration stresses the need for development of process simulation tools to identify optimal and efficient processes that can be easily scaled up. Up to now, in tablet production little attention has been paid to the measurement of die-wall pressure. Die-wall instrumentation[19–21] would be essential to understand the deformation of particles under axial pressure during the compaction cycle. It would be also of great help to investigate particle–die-wall shear stresses or friction, which is the cause of many tableting problems such as capping, lamination, tooling wear, and sticking[17]. Residual die-wall pressure (RDP) was reported as one of the key factors for capping, like elastic recovery during decompression[22,23].

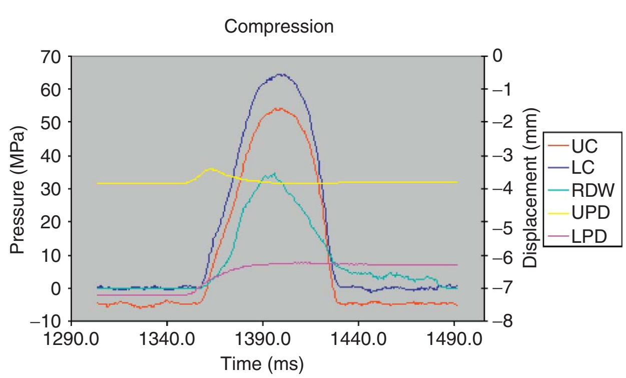

Figure 1. Compression waveform of the Presster™ showing 1. upper and 2. lower compression (UC/LC), 3. upper and 4. lower punch displacement (UPD/LPD), and 5. radial die-wall pressure (RDW) curves.

Figure 2. Die-wall instrumentation.

The aim of this study was to use RDW pressure as a tool for characterizing the compaction behavior of pharmaceutical powders as well as to predict capping tendency during compaction. Further, to correlate various physical tablet properties such as tensile strength and elastic recovery to RDW pressure.

Materials and methods

Materials

Microcrystalline cellulose (Avicel® PH102, FMC Corporation, DE, USA), directly compressible mannitol (Parteck® M200, Merck KGaA, Darmstadt, Germany), calcium hydrogen phosphate dihydrate (Emcompress®, JRS Pharma, Rosenberg, Germany), pre-gelatinized starch (Sta-Rx® 1500, Colorcon, Idstein, Germany), spray-dried lactose monohydrate (Flowlac® 100, Meggle, Wasserburg, Germany), and magnesium stearate (N.F. Novartis, Basel, Switzerland) were used in the present study.

Methods

Powder characterization

Apparent particle density

Apparent particle density of powders was measured by AccuPyc 1330 helium pycnometer (Micrometrics, Norcross, GA, USA). A known weight (2.5 mg) of the samples was placed into the sample cell. Values were expressed as the mean of five parallel measurements (Table 1).

Table 1. Apparent particle density and mean particle size of the powders.

Material	Apparent particle density (g/cm^3) ± standard deviation ($n = 5$)	Mean particle size (μm) ± standard deviation ($n = 3$)
Microcrystalline cellulose	1.5589 ± 0.0009	127.6 ±0.33
Mannitol (spray dried)	1.4902 ± 0.0005	146.3 ± 6.20
Calcium hydrogen phosphate dihydrate	2.4741 ± 0.0028	191.206 ± 7.077
Lactose (spray dried)	1.5419 ± 0.0012	131.44 ± 1.005
Pre-gelatinized starch	1.4790 ± 0.0018	93.74 ± 0.13

Particle-size distribution

The average particle size was determined with a Malvern Mastersizer X (Malvern Instruments, Worcestershire, UK). The measurements were carried out three times for each sample. Obscuration value was between 10% and 30% in all measurements. The function 'polydisperse' was activated (Table 1).

Powder compaction

Powder compaction was carried out using a compaction replicator (Presster™, Metropolitan Computing Corp., NJ, USA) simulating the tablet-press Korsch PH336 (36 stations). The compaction rolls used were 300 mm in diameter. Accordingly, a flat-faced B-tooling with a diameter of 10 mm was used to make tablets of 250 mg in weight. Powder feed was manually done. Punches and dies were dusted with magnesium stearate powder before each compaction cycle for lubrication. The machine was set to perform compaction pressures in the range of 50–300 MPa at the compaction speeds of 0.5 and 2.147 m/s corresponding to the dwell times 19 and 4.4 ms, respectively. Six tablets were compressed in the same experimental conditions and the mean of each parameter was calculated. During RDW sensor calibration, the radial force was calculated as a product of the applied axial pressure by the area of cylindrical portion of the tablet. Calibration factor was calculated as RDW force per voltage output (10.08 kN/volt). During tablet compaction, the measured voltage output was multiplied by calibration factor and the product RDW force value was referred to the area of cylindrical portion of the tablet to obtain the RDW pressure value. The transducer was calibrated with a polyurethane 4.5 mm height insert and B-type 10 mm round flat face punch.

RDP and maximum die-wall pressure (MDP) were measured and RDP/MDP ratio was calculated. The die-wall pressure reaches a maximum value, MDP, just after the upper and lower punches show maximum compression values, and shows a constant residual value, RDP, after upper and lower punch forces become zero. Axial to radial stress ratio (SR) (the average of upper and lower compression pressures to MDP) was also calculated. To study the effect of different compaction variables, runs were generated according to an experimental design using STAVEX® 5.0 (Aicos, Switzerland) applying Pentagon factorial design and optimization mode (Table 2).

Table 2. Pentagon factorial design for compaction variables.

Run	Compaction pressure C (MPa)	Precompaction pressure P (MPa)	Compaction speed S (m/s)
1	50	50	0.5
2	50	50	2.0
3	80	10	0.5
4	80	10	2.0
5	120	30	0.5
6	120	30	2.0
7	120	70	0.5
8	120	70	2.0
9	170	10	0.5
10	170	10	2.0
11	200	50	0.5
12	200	50	2.0

Compact's characterization

Radial tensile strength. Crushing strength of a compact was determined by pressing it diametrically[24] on a Pharmatron tablet tester (model 8D, Dr Schleuniger Pharmatron, Inc., Solothum, Switzerland). Radial tensile strength (RTS) σ (MPa) was calculated according to:

$$\sigma = \frac{2F}{\pi dh}, \tag{1}$$

where F is the force required to cause failure in tension (N), d the compact's diameter (mm), h the compact's thickness (mm), and π a constant that equals 3.1416.

Elastic recovery. The elastic recovery within the die at zero pressure (% ER_0) for a compact was calculated from 'zero pressure thickness' that could be seen from the force versus thickness plot, and 'minimum punch gap' (thickness at maximum compression) features of Presster™ software.

$$\textit{Change in void fraction } VC = \frac{\Delta\varepsilon}{1-\Delta\varepsilon}, \tag{2}$$

where $\Delta\varepsilon$ is the change in porosity of the compact (difference between out and in die porosities).

Data interpretation

Statistical analysis was done using STAVEX® 5.0 (Aicos, Switzerland) and Graph Pad Prism v.5.00.

Results and discussion

Effect of compaction pressure on radial die-wall parameters

Table 3 shows the models suggested for different materials showing the compaction variables, compression, precompression and compaction speed and their interactions. A qualitative classification for the materials under investigation regarding their deformation behavior[25–29] is given in Table 4. For all materials, increasing compaction pressure significantly increased both RDP ($P < 0.0001$) and MDP ($P < 0.0001$), whereas decreased both RDP/MDP ratio ($P < 0.003$) and SR ($P < 0.0001$). Figure 3 shows that the plastic material mannitol had the highest RDP followed by lactose (plastic/brittle) then calcium hydrogen phosphate dihydrate (brittle), and finally microcrystalline cellulose and pre-gelatinized starch (plastic/elastic). It is clear that plastic materials displayed the highest RDP, whereas materials with an elastic component displayed the lowest RDP and materials with brittle character laid in between. Regarding MDP, (Figure 4) at higher pressures (200 MPa and above) materials with plastic/elastic behavior (microcrystalline cellulose and pre-gelatinized starch) showed the highest MDP values followed by the plastic material mannitol then the plastic/brittle lactose, and finally the brittle calcium hydrogen phosphate dihydrate. MDP describes both elastic and plastic components, where it was clear in Figure 4 that MDP could not clearly differentiate between materials at lower pressures, whereas RDP shows only permanent deformation after compaction[30]. RDP was used as a guide to detect capping problem in some formulations[15,31]. The relation between compaction pressure and RDP/MDP ratio (Figure 5) followed the same sequence for different materials' behavior with RDP but in a decreasing trend, where materials with plastic behavior (mannitol and lactose) showed the highest ratio values and materials with elastic component (microcrystalline cellulose and pre-gelatinized starch) showed the least ratio values. Plastic behavior increases RDP whereas elastic behavior decreases RDP[32]. RDP/MDP ratio could be more useful in describing the compaction behavior as it involves both die-wall-related parameters, which provide a thorough profile regardless of the compaction pressure or speed. Generally, in tableting it would be desirable to have low RDP and high MDP values, hence low RDP/MDP values. This is in accordance with the results reported by Takeuchi et al.[33] On the other hand, compaction pressure showed no effect on SR for the brittle calcium hydrogen phosphate dihydrate, but in case of materials with elastic component (microcrystalline cellulose and pregelatinized starch) SR values were the lowest (i.e., low axial to radial

Table 4. Classification of the materials regarding their deformation behavior upon compaction.

Material	Deformation behavior		
	Plastic	Elastic	Brittle
Calcium hydrogen phosphate dihydrate	–	–	+++
Microcrystalline cellulose	++	++	–
Mannitol (spray dried)	++	–	–
Lactose (spray dried)	+	–	+
Pre-gelatinized starch	++	+++	–

+++, high; ++, medium; +, low; –, not present.

Table 3. Models suggested for different materials showing the compaction variables, compression (C), precompression (P), compaction speed (S), and their interactions.

Material	Equation	Goodness of fit	
		R^2	$R_c^{\ 2}$
Calcium hydrogen phosphate dihydrate	RDP = –1.757 + 0.09243C + 0.02666P + 0.08435S + 5.374E – 05C^2 – 0.0002014P^2 – 0.0001033CP – 0.001225CS – 0.00197 PS	0.9981	0.9931
	MDP = –8.585 + 0.4103C + 0.1826P – 6.662S + 0.0009373C^2 – 0.0007913P^2 – 0.001214CP + 0.002614CS – 0.02599PS	0.9956	0.9838
Microcrystalline cellulose	RDP = 4.327 + 0.02462C – 0.05231P – 0.2226S – 7.245E – 05C^2 + 0.0002541P^2 + 0.0001992CP – 0.001599CS + 0.003609PS	0.976	0.9122
	MDP = 0.6125 + 0.5372C – 0.2768P – 1.357S + 0.0008899C^2 + 0.003295P^2 – 0.0003050CP – 0.02209CS – 0.007288PS	0.9996	0.9985
Mannitol (spray dried)	RDP = 2.145 + 0.08482C – 0.05365P + 0.1784S + 0.0001936C^2 + 0.0004361P^2 + 6.694E – 05CP – 0.01017CS + 0.001765PS	0.9995	0.9982
	MDP = –0.1144 + 0.4770C – 0.09218P – 0.9937S + 0.0009111C^2 + 0.001167P^2 – 0.0002378CP – 0.02897CS – 0.02950PS	0.9994	0.9978
Lactose (spray dried)	RDP = 1.956 + 0.08445C – 0.04192P – 1.010S + 2.443E –05C^2 + 0.0001850P^2 + 0.0001275CP – 0.004313CS + 0.01027PS	0.9995	0.9983
	MDP = 10.38 + 0.2405C – 0.1535P – 3.895S + 0.001192C^2 + 0.001094P^2 + 3.639E – 05CP – 0.03444CS + 0.01328PS	0.9990	0.9962
Pre-gelatinized starch	RDP = 8638 + 0.03348C + 0.001427P – 0.2748S – 8.650E – 05C^2 – 7.135E – 05P^2 – 1.389E05CP – 0.0008719CS + 0.005358PS	0.9799	0.9263
	MDP = –14.61 + 0.6541C + 0.2226P – 3.103S + 0.001214C^2 – 0.001357P^2 – 0.001385CP – 0.05388CS+0.05732PS	0.9999	0.9995

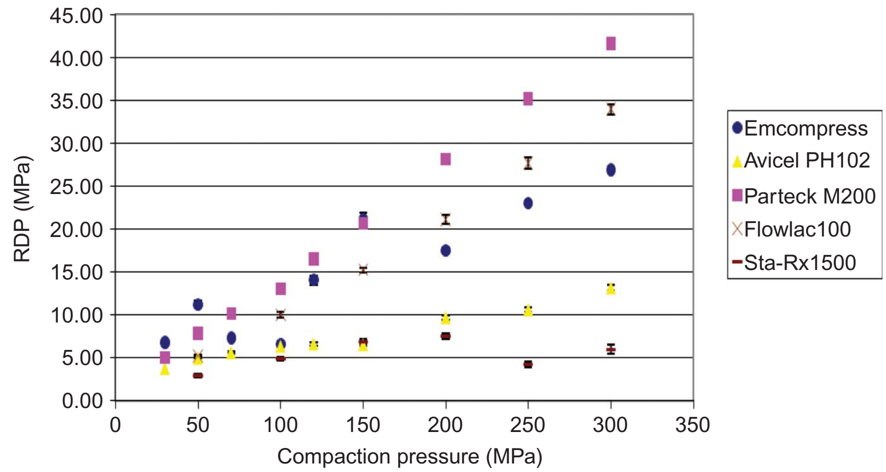

Figure 3. Effect of compaction pressure on RDP at compaction speed 0.5 m/s.

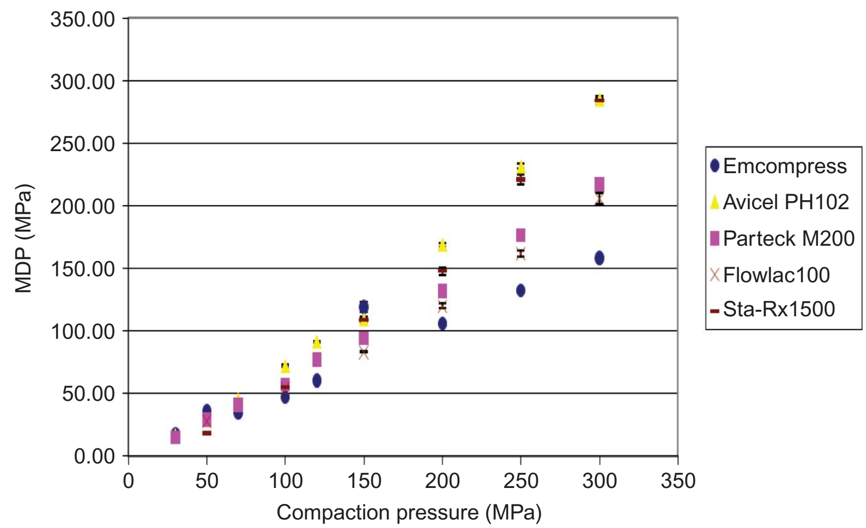

Figure 4. Effect of compaction pressure on MDP at compaction speed 0.5 m/s.

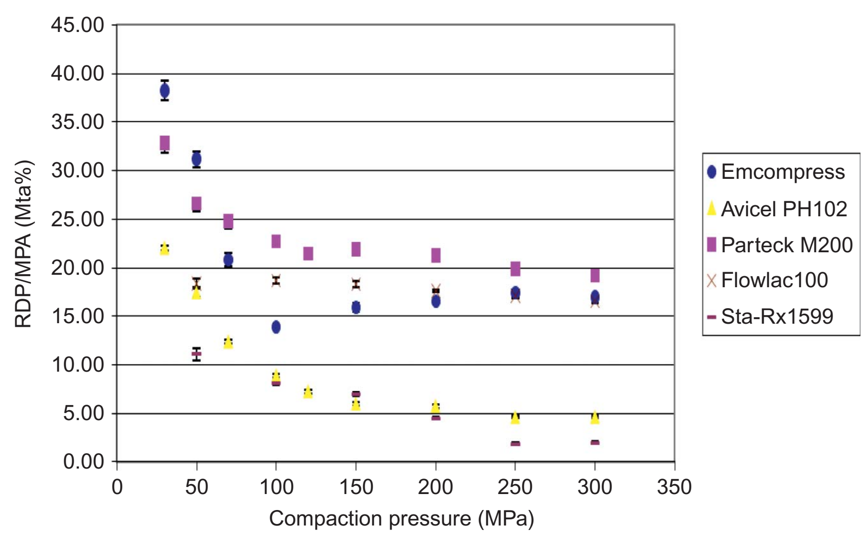

Figure 5. Effect of compaction pressure on RDP/MDP ratio at compaction speed 0.5 m/s.

stress transmission), whereas materials with only plastic behavior such as mannitol and lactose (no elastic component) showed the highest SR values (i.e., high axial to radial stress transmission), which is a typical indicator for plasticity (Figure 6).

Effect of precompaction pressure on radial die-wall parameters

Precompression had no effect on RDP and SR for microcrystalline cellulose and pregelatinized starch as well as calcium hydrogen phosphate dihydrate but for plastic materials (mannitol and lactose) RDP decreased (Table 3) and SR increased ($P < 0.05$). On the other hand, precompression had no effect on MDP and RDP/MDP ratio for all materials except for microcrystalline cellulose (MDP decreased) (Table 3). Precompression helped in particles rearrangement (powder densification) and hence ease of contact and bonding between particles leading to a cohesive mass with less tendency for radial deformation upon compression. This explains the decrease of MDP for microcrystalline cellulose. Precompression also helps in removal of entrapped air and thus improves bonding between particles during the compaction phase[34]. Precompression had the most significant effect on materials that showed the highest RDP (mainly plastic), where precompression decreased radial stress relative to axial during compaction (increased SR) and decreased radial relaxation after decompression (decreased RDP).

Effect of compaction speed on radial die-wall parameters

Increasing speed decreased MDP for all materials ($P < 0.05$). However, increasing speed led to the increase of RDP for mannitol ($P < 0.001$) and the decrease of RDP for microcrystalline cellulose lactose and pregelatinized starch ($P < 0.05$), and no effect for Emcompress® (Table 3). The decrease of dwell time (increase of speed) decreased the time of deformation for all types of materials during compaction and so led to a decrease in MDP. On the other hand, the increase of speed led to increase of radial recovery for mannitol like the same effect produced by speed on elastic recovery for materials with axial elastic component. All materials with elastic component showed a decrease in radial recovery (low RDP) as they experienced higher axial recovery (high elastic recovery). Finally, speed had no effect on the radial recovery of materials with brittle behavior because of the fracture of particles rather than deformation.

The effect of radial die-wall pressure changes on compacts' physical properties

Materials with an elastic component (microcrystalline cellulose and pregelatinized starch) during decompression showed highest elastic recovery ($P < 0.0001$) within the die at zero pressure ER_0 as well as the highest void volume change ($P < 0.0001$) with the least RDP values (Figures 7 and 8). Thus, they had the greatest probability for capping. ER_0 would be more accurate to describe any tableting problem like capping and lamination on deloading in comparison to measuring elastic recovery like after 48 hours as the problem would have been already occurred. Viscoelastic materials like microcrystalline cellulose have high energy in compacts[28], so on relaxation during deloading they would be liable for capping, especially at high speeds, unless they show strong bonding between particles. Moreover, high frictions between the die-wall and the compact may prevent the newly formed compact from relaxation and the relief of stored energy which would probably lead to capping or lamination[2]. Microcrystalline cellulose and pregelatinized starch showed the lowest RDP values and highest void volume change (lowest friction and highest porous structures during ejection) and thus fewer tendencies for capping or lamination. These were in accordance with

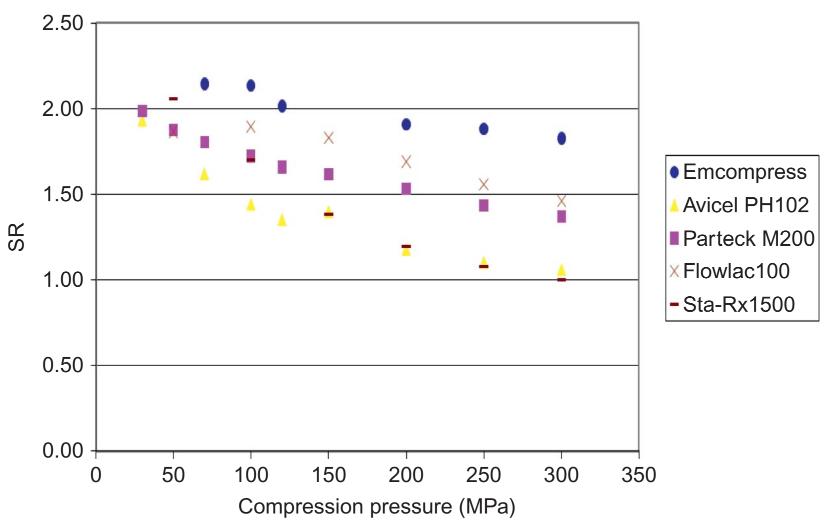

Figure 6. Effect of compaction pressure on axial to radial stresses ratio SR at compaction speed 0.5 m/s.

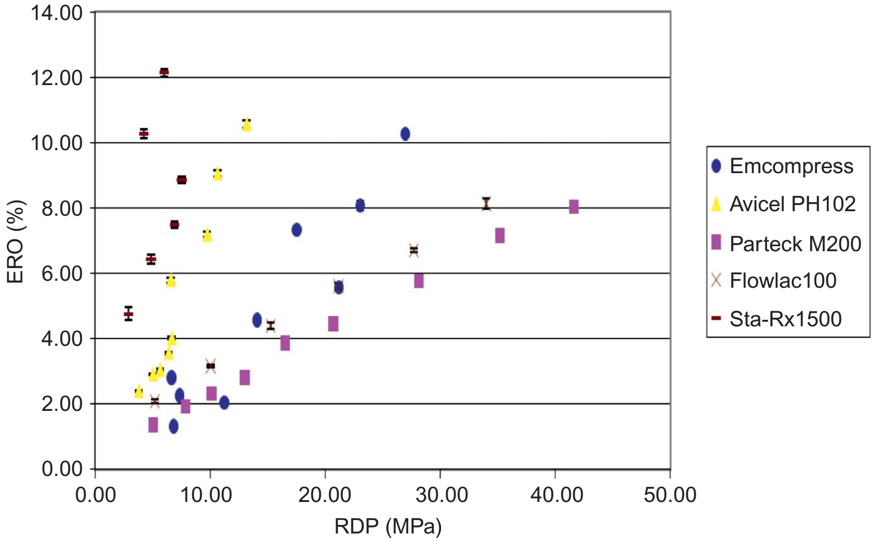

Figure 7. Change of RDP with ER0 at compaction speed 0.5 m/s.

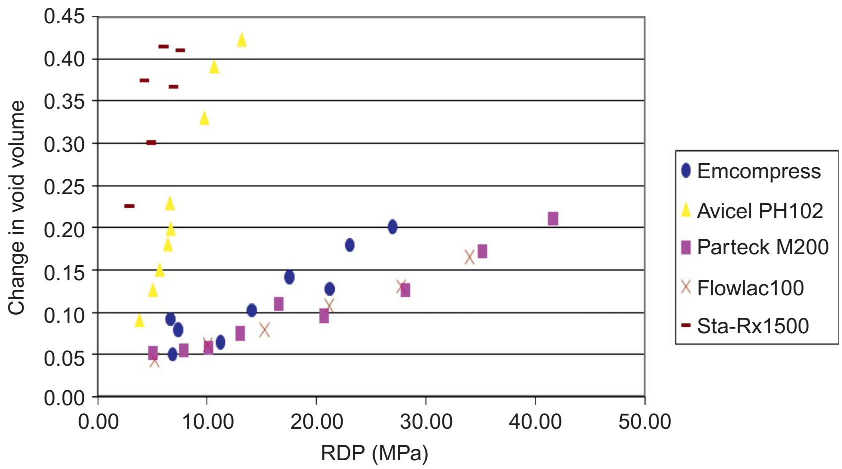

Figure 8. Change of RDP with void volume change at compaction speed 0.5 m/s.

the results of Sugimori et al.[35], where they stated that RDP depends on the elasticity and the use of powders with low RDP like microcrystalline cellulose reduced capping tendency. Although microcrystalline cellulose showed highest elastic recovery, but in comparison to pregelatinized starch and other materials, it showed the highest RTS (P < 0.0001) (Figure 9). RTS indicates the force required to break bonds between particles. In case of microcrystalline cellulose, the high bonding between particles limits the disruptive effect of elastic recovery[30]. However, materials with high elastic recovery at high compaction speeds during decompression would be still at high risk for capping[36–38]. Plastic materials (mannitol and lactose) showed the least values for ER_0 and void volume change (P < 0.0001) and the highest RDP values (higher tendencies for friction). This was practically observed where compaction of microcrystalline cellulose and pregelatinized starch did not need any external lubrication (low ejection forces did not exceed 200 N), whereas it was completely unavoidable to use external lubrication with mannitol and lactose (very high ejection forces more than 1500 N). However, mannitol showed stronger compacts (higher RTS) than lactose because of the brittle component of the latter. The brittle calcium hydrogen phosphate dihydrate showed intermediate values between viscoelastic and plastic materials for ER_0, void volume change, and low RTS, which makes it highly liable for decompression defects like capping, lamination, or chipping. Table 5 summarizes the compaction parameters previously discussed in relation to materials deformation behavior.

Conclusion

Die-wall pressure investigation is of help to monitor compact formation at two critical steps: decompression (elastic recovery) and ejection phases (friction). RDW pressure reflects radial relaxation and so probability for

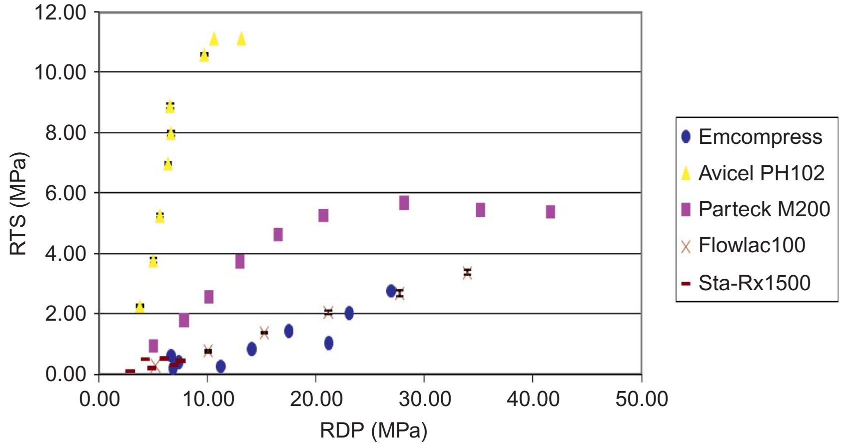

Figure 9. Change of RDP with RTS at compaction speed 0.5 m/s.

Table 5. Different levels for compaction parameters in relation to materials' deformation behavior.

	Materials		
Parameter	Elastic/plastic	Plastic	Plastic/brittle
RDP	↑	↑↑↑	↑↑
MDP*	↑↑↑	↑↑	↑↑
RDP/MDP	↓↓↓	↓↓	↓↓
SR	↓↓↓	↓↓	↓/–
ER_0	↑↑↑	↑	↑/↑↑
VC	↑↑↑	↑	↑/↑↑
RTS	↑↑↑**	↑↑	↑

↑↑↑, High; ↑↑, medium; ↑, small; –, no effect; ↑, increasing; ↓, decreasing. *At high pressures >200 MPa. **Only microcrystalline cellulose as pregelatinized starch showed very low values.

friction. An increasing RDP value during compaction would indicate higher tendency for friction, whereas an increased or constant value of MDP would provide an evidence for plastic behavior, a character always desired in powder formulations. We highly recommend using RDW pressures for setting limits for high-speed tableting machines to give a continuous control feedback for problems arising during manufacture, such as lamination and capping by detecting friction phenomena in early stages of development.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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