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Research paper

Application of multivariate methods to compression behavior evaluation of directly compressible materials

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ABSTRACT

The present study is an approach to describe and predict compaction and tablet properties by a combination of a set of commonly used mathematical descriptors and multivariate methods based on continuous compression profiles. Effects of formulation and process parameters (e.g. composition, powder properties, compression speed) of well-known direct compression excipients of widely plastic, elastic, and fragmentary properties, and binary mixtures thereof were characterized. 2^3-Full factorial designs with three centre points were applied for Avicel® PH 102, Starch 1500® and Spherolac® 100. Tablets (11 mm diameter) were compressed from hand-weighed powder (of constant true volume) at 104.1 ± 0.2 MPa using a compaction simulator, yielding highly repeatable data. Heckel equation and work-related parameters were derived. Data were evaluated by multivariate analysis (principal component analysis (PCA) and partial least squares (PLS-2, PLS-1) models). The PCA indicated that Hausner ratio, work of compression (WoC), and tensile strength (TS) are negatively correlated to yield pressure of plastic (YPpl) and elastic deformation (YPel), Emcompress® fraction, helium-, bulk-, and tapped density, and particle size. PLS-2 model correlated all design variables, their interaction and square effects with all response variables. These correlations were further quantified for the most important responses (e.g. WoC, TS, YPpl, and YPel) by optimizing separate PLS-1 models. The results were found in accordance with expectations and show the ability of this approach to quantify compression behavior, as a step towards a 'formulation development tool' for tablets.

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1. Introduction

Still the development of new tablet formulations is empirical, requires numerous experiments, and does not necessarily lead to the optimum formulation. The ultimate goal, therefore, is a formulation development tool that would allow the formulation scientist to predict compression behavior on industrial scale as well as on tablet properties based on a limited number of simple experiments and quick evaluation methods.

There is no single and simple function or equation that may serve as a general compaction equation capable to explain all the mechanisms of an entire compression process. It is yet not even likely to be achieved in the near future, if possible at all. An alternative approach is to use a set of frequently used functions and descriptors that only cover some of the aspects (such as Heckel, Kawakita, Cooper-Eaton, and work-related parameters) and establish a 'compression database' with the most important parameters derived for the wide range of tableting excipients. The parameters from such database may then serve as 'fingerprints' for the prediction and optimization of the tableting properties of new tablet formulations. It is a prerequisite that the compression parameters derived are accurate, and both the experiments and the evaluation should be quick and simple to carry out.

In order to develop such a tool, it should be an advantage to start with accurate time-resolved force and displacement data (compression profiles) obtained from a compaction simulator, and apply commonly used and accepted mathematical models on a set of well-known pharmaceutical excipients of widely different deformation nature. Evaluation of the deformation behavior by multivariate methods is a useful way of mapping common trends, describe and quantify the behavior of variables and responses and to develop models suitable for the prediction of behavior within a predefined design space. The aim of the present work was therefore to study the compression behavior of four commercially available direct compression materials of mainly plastic, elastic and fragmentary properties and their respective binary blends, to cover a wide range of properties. A compaction simulator was used to produce highly accurate and reproducible data [1]. The objective was to evaluate continuous compaction profiles in response to process and formulation parameters from force–displacement curves, work related descriptors and from the Heckel equation, and to

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quantify relationships by multivariate methods. In order to keep the procedure quick and simple, "in-die" methods were preferred instead of more time consuming "out of die" methods.

2. Materials

Microcrystalline cellulose, Avicel® PH 102 (Batch K.W. 907014), was a free sample from FMC biopolymer, Belgium. Dibasic calcium phosphate dihydrate, Emcompress® (Batch A740 57A) was donated by JRS Pharma, Germany. A partially pregelatinized starch, Starch 1500® (Batch IN 509959), was a free sample from Colorcon, England, and Spherolac® 100 (Batch L.9909 A4132), which is α-lactose monohydrate, was donated by Meggle Pharma, Germany. Magnesium sterate (Batch MF19/70089) was purchased from NMD, Norway.

3. Methods

3.1. Basic powder characterization of excipients as received

3.1.1. Particle size distribution

Analytical sieving was performed according to Ph.Eur. 2008 [2], using a mechanical sieve shaker (Retsch VE 1000, Retsch GmbH and Co. Kg, Hann, Germany).

3.1.2. Particle shape

Samples were mounted on an aluminum base with adhesive carbon tape and sputtered with gold under vacuum for 120 s prior to SEM examination (JSM-6300 SEM, Japan Electron Optics Laboratory, Ltd., Tokyo, Japan).

3.1.3. Flowability

Flowability of the powders was determined by indirect method using Hausner factor (HF), which is a ratio of tapped to bulk density of powder [3]. Bulk and tapped densities were determined according to Ph.Eur.2008 [4] with three repetitions (Erweka® Tapped Volumeter, Typ Svm, Heusenstamm, Germany).

3.1.4. Helium density

The helium density of the powder particles was determined by using gas pycnometer in a Micromeritics AccuPyc™1330 Pycnometer (Micromeritics GmbH, Neuss, Germany). Ten repetitive purge cycles were performed before recording results in three repetitions.

3.2. Preparation and characterization of physical blends

Binary blends were prepared in 200 g lots in a Turbula mixer (Turbula® System Schatz, Basel, Switzerland) for 3 min at 23 rpm. Lubrication of plain excipients and their binary blends with 1% magnesium sterate was performed under the same conditions.

3.3. Experimental design for the evaluation of compression behavior

The effect of punch velocity (saw tooth profile, 10.0 and 50.0 mm/s), lubricant level (0% and 1.0%), and added material Emcompress® (0% and 50.0%) as process and formulation parameters was investigated with respect to compression responses, namely yield pressure value of plastic deformation (YPpl), YP of elastic recovery (YPel), work of compression (WoC), work of elastic recovery (WoE) and tablet tensile strength (TS). The independent variables and their levels are presented in Table 1.

Three excipients (Avicel® PH 102, Starch 1500®, and Spherolac® 100 (Table 2)) were tested in a 2^3-full factorial design with three centre points each, resulting in 11 experiments per excipient. A total of 37 experiments were performed; 33 experiments from 3 excipients and 4 additional control experiments containing Emcompress® as main excipient.

Table 1
Design variable levels in the 2^3-full factorial design with three centre points.

Design variables	Experimental levels		
	Low	Intermediate	High
Punch velocity (mm/s)	10.0	30.0	50.0
Lubricant fraction (%)	0.0	0.5	1.0
Emcompress® fraction (%)	0.0	25.0	50.0

3.4. Tablet preparation

In order to compare the compression properties of different materials and different blends of materials, constant true volume (calculated from the helium density) should be used instead of constant weight since the response to punch movement (i.e. punch force) is a function of volume of solid in the die and not its weight [5]. Cylindrical 11 mm tablets of theoretically constant volume were prepared on a calibrated and validated compaction simulator (ServoPress 450, Schmidt Technology, St. Georgen, Germany; IRB, Waldkirch, Germany) [1]. Helium density value was used to calculate the mass of powder required for each tablet to be 0.2552 ± 0.01 cm^3. Prior to each compression, the punch tips and the die wall were lubricated with a 0.5% suspension of magnesium sterate in acetone. The weighed amount of powder mass was poured manually into the die and compacted at pressure 104.1 ± 1.7 MPa at constant punch velocities (as given in Table 1). Tablet mass was measured immediately after production (CP225D, Sartorius AG, Göttingen, Germany) while its dimensions (diameter and thickness) were measured 24 h after production (0.01 mm micrometer IP54, Wilson Wolpert, Netherlands). The tablets were stored for at least 24 h in desiccators at 24.6 ± 1.5 °C and a relative humidity of 22.5 ± 5.5%.

Crushing force of the tablets was determined (Erweka® GmbH, model TBH20, Heusenstamm, Germany) and tensile strengths (TS) were calculated according to the following (1) [6]:

$$TS = \frac{2F}{\pi D t} \quad (1)$$

where F is the crushing force in N, D diameter, and t is the thickness of tablet in mm.

3.5. Determination of compression parameters

Compression behavior was studied using the *in-die* method for Heckel Eq. (2) [7]:

$$\ln\left[\frac{1}{1-D}\right] = kP + A \quad (2)$$

where D is the relative density of the compact at pressure P.

The reciprocal of the slope (k) of the linear portion of the compression phase and the decompression phase, respectively (i.e. mean YP of plastic deformation (YPpl) and elastic recovery (YPel), respectively) was calculated by linear regression between 20 and 80 MPa for the compression phase, and between 20 and 90 MPa for the decompression phase.

Also, the apparent work of compression (WoC) and elastic recovery (WoE) values was determined from the force–displacement data recorded during the compression-cycle [8].

3.6. Statistical analysis

Principal component analysis (PCA) followed by partial least square regression (PLS-1 and PLS-2) was performed to identify

Table 2
Investigated excipients, given with measured particle size and particle shape.

Sr. No.	Brand name	Chemical name	Main compression behavior[a]	Particle size[b] [μm]		Particle shape[c]
				D_{50}	D_{90}	
1	Avicel® PH 102	Microcrystalline cellulose	Plastic deformation	84	177	Rod
2	Spherolac® 100	α-Lactose monohydrate	Low fragmentation	118	204	Cube + round
3	Starch 1500®	Pregelatinized starch	Elastic deformation	140	171	Cube
4	Emcompress®	Dicalcium phosphate dihydrate	High fragmentation	81	249	Spherical

[a] As described in the literature.
[b] According to Ph.Eur. [2].
[c] Determined in SEM examination.

the most important factors and quantify their influence (The Unscrambler® 9.7, CAMO AS, Norway). The models were calculated using systematic cross-validation. Jack-knifing was used to estimate the approximate uncertainty variance of the PLS regression coefficients [9]. Further information on the method can be found elsewhere [10,11].

4. Results and discussion

The basic powder characteristics of Avicel® PH 102, Starch 1500®, Spherolac® 100 and Emcompress® are summarized in Tables 2 and 3. According to their size distribution (D_{90} values) the excipients (Table 2) can be arranged in the following order:

$$\text{Emcompress}^{®} > \text{Spherolac}^{®}\ 100 > \text{Avicel}^{®}\ \text{PH}\ 102 \approx \text{Starch}\ 1500^{®}$$

where the D_{90}-values range from 170 to 250 μm. The scanning electron microscopy (SEM) study was carried out to point out differences in the particle morphology and the surface characteristics (Fig. 1 and Table 2). The study showed that Emcompress® consists of microagglomerates, while the particles of the other materials are single entities. Emcompress® showed the highest bulk and tapped densities followed by Spherolac® 100, Starch 1500® and Avicel® PH 102. Lubrication and addition of Emcompress® showed an increment in both densities of plain excipients and their binary mixture (Table 3). Addition of Emcompress® also increased the helium density of blends. The powder flow properties were assessed by HF: a value less than 1.20 indicates good flowability, whereas values higher than 1.50 indicates poor flowability [3]. For all plain excipients, Emcompress® and Avicel® 102 showed the lowest and highest HF value, respectively. Generally, an addition of 1% magnesium sterate improved the flow properties of plain excipient except for Emcompress®. The best flowability, i.e. lowest HF, was found for the combinations of 49% Spherolac® 100 + 50% Emcompress® + 1% MgSt.

Deformation properties were assessed by porosity-pressure profiles. '*In-die*' Heckel analysis method was used for both compression and decompression phase because it is a fast and simple method. Fig. 2 shows a typical Heckel plot for Avicel® PH 102, Starch 1500®, Spherolac® 100 and Emcompress®, respectively. In order to characterize the deformation properties of materials,

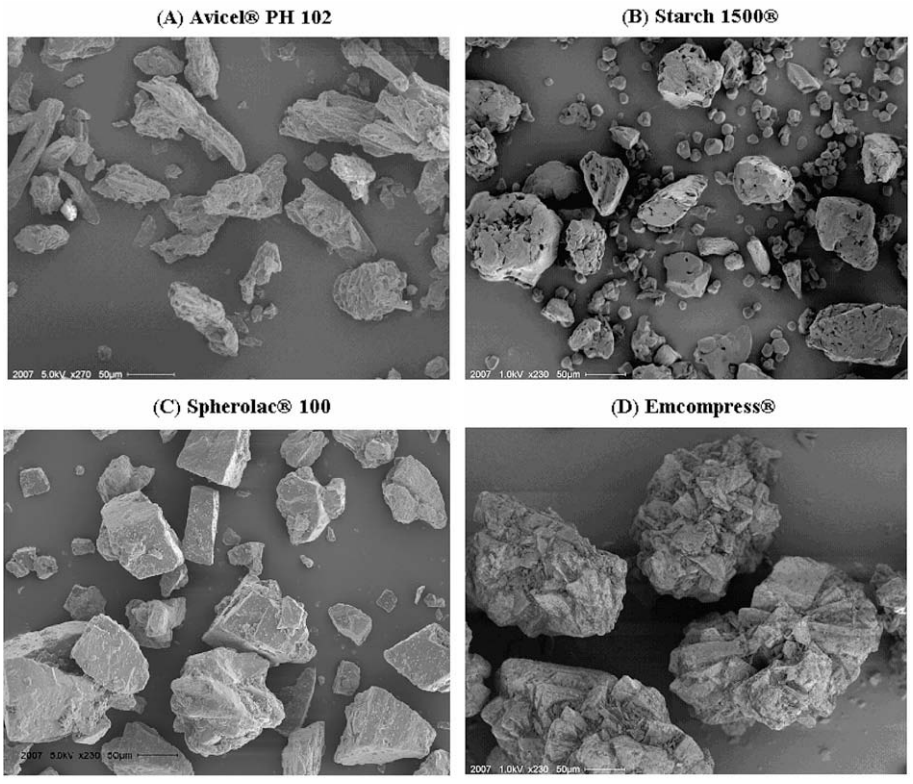

Fig. 1. SEM micrographs for plain excipients (A) Avicel® PH 102, (B) Starch 1500®, (C) Spherolac® 100, (D) Emcompress® (three replicate strokes plotted).

Table 3
Experimental matrix and some responses from the 2^3-full factor designs.

No.	A	B	C	D	Bulk density, g/cm^3	Tapped density, g/cm^3	Helium density, g/cm^3	Hausner ratio (HF)	YPpl, MPa	YPel, MPa	WoC, Nm	WoE, Nm	TS, MPa
1	Avicel® PH 102	10	0	0	0.3603	0.4732	1.558	1.3133	51.81	120.77	7.95	0.63	8.6
2	Avicel® PH 102	50	0	0	0.3603	0.4732	1.558	1.3133	55.33	146.48	8.49	0.68	8.18
3	Avicel® PH 102	10	1	0	0.4045	0.4898	1.5461	1.2109	49.69	104.35	7.66	0.7	4.64
4	Avicel® PH 102	50	1	0	0.4045	0.4898	1.5461	1.2109	51.3	118.82	8.05	0.71	4.52
5	Avicel® PH 102	10	0	50	0.5574	0.7332	1.8945	1.3154	88.49	383.15	6.5	0.6	3.94
6	Avicel® PH 102	50	0	50	0.5574	0.7332	1.8945	1.3154	90.73	408.95	6.7	0.63	3.87
7	Avicel® PH 102	10	1	50	0.6274	0.7282	1.8718	1.1606	71.56	240.77	5.9	0.63	2.26
8	Avicel® PH 102	50	1	50	0.6274	0.7282	1.8718	1.1606	72.71	244.92	6.33	0.67	2.04
9	Avicel® PH 102*	30	0.5	25	0.483	0.6088	1.6949	1.2604	69.3	230.96	7.76	0.58	3.23
10	Avicel® PH 102*	30	0.5	25	0.483	0.6088	1.6949	1.2604	69.46	232.4	7.73	0.57	3.21
11	Avicel® PH 102*	30	0.5	25	0.483	0.6088	1.6949	1.2604	69.91	232.04	7.75	0.58	3.12
12	Spherolac® 100	10	0	0	0.6835	0.8359	1.541	1.223	82.53	251.28	3.77	0.59	1.05
13	Spherolac® 100	50	0	0	0.6835	0.8359	1.541	1.223	86.83	272.74	3.8	0.62	0.93
14	Spherolac® 100	10	1	0	0.7447	0.8676	1.5288	1.165	73.23	193.68	3.42	0.64	0.51
15	Spherolac® 100	50	1	0	0.7447	0.8676	1.5288	1.165	75.67	199.96	3.51	0.66	0.44
16	Spherolac® 100	10	0	50	0.8237	0.9445	1.852	1.1467	89.56	307.1	3.8	0.62	1.2
17	Spherolac® 100	50	0	50	0.8237	0.9445	1.852	1.1467	90.08	311.95	3.88	0.65	1.16
18	Spherolac® 100	10	1	50	0.846	0.9583	1.8337	1.1327	85.35	266.91	3.42	0.63	0.74
19	Spherolac® 100	50	1	50	0.846	0.9583	1.8337	1.1327	86.33	271.59	3.55	0.67	0.66
20	Spherolac® 100*	30	0.5	25	0.773	0.8853	1.6701	1.1453	80.66	244.1	3.65	0.59	0.63
21	Spherolac® 100*	30	0.5	25	0.773	0.8853	1.6701	1.1453	80.33	241.96	3.65	0.6	0.66
22	Spherolac® 100*	30	0.5	25	0.773	0.8853	1.6701	1.1453	80.17	244.13	3.62	0.62	0.66
23	Starch 1500®	10	0	0	0.6378	0.8182	1.499	1.2828	72.8	121.31	4.28	0.7	0.45
24	Starch 1500®	50	0	0	0.6378	0.8182	1.499	1.2828	76.03	134.17	4.37	0.8	0.32
25	Starch 1500®	10	1	0	0.7624	0.9621	1.4898	1.2619	70.54	99.05	3.07	0.8	0**
26	Starch 1500®	50	1	0	0.7624	0.9621	1.4898	1.2619	72.98	108.2	3.16	0.85	0**
27	Starch 1500®	10	0	50	0.8833	1.0802	1.851	1.2229	106.2	286.81	3.77	0.66	0.46
28	Starch 1500®	50	0	50	0.8833	1.0802	1.851	1.2229	110.5	313.49	3.92	0.72	0.43
29	Starch 1500®	10	1	50	0.9903	1.1401	1.8289	1.1513	85.35	187.15	3.03	0.7	0**
30	Starch 1500®	50	1	50	0.9903	1.1401	1.8289	1.1513	88.08	206.03	3.1	0.73	0**
31	Starch 1500®*	30	0.5	25	0.8563	1.0128	1.6507	1.1828	81.73	138.13	3.33	0.71	0**
32	Starch 1500®*	30	0.5	25	0.8563	1.0128	1.6507	1.1828	81.99	137.31	3.32	0.72	0**
33	Starch 1500®*	30	0.5	25	0.8563	1.0128	1.6507	1.1828	82.46	137.43	3.32	0.72	0**
Control experiments													
35	Emcompress®	10	0	100	0.9486	1.1436	2.3692	1.2056	112.7	491.53	3.7	0.61	1.21
36	Emcompress®	50	0	100	0.9486	1.1436	2.3692	1.2056	115.7	499.19	3.86	0.67	1.17
37	Emcompress®	10	1	99	0.9636	1.1604	2.3481	1.2042	103.4	406.53	3.47	0.64	0.98
38	Emcompress®	50	1	99	0.9636	1.1604	2.3481	1.2042	103.7	407.65	3.52	0.67	0.94

Results are given as mean of three measurements.
A = type of excipient, B = punch velocity (mm/s), C = lubricant fraction (%), D = Emcompress® fraction (%), * = centre point three replicate, ** = tablet of insufficient TS was formed, which cannot be taken out of the die.

and subsequent prediction of tablet properties, there is an absolute imperative to have highly accurate and reproducible force–displacement data, which can be obtained, for example, from the compaction simulator used. The plots in Fig. 2 are all depicted in triplicate, which confirms the previously described [8] good reproducibility. The plots are in good agreement with what has been described in the literature for the materials investigated [12]: the predominantly plastically deforming material Avicel® PH 102 is characterized by a high slope of the linear portion of the compression phase (Fig. 2A). However, relatively elastic materials such as Starch 1500® show a higher slope of a linear portion of the decompression phase (Fig. 2B). Emcompress® is an extensively fragmenting material, of which higher initial curvature in a low-pressure region of the Heckel plot is characteristic (Fig. 2D). Spherolac® 100 with less fragmenting propensity shows less initial curvature than Emcompress® (Fig. 2C).

A PCA of all results from the basic powder characteristics as well as the compression characteristics is used to give an overview over groups and the trends in the data (Fig. 3). It is possible to simplify the responses into latent variables (principal components), which explain the main variance in the data. In the present study, the first two principal components were able to describe 45% and 30%, respectively, totally 75% of the variation in the data. Samples and variables located on the same side and same direction of the co-ordinate system formed by the principal components (PCs) are positively correlated, while the ones placed diagonally on the two sides of the origin are inversely correlated. In the score plot shown in Fig. 3A, the data show a distinct grouping related to the different excipients. The loading plot (Fig. 3B) indicates which of the factors is indicative of the grouping. The variables YPpl, YPel, helium density, and particle size are positively correlated along PC1 and inversely correlated to WoC, TS, and HF along the same PC. This means that low particle size and helium density as well as both low plastic and elastic yield pressure (YP) correlate to high tensile strength (TS) and high work of compression (WoC). The addition of Emcompress® caused an increase in the helium density and due to the spherical particle shape, also better flowability, i.e. a reduction in HF. This corresponds to the grouping in the score plot when comparing Fig. 3A and B. Spherical or rounded particles pack more closely than flat or elongated particles, they have less interparticular spaces [13], and show better flowability. Both the control experiments with pure Emcompress® and experiments with a high fraction of Emcompress® within each class of excipients are located towards the lower left corner of the plot. WoE is mainly

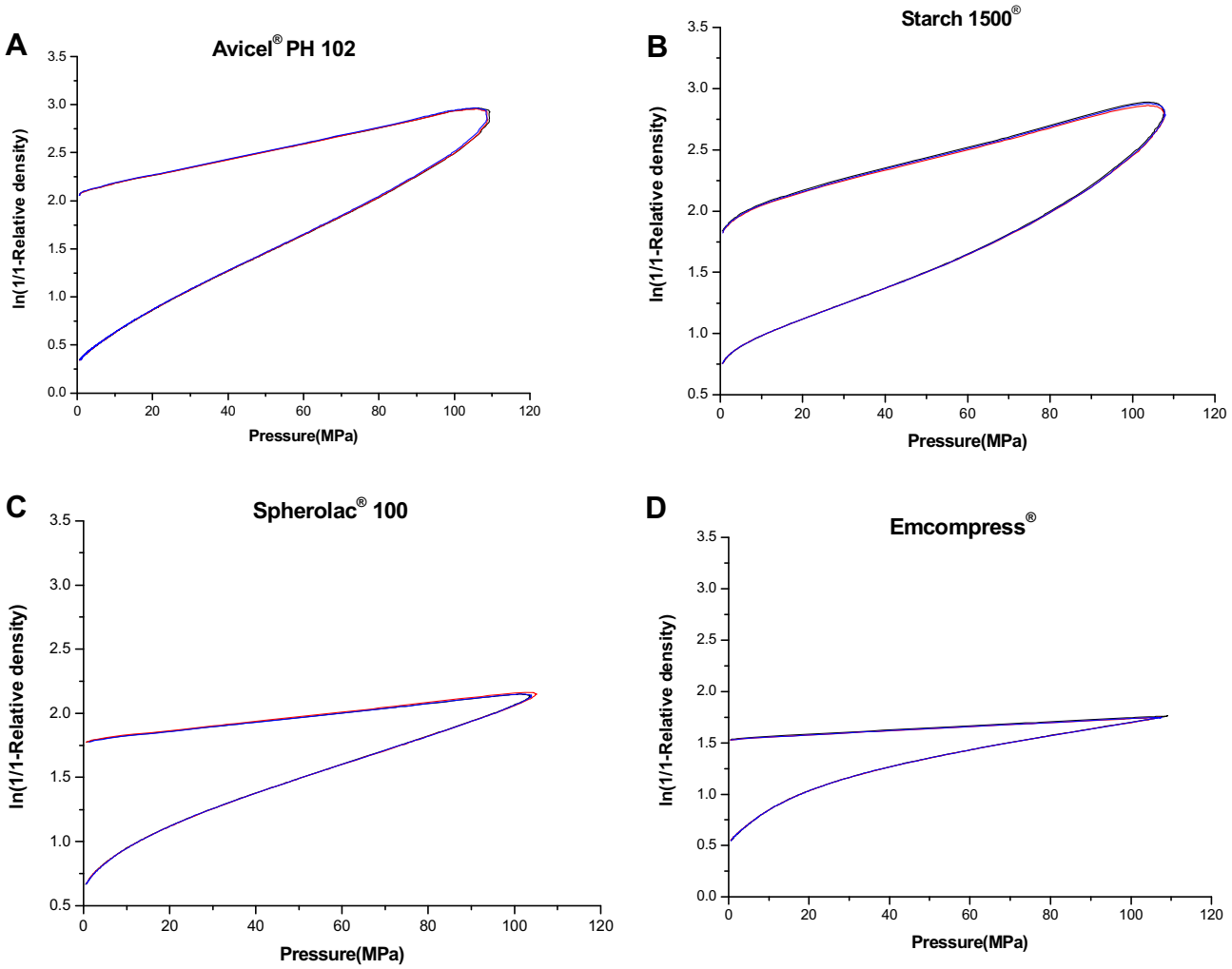

Fig. 2. Heckel plots obtained for plain excipients (A) Avicel® PH 102, (B) Starch 1500®, (C) Spherolac® 100, (D) Emcompress® (three replicate strokes plotted).

explained by PC2 and is inversely correlated to WoC and TS along this component as expected.

The above discussed PCA is made based on results from four excipients, i.e. three of excipients in a 2^3-full factorial design with centre points (Avicel® PH 102, Starch 1500®, Spherolac® 100), and the additional 4 control experiments for Emcompress®. Since Emcompress® also is included as a design variable in the factorial designs for the other excipients this could cause problems with the interpretation. In the following Emcompress® content is treated as a design variable and not as an excipient in order to balance the data matrix, the control experiments are therefore removed before further analysis takes place.

PLS models were developed to determine a quantitative regression between the design variables (*X*-data structure, the *X*-variance) and response variables (*Y*-data structure, the *Y*-variance), which uses the *Y*-data structure in decomposing the *X*-data structure. The regression results were calculated by Martens' uncertainty test [9], which is performed by full cross-validation and based on the Jack-knifing principle. In this method, same samples are used for both model estimation and testing. During this, one sample is kept out of the calibration data set and the model is calibrated on the remaining data points. Then the value for the left out sample is predicted and the prediction residuals are computed. This is repeated until all samples have been kept out once. The respective PLS-2 model for all compression responses is shown in Fig. 4. The model is based on three 2^3-full factorial designs with the three excipients defined as category variables coded 1 and 0. The category variables were split during modeling in order to investigate the influence of each excipient separately. The plot (Fig. 4) indicates the first two PLS-components, which are able to explain 73% (46% and 27%) of the *Y*-variance (response) based on 26% (13% and 13%) of the *X*-variance (design). The influence of the investigated factors on the regression coefficients can be identified in the plot. It is worthy noticing that several factors are located close to the origin. This indicates that those factors are of no relevance in the model, i.e. not significant factors. In the present study, punch velocity and the interactions of punch velocity with fractions of lubricant and Emcompress®, respectively, are found not significant; neither is the square effect of punch velocity nor the square effect of lubricant fraction significant, meaning that no nonlinear behavior was identified. Separate models (PLS-1) were optimized for each of the following responses YPpl, YPel, WoC, WoE and TS. The influence of all regression coefficients ($p < 0.05$) obtained from the PLS-1 models is summarized in Table 4. It should be noted that the explained *X*-variance is quite low for all models (as also for the PLS2 above), whereas the explained *Y*-variance is much higher. The low degree of explanation within *X* is due to the organization of the *X*-matrix. The fact that the different excipients are organized as category variables coded 1 and 0 and a further splitting is performed to achieve the separate effects, results in a forced low degree of the total *X*-matrix utilized to explain most of the variation in the *Y*.

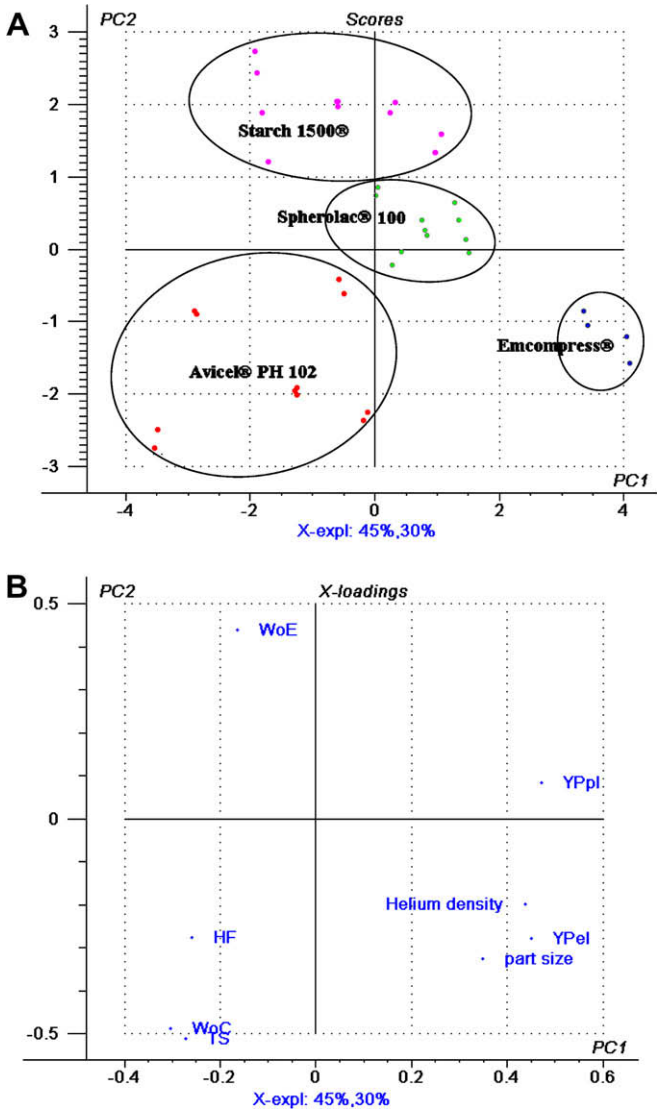

Fig. 3. (A) score plot from PCA of all powder characteristics and compaction characteristics showing grouping of scores representing different materials. The two displayed PCs explain 45% and 30%, respectively. (B) Loading plots from PCA of all powder characteristics and compaction characteristics show the variables explaining the two PCs. The two displayed PCs explain 45% and 30%, respectively.

Employing Avicel® PH 102 as the main excipient result in a large negative regression coefficient for yield pressure value of plastic deformation YPpl, meaning large plastic deformation, whereas no significant influence was found on the YPel. Further Avicel® PH 102 shows a large positive regression coefficient for WoC as well as a large positive coefficient for TS. This corresponds to high work of compaction and strong tablets, whereas work of elastic recovery shows a negative regression coefficient as expected from MCC properties. Avicel® is a microcrystalline cellulose known for high plastic deformation [14]. It has been discussed in the literature that microcrystalline cellulose particles show the presence of slip planes, dislocations and individual microcrystals, which facilitates high degree of plastic deformation [15]. This plastic deformation consumes more energy during compression. Avicel® PH 102 has higher bulkiness than the two other excipients studied (Starch 1500® and Spherolac® 100), probably due to its smaller particle size. Adjacent cellulose particles from MCC may form hydrogen bonding, and during plastic deformation, these hydrogen bonds on the extremely large surface area are brought into close contact, which provides extremely good compactability of MCCs [16]. As a result, the excipient with high bulkiness and plastic deformation requires high WoC and might also produce tablets with high TS.

Spherolac® 100 shows a positive regression coefficient for both YPpl and YPel, which indicates that the material undergoes fragmentation in the compression phase, followed by low elastic recovery in the decompression phase. WoC, WoE and TS all have a negative regression coefficient, which further confirms that there is a low work of compression, less elastic recovery and less strong tablets are formed by using Spherolac® 100. It has been described in the literature that Spherolac® 100 undergoes fragmentation at relatively low compression pressures [17]. Spherolac® 100 also showed relatively high bulk density (i.e. lower bulkiness, Table 3). The powder with lower bulkiness has close initial packing of the particles, which results in a relatively high in-die working density. In conclusion, these powders will acquire less total volume reduction (i.e. low value of WoC). The material undergoing particle fragmentation or an elastic deformation forms weaker inter-particulate bonds than a plastically deforming material, due to creation of small new bonding surface area [18]. This might be a reason for a negative influence of the Spherolac® 100 on the TS.

Finally, Starch 1500® as an excipient of the mixture, resulted in a positive regression coefficient for YPpl and a negative for YPel, meaning that the material shows most elastic deformation of the studied materials. This is also seen in a large positive coefficient for WoE. In the literature, a (slow) plastic deformation followed by pronounced (fast) elastic recovery in the decompression phase is the most prominent feature of the Starch 1500®. These unique properties of the Starch 1500® are recognized in its positive influence on the YPpl and WoE, and negative influence on the YPel. Even the simple "in-die" methods used in this study is able to recognize the elastic recovery of this material. In the PLS-2 model, Starch 1500® is therefore placed close to the WoE parameter. The low plastic deformation tendency can explain the negative influence of the Starch 1500® on the WoC. Starch 1500® may form weaker inter-particulate bonds, due to an extensive elastic recovery in the decompression phase which in turn explains its negative effect on the TS.

As indicated in Fig. 4, neither the investigated design variable punch velocity as main factor nor any of its interactions has significant influence on whether yield pressure (plastic nor elastic deformation) or WoC. This might be due to the selection of a narrow range of this variable in the present study due to technical reasons, and should be kept in mind when designing further studies. However, the punch velocity and its square effect show a positive influence for WoE and TS, respectively (Table 4). This confirms the importance of this design variable in compression studies and the necessity to select an appropriate design space.

The formulation parameter, 'lubricant fraction', showed a significant reduction of the YPpl, YPel, WoC and TS and an increment in the WoE. The lubricant generally reduces inter-particulate friction resulting in better plastic deformation. The elastic recovery of the material in the decompression phase is normally considered as a balance between stored elastic energy for relaxation, and bonds between particles as the counteracting force [19]. However, inter-particulate bonding becomes weaker by lubrication [20]. The weaker inter-particulate bonding yields less resistance to relaxation by elastic recovery in the decompression phase. These can be the possible reasons for the negative influence of high lubricant fraction on the YPpl, YPel, WoC and TS and a positive influence on the WoE.

Finally, the addition of Emcompress® showed an extra large positive influence on the YPpl and YPel. A decrease in the WoE and TS compared to plain excipients was also found. It indicated that excipients mixed with Emcompress® showed reduction in the plas-

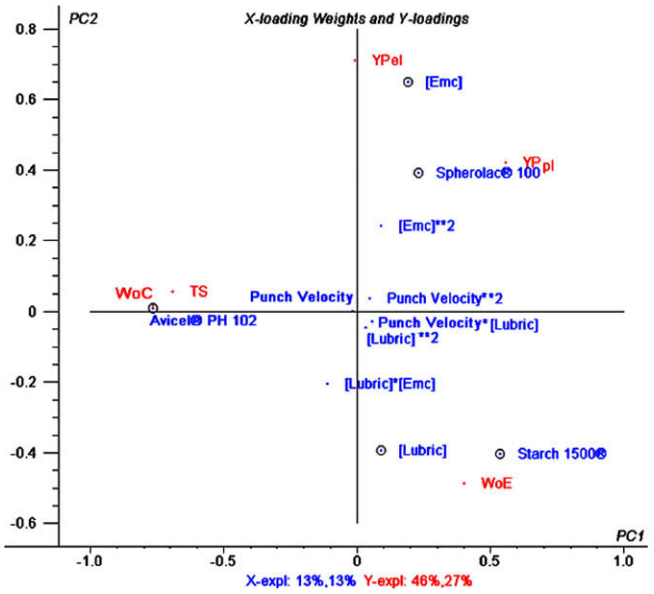

Fig. 4. *X*-loading weights and *Y*-loading plot from a PLS-2 of all compaction responses showing correlation between the variables, their interactions and square effects as well as the excipients investigated [Avicel® PH 102, Starch 1500®, Spherolac® 100]. The two principal components of the plot, PC1 and PC2, together explained 26% and 73% variation in the *X* and *Y*-data, respectively.

Table 4
Trends of the regression coefficients of the design variables, their interaction and square effects on the different response variables obtained in separate PLS-1 models.

Design variables (*X*)	Effect on response variables (*Y*)				
	YPpl	YPel	WoC	WoE	TS
Avicel® PH 102	↓↓	X	↑↑	↓	↑↑
Spherolac® 100	↑	↑	↓	↓	↓
Starch 1500®	↑	↓	↓	↑↑	↓↓
Punch velocity	X	X	X	↑	X
Lubricant fraction	↓	↓	↓	↑	↓
Emcompress® fraction	↑↑	↑↑	X	↓	↓
Punch velocity*[Lubric]	X	X	X	X	X
Punch velocity*[Emc]	X	X	X	X	X
[Lubric]*[Emc]	X	↓	X	X	X
Punch velocity^2	X	X	X	X	↑
[Lubric]^2	X	X	X	X	X
[Emc]^2	X	X	X	X	X
Expl. variance in *X* (%)	39	37	37	40	30
Expl. variance in *Y* (%)	79	77	95	76	82

↑ = positive significance, ↓ = negative significance, ↑↑ = extra large positive significance, ↓↓ = extra low significance, X = not significant coefficient (error bars passing through origin). The significance of regression coefficients has been determined by Jack-knifing and corresponds to $p = 0.05$.

tic deformation and subsequent elastic recovery. Emcompress® is known for its high fragmentation propensity, and undergoes particle fragmentation already in an early stage of the compression phase. It may shield particles of other materials and hamper their original deformation tendency resulting in 'Emcompress® deformation dominance'. The low TS may be the results of Emcompress® dominance. The phenomenon is also confirmed by the close location of the parameters Emcompress® fraction, YPpl and YPel in the *X*-loading weight and *Y*-loadings plot of the PLS-2 (Fig. 4). Similar to Spherolac® 100, Emcompress® shows low WoC, probably because of its high *in-die* working density.

Multivariate analysis tool is also useful to quantify the effect of interaction between the various design variables on the responses. An example is the interaction effect of lubricant and Emcompress® addition showed increased elasticity expressed as negative influence on YPel. This may be explained by better lubricant film formation around the excipient particles in the presence of Emcompress®, due to improved flowability [20] and possibly also due to higher density. In order to investigate this interaction effect in more detail, separate PLS-1 models were optimized for the response YPel for Avicel® PH 102, Spherolac® 100 and Starch 1500®. As can be seen in Table 5, this effect was only prominent for Avicel® PH 102 and not recognized for the two other excipients. This might be due to the greater influence of Emcompress® on the flowability of Avicel® PH 102 (i.e. decrease in HF after Emcompress® addition) compared to the other excipients.

Table 5
Trends of the regression coefficients of the design variables, their interaction and square effects on the response variable YPel obtained in separate PLS-1 models.

Design variables (*X*)	Effect on response variables YPel		
	Avicel® PH 102	Spherolac® 100	Starch 1500®
Punch velocity	X	X	X
Lubricant fraction	X	X	X
Emcompress® fraction	↑↑	↑↑	↑↑
Punch velocity*[Lubric]	X	X	X
Punch velocity*[Emc]	X	X	X
[Lubric]*[Emc]	↓	X	X
Punch velocity^2	X	X	X
[Lubric]^2	X	X	X
[Emc]^2	X	X	X
Expl. variance in *X* (%)	53	55	55
Expl. cariance in *Y* (%)	91	82	82

↑ = positive significance, ↓ = negative significance, ↑↑ = extra large positive significance, ↓↓ = extra low significance, X = not significant coefficient (error bars passing through origin). The significance of regression coefficients has been determined by Jack-knifing and corresponds to $p = 0.05$.

5. Conclusion

This study has shown that it is possible to quantify differences between materials of different deformation nature and their blends by a quick and simple screening method. Well-known descriptors based on the Heckel equation and work-related parameters were used, taking advantage of highly accurate measurement of time-resolved force and displacement data. It was possible to use "in-die" methods for the evaluation of deformation behavior instead of more laborious "out of die" methods. In combination with multivariate evaluation methods such as PCA and PLS, this approach has shown to be successful in distinguishing, quantifying and predicting the compression behavior of pure excipients and binary blends. Well-known behavior and relationships described in the literature were confirmed. Furthermore, the multivariate approach made it possible to identify interactions and nonlinear behavior of the variables. Based on these findings the present approach serves as the first step towards a 'formulation tool' for optimizing tablet properties, for example to balance brittleness and plasticity, with respect to tablet tensile strength. The ultimate goal is to predict compression behavior and tablet properties on industrial scale based on few simple experiments and quick evaluation methods.

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