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Research paper

The difficulty in the assessment of the compression behaviour of powder mixtures: Double layer tablets versus arithmetic additivity rule

Petra M. Belda, Jobst B. Mielck*

Department of Pharmaceutical Technology, Institute of Pharmacy, University of Hamburg, Hamburg, Germany

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Abstract

The weighted arithmetic mean from values of a feature derived from the individual components is often used to calculate the theoretically expected compression behaviour of powder mixtures if no interparticulate interactions between the components occur. Alternatively, simulated and experimental double layer tablets are presented. The suitability of the various methods to serve as a reference for the assessment of the compression behaviour of powder mixtures shall be compared. Narrow and similar sieve fractions of maltitol and metamizol were mixed in various ratios of true volumes. Constant total true volumes of the single substances, powder mixtures, and layered powders of the same composition were compressed on an eccentric tabletting machine to a constant maximum geometric mean punch force. In addition, the compression of double layer tablets was mathematically simulated from the dynamic relative density–force data of the pure materials. At a given momentary force, the relative density of a simulated double layered powder bed is given by the harmonic mean of the relative density values of the pure materials weighted by their true volume fractions. The results show that the total, the net, and the expansion work change indeed almost linearly with the true volume fraction of the components in the double layer tablets, with the consequence that the plasticity index (=net work/total work × 100) proceeds non-linearly. The slope of the Heckel plot 'at pressure' and the apparent mean yield pressure obtained from these Heckel data are non-linearly related to the true volume fraction. If the weighted arithmetic mean is used to analyse the compression behaviour of the powder mixtures, results are obtained which are incompatible or even contradictory between interrelated features. On the other hand, the double layer model provides a consistent evaluation. A good agreement between the results of the experimental and the simulated double layer tablets is found.

Keywords: Tabletting of powder mixtures; Double layer tablets; Relative density; Work of compression; Heckel parameters

1. Introduction

The preparation of tablets composed of two or more components is still an interesting area in pharmaceutical technology. Due to physical interactions between the components, positive or negative effects in the tabletting behaviour of powder mixtures may be obtained. In his literature review, Fell observed a variety of relationships between component proportion and compaction features like the tablet strength [1]. However, the complexity of the systems and the influence of experimental variables made it difficult to deduce inherent behavioural patterns. So, he recommended the use of at least well defined materials of simple reproducible shape and size distribution.

Due to the inevitable diversity in experimental conditions and in analysis methods, there arises another demand, namely to properly define which relationship between the component proportion and the feature is theoretically expected if no interparticulate interaction between the components occurs. This is an important aspect because the theoretically expected behaviour serves as a reference for the assessment of the experimental results. It is usually computed by arithmetic additivity. From the force and/or displacement data sampled when the components were compressed separately, the values of a characteristic feature, e.g. the work of compression, are calculated. These values are weighted by the mass or true volume fraction of

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* Corresponding author. Department of Pharmaceutical Technology, Institute of Pharmacy, University of Hamburg, Bundesstrasse 45, D-20146 Hamburg, Germany. Tel.: +49 40 42838 3479; fax: +49 40 42838 6573.
E-mail address: mielck@chemie.uni-hamburg.de (J.B. Mielck).

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the components in the mixture and then simply added up. Of course, this is an easy method. But what is the meaning behind it? Is this method so fundamental that it can be applied as a reference relationship generally to all features under any experimental condition? Only few examples could be found in the literature where the reference behaviour presented is mathematically or physically deduced.

Leuenberger [2] investigated the compressibility and compactibility of powders and powder mixtures. He developed an equation including both, the compactibility, described by the maximal possible deformation hardness $P_{\max}$, and the compressibility, represented indirectly by the compression susceptibility γ. Based on mathematical considerations he concluded that, for a binary system, γ is given by the weighted arithmetic mean from the individual components while $P_{\max}$ is calculated by the weighted geometric mean if no interaction occurs between the components. Thus, for $P_{\max}$ a non-linear relationship with mixture composition is expected even if the materials do not interact. However, no definite statement is given by which quantity the portions of the components should be specified.

Führer and Schmidt [3] prepared binary mixtures from several pharmaceutical excipients in varying mass fractions with a small constant amount of lubricant. The mixtures were compressed to a constant punch force. In a first series, the filling volume of the powder was held constant, while in a second series constant true volumes of material were tabletted. In addition, various masses of the single excipients were compressed to the same maximum punch force to derive a relationship between the powder mass and the net energy for each of the excipients. These individual relationships were used to calculate the reference values by adding up the energies related to the actual masses of the components in the mixture. The dependency between the reference values and the mass fraction of the components was in many cases non-linear. However, due to friction and surface effects, a small portion of material compressed separately may not exactly reflect the behaviour of a small portion within a big tablet. A further drawback of this method is that the rule of additivity must be known a priori.

Ramaswamy et al. [4] compressed binary mixtures of several organic and inorganic substances to graded maximum pressures. They considered volume to be an additive property if each component behaves independently from the other in mixture.

$$V_{\mathrm{mix}} = V_{\mathrm{A}} + V_{\mathrm{B}} \tag{1}$$

$$\frac{v_{\mathrm{mix}}}{1-\varepsilon_{\mathrm{mix}}} = \frac{v_{\mathrm{A}}}{1-\varepsilon_{\mathrm{A}}} + \frac{v_{\mathrm{B}}}{1-\varepsilon_{\mathrm{B}}} \tag{2}$$

where V is the compact volume, v is the true volume of the material, and ε represents the porosity of the compact. Eq. (2) means that the relative density $(1-\varepsilon)$ of the tablets from the mixtures compressed to a given maximum pressure can be computed theoretically by the harmonic mean weighted by the true volume fractions of the components. However, from a mathematical simplification they concluded that the porosity of a compact is obtained approximately from the weighted arithmetic mean if the components do not interact. The experimentally derived porosity of tablets from powder mixtures was then compared to the porosity calculated this way and a good agreement was found.

It is obvious from Eq. (2) that the arithmetic mean fails with a comparatively simple quantity like the relative density (1–ε). So, what mathematical relationship will be obtained if for example logarithmic transformations of the displacement are used for data analysis, e.g. the Heckel function [5] (see Eq. (6) in the following)? Even for the porosity, a quite simple quantity, Ramaswamy et al. [4] obtained an additivity rule only approximately by mathematical simplifications. Therefore, it may be difficult to theoretically deduce additivity rules for other features.

The attempt of Ramaswamy et al. [4] is the simplest method to model an ideal mixture where the components do not interact [6]. While the idea of an ideal mixture is less clearly reflected by Eq. (1), this model can be easily visualised as a system where the components are not statistically distributed within the powder bed but separated as bulk in two compartments, namely in two horizontal layers (Fig. 1). During compression, both layers reduce in volume according to their individual resistance to densification. At every moment during compression an equilibrium establishes between the layers with respect to the resistance to densification. This means, at every moment each layer is densified to an extent that equal forces act in both layers. Thus, strictly speaking, the components do not densify independently from each other. But the interaction is limited to a macroscopic scale, to a level that must be expected.

From a physical point of view, the model described above couples the components in series with respect to the direction of the applied force. This arrangement of the components describes a pliable system where the components can accommodate in concert with each other to

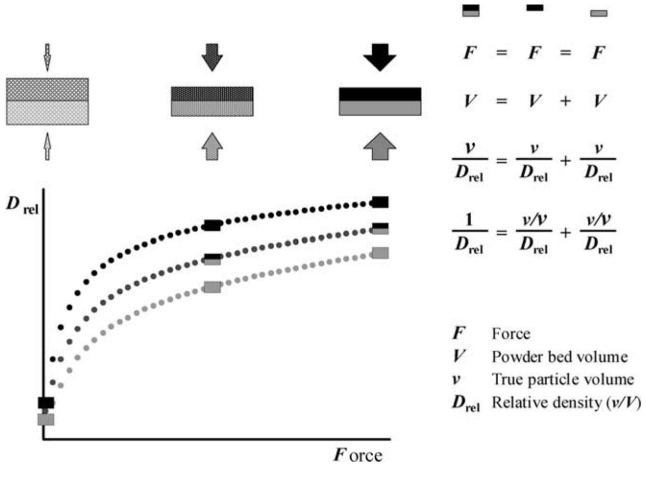

Fig. 1. The double layer model.

the constraint. This leads to a force balance between the layers. In contrast, one can also imagine the components arranged in parallel as powder columns. However, this model requires that the columns are rigid against the constraint so that each column can bear the load on its own. Otherwise, the columns would deform radially during compression thus pressing against the neighbouring column. If the columns interact this way, the originally parallel model turns into a serial model, however, with the radial pressure of the columns in equilibrium. So, only at high densification, when the ability to yield is restricted by the dense structure of the powder bed, the parallel model may become important.

Ramaswamy et al. [4] applied their model originally to the porosities of the ejected tablets. However, from the above considerations it is obvious that this model can be easily adapted to the compression event itself. From the force and the displacement data sampled during compression of the pure materials, the resulting course of the densification of a layered system can be simulated for the compression process using Eq. (2). Features such as the slope of the Heckel plot ‘at pressure’ [5] can be calculated from these profiles in the usual way. Thus, it is not necessary to deduce mathematical additivity rules for each feature in order to describe the compression behaviour theoretically expected for a powder mixture. As the contact area between the components is very small in such a layered system, the possibility of interparticulate interactions between the components is also small. Then, it becomes possible to realise the model experimentally by double layer tabletting, however, without the pre-compression of the first layer. The values of a feature obtained from simulated or experimental double layer tablets may then serve as reference values for the assessment of the compression behaviour of binary powder mixtures of the same compositions instead of an arbitrarily chosen arithmetic mean.

The aim of this study is to compare the values of features obtained from simulated and from experimental double layer tabletting with their respective commonly used weighted arithmetic mean values. In addition, the various references will be used to evaluate the compression behaviour of binary powder mixtures. From the results it shall be deduced which of the reference methods provides a suitable basis for the assessment of the compression behaviour of powder mixtures.

2. Materials and methods

2.1. Materials

Crystalline maltitol (Maltisorb P200®, Roquette Freres, Lestrem, France, batch E956N) and crystalline metamizol sodium monohydrate (Metamizol-Natrium T $1H_20$, Fährhaus Pharma GmbH, Hamburg, Germany, batch FP02259M) were used as components. Magnesium stearate (Riedel-de Haen AG, Seelze, Germany, Lot 91320) was used as external lubricant.

2.2. Sieving

Narrow particle size fractions of 0.100–0.125 mm were prepared by air jet sieving (A200LS, Alpine AG, Augsburg, Germany). Samples of 5–10 g were sieved for 5 min at 1500–2500 Pa subpressure.

2.3. True density

The sieved materials were dried one day over silica gel. The true densities of three samples of maltitol (84–91 g) and of two samples of metamizol (72 g) were determined by Helium pycnometry (Stereopycnometer SPY-2, Quantachrome Corp., Syosset, NY, USA) at a room temperature of 20–23 °C. Each sample was analysed in triplicate.

True densities of 1.615 ± 0.012 and 1.415 ± 0.011 g/cm^3 were obtained for maltitol and metamizol, respectively. The standard uncertainty considers the standard deviation of the mean of repeated measurements as well as the specifications of the pycnometer and of the analytical balance (AE 166/9, Mettler, Gießen, Germany) according to DIN 1319-4 [7].

2.4. Particle volume

Two samples of each of the sieved materials were dispersed on slides and the number of particles was determined from pictures taken with an image analysis system (KS400 software, Matrox Meteor RGB framegrabber, 3-CCD Hitachi colour camera HV-C20, Carl Zeiss Vision GmbH, Hallbergmoos, Germany) at low magnification (Micro-Nikkor objective, 55 mm, 1:3.5, Nikon).

From the weight of the samples (1.6–2.7 mg), their true density, and the number of particles, the particle volume was calculated to be 1.00 ± 0.03 and 0.88 ± 0.02 nl for maltitol and metamizol, respectively. The given standard uncertainty according to DIN 1319-4 [7] considers the standard deviation of the mean of repeated measurements, the specifications of the analytical balance (1712 MP8, Sartorius GmbH, Göttingen, Germany) and a possible counting error.

2.5. Mixing

Maltitol and metamizol were combined to binary powder mixtures in percentages by true volume ranging from 90 to 10% in steps of 10% using a tumbling mixer (Turbula T2A, W. Bachofen, Basle, Switzerland). Total masses corresponding to 12 times the target tablet weight were filled into 12 ml vials and mixed for 30 min at 54 rpm. Each mixture was prepared twice.

2.6. Tabletting

An eccentric tabletting machine (Hanseaten Exacta E1, W. Fette, Schwarzenbek, Germany) was used, equipped with sharp-edged punches of 10 mm diameter. The filling depth was set to 11 mm. The machine was instrumented with two inductive displacement transducers for the measurement of the distance between the punches. Piezoelectric load washers were installed for the measurement of the upper and lower punch forces. The instrumentation, their qualification, and their calibration is described in detail elsewhere [8–10].

The die wall was lubricated externally with magnesium stearate applied on a rotating felt point of a dental technique instrument (Contra Angle 1:1, 30,000 rpm with Bravo TD motor, Hager & Werken GmbH & Co. KG, Duisburg, Germany) for 10 s at 10,000 rpm. Powder samples were weighed on an analytical balance (AE 166/9, Mettler) and filled manually into the die. The total powder mass in the die corresponded to a true volume of 0.2356 ± 0.0003 cm^3 (target ± range). The surface of the powder bed was carefully flattened with a Teflon®-punch. When double layer tablets were prepared, the powder bed was flattened twice, after the first layer was poured in and after the second one. In order to avoid artefacts due to the uneven stress distribution within the powder bed caused by die wall friction, half of the experiments with double layer tablets were conducted with maltitol as the lower layer and the other half of the experiments with maltitol as the upper layer. In addition, pseudo double layer tablets were tabletted as a control. They were composed of equal parts of the same component but filled into the die in two separate layers. Each layer was flattened as described above.

The powders were compressed at 30 strokes per min to 10.0 ± 0.1 kN (target ± range) maximum geometric mean punch force in sets of four successive tablets. Tablets of the single substances, freshly prepared powder mixtures, and double layer tablets with the same composition as the powder mixtures were prepared. All tablets were prepared from the sieve fraction 0.100–0.125 mm. The experiments were carried out in random order. After the first block of experiments was finished, all trials were repeated again in random order. New powder mixtures were prepared for the second block. All experiments were performed in an air-conditioned room at 22–23 °C and 48–50% r.h.

During tabletting 700 sets of data were recorded at 1.5 kHz using a data acquisition device with a 16-bit A/D-converter (PCI-MIO-16XE-10, National Instruments, Munich, Germany) and LabVIEW software (version 5.1, National Instruments).

2.7. SEM

Samples of powders and broken tablets were sputtered with gold and examined with a scanning electron microscope (Leo 1525, Leo, Oberkochen, Germany) at 5 kV.

2.8. Data analysis

2.8.1. Compression profiles

Data analysis was performed with LabVIEW (version 5.1, National Instruments). The displacement signals were transformed to punch separation corrected for punch deformation and to relative density (D_{rel}), which is the quotient of the true particle volume (v) and the powder bed volume (V).

$$D_{\mathrm{rel}} = \frac{v}{V} = \frac{m/\rho}{\Pi r^2 s} \qquad (3)$$

where m is the tablet weight, ρ the true density, r the radius of the die, and s the punch separation.

From the upper and lower force signals, geometric mean punch forces and geometric mean punch pressures were calculated. The geometric mean punch force was chosen to reduce the influence of the die wall friction on the results. These data are called the 'original data' in the following.

While the original data are evenly spaced with respect to time, the construction of the profiles of simulated double layer tablets needs data that are evenly spaced with respect to force and that have identical force levels. So, a ramp was generated for the force that starts at 75 N, increases in steps of 50 N up to maximum force, and then decreases in steps of 50 N until it reaches 75 N again at the end of the profile. To aid the subsequent interpolation procedure, the noise in the original force and displacement data was smoothed by means of a finite impulse response windowed low pass filter. Relative densities were calculated from the smoothed displacement. The relative densities corresponding to the force ramp were then obtained by linear interpolation. The pressure was computed from the evenly spaced force, and the punch separation from the interpolated relative density. These profiles are called 'interpolated data'. This procedure was applied to all tablets.

2.8.2. Simulated double layer tablets

The interpolated data of the geometric mean force and the relative density from the pure materials were used to simulate the relative density of tablets where the materials are combined in separate horizontal layers. In such an imaginary layered powder bed each layer is densified to an extent that equal forces act in both layers at every moment during compression. The relative density (D_{rel}) of the whole powder bed at a given force level is then calculated as the harmonic mean of the relative density of the single layers A and B weighted by the true volume fractions (c) of the layers.

$$D_{\mathrm{rel,AB}} = \frac{1}{\frac{c_{\mathrm{A}}}{D_{\mathrm{rel,A}}} + \frac{c_{\mathrm{B}}}{D_{\mathrm{rel,B}}}} \qquad (4)$$

This formula is derived from Eq. (2) by substituting $(1-\varepsilon)$ by D_{rel} and by division by v_{mix}, with v/v_{mix} being the true volume fraction c. The same true volume fractions that were used for the experimental double layer tablets were chosen for the simulated ones. Only data sets of the pure materials that have exactly the same interpolated maximum force can be combined in pairs to perform the simulation.

2.8.3. Parameters describing the compression behaviour

Characteristic parameters describing the tabletting process were computed from the original and the interpolated data. All calculations were limited to the data within contact time, namely the time span where the force is equal to or higher than 75 N.

From the geometric mean punch force–punch displacement curves, the total work of compression at minimum punch separation, the net work at the end of contact time, and the expansion work (= net work − total work) were calculated by integration using the trapezoidal rule. It was shown by numerical simulation that the trapezoidal rule can account for the curvature of the force–punch separation profiles with an accuracy of 0.0002 J. The work parameters were expressed as absolute values. The plasticity index according to Stamm and Mathis [11] was computed by Eq. (5).

$$\text{Plasticity} = \frac{\text{net work}}{\text{total work}} \times 100 \qquad (5)$$

Heckel [5] found that the course of the densification with pressure of metal powders can be described by a linear function if the relative density is transformed logarithmically (Eq. (6)). A more or less linear dependency can usually also be found with pharmaceutical materials. The slope K_{Heckel} of a sufficiently linear region in the increasing part of the Heckel plot ‘at pressure’ was obtained by linear regression.

$$\ln \frac{1}{1 - D_{\mathrm{rel}}}(p) = K_{\mathrm{Heckel}} p + A \qquad (6)$$

where D_{rel} is the relative density and p is the geometric mean punch pressure. The linear range was located by firstly determining the interval with the smallest slope in the upward part of the Heckel plot. Successive intervals of 40 data points were cut out from the interpolated profiles. The intervals overlapped by 35 values. The interval length was reduced to 20 values regarding the original and the smoothed data in order to account for the variation in the density of the data points. The intervals overlapped by 15 data points. Linear regression was performed within each interval. From the interval with the smallest slope, the mean absolute deviation from the regression line was calculated. All data points in the upward part of the plot that differ from this regression line by less than the mean deviation multiplied by a tolerance factor of 25 and that form a successive series were considered to be within the linear range. The robustness of this method was checked by varying the tolerance factor by ±10. This changed the Heckel slope and the apparent mean yield pressure of the interpolated data by about ±0.6%.

The so-called apparent mean yield pressure, p_{yield}, was estimated from the inverse Heckel function, where the pressure is the dependent variable.

$$p\left(\ln \frac{1}{1 - D_{\mathrm{rel}}}\right) = p_{\mathrm{yield}} \ln \frac{1}{1 - D_{\mathrm{rel}}} + B \qquad (7)$$

The linear regression was performed over the same linear region as in case of the normal Heckel plot. However, it is questionable whether the apparent mean yield pressure can really provide a measure of the yield strength of the material compressed [12].

2.8.4. Uncertainty of measurement

The standard deviation of the mean of 8 repeated tabletting experiments was calculated for the parameter values and used for a t-test ($\alpha = 0.05$). Additionally, the standard uncertainty was computed according to the German norm DIN 1319-4 [7]. The standard uncertainty (u) presented considers not only the standard deviation of the mean but also the uncertainty derived from the calibration and validation of the measuring devices and, if involved, the uncertainty for the parameters resulting from curve fitting. An in-depth description and discussion of the methods used in DIN 1319-4 [7] is given by Weise and Wöger [13]. In brief, random and systematic uncertainties were handled in a consistent way based on Bayesian statistics and on the principle of maximum entropy as variances of normal and rectangular probability distributions, respectively. By propagation of the uncertainties, it is thus possible to include random as well as systematic uncertainties known from preceding experiments in the results of the actual tabletting experiments. As far as possible, the propagation of the uncertainties was done by means of the partial derivatives. In case of linear regression or non-linear curve fitting, the change in the coefficients of the function with changes in the values of the dependent and independent variables was determined numerically.

In line with the Bayesian theory of measurement uncertainty, Weise and Wöger recommended a factor of $\beta^2 = 2$ for a critical comparison between results so that

$$|x_1 - x_2| \le \beta \sqrt{u^2(x) + u^2(x_2)} \qquad (8)$$

This strict significance test needs no choice of a probability.

Recently, Belda and Mielck [14] published an evaluation of these methods with respect to the analysis of some characteristic tabletting parameters, some of which were selected for the present study as well.

3. Results and discussion

3.1. Compression behaviour of single components

Both model substances selected are crystalline materials. Maltitol has a more isotropic particle shape, while metamizol is more elongated. Column-shaped and plate-like metamizol particles with a layered structure were observed by SEM. The shape of the maltitol particles is less well defined. A few crystals with a pyramidal or octahedral habit were found besides crystal lumps. However, the particle volumes of both substances are quite similar, 1.00 ± 0.03 and 0.88 ± 0.02 nl for maltitol and metamizol, respectively. Despite the difference in the shape of the particles, the packing at the beginning of contact time is similar for both materials. Initial relative densities of 0.513 and 0.548 were observed for maltitol and metamizol, respectively. However, the arrangement of the particles will change when they are deformed during compression, in fact in a different manner for each material.

Preliminary tabletting experiments to constant levels of maximum relative density using a slightly coarser sieve fraction (0.125–0.180 mm) revealed that maltitol behaves similar to α-lactose monohydrate during tabletting with respect to its kinetic and dynamic profiles. Only a slightly higher resistance to densification and lower elastic recovery were found for maltitol compared to lactose. Therefore, maltitol may deform similar to lactose with its initially brittle behaviour and its transition to ductile deformation when comminution proceeds [15]. Metamizol, on the other hand, is much more easily densified than maltitol. In the literature, metamizol is described as a ductile material by Jetzer and Leuenberger [16]. This deformation mechanism was deduced from the relation between the Brinell hardness and the tensile strength of tablets. The intensive fragmentation of maltitol and the plastic deformability of metamizol with a tendency to twin formation were confirmed by SEM.

Table 1 lists the parameter values obtained for the substances when compressed to 10 kN maximum pressure. The high maximum relative density, the low apparent mean yield pressure, and the low work needed to densify metamizol give evidence of its easy deformability. However, due to the high degree of densification of 97%, the metamizol tablets tend to recover elastically. The expansion work is twice as high for metamizol compared to maltitol and the plasticity index, which characterises the fraction of the effectively used energy, is comparatively low.

3.2. Compression behaviour of two-component systems

Two methods are proposed to calculate the theoretically expected value of a feature if no interparticulate interactions between the components of a powder mixture occur during compression: the weighted arithmetic mean on the one hand and the double layer system on the other. Fig. 2 compares the parameter values of the powder mixtures with the different reference systems. For clarity, the bars of standard uncertainty are omitted but the statistical evaluation by the *t*-test is indicated. A detailed statistical comparison between the data is given in Tables 2 and 3. As a control, the border points of the experimental double layer tablets (0 and 100%) contain the data of the double layer tablets composed of equal portions of the same substance.

3.2.1. Maximum relative density

In Fig. 2(a) it can be seen that the maximum relative density of the simulated and the experimental double layer reference tablets is lowered compared to the weighted arithmetic mean. The double layer systems differ significantly from the arithmetic mean if analysed by the *t*-test. If the statistical comparison is extended to include the uncertainty of the measuring instruments, the deviation is not significant (Table 2: SimRef–AMean, ExpRef–AMean). However, a systematic deviation from the arithmetic mean must be expected since the relative density is given theoretically by the weighted harmonic mean (Eq. (4)). Nevertheless, if the maximum relative density is closely examined, there is even a slight but not significant deviation from the harmonic mean of up to 0.00016. This deviation results from the individual relaxation behaviour of the formulations. The consequence of the relaxation is that the maximum relative density takes place at slightly different

Table 1

Values of characteristic parameters and their standard uncertainty, for constant true volumes of the single substances and some powder mixtures (MixTab) compressed to constant maximum geometric mean punch force, and for the corresponding simulated double layer tablets (SimRef)

Parameter[a]	Maltitol	80 + 20[b]		50 + 50		20 + 80		Metamizol
		MixTab	SimRef	MixTab	SimRef	MixTab	SimRef	
$F_{\max}$ (kN)	9.99 ± 0.02	9.98 ± 0.01	9.99 ± 0.02	9.98 ± 0.01	9.99 ± 0.02	9.99 ± 0.02	9.99 ± 0.02	9.99 ± 0.02
$s_{\min}$ (mm)	3.449 ± 0.002	3.360 ± 0.002	3.376 ± 0.001	3.235 ± 0.002	3.266 ± 0.001	3.135 ± 0.002	3.155 ± 0.001	3.082 ± 0.002
$D_{\mathrm{rel,max}}$	0.870 ± 0.007	0.893 ± 0.006	0.889 ± 0.006	0.927 ± 0.006	0.919 ± 0.005	0.957 ± 0.007	0.951 ± 0.006	0.974 ± 0.008
W_{total} (J)	5.16 ± 0.02	4.82 ± 0.02	4.76 ± 0.01	4.23 ± 0.01	4.17 ± 0.01	3.59 ± 0.02	3.58 ± 0.01	3.19 ± 0.02
W_{net} (J)	5.00 ± 0.01	4.63 ± 0.01	4.57 ± 0.01	3.98 ± 0.02	3.92 ± 0.01	3.29 ± 0.02	3.27 ± 0.01	2.84 ± 0.01
W_{exp} (J)	0.16 ± 0.01	0.19 ± 0.01	0.19 ± 0.00	0.25 ± 0.01	0.24 ± 0.00	0.30 ± 0.01	0.30 ± 0.01	0.34 ± 0.01
Plasticity (%)	97.0 ± 0.5	96.0 ± 0.5	96.0 ± 0.5	94.2 ± 0.7	94.1 ± 0.5	91.6 ± 0.7	91.5 ± 0.6	89.2 ± 0.8
K_{Heckel} (10^{-3} MPa^{-1})	6.5 ± 0.3	7.4 ± 0.4	7.0 ± 0.3	9.4 ± 0.5	8.3 ± 0.4	12.1 ± 1.1	11.0 ± 0.9	14.8 ± 2.1
p_{yield} (MPa)	155 ± 7	136 ± 6	142 ± 6	107 ± 6	120 ± 6	83 ± 8	91 ± 8	68 ± 9

$F_{\max}$, maximum geometric mean punch force; $D_{\mathrm{rel,max}}$, maximum relative density; $s_{\min}$, minimum punch separation; W_{total}, total work; W_{net}, net work; W_{exp}, expansion work; plasticity index = net work/total work × 100; K_{Heckel}, slope of the Heckel plot; p_{yield}, apparent mean yield pressure.

[a] The parameter values were derived from the data profiles interpolated from forces and relative densities during tabletting.

[b] True volume fraction of maltitol and metamizol, respectively, in maltitol–metamizol tablets (%).

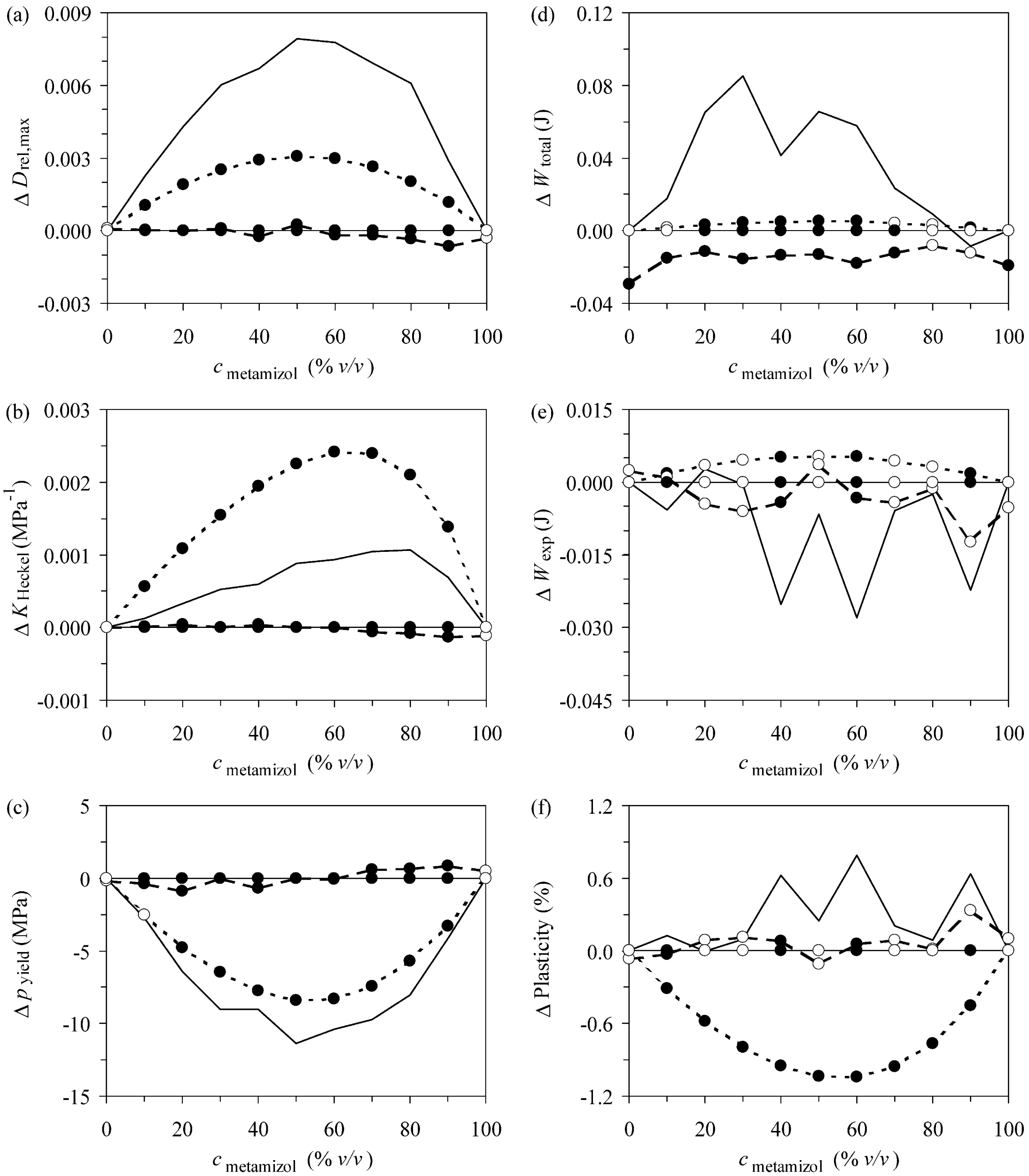

Fig. 2. Difference between the maltitol–metamizol tablets and the simulated double layer tablets (base line) in dependence on the true volume fraction of metamizol. (—) Tablets from the powder mixtures, (– –) experimental double layer tablets, and (- - -) weighted arithmetic mean from the one-component tablets. (●) Significantly and (○) not significantly different from the tablets from the powder mixtures (*t*-test, $\alpha = 0.05$). Parameter values were derived from the data profiles interpolated from forces and relative densities during compression to 10 kN maximum geometric mean punch force. (a) Maximum relative density, $D_{\text{rel,max}}$, (b) slope of the Heckel plot, K_{Heckel}, (c) apparent mean yield pressure, p_{yield}, (d) total work, W_{total}, (e) expansion work, W_{exp}, and (f) plasticity index (=net work/total work × 100).

forces for each formulation (e.g. 9.3 and 9.8 kN for maltitol and metamizol, respectively). If this occurs, Eq. (4) is strictly speaking not valid with respect to the maximum relative density since it assumes equal forces.

The densification of the powder mixtures is significantly enhanced compared to the double layer systems (Fig. 2(a)). At low volume fractions of maltitol or metamizol, the increase in the maximum relative density is steep. Between 30 and 80% of metamizol, the change in the enhancement of the maximum relative density with mixture composition levels out. As the uncertainty of the true density influences the standard uncertainty to a great extent, all effects are only significant with respect to the *t*-test (Table 3: MixTab–SimRef, MixTab–ExpRef). If the minimum punch separation is taken as a measure of volume reduction, the deviation of the powder mixtures from the double layer tablets is significant with respect to both tests (data not shown). However, if the maximum relative density of

Table 2
Statistical comparison between the reference systems by the *t*-test ($\alpha = 0.05$) and the significance test according to Eq. (8) (first sign and second sign, respectively)

Parameter[a]	Systems	Significance[b]										
		0[c]	10	20	30	40	50	60	70	80	90	100
$D_{rel,max}$	SimRef–AMean	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	ExpRef–AMean	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	ExpRef–SimRef	− −	− −	− −	− −	− −	− −	− −	− −	− −	+ −	− −
K_{Heckel}	SimRef–AMean	− −	+ −	+ +	+ +	+ +	+ +	+ +	+ +	+ −	+ −	− −
	ExpRef–AMean	− −	+ −	+ +	+ +	+ +	+ +	+ +	+ +	+ −	+ −	− −
	ExpRef–SimRef	− −	− −	+ −	− −	− −	− −	− −	− −	− −	+ −	− −
p_{yield}	SimRef–AMean	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	ExpRef–AMean	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	ExpRef–SimRef	− −	− −	+ −	− −	− −	− −	− −	− −	− −	+ −	− −
W_{total}	SimRef–AMean	− −	− −	− −	− −	− −	− −	− −	− −	− −	− −	− −
	ExpRef–AMean	+ −	− −	+ −	+ −	+ −	+ −	+ +	− −	− −	+ −	+ −
	ExpRef–SimRef	+ −	− −	− −	− −	− −	− −	+ −	− −	− −	− −	+ −
W_{exp}	SimRef–AMean	− −	− −	+ −	+ −	+ −	+ −	− −	− −	− −	− −	− −
	ExpRef–AMean	− −	− −	+ −	+ +	+ −	− −	− −	− −	− −	+ +	− −
	ExpRef–SimRef	− −	− −	+ −	+ −	− −	− −	− −	− −	− −	− −	− −
Plasticity	SimRef–AMean	− −	+ −	+ −	+ −	+ +	+ +	+ −	+ −	+ −	+ −	− −
	ExpRef–AMean	− −	+ −	+ −	+ −	+ +	+ −	+ −	+ −	+ −	+ −	− −
	ExpRef–SimRef	− −	− −	+ −	+ −	− −	− −	− −	− −	− −	− −	− −

$D_{rel,max}$, maximum relative density; K_{Heckel}, slope of the Heckel plot; p_{yield}, apparent mean yield pressure; W_{total}, total work; W_{exp}, expansion work; plasticity index = net work/total work × 100. SimRef, simulated double layer reference tablets; ExpRef, experimental double layer reference tablets; AMean, weighted arithmetic mean from the one-component tablets.

[a] The parameter values were derived from the profiles interpolated from forces and relative densities during tabletting to 10 kN maximum geometric mean punch force.

[b] +, significantly different; −, not significantly different.

[c] True volume fraction of metamizol in maltitol–metamizol tablets (%).

Table 3
Statistical comparison between the tablets from the powder mixtures and the reference systems by the *t*-test ($\alpha = 0.05$) and the significance test according to Eq. (8) (first sign and second sign, respectively)

Parameter[a]	Systems	Significance[b]										
		0[c]	10	20	30	40	50	60	70	80	90	100
$D_{rel,max}$	MixTab–SimRef	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	MixTab–ExpRef	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	MixTab–AMean	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
K_{Heckel}	MixTab–SimRef	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	MixTab–ExpRef	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	MixTab–AMean	− −	+ −	+ −	+ −	+ +	+ −	+ −	+ −	+ −	+ −	− −
p_{yield}	MixTab–SimRef	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	MixTab–ExpRef	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
	MixTab–AMean	− −	− −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	+ −	− −
W_{total}	MixTab–SimRef	− −	− −	+ +	+ +	+ +	+ +	+ +	+ −	− −	− −	− −
	MixTab–ExpRef	+ −	+ +	+ +	+ +	+ +	+ +	+ +	+ +	− −	− −	+ −
	MixTab–AMean	− −	− −	+ +	+ +	+ +	+ +	+ +	− −	− −	+ −	− −
W_{exp}	MixTab–SimRef	− −	+ −	− −	− −	+ +	− −	+ +	− −	− −	+ +	− −
	MixTab–ExpRef	− −	− −	− −	− −	+ +	− −	+ +	− −	− −	− −	− −
	MixTab–AMean	− −	+ −	− −	− −	+ +	− −	+ +	− −	− −	+ +	− −
Plasticity	MixTab–SimRef	− −	+ −	− −	− −	+ −	− −	+ −	− −	− −	+ −	− −
	MixTab–ExpRef	− −	+ −	− −	− −	+ −	− −	+ −	− −	− −	− −	− −
	MixTab–AMean	− −	+ −	+ −	+ −	+ +	+ +	+ +	+ −	+ −	+ −	− −

$D_{rel,max}$, maximum relative density; K_{Heckel}, slope of the Heckel plot; p_{yield}, apparent mean yield pressure; W_{total}, total work; W_{exp}, expansion work; plasticity index = net work/total work × 100. MixTab, tablets from powder mixtures; SimRef, simulated double layer reference tablets; ExpRef, experimental double layer reference tablets; AMean, weighted arithmetic mean from the one-component tablets.

[a] The parameter values were derived from the profiles interpolated from forces and relative densities during tabletting to 10 kN maximum geometric mean punch force.

[b] +, significantly different; −, not significantly different.

[c] True volume fraction of metamizol in maltitol–metamizol tablets (%).

the powder mixtures is compared to the weighted arithmetic mean from the one-component tablets, the synergistic effect exerted by the powder mixtures is clearly underestimated (Fig. 2(a)).

The minimum porosity (1 − maximum relative density) reflects the deviation observed for the maximum relative density but with opposite sign (data not shown). This means that for the minimum porosity a linear reference line is also unsuitable.

3.2.2. Heckel parameters

The slope of the Heckel plot at pressure characterises the rate of densification as a fraction of increasing pressure during a late stage in the course of increasing densification. The development of the resistance to densification in this phase is described by the apparent mean yield pressure. The Heckel slope and the apparent mean yield pressure of the simulated and the experimental double layer tablets proceed non-linearly with true volume fraction as obvious from Fig. 2(b) and (c). The deviation from the arithmetic mean is significant with the *t*-test for all volume fractions. With respect to the Heckel slope, significance is also obtained in many cases with the extended significance test (Table 2: SimRef–AMean, ExpRef–AMean). According to van Veen et al. [17], the yield pressure of a mixture should be described by linear interpolation of the values of the individual components with respect to their volume fractions if no mutual interactions occur. On the other hand, Sheikh-Salem and Fell [18] proposed a linear relation between the slope of the Heckel plot and the volume proportion of the components. Because the Heckel slope and the apparent mean yield pressure are inversely related to each other, only one of the parameters can theoretically follow a linear rule. However, from Fig. 2(b) and (c) it seems that in practice none of the parameters follows a simple linear rule, at least if the parameters are calculated from the dynamic data. Mitrevej et al. [19] expected a linear dependency for the Heckel slope with weight fraction. If the double layer tablets are analysed with respect to the arithmetic mean weighted by the weight fraction, the deviation from linearity even increases.

Contradictory results must be noted if the behaviour of the tablets from the powder mixtures is compared to the weighted arithmetic mean. The apparent mean yield pressure points to a lower resistance to compression and thus to an enhanced compressibility of the powder mixtures (Fig. 2(c)). Yet, the Heckel slope indicates that the compressibility is lowered as the rate of densification is impeded for the powder mixtures (Fig. 2(b)). On the other hand, the results are unambiguous if the double layer tablets are used for the comparison. Both parameters point to a significant enhancement in the densification of the powder mixtures during the compression phase corresponding to the linear region in the Heckel plot. However, the significance is limited mainly to the *t*-test (Table 3: MixTab–SimRef, MixTab–ExpRef) due to the high impact of the uncertainty of the true density on the Heckel parameters [14]. With respect to the apparent mean yield pressure, the difference between the powder mixtures and the double layer tablets resembles quite well the trend seen with the maximum relative density (Fig. 2(a) and (c)). Regarding the slope of the Heckel plot, the course of the deviation shows a shift of the maximum deviation to higher portions of metamizol (Fig. 2(b)). At first sight, this seems to point to an inadequacy of the double layer model to serve as a reference. However, it must be emphasised that a simple non-linear mathematical transformation as the calculation of a reciprocal value can lead per se to such curious effects. Thus, the model used is not to be questioned by this observation.

3.2.3. Work

Based on the physical model chosen, the work should be linearly related to the true volume fraction since the change in the work during compression is proportional to the incremental punch travel and thus to the change in the powder bed volume. This rule of additivity holds indeed for the total work applied to the powder bed. In Fig. 2(d), the values of the simulated double layer tablets follow quite precisely the weighted arithmetic mean. On the other hand, the expansion work exerted by the compact seems to deviate from linearity (Fig. 2(e)). However, the absolute deviation of the simulated double layer systems from linearity is in both cases at most 0.005 J. This deviation is mainly a consequence of the fact that maximum densification is observed at slightly different forces for the two materials as a result of their individual relaxation behaviour. This means that the force–displacement curves are split at slightly different forces if different formulations are analysed with respect to the total work before maximum densification as well as for the expansion work behind it. Integration is thus performed over differing force ranges. If the net work is considered, which covers the whole contact time for all formulations, the deviation from linearity vanishes. However, the differences between the simulated double layer system and the arithmetic mean are only in some cases statistically significant for the expansion work and in no case for the total work (Table 2: SimRef–AMean). Therefore, the arithmetic mean from the values of the pure materials weighted by the true volume fraction appropriately reflects the theoretically expected behaviour of powder mixtures.

The course of the plasticity index with true volume fraction is by far not linear for the simulated and the experimental double layer tablets (Fig. 2(f)), which is supported by the *t*-test (Table 2: SimRef–AMean, ExpRef–AMean). This is to be expected, because the plasticity index is defined as the quotient of the net work and the total work. Since the net work and the total work are both linearly related to the true volume fraction, their quotient cannot show a linear relationship. In order to assess the plasticity of compressed powder mixtures, the reference line can be calculated roughly as the quotient of the weighted arithmetic means of the net work and the total work, but not as the arithmetic mean of the quotients.

As the theoretically expected work is almost linearly related to the true volume fraction, the conclusions drawn are about the same regardless whether the behaviour of the powder mixtures is compared to the double layer tablets or to the weighted arithmetic mean. The enhanced densification of the powder mixtures leads to an increase in the total work applied to the powder bed since increased punch travel requires extra energy. However, the deviation of the total work seen in Fig. 2(d) with the powder mixtures does not exactly reflect the course of the effects of the maximum relative density (Fig. 2(a)). It is the development of the force that also influences the consumption of energy. So, at high portions of metamizol the resistance to densification is comparatively low during compression. These powder mixtures require no extra energy to reach a higher degree of densification.

When maltitol or metamizol are compressed separately to increasing maximum relative densities, the expansion work exerted by the compact increases due to increased elastic deformation of the particles (data from preliminary trials). However, although the maximum relative density of the powder mixtures is enhanced compared to the double layer tablets, the expansion work is even lowered for some true volume fractions (Fig. 2(e)). Therefore, it can be concluded that the energy applied to the powder mixtures is effectively used for permanent deformation.

The plasticity index, which expresses the fraction of the energy successfully used, is strongly correlated with the expansion work. Therefore, it is not surprising that the same conclusions can be drawn from the expansion work and from the plasticity index if the behaviour of the powder mixtures is compared to the double layer tablets (Fig. 2(e) and (f)). However, the energy effectively used due to interparticulate effects between the components is clearly overestimated if the plasticity index of the powder mixtures is compared to the weighted arithmetic mean. Because of that, the assessment of the behaviour of the powder mixtures becomes inconsistent with respect to the expansion work on the one hand and the plasticity index on the other hand.

3.2.4. Comparison between the simulated and the experimental double layer tablets

The values of the simulated and the experimental double layer tablets are in good agreement with each other with respect to all parameters (Table 2, ExpRef–SimRef). Only at some true volume fractions, which vary with the parameter, significant deviations are observed. Systematic differences between the simulated and the experimental double layer tablets are conceivable since both methods have their shortcomings. The weak point of the experimental realisation of the model is the interface between the layers, where the components directly interact with each other and where some ‘diffusion’ of the components may occur. Although the contact area at the interface is small compared to the total internal surface of the tablet, problems can arise especially in the decompression phase if the adherence between the layers is weak. If this occurs, the elastic recovery of the compact should be enhanced. However, a general systematic increase of the expansion work is not observed in Fig. 2(e) and Table 2 (ExpRef–SimRef) for the experimental double layer tablets compared to the simulated ones. A further problem with the experimental double layer tablets is related to their preparation. After the first layer was poured in, the surface was flattened. The smoothing of the interface may not influence the adherence of the layers. Yet, the additional application of a small force can affect the densification profile in the early phase. Indeed, a systematic increase in the relative density of about 0.004 at the beginning of contact time must be noted when tablets were prepared from one material in two layers compared to the usual method with a single filling and a single smoothing step. This may explain the significant deviations between the simulated and the experimental double layer tablets with respect to the total work in Table 2 (ExpRef–SimRef).

A drawback of the simulated double layer tablets is that they require modification of the data. Before the simulated force–relative density profiles can be calculated by Eq. (4), the data structure must be adjusted to the underlying principle since Eq. (4) is only applicable at constant force. This means fine graded and identical force levels instead of an evenly spaced time course as obtained from fast data acquisition. Such a data structure can be generated from the original force–relative density data by linear interpolation. However, this treatment can distort the data as the relative density is non-linearly related to the force. In addition, the interpolated data profiles are cut above the highest preset force level. So, the maximum force of the interpolated data profiles is at most 50 N below the original maximum force. A small part of the compression event is cut off this way. Finally, the change in the data structure can have an effect on the results of the regression analysis used for the estimation of the Heckel parameters. In addition, the smoothing procedure performed to aid the interpolation can slightly distort the data, although it must be noted that it primarily levels the noise. However, the deviation resulting from the modification of the data is generally acceptable considering the standard uncertainty of the results (Table 4). A further shortcoming of the simulation is given by the fact that it represents a dynamic model, which does not consider kinetic effects. Such effects occur if the time course of the force development changes for the components by the equilibrium built up between the layers. For example, when a material with a short contact time is combined with a material that develops a measurable resistance very early in the compression process, the first mentioned material is also stressed to an earlier time. So, the contact time for this substance is prolonged and there is more time for plastic deformation. The mathematical modeling of

Table 4
Values of characteristic parameters and their standard uncertainty, for constant true volumes of the single substances compressed to constant maximum geometric mean punch force, calculated from original, smoothed, and interpolated data, respectively

Parameter	Maltitol			Metamizol		
	Original[a]	Smoothed[b]	Interpolated[c]	Original	Smoothed	Interpolated
F_{max}	10.007±0.045	10.007±0.018	9.988±0.019	10.010±0.045	10.010±0.019	9.988±0.019
$D_{rel,max}$	0.8700±0.0069	0.8697±0.0068	0.8697±0.0068	0.9739±0.0083	0.9735±0.0081	0.9735±0.0081
W_{total} (J)	5.165±0.041	5.156±0.012	5.157±0.015	3.192±0.041	3.184±0.012	3.186±0.015
W_{net} (J)	4.998±0.034	4.999±0.011	5.000±0.014	2.841±0.032	2.841±0.009	2.843±0.013
W_{exp} (J)	0.167±0.021	0.157±0.005	0.157±0.005	0.351±0.024	0.343±0.007	0.343±0.007
Plasticity (%)	96.77±1.36	96.95±0.34	96.95±0.48	89.00±2.05	89.23±0.53	89.24±0.77
K_{Heckel} (10^{-3} MPa^{-1})	6.79±0.32[d]	6.44±0.31	6.45±0.30	15.74±2.33[d]	14.81±2.10	14.76±2.08
p_{yield} (MPa)	147.1±7.0[d]	155.2±7.3	155.0±7.3	63.4±9.4[d]	67.5±9.4	67.8±9.5

F_{max}, maximum geometric mean punch force; $D_{rel,max}$, maximum relative density; W_{total}, total work; W_{net}, net work; W_{exp}, expansion work; plasticity index = net work/total work × 100; K_{Heckel}, slope of the Heckel plot; p_{yield}, apparent mean yield pressure.

[a] The parameter values were derived from the original data of forces and displacements during tabletting.

[b] The parameter values were derived from the smoothed original data of forces and displacements during tabletting.

[c] The parameter values were derived from the data profiles interpolated from the smoothed forces and displacements during tabletting.

[d] The range over which regression was performed exceeded slightly the linear range as the tolerance factor of 25 was too large.

the consequences of this expected change in the time course is, however, very difficult and not considered in this work.

3.2.5. The course of the densification

Fig. 3 shows the characteristic course of the relative density of the powder mixtures compared to the simulated profiles of double layer tablets during contact time. A small dark band at the very beginning of the compression process points to a slight decrease in the relative density of the powder mixtures compared to the layered powder beds. This is presumably a result of impeded packing of the combined crystal types. Afterwards, the density of the powder bed is slightly increased. As this effect is more pronounced at medium to high fractions of metamizol, this may be caused by first fragments of maltitol occupying the still large pores easily [18]. At high portions of maltitol, a zone of stagnancy can be observed. The brittle maltitol may improve the plastic deformation of metamizol as it exerts stress on the soft particles more locally. However, sharp fragments are less advantageous for the deformation of metamizol because it requires a high flexibility of the soft particles to follow the indents of splinters [20]. Thus, with increasing portions of metamizol, the situation becomes more favourable for metamizol as the breakage of maltitol is hindered more efficiently by damped stresses [18]. This means fewer and larger fragments. Therefore, only at higher parts of metamizol this mechanism supports the densification accompanied by enhanced packing of particles as long as the fragments of maltitol are small enough to fill the shrinking void space effectively. This may explain why at low forces of 1–2 kN the relative density is most improved at 70–80% of metamizol (Fig. 3). With increasing densification, the effective filling of voids by further fragmentation proceeds as long as sufficient mobility is in the powder bed. At high portions of metamizol, however, the matrix becomes quickly dense, thus impeding this process. This may be one reason that causes the most effective densification to shift to lower fractions of metamizol. The second factor may also be related to the porosity of the powder bed. In a dense matrix, the ability to deform is limited for metamizol. But with decreasing parts of metamizol the density decreases. For example, at 5 kN the relative density of pure metamizol is 0.92 while at equal portions of both materials a relative density of only 0.86 is achieved. So, there is more space for metamizol to deform and to occupy the pore volume around the fragmented particles [21]. However, as the porosity within clusters of

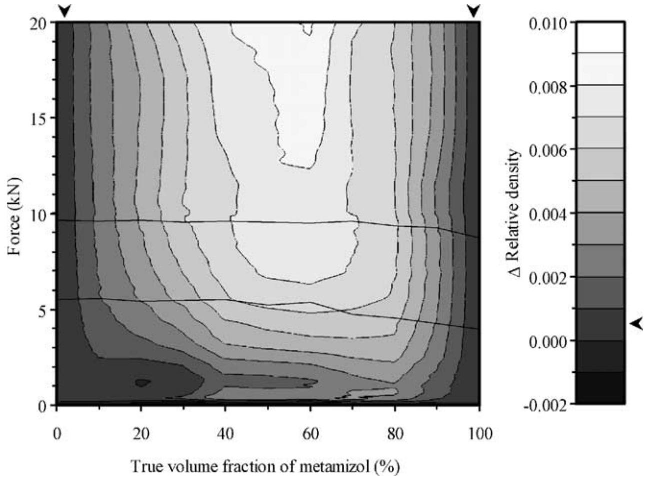

Fig. 3. Projection plot of the difference in relative density (D_{rel}), during compression and decompression, between the tablets from the powder mixtures composed of maltitol and metamizol and the respective simulated double layer tablets in dependence on the true volume fraction of metamizol and on the geometric mean punch force. The contact time starts at the lower border of the graph and ends at its upper border. The height of the difference (D_{rel}(mixture) − D_{rel}(reference)) is given by the grey scale. The data profiles were interpolated from forces and relative densities during compression to 10 kN maximum geometric mean punch force. The plot is based on the mean profiles of eight data sets for each composition. The beginning and the end of the linear region in the Heckel plot with respect to the powder mixtures and the pure substances are given by the additional lines drawn.

maltitol is not accessible for metamizol [20], the densification is most effective where both components are distributed equally. This behaviour is clearly reflected in the maximum relative density (Fig. 2(a)) and in the apparent mean yield pressure (Fig. 2(c)). The irregular effects with the total work observed in Fig. 2(d) are more difficult to explain by Fig. 3 as the work adds up the behaviour over the course of the densification. However, it seems that the course of the deviation depicted in Fig. 2(d) for the total work is especially related to the zone at 1–2 kN in Fig. 3. The dark region points to less facile densification at higher portions of maltitol, which requires energy. The minima found with the expansion work at medium volume fractions (Fig. 2(e)) are reflected in Fig. 3 by the change in the grey level during decompression at these compositions. This means that the enhancement in the densification of the powder mixtures relative to the double layer systems progresses further during decompression for these mixtures due to reduced fast elastic recovery. Effective densification during compression by successful packing and deformation may contribute to this effect.

4. Conclusions

The weighted arithmetic mean from values of a feature derived from the individual components is often used to calculate the theoretically expected compression behaviour of powder mixtures if no interparticulate interactions between the components occur. Alternatively, the authors propose a double layer model, which is based on a fundamental principle of densification. A simple linear dependency between the values of a feature and the true volume fraction of the components cannot be generally confirmed by the double layer model. So, if the actual relationship between a feature and the ratio of the components cannot be deduced mathematically, the double layer model seems to be a valuable alternative to an arbitrarily chosen weighted arithmetic mean. The benefit of the double layer model is demonstrated by the evaluation of the compression behaviour of powder mixtures. Using the weighted arithmetic mean indiscriminately to assess the compression behaviour of powder mixtures can lead to incompatible or even contradictory results between interrelated features and to misleading interpretations. However, the results are consistent if the compression behaviour of powder mixtures is compared to the double layer tablets.

The experimental realisation and the mathematical simulation of the double layer model lead to about the same results. Therefore, experimental double layer tabletting can be used if the mathematical simulation is not applicable, namely if tabletting is performed to constant maximum relative density. In this case, the component with the lower resistance to densification lacks force data near the lower turning point of the punches compared to the component with the higher resistance to densification. Furthermore, the experimental reference takes kinetic effects into consideration, which are difficult to model mathematically.

The model can be extended to systems of three or more components. However, problems might arise with very small portions of a substance when layered tablets have to be experimentally produced due to the difficulty in the preparation of very thin even layers. In addition, multiple flattening of the powder surface might noticeably increase the initial density of the powder bed.

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