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Research paper

Considerations about the theoretically expected crushing strength of tablets from binary powder mixtures: Double layer tablets versus arithmetic additivity rule

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Abstract

The theoretically expected breaking strength of tablets from powder mixtures is often calculated by the weighted arithmetic mean from the breaking strength of the single components, which corresponds to a linear interpolation. The validity of this additivity of fracture strength shall be evaluated by the underlying model of parallel couplings. It assumes the components linked in parallel with respect to the direction of loading during diametrical strength testing. Parallel couplings were experimentally realised by the preparation of double layer tablets from crystalline and spray-dried lactose on the one hand and from maltitol and metamizol-sodium on the other. Constant total true volumes of the single substances and of layered powders in varying ratios of true volume were compressed on an eccentric tabletting machine to constant geometric mean punch force. Simulated crushing profiles of parallel couplings were derived from force–displacement profiles measured during diametrical compression of the one-component tablets. At given finely graded deformation levels, the forces exerted by the components during loading were added in the proportion of the true volume fractions of the components in the coupling. The results from the experiments and from the simulations are in good accordance. They demonstrate that a linear change of the crushing strength in dependence on the true volume fraction of the components can only be assumed if the single components deform to the same extent up to the point of fracture. This behaviour was approximately found with the parallel lactose system. In all other cases it must be expected that the crushing strength of parallel systems will be lowered beneath the weighted arithmetic mean values or even below the crushing strength of the single components. The latter was observed with the maltitol–metamizol combinations. Thus, if tablets from binary powder mixtures exhibit a crushing strength depression, this is not necessarily an indication of weak bonding between the components or of structural defects.

Keywords: Double layer tablets; Powder mixtures; Crushing strength; Additivity rule; Parallel couplings

1. Introduction

Direct compression offers a convenient method for the production of tablets. The ingredients are simply mixed and then compressed. As the tablets must withstand the packaging and the normal handling by the patient, they must possess sufficient mechanical strength. However, the intimate contact of the different substances combined in the tablets can result in unexpected detrimental physical interactions between the components. In his literature review, Fell [1] gives an overview of the effects observed. The breaking strength of tablets from powder mixtures can be lowered or enhanced compared to the strength expected. However, what strength is actually expected from the properties of the single components?

Using a simple mathematical principle, the breaking strength S_{mix} theoretically expected for tablets from binary powder mixtures may be calculated by the weighted arith-

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metic mean from the strengths S_1 and S_2 of the tablets from the pure components 1 and 2, respectively.

$$S_{mix} = S_1 f_1 + S_2 f_2, \quad (1)$$

where f_1 and f_2 represent the fractions of the components in the mixture. This means that a linear dependency between the breaking strength and the composition of the tablets is theoretically expected if no interaction between the components occurs. This additivity rule is often used for the evaluation of the compaction behaviour of binary powder mixtures [2,3]. However, where does this additivity rule come from and what does it physically mean?

In elasticity theory, two simple couplings of two elements are conceivable. Firstly, the elements can be coupled in series with respect to the direction of the stress applied as illustrated in Fig. 1a. When a tensile or compressive stress is applied to the assembly, the stress is transmitted through the elements. So, the stress acting in each element is the same as the stress between the supports. To accommodate to the stress, the elements deform in their individual manner. The deformation of the elements sums up to the total deformation of the arrangement. In this serial coupling there is strictly speaking no additivity of stress. In the parallel coupling (Fig. 1b), the elements deform to the same extent when a tensile or compressive stress is applied. But an individual stress arises in each element in dependence on its deformation resistance. At a given degree of deformation the stresses of the elements sum up to the total stress of the arrangement. This additivity of stresses in a parallel coupling of components seems to be reflected in Eq. (1).

In reality, the situation is of course more complex. In tablets from powder mixtures the elements, namely the particles of the components, can be coupled in parallel and in series to each other. Such structural circumstances are considered in the equivalent box model used by Kolarik [4] to describe the yield strength of polymer blends. Later he extended it to the tensile strength of such systems [5].

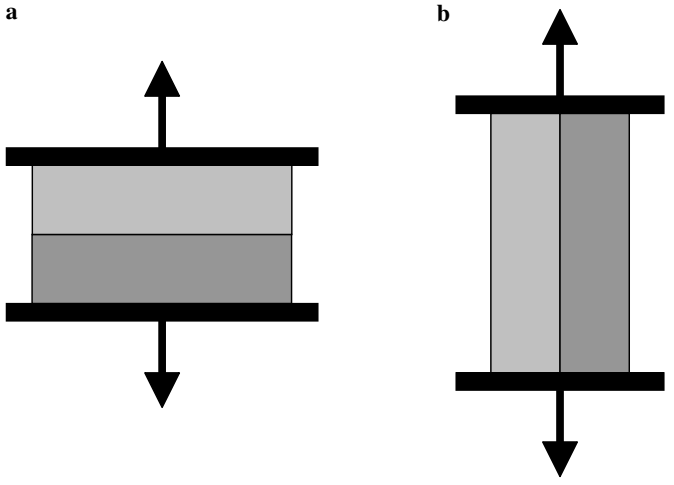

Fig. 1. (a) Serial and (b) parallel coupling of two elements.

Recently, van Veen et al. [6] applied this model to the elastic modulus and the tensile strength of tablets from mixtures of pharmaceutical substances. The equivalent box model assumes a parallel and a serial branch that are coupled in parallel. This simple model cannot reflect the complex structure within the tablets from powder mixtures but should model the overall mechanical response. The equivalent box model can be mathematically described by:

$$S_{mix} = (S_1 f_{1p} + S_2 f_{2p}) + A S_1 f_s, \quad (2)$$

where the first term (in parentheses) refers to the parallel branch and the last term stands for the serial branch. S_{mix} is the tensile strength of the tablets from powder mixtures. S_1 and S_2 denote the tensile strength of the tablets from the single components 1 and 2, respectively. A is an interaction factor. The volume fractions of the components 1 and 2 in the parallel branch, f_{1p} and f_{2p}, respectively, represent the portion of the particles of each component that build a continuous path through the whole specimen in the direction of the acting stress. When this branch ruptures, the stresses in the continuous phases of the components add up. The volume fraction of the serial branch f_s represents the sum of the portions of the components that are discontinuous in the direction of the tensile stress. This means that the path of particles of one component is interrupted by particles of the other component in the direction of the acting stress. The serial branch ruptures when the strength limit of the weaker component (component 1 in Eq. (2)) is reached, provided that the interfacial adherence between the components is strong enough to resist the tensile stress. Then, A in Eq. (2) is equal to 1. If however, the interfacial adherence is lower than the strength of the weakest component, the serial branch breaks at the interface between the components and A decreases. So, A indicates the extent of the interfacial interaction between the particles of the components.

Eqs. (1) and (2) assume that the breaking strength of the components, namely the *stresses at the point of fracture* measured when each component is separately tested, can be simply added in order to obtain the fracture stress of a parallel coupling of the components. However, from the explanations above it is obvious that the addition of stresses is only valid at a given common degree of deformation if the components are physically linked up. Therefore, Eqs. (1) and (2) hold strictly speaking only if both components have the same deformation at rupture. But what happens if the single components deform to a different degree before their fracture strength limit is reached? Fig. 2a illustrates this case by idealised sawtooth stress-deformation profiles for elastic/brittle failure. Both components have the same tensile strength but component 1 is stiffer than component 2. So, component 1 fractures before component 2 and does not longer contribute to the stress measured at the supports of the testing device. If the profiles of the single components are added to simulate the stress-deformation curves of a parallel system consisting of each 50% of the components, a double sawtooth profile results as

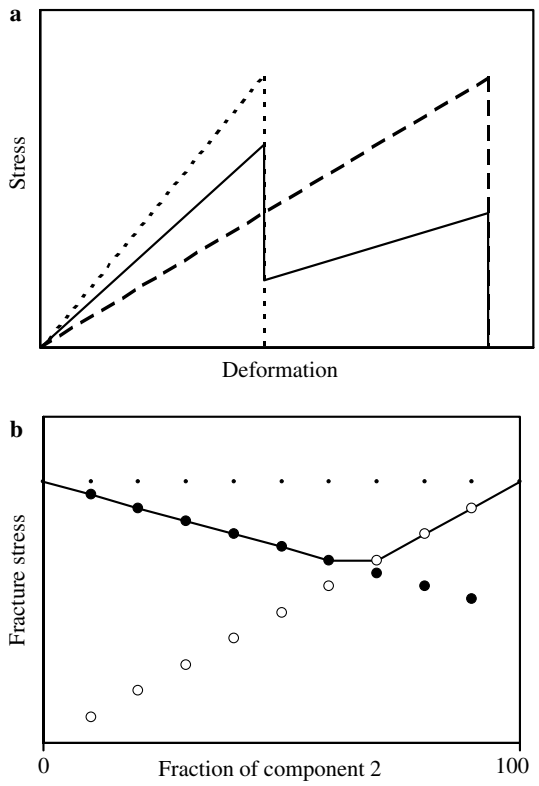

Fig. 2. (a) Idealised stress–deformation profiles for elastic/brittle failure of (-----) component 1, (— —) component 2, and (———) a parallel coupling of each 50% of the components. (b) Fracture stress of parallel couplings of two components. (●) First maximum in the stress-deformation profiles, (○) second maximum, (———) absolute maximum, and (· · · ·) expected maximum according to Eq. (1) and to Eq. (2) if $A = 1$.

depicted in Fig. 2a. This profile shows two breaking events, the first one at the fracture of the first component and the second fracture when the deformation limit of the second component is reached. Such profiles were calculated for several component proportions with increments of 10%. The height of the first, of the second, and of the absolute maximum (the first or second one, whichever is higher) is shown in Fig. 2b. It can be seen that none of the curves corresponds to a linear interpolation obtained from the breaking strength of the single components. All curves are lowered beneath the strength of the components although the mechanical properties of parallel systems are independent of interfacial adhesion. Note, in the special case where the breaking strengths of the components are identical ($S_1 = S_2$) and where the interfacial adhesion between the components is good ($A = 1$), Eq. (2) reduces to Eq. (1) [4]. In this case, the fracture strength should be independent of the composition of the system. However, concerning the simulations this seems to be obviously not the case. So, what is valid in practice?

The aim of this study is to experimentally elucidate the additivity of the breaking strength of tablets composed of two components with the aid of double layer tablets. The components are separated in the different layers of the tablets. The layers are arranged in parallel with respect to the direction of the diametrical loading during the strength test and with respect to the tensile stresses ideally rupturing the tablets. The deformation in the direction of the tensile stresses, however, is difficult to measure because the tensile stresses develop in the direction normal to the loading by the platens. Therefore, this study is limited to the force and the deformation in the line of loading. In this way it should be possible to compare the fracture behaviour of double layer tablets with the strength of simulated parallel couplings of the components. The simulations will be based on force–displacement profiles of the single components measured during the crushing of the tablets.

2. Materials and methods

2.1. Materials

Crystalline maltitol (Maltisorb P200®, Roquette Freres, Lestrem, France), crystalline metamizol sodium monohydrate (Metamizol-Natrium T $1H_20$, Fährhaus Pharma GmbH, Hamburg, Germany), crystalline α-lactose monohydrate (Pharmatose 100M®, DMV, Veghel, Netherlands), and spray-dried lactose (Flowlac®, Meggle GmbH, Wasserburg, Germany) were used as components. Magnesium stearate (Riedel-de Haen AG, Seelze, Germany) was used as external lubricant.

Narrow particle size fractions of 0.100–0.125 mm were prepared from Maltisorb®, metamizol, Pharmatose®, and Flowlac® by air jet sieving as described by Belda and Mielck [7] and used for tabletting.

2.2. True density

True densities of 1.615 ± 0.012, 1.415 ± 0.011, 1.547 ± 0.015, 1.545 ± 0.018 g/cm^3 (mean ± standard uncertainty) were obtained from the fractionated powders for Maltisorb®, metamizol, Pharmatose®, and Flowlac®, respectively, according to the procedure described in [7].

2.3. 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. Piezo-electric load washers were installed for the measurement of the upper and lower punch forces. The instrumentation and their qualification is described in detail elsewhere [8–10].

The die wall was externally lubricated with magnesium stearate as described by Belda and Mielck [7]. Powder samples were weighed on an analytical balance (AE 166/9, Mettler, Gießen, Germany) and manually filled into the lubricated 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 the first component as the lower layer and the other half of the experiments with the first component 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 were filled into the die in two separate layers. Each layer was flattened.

The powders were compressed at 30 strokes per min to 10.0 ± 0.1 kN (target ± range) maximum geometric mean punch force. No pre-compression of the first layer was performed. Tablets of single substances and double layer tablets with varying compositions in percent of true volume were prepared. All trials were repeated on another day. The tablets were stored in a closed container.

Tabletting as well as the experiments described below were performed in an air-conditioned room at 22–24 °C and 47–52% r.h.

2.4. Tablet thickness

After 1 week the height at the centre of the tablets was measured with a digital micrometer (Digimatic Indicator ID-110M, Mitutoyo Corp., Tokyo, Japan) using a spherical probe.

2.5. Crushing strength

One week after the preparation of the tablets their radial breaking strength was measured with a crushing strength tester (TBH 28, Erweka Apparatebau GmbH, Heusenstamm, Germany). The testing device was calibrated against weights and quasi-statically against a reference load cell in accordance with DIN 51301 [11]. The uncertainty of the calibration was determined in accordance with DIN 1319-4 [12]. The contribution of the calibration to the measuring uncertainty is 0.3 N.

2.6. Fracture profiles

One week after the preparation of the tablets, force–punch distance profiles were recorded during diametrical loading of the tablets on the same tabletting machine as used for tabletting but without the die. Although the tabletting machine was not instrumented and calibrated for the purpose of crushing tablets, the piezo-electric force transducers with their low noise and their low response threshold justify its use. The uncertainty of the calibration of the force transducers was determined to be 5 N. The uncertainty of the calibration of the displacement transducers was 3 μm. However, it must be assumed that the uncertainty of the calibration of the force transducers overestimates the measuring uncertainty during crushing because the calibration set-up was not intended for the small forces during crushing. Hence, it will not be used in the statistical evaluation of the data.

The lower turning point of the upper punch was adjusted to 9.89–9.91 mm punch distance. The tablets were placed on the lower punch of the tabletting machine and diametrically compressed between the punches at a machine speed of 30 strokes per min. Because the displacement–time profile of the tabletting machine is a sine wave, the punch speed was not constant during testing. However, near the lower turning point of the upper punch the change in the velocity with time is small and almost linear. Table 1 summarises the punch speed at first contact with the tablets and the speed when the tablets fracture.

During testing 1500 sets of data were recorded at 10 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 7.0, National Instruments).

2.7. Data analysis

Data analysis was performed with LabVIEW (version 7.0, National Instruments). The displacement signals were filtered by a median filter to eliminate sharp noise peaks caused by the machine drive. The filtered signal was transformed to punch distance, which reflects the absolute deformation of the tablet across its diameter. The unfiltered upper punch signal was transformed to force. The beginning of the contact between the upper punch and the tablet was defined as the data point where the force remained 0.3 N above the noisy base line for a period of at least 10 successive data points. The punch distance at this point gave the initial diameter of the tablet. By normalising the change in the tablet diameter to this initial diameter, the engineering strain ε was obtained

$$\varepsilon_i = (s_i - s_0)/s_0 \times 100;\ (i = 1, \ldots, n), \tag{3}$$

where s_i and s_0 are the actual and the initial punch distance, respectively. These force and deformation data will be called 'original' data in the following.

While the measured data are evenly spaced with respect to time, the construction of simulated force–deformation profiles of a parallel coupling needs data that are evenly

Table 1
Mean upper punch speed and standard deviation of the mean ($n = 8$) during strength testing on the tabletting machine

Material	Initial speed (mm/s)	Speed at fracture (mm/s)
Pharmatose®	9.8 ± 0.3	7.5 ± 0.3
Flowlac®	10.0 ± 0.2	7.0 ± 0.4
Maltitol	9.2 ± 0.3	7.0 ± 0.2
Metamizol	8.4 ± 0.3	6.6 ± 0.3

spaced with respect to the deformation and that have identical deformation levels. The required force profiles were obtained by linear interpolation to graded punch distance on the one hand and to graded strain on the other. In order to preserve the sharp course of the fracture in the interpolated data, the forces were interpolated with respect to very small increments in the punch distance and in the strain of 0.0002 mm and 0.002%, respectively. The data interpolation caused a deviation of no more than 0.2 N with respect to the crushing force. The punch distance and strain at break deviate from the original data by at most 0.0001 mm and 0.001%, respectively. The interpolation procedure was applied to the data of all tablets.

The force profiles of parallel couplings of the components 1 and 2 were obtained by adding the interpolated forces of each component (F_1 and F_2) at a given punch distance or strain (s_1 and s_2) in the proportion of the true volume fraction of the components (f_1 and f_2).

$$F_{p_i} = F_{1_i} f_1 + F_{2_i} f_2; \quad s_{1_i} = s_{2_i}; \quad (i = 1, \ldots, n). \tag{4}$$

The simulation was performed for true volume fractions ranging from 10% to 90% in increments of 10%. The crushing strength of a simulated coupling was defined as the absolute maximum of its force profile, namely the maximum of the first or of the second fracture event whichever is higher.

2.8. Statistical analysis

The standard deviation of the mean from each eight replicate tablets was used for a Student's t-test ($p = 0.95$).

The standard uncertainty u was calculated in accordance with DIN 1319-4 [12]. The standard uncertainty considers the standard deviation of the mean from eight repeated measurements as well as the uncertainty derived from the calibration. In line with the Bayesian theory of measurement uncertainty, Weise and Wöger [13] recommended a factor of $\beta^2 = 2$ for a critical comparison between results so that

$$|x_1 - x_2| \leqslant \beta \sqrt{u^2(x_1) + u^2(x_2)}. \tag{5}$$

This strict significance test needs no choice of a probability.

3. Results and discussion

Double layer tablets were prepared in order to experimentally elucidate the additivity of the crushing strength of binary component systems. During diametrical compression they represent a parallel coupling of the components by the platens or punches of the testing device. In addition, the components are laterally linked up in double layer tablets. The latter may give rise to problems. However, none of the tablets laminated at the interface between the layers, which might have produced interfering fracture signals during testing. Furthermore, the preparation of the layers had no influence on the crushing strength. Tablets from one substance but prepared like the double layer tablets in two layers show no significantly different crushing strength compared to tablets conventionally prepared in one filling and smoothing step. However, if double layer tablets were prepared from two different components, the standard deviation of the crushing strength is on average nearly twice as high as the standard deviation from one-component tablets. This may result from some diffusion of the components at the interface between the layers. In addition, the layers may not be perfectly plane-parallel.

The lower graph in Fig. 3 depicts the crushing strength obtained on the crushing strength tester for double layer tablets composed of Pharmatose® and Flowlac®. The crushing strength of the double layer tablets is almost linearly related to the true volume fraction of the components. Only at 25% (v/v) of Flowlac® the strength is slightly but significantly lowered beneath the weighted arithmetic mean calculated from the crushing strength of the tablets from the single components. This is confirmed by both statistical tests. All in all, the results are in good accord with Eq. (1), which describes a linear relationship between breaking strength and composition. So, the question arises: Is the deformation of the single materials up to the point of fracture similar as stated in the introduction for the validity of Eq. (1)? To clarify this, force–displacement profiles were recorded during diametrical loading of the tablets on the tabletting machine. Profiles of single tablets are shown in Fig. 4. Indeed, the tablets from Pharmatose® and Flowlac® deform to about the same extent during loading. However, the curve of Pharmatose® is slightly shifted to a lower punch distance. Although the double layer tablets are com-

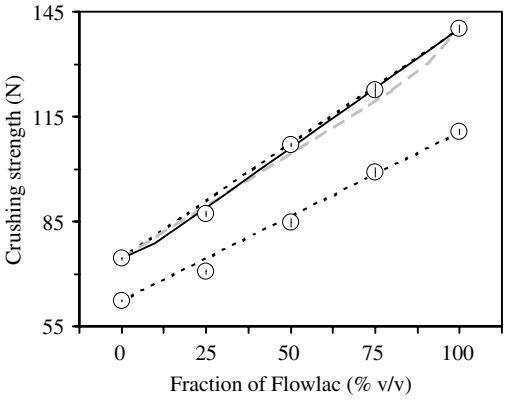

Fig. 3. Crushing strength of Pharmatose®–Flowlac® tablets in dependence on the true volume fraction of Flowlac®. The vertical bars within the symbols represent the standard deviation of the mean. Lower graphs: The measurements were performed on the crushing strength tester. (○) Measured crushing strength of one-component and double layer tablets and (-----) weighted arithmetic mean from the strength of the one-component tablets. Upper graphs: The measurements were performed on the tabletting machine. (○) Maximum of the interpolated upper punch force–punch distance profiles of one-component and double layer tablets, (-----) weighted arithmetic mean from the maxima of the one-component tablets, as well as absolute maximum of the force profiles of parallel couplings (———) simulated from the interpolated force–punch distance profiles and (— —) simulated from the interpolated force–strain profiles.

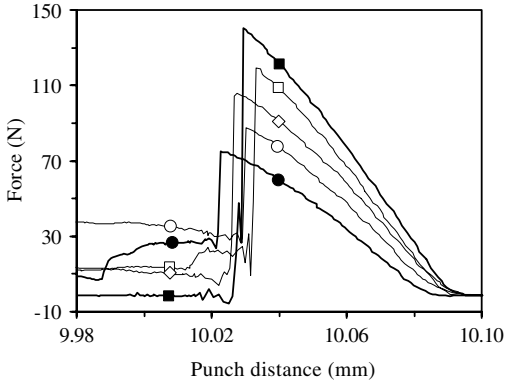

Fig. 4. Original upper punch force–punch distance profiles during diametrical loading of the tablets on the tabletting machine. (●) Pharmatose® tablets (■) Flowlac® tablets, as well as double layer tablets composed of Pharmatose® and Flowlac® in true volume fractions of (○) 75 + 25%, (◇) 50 + 50%, and (□) 25 + 75%.

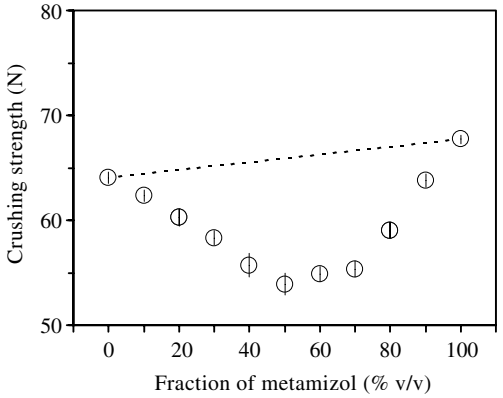

Fig. 5. Crushing strength of maltitol–metamizol tablets in dependence on the true volume fraction of metamizol. The measurements were performed on the crushing strength tester. (○) Measured crushing strength of one-component and double layer tablets including the standard deviation of the mean and (---) weighted arithmetic mean from the strength of the one-component tablets.

posed of two components, they exhibit only one clear fracture event. The punch distance at fracture of the double layer tablets does not significantly diverge from the punch distance at the fracture of Flowlac®, irrespective of the composition of the tablets. This is shown by both statistical tests. Yet, at all compositions there is a significant deviation of the punch distance at fracture of the double layer tablets from the punch distance at the fracture of Pharmatose® if the data are assessed by the *t*-test. Thus, the crack initiated in the Flowlac® layer obviously propagates through the whole tablet as expected from fracture mechanics. The maximum force of the double layer tablets measured on the tabletting machine (Fig. 3, upper graphs) shows the same pattern as the crushing force obtained by the crushing strength tester (Fig. 3, lower graphs). But the forces measured on the tabletting machine are higher. This may be a result of the velocity of the testing devices [14,15] as well as of the uncertainty of their calibration. Again, only the crushing strength of double layer tablets containing 25% (v/v) Flowlac® is significantly lowered beneath the weighted arithmetic mean. This behaviour, however, is expected. The upper graphs in Fig. 3 include the maximum force of profiles that simulate parallel couplings of the components according to Eq. (4). The simulations from force–punch distance profiles exhibit the same trend as observed for the experimental double layer tablets, namely a significant decrease in the crushing strength at low true volume fractions of Flowlac®. This is a result of the slightly shifted course of the punch distance of Pharmatose® and Flowlac® tablets during loading. The *t*-test shows that the maximum force of the double layer tablets does not significantly diverge from the maximum force of the simulated force–punch distance profiles with respect to all compositions. On the other hand, the simulation from the force–strain curves cannot reflect the behaviour of the double layer tablets. The difference between both simulation methods will be explained below.

Fig. 5 depicts the crushing strength of double layer tablets composed of maltitol and metamizol. Although the strength of tablets from the single components is similar, the crushing strength of all double layer tablets is noticeably and significantly lowered beneath the weighted arithmetic mean calculated from the crushing strength of the tablets from the single components by Eq. (1). This is confirmed by both statistical tests. The course of the crushing strength with the true volume fraction is qualitatively equivalent to the behaviour illustrated in Fig. 2b. Hence, it may be assumed that tablets from maltitol and metamizol deform to a quite different degree during strength testing. Fig. 6 shows force–punch distance profiles of single tablets during diametrical loading on the tabletting machine. Indeed, the deformation up to the fracture event is nearly twice as high for metamizol compared to maltitol (see also Table 2). Nevertheless, the double layer tablets break only once. The tight lateral coupling of the component layers in double layer tablets caused the parallel systems to behave like a single entity. Both statistical tests indicate that the punch distance at fracture of the double layer tablets containing 20% and 50% (v/v) of metamizol does not significantly deviate from the punch distance at the fracture of maltitol. However, tablets containing 80% (v/v) of metamizol show no sign of fracture in the force–punch distance profiles at the deformation limit of maltitol. A possible crack initiated in the maltitol layer may not be able to propagate completely through the thick metamizol layer. Yet, it may weaken the tablet and induce a terminal crack before the deformation limit of the metamizol layer is reached. Nevertheless, the crushing strength of these tablets containing 80% metamizol almost corresponds to the crushing strength expected from the simulated force–deformation profiles (Fig. 7). At this composition, the absolute maximum of the simulated force–deformation profiles is located at the deformation limit of metamizol. The deformation limit of metamizol, however, is not reached in practice.

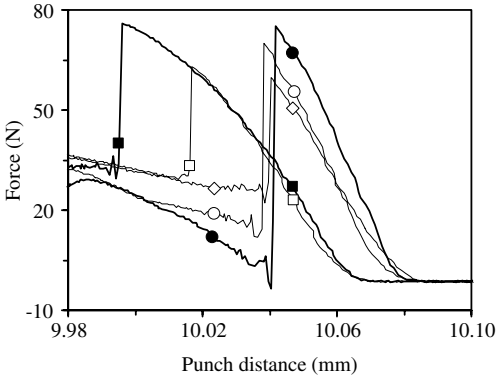

Fig. 6. Original upper punch force–punch distance profiles during diametrical loading of the tablets on the tabletting machine. (●) Maltitol tablets (■) metamizol tablets, as well as double layer tablets composed of maltitol and metamizol in true volume fractions of (○) 80 + 20%, (◇) 50 + 50%, and (□) 20 + 80%.

The simulations of parallel couplings were performed with interpolated force–punch distance profiles on the one hand and with interpolated force–strain profiles on the other. In dependence on the simulation method, divergent maximum forces are obtained especially at low to medium fractions of metamizol (Fig. 7). The crushing strength of all double layer tablets significantly differs from the maximum force of simulated force–punch distance curves. But only the crushing strength of tablets containing 50% (v/v) of metamizol shows a significant deviation from the maximum force of simulated force–strain profiles. So, what is the difference between both simulation methods and why can none of the methods fully explain the behaviour of the double layer tablets? The problem with the maltitol–metamizol system is that the tablets of these components diverge noticeably in their initial diameters. The difference amounts to 13 μm (Table 2). The consequence for the double layer tablets is that the components influence each other with respect to their relaxation and recovery after ejection from the die if they are tightly bound in double layer tablets. The layers, therefore, presumably do not possess exactly the same properties that the components have if they are tabletted separately. The consequence for the simulations is that the force profiles of the components are shifted relative to each other if the punch distance profiles are normalised with respect to the initial diameters. Differences in the initial diameters are removed in this way. This may correspond to relaxation and recovery effects that may level out the diameter of the laterally coupled layers in double layer tablets. However, differences in the diameters of the bonded layers may remain at some distance from the interface between the layers. Then, one must assume a perfect lateral transfer of the deformation during strength testing from one layer to the other to guarantee equal strain in the component layers. Diameter adaptation and strain transfer are of course only partially possible within experimental double layer tablets. This may explain differences between the crushing behaviour of double layer tablets and the simulations from force–strain curves. In powder mixtures, however, the components are more homogeneously distributed. So, the tablets relax more homogeneously and the strain can be more easily transferred between the components during strength testing. This fact gives the simulation of parallel couplings from force–strain profiles practical relevance. On the other hand, the simulation from force–punch distance profiles represents the pure theoretical case. It assumes that the component layers do not influence each other. One must imagine the layers arranged as laterally separated specimens only coupled in parallel by the punch faces during strength testing. This is certainly not the case in double layer tablets. Yet, this method loses its practical value only if the difference in the diameters of the components becomes too large. Looking back to the lactose system, the difference in the initial diameters of the components is only 8 μm (Table 2). With respect to this example, only the simulation from force–punch distance curves can reflect the behaviour of double layer tablets (Fig. 3, upper graphs). On the other hand, the breaking behaviour of double layer tablets from maltitol and metamizol represents an intermediate case between the simulation methods (Fig. 7). Besides the difference in the diameters of the components there may be a further reason why none of the simulation methods can fully explain the behaviour of the

Table 2
Tablet thickness before crushing and features derived from the original data profiles measured during diametrical compression of one-component and double layer tablets on the tabletting machine (mean values and standard deviation of the mean, $n = 8$)

		Thickness (mm)	Initial diameter (mm)	Diameter at break (mm)	Strain (%)	Maximum force (N)
Pharmatose®	–	3.513 ± 0.001	10.088 ± 0.001	10.027 ± 0.001	0.61 ± 0.01	74 ± 0.4
75%[a]	25%	3.551 ± 0.001	10.095 ± 0.002	10.033 ± 0.001	0.61 ± 0.02	87 ± 0.7
50%	50%	3.597 ± 0.001	10.096 ± 0.001	10.030 ± 0.001	0.65 ± 0.01	107 ± 0.6
25%	75%	3.637 ± 0.002	10.095 ± 0.001	10.031 ± 0.002	0.63 ± 0.02	123 ± 1.9
–	Flowlac®	3.681 ± 0.001	10.096 ± 0.001	10.031 ± 0.001	0.65 ± 0.01	140 ± 1.1
Maltitol	–	3.518 ± 0.001	10.075 ± 0.002	10.035 ± 0.002	0.40 ± 0.01	74 ± 0.3
80%	20%	3.463 ± 0.005	10.074 ± 0.002	10.033 ± 0.002	0.41 ± 0.01	70 ± 0.8
50%	50%	3.369 ± 0.004	10.078 ± 0.002	10.034 ± 0.002	0.43 ± 0.01	61 ± 0.6
20%	80%	3.272 ± 0.004	10.065 ± 0.001	10.013 ± 0.001	0.52 ± 0.01	64 ± 0.5
–	Metamizol	3.216 ± 0.001	10.062 ± 0.002	9.992 ± 0.001	0.69 ± 0.01	76 ± 0.4

[a] True volume fraction.

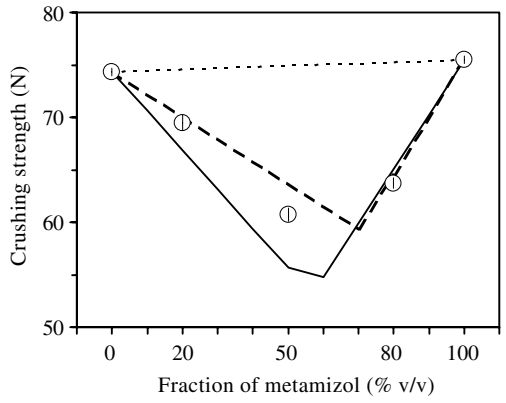

Fig. 7. Crushing strength of maltitol–metamizol tablets in dependence on the true volume fraction of metamizol. The measurements were performed on the tabletting machine. (○) Maximum of the interpolated upper punch force–punch distance profiles of one-component and double layer tablets including the standard deviation of the mean, (-----) weighted arithmetic mean from the maxima of the one-component tablets, as well as absolute maximum of the force profiles of parallel couplings (———) simulated from the interpolated force–punch distance profiles and (— —) simulated from the interpolated force–strain profiles.

double layer tablets from maltitol and metamizol. Tablets ideally rupture by tensile stresses that develop in the direction normal to the line of loading during diametrical compression. In this direction, the deformation may be different from the deformation measured along the line of loading. However, the *t*-test gives evidence that not only the maximum force of the profiles simulated from maltitol and metamizol tablets significantly diverges from the weighted arithmetic mean, but also the maximum force during crushing of the experimental double layer tablets. And the double layer tablets do not suffer from deficiencies of the model calculations.

4. Conclusions

The addition of the breaking strength performed in Eqs. (1) and (2) reflects parallel couplings of components only in the case that the single components deform to the same extent up to the point of fracture. In all other cases it must be expected that the breaking strength of the parallel two-component systems will be lowered beneath the weighted arithmetic mean from the one-component tablets or even below the breaking strength of the one-component tablets. Yet, it must be emphasised that this strength depression does not indicate weak interfacial adherence between the components. Using Eqs. (1) and (2) can therefore lead to false interpretations of the behaviour of tablets from binary powder mixtures. The knowledge of the force–punch distance profiles of the components during crushing enables a more reliable assessment of the compactibility of powder blends. If the measurement of such profiles is not possible with the devices available, double layer tablets seem to be an interesting alternative as they behave like a single entity. However, the parallel coupling of components reflects only one facet of the complex structure within tablets from powder mixtures.

From the point of view of a practitioner there arises another conclusion. As far as possible, components should be combined in tablets from powder mixtures that equally deform during loading to avoid negative trends in the mechanical strength of the tablets.

References

[1] J.T. Fell, Compaction properties of binary mixtures, in: G. Alderborn, C. Nyström (Eds.), Pharmaceutical Powder Compaction Technology, Marcel Dekker, New York, NY, USA, 1996, pp. 501–515.
[2] B. van Veen, K. van der Voort Maarschalk, G.K. Bolhuis, K. Zuurman, H.W. Frijlink, Tensile strength of tablets containing two materials with a different compaction behaviour, Int. J. Pharm. 203 (2000) 71–79.
[3] H. Vromans, C.F. Lerk, Densification properties and compactibility of mixtures of pharmaceutical excipients with and without magnesium stearate, Int. J. Pharm. 46 (1988) 183–192.
[4] J. Kolarik, A model for the yield strength of binary blends of thermoplastics, Polymer 35 (1994) 3631–3637.
[5] J. Kolarik, Evaluation of the extent of interfacial debonding in polymer blends, Polymer 37 (1996) 887–891.
[6] B. van Veen, K. van der Voort Maarschalk, G.K. Bolhuis, H.W. Frijlink, Predicting mechanical properties of compacts containing two components, Powder Technol. 139 (2004) 156–164.
[7] P.M. Belda, J.B. Mielck, The difficulty in the assessment of the compression behaviour of powder mixtures: double layer tablets versus arithmetic additivity rule, Eur. J. Pharm. Biopharm. 60 (2005) 133–145.
[8] P.H. Krause, Einflüsse des Geschwindigkeitsverlaufs in Exzenter-Tablettiermaschinen auf die Verdichtungseigenschaften von pharmazeutischen Haufwerken, Ph.D. thesis, University of Hamburg, Germany, 1991.
[9] P.M. Belda, J.B. Mielck, The tabletting machine as an analytical instrument: qualification of the measuring devices for punch forces and validation of the calibration procedures, Eur. J. Pharm. Biopharm. 46 (1998) 381–395.
[10] P.M. Belda, J.B. Mielck, The tabletting machine as an analytical instrument: qualification of the tabletting machine and the instrumentation with respect to the determination of punch separation and validation of the calibration procedures, Eur. J. Pharm. Biopharm. 47 (1999) 231–245.
[11] DIN 51301, Kraftmessgeräte für statische Kräfte zur Prüfung von Werkstoffprüfmaschinen, Beuth, Berlin, 1986.
[12] DIN 1319-4, Grundlagen der Messtechnik - Teil 4: Auswertung von Messungen, Messunsicherheit, Beuth, Berlin, 1999.
[13] K. Weise, W. Wöger, Messunsicherheit und Messdatenauswertung, Wiley-VCH, Weinheim, 1999, 247–251.
[14] J.E. Rees, J.A. Hersey, E.T. Cole, The effect of rate of loading on the strength of tablets, J. Pharm. Pharmacol. 22 (Suppl.) (1970) 64S–69S.
[15] S. Edge, D.F. Steele, A. Chen, M.J. Tobyn, J.N. Staniforth, The mechanical properties of compacts of microcrystalline cellulose and silicified microcrystalline cellulose, Int. J. Pharm. 200 (2000) 67–72.