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Tabletting of pellet–matrix systems: ability of parameters from dynamic and kinetic models to elucidate the densification of matrix formers and of pellets

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Abstract

Two different types of pellets, i.e. drug-free sugar spheres, and pellets, spray-layered with crystalline theophylline and coated with Eudragit RS/RL, were tabletted each in combination with matrix-forming powder mixtures of Avicel PH200 and PEG 4000. The die fills from pellets and powder mixtures were regarded as two-compartment systems with a volume fraction of the pellets being limited to 0.52 corresponding to a cubic lattice, and the maximum degrees of densifications were adjusted related to the matrix. To data measured during single compression cycles on an instrumented eccentric tabletting machine and transformed appropriately, the Kawakita equation, the Heckel function, and a modified Weibull function were fitted, and the total work of compression was calculated. The Kawakita model fitted well systems with both types of pellets. Its parameters reflected the additional densification of the theophylline pellets separately from that of the matrix formers. The Heckel function could only be applied to systems containing non-porous sugar spheres, since the theophylline pellets underwent considerable densification and deformation. Only, when the Heckel porosity function was related to the volume fraction of the matrix, excluding the sugar spheres, the approximately linear regions for mixtures with increasing volume proportions of sugar spheres occured in comparable regions of densification. Parameters of the modified Weibull function demonstrated an increasing resistance against densification with increasing amounts of pellets. The total work of compression increased steeply with increasing volume fractions for pellets from 0.42 to 0.46 indicating, that the resistance against densification already rose when the pellets were still isolated. In conclusion, the combination of dynamic and kinetic models provides a comprehensible insight into the process of tabletting powder mixtures with pellets. Particularly, the Kawakita model was a suitable tool to differentiate the actual changes in porosity during compression from the compressibility of such complex systems.

Keywords: Tabletting; Pellets; Matrix former; Heckel; Kawakita; Work of compression; Degree of densification

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1. Introduction

Coated pellets are chosen as drug units when high standards are set to the reproducibility of drug release and when drug safety should be assured (Bechgaard, 1982; Krämer and Blume, 1994). Considerations to use the tablet as a carrier system for multiple unit dosage forms instead of the commonly used capsule led to many investigations in tabletting of pellets. The use of already existing tabletting capacities could be the most important reason for preferring the development of a tablet instead of a capsule.

However, the tabletting process represents the potential risk of damaging pellets by the mechanical load during compaction.

For tabletting, pellets are usually combined with excipients which are able to embed, cushion and isolate the pellets within a matrix. A coherent matrix formed by easily deformable and fluffy excipients can prevent pellets from auto-adhesion and consequently from problems in disintegration (Bodmeier, 1997). Moreover, the matrix protects the pellets from mechanical threat and is responsible for tablet strength. But due to the propensity to segregate during tabletting within the filling device and even within the die, especially at high production speed, the risk of pellet damage still remains (Haubitz et al., 1996; Wagner et al., 1999).

Most of the studies on tabletting of pellets dealt with the impact of the compression process on the properties of the compacts obtained and the alterations in the properties of the pellets. The amount (Béchard and Leroux, 1992; Sarisuta and Punpreuk, 1994; Torrado and Augsburger, 1994; Beckert et al., 1996; Mount and Schwartz, 1996) and size (Ragnarsson et al., 1987; Haslam et al., 1998) of pellets, the level of compression load (Aulton et al., 1994; Sarisuta and Punpreuk, 1994; Beckert et al., 1996; Mount and Schwartz, 1996) and the materials used for matrices (Sarisuta and Punpreuk, 1994; Beckert et al., 1996; Mount and Schwartz, 1996) were the subjects in comparative studies. In most cases, the level of compression load was adjusted to a distinct maximum pressure. In cases where no matrix excipients were added to the pellets, the degree of densification was adjusted according to the entire porosity of the compacts. Thereby, the compression behaviour of the pellets themselves could be described (Maganti and Çelik, 1993).

Since the pressure during the compression cycle has to be regarded as a reaction of the material on the volume reduction enforced by the punches (Marshall, 1989; Mielck and Stark, 1995), the maximum pressure cannot represent an independent parameter within a study design. This is the reason why in different studies the assessment of an optimal pellet concentration did not come to the same result. Furthermore, comparing the properties of compacts containing different portions and different types of pellets on the basis of the same maximum pressure can only lead to quite limited interpretation.

In addition, the concentrations of pellets chosen were always mass-related percentages, without considering that different types of pellets variate in their apparent densities due to different manufacturing processes and materials.

We therefore consider the degree of densification as an independent variable instead of the force, which can be adjusted by aid of the actual volume proportions of pellets to matrix. The volume fraction of pellets is calculated using their apparent density. The compression cycle is then analyzed with respect to the changing volume proportions of pellets to matrix. The method should enhance the understanding how the amount, size and type of pellets affect the compression properties of a certain matrix. A further purpose is to find parameters for assessing the compressibility of different systems and for the control of the tabletting process.

1.1. Theory of compression data analysis

The Kawakita equation (Kawakita and Lüdde, 1970/71) relates the reduction of volume between the punches at a certain pressure to the initial volume at a defined pressure threshold (Eq. (1)). Thus, the course of displacement of the upper punch with pressure is described independently from any calculated relative densities of the powder. In this equation the densification process is regarded as a relative reduction of volume between the punches related to the initial volume

at a defined pressure threshold.

$$C = \frac{V_0 - V_P}{V_0} = \frac{a * b * P}{1 + b * P} \quad (1)$$

The constant 'a' is equal to the initial porosity which corresponds to the total portion of reducable volume at infinitely high pressures. The degree of curvature of the generated curves of volume reduction versus pressure is expressed by the constant 'b'. Reciprocal values of 'b' represent the pressure necessary to reduce the porosity by half. For different materials, both parameters correlated well with some of their physical properties. In addition, for uniaxial densifications of packed beds from solid agglomerates, Adams and McKeown (1996) were able to show a correlation between the strength of single agglomerates and the parameters of the Kawakita equation obtained from the powder bed. In this study the suitability of the Kawakita equation shall be investigated for detecting the porosity of a pellet-embedding matrix and for distinguishing between the compression behaviour of the matrix and the effect of the pellets on it.

Another method used widely to analyse compression data is to apply the Heckel equation (Heckel, 1961) to displacement–pressure profiles:

$$\ln(1/(1-D_{rel})) = kP + A \quad (2)$$

The current distance between the punches is transformed into a relative density D_{rel} of the powder bed which requires the knowledge of the true densities of all components. The calculated relative densities in-die are then transformed into the term $\ln 1/(1-D_{rel})$, which is the negative log of porosity, in order to obtain a certain linear region in Heckel plots for which a slope and an intercept can be estimated. Duberg and Nyström (1986) and Humbert-Droz et al. (1983) used such Heckel plots to interpret the densification mechanism of several pharmaceutical excipients and drugs. However, the extent and position of the linear region can variate widely, as was shown by Konkel and Mielck (1997), who determined a region within a Heckel plot with acceptable linearity by an algorithm with an appropriate statistical deviation criterion.

Based on differences between published Heckel parameters, Sonnergaard (1999, 2000) accentuated the great sensitivity of Heckel plots to small errors in the true density and criticized the validity of the concept of yield pressures derived from slopes of such plots.

For the present problem, as a first assumption, the pellets were regarded to be mechanically stiff in contrast to the matrix-forming materials, which were purposely selected to be easily and irreversibly deformable. Then, the compression behaviour of the matrix in dependence on different concentrations, sizes and types of pellets might be assessed better, when the volume parts occupied by the pellets are excluded from the calculation of relative densities. Such corrected Heckel plots are supposed to show a better performance in characterizing the compressibility of systems consisting of matrix with different volume fractions of pellets.

While both models cited above consider a specific function of volume in dependence of force or pressure, the modified Weibull function (Dietrich and Mielck, 1984), further modified by Konkel and Mielck (1997) is as a function, which relates force or pressure to time for known initial volumes being densified to known maximum relative densities. This function provides a capable method to characterize the force or pressure at the upper punch, but requires the knowledge of true densities of the materials compressed as well. A fixed time span of data to be analysed can be taken as the contact time (t_c). Within this contact time, the pressure exceeds a certain threshold of minimum pressure. The function fitted is derived from an iterative approximation of the maximum pressure (P_{max}), the time at the fitted maximum pressure (t_{max}) and the shape factor γ:

$$P(t) = P_{max}\left(\frac{t_{end} - t}{t_{end} - t_{max}}\right)^{\gamma} e^{1-\left(\frac{t_{end}-t}{t_{end}-t_{max}}\right)^{\gamma}} \quad (3)$$

The parameter γ describes how steeply the pressure rises up to P_{max}. The relative position of t_{max} within the contact time is expressed by the parameter β which is defined as the percentage of time remaining from t_{max} to the end of contact

time (t_{end}). Both parameters, β and γ, proved to be suitable for characterising the densification behaviour of different excipients, drugs and mixtures of them, particularly by using γ/β diagrams (Mielck and Stark, 1995; Haaks, 1988; Krause, 1991). The parametrisation provides the possibility to discern whether fragmentation or plastic deformation dominates the densification behaviour. For the compression of matrix systems containing different concentrations of pellets the capability of a parametrisation with the aid of Eq. (3) was investigated with respect to the purpose to characterise the impact of the pellets on the compression behaviour.

Krycer and Pope (1982) in an early review of approaches to interpret powder compaction data, proposed the use of energies, in particular energies of compaction. While these authors recommended to relate the work required to cause tablet failure to the lower punch work of compaction in order to evaluate the energy utilization of compaction, in the present work the focus is on the interpretation of data from the densification process only. Therefore, the evaluation is restricted to a work of compression and a work of fast elastic expansion, which can be obtained by integration, when forces are multiplied by the respective rates of densification, ds/dt, and by the time increment, dt. This kind of analysis considers the entire force-time profile of a compression cycle, as does the modified Weibull function.

In order to provide an additional and sensitive method to detect and quantify the occurence of deformation of pellets, the types of pellets containing theophylline as a model drug were coated with a purposly thin layer of polymers, with two different contents of a plasticizer, able to retard the release of drug when not disrupted. Acceleration of the release of drug from tablets even with deformed, but still coherent pellets, would reflect mechanical stress mainly at the surface of the pellets during tabletting. However, release studies with these compacts will be subject of a subsequent publication. Simultaneously, these film coats represent some part of the mechanical stability of these pellets, which will be included in any response of the tabletting mixtures to densification.

2. Materials and methods

2.1. Materials

Excipients used for forming matrices were microcrystalline cellulose, MCC (Avicel PH200, batch M539C, Lehmann & Voss, Hamburg, Germany) and polyethylene glycole 4000, PEG 4000 (Polyglykol Powder, batch 106307869, Clariant, Frankfurt, Germany). Image analysis (KS 400 Imaging System 3.0, Carl Zeiss Vision, Eching, Germany, with digital camera Hitachi 3-CCD, HV-C20E/K-S4, Hitachi Denshi, Rodgau, Germany, calibrated with objectmicrometer fo calibration, 50 mm/0.1 mm and 50 mm/0.01 mm, Leica Mikroskopie, Wetzlar, Germany, validated with steel balls RB-1, precision class G20W, SKF Maschinenbau u. Handel, Hamburg, Germany) of $>20{,}000$ particles resulted in the following, characterizing parameters: MCC: fines <40 μm: 8%, d_{50} 170 μm, d_{90} 310 μm, and PEG 4000: fines <40 μm 16%, d_{50} 240 μm, and d_{90} 390 μm. As model pellets, drug-free sugar spheres (Neutral Pellets, H.G. Werner, Tornesch, Germany), and as drug-containing pellets, theophylline-coated pellets were used. Narrow size fractions of pellets were obtained by careful sieving. The sugar spheres were divided into the fractions 0.63–0.80, 0.80–1.00 and 1.00–1.25 mm, and theophylline pellets into the fractions 0.80–1.00 and 1.00–1.25 mm. The uniformly sized fractions of both types of pellets of 1.00–1.25 mm in diameter were used for tabletting.

Theophylline pellets were prepared by suspension-layering with a mixture, containing the equivalent of 66% (w/w) crystalline theophylline, (theophylline anhydrous, lot # 92577, Knoll AG, Germany, recrystallized from water at room temperature to the monohydrate, and micronized by an air jet mill to $d_{90}<10$ μm), 22.6% (w/w) tribasic calcium phosphate (calcium phosphate, lot # 96030180, Synopharm, Barsbüttel, Germany), and 11.4% (w/w) HPMC (Pharmacoat 603, lot # 510480, Syntapharm, Germany), dispersed in water to a total solids content of 30% (w/w), on sugar spheres of 0.63–0.80 mm in diameter as starter cores in a fluidized bed, using a bottom

spray process (Uniglatt, Glatt GmbH, Binzen, Germany, equipped with a Wurster column).

Subsequently, the drug-loaded pellets were coated with a thin film layer (about 22±4 μm) using the same process as for suspension-layering of drug with a dispersion of Eudragit RS/RL 30 D (4:1) (Röhm Pharma Polymers, Darmstadt, Germany). Two different levels of plasticizer, 10 and 20% triethyl citrate (TEC) related to the polymer mass, were used in order to obtain film coats with different mechanical properties. Beside the impact of the plasticizer concentration on the integrity of the pellets during tabletting, the compression behaviour of the pellets will include effects of these film coats.

2.2. Densities of materials

The true densities of the matrix materials and of the sugar spheres were determined by gas pycnometry (Stereopycnometer SPY-2, Quantachrome, New York). In contrast, coated theophylline pellets had to be investigated in a fluid medium, because significant permeation of gas into the drug layer was observed during gas pycnometry. Therefore the determination was carried out with a pycnometer (Brand, Wertheim, Germany) filled with subliquid paraffine (Ph. Eur.). The comparability of the results between the gas and the fluid method was demonstrated by determining the true density of glass beads with both methods. Glass beads can be regarded as a material having neither any internal porosity nor any interactions with the fluid medium. Since the gas method was capable to detect a difference in the density between intact and grinded sugar spheres equal to 2% internal porosity, this method was found to be more accurate than the fluid method. The relevant densities used for the compression studies are listed in Table 1.

Bulk and tapped densities were determined in compliance with the Ph. Eur. method (STAV2003, Engelsmann AG, Ludwigshafen, Germany).

2.3. Mechanical strength of pellets

The mechanical strength of sugar spheres and of pellets was analyzed by a Texture Analyzer (TA XT2, Stable Micro Systems, Haslemere, UK, with load cell 5 kg, sensitivity ±0,1 g, displacement sensitivity ±2.5 μm, loading with plane head of 2 mm diameter over a distance of 0.5 mm at a rate of 0.1 mm s^{-1}, recording rate 100 values s^{-1}). Seven specimens each were analyzed. Stable fracturing was observed and a deformation factor calculated as the reciprocal of the slope of a linear regression of the force vs. compression curve. The maximum surface stress according to Shipway and Hutching, $\sigma_f(s)$, as proposed by Salako et al., 1998, was calculated, using the maximum force and the mean diameter (Digimatic Indicator 543, Mitutoyo Corp, Tokyo, Japan, $n = 50$ for each pellet type, mean relative S.D. = 5.6%), by Eq. (4). It has to be noted, that with theophylline pellets fracture occurred primarily of the drug layer. The maximum force therefore relates always to the first fracturing event. The values are collected in Table 2.

$$\sigma_f(s) = 0.4F_{max}/(\pi r^2) \quad (4)$$

Table 1
Densities of raw materials (MCC (AvicelPH200), PEG 4000, and sugar spheres), glass spheres as test material, and different pellets, determined with a gas pycnometer ($n = 9$) and a fluid pynometer ($n = 3$) (means±S.D.; n.d.: not determined)

Material	Gas pycnometer (helium) (g/cm^3)	Fluid pycnometer (subliquid paraffine) (g/cm^3)
MCC	1.564±0.006	n.d.
PEG 4000	1.229±0.005	n.d.
Sugar spheres	1.544±0.004	n.d.
Sugar spheres, ground	1.575±0.006	n.d.
Glass beads	2.940±0.007	2.931±0.030
Theophylline pellets with 10% TEC	n.d.	1.240±0.001
Theophylline pellets with 20% TEC	n.d.	1.217±0.005

2.4. Preparation of mixtures

Microcrystalline cellulose (MCC) was chosen as the main component for the matrix forming mixtures due to its capability to built already firm comprimates at relatively low degrees of

Table 2
Size (mean ± S.D., $n = 50$) and parameters for mechanical strength (mean ± S.D., $n = 7$) of sugar spheres (size fractions 630–800 and 1000–1250 μm) and coated theophylline pellets (with 10 and 20% triethylcitrate as plasticizer)

Material	Size ($n = 50$) (μm)	Crushing strength (N)	Maximum surface stress[a] $\sigma_t(s)$ (MPa)	Deformation factor[b] (μm N^{-1})
Sugar spheres	701 ± 70	3.0 ± 1.1	3.1 ± 1.1	16 ± 2
	1043 ± 49	7.2 ± 1.0	3.4 ± 0.6	15 ± 1
Theophylline pellets (10% TEC)	1133 ± 56	9.9 ± 0.8	3.9 ± 0.3	19 ± 1
Theophylline pellets (20% TEC)	1132 ± 47	9.4 ± 1.3	3.7 ± 0.5	20 ± 1

[a] Calculated according to Shipway and Hutchings from maximum force at loading, and the mean diameter: $\sigma_t(s) = 0.4F_{max}/(\pi r^2)$.
[b] Reciprocal of the slope (linear regression up to 1st breaking event) of the force–compression curve.

densification. The high porosity of MCC was regarded as being compellingly required for isolating sufficiently the pellets in the matrix. Small portions of polyethylene glycole (PEG 4000) were added to the MCC for modifying the properties of the matrix forming mixtures by a plastically deformable material. All excipients were equilibrated under the same climatic conditions as the tabletting was carried out. The mixtures of matrix formers containing 5, 15 and 30% (w/w) PEG 4000 in MCC were prepared in a shaking mixer (Turbula T2 C, Bachofen, Basel, Switzerland) by blending total amounts of 50 g in a 300 ml wide necked flask at 54 rpm for 5 min. Calculated masses of matrix formers and pellets for every single amount required for 1 tablet were then blended in a 7.5-ml vial by a manual operation standardized as far as possible. The vial was closed by a self-constructed stopper, then it was put upside down on the opening of the die and the closure strap of the stopper was momentarily pulled to deliver the content into the die by mass flow. This procedure was established in order to avoid segregation phenomena within the die fill.

2.5. Tabletting

Tabletting was performed on an instrumented eccentric tabletting machine (Hanseaten Exacta XI, W. Fette, Schwarzenbek, Germany) at a speed of 25 rpm under constant climate (21.5 ± 1 °C, 39 ± 1% r.h.). The upper piston and the lower punch holder of this machine are equipped with strain gauges (6/350 LY11, Hottinger Baldwin Messtechnik, Germany). The distance between the surfaces of upper and lower punch was measured by two inductive displacement transducers (W10, Hottinger Baldwin Messtechnik) mounted diagonally. Flat-faced punches of 14 mm in diameter (Ritter Pharma-Technik GmbH, Hamburg, Germany) were used.

The signals of force and displacement were amplified by a digital amplifier (MGC, Hottinger Baldwin Messtechnik) with a carrier frequency of 9.6 kHz, and were digitized by an analogue-to-digital converter (DT2827; Data Translation Inc., Marlboro, USA) at an acquisition frequency of 1.5 kHz. Acquisition and processing of data were carried out by ASYST (Macmillan Software Co., New York).

The complete measuring system was calibrated quasi-statically, while the elastic deformation of the punches for the correction of displacement values was obtained from dynamic calibration (Kühl, 1999). Data recorded for forces were divided by the surface area of the punches to obtain the respective pressures.

2.6. Principles of compression

A two compartment model was used, where it is assumed, that the outer coherent compartment of matrix is the only one which is densified during compression (Fig. 1). The pellets represent the inner, incoherent compartment, which occupies a nearly constant volume during densification.

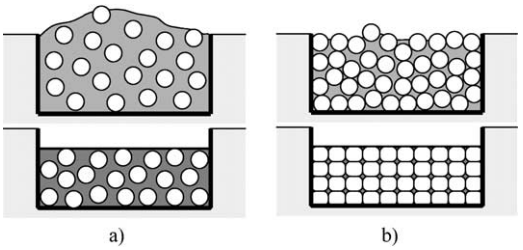

Fig. 1. Model of two compartments, two cases illustrated: (a) amount of pellets does not reach its bulk density after compaction, (b) amount of pellets exceeds the critical limit.

For all compression experiments, the minimum punch separation was adjusted to a constant distance of 4.50 mm (±10 μm), which corresponds to a minimum volume of 0,693 cm^3. The compressions were thus performed as a densification to defined maximum relative densities of the matrices ($D_{rel,max}$). To obtain a certain value of $D_{rel,max}$, the masses of powders to obtain the matrix, and of the pellets to obtain a certain percentage (w/w) had to be calculated. Fig. 2 shows the relationship between the mass concentrations of sugar spheres and the calculated total masses of pellets and matrix for the lowest and highest values chosen for $D_{rel,max}$. It is obvious that, the lower $D_{rel,max}$ the less linear the relationship due to a higher effect of the total amount of gas volume in the mixtures. For the calculation, the true densities of the matrix-forming powder materials and the apparent densities of pellets are required. The two-compartment situation limits the amount of pellets, which can be chosen, to a percentage at which their theoretical bulk density is reached and the matrix fills only the voids between the pellets without separating them. For a cubic packing of spheres the corresponding volume fraction is reached at 52% (V/V).

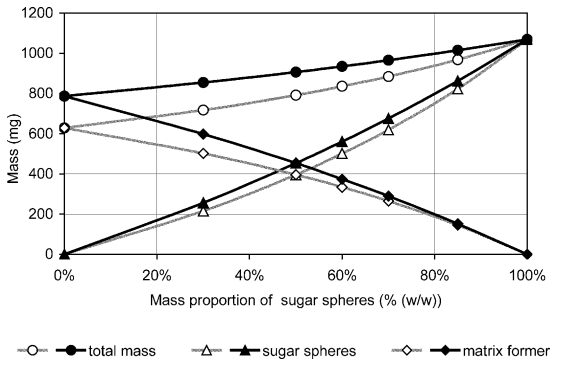

Fig. 2. Masses of sugar spheres and matrix (MCC (Avicel PH200) with 15% PEG 4000) to be weighed for a single compact in dependence of the mass proportion of sugar spheres at the lowest and highest degree of densification related to the matrix (open symbols: $D_{rel,max} = 0.60$; closed symbols: $D_{rel,max} = 0.75$).

2.7. Compression studies

Matrices containing concentrations of 5%, 15% and 30% PEG 4000 in MCC were combined with 0, 30, 50 and 60% (w/w) sugar spheres and compressed to $D_{rel,max}$ of 0.60, 0.65, 0.70 and 0.75, respectively. In addition, theophylline pellets were compressed with the same matrix-forming materials to the higher $D_{rel,max}$ of 0.70 and 0.75, respectively. The mass concentrations of theophylline pellets and sugar spheres occupying the same volume fractions in the bulk mixture at the beginning of a compression cycle are different due to the difference in their apparent densities. Theophylline pellets (44 and 54% (w/w)) correspond to 50 and 60% (w/w), respectively of sugar spheres.

2.8. Analysis of compression data

The Kawakita equation, the Heckel function and the modified Weibull function were approximated to the respective transformations of displacements as functions of the pressures for the two former models, and to pressures and time for the latter, using a program written in ASYST. For calculating the volume reduction of the Kawakita equation, C, the initial volume V_0 was determined at the point where at least five pressure data had exceeded the pressure threshold of 1 MPa. Curve fitting was then applied to the whole section up to the maximum pressure at the upper punch (P_{max}). The algorithm for determining a sufficiently linear region within Heckel plots was taken from Konkel and Mielck (1997). For the fitting of the modified Weibull function by means of a Gauß–Newton method the sequence of data (pressure, time) to be analysed started and ended when 50 subsequent pressure values at first lied above 1 MPa. The time

interval between these limits is termed the contact time.

In addition, the work of compression, W_{comp}, was calculated. After smoothing the profiles of the rate of displacement *vs*. time of the upper punch, and calculating values for power by using the respective forces, integration of the area under the resulting power/time curves from the beginning of the contact time to the time of maximum displacement resulted in W_{max}, and from that time to the end of the contact time in W_{elast}. The difference of these energies gave the net work of compression.

3. Results and discussion

3.1. Kawakita equation

Fitting the Kawakita equation to the data transformed accordingly allows the analysis of the entire pressure rise from the threshold value of 1 MPa up to the pressure at maximum displacement of the upper punch. In Fig. 3, the percentage volume reduction, C, is represented in relation to the corresponding pressure for single compression cycles of mixtures of 0, 30, 50 and 60% (w/w), respectively, sugar spheres with the matrix former containing 30% (w/w) PEG 4000. A different progression in densification is noted at initial, low pressures. The maximum of volume

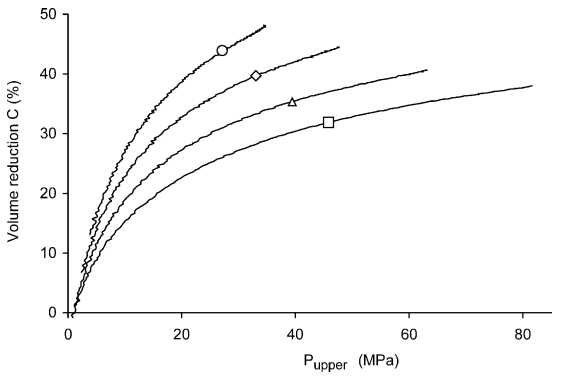

Fig. 3. Volume reduction C from the Kawakita equation in relation to the pressure of the upper punch P_{upper} between 1 MPa and maximum pressure; matrix: MCC (Avicel PH200) with 30% (w/w) PEG 4000; pellet concentrations (w/w): 0% (□), 30% (◇), 50% (△), 60% (○).

reduction as estimated by the parameter a, seems to be dependent on the porosity of the bulk mixture. Table 3 collects the data for parameter a in comparison to the respective bulk porosities for all matrices and all proportions of sugar spheres at the highest $D_{rel,max}$ of 0.75. Comparing parameter a to the corresponding bulk porosity with regard to the proportion of sugar spheres, the curve fitting led to a slight overestimation of the porosity for the pure matrices. In contrast, for mixtures containing sugar spheres, the parameter a is underestimated to an extent that is dependent on the amount of sugar spheres. Most probably the assumption is not correct, that the acquired compression data built a representative part of a totally homogeneous pressure curve obeying the Kawakita equation. In fact, the proportion of pellets affects the pressure course in a way that the porosity is underestimated. This can be interpreted as an increase in the resistance against compression of the total mixture. The sugar spheres can not be densified to a significant extent since their inner porosity was determined approximately to be only 2%. As a consequence of deriving too low values of parameter a for mixtures containing sugar spheres, the reciprocal of b is too low in relation to the pure matrices as well. Both parameters are illustrated in Fig. 4 for the concentrations of 0, 30, 50 and 60% (w/w), respectively, at $D_{rel,max}$ 0.75. The underestimated porosity of sugar spheres containing mixtures is illustrated in form of too low left positions of the data points in the plot. The values $1/b$, indicating the ability to resist against volume reduction, increase strongly from 30 to 60% (w/w) of pellets.

From the consideration above, it is likely that the type of pellets influences the compression behaviour of the mixtures due to the mechanical properties of the pellets.

For that reason an evaluation was performed by fitting the Kawakita equation to pressure profiles of mixtures with equal volume amounts of sugar spheres and theophylline pellets, respectively, at the highest target degree of densification, $D_{rel,max} = 0.75$. If it is assumed that the load of the threshold value of 1 MPa is still not high enough to affect the porosity of the theophylline pellets significantly, the volume fraction of the

Table 3
Kawakita parameter a (mean ± S.D, $n = 7$) from tabletting graded mixtures of MCC (Avicel PH200) with PEG 4000 as a matrix, mixed with graded proportions of suguar spheres, to $D_{rel,max}$ of 0.75, in comparison to the corresponding bulk porosity of the systems

Matrix PEG 4000 in MCC (% (w/w))	Mass proportion of sugar spheres (% (w/w))	Parameter a	Bulk porosity
5	0	0.789 ± 0.005	0.736
	30	0.643 ± 0.005	0.658
	50	0.557 ± 0.003	0.590
	60	0.522 ± 0.003	0.549
15	0	0.771 ± 0.006	0.715
	30	0.628 ± 0.004	0.638
	50	0.543 ± 0.006	0.562
	60	0.502 ± 0.004	0.535
30	0	0.744 ± 0.005	0.682
	30	0.601 ± 0.004	0.612
	50	0.515 ± 0.005	0.537
	60	0.480 ± 0.006	0.514

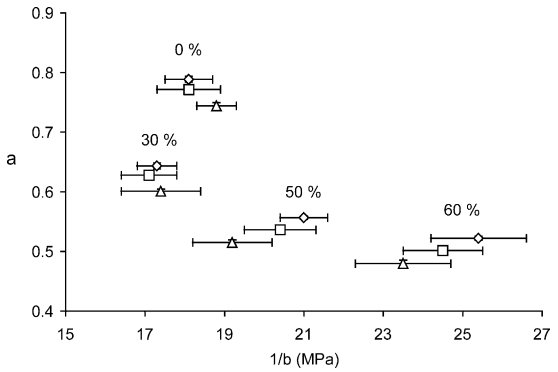

Fig. 4. Kawakita parameters $a \pm$S.D. and $1/(b \pm$S.D.) from tabletting the pellet concentrations 0, 30, 50 and 60% (w/w) in matrices of MCC (Avicel PH200) with 5% (◇), 15% (□) and 30% (△) (w/w) PEG 4000, at $D_{rel,max}$ of 0.75; mean values from $n = 7$.

pellet load in the die can be calculated at this pressure: 50% (w/w) sugar spheres and 44% (w/w) theophylline pellets both correspond to 25% (V/V), while 60% (w/w) sugar spheres and 54% (w/w) theophylline pellets , respectively, occupy 32% (V/V) at 1 MPa. In Table 4, all values of parameter a and $1/b$ are collected in order to compare between the different pellet types. A potential effect of the mechanical properties of the polymeric coat on the compression data could be assessed by investigating theophylline pellets coated with two differently plasticised film materials, namely 10% TEC and 20% TEC. The values of the parameter a for mixtures with theophylline pellets were distinctly higher than for mixtures with sugar spheres. Hence, an additional porosity of the pellets was detected in the pressure profile. This might indicate that the theophylline pellets were not only deformed and potentially broken but also densified during compression. The difference between the values of parameter a for mixtures with sugar spheres and those with theophylline pellets corresponds to a volume difference of 7.5–8%. However, this value will overestimate the porosity available for densification of the theophylline pellets, since the range of densification available for fitting of the Kawakita equation considered only the densification of the porous drug layer, but not yet that of the pellet cores, which are sugar spheres as well, although of a smaller size fraction, namely 630–800 μm.

In contrast to parameter a, parameter b changed only slightly between mixtures with different types and amounts of pellets, although clearly different maximum pressures were achieved during the compressions. Fitting the Kawakita equation proved to be an effective means to distinguish between different original porosities. The difference in the flexibility of the film could not be detected by the Kawakita parameters. Film coats with 20% TEC will have a distinctly higher flexibility than films with 10% TEC (Lehmann et al., 1993). The deformation of the film is a prerequisite for any potential densification of the

Table 4
Kawakita parameters a and $1/b$ (mean ± S.D., $n = 7$) for different pellet types and two different volume fractions of pellets from tabletting to $D_{rel,max}$ of 0.75

Volume fraction of pellets at 1 MPa (% (v/v))	Mass proportion of pellets (% (w/w))	Kawakita parameter a	Kawakita parameter $1/b$ (MPa)
25	50 SP	0.515 ± 0.005	19.2 ± 1.0
	44 TP10	0.588 ± 0.011	20.9 ± 1.8
	44 TP20	0.590 ± 0.009	21.6 ± 1.6
32	60 SP	0.480 ± 0.006	23.5 ± 1.2
	54 TP10	0.556 ± 0.008	21.2 ± 0.8
	54 TP20	0.562 ± 0.004	22.3 ± 1.1

SP: sugar spheres; TP10: theophylline-layered pellets, coated with Eudragit RL/RS 30D with 10% triethylcitrate; TP20: similar theophylline-containing coated pellets, containing 20% triethyl citrate.

porous drug layer. Nevertheless, due to the very low thickness of the film coats, which are only about 20 μm thick, their mechanical properties have no discernible impact on the observed compression behaviour.

3.2. Heckel function

The same data for pressure and displacement, the latter after appropriate transformation with the aid of the true densities, can also be presented in form of Heckel plots in order to support the interpretation of the compression mechanisms. In the Heckel term $1/(1-D_{rel})$, the relative density considers the total mass of the tabletted mixture. In Fig. 5 Heckel plots are presented for mixtures of MCC with 5% (w/w) PEG 4000 as matrix forming agent, and with sugar sphere contents increasing from 0 to 60% (w/w). It is seen clearly, that in the initial compression phase the curvature of the profile increases with increasing proportion of pellets. This can be interpreted as a rearrangement of the powder bed. The pellets markedly disturb the packing of matrix particles. As a consequence, the pellets will change their location within the powder bed during the early phase of densification. Furthermore, the slopes of the apparently linear regions decrease with increasing pellet content. However, when the Heckel terms $1/(1-D_{rel})$ are related solely to the matrix as in Fig. 6, the extensive reduction in the compressibility with increasing amount of sugar pellets becomes evident. The rise in pressure sets in at almost the same relative density of the matrix for all proportions of

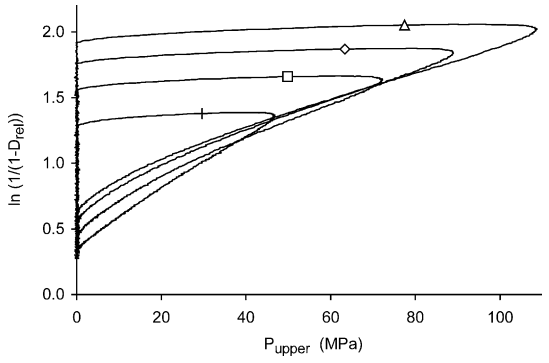

Fig. 5. Heckel plots from single densifications of matrix of Avicel PH200 with 5% PEG 4000, mixed with 0% (+), 30% (□), 50% (◇) and 60% (△) (w/w) sugar spheres, at $D_{rel,max}$ of 0.75; the relative density D_{rel} is related to the total volume between the punches.

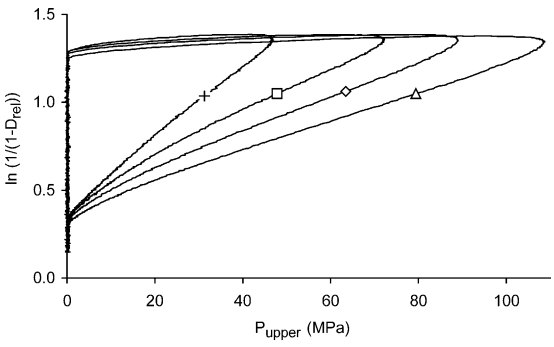

Fig. 6. Heckel plots, with the relative density D_{rel} solely related to the volume of the matrix, from single densifications of matrix of MCC (Avicel PH200) with 5% (w/w) PEG 4000, mixed with 0% (+), 30% (□), 50% (◇) and 60% (△) (w/w) sugar spheres, at $D_{rel,max}$ of 0.75.

sugar pellets, what is to be expected when the pellets are supposed to be isolated in the matrix as presumed in the model of two compartments. Nevertheless, slight differences can be observed in the initial pressure rise. The difference increases with a lower porosity of the matrix corresponding to a higher concentration of PEG 4000. In Fig. 7, the calculated mean values of the slope parameter kH are presented for all three matrices investigated (5, 15 and 30% (w/w) PEG 4000) at the highest degree of densification ($D_{rel,max} = 0.75$). For all matrices, the compressibility is found to be impaired to a similar extent. In order to compare the compression behaviour of mixtures with almost porosity-free sugar spheres and mixtures with theophylline pellets carrying a porous drug layer, Heckel plots were generated from densifications of equal volume proportions of pellets, as shown in Fig. 8 for compacts with the matrix containing 30% (w/w) PEG 4000. Already at a very low stage of densification, the Heckel functions of mixtures containing theophylline pellets with 10% TEC deviate from those of mixtures with sugar spheres. In contrast to mixtures containing sugar spheres, no regions in their Heckel functions can be identified to be sufficiently linear. It seems, thus, that the curves reflect two different and superimposed compression mechanisms. Consequently, no slope parameter kH should be determined. In addition to the Heckel functions of mixtures containing pellets, the graph includes the curve of the pure matrix with 30% (w/w) PEG 4000. The

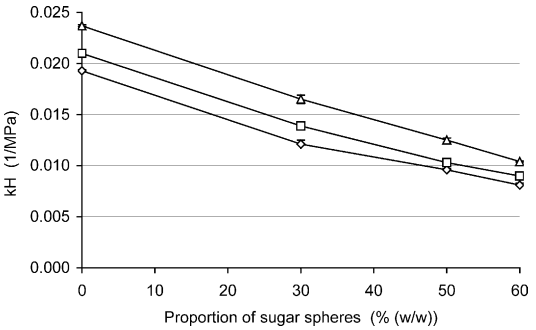

Fig. 7. Heckel slope parameter kH from the regions of fitted Heckel function at $D_{rel,max}$ of 0.75; matrices of MCC (Avicel PH200) with 30% (△), 15% (□) and 5% (◇) (w/w) PEG 4000 (mean values ± S.D. from $n = 7$).

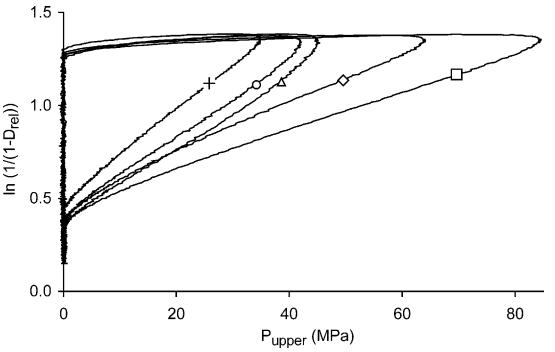

Fig. 8. Heckel plots, with the relative density D_{rel} solely related to the volume of the matrix, from systems with two different volume fractions of pellets and from pure matrix (MCC (Avicel PH200) with 30% (w/w) PEG 4000) at $D_{rel,max}$ of 0.75; pellet proportions: 60% sugar spheres (SP) (□), 50% SP (◇), 54% theophylline pellets (TP) (△), 44% TP (○) and pure matrix (+).

latter matrix clearly reveals the strong influence of the type of pellet in comparison to that of the proportion of pellets. The very early difference in the pressure rise between the two pellet types indicates that the lower resistance of theophylline pellets with 10% TEC against compression is based on a dynamic interaction between the matrix and the pellets during the entire compression cycle. The behaviour of theophylline pellets during compression can be explained as permanent, pressure dependent yielding due to deformation and densification of the porous drug layer. To the same extent as the pellets are densified, the matrix can evade densification.

3.3. Modified Weibull function

The parameters of fitting, β and γ, are shown in Fig. 9 for the matrix comprising of MCC and 5% (w/w) PEG 4000 at four different $D_{rel,max}$ and at the pellet concentrations of 0, 30, 50 and 60% (w/w), respectively. Whereas for the pure matrix only the values of β, but not those of γ, change with $D_{rel,max}$, an increasing proportion of sugar spheres led to an increase of γ. Since, within the contact time, the time proportion of the rising pressure increases with an increasing $D_{rel,max}$, the decrease in β observed means a shift of the relative position of maximum pressure. An increasing value of γ

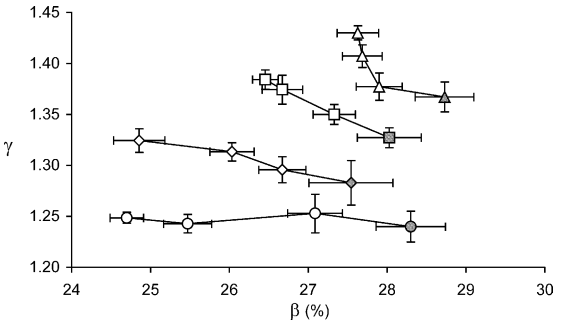

Fig. 9. Modified Weibull parameters β and γ derived from the fitting of the function for different pellet concentrations: 0% (○), 30% (◇), 50% (□) and 60% (△) (w/w) sugar pellets; matrix: MCC (Avicel PH200) with 5% (w/w) PEG 4000, $D_{rel,max}$ increasing from 0.60, 0.65, 0.70 to 0.75, lowest $D_{rel,max}$ indicated with grey filled symbols; mean values ± S.D. from $n = 7$.

reflects the fact that the pressure rise up to the maximum pressure becomes steeper with higher pellet proportions and increasing $D_{rel,max}$. The final phase of compression is strongly affected by the extent of direct and indirect interactions between pellets which cause a stronger resistance against the densification.

The increasing proportion of sugar spheres reduces the bulk height of the mixture in the die. Hence, the upper punch passes through the same stages of densification of the matrix within a shorter distance.

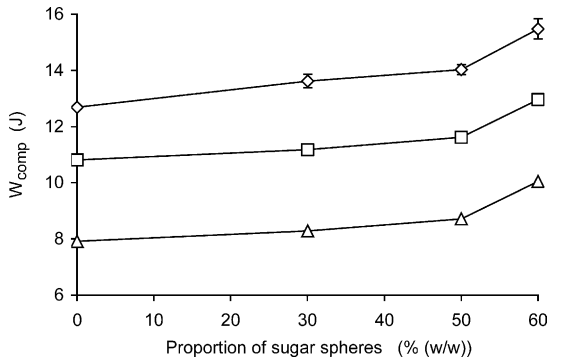

Fig. 10. Work of compression in relation to the proportion of sugar spheres at $D_{rel,max}$ of 0.75; matrices of MCC (Avicel PH200) with 5% (△), 15% (□) and 30% (◇) (w/w) PEG 4000; mean values ± S.D. from $n = 7$.

3.4. Work of compression

In Fig. 10, the work of compression, $W_{comp,}$ is shown for all three matrices used in combination with sugar pellets at $D_{rel,max} = 0.75$. When the concentration of sugar pellets exceeds a mass proportion of 50%, which corresponds to a volume fraction of 0.42, W_{comp} increases much more than proportionally. Hence it can be assumed that in reality the critical portion of pellets, at which direct interactions between the pellets occur, is reached at much lower volume fraction than it is expected with regard to the theoretical cubic packing of spheres corresponding to a volume fraction of 0.52. This should be seen in light of the fact that the pellets will never be homogeneously distributed within the matrix in an ideal manner.

4. Conclusion

The Kawakita equation was able to indicate for nearly porosity-free sugar spheres that compressions with increasing amounts of pellets lead to an increasing resistance of the matrix system against the compression. At the same time the decreased, total porosities of the systems were also detected, but they were increasingly underestimated with increasing amount of pellets. For compressions with theophylline pellets having an additional porous drug layer, the higher porosities of the systems are reflected in the values derived from the applied Kawakita equation. This observation leads to the conclusion that the coated drug layer is densified during compression. In contrast to the differences in porosity no significant differences were found in the resistance against compression between sugar spheres and theophyllline pellets. The mechanical flexibility of the film coats did not affect discernably the compression data.

The porosity term of the Heckel function can be related solely to the matrix as long as the pellets are known to be nearly without any porosity. For tabletting mixtures with sugar spheres the applied method of analysis enables to show how obviously the compressibility of the matrix forming system decreases with increasing portions of pellets. The Heckel plots from compressions of matrix systems

with theophylline pellets show a large difference in the curvature in comparison to mixtures containing sugar spheres demonstrating that a constant interaction between pellets and matrix occurs already at very low pressures. The courses of the Heckel plots imply the assumption that a rearrangement of pellets in the powder bed might take place.

A parametrization of the compression behaviour was performed with aid of the modified Weibull function. Particurlarly, the different changes in the compression behaviour in dependence on an increasing degree of densification could be described for the different pellet concentrations. The work of compression represents a suitable tool for determining the critical proportion of pellets in the matrix. For sugar spheres, at a volume ratio of 0.42 a concentration is reached where the work of compression increases steeply indicating the beginning of stronger mechanical interactions between the pellets.

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