Pressure Susceptibility of Polymer Tablets as a Critical Property: A Modified Heckel Equation

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Abstract □ The pressure susceptibility (χ_p), which is defined as the decrease of porosity (ϵ) under pressure was investigated. Of special interest are compacts obtained at very low pressures, because of the transition between the state of a powder and the state of a tablet. This range was found to be critical in respect to a diverging pressure susceptibility. Above a critical porosity (ϵ_c) or below the corresponding relative density (ρ_c), no pressure susceptibility can be defined, because of no rigid structure exists. To take this into account, a simple function was proposed for the pressure susceptibility: $\chi_p \propto 1/(\epsilon_c - \epsilon)$. This proposal leads to a new porosity vs pressure relationship. The new model was compared to the Heckel equation that involves a constant pressure susceptibility. Various polymers were tested from "out of die" measurements, and the new relationship was found superior to the Heckel equation. As a conclusion, the pressure susceptibility exhibits a curvature that can be called critical at low relative densities. Consequently, a better understanding evolves as to why the Heckel equation is not valid at low pressures. The new model has proven to be adequate for polymer tablets but, so far it is not clear whether other substances exhibit the same performance. Especially tableting materials exhibiting brittle fracture will be of interest considering their importance in compaction technology.

Introduction

Porosity–Pressure Relationship—A tablet can be considered as a special type of dispersion. The solid fraction and the air in pores constitute two phases of the system. This heterogeneous character of such a particulate material leads to a very complex mechanical behavior. In case of low packing fractions, rheological properties can be found. Thus, individual particles are movable to some extent, enabling many possible configurations. This aspect of a disordered structure holds for an analogy to liquids, and even an entropy S_t can be attributed to a particle packing.[1] Yet, the individuality of particles gets lost in tablets compacted at higher pressures. Consequently, also the entropy of the diverse particle configurations vanishes. Such very dense compacts can approach a continuum of the solid fraction, and therefore mechanics of practically homogeneous solids will evolve.

As a result, the character of the system undergoes dramatic changes as a function of the relative density. Particle rearrangements, occurrence of plastic flow, and possible brittle fracture contribute to a vast complexity. Hence, there is a number of different mathematical models, which are mostly empirical or contain at least some *heuristic* elements.

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The most widespread models used in the field of pharmaceutical technology are the Kawakita equation,[2] the approach according to Cooper and Eaton,[3] and the Heckel equation.[4,5] The latter model is of special interest for the present study:

$$\ln\left(\frac{1}{1-\rho}\right) = K\sigma + A \qquad (1)$$

where ρ equals the relative density and σ is the compression pressure, whereas K and A are constants. It is known that tablets compressed at higher pressures fulfill the relationship properly.[6] In a plot of $\ln(1/(1-\rho))$ versus applied pressure, K is determined from the slope, and A from the intercept. The general limitations of Heckel plots have been analyzed rigorously by Rue and Rees.[7]

Recent Developments—The lacking adequacy of the classical compression equations stimulated efforts for current investigations. Yu and Hall[8] analyzed very porous particle packings, using a double-logarithmic form of the Heckel plot. The fit of the new model was better than the original Heckel equation. Yet, the empirical nature of this approach lacking any theoretical background can be considered as a drawback. The same also can be remarked for the *heuristic* equation proposed by Lordi et al.[9]

An interesting modification of the original Heckel equation was attained by Carstensen et al.[10] They assumed the final compact of a pharmaceutical powder to always possess some residual porosity. Accordingly, the void volume decreases exponentially toward a value different from zero. The resulting model seemed capable to also describe experimental data in the nonlinear part of the Heckel plot and can potentially be extended to more than a one-component system.

Confined compression of particle agglomerates is mainly focused by an approach of Adams et al.[11] The bed in the die was modeled as a series of parallel columns, where only processes of friction were allowed. Thus, any system where elastic energy also is stored is not covered by this theory. However, the assumptions lead to a result that took approximately the same form as the Kawakita equation and therefore enabled a physical interpretation of its parameters.

Coming finally to a microscopic theory, Duncan–Hewitt[12] attempted a model of the compression process, where compact properties were predicted by the characteristics of single crystals. The behavior of brittle particles was found to be substantially different from the one of more ductile crystals, and so two distinct models evolved. However, the main problem of any microscopic theory can be understood in the change of relevant binding points. The tablet is heterogeneous, built up by particles whose binding points are distributed randomly to some extent. Consequently, disorder has to be taken into account by any theoretical approach.

The aspect of disorder is most interesting in that some very different physical problems can be treated similarly

from a theoretical point of view.[13] Modern physics of phase transitions and critical phenomena[14] provides interesting new concepts that can potentially be applied to many scientific fields. Yet, an analogy between relevant physical problems may not always be obvious at first, but similarities can be revealed by studying the *response functions* of a system. The present paper introduces such a function in the context of powder compaction.

Theoretical Section

Pressure Susceptibility—For particle systems, a pressure susceptibility can be defined as a function of the porosity and compression pressure as stated below:

$$\chi_p \equiv -\frac{1}{\epsilon}\frac{d\epsilon}{d\sigma} \tag{2}$$

The porosity can equally be expressed by the relative density:

$$\rho = 1 - \epsilon, \quad \text{or in differential form:} \quad d\rho = -d\epsilon \tag{3}$$

Hence, eq 2 reads:

$$\frac{d\rho}{d\sigma} = \chi_p(1 - \rho) \tag{4}$$

In case of a constant χ_p, eq 4 just holds for the differential form of the Heckel equation where χ_p equals K. Thus, a constant pressure susceptibility is the base of the theoretical concept of Heckel. Physically, this can be motivated by thinking of uniformly shrinking pores in a solid continuum. However, at low relative densities and pressures, the compacts are essentially particle agglomerates rather than homogeneously dispersed holes in a solid matrix. Consequently, a very different physical behavior can be expected.

Critical Behavior of the Pressure Susceptibility— Especially in the initial stage of the compression process, particle rearrangements dominate in many cases. In addition, fine particle systems can exhibit very porous structures by arching and formation of very loose agglomerates. Such structures are highly unstable and can collapse if only a minimal force is applied. Thus, the susceptibility to an external pressure can theoretically take any high value. Yet, it needs to be highlighted that in the case of a total lack of mechanical rigidity between the punches, the possibility to define pressure susceptibility is not available. Accordingly, a threshold value of the porosity ϵ_c or corresponding relative density ρ_c can be introduced, where a rigidity starts to evolve. The property χ_p exists therefore only for porosities lower than ϵ_c or relative densities higher than ρ_c. Hence, from these characteristics of the pressure susceptibility, the range in vicinity of the threshold can be called *critical*.

In line with these considerations, the Heckel model, where χ_p equals a constant K, needs to be replaced by an alternative approach, taking better account of the characteristics of pressure susceptibility. A related conjecture is an equation describing a hyperbola:

$$\chi_p = \frac{C}{\epsilon_c - \epsilon} = \frac{C}{\rho - \rho_c} \tag{5}$$

Where, C holds for a constant. Considering eq 5, it is interesting to notice that very different physical systems exhibit similar critical behavior. For example, the van der Waals theory expresses the compressibility (χ_T) of a gas as being proportional to $(T - T_c)^{-1}$, where T is the temperature and T_c is the critical temperature. Another example

is the Curie−Weiss law that states the same for the magnetic susceptibility (χ_m). Here the critical temperature (T_c) is known in textbooks as the Curie temperature. However, the latter cases both hold for thermal phase transitions, whereas for tablets the relative density holds for an *order parameter*,[14] describing a geometric phase transition. Yet, it should be mentioned that such simple functions for χ_T or χ_m are based on a so-called *mean field approach*.[14] This theoretical view implies a simple mean potential, approximating the molecular interaction. In the context of compaction, the mean field can correspond to a mean pressure. A mean field approximation usually provides a rather good model and is valid in a broad range.

It should further be mentioned that percolation theory[15−18] assumes a power law for modeling a critical property. Unfortunately, such a power law has an unknown range of validity in the critical range. Keeping in mind the goal to find a new relationship between pressure and relative density, we used eq 5 for the present model.

A Modified Heckel Equation—Combination of eqs 2 and 5 results in the differential equation given below:

$$-\frac{1}{\epsilon}\frac{d\epsilon}{d\sigma} = C\frac{1}{\epsilon_c - \epsilon} \tag{6}$$

after separation of variables, it reads:

$$-\frac{\epsilon_c - \epsilon}{\epsilon}d\epsilon = Cd\sigma \tag{7}$$

Integration can be performed starting from the critical porosity ϵ_c at a negligible resting pressure $\sigma_0 \cong 0$:

$$\int_{\epsilon_c}^{\epsilon}\frac{\epsilon - \epsilon_c}{\epsilon}d\epsilon = C\int_0^{\sigma}d\sigma \tag{8}$$

$$[\epsilon - \epsilon_c \ln(\epsilon)]|_{\epsilon_c}^{\epsilon} = C\sigma \tag{9}$$

$$\epsilon - \epsilon_c \ln(\epsilon) - [\epsilon_c - \epsilon_c \ln(\epsilon_c)] = C\sigma \tag{10}$$

$$\epsilon - \epsilon_c + \epsilon_c [\ln(\epsilon_c) - \ln(\epsilon)] = \epsilon - \epsilon_c + \epsilon_c \ln\!\left(\frac{\epsilon_c}{\epsilon}\right) = C\sigma \tag{11}$$

$$\sigma = \frac{1}{C}\left[\epsilon - \epsilon_c - \epsilon_c \ln\!\left(\frac{\epsilon}{\epsilon_c}\right)\right] \tag{12}$$

Hence, replacing porosity ϵ with the relative density ρ, a modified Heckel equation results:

$$\sigma = \frac{1}{C}\left[\rho_c - \rho - (1 - \rho_c)\ln\!\left(\frac{1 - \rho}{1 - \rho_c}\right)\right] \tag{13}$$

Materials and Methods

Tablets (round, flat, 11 mm diameter, 400 ± 1 mg weight) were manufactured with a Zwick 1478 Universal Testing Instrument (Zwick GmbH, Ulm, Germany). Different pharmaceutical polymers were chosen as model substances, because of their ability to form tablets in the interesting critical range at comparatively low relative densities (Table 1). True density was determined with an Beckman Air Comparison Pycnometer Model 930 and the particle size assayed using a Malvern Mastersizer X.

For each powder system, five tablets were compressed at different pressure levels ranging from 1.05 MPa up to 105.23 MPa at a relative humidity of $45\% \pm 10\%$. The compression speed was 10 mm/min and tablets' geometry was assessed 48 h after manufacture ("out of die" determination).

All data of different substances were used for statistical evaluation, except for Klucel, where only values to a pressure of

Table 1—Characterization of the Polymer Substances

substance	true density [g/cm³]	relative bulk density	relative tapped density	mean particle size (Sauter)[μm]
Emcocel 50M[a]	1.57	0.207	0.250	54
Avicel PH101[a]	1.57	0.205	0.260	48
Avicel PH102[a]	1.56	0.213	0.258	81
Klucel[b]	1.20	0.358	0.388	307
Pharmacoat 606[c]	1.33	0.275	0.357	45
Ac-Di-Sol[d]	1.57	0.317	0.393	41
Kollidon K17[e]	1.19	0.405	0.436	73
Kollidon CL[e]	1.26	0.283	0.345	41
Kollidon K90F[e]	1.22	0.427	0.466	138
PEG 8000[f]	1.23	0.466	0.543	50
PEG 10000[f]	1.22	0.525	0.572	158
PEG 20000[f]	1.22	0.522	0.558	229

[a] Type of microcrystalline cellulose. [b] Type of hydroxypropyl cellulose. [c] Type of hydroxypropyl methylcellulose. [d] Type of croscarmellose sodium. [e] Type of poly(vinylpyrrolidone). [f] Type of poly(ethyleneglycol)s.
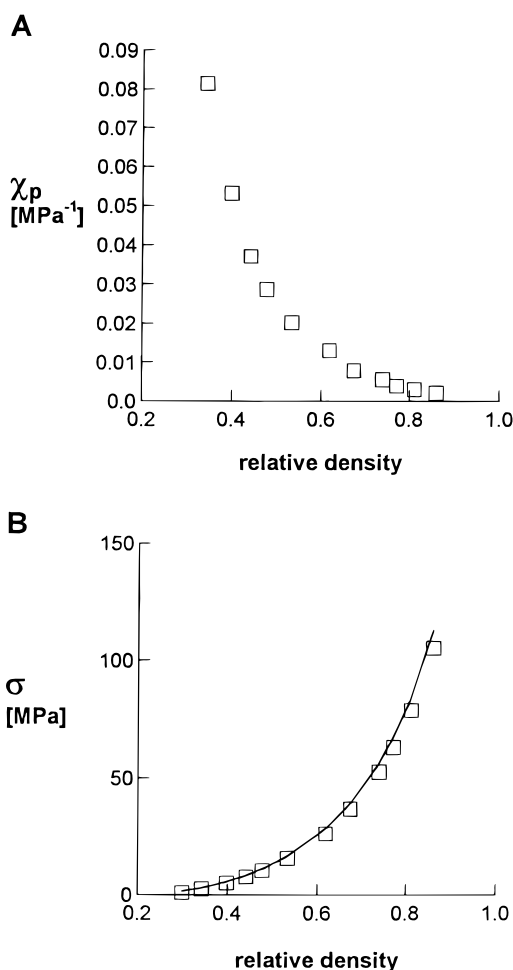

Figure 1—Avicel PH101: (A) Pressure susceptibility χ_p (MPa^{-1}) vs relative density (□). (B) Compression pressure σ (MPa) as a function of the relative density (□). The solid line represents the model according to eq 13.

36.8 MPa were evaluated. The program used for all calculations was SYSTAT for Windows Version 7.0 (SPSS Inc.).

Results and Discussion

The pressure susceptibility was calculated from experimental data according to eq 4 using finite differences for the differential quotient and plotted against ρ (see Figures1−4A). The graphs show that very high compressibility
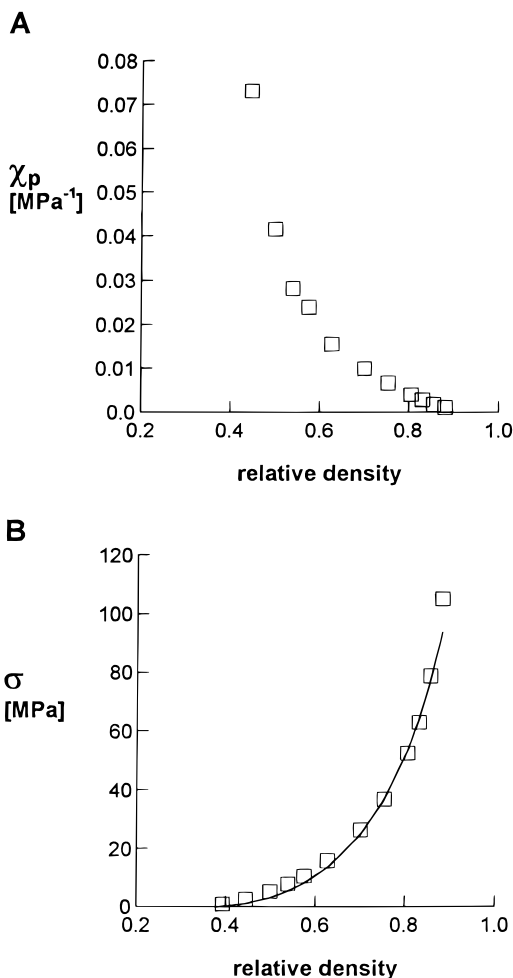
Figure 2—Pharmacoat 606: (A) Pressure susceptibility χ_p (MPa^{-1}) vs relative density (□). (B) Compression pressure σ (MPa) as a function of the relative density (□). The solid line represents the model according to eq 13.

decreases sharply with increasing relative densities. Thus, the assumption of Heckel to use a constant pressure susceptibility is only acceptable as a first approximation for comparatively dense compacts. Still, further changes of the property χ_p will take place, until a minimum is achieved at about zero porosity. Note that for the slight changes in this range, the experimental accuracy is a limiting factor. This is reflected by the scatter of the values for PEG 8000 (see Figure 4A).

Very porous tablets produce considerable porosity changes under strain. Such high compressibility can only be explained by particle displacement, i.e., particle rearrangements in the initial stages of compression. As long as a large extraparticulate void volume exists, a reduction of porosity can be achieved by a small pressure. The consequence is a high value of χ_p that was also observed in the experimental results (Figure 1−4A). Theoretically, the curve close to ρ_c can even extend to infinity but directly at the threshold and below the function χ_p vanishes. As a conclusion, the assumption of a hyperbola for χ_p eq 5 appears very suitable, whereas the approximation of a constant value for χ_p is clearly not correct for low-density tablets.

Focusing on the relationship between pressure and relative density,we compared the new model eq 13 and the Heckel eq 1, on the basis of "out of die" measurements (Table 2). A nonlinear fit was conducted with all substances using the new model equation (See Figure 1−4B). It shows that eq 13 is in good agreement with experimental results.
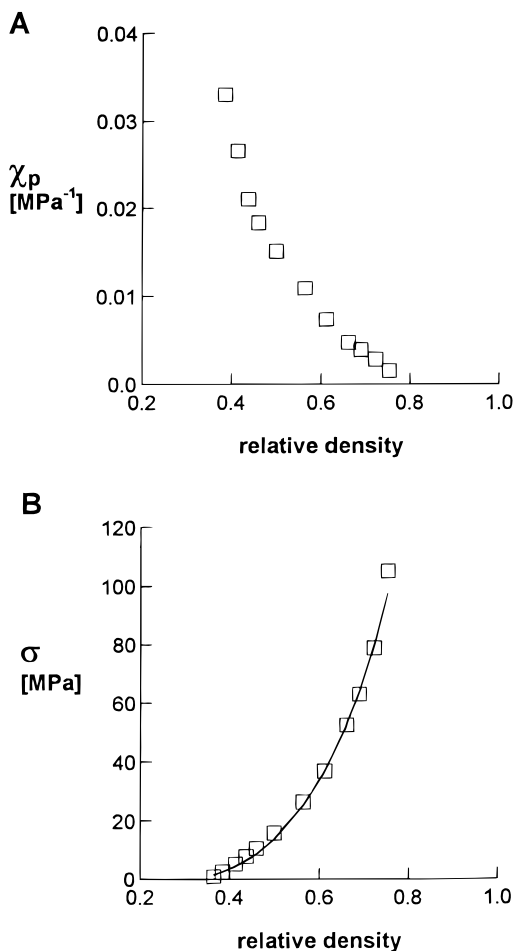
A

B

Figure 3—Kollidon CL: (A) Pressure susceptibility χ_p (MPa^{-1}) vs relative density (□). (B) Compression pressure σ (MPa) as a function of the relative density (□). The solid line represents the model according to eq 13.

A

B

Figure 4—PEG 8000: (A) Pressure susceptibility χ_p (MPa^{-1}) vs relative density (□). (B) Compression pressure σ (MPa) as a function of the relative density (□). The solid line represents the model according to eq 13.

In addition, the comparison with the Heckel equation (Table 2) clearly showed a better goodness of fit of the new model. Yet, in some cases such as for Pharmacoat 606 (Figure 2) and Kollidon CL (Figure 3), the highest pressure did not properly match the new model.

It should be noticed that the number of parameters is the same for the Heckel equation and the new model. This low number of parameters, i.e., the simplicity of a model, is an important aspect. Yet, the complexity of the compression process is awesome, involving several physical phenomena of changing significance in different stages.[19,20] Thus, the proposal of a *power series* might be most adequate to describe the change of pressure susceptibility close to the threshold ρ_c. On the other hand, new parameters would be introduced and the problem of an a priori limited range of validity is still present. Therefore, a simple approximation on the average, as proposed by eq 5, is justified.

Comparing the constants C and K (Table 2), values for the new parameter C were all smaller than those of K by a factor of roughly between 2 and 4. Qualitatively it can be said that both parameters incorporate an experimental minimal susceptibility (χ_{pmin}) close to zero porosity. This parameter is independent of the tablet's pore structure because it is a characteristic of the solid continuum. The constant C is proportional to χ_{pmin} but further involves the threshold value ρ_c, which becomes apparent evaluating eq 5 at unity density. Thus, C depends on the initial structure of the particle packing.

Considering the parameter ρ_c, this value was defined in the theoretical section as a rigidity threshold. Thus, this
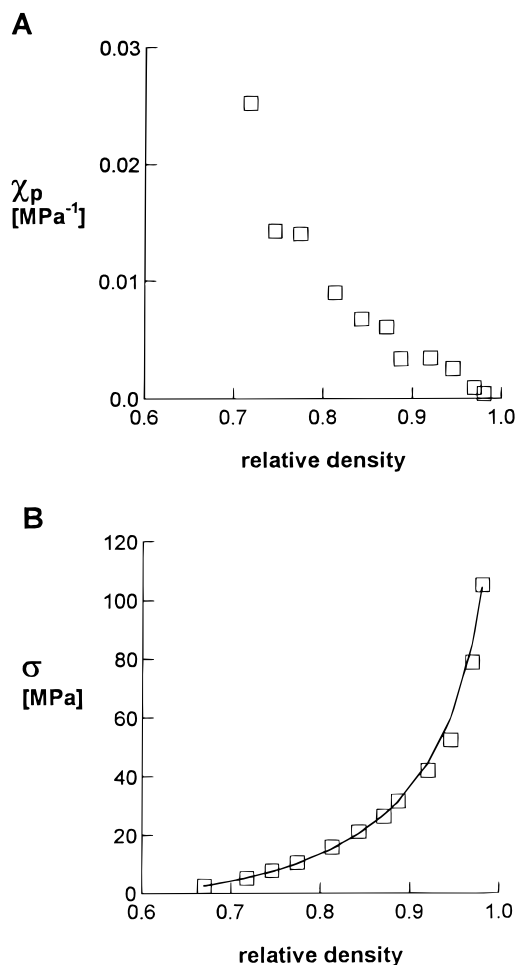
Table 2—Comparison between the Heckel Equation and the Proposed Modified Equation

	Heckel equation			Modified Heckel equation		
	K	A	$r^{2\,a}$	C	ρ_c	$r^{2\,a}$
Emcocel 50M	0.015	0.449	0.960	0.006	0.217	0.998
Avicel PH101	0.016	0.453	0.978	0.007	0.167	1.000
Avicel PH102	0.016	0.442	0.969	0.007	0.180	0.998
Klucel	0.044	0.682	0.934	0.014	0.379	0.986
Pharmacoat 606	0.017	0.638	0.952	0.006	0.356	0.993
Ac-Di-Sol	0.007	0.503	0.978	0.002	0.291	0.999
Kollidon K17	0.021	0.593	0.989	0.012	0.195	0.996
Kollidon CL	0.010	0.505	0.965	0.003	0.284	0.996
Kollidon K90F	0.011	0.621	0.986	0.003	0.323	0.998
PEG 8000	0.028	1.200	0.979	0.010	0.528	0.995
PEG10000	0.029	1.292	0.953	0.008	0.601	0.984
PEG 20000	0.028	1.127	0.933	0.009	0.560	0.971

[a] Corrected squared correlation coefficient.

critical value holds for the packing fraction, producing a negligible mechanical resistance between the punches. In a strictly geometric interpretation, this threshold ρ_c demonstrates the transition between dispersed solid in air and voids in a solid matrix. The coherent contact within the powder column will be already present only when the powder is poured in the die. Yet, it can be argued that contact between particles might not be enough for establishing a relevant rigidity.[21] Some initial particle rearrangements might require only minimal forces that can be

neglected. Thus, the rigidity threshold ρ_c can be higher than the relative density needed for coherent contact.

The values for ρ_c (Table 2) according to eq 13 ranged for all substances close to the interval of the relative bulk density and tapped density (Table 1). It is interesting to notice that the different types of microcrystalline cellulose and poly(vinylpyrrolidone) displayed a trend for lower thresholds. This tendency seemed especially pronounced for Avicel PH102, Kollidon K17, and K90F, where values for ρ_c were even lower than the relative bulk density. The poly(ethylene)glycol)s showed reversed tendency, where critical rigidity was achieved close to the relative tapped density or slightly above as produced by PEG 10000 and PEG 20000. In line with these considerations, it can be concluded that the microstructure, being specific for a given substance, plays an important role for ρ_c.

The Heckel constant K in eq 1 can be used to characterize substances.[22] The question can therefore be asked if a similar information can also be acquired from the new parameters ρ_c and C. In line with the considerations so far, ρ_c appears to be a parameter being strongly affected by the microstructure of the powder system. Of further special interest is that particle systems can behave differently under compression or tension. The behavior under compression gives information on rigidity, whereas a behavior under tension is related to compact strength. Thus, the compressibility of a particle assembly can therefore be considered as a characteristic on its own apart from the binding capabilities. Yet again the situation is different for the dense compacts. If the applied pressure is high enough, plastic flow occurs at a compressive yield pressure (σ_Y). Accordingly, the value for χ_{pmin} can be expected to depend on σ_Y. This aspect can further be stressed by defining a compression modulus (G):

$$G \equiv \frac{1}{\chi_p} \quad (14)$$

The property G expresses the pressure needed to reduce porosity of a tablet. A maximal value (G_{max}) will therefore be limited by a compressive yield strength. Alternatively, it can be stated that the maximal compression modulus equals the maximal hardness (P_{max}) of the material if exclusive plastic flow occurs.

The inverse of the constant K can also be regarded as a compression modulus G. Its determination only from the linear part of the Heckel plot, results again in an estimate of compressibility at high pressures and therefore approximates G_{max}. Note that the constant K was assessed instead over the entire range of the relative density.

However, Heckel already conjectured that the inverse of the Heckel slope was proportional to the yield point of the particles with a proportionality factor equal to three.[5] This observation agrees with our considerations that maximal compressibility is limited by a compressive yield pressure. Furthermore, it should be mentioned that the yield point of a plastic material is known to equal one-third of the indentation hardness.[23] This again supports the view that for plastic substances, the inverse Heckel slope can also be regarded as a measure of maximal hardness. From these considerations it can be qualitatively concluded that G_{max} is a specific property of a substance and can potentially be used for characterization of a tableting material. Yet, it needs to be stressed that experimentally the zero porosity state can hardly be achieved even at highest pressures.[24] Therefore, arguments on G_{max} should be understood qualitatively first.

It is interesting to normalize the compression modulus G by its maximum G_{max}. This quotient only depends on the structure of the tablet. Using eq 5, one obtains:

$$\frac{G}{G_{max}} = \frac{\chi_p^{-1}}{\chi_{pmin}^{-1}} = \frac{(\rho - \rho_c)C}{(1 - \rho_c)C} = \frac{1}{1 - \rho_c}(\rho - \rho_c) \quad (15)$$

This result is consistent with the model of Leuenberger and Leu[25] based on the percolation theory. The eq 15 was previously pointed out to be consistent with a so-called *effective medium approximation*,[26–28] where a disordered medium is replaced on the average by a hypothetical homogeneous one.

Conclusions

It was shown that the pressure susceptibility exhibits very high values at comparatively low relative densities. The property χ_p was expected to be divergent in this range having a singularity at a critical relative density ρ_c. As a consequence, the Heckel equation, assuming a constant value for χ_p, is inadequate in this critical range. The proposal of a simple hyperbola function leads in the integrated form to a modified Heckel equation. This model has shown to be superior in describing different polymer tablets from "out of die" measurements. The understanding of the pressure susceptibility as a critical property links the process of compression to the theory of phase transitions. Thus, the present concept provides not only a new equation for the relationship between pressure and relative density, but contributes also to further insights in the complex nature of the compaction process.

Additional studies are needed for a complete evaluation of the proposed model equation. So far in this study, porosity was determined after manufacture and storage. Additional "in die" measurements would be of interest because no elastic recovery or other postcompressional changes are allowed under these conditions. Plus, brittle substances should be tested. This is especially of interest, regarding the importance of tableting material undergoing fragmentation during compaction.

Glossary

ϵ, ϵ_c	Porosity and critical porosity. The latter value is defined as the threshold porosity of a vanishing rigidity between the punches
ρ, ρ_c	Relative density and critical relative density. The threshold density corresponds to $1 - \epsilon_c$
σ	Applied pressure (MPa)
K, A	Constants of the Heckel equation, where K (MPa^{-1}) equals the slope, and A the intercept of the plot $\ln(1/(1 - \rho))$ with respect to σ
χ_p	Pressure susceptibility or compressibility, defined as $\chi_p \equiv -(1/\epsilon)(d\epsilon/d\sigma) = [1/(1 - \rho)](d\rho/d\sigma)$ (MPa^{-1})
χ_{pmin}	Minimal value of the pressure susceptibility (MPa^{-1}) at zero porosity
C	Proportionality constant (MPa^{-1}) that links the porosity with the pressure susceptibility $\chi_p = C/(\epsilon_c - \epsilon) = C/(\rho - \rho_c)$. Hence, C can also be related to with the minimal pressure susceptibility at zero porosity: $C = \chi_{pmin}\epsilon_c = \chi_{pmin}(1 - \rho_c)$.
χ_T	Isothermal compressibility of a gas defined by a relation to the volume V (m^3), pressure P (Pa) and gas density ρ_g (kg m^{-3}): $\chi_T \equiv -(1/V)(dV/dP) = (1/\rho_g)/(d\rho_g/dP)$
χ_m	Magnetic susceptibility, defined over the relationship: $\chi_m \equiv (dM/dH)$, where M (A m^{-1}) is the magnetization and H (A m^{-1}) the magnetic field.

T, T_c	Temperature and critical temperature. The threshold temperature can hold, for example, for the singularity at the end of the vapor vs pressure curve, or in case of magnetic systems, it marks the transition of ferromagnetism and paramagnetic behavior.
G	Compression modulus (MPa) is by definition the reciprocal of χ_p.
G_{max}	Maximal compression modulus (MPa) defined over the reciprocal of χ_{pmin}.
σ_N	Compressive yield pressure (MPa).
P_{max}	Maximal value of the deformation hardness (MPa).

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