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The application of percolation theory to the compaction of pharmaceutical powders

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Summary

Based on the concepts of percolation theory the compaction process is interpreted as a site-bond percolation phenomenon. The combination of the Heckel equation with an equation derived earlier yields a simple relationship between the tensile strength σ_t or the deformation hardness P and the relative density. This mathematical model is identical with the fundamental law of percolation theory, i.e., $X = s(p - p_c)^q$ with X = system property equivalent to tensile strength or deformation hardness, S = scaling factor, p = site occupation or bond formation probability corresponding to the relative density ρ, p_c = percolation threshold and critical exponent $q = 1$ according to percolation on a Bethe lattice. In the case of the tensile strength σ_t and the deformation hardness P, two percolation thresholds $p_c(1)$ and $p_c(2)$ corresponding to $\rho_c(1)$ and $\rho_c(2)$ could be identified. The relative density $\rho_c(1)$ which is close to the relative poured or relative tapped density can be interpreted as a bond percolation threshold. The particles are bonded by weak interparticulate forces and form only loose compacts as used for filling of capsules. The relative density $\rho_c(2)$ is the relative density where the first stable pharmaceutical compact is achieved which can no longer be disintegrated mechanically into its primary particles. It is of special interest that the above equation is also valid for the elastic modulus with the only percolation threshold $p_c(1) = \rho_c(1)$.

Introduction

Theoretical aspects

Percolation theory (Stauffer, 1985) is based on the formation of clusters and on the existence of a site and/or bond percolation phenomenon. It can be applied if a system can be sufficiently well described by a lattice, where the sites are occupied at random (site-percolation) or, in the case that all sites are already occupied, where bonds between neighbouring sites are formed at random (bond-percolation).

Tablet formation can be imagined as a combination of site and bond percolation phenomena. The volume of the die is supposed to be spanned by a three-dimensional virtual lattice with a lattice spacing of the order of a molecular diameter. This interpretation is much more rigorous than an earlier one assuming a lattice spacing of approximately mean particle size (Leuenberger et al., 1992) and takes into account a particle size

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distribution, i.e. a distribution of cluster sizes. After pouring particles/granules to be compacted into the die the lattice sites are either empty forming pores or occupied by molecules forming clusters. During the uniaxial compression the number of lattice sites to be finally occupied are continously reduced until the final dimension of the tablet is achieved. In the beginning the fine particles are bonded by weak inter-particulate forces. Thus, there is a bond percolation throughout the powder bed as soon as the particles are in contact. The cohesive property of the powder bed starts to become evident at a relative density $\rho_c(1)$ which is close to the relative poured (ρ_p) or relative tapped (ρ_t) density. The relative density $\rho_c(1)$ can be interpreted as the bond percolation threshold. During the compaction process the relative density $\rho_c(2)$ is reached at which the particles are no more easily displaced and an important build-up of compressional force must be expected. Such a situation is typical for a site percolation phenomenon with the site percolation threshold $\rho_c(2)$. By the end of the compaction the pore volume is more and more reduced until at a certain relative density $\rho_c(3)$ the pore system will no longer form a continuous network. Thus, $\rho_c(3)$ represents the percolation threshold for the pores. Due to effects of different particle size and shape, effects of brittle fracture, plastic flow and finite size of the tablet no sharp percolation thresholds can be expected however.

The fundamental equation of percolation theory

According to percolation theory a system property X at the percolation threshold p_c, follows a power law:

$$X = S(p - p_c)^q \qquad (1)$$

where S denotes the scaling factor and q the critical exponent. Eqn 1 is strictly valid only close to the percolation threshold. In practical cases (Ehrburger and Lahaye, 1989), Eqn 1 often showed a much larger range of validity than originally anticipated.

The Heckel equation

In powder technology, the Heckel equation (Heckel, 1961) has been widely used. It can be described after algebraic rearrangement of the usually applied equation as follows

$$\epsilon(\sigma_c) = \epsilon_0 \exp(-a\sigma_c) \qquad (2)$$

where ϵ is the porosity, ϵ_0 the porosity at $\sigma_c = 0$, $\rho_r = 1 - \epsilon$, σ_c is the compressional stress and a represents a powder/substance specific constant.

An equation derived earlier

In earlier publications (Leuenberger, 1982, 1985; Leuenberger and Rohera, 1986a; Blattner et al., 1990; Leuenberger et al., 1987, 1992) the following equations were derived and successfully applied:

$$P = P_{\max}[1 - \exp(-\gamma\sigma_c\rho_r)] \qquad (3)$$

where P denotes the deformation hardness, $P_{\max}$ the deformation hardness at $\sigma_c \to \infty$ and $\rho_r \to 1$, σ_c is the compressional stress and γ represents the compression susceptibility parameter. It could be shown that the compression susceptibility γ of Eqn 3 is practically identical with the powder/substance specific constant a of the Heckel equation (Eqn 2). The mathematical model, Eqn 3, is very elastic concerning the fitting of data. Due to a flip-flop phenomenon, i.e., the correlation between γ and $P_{\max}$, a higher estimate of $P_{\max}$ is related to a lower estimate of γ (Leuenberger and Rohera, 1986b). During the compaction process the relative density ρ_r varies usually in the range of $0.6 < \rho_r < 1$. Thus, the following expression (Leuenberger and Jetzer, 1984) yields a good approximation of Eqn 3

$$P = P_{\max}[1 - \exp(-\gamma\sigma_c)] \qquad (4)$$

Due to the flexibility of this equation other properties related to the strength of the compact such as tensile strength σ_t and the modified Young's modulus E' fulfil the mathematical models, Eqns 3 and 4, without problems. The modified Young's modulus E' is defined as $E' = E/(1 - \nu^2)$ with Young's modulus E and Poisson ratio ν.

Derivation of the power law for deformation hardness P and tensile strength σ_t

As shown in a recent paper (Leuenberger and Leu, 1992) the combination of the Heckel equation (Eqn 2) and Eqn 4 leads to the following equations for the deformation hardness P, the tensile strength σ_t and the modified Young's modulus E':

$$P = \frac{P_{\max}}{(1-\rho_c)}(\rho_r - \rho_c) \tag{5}$$

$$\sigma_t = \frac{\sigma_{t\max}}{(1-\rho_c)}(\rho_r - \rho_c) \tag{6}$$

$$E' = \frac{E'_{\max}}{(1-\rho_c)}(\rho_r - \rho_c) \tag{7}$$

were P is the deformation hardness, σ_t tensile strength, E' modified Young's modulus of elasticity, ρ_r relative density and ρ_c critical relative density (percolation threshold). It is evident that these Eqns 5–7 are formally identical with the fundamental law of percolation theory (Eqn 1) with a percolation threshold $p_c = \rho_c$ and with the exponent $q = 1$ corresponding to percolation in a Bethe lattice (Stauffer, 1985).

The general relationships Eqns 5–7, can be specified on the one hand for the formation of loose compacts and, on the other, for the formation of dense compacts. For loose compacts, i.e., at a low pressure range, ρ_c equals the bond percolation threshold $\rho_c(1)$. $P_{\max}$ and $\sigma_{\max}$ describe the strength of the substance specific particle-particle interaction at low densities where the primary particles have not yet lost their identity. In this stage the compact can still be separated into the original particles. For the formation of dense compacts, i.e., at median pressure ranges, ρ_c is equivalent to the site percolation threshold $\rho_c(2)$. In this case $P_{\max}$ and $\sigma_{t\max}$ correspond to the maximum deformation hardness or tensile strength of the substance at $\rho_r \to 1$.

Eqn 7 is proposed by virtue of the sometimes observed analogy (Mashadi and Newton, 1987) of the elastic modulus to the deformation hardness or tensile strength.

Materials and Methods

Materials

Tablets (round, flat, diameter 11 mm, weight 400 ± 1 mg) were prepared of different substances (Table 1) and the deformation (Brinell) hardness, tensile strength and modified Young's modulus of elasticity were tested using the Zwick 1478 Universal Testing Instrument (Zwick GmbH, Ulm, Germany) (Leuenberger and Leu, 1992).

Methods

Heckel plots are established on the basis of the relative densities ρ_r of the compacts meas-

TABLE 1

Physical characterization of the substances used

Substances	Densities					Mean particle size (μm)
	True (g/ml)	Poured (g/ml)	ρ_p (rel)	Tapped (g/ml)	ρ_t (rel)	
Avicel® PH 102 FMC 2843	1.58	0.325	0.206	0.439	0.278	97.0
Caffeine anhydrous Sandoz 88828	1.45	0.323	0.223	0.417	0.288	55.0
Emcompress® Ed. Mendell E27B2	2.77	0.714	0.258	0.870	0.314	106.0
Lactose α-monohydrate DMV 171780	1.54	0.562	0.365	0.735	0.477	53.2
PEG 10000 Hoechst 605331	1.23	0.568	0.462	0.719	0.585	135.8
Sta-RX 1500® Sandoz 86823	1.50	0.606	0.404	0.741	0.494	68.1

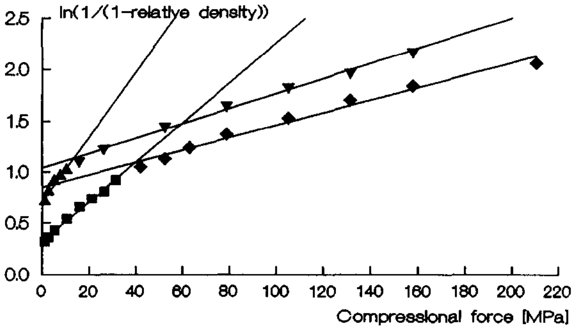

Fig. 1. Heckel plot. Caffeine: median (▼) and (▲) low pressure range; Avicel: median (◆) and (■) low pressure range.

ured 24 h after being manufactured. The data of the deformation hardness, the tensile strength and modified Young's modulus are evaluated according to Eqns 5–7. For all data dummy variables are used to determine the partition in two linear sections with the best overall fit.

The thresholds resulting from the intercepts of the straight lines of the Heckel plots and of Eqns 5–7 are compared.

Results and Discussion

Deformation hardness and tensile strength

As described earlier, the Heckel plots are approximated with two linear sections (Fig. 1). According to Eqns 5 and 6, which are a special case of Eqn 1 with $q = 1$, P and σ_t are plotted against the relative density and linearized by two regression lines (Figs 2 and 3).

As expected, no sharp percolation threshold can be observed. In Table 2 the experimentally determined percolation threshold from the Heckel plot, from the deformation hardness (Eqn 5) and from the tensile strength (Eqn 6) and the P_{max} and σ_{tmax} values at the median pressure range are summarized. To a first approximation the bond percolation threshold $\rho_c(1)$ is in the range of the relative tapped density ρ_t. The estimates for the site percolation thresholds $\rho_c(2)$ are within the range of 0.5 and 0.8.

Taking into account the assumptions made and the theoretical expectations allowed, the experimental results are in good agreement with the established mathematical model.

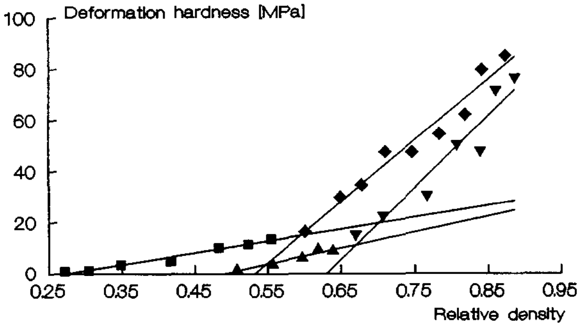

Fig. 2. Deformation hardness as a function of relative density according to Eqn 5. Caffeine: median (▼) and (▲) low pressure range; Avicel: median (◆) and (■) low pressure range.

Modified Young's modulus of elasticity

The evaluation of the data of elasticity according to Eqn 7 shows that in this case the approximation by one linear range is more reasonable than by two linear ranges (Fig. 4). This result is not surprising as the elastic properties are already present at low relative densities and do not disappear or change their magnitude at higher relative densities. In Table 3 the results are compiled.

Comparing the percolation thresholds ρ_c in this case with the ρ_c values determined for the deformation hardness and the tensile strength it can be seen that they are in general lower. Except

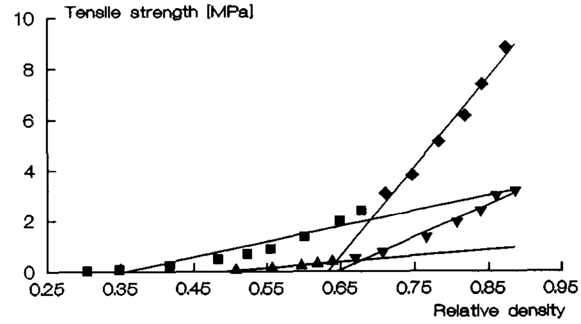

Fig. 3. Tensile strength as a function of relative density according to Eqn 6. Caffeine: median (▼) and (▲) low pressure range; Avicel: median (◆) and (■) low pressure range.

TABLE 2

Experimentally determined values for $\rho_c(1)$ and $\rho_c(2)$ according to the Heckel plot, Eqns 5 and 6 and the values of P_{max} and σ_{tmax} for dense compacts

	Heckel plot		
	$\rho_c(1) \pm$ s	$\rho_c(2) \pm$ s	r^2
Avicel®	0.270 ± 0.010	0.551 ± 0.033	0.997
Caffeine	0.506 ± 0.024	0.644 ± 0.035	0.992
Emcompress®	0.411 ± 0.023	0.547 ± 0.016	0.988
Lactose	0.639 ± 0.026	0.741 ± 0.032	0.991
PEG 10000	0.577 ± 0.022	0.718 ± 0.085	0.994
Sta-RX 1500®	0.531 ± 0.014	0.774 ± 0.153	0.989

	Deformation hardness (Eqn 5)			
	$\rho_c(1) \pm$ s	$\rho_c(2) \pm$ s	$P_{max} \pm$ s (MPa)	r^2
Avicel®	0.275 ± 0.051	0.533 ± 0.014	111.9 ± 3.9	0.986
Caffeine	0.521 ± 0.036	0.696 ± 0.021	127.7 ± 11.6	0.970
Emcompress®	0.454 ± 0.062	0.564 ± 0.028	89.6 ± 21.5	0.948
Lactose	0.644 ± 0.052	0.744 ± 0.013	76.4 ± 5.8	0.979
PEG	0.591 ± 0.035	0.902 ± 0.007	36.9 ± 3.2	0.969
Sta-RX 1500®	0.499 ± 0.012	0.595 ± 0.070	30.3 ± 5.1	0.939

	Tensile strength (Eqn 6)			
	$\rho_c(1) \pm$ s	$\rho_c(2) \pm$ s	$\sigma_{tmax} \pm$ s (MPa)	r^2
Avicel®	0.357 ± 0.028	0.633 ± 0.012	12.96 ± 0.51	0.990
Caffeine	0.526 ± 0.021	0.697 ± 0.009	5.47 ± 0.22	0.994
Emcompress®	0.454 ± 0.022	0.581 ± 0.006	1.45 ± 0.10	0.987
Lactose	0.676 ± 0.016	0.804 ± 0.004	3.00 ± 0.15	0.992
PEG	0.602 ± 0.064	0.812 ± 0.008	2.69 ± 0.10	0.990
Sta-RX 1500®	0.551 ± 0.030	0.738 ± 0.020	5.18 ± 0.25	0.989

for Emcompress® and lactose the values are between the relative poured and the relative tapped densities. It is reasonable that the percolation threshold for the modified Young's modulus is close to the bond percolation threshold $\rho_c(1)$ as the compressional stress is transmitted by the contact (bond) points within the powder compact. E'_{max} can be interpreted as the modified Young's

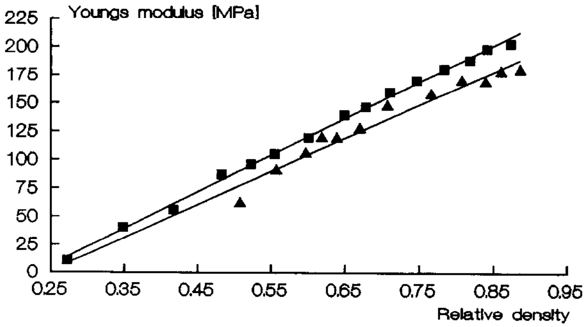

Fig. 4. Young's modulus as a function of relative density according to Eqn 7. (▲) Caffeine; (■) Avicel.

TABLE 3

Evaluation of the Young's modulus according to Eqn 7

	$\rho_c \pm$s	$E_{max} \pm$s (MPa)	r^2
Avicel®	0.288 ± 0.066	249.08 ± 2.00	0.997
Caffeine	0.244 ± 0.031	221.10 ± 6.14	0.958
Emcompress®	0.385 ± 0.023	369.39 ± 29.23	0.887
Lactose	0.567 ± 0.017	215.67 ± 9.61	0.940
PEG 10000	0.488 ± 0.012	133.59 ± 2.68	0.985
Sta-RX 1500®	0.488 ± 0.009	141.03 ± 3.22	0.988

modulus of a compact with zero porosity, i.e., $\rho_r \to 1$.

The Bethe lattice approximation

Eqns 5–7 resulting from the combination of Eqns 2 and 4 are formally identical with the fundamental law of percolation assuming a critical exponent $q = 1$. The only theoretical model showing $q = 1$ is the Bethe lattice.

Thus, assuming that the densification of powder can be described to a first approximation by a percolation process on a Bethe lattice, it is of interest to interpret the bond and site percolation thresholds as thresholds in a Bethe lattice. From the following equation determining the percolation threshold for both bond and site percolation in a Bethe lattice

$$p_c = \frac{1}{z-1} \tag{8}$$

it is possible to calculate the coordination number z.

The resulting values shown in Table 4 are rather low. Although it may be of interest in the case of site percolation to take into account that the uniaxial compression leads to a two-dimensional situation, higher coordination numbers are expected. Concerning this point the approximation by a normal Bethe lattice is not quite satisfying.

TABLE 4

Coordination numbers resulting from Eqn 8 for the percolation thresholds according to Eqns 2 and 5–7

	Bond percolation threshold $\rho_c(1)$			
	Eqn 2	Eqn 5	Eqn 6	Eqn 7
Avicel®	4.70	4.64	3.80	4.47
Caffeine	2.98	2.92	2.90	5.10
Emcompress®	3.43	3.20	2.20	3.60
Lactose	2.56	2.55	2.48	2.76
PEG 10000	2.73	2.69	2.66	3.05
Sta-RX 1500®	2.88	3.00	2.81	3.05

	Site percolation threshold $\rho_c(2)$		
	Eqn 2	Eqn 5	Eqn 6
Avicel®	2.81	2.88	2.58
Caffeine	2.55	2.44	2.43
Emcompress®	2.83	2.77	2.72
Lactose	2.35	2.34	2.24
PEG	2.39	2.11	2.23
Sta-RX 1500®	2.29	2.68	2.36

Fisher and Essam (1961) show that for decorated Bethe lattices, i.e., more complex lattices of the type of a Bethe lattice, where q still equals 1, the relationship between the coordination number and the percolation threshold is more complicated than Eqn 8. Depending on the type of the decorated Bethe lattice the bond percolation threshold of a lattice with coordination number $z = 4$ becomes, e.g., 0.403 instead of 0.333 for the normal Bethe lattice or the bond percolation threshold of a lattice with $z = 3$ becomes, e.g., 0.637 instead of 0.500. Thus, for a given coordination number the thresholds are higher for decorated Bethe lattices than for normal Bethe lattices. Therefore, the approximation by decorated Bethe lattices would yield more reasonable values for the coordination number. The determination of the most appropiate decorated Bethe lattice for the given bond percolation and site percolation problem remains the object of further investigations.

Conclusion

The combination of the Heckel equation with the compactibility/compressibility equations derived earlier yield a mathematical model which is identical to the power law of percolation theory with a critical exponent $q = 1$. The data of deformation hardness, tensile strength and modified Young's modulus are evaluated according to this new equation. Taking into account on the one hand the complexity of the formation of a tablet and, on the other, the plainness of the equation the agreement of the experimental data with the model is very satisfactory.

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