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Research paper

Application of percolation model to the tensile strength and the reduced modulus of elasticity of three compacted pharmaceutical excipients

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Abstract

Percolation theory has been applied to several mechanical properties of pharmaceutical tablets. This power law describes the change of tablet's properties with the relative density. It defines critical tablet densities from which the mechanical properties start to change. The exponent in the law is expected to be universal for a mechanical property and numerical values are proposed in the literature. In this work, the percolation model was applied to the tensile strength and the reduced modulus of elasticity (obtained from surface indentation test) of three compacted pharmaceutical excipients (a microcrystalline cellulose, a lactose and an anhydrous calcium phosphate). Two approaches were proposed. First, the exponent was kept constant and equal to the values used in the literature (2.7 for the tensile strength and 3.9 for the reduced modulus of elasticity). Secondly, the critical tablet density (*i.e.* the percolation threshold) and the exponent were determined from the model. In the first approach, the percolation thresholds were higher than the relative tapped density. Using the second approach, the experimentally determined exponents were not close to the values of the literature and the critical relative densities were higher than the relative tapped density or equal to zero. Then, this study showed that the exponent seems not universal and that the model must be used carefully.

Keywords: Percolation theory; Percolation threshold; Tensile strength; Reduced modulus of elasticity; Porosity; Relative density

1. Introduction

The percolation theory is applied in different scientific disciplines [1]. For pharmaceutical application, it was introduced by Leuenberger et al. in 1987 to characterize tablet properties [2,3]. In this first definition, through the compaction process to form a pharmaceutical tablet, a site-percolation and a bond-percolation may be observed. The sites can be occupied by particles or pores and, bonds can exist between neighbouring particles. This theory assumes that at a specific solid/pores composition in the tablet, *i.e.* when particles or pores form a continuous network in the system, a sudden change in the tablet properties is observed. This particular ratio corresponds to the percolation threshold. In a compacted system consisting of particles and pores, the composition is expressed in terms of relative density and, different percolation thresholds can be observed depending on the compaction pressure. At very low relative density, particles form a loose powder bed. It is generally considered that when the relative density becomes larger than the relative tapped density (ρ_{rt}) of the powder bed, the first cohesive compact is formed. The relative tapped density is often regarded as

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Nomenclature

A, A'	constants
D	diameter of cylindrical compact
E^*	reduced modulus of elasticity
E_0^*	reduced modulus of elasticity obtained from exponential extrapolation of $\varepsilon \to 0$
E_{max}^*	reduced modulus of elasticity obtained from linear extrapolation of $\rho_r \to 1$
F_r	maximal diametrical crushing force
h	height of cylindrical compact
q	critical exponent
ε	porosity
ρ_c	critical relative density
ρ_r	relative density
ρ_{rb}	relative bulk density
ρ_{rt}	relative tapped density
σ_{r0}	tensile strength obtained from exponential extrapolation of $\varepsilon \to 0$
σ_{rmax}	tensile strength obtained from linear extrapolation of $\rho_r \to 1$
σ_r	tensile strength

the percolation threshold of the network formed by particles. Above a second critical relative density (which is a relative density close to 1), the pores do not form anymore a continuous network. This is the percolation threshold of pores [4]. In practice, the percolation threshold of particles is the most studied. Nevertheless, the percolation threshold of pores is also interesting to consider in the compaction process, since it corresponds to a pressure which is not to be exceeded. In later articles [5–7], a new concept of percolation theory was applied and a definition of a mechanical percolation threshold was given. In this version, the system is supposed to be composed of springs. At the percolation threshold, two sides of the system are connected by a network of relevant contact points which spans the system. Then, any mechanical property becomes different of zero above this threshold. The threshold's values estimated from this new approach lead to higher values than from the first approach. More, for a same material, the value depends on the mechanical property considered. For example, the network of contact points for the elasticity is not the same as for the tensile strength. This leads to the observation in the literature of lower value for the elasticity than for the tensile strength [7].

According to the percolation theory, a property X of a compact varies, close to the percolation threshold of the particles, following this relationship:

$$X = A \cdot (\rho_r - \rho_c)^q \quad (1)$$

with, ρ_r the relative density of the tablet, ρ_c the critical relative density corresponding to the percolation threshold, q the critical exponent and A, a constant.

In theory, Eq. (1) is only valid close to the percolation threshold, but, in most applications (for example, mechanical properties of tablets), it is also valid for a range of relative densities higher than the percolation threshold [6–8]. In practice, the authors agree that the percolation threshold (ρ_c) is comprised in the range of the relative bulk density (ρ_{rb}) and the relative tapped density (ρ_{rt}). The exponent, q, is expected to be universal. For the mechanical strength and the elasticity of a theoretical lattice, its theoretical values are, respectively, 2.7 and 3.9 [9]. Experimental studies performed by Kuentz et al. [5,7] on pharmaceutical tablets composed of various microcrystalline celluloses show exponent values of 3.2 for the tensile strength and 3.95 for the reduced modulus of elasticity. Far away, the percolation threshold (*i.e.* $\rho_r \gg \rho_c$), the same authors [2,5,7] consider a linear relationship between one of the two properties (*i.e.* tensile strength or reduced modulus of elasticity) and the relative density in reference to the "effective medium approximation" (EMA). The maximal value (X_{max}) is obtained for a relative density of 1. In these works [5,7], the linear relationship is applied for a compaction pressure higher than 80 MPa which corresponds to a relative density of tablet higher than 0.7–0.75.

In practice, two approaches are possible: (1) use the exponent proposed by previously published works (which are those of Leuenberger and Kuentz for pharmaceutical application [2,5,7]); (2) try to adjust all parameters in the power law (which was the strategy used by Kuentz and Leuenberger) to establish the exponents in the case of microcrystalline cellulose tablets [5,7]. In this paper, these two approaches are applied to two mechanical properties of three compacted pharmaceutical excipients. The percolation threshold and the critical exponent were determined from the experimental values and compared to the expected values of the literature. Then, the validity of the obtained results is discussed.

2. Materials and methods

2.1. Excipients

Granular fractions (between 100 and 180 μm) of a microcrystalline cellulose (Vivapur 12®, 5601210932, JRS, Germany), a partly amorphous lactose (Fast Flo®, 8500042062, Foremost, US) and an anhydrous calcium phosphate (A TAB®, GW930187, Rhodia, France) were used as materials. The mean particle sizes in volume were obtained by laser diffraction (Coulter LS 230, Beckman Coulter, US). The fractions were mixed with 0.5% w/w (Vivapur 12® and Fast Flo®) or 1% w/w (A TAB®) of magnesium stearate (NF-BP-MF2 039445, Akcros Chemicals v.o.f, Netherlands) in a Turbula mixer at 50 rpm for 5 min (type T2C, Willy A. Bachofen, Basel, Switzerland).

The apparent particle densities of the mixtures were obtained by helium pycnometry (Accupyc 1330, Micromeritics, US).The bulk densities were obtained from the mass of powder used to fill manually a defined die volume which has a normalised value of 1 cm^3. The tapped densities were deduced from the mass of powder used to fill the die of 1 cm^3 and the punch's displacement corresponding to a force of 16 N recorded with an eccentric instrumented Frogerais OA tableting press [10]. This force of 16 N is the defined limit of detection of the upper punch's sensor. All these parameters are reported in Table 1.

2.2. Formation of compacts

Cylindrical compacts were obtained using an eccentric instrumented Frogerais OA tableting press [10]. The volume of the die was kept constant (1 cm^3) and the powders were manually poured into the die. The applied compaction pressures varied between 5 and 280 MPa (*i.e.* 18 compaction pressures). At least three days after compaction (*i.e.* after total elastic recovery), the section, the height, the weight of tablets were measured, and the mean porosity ε of the compacts was calculated knowing the apparent particular densities of the fractions. The relative density ρ_r corresponds to $1-\varepsilon$.

2.3. Measurement of mechanical properties

Mechanical properties were studied after total elastic recovery of the compacts. The tensile strength (σ_r, expressed in MPa) was obtained by a diametrical test using a texture analyser (model TAXT2, Stable Microsystems, UK) equipped with 250 N load cell and calculated from the maximal diametrical crushing force (F_r), the diameter (D) and the height (h) of the cylindrical compacts [11]:

$$\sigma_r = \frac{2 \cdot F_r}{\pi \cdot D \cdot h} \tag{2}$$

A reduced modulus of elasticity (E^*, expressed in GPa) is obtained with a microindentation test using a micropress prototype [12]. A stress was applied on the top side of the compact by a spherical indentor with a 2.38 mm diameter at a rate of 0.06 mm min^{-1}. The maximal displacement of the indentor and the relaxation time were adjusted to the excipients [13]. The force–displacement curves were recorded and then, E^* was obtained as the slope of the linear zone during unloading.

It can be noticed that tensile strength characterizes the sample volume whereas the reduced modulus of elasticity is a surface mechanical property.

2.4. Mechanical properties versus porosity, ε (or relative density, $\rho_r = 1-\varepsilon$)

2.4.1. Exponential relationship

For pharmaceutical field, mechanical properties of a tablet are generally plotted versus porosity and are often fitted with an empiric exponential relationship [14,15]:

$$X = X_0 \cdot e^{-b\cdot\varepsilon} \tag{3}$$

where X is σ_r or E^* in this work, ε is the mean compact porosity and X_0 is the mechanical property at $\varepsilon = 0$ or $\rho_r = 1$ (σ_{r0} or E_0^*), b is a constant.

X_0 is currently used to compare mechanical properties of various compacted materials.

2.4.2. Percolation model

The percolation model (Eq. (1)) was used to relate the mechanical properties (σ_r and E^*) to the relative density, in order to determine the model's parameters (ρ_c and q), in the vicinity of the percolation threshold. Far away from the percolation threshold (*i.e.* for $\rho_r > 0.8$ in the case of microcrystalline cellulose and lactose, for $\rho_r > 0.6$ in the case of anhydrous calcium phosphate), a linear relationship between σ_r or E^* and ρ_r was employed. The values of mechanical properties for $\rho_r = 1$ were determined (σ_{rmax} and E^*_{max}). The use of this model was based on the approach proposed by Kuentz et al. in [5,7]. Then, the experimental values of the two mechanical properties were normalised by the maximal values of the corresponding properties σ_{rmax} and E^*_{max} obtained from linear extrapolation of $\rho_r \to 1$ using the experimental values from the highest compaction pressures (*i.e.* higher than 80 MPa). The data used for the linear extrapolation were omitted for the application of the percolation model. This leads to Eq. (4):

$$\frac{X}{X_{max}} = A' \cdot (\rho_r - \rho_c)^q \tag{4}$$

Table 1
Physical characterization of the three excipients mixed with magnesium stearate

	Microcrystalline cellulose	Lactose	Anhydrous calcium phosphate
Apparent particle density (g cm^{-3})[a]	1.5380 ± 0.0007	1.5287 ± 0.0003	2.7682 ± 0.0004
Mean particle size (μm)[b]	152 ± 48	134 ± 36	162 ± 35
Bulk density (g cm^{-3})[c]	0.362 ± 0.004	0.604 ± 0.007	0.731 ± 0.004
Tapped density (g cm^{-3})[c]	0.387 ± 0.004	0.626 ± 0.002	0.767 ± 0.006
Relative bulk density	0.236	0.395	0.264
Relative tapped density	0.252	0.409	0.277

[a] $n = 3$.
[b] Mean particle size obtained without magnesium stearate, $n = 3$.
[c] $n = 8$.

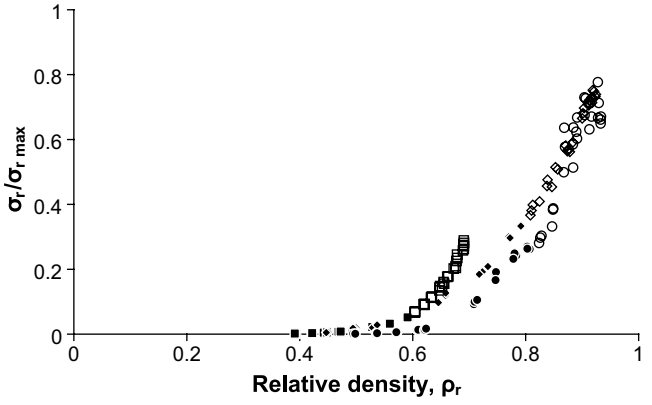

Fig. 1. Normalised tensile strength (σ_r/σ_{rmax}) as a function of relative density and in the case of microcrystalline cellulose (♦/◇), lactose (●/○) and anhydrous calcium phosphate (■/□) tablets. Closed symbols correspond to experimental data used for the application of the percolation model (Eq. (4)) and open symbols correspond to experimental data used for the linear extrapolation.

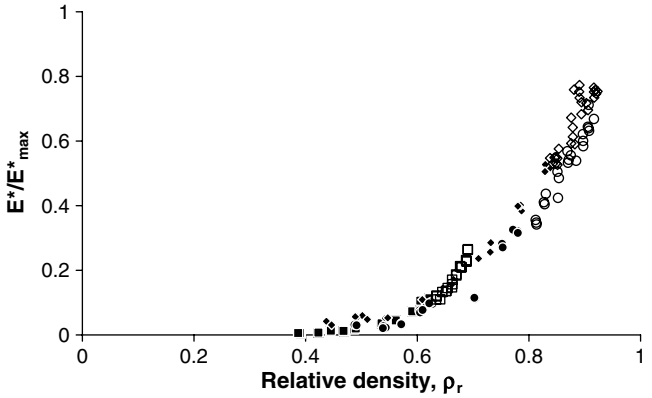

Fig. 2. Normalised reduced modulus of elasticity $\left(\frac{E^*}{E^*_{max}}\right)$ as a function of relative density and in the case of microcrystalline cellulose (♦/◇), lactose (●/○) and anhydrous calcium phosphate (■/□) tablets. Closed symbols correspond to experimental data used for the application of the percolation model (Eq. (4)) and open symbols correspond to experimental data used for the linear extrapolation.

The constant A in Eq. (1) is only affected by the value of X_{max} (this corresponds to the constant A'). On the contrary, the threshold ρ_c and the exponent q are not influenced by the normalisation. Data fitted with Eq. (4) are shown in closed symbols in Figs. 1 and 2 whereas open symbols in the same figures correspond to data used for determination of σ_{rmax} and E^*_{max}.

All the experimental data were fitted using the program Origin 5.0 (OriginLab, Northampton, USA) and the validity of the model was estimated with a χ^2 test. We proceed in two stages. In a first step, the exponent q was kept constant and equal to the values proposed in the literature [2], *i.e.* 2.7 for the tensile strength and 3.9 for the reduced modulus of elasticity. Then, only A' and ρ_c were deduced from the model. Second, all the parameters (A', ρ_c and q) were obtained from the model.

3. Results and discussion

3.1. Discussion about linear and exponential extrapolations

For the two mechanical properties (σ_r and E^*), the X_0 values obtain with an exponential extrapolation are higher than the X_{max} values obtained with a linear relationship (Table 2). In fact, in the two cases, the validity of the X_{max} and X_0 values must be debated since it is difficult to obtained tablets with porosity near zero. First, the minimal value of porosity observed with anhydrous calcium phosphate tablets is 31% (*i.e.* $\rho_r = 69\%$). Secondly, the porosity values observed with cellulose and lactose compacts seem to remain stable for the highest compaction pressures (see Fig. 3). It then should be supposed that a zero porosity could not be obtained even under highest pressures. In this particular case, a linear or exponential extrapolation to a zero porosity seems critical. More, the use of these relationships with E^* may also be discussed. The porosities or relative densities used in Eq. (1) and in the linear relationship

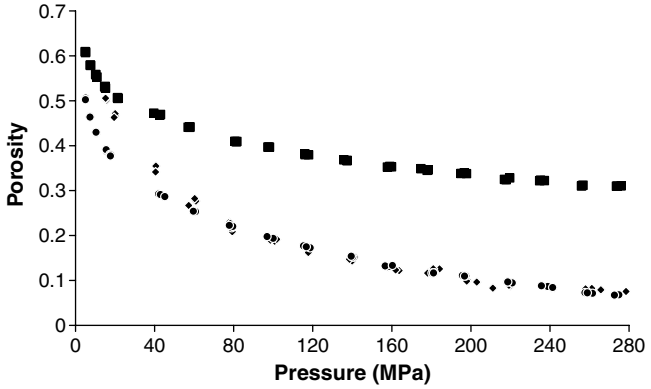

Fig. 3. Evolution of porosity with the compaction pressure in the case of microcrystalline cellulose (♦), lactose (●) and anhydrous calcium phosphate (■) tablets.

Table 2
Comparison between X_{max} obtained with a linear extrapolation and X_0 obtained with an exponential relationship

	Linear relationship		Exponential relationship	
	σ_{rmax}	E^*_{max}	σ_{r0}	E^*_0
Microcrystalline cellulose	4.9 (0.9863)	5.2 (0.8002)	9.3 (0.9711)	7.5 (0.9861)
Lactose	4.0 (0.8148)	51.0 (0.9414)	12.9 (0.9605)	77.6 (0.9665)
Anhydrous calcium phosphate	7.7 (0.9559)	184.0 (0.9907)	376.3 (0.9981)	2483.1 (0.9369)

Values in brackets refer to R^2 values.

are properties which characterize the tablet's volume (*i.e.* it is a mean value porosity). On the contrary, E^* is a surface tablet property and a recent study shows that the surface and mean volume porosities are different [16]. In regard of these results, the analysis of extrapolated values for E^* is difficult. In fact, mechanical properties extrapolated to $\varepsilon = 0$ (*i.e.* $\rho_r = 1$) with a linear or an exponential relationship are not suitable to compare the mechanical properties of the single materials.

Nevertheless, in the following parts concerning the use of percolation model, the extrapolated values obtained with a linear relationship are used to normalise mechanical properties. This choice was not justified by the superiority of one relationship. It was made to be comparative with previously published works [2,5,6].

3.2. Parameters obtained from the percolation model

In theory, Eqs. (1) and (4) are only valid close to the percolation threshold. For pharmaceutical compaction process, it is admitted that the range of application of Eq. (4) is relatively broad [2] (see part 1). No rules have been found in the literature concerning the range of relative densities applicable, and more, it depends on the authors [5,7,17]. In this work, the range of application of the model was determined graphically; it is below a relative density of about 0.8 for lactose or microcrystalline cellulose and about 0.6 for anhydrous calcium phosphate. However, it must be kept in mind that the parameters fitted from the percolation model strongly depend on the range of relative densities used [7]. For the two approaches, the statistical correlation of the fit is given by χ^2 values in Tables 3–6.

3.2.1. First approach ($q = 2.7$ or 3.9)

Figs. 4 and 5 show the normalised mechanical properties (tensile strength and reduced modulus of elasticity) *vs.* the relative density of the corresponding tablets for the range of relative densities chosen for the use of percolation model. The relative tapped density is generally used as an approximation of the thresholds ρ_c [2]. For the tensile strength, the thresholds are higher than the relative tapped densities of the three excipients (Table 3). As a comparison, in a study performed by Kuentz et al. [7], the thresholds corresponding to the tensile strength of microcrystalline cellulose tablets were equal to the relative bulk densities or between the relative bulk and tapped densities. Concerning the reduced modulus of elasticity, the threshold values are smaller than the relative bulk densities of the excipients and then, lower than values obtained with the tensile strength (Table 4). The same trend was observed by Kuentz and Leuenberger [5] in a study concerning the elasticity modulus of microcrystalline cellulose tablets. The authors hypothesized that regarding the critical values obtained for the two mechanical properties, higher values of relative densities are needed for a minimal tensile strength than for a minimal reduced modulus of elasticity. Nevertheless, some recent results about the density in tablets [16] show higher density in surface than the mean tablet density. Then, if we consider the relative density of the surface, the threshold values should be displaced to higher values of relative densities.

Table 3
Parameters obtained with Eq. (4) for the tensile strength when $q = 2.7$

	Microcrystalline cellulose	Lactose	Anhydrous calcium phosphate
σ_{rmax}	4.9	4.0	7.7
ρ_c	0.38 ± 0.01	0.49 ± 0.01	0.34 ± 0.01
A'	3.5 ± 0.2	6.6 ± 0.7	1.9 ± 0.3
χ^2	0.00135	0.00251	0.00017

Table 4
Parameters obtained for the reduced modulus of elasticity with Eq. (4) when $q = 3.9$

	Microcrystalline cellulose	Lactose	Anhydrous calcium phosphate
E^*_{max}	5.2	51.0	184.0
ρ_c	0.12 ± 0.02	0.23 ± 0.03	0.25 ± 0.02
A'	1.9 ± 0.2	3.1 ± 0.6	5.2 ± 0.9
χ^2	0.00628	1.88458	1.86725

Table 5
Parameters obtained for the tensile strength with Eq. (4) when q is obtained from the percolation model

	Microcrystalline cellulose	Lactose	Anhydrous calcium phosphate
σ_{rmax}	4.9	4.0	7.7
ρ_c	0.25 ± 0.08	0.54 ± 0.01	0 ± 0.23
A'	3.6 ± 0.5	4.6 ± 0.8	5.3 ± 7.7
q	3.8 ± 0.7	2.1 ± 0.2	8.8 ± 7.9
χ^2	0.00004	0.00013	1.3202×10^{-6}

Table 6
Parameters obtained for the reduced modulus of elasticity with Eq. (4) when q is obtained from the percolation model

	Microcrystalline cellulose	Lactose	Anhydrous calcium phosphate
E^*_{max}	5.2	51.0	184.0
ρ_c	0 ± 0.22	0 ± 0.9	0 ± 0.49
A'	1.2 ± 1.2	1.8 ± 10.4	6.2 ± 19.2
q	4.8 ± 1.5	6.8 ± 9.3	8.3 ± 7.4
χ^2	0.00019	0.00064	0.00003

3.2.2. Second approach (all the parameters are fitted)

Figs. 6 and 7 show the percolation model (dashed line) and ρ_c in the case of the second approach. The simultaneous determination of the three parameters could be sensitive. More, curve fittings can produce very different results depending on the starting values. To test the Origin 5.0 program, other trials were performed by different people with other fitting programs. The obtained results con-

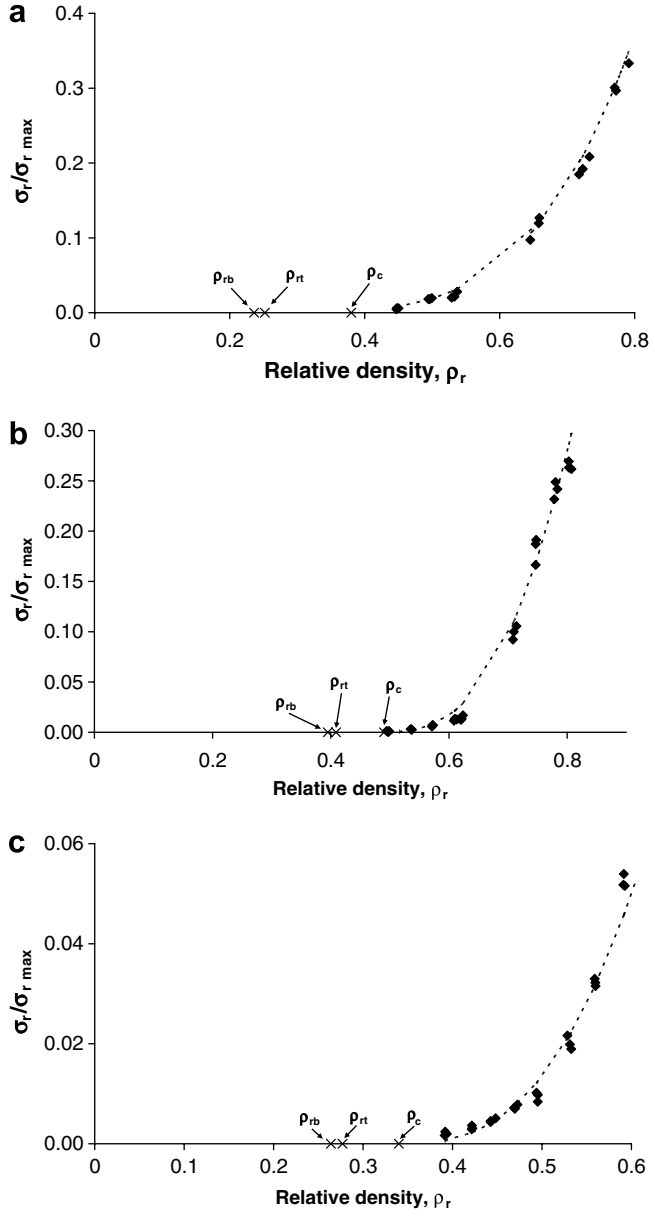

Fig. 4. Normalised tensile strength (σ_r/σ_{rmax}) as a function of relative density when $q = 2.7$ and in the case of microcrystalline cellulose (a), lactose (b) and anhydrous calcium phosphate (c) tablets. Dashed line corresponds to the percolation model (Eq. (4)).

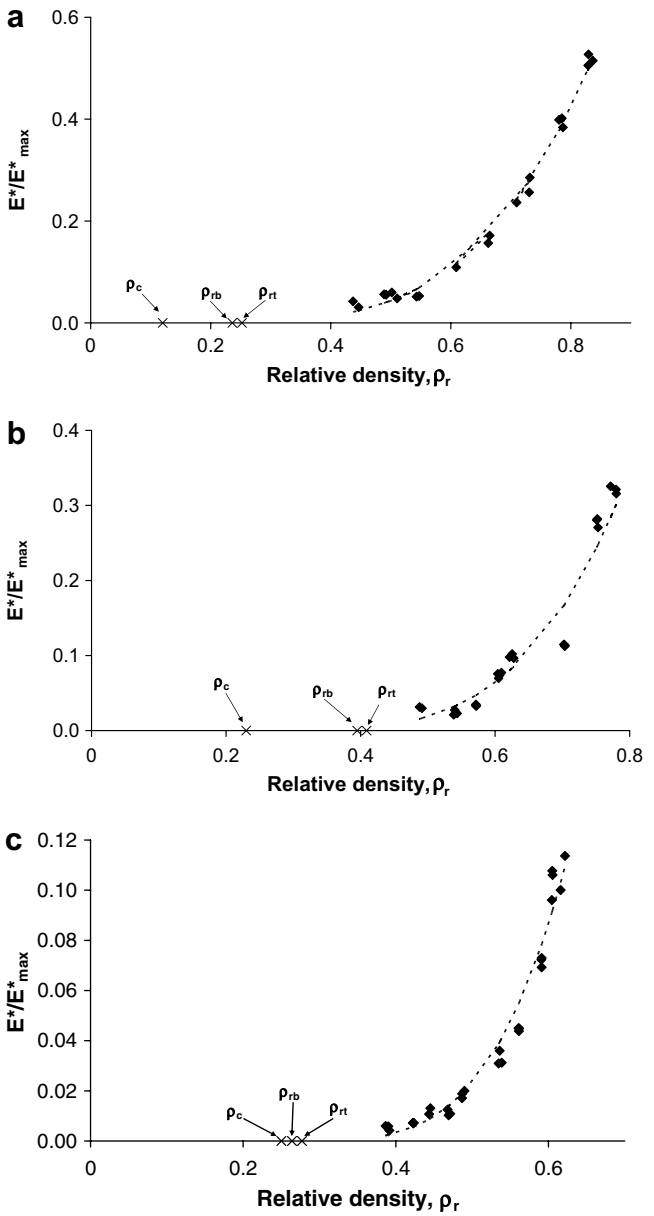

Fig. 5. Normalised reduced modulus of elasticity $\left(\frac{E^*}{E^*_{max}}\right)$ as a function of relative density when $q = 3.9$ and in the case of microcrystalline cellulose (a), lactose (b) and anhydrous calcium phosphate (c) tablets. Dashed line corresponds to the percolation model (Eq. (4)).

firmed those obtained using Origin 5.0 and validated the use of this fitting program. Depending on the excipients, the values of the exponent q may highly differ from the theoretical values of 2.7 for tensile strength and 3.9 for reduced modulus of elasticity. For tensile strength, values of 2.1 and 3.8, coherent with theoretical and previous experimental values (2.7 and 3.2, respectively, [7]) are obtained with lactose and microcrystalline cellulose tablets. The exponent obtained with anhydrous calcium phosphate tablets is higher than the expected value of 2.7 ($q = 8.8$, see in Table 5). For the reduced modulus of elasticity, the experimental values of q are always higher than 3.9 (Table 6). But, a closest value is obtained with microcrystalline cellulose tablets since $q = 4.8$. Previously, Kuentz and Leuenberger [5] found q values ranged from 3.8 to 4.1 for the reduced modulus of elasticity of four compacted cellulose. For the two other products, q values are very different than the theoretical value and the uncertainties about q are significant.

The second parameter studied is the threshold ρ_c. In two investigations on microcrystalline cellulose tablets performed by Kuentz and Leuenberger [5,7], the thresholds were close to the interval of the relative bulk density and relative tapped density and the thresholds were lower for the reduced modulus of elasticity than for the tensile

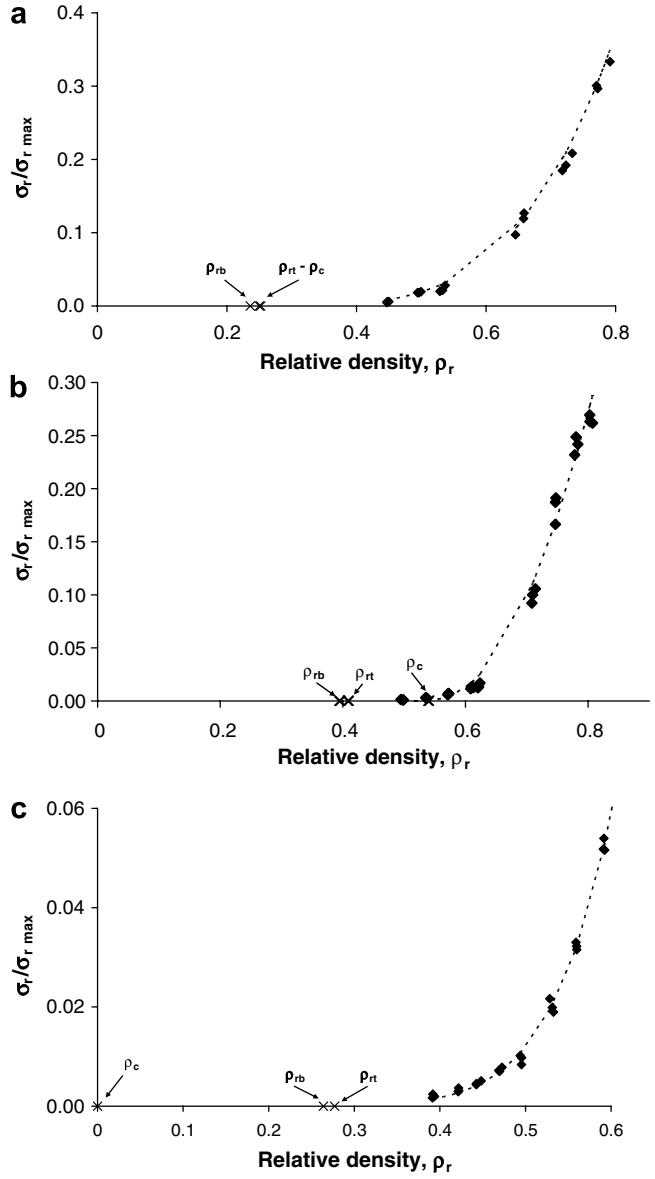

Fig. 6. Normalised tensile strength (σ_r/σ_{rmax}) as a function of relative density when q is obtained from the percolation model and in the case of microcrystalline cellulose (a), lactose (b) and anhydrous calcium phosphate (c) tablets. Dashed line corresponds to the percolation model (Eq. (4)).

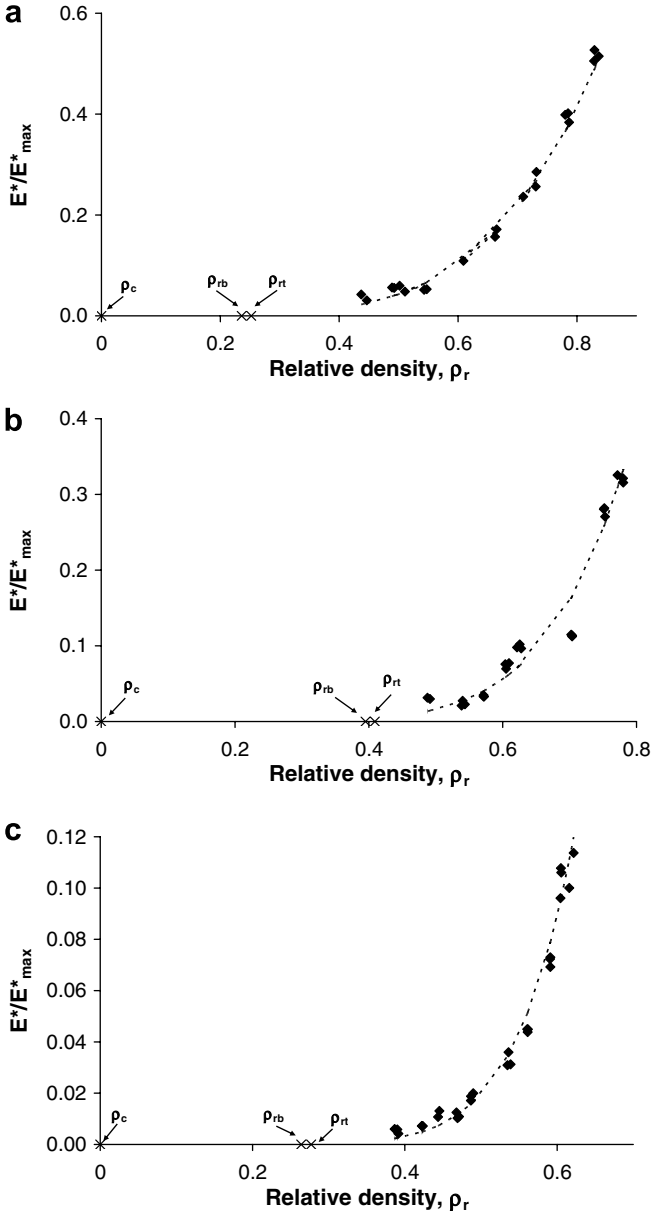

Fig. 7. Normalised reduced modulus of elasticity $\left(\frac{E^*}{E^*_{max}}\right)$ as a function of relative density when q is obtained from the percolation model and in the case of microcrystalline cellulose (a), lactose (b) and anhydrous calcium phosphate (c) tablets. Dashed line corresponds to the percolation model (Eq. (4)).

strength. In this work, ρ_c are lower in the case of E^* and could even be a zero value (in the case of anhydrous calcium phosphate, $\rho_c = 0$ for the two mechanical properties). However, zero values which are inconsistent with values of relative density are observed for the thresholds of the reduced modulus of elasticity. More, it is obvious that the minimal solid fraction needed to have a minimal value of tensile strength or reduced modulus of elasticity could not be much lower than the relative bulk density. Concerning the tensile strength of cellulose tablets, the threshold value is the most coherent with those expected ($\rho_c \sim \rho_{rt} \sim 0.25$). For lactose tablets, ρ_c corresponds to a relative density where cohesion was already experimentally observed; whereas, it is a zero value for anhydrous calcium phosphate tablets.

4. Conclusions

The percolation model is more and more use in the field of pharmaceutical compaction [5–7,17]. In this work, this model was applied to the tensile strength and the reduced modulus of elasticity of three compacted pharmaceutical excipients. In these particular cases, this model presents some limits. In fact, for a mechanical property and in the proximity of a critical relative density, the exponent of

the percolation law seems not universal. The best results are obtained with microcrystalline cellulose and lactose (*i.e.* q closer to the theoretical values). The results of the critical relative density for the two mechanical properties are not always in accordance with expected relative tapped density or relative bulk density when the two proposed approaches are tested. For example, in some cases, ρ_c could be equal to zero. Then, having regard to the presented results, the percolation model must be applied carefully to the tablet's mechanical properties.

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