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ORIGINAL ARTICLE

Changes in the specific surface area of tablets composed of pharmaceutical materials with various deformation behaviors

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Abstract

Objective: The aim of this work is to study the effect of compaction on the specific surface area of tablets composed of various pharmaceutical materials (microcrystalline cellulose, lactose, and anhydrous calcium phosphate) compacted under seven degrees of compaction pressure. *Methods*: In a first part, the influence of the deformation behavior of the compacted materials on the evolution of the specific surface area is observed. In a second part, the brittle and ductile abilities of the materials are calculated using the specific surface area values. The experimental results are used to calculate the number and the force of interparticulate bonds inside the tablet. *Results and Discussion*: Tablets made of microcrystalline cellulose, which deform plastically, have specific surface areas that fall under pressure. In the case of lactose, the tablet specific surface area first increases to reach a maximum value at a pressure of 150 MPa. At higher pressure, however, the specific surface area decreases. The specific surface area of tablets composed of anhydrous calcium phosphate consistently increases, whatever the compaction pressure applied. Moreover, the evolution of the specific surface area is correlated with the tensile strength of the corresponding tablets. The number and the force of interparticulate bonds make it possible to classify the materials according to their deformation behavior and to quantify their ability to form cohesive tablets.

Key words: Compaction, deformation behavior, excipients, specific surface area, tensile strength

Introduction

Direct compaction is commonly used to produce pharmaceutical tablets. The porous structure of the produced tablets depends on the behavior of powder during compaction, on interparticle frictions, and on die wall frictions. The tabletting behavior of pharmaceutical materials may be studied by taking into account the characterization of the deformation behavior of the materials under pressure. Commonly, it may be evaluated by using the parameters measured during the compression cycle. One of the most studied correlations is the degree of porosity variation as a function of the applied pressure. In the pharmaceutical field, the model proposed by Heckel[1,2] is commonly used. The porosity of tablets can also be studied with some other techniques, like nitrogen adsorption or mercury porosimetry[3]. With the nitrogen adsorption experiments, it is possible to obtain the specific surface area by using the BET model[4]. Recently, we studied the porous structure of pharmaceutical tablets using the pulsed-gradient stimulated echo NMR experimental technique[5]. We showed that the diffusion in the pore space depends on the compaction behavior of the compacted materials. The measurement of the surface area of tablets obtained with various degrees of compaction pressure is a continuation of this work, as it may give information on the tabletting behavior of pharmaceutical materials. Different kinds of specific surface area evolution with pressure have been observed and reported in the literature. (i) The specific surface area increases at a low pressure corresponding to the fragmentation of the initial particles. A maximum is reached at a given pressure. Beyond this level of pressure, a decrease in the specific surface area because of the plastic deformation of particles is observed[6]. (ii) For materials which only deform owing to a plastic phenomenon without fragmentation, only a decrease in the specific surface area is observed[7]. (iii) For brittle materials, the specific surface area increases with compaction pressure indicating continual formation of new surfaces[8]. (iv) In

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some cases, a second rise may be observed at high pressure with materials characterized by a high degree of elastic recovery[9].

The aim of this work was first to study the effect of compaction on the surface area of tablets obtained with three pharmaceutical materials. In a second part, the results of specific surface area were correlated with the compaction behavior of the materials under pressure. For this purpose, the fragmentary ability[6], the number of interparticulate bonds formed during compression, and the force of interparticulate bonds[10] were obtained.

Materials and methods

Materials

The materials were microcrystalline cellulose (Vivapur 12®, 5601210932, JRS Pharma, Rosenberg, Germany), partly amorphous lactose (Fast Flo®, 8500042062, Sheffield Bio-Science, Norwich, NY, USA), and anhydrous calcium phosphate (A TAB®, GW930187, Innophos, Cranbury, NJ, USA). These materials were chosen as models of materials with different behaviors in terms of fragmentation and deformability propensity. Microcrystalline cellulose consolidates by plastic deformation and anhydrous calcium phosphate by fragmentation[11,12]. Lactose has an intermediate behavior[13]. The 100–180 µm sieved fractions were used in all cases. The particle size distributions of the three fractions were characterized by laser diffraction (Mastersizer 2000, Malvern Instrument, Worcestershire, UK) in the validity conditions of Fraunhofer theory. Other main characteristics of the three fractions were previously determined[14] and reported in Table 1. Before use, the fractions were stored in a closed chamber with a saturated $NaHSO_4$, H_2O solution corresponding to a relative humidity of 48 ± 6%, and kept at room temperature (about 20°C) for at least 3 days.

Compaction

Cylindrical tablets of materials mixed with 0.5% (microcrystalline cellulose and lactose) or 1% (calcium phosphate) by weight of magnesium stearate (NF-BP-MF2, Akcros Chemicals Ltd., Manchester, UK) were obtained using an eccentric instrumented Frogerais OA tabletting press. The powders were manually poured into the cylindrical die (8 mm in diameter and 1 cm in height). The target compressions (σ_c) used were 40, 80, 120, 150, 200, 240, and 280 MPa. The press and the method of compaction were described in more detail in a previous paper[15]. After compaction, the compacts were stored for at least 3 days in a closed chamber at a relative humidity of 48 ± 6% and kept at room temperature. The mean porosity of tablets was calculated after relaxation from the apparent particular density, the dimensions, and the weight of each tablet.

Determination of the specific surface area of powders and tablets

Samples were first vacuum outgassed at a temperature below 30°C. The outgassing was stopped when a pressure of 10^{-3} mmHg was reached in the cell containing the sample[16,17]. After that, the specific surface area of powders and tablets was measured in triplicate using nitrogen adsorption (Coulter SA 3100, Beckman Coulter, Inc., Brea, CA, USA). The specific surface area was calculated according to the BET equation[4]. The measurements were performed at the relative nitrogen pressure range P/P_0 from 0.05 to 0.20 (at 10 values of P/P_0) and at a temperature of −196°C. By following this procedure, the best linear fit is obtained for the BET model[17]. Because of the surface area of one tablet (which is below 0.5 m^2), each measurement was made on a sample containing several compacts (10 for microcrystalline cellulose or lactose and 5 for calcium phosphate). Taking larger sample quantities (equivalent to 1 m^2 or greater total surface) compensates for the risk of errors in determining low surface areas by nitrogen adsorption[18].

Measurement of tensile strength

The tensile strength, σ_r (MPa) was obtained by a Brazilian test using a texture analyzer (model TAXT2, Stable Microsystems Ltd., Surrey, UK) equipped with a 250 N sensor load and was calculated from the diametrical crushing force (F_r), the diameter (D), and the height (h) of the cylindrical compacts[19]:

Table 1. Physical properties and characteristics of the three materials studied (values are expressed as mean ± standard deviation).

Excipient	Apparent particle density (g/cm³)[a]	Mean particle size (µm)[b]	dv10 (µm)[b]	dv50 (µm)[b]	dv90 (µm)[b]	Specific surface area (m²/g)[c]	Mean yield pressure (MPa)[d]	BDA
Calcium phosphate (A TAB®)	2.7682 ± 0.0004	162 ± 1	115 ± 1	158 ± 1	217 ± 1	9.847 ± 0.212	672 ± 4	+0.05
Lactose (Fast Flo®)	1.5287 ± 0.0003	126 ± 2	84 ± 1	121 ± 2	175 ± 5	0.221 ± 0.003	118 ± 1	+1. 59
Microcrystalline cellulose (Vivapur 12®)	1.5380 ± 0.0007	171 ± 0	110 ± 0	163 ± 0	242 ± 0	1.127 ± 0.009	59 ± 1	−0.65

[a]Helium pycnometry (Acupyc 1330, Micrometics); $n = 3$, materials with magnesium stearate[14].
[b]Laser diffraction granulometry (Mastersizer 2000, Malvern); $n = 3$.
[c]Nitrogen adsorption, BET method (Coulter SA 3100); $n = 3$, materials with magnesium stearate.
[d]Obtained from the Heckel plot, $n = 3$, materials with magnesium stearate[14].

$$\sigma_r = \frac{2F_r}{\pi Dh}. \quad (1)$$

Results and discussion

Specific surface area of powders

The BET specific surface areas of the three raw materials are reported in Table 1. Particles of cellulose and lactose are characterized by low specific surface areas, whereas the value is far greater for particles of anhydrous calcium phosphate. These differences are not in relation with the particle size distributions. Because of sieving, the fractions are characterized by close size distributions (Figure 1d). Moreover, the specific surface areas calculated from laser diffraction in the case of smooth spherical particles are, respectively, 0.025, 0.034, and 0.014 m^2/g for microcrystalline cellulose, lactose, and anhydrous calcium phosphate. The changes in the specific surface area are probably correlated with the roughness of the particles' surfaces[11] and the existence of microporosity, which differs for the three materials (Figure 1).

Relationship between porosity and specific surface area versus compaction pressure

The decrease in the calculated mean porosity of the cylindrical compacts as a function of the increase in the compaction pressure is shown in Figure 2. Because of its brittle and fragmenting behavior, the decrease in porosity is the lowest in the case of calcium phosphate tablets. In fact, among all the different types of pressure applied, the pressure corresponding to its mean yield pressure (P_y evaluated as 672 MPa[14]) could not be obtained. Then, the porosity under the maximal pressure is slightly under those observed in the dense packing of equal spheres[20]. A porosity of about 32% is obtained under the maximal compaction pressure because of the existence of different particle sizes[21].

On the contrary, for the other two materials, the porosity decrease during compaction is more prominent. In fact, cellulose and lactose deform plastically when the applied pressure is higher than their mean yield pressure (i.e., 59 MPa for microcrystalline cellulose and 118 MPa for lactose)[14]. In both cases, the plastic deformation makes possible a greater decrease in porosity under

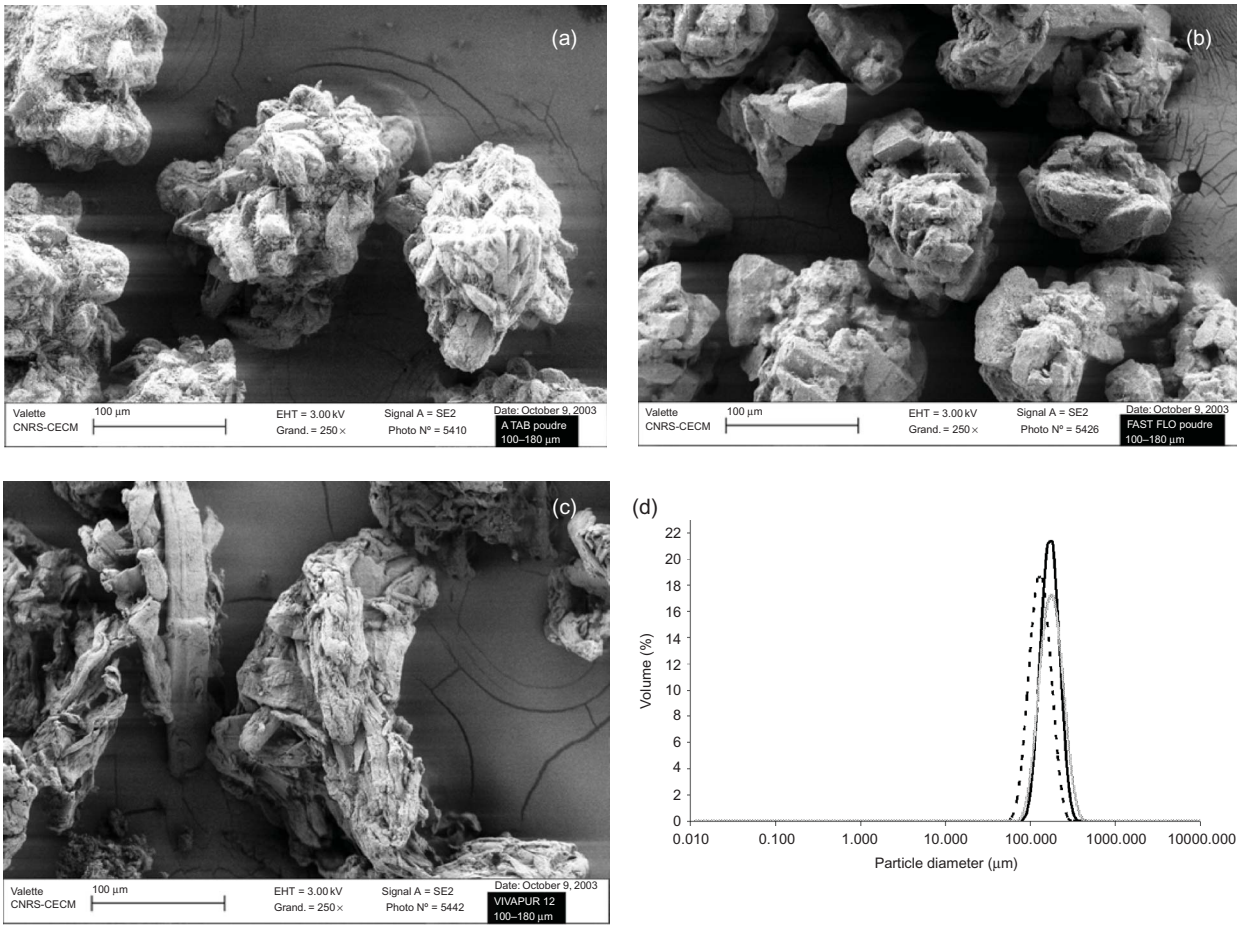

Figure 1. SEM photographs of powders (a) anhydrous calcium phosphate, (b) lactose, (c) microcrystalline cellulose, and (d) particle size distribution in volume % (gray line, microcrystalline cellulose; dotted line, lactose; black line, anhydrous calcium phosphate).

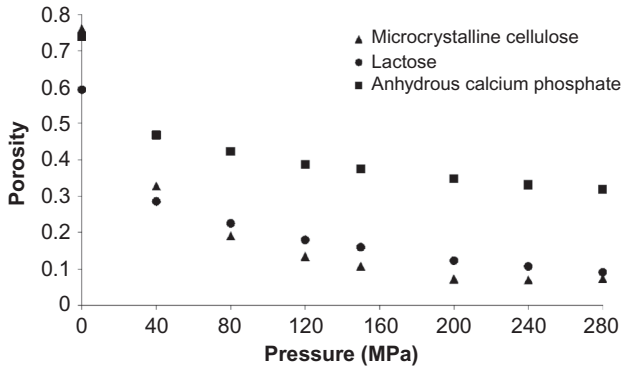

Figure 2. Evolution in the porosity of tablets as a function of compaction pressure. ▲, microcrystalline cellulose; ●, lactose; ■, anhydrous calcium phosphate.

pressure (7% for microcrystalline cellulose and 9% for lactose under 280 MPa).

The evolution in specific surface areas according to the degree of applied pressure is shown in Figure 3. As presented in the Introduction, the specific surface area evolves differently depending on the excipient used. It can increase at a low pressure because of the fragmentation of the initial particles and take a maximum value at a given pressure. When the compaction pressure becomes higher, the specific surface area falls as a consequence of particle plastic deformation[6]. When the particles are only plastic under pressure, a decrease in the specific surface area is observed[7]. In the case of brittle materials, the specific surface area continuously increases with the compaction pressure[8]. Sometimes, the specific surface area can rise at a high compaction pressure because of elastic recovery[9].

It is known that the particle size of the initial material affects the degree of fragmentation during compaction[22–24]. In our work, we tried to reduce the effect of the initial particle size by using the same size fractions for all tested materials. The size distribution parameters reported in Table 1 show that the initial particle distribution are quite the same and not very large.

The specific surface area of cellulose tablets decreases with increasing compaction pressure because of the plastic deformation of particles[7] (Figure 3a). The total decrease (when considering both the powder's specific surface area and the specific surface area of the most compacted tablet) is about 0.7 m^2/g (i.e., a relative decrease of 65% in the initial specific surface area) with a variation of 0.5 m^2/g for a pressure lower than 120 MPa and only 0.2 m^2/g when the pressure becomes higher than 200 MPa. The same trend is observed for the decrease in the mean porosity of the corresponding tablets when the pressure gets near 200 MPa. These two results can probably be explained by a percolation of the tablet porosity[25].

In the case of lactose tablets, the graph entitled 'surface area as a function of compaction pressure' shows results which can be divided into two main categories. For a pressure lower than 150 MPa (which corresponds to a pressure lower than the mean yield pressure of lactose),

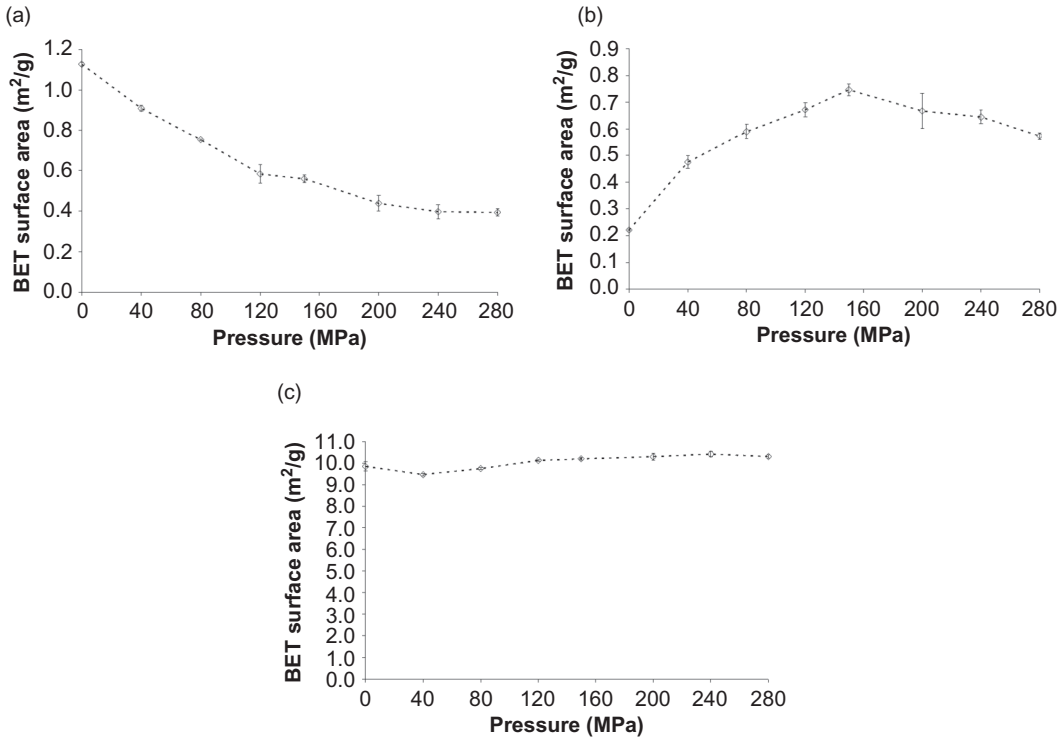

Figure 3. Changes in BET surface area with compaction pressure in the case of (a) microcrystalline cellulose tablets, (b) lactose tablets, and (c) anhydrous calcium phosphate tablets.

an increase in the specific surface area is observed (at 150 MPa, the tablets have a specific surface area that is 3.5 times higher than the powder's specific surface area). This clearly indicates the fragmentation of particles and formation of new surfaces. This effect is more marked for pressure between 0 and 40 MPa, probably because of the fragmentation of powder agglomerates. For a pressure higher than 150 MPa, a decrease in the surface area with increasing compaction pressure is observed (25% of the highest specific surface area is lost). For this range of pressure, the mean yield pressure of lactose is exceeded and particles deform plastically, leading to a decrease in the tablet's surface area. The same trend was previously observed by Masteau and Thomas[6] for tablets of lactose and materials with a similar behavior under pressure. These authors also observed a maximum value in the specific surface area of lactose tablets at a pressure of about 150 MPa.

For tablets of anhydrous calcium phosphate, an increase in the BET surface area is observed except at a pressure lower than 50 MPa. This first step in the decrease could correspond to the formation of interparticular bonds between the initial particles. Then, the surface area of tablets obtained at a lower pressure is lower than that of initial particles. For a pressure higher than 50 MPa, the surface area increases continually with increasing pressure. This illustrates the brittle behavior of anhydrous calcium phosphate particles[8]. Nevertheless, the increase in the surface area seems reduced in comparison with that observed with lactose. This is because of the specific surface areas of the initial powders (less than 0.5 m^2/g in the case of lactose but about 10 m^2/g in the case of anhydrous calcium phosphate). Then, the relative increase in the specific surface area is 1 m^2/g but represents about 6% of the powder's specific surface area in the case of calcium phosphate. For lactose, even if the increase is 0.5 m^2/g, it accounts for about 240% of the initial specific surface area. The difficulty in the comparison of lactose and calcium phosphate arises from a great difference between the two initial specific surface areas. As previously reported by Alderborn and Nyström[22], the absolute and the relative increases in the specific surface area of tablets under pressure are dependent on the specific surface area of the initial materials. As a consequence, it can be used only when the surface areas of powders are the same for all the compared materials.

Relationship between tensile strength and specific surface area

The amount of variation in the tensile strength according to the specific surface area is shown in Figure 4. In the case of anhydrous calcium phosphate, the increase in the tensile strength is correlated with an increase in the specific surface area, except for tablets obtained at the highest degrees of pressure. For lactose, the evolution in the tensile strength is first related to a slight increase in the specific surface area. For a pressure higher than P_y, the tensile strength increases but the specific surface area remains constant. For tablets composed of microcrystalline cellulose, the tensile strength increases when the specific surface area decreases. The tablet's tensile strength results from the presence of interparticulate bonds and the force of these bonds. A rise in the tablet's surface area theoretically increases the number of interparticulate bonds[9]. Therefore, the first hypothesis may be that concerning anhydrous calcium phosphate, the important parameter for cohesion is the number of interparticulate contacts. On the contrary, for microcrystalline cellulose, the parameter to consider may be the strength of the contacts. In the case of lactose, it depends on the applied pressure (lower or higher than its P_y).

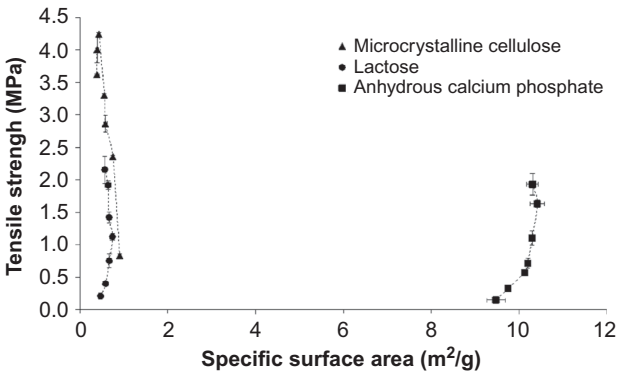

Figure 4. Evolution in tensile strength of tablets as a function of specific surface area. ▲, microcrystalline cellulose; ●, lactose; ■, anhydrous calcium phosphate.

Classification of the materials according to their brittle and ductile abilities

As the evolution of the specific surface area of tablets under pressure depends on the compaction behavior of the compacted materials (i.e., fragmentation and/or plastic deformation), Masteau and Thomas[6] proposed a classification of the materials according to their fragmentation ability. This parameter is originally calculated with the following equation:

$$FA = \frac{S_m - S_0}{S_0}, \quad (2)$$

where S_m represents the maximum value of the specific surface area and S_0 the specific surface area of the powder.

Equation (2) was previously applied successfully only with materials which deform first by fragmentation (i.e., when $\sigma_c < P_y$) and second by plastic deformation for a pressure higher than the mean yield pressure. For ductile materials, the maximum specific area is the powder's specific area and, in that case, FA takes a zero value. For brittle materials, the specific surface area increases continuously with pressure (if we consider the range of

pressure used in the pharmaceutical field, which is generally not higher than 300 MPa). In our study, the fragmentation ability expressed by Equation (2) could only be used with lactose (FA = 2.4). In the case of microcrystalline cellulose and anhydrous calcium phosphate, a maximum value was not observed because the specific surface area continually decreases or increases. Consequently, a change in Equation (2) may be proposed to make the evaluation of materials' behavior more universal for the different degrees of pressure used. The parameter BDA (for brittle and ductile ability) is then proposed and defined by Equation (3):

$$\mathrm{BDA} = \frac{S_{\mathrm{p\,max}} - S_0}{S_0}, \tag{3}$$

where $S_{\mathrm{p\ max}}$ is the specific surface area of the tablet obtained under the highest compaction pressure (in this case, 280 MPa) and S_0 the specific surface area of the powder.

The values of BDA obtained for the three materials are reported in Table 1. As expected, BDA is negative for microcrystalline cellulose. This negative value characterizes the decrease in the specific surface area and the plastic deformation of cellulose. BDA is positive for lactose and anhydrous calcium phosphate. This means that these two materials fragment under pressure. BDA is higher for lactose than for anhydrous calcium phosphate, which means that according to this parameter, the fragmentation ability should be lower in the case of calcium phosphate. This conclusion is not in accordance with what could have been expected as calcium phosphate is known to fragment at all degrees of pressure, whereas lactose has an intermediate behavior (i.e., fragmentation or plastic deformation depending on the applied pressure). In the case of lactose, BDA results in fact from fragmentation and plastic deformation. For calcium phosphate, it is only because of its brittle behavior. But, as previously observed, the specific surface area values show that even if an increase of 1 m^2/g is observed for anhydrous calcium phosphate, the relative variation is lower than in the case of lactose (see Section 'Relationship between porosity and specific surface area versus compaction pressure'). This may be explained by the characteristics of the calcium phosphate particles. In fact, if we first hypothesize spherical particles of lactose and phosphate, the surface area of calcium phosphate particles is more than 100 times superior to that of lactose particles. Second, we suppose that each particle breaks down into two parts and that the created surfaces correspond to those of two smooth disks. In this over-simple case, the created surfaces represent less than 0.1% of the total particle surface area for anhydrous calcium phosphate and almost 7% for lactose. Even if anhydrous calcium phosphate particles fragment in the whole range of pressure, the impact of the created surfaces on the total surface area remains limited. We can therefore conclude that the BDA parameter is not totally adapted to characterize the propensity of calcium phosphate to fragment and to a larger extent for particle systems with a high specific surface area.

Theory of interparticulate bond-formation process

A tablet is obtained under pressure by the formation of interparticulate bonds. The number of bonds depends on the deformation behavior of particles and indirectly on the tablet's surface area. The tensile strength of the corresponding tablets is controlled by the number of bonds and the bonding forces. Eriksson and Alderborn[9] proposed a study of particle deformation and fragmentation during compression with the theory of interparticulate bond-formation process. In this work, the authors supposed that the tensile strength of a tablet is theoretically governed by the sum of the bonding forces of all individual interparticulate bonds in the failure plane. This could be expressed by the following equation:

$$\sigma_{\mathrm{r}} = n_{\mathrm{b}} F_{\mathrm{b}}, \tag{4}$$

where σ_{r} is the tensile strength (MPa), n_{b} the number of bonds per cross-sectional area of the tablet's fracture surface (mm^{-2}), and F_{b} the bonding force of interparticulate bonds (N).

The authors consider that Equation (4) is valid for relatively porous compacts defined in their study by $\sigma_{\mathrm{c}} \leq 150$ MPa[9].

Secondly, an approximation of the number of bonds per cross-sectional area of the tablet fracture surface (n_{b} expressed in mm^{-2}) was proposed. It was obtained by Equation (5):

$$n_{\mathrm{b}} \propto \left[\frac{1-\varepsilon}{\varepsilon}\right] S_{\mathrm{v}}^2, \tag{5}$$

with ε, the porosity of the tablet and S_{v}, the volume specific surface area of the tablet (mm^{-1}).

The authors observed that plastic materials generally have a considerably lower number of bonds compared to fragmenting materials. Here, n_{b} was calculated for the three materials studied and reported in Figure 5. For microcrystalline cellulose (i.e., the plastic material), an increase in the number of bonds is observed for any pressure lower than 50–60 MPa, which is a range of pressure corresponding to that of the mean yield pressure ($P_{\mathrm{y}} = 59$ MPa). At a higher pressure, the variation of n_{b} is limited with values around $5\text{–}6 \times 10^{10}$ mm^{-2}. For lactose, which is characterized by an intermediate mean yield pressure ($P_{\mathrm{y}} = 118$ MPa), n_{b} increases almost linearly up to a pressure of 150 MPa. Beyond this pressure level, n_{b} is almost constant with values around $7\text{–}8 \times 10^{10}$ mm^{-2}. This is in accordance with the behavior of lactose under

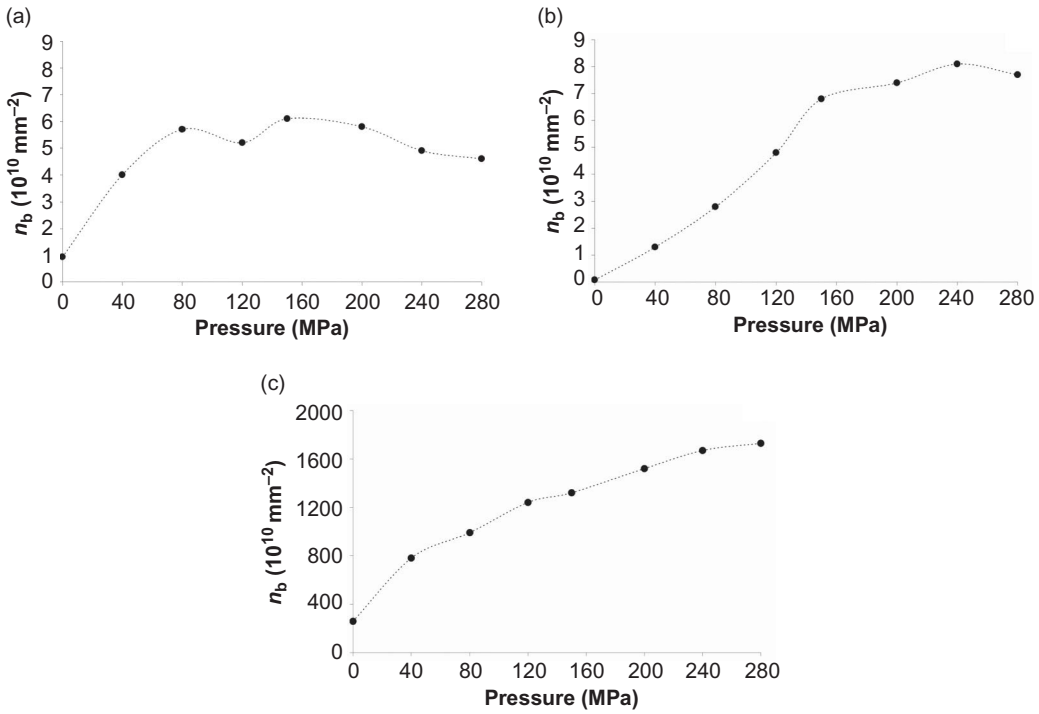

Figure 5. Number of bonds per cross-sectional area of tablet's fracture surface (n_b) as a function of the compaction pressure in the case of (a) microcrystalline cellulose tablets, (b) lactose tablets, and (c) anhydrous calcium phosphate tablets.

pressure in relation with its mean yield pressure. Values of n_b observed with anhydrous calcium phosphate rise, whatever the pressure applied. At 280 MPa, the n_b values may be classified in the following order: *anhydrous calcium phosphate* >> *lactose* > *microcrystalline cellulose*. This classification remains the same when considering mean yield pressure.

Considering Equation (4), it is possible to infer the bonding force of interparticulate bonds (F_b) from the graph of tensile strength versus n_b (Figure 6). With reference to Eriksson and Alderborn[9], Equation (4) is valid for relatively porous compact. Moreover, this relationship supposes a variation of n_b with the compaction pressure and then with the tensile strength. Therefore, in our work, Equation (4) could not be applied for the whole range of pressure used (see variation of n_b with compaction pressure in Figure 5). Therefore, it was decided to apply Equation (4) for a pressure between 40

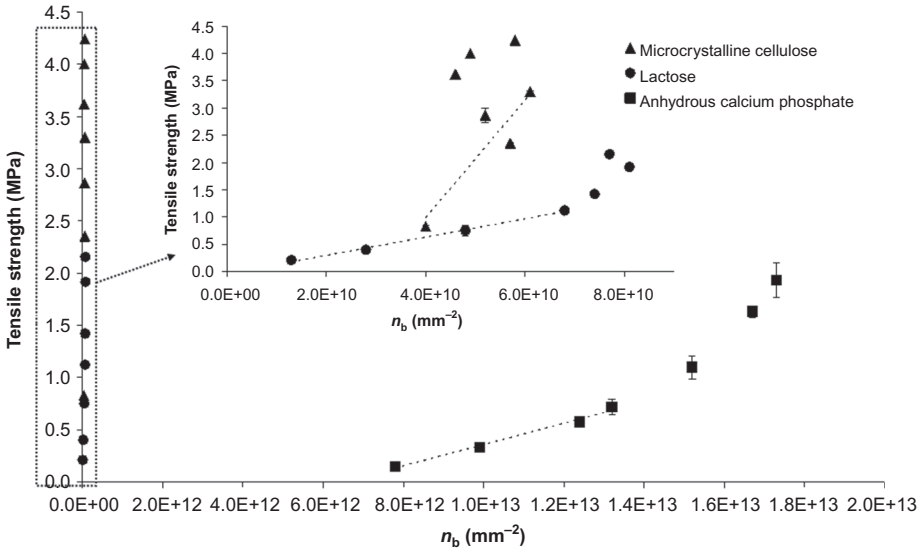

Figure 6. Evolution of tensile strength as a function of n_b. ▲, microcrystalline cellulose; ●, lactose; ■, anhydrous calcium phosphate.

Table 2. Values of n_b and F_b for the three materials studied.

Excipient	n_b obtained from the bulk powder (10^{10} mm^{-2})	n_{b0} (10^{10} mm^{-2})	F_b (10^{-13} N)
Calcium phosphate (A TAB®)	260.00	650.00	1.02
Lactose (Fast Flo®)	0.08	0.20	1.67
Microcrystalline cellulose (Vivapur 12®)	0.94	3.10	1080.00

and 150 MPa. Secondly, Equation (4) supposed that when $\sigma_r = 0$, $n_b = 0$. Nevertheless, it was generally observed that the compaction pressure needed to form a coherent compact differs from zero. As a consequence, n_b is probably greater than zero at this critical pressure and greater than n_b calculated for bulk powder (i.e., values of n_b for $\sigma_c = 0$ in Figure 5). To take these observations into account, the expression derived by Eriksson and Alderborn[9] was modified in the following way:

$$\sigma_r = n_b F_b - (n_{b0} F_b), \quad (6)$$

with σr the tensile strength (MPa), n_b the number of bonds per cross-sectional area of the tablet's fracture surface (mm^{-2}), F_b the bonding force of interparticulate bonds (N), and n_{b0} the number of bonds per cross-sectional area of the tablet's fracture surface (mm^{-2}) when $\sigma_r = 0$.

F_b and n_{b0} are graphically obtained from Figure 6 and reported in Table 2. As expected, n_{b0} are higher than n_b obtained with bulk powder. The bonding force of interparticulate bonds is the highest in the case of microcrystalline cellulose, intermediate for lactose, and the lowest in the case of anhydrous calcium phosphate. These results confirm the inferences of Section 'Relationship between tensile strength and specific surface area', that is, (i) in microcrystalline cellulose tablets, the cohesion is mainly because of a considerable force between particles; (ii) in anhydrous calcium phosphate tablets, the cohesion is correlated with an increase in the number of interparticulate bonds; (iii) in lactose tablets, both aspects account for the fact that the level of cohesion varies depending on the amount of pressure applied (lower or higher than the mean yield pressure).

Conclusion

Three pharmaceutical materials were chosen as material models and compacted under seven different levels of pressure. The specific surface area of tablets was measured and reported according to the amount of pressure applied. It appeared that the variation in the specific surface area of tablets under pressure was related to the deformation behavior (fragmentation and/or plastic deformation) of the compacted material. The results obtained in relation with the specific surface area of tablets also enabled us to calculate the brittle and ductile abilities of the materials. The calculated values confirmed the results obtained with the Heckel plot. Nevertheless, this parameter seemed less adapted when the material particles showed a large specific surface area, like anhydrous calcium phosphate. At the end, the specific surface area data were correlated with the theory of interparticulate bond-formation process. The number of bonds per cross-sectional area of tablets was calculated. The evolution of this number according to the amount of pressure applied reflected the behavior of the material under pressure. Therefore, parameters obtained are correlated with the cohesion of tablets. Concerning anhydrous calcium phosphate, cohesion occurs by increasing the number of interparticulate contacts over the whole range of pressure studied. For microcrystalline cellulose, the parameter to consider is the force of interparticulate contacts. The cohesion of lactose tablets depends on an increase in the number of interparticulate contacts when the applied pressure is lower than its mean yield pressure. With pressures higher than the mean yield pressure, cohesion results from the force of interparticulate contacts.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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