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1 **Quantification of tablet sensitivity to a stress concentration: generalization of**  
2 **Hiestand's approach and link with the microstructure**

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11 **Abstract**

12 Sensitivity to a stress concentration is important for the development of pharmaceutical  
13 tablets as it is related to defects like capping. The Brittle Fracture Index (BFI) was  
14 introduced by Hiestand *et al.* to test this sensitivity. Recently, a more general index,  
15 based on the average stress criterion, was proposed as a generalized Hiestand  
16 approach. In this work, this new approach is tested on tablets obtained for several  
17 products and pressure levels, and results show the wide applicability of the new  
18 criterion.

19 Furthermore, X-ray micro-computed tomography was used to link the tablet  
20 microstructure and the sensitivity to a stress concentration. A strong correlation was  
21 found between the size of the largest pores in the structure and the value of  $a_0$  which  
22 quantify the sensitivity to a stress concentration in the generalized Hiestand approach.

23 These results constitute the first attempt to link the brittle fracture propensity of tablets  
24 with their effective microstructure.

25 **Keywords** : tableting, capping, BFI, brittle fracture propensity, microstructure, X $\mu$ CT

26

## 27 **1. Introduction**

28 Tableting is a common process for the production of pharmaceutical dosage forms.

29 Manufacturing of tablets using die compaction have been used for more than a century.

30 Nevertheless, despite an apparent simplicity, the process of compaction involves

31 complicated mechanical phenomena, both reversible and non-reversible. The properties

32 of the final tablets are the consequence of complex interactions between the powder

33 properties (material parameters) and the process parameters. The characterization of

34 the behavior of a formulation during compaction is generally performed by studying the

35 evolution of the tablet porosity and mechanical strength (measured generally by

36 diametral compression) as a function of the pressure used to make the tablet [1]. These

37 characterizations are now summarized in the US Pharmacopeia under the terms

38 compressibility, tableability and compactibility [2].

39 One of the main challenge for the manufacturing of pharmaceutical tablet is to avoid the

40 occurrence of classical problems like capping or lamination during scale-up [3].

41 Unfortunately, the previously described characterizations are not always sufficient to

42 predict the occurrence of these kinds of defects. The case of capping, which, in the case

43 of biconvex tablet, corresponds to the breakage of at least one of the tablet cups, is

44 particularly difficult to predict. From a mechanistic point of view, it is due to the

45 development, during the unloading phase, of a high shear stress at the limit between the

46 land and the cup of the tablet (Hiestand et al., 1977; Mazel et al., 2015; Wu et al., 2008).  
47 This stress is highly concentrated and it is well known that the prediction of the breakage  
48 of a solid under concentrated stress is more difficult than in the case of homogeneous  
49 stresses [7].

50 To overcome this problem, Hiestand et al. proposed the introduction of another  
51 parameter for the characterization of a formulation: the brittle fracture index (BFI) [4].  
52 This index is calculated by comparing the tensile stress of a tablet with the apparent  
53 tensile strength of a tablet obtained under the same conditions but containing a hole at  
54 its center. The presence of the hole promotes the development of stress concentrations  
55 near the hole edge. By comparing the two values it becomes possible to study the  
56 sensitivity of a formulation concentrated stresses. Several examples of studies using this  
57 approach can be found in the literature [8–13]. It can be noted that the sensitivity to a  
58 stress concentration is sometimes called brittleness [14]. Nevertheless, other articles in  
59 the pharmaceutical literature refers also to brittleness with a slightly different meaning.  
60 For example, in some cases, a more brittle tablet is said to be more friable [15–18]. In  
61 other studies the brittleness of a tablet is directly linked with the stress intensity factor  
62 (resistance of a material to the propagation of a crack)[19]. The sensitivity to a stress  
63 concentration do not correspond to neither of these concepts. For this reason, the term  
64 brittleness will be avoided in the present paper.

65 If BFI is of interest, it is unfortunately dependent of the size of the hole introduced in the  
66 tablet. As a consequence, results published in the literature are difficult to compare one  
67 to another. For this reason, we recently proposed to introduce a new index, calculated  
68 using different hole sizes, in order to generalize Hiestand's approach [20]. Using the

69 average stress criterion introduced by Whitney et al.[7], it was found possible to  
70 characterize the evolution of the strength of the tablet as a function of the hole size. A  
71 new parameter,  $a_0$ , which is a characteristic distance, could be used to replace the BFI  
72 and quantify the sensitivity of a product to a stress concentration. In our previous work,  
73 only two products compacted at one compaction pressure were studied to see the  
74 applicability of the criterion. In the present work, the criterion is applied to tablets  
75 obtained for five different products under at least three different compaction pressures to  
76 verify the applicability of the criteria using a broader set of samples. Changing the  
77 compaction pressure would also make it possible to study the evolution of the sensitivity  
78 to a stress concentration as a function of the porosity of the tablet.

79 Then, the second objective of this study is to go further than only a descriptive index and  
80 to try to understand the relationship between the sensitivity to a stress concentration and  
81 the microstructure of the tablet. For this purpose, X-ray microcomputed-tomography  
82 ( $X\mu$ CT) was used to study the tablet microstructure as commonly done in the literature  
83 [21–24]. A special focus was made on the size of the biggest pores in the structure that  
84 are susceptible to play an important role in the failure mechanism [25,26].

## 85 **2. Material and methods**

### 86 **2.1. Powders**

87 Five different powders were used to produce compacts: calcium phosphate dihydrate  
88 (DCP) (Dicafos D160, Chemische Fabrik Budenheim Budenheim, Germany), granulated  
89  $\alpha$ -lactose monohydrate (MLac) (Excipress, Armor Pharma, France), anhydrous  $\beta$ -lactose  
90 (ALac) (Duralac, Meggle, Wasserburg, Germany), spray-dried lactose monohydrate  
91 (SDLac) (SuperTab 14SD, FSD) and spray-dried mannitol (SDMan) (Pearlitol, Roquette,

92 Lastreme, France). Table 1 and figure 1 present the particle size distribution data and  
93 photographs obtained using scanning electron microscope for the different products. It is  
94 worth noting that tablets of these products present brittle failure when broken in  
95 diametral compression. To perform the compaction experiments, the products were  
96 mixed with 1% (w/w) of magnesium stearate (Cooper, Melun, France) to minimize the  
97 frictions in the die. The blending was performed at 49 rpm for 5 min using a turbula  
98 mixer (Type T2C, Willy A Bachofen, Muttenz, Switzerland).

## 99 **2.2. Tablet compaction**

100 All the compacts were produced using a compaction simulator Stylcam® (Medelpharm,  
101 Beynost, France). This tableting press is a single station press. It is equipped with force  
102 sensors (accuracy 10 N) and the displacements of the punches are monitored with an  
103 accuracy of 0.01 mm.

104 For the application of the generalized Hiestand's approach, a special set of flat faced  
105 Euro B tooling was used as described previously [20,27]. These tooling made it possible  
106 to obtained a so-called flattened geometry. In the present study, tablets with a diameter  
107 of 11mm were used with a flat end of 30°[27]. All the compacts were obtained using the  
108 same compaction kinematic (total compression time of about 100 ms). Compression  
109 pressures of 100, 200, 300 and 400 MPa were used to produce the tablets. For SDLac  
110 and SDMan, tablets obtained under 400 MPa were too strong to be broken on the  
111 device described thereafter and were, as a consequence, not used. To avoid any effect  
112 due to the thickness, all the compacts manufactured had similar thicknesses around 3.0  
113 mm. The density was calculated using the weight and dimensions of the compacts.

114 For X $\mu$ CT, tablets with a diameter of 8 mm and a thickness of 2mm were produced  
115 under the same compaction conditions. Tablets were then cut using a sharp blade knife  
116 to obtain small cubes of about 2x2x2 mm<sup>3</sup>. The small cubes were taken from the center  
117 of the tablet as shown in figure 2.

### 118 **2.3. Tablet machining**

119 As described elsewhere [20], the holes in the tablets were inserted using a drill Micromot  
120 50 E/EF (PROXXON S.A., Luxembourg). Three drill diameters (0.5, 0.8 and 1 mm) were  
121 used to make the holes. Machining speed was adapted for each product and each  
122 compaction pressure. The tablets were maintained using a specially designed polymeric  
123 holder obtained by 3D printing. Furthermore, a Polytetrafluoroethylene sheet was used  
124 to limit friction between the tablet and the piece holder. To avoid defects at the back of  
125 the tablet during machining holes, two tablets were placed together and only the upper  
126 one was finally used for experiments.

### 127 **2.4. Tablet mechanical characterization**

128 The diametral compression test was performed using a TA.HDplus texture analyzer  
129 (Stable microsystems, Surrey, United Kingdom). Compacts were compressed between  
130 two flat surfaces at a constant speed of 0.1 mm.s<sup>-1</sup> with an acquisition frequency of 500  
131 Hz. For each condition, ten compacts were broken.

132

### 133 **2.5. X-ray tomography**

134 Tablets were scanned using a lab-based system at PLACAMAT (UMS 3626, Pessac,  
135 France). The facility used was a GE VTomex-s with a xs-180-nf transmission source and

136 a diamond target. The scan parameters (voltage and intensity) were adapted for each  
137 sample. The 1800 projections for a 360° rotation were recorded using a binning factor of  
138 1 and an exposure time of 1 second (total scanning time of two hours). The final voxel  
139 size was about 2.5µm for all the samples. Tomographic reconstructions were performed  
140 using phoenix-datos-x2 software with default parameters. Following image treatments  
141 were performed using the software Avizo V9 (Thermo Fisher Scientific, Waltham, USA).  
142 A cube of about 1.5x1.5x1.5 mm<sup>3</sup> was extracted from the data and submitted to further  
143 analyses. Details about the analyses will be given in the result part of the article.

### 144 **3. Results and discussion**

#### 145 **3.1. Application of the average stress criterion as a generalized Hiestand's** 146 **approach**

147 The five products were tested according to the methodology defined in our previous  
148 work [20]. For each product and each pressure point, tablets without hole and with holes  
149 of 0.5, 0.8 and 1 mm were broken and the breakage force was recorded. As all the  
150 tablets had the same size, analysis could be performed without transforming the forces  
151 into stresses. The ratio of the force needed to break the tablet with a hole to the force  
152 needed to break the tablet without a hole was then plotted as a function of the hole  
153 radius. Results can be found in figure 3. As expected, the ratio calculated is always  
154 below 1, which means that introducing a defect in the structure render the structure  
155 weaker. Moreover, the ratio is decreasing with increasing hole size in nearly all the  
156 cases (except for MLac between 300 MPa and 400 MPa for which the trend was not so  
157 clear). These results confirms the results published previously [20]. It also confirms that



158 the BFI defined by Hiestand *et al.*, which is calculated using the ratio, is dependent on  
159 the hole size. This is true for all the products and for all the pressure points.

160 The other result is that, for each hole size, the ratio is decreasing with increasing  
161 compaction pressure, i.e. with decreasing tablet porosity in nearly all the cases (except  
162 for DCP at 100 and 200 MPa). This means that when the porosity decreases, the tablets  
163 becomes more sensitive to a stress concentration. Similar results can be found in the  
164 literature [4,11]. These results emphasize the relation between tablet microstructure and  
165 sensitivity to a stress concentration. This aspect will be discussed in the last part of the  
166 article.

167 The average stress criterion previously discussed was then used to represent the  
168 evolution of the breakage force ratio as a function of the hole size. Results of the curve  
169 fitting with the equation of the average stress criterion[20] can be seen in figure 3. As the  
170 curve used to fit the data is non-linear, it is tedious to judge the quality of the fit using R<sup>2</sup>  
171 [28]. As an alternative, the value of the residual standard deviation (Se) is reported in  
172 table 2 and was calculated as follow[29,30]:

173

$$Se = \sqrt{\frac{\sum_{i=1}^N (y_i - \hat{y}_i)^2}{N - 1}}$$

174 With N the number of points used for the regression (3 in our case, for the 3 holes  
175 sizes),  $y_i$  the  $i^{\text{th}}$  experimental value and  $\hat{y}_i$  the  $i^{\text{th}}$  value predicted by the model. As it can  
176 be seen in most of the cases, the curve fits correctly the experimental data. For  
177 example, the agreement is very good for ALac and SDMan, and MLac gives the poorest  
178 agreement especially for the highest pressure.

179 As the criterion makes it possible to correctly represent the evolution of the force ratio as  
180 a function of the hole size, the  $a_0$  parameters was extracted for each tablet set. Results  
181 can be found in table 2. In accordance with the previous discussion,  $a_0$  values  
182 decreased (i.e. the sensitivity to a stress concentration increased) with increasing  
183 compaction pressure (except for DCP at 100 and 200 MPa as previously). This  
184 parameter can also be used to compare the products one to the other. For example, if  
185 we compare the tablets obtained under 200MPa for each product, DCP has the highest  
186  $a_0$ , i.e. is the less sensitive to a stress concentration, whereas the lowest value of  $a_0$  is  
187 obtained for SDMan. In a similar way we can see that MLac and ALac have a similar  
188 behavior regarding the stress concentration (except at the lowest pressure where ALac  
189 is a more sensitive).

190 The results presented previously show that the average stress criterion can be used as  
191 a generalized Hiestand's approach to characterize the sensitivity of a tablet to a stress  
192 concentration. It would now be interesting to understand this sensitivity. From a  
193 fundamental point of view, the sensitivity to a stress concentration should be related to  
194 the tablet microstructure. The pores that are present in the microstructure play the role  
195 of defects and are responsible of stress concentrations. If a structure has a lot of pores,  
196 it means that it has a lot of defects. We can thus anticipate that it will be less sensitive to  
197 the introduction of a hole in terms of strength (because it is already weakened by the  
198 presence of the pores). This explains why, when the pressure increases,  $a_0$  decreases.  
199 When the pressure increases, the porosity of the tablets decreases (table 2) which  
200 means that the concentration of defects in the structure decreases. As a consequence,

201 the tablet becomes more sensitive to a defect introduction and  $a_0$  decreases, as it can  
202 be observed in table 2.

203 This interpretation gives a first link between the tablet microstructure and its propensity  
204 to brittle fracture. Nevertheless, global porosity is only a macroscopic description of the  
205 microstructure in terms of global defect concentration. It does not give any information of  
206 the actual geometry of the pores for example. When comparing the same product at  
207 different porosity level, it can be supposed that the pores in the structure would be  
208 comparable in terms of geometry. Nevertheless, when comparing two different products,  
209 even if they have the same porosity level, it does not mean that the pore structure is the  
210 same in terms of pore size for example. To illustrate this fact, table 3 present an  
211 extraction of table 2 with all the tablets having a porosity level around 12.5% (11.3 to  
212 13.8%). As it can be seen, very different  $a_0$  values are obtained for the different  
213 products, and no correlation can be found with the porosity variation. Porosity is thus not  
214 a sufficient parameter to explain the sensitivity to a stress concentration of a tablet.

215

216 To understand the difference between the products at least two factors can be  
217 considered. First it could be related with microscopic interaction between the grains.  
218 This interaction being different from one product to another, it could explain the different  
219 sensitivity to a stress concentration. The second factor could be related with the pore  
220 structure itself. For example, the pore size varies from one product to another, even if  
221 the global porosity is the same. Pores of different sizes represent very different kinds of  
222 defects in the structure and might have different influence in terms of sensitivity to a

223 stress concentration[25]. To further explore the influence of pore structure on the  
224 mechanical behavior of the tablet, X $\mu$ CT was used in the following part.

### 225 **3.2. Analysis of the pore structure using X $\mu$ CT and link with the sensitivity to** 226 **stress concentration**

227 The purpose of this part was to further explore the influence of the pore structure on the  
228 sensitivity to stress concentration. For the characterization of the pore structure we  
229 focused our attention on the size of the pores, and more exactly on the size of the  
230 biggest pores in the structure. The reason for that is the following. In terms of defects, it  
231 is well-known the large defects have more influence on the actual strength of a structure  
232 than small defects [25,26]. This was, for example, seen on the results shown above,  
233 where larger hole diameters promote a larger decrease of the force needed to break the  
234 tablet. It can thus be supposed that if a tablet contains large pores, it is already  
235 weakened by these pores and as a consequence, it should be less sensitive to the  
236 introduction of the central hole. We can thus suppose that a tablet with larger pores will  
237 have a larger value of  $a_0$  than a tablet that has smaller pores (supposing that the global  
238 porosity is constant). The aim of this part was to test this hypothesis.

#### 239 **3.2.1. X $\mu$ CT analysis protocol of the tablet**

240 A procedure was thus defined in order to have an estimation of the dimensions of the  
241 largest pores in the structure. The first step was to isolate the porosity in the X $\mu$ CT  
242 images. This required the use of a threshold in terms of grayscale that will separate the  
243 solid from the pores. In the present study, the threshold was chosen in order to have, in  
244 the numerical analysis of the X $\mu$ CT images, a total porosity equal to the global porosity

245 measured on the analyzed tablets as presented in table 2. A typical example of the pore  
246 localization using this procedure can be found in figure 4. It is important to note that, in  
247 our case, only the biggest pores will be taken into consideration. These pores are those  
248 which are the less influenced by the thresholding procedure.

249  
250 Afterwards, automatic procedures of the Avizo software were used to analyze the  
251 obtained pores in terms of size. First a complete 3D analysis was intended.  
252 Nevertheless, analysis showed a large connectivity of the pore structure (i.e. more of  
253 60% of the pores was considered to be one single pore) and this did not make it  
254 possible to isolate easily the different pores in the structure. So instead of a real 3D  
255 analysis, a 2D+1 analysis was performed (i.e. a 2D analysis of images positioned along  
256 the third direction). For each slice of the X $\mu$ CT results (each analysis contained  
257 approximately 600 slices), a 2D analysis of the pores was performed. For each pore an  
258 equivalent diameter was calculated which corresponds to the diameter of the disc that  
259 would have the same surface as the pore. This diameter was taken as the characteristic  
260 size of the pores. Other parameters like the form factor were also calculated.  
261 Nevertheless, no significant results could be found with those parameters as no  
262 differences were obtained from one product to another. As a consequence, only the pore  
263 size will be discussed in the present work.

### 264 **3.2.2. Link between microstructure and sensitivity to a stress concentration**

265 Once the pore sizes were extracted for all the slices of the X $\mu$ CT results, a frequency  
266 distribution was drawn using for one sample all the pores of all the slices. Results shown  
267 below will focus on the big pores of the distribution. 10 different samples were analyzed

268 using this procedure. Two pressure points were chosen for each product. The first was  
269 100 MPa for all the samples and the second was the pressure point that gave a global  
270 porosity around 12.5% for the tablet, i.e. 200 MPa for all the products except for DCP for  
271 which the pressure was 400MPa (cf. table 3).

272 First, the evolution of the pore size distribution as a function of the applied pressure was  
273 monitored for each product. Results can be seen in figure 5. In each case, the pore size  
274 distribution is shifted to lower sizes when the pressure increases and for each case, the  
275 size of the largest defects decreases with increasing pressure. This result was expected  
276 and can be used as a validation of the data treatment methodology used in this work.  
277 Moreover, in the previous section of the article, we showed that increasing the pressure  
278 increased the sensitivity to stress concentration for each product. This could be  
279 explained by the fact that the pore size in the structure are smaller when the pressure  
280 increases. Of course the global porosity is also different and the defects concentration  
281 could also play a role in the sensitivity to stress concentration.

282 To separate the effect of global porosity and pore size, tablets with approximately the  
283 same porosity were compared. The case of the tablets presented in table 3 was  
284 considered. Pore size distribution for all the 5 tablets can be found in figure 6. It is  
285 interesting to note that, as expected, even if these tablets have a similar global porosity,  
286 the pore size distribution differs from one product to another. This confirms that global  
287 porosity is not a sufficient descriptor of the tablet microstructure. But the most interesting  
288 point is that there is a correlation between the pore size distribution and the sensitivity to  
289 defects. If we compare the values of  $a_0$  given in table 3 to the position of the pore size  
290 distribution, we can see that the lower  $a_0$ , the smaller the size of the biggest pores. To

291 better visualize this fact, the mean diameter of the 10 largest defects in the structure  
292 (noted  $\langle D \rangle_{10}$ ) was calculated for each tablet and is reported in table 3 along with  $a_0$   
293 values (the value of 10 was chosen arbitrarily for the sake of the demonstration).  
294 Evolution of  $a_0$  as a function of  $\langle D \rangle_{10}$  was then drawn on figure 7. Again, we can see  
295 that the lower  $a_0$ , the lower the mean diameter of the largest pores.

296 These results show the strong correlation between the pore size and the sensitivity to a  
297 stress concentration for the products considered in this studies. This sensitivity is directly  
298 related to the microstructure itself, which is dependent on the deformation behavior of  
299 the products under compression. This correlation does of course not mean that the  
300 microstructure is the only parameter influencing the sensitivity to defects. Some material  
301 related properties (i.e. surface energy) might also play a significant role and were not  
302 included in the present study.

303 Moreover, it is worth noting here that the products studied in the present work present a  
304 brittle fracture behavior during diametral compression. For other more ductile products  
305 (e.g. microcrystalline cellulose), some other effects may take place (large plastic  
306 deformation ahead the crack tip, etc.) that might render the correlation more  
307 complicated. Present results might thus not be directly applicable to this kind of tablets.  
308 Nevertheless, these results represent a first effort of explaining, from a more  
309 fundamental point of view, the sensitivity of a tablet to the presence of defects.

## 310 **Conclusion**

311 In this work, 5 different pharmaceutical excipients were studied in terms of sensitivity to  
312 a stress concentration. The average criterion method, developed in a precedent work,

313 was successfully applied to tablets of the different excipients made under several  
314 pressure points. Because it takes into account the size of the hole placed in the tablet,  
315 this criterion can be considered as a generalization of Hiestand's approach to  
316 characterize the sensitivity of a tablet to stress concentration.

317 Moreover, using X $\mu$ CT, the microstructure of the tablets was studied. A special attention  
318 was paid to the size of the largest pores in the structure. Analysis of the pore size  
319 distribution for the different products showed a direct correlation between the size of the  
320 largest pores and the sensitivity to a stress concentration: the largest the defects, the  
321 lower the sensitivity. These results show the importance of the microstructure to explain  
322 the sensitivity to stress concentration and, as a consequence to understand the capping  
323 tendency of formulations. This study constitutes a first step in the fundamental  
324 understanding of the sensitivity to stress concentration of pharmaceutical tablets.

### 325 **Acknowledgment**

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### 329 **Legend to figures**

330 Figure 1: photographs of the powder obtained under scanning electron microscope.  
331 Pictures were taken using a Hitachi TM 3000 (Hitachi, Tokyo, Japan). (a) DCP, (b)  
332 MLac, (c) ALac, (d) SDLac, (e) SDMan.

333 Figure 2: Localization of the sampling zone for X-ray tomography analysis: (a) top view;  
334 (b) side view.



335 Figure 3: Application of the average stress criterion to the different products : (a) DCP,  
336 (b) MLac, (c) ALac, (d) SDLac et (e) SDMan.  $F_{\text{applied}}$  is the force needed to break the  
337 tablet with a hole and  $F_{0 \text{ applied}}$  is the force needed to break the tablet without a hole.

338 Figure 4: Example of X $\mu$ CT image before (left) and after (right) thresholding. Blue pixels  
339 on the right picture represent the pore structure that will be analyzed afterward

340 Figure 5: evolution of the pore size distribution with increasing pressure

341 Figure 6: pore size distribution for tablets with an global porosity around 12.5%.

342 Figure 7: evolution of  $a_0$  as a function of the mean diameter of the 10 biggest defects in  
343 the structure.

344

345

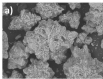
346

## 347 **Bibliography**

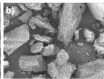
- 348 [1] G. Alderborn, Tablets and compaction, in: Aulton's Pharm. Des. Manuf. Med., Churchill Livingstone,  
349 London, 2001.
- 350 [2] U.S. Pharmacopeia, <1062> Tablet Compression Characterization, (2018).
- 351 [3] S.C. Gad, Pharmaceutical manufacturing handbook: production and processes, John Wiley & Sons,  
352 2008.
- 353 [4] E.N. Hiestand, J.E. Wells, C.B. Peot, J.F. Ochs, Physical processes of tableting, J. Pharm. Sci. 66  
354 (1977) 510–519.
- 355 [5] V. Mazel, H. Diarra, V. Busignies, P. Tchoreloff, Evolution of the Die-Wall Pressure during the  
356 Compression of Biconvex Tablets: Experimental Results and Comparison with FEM Simulation, J.  
357 Pharm. Sci. 104 (2015) 4339–4344.
- 358 [6] C.-Y. Wu, B. Hancock, A. Mills, A. Bentham, S. Best, J. Elliott, Numerical and experimental  
359 investigation of capping mechanisms during pharmaceutical tablet compaction, Powder Technol.  
360 181 (2008) 121–129.
- 361 [7] J.M. Whitney, R.J. Nuismer, Stress Fracture Criteria for Laminated Composites Containing Stress  
362 Concentrations, J. Compos. Mater. 8 (1974) 253–265.

- 363 [8] C. Imbert, P. Tchoreloff, B. Leclerc, G. Couarraze, Indices of tableting performance and application  
364 of percolation theory to powder compaction, *Eur. J. Pharm. Biopharm.* 44 (1997) 273–282.
- 365 [9] O.A. Itiola, N. Pilpel, Tableting characteristics of metronidazole formulations, *Int. J. Pharm.* 31  
366 (1986) 99–105.
- 367 [10] S. Majuru, D.E. Wurster, The Effect of Composition on the Tableting Indices of Binary Powder  
368 Mixtures, *Pharm. Dev. Technol.* 2 (1997) 313–321.
- 369 [11] R.S. Okor, F.E. Eichie, C.N. Ngwa, Correlation Between Tablet Mechanical Strength and Brittle  
370 Fracture Tendency, *Pharm. Pharmacol. Commun.* 4 (1998) 511–513.
- 371 [12] R.J. Roberts, R.C. Rowe, Brittle fracture propensity measurements on ‘tablet-sized’ cylindrical  
372 compacts, *J. Pharm. Pharmacol.* 38 (1986) 526–528.
- 373 [13] M.D. Schulze, J.W. McGinity, Indices of Tableting Performance for Acrylic Resin Polymers with  
374 Plastic and Brittle Drugs, *Drug Dev. Ind. Pharm.* 19 (1993) 1393–1411.
- 375 [14] H.E.N. Hiestand, D.P. Smith, Indices of tableting performance, *Powder Technol.* 38 (1984) 145–159.  
376 [https://doi.org/10.1016/0032-5910\(84\)80043-1](https://doi.org/10.1016/0032-5910(84)80043-1).
- 377 [15] X. Gong, C.C. Sun, A new tablet brittleness index, *Eur. J. Pharm. Biopharm.* 93 (2015) 260–266.  
378 <https://doi.org/10.1016/j.ejpb.2015.04.007>.
- 379 [16] X. Gong, S.-Y. Chang, F. Osei-Yeboah, S. Paul, S.R. Perumalla, L. Shi, W.-J. Sun, Q. Zhou, C.C. Sun,  
380 Dependence of tablet brittleness on tensile strength and porosity, *Int. J. Pharm.* 493 (2015) 208–  
381 213. <https://doi.org/10.1016/j.ijpharm.2015.07.050>.
- 382 [17] S. Paul, C.C. Sun, Lubrication with magnesium stearate increases tablet brittleness, *Powder  
383 Technol.* 309 (2017) 126–132. <https://doi.org/10.1016/j.powtec.2016.12.012>.
- 384 [18] J.M. Sonnergaard, A New Brittleness Index for Compacted Tablets, *J. Pharm. Sci.* 102 (2013) 4347–  
385 4352. <https://doi.org/10.1002/jps.23741>.
- 386 [19] P. York, F. Bassam, R.C. Rowe, R.J. Roberts, Fracture-Mechanics of Microcrystalline Cellulose  
387 Powders, *Int. J. Pharm.* 66 (1990) 143–148.
- 388 [20] B. Croquelois, J. Girardot, J.B. Kopp, C. Cazautets, P. Tchoreloff, V. Mazel, Breaking pharmaceutical  
389 tablets with a hole: Reevaluation of the stress concentration factor and influence of the hole size,  
390 *Powder Technol.* 317 (2017) 126–132.
- 391 [21] V. Busignies, B. Leclerc, P. Porion, P. Evesque, G. Couarraze, P. Tchoreloff, Quantitative  
392 measurements of localized density variations in cylindrical tablets using X-ray microtomography,  
393 *Eur. J. Pharm. Biopharm.* 64 (2006) 38–50.
- 394 [22] D. Markl, A. Strobel, R. Schlossnikl, J. Bøtker, P. Bawuah, C. Ridgway, J. Rantanen, T. Rades, P. Gane,  
395 K.-E. Peiponen, J.A. Zeitler, Characterisation of pore structures of pharmaceutical tablets: A review,  
396 *Int. J. Pharm.* 538 (2018) 188–214.
- 397 [23] D. Markl, P. Wang, C. Ridgway, A.-P. Karttunen, M. Chakraborty, P. Bawuah, P. Pääkkönen, P. Gane,  
398 J. Ketolainen, K.-E. Peiponen, J.A. Zeitler, Characterization of the Pore Structure of Functionalized  
399 Calcium Carbonate Tablets by Terahertz Time-Domain Spectroscopy and X-Ray Computed  
400 Microtomography, *J. Pharm. Sci.* 106 (2017) 1586–1595.
- 401 [24] A.M. Miguélez-Morán, C.-Y. Wu, H. Dong, J.P.K. Seville, Characterisation of density distributions in  
402 roller-compacted ribbons using micro-indentation and X-ray micro-computed tomography, *Eur. J.  
403 Pharm. Biopharm.* 72 (2009) 173–182.
- 404 [25] K. Kendall, A.J. Howard, J.D. Birchall, P.L. Pratt, B.A. Proctor, S.A. Jefferis, P.B. Hirsch, J.D. Birchall,  
405 D.D. Double, A. Kelly, G.K. Moir, C.D. Pomeroy, The relation between porosity, microstructure and  
406 strength, and the approach to advanced cement-based materials, *Philos. Trans. R. Soc. Lond. Ser.  
407 Math. Phys. Sci.* 310 (1983) 139–153.
- 408 [26] V.D. Krstic, Effect of microstructure on fracture of brittle materials: Unified approach, *Theor. Appl.  
409 Fract. Mech.* 45 (2006) 212–226.

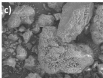
- 410 [27] V. Mazel, S. Guerard, B. Croquelois, J.-B. Kopp, J. Girardot, H. Diarra, V. Busignies, P. Tchoreloff,  
411 Reevaluation of the diametral compression test for tablets using the flattened disc geometry, *Int. J.*  
412 *Pharm.* 513 (2016) 669–677.
- 413 [28] A.-N. Spiess, N. Neumeyer, An evaluation of R2 as an inadequate measure for nonlinear models in  
414 pharmacological and biochemical research: a Monte Carlo approach, *BMC Pharmacol.* 10 (2010) 6.
- 415 [29] T.O. Kva<sup>o</sup>Lseth, Note on the R2 measure of goodness of fit for nonlinear models, *Bull. Psychon. Soc.*  
416 21 (1983) 79–80. <https://doi.org/10.3758/BF03329960>.
- 417 [30] H.S. Bennett, J.J. Filliben, A Systematic Approach for Multidimensional, Closed-Form Analytic  
418 Modeling: Effective Intrinsic Carrier Concentrations in Ga<sub>1-x</sub>Al<sub>x</sub>As Heterostructures, *J. Res. Natl.*  
419 *Inst. Stand. Technol.* 107 (2002) 69–81. <https://doi.org/10.6028/jres.107.008>.
- 420



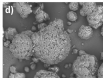
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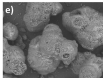
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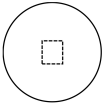
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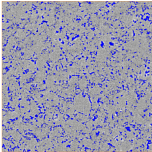
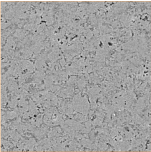
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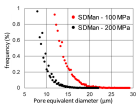
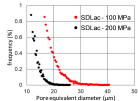
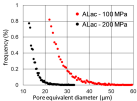
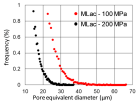
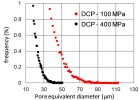


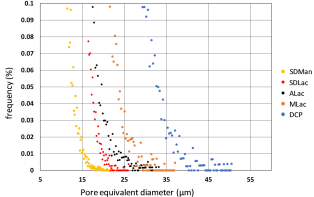
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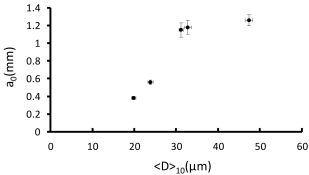
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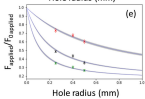
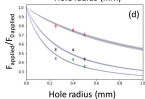
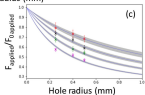
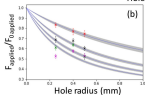
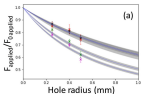












(x) 100 MPa (x) 200 MPa (x) 300 MPa (x) 400 MPa

Table 1: Parameters of the particle size distribution of the powders used in the present study. The analysis were performed by laser diffraction using a Mastersizer 2000 (Malvern, Malvern, UK). All parameters were measured on the volume distribution.

Product	Mean diameter ( $\mu\text{m}$ )	D <sub>10</sub> ( $\mu\text{m}$ )	D <sub>50</sub> ( $\mu\text{m}$ )	D <sub>90</sub> ( $\mu\text{m}$ )
DCP	209	120	196	316
Alac	181	37	165	342
MIac	153	52	136	281
SDMan	156	98	155	235
SDLac	140	52	129	241

Table 2: value of  $a_0$  parameter and porosity for each product and each pressure point.  $Se$  is the residual standard deviation.

Product	Pressure	$a_0$ (mm)	Se	Porosity (%)
DCP	100	2.44 ± 0.35	$2.4 \cdot 10^{-2}$	23.2
	200	2.55 ± 0.22	$1.3 \cdot 10^{-2}$	18.1
	300	1.51 ± 0.1	$3.8 \cdot 10^{-2}$	15.1
	400	1.26 ± 0.06	$3.7 \cdot 10^{-2}$	13.4
Alac	100	1.63 ± 0.2	$1.4 \cdot 10^{-2}$	17.7
	200	1.15 ± 0.08	$2.0 \cdot 10^{-2}$	11.3
	300	0.85 ± 0.047	$1.1 \cdot 10^{-2}$	8.7
	400	0.59 ± 0.025	$3.0 \cdot 10^{-2}$	7.1
Mlac	100	2.14 ± 0.22	$1.2 \cdot 10^{-2}$	18.1
	200	1.18 ± 0.08	$4.4 \cdot 10^{-2}$	12
	300	0.82 ± 0.05	$6.7 \cdot 10^{-2}$	9.1
	400	0.7 ± 0.038	$7.1 \cdot 10^{-2}$	7.1
SDMan	100	1.18 ± 0.07	$2.0 \cdot 10^{-2}$	21.3
	200	0.38 ± 0.018	$2.6 \cdot 10^{-2}$	13.8
	300	0.19 ± 0.011	$1.2 \cdot 10^{-2}$	9.3
SDLac	100	1.82 ± 0.13	$1.7 \cdot 10^{-2}$	20.3
	200	0.56 ± 0.024	$5.2 \cdot 10^{-2}$	12.4
	300	0.36 ± 0.013	$4.4 \cdot 10^{-2}$	8.9

Table 3: Value of  $a_0$  and  $\langle D \rangle_{10}$  for product having an overall porosity around 12.5%.  $\langle D \rangle_{10}$  is the mean diameter of the 10 largest pores in the structure as found by  $x\mu CT$ .

Product	Pressure	$a_0(\text{mm})$	Porosity (%)	$\langle D \rangle_{10}(\mu\text{m})$
DCP	400	1.26 $\pm$ 0.06	13.4	47.4 $\pm$ 0.87
Alac	200	1.15 $\pm$ 0.08	11.3	31.2 $\pm$ 0.5
Mlac	200	1.18 $\pm$ 0.08	12	32.8 $\pm$ 0.9
SDMan	200	0.38 $\pm$ 0.018	13.8	19.9 $\pm$ 0.5
SDLac	200	0.56 $\pm$ 0.024	12.4	23.9 $\pm$ 0.65

