Comparing failure tests on pharmaceutical tablets: Interpretation using experimental results and a numerical approach with cohesive zone models

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A B S T R A C T

The mechanical strength is an important quality attribute of pharmaceutical tablets. It can be determined using different failure tests like the Brazilian test or the three-point bending test. Nevertheless, literature shows that different failure tests often give conflicting values of tensile strengths (TS), which are generally calculated using the maximum stress criterion as a failure criterion. This work started from the hypothesis that these discrepancies are in fact due to the application of this criterion which is not suited to study pharmaceutical tablets, first due to heterogeneity of the stress distributions during the tests and second due to the quasi-brittle nature of pharmaceutical tablets. As an alternative, a numerical fracture criterion which is known to be well-suited for quasi-brittle solids (cohesive zone model, CZM) was used and calibrated using experiments. Using this approach, the breaking forces obtained numerically were shown to be in fair agreement with the experimental ones. Above all, the numerical results made it possible to catch the trends when comparing the different failure tests one to another. Especially, the model made it possible to retrieve the factor 2 between the TS obtained by three-point bending and by diametral compression found in the literature.

1. Introduction

The tablet is the most common pharmaceutical form and is produced using a die compaction process. As any pharmaceutical products, it must fulfill a number of requirements. Among then, mechanical strength is of particular interest. Indeed, between the ejection from the die and the packaging, the tablets can be submitted to various stresses that could lead to their deterioration if their mechanical strength was not sufficient. Being able to correctly assess the mechanical strength of a tablet is thus of particular interest.

As for any material, one way of measuring the mechanical strength of a tablet is to perform failure tests. Two tests are mainly described in the case of pharmaceutical tablets: the diametral compression test (Brazilian test) and the three-point bending test (U.S. Pharmacopea, 1217). The diametral compression test is, by far, the more used in the pharmaceutical industry, especially because it is very easy to perform and because it is well suited to the usual shape of pharmaceutical tablets. If three-point bending is less used it can also be useful especially for elongated tablets or in the case of scored tablets for example (Gold et al., 1980).

Whatever the test, the result obtained is a force needed to break the tablet. This force is in fact related with two different kinds of parameters: the intrinsic cohesion of the material and the geometrical features of the tablet. Only the former is of interest in order to have a proper idea of the tablet cohesion and to be able, for example, to compare tablets of different shapes. In order to get rid of the geometrical features, it is important to calculate the actual stresses inside the tablet during the test, taking into account the applied force and the geometry. This can be done analytically or numerically depending on the geometry of the tablet. The two tests mentioned above promote a tensile failure of the specimen so tensile stresses are considered and used in order to calculate the tensile strength of the tablet. In the case of a cylindrical tablet of diameter D, thickness h and a failure force F_f, the tensile strength obtained during diametral compression (σ_d) and the one obtained during three point bending test (σ_{3pt}) are generally calculated using the following equations (U.S. Pharmacopea, 1217):

$$\sigma_d = \frac{2F_f}{\pi D h} \tag{1}$$

$$\sigma_{3pt} = \frac{3F_f L}{2h^2 D} \tag{2}$$

where L is the distance between the supports in the three-point

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bending test.

In fact, equations (1) and (2) give the value of the maximum tensile stress in the tablet, and are derived from linear elastic theory, i.e. the behavior of the tablet is supposed to correspond to an elastic body until failure. If this last point can be questionable for some products like microcrystalline cellulose, it gives a fair approximation of the mechanical behavior for a lot of different products. Nevertheless, it is important to notice that, in order to link the value of the maximal stress in the structure to the tensile strength of the specimen, it is necessary to determine a failure criterion. In the case of equations (1) and (2), the failure criteria chosen is the maximum stress criterion, i.e. the tablet breaks when the maximum tensile stress in the structure is equal to the tensile strength of the material.

If this failure criterion can be used in the case of tests giving a relatively homogeneous stress distribution, its application in cases were the stress distribution is very heterogeneous or in the presence of stress concentration is problematic. An example of the limits of the application of this criterion can be found in the literature considering the comparison between the results of diametral compression and three-point bending. Indeed, several authors have shown that the value of the tensile strength obtained using diametral compression was around half of the value obtained using three-point bending (Amin and Fell, 2002; Amorós et al., 2008; Podczeck, 2012; Mazel et al., 2014; Hilden et al., 2016).

The problem of the failure of materials submitted to stress concentrations was introduced in the pharmaceutical field by Hiestand with the concept of Brittle fracture index (BFI) (Hiestand et al., 1977). Hiestand's approach consisted in introducing a hole at the center of a tablet and comparing the apparent tensile strength of the tablet without and without the hole using the following equation:

$$BFI = \frac{1}{2}\left(\frac{TS_0}{TS_h} - 1\right) \tag{3}$$

With TS_0 the tensile strength without hole and TS_h the tensile strength with a hole.

Initially, in the works of Hiestand, the tablet was a square, but the concept can be generalized to the cylindrical shape (Roberts and Rowe, 1986) or to the case of the flattened Brazilian disk (Croquelois et al., 2017). The introduction of the hole promotes a stress concentration at the hole edge during the test with a stress which is 6 times higher than the stress that would be present without the hole (Croquelois et al., 2017). Note that Hiestand wrongly considered that the stress concentration was 3 but this had no influence on the logic and applicability of the BFI. Hiestand remarked that the force needed to break a tablet with a hole was not 1/6 (in fact he considered 1/3) of the force needed to break a tablet of the same characteristics but without a hole. Its interpretation was that it meant that the tablets were not perfectly brittle and that some plastic deformation was occurring at the hole edge.

This reasoning is in fact not really correct. A breaking force equal to 1/6 of the original breaking force would be obtained only if the maximum stress criterion was correct. But even in purely brittle material, the criterion is not applicable. Let's consider a solid with a sharp crack. If the solid is stressed in tension, the stress field at the crack tip will tend to infinity whatever the tensile stress applied (Anderson, 2017). So if the maximum stress criterion is applied, the solid would not withstand any applied stress. This problem is overcome by the use of linear elastic fracture mechanics (LEFM) and the concept of fracture toughness (Anderson, 2017). Of course, it is true that if plastic deformation occurs at the crack tip, this will also influence the fracture behavior. This means that the BFI defined by Hiestand is not directly a measure of the brittleness, but is in fact impacted by both the fracture toughness and the presence of plastic deformation, i.e. by the presence of a non-linear zone at the crack tip. It is thus complicated to interpret.

Other authors have tried to study pharmaceutical tablets using the concept of linear fracture mechanics (Mashadi and Newton, 1987; Mashadi and Newton, 1988; Roberts et al., 1993; Roberts and Rowe, 1989). These studies are based on the use of classical tests like the single notched beam broken using the three-point bending test and use the failure load to calculate the critical stress intensity factor (K_{IC}). Nevertheless, this approach is only valid in the case of brittle solids. But in fact, a pharmaceutical tablet cannot be considered as a brittle solid. It was recently demonstrated in the case of anhydrous calcium phosphate tablets, that are generally considered as brittle, that the tablets should be treated as quasi-brittle materials (Girardot et al., 2023).

By definition, quasi-brittle materials are a class of solids for which a fracture process zone (FPZ) develops during the test before the formation of a macroscopic crack. The phenomena occurring in the FPZ can be related to plastic deformation or to micro-cracking for example. The size of the FPZ compared to the size of the sample can be used to characterize the brittleness of the sample (Bažant, 2002). If the FPZ is very small compared to the sample size, the solid will nearly behave like a brittle solid (and can be treated with LEFM) whereas as the size of the FPZ becomes closer to the sample size, the solid behave more and more like a ductile material (Bažant, 2002; Morel and Dourado, 2011). Quasi-brittle failure needs to be described in the non-linear fracture mechanics (NLFM) framework (Bažant, 2002).

Since the tablets are quasi-brittle solids, their failure cannot be treated using simple criteria like the maximum stress criterion, and it is thus normal that, using this criterion, the different failure tests give conflicting results. It is thus necessary to use other criteria. Analytical criteria like the average stress criterion can be used in the case of stress concentration as demonstrated earlier (Croquelois et al., 2017; Croquelois et al., 2020). Nevertheless, they necessitate to know analytically the stress field in the tablet during the test and they are difficult to use in 3D. An alternative to analytical criteria is the use of numerical simulation to implement more complex criteria. In the case of quasi-brittle solids, the use of a cohesive zone model (CZM) in finite element method (FEM) simulations (Hillerborg et al., 1976) is one of the most popular and also one of the most simple.

The aim of this article was to study if the implementation of a cohesive zone model in FEM could make it possible to interpret the conflicting results found in the literature when different failure tests are compared for the measurement of the strength of pharmaceutical tablets. For this purpose, four different failure tests were performed experimentally on classical pharmaceutical excipients. The results of the experiments were then used to calibrate CZM models in order to simulate the different tests. Finally, the apparent paradoxes published in the literature, were interpreted using the results of the simulations.

2. Materials and methods

2.1. Experiments

2.1.1. Powders

Five classical pharmaceutical excipients were used: Anhydrous lactose (ALac) (SuperTab22AN, DFE pharma, Goch, Germany), Spray-dried lactose monohydrate (SDLac) (SuperTab14SD, DFE pharma, Goch, Germany), anhydrous calcium phosphate (ACP) (Anhydrous Emcompress, JRS pharma, Rosenberg, Germany), granulated lactose monohydrate (GLac) (SuperTab 30GR, DFE Pharma, Goch, Nordrhein-Westfalen, Germany) and isomalt(IsM) (GalenIQ 721, Beneo, Tienen, Belgium). The choice of these products was based on their apparent brittle behavior during failure tests (i.e. no sign of plastic deformation on the strain–stress curves during diametral compression, see supplementary material). They also present different BFI as it will be shown below. Products with an apparent ductile behavior like microcrystalline cellulose were not included because the interpretation of the Brazilian test is complicated for such products as the maximum force measured might not correspond to the crack initiation (Jonsén et al., 2007). This kind of problems surpasses the objective of this work. Neverthless, in principle, the model used in the present article is applicable to products that

present a more ductile failure.

To lower the frictions during compaction, the powders were lubricated using Magnesium stearate (Mgst) (Ligamed MF-2-V, Peter Greven France, Rueil Malmaison, France). The quantity of MgSt was set to 1% (w/w) for ALac, SDLac, MLac and IsM and to 2%(w/w) for ACP. Blending was performed for 5 min at 49 rpm in a Turbula mixer (Type T2C, Willy A. Bachofen AG, Muttenz, Switzerland).

2.1.2. Tablet manufacturing

All tablets were prepared using a compaction simulator Stylcam (Medelpharm, Beynost, France). This device is a single station instrumented tableting machine. It is equipped with force sensors (strain gauges) on both punches and the displacements of the punches are monitored using LVDT sensors.

The machine was operated in the direct cam mode at a compaction speed of 20 compacts per minutes. A special set of flat faced Euro B tooling was used as described previously (Mazel et al., 2016). This tooling made it possible to obtain a so-called flattened geometry. In the present study, tablets with a diameter of 11 mm were used with a flat end of 30° (Mazel et al., 2016). For all the tablets, the applied pressure was set to 200 MPa. The filling height was fixed for each product to obtain a final tablet height around 2.5 mm. At least 50 tablets were made for each product in order to be able to perform all the failure tests.

2.1.3. Tablet machining

For each product, ten tablets were drilled with a hole of 1 mm at the center. The holes in the tablets were inserted using a drill Micromot 50 E/EF (PROXXON S.A., Luxembourg). During the drilling process, the tablets were maintained using a specially designed polymeric holder obtained by 3D printing. To avoid defects at the back of the tablet during the machining of the holes, two tablets were placed together and only the upper one was finally used for experiments. It was shown previously that this process does not damage the tablet (Croquelois et al., 2017).

2.1.4. Failure tests

All the failure tests were performed using a TA.HDplus texture analyzer (Stable microsystems, Surrey, United Kingdom). In all experiments, the mobile arm was moved at a constant speed of 0.1 $mm.s^{-1}$ and the acquisition frequency was set to 500 Hz.

For the Brazilian test, compacts were compressed between two flat surfaces. Three Brazilian tests were performed. In the first case, a tablet without a hole was compressed diametrically on the two flat ends of the tablet. This test will be referred to as flattened Brazilian test (FBT). The same was performed on the tablets with a hole (HFBT). Finally tablets without holes were also broken by applying the force on a diameter normal to the one used for the FBT. This corresponds to the classical configuration of the Brazilian test and will be called Classical Brazilian test (CBT) (Mazel et al., 2016). In each case, 10 tablets were broken for each product.

Three-point bending test (TPBT) was performed on a home-made setting. Supports were cylinders (top) or half cylinders (bottom) with a diameter of 2 mm. Distance between the support was 6 mm. Fig. 1 gives a schematic representation of all the tests used in this study.

2.1.5. Determination of elastic moduli using impulse excitation

In order to determine the apparent elastic moduli of the tablets, impulse excitation technique was used as described elsewhere (Mazel and Tchoreloff, 2020; Meynard et al., 2021). The impulse excitation is obtained for a sample by dropping it from a 1 cm height, so the band of the tablet impacts a hard surface. The sample free vibrations induced by the impact were recorded using a microphone MM310 (Microtech Gefell GmbH, Gefell, Germany). The data acquisition system was a DEWE-43 coupled with the software Dewesoft X3 (Dewesoft, Trbovlje, Slovenia). Acquisition frequency was set to 200 kHz and as a consequence the maximal detectable frequency was 78.1 kHz. Time domain amplitude signal was converted into a frequency domain signal to measure the resonance frequencies using a fast Fourier transform (FFT) algorithm. A Blackman window with 4096 points was used. The frequency resolution was 24.4 Hz. Note that this technique makes it possible to determine the dynamic elastic modulus of the product. This modulus might be higher than the static one. Nevertheless as the products used in this study do not present important viscoelasticity (Meynard et al., 2022), we can expect that this difference should not be too important.

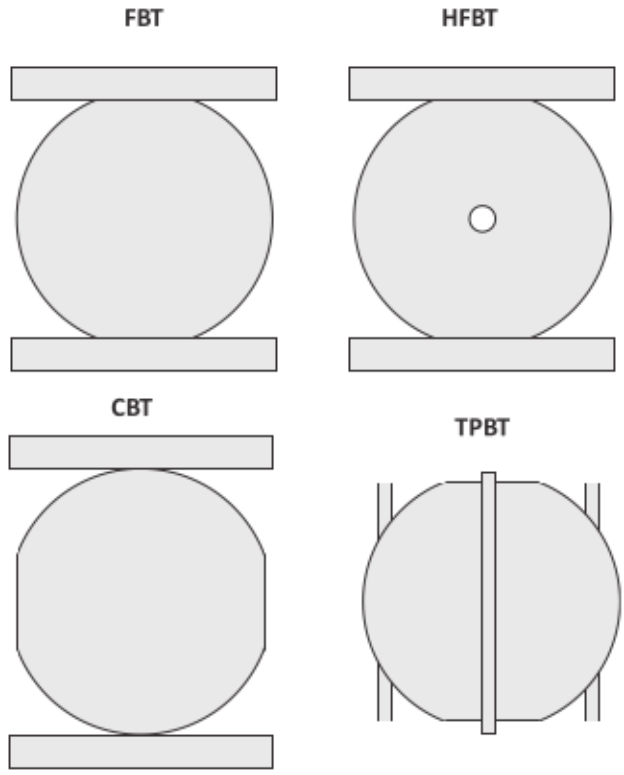

Fig. 1. Schematic representation of the different failure tests used. For a better readability, the representation for FBT, HFBT and CBT are front views whereas a top view is presented for TPBT.

2.2. Numerical methods

2.2.1. Determination of elastic moduli

Determination of the elastic moduli from the spectra obtained by impulse excitation was made using a manual numerical inverse identification. Undamped modal analysis was realized using the finite element software Abaqus® 6.13 (Dassault Syst'emes, Vélizy-Villacoublay, France) with the Lanczos algorithm. The tablet was treated as an apparent isotropic elastic body.

2.2.2. General numerical framework for failure tests

All the failure tests presented above were simulated using FEM simulation on Abaqus® 6.13 (Dassault Systèmes, Vélizy-Villacoublay, France). In each case, the tablet was represented by an elastic isotropic body with the elastic properties determined using impulse excitation. A 3D simulation was performed, and penalty contacts were chosen to match as much as possible the experiments. Hexahedral meshes were used using C3D8R elements. The mesh was adapted for each test. Using the symmetries of the system, it was possible to represent only a quarter of the whole tablet for the Brazilian test and half of it for the three-point bending. For the Brazilian test the mobile surfaces that applied the force were modeled using a non-deformable analytical surface. For three-point bending, the supports and loading rods were modelled deformable solids using half cylinders with the properties of steel ($E = 220$ GPa and $\nu = 0.3$).

In order to model the failure tests, the tablet was initially split into two halves separated by the surface finally obtained after failure (i.e. a surface along the diameter of the tablet. The two halves were then connected together using a cohesive zone model. The model is described in the next section. A static analysis was performed and the stresses were applied by imposing a displacement to the platens in the Brazilian test and to the upper rod in the three-point bending test.

2.2.3. Cohesive zone model

In a cohesive zone model, the behavior of the interface between the two parts is govern by a traction-displacement curve between the nodes of each surface. In this work, a triangular curve was chosen as presented in Fig. 2. This is the base model that can be used for this kind of approach and it was shown to provide a correct approximation of the quasi-brittle fracture (Hillerborg et al., 1976). Of course, more elaborated models can be used but they surpass the objective of this study. Further justifications of the use of the simplest model will be provided below.

Initially, the stress at the interface increases according to the k_i slope where k_i corresponds to the initial stiffness of the cohesive interface. When the stress reaches the value σ_t, it then decreases progressively until a total separation of the two opposite nodes of the interface. This progressive separation is obtained from the progressive decrease of the interface stiffness associated with a progressive release of the elastic energy. In our case, the slope of the decreasing part (also called as softening part) was fixed using G_f which represent the area below the curve.

In this work, only failure according to mode I (i.e. tension) was considered. So parameters for shear failure were set at very high values (several orders of magnitude above mode I parameters) in order not to influence the results. According to Fig. 2, the model seems to be defined by three parameters. In fact, in our case, only two of them, σ_t and G_f, have a real physical meaning because the initial stiffness of the interface k_i must tend towards infinity due to the zero thickness of the interface. In the simulation, the value of k_i must just be put as high as possible (penalty stiffness) in order not to impact the elastic stiffness of the specimen in the absence of damage of the interface. The software Abaqus provides the option to use a default contact enforcement method, for which the value of k_i is based on the underlying element stiffness (Vervloet et al., 2019). This option was used. It was verified that it did not alter the elastic stiffness of the specimen (results not shown). Using this option, the model looked like the one presented in Fig. 2b and it finally required two parameters to be determined. The procedure for this determination is presented below, in the result section.

It is important to note that σ_t and G_f have direct physical meaning. σ_t is the tensile strength of the material, i.e. if a tensile test is performed numerically, the failure stress obtained will be σ_t. G_f corresponds to the cohesive energy required to completely separate two opposite nodes of the interface. In other terms, G_f is corresponds to the fracture energy (J/m^2) of the material (Morel et al., 2010). These parameters will be interpreted this way in the following text.

3. Results and discussion

3.1. Experimental results

3.1.1. Elastic moduli

The determination of the elastic moduli was performed using impulse excitation as explained above. As an apparent isotropic behavior was considered, it is only necessary to measure the frequency of the two first modes (Mazel and Tchoreloff, 2020). Contrary to previous studies (Mazel and Tchoreloff, 2020; Meynard et al., 2021), the tablets studied in this work were not perfectly cylindrical but presented two flat ends. The main consequence is the doubling of the peak of the first mode (i.e. the mode with the lowest frequency). Examples of spectra for three of the products are presented in Fig. 3. As it can be seen, the peaks associated to each of the two first modes are clearly visible and the first mode gives in fact a double peak due to the tablet geometry.

Using FEM, Young's modulus (E) and Poisson's ratio (ν) were determined for each product and are presented in Table 1. These values will be used for the simulations of the failure tests.

3.1.2. Results of failure tests

The four different failure tests were performed on each set of tablets. Results are summarized in Table 2. For each test, Fr is the failure force obtained during the experiment. From this force an apparent tensile strength is calculated (σ_T). For CBT, the apparent tensile strength is calculated from equation (1) and for TPBT equation (2) is used. In the case of FBT and HFBT, the apparent tensile strength is calculated by multiplying the results of Equation (1) by 0.87 to take into account the presence of the flat ends as demonstrated in a previous (Mazel et al., 2016). Note that the use of this correcting factor will be further discussed below. For FBT, CBT and TPBT, the apparent tensile strength is supposed to represent the highest tensile stress in the structure when failure occurs. In the case of HFBT, the apparent tensile stress does not represent a real physical quantity, but it is the value used in Hiestand's approach to calculate the BFI (Hiestand et al., 1977).

Several comments can be made concerning the results. As generally found in the literature, the values obtained with the TPBT are much higher than the values obtained with the CBT. The ratio is between 2.1 and 2.7 which is coherent with previously published results (Hilden et al., 2016). This confirms that calculating the tensile strength using the maximal stress criteria cannot make it possible to compare the results obtained with these two tests.

Another point is that the value obtained with FBT is higher than the one obtained with CBT and that the ratio between the two values is dependent on the product. The value of the ratio is 1.19 for ACP, 1.47 for ALac, 1.74 for SDLac, 1.14 for GLac and 1.28 for IsM which is also coherent with results previously published (Mazel et al., 2016).

Finally, as mentioned before, the five products present different BFI, SDLac being the most sensitive to stress concentration and, ACP and GLac being the less sensitive. These values cover most of the range generally obtained for pharmaceutical products. Lower values of the BFI can be obtained for product like microcrystalline cellulose but as

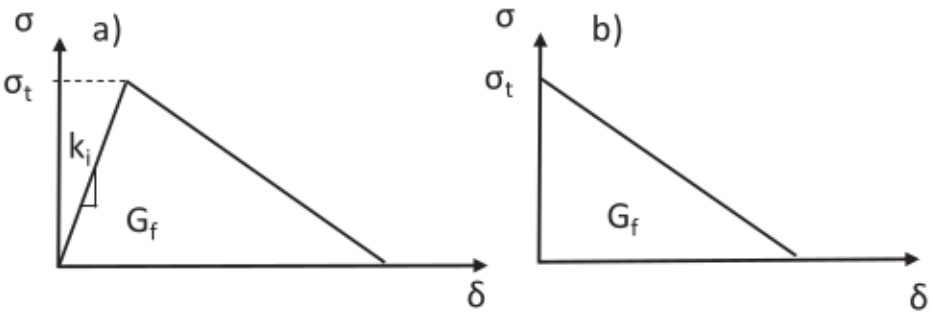

Fig. 2. Triangular model for a traction separation curve. σ represents the stress and δ represents the displacement. (a) general model and (b) model used in this work.

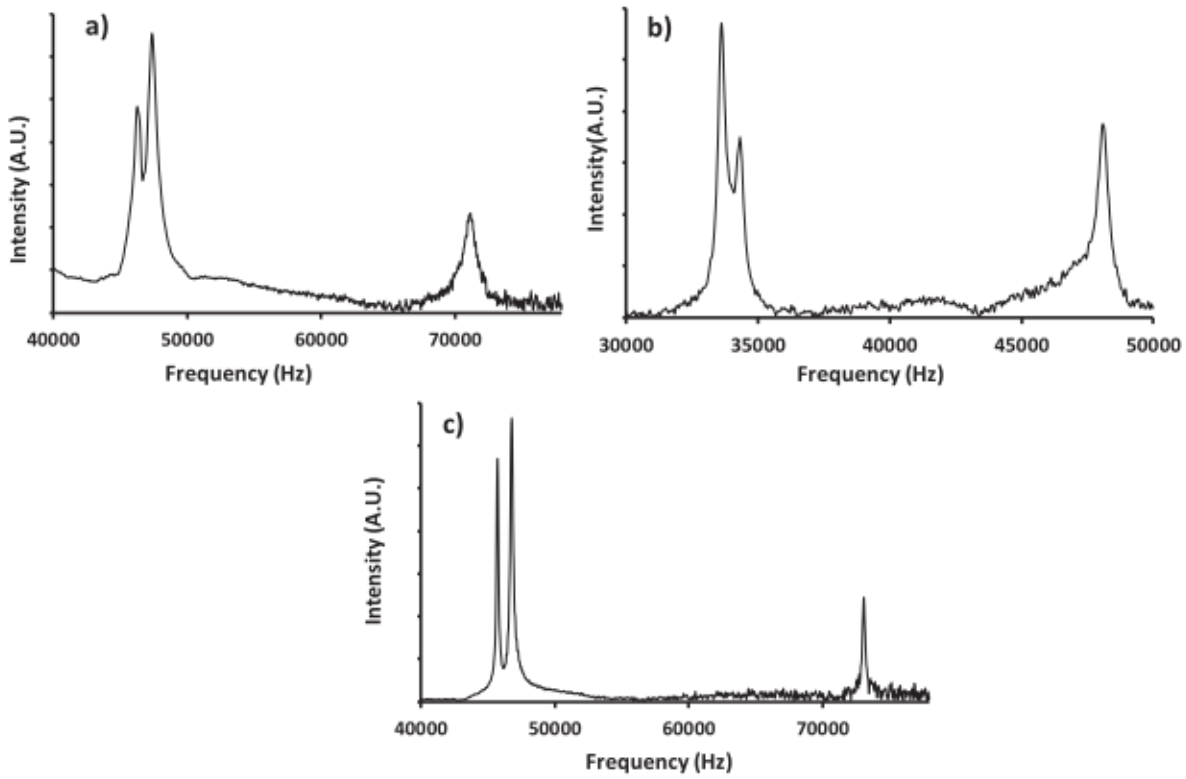

Fig. 3. Examples of spectra obtained by impulse excitation for: (a) ALac; (b) ACP and (c) SDLac.

Table 1
Elastic constants found for the products used.

Product	Young's modulus (GPa)	Poisson's Ratio
ALac	9.1	0.235
SDLac	9.37	0.283
ACP	5.95	0.135
GLac	4.99	0.209
IsM	6.86	0.253

mentioned above interpretation of the failure test for these products are complicated and as such they could not be included in the present study.

3.2. Numerical results

The numerical simulation of the various test was performed in order to see if, using CZM it was possible to reproduce numerically the experimental results. In each simulation the exact sample geometry was implemented as well as the previously determined elastic moduli. The output considered in the simulation was the maximum applied force obtained during the failure test. The idea was to compare the forces obtained numerically to the forces obtained experimentally for the four different tests.

As said above, in our case, CZM is defined by two parameters, σ_t and G_f which have to be determined. To determine the two cohesive parameters, only the results of two of the tests had to be used. This point is one of the reasons of the choice of the simplest CZM. As one of the aim of the study was to understand the difference found in the literature between CBT and TPBT and to show that this was due to the quasi-brittle nature of the tablet, these two tests were not used for the calibration. So only FBT and HFBT were used to determine σ_t and G_f.

The parameters were obtained after a manual optimization until attaining values of the breaking forces for the simulation of FBT and HFBT that presented less than 1% difference with the experimental values. The process was made as follows. First, as it was found that FBT was mainly influenced by σ_t, this parameter was set to the value found in Table 2 as first approximation. Then G_f was modified to try to match HFBT. Then σ_t was modified in order to match FBT. An iterative calculation was then manually performed alternatively on both parameters until attaining the objective of less than 1% difference between the experimental and numerical values of the forces. This objective was fulfilled for each product. Note that the values obtained for the two parameters are dependent on the way calibration was performed and that a different methodology might have given a different result. Nevertheless, the confirmation of the consistency of this methodology will be given by the results found and their coherence with the experimental results ans well as with the existing literature as shown below.

Then, these parameters were used for the simulation of CBT and TPBT to obtain numerical breaking forces for these two tests. The values

Table 2
Results of the different failure tests. For each test, F_r represents the failure force and σ_r represents the apparent tensile strength.

	FBT		HFBT		CBT		TPBT		BFI
Product	F_r (N)	σ_r (MPa)	F_r (N)	σ_r (MPa)	F_r (N)	σ_r (MPa)	F_r (N)	σ_r (MPa)	
ALac	192.9 ± 3.4	3.92 ± 0.07	106 ± 2.15	3.32 ± 0.07	122.8 ± 4.4	2.86 ± 0.10	48.6 ± 2.86	6.47 ± 0.37	0.41
SDLac	337.3 ± 9.6	6.97 ± 0.20	110 ± 2.3	4.53 ± 0.09	169.2 ± 9.4	4.00 ± 0.22	69.1 ± 4.5	9.57 ± 0.62	1.03
ACP	98.6 ± 1.8	2.00 ± 0.03	63.1 ± 1.3	2.52 ± 0.05	72.7 ± 3.2	1.68 ± 0.06	28.5 ± 1.7	3.81 ± 0.23	0.28
Glac	128.9 ± 3.5	2.59 ± 0.07	82.2 ± 1.7	1.65 ± 0.07	79.9 ± 4.1	1.84 ± 0.1	38.6 ± 1.2	5.07 ± 0.15	0.28
IsM	225.6 ± 4.4	4.51 ± 0.11	77.5 ± 1.6	1.56 ± 0.11	152.3 ± 3.5	3.51 ± 0.08	57.5 ± 6.1	7.49 ± 0.80	0.94

obtained for the two parameters are given in Table 3 whereas the results for the obtained breaking forces are presented in Fig. 4.

The first comment is that, as expected, CZM makes it possible to represent the influence of the hole in the structure and that it is possible to find, for each product, a set of cohesive parameters that gives numerical values close to the experimental values for FBT and HFBT at the same time. The model chosen is then well suited to represent this case. It is also interesting to note that the values of G_f, which is supposed to represent the fracture energy, are in the order of magnitude of the values presented in the literature for pharmaceutical products (Girardot et al., 2023; Croquelois et al., 2021).

The results obtained for TPBT show that the numerical model systematically slightly underestimates the breaking force. The difference between numerical and experimental force is between 11 and 24.4% depending on the product. Despite this underestimation, the numerical model makes it possible to obtain the good order of magnitude for the breaking force. It also shows that, if this breaking force is used in Equation (2) to calculate a tensile strength, the value obtained is much higher than real value of the tensile strength (even if it is underestimated by the model). The values obtained, that have to be compared with the value of the tensile strength (σ_t) used in the model as shown in Table 3 are 5.8 (+59%), 8.5 (+33%), 3.3 (+79%), 4.1 (+71%) and 5.7 (+31%) MPa for ALac, SDLac, ACP, GLac and IsM.

Concerning the results of the CBT, it is interesting to note that the numerical results also catches the decrease of the force compared to the case of FBT. Again experimental and numerical results are in fair agreement even if the numerical model slightly over estimate the breaking force except in the case of IsM where the force is underestimated. The difference between numerical and experimental force is between 6.5 and 28.2% (absolute value) depending on the product. These results will be further discussed in the next section.

3.3. Discussion

The results presented above show that using a CZM in an FEM simulation it is possible to obtain a fair agreement between numerical and experimental values and above all to catch the evolution of the breaking force from one test to the other. Nevertheless, the agreement is not perfect and in some cases discrepancies around 25% can be observed. The first reason may be the simplifications used in the model. First, the tablet was described as a homogeneous isotropic body which is clearly a simplification of the reality (Meynard et al., 2021). It is known that tablet might be anisotropic but it is also possible that modulus in flexion/compression and traction might in fact differ like in other materials. The other point is the CZM used. The triangular model is the simplest model and more complex forms like bilinear or exponential might improve the agreement. But the use of these model clearly surpasses the aim of the present work. Moreover, it is possible that different models should be used for the different geometries especially due to the effect of confinement of the process zone due to the complex stress distribution in the tests used.

Another point is the fact that the tablet is considered as homogeneous. It is known that the surface layer of the tablet has properties that are different from the bulk because, as in the surface layer particles are much more deformed than the bulk ones (Mazel et al., 2013). It is thus possible that the surface might in fact be more resistant than the bulk.

Table 3
Cohesive parameters used in the numerical CZM.

Product	σ_t (MPa)	G_f (J/m^2)
ALac	3.65	3.2
SDLac	6.65	3.15
ACP	1.84	2.3
GLac	2.40	3.85
IsM	4.35	2

This could explain the fact that the model systematically underestimates the breaking force during TPBT. During TPBT, the maximum stresses are located near the surface and this test is thus more susceptible to be influenced by this effect than the other ones.

One of the interest of the quasi-brittle behavior represented by the CZM model is that it makes it possible to catch the influence of the stress distribution of the failure load. For the failure of a quasi-brittle solid a FPZ must develop before the appearance of a macroscopic crack. The sample is thus sensitive to the stress distribution and the stress should thus develop on a large zone of the sample in order to promote the failure. This means that when the failure occurs, the apparent maximum stress in the structure (i.e. the maximum stress calculated supposing a perfect elastic behavior) will be higher than the real tensile stress. The more heterogeneous the stress is, the higher will be this difference. This explain why in the TPBT, the apparent tensile strength calculated using Equation (2) is much higher than the real tensile strength as the stress distribution is very heterogeneous (Mazel et al., 2014).

The same occurs in a lesser extend to the FBT. Even if the stress is more homogeneous than in TPBT, it is also not uniform in the sample. The apparent tensile strength calculated in Table 2 using this stress, is thus also larger than the effective tensile strength obtained numerically (Table 3). Depending on the product, the overestimation was between 4.8 and 8.7%. This difference is relatively small and is in fact due to the coefficient used to correct Equation (1). In this work we used 0.87 as suggested elsewhere (Mazel et al., 2016). But this value comes in fact from numerical simulations and was determine to obtained, using the force, the value of the maximum stress in the flattened tablet. So again it was based on a maximum stress failure criterion. This might be corrected in future works, for example by lowering this coefficient. In the present case, the use of a coefficient 0.82 instead of 0.87 would have given a difference lower than 2.5% in each case between the value obtained in the FBT and the numerical parameter of the CZM. This would need to be confirm on a larger set of samples, but it confirms that the FBT is a good way to determine the tensile strength.

The case of CBT is more complex. In a previous work, we assumed that the difference between CBT and FBT was due to the development of large stresses away from the center of the tablet (Mazel et al., 2016). These stresses could promote the development of the crack away from the center as observed experimentally. It was also demonstrated that these stresses were fairly concentrated, which means these stresses need to develop on a large area before failure could occur. Depending on the product (i.e. on the fracture behavior), the extension needed for the stress distribution might be different. It must be noted, that these stresses are largely influenced by the contact area and thus by the local deformation of the tablet near the platens. So, in the simulation results, they are sensitive to Young's modulus. Due the very high stresses occurring initially at the contact and to the porous structure of the tablet, it is possible that a simple linear elastic model might not correctly represent this contact, which could explain part of the disagreements. All this could also explain why the difference between the apparent tensile strength obtained by CBT and the one obtained by FBT depends on the product. A complete understanding of the parameter influencing this difference is still to build. Nevertheless, the consequence is that, using CBT to calculate the tensile strength of a tablet is tedious because, depending on the product, the value obtained might be correct or not. For example, comparing the values in Tables 2 and 3, we can see that for ACP the value of the CBT is close to the tensile strength (-8%) whereas for SDLac, the value of CBT largely underestimates the tensile strength (-40%). These results seems to confirm that the use of CBT to determine the tensile strength of a tablet is complicated and might be misleading.

Finally, as mentioned before, literature results indicate that the ratio between the tensile strengths obtained in TPBT and CBT are around 2 (Hilden et al., 2016). In the numerical results, this ratio is found between 1.72 and 1.98. The model catches thus correctly this discrepancy. This confirms that this difference is due to the fracture behavior of the tablet, that is complex and cannot be treated using a simple maximum stress

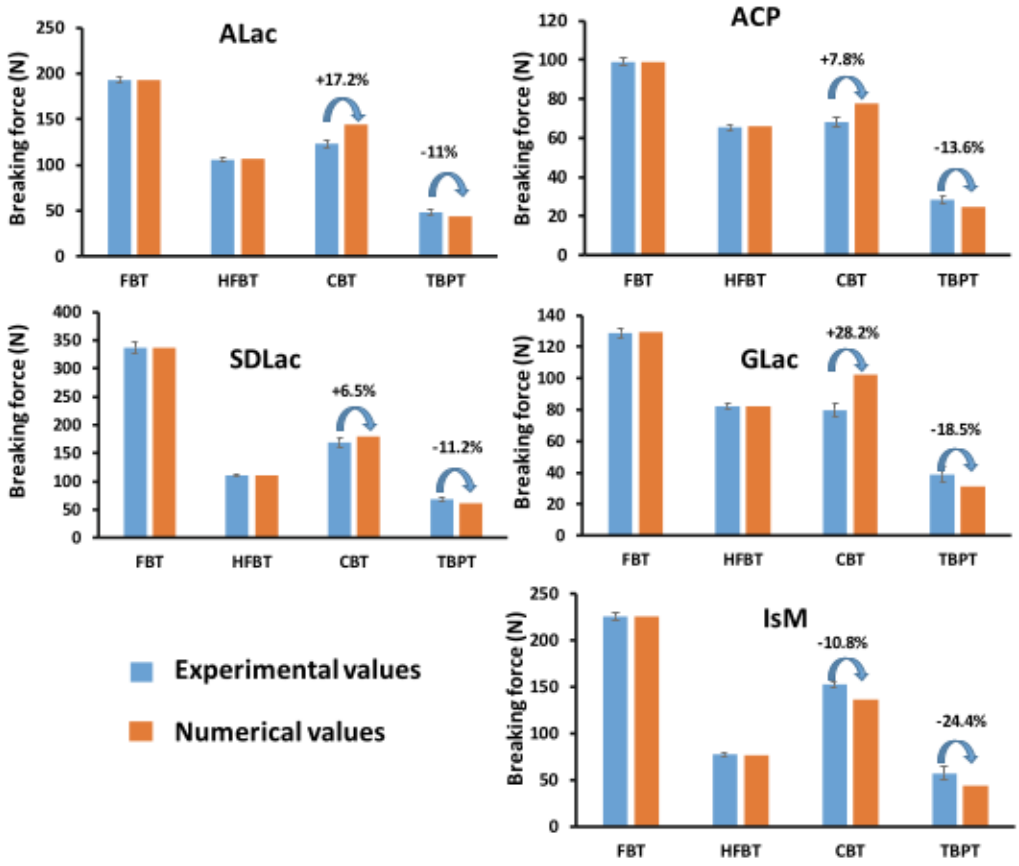

Fig. 4. Comparison between experimental and numerical results obtained for the breaking forces in the different tests.

criterion, and not to non-ideal loading conditions or shear failure as sometimes mentioned elsewhere (Hilden et al., 2016).

4. Conclusion

The quantification of tablet strength is of particular importance for the pharmaceutical industry. The tensile strength is generally the parameter used for this quantification. Several publications showed that different tests (Brazilian test, three-point bending, etc.) generally lead to different values of the tensile strength for the same tablet. The results presented in the present article indicate that the reason for the lack of agreement between the tests was the use of the maximum stress criteria to derive the tensile strength from maximum force obtained during the test. In fact, the stress distribution in the sample plays a fundamental role in the failure mechanism.

In order to take this stress distribution into account but also the fact that tablets are quasi-brittle solids, it is possible to use CZM in FEM simulation. In this paper, using the simplest model possible (a triangular CZM or in other terms a linear softening behavior), it was possible to obtain a fair agreement between the failure forces obtained experimentally and numerically for four different test configurations (different versions of the Brazilian test and three-point bending test). Above of all, the model used made it possible to catch the trends when comparing the different tests.

The simulation results correctly catch the fact that equation (2) applied to the TPBT overestimates the value the tensile strength. They also show that CBT underestimate the tensile strength to an extent that depends on the product which is coherent with previous results (Mazel et al., 2016; Fell and Newton, 1970). Both results are due to the heterogeneous stress distributions obtained during the test coupled with the fracture behavior, i.e. quasi-brittle nature, of the tablets. On the contrary the version of the Brazilian test using a flattened tablet (FBT) shows more consistent data even if it tends to slightly overestimate the tensile strength. A lowering of the correction factor used in combination with equation (1) might be a good option to obtain a better estimation of the tensile strength.

CRediT authorship contribution statement

Vincent Mazel: Methodology, Investigation, Conceptualization, Writing – original draft. **Jérémie Girardot:** Writing – review & editing. **Jean-Benoit Kopp:** Writing – review & editing. **Stéphane Morel:** Conceptualization, Writing – original draft. **Pierre Tchoreloff:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A: List of Abbreviations

CBT: classical Brazilian test
CZM: cohesive zone model
FBT: Flattened Brazilian test
FPZ: fracture process zone
HFBT: Flattened Brazilian test made on tablets with a hole
TPBT: three-point bending test

Appendix B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2023.123166.

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