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Abstract

Elastic properties are of particular interest during the development of tablets especially for the definition of the formulation and of the process parameters. Impulse excitation, which is used in several industrial fields to determine elastic properties of materials, is presented in this article as a new fast and relatively cheap technology for the determination of elastic constants of pharmaceutical tablets. This technique is based on the detection of the natural resonance frequencies of solids. It was found in the present work that, for tablets obtained using different products under different compaction pressures, it was possible to detect clearly at least 3 resonance frequencies. Moreover, the shape of the resonance peaks obtained in the spectrum could be a sign of the viscoelastic nature of the tablet. With the two first resonance frequencies, it was possible, under the assumption of isotropy, to calculate Young's modulus and Poisson's ratio for each tablet using the methodology presented in the norm ASTM E1876-01. The value obtained were found independent of the tablet size as expected, and were

consistent with those presented in the literature using other methodologies. Moreover, using FEM simulation, it was found that the difference between the experimental value of the third resonance frequency and the value obtained numerically was well correlated with the expected anisotropy of the tablet. Impulse excitation could thus be an interesting methodology to study tablet anisotropy.

Keywords: tablet; compression; elasticity; young's modulus; Poisson's ratio; viscoelasticity; anisotropy

1. Introduction

The tablet is the most common pharmaceutical form. Nevertheless, the successful development of a tablet involves a lot of critical steps from the formulation to the final definition of the process parameters to ensure the desired quality attributes. During the development, mechanical properties of tablets are important parameters. They are the result of both the mechanical properties of the powders used and the process parameters used to obtain the tablet. They play a key role in the success of tablet production. Among these properties, elasticity is of particular importance. For example, it is well-known that elastic properties are linked with the stress evolution during compression (Diarra et al., 2018; Hiestand et al., 1977) and with adverse phenomena like capping or chipping (Hiestand et al., 1977). A good measurement of tablet elasticity is thus of particular interest. This article presents a new methodology for the characterization of the elastic behavior of pharmaceutical tablets.

Elasticity can be characterized directly in the die (Cunningham et al., 2004; Hagelstein et al., 2019; Mazel et al., 2012). In this case it might help to understand the stresses

evolution during the compression. This characterization is also useful for the calibration of numerical models (Cunningham et al., 2004; Diarra et al., 2012). Another, complementary approach is to characterize the elasticity of the final tablets. Several methodologies have been presented in the literature to measure elastic moduli but also to characterize the viscoelastic behavior or the elastic anisotropy. These methodologies can be separated into two main categories.

First, classical mechanical tests are used to determine the quasi-static values of elastic moduli. In most of the studies, only young's modulus is determined. For this purpose, three or four points bending tests as well as indentation tests can be used (Bassam et al., 1990; Busignies et al., 2006; Kuentz and Leuenberger, 1998). A torsion test on specific geometries was also presented to obtain the shear modulus (Radebaugh et al., 1989; Roberts et al., 1994). Using both moduli it is possible to calculate Poisson's ratio (Roberts et al., 1994) but the results obtained showed surprising values of Poisson's ratio that could even become negative (Mazel et al., 2012). So if the Young's moduli reported in the literature using these techniques are consistent, Poisson's ratio values are to be taken with caution.

The second category of tests study the dynamic elastic moduli. It must be noted that in the case of viscoelastic materials, dynamic elastic moduli might differ from quasi-static ones. This can be performed by measuring wave propagation in the tablets using either ultrasonic (Akseli et al., 2009b, 2009a) or photoacoustic waves (Ketolainen et al., 1995). These methodologies can make it possible to determine both Young's modulus and shear modulus and to deduce Poisson's ratio. In the case of Photoacoustic evaluation, a large dispersion is obtained for Poisson's ratio (Ketolainen et al., 1995). Moreover, in the

case of ultrasound, anisotropy can also be assessed (Akseli et al., 2009b). Nevertheless, the technique is quite expensive and complicated to use which might explain why only few articles have been published on the subject even if the technique is used for more than 10 years.

Another possibility is the use of dynamic mechanical analysis (DMA) to measure both Young and shear moduli as a function of the frequency (Hancock et al., 2001; Radebaugh et al., 1989). Nevertheless, it is the author experience that due to the small size and relatively high values of elastic moduli, pharmaceutical tablets are difficult to test on commercial apparatus. This might explains the strangely low values for young's moduli obtained in some publications (Ascani et al., 2019). Finally, Maranzano et al. presented an interesting technique using drop tests on a piezo electric force sensor (Maranzano et al., 2013). Thanks to the transformation of the force signal obtained, it is possible to calculate Poisson's ratio and young's modulus. If this technique is very interesting, the results show large errors bar on young's modulus and values of Poisson's ratio that are sometimes higher than 0.5, which is physically impossible, at least for isotropic tablets as supposed in the article.

Impulse excitation technique, is used from a long time in different scientific fields to characterize the elastic properties of materials. It can be applied to a lot of different materials like ceramics or composites (Swarnakar et al., 2009; Tognana et al., 2010). The principle is to measure the natural resonance frequencies of a material. These frequencies are linked with the dynamic elastic properties of the material and with the geometry of the sample used for the characterization. These relations are given for example in the norm ASTM E1876-01. Excitation of the resonance frequencies is

achieved by submitting the sample to a very short impact. This technique is easy to implement and relatively cheap compared to others (like ultrasonic measurement for example). To our knowledge, it was never applied to pharmaceutical tablets, but it could constitute an easy methodology to study the elastic properties of tablets. The aim of this article is thus to study the applicability of this technique to pharmaceutical tablets and to give a first overlook of the possibilities offered in terms of characterization. It thus constitutes a first step in the development of this technique in the pharmaceutical field.

2. Materials and method

2.1. Powders

Four classical pharmaceutical excipients were used in this study: anhydrous lactose (Alac) (Duralac H, Meggle, Wasserburg, Germany), Lactose monohydrate (MLac) (Excipress 150Gr, Armor Pharma, France), Anhydrous calcium phosphate (ACP) (Anhydrous Emcompress, JRS pharma, Rosenberg, Germany) and microcrystalline cellulose (MCC) (Vivapur 12, JRS pharma, Rosenberg, Germany). To perform the compaction experiments, MLac, MCC and Alac were mixed with 1% (w/w) of magnesium stearate (Cooper, Melun, France) to minimize the frictions in the die. ACP was mixed with 2% Magnesium stearate. The blending was performed at 49 rpm for 5 min using a turbula mixer (Type T2C, Willy A Bachofen, Muttenz, Switzerland).

2.2. Tablet manufacturing

All tablets were manufactured on a compaction simulator Styl'One Evolution (Medelpharm, Beynost, France). This device is a single station instrumented tableting machine. It is equipped with force sensors (strain gauges) on both punches and on the

die wall, and the displacements of the punches are monitored using incremental sensors. It is equipped with a separate engine for each punch. Punches can thus be moved independently. Euro B flat faced punches with a diameter of 16 mm were used for all the products and Euro B flat faced punches with a diameter of 11.28 mm were used to produce a supplementary group of MCC tablets. For each product, three compression pressures were used: 100, 150 and 200 MPa. Filling height was modified in each case to obtain a final tablet thickness of 3 mm for the 16 mm tablets and of 2 mm for 11.28 mm tablets. This selection was made to maintain a thickness to radius ratio below 0.5 as recommended by the norm ASTM E1876-01. For each condition (product/pressure/size) 5 tablets were manufactured and analyzed using the impulse excitation method.

2.3. Impulse Excitation method setup

The signal for the impulse excitation method was acquired using a microphone MM310 (Microtech Gefell GmbH, Gefell, Germany). This device makes it possible to measure frequencies from 20 Hz to 100 kHz. The data acquisition system was a DEWE-43 coupled with the software Dewesoft X3 (Dewesoft, Trbovlje, Slovenia). Acquisition frequency was set to 200kHz 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 4069 points was used. The final frequency resolution was25Hz. A complete description of the experimental procedure is given below in the results section.

2.4. Numerical method

Numerical calculation of the resonance frequencies of tablets was performed using Finite element method (FEM). The FEM modelling was performed using Abaqus® software (Abaqus® Standard 6.13, Dassault Systèmes, Vélizy-Villacoublay,France). The Lanczos method was used in conjunction with isotropic linear elastic properties as proposed in the literature (Akseli and Cetinkaya, 2008). This method is already implemented in the Abaqus code.

3. Results and discussion

3.1. Measurement of resonance frequency

The methodology developed in this article was based on the norm ASTM E1876-01. Nevertheless, due to the small size of pharmaceutical compacts, some improvements were necessary to obtain a good measurement of the vibration frequencies.

The principle of the technique is to submit the tablet to an excitation and to record the response of the tablet in terms of vibrational waves (sound or ultrasound). In the norm ASTM E1876-01, the excitation is given by an impulser that will impact the sample. Moreover, a support is also needed to set the tablet. Another common alternative is to set the tablet on a foam. Preliminary results using this methodology showed that for some products (especially MCC in the present case), the resonance frequencies could not be measured.

In the case of pharmaceutical tablets, we found that it was suitable to drop the tablet, from a height around 5 cm, on a hard surface (ceramic) and to record the sound promoted by the shock between the tablet and the hard surface. Using this

159 methodology, it was possible to measure the resonance frequencies of all the products
160 compressed at all the pressure levels used in this study. Different ways of dropping the
161 tablet (on the band, on the surface, on the edge) were tested. Recorded spectra
162 indicated that resonance frequency peaks were better recorded when the tablet was
163 dropped on the band. Finally, in the present methodology, noise can be obtained in the
164 sound range especially below 15kHz. As a consequence, resonance frequency in this
165 range could be difficult to measure.

166 Figure 1 shows examples of frequency spectra obtained for the different products, using
167 the tablets obtained under a compaction pressure of 150 MPa. For all the products
168 vibration frequencies are clearly seen on the spectra. Depending on the product, the
169 number of frequencies detected ranged from 3 to 7. For each tablet, at least five spectra
170 were recorded. By comparing the spectra, it was found that, the variation of the
171 frequency from one spectrum to the other, was never higher than 0.1 kHz. The norm
172 ASTM E1876-01 only considers the two lower frequencies (F_1 and F_2 in table 1) for the
173 calculation of Young's modulus and Poisson's ratio. Nevertheless, the other frequencies
174 can also be of interest as it will be shown below. From the graph, it can be seen that
175 each product has a specific set of vibration frequencies that corresponds to its own
176 elastic properties. The methodology makes it thus possible to differentiate the different
177 products one from the other.

178 In the case of MCC, two tablet sizes were used. The resonance frequencies of a tablet,
179 depends on its elastic properties but also on its dimension. Reducing the diameter of the
180 tablet promotes a shift of the resonance frequency towards higher values as it can be
181 observed in Figure 1. This can be interesting in the cases where the vibration

182 frequencies are very low and could thus be mixed with the noise present below 15kHz.
183 Depending on the elastic properties of the studied product, tablet shape can thus be
184 varied in order to obtain correctly measureable frequencies.

185 Finally, another interesting point is the shape of the peaks obtained for the different
186 products. If we consider the first peak of the spectra, very narrow peaks are obtained for
187 ACP, Alac and Mlac. On the contrary, MCC presents much broader peaks. The width of
188 the peak is in fact linked with the viscoelastic properties of a product (Bernard et al.,
189 2014). Indeed, viscoelasticy corresponds, in terms of vibration, to a damping factor. In
190 general, for oscillators, the result of damping is an increase of the width of the
191 resonance peak. This is exactly what is observed in Figure 1. Whereas ACP, Mlac and
192 Alac are not considered as viscoelastic, MCC is a viscoelastic product (Hancock et al.,
193 2001). This explains the larger peaks obtained for this product. The damping due to
194 viscoelasticity could also explain why only 3 frequencies are obtained for MCC contrary
195 to the other products. For the moment, this observation is not quantitative and work is
196 necessary to develop this aspect. But it indicates that further development could make it
197 possible to use, in the future, Impulse excitation technique for the characterization of the
198 viscoelasticity of pharmaceutical tablets.

199 ### 3.2. Elastic constant determination

200 As shown before, the methodology developed makes it possible to detect the two lower
201 frequencies of vibration of pharmaceutical tablets. According to the norm ASTM E1876-
202 01, Young's modulus and Poisson's ration could be determined for each tablet using
203 these two frequencies. The calculation was thus made for all the tablets according to the

204 recommendation of the norm. The following paragraphs only give a short summary of
205 the methodology. A complete development can be found in the norm ASTM E1876-01.

206 Derivation of the elastic moduli was performed in two steps. First, thanks to the ratio
207 between the two resonance frequencies, Poisson's ratio could be determined using a
208 table given in the norm that accounts also for the tablet dimensions. Once Poisson's
209 ratio is determined, other tables, given in the norm ASTM E1876-01, made it possible to
210 determine two constants, K_1 and K_2, which were used to calculate Young's modulus. In
211 fact, Young's modulus could be calculated from any of the two frequencies using the
212 following equation:

213 $$E_i = \frac{37.6991 f_i^2 D^2 m(1-\upsilon^2)}{K_i^2 t^3}$$

214 were i=1 or 2, f_i is the i^{th} resonance frequency, υ is the Poisson's ratio and D, m and t
215 are respectively the mass, the diameter and the thickness of the tablet. As
216 recommended in the norm, Young's modulus was determined using the two frequencies
217 and the mean of the two values was finally considered. It must be noted that for round
218 tablets, the use of tables generates an imprecision in the results. To obtain results as
219 precise as possible, 2D curve fitting of the tables was performed using the software
220 Origin 7.5 (Originlab, Northhampton, USA).

221 Young's moduli and Poisson's ratios for all the tablets as a function of the porosity are
222 presented in Figure 2. As mentioned previously, for each condition a batch of five tablets
223 was analyzed. The results of all the tablets are presented in figure 2. As it can be seen
224 the dispersion of the results for each batch is quite small, especially for Young's
225 modulus. From a more quantitative point of view, the standard deviation was calculated

for each batch. It was found that it was always below 0.06 GPa for Young's modulus and 0.01 for Poisson's ratio. The reproducibility is thus good and comparable with the one obtained with other techniques (Mazel et al., 2012).

The results give trends as a function of the porosity that are similar to those presented in the literature. Young's modulus and Poisson's ratio are increasing with a decreasing porosity. Another interesting point is the comparison for MCC between the two sizes of tablets. For both sets, the value of Young's modulus and Poisson's ratio are well superimposed. This constitute an important confirmation that the methodology can indeed be applied consistently to pharmaceutical tablets.

Concerning, the numerical values, as the moduli are obtained out of die, it is complicated to compare the obtained values with studies performed in die (Cunningham et al., 2004; Mazel et al., 2012). The ejection process could indeed promote large modifications of the tablet structure. Comparison should thus be limited to studies that performed out of die characterization of tablets.

For Young's modulus, comparison can be made with studies using three point bending tests (Bassam et al., 1990; Busignies et al., 2006, 2004). Nevertheless, the present methodology measures the dynamic elastic moduli. In a case of a viscoelastic product, like MCC, the dynamic values could be higher than the quasi-static values measured in three point bending for example. The values shown in Figure 2 are in the same order of magnitude than those presented for example by Busignies et al.(Busignies et al., 2006). Larger values for anhydrous lactose than for lactose monohydrate were also reported in the literature (Busignies et al., 2004). Globally, Young's modulus values are thus in the expected range, considering also the variability of the results presented in the literature.

For Poisson's ratio, as mentioned in the introduction, it is difficult to find experimental values to compare our results. The values presented in Figure 2 are rather low compared to those presented by Maranzano et al.(Maranzano et al., 2013) which are, as said before, to be taken with caution. Nevertheless, the trend as a function of the porosity seems to be consistent and the dispersion of the results is quite small.

To conclude on this part, the methodology makes it possible to obtain reproducible results in terms of elastic moduli. Moreover, the results are not affected by the size of the sample used.

3.3. Effect of anisotropy

In the application of the norm ASTM E1876-01, it is supposed that the solid is isotropic. In the case of pharmaceutical tablets, this hypothesis is questionable as reported by several authors (Akseli et al., 2009b; Galen and Zavaliangos, 2005; Porion et al., 2009). This anisotropy should nevertheless depend on the product. It was shown for example that MCC tablets are more anisotropic than ACP tablets (Porion et al., 2009). If the anisotropy of the tablet is important, the previously determined moduli should then be considered as apparent isotropic moduli, as in the case of the elastic moduli measured in die during compression.

The previous methodology only used the two first frequencies. Nevertheless, it was shown in Figure 1 that at least 3 frequencies could be determined for all products. The vibration modes corresponding to these three first frequencies can be seen in Figure 3 (FEM calculation). Knowing the elastic properties, it is possible to predict all the resonance frequencies of a solid, for example using FEM simulation. So if the elastic

constants determined previously are correct, all the frequencies of the spectrum should be predicted correctly using FEM simulation and not only the two first ones.

The test was performed using the third frequency of the spectrum that can be seen for all the products. First the elastic parameters obtained previously were entered in the simulation to calculate the two first frequencies. It was found necessary to slightly adjust these elastic parameters to obtain exactly the experimental frequencies by numerical simulation. This is understandable as the determination of Poisson's ratio, K_1 and K_2 are made using tables and not analytical equations. This method promotes some uncertainties on the final results. Once the final elastic moduli obtained, the three first frequencies could be obtained in the simulation. This methodology was applied for one tablet obtained under 150 MPa for each product. The comparison between the experimental and numerical frequencies is given in table 1.

As mentioned above, experiments showed that the error on the measurement of a frequency in the spectrum was around 0.1 kHz. Any difference below this value should thus be considered as insignificant. The two first frequencies are well predicted, which means the elastic parameters are correctly set in the simulation. On the contrary, the quality of prediction of the third frequency depends on the product. For ACP, the third frequency is well predicted whereas this prediction is not so good for Alac and Mlac and is even worse for MCC. It is known from the literature that MCC is strongly anisotropic (Akseli et al., 2009b; Galen and Zavaliangos, 2005; Porion et al., 2009). Mlac is also known to present some anisotropy but to a smaller extend than MCC (Akseli et al., 2009b). Studies on ACP showed isotropy in terms of porous network (Porion et al.,

293 2009). There is thus a good correlation between ΔF_3 and the expected anisotropic
294 behavior.

295 This result has two main consequences. In the case of anisotropic tablets, the
296 methodology developed in section 3.2 gives apparent isotropic elastic constant which
297 might not represent exactly the true elastic constant values. Second, the methodology
298 presented in the present paper could be an interesting mean to study the anisotropy of
299 tablets in terms of elastic properties. Further work is needed to develop the
300 characterization of anisotropic properties using this technique.

301 **4. Conclusion**

302 As shown in this paper, impulse excitation can be applied to pharmaceutical tablets to
303 determine their resonance frequencies. For all the product studied, at least 3 resonance
304 frequencies could be detected. Moreover, depending on the product, the size of the
305 tablet could be adjusted to obtain the frequencies in the measuring range.

306 The shape of the peaks can give some information on the viscoelastic nature of the
307 studied tablet. Indeed, viscoelastic products give much broader peaks in the spectrum.
308 This information is for the moment very qualitative, nevertheless, developments could be
309 made to use impact excitation to study viscoelasticity.

310 Using the two first frequencies of the spectrum, it is possible to calculate the elastic
311 properties of the tablet, under the assumption of isotropy, using for example the ASTM
312 norm E1876-01. Young's modulus and Poisson's ratio were obtained for tablets made of
313 several products and manufactured under several pressure points. The values for
314 young's moduli were coherent with published data. Values for Poisson's ratio were low

315 but there are not enough data published on this topic to make a useful comparison.
316 Moreover, the size of the tablet had no influence on the value of the moduli.

317 Finally, by looking at the third frequency of the spectrum and by comparing it with
318 numerical modelling results, we found that differences between measured and
319 calculated values could be a sign of tablet anisotropy. These results are very
320 preliminary, but impulse excitation could be an interesting technique to study the
321 anisotropy in the elastic properties of tablets.

322 **Acknowledgement**

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325 **Legend to figures**

326 **Figure 1**: Examples of frequency spectra.(a) ACP; (b) Alac; (c) Mlac and (d) MCC (two
327 tablet diameters).

328 **Figure 2**: Evolution of Young's moduli (left) and Poisson's ratios (right) as a function of
329 the porosity.

330 **Figure 3:** Deformation patterns corresponding to the three first frequencies (FEM
331 calculation). Resonance frequencies increase from left to right.

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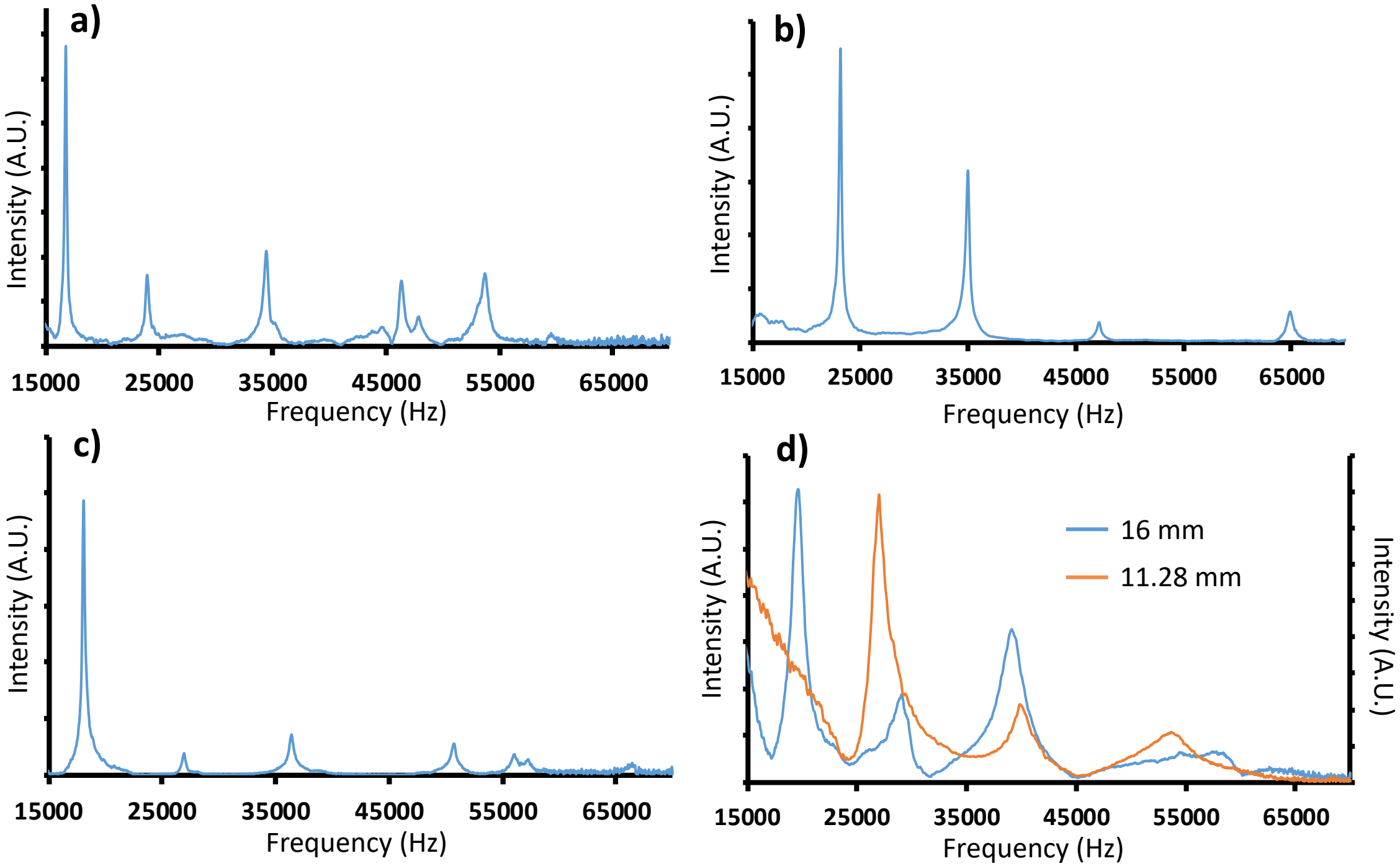
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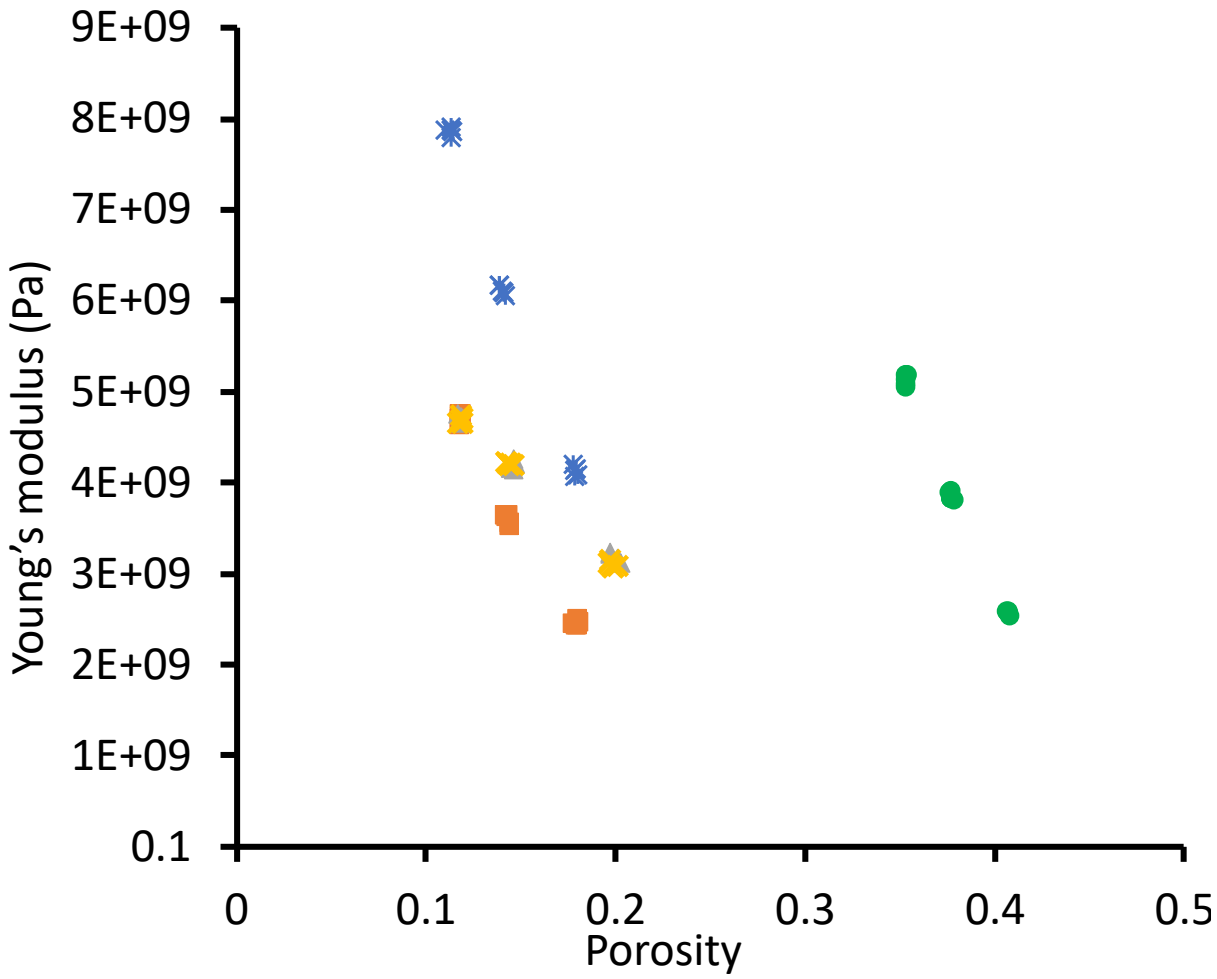
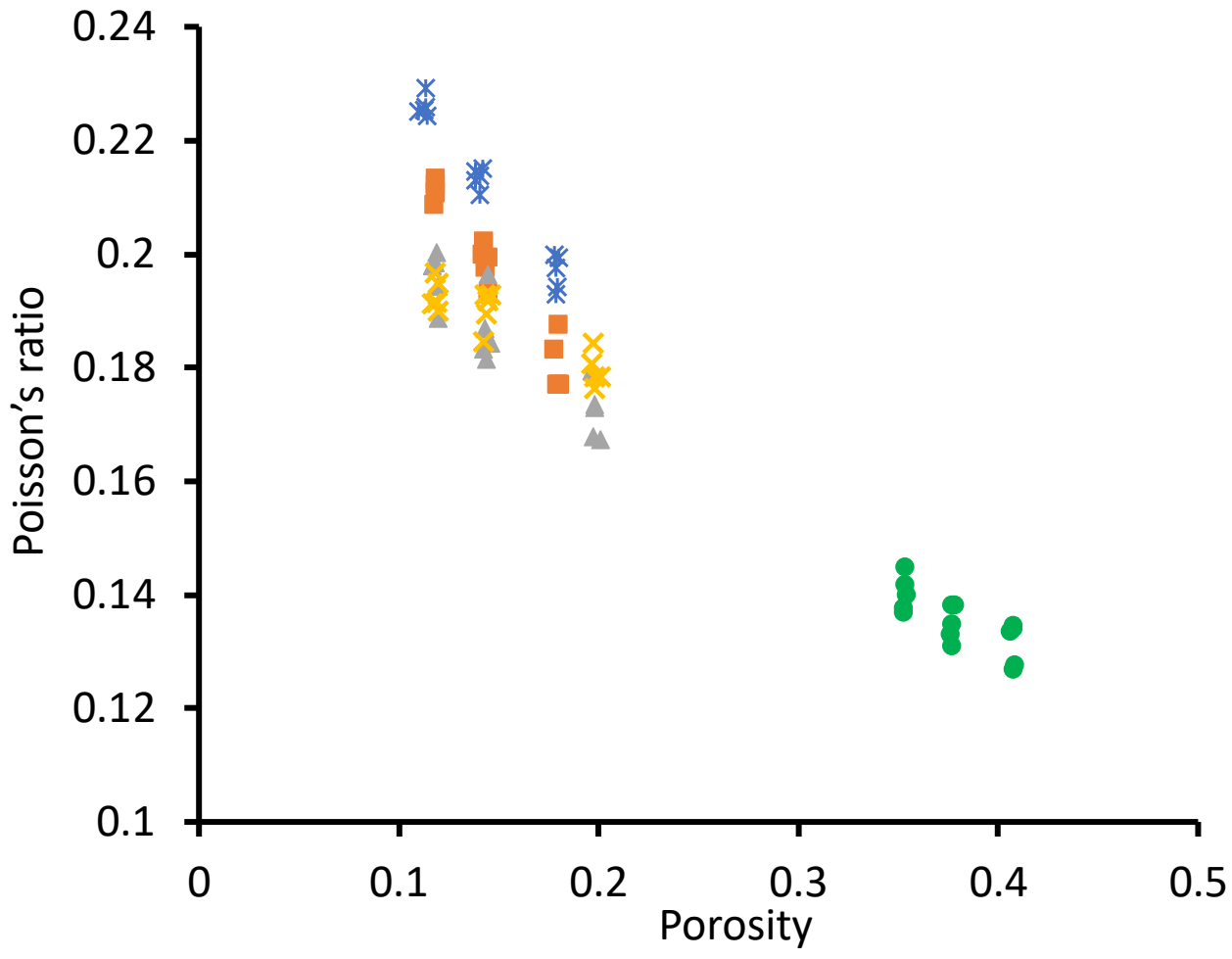




Mlac MCC_16mm MCC_11.28mm Alac ACP

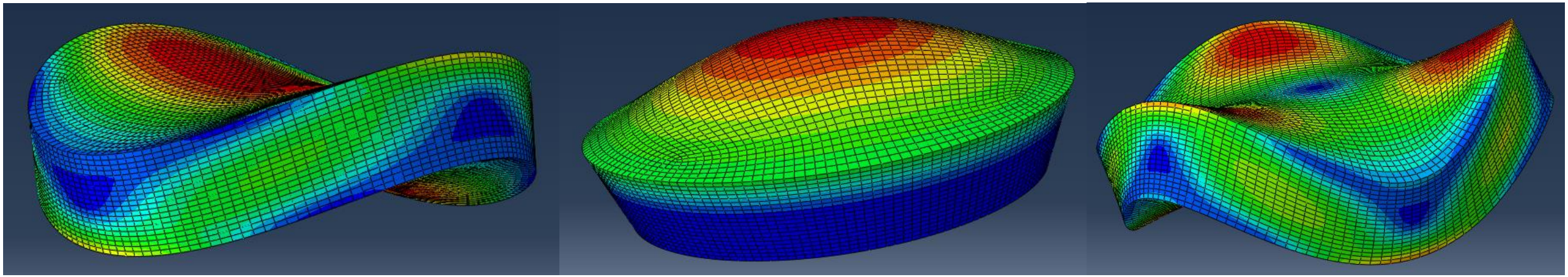
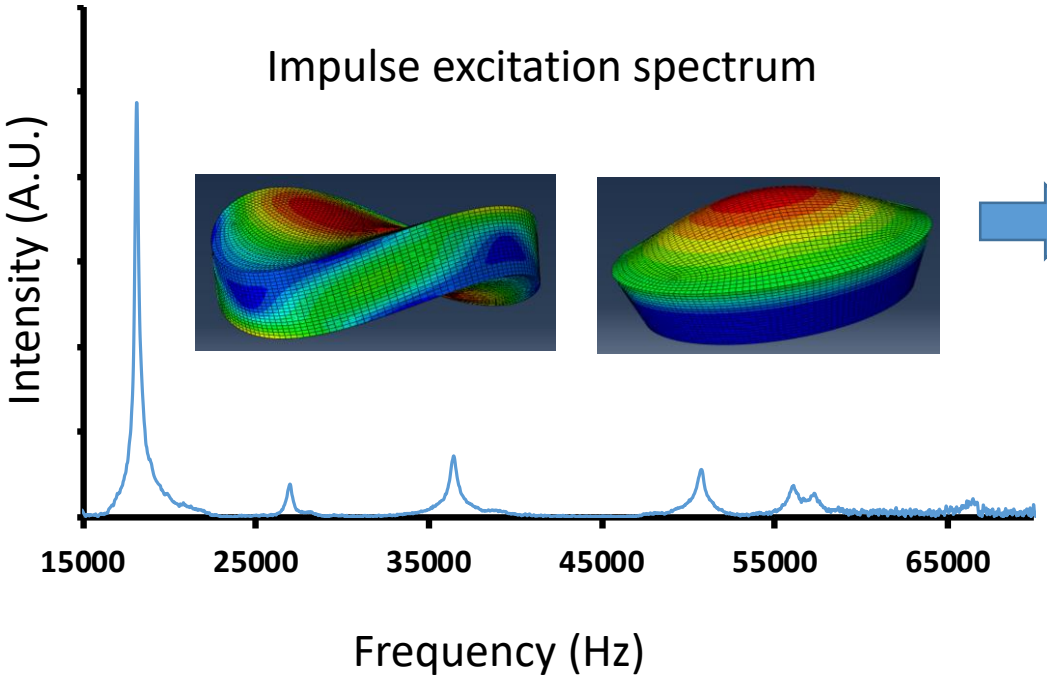
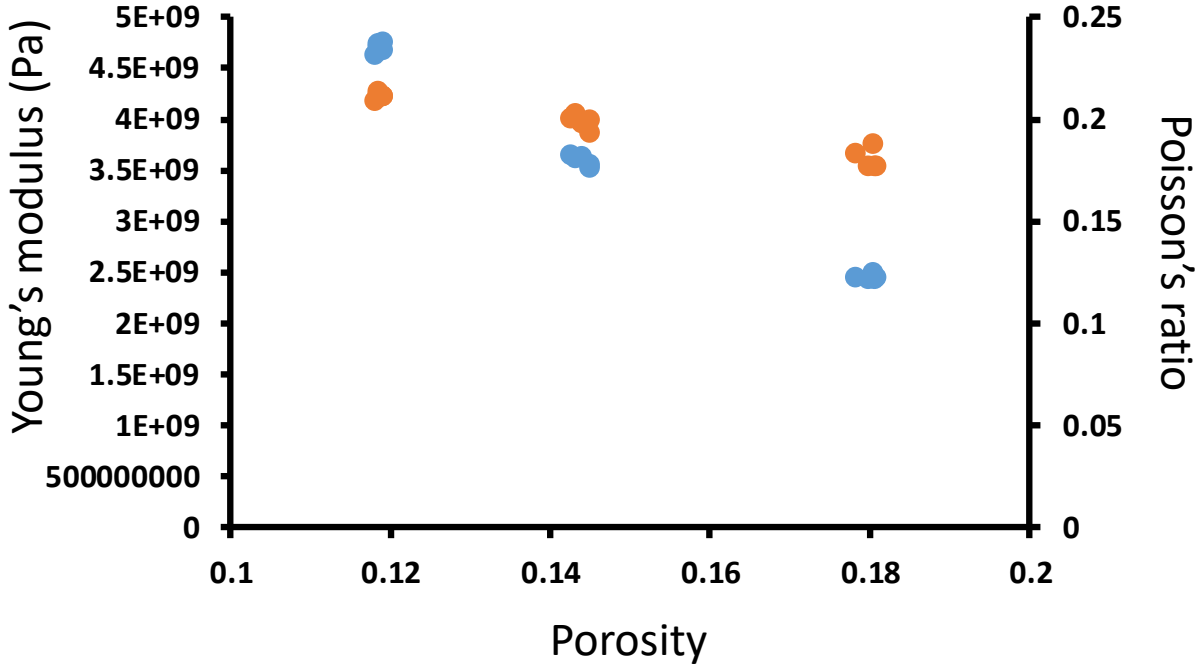


Table 1: comparison between experimental (exp) and numerical (FEM) frequencies for tablets obtained under 150MPa. F_1, F_2 and F_3 correspond to the three first resonance frequencies in ascending order. ΔF_i correspond to the absolute difference between experimental and numerical value for the frequency F_i.

Product	F_1(kHz)			F_2(kHz)			F_3(kHz)		
	Exp	FEM	ΔF_1	Exp	FEM	ΔF_2	Exp	FEM	ΔF_3
ACP	16.8	16.81	-0.01	23.9	23.91	-0.01	34.52	34.58	-0.06
Alac	23.17	23.17	0	34.99	34.99	0	47.14	47.86	-0.72
Mlac	18.02	18	0.02	26.9	26.91	-0.01	36.45	37.13	-0.68
MCC	19.6	19.61	-0.01	29.05	29.05	0	39.14	40.4	-1.26


Impulse excitation spectrum
Intensity (A.U.)
15000
25000
35000
45000
55000
65000
Frequency (Hz)


Young's modulus (Pa)
5E+09
4.5E+09
4E+09
3.5E+09
3E+09
2.5E+09
2E+09
1.5E+09
1E+09
500000000
0
0.1
0.12
0.14
0.16
0.18
0.2
Porosity
0.25
0.2
0.15
0.1
0.05
0
Poisson's ratio