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Effect of the compaction parameters on the final structure and properties of a press-coated tablet (Tab-in-Tab): Experimental and numerical study of the influence of core and shell dimensions

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ABSTRACT

With increasing interest in chronopharmaceutics, press-coated tablets have become a key technology in the field of modified release drug delivery systems. Although their benefits in terms of drug release have been largely studied, the comprehension of the compaction process of press-coated tablets is yet to complete. Particularly, the effects of geometrical parameters like the ratios between the thickness/diameter of the core and the thickness/diameter of the whole tablet were so far not much considered. Moreover, there is only few studies in the literature about the effect of the press-coating compression on the final structure and properties of the core. The present work consists in a joint experimental and numerical study that aims to assess these points. The study revealed high stress concentrations on the core during compression, causing high permanent deformations of the core, especially when the ratio between the core thickness and the total tablet thickness was high. The mechanical properties of the core tablet were also shown to be impacted: its density and strength were found to decrease before increasing again along the coating-compression. This effect was highlighted to be dependent on the triaxiality of the stress state (i.e. the ratio between the stresses in the different directions), itself depending on the two studied geometrical parameters. As the properties of the core affect the release attributes, ratios between the dimensions of the core and the dimensions of the whole tablet (thickness, diameter) should be taken into account as critical parameters for the manufacture of press-coated tablets.

1. Introduction

Press-coated tablet is a solid dosage form for controlled release that consists of a “core-shell” structure (Foppoli et al., 2017). Although a variety of release profiles may be obtained, in most of the cases, the active ingredient is contained in a core coated with an inactive shell (Jagdale et al., 2014; Kaljević et al., 2016; Sawada et al., 2004; Wu et al., 2007). In this case, the active ingredient can only be released when the shell itself releases the core, allowing a lag-time before the release of the drug (Conte et al., 1993; Fukui et al., 2000). This kind of pharmaceutical drug delivery system is currently produced at an industrial scale and used to treat patients, especially for applications that needs a precise release place like the colon (Maity and Sa, 2016), or that needs a long term release, for example during the night (Lin and Kawashima, 2012). The therapeutic advantages of pulsatile drug delivery have been widely studied (Gandhi et al., 2011; Lin and Kawashima, 2012), demonstrating high added value in the field of healthcare.

The specific structure of the press-coated tablets also makes the press-coating process a very particular case of powder compaction. The process begins with the production of the core, and the second step is the manufacture of the shell by compaction of a free powder surrounding the core (Kaljević et al., 2016). In spite of the long use of the technique and the complexity of the phenomena occurring during this process, there is still very few studies concerning the press-coating manufacturing process and its effects on the mechanical resistance and the functional performance of press-coated tablets.

A precursor work (Ascani et al., 2019) started a new interest for the mechanical side of press-coating. The attention was drawn on the influence of core and shell mechanical properties, like stiffness and viscoelastic properties. These properties are confirmed to have large effects on the final product attribute like mechanical resistance, coat defects, and density distribution.

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Another recent following work also provided links between process parameters, formulation parameters and final properties in the case of press-coated tablets (Nguyen et al., 2020). In this study, several parameters were studied like the core and shell materials, core initial density and compression speed. Through a systematic understanding approach, the influence of these parameters on the layer adhesion, lamination tendency and tablet microstructure were studied.

Particularly, in the case of Tab-in-Tab tablets (i.e. press-coated tablets), the release profile should be considered as a critical quality attribute and has to be controlled. As this attribute partly depends on the core which contains the active ingredient, it is necessary to understand how and to what extent the coating-compression impacts the core.

The present study aims to evaluate the evolution of the core during the coating-compression. Cores recovered from press-coated tablets, manufactured at different pressures, were characterized in dimensions, density and mechanical strength. As the geometry effects are yet not described in the literature, the diameter ratio between the core and the shell was studied, as well as the thickness of the layer above the core (i.e. the distance between the core surface and the shell surface). These parameters may be critical process parameters that were so far not considered in the design of press-coated tablets and should be extensively studied. Finally, FEM numerical simulation, more and more used in the field of pharmaceutical compaction(Cunningham et al., 2004; Diarra et al., 2012; Sinka et al., 2004; Wu et al., 2005), was carried out as a tool to understand the mechanical phenomena occurring during the coating compression.

2. Materials and methods

2.1. Powders and blend

Classical pharmaceutical excipients were used as model products for this study. Two mixtures were used for the compaction of cores. The first was composed of 99% granulated lactose monohydrate (GLac) (Excipress GR150, Armor Pharma, Loudéac, France) and 1% Magnesium Stearate (Partek Mg Lub, Merck, Darmstadt, Germany). The second was composed of 99,5% (w/w) Microcrystalline Cellulose (MCC) (Vivapur 200, JRS Pharma GmbH, Rosenberg, Germany) and 0.5% Magnesium Stearate. The choice of the two products was based on their different mechanical behavior, lactose being generally considered as brittle and MCC as plastic (Roberts and Rowe, 1987). This will make it possible to broaden the applicability of the presented results.

The same MCC mix was used for every shell compression. Lactose mix was not used as a shell for two reasons. First, in the case of MCC cores it led to quasi-systematic lamination upon the ejection. Second, in the case of Lactose, it was found impossible to extract the core from the final form without damage.

The powders were blended using a Turbula mixer (Wab, Muttenz, Switzerland) at 49 rpm during 5 min and then stored at a constant relative humidity (RH) of 45% until the compaction.

2.2. Tablet manufacturing

2.2.1. Compaction simulator

All experiments were performed 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 (accuracy 10 N) on both punches, and the displacements of the punches are monitored using incremental sensors. The die was filled automatically with a gravity flow feeder containing the powder.

2.2.2. Core compression

The cores were manufactured in three sizes with diameters of 6 mm; 8 mm; 11.28 mm respectively, using for each a set of Euro B round flat punches of the selected diameter. Thicknesses of the cores were set to keep a constant Diameter/Thickness ratio of 8/3. Lactose cores were compacted at a pressure of 300 MPa and MCC cores were compacted at a pressure of 150 MPa. Compression forces were adjusted to get the same pressure for each size. These manufacturing parameters are reported in the Table 1.

The core-tablets were let 48 h at 45% RH for relaxation before the coating compression.

2.2.3. Coating-compression

All press-coated tablets were manufactured using Euro B round flat punches of 16 mm diameter. After first filling, the core was manually placed on the center of the powder bed. A minimal tamping force was applied to place the top of the core at the level of the powder bed, before the second filling and main compression. The configuration of the resulting press-coated tablet is presented in Fig. 1.

The filling heights were adjusted to have the target thickness of 0.6 mm, 1.0 mm or 1.8 mm for both upper and lower layers after the compression. In the further text, both upper and lower layers will be referred as "layer", as they have the same thickness.

Two series of press-coated tablets were made. The first one used a constant 8 mm diameter core with three different layer thicknesses of 0.6 mm, 1.0 mm and 1.8 mm. The second one used three sizes of core, respectively 6 mm, 8 mm, 11.28 mm, while keeping a constant layer thickness of 1.0 mm.

For each "Core diameter/Layer thickness" set, symmetrical coating-compression was performed at five different compression pressures, respectively 25 MPa, 50 MPa, 75 MPa, 100 MPa and 150 MPa.

As mentioned above, these experiments were performed on two systems. Each system had MCC as shell and the core was MCC for one of them and Lactose for the other.

To ensure the reproducibility of the results, four press-coated tablets were made for each "Core diameter/Layer thickness/Pressure" set. The press-coated tablets were let to relax 48 h at 45% RH before the characterization.

2.3. Characterization

2.3.1. Recovery and measurements of the core

Right before the coating-compression, the cores were individually measured in diameter and thickness using an ABS Digital Thickness Gauge (Mitutoyo, Japan, accuracy 3 μm), and weighted using a precision scale (AT261, Mettler Toledo, Switzerland, accuracy 0.015 mg). After press-coating and relaxation, the press-coated tablets were opened by applying a scalpel on the side of the tablet to remove a layer, the cores were then recovered manually to keep them intact. This operation was quite easy to perform and the dimensions of the cores were then measured again following the same process.

As the tablets were all cylindrical, the density was calculated from the dimensions and mass:

$$\rho = \frac{4 \cdot m}{\pi \cdot d^2 \cdot t} \quad (1)$$

where m is the mass of the tablet, d its diameter and t its thickness.

For a maximum of precision, every recovered core was compared to its own initial dimensions and density.

2.3.2. Breaking test of the core

The diametral compression test was performed using a TA.HDplus texture analyzer (Stable microsystems, Surrey, United Kingdom). Compacts were diametrically compressed between two flat surfaces at a constant speed of 0.5 mm. s^{-1}. To be able to compare the strength of tablets with different sizes, the tensile strength of the core was calculated with the following equation (Fell and Newton, 1970):

$$\sigma = \frac{2 \cdot F}{\pi \cdot D \cdot t} \quad (2)$$

Table 1
Manufacturing parameters of the cores.

Core diameter (mm)	Core thickness (mm)	Target compression force on MCC (kN)	Equivalent pressure (MPa)	Target compression force on Lactose (kN)	Equivalent pressure (MPa)
6	2.25	4.2	150	8.4	300
8	3.00	7.5	150	15.0	300
11.28	4.23	15.0	150	30.0	300

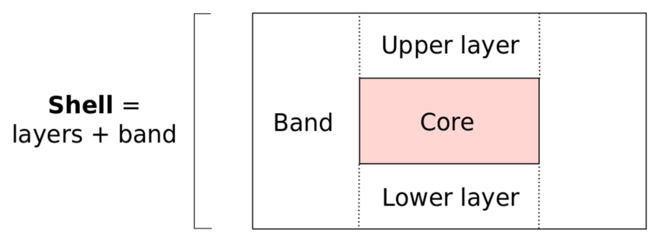

Fig. 1. Schematic cross section view of a press-coated tablet, and region names used in the study.

where F is the maximum force reached in the test, D is the tablet diameter and t is the tablet thickness.

2.4. Numerical modeling

Numerical modeling is nowadays increasingly used in the pharmaceutical industry to study the processes. In the case of compaction, the Finite element method is the most widely used (Cunningham et al., 2004; Diarra et al., 2012; Sinka et al., 2004; Wu et al., 2005). It considers the powder as continuous medium which properties are dependent on the relative density. Results published in the literature show good agreement between experimental results and simulation.

Finite Elements Modeling Abaqus® software (Dassault Systèmes, Vélizy-Villacoublay, France) was used to undergo numerical simulations of the die compression of press-coated tablets.

An axisymmetric modeling was chosen as the geometry, border limits, and loads are all axisymmetric. The dimensions of the core, shell, die and punches were chosen equal to the ones that were used for the experiments. However, a light chamfer ($32^\circ \times 0.6$ mm) was introduced on the core geometry to prevent excessive element distortion on the edge of the core. It was considered to have an acceptable impact on the results.

The MCC core/MCC shell tablet was chosen to be numerically reproduced, so both core and shell were affected with Drucker-Prager-Cap (DPC) model properties of MCC according to previous results and calibration work (Diarra et al., 2013).

A different initial relative density was applied to core and shell: 0.862 for the core which corresponds to a compaction under 150 MPa and 0.474 for the shell which is the minimum acceptable density for the modeling and corresponds to a tamping pressure around 12 MPa.

3. Results

In the whole following text, the expression "apparent pressure" will be used and refers to the applied axial compression force of the punches divided by their surface. This variable represents the mean axial pressure on the punches at the compression peak. This expression was chosen to differentiate this value from the effective pressure at a particular location of the core tablet (e.g. in the core). As it will be demonstrated below, the effective pressure can be very different from the apparent one.

3.1. Influence of the layer thickness

In this part, we studied the variations of the core diameter and thickness as a function of the applied apparent pressure and the influence of the layer thickness on these variations. For this purpose, a series of experiments was led with the layer thickness as the variable parameter, only using cores of 8 mm diameter. By measuring the cores before and after the compression, the diameter, thickness and density variations were obtained. The results are presented in Fig. 2.

First of all, in every case the core diameters increased and their thickness decreased in a high proportion after the coating-compression (Fig. 2A-B-D-E). These dimension variations are both increasing with the compression pressure. With a diameter variation up to +15% for MCC cores and to +20% for lactose cores and a thickness up to −30% variation, the "flattening-like" effect is perceptible to the naked eye. Secondly, it appeared that these effects were more important when the layer was thin. Thus, a thin layer acts as an aggravating factor, making the cores to achieve significant deformations even at very low apparent pressure levels compared to their initial compression pressure of 150 MPa and 300 MPa, for MCC and lactose respectively.

Afterwards, the density variations depending on the pressure were studied, with the same three layer thicknesses. The results are reported in Fig. 2C-F.

For the three studied layer thicknesses, the evolution of the density followed the same trend when the compaction pressure increased. First, the density decreased, then after a certain "apparent pressure", the density increased again. A decrease of the density is something which is normally not observed during the compaction of powders. Such a loss of density can be interpreted as a partial failure of the core within the shell. As the failure is confined in the shell, the core can undergo further compaction at higher apparent pressures. In the case of MCC core, it even makes it possible to reach density levels higher than the initial one.

The influence of the layer thickness is also visible on the density curves. The minimum of core density is reached at a higher level of apparent pressure when the thickness of the layer increases. Thus, the density changes can be observed regardless of the layer thickness, but this parameter has a "shifting" role on the apparent pressure axis. For MCC core, the minimum density is obtained for an apparent pressure around 25 MPa for a layer thickness of 0.6 mm but for layer of 1.8 mm, this minimum is reached between 50 and 75 MPa. The same trend can be seen for Lactose cores. It is therefore clear that the layer thickness is an important parameter that strongly affects the stress state inside the core.

As the density of the core varies along the coating-compression path, it is important to study its mechanical resistance since these properties are strongly linked. The diametrical compression test was applied on the recovered cores to assess their mechanical strength. The results are given in Fig. 3. It is worth noting that the MCC cores recovered from 150 MPa tablets with 0.6 mm layer thickness are not presented on these curves. The reason is that these cores did not break diametrically, but chipped during the text. Thus, the maximal force reached could not be converted in tensile strength and compared with the other values.

As a reference, a series of 8 mm diameter tablets was manufactured at different pressure levels using simple die compression. The obtained tablets were measured and tested to assess the tabletability and the compactibility of the powder (Tye et al., 2005).

The strength of the core tablets (Fig. 3A,C) follows the same tendency as the one previously seen for their density, with a minimum reached at a thickness-dependent apparent pressure and then a further increase.

On Fig. 3B,D the same values of tensile strength are plotted as a function of the densities of the cores out of press-coated tablets. The

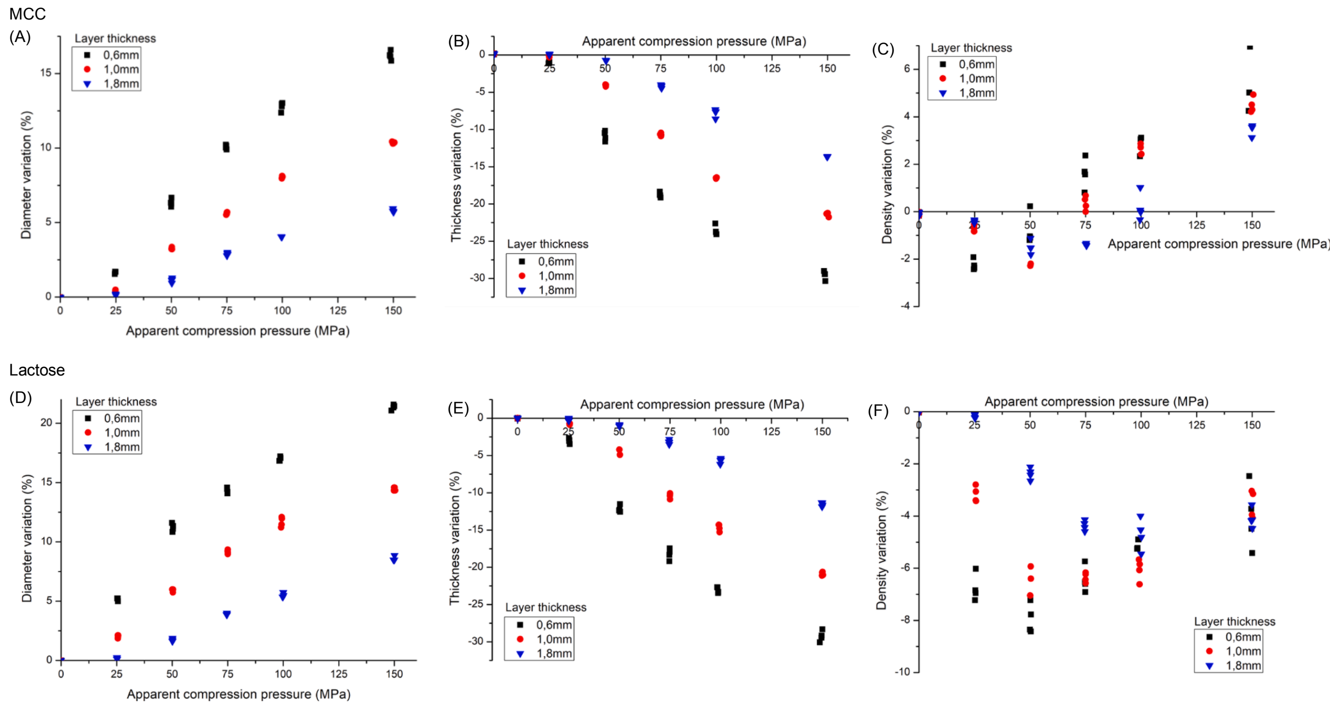

Fig. 2. Dimension and density variation of the MCC (A,B,C) and Lactose (D,E,F) cores versus coating-compression pressure for different layer thicknesses: Core diameter (A,D) Core thickness (B,E) Core density (C,F).

compactibility curve, obtained in a simple die compaction, is also plotted as a reference. This comparison shows that the core tablets that lost density at low apparent pressure are less resistant than tablets of the same density obtained by a simple compression, which agrees with the hypothesis of a failure of the core in the early-compression. The strength loss is even more pronounced with the lactose cores, that are reduced to an extremely low resistance after a coating-compression at only 25 MPa, despite being compacted at an initial 300 MPa pressure.

On the contrary, at higher apparent pressures, the cores have a higher tensile strength than the tablets of the same density obtained by a simple compression. This effect does not seem to be strongly dependent on the external layer thickness. It reveals that the loading path obtained during the coating-compression is able to modify the inner structure of the core tablets in a way which is different from the simple die compaction. As a consequence, two tablets of the same density obtained by press coating or by simple die compaction can have different tensile strengths. This point will be further discussed in the discussion part of the manuscript.

In the next part, following the same methodology, another geometrical parameter of the press-coated tablet was studied: the ratio between the shell diameter and the core diameter.

3.2. *Influence of the core-shell diameters ratio*

To isolate the influence of the ratio between the core and shell diameters, the same experiments series were undergone with fixed shell-diameter and layer thickness parameters, respectively d = 16 mm and t = 1.0 mm. The only varying parameter was the core size, which was chosen at 6 mm, 8 mm, and 11.28 mm. As previously, the results are given in relative variations to make the different sizes comparable. They are presented in Fig. 4.

As previously, there is an increase of the diameter and a decrease of the thickness of the cores when the apparent pressure increases. Nevertheless, compared to the case of the layer thickness, the size of the core seems to have a smaller influence on the relative deformations. Whereas the three layer thicknesses resulted in three well distinct lines for the core dimensions, the three core sizes showed nearly identical relative deformations (Fig. 4A,B,D,E). Even if there is a slight shift, the results are not showing a consistent trend regarding the diameter. For example, at an apparent pressure of 150 MPa, the medium core diameter of 8 mm shows the highest deformations for both MCC and lactose cores. Another example is the evolution of the diameter of the core of 11.28 mm. For MCC cores, it seems to be the diameter with the lowest variations but for lactose cores, the result is much more complex. Considering the present results, it is thus difficult to understand exactly the influence of the core diameter on diameter and thickness variations.

For the density variations, again the same trend is obtained for all diameters with a decrease of the density followed by an increase after a certain pressure. Nevertheless, contrary to the case of the layer thickness, the core-shell diameters ratio seems to have no influence on the apparent pressure corresponding to the density minimum (Fig. 4C,F). Again, a clear trend is complicated to observe. Nevertheless, the results for the 11.28 mm diameter seems different, especially with a higher density for the high apparent pressures for both cores. For lactose cores it seems that at the lowest apparent pressure (25 MPa) the density of the core is inversely proportional to the core diameter whereas the opposite results are obtained at the highest apparent pressure (150 MPa). This trend is not so clear for MCC cores. So to conclude, it seems that the core diameter can have an influence on the density evolution but the results presented do not make it possible to clearly define the trend.

As for the previous series, the tensile strength of the recovered cores was then assessed performing diametral compression tests. The results are presented in Fig. 5A,C depending on the apparent pressure and Fig. 5B,D depending on the density, in which the path of growing apparent pressure is represented by the lines.

First of all, a slight difference of density has been measured between the initial MCC cores of different diameters, even if manufactured at the same pressure. To confirm this fact, the experiment was reproduced several times by changing the measuring tools and the powder, but the same result was obtained each time. This trend was not observed for lactose cores. We have for the moment no explanation for the difference between the MCC cores, and more systematic studies are needed to explain this point, but these studies overpass the objectives of the present work. However, this initial difference is considered acceptable as

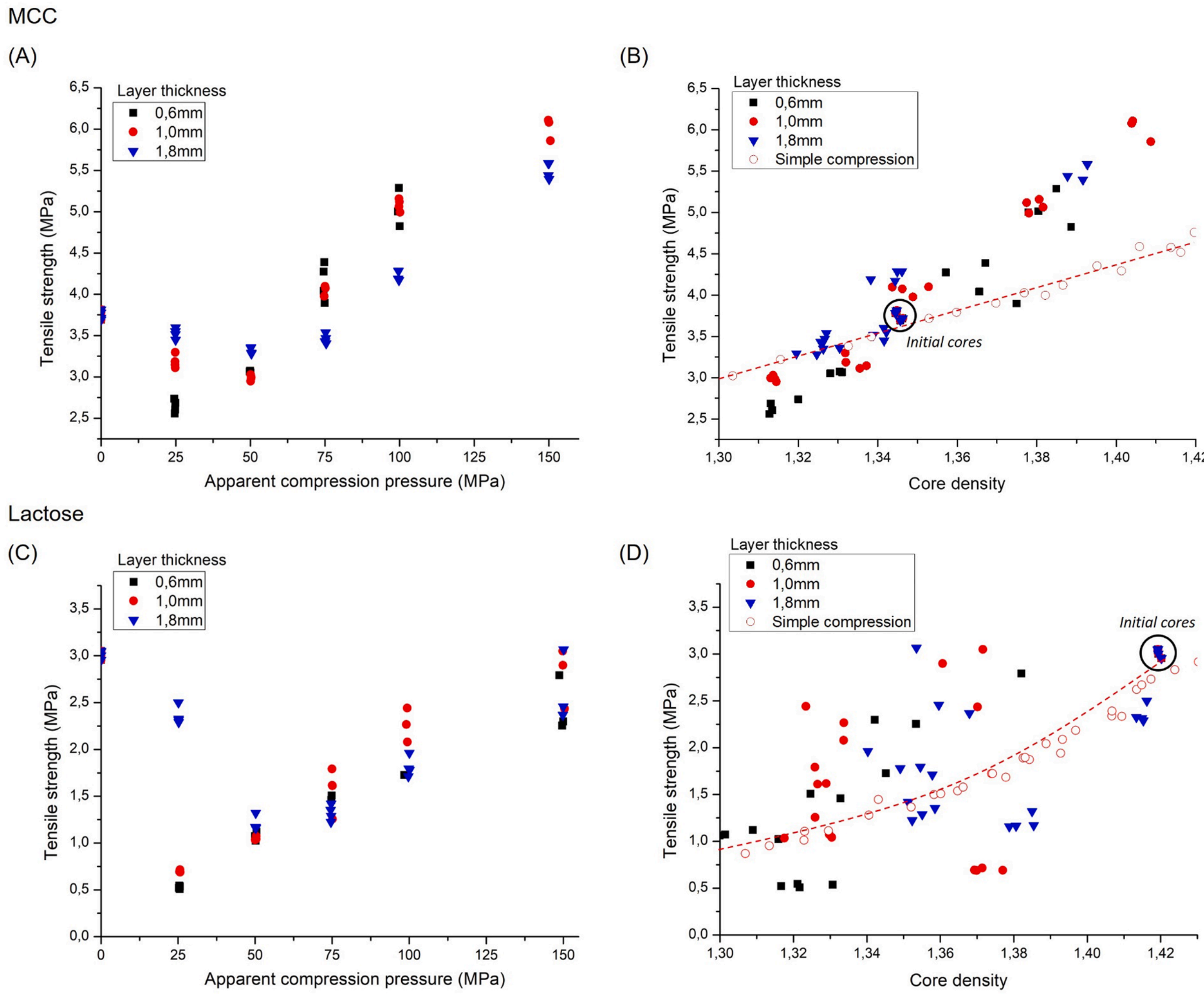

Fig. 3. Tensile strength of the MCC (A,B) and Lactose (C,D) cores after compression depending on the apparent pressure (A,C) and on their density (B,D).

the results rely on the individual variation of density of each core tablet and not on the comparison of the density between cores of different diameters.

For all the cores, as it can be seen in the tabletability profile (Fig. 5A and C), there is an initial decrease of the tensile strength followed by an increase when the apparent pressure further increases. Nevertheless, the compactibility graphs (Fig. 5B and D) show very different behavior depending on the core diameter. As seen previously, the 6 mm and 8 mm cores strengthen to a higher resistance than the usual resistance of tablets obtained by simple compression of the same density. The curves show the opposite behavior for the 11.28 mm cores: after the dedensification and loss of resistance in early-compression, the tensile strength stays inferior to the usual level for a simple die compression until the high apparent coating-pressure of 150 MPa. Thus, it is clear that the core diameter has an influence on the triaxial stress state that modifies the structure of the core and consequently, on the final properties of the core.

The results of this part highlight again the fact that strength of the powder compact is not a bijection of the density, as it is often assumed in the case of a simple die compression. The strength also depends on the loading path that the tablet has undergone, which is affected by the type of compression, and in the case of the press-coating by the core diameter.

The triaxiality of the stresses (i.e. the ratio between the stresses in the different directions) will be discussed in the next part with the use of numerical modelling, explaining how the stress states depend on the studied parameters and can cause the previously seen effects.

4. Discussions

The described changes of the core and the influence of the layer thickness and core diameter during the press-coating manufacturing process indicate different stress states in different regions of the tablet depending on these two parameters. A series of numerical simulations was made to interpret the experimental results and understand their mechanical origin. The numerical simulation of the coating-compression allows to access local variables inside the compact at a given compression pressure, like stress fields in different directions and relative density field in the shell, which are difficult to assess experimentally. It is well known that FEM simulation might not be completely quantitative as some physical phenomena are not taken into account. Nevertheless, it makes it possible to obtain trends and order of magnitude which are useful to compare the different situations.

4.1. Influence of the layer thickness

The modeling was set with a punch force of 10.05kN to simulate a compression with an apparent pressure of 50 MPa. The pressure was chosen to avoid excessive mesh deformation during simulation. The simulated stress state in the compact at this pressure is presented in Fig. 6 for the three layer thicknesses of the experiments.

The material parameters used are known to correctly describe the

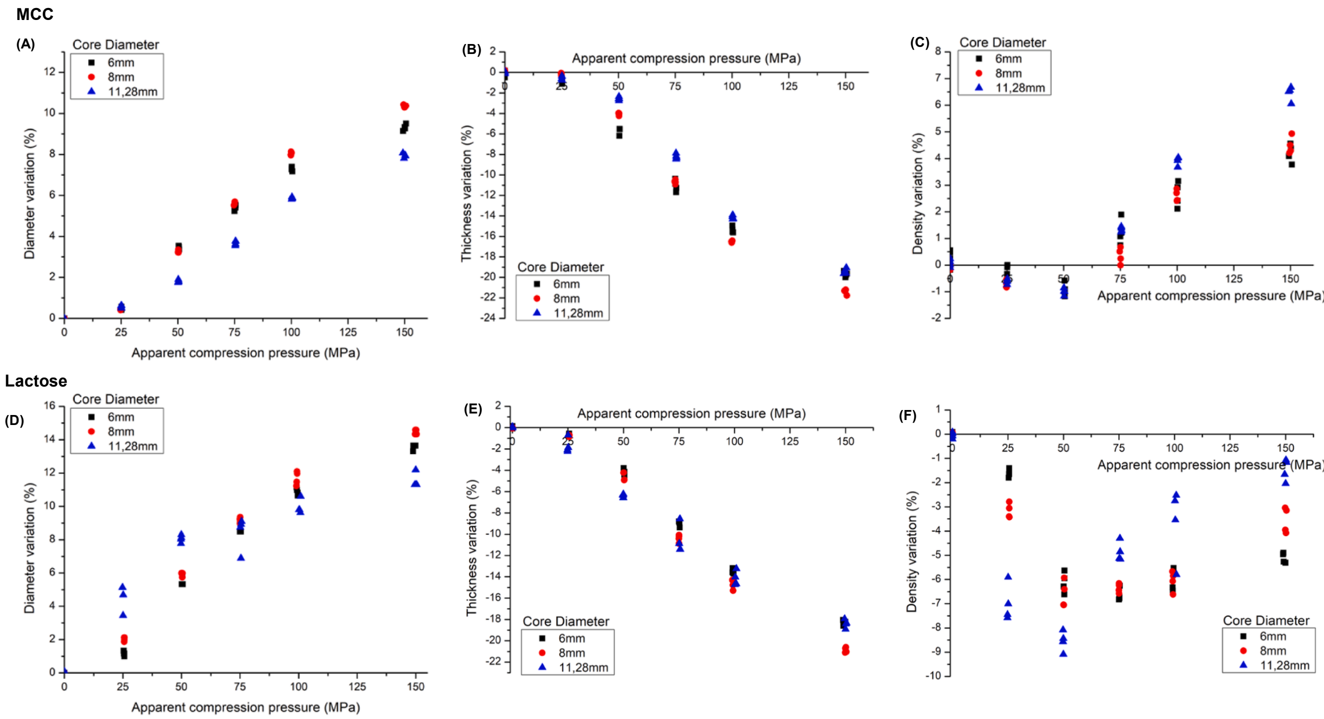

Fig. 4. Dimensions and density relative variations of different sizes of cores of MCC (A,B,C) and Lactose (D,E,F) after coating-compression: Core diameter (A,D); Core thickness (B,E); Density (C,F).

densification behavior (Diarra et al., 2013). However, no decrease of core density was observed. This reveals that the calibration of the failure line does not describe well the material behavior which is not really surprising as the failure criterion used (Drucker Prager) might not represent accurately the fracture behavior of a powder bed (Mazel et al., 2014). Thus, the results on the core dimensions and densities were not taken into account. We cannot discard an influence of the changes of the core dimensions on the final results. Nevertheless, the changes in dimension of the core are much smaller than the changes occurring in the shell. We can thus reasonably suppose that these should not have a large influence on the stress and density fields in the shell.

The results showed that unlike the case of the simple compression (Diarra et al., 2012), the stress distribution is strongly heterogeneous in the press-coated tablet during compression. Indeed, the axial stress (Fig. 6A) is highly concentrated on the core with values that exceed twice the mean axial stress of 50 MPa. This stress concentration is explained by the structure of the system: the core which is very stiff with respect to the loose powder exhibits negligible deformation in the early compression, which means that the thickness change induced by the punch displacement is in fact mainly absorbed by the thin thickness of the upper and lower layers. The layer is thus submitted to a very high strain (relative change in thickness). In the band (i.e. on the side region of the shell), the same thickness change affects the whole height of the tablet, resulting in a smaller relative deformation and then to a less dense and stiff compact in this location than in the layers over the core. This effect is more pronounced when the layer is thin. As a consequence, the pressure on the core increases when the thickness of the layer decreases, explaining the higher deformations of the core with a thin layer, as seen previously (Fig. 2). Moreover, the radial stress in the band (Fig. 6B) has an additive effect: the highest axial stress concentration on the core corresponds to the case with the lowest radial stress (Fig. 6B). Thereby, the band opposes less to the diametral extension and the core deforms more easily in the radial direction.

4.2. *Influence of the core diameter*

The stress states in both axial and radial directions are presented in Fig. 7 for the same apparent pressure of 50 MPa.

As for the layer thickness, the diameter of the core modifies the concentrated axial stress on the core (Fig. 7A) which should increase the deformation of the core. However, it has an inverse effect on the radial stress which is also higher for small diameter (Fig. 7B) which should decrease the core deformation. Whereas the effects were additive in the case of the layer thickness, they are opposite in the case of the diameter. This might explain why it was more difficult to extract a consistent trend from the experimental results presented above.

Thereby, the particular distributions of stresses applied on the core have been highlighted, in regards to the layer thickness and the core diameter. The stress distribution analysis gives a mechanical interpretation to the cause of the core deformations, but it also raises the interest on the shell heterogeneity, which will be studied in the following section.

4.3. *Density distribution in the shell*

As well as the stresses, the density in the shell is not homogeneous, as it has been observed visually (Ascani et al., 2019) and with X-ray microcomputed tomography (Nguyen et al., 2020). Regarding these results, the regions of the shell that are denser are those that underwent the highest relative deformation: the layers above the core. The distribution of densities in the shell can be extracted from the numerical simulations and is presented in Fig. 8.

These simulations are in full agreement with the previous observations in the literature and with the results of the present work. In all cases, the band is less dense than the layers, and the stress distributions correlate well with the density field in the shell. Indeed, the denser regions are stiffer and are submitted to higher stresses than the less dense ones.

The density distribution in the band also makes it possible to validate the interpretation presented above for the core deformation.

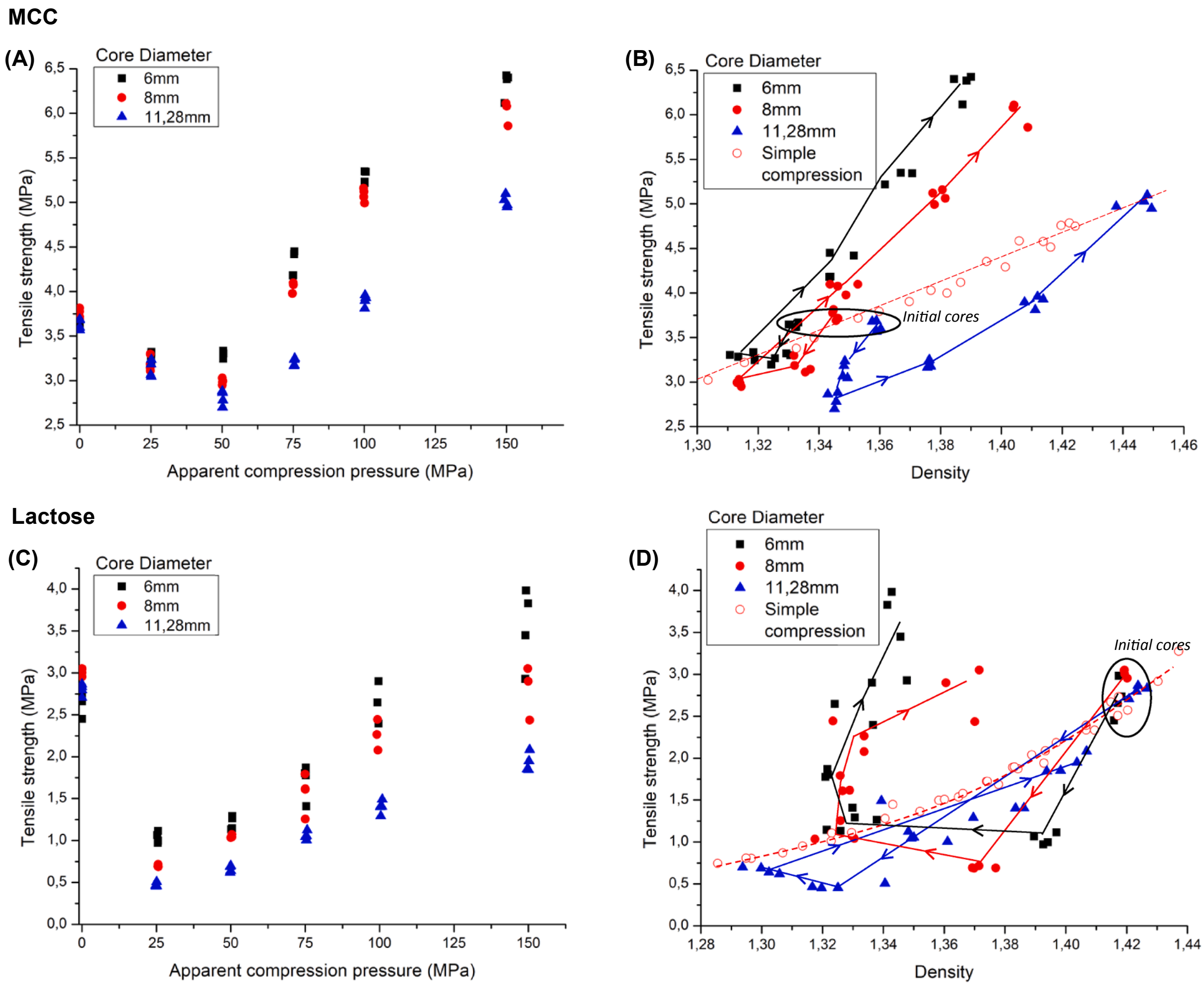

Fig. 5. Tensile strength of the cores of different diameters after compression depending on the apparent compression-pressure (A,C) and on the core density (B,D).

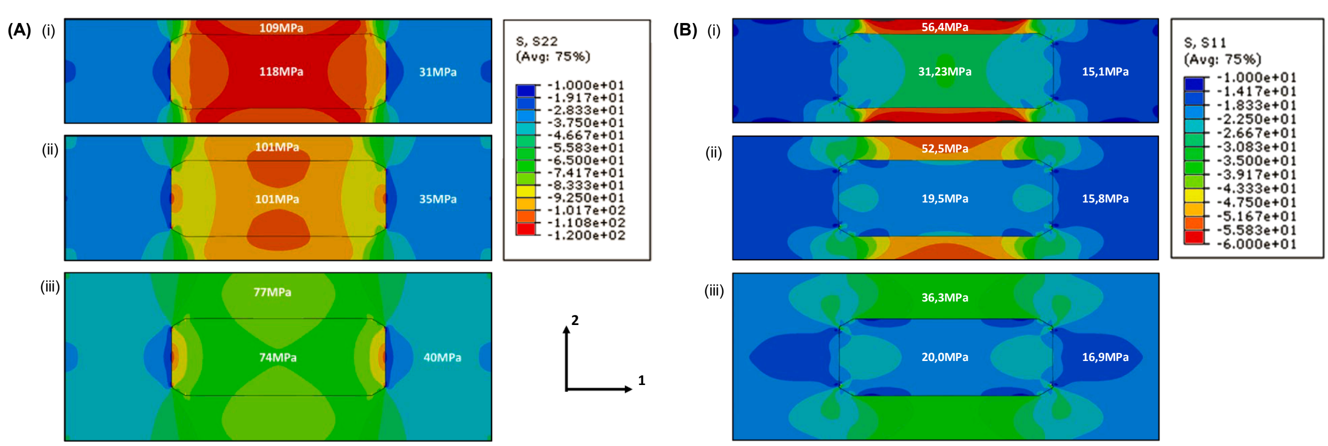

Fig. 6. Simulated axial stress (A) and radial stress (B) fields at an apparent axial pressure of 50 MPa obtained with different layer thicknesses of 0.6 mm (i) 1.0 mm (ii) and 1.8 mm (iii).

Considering the layer thickness, a small thickness, which corresponds to a high applied stress, also corresponds to a small density of the band, which will less resist to the core deformation. The two effects are thus additive. Considering the diameter, the smallest diameter, which corresponds to the highest axial stress on the core, also corresponds to the highest band density which will add resistance against the core deformation. The two effects are thus opposite in this case, and the trends are more complicated to extract.

In order to have an experimental confirmation of the simulation, it is possible to observe experimentally the density heterogeneity on the surface of press-coated tablets. Scanning Electron Microscopy (SEM) was used (TM3000, Hitachi, Tokyo, Japan) on a press-coated tablet with a

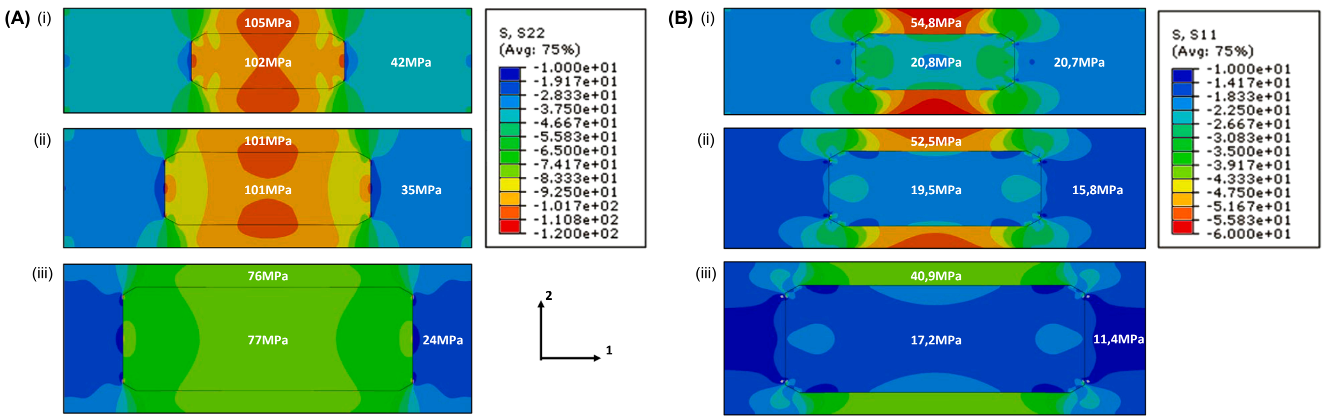

Fig. 7. Simulated axial stress (A) and radial stress (B) fields at an apparent axial pressure of 50 MPa obtained with different core diameters of 6 mm (i) 8 mm (ii) and 11.28 mm (iii).

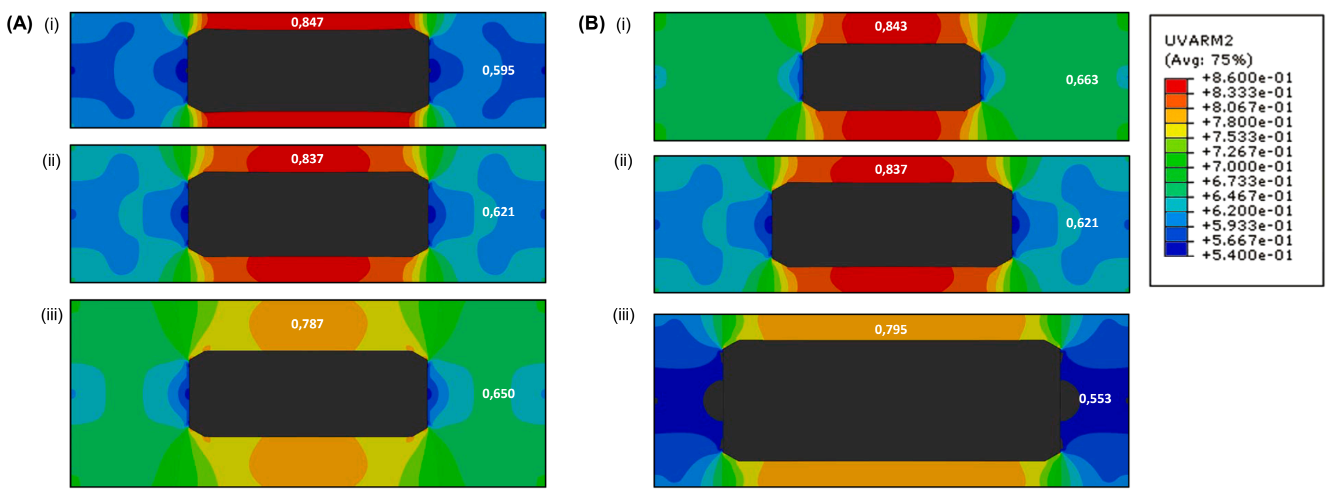

Fig. 8. Simulated relative density field at an apparent compression pressure of 50 MPa with different layer thicknesses (A) of 0.6 mm (i) 1.0 mm (ii) and 1.8 mm (iii) and with different core diameters (B) of 6 mm (i) 8 mm (ii) and 11.28 mm (iii).

MCC core of 8 mm diameter and layer thickness of 1.0 mm, compacted at a 50 MPa apparent pressure, to observe its surface porosity. The output images are shown on Fig. 9.

Both images are taken on the exact same tablet, but on regions with different densities in the simulations results: the band surface (Fig. 9A) and the layer surface (Fig. 9B). This observation confirms the high density gradient from the simulations results: the layer above the core is much denser than the band.

4.4. Consequences

The results presented above give new insights in the understanding of the compression of press-coated tablets.

The first important result presented above is that, even at very low apparent pressure, the final compression step promotes a significant change in the structure of the core, in terms of density/porosity and mechanical strength. It is well-known that these parameters play a key role in the final release profile of a tablet. As a consequence, as its structure is largely modified, the release profile of the core after press-coating might be very different from the release profile of the original core. This is an important result that should be taken into account during the development and process parameters definition. Moreover, the geometrical features of the final form, i.e. layer thickness and core diameter, have both an influence on the final properties of the core. As a consequence, they might also influence the final release profile of the core.

Of course, the release profile of a core-coated tablet is also largely influenced by the properties of the shell, in terms of density and mechanical resistance. These two parameters are of course influenced by the apparent pressure used for the final compression step. Nevertheless, as shown in Fig. 9, the density in the shell is also largely influenced by the thickness of the upper and lower layers and by the ratio between the diameter of the core and the diameter of the final tablet. These two parameters have then again an influence on the final release profile of the press-coated tablet. They should thus be considered as critical parameters during the design and development of a press-coated tablet.

The second point we would like to emphasize is related to a more fundamental understanding of the compression of powders. It is usual to characterize the compaction behavior of a powder using the compactibility, i.e. the tensile strength of a tablet as a function of the density (or porosity). There is in fact no strict bijection between density and tensile strength, i.e. it is possible to obtain different tensile strengths for the same porosity, if the compression path is different. This phenomenon is often called "path dependence" in the literature and has been demonstrated for various powders (Galen and Zavaliangos, 2005; Koerner, 1978). Usually, this phenomenon is demonstrated using triaxial compression. The case of core coating is another interesting example of the path dependence. Indeed, the triaxiality of the stress on the core is not the same as the one during closed die compaction. As a consequence, the relation between the strength of the core and its density is not the

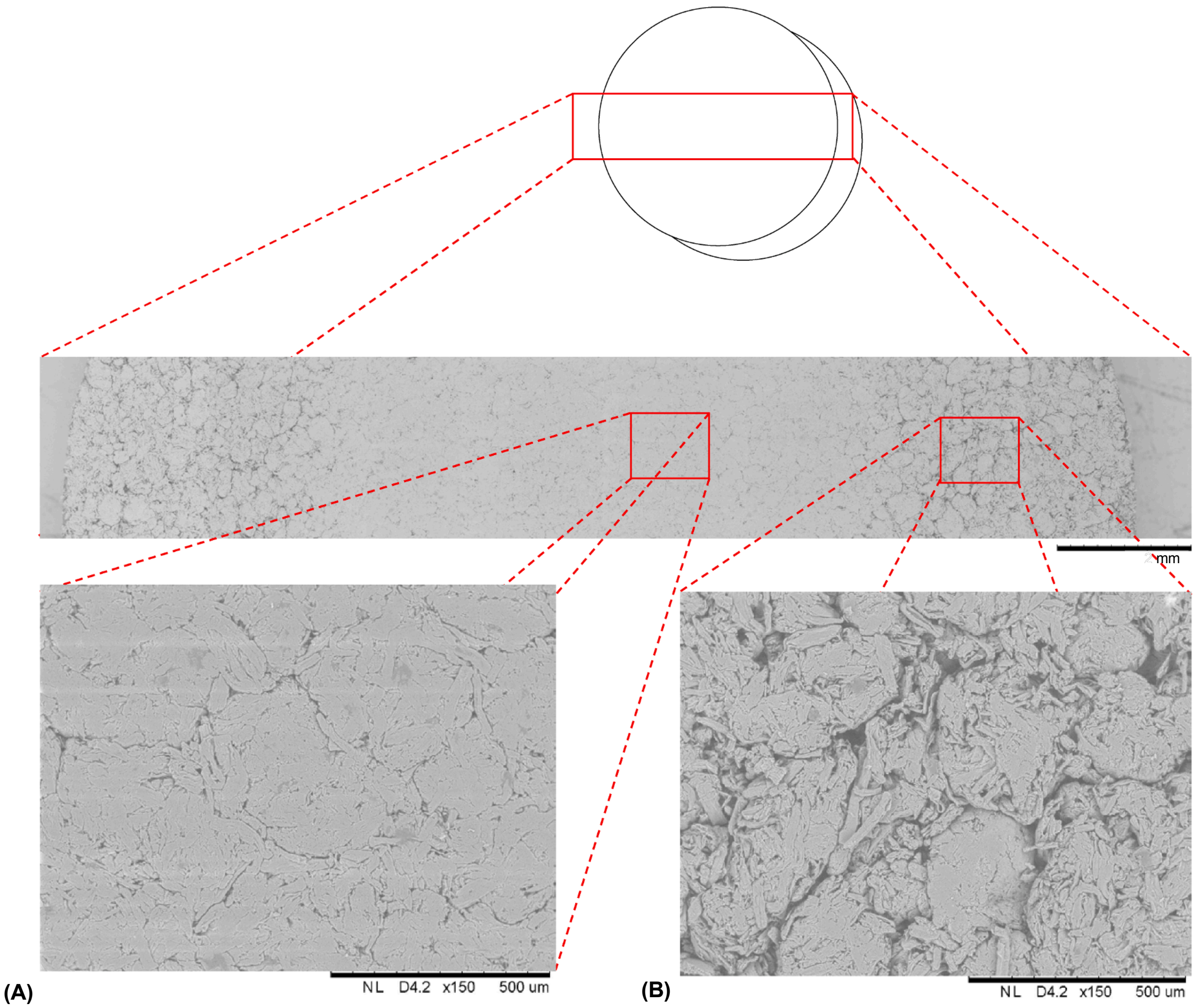

Fig. 9. SEM images of the surface of a press-coated tablet (MCC core and MCC shell; 8 mm core diameter; 1.0 mm thickness; 50 MPa apparent compression pressure) upon the center region (A) and on the band region (B).

same as in normal die compaction as it can be seen in Figs. 3 and 5. Moreover, it can be easily foreseen that the triaxiality of the stress on the core depends on the mechanical properties of the powder used in the shell. This was already used in the past in a paper (Carstensen et al., 1985) where the authors used core-coating technique with a shell composed of small polymer beads in order to obtain a different triaxiality to avoid capping. So, as the mechanical properties of the shell might influence the stress triaxiality on the core during the final compression, they will also influence the final state of the core (density, strength) and, as a consequence, its release profile. This is important to consider during the development of a press-coated tablet.

5. Conclusion

In this study, it has been highlighted that, during coating-compression, the structure of the core is modified both in terms of density and of mechanical strength. This occurs even if the final apparent pressure used is much lower than the pressure used to manufacture the core. Due to stress concentration phenomena that are peculiar to this type of compression, the physical state of the core is highly modified along the compression process. It has been shown that the layer thickness and the core-shell diameter ratio are critical parameters that influence the stress distribution and triaxiality that are specific to the press-coating. The dimensions and mechanical properties of the core after the coating-compression are thus strongly dependent on these parameters. Both shall thus be considered as critical process parameters and be taken in account in the design of press-coated tablet to reach the aimed quality attributes.

CRediT authorship contribution statement

Léo Picart: Methodology, Investigation, Writing - original draft. **Vincent Mazel:** Methodology, Conceptualization, Writing - review & editing. **Aline Moulin:** Conceptualization, Writing - review & editing. **Pierre Tchoreloff:** Conceptualization, 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.

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