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Effect of geometrical features on the capping behavior of biconvex tablets

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ABSTRACT

Capping is a common industrial issue during the manufacturing of pharmaceutical tablets. It is influenced by both process and formulation parameters. In this work, a systematic study of the influence of the geometrical features of biconvex tablets on capping occurrence was performed on a model formulation, using a design of experiment. Capping was characterized by the pressure at which half of the produced tablets were capped. The influence of the tablet geometry was assessed by varying three parameters: the diameter (D), the band thickness (W) and the ratio between the radius of curvature (R) and the diameter, i.e. R/D. Results showed that having a large diameter, a low band thickness and a high curvature (i.e. a low R/D) favored capping occurrence. Moreover, the effects are not independent as cross-effect were detected. Finally, even for homothetic tablets (i.e. same R/D and W/D) it is shown that a large diameter increases capping occurrence. These results could be used in the future as a guideline for punch selection during tablet development.

1. Introduction

Capping is a common industrial issue during the manufacturing of pharmaceutical tablets which is known for more than a century (Wood, 1906). In the case of biconvex tablets, it corresponds to the failure of one or both cups of the tablet (Alderborn, 2001). It differs from another classical tablet defect, lamination, which corresponds to a failure of the tablet with a failure plan passing through the tablet band (Alderborn, 2001; Mazel and Tchoreloff, 2021). There is a large literature dealing with capping problems, nevertheless, it is sometimes to be taken with caution as in some papers, defects called capping in fact correspond to lamination as in (Tanino et al., 1995; Osamura et al., 2018).

The occurrence of capping during the manufacturing of tablets results from a complex interaction between the product properties and the process parameters. Concerning the properties of the formulations that may influence the occurrence of capping there is no general consensus in the literature. As an example, a high residual die wall pressure is often cited as a factor that favors the occurrence of capping (Hiestand et al., 1977; Sugimori et al., 1989; Sugimori and Kawashima, 1997) but other authors presented inverse trends (Paul and Sun, 2017). Parameters like low plastic energy during the cycle have also be found to correlate well with capping occurrence (Nakamura et al., 2012; Meynard et al., 2022a). Nevertheless, there is for the moment no definitive approach to predict capping based on the formulation properties and capping prediction remains a complex challenge (Meynard et al., 2022a).

Concerning the process parameters, some of them are clearly identified as factors that promote capping. The first one is the applied pressure as it is well-known that capping increases along with the compaction pressure (Ritter and Sucker, 1980; Akseli et al., 2014; Meynard et al., 2022b). The compaction speed is also known to have a great influence on capping (Ritter and Sucker, 1980; Garr and Rubinstein, 1991; Sarkar et al., 2015; Meynard et al., 2022b). Precompression is also an important parameter when capping occurs as it can be used to suppress it, even if the mechanism behind this mitigation is still not well understood (Mann et al., 1982; Vezin et al., 1983; Mazel and Tchoreloff, 2020).

Another important factor in the occurrence of tablet capping is the tablet shape. Nevertheless, there are not so many articles in the literature that tried to completely understand this link, especially in the case of biconvex tablets. Desai et al. studied the case of flat faced bevel edge (FFBE) and flat faced round edge tablets (FFRE) showing that FFRE led to lesser capping than FFBE. In a study on flat faced tablets, Ritter and Sucker showed that capping increased with tablet thickness (Ritter and Sucker, 1980). This is in contradiction with the results presented by Sugimori and Kawashima who wrote that capping tendency increase with the ratio between Tv (thickness of the flat tablet having the same volume as the convex faced tablet) and the band thickness of the convex faced tablet (Sugimori and Kawashima, 1997). For tablets with a

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constant diameter and curvature radius, this ratio decreases when the band thickness increases, meaning that increasing the band thickness should decrease the capping tendency. Using the same ratio, it can also be deducted that increasing the radius of curvature will favor tablet capping as it is generally known from the common practice (Sixsmith and Mccluskey, 1981; Sugimori and Kawashima, 1997; Gad, 2008). This was recently confirmed (Patel et al., 2023).

A biconvex tablet can be described from a geometrical point of view by 4 geometrical features as described in Fig. 1: diameter (*D*), total thickness (*T*), band thickness (*W*) and radius of curvature (*R*) (Note that here the land of the tablet is neglected for the sake of simplification). Nevertheless, only three of them are independent as, for example, the total thickness can be expressed as a function of the other variables as follows:

$$T = W + 2\left(R - \sqrt{R^2 - \left(\frac{D}{2}\right)^2}\right) \tag{1}$$

If the land of the tablet *l* is taken into account, the variable *D* in Equation (1) must be replaced by (*D-l*). In order to compare punches of different sizes and shapes, instead of using *R*, the variable *R/D* is often used and the punches are generally classified as standard ($R/D = 1$), shallow ($R/D > 1$) or deep ($R/D < 1$) (Bauer-Brandl, 2015). As a consequence, the geometry of the tablet can be described using the three following variables: *R/D*, *D* and *W*.

As only the influence of R/D seems to have been consistently studied in the literature, the aim of the present paper is to present a systematic study of the influence of these three parameters as well as their interaction on the capping behavior of a model formulation.

2. Material and methods

2.1. Powders

The study was performed on a formulation chosen for its capping tendency. The products used were: micronized Paracetamol “Para” (Novacyl, Lyon, France), Microcrystalline cellulose “MCC” (Vivapur 12, JRS Pharma, Rosenberg, Bade-Wurtemberg, Germany), granulated lactose monohydrate “MLac” (SuperTab 30GR, DFE Pharma, Goch, Nordrhein-Westfalen, Germany), sodium crosscaramellose “CCNa” (Vivasol, JRS Pharma, Rosenberg, Bade-Wurtemberg, Germany), and magnesium stearate “MgSt” (Ligamed MF-2-V, Peter Greven, Bad Münstereifel, Nordrhein-Westfalen, Germany). The formulation prepared contained (%w/w): 20% Para, 49% MLac, 25% MCC, 5% CCNa, 1% MgSt.

Batches of 1.5 kg were prepared using a Turbula Mixer T10B with a container of 5 L (Willy A. Bachofen, Muttenz, Switzerland) at 32 rpm. First Para, MCC and MLac were premixed for 10 min, then CCNA and MgSt were added and mixed for an additional 5 min.

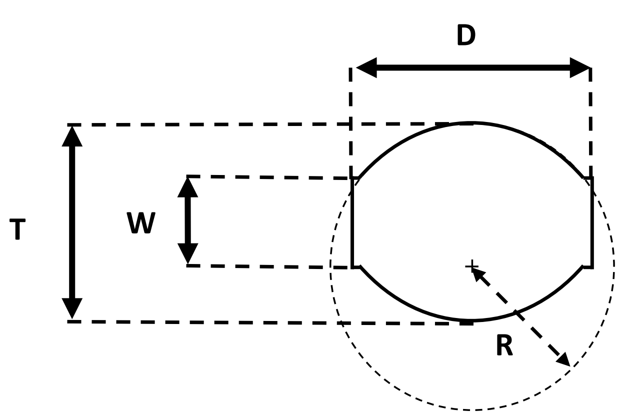

Fig. 1. Geometrical features of a biconvex tablet. *T*: total thickness, *W*: band thickness, *D*: diameter, *R*: radius of curvature.

2.2. Tablet manufacturing

All the tablets were made on a compaction simulator Stylcam (Medelpharm, Beynost, France). The profile was set to simulate a Fette P1200 at a rotation speed of 60 RPM. Several sets of punches were used. For each punch the classical naming XRY will be used with X the punch diameter and Y its radius of curvature. The punch used were the following:

- 4 standard punches ($R/D = 1$): 8R8, 10R10, 11R11 and 12R12
- 3 shallow punches ($R/D = 1.25$): 8R12, 10R15 and 12R18
- 3 deep punches ($R/D = 0.75$): 8R6, 10R7.5 and 12R9.

To study the influence of the band thickness, the mass was adapted for each punch set to obtain, under a compaction pressure of 150 MPa, a target band thickness (*W*) of: 1.7 mm, 2.6 mm or 3.7 mm. For each batch of tablets produced, three tablets obtained at 150 MPa were taken for band thickness measurement under an optical binocular (Meiji Techno, Chikumazawa, Japan) equipped with a digital camera Invenio-3SII (Deltapix, Hassellunden, Denmark). The mean value of the three tablets was taken as the final band thickness value for the batch.

2.3. Capping quantification

The capping quantification of a set of tablets (i.e. 1 set of punches, 1 mass and 1 pressure) was performed, on 10 tablets as described elsewhere (Meynard et al., 2022b). A first macroscopic examination of the tablets after manufacturing was made in order to detect capping. A tablet with one or both of its cups coming off after manufacturing was considered as capped. If no capping was visible, tablets were then broken using the diametral compression test (ST 50, Sotax, Saint Louis, France). A tablet presenting one or both of its cups coming off during the diametral compression test was also considered as capped. In some cases, it was necessary to pull gently on the cup to see capping. In these cases, the tablet was also considered as capped. For a batch, the capping behavior was quantified by a parameter called capping index (CI) corresponding to the total number of tablets presenting capping defects (after ejection and after diametral testing) among the 10 produced tablets (in %).

2.4. Design of experiment and statistical analysis

To test the effect of the variables *R/D*, *W* and *D* on the capping tendency, a design of experiment was performed. A full factorial design was used with two levels for *R/D* (0.75 and 1.5), two levels for *W* (1.7 and 3.7 mm, value measured for a compaction pressure of 150 MPa) and 3 levels for *D* (8, 10 and 12 mm). This resulted in 12 sets of experiments. 4 additional points were performed with $R/D = 1$ (using 11R11 and 10R10 punches). The complete list of experiments is given in Table 1. The response chosen was the pressure at which 50% of the tablets were cap (*P50*). The reason for this choice and the way this pressure was determined is explained below in the first part of the results.

The statistical analysis of the results was performed using the software MODDE (Umetrics, Malmö, Sweden). The relationship between the factors and the response was obtained by fitting with MLR (multiple linear regressions). First, the complete equation containing all the single and interaction terms was used in order to identify the significant terms. As 3 levels were used for D, the term D^2 was also included in the model. The model parameters were considered as significant if their p value was lower than 0.05 (confidence level of 95%). Then, the insignificant parameters were removed and the final model was built. The quality of the final model was evaluated with a summary of the fit method which included the goodness of fit(R^2) and the goodness of prediction (Q^2). The model was considered good (goodness of fit and goodness of prediction)

Table 1
Values of the different factors used for the DOE and the response obtained.

Factors			Response
D (mm)	W (mm)	R/D	P50 (MPa)
8	1.69	0.75	140
12	1.70	0.75	58
10	1.74	1.5	99
10	1.74	0.75	88
10	1.74	1	88
12	1.77	1.5	70
8	1.78	1.5	153
11	2.65	1	106
10	2.66	1	121
8	3.56	0.75	161
8	3.57	1.5	220
12	3.64	0.75	112
10	3.67	1	141
10	3.72	1.5	182
10	3.72	0.75	133
12	3.72	1.5	159

if the difference R^2-Q^2 was lower than 0.2, Q^2 was higher than 0.5 (Eriksson et al., 2013).

3. Results and discussion

3.1. Preliminary results and choice of the response for the DOE

In order to run the design of experiment, it was necessary to choose a response that was quantitative but also that had values that are not limited in the high or low range. For example, the capping index at one compaction pressure could not be used as a response as it would give, for example, the same response to all the case without capping at this pressure, without being able to classify these different cases. We therefore chose a different approach inspired by works performed previously on lamination and capping (Mann et al., 1982; Mazel et al., 2015a). If changing one of the parameters (e.g. punch curvature) is favorable to mitigate capping, it should be seen that the pressure at which capping begins increases. So, the pressure at which capping happens could be a good indicator of the influence of the parameters on capping. To verify this point, a preliminary experiment was performed by studying the influence of the punch curvature at a constant tablet diameter (10 mm) and tablet band thickness (around 2.7 mm at 150 MPa). This parameter was chosen because, as said above, it is known that when the radius of curvature decreases, capping propensity should increase. The capping index was determined as a function of the compaction pressure for three different punch curvature (7.5,10 and 15 mm) and the results are presented in Fig. 2.

The results show clearly the expected trend, i.e. when the radius of curvature increases (i.e. the curvature decreases), capping appears at a higher pressure. This means that this methodology is suitable to classify

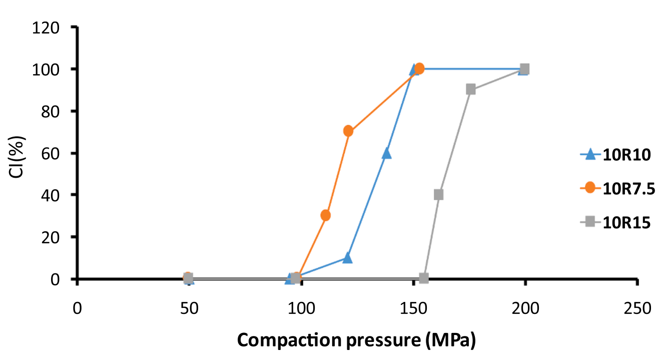

Fig. 2. Evolution of the capping index (CI) as a function of the compaction pressure for *W* = 2.7 mm, *D* = 10 mm and three punch curvatures.

capping situations. It is also interesting to note that CI goes rapidly from 0 to 100%, i.e. in less than 50 MPa, and that the curves look like a S-shaped curve. Knowing this, it was necessary to make a choice about which pressure to choose to represent the capping behavior of one experiment. Considering the S-shape of the curve and in order to limit the uncertainty on the results, it was logical to choose the pressure at which the slope is maximum, i.e. around CI = 50%.

So the final methodology was the following. The capping index was determined as a function of the pressure. It would have been very complicated to find, for each configuration a pressure where CI was exactly 50%. So instead, by using pressure step of 12.5 MPa (lower step size was complicated considering the variability during filling), the pressure domain was explored to find a pressure where CI was between 0 and 50 % and a pressure where it was between 50% and 100%. A linear interpolation between these two pressures on the graph P as a function of CI was then performed. The obtained equation was then utilized to calculate P50 with CI set to 50. For each case presented below it was found that the difference between the two pressures corresponded to the step size (i.e. 12.5 MPa). This means that the precision on *P50* is around ± 5 MPa. The results for *P50* are presented in Table 1.

3.2. Results of the DOE

Using the methodology described in the previous paragraph, the DOE described in part 2.4. was performed and the results from Table 1 were statistically analyzed. The results for the significant effects are presented in Fig. 3. For a better visualization of the results, contour pots are presented in Fig. 4.

The performance of the model can be judged using the values of R^2 and Q^2. Using the model with the coefficient presented in Fig. 3, we obtained $R^2 = 0.997$ and $Q^2 = 0.979$. As said above, this means that the model is well suited to represent the data. As a consequence, the effect of the different parameters can be assessed using this model.

These results make it possible to understand the effect of the different variables. First, *W*, *R/D* and *D* have a significant effect on *P50*. As expected and already seen in Figure 2, P50 decreases when *R/D* decreases, which means a high curvature promotes capping as it is already known from practical experience. If this point is not new, it shows that the methodology chosen gives consistent results. *W* has also an important effect on P50. If *W* increases, then *P50* also increases. This means that having a small band thickness promotes capping occurrence. Finally, the effect of *D* can also be seen very clearly in Fig. 4. When the diameter of the tablet increases, *P50* decreases, meaning that tablets with a large diameter are more prone to cap.

The results also show cross effects between *R/D* and *W* and between *D* and *W*. From the results in Fig. 3, the most important cross effect is the one between *R/D* and *W*. It shows that the effect of the curvature (*R/D*) on capping is more important when *W* has a large value. This can be seen clearly in Fig. 4. On the contour plot for *W* = 1.7 mm, the *iso*-value lines are nearly vertical, meaning that the effect of *R/D* (which is on the vertical axis) is very limited in this case. This is not the case at *W* = 3.7 mm. To take an example, at *D* = 8 mm and *W* = 1.7 mm, the model gives *P50* = 139 MPa at *R/D* = 0.75 (deep punches) and *P50* = 149 MPa at *R/D* = 1.5 (shallow) (+7.2%). At *D* = 8 and *W* = 3.7 mm, the models gives *P50* = 169 MPa for *R/D* = 0.75 and *P50* = 220 MPa for *R/D* = 1.5 (+17.8%).

Another cross-effect is obtained between *W* and *D*. It shows that the effect of the band thickness is more important when the diameter is high. To illustrate this point, we can choose the case *R/D* = 1 (standard curvature). When *D* = 8 mm, then *P50* = 143 MPa for *W* = 1.7 mm and *P50* = 186 MPa when *W* = 3.7 mm (+30%). When *D* = 12 mm, the model gives *P50* = 61 MPa for *W* = 1.7 mm and *P50* = 128 MPa for *W* = 3.7 mm (+110%).

The results presented above are clear about the effect of the different parameters. Nevertheless, one could wonder if the effect of *D* and *W* are really uncorrelated. It could for example be imagined that two tablets of

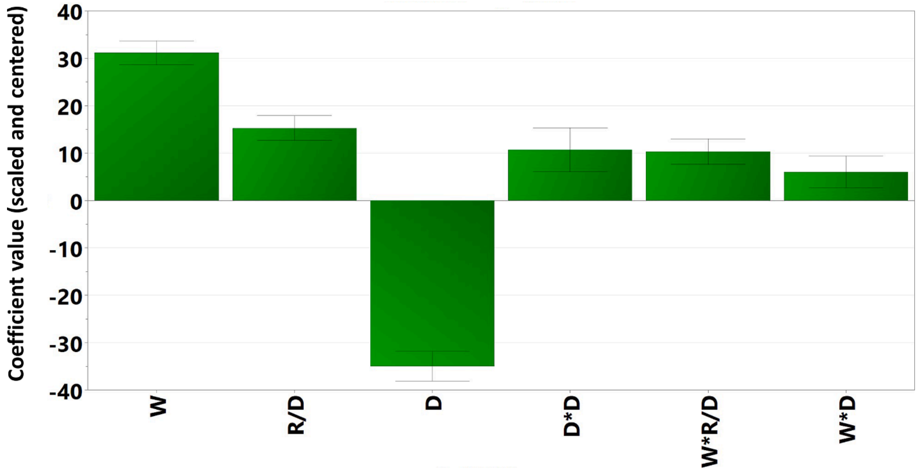

Fig. 3. Statistical analysis of the results: values of the coefficients of the model associated to each factor.

different sizes but with the same proportions (i.e. with homothetic dimensions) could have the same behavior. This would mean that tablets having at the same time the same R/D and W/D, even with different W and D, would have the same $P50$. From a mathematical point of view, it would mean that on a graph P50 as a function of W/D, all the points should fall on the same curve whatever the diameter. The curve $P50$ as a function of W/D can be drawn from the model developed above for the three diameters used. The case of $R/D = 0.75$ was chosen. In order to use points that could be interpolate inside the domain studied, the values of W used were kept between 1.7 and 3.7 mm. Results are presented in Fig. 5. It is clear that the curves for the different diameters do not overlap. For a constant R/D and W/D (i.e. homothetic tablets which correspond to a vertical line on the graph), P50 increases when the diameter decreases. This means that even for homothetic tablets, increasing the diameter favors the occurrence of capping.

To provide an experimental example of this phenomenon, a complementary experiment was performed using tablets with $R/D = 1$, $W/D = 0.23$ and, $D = 8$ and 12 mm. The complete curve of CI as a function of the compaction pressure for the two sets of tablets in presented in Fig. 6. As expected, the pressure range where capping begins is higher for the tablet with a diameter of 8 mm than for the tablets with a diameter of 12 mm. This confirms the trend observed above, i.e. the size effect observed for W and D cannot be reduced to an effect of W/D. As a consequence, for a given formulation, homothetic tablets of different diameters will not have the same capping behavior.

3.3. Discussion

The results presented in part 3.2 clearly gave the influence of each parameter on capping. In order to mitigate capping, curvature should be low, band thickness high and diameter low. Moreover, the effects of W and D cannot be reduced to a single one as even if the ratio W/D is taken constant together with R/D (i.e. homothetic tablets), the capping behavior still depends on D.

In order to explain these results, it is important to consider the mechanism that leads to capping. This mechanism can be found in the literature (Hiestand et al., 1977; Wu et al., 2008; Mazel et al., 2015b). At the end of the unloading part of the compaction cycle, a shear stress appears at the limit between the land of the tablet and the cup. This shear stress is due to the fact the cup can expand radially during unloading contrary to the band. Moreover, this stress is fairly concentrated. Considering this mechanism it seems logical to consider that the residual die-wall pressure (RDP), which is the pressure acting on the band at the end of the unloading might impact the value of the shear stress and, as a consequence, the capping behavior (Sugimori et al., 1989). This is coherent with recent results showing that, in some cases, capping is favored by a high in die elastic recovery together with a high residual die-wall pressure (Meynard et al., 2022a).

Based on this mechanism it is possible to try to interpret the experimental trends found. First the effect of the curvature was expected considering the literature (Sixsmith and Mccluskey, 1981; Sugimori and Kawashima, 1997; Gad, 2008; Patel et al., 2023). When the curvature increases, there is more material in the cup and it can be foreseen that this might increase the elastic recovery of the cup. Moreover, increasing the curvature also increases the RDP (Sugimori et al., 1989). Numerical results published by Wu et al. seem to confirm that, as a consequence, increasing the curvature promote an increase of the shear stress (Wu et al., 2008). It is thus logical that this increases also the capping tendency.

The effect of the band thickness is more complex. It was demonstrated before that, contrary to the case of flat tablets, changing the band thickness of a biconvex tablet (while keeping R/D and D constant) has both an effect on the residual die-wall pressure (Sugimori and Kawashima, 1997) and on the density distribution inside the tablet (Diarra et al., 2015). When the band thickness decreases, RDP increases and the density distribution inside the tablet becomes more heterogeneous. The increase of the RDP points toward the increase of capping tendency. The role of the density distribution is more difficult to interpret even if it is mentioned in the literature that heterogeneity in the density distribution might be associated with an increase in defect propensity (Kadiri and Michrafy, 2013). It has to be noted that the effect found in the present work is in contradiction with the one found by Ritter and Sucker (Ritter and Sucker, 1980). Reasons for this discrepancy is difficult to understand, and the lack of experimental details in the cited reference does not make it possible to study this point in details.

Finally, the effect of diameter is of particular interest and was, to our knowledge, never cited in the literature. Interestingly, it was found that even for homothetic tablets (i.e. same R/D and W/D), a large diameter increases the capping propensity. The most probable explanation is linked with the concentration of the shear stress that promote the failure. The cases of failure under a concentrated stress are strongly influenced by the extent of the region submitted to the high stress. A practical case for the pharmaceutical tablets can be found in the example of the diametral compression test performed on tablets presenting a hole at the center (Croquelois et al., 2017). When such a tablet is submitted to diametral compression, a stress concentration can be found at the hole edge. If the diameter of the hole is small enough compared to the tablet size, it has no influence on the maximum value of the stress. Nevertheless, it changes the size of the zone in the tablet submitted to high stresses. As increasing the hole size enlarge the zone under stress, it promotes a decrease of the force needed to break the tablet (i.e. the tablet appears to be weaker). This can be seen as a Weibull effect. This

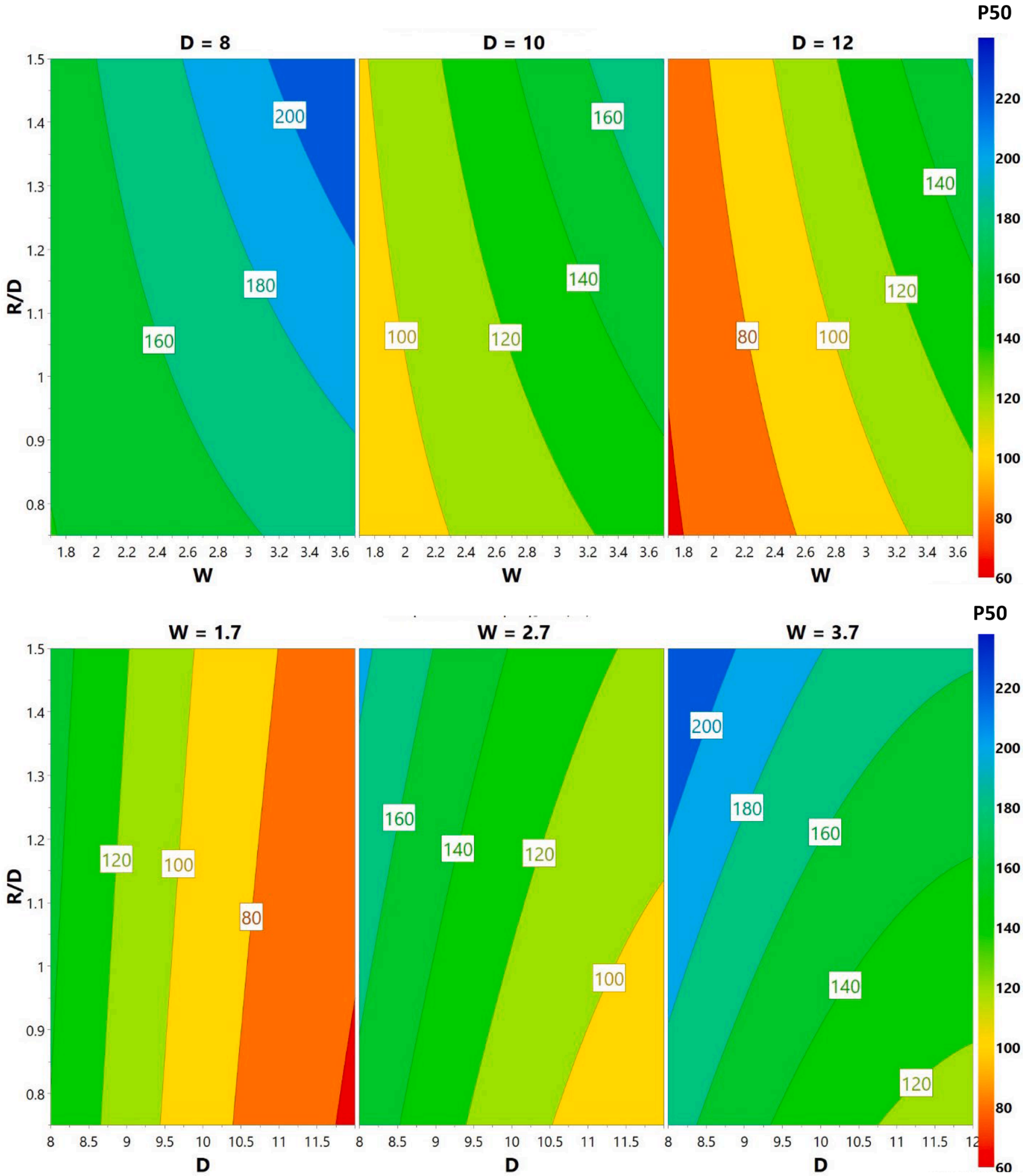

Fig. 4. Contour plots obtained for *P50* according to the statistical analysis.

effect makes it possible to explain what happens when comparing two homothetic tablets of different diameters. The stresses obtained during compaction for both cases will be identical and distributed in homothetic distributions. As a consequence, the zone submitted to a high stress will also be homothetic. This means that, for the tablet with the higher diameter, the zone submitted to the high shear stress will be larger (in absolute value) than the one in the tablet with the smaller diameter (even if the ratio between the size of the zone and the diameter is constant). As a consequence, the tablet with the large diameter will break more easily (i.e at a lower stress) than the tablet with the small diameter as demonstrated in the results above. This explains the decrease of *P50*.

4. Conclusion

In this work, we presented a systematic approach to assess the effect of the geometrical features of biconvex tablet on their capping tendency. It was found that increasing the curvature, decreasing the band thickness and increasing the tablet diameter were facts that increased the capping propensity by decreasing the pressure at which capping happened for a given formulation. Interestingly, for cases studied in this paper, *P50* (pressure at which half of the tablets are capped) could vary from 58 MPa to 220 MPa, depending on the parameters chosen. Moreover, there are cross-effects between the parameters, meaning, for example, the effect of curvature is more important when the tablet has a high band thickness.

These results have different practical consequences. First, in the industrial context, they can be used as a guideline for punch selection. Indeed, the mass of the tablet is generally fixed before punch selection. But for a fix tablet mass, effect of changing one geometrical feature (R/D or D) generally has a cumulative effect. For example, increasing the curvature at constant diameter will promote a decrease in tablet band

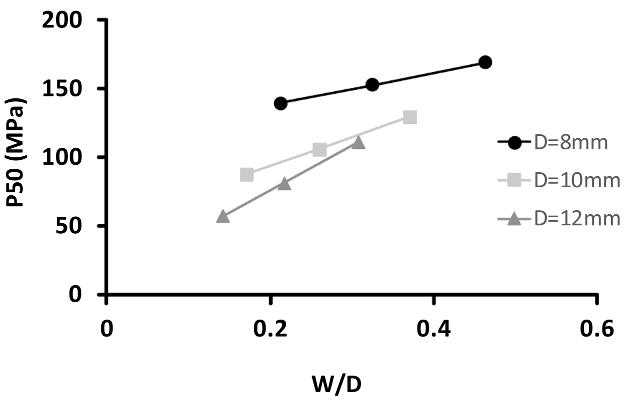

Fig. 5. Evolution of *P50* as a function of *W/D* for the case $R/D = 0.75$. All the points were calculated using the model obtain in the DOE.

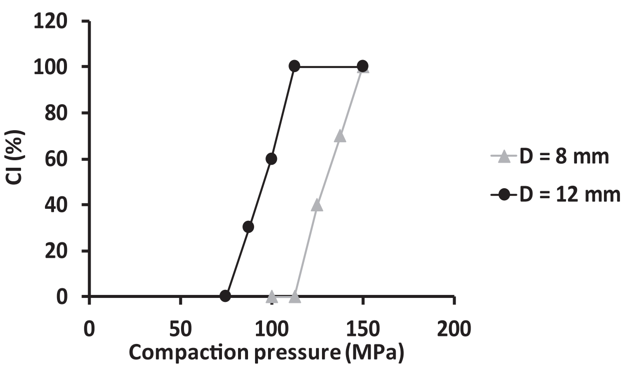

Fig. 6. Experimental evolution of CI as a function of the compaction pressure in the case of $R/D = 1$ and $W/D = 0.23$.

thickness and as such it adds two deleterious effects. On the contrary, at a constant R/D, decreasing the tablet diameter will increase the band thickness and both effect can help mitigating capping.

It is also often possible to have for the same formulation two different tablet sizes in order to have different dosages or for a pediatric adaptation. The results presented here shows that it could be possible to have more capping on the large size than on the small one even with the same formulation. This has to be kept in mind when developing this kind of products.

CRediT authorship contribution statement

Vincent Mazel: Methodology, Investigation, Conceptualization, Writing – original draft. **Cléo Garcia:** Investigation. **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.

References

Akseli, I., Stecuła, A., He, X., Ladyzhynsky, N., 2014. Quantitative Correlation of the Effect of Process Conditions on the Capping Tendencies of Tablet Formulations. J. Pharm. Sci. 103, 1652–1663. https://doi.org/10.1002/jps.23951.

Alderborn, G., 2001. Tablets and compaction, in: Aulton's Pharmaceutics: The Design and Manufacture of Medicines. Churchill Livingstone, London.

Bauer-Brandl, A., 2015. Tooling for Tableting, in: Encyclopedia of Pharmaceutical Science and Technology, Six Volume Set (Print). CRC Press.

Croquelois, B., Girardot, J., Kopp, J.B., Cazautets, C., Tchoreloff, P., Mazel, V., 2017. Breaking pharmaceutical tablets with a hole: Reevaluation of the stress concentration factor and influence of the hole size. Powder Technol. 317, 126–132.

Diarra, H., Mazel, V., Busignies, V., Tchoreloff, P., 2015. Investigating the effect of tablet thickness and punch curvature on density distribution using finite elements method. Int. J. Pharm. 493 (1-2), 121–128.

Eriksson, L., Byrne, T., Johansson, E., Trygg, J., Vikström, C., 2013. Multi- and Megavariate Data Analysis Basic Principles and Applications. Umetrics Academy.

Gad, S.C., 2008. Pharmaceutical manufacturing handbook: production and processes. John Wiley & Sons.

Garr, J.S.M., Rubinstein, M.H., 1991. An investigation into the capping of paracetamol at increasing speeds of compression. Int. J. Pharm. 72 (2), 117–122.

Hiestand, E.N., Wells, J.E., Peot, C.B., Ochs, J.F., 1977. Physical processes of tableting. J. Pharm. Sci. 66 (4), 510–519.

Kadiri, M.S., Michrafy, A., 2013. The effect of punch's shape on die compaction of pharmaceutical powders. Powder Technol. 239, 467–477.

Mann, S.C., Roberts, R.J., Rowe, R.C., Hunter, B.M., 1982. The Influence of Precompression Pressure on Capping. J. Pharm. Pharmacol. 34, 49P–P.

Mazel, V., Tchoreloff, P., 2021. Lamination of Pharmaceutical Tablets: Classification and Influence of Process Parameters. J. Pharm. Sci. 111 (5), 1480–1485.

Mazel, V., Busignies, V., Diarra, H., Tchoreloff, P., 2015a. Lamination of pharmaceutical tablets due to air entrapment: direct visualization and influence of the compact thickness. Int. J. Pharm. 478 (2), 702–704.

Mazel, V., Diarra, H., Busignies, V., Tchoreloff, P., 2015b. Evolution of the Die-Wall Pressure during the Compression of Biconvex Tablets: Experimental Results and Comparison with FEM Simulation. J. Pharm. Sci. 104, 4339–4344. https://doi.org/10.1002/jps.24682.

Mazel, V., Tchoreloff, P., 2020. Role of Precompression in the Mitigation of Capping: A Case Study. J. Pharma. Sci 109, 3210–3213. https://doi.org/10.1016/j.xphs.2020.07.021.

Meynard, J., Amado-Becker, F., Tchoreloff, P., Mazel, V., 2022a. On the complexity of predicting tablet capping. Int. J. Pharm. 623, 121949 https://doi.org/10.1016/j.ijpharm.2022.121949.

Meynard, J., Amado-Becker, F., Tchoreloff, P., Mazel, V., 2022b. Impact of unloading kinematics on the occurrence of capping during the production of pharmaceutical tablets. Int. J. Pharm. 621, 121818 https://doi.org/10.1016/j.ijpharm.2022.121818.

Nakamura, H., Sugino, Y., Watano, S., 2012. In-Die Evaluation of Capping Tendency of Pharmaceutical Tablets Using Force-Displacement Curve and Stress Relaxation Parameter. Chem Pharm Bull Tokyo 60, 772–777. https://doi.org/10.1248/cpb.60.772.

Osamura, T., Takeuchi, Y., Onodera, R., Kitamura, M., Takahashi, Y., Tahara, K., Takeuchi, H., 2018. Formulation design of granules prepared by wet granulation method using a multi-functional single-punch tablet press to avoid tableting failures. Asian J. Pharm. Sci. 13, 113–119. https://doi.org/10.1016/j.ajps.2017.08.002.

Patel, V.D., Patel, D.B., Sturgis, J.C., Queensen, K., Sedlock, R., Haware, R.V., 2023. Assessing the Impact of Punch Geometries on Tablet Capping Using a Newly Proposed Capping Index. Pharm. Res. https://doi.org/10.1007/s11095-023-03555-4.

Paul, S., Sun, C.C., 2017. Gaining insight into tablet capping tendency from compaction simulation. Int. J. Pharm. 524 (1-2), 111–120.

Ritter, A., Sucker, H.B., 1980. Studies of variables that affect tablet capping. Pharm. Technol. 4, 56–65.

Sarkar, S., Ooi, S.M., Liew, C.V., Heng, P.W.S., 2015. Influence of Rate of Force Application During Compression on Tablet Capping. J. Pharm. Sci. 104 (4), 1319–1327.

Sixsmith, D., Mccluskey, D., 1981. The effect of punch tip geometry on powder movement during the tableting process. J. Pharm. Pharmacol. 33, 79–81. https://doi.org/10.1111/j.2042-7158.1981.tb13715.x.

Sugimori, K., Kawashima, Y., 1997. A new practical index to predict capping occurring during the tableting process. Eur. J. Pharm. Biopharm. 44, 323–326. https://doi.org/10.1016/S0939-6411(97)00131-8.

Sugimori, K., Mori, S., Kawashima, Y., 1989. Characterization of die wall pressure to predict capping of flat- or convex-faced drug tablets of various sizes. Powder Technol. 58 (4), 259–264.

Tanino, T., Aoki, Y., Furuya, Y., Sato, K., Takeda, T., Mizuta, T., 1995. Occurence of capping due to insufficient air escape during tablet compression and a method to prevent it. Chem. Pharm. Bull. (Tokyo) 43, 1772–1779.

Vezin, W.R., Pang, H.M., Khan, K.A., Malkowska, S., 1983. The effect of precompression in a rotary machine on tablet strength. Drug Dev. Ind. Pharm. 9, 1465–1474. https://doi.org/10.3109/03639048309052388.

Wood, J.R., 1906. Tablet Manufacture: Its History. Pharmacy and Practice, JB Lippincott Company.

Wu, C.-Y., Hancock, B.C., Mills, A., Bentham, A.C., Best, S.M., Elliott, J.A., 2008. Numerical and experimental investigation of capping mechanisms during pharmaceutical tablet compaction. Powder Technol. 181 (2), 121–129.