Impact of unloading kinematics on the occurrence of capping during the production of pharmaceutical tablets

J. Meynard[a], F. Amado-Becker[b], P. Tchoreloff[a], V. Mazel[a,*]

[a] Univ. Bordeaux, CNRS, Arts et Metiers Institute of Technology, Bordeaux INP, INRAE, I2M Bordeaux, F-33400 Talence, France
[b] Research and Development Division, F. Hoffmann-La Roche AG, Basel, Switzerland

ABSTRACT

Capping is a common defect that can occur during the manufacturing of pharmaceutical tablets. Several studies showed that decreasing the unloading speed of the manufacturing cycle plays a role in the occurrence of such defects. Following this idea, we study in this work the influence of the unloading step on capping using a compaction simulator.

Measuring the die wall pressure made it possible to detect precisely that tablets capped just after the unloading (some milliseconds only). To evaluate the impact of the unloading speed on capping, we developed a two-step unloading phase controlled by three manufacturing parameters. It was possible to mitigate capping by decreasing the speed at which the contact between the punches and the tablet was lost. Capping seemed due to dynamical effects related to the release of the axial pressure. The modification of the unloading step to mitigate capping led to significant changes in tablet density but no clear trends were found for the residual die-wall pressure and tablet strength.

This work made it possible to improve the understanding of capping. Moreover, the two-step unloading cycle gave a new idea for possible modifications that could be done on rotary presses in order to mitigate capping.

1. Introduction

Capping is a classical problem that can occur during the production of pharmaceutical tablets. It corresponds to a specific kind of failure pattern of the tablet, which is usually observed on a tablet after its ejection from the die. In the case of a biconvex tablet, which is the form that is the most prone to capping, it can be described as the separation of one or both cups from the tablet body (Alderborn, 2001). It should not be confused with lamination, which is another kind of tablet defect, but with failure planes passing through the tablet band (Alderborn, 2001). Even if capping is known for more than a century (Wood, 1906), its mitigation can still be challenging today.

The mechanism of capping is well described in the literature. At the very end of the unloading part of the compaction cycle, due to the elastic recovery of the cup and to the presence of the residual die wall pressure, a highly localized shear stress develops at the limit between the land and the cup of the tablet and this shear stress can, in some cases, promote the failure of the tablet (Hiestand et al., 1977; Mazel et al., 2015; Wu et al., 2008). This mechanism was confirmed recently by showing that if the unloading part of the cycle was modified in such a way that the shear stress cannot occur, capping disappeared (Mazel et al., 2019).

As any breakage event, capping corresponds to a balance between the strength of the material and the stresses present in its structure. Tablet strength is generally characterized by the tensile strength measured by diametral compression (Fell and Newton, 1970) but other parameters might also be of interest like the brittle fracture index (BFI) (Hiestand et al., 1977), the shear strength (Mazel et al., 2017) or the strength anisotropy (Nyström et al., 1978). The final stress distribution inside the tablet is mainly determined by the residual die-wall pressure, tablet elastic behavior (through its elastic recovery and moduli of elasticity) and also by the viscoelastic nature of the product (i.e. extent of time-dependent elastic deformation under applied stress). In order to avoid capping, one should try to increase the material strength and/or to decrease the internal stresses at the end of the unloading. To do so, the first option is to adapt the powder formulation by choosing other components and/or by changing the proportions of each product in the formulation. The second option is to modify the manufacturing conditions. It is thus possible to manufacture capping-free tablets by modifying the compaction cycle itself, e.g. using the concept of loaded ejection (Funakoshi, 1975; Funakoshi et al., 1969; Mazel et al., 2019) or

---

* Corresponding author at: Université de Bordeaux, CNRS, I2M Bordeaux, 146 rue Léo Saignat, F-33000 Bordeaux, France.
E-mail address: vincent.mazel@u-bordeaux.fr (V. Mazel).

even by modifying the machine itself for example by using flexible die-walls (Amidon et al., 1981). In this work, we will focus on possible modifications of the compaction cycle in order to prevent capping.

For a given compaction cycle, the three main process parameters that are known to affect capping are the compaction pressure, the use of a precompression and the tableting speed. It is well-known that capping is more likely to occur at high compaction pressures. In fact, even if increasing the pressure both increases the material strength and its residual stresses, at some point, the increase of tablet strength might not counterbalance the increase of the residual stresses. Moreover, increasing the compaction pressure leads to a decrease of tablet porosity which increases the brittle fracture index of the formulation which may lead to an increase of capping occurrence (Croquelois et al., 2020; Hiestand et al., 1977).

The use of a precompression step is also an important tooling in the mitigation of capping but the phenomena responsible for this mitigation are still not clear from the literature. Some authors claim that the effect of precompression on capping comes from the removal of air from the formulation (Mann et al., 1982, 1981; Peeters et al., 2018; Swarbrick, 2006). Nevertheless, there are no convincing proofs in the literature that air entrapment might play a significant role in capping occurrence (Hiestand, 1997; Ritter and Sucker, 1980). Another argument is that it increases the time during which the formulation is under pressure and as such it could increase tablet strength (Augsburger and Hoag, 2008; Peeters et al., 2018; Swarbrick, 2006; Wray, 1992). This idea led to the development of devices or presses that could hold the pressure on the tablet between precompression and main compaction in order to maximize the time during which tablets were under pressure, e.g. the Comprima 300 from IMA or the dwell bar on Korsch machines. Nevertheless, it was proven that holding the precompression might in fact cancel its positive effects (Mazel and Tchoreloff, 2020). The effect of precompression therefore seems to stem from having two compaction events separated by a sufficiently long time period (Vezin et al., 1983) which backs up the idea that its effect is in fact related to phenomena of stress relaxations especially in terms of viscoelasticity (Hiestand, 1997). Unfortunately, precompression is not always sufficient to prevent capping occurrence.

Finally, the tableting speed was long recognized as one of the main factors in capping occurrence. It is well-known that capping increases when the tableting speed increases (Garr and Rubinstein, 1991; Ritter and Sucker, 1980; Ruegger and Çelick, 2000). Multiple explanations can be found regarding this influence. The first one comes from the influence of this speed on tablet strength as it is known that increasing the speed might lower tabletability (Tye et al., 2005). It could also be linked with stress relaxation phenomena due to viscoelasticity, e.g. a slower compaction might provide more time for internal stresses to relax (Hiestand, 1997). However, it is important to note that the compaction cycle on rotary presses can be separated into 3 steps (loading, dwell-time -i.e. the duration during which the punch flat head is under the main compression roller- and unloading) and the kinematics of each step is determined by the turret rotation speed and by the shape of the punch head. A lot of attention has been paid to the size of the punch flat head in order to increase the dwell-time but it is also known that the loading and unloading speed can be modified by changing the curvature of the punch head. These modifications might change tablet final properties. Indeed, (Ruegger and Çelick, 2000) showed that slowing the unloading and loading speeds made it possible to increase tablet crushing strength when both parameters were not taken identical. (Ritter and Sucker, 1980) evaluated the influence of the loading and unloading speed on capping and concluded that the unloading speed had the most impact on capping occurrence. Their conclusion was that "this fact should prompt changes in the design of high speed tableting machines". Nevertheless, this idea of the importance of the unloading speed on capping was not really followed afterwards.

The goal of the present paper was to study the influence of the unloading step on capping using a compaction simulator. Afterwards, a new manufacturing cycle with a modified unloading step was proposed in order to mitigate capping. The parameters of this cycle were then studied. This made it possible on the one hand to improve the understanding of capping phenomena and on the other hand to give a new idea of possible modifications that could be made on a rotary press in order to avoid capping.

2. Materials and methods

2.1. Formulations

2.1.1. Raw materials

The following products were used for this study:

- calcium sulfate dihydrate "Comp" (Compactrol, JRS Pharma, Rosenberg, Bade-Wurtemberg, Germany),
- mannitol "Man" (Mannitol, Cooper, Melun, Seine-et-Marne, France),
- microcrystalline cellulose "MCC" (Vivapur 12, JRS Pharma, Rosenberg, Bade-Wurtemberg, Germany),
- granulated lactose "MLac" (SuperTab 30GR, DFE Pharma, Goch, Nordrhein-Westfalen, Germany),
- crosscaramellose sodium "CCNa" (Vivasol, JRS Pharma, Rosenberg, Bade-Wurtemberg, Germany),
- magnesium stearate "MgSt" (Ligamed MF-2-V, Peter Greven, Bad Münstereifel, Nordrhein-Westfalen, Germany).

2.1.2. Blending process of the formulations

Two formulations were studied: a) a lubricated pure product (Comp-l = 99 %w/w Comp and 1 %w/w MgSt) and b) a mixture similar to what is used in the industry with Man acting as an active principle (F-40Man = 40 %w/w Man, 18 %w/w MCC, 36 %w/w MLac, 5 %w/w CCNa and 1% w/w MgSt).

Mixtures of 900 g were weighed directly on a 3L recipient using a PB3002-S/PH balance (J.P., Mettler Toledo, Hospitalet De Llobregat, Catalonia, Spain). Blends were then performed using the T10B turbula mixer (Willy A. Bachofen, Muttenz, Switzerland) at 32 rpm. All the products for Comp-l were mixed together during 6 min. For F-40Man, a first blend of 6 min was performed with the main ingredients (Man, MLac and MCC) then followed by a second blend of 6 min with the remaining raw materials (CCNa and StMg). Blends were stored under controlled atmosphere (20 °C and 44% RH) during at least 48 h before tablet manufacturing.

2.1.3. Formulation characterization

Before manufacturing, each formulation was characterized. The apparent particle density ρ_{pyc} of each powder was determined using a gaz pycnometer (Helium AccuPyc 1330, Micromeritics, Norcross, Georgia, USA) with helium. Each run (corresponding to 10 purges and 10 runs) was performed at (22 ± 1)°C in a cell of 10 cm^3 with an equilibration rate of 0.05 psig/min and a pressure of 19.5 psig. For this characterization, a mass of about 9.5 g was used for Comp-l and 5.5 g for F-40Man. Particle size distribution measurements were done by laser granulometry using a Mastersizer 3000 instrument (Malvern Panalytical, United-Kingdom, dry dispersion unit, measurement during 10 s) . Powder size parameters (D_{10}, D_{50} and D_{90}) were then estimated. For both characterizations, measurements were performed in triplicate for each formulation studied (Comp-l and F-40Man). The results are

Table 1
Particle size parameters and pycnometric density for each formulations studied.

	Particle size parameters (µm)			Density ρ_{pyc} (kg/m^3)
	D_{10}	D_{50}	D_{90}	
Comp-l	36 ± 5	278 ± 2	488 ± 3	2287 ± 1
F-40Man	25 ± 1	117 ± 1	288 ± 2	1519 ± 1

presented in Table 1.

2.2. Tablets

2.2.1. Tablet manufacturing

All the tablets were manufactured on a Styl'One Evolution compaction simulator (Medelpharm, Beynost, France). This device is a single station instrumented tableting machine. It is equipped with strain gauge force sensors to measure the force on both punches. The displacement of each punch is monitored using incremental sensors. During the acquisition, the sampling rate was 10 kHz. An instrumented die using strain gauge technology was used to monitor the die-wall pressure. For all experiments, the filling height was set to obtain 800 mg for Comp-l and 600 mg for F-40Man and the filling was performed using a gravimetric feeder. The compaction thickness was set to obtain the targeted axial pressure at the peak of compaction. For the purpose of the study, two pairs of Euro B punches were used: a) round concave punches with a diameter of 11.28 mm and a radius of curvature of 11 mm to obtain biconvex tablets and b) flat punches with a diameter of 11.28 mm to obtain flat-faced cylindrical tablets. The manufacturing cycles were set-up using the Profil'One software (Medelpharm, France). The different cycles used and the targeted compaction pressures P_{comp} will be presented below in the article along with the results. For each batch made using a specific manufacturing condition (i.e. with a specific manufacturing cycle and a fixed compaction pressure), ten tablets were manufactured and then characterized.

2.2.2. In-die measurements

The residual die-wall pressure of a tablet was measured as the die-wall pressure measured when the axial pressure on the lower punch reached the value of 0.05 MPa during the unloading step. The compaction duration t_{comp} of a manufacturing cycle was measured as the time interval between which the axial pressure on the lower punch was higher or equal to the value of 0.05 MPa. The compaction dwell-time t_{DT} was measured as the duration during which the axial pressure was equal or above 90% of the maximum compaction pressure P_{comp}.

2.2.3. Estimation of tablet solid fraction

Tablet solid fraction was estimated as the ratio between tablet density ρ_{tab} (evaluated with the measurements of tablet dimensions and mass) and the pycnometric density $\rho_{pyc.}$.

2.2.4. Diametral compression test

Diametral compression tests were performed using a TA.HDplus texture analyzer (Stable microsystems, United Kingdom). Compacts were compressed between two flat surfaces at a constant speed of 0.10 mm/s with an acquisition rate of 500 Hz. The breaking force F_r of each tablet was recorded. The tensile strength σ_T of each flat-faced tablet was evaluated using the equation of (Fell and Newton, 1970):

$$\sigma_T = \frac{2F_r}{\pi D t}$$

where t and D are respectively the tablet thickness and diameter.

2.2.5. Capping quantification

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. An example of the defects that we considered as capping ones can be seen in Fig. 1.

If no capping was visible, tablets were then broken using the diametral compression test using the same idea as in (Akseli et al., 2013). Indeed, for tablets presenting capping defects, the use of diametral compression test makes it possible to propagate an already existing crack leading to tablet cup failure and the registered breaking force will be lower than the one expected for a capping-free tablet. Thus, a tablet presenting one or both of its cups coming off during the diametral compression test 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 tablet presenting capping defects (after ejection and after diametral testing) among the total number of produced tablets.

3. Results

3.1. Compaction behavior of the formulations

Before evaluating the influence of the unloading part of the compaction cycle on capping, a characterization of the formulations studied and their compaction behaviour was performed.

3.1.1. Formulation compaction with flat punches: Global compaction behavior

To study the formulation compaction ability, we chose to use as a baseline manufacturing cycle based on the compaction cycle of a Korsch XL 100 at 25 rpm that was modified in order to be able to change the unloading part. The compaction phase corresponded to a compaction using a roller with a diameter of 150 mm (like on the Korsch XL 100). To simulate a dwell-time, the punches were then maintained at the positions they reached when the axial pressure hit P_{comp} during 80 ms which is similar to the dwell-time t_{DT} obtained with Euro D punches on the Korsch XL 100 at 25 rpm. The unloading was then performed at a constant speed s_U (using the "free motion punches" option of the software) that was set at 15 mm/s for the base cycle (which gives an unloading time similar to the one obtained on the Korsch XL 100). Fig. 2 shows the profiles of punch displacements and axial pressures on the example of Comp-l compacted at 200 MPa. This cycle will be referred as the baseline cycle (BS) for the studies presented in the sections below.

Flat-faced tablets were manufactured using this cycle with Comp-l and F-40Man in order to study their compaction behaviour. Fig. 3 shows their compressibility, tabletability and compactibility for a range of compaction pressure P_{comp} from 50 up to 300 MPa.

It can be seen that the two formulations studied presented different compaction behavior especially in terms of compressibility. Thus, tablet microstructures and properties obtained using these two formulations can be expected to be also different which makes it two interesting cases in order to evaluate the influence of the unloading on capping defects.

Moreover, for both formulations, relatively high compaction

Fig. 1. Examples of capped tablets characterized a) out-of-the die and b) after the diametral test (both cups came off).

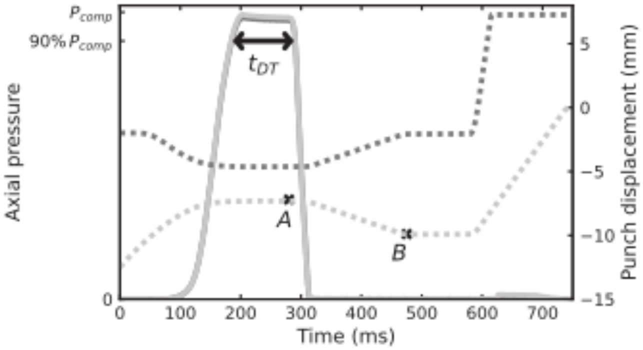

Fig. 2. BS profiles of axial pressures (solid lines) and punch displacements related to the compaction of Comp-I at 200 MPa (dotted lines) for the upper and lower punches (respectively dark gray curves and light gray curves). The speed s_U corresponds to the speed of the portion from the point A to B.

pressures (around 300 MPa for Comp-I and 270 for F-40Man) were required to obtain a tensile strength of 2 MPa, which is a common mechanical target for the development of tablets in the industry. Note that the tensile strength was increasing on the whole pressure range studied. The pressure range studied corresponds thus to a domain where the formulation cannot be considered as overcompressed (i.e. compressed in a domain where an increase of the compaction pressure does not lead to an increase in solid fraction).

These characterizations gave a general idea of the compaction behavior of the two formulations. In order to study their capping behavior, biconvex tablets were then produced, as capping rarely occurs on flat tablets.

3.1.2. Formulation compaction with curved punches: Capping behavior

In order to estimate the formulation capping behaviour with the BS cycle, biconvex tablets were manufactured for a range of compaction pressure P_{comp} from 50 up to 300 MPa and the presence of capping defects on those tablets was quantified. Fig. 4 shows the influence of the compaction pressure P_{comp} on capping occurrence for both formulations studied.

Note that both formulations presented capping in the range of compaction pressure studied. It can be noticed that, for each product, there was a certain compaction pressure below which tablets remained capping-free. Above this pressure, capping defects were observed and the proportion of capped tablets increased with the compaction pressure until reaching a *CI* of 100% (i.e. no defect-free tablets remaining). The increase of capping occurrence with P_{comp} is coherent with literature (Akseli et al., 2014; Paul et al., 2021). Note that both formulations started to cap for a rather similar compaction pressure (between 100 and 160 MPa), however Comp-I seemed to be more sensitive to capping than F-40Man as at 160 MPa the Comp-I batch had a CI of 80% compared to 20% for F-40Man.

The influence of the compaction pressure on tablet capping occurrence (Fig. 4) was used as a starting point to investigate below the influence of the unloading speed on tablet capping.

3.1.3. Parameters selected for the capping analysis and the relevance of studying the unloading step

As mentioned above, the idea of this article was to evaluate the influence of the unloading part of the cycle on capping. Therefore, using the results presented on Fig. 4, we chose to make tablets at two different compaction pressures P_{comp} leading to capping tablets, referenced hereinafter as P_A and P_B. For each formulation, the condition P_A was chosen to be in the transition zone between fully capping-free tablets and fully capped tablets, i.e. with a capping index *CI* between 50% and

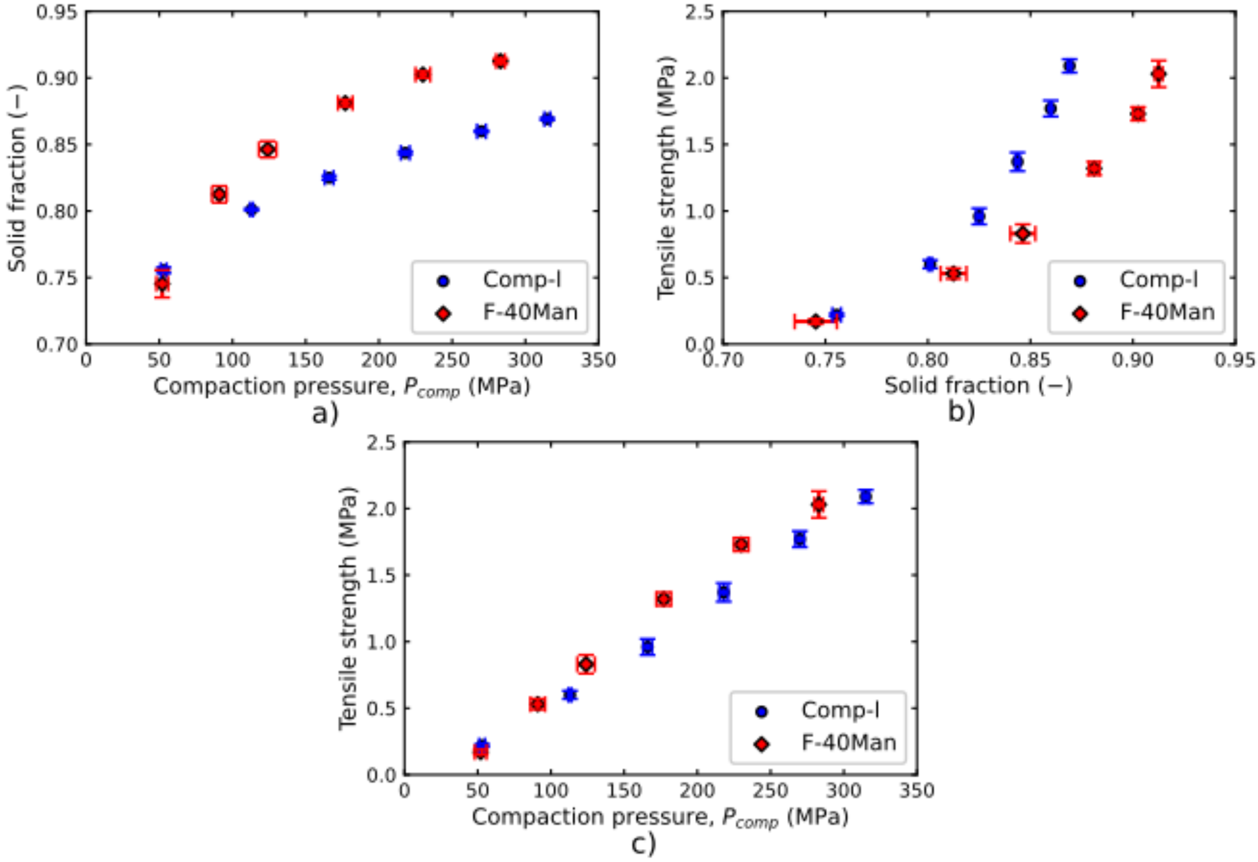

Fig. 3. Compaction behavior of Comp-I and F-40Man in terms of a) compressibility, b) compactility and c) tabletability.

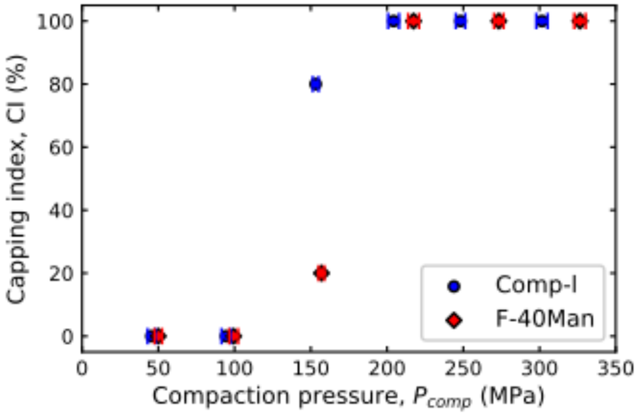

Fig. 4. Influence of the compaction pressure on the capping index of Comp-l and F-40Man made with the BS cycle.

100%, whereas P_B was selected in order to have a worse case than P_A with only capped tablets (i.e. a CI of 100%).

Tablets were manufactured with the BS cycle for each formulation at the chosen P_A and P_B. For each BS cycle performed, the compaction duration t_{comp} was determined and the capping index of each formulation was estimated. The chosen pressure set points and the characteristics of each BS cycle used are shown in Table 2.

This set of experiments also made it possible, thanks to the use of the radial pressure sensor, to have more information on the moment when capping failure arises. Results previously published, suggested that the breakage took place after the end of the unloading (Mazel et al., 2019). Nevertheless, the precise moment during which capping takes place was never shown, to our knowledge, in the literature.

It was possible to evaluate this moment, using the die-wall pressure signal of tablets made at P_A. Indeed, at this pressure, 20% of the manufactured biconvex tablets were found capping-free and 80% capped. Fig. 5 shows, for both formulations, a comparison of the die-wall pressures of two tablets (one capped and one without defects) made at the same axial pressure P_A.

It can be noticed that, the tablets compared on each graph were made at the same compaction pressure and the die-wall pressures of the capped tablets were superposed to the ones of tablets presenting no defects until the end of the unloading. Then, a sudden drop of the die-wall pressure was observed for capped tablets and not for capping-free tablets and it can be thus related to capping. It can be explained by the fact that the failure of the tablet cup led to a release of some of the tablet internal stresses which was detectable by the strain gauges in the die. Therefore, the detection of this drop made it possible to identify the moment when tablet failure occurred. Note that identifying the drop on the residual die-wall pressure is a simple way to identify capping during stages of development or manufacturing. Cup failure happened for both formulations just after the unloading part of the cycle: it occurred about 5 ms for Comp-l and 20 ms for F-40Man after the axial pressure dropped to zero. Thus, the proximity of the release of the axial pressure and tablet failure seemed to indicate that the unloading part played a role on capping. This result justifies our focus on the impact of the unloading step on capping in the rest of the article. First, the impact of the unloading speed related to the BS cycle on tablet capping was investigated.

Table 2
Compaction pressures studied in this article for Comp-l and F-40Man as well as capping index and compaction durations.

	Comp-l			**F-40Man**		
	Pressure (MPa)	*CI* (%)	t_{comp} (ms)	Pressure (MPa)	*CI* (%)	t_{comp} (ms)
P_A	170	80	218 ± 1	200	80	245 ± 1
P_B	200	100	226 ± 1	250	100	255 ± 1

3.2. Impact of the unloading speed on capping

The modification of the unloading speed was performed on the BS cycle by changing the value of the parameter s_U presented on section 2.1.1.

3.2.1. Study of the unloading speed using the compaction simulator

Fig. 6 shows the influence of the parameter s_U on the occurrence of capping for tablets made at P_A and P_B with Comp-l and F-40Man. First of all, it can be seen that, for each formulation and each compaction pressure, it was possible to find a s_U for which capping was not observed. This confirms the interest of studying the unloading part of the compaction cycle.

Nevertheless, the speed necessary to obtain a capping index equal to zero was dependent of the product and on the pressure. In fact, the first value of s_U leading to capping-free tablets was higher for:

- F-40Man tablets than for Comp-l ones made at a fixed compaction pressures (at 200 MPa, it was 0.07 mm/s for Comp-l and 1.00 mm/s for F-40Man). As capping is a product-dependent phenomenon, it was expected to obtain different capping behaviour of each formulation studied.
- Tablets made with a specific formulation at P_A compared to the ones made at P_B (e.g., for Comp-l, it was 0.25 mm/s at P_A compared to 0.07 mm/s at P_B). As mentioned in section 2.1.3, the pressure P_B was chosen to represent a more dramatic capping case compared to P_A.

Therefore, reducing sufficiently the parameter s_U driving the unloading speed associated to the BS cycle is a solution to mitigate capping. Nevertheless, it is worth noting that the decreasing of s_U has in fact two consequences. First this parameter slows down the unloading part of the cycle, but second, it also increases the dwell-time. Indeed, with the definition of the dwell-time used, the beginning of the unloading, until the axial pressure becomes lower than 90% of the maximum pressure, is in fact included in the dwell-time. Fig. 7 shows the influence of the parameter s_U on the dwell-time t_{DT} for the same tablets used on Fig. 6.

As it can be seen in this figure, for a specific formulation at a specific compaction pressure, a decrease of s_U led to a significant increase of t_{DT}. Thus, modifying the parameter s_U led to modifications of the unloading speed and the dwell-time. However, in the pharmaceutical field, increasing t_{DT} is also said to be a solution that can lead to capping-free tablets. Therefore, as both effects of the unloading speed and the dwell-time were coupled in the experiments presented in this section, it was not possible to conclude, with only these results, on the impact of the unloading speed on capping occurrence. Therefore, in order to separate the effects of the unloading speed and of the dwell-time, the influence of the dwell-time was determined.

3.2.2. Impact of the dwell-time on capping occurrence

The objective of this section was not to perform a complete study of the impact of dwell-time on capping. It was only to assess if the effect previously observed on capping could be attributed to the dwell-time modification or to the change of the unloading speed. Fig. 8 shows an example of the cycles used to study the impact of the dwell-time on capping.

On this figure, two conditions were presented: "Low s_U" and "Long t_{DT}". For each compaction pressure studied, the tablets with the highest s_U leading to capping-free tablets were chosen from Fig. 4 for the "Low s_U" case. For the "Long t_{DT}" case, tablets were manufactured with s_U = 15 mm/s and an added dwell-time, chosen to at least double the dwell-time of the case "Low s_U" to which it will be compared. Table 3 shows the comparison of both cycles studied in terms of capping occurrence for

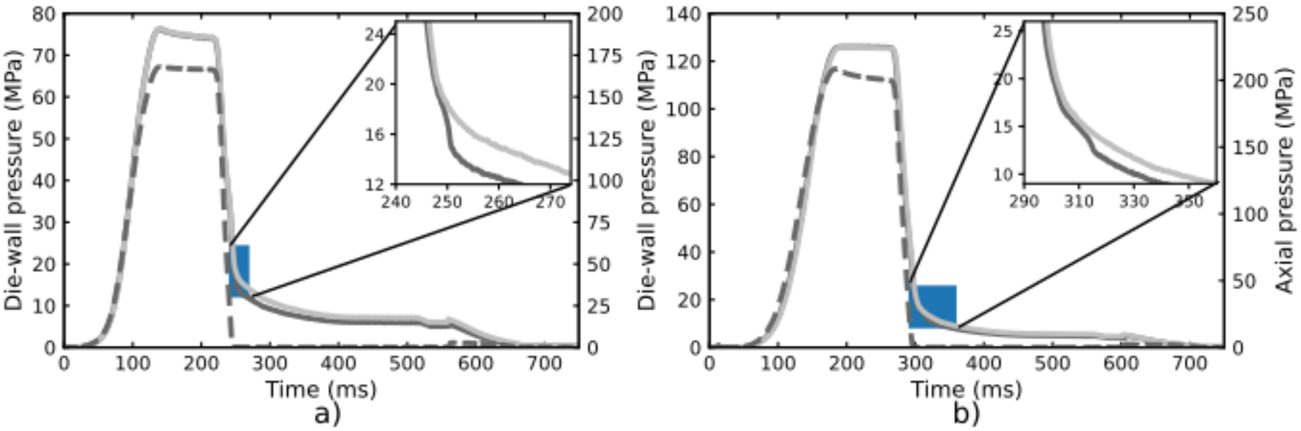

Fig. 5. Comparison of the die-wall pressures (solid lines) and the axial pressure related to the lower punch (dashed lines) of capped (dark grey) and capping-free (light grey) tablets made at P_A with a) Comp-l and b) F-40Man. The insert on each graph corresponds to a zoom of the colored area.

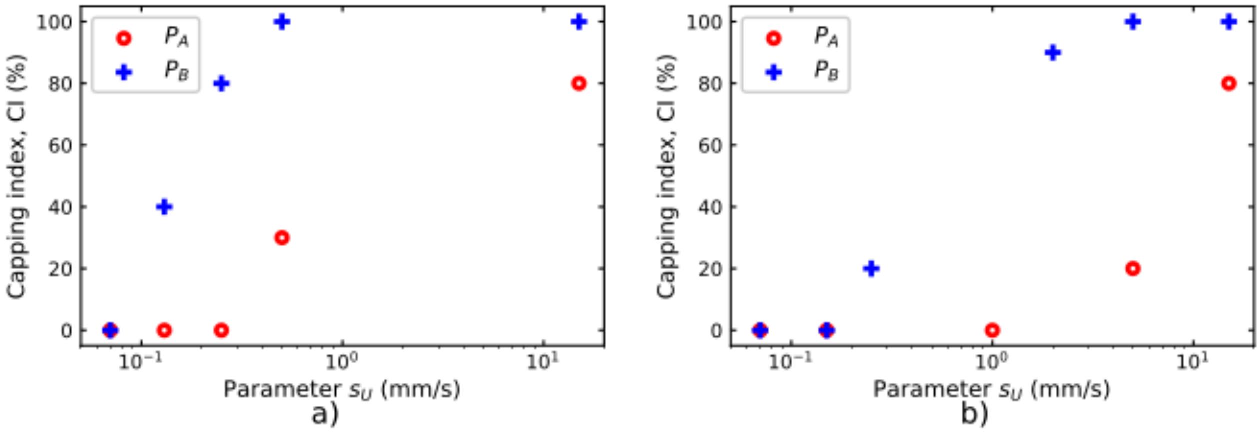

Fig. 6. Influence of the parameter s_U on the capping index at P_A and P_B for a) Comp-l and b) F-40Man.

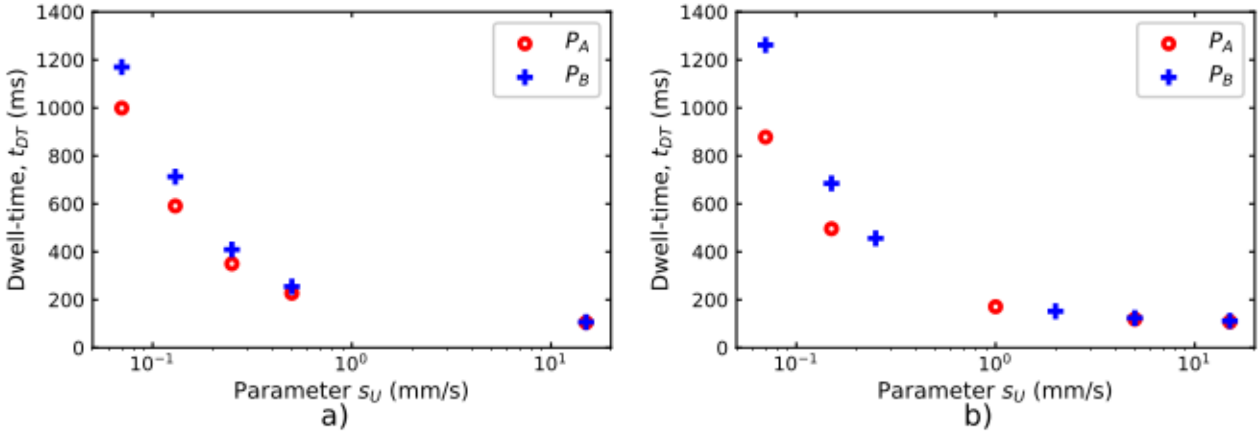

Fig. 7. Influence of the parameter s_U of the standard cycle on the dwell-time at P_A and P_B for a) Comp-l and b) F-40Man.

tablets made of Comp-l and F-40Man at P_A and P_B.

This table shows that, in "Long t_{DT}" cases, the tablets obtained were all or nearly all capped. Therefore, no significant impact of the dwell-time was observed on capping for those cases. Note that the elongated dwell-times used were far longer than what can be obtained in industry by modifying the punch head (only few milliseconds can be added) and no drastic change of the capping occurrence was observed even with those long and non-industrially applicable durations. These results suggest that only modifying the dwell-time is not a practicable solution at the industrial level to mitigate capping which is coherent with the results obtained by (Sarkar et al., 2015) who estimated that the effect of the compaction rate predominated on the impact of the dwell-time.

Again, the dwell-times of "Low s_U" cases were much smaller than those of "Long t_{DT}" cases (Table 3), for which no impact of the dwell-time on capping was observed. Therefore, if there was an influence of the dwell-time on capping occurrence in the "Low s_U" cases, it was

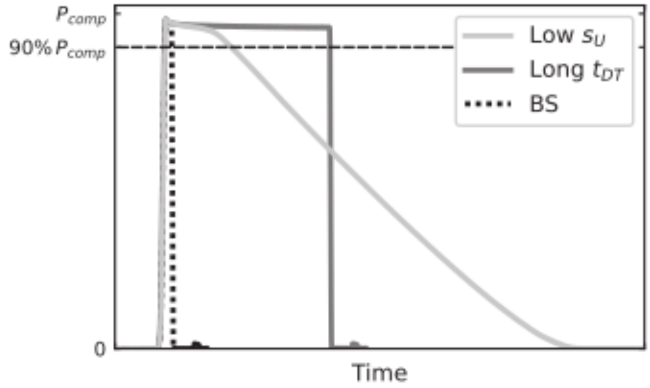

Fig. 8. Example of the cycles studied in order to study the impact of the dwell-time (solid lines). The dark gray line (Long t_{DT}) corresponds to $s_U = 15$ mm/s with an elongated dwell-time and the light gray line (Low s_U) corresponds to a s_U much lower than 15 mm/s. The BS cycle (dashed line) is also presented as a reference curve.

clearly negligible compared to the impact of the unloading speed. These results confirmed the influence of the unloading speed on capping as already mentioned in the literature (Ritter and Sucker, 1980; Ruegger and Çelick, 2000).

Even if decreasing the unloading speed makes it possible to mitigate capping, the manufacturing durations are very long. As a result, even if this solution is efficient, it won't be implemented on industrial rotary presses. To decrease the manufacturing durations and understand what occurred during the unloading step, we chose to develop a new way of performing the unloading step.

3.3. Influence of the final unloading speed on capping using the compaction simulator

3.3.1. Presentation the two-step unloading cycle

As shown previously, decreasing the unloading speed makes it possible to mitigate capping. However, the manufacturing durations of the cycles obtained were very long. The idea was to evaluate if it was necessary to slow down the whole unloading phase or if only slowing down the last part of the unloading (during which the contact between the punches and the tablet gets lost) was sufficient to mitigate capping. Based on this idea, we modified the unloading part of the BS cycle presented in section 2.1.1 and developed a manufacturing cycle called two-step unloading (2SU) that is shown in Fig. 9.

The filling, compaction and ejection steps (respectively steps a, b and e in Fig. 9) were kept identical to the BS cycle. The unloading phase was split into two steps (steps c and d in Fig. 9) in the 2SU cycle (hence its name).

In the first unloading part (step c), the punches move back to a set point position with a speed (driven by a parameter called $s_{U,1}$ similar to s_U in the BS cycle) and remain in that position for a set point duration. Note that $s_{U,1}$ is related to the speed of the lower punch from the end of step b to point C*. The positions used were chosen so that the punches are still in contact with the manufactured tablet inducing a remaining axial pressure maintained on the tablet. Therefore, the step c corresponds to a partial unloading. The set point duration between the point C* and the end of the step c will be called partial unloading duration t_{PU}. The minimal value of the pressure during step c (Fig. 9) will be called the partial unloading pressure P_{PU}. In the second and final unloading step d, the punches move away from the tablet with a speed driven by a parameter called $s_{U,2}$ releasing then the axial pressure.

Note that, if the partial unloading pressure is set as P_{comp}, the manufacturing cycle is no longer a two-step unloading one and is similar to the BS cycle with an unloading speed $s_U = s_{U,2}$ and an extended dwell-time as t_{PU} is not zero.

Due to the compaction simulator used, it was not possible to modify the unloading speed from $s_{U,1}$ to $s_{U,2}$ without making a pause, i.e. using $t_{PU} = 0$. The minimal value of t_{PU} was 1 ms. Moreover, it took a certain time for the speed of the punches ($s_{U,1}$ as well as $s_{U,2}$) to reach the set point value. Those specifications due to the device used had to be taken into account in the following studies.

As our objective was to study the impact of $s_{U,2}$ on capping occurrence, we chose hereinafter to set the parameter $s_{U,1}$ related to the partial unloading speed equivalent to the unloading speed of the BS cycle, i.e. $s_{U,1} = 15$ mm/s. Thus, the 2SU cycle is similar to the BS cycle until the axial pressure reaches P_{PU} (in fact they begin to differ slightly before because, in the 2SU cycle, the press needs to slow down in order to stop the punches when the pressure is P_{PU}). Therefore, the parameters of the 2SU cycle for this study were $s_{U,2}$, P_{PU} and t_{PU}.

The first point was to verify if it was possible to decrease capping occurrence by using the 2SU cycle.

3.3.2. Proof of concept

To check the possible use of the 2SU cycle in order to decrease capping occurrence, for a specific compaction pressure P_{comp}, tablets were manufactured at different P_{PU} with:

- t_{PU} set to its minimal value, i.e. 1 ms.
- $s_{U,2}$ chosen as the highest unloading speed s_U used in section 2.2.1 leading to capping-free tablets.

Table 4 shows the influence of the cycle on capping occurrence and on the manufacturing durations for Comp-l and F-40Man at P_A and P_B.

For each formulation at a specific compaction pressure, it was possible to prevent the formulations studied to cap for whatever unloading partial pressure P_{PU}. This result shows that the 2SU cycle with $s_{U,2}$ taken as a capping-free speed s_U (see section 2.2.1) makes it possible to manufacture capping-free tablets. The final part of the unloading (step d on Fig. 9a) has thus a significant impact on capping occurrence and it does not seem to be necessary to slow down the complete unloading part.

Thanks to the structure of the 2SU cycle, in the case studied in Table 4, for each formulation and compaction pressure, decreasing the partial unloading pressure P_{PU} induced a significant decrease of the compaction duration. However, note that, for all the 2SU cycles studied,

Table 3
Comparison for Comp-l and F-40Man at P_A and P_B between tablets made with "Low s_U" and "Long t_{DT}".

		Characteristics of the cycles studied			Capping index, *CI* (%)
		Case	s_U (mm/s)	Dwell-time, t_{DT} (ms)	
Comp-l	P_A	Low s_U	0.25	350	0
		Long t_{DT}	15.00	1624	90
	P_B	Low s_U	0.07	999	0
		Long t_{DT}	15.00	2506	90
F-40Man	P_A	Low s_U	1.00	171	0
		Long t_{DT}	15.00	1627	100
	P_B	Low s_U	0.15	685	0
		Long t_{DT}	15.00	2511	100

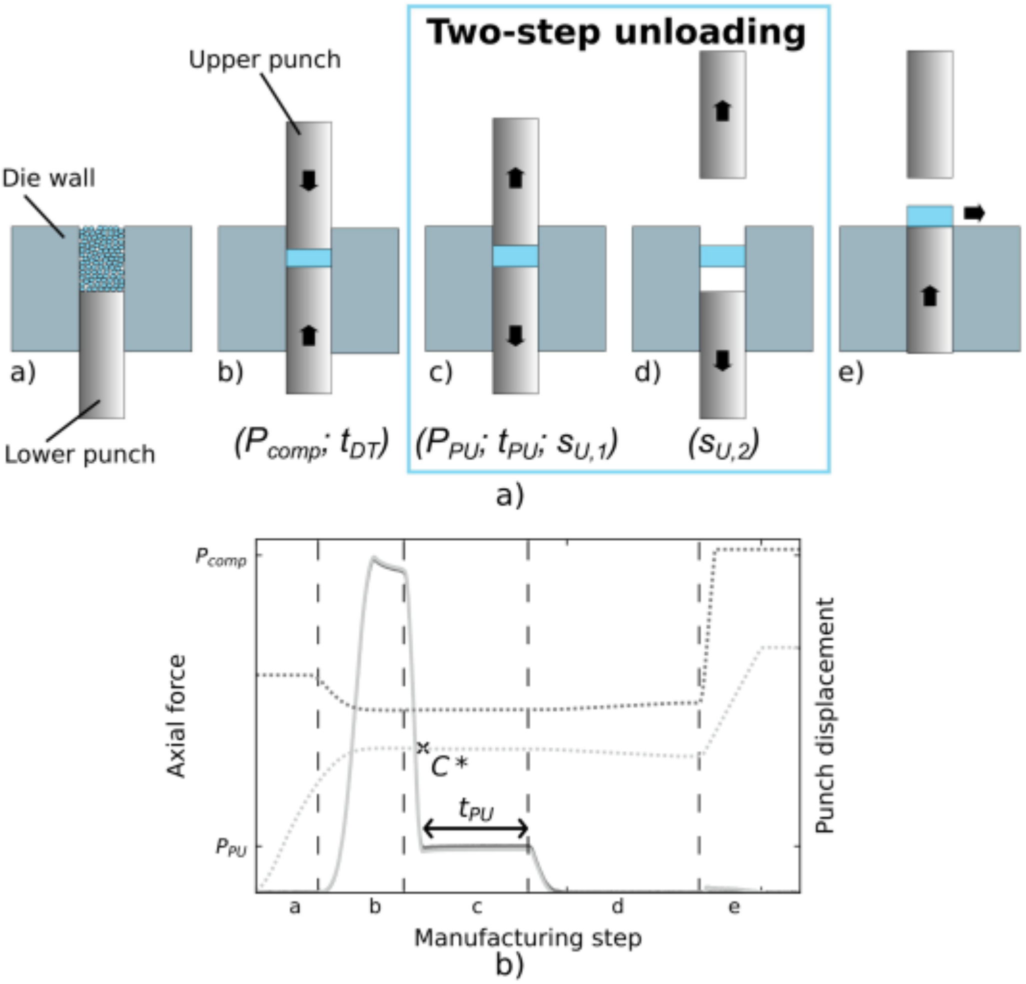

Fig. 9. 2SU cycle. a) Scheme of the manufacturing steps and b) example of the axial forces (solid lines) and the punch displacement (dotted lines) for the upper and lower punches (respectively dark gray and light gray curves).

Table 4
Impact of the 2SU cycle (different P_{PU}, $t_{PU} = 1$ ms and $s_{U,2}$ taken as a capping-free condition s_U in Fig. 6) on the capping index and manufacturing duration of Comp-I and F-40Man at P_A and P_B.

Comp-I	At P_A with $s_{U,2} = 0.25$ mm/s			At P_B with $s_{U,2} = 0.07$ mm/s		
	P_{PU} (MPa)	t_{comp} (ms)	CI (%)	P_{PU} (MPa)	t_{comp} (ms)	CI (%)
	171 ± 2	1715 ± 15	0	201 ± 3	6398 ± 91	0
	143 ± 2	1434 ± 12	0	164 ± 2	5031 ± 61	0
	94 ± 2	1098 ± 12	0	104 ± 2	3596 ± 57	0
	51 ± 1	783 ± 12	0	60 ± 3	2410 ± 75	0
	15 ± 2	468 ± 17	0	13 ± 1	954 ± 57	0
F-40Man	At P_A with $s_{U,2} = 1.00$ mm/s			At P_B with $s_{U,2} = 0.15$ mm/s		
	P_{PU} (MPa)	t_{comp} (ms)	CI (%)	P_{PU} (MPa)	t_{comp} (ms)	CI (%)
	201 ± 2	658 ± 5	0	251 ± 2	3804 ± 36	0
	159 ± 3	587 ± 6	0	238 ± 4	3365 ± 42	0
	106 ± 3	505 ± 6	0	151 ± 3	2474 ± 41	0
	60 ± 3	429 ± 6	0	76 ± 3	1571 ± 40	0
	18 ± 1	348 ± 2	0	13 ± 1	692 ± 21	0

the compaction durations were still way higher (at least 42%) than those of the BS cycles, whose t_{comp} were presented in Table 2. Nevertheless, the 2SU cycle is a solution for capping mitigation which gives shorter compaction cycles compared to the use of the BS cycle with a low s_U (as presented in section 2.2) as only the last part of the unloading was slowed down. In order to use cycles giving capping-free tablets with the lower compaction durations, we chose to study hereinafter the 2SU cycle with the lower P_{PU} studied (the values chosen for each compaction pressure and formulation can be seen in Table 4).

As explained above, it was not possible to set t_{PU} to zero. It was thus not possible to change the unloading speed without maintaining a remaining P_{PU} during t_{PU}. Thus, we chose to study the influence of t_{PU} in order to estimate if the capping-free conditions obtained with the 2SU cycle (Table 4) was due to either the decrease of $s_{U,2}$ and/or the duration

t_{PU} of the plateau on the axial force during the partial unloading.

3.3.3. Impact of the partial unloading duration on capping

To evaluate only the impact of the partial unloading duration, the 2SU cycle with $s_{U,2}$ set up as $s_{U,1}$ (i.e. 15 mm/s) was used to manufacture tablets (P_{PU} values being fixed in section 2.3.2) and only the parameter t_{PU} was modified in order to obtain capping-free tablets. Table 5 shows the compaction durations and capping occurrence of the characterized tablets made of Comp-l and F-40Man at P_A and P_B.

It can be seen in this table that it was possible to obtain capping-free tablets by increasing the partial unloading duration for each condition studied. Thus, the parameter t_{PU} had an impact on capping. Besides, Table 5 shows that the higher the compaction pressure is, the higher the t_{PU} required to mitigate capping is. This might be explained with the fact that, as P_B led to a worst capping case, the time required by the material to mitigate capping is longer.

As explained above, this experiment was performed because, in the results presented in section 2.3.2, the effects of t_{PU} and s_{u2} were coupled as it was not possible to set t_{PU} to zero. Results presented in Table 5 indicated that t_{PU} can have an effect on capping if it takes very high values (at least 2 s). As in part 2.3.2, the value of t_{PU} was 1 ms, it can be considered that its effect on capping was in fact negligible. Thus, this result showed that it was the decrease of the final unloading speed driven by $s_{U,2}$ which made possible to mitigate capping in the experiments of section 2.3.2. The moment during which the punches and the manufactured tablet loose contact seems to have a crucial impact on tablet properties and its propensity to cap.

Thus, all the results presented above indicated that it was possible to mitigate capping using the 2SU cycle (by slowing the final unloading speed and/or increasing the partial unloading duration). Nevertheless, for the moment, no explanation was given for those mitigations. Therefore, for the last part of the results, we tried to see if we could understand the impact of these modifications of the unloading part on capping occurrence by studying their influence on the properties of the tablets.

3.4. Impact of the capping-free conditions used on tablet properties

As tablet tensile strength and residual-die wall pressures are parameters known to play an important role on capping, it was interesting to study the influence of the different compaction cycles developed on these two properties. Unfortunately, because of capping, concave tablets could not be used for this study, because it is not possible to assess correctly the tensile strength of capped tablets. We thus chose to characterize those mechanical properties on flat-faced tablets at P_A (which is a compaction pressure where capping occurred) to make this study. Of course, it is important to remember that the results obtained might not be completely transferable to the case of biconvex tablets. Anyway, they will give some information about the influence of the compaction cycle on the final tablet properties.

Four manufacturing cycles were selected to conduct this study. Two 2SU cycles were studied: the cycle with a low $s_{U,2}$ and the minimal value of t_{PU} (case a) as well as the cycle with $s_{U,2} = s_{U,1}$ and an elongated t_{PU} (case b, Table 5). We chose to compare those cycles with: the BS cycle with $s_U = 15$ mm/s (Fig. 2) which will serve as a baseline and a cycle with a low s_U which gave capping-free tablets at P_A and P_B (case c, Fig. 6) to compare what varies between slowing the whole unloading part or only the final part. Table 6 summarizes all the cycles studied in this section in order to study the impact of the 2SU cycle on tablet mechanical properties.

Table 5
Influence of the partial unloading duration t_{PU} on the capping index ($s_{U,2} = s_{U,1}$).

Comp-l	Conditions	At P_A with $P_{PU} = 15$ MPa		At P_B with $P_{PU} = 13$ MPa	
	t_{PU} (ms)	1667	2000	2667	3333
	CI (%)	20	0	20	0
F-40Man	Conditions	At P_A with $P_{PU} = 18$ MPa		At P_B with $P_{PU} = 13$ MPa	
	t_{PU} (ms)	1667	2000	4667	5000
	CI (%)	30	0	30	0

The manufactured tablets were characterized by diametral compression and the residual die-wall pressure for each tablet was determined.

Table 7 shows the solid fractions, tensile strengths and residual die-wall pressures of flat-faced tablets made at P_A obtained with the four manufacturing cycles studied.

Interestingly, both formulations gave different results. In the case of F-40Man, all the modified cycles gave a higher solid fraction, a higher tensile strength and a lower residual die-wall pressure than the BS cycle. These trends were not so clear for Comp-l. For example, case b gave no significant difference for all the measured parameters compared to the BS cycle. So even if the modified cycles can promote a change in the tablet structure, the modifications observed do not make it possible to explain the influence of the unloading conditions on capping mitigation.

4. Discussion

In the section above, starting from the premise that decreasing the unloading speed led to capping-free tablets, a two-step unloading (2SU) cycle was developed. After taking the partial unloading speed equal to BS cycle, the cycle parameters were the final unloading speed driven by the parameter $s_{U,2}$ as well as the partial unloading duration t_{PU} and pressure P_{PU}. It resulted that, for whatever P_{PU}, reducing the final unloading speed and/or increasing the t_{PU} led to capping-free tablets. It can be noticed that the compaction durations in Table 4 were still far higher than the ones of the BS cycle (Table 2). However, as t_{comp} is directly related to the value of P_{PU} and $s_{U,2}$, lower manufacturing durations can be obtained by optimizing the parameters used. It is recommended to choose P_{PU} as low as possible (but not equal to 0 MPa) and $s_{U,2}$ as high as possible. As in this article the objective was to present the cycle and provid a proof of concept of a solution to mitigate capping, we did not deal with this parameter optimization. However, preliminary results seemed to be encouraging and might be investigated in a future article.

The use of the developed 2SU cycle can be considered for testing new formulations on development presses. Moreover, slowing only the final unloading speed can be of great interest as it makes it possible to obtain capping-free tablets without changing too much the BS cycle compared to other capping-free manufacturing cycles proposed in the literature (Funakoshi, 1975; Funakoshi et al., 1969). Thus, slight modifications of commercial manufacturing rotary could be considered and similar results to those presented in this study might be expected.

Moreover, it was shown that slowing down only the final unloading part made it possible to mitigate capping. Therefore, the crucial moment for capping seemed to be the one during which the contact between the punches and the manufactured tablet got lost. This result was coherent with the fact that capping cannot occur if this contact is never lost

Table 6
Conditions of the cycles used for the study of the capping-free conditions on tablet properties.

		Comp-l	**F-40Man**
BS		$s_U = 15$ mm/s	$s_U = 15$ mm/s
2SU cycle	Case a ($t_{PU} = 1$ ms)	$s_{U,2} = 0.07$ mm/s, $P_{PU} = 15$ MPa	$s_{U,2} = 0.15$ mm/s, $P_{PU} = 18$ MPa
	Case b ($s_{U,2} = 15$ mm/s)	$t_{PU} = 2000$ ms, $P_{PU} = 15$ MPa	$t_{PU} = 2000$ ms, $P_{PU} = 18$ MPa
Case c (Low s_U)		$s_U = 0.07$ mm/s	$s_U = 0.15$ mm/s

Table 7
Impact of the manufacturing cycles on the solid fraction, tensile strength and residual die-wall pressures of flat-faced tablets of Comp-l and F-40Man made at P_A.

		Solid fraction (–)	Tensile strength σ_T (N)	Residual die-wall pressure (MPa)
Comp-l	BS	0.827 ± 0.001	0.98 ± 0.05	18.4 ± 0.3
	Case a	0.830 ± 0.002	1.12 ± 0.06	17.3 ± 0.3
	Case b	0.830 ± 0.002	1.00 ± 0.03	18.9 ± 0.5
	Case c	0.833 ± 0.001	1.12 ± 0.05	18.4 ± 0.1
F-40Man	BS	0.893 ± 0.002	1.47 ± 0.05	22.0 ± 0.2
	Case a	0.904 ± 0.003	1.81 ± 0.12	15.5 ± 0.4
	Case b	0.908 ± 0.004	1.79 ± 0.04	18.5 ± 1.0
	Case c	0.908 ± 0.003	1.86 ± 0.05	18.3 ± 0.2

(Mazel et al., 2019). This result might give an insight on how capping works. As the capping occurrence (of a formulation at a given compaction pressure) depends on the unloading speed (Fig. 6), this phenomenon seemed to be related to dynamical effects related to the release of the contact between punches and the manufactured tablet. Following this idea, an amount of energy seems to be given to the tablet when the contact with the punches is released leading to internal stresses. To dissipate those stresses, some local relaxations phenomena might take place due to viscoelasticity or some local modifications of tablet microstructures with the creation of some fracture process zones (Grassl et al., 2012), i.e. leading to the creation of individual micro cracks in a region which made it possible to dissipate some energy. If the tablet internal stress reached a material stress limit, those micro cracks can merge and give rise to a macroscopic crack that can lead to tablet failure. This hypothesis needs to be further explored in future studies by studying the local impact of the manufacturing cycle on tablet microstructures and by evaluating the impact of the dynamical effects on their properties.

5. Conclusion

In this study, different kinds of capping-free conditions obtained by modifying tablet unloading were studied in order to understand capping occurrence. Two formulations were studied on a range of compaction pressure between 50 and 300 MPa which presented capping defects for pressures higher than 100 MPa.

The use of a strain gauge on the die wall made it possible to detect capping in-die as there was a drop of the die wall pressure for capped tablets. For the formulations studied, capping was shown to occur just after the unloading (at most 20 ms). To the author knowledge, it was the first time that the precise moment where capping occurred was determined.

A new manufacturing cycle was developed with two (partial and final) unloading steps and it was shown that capping-free tablets could be obtained with this cycle by lowering the speed on the part during which the contact between the punches and the tablet got lost and/or increasing the partial unloading duration. By taking the partial unloading pressure and duration as low as possible and the final unloading speed as high as possible, it was possible to reduce the compaction durations compared to the solution for mitigating capping by slowing the whole unloading part. Optimization of the parameters might result in compaction cycle durations that could be compatible with the ones used on industrial rotary presses. This could lead to a reflection on new developments on rotary presses to avoid capping.

The study of the developed cycle showed that capping occurrence was directly linked to the moment during which the contact between the punches and the manufactured tablet got lost. This observation seemed to indicate that capping might be related to dynamical effects. This study challenges the conceptualization of how capping works and paves the way towards the study of how tablet microstructures are impacted locally by the manufacturing cycle and the study of dynamical effects on tablets.

CRediT authorship contribution statement

J. Meynard: Methodology, Investigation, Conceptualization, Writing – original draft. **F. Amado-Becker:** Conceptualization, Writing – review & editing. **P. Tchoreloff:** Writing – review & editing. **V. Mazel:** Methodology, 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.

References

Akseli, I., Ladyzhynsky, N., Katz, J., He, X., 2013. Development of predictive tools to assess capping tendency of tablet formulations. Powder Technol. Special Issue: Pharm. Powders 236, 139–148. https://doi.org/10.1016/j.powtec.2012.04.026.

Akseli, I., Stecula, 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 (6), 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.

Amidon, G.E., Smith, D.P., Hiestand, E.N., 1981. Rotary press utilizing a flexible die wall. J. Pharm. Sci. 70 (6), 613–617.

Augsburger, L.L., Hoag, S.W., 2008. Pharmaceutical Dosage Forms - Tablets: Manufacture and Process Control, 3rd ed. CRC Press, New York.

Croquelois, B., Girardot, J., Kopp, J.B., Tchoreloff, P., Mazel, V., 2020. Quantification of tablet sensitivity to a stress concentration: Generalization of Hiestand's approach and link with the microstructure. Powder Technol. 369, 176–183. https://doi.org/10.1016/j.powtec.2020.05.002.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 59 (5), 688–691.

Funakoshi, Y., 1975. Some Observation on the Capping Properties Detected in the Tablet Making Compaction Process. J. Soc. Mater. Sci. Jpn. 24, 673–676.

Funakoshi, Y., Kajiura, T., Asogawa, T., 1969. Ruling Factors of Capping in the Compressing Process and the Method of Preventing Capping. J. Soc. Mater. Sci. Jpn. 18 (189), 547–553.

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.

Grassl, P., Grégoire, D., Rojas Solano, L., Pijaudier-Cabot, G., 2012. Meso-scale modelling of the size effect on the fracture process zone of concrete. Int. J. Solids Struct. 49 (13), 1818–1827. https://doi.org/10.1016/j.ijsolstr.2012.03.023.

Hiestand, E., 1997. Principles, tenets and notions of tablet bonding and measurements of strength. Eur. J. Pharm. Biopharm. 44 (3), 229–242.

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

Mann, S.C., Bowen, B.M., Roberts, R.J., Rowe, R.C., Tracy, R.H.T., 1981. The influence of punch tolerance on capping. J. Pharm. Pharmacol. 33, 25P.

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-49P.

Mazel, V., Desbois, L., Tchoreloff, P., 2019. Influence of the unloading conditions on capping and lamination: Study on a compaction simulator. Int. J. Pharm. 567, 118468. https://doi.org/10.1016/j.ijpharm.2019.118468.

Mazel, V., Diarra, H., Busignies, V., Tchoreloff, P., 2017. Shear strength of pharmaceutical tablets: Theoretical considerations, evaluation and relation with the capping tendency of biconvex tablets. Int. J. Pharm. 532 (1), 421–426.

Mazel, V., Diarra, H., Busignies, V., Tchoreloff, P., 2015. Evolution of the Die-Wall Pressure during the Compression of Biconvex Tablets: Experimental Results and Comparison with FEM Simulation. J. Pharm. Sci. 104 (12), 4339–4344.

Mazel, V., Tchoreloff, P., 2020. Role of Precompression in the Mitigation of Capping: A Case Study. J. Pharm. Sci. 109 (10), 3210–3213. https://doi.org/10.1016/j.xphs.2020.07.021.

Nyström, C., Malmqvist, K., Mazur, J., Alex, W., Hölzer, A., 1978. Measurement of axial and radial tensile strength of tablets and their relation to capping. Acta Pharm. Suec. 15, 226–232.

Paul, S., Baranwal, Y., Tseng, Y.-C., 2021. An insight into predictive parameters of tablet capping by machine learning and multivariate tools. Int. J. Pharm. 599, 120439. https://doi.org/10.1016/j.ijpharm.2021.120439.

Peeters, E., Silva, A.F.T., Fonteyne, M., De Beer, T., Vervaet, C., Remon, J.P., 2018. Influence of extended dwell time during pre- and main compression on the properties of ibuprofen tablets. Eur. J. Pharm. Biopharm. 128, 300–315. https://doi.org/10.1016/j.ejpb.2018.05.007.

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

Ruegger, C.E., Çelick, M., 2000. The effect of compression and decompression speed on the mechanical strength of compacts. Pharm. Dev. Technol. 5 (4), 485–494.

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. https://doi.org/10.1002/jps.24328.

Swarbrick, J., 2006. Encyclopedia of Pharmaceutical Technology, third ed. (Print). Taylor & Francis.

Tye, C.K., Sun, C., (Calvin), Amidon, G.E., 2005. Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction. J. Pharm. Sci. 94, 465–472. https://doi.org/10.1002/jps.20262.

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 (8), 1465–1474. https://doi.org/10.3109/03639048309052388.

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

Wray, P.E., 1992. The Physics of Tablet Compaction Revisited. Drug Dev. Ind. Pharm. 18 (6-7), 627–658.

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.