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Role of precompression in the mitigation of capping: a case study

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Abstract

Capping is an important industrial problem that can arise during the manufacturing of pharmaceutical tablets. It corresponds, for biconvex tablets, to the detachment of one of the cups of the tablet during the ejection from the press or after relaxation. Solutions to this problem remain mainly empirical. Among them, precompression is widely used.

One of the most popular explanation of the role of precompression in the mitigation of capping is that it increases the total time under compression. Following this interpretation, press manufacturers developped devices or machines that make it possible to maintain the pressure between precompression and main compression.

In this note, we present a case study of capping. For the formulation proposed, a precompression that was maintained until the compression gave similar results as no precompression at all, i.e. capping of all the tablets. On the contrary, if the precompression was released before compression, capping stops completely. In this case, the effect of precompression is thus due to the separation of two compression events. Moreover, results prove that this separation must last long enough for the precompression to be

efficient. This example shows that effect of precompression is more complex than often described in the literature.

Keywords: tableting; capping, precompression, tablet.

1. Introduction

Compaction is the most popular process to produce solid dosage forms in the pharmaceutical industry. Despite this popularity and a long use, problems still occur at the industrial level. Among them, the problems of cracks or tablet failure upon the ejection from the press are described for more than a century[1]. The cases of tablet failure can be separated into two kinds: capping and lamination. In the case of biconvex tablets, capping corresponds to the separation of at least one of the two cups of the tablets whereas lamination correspond to a failure in the band of the tablet[2]. This work is focused on capping.

The mechanism of capping for biconvex tablets was first proposed by Hiestand *et al.*[3]. At the end of the unloading part of the compaction cycle, during the elastic recovery, a highly concentrated shear stress develops at the limit between the land and the cup of the tablet. Different numerical studies have confirmed the development of such a shear stress[4,5]. Moreover, it was recently shown that if the unloading conditions were modified in order to avoid the development of the shear stress, capping was suppressed, which confirmed the mechanism[6].

Air entrapment is also commonly cited as a cause of capping[7,8]. Nevertheless, to our knowledge, it was shown that air entrapment can promote lamination[9–11], but there is no proof that it can indeed promote capping. In their study about capping, Ritter and Sucker[12]

showed that, in the case of Phenazone tablets, even a compression under vaccum had no effect on capping. They concluded: “air cannot be considered to be the cause of capping in compacts produced in an air atmosphere”. Moreover, there is sometimes in the literature a confusion between capping and lamination, and the effect of air entrapment on lamination is, in some articles, wrongly assigned to capping. This is for example the case for the study of Tanino et al. (Tanino, 1995). The photographs presented in the article indicate clearly that the problem is lamination and not capping.

Precompression is considered as a very effective means to mitigate capping[13]. In the literature two main mechanisms are cited to explain its role. The first one is the reduction of air entrapment[7,8,14,15]. If this mechanism might be effective for lamination when air entrapment is involved, there is, as explained before, no solid proof that air entrapment can be related with capping. The second mechanism proposed is that precompression increases the amount of time the material is under pressure. Consequences could be an increase in the cohesion[7,15–17] or a longer time for stress relaxation before the main compression[3,7]. In both cases, the longer time under compression seems to be the reason of capping mitigation.

This idea had direct consequences on the development of tableting machines. Indeed, following the idea that the effect of precompression was due to an increase of the total compression time, several manufacturers have proposed solutions to increase the precompression time. For example, thanks to an air compensator system, some GEA presses make it possible to extend the dwell time during precompression[15]. At least two press manufacturers have even gone further and developed machines or devices that make it possible to hold the pressure between precompression and main compression.

This is the case for the IMA Comprima 300 and it can also be done on Korsch machines using a so-called “dwell bar”.

Nevertheless, this extended dwell-time effect was questioned at the beginning of the 80’s by Vezin et al. (Vezin 1983). In their study, the authors modified both the precompression and the rotary speed of the press to have equivalent dwell-times with and without precompression. The conclusion of their study was:” It appears that advantages of precompression arise more from separation of two distinct compression events by a relatively long interval of time, and not generally from increase in contact or dwell times”. They attributed this to slow time-dependent phenomena during the time between precompression and main compression.

The idea that at least part of the effect of the precompression on capping was due to the separation between precompression and main compression was not demonstrated by Vezin et al. and is nearly completely forgotten nowadays in the literature. The objective of this note is to show, on a case study, that this idea was correct.

2. Material and method

2.1. Powders

The powders used in this work were Mannitol (Pearlitol 200SD, Roquette Frère, Lesterme, France), Kollidon CL (BASF, Ludwighafen, Germany) and magnesium stearate (Partek Mg Lub, Merck, Darmstadt, Germany). The formulation studied was: 94% (w/w) of mannitol, 5%(w/w) of Kollidon CL and 1%(w/w) of magnesium stearate. Blending was performed using a Turbula Mixer (Type T2C, Willy A Bachofen, Muttenz, Switzerland) at

49 rpm during 5 min (total mass of powder: 300 g). The formulation was chosen, based on in-house experience, for the sake of the demonstration.

2.2. Tablet manufacturing

All tablets were obtained on a compaction simulator Styl'One Evolution (Medelpharm, Beynost, France) using Euro B round concave punches with a diameter of 11.28 mm and a radius of curvature of 11 mm (11.28R11). The compaction kinematics were set-up using the Profile One® software (Medelpharm, Beynost, France). They were based on the profile of the Kilian Synthesis 500 with Euro B punches (pitch diameter of 415mm, roller diameter of 210 mm). Tablet mass was set to 600mg. The main compression was set to 200 MPa.

The parameters investigated are reported in table 1. A total of 14 runs (named A1 to D4) were performed. The dwell-time reported in the table corresponds to the time when the axial pressure is above 90% of the maximal value of the maximal axial pressure. When precompression was on, two cases occurred. First, the precompression could be released like on a normal rotary press. In this case the lag-time, i.e. the time between the end of precompression and the beginning of compression, was reported in the table (runs B1, B2, B3, B4, B5, B6, B7, D1, D2, D3 and D4). Second, the precompression could be hold. In this case, the hold time is reported in the table (run C1). For each run, 10 tablets were manufactured.

2.3. Capping Quantification

For each run, the tablets produced were carefully examined to detect capping. If no capping was seen, the tablet was broken by diametral compression using a texture

analyser TAHD-plus (Stable microsystems, Surrey, UK). Flat platens were used and the mobile platen was moved at 0.1mm/s. A capping index was then calculated based on the equation proposed by Akseli et al.[18]:

$$capping\ index = \frac{\left(5N_{op} + N_h\right)}{N_t}$$

where N_{op} is the number of tablets capped directly on the press, N_h is the number of tablets capped during hardness testing, and N_t is the total number of tablets tested (10 in our case).

Moreover, the breaking force of the tablets was also included in table 1. It can be easily seen that the capping index is negatively correlated with the breaking force. The reason is simple. When capping occurs during the breaking test, the breaking force obtained is lower than the one obtained for intact tablets. It must be noted that all the tablets without defects before or during the breaking test had approximately the same dimensions. Breaking force can thus be used to compare their strength.

3. Results and discussion

All the results in terms of capping behavior are presented in Table 1. The discussion presented below refers to these results.

3.1. General capping behavior

Runs A1 to B7 make it possible to obtain the general capping behavior of the model formulation. At low speed (run A1) no capping was observed. Nevertheless, when the turret speed increased (run A2), all the tablets ejected from the press were capped. This is a classical capping behavior. It is worth noting that between the two runs, not only the

dwell-time is modified but also the loading and unloading time. We do not intend to explain the role of speed on capping in the present note.

Then, several precompression pressures were tested (runs B1 to B7). For low precompression pressures (runs B1 and B2) capping remained a problem. At a precompression of 19MPa, capping was completely solved (run B3). A further increase of the precompression pressure up to a value of 110MPa (runs B3, B4 and B5) gave also defect free tablets. Nevertheless, when the precompression pressure reached 135MPa and above, defects were seen again (run B6 and B7). This formulation presents thus a classical capping behavior. A precompression pressure of 45MPa, which is inside the range of the defect free tablets was selected for the other experiments.

3.3. Effect of precompression holding

As mentioned previously, some manufacturers propose machines or devices that makes it possible to maintain the pressure between precompression and compression. According to the argument that precompression increases the time under pressure and also the time for stress relaxation, maintaining the precompression pressure should be efficient to mitigate capping.

Effect of this hold-time can be seen by comparing runs B4 and C1. The only difference between this two runs is that the precompression is released in run B4 and maintained in run C1. Figure 1 presents the evolution of the pressure on the upper punch versus time for these two runs. Whereas in run B4 no capping is detected, in run C1 the capping index is 5. This means that maintaining the pressure between precompression and compression gives the same result as having no precompression at all. In our case, the hold-time

cancelled completely the positive effect of precompression on capping. This is, to our knowledge, the first time that such a result is presented. It clearly indicates, that, at least in the case of this formulation, the effect of precompression has nothing to do with a contact time increase. It is also an experimental proof of the comment of Vezin et al.[19] reported above.

As a consequence, in case of capping, using a device that maintains the pressure between precompression and compression might in fact be detrimental.

3.4. Effect of the lag-time

In the case of our formulation, the benefit of precompression comes thus from the fact of having two separate events. The last point studied was the influence of the lag-time (time between-precompression and compression) on this effect. In the runs D1 to D4, the lag-time was varied to find if there was a minimum value under which precompression stopped to be efficient for capping mitigation.

No effect of the lag-time was seen until a value around 25 ms. From this value and below, capping appears again, especially for the shorter time (20ms). It must be noted that 20ms was the shortest time that could be obtained during the experiment due to machine limitations. On a rotary press, the lag-time is influenced by the turret speed but it depends also on the distance between the two rollers. This distance varies from one machine to the other. As a consequence, this parameter must be considered, with many others, when a product is transferred from one press to another.

4. Conclusion

In this study, the capping behavior of a model formulation was studied as well as the influence of process parameters related to precompression. The results generated are specific to the formulation used in the study and might not be exactly transferrable to other formulations. Nevertheless, it made it possible to emphasize some aspects of the effects of the precompression on the mitigation of capping.

The main result was that holding the precompression pressure until the compression might suppress totally the benefits of the precompression. In our case, holding the precompression pressure gave the same results than having no precompression at all. In case of capping, devices or machines that hold the precompression pressure should thus be used with caution.

Another important factor is the lag-time between precompression and compression. The results indicate that there is a threshold lag-time under which precompression stops to be efficient. This parameter is especially influenced by the geometry of the machine itself (angle between the rollers of precompression and compression) that are not similar from one machine to the other. This has to be kept in mind when transferring a product form one machine to the other.

In the case of the formulation presented in this article, part of the effect of precompression was clearly due to the separation of two distinct compression event by a sufficient amount of time as predicted by Vezin et al.[19]. Further work is now needed to understand what happens to the tablet during this lag-time that makes it possible to mitigate capping.

Acknowledgement

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Legend to figures

Figure 1: Evolution of the pressure on the upper punch versus time for runs B4 and C1.

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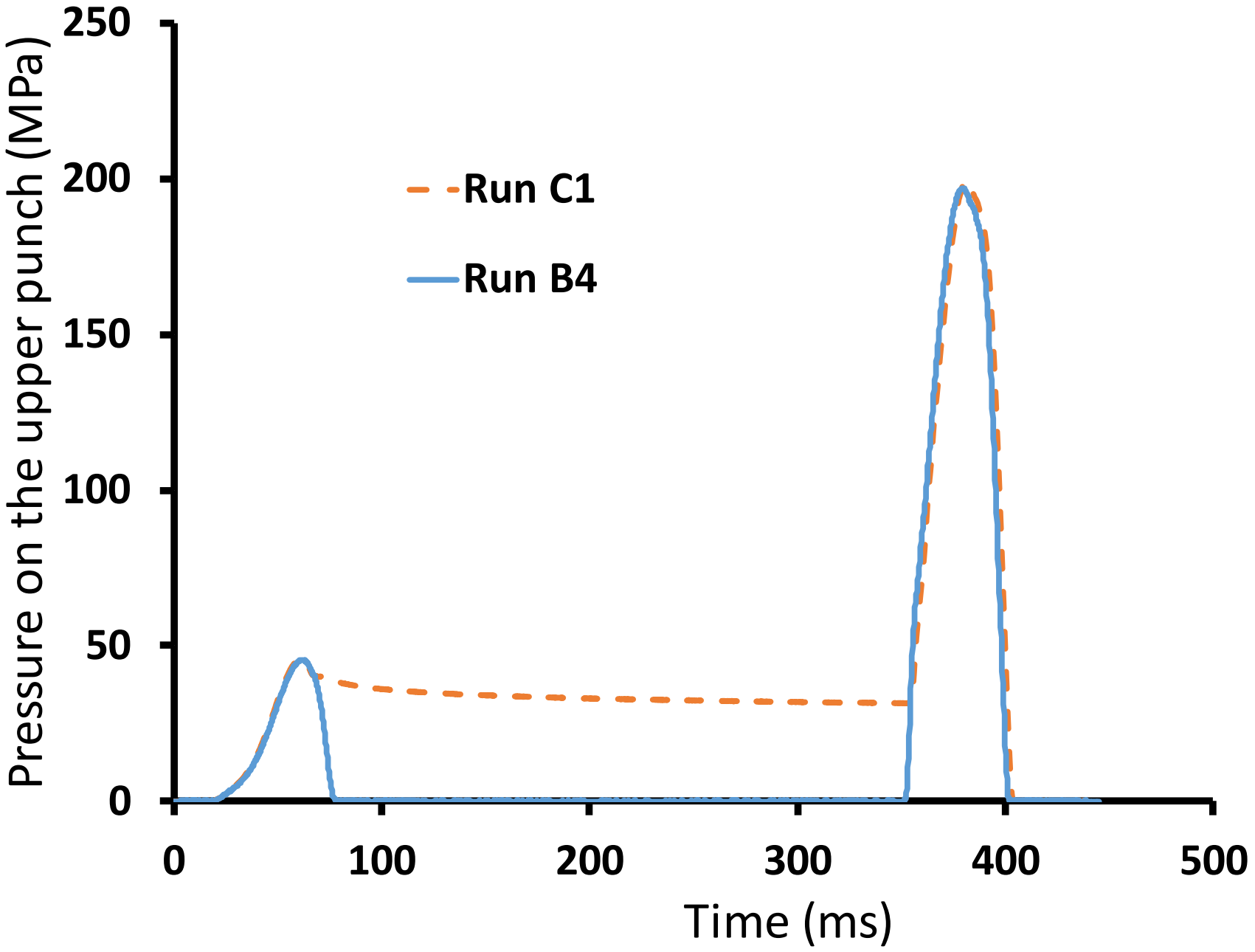
Pressure on the upper punch (MPa)
250
200
150
100
50
0
Run C1
Run B4
0
100
200
300
400
500
Time (ms)

Table 1: Description of the runs performed in the study and results in terms of capping. Nop is the number of tablets capped directly on the press, Nh is the number of tablets capped during hardness testing.

Run	Simulated Turret Speed (rpm)	Precompression pressure (MPa)	Lag-time (ms)	Compression dwell-time (ms)	Precompression holdtime (ms)	N_{op}	N_h	Capping index	Breaking force (N)
A1	5	x	x	130	x	0	0	0	256 ± 9
A2	30	x	x	17	x	10	0	5	X
B1	30	4.5	262	16	x	9	1	4.6	x
B2	30	9	265	17	x	0	9	0.9	167 ± 27
B3	30	19	269	17	x	0	0	0	229 ± 5
B4	30	45	273	17	x	0	0	0	222 ± 14
B5	30	110	274	16	x	0	0	0	217 ± 6
B6	30	135	274	16	x	0	6	0.6	160 ± 43
B7	30	170	273	15	x	4	5	2.5	135 ± 37
C1	30	45	x	17	290	10	0	5	x
D1	30	45	125	17	x	0	0	0	215 ± 7
D2	30	45	72	16	x	0	0	0	218 ± 7
D3	30	45	24	17	x	0	3	0.3	193 ± 24
D4	30	45	20	17	x	0	6	0.6	170 ± 43