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MULTIVARIATE DATA ANALYSIS FOR TABLETING PERFORMANCE IMPROVEMENT AT INDUSTRIAL SCALE. A CASE STUDY FOCUSED ON UNDERSTANDING AND AVOIDING THE OCCURRENCE OF CAPPING AND LAMINATION

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Abstract

The objective of this work was to investigate the granule properties and processing conditions leading to capping and lamination phenomena occurred for a high drug load, wet granulated, film coated product. Assessment of historical industrial data was combined with parameters resulting from compaction simulator testing of representative samples. A systematic approach, based on batch statistical modelling, was applied to identify patterns between batches linked to changes in input variables. Batch evolution modelling revealed the typical process fingerprint and expected variability and confirmed that defects were not linked to process evolution excursions. Class-based modelling and ANOVA allowed the identification of statistically significant differences between input variables (active ingredient particle size and granulation water amount) and adjustments to be done to improve the process. The model built with the parameters resulting from the compaction simulator confirmed the inter-batch differences and suggested the mechanism for capping/lamination - higher elastic recovery rate. The strain rate sensitivity (SRS) values showed a product sensitivity to certain processing conditions, including dies wear. SRS and bulk density showed a negative correlation and could be used to predict the appropriate tableting conditions to increase tablet hardness.

Rezumat

Obiectivul acestui studiu a fost investigarea proprietăților granulatului și a condițiilor de procesare care au determinat decaparea și laminarea unui produs cu conținut ridicat de substanță activă, obținut prin granulare umedă. Evaluarea datelor istorice industriale a fost combinată cu parametri obținuți cu simulatorul de comprimare pentru probe reprezentative. S-a aplicat o abordare sistematică, bazată pe modelarea statistică a loturilor, pentru identificarea grupărilor de loturi corelate cu schimbări ale variabilelor de intrare. Modelele de evoluție au dezvăluit amprenta şi variabilitatea tipică a procesului și au confirmat că defectele nu erau cauzate de abateri ale evoluției procesului. Modelarea pe clase și ANOVA au permis identificarea diferențelor semnificative statistic între variabile de intrare (dimensiunea particulelor substanței active și cantitatea de apă de granulare) și ajustări necesare pentru îmbunătățirea procesului. Modelul construit cu parametri generați de simulatorul de comprimare a confirmat diferențele inter-loturi și a sugerat mecanismul pentru decapare/laminare – o rată mai mare de revenire elastică. Valorile sensibilității la viteza de aplicare a stresului (SRS) au arătat tocmai o sensibilitate a produsului la anumite condiții de procesare, inclusiv la uzura matrițelor. SRS și densitatea aparentă au arătat o corelație negativă și ar putea fi utilizate la prezicerea condițiilor de comprimare pentru creșterea durității comprimatelor.

Keywords: batch modelling, capping, lamination, strain rate sensitivity

Introduction

Performance improvement is one of the main targets of the pharmaceutical industry, without affecting the quality standards. Multivariate data analysis applied to sets of data acquired during routine commercial manufacturing can be one of the strategies applied for a systematic approach to product and process continuous improvement, based on scientific rationale and quality risk management which would be equivalent also with the implementation of Quality by Design (QbD) principles to legacy products in order to enable the continuous delivery of high quality products, despite the multiple changes occurring during a product's lifecycle [10, 13, 19, 30].

If the process and product development phase hasn't or couldn't fully assess the impact of raw materials variability, during the product lifecycle there are high chances for offsets from the quality target product profile [10]. In such cases, the historical data from routine manufacturing could be used to identify sources of variation and to propose science-based solutions to the problems identified, because the more batches are manufactured at industrial scale, the more common and special cause variability can be observed in both raw materials and intermediate and final products [19].

On the other hand, the diverse datasets makes it difficult to properly interpret the data, therefore advance data analysis tools would be required [4, 17]. For these reasons, Quality by Control concept having PAT methods as part of it for process monitoring purposes, would represent the highest level of control to avoid deviations [3, 6, 15].

Tableting is one of the most widely used technological processes in the pharmaceutical industry, as tablets increase patient acceptability and treatment adherence, they ensure an improved chemical and physical stability of the formulation, due to the lower contact surface area and they can be generally obtained at low costs with decent throughput [20, 21].

Tablet attributes (weight uniformity, hardness or tensile strength, disintegration time, friability, dissolution) have to be ensured through the formulation, environmental conditions, appropriate tooling design and the applied manufacturing process, but during routine manufacturing they can be strongly influenced by raw material properties and the performance of upstream processes, all these factors being mostly inter-dependent, meaning that multivariate data analysis techniques are needed [9, 20, 23, 24].

There are various types of defects occurring during the tableting process or in the downstream process steps of film-coating and packaging and the most frequent ones are: edge chipping or breakage (caused by mechanical impact during handling or successive processing), sticking or picking, variable disintegration time affecting dissolution and capping (complete removal of tablet upper part) or lamination (microcracks on the side of the tablet or separation into multiple layers) [23].

If capping or lamination tendency is identified during initial development studies, there is still the option to adjust the formulation in order to mitigate this risk, if there is no other impact on the tablet's critical quality attributes [23]. If this tendency is observed during routine manufacturing in recurring manner, this has to trigger an investigation for potential root causes of changes appeared in the potential influencing factors: raw materials, tooling and processing conditions [29]. There are several mechanisms which can explain the capping or lamination defect and they depend on the elastic recovery rate of the compact during the decompression phase (higher than the inter-particles bonding strength), air entrapment during the compaction phase, formation of shear bands during the decompression phase, volume reduction mechanisms, compression speed, stress and density distribution, internal shear stress caused by die wall pressure and friction [1, 27-29].

Most of the mechanisms listed above are related to the stress applied to the tableting mass and products respond differently to stress application at different rates. This sensitivity can be assessed numerically through the strain rate sensitivity of the tableting mixture. This results from the difference between the rate at which the stress is applied and the rate at which this can be relieved by the compacted material, being therefore more visible in case of industrial scale rotary presses, when the entire compaction process takes place in a matter of milliseconds. The rate of stress relief is dependent on the elastic recovery of the materials. During compaction the bulk density of the powder bed increased towards the true density of the mixture and this change in density depends on the consolidation and relaxation of the material [11].

Considering all the potential causes listed above, the objective of this work was to identify the root causes leading to appearance of capping and lamination defects during tableting of a legacy product, with no known previous occurrences of similar issues. A systematic approach was applied, based on batch statistical modelling in order to identify patterns between compliant and non-compliant batches, which could be traced back to a change in the properties of raw materials, processing conditions or equipment and tooling.

The novelty of this study is the use of multivariate data analysis for identifying raw materials, process variables or intermediate product properties with the highest impact on the tablet appearance from routine manufacturing data. Another element of complexity and novelty is the combination of the historical data assessment with small scale studies using a compaction simulator for final blend samples in order to understand differences between extreme batches, under identical conditions. This approach was chosen as historical data from routine manufacturing was partially confounded because typical process adjustments were performed in order to optimize tablet attributes and avoid or minimize the capping or lamination and increase tablet mechanical resistance, like lowering of tableting speed to increase dwell time, changes in compression force values [2, 7].

A wide data set was used for modelling and the pre-assessment part and was composed of numerical attributes of raw materials, processing conditions during granulation and tableting and intermediate product characteristics from 287 industrial scale batches, manufactured for three years. After preliminary grouping based on tableting behaviour, several batches were selected for compaction simulation comparison as part of the pre-assessment. Ultimately, 8 batches were selected for a more in-depth analysis of strain rate sensitivity correlation with density measurements, as a means for predicting the adjustments needed to the tableting process parameters in order to reduce or even remove the defect of capping or lamination.

Materials and Methods

Product and Process summary

In scope of this study was a high dose immediate release film-coated tablet formulation, composed of one active ingredient (approx. 70%) and well-known

excipients: polyvinylpyrrolidone (binder), micro-crystalline cellulose (diluent), sodium starch glycolate and sodium croscarmellose (disintegrants), magnesium stearate and stearic acid (lubricants).

The typical product and process performance with respect to tableting step is presented in Figure 1, with regular tableting speeds in the upper half of the equipment's capacity, representing therefore a high performer from throughput point of view and hardness values in the upper half of the established range, which ensured optimal downstream processability. Both performance indicators have a narrow distribution, suggesting a stable and robust product and process.

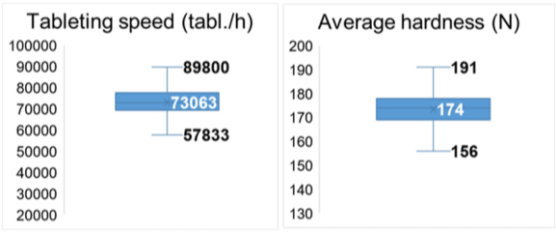

Figure 1.
Historical tableting performance for tableting speed (left) and average hardness (right) - statistics calculated on 143 batches

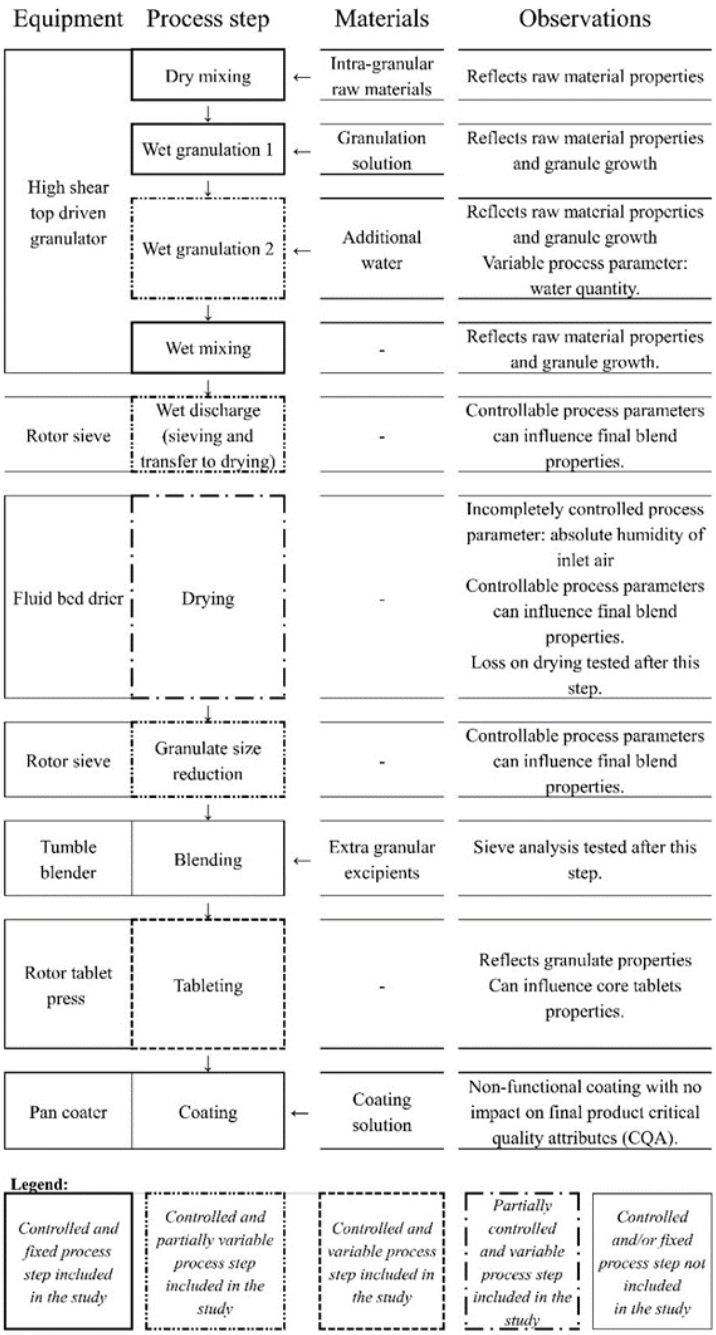

Figure 2.
Manufacturing process flowchart

The manufacturing process consisted of high shear wet granulation with binder solution, followed by wet granulate sieving and closed transfer to fluid bed dryer, milling, blending, compression and film-coating. The outline of the manufacturing process flowchart and process adjustment opportunities allowed by the registration file are presented in Figure 2.

Other details regarding the composition, raw material suppliers, batch size and equipment used couldn't be disclosed, but all the batches included in the study are similar from this point of view.

Historical dataset

Data generated during routine manufacturing of 287 batches (27 manufacturing campaigns) were compiled and used for pre-assessment and root cause analysis. The variables of interest (with highest observed variability) are presented in Table I and they were organized as follows [8]: batch conditions data (BC – one row *per* batch); batch evolution data (BE – multiple rows *per* batch) and in-process controls (IPC – one row *per* batch).

Table I

Data collection plan

Variable type	Attribute (unit of measure)		Data source	Matrix
Raw material	API	Particle size distribution (PSD) by sieving (< 20 and < 20 μm)	Certificate of analysis; one value/batch	BC
Process parameters	Wet granulation	Torque value (Nm)	Equipment report; datapoints at 30 seconds interval	BE
		Final torque value (Nm)	Equipment report	BC
		Quantity of granulation water (kg)	Batch records	BC
	Granule drying	Inlet air flowrate (m^3/h)	Equipment report; datapoints at 30 seconds interval	BE
		Inlet air humidity (g/kg)		
		Product temperature (ºC)		
		Product and filter differential pressures		
		Drying time (min)	Equipment report - endpoint	BC
	Tableting	Speed (tablets/hour)	Batch records	BC
		Fill depth (mm)		BC
		Compression force (kN)		BC
		Compression mode		BC
		Die set (D1 or D2)	n/a	BC
Granule properties		Dry granules loss on drying (LOD) (%)	Batch records	IPC
		Particle size analysis by sieving (%)		
Core tablet properties		Average hardness/batch (N)		
		Capping/lamination		

D1 – initial dies set; D2 – second dies set, replacing the initial one

Considering the stable historical performance of the product, extensive data collection for time dependent process parameters from granulation and drying steps was only performed for the last six campaigns before the occurrence of the tablet defects, summing up 58 batches.

Several process adjustments were performed in order to counter the tablet appearance defects; therefore batches were grouped into 7 main categories, based on the qualitative variables which were part of this analysis: defect occurrence (NO/YES/YES*), compression mode (STANDARD/CONSTANT DISPLACEMENT) and die set (D1/D2) used. Defect occurrence classified with YES* meant that a certain combination of tableting parameters could be identified in order to completely avoid the capping or lamination defects, while NO classification meant total absence of the defect, regardless of the process parameters used and YES classification meant that some tablets still presented the defects.

The two compression modes used during manufacturing of the batches are allowed by the equipment and the role of the later operating mode is to ensure a prolonged compression of the granules in the dies, which theoretically should be beneficial in case of capping or laminations issues [12].

Two sets of dies were used during manufacturing of the batches because at a certain moment during the investigation of root causes for tableting issues, ringing was observed in the dies and the initial set was replaced with a new one. After the introduction of the new dies the capping and lamination defects didn't appear anymore, but there was still some variability between the batches with respect to hardness values, tableting speed and need to use the constant displacement compression mode, which was not typical to the product. This variability and the one observed between the batches in the groups belonging to the initial dies triggered the additional data analysis.

Compaction simulation studies

For initial screening purposes, representative batches, with extreme industrial scale performance, from each of the groups presented above were studied at small scale using a compaction simulator (single punch

Gamlen GTP, series D tablet press – Gamlen Tableting Ltd., Biocity Nottingham, UK). In order to mimic the worst-case operating conditions, compaction profiles were generated at high speed (150 mm/min), high load (500 kg) and high granulate quantity (150 mg) on samples belonging to 20 batches. For each sample the force-displacement curves from the three steps, compaction, detachment, and ejection, were used to generate the compaction performance indicators: work of compression (J), elastic recovery (%), compaction pressure (MPa), tensile strength (MPa), detachment stress (MPa), ejection stress (MPa), solid fraction and porosity. For calculation of Tensile strength, the tablet diameter, thickness and hardness were also determined. In order to compute the last two parameters, true density of the granulate was estimated based on data for individual components taken from literature. All these parameters were included in a PCA model to identify whether the groups of batches show similar behaviour at small scale.

For the second level assessment, the porosity pressure relationship defined by the Heckel equation (Equation 1) was used to calculate the mean yield pressure (Py – Equation 2), as reciprocal of the slope for batches with extreme density values and belonging to different groups based on the industrial scale performance. This parameter can be used to classify the compression behaviour according to the system proposed by Dai *et al*. (Py < 40 – very soft products; 40 < Py < 80 – soft products; 80 < Py < 200 – moderately hard products; Py > 200 – hard products) [5].

$$\ln(1/\varepsilon)=kP + A, \text{ (Equation 1 – Heckel equation),}$$

where, ε – porosity; P – compressure pression; k, A – constants;

$$Py = 1/k, \text{ (Equation 2 – Mean yield pressure calculation).}$$

Mean yield pressure values determined at two compaction speeds (9 and 180 mm/min) were used for the calculation of the strain rate sensitivity (SRS) a parameter which can be used to assess the sensitivity of the material to compression speed [26].

$$SRS = [Py (180 \text{ mm/min}) - Py (9 \text{ mm/min})]/[Py (9 \text{ mm/min})] \times 100, \text{ (Equation 3 – Strain rate sensitivity calculation).}$$

The strain rate sensitivity assessment was performed in correlation with bulk density measurements, as the later can be easily measured during routine manufacturing and could be used as a surrogate for SRS for predicting tableting behaviour with respect to capping and lamination risks.

Data analysis

Batch evolution models (OPLS-Class) were developed using the data compiled for the batches before the occurrence of capping and lamination defects in order to assess the typical process evolution fingerprint. The other batches were used as test batches in order to detect deviating evolutions which could explain the variability noticed during tableting step.

OPLS-DA models were built with historical data in order to identify other differences between the 7 groups of batches and ANOVA was applied to highly correlated variables in order to discern statistically significant differences.

In the next step of modelling, the compaction simulator data was added to the historical dataset of the studies batches and another round of PCA models were developed for a deeper understanding of the observed variability at industrial scale.

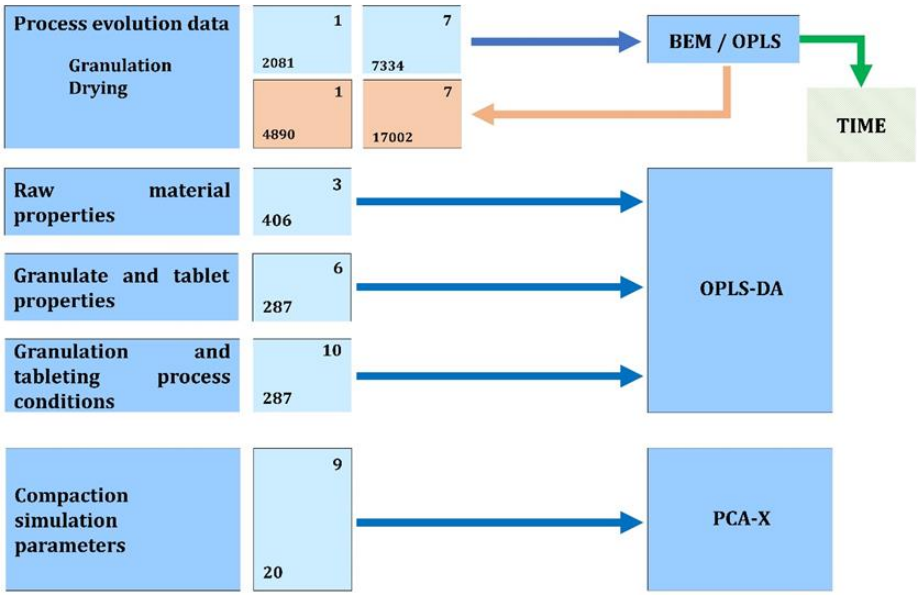

Figure 3.
Model building strategy (blue (smooth) zone – input (X) variables; green (\\\) zone – output (Y) variables; orange – prediction set

In order to evaluate the performance of the models, the percentage of explained variability in X (R2X) and Y (R2Y) and the predictive ability (Q2) were considered. In order to avoid model over-fitting, the number of latent variables was selected based on the cross-validation criteria. All the models were developed using Simca 17 (Sartorius Stedim Data Analytics AB, Sweden).

The complete overview of the model building strategy is presented in Figure 3.

Results and Discussion

Batch Statistical Modelling

Reference process evolution was obtained by developing BEM models for the 58 batches manufactured before the occurrence of the tableting defects. Torque evolution during the liquid addition phase showed a strong time dependence (Q2 = 0.871) proving the similarity between batches and the known robustness of the product. Drying process parameters showed a lower time dependence, as more variability is typical to this process, but without having an impact on the final product attributes.

The rest of the batches in the analysis were included in the prediction set and were compared with the control limits for process evolution. There were no consistent excursions from the ± 3s control limits of batches showing poorer tableting performance, therefore the difference in tableting behaviour couldn't be related to atypical process evolution. As an example, in Figure 4, the torque evolution is presented for batches included in the model and for the prediction set.

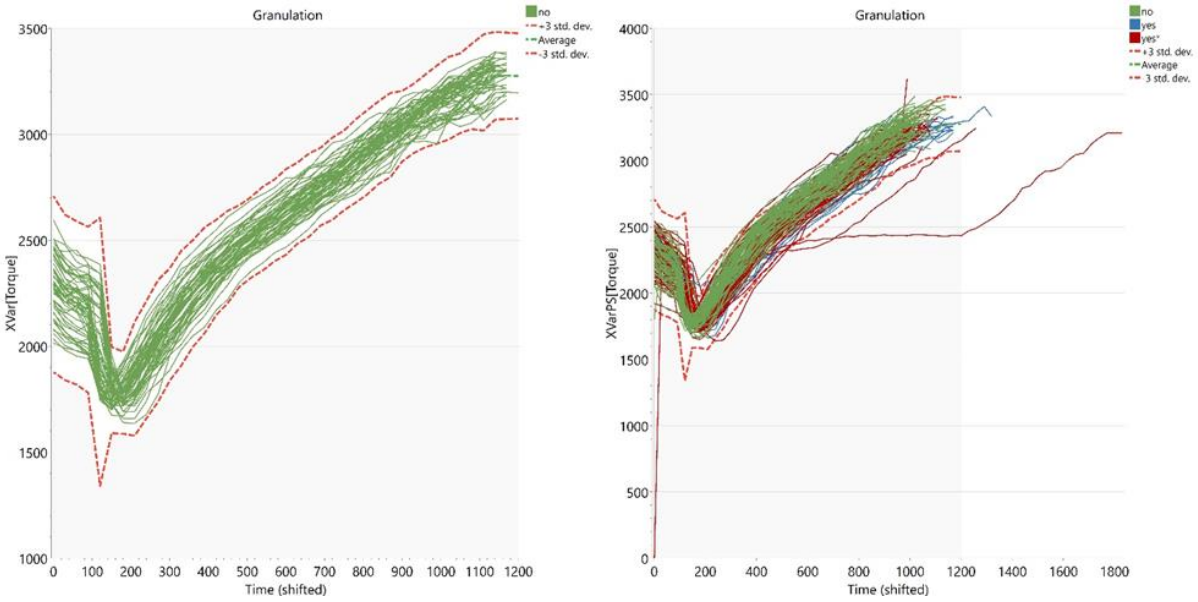

Figure 4.
Reference (left) and prediction set (right) – torque evolution during granulation

The next step in modelling was to compare the 7 groups of batches in terms of single value variables, through building an OPLS-DA model using all the variables except the ones used for grouping (Figure 5). This model explained 68.2% of the observed variability and there was a decent separation between the different groups (Q2 = 0.31).

Groups 2 and 3 showed the clearest separation from the other groups. Group 3 presents the lowest core tablets hardness value and tableting speed and batches from group 2 are the only ones presenting no capping or lamination tendency before the change of dies, independent of the tableting process parameters applied. The variables listed in Table II were selected for ANOVA testing. Most of them presented statistically significant differences between the seven groups ($p < 0.05$). The API particle size distribution results showed the finest results in case of group 7, significantly different from groups 1 and 6, which could explain the different compression behaviour, in the context of new dies. Batches belonging to group 7 presented better tableting performance when they were granulated with less water quantity, which could be explained by the higher water uptake of finer API particles leading to slight over-granulation in case more granulation water quantity was used, which could lead to more difficult tableting set-up in order to optimize hardness value and therefore a lower tableting throughput. Although, under-granulation is more frequently linked to capping/lamination and hardness issues, the actual behaviour depends on the product and through such an extensive investigation, exceptions can be identified. The correlation between the water amount and the API particle size and their common influence on the tableting throughput was confirmed by groups 2 and 3.

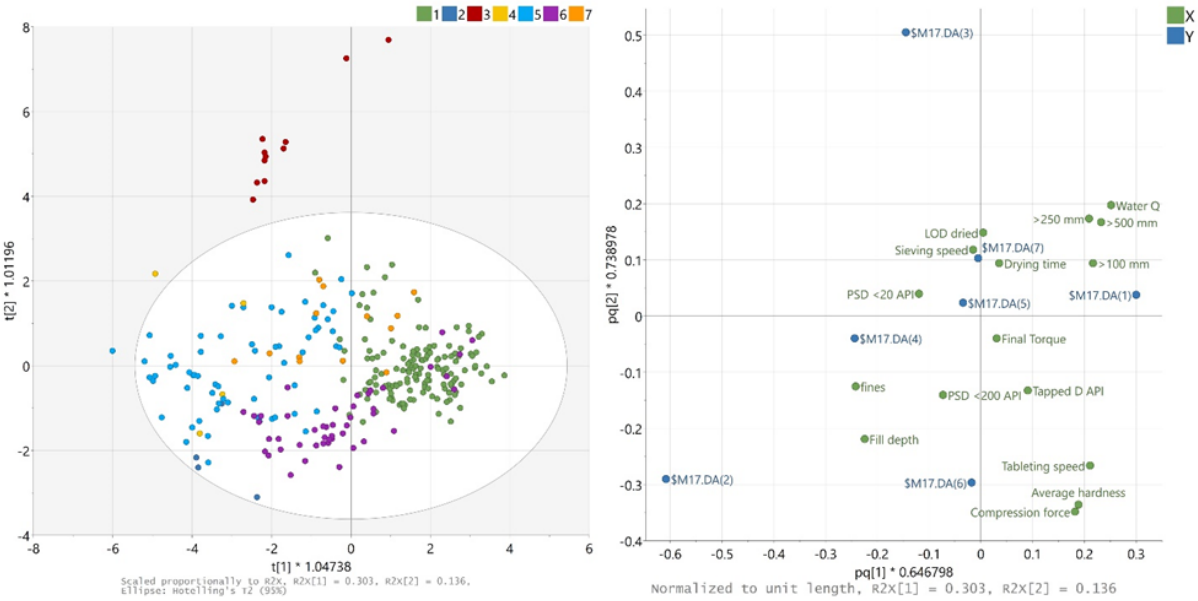

Figure 5.

Score (left) and loading (right) plots of OPLS-DA model build for variable influence screening

Table II

Statistical comparison of relevant variables

		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	
Capping / lamination		**NO**	**NO**	**YES**	**YES**	**YES***	**NO**	**NO**	
Compression mode		**STD**	**CD**	**STD**	**CD**	**CD**	**STD**	**CD**	
Dies		**D1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D2**	
Variable									**p**
API	< 20 microns (%)	56.25 ± 1.08	59.33 ± 3.36	59.58 ± 4.01	59.74 ± 2.15	57.03 ± 1.44	57.30 ± 1.50	62.10 ± 3.76	2.98E-02
	< 200 microns (%)	94.87 ± 0.99	99.80 ± 0.28	91.17 ± 3.72	99.77 ± 0.29	99.94 ± 0.05	98.65 ± 0.52	99.46 ± 0.55	3.81E-06
Granulation	Wet Granulation - Water Quantity (kg)	99.06 ± 0.19	81.65 ± 2.49	101.84 ± 2.96	82.85 ± 2.44	84.62 ± 1.18	89.81 ± 1.20	91.94 ± 1.62	1.52E-97
	Milling - Sieving speed (rpm)	645 ± 13	625 ± 49	655 ± 48	675 ± 94	653 ± 22	611 ± 13	631 ± 41	0.12
Granules	LOD after drying (%)	3.13 ± 0.04	3.08 ± 0.46	3.36 ± 0.08	3.15 ± 0.06	3.04 ± 0.06	3.09 ± 0.09	3.30 ± 0.09	2.06E-04
	> 500 mm (%)	7.70 ± 0.15	4.65 ± 0.33	7.29 ± 1.20	4.93 ± 0.62	5.70 ± 0.38	5.94 ± 0.31	6.95 ± 0.60	9.40E-30
	> 250 mm (%)	5.83 ± 0.17	2.58 ± 0.24	6.08 ± 1.81	2.90 ± 0.45	4.35 ± 0.42	4.35 ± 0.55	4.32 ± 1.83	7.54E-13
	> 100 mm (%)	49.67 ± 1.12	29.15 ± 6.63	47.02 ± 5.98	42.39 ± 19.65	37.99 ± 2.71	45.52 ± 3.61	53.36 ± 7.17	3.36E-14
	Fines (%)	36.79 ± 1.28	63.62 ± 6.64	39.61 ± 7.62	49.79 ± 20.38	51.96 ± 3.11	44.19 ± 4.01	35.37 ± 8.06	4.20E-18
Tableting	Tableting speed (tabl./h)	72733 ± 1378	67354 ± 9210	23461 ± 2018	45062 ± 18881	51430 ± 2319	61889 ± 2177	54223 ± 3504	9.88E-65
	Compression force (kN)	15.0 ± 0.2	14.6 ± 0.8	9.9 ± 0.4	12.6 ± 1.6	13.0 ± 0.2	15.8 ± 0.2	13.8 ± 0.4	1.88E-67
	Fill depth (mm)	10.00 ± 0.08	11.98 ± 0.80	9.43 ± 0.18	11.28 ± 0.75	10.81 ± 0.16	10.40 ± 0.15	9.99 ± 0.26	4.03E-28
Tablets	Hardness (N)	173 ± 1	159 ± 11	119 ± 7	142 ± 16	149 ± 2	171 ± 2	158 ± 6	1.92E-78

STD – standard compression mode; CD – constant displacement compression mode

Group 2 used a water amount at the low end of the range and could be compressed without capping or lamination issues at decent tableting speeds even with the old set of dies, while group 3 used the typical water amount and presented the poorest tableting performance for standard compression mode. This was the group which triggered the extensive investigation, showing at that time also finer API particles than for previous manufacturing campaigns. Group 4, despite being similar to group 2 from API particle size point of view presented a different tableting behaviour, which was investigated further in compaction simulation studies, as they were manufactured in the same period ad group 5 batches, which were compressed with a better overall performance from both tableting speed and average hardness point of view.

Groups 5 and 6 presented similar API properties, but were granulated with different water amounts due to the fact that lower water amounts were identified as beneficial before identifying the ringing defect of the dies. Once the dies were exchanged, a return to the typical granulation water quantity was targeted and was implemented for the second half of the group 6 batches, with good tableting performance.

From this assessment it was concluded that the main impact on the capping and lamination phenomenon was the ringing defect of the dies, but also the API properties and granulation water amount could influence the tableting behaviour. This was supported by the fact that the defect of capping and lamination appeared suddenly, and the dies wear was progressive, so it couldn't have generated alone the clear difference between group 1 and group 3 batches, which belonged to consecutive manufacturing campaigns.

Compaction simulation studies

Initial screening

In order to assess the between and withing groups differences, the following batches were tested in compaction simulation studies, covering batches with high and low performance at industrial scale.

Table III

Composition and codification of metronidazole gel formulations

Batch no.	Group	API PSD (< 20 microns)	Granulation water quantity (kg)	Tableting speed (tabl./h)	Average hardness (N)
L-2019-6-18-1	3	71.0	99.8	25007	130
L-2019-7-4-1	3	51.1	99.8	25079	110
L-2019-7-8-1	3	51.1	108.2	25007	103
L-2019-7-9-1	3	56.9	114.8	25016	99
L-2019-7-10-2	5	58.4	80.0	55000	170
L-2019-12-7-1	5	47.2	82.8	56278	167
L-2019-12-9-1	5	49.8	80.6	30543	136
L-2019-12-10-2	5	63.0	83.0	63085	167
L-2019-12-12-2	5	48.4	84.0	65564	153
L-2019-12-13-1	5	47.5	84.0	64472	155
L-2020-1-10-2	5	48.9	90.0	53901	139
L-2020-2-10-1	5	66.9	81.0	30386	137
L-2020-2-10-2	5	63.6	81.0	26347	141
L-2020-2-14-1	2	54.2	81.0	55950	174
L-2020-2-14-2	4	56.5	81.0	22172	136
L-2020-4-8-3	6	62.1	85.0	58954	180
L-2020-6-16-3	7	73.9	89.4	56075	177
L-2020-6-16-4	7	73.9	89.0	47383	170
L-2020-6-18-2	7	58.6	89.0	49954	155
L-2021-1-18-2	6	55.8	99.6	68549	165

A PCA-X model was built for these batches with the parameters determined through compaction simulation studies. The model was fitted with 1 PC, due to the inter-correlation of the compaction simulation parameters and it explains 47% of the variability between the batches. The groups are clearly separated on the score plot. The combined assessment of the score and loadings plots (Figure 6), suggests that batches with lowest hardness values and highest occurrence of capping and lamination defects are characterized by higher elastic recovery rates, which could explain the potential impact of any wear at dies level (*e.g.* ringing) as the tablet has the tendency to expand after compression, during ejection [16, 27], and any irregularities in the internal surface of the dies could lead to micro-cracks on the sides of the tablet leading to caping or lamination. The same batches are characterized by lower porosity, tensile strength and ejection stress. On the other hand, batches with best tableting performance (highest speeds and typical hardness values) showed lower elastic recovery rates and higher porosity, tensile strength and ejection stress. Extreme behaviours could be therefore explained by this model and supported by literature data [22, 23], but for intermediate performance batches, no clear correlations could be identified. This could be due to the fact that in the compaction simulation studies the tablets obtained are small and round, whereas the product in scope is oblong and a with a

target weight around 5.5 times larger than that of the tablets obtained during these studies and it is known that the shape of the tablet can influence the behaviour of the powders during compaction [14, 18]. In addition to this, the dies wear hypothesis was tested on a small sample after the first manufacturing campaign with new dies and by using the same process parameters the capping and lamination phenomenon reappeared. Therefore, even batches with good performance after the change of dies, could have been similar to intermediate performance batches, due to the intrinsic properties of the tableting mixture (*e.g.* group 5).

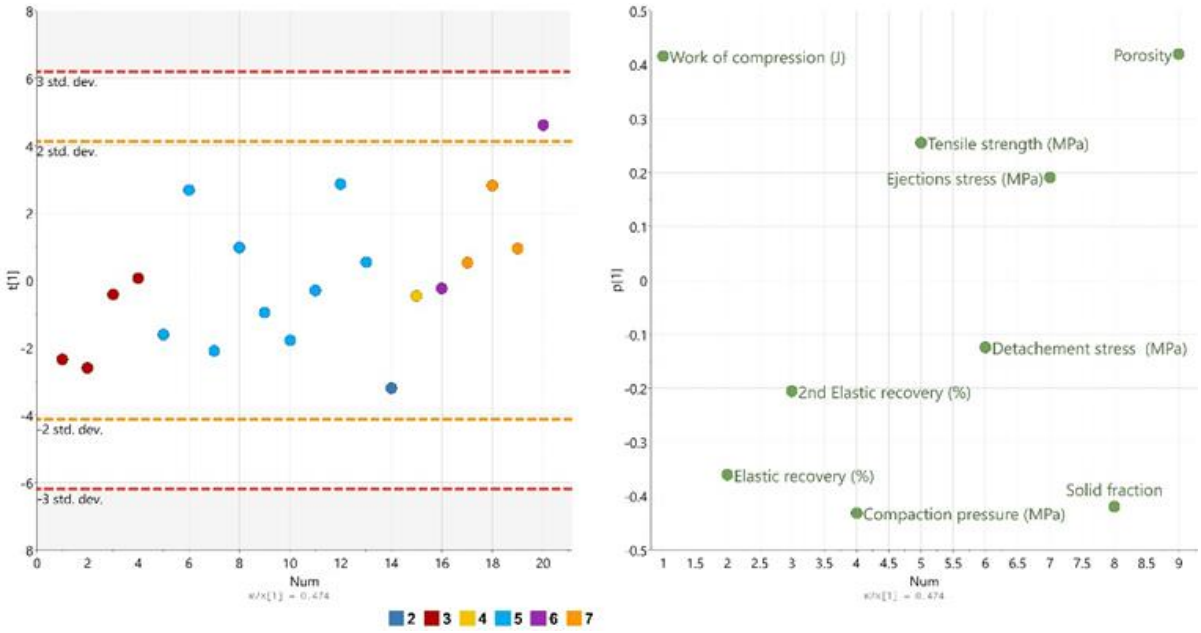

Figure 6.

Score (left) and loadings (right) plots for parameters resulting from the compaction simulation screening studies

Correlation between bulk density and strain release sensitivity for predicting tableting process conditions

For the extended assessment of the granule properties through compaction simulation studies, 26 batches were selected for bulk density measurements (Table IV) and 9 batches with extreme values were further characterized using the compaction simulator in order to calculate the strain rate sensitivity value.

Table IV

Composition and codification of metronidazole gel formulations

Batch no.	Group	Bulk density (g/mL)	Batch no.	Group	Bulk density (g/mL)
L-2020-2-14-1	**2**	**0.526**	**L-2020-9-17-1**	**6**	**0,509**
L-2019-12-7-1	2	0.530	L-2020-9-17-2	6	0.513
L-2019-12-10-2	2	0.496	L-2020-9-18-1	6	0.527
L-2019-7-10-2	**2**	**0.482**	L-2020-9-18-2	6	0.517
L-2019-12-12-2	2	0.535	L-2020-9-18-3	6	0.510
L-2019-12-13-1	2	0.529	L-2021-1-13-1	6	0.576
L-2019-6-18-1	**3**	**0.528**	L-2021-1-15-2	6	0.576
L-2019-7-4-1	3	0.528	**L-2021-1-14-1**	**6**	**0.585**
L-2019-7-8-1	**3**	**0.594**	L-2021-1-16-1	6	0.584
L-2019-7-9-1	**3**	**0.593**	L-2021-1-18-2	6	0.565
L-2020-2-14-2	**4**	**0.513**	L-2021-1-18-1	6	0.578
L-2020-2-10-1	4	0.487	L-2020-4-7-1	6*	0.488
L-2020-1-10-2	4	0.561	L-2020-4-8-1	6*	0.507
L-2020-2-11-1	**4**	**0.484**	L-2020-4-8-2	6*	0.506
L-2020-2-13-3	4	0.533	L-2020-4-8-3	6*	0.496
			L-2020-4-8-4	6*	0.502

*first batches manufactured with new dies; old dies would have caused tablet defects at same tableting parameters; included for comparison purposes at granule level; **bold** – selected for strain release sensitivity calculation

Batches classified as group 6* presented similar density values as the ones in groups 2 and 4 (Figure 7), confirming the similarity between the granulates and the decisive influence of the dies.

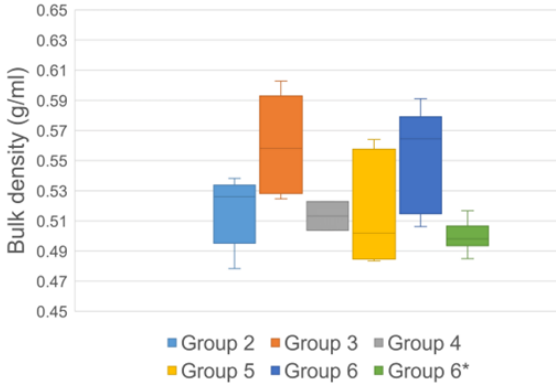

Figure 7.
Comparison of bulk densities between groups

The batches with extreme bulk density values were characterized at two different speeds and at five load levels, in order to generate the data needed for the SRS calculation.

By assessing the industrial behaviour of the batches, the appearance of capping and lamination defects can be explained thorough the SRS values and are consistent with existing data in the literature, as highly plastic deforming materials have low SRS values showing compactability and compressibility, while materials having high SRS values present a higher elastic recovery after compaction [1, 25]. Also, materials which are strain rate sensitive, show capping and lamination issues after ejection [16], which is what was also observed at industrial scale and show a sensitivity of the product to tooling wear.

Table V
Composition and codification of metronidazole gel formulations

Batch no.	Group	P_y (180 mm/min)	P_y (9 mm/min)	SRS	Comments
L-2020-2-14-1	2	152.798	133.678	12.5	Low SRS value, consistent with observed tableting behaviour. Mildest granulation conditions applied for this batch, based on previous observations.
L-2019-7-10-2	2	167.330	141.199	15.6	Intermediate SRS value, CD compression mode removed the occurrence of defects
L-2019-6-18-1	3	166.716	142.310	14.6	Intermediate SRS value, leading to capping and low hardness values in case of STD compression mode, which could be more intense when ringing wear starts to appear
L-2019-7-8-1	3	159.409	131.785	17.3	High SRS value, leading to more frequent capping defects and even lower hardness values
L-2019-7-9-1	3	164.765	135.710	17.6	
L-2020-2-14-2	4	160.464	140.619	12.4	Unexpected SRS value compared to tableting behaviour. Higher variability is observed in compaction profiles between the different runs. Mildest granulation conditions applied for this batch, similar to batch no L-2020-2-14-1, but more intense drying was applied and different granulate particle size distribution is observed.
L-2020-2-11-1	4	161.991	133.775	17.4	High SRS value, leading to more frequent capping defects and even lower hardness values
L-2020-9-17-1	6	150.746	135.167	10.3	Low SRS value, consistent with observed tableting behaviour
L-2021-1-14-1	6	149.842	133.678	10.8	

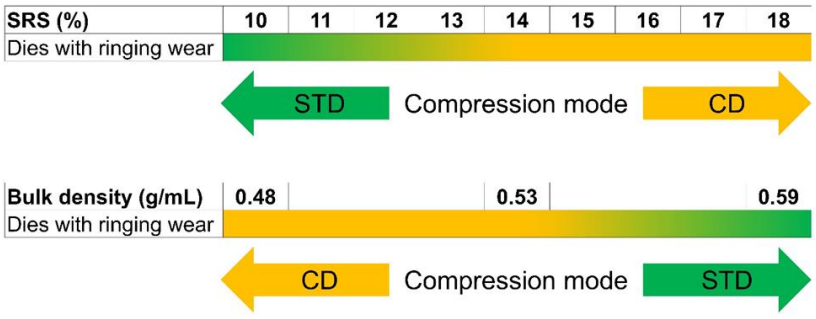

Figure 8.
Prediction of compression mode to be applied based on SRS value (top) and bulk density value (bottom)

Based on the data presented above, SRS values could be used to predict the tableting conditions to mitigate the influence of higher die-wall pressure during ejection, as it can happen in case of worn dies or simply due to final blend characteristics. In case of this product, a SRS value below 14% can be processed in standard compression mode, without capping of lamination issues, while between 14% and 17%, the constant

displacement mode would be desirable and managed to avoid the tablet defect. At values above 17%, the likelihood for capping of lamination defects is high, but the use of the constant displacement mode improved tablet hardness and tableting throughput.

A decent negative correlation (R^2 = 0.7) could be identified between SRS and bulk density values, with the exception of three batches. This could imply that batches with low bulk density (< 0.53 mg/mL) should be compressed using the CD mode in order to avoid capping or lamination issues.

Two atypical batches had a higher bulk density and also a high SRS and presented capping and lamination in STD compression mode. Both batches were granulated with a larger water amount, as they were part of a trial regarding adjustments to be performed to this parameter in order to avoid tableting issues. The higher water quantity led to higher granule sizes, which most probably lead to higher densities values. Higher water quantity was already shown as non-beneficial for this product in case of finer API particles, as means of avoiding capping or lamination issues. If bulk density values would be used to predict tableting conditions, these batches would be a false-negative situation, as the need for CD mode would be identified only after initial set-up issues, in a feed-back manner. The third atypical batch (low density, low SRS) was granulated with 10% less water compared to another batch with similarly SRS value, which could explain the difference in bulk density value. Nevertheless, this batch would present a false-positive situation, as batches that can be processed in STD mode, can also be processed without issues in CD mode, the only difference being the setting-up of the proper displacement value at the compression station.

Therefore, through this small-scale study, a potential feed-forward control strategy could be identified with a prediction accuracy of 78%.

Conclusions

The purpose of this study was to identify and understand the root causes leading to capping and lamination defects during the tableting step of an industrial scale legacy product, by applying a systematic multivariate analysis of routine manufacturing data compiled for 279 batches. The industrial dataset was amended with several small-scale studies of batches with extreme behaviour using a compaction simulator.

During the investigation, one major factor influencing the occurrence of the defects was identified as being a ringing wear of the dies set, which was afterwards replaced with a new set of dies. But due to the sudden appearance of the capping and lamination defects and the fact that several batches could be processed without appearance issues, a more detailed assessment of the impact of several input variables was desired.

The multivariate data analysis tools were used to assess the typical process evolution fingerprint and to identify differences between several groups of batches, classified according to three factors: defect occurrence, compression mode and dies set. The batches showing poor tableting performance were compared against the desired pattern of process evolution built though BEM modelling and no consistent process evolution deviations outside the $\pm 3\sigma$ control limits were observed.

OPLS-DA models and ANOVA testing were used to assess the differences between 7 groups of batches and the API particle size distribution was identified as an additional influencing factor, leading to adjustments needed to granulation water amount, in order to allow proper processing of the batches even when dies presenting the ringing wear were used.

Compaction simulation studies were used for both screening purposes and assessment of strain rate sensitivity, including its correlation to bulk density value.

A PCA model was built using compaction simulation parameters and showed that the batches with the lowest hardness values and capping/lamination defects during industrial manufacturing, presented higher elastic recovery rates and lower porosity, tensile strength and ejection stress, being consistent with existing literature data and explaining the potential impact of the dies wear during the tablet ejection phase.

An extended assessment of extreme batches was done thorough calculation of strain rate sensitivity and the results obtained confirmed the differences observed in practice between most of the batches and enabled to identify some intervals for SRS value which could predict the tableting conditions to be applied. High SRS values, above 17%, were an indication of high probability of capping and lamination, while for batches having intermediate SRS values, the constant displacement compression mode could be used to optimize tableting performance. A decent negative correlation was identified between SRS and bulk density values. This could be used as a feed forward control strategy for establishing tableting conditions, using an easy to measure in-process control parameter.

Conflict of interest

The authors declare no conflict of interest.

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