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Mahamadou Dembélé
Sophie Hudon
Jean-Sébastien Simard
Nicolas Abatzoglou
Ryan Gosselin

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RESEARCH ARTICLE

A multivariate data analysis approach to tablet sticking on an industrial scale: a qualitative case study of an ibuprofen-based formulation

Mahamadou Dembélé[a,b], Sophie Hudon[b], Jean-Sébastien Simard[b], Nicolas Abatzoglou[a] and Ryan Gosselin[a]

[a]Department of Chemical and Biotechnological Engineering, Université de Sherbrooke, Sherbrooke, Quebec, Canada; [b]Pfizer Canada, Kirkland, Quebec, Canada

ABSTRACT

Objectives: Sticking is one of the most common and damaging issues that occur during tablet manufacturing. Sticking is the adhesion of powder onto tooling surfaces during compression. Because of the numerous factors involved in its occurrence, understanding tablet sticking requires the simultaneous investigation of these factors to clarify their possible interactions. However, conducting such a study experimentally can present a significant financial and technical burden. In this study, we aimed to leverage the large amount of data that is usually generated during industrial manufacturing to gain insights into sticking.

Methods: This was achieved by collecting and analyzing a total of 71 historical batches that used an ibuprofen-based formulation. We associate each batch with a hundred parameters, including a qualitative descriptor of sticking, and employ a predefined methodology based primarily on multivariate data analysis.

Results and Conclusions: Our results highlight the role of lubrication, water content, and the low melting point of ibuprofen in its sticking tendency. Based on these findings, we propose and discuss an industrial manufacturing data analysis approach to sticking and its associated systematic methodology, consisting of collection, exploration, and data modeling.

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1. Introduction

Tablets are the most prevalent form of medication (Tita-Goldstein 2013; Chattoraj et al. 2018). This is primarily due to their physical and chemical stability under various conditions, as well as their ease of use and manufacturing (Boussaoud 2003; Santos and Sousa 2008; Iqubal et al. 2014). Tablet production consists of compressing a defined quantity of powder formulation on a tablet press. The formulation is a powder blend of an active pharmaceutical ingredient (API) and excipients that are often dried or wet-granulated to enhance their compressibility and compactability. Compression involves the application of a uniaxial force on the formulation powder that is embedded in the die cavity of the tablet press. Under pressure, the density of the powder blend is increased by expelling air from between the particles (Saniocki 2014; Thomas 2015). The powder then consolidates *via* a series of plastic and elastic deformations and particle fragmentations, leading to the formation of bonds between them (Kadiri 2004; Saniocki 2014).

One of the most common issues that arise during this process is the adhesion of powder onto the surfaces of the press tooling (die and punches); this is referred to as sticking (Chattoraj et al. 2018). This phenomenon can occur at any stage of drug manufacturing, but it is more prevalent and damaging during the industrial production phase, during which, possible changes to the formulation and process are limited (Chattoraj et al. 2018). When sticking appears at this stage, it causes tablet defects and reduces quality and yield. Operators generally stop the press and then remove, clean, and polish the tooling before continuing production. Thus, sticking significantly affects manufacturing costs and production times. It also limits the age of compression tools because of premature wear (Kadiri 2004; Saniocki 2014). Because of these serious consequences for productivity, research has been performed on powder sticking, especially the adhesion of powder to the punch surface (referred to as punch sticking).

Sticking was first described as the result of two opposing forces: first, the adhesive forces between the formulation powder and punch surfaces, and second, the inner cohesive forces between the particles of the formulation powder (Tita-Goldstein 2013; Chattoraj et al. 2018). This simple model states that particles detach from the powder bed and stick onto the punch surface when the strength of the adhesive forces between particles and the surface exceeds that of cohesive forces between the formulation powder particles.

In 2017, another model for sticking was introduced (Paul, Taylor, et al. 2017a). They assert that a model involving two opposing forces cannot explain several well-established observations about sticking: multiple layers of powder accumulate on punch surfaces and API particles make up a high proportion of the powder in these layers (Waimer et al. 1999a; Saniocki et al. 2013; Paul, Taylor, et al. 2017a). Based on their experimental results, (Paul, Taylor, et al. 2017a) propose a more complete model that involves two kinds of sticking and three forces. The first type of sticking (type I) corresponds to light sticking, in which only one layer of powder builds up on the punch surfaces, while the second type (type II) refers to major sticking, with several layers of accumulation. These two kinds of sticking arise from the interplay of three forces, designated as F1, F2, and F3. F1

CONTACT Ryan Gosselin Ryan.Gosselin@usherbrooke.ca Department of Chemical and Biotechnological Engineering, Université de Sherbrooke, Sherbrooke, Quebec, Canada

represents the strength of adhesive forces between API particles and punch surfaces, while F2 is the strength of inner cohesive forces between API particles, and F3 denotes the strength of adhesive forces between API particles and the excipients matrix (Paul, Taylor, et al. 2017a). Sticking only occurs if F1 is greater than the sum of F2 and F3, when the adhesive forces of API particles to the punches predominates . The occurrence of light sticking (type I) or severe sticking (type II) would then depend on the strength ratio between F2 and F3. Accordingly, light sticking is observed if F2 is weaker than F3, in which case a single layer that is rich in API would cover punch surfaces. Severe sticking is observed when F2 is greater than F3. The intensity of these three forces is determined by various interactions, such as van der Waals forces, electrostatic interactions, capillary bonds, and mechanical locking, which all depend on the chemical and structural properties of the particles in the formulation (API and excipients) and the compression conditions, such as the properties of punches surfaces, the compression force, the compression speed, and the environmental conditions. Furthermore, the ratio between the three forces is dynamic and constantly evolving. Therefore, sticking is a complex phenomenon that involves various factors, particularly to evaluate the severity or level of sticking.

A broad range of factors have been investigated to elucidate the sticking mechanism, and clear effects have been found for some. Several studies with different methodologies and formulations have shown that sticking is primarily dependent on the API particles (Kakimi et al. 2010; Saniocki et al. 2013; Paul, Taylor, et al. 2017a; Paul and Sun 2018). In many ways, such findings are predictable, as excipients are chosen for their suitability in manufacturing (mechanical, electrical, and chemical properties), whereas the API is chosen largely for its pharmacological properties. Paul, Taylor et al. (2017a) studied the sticking kinetics of 24 API formulations, finding that the stickiest formulations containing 10% API resulted in a stuck crust containing a 93–96% concentration of API. Similar conclusions with other APIs and methodologies have been reported (Mcdermott et al. 2011; Saniocki et al. 2013). These observations were attributed primarily to the specific physical, chemical, and electrostatic properties of the API particles (Mcdermott et al. 2011; Šupuk et al. 2012; Saniocki et al. 2013; Paul, Taylor, et al. 2017a; Paul and Sun 2018). The results show that—due to their polarity, generally small size, and hydrophobic behavior—API particles are susceptible to triboelectric charging during handling, mixing, and compression (Šupuk et al. 2012; Ghori et al. 2014). This electrostatic behavior, especially the slow dissipation of charge, has been identified as a key factor promoting sticking (Ghori et al. 2014; Samiei et al. 2017). Because of their more suitable electrostatic behavior, excipients can enhance the electrostatic behavior of the whole formulation, thereby reducing sticking relative to API particles alone (Šupuk et al. 2009; Šupuk et al. 2012). In addition to the central role of API particles in sticking, compression speed and duration can promote sticking (Waimer et al. 1999a; Kakimi et al. 2010; Bunker et al. 2011; Paul, Taylor, et al. 2017b; Al-Karawi et al. 2017).

Despite these clear findings, no root causes of sticking have been identified (Al-Karawi 2018; Chattoraj et al. 2018; Costa et al. 2020). The reason is simple: sticking is multifactorial and involves several interactions between the parameters, which can also change over time. For instance, lubrication with magnesium stearate is known to help decrease sticking for numerous formulations (such as mannitol, pozanicline, and macrogol), but increases it for ibuprofen-based formulations (Sendall and Staniforth 1986; Toyoshima et al. 1988; Roberts et al. 2003; Roberts et al. 2004). Another example is the effect of compression force. An increase in the compression force leads to increased sticking for celecoxib or sorbitol-based formulations, but it decreases sticking in acetylsalicylic acid-based formulations (Waimer et al. 1999a; Kakimi et al. 2010; Paul, Wang, et al. 2017). In addition, for ibuprofen-based formulations, the effect of compression force also changes according to the properties of punch surfaces (Toyoshima et al. 1988; Waimer et al. 1999b; Saniocki et al. 2013; Al-Karawi et al. 2017; Al-Karawi and Leopold 2018).

Therefore, recent studies have focused on the simultaneous study of several parameters to understand sticking (Al-Karawi 2018; Costa et al. 2020). Paul, Taylor, et al. (2017a) simultaneously assessed the effect of powder properties and compression parameters on the sticking of 24 different API formulations. They identified the surface area of the API particles, tablet tensile strength, ejection force normalized by particle size, take-off force normalized by tablet tensile strength, and the die wall pressure. Studies by Roberts (Roberts et al. 2003; Roberts et al. 2004) and Al-Karawi (Al-Karawi et al. 2017; Al-Karawi and Leopold 2018) also illuminate the role of compression forces in sticking for ibuprofen-based formulations. These studies describe the significant interactions between the compression force and several properties of the punch surface. An increase in the compression force led to more sticking when the punch surface was smooth, while no effect on sticking was observed when the punch surface was rough (Roberts et al. 2003; Roberts et al. 2004). Punch coating only appears to influence sticking for low compression forces, where uncoated or hard chromium-coated punches generated more sticking than punches coated with titanium nitride or chromium nitride, whereas no difference in their sticking propensity was observed for high compression forces (Schumann and Searle 1992; Roberts et al. 2003; Roberts et al. 2004; Uemura et al. 2007; Al-Karawi et al. 2017; Al-Karawi and Leopold 2018). This interaction was attributed to the increased internal cohesive forces induced by the high compression force, which subsequently overcome the specific adhesive forces between powder particles and each coating (Roberts et al. 2003; Roberts et al. 2004; Bunker et al. 2011).

More multivariate studies that simultaneously investigate the effects of various parameters are necessary to fully understand tablet sticking. However, performing a dedicated experimental study can present a significant technical and financial burden. Indeed, increasing the number of parameters under study inevitably requires a greater number of experiments. Some parameters are also more difficult to obtain and test experimentally, such as punch age and wear, long compression times, high compression speeds, and low dwell times. Nevertheless, substantial data is usually generated during industrial-scale tablet manufacturing, where sticking is inherently prevalent. Accounting for all this data comprehensively may provide insights into the causes of tablet sticking.

In this study, we introduce an industrial data analysis approach to examine tablet sticking. We present a qualitative case study, followed by a deep discussion on the overall approach and methodology. In the case study, we investigate the sticking of an ibuprofen-based formulation by collecting and analyzing industrial manufacturing data. A total of 104 variables were gathered from the production of 71 historical batches, for which sticking behavior was assessed directly as a categorical variable (with either the presence or absence of sticking during compression). Our methodology is based primarily on multivariate data analysis (MVDA) techniques. The specific objectives of this work are expressed as follows:

1. Identifying the key parameters contributing to the occurrence of sticking using an ibuprofen-based formulation.
2. Developing a classification model to predict the occurrence of sticking on a batch during its compression.
3. Discussing the industrial data analysis approach and methodology to provide insights into tablet sticking.

2. Materials and methods

2.1. Formulation

The active pharmaceutical ingredient of the formulation is ibuprofen, a common non-steroidal anti-inflammatory drug. The other substances present in the formulation include aspartame, mannitol, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, modified corn starch, natural and artificial flavors, sodium starch glycolate, and coloring agents. Tablets are manufactured through a direct compression process involving mixing and sieving operations before compression using a tablet press. Due to confidentiality concerns, no further details regarding the manufacturing process are provided.

2.2. Data collection and preparation

During the industrial manufacture of these confidential-formulation tablets, copious volumes of data regarding the processing steps are generated. For this study, we collected this data from various sources such as master batch record files, certificates of analysis for raw materials, and the records on temperature and relative humidity in the operating rooms and warehouses. A total of 104 variables were gathered for 71 historical batches.

The raw data were cleaned and prepared before analysis. First, some variables were found to be nearly constant or to present a high proportion of missing data ($>$ 50%). Therefore these were discarded. For quantitative variables, the coefficient of variation (ratio of the standard deviation to the mean) was employed to set a low variation criterion (1%). Thus, quantitative variables displaying a coefficient of variation of less than 1% were discarded from the data. For qualitative variables, the low variation criterion was set as the presence of a maximum of two observations among all batches with modalities different from the mode of the concerned variable.

Second, after the cleaning operations, only a few missing values remained in the data. Notably, the main analysis algorithms employed in this study—namely, the principal component analysis (PCA) and partial least squares-discriminant analysis (PLS-DA)—can be adapted to account for the presence of missing data, and thus, the few missing values were imputed from the mean of the corresponding variable when necessary.

The final dataset consists of 71 batches described by a set of 46 variables, referred to herein as V1 to V45, plus a qualitative **y** variable describing the sticking behavior of each batch. This **y** variable separates the 71 batches into two classes consisting of batches that were not affected by sticking and those that were affected. The first class is composed of batches for which no sticking was observed during compression, and the second class consists of batches for which sticking issues were observed during compression. Except for the qualitative **y** variable, all the remaining 45 variables were quantitative. These can be divided into five different groups:

- Group 1: V1–8 are related to materials (API + excipients).
- Group 2: V9–16 give information about the mixing step, including the cleaning methods used on machines and the durations of various mixing operations.
- Group 3: V17–36 relate to the environmental conditions in different rooms where manufacturing operations, from dispensing to compression, take place.
- Group 4: V37–39 represent the tablet dimensions and weight.
- Group 5: V40–45 relate to the parameters of compression operations.

During the collection campaign (encompassing 71 batches), environmental conditions variables (V17–36) were unavailable for some batches (batches 1–46). To study the impact of these environmental variables, two datasets were generated: dataset1 and dataset2. Dataset1 includes all batches and all variables except those related to the environmental conditions while dataset2 only comprises batches for which data was available for all variables including environmental conditions. The resulting sizes of both datasets were 71 batches $\times$ 26 variables (dataset1) and 25 batches $\times$ 46 variables (dataset2). These were scaled and centered to unit variance prior to analysis.

2.3. Analysis methodology

Both dataset1 and dataset2 were analyzed in three main steps, using the Python programming language (version 3.7) along with MVDA software, namely SIMCA (version 16.0.2.10561) from Sartorius.

The first step involves univariate and bivariate analysis of both datasets to determine whether any single variable could significantly explain or predict the observed sticking behavior. For this purpose, scatter plots of input variables are colored according to the occurrence of sticking.

The second step consists of a multivariate investigation of both datasets using PCA to check for the presence of clusters of observations representing sticking. PCA is a well-established multivariate method employed to reduce the dimensionality of large datasets by capturing the highest amount of variation in the datasets in a few orthogonal components. It facilitates the visualization and investigation of similarities between observations, following linear combinations of the input variables along the principal components. PCA was well-described and discussed by (Eriksson et al. 2001; Johnson and Wichern 2002; Shaffer 2002).

The third step consists of discriminant analysis (DA). Linear discriminant analysis (LDA) is applied to dataset1, while the DA version of partial least squares regression (PLS-DA) is used for dataset2. These analyses use a supervised approach to yield insights into sticking.

LDA is a classification technique that allows for the development of multivariate models to classify observations among modalities of a qualitative **y** variable. It is aimed at finding a linear combination of the original predictive variables that separate the different modalities of the **y** variable. This modeling technique is generally referred to in the literature as factorial DA or canonical DA (when the objective is strictly descriptive). For predictive purposes, LDA modeling provides a classification function for predicting the membership of a new batch among the modalities of the qualitative **y** variable. Both descriptive and predictive attributes of LDA have been reviewed and discussed previously (Johnson and Wichern 2002; Xing et al. 2003; Lammertyn et al. 2004; Huberty and Stephen 2006; Rakotomalala 2020).

For dataset2, there are more variables than the number of observations available, which precludes the use of LDA because the degree of freedom is too low to proceed, also owing to the risk of multicollinearity issues (Yendle and MacFie 1989; Rännar et al. 1995; Naes and Mevik 2001; Nørgaard et al. 2006; Dormann et al. 2013). Instead of LDA, we employ PLS-DA, a different

technique for discrimination. Broadly speaking, this technique has the same objective as LDA, but the extracted components for the descriptive model and the independent variables used for predictive modeling are different. PLS-DA employs latent variables extracted from the original predictor matrix by PLS, a well-known multivariate procedure. These latent variables facilitate the visualization and description of the discrimination as per descriptive outcomes of LDA. However, the latent variables are also used as predictors in PLS-DA predictive modeling, instead of the original variables for LDA. PLS-DA has been extensively described previously (Eriksson et al. 2001; Johnson and Wichern 2002; Huberty and Stephen 2006).

3. Results and discussion

3.1. Sticking data

When sticking occurs during the compression of a batch, operators generally stop the press, note the cause of the interruption, assess the situation, and fix the issue before restarting. Since the operators did not specifically report the severity of individual sticking events, we utilized their notes to set up a qualitative y variable to assess the sticking behavior of batches. According to this qualitative y variable, batches were split into two classes: batches unaffected by sticking and batches that were affected by sticking (as assessed by the operators). Table 1 presents a breakdown of the number of observations in both datasets.

Table 1. Repartition of the number of batches following the qualitative **y** variable modalities.

	Modalities of the qualitative **y** variable				
Datasets	Batches unaffected by sticking		Batches affected by sticking		Total
Dataset1	51	71.8%	20	28.2%	71
Dataset2	18	72%	7	28%	25

3.2. *Univariate* data analysis

3.2.1. Dataset1

Scatter plots of the input variables were color-coded according to the presence of sticking during the compression (**y** variable). An excerpt of this representation is given in Figure 1. These variables (V8 and V13) were chosen because they exhibit the highest correlation with the **y** variable.

Examining the scatter plots of individual variables reveals no clear trend of discrimination between batches affected or unaffected by sticking (Figure 1). Thus, no single variable—nor any of the bivariate combinations assessed—can explain the occurrence of sticking. Furthermore, univariate data analysis is used to check for outliers from each variable. To this end, we identified several possible outliers. However, after evaluating different raw data sources, no data reporting error was noted, and all of the values were compliant with reglementary standards when needed. Therefore, no action has been taken to treat or remove them. This decision is also motivated by the fact that none of these outliers were physically unreasonable considering the reality of a day-to-day tablet manufacturing processes.

3.2.2. Dataset2

For dataset2, only scatter plots of variables representing environmental conditions (V17 to V36) were considered, since the remaining input variables were already assessed in dataset1. As with dataset1, no clear trend of discrimination was observed between the batches affected by sticking and those unaffected by sticking. Thus, no single variable related to environmental conditions can explain the occurrence of sticking. Several possible outliers were identified, but after verification of the raw data, they were also kept in data for the same reasons described for dataset1.

The results of the univariate analyses may be expected because sticking is known to be a highly multivariate phenomenon (Al-Karawi 2018; Chattoraj et al. 2018). Consequently, combined information from several variables is required. However, it

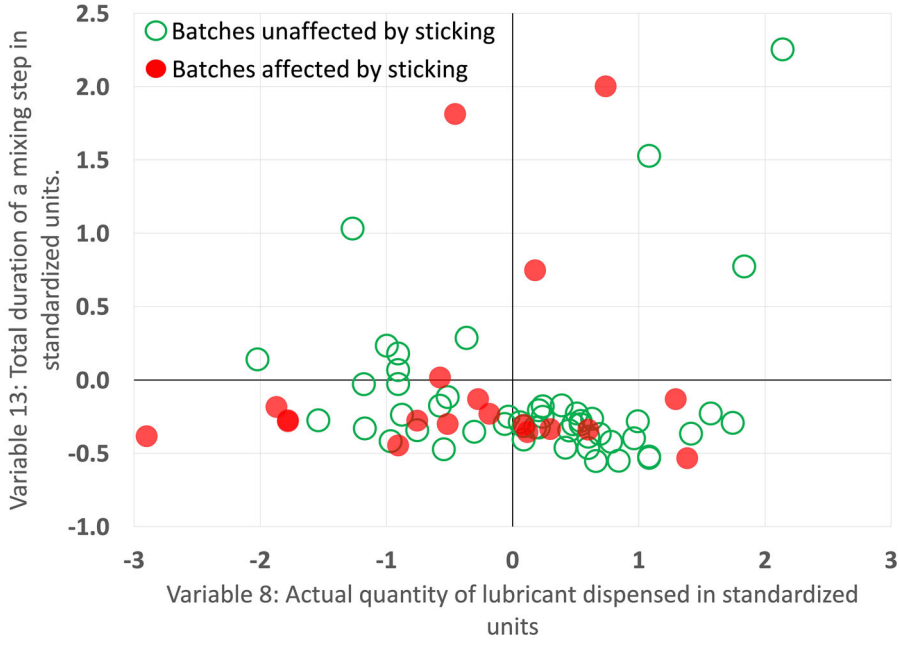

Figure 1. Scatter plot of input variables in dataset1 colored according to the presence of sticking (**y** variable). This excerpt corresponds to V8 and V13, which are the actual quantity of lubricant dispensed and mixing step duration, respectively.

remains important to systematically use univariate data analysis to fully understand the data and to treat eventual outliers when they reflect errors or could induce noise in the data. To yield further insights regarding sticking, we employed MVDA techniques, beginning with PCA followed by DA.

3.3. Principal component analysis

3.3.1. Dataset1

The first PCA model was built on dataset1. According to an analysis of the scree plot, a total of 10 components were exploited. These account for approximately 70% of the variance in dataset1. Figure 2 displays the score plot of the two first components of this PCA model.

In the score plot, the batches affected and unaffected by sticking overlap (Figure 2). The same conclusion can be drawn from the analysis of the subsequent eight PCA components. Therefore, this first PCA model does not reveal any clear discrimination according to the observed sticking in dataset1. This does not mean that dataset1 cannot be used to explore sticking. It simply means that these first components explain other phenomena that account for more variance within the data than sticking.

3.3.2. Dataset2

A PCA model was also built on dataset2, including all available information. A total of eight components were retained according to the analysis of the scree plot, but no clear trend regarding sticking was found in dataset2.

The failure of PCA to explain the observed sticking is unsurprising. PCA is an unsupervised learning technique that tends to reveal spontaneous clusters for successive components that are decreasingly extracted following the most important dimension of variance in the data (Shaffer 2002). Therefore, PCA components describe the sticking phenomenon only if it represents one of the most important dimensions of variance retained. This was not the case for either dataset1 or dataset2. To overcome this limitation, we employ supervised learning techniques, particularly DA, in which the qualitative **y** variable (the occurrence of sticking) guides component extraction.

3.4. Linear discriminant analysis of dataset1

3.4.1. Descriptive outcomes

The first descriptive DA model was developed for all variables and observations in dataset1 (71 batches x 25 variables). The corresponding score, loading, and variable importance plots are depicted in Figure 3.

The significance of an LDA model is evaluated using Wilks' lambda, a well-known statistical parameter (Johnson and Wichern 2002; Rakotomalala 2020). This statistical value represents the overall quality of discrimination results. It allows for the simultaneous comparison of several averages by assessing the part of intraclass inertia in the total variance. It corresponds to the ratio between the determinant of the intraclass variance-covariance matrix and the determinant of the total variance-covariance matrix. In this way, Wilks' lambda always varies between 0 and 1, where 0 represents more reliable discrimination because of a better interclass separation. A test with a null hypothesis, positing equality of the class averages, is performed to assess the significance of the observed Wilks' lambda value with regard to the number of observations, variables, and classes of the target variable. Wilks' lambda follows a complex distribution and, generally, a transformation is first computed to approximate more common distributions. The transformed statistic (RAO transformation and Bartlett transformation of Wilks' lambda) is then compared to a Fisher distribution and χ^2 distribution (Johnson and Wichern 2002; Huberty and Stephen 2006).

The first DA model built on dataset1 relies on one canonical component, with a Wilks' lambda value of 0.7424, which is insignificant with a *p* value over .8 (Figure 3(A)). Therefore, the discriminating power highlighted by this first model does not lead to a significant separation between the batches affected by sticking and those unaffected by sticking. Although the separation is insignificant, the batches affected by sticking exhibited a slightly lower score, along with component 1, than batches unaffected by sticking (Figure 3(A)). The corresponding loading plot (Figure 3(B)) indicates that the batches affected by the sticking cluster, aside from those unaffected by sticking, based on their relatively high values for V6, V13, and V45 and their relatively low values for V8 and V44. V3, V9, V10, V14, V16, and V37, may also be important.

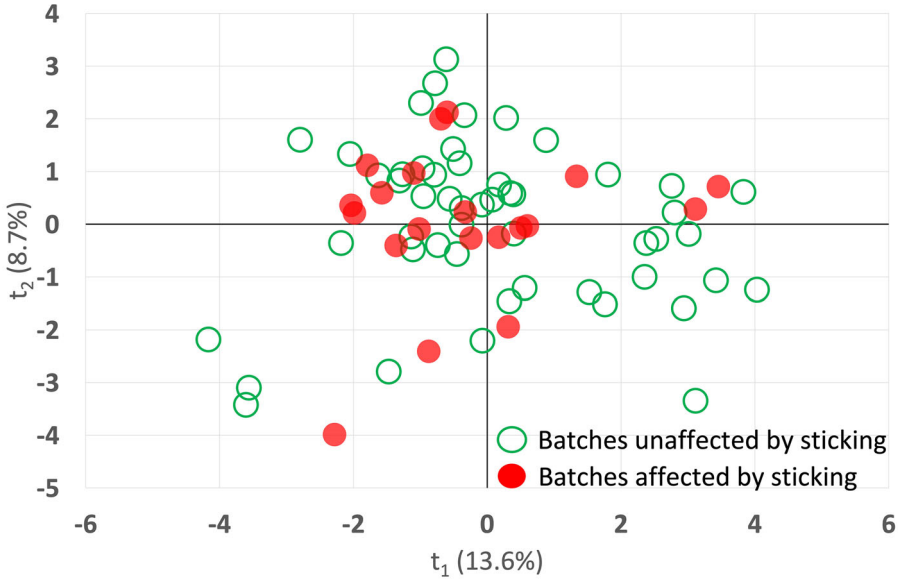

Figure 2. The score plot of the PCA model built on dataset1.

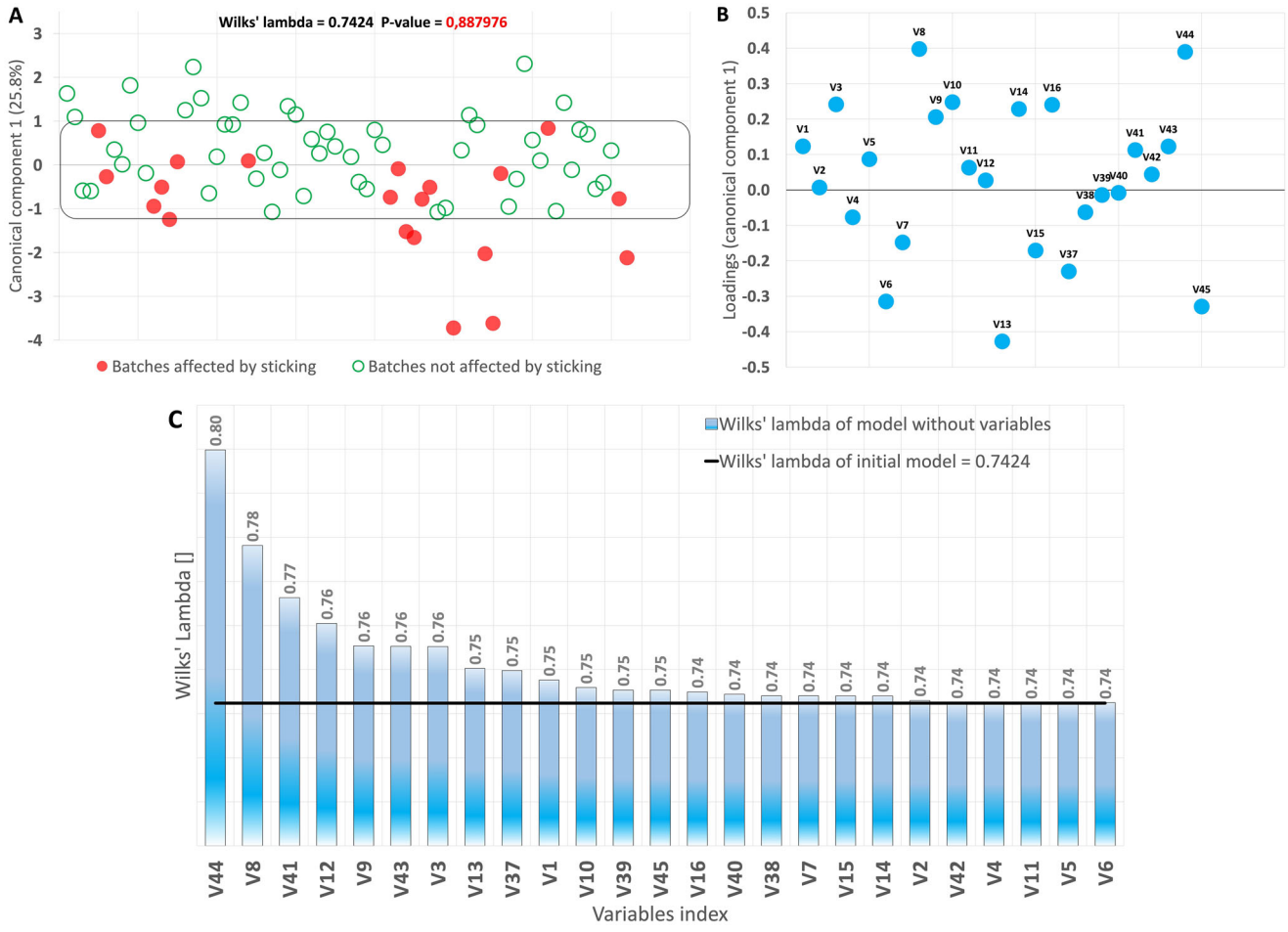

Figure 3. Score (A), loading (B), and variable importance (C) plots of the first descriptive LDA model developed on dataset1. The frame on the score plot (A) indicates the overlapping.

The importance of each variable is given by the variable importance graphic (Figure 3(C)). This graphic displays the variation induced in the initial Wilks' lambda of the model by the removal of each variable, thereby preventing the misinterpretation that can sometimes arise with a direct lecture of low loadings, as observed in Figure 3(B). As Wilks' lambda increases with the withdrawal of a specific variable, that variable becomes more relevant for discrimination. Following this graphic, some variables are relevant while many others account for nothing in the model. These results suggest that there is some information in dataset1 that is useful in distinguishing the two groups of batches, although its significance is probably masked by the presence of several variables that account for little or nothing in the discrimination. For instance, the Wilks' lambda value of the model does not change when some variables, such as V2 or V4, are discarded from the model; in contrast, it increases when V8, V41, or V44 are removed (Figure 3(C)).

Thus, we executed a well-known backward variable-selection strategy to optimize the LDA model (Johnson and Wichern 2002; Huberty and Stephen 2006; Rakotomalala 2020). We computed the first LDA model, including all of the variables, and calculated the initial Wilks' lambda value. The model was then optimized by recursively removing the variable contributing least to the Wilk's lambda value. Thus, seven variables were selected, and a second LDA model was then built with these variables. The corresponding score, loading, and variable importance plots are depicted in Figure 4.

Unlike the first LDA model, a clear trend of discrimination is now observed in the score plot (Figure 4(A)), even if an overlap is still observed in the center of the graph, albeit to a lesser extent than in the first model (Figure 3(A)). Moreover, discrimination is observed using only seven variables, as opposed to using 25 variables in the first LDA model. Consequently, this second optimized model results with a slightly higher Wilks' lambda value of 0.8044, which is still significant with a p value below .05. This indicates the existence of relevant information in dataset1 that distinguishes the batches affected by sticking from those unaffected by sticking. According to the loading plot in Figure 4(B), the LDA component—along which several batches affected by sticking stand out from some unaffected by sticking on the score plot—is positively correlated with V8 and V44 and negatively correlated with V13 and V37. The variable importance plot in Figure 4(C) illustrates that all seven variables in the optimized model are important for achieving the observed discrimination. Nevertheless, only two of them significantly contribute to the separation. These are V8 (corresponding to the total quantity of lubricant dispensed in the formulation) and V44 (the total duration of stops during the compression of the whole batch). The influences of V8 and V44 indicate that a batch is more likely to be affected by sticking when there is less lubricant dispensed (V8) in the formulation and when there are fewer stops during compression (V44). Similar results were obtained when using the PLS-DA method (Appendix A). The effects of these two variables on sticking occurrences are discussed in detail in section 3.6. For the other variables that

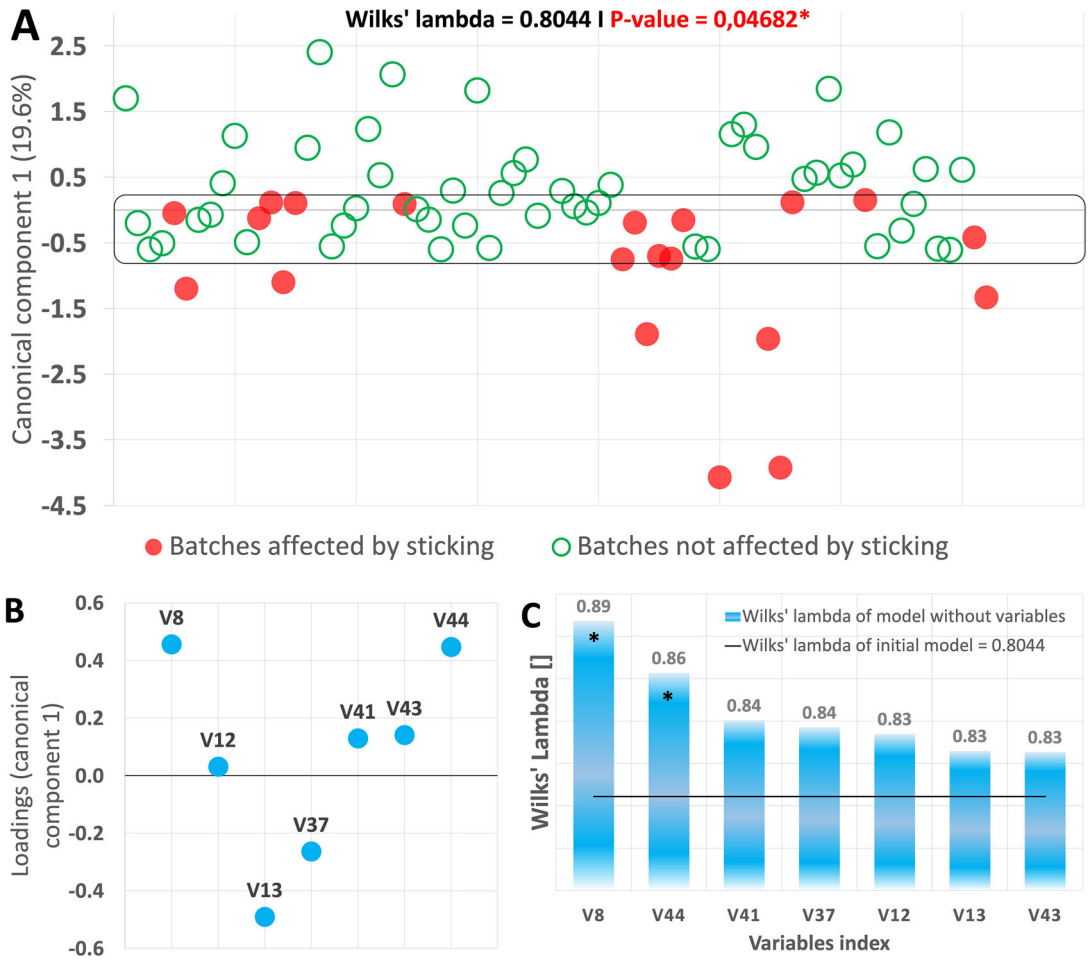

Figure 4. Score (A), loading (B), and variable importance (C) plots of the optimized descriptive LDA model developed on dataset1. The frame on the score plot (A) indicates the overlapping. (*) indicates the statistical significance of the change induced in Wilks' lambda by the withdrawal of corresponding variables (C).

were identified as important but not significant, more data are necessary to confirm their role in sticking.

Although some insights regarding sticking were found, only a small portion of the difference between affected and unaffected batches is explained by the presented models, since the high values of Wilks' lambda (0.7424 and 0.8044) in both models indicate a low interclass variance in dataset1. This is probably because some important factors contributing to sticking are not included in dataset1. Furthermore, since the data were obtained from historical batches, data on some variables that are potentially important for the occurrence of sticking were unavailable. These variables include punch surface conditions, several specific properties of materials at defined steps of the process (such as the water content, the electrostatic properties, and particle size), and several compression parameters that are not systematically recorded, such as the actual compression force over time. Moreover, no variables related to environmental conditions at the manufacturing plant are present in dataset1, exacerbating the lack of potential information that can help explain the observed sticking. Data collection that addresses more variables may yield more complete and precise interpretations.

However, unlike the PCA model, the LDA model does provide insights about sticking, even if these do not account for the most important portion of the total variance in this specific data. This is due to the way that DA extracts its components. Instead of extracting the components with the greatest variance in data one after another, DA searches for the dimensions that maximize the separation between the centers of two classes. This has been achieved here, even if only a small portion of the phenomenon was captured.

3.4.2. Predictive outcomes

A classification function is associated with the LDA models developed before and after optimization. The performances of these two classification models in predicting sticking during compression are presented in Figure 5.

According to these results, the first LDA model (computed before optimization) classifies the 71 batches with error rates of 23% and 46% in calibration and validation, respectively (Figure 5). This indicates overfitting, as the model is better at classifying batches when they are included in its construction (calibration) than when they are excluded (validation). Strong overfitting is an indicator of variables in the dataset that contribute little or nothing to the actual explanation and prediction of the studied phenomenon, following the descriptive model discussion. After optimization, the new model led to a slightly lower error rate in calibration, with a 20% misclassification rate. However, the cross-validation error rate decreases significantly from 46% to 23%, which is closer to the new calibration error (Figure 5). Therefore, unlike the first model, the optimized model predicts both the batches used in its construction and new batches.

The optimized model possesses the necessary performance to predict sticking in production, or for providing an early indication. However, a detailed examination reveals that the prediction error

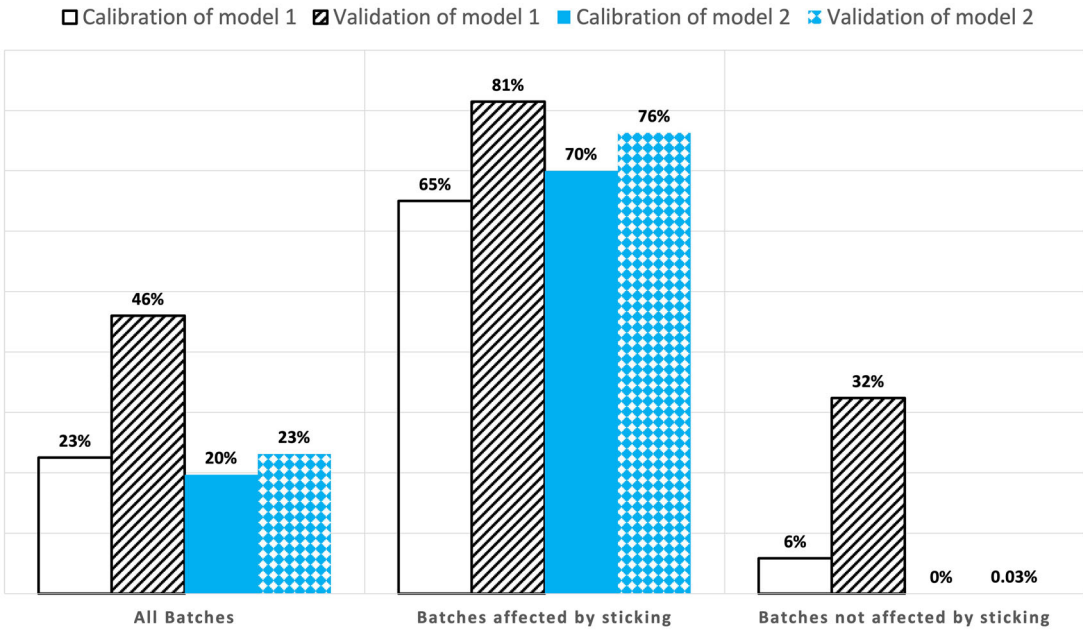

Figure 5. Histogram of the classification error rate for the predictive LDA models. Model 1 and Model 2 represent the model before optimization (71 batches × 25 variables) and the optimized model (71 batches × 7 variables), respectively. The validation error rate corresponds to the result of a seven-folds cross-validation procedure.

rate of the model depends on the class of batches, indicating the existence of bias. Moreover, batches affected by sticking are systematically the worst-classified batches, with an error rate of 65–81%, compared to an error rate of 0–30% for batches unaffected by sticking (see Figure 5).

In light of the results and raw data, the observed bias appears to be understandable. This is probably due to the very definition of batches affected by sticking. We found that 60% of these batches involve only one sticking event reported during their whole compression. Based on the importance of these single sticking events, some of these batches may be regarded as unaffected by sticking. However, without any other information on the importance of the single sticking events, sorting is not possible. Therefore, all of these were classified as affected by sticking, which probably prevents the models from correctly predicting batches affected by sticking. Thus, the developed models have trouble distinguishing some batches affected by sticking from those unaffected by sticking. The overlap observed in the center of the score plots in explicative models (Figures 3(A) and 4(A)) is probably related to this issue.

This fine line between sticky and not-sticky batches constitutes a major limitation of our study on two levels. First, since some of the batches affected by sticking are difficult to separate from those unaffected by sticking, variables identified as significant contributors to sticking may just be artifacts caused by the outlying behavior of a few sticking batches. Fortunately, this can be assessed by analyzing the raw data on the identified variables. The results of this analysis are presented in a dedicated section of this paper (see section 3.6). Second, such a bias definitively prevents the developed model from determining whether a new batch is likely to have sticking issues, potentially making multiple false predictions for batches affected by sticking. To overcome this limitation, stickier batches can be gathered and included in the study, thereby preventing confusion between the two classes. Furthermore, a quantitative **y** variable with a large range of sticking behavior may be a more effective means for preventing the observed bias. Using several distinct profiles of sticking in the data may prevent eventual bias due to categorization. Moreover, it can be more informative because the relationships between input variables and sticking events can be described from multiple perspectives. Another means of preventing the observed bias is to perform planned data collection, where a systematic evaluation of sticking event intensity is conducted. This can be achieved in several ways. For instance, an intensity scoring methodology can be developed and adopted by manufacturers. Moreover, a procedure that allows operators to quickly take a photo of the punch surface before cleaning it—or even to preserve the stuck powder for subsequent analysis—could be implemented.

3.5. Partial least squares-discriminant analysis of dataset2

3.5.1. Descriptive outcomes

The first PLS-DA model was built on dataset2, including all batches and variables available (25 batches × 45 variables). For simplicity, the outcomes of this first PLS-DA model are not presented here. Like the first LDA model, the first PLS-DA model consists of one latent component that was also subject to overfitting according to classification errors. Therefore, a variable-selection strategy was also conducted to optimize the model. The employed strategy is quite different from the one conducted for the LDA models with dataset1. The PLS-DA model is optimized based on the variable importance in the projection (VIP), which is a well-known statistic in partial least squares procedures (Eriksson et al. 2001; Mehmood et al. 2020). VIP is a dimensionless parameter that enables estimation of the importance of each variable in the projection along with the latent variables extracted by the PLS procedures. A threshold value of 0.8 or 1 for VIP is generally accepted as heuristic of a particular variable's importance. This parameter is often used to perform variable selection when PLS-based models are overfitted (Eriksson et al. 2001; Shaffer 2002; Mehmood et al. 2020). The strategy excludes variables exhibiting a VIP value significantly lower than a predefined threshold. Because of their low contribution to the projection on latent structures, these variables are probably just modeling noise and

data, rather than representing physics, leading to a good performance in calibration but poor performance in validation.

The VIP-based selection strategy was computed to optimize the first PLS-DA model. The first selection was operated by filtering all variables exhibiting a VIP score lower than 0.8. Then, a new PLS-DA model was built on the remaining variables. This model also exhibits overfitting issues. Thus, a second variable-selection operation was conducted by filtering out all of the variables that failed to display a VIP score significantly greater than 0.8. This led to the selection of a set of 10 variables (V8, V11, V13, V21, V22, V29, V33, V34, V42, and V44). Using these 10 variables and the 25 observations available in dataset2, we built an optimized PLS-DA model. The corresponding score, loading, and VIP plots are presented in Figure 6.

The optimized PLS-DA model distinguishes batches affected by sticking from those unaffected by sticking, even if an overlap is observed in the center of the score plot (Figure 6(A)). This model allows for discrimination with an overall multiple analysis of variance *p* value of .01. According to the score and loading plots given in Figure 6, some batches affected by sticking stand out from many batches unaffected by sticking, which is based on their relatively high values for V29 and V33, as well as their low values for V34. The VIP plot for more precision (Figure 6(C)) shows that all 10 variables are important for explaining the observed discrimination, although only seven of them, depicted in green, are identified as contributing significantly to sticking (in order of importance: V33, V29, V22, V34, V42, V21, and V44). Their effects are discussed in detail in section 3.6. For V8, V11, and V13, which were identified as important but not statistically significant, more data are needed to confirm their impact on sticking.

3.5.2. Predictive outcomes

The predictive performances in the calibration and validation of the optimized PLS-DA model are presented in Figure 7.

The optimized PLS-DA model misclassifies 24% and 28% of batches in calibration and validation, respectively. These reasonable performances suggest that they can be useful in industrial production to predict sticking during the compression of a new batch, or at least to give an early indication of sticking. However, a detailed examination of the calibration and validation scores highlights the same bias observed in the prediction of affected batches by the LDA-optimized model. The PLS-DA model also made more errors predicting the affected batches versus unaffected batches, with error rates of 57% and 71% for affected batches in calibration and validation, respectively, versus an error rate of 11% for unaffected batches (Figure 7). This leads to the same bias as discussed with the optimized LDA model. Therefore, using the optimized PLS-DA model as a predictive tool carries a high risk of misprediction of batches affected by sticking. In addition, the sharp gap between the error rates in calibration (57%) and validation (71%) also suggests overfitting for these batches. This is probably due to the low number of batches affected by sticking in dataset2, potentially leading to a lack of generalization.

3.6. Discussion of the significant insights identified

Our analyses of dataset1 and dataset2 have identified a total of eight variables (V8, V21, V22, V29, V33, V34, V42, and V44) as significantly contributing to sticking in the ibuprofen-based formulation. Due to the observed bias in the developed models, the importance of these variables may be artifacts, resulting from the presence of outliers in

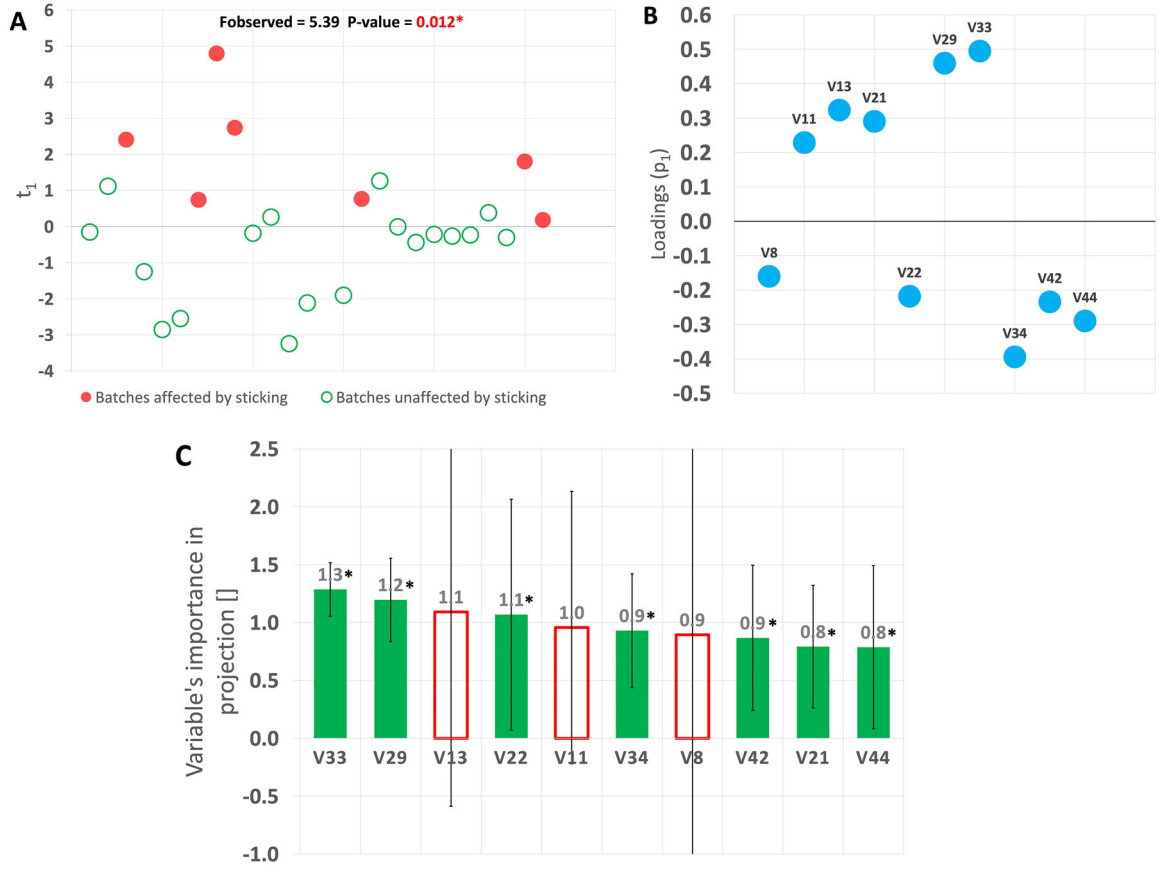

Figure 6. Score (A), loading (B), and VIP (C) plots of the optimized PLS-DA model. (*) indicates the statistical significance (95%) of the VIP scores (C).

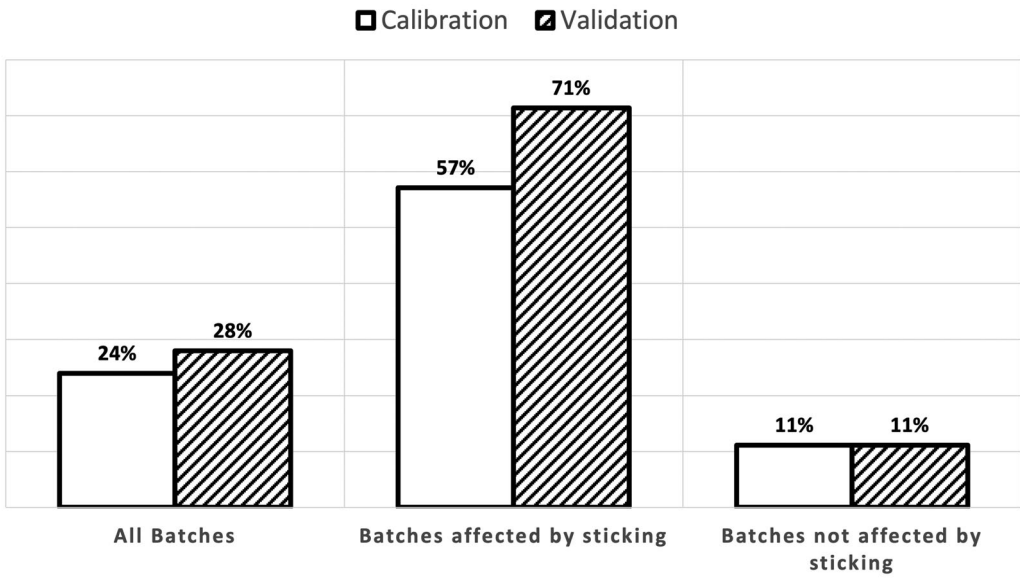

Figure 7. Histogram of the classification error rate for optimized PLS-DA (25 batches × 10 variables). The validation error rate corresponds to the result of a seven-folds cross-validation procedure.

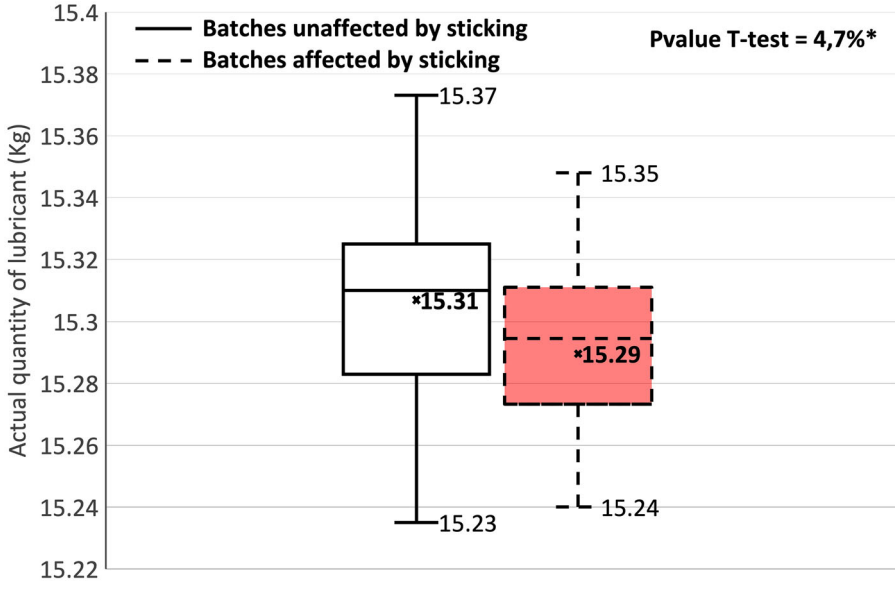

Figure 8. Box plot of mean comparison between batches affected by sticking and those unaffected by sticking for the actual quantity of lubricant dispensed in the formulation (V8) in Kg. (*) indicates the statistical significance (95%) of the Student's t-test.

the data or the low number of batches affected by sticking in dataset2. To evaluate these possibilities, the raw data for the identified variables are represented in Figures 8–11 to assess the differences more precisely between the two classes and detect the potential bias. In this section, the identified variables are also discussed in regard to findings reported in the literature.

3.6.1. The quantity of lubricant dispensed in the formulation (V8)

The quantity of lubricant dispensed in the formulation was identified through the analysis of dataset1 as a significant contributor to sticking. It was also identified as important in the analysis of dataset2, although this relationship was not significant ($p > .05$). A box plot highlighting the mean comparison of this variable for affected batches versus unaffected batches is depicted in Figure 8.

The examination of the raw data (Figure 8) confirms that slightly less lubricant is dispensed in the formulations for batches affected by sticking, with a statistically significant difference of approximately 20 g of lubricant on average (p value of .047). No outlying behavior appears in the box plot, indicating that V8 is not impacted by the observed bias. Therefore, the actual quantity of lubricant probably plays an important role in the occurrence of sticking in the ibuprofen-based formulation. Moreover, this effect is largely confirmed by other studies. Sendall and Staniforth (1986), Toyoshima et al. (1988), and Mcdermott et al. (2011) reported on the benefits of lubricants in mitigating sticking issues with various kinds of formulations, such as pozanicline, acid acetylsalicylic, and macrogol. It is generally established that magnesium stearate, a common lubricant used in formulations, reduces sticking occurrences by covering API particles in the formulation, thus making them less available for adhesion to the punch surface (Toyoshima et al. 1988; Mcdermott et al. 2011). However, some studies using ibuprofen-based formulations revealed the opposite effect, especially for magnesium stearate, where an

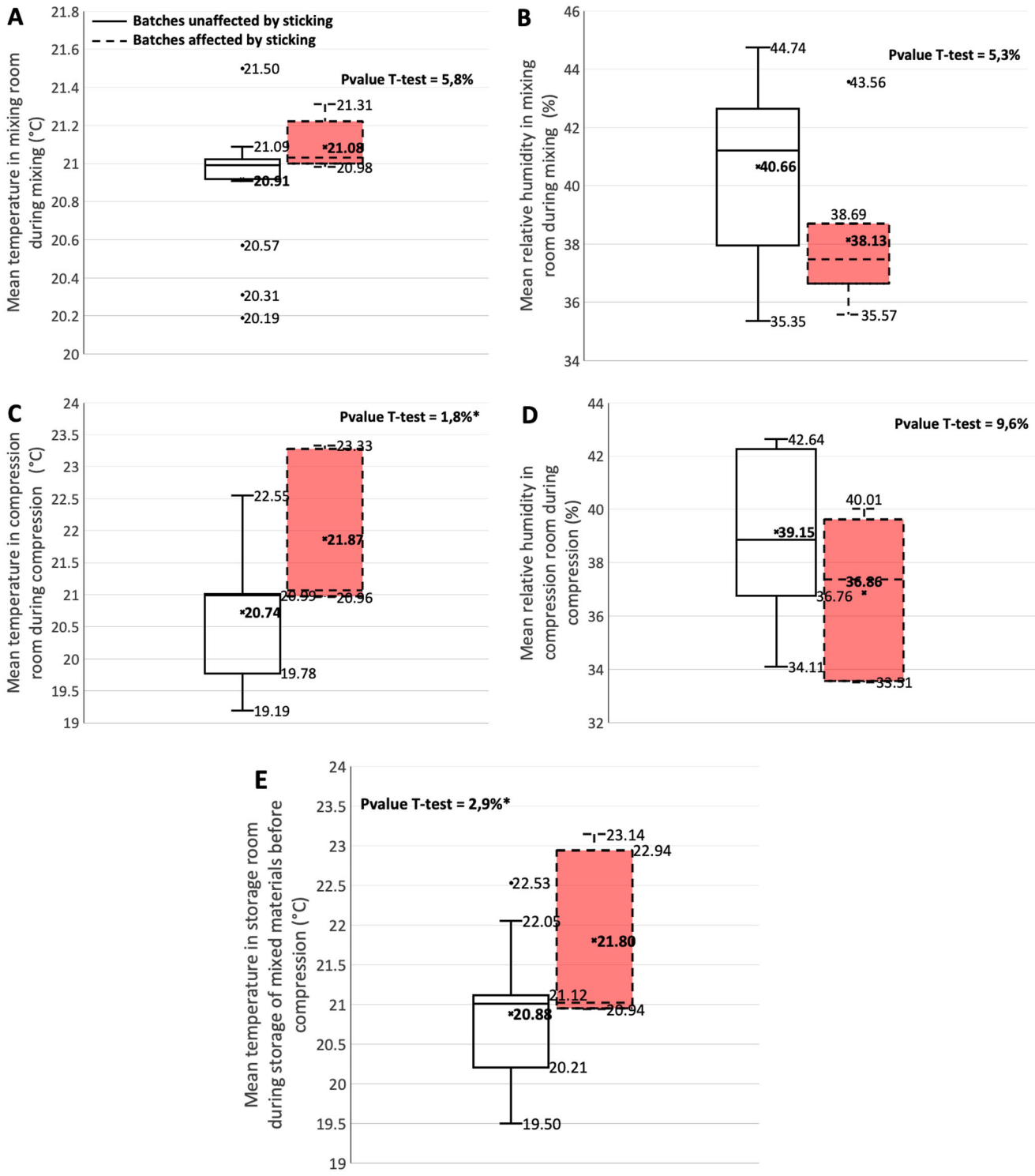

Figure 9. Box plots of mean comparison between affected batches and unaffected batches for the environmental-related parameters V21, V22, V33, V34, and V29 presented in A, B, C, D, and E, respectively. (*) indicates the statistical significance (95%) of the Student's t-test.

increase in its proportion leads to more sticking (Gordon et al. 1984; Roberts et al. 2003; Roberts et al. 2004). It may be interesting to experimentally investigate why and how lubrication enhanced sticking behavior for the ibuprofen-based formulation studied in this work. Moreover, the average difference between the two classes of batches in this study was quite small. This represents ~0.1% of the targeted lubricant weight added to the formulation. Such levels of accuracy might not be addressable at an industrial scale and are practically irrelevant to prevent sticking on their own. The literature also revealed that the lubricant effect depends on punch surface properties (Al-Karawi et al. 2017). Therefore, an experimental validation assessing the lubricant effect in coordination with the other parameters may be valuable to support further improvements or new formulation development efforts.

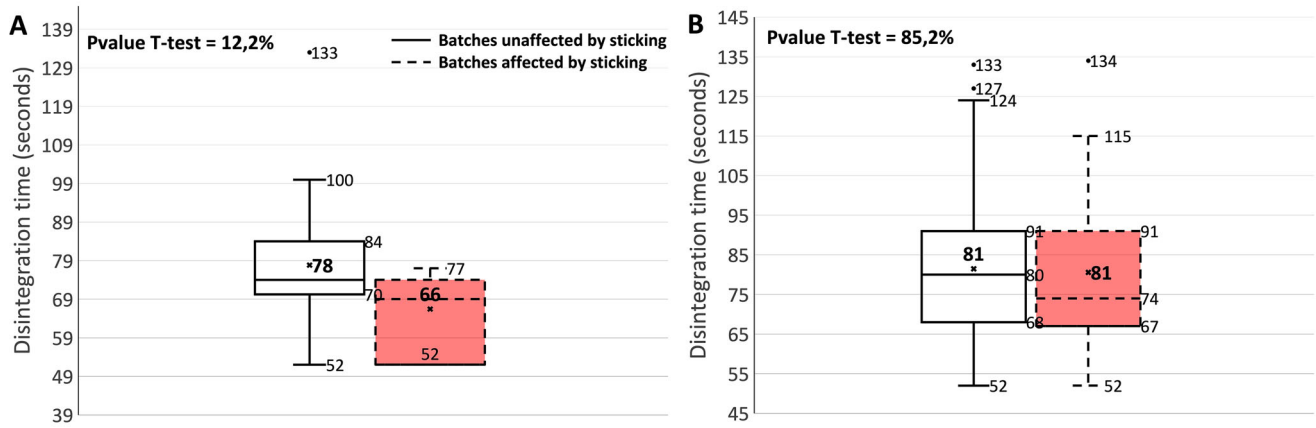

Figure 10. Box plots of the mean comparison between affected and unaffected batches for the average disintegration time (V42). Figure 10(A,B) uses the information from dataset2 and dataset1, respectively.

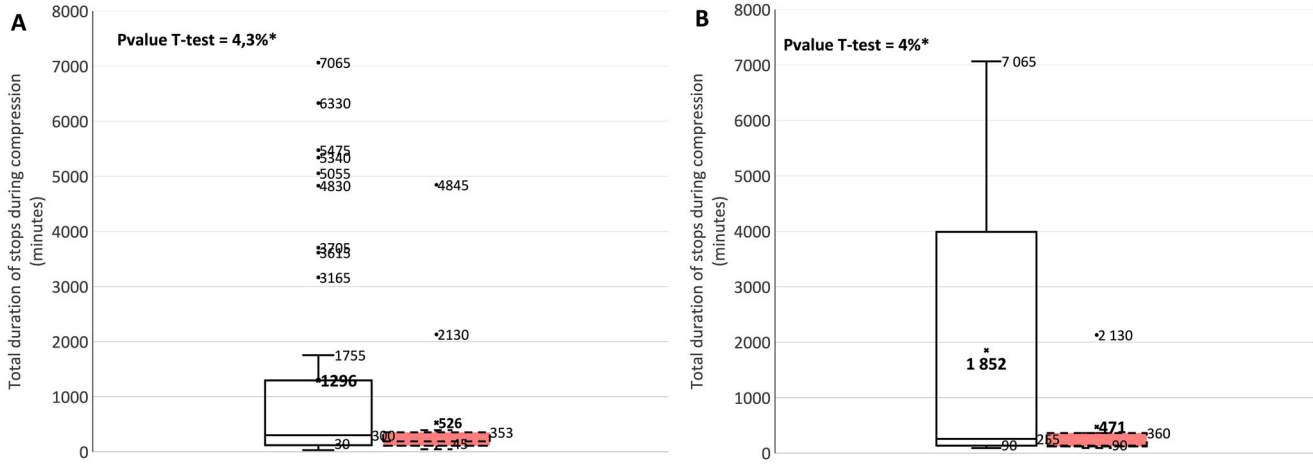

Figure 11. Box plots of the mean comparison between affected and unaffected batches for the total duration of stops during compression, in minutes (V44). Figure 11(A,B) uses the information from dataset1 and dataset2, respectively. (*) indicates the statistical significance (95%) of the Student's t-test.

3.6.2. Average temperatures and relative humidity (V21, V22, V29, V33, and V34)

Five of the variables identified as significantly contributing to sticking relate to the environmental conditions of manufacturing. V21 and V22 are the averages of the temperature and relative humidity, respectively, in the mixing room during mixing. V33 and V34 represent the same parameters in the compression room during compression. The final environmental variable is V29, the temperature average in the storage room during the storage of intermediate materials before compression. Figure 9 presents box plots displaying the comparison of these five variables for affected batches versus unaffected batches.

As shown in the DA models, high temperatures in the mixing, compression, and storage rooms (V21, V33, and V29, respectively) are associated with more sticking, and the opposite relationship is observed for relative humidity in the mixing and compression rooms (V22 and V34, respectively) (Figure 9). Some moderate outliers are identified regarding V21, V22, and V29, although these may only induce misinterpretation for V21, where three batches appear to contribute to the direction of discrimination (Figure 9). For this variable, more data or an experimental study are necessary to confirm that the relationship with sticking is not an artifact induced by the three outlying batches, which would not be representative of general observations. For V22 and V29, the observed outliers even tend to oppose the mean difference, so they are not problematic in terms of bias (Figure 9). Therefore, except for V21, all the other environmental variables identified (V22, V29, V33, and V34) probably play important roles in sticking, even if some are not statistically different on average—especially V34, with a p value of .096. This simply indicates that the effect of V34 alone is insufficient to explain a significant part of the difference between sticky and not-sticky batches, highlighting the power of MVDA. Moreover, V34 probably interacts with other important parameters to better explain sticking.

Notably, temperature and humidity are interdependent parameters. Previous reports clearly state that exposition of powders, even to low relative humidity values, can favor the increase of its water content, which was subsequently correlated with sticking (Aoki and Danjo 1998; Shimada et al. 2003; Bunker et al. 2011; Mullarney et al. 2012). Danjo et al. showed that sticking increases with the water content of pharmaceutical powder up to 3% (w/w) and then decreases with further increases in water content, where it starts to behave as a lubricant at the interface between particles and punch surfaces (Danjo et al. 1997). For the formulation studied here, it is then probable that the slightly higher temperature, favoring a slightly lower relative humidity induces the water uptake necessary to give a specific level of water content, which promotes sticking according to processing times. Experiments are necessary to elucidate the postulated mechanism of action. Herein, the slight difference in temperature and relative humidity observed between the affected and unaffected batches may not be exploitable to mitigate sticking issues at the industrial scale.

Therefore, clarifying the mechanism may help identify a practical level of environmental conditions addressable by HVAC systems that can subsequently mitigate sticking of the formulation.

Additionally, environmental conditions measured during compression can be more of a consequence than a cause. For example, the low melting point of ibuprofen promotes sticking if an important increase in temperature occurs in the powder bed during compression (Gordon et al. 1984; Roberts et al. 2003; Roberts et al. 2004; Al-Karawi and Leopold 2018). Thus, the slightly higher temperature measured during compression, translating into the slightly lower relative humidity may be indicative of a high cadence of operations inducing a local increase of temperature above the melting point of ibuprofen, promoting sticking. This hypothesis is corroborated by the total duration of stops during compression. For instance, less time was spent stopping during the compression of batches that were affected by sticking, which may also indicate a higher operational cadence with a higher probability of localized temperature increase at the interface between the powder bed and punch surface.

3.6.3. Average disintegration time (V42)

Although it was included in dataset1, the average tablet disintegration time (V42) was identified as an important contributor to sticking only in the analysis of dataset2. Thus, the observation of this effect may be due to the lower number of observations in dataset2, especially for batches affected by sticking, which are also subject to the bias observed in the developed models. To assess this aspect, two box plots displaying the comparison of the average disintegration time between affected and unaffected batches are presented in Figure 10. The first plot utilizes data present in dataset2 and the second plot presents the same comparison for dataset1.

As indicated by the DA models, the average disintegration time for dataset2 appears to be associated with sticking (Figure 10(A)). However, it may be a consequence, rather than a cause, because batches affected by sticking may yield tablets with lower internal cohesion, thus lowering their disintegration time. But an examination of this variable with a greater number of observations in dataset1 reveals a potential bias. Distributions for the two classes are quite similar in dataset1 (Figure 10(B)), indicating that the average disintegration time is probably identified as a factor in sticking due to the small number of observations in dataset2. Moreover, even fewer batches are affected by sticking in dataset2. This is highlighted by the change in the average values between the two datasets. The average disintegration time for batches unaffected by sticking is similar between dataset1 (81.47 s) and dataset2 (77.83 s), while it is significantly different for batches affected by sticking—81.55 s in dataset1 versus 66.43 s in dataset2 (Figure 10). Therefore, the average disintegration time may be an artifact, induced by both the subsampling operated to study environmental conditions variables and the inherent observed bias in the models. An experimental study may help to clarify the effect of sticking on the tablet disintegration time.

3.6.4. The total duration of stops during compression (V44)

The total duration of stops during compression was identified as a significant contributor to sticking, which was apparent in the analyses of dataset1 and dataset2. Figure 11 presents two box plots displaying the comparison of the total duration of stops during compression between affected and unaffected batches for the two datasets.

Our examination of the raw data concerning the total duration of stops during compression confirms the relevance of this variable's relationship to sticking, both in dataset1 and dataset2 (Figure 11). The batches are not affected by sticking when the tablet press spends more time stopped (1296 and 1852 min on average) and the batches are affected when less time is spent stopping (526 and 471 min, on average). Notably, the total duration of stops during compression does not include the stop time due to sticking. It only accounts for sporadic stops due to different breaks of operators and other activities necessary for monitoring the manufacturing process. Because this condition differs significantly from one batch to another, several outliers in its distribution are identified for the affected and unaffected batches (Figure 11). Considering the nature of V44, the presence of outliers cannot be considered an indicator of artifacts. In addition, we observe a highly similar distribution for V44 across both datasets (Figure 11). Furthermore, the difference in the average for V44 between affected and unaffected batches remains significant, with a p value always below .05 in dataset1 and dataset2. This difference even persists when all batches that appear to be outliers are removed. Therefore, the total duration of stops due to sticking probably plays an important role in sticking.

No work in the literature has reported such a direct link. A potential explanation may be an indirect correlation involving the influence of temperature in sticking for the ibuprofen-based formulation. Several authors have reported on the low melting point of ibuprofen particles and a potentially sharp temperature increase in the powder bed during compression, which could lead to the sticking of particles onto punch surfaces (Gordon et al. 1984; Roberts et al. 2003; Roberts et al. 2004; Al-Karawi and Leopold 2018). The high cadence and duration of a continued compression would result in temperature increases in the powder bed, and more time stopped during compression would have a cooling effect on tooling, thus mitigating sticking occurrences on ibuprofen-based formulations. This postulated mechanism aligns well with the discussions about temperature and relative humidity measures during compression. A detailed experiment is necessary to confirm the hypothesis. If this is supported, it is worth mentioning that the intentional introduction of more stops during compression is not a viable solution from an industrial perspective, but cooling down the tablet press (especially the die cavity and the surfaces of punches) may be an interesting approach to mitigate sticking.

3.7. A new approach to studying tablet sticking and its related systematic methodology

This study validates a new approach to evaluate tablet sticking, consisting of collecting and analyzing industrial manufacturing data. This approach presents two main advantages. First, it allows the simultaneous assessment of numerous factors for their implications in sticking, to a greater extent than experimental studies. For instance, this study involves up to approximately 50 variables after data cleaning, even though only six of these were found to significantly contribute to sticking. Since sticking is known to be a multifactorial phenomenon, this approach may greatly enhance our understanding of sticking, or at least enable the informed selection of a few factors to assess in subsequent experimental studies. Second, another benefit of the industrial data analysis approach is the emphasis on actual factors that primarily contribute to sticking. One challenge in sticking studies is observing or reproducing this phenomenon on an experimental scale (Chattoraj et al. 2018; Costa et al. 2020). Many factors usually do not appear until the formulation is scaled up to the industrial stage (Saniocki 2014). Thus, an analysis based on this scale is

likely to be more informative. Moreover, many factors have tight tolerances and are strictly controlled during industrial manufacturing, allowing for a focus on variables for which sticking is very sensitive.

Based on our experiences conducting this study, we propose a systematic methodology to proceed with the new approach. This methodology is based on MVDA techniques. These are adequate tools for the new approach's purpose because of the limited number of batches performed at an industrial scale and the commonly large number of factors. Such datasets generally lack degrees of freedom to facilitate the correct use of common regression and classification techniques directly with original variables. Furthermore, they often lack enough observations to perform more complex modeling, such as artificial intelligence models like neural networks. Therefore, MVDA is the best fit, particularly for dimensionality reduction techniques such as PCA and partial least squares regression.

The proposed methodology involves three major steps: data collection and preparation, followed by an exploratory step, and then explicative and predictive modeling. The first step involves gathering, cleaning, and preparing relevant variables regarding the manufacturing process and tablet sticking. Special attention must be devoted to the choice of the **y** variable(s) for assessing the sticking behavior of the batches because this predetermines all eventual outputs. For this first step, well-planned and detailed data collection can be more informative (when it is possible) than a historical study. Regardless of the collection mode, data must be cleaned and prepared prior to analysis. This involves handling missing data, feature engineering, evaluating multicollinearity, and standardizing methods.

The resulting dataset from the first step is then assessed using univariate data analysis methods and PCA. Univariate data analysis reveals whether sticking is dependent on any single variable, although it also helps in finding, investigating, and processing eventual outliers, thereby completing data cleaning. PCA finalizes the investigation on a multivariate stage. The existence of spontaneous clusters according to the observed sticking is assessed, and the most important dimensions of variance in the data are analyzed to detect eventual multivariate outliers and ensure that there is no other phenomenon captured in the data that could impact sticking. If clear clustering with sticking is observed on the PCA components, there is effectively no need to proceed to the third step of the proposed methodology. The loading and contribution plots of these components will be sufficient to identify the important contributors to sticking. They can also be used in conjunction with multivariate linear regression to develop a predictive model. In contrast, if no clear trend regarding sticking is apparent after PCA, the final step of the proposed methodology must be performed, consisting of supervised learning techniques. These modeling techniques will definitively provide explicative and predictive models that may assist in understanding the observed sticking, even if they rely on a limited part of the data. This systematic methodology can be adapted and employed for a broad range of cases by integrating any other necessary analysis techniques at each stage.

However, two major limits related to this proposed approach remain. Since this entire approach is based on data analysis, there must be relevant and sufficient data. This is the most important limit because when data do not contain relevant information about sticking, no analysis method would reveal helpful information. This occurred partially in this study because only a small portion of the observed sticking can be explained, probably due to missing data regarding important variables. The proposal of a well-planned and detailed data collection may be useful for mitigating this limitation. The second limitation is related to the inability to fundamentally describe the observed relationship between sticking and the identified variables. Future experimental studies should be considered to address this deficiency. For instance, researchers can implement a design that includes the identified variables along with potentially important variables that were not included in this data analysis approach. Such a study may yield a more complete and useful multivariate understanding of tablet sticking. Furthermore, integrating the results of several such studies involving different formulations may further assist the effort to generalize results and establish the root causes of tablet sticking.

4. Conclusion

The purposes of this study were to introduce, assess, and discuss a manufacturing data analysis approach to gain insights into tablet sticking on the industrial scale.

In the first step, we obtained industrial manufacturing data on approximately 100 variables, encompassing information about raw materials, processing machines, tablet properties, environmental conditions during production, and processing parameters.

Second, the relevance of the proposed approach in studying tablet sticking by directly assessing industrial data was determined. Using a predefined methodology based largely on MVDA, a total of six variables were identified as significant contributors to sticking for the proprietary ibuprofen-based formulation. Among these variables, the average temperatures during compression and storage of intermediate materials before compression were found to be positively correlated with sticking. Specifically, higher temperatures are associated with enhanced sticking. The actual quantity of lubricant dispensed in the formulation, the relative humidity in the mixing and compression rooms during these steps, and the total duration of stops during compression were found to be negatively correlated with sticking. Specifically, increases in these parameters mitigated sticking. These insights point out the role of lubrication, water content, and the low melting point of ibuprofen in its sticking tendencies. Therefore, the proposed approach is suitable to identify the impact of variations within closely defined tolerances, as observed in industrial pharmaceutical manufacturing processes.

Third, because of a large bias in the developed models for batches affected by sticking, these models were not suitable for predicting sticking. The descriptive outcomes exploited to identify important variables were also affected, since only a small portion of interclass separation could be explained, and several variables turned out to be artifacts. A study including batches with more severe sticking may prevent confusion between the two classes and address this limitation. Furthermore, a continuous **y** variable relying on a large range of sticking behavior may definitively prevent this kind of bias. Moreover, this can help describe the effects of variables on sticking, allowing for further determination of an optimal operating range for the identified parameters.

Finally, based on our experiences in conducting this work, we have proposed and discussed a systematic methodology for industrial manufacturing data analysis. We suggested a plan for data collection and an experimental design after data analysis to create a more complete description and multivariate understanding of tablet sticking.

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Disclosure statement

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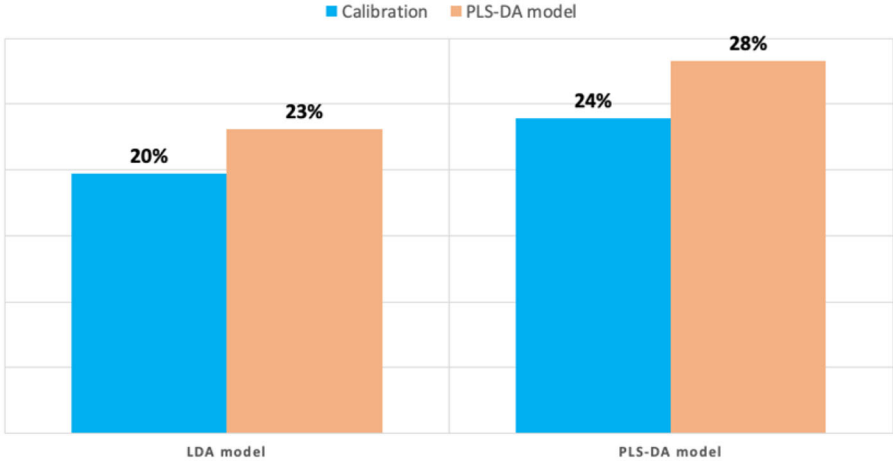
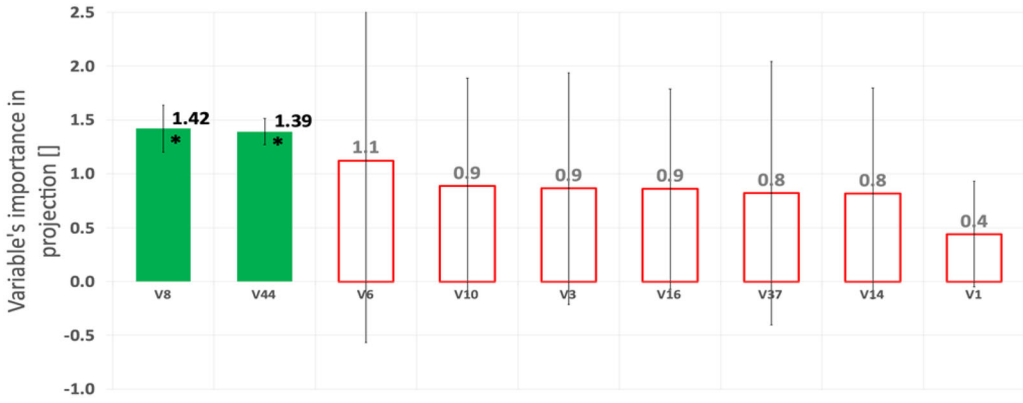
Appendix A

Summary of the results from dataset1 using LDA and PLS-DA

PLS-DA was also used to analyze dataset1 and similar results as per LDA was obtained. Below are the results.



Error rates of both LDA and PLS-DA models using dataset 1.



Variables importance plot for PLS-DA model

Both LDA and PLS-DA models provide similar results in terms of predictive and descriptive outcomes. LDA model has slightly better performance in classification of about 3–5%. This is probably due the difference in final set of variables selected throughout the two different optimization processes.