

# Machine learning modelling of wet granulation scale-up using compressibility, compactibility and manufacturability parameters

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## Abstract

The purpose of this extensive study is to use a quality by design (QbD) approach and multiple machine learning algorithms in facilitating wet granulation process scale-up. This study investigated the extent of influence of both formulation and process variables. Furthermore, measured responses covered compressibility, compactibility and manufacturability of a powder blend. Finally, the models developed on laboratory scale samples were tested on pilot and commercial scale runs. Tablet detachment and ejection work were calculated from force-displacement measurements. Significant numerical and categorical input variables were identified by using a stepwise regression model and their importance evaluated by using a boosted trees model. Pilot scale runs resulted in the highest tablet tensile strength and compaction work as well as the highest detachment and ejection work. Critical quality attributes (CQAs) that were the most successfully predicted were the compaction, decompaction, and net work, as well as the tablet height. The most important input variable influencing all CQAs was the compaction force. Application of the boosted regression trees model resulted in the lowest Root Mean Square Error (RMSE) values for all of the responses. This work demonstrates reliability of predictions of developed models that can be successfully used as a part of a QbD approach for wet granulation scale-up.

**Keywords:** *quality by design; artificial intelligence; compaction work; decompaction work; elastic recovery*

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## 1. INTRODUCTION

Quality by design (QbD) is a pharmaceutical design, development and research concept using a systematic, risk-based, holistic approach [1]. It is based on proactive identification and definition of a desired quality target product profile (QTPP) by using the existing scientific knowledge [2]. After establishing QTPPs, product formulation and manufacturing process design should be developed together with defining the critical quality attributes (CQAs), which are characteristics that reflect the final process and product qualities. Defining all critical sources of variability in a formulation and manufacturing process will provide development of the design space [3] while defining critical material attributes (CMAs) and critical process parameters (CPPs) will provide control of the manufacturing process to produce a product of a constant quality [4].

Wet granulation is a complex manufacturing process influenced by formulation variables (ingredient concentration, particle shape, particle size distribution, solubility, hygroscopic nature *etc.*), and process conditions (impeller speed, milling speed, screen size, mixing time, amount and rate of liquid addition [5], moisture of granules *etc.*). All those variables can directly influence the behavior of granules (flow, compressibility, compactibility, surface area *etc.*) as well as the tablet

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properties (porosity, tensile strength, disintegration time, elastic recovery, dissolution *etc.*). It is important to define variables that have a significant impact on the product quality and to distinguish them from those which impact is minimal.

It is very rare to have the ideal wet granulation scale-up in the real production environment. Challenges of wet granulation scale-up should be approached with the knowledge and experiences gained from prior stages of the process development with QbD principles applied [6]. For scale-up study purposes, two processes may be considered similar if there is a geometrical (the same ratio of linear dimensions and shape), a kinematic (the same ratio of velocities between corresponding system points) and a dynamic (the same ratio of forces between corresponding system points) similarity [7]. There are often differences in granulation or milling equipment across scales (e.g. different blade shape, diameter, milling mechanism *etc.*). Even when the equipment from the same manufacturer is used, with the same geometrical properties, the scale-up process of wet granulation can be a challenge [8]. Nevertheless, by developing a progressive design space with a QbD risk based approach, production of pharmaceutical products is robust enough to allow for scale-up adjustments of process parameters [9,10].

Critical evaluation of input variables, which are defined by risk assessment, would be traditionally performed by varying one factor at a time (OFAT), while keeping the others constant. This approach exhibits several problems, one of which is not considering interactions between different variables. The Design of Experiments (DoE) approach is capable of examining systemic variation of multiple variables, creating mathematical models of a process in order to predict the process performance. Results obtained by DoE statistical analysis using the Response Surface Method (RSM) can be utilized to generate an effective design space [11]. A reliable design space for a scale-up study should be based on experiments carried out on each scale, which is not always practical and can incur high costs. DoE is almost always performed on a smaller rather than on a commercial scale. Using multivariate data analysis (MVDA) models, process parameters can be summarized by a few critical variables instead of a great number of variables with limited significances [12]. There are many examples of machine learning techniques used in product/process development and optimization [4,13-15]. The choice of a model depends on number of factors including the type of variables (numerical or categorical), the number of responses and the effects that inputs create on those responses. The effect of inputs on responses is often not known in advance, so different modeling techniques should be applied to determine which technique is optimal for a certain data set. Otherwise, a model could be under-fitting (would not perform on the training data set and would not have satisfactory predictions for a new data set) or over-fitting (the model would have 'too good' performance with the training data set, so the prediction would not be precise with a new data set).

Studies utilizing the QbD approach and machine learning modeling for scale-up of wet granulation processes often use either process parameters or formulation factors [16]. Furthermore, responses being observed are usually related to granule properties (particle size distribution [17], porosity [18], size and bulk density [19]). In studies conducted by Aikawa *et al.* [10] and Badawy *et al.* [20] the analyzed responses were tablet properties. Those studies, however, did not utilize machine learning techniques. Previous studies with machine learning modeling involved testing of the prediction capability of developed methods on either laboratory [4] or pilot scale runs [21]. In this study, for the first time, the developed models were tested using a large data set obtained from both pilot and commercial scale runs. We also utilized and compared multiple machine learning techniques (regression, regularization, decision tree and ensemble algorithms). Both formulation and process parameters were used as input variables. Analyzed responses are quality attributes of granules and tablets relevant in the context of the complex system of the wet granulation process scale-up – compactibility [22], compressibility and manufacturability. This article provides an extensive example of how different machine learning techniques can be utilized to determine significant variables (both categorical and numerical) and the magnitude of their influence on tablet CQAs.

## 2. EXPERIMENTAL

### 2. 1. Experimental design

Tablets were made by varying concentrations of tribasic calcium phosphate (TCP) (Innophos Inc., Cranbury, New Jersey, USA) that was used as a filler and sodium starch glycolate (SSG) (DFE Pharma, Goch, Germany) that was used as

a disintegrator. SSG was added extragranularly. The binder solution was made using water as a solvent and povidone (ISP Technologies, Inc., Wayne, New Jersey, USA) as a binding agent. Tablets were lubricated with 1% of magnesium stearate (FACI S.p.A., Carasco, Italy).

The mixer fill level was at 80% for all scales. The impeller speed was constant for all experiments on each scale level. Laboratory scale experiments were conducted on a Hobart planetary bench mixer, model N50-60 (Troy, Ohio, USA), and the pilot and commercial scale experiments were conducted on a Diosna mixer-granulator, model P 300 (Osnabrück, Germany). Wet granules were dried at 45°C in a Glatt fluid bed dryer (Binzen, Germany), model TR2 for laboratory scale experiments and model WSG 60, for pilot and commercial scale experiments. Loss on drying (LOD) was measured using a O'Haus, model MB35 (Parsippany, New Jersey, USA), drying granules for 10 minutes, at 80°C. Mill Powder Tech (knives positioned around the horizontal axis), model RT-10HS (Tainan City, Taiwan), was used for laboratory scale experiments. For pilot scale experiments a Quadro Comil (impeller spinning around the vertical axis), model 194 (Waterloo, Ontario, Canada) was used with different shapes of impeller bars (round bar impeller '1601' and square bar impeller '1607'). Fitz mill (knives were positioned around the horizontal axis, using the 'Knives forward' setting), model D (Elmhurst, Illinois, USA) was used for commercial scale experiments. The laboratory scale mill had a constant speed. The Quadro Comil was operating at speeds of 200, 300 and 400 rpm, and the Fitz mill was operated with slow, medium and fast speeds. Screens used for milling were 0.69, 0.81, 0.84, 1.00, and 1.04 mm with round shaped holes, with the exception of 1.00 mm which had square shaped holes.

Bulk powders were compressed into round tablets, 6 mm in diameter, and weight of 110 mg using a compaction simulator Gamlen tablet press (Gamlen Tableting, UK) [23]. The compaction speed was constant (60 mm/min) with the graph sampling rate of 200 Hz. There were total 84 laboratory, 48 pilot and 36 commercial scale runs. Each bulk powder sample was compressed using compaction pressures of 70, 105, 140, and 175 MPa. Each samples was compressed in triplicates for every given compaction pressure.

## 2. 2. Testing & data analysis

Particle size distribution was determined using sieves Endecotts Ltd. (London, UK) with hole sizes 150, 250, and 500 µm. Tablet breaking force was measured by a tablet hardness tester, Erweka, model TBH 30 (Heusenstamm, Germany).

Tablet in-die tensile strength was calculated using the Equation 1:

$$\sigma_{in} = \frac{2F}{\pi D_{in} H_a} \quad (1)$$

where  $\sigma_{in}$  is the tablet in-die tensile strength,  $F$  is the tablet breaking force,  $D_{in}$  is the in-die tablet diameter, and  $H_a$  is the minimum in-die tablet height under the maximum compaction pressure.

Tablet out-of-die tensile strength was calculated using the Equation 2:

$$\sigma_{out} = \frac{2F}{\pi D_{out} H_c} \quad (2)$$

where  $\sigma_{out}$  is the tablet out-of-die tensile strength,  $D_{out}$  is the out-of-die tablet diameter, and  $H_c$  is the out-of-die tablet height.

Compaction pressure was calculated per the Equation 3:

$$P = \frac{F_c}{\pi \left(\frac{D_{in}}{2}\right)^2} \quad (3)$$

where  $P$  is the pressure applied by a punch, and  $F_c$  is the compaction force.

"In-die" elastic recovery was calculated as immediate axial recovery (IAR), using the following equation:

$$IAR = \frac{H_b - H_a}{H_a} 100 \quad (4)$$

where  $H_b$  is the tablet height at the end of the decompaction phase.

Out-of-die elastic recovery, which occurs after ejection, is described by the cumulative axial recovery [24], and the volumetric strain recovery (which accounts for changes in both tablet height and diameter). Cumulative axial recovery (CAR) was calculated using the following equation [24]:

$$CAR = \frac{H_c - H_a}{H_a} 100 \quad (5)$$

Volumetric strain recovery (VSR) was calculated using the Equation 6 [25]:

$$VSR = \frac{(D_{out}^2 H_c - D_{in}^2 H_a)}{D_{in}^2 H_a} 100 \quad (6)$$

Compaction work ( $W_c$ ), decompaction work ( $W_{dc}$ ), net work ( $W_n$ ), detachment work ( $W_a$ ) and ejection work ( $W_e$ ) were calculated as the area under the curve (AUC) of the respective force-displacement diagram (Fig. 1). The decompaction curve represents elastic relaxation of the material. Net work is the effective work, which is spent on compaction after reversible energy is returned during the decompaction stage.

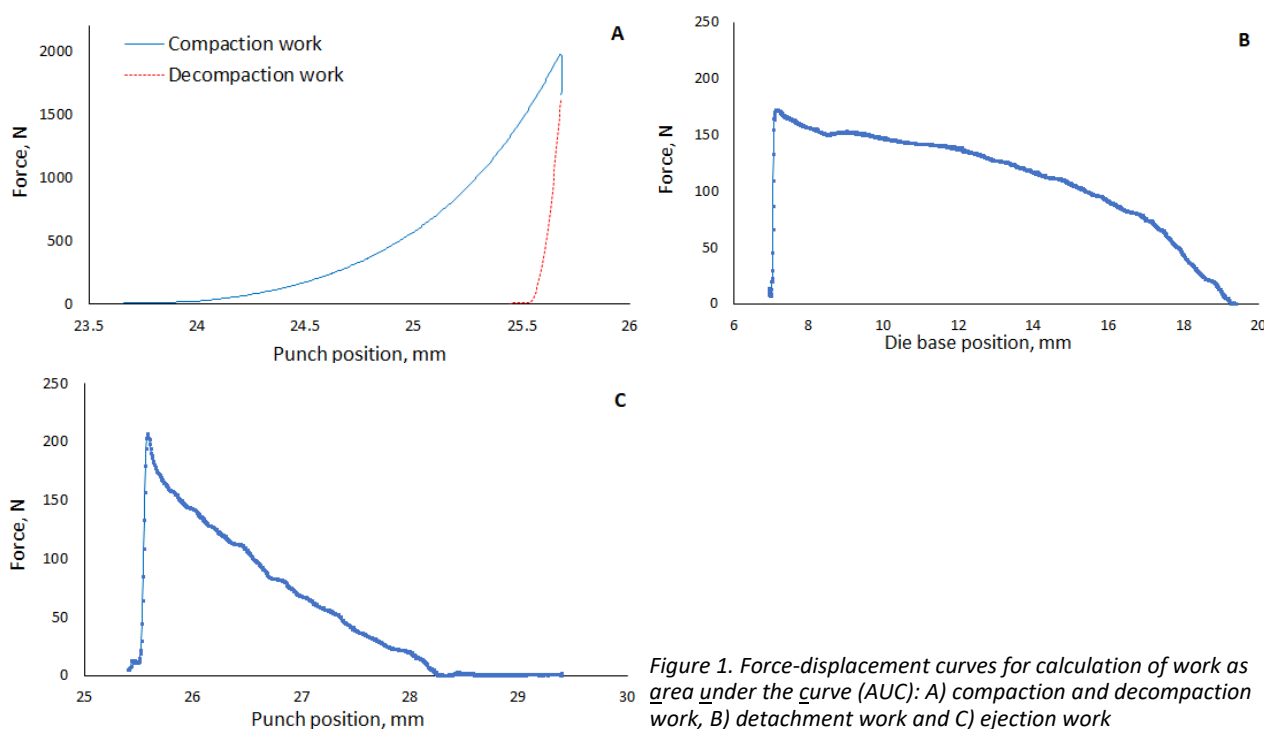


Figure 1. Force-displacement curves for calculation of work as area under the curve (AUC): A) compaction and decompaction work, B) detachment work and C) ejection work

### 2. 3. Modeling techniques

Machine learning techniques used in this study are suitable for different types of variables (Fig. 2): linear regression, stepwise regression, lasso regression [26], ridge regression [27], elastic net [28], regression trees [29] and boosted regression trees [30] modeling techniques. The software used was MATLAB® 2013b (MathWorks, USA).

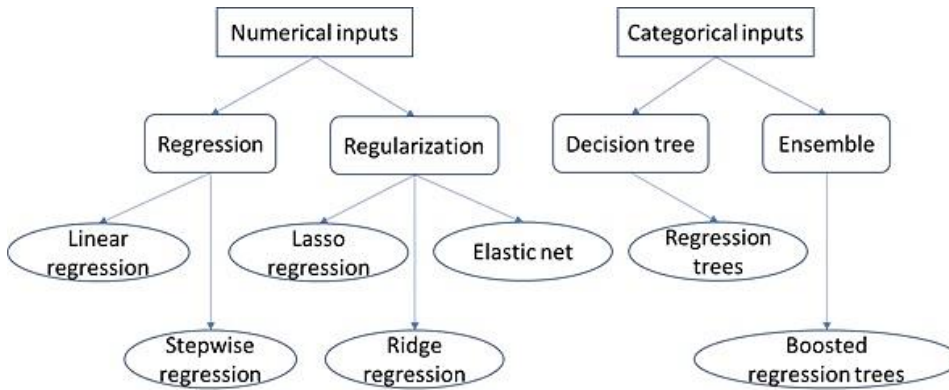


Figure 2. Machine learning models used for wet granulation scale-up modelling

To examine normality and relation between input variables and responses the Shapiro-Wilk test [31] and the Kruskal-Wallis rank sum test [32] were performed. The Shapiro-Wilk test has a significant value  $W$ , which is equal to 1 for normal data distribution and lower than 1 for non-normal data distribution.  $W$  is calculated using the following equation:

$$W = \frac{\left(\sum_{i=1}^n a_i x_{(i)}\right)^2}{\sum_{i=1}^n (x_i - \bar{x})^2} \tag{7}$$

where  $x_{(i)}$  is the  $i^{\text{th}}$  order statistic, and  $n$  is the number of examples used for model training.

Models were evaluated by comparison of root-mean-square-error (RMSE) values (root of the mean square error – MSE), which are calculated by the following equation:

$$RMSE = \sqrt{MSE} = \sqrt{\frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{n}} \tag{8}$$

where  $y_i$  is the actual response value and  $\hat{y}_i$  is the model predicted value. Factors with p-value <0.05 were considered statistically significant [33].

### 3. RESULTS

Results show that tablet  $\sigma$ ,  $W_c$ ,  $W_{dc}$  and  $W_n$  increase as the applied compaction pressure increases (Fig. 3). Significant differences between  $\sigma_{in}$  and  $\sigma_{out}$  were not found at any of the applied compaction pressures. The tensile strength and compaction work are the highest for the pilot scale samples, as compared to laboratory and commercial scale data. The difference between  $W_c$  and  $W_n$  increases with the increased applied compaction pressure, which points to an increase in the decompaction work (Fig. 3). The decompaction work has a negative value compared with  $W_c$  and  $W_n$  and is shown as an absolute value.

Variations in the tablet height were monitored at the end of the compaction stage, the end of the decompaction stage and outside of the die. Tablet height and its correlation with the applied compaction pressure at different time points, at laboratory, pilot and commercial scales are shown in Figure 4. Tablet height is negatively correlated to the compaction pressure. Significant differences were not found between  $H_b$  and  $H_c$ . The only difference between  $H_b$  and  $H_c$  is noticed in commercial scale experiments, at compaction pressures of 70 and 105 MPa.

Elastic recovery increases with the increase in the compaction pressure (Fig. 5). Significant differences between CAR and VSR were not found at all scale levels. IAR is the highest for commercial scale samples although these data show the highest standard deviation (SD).



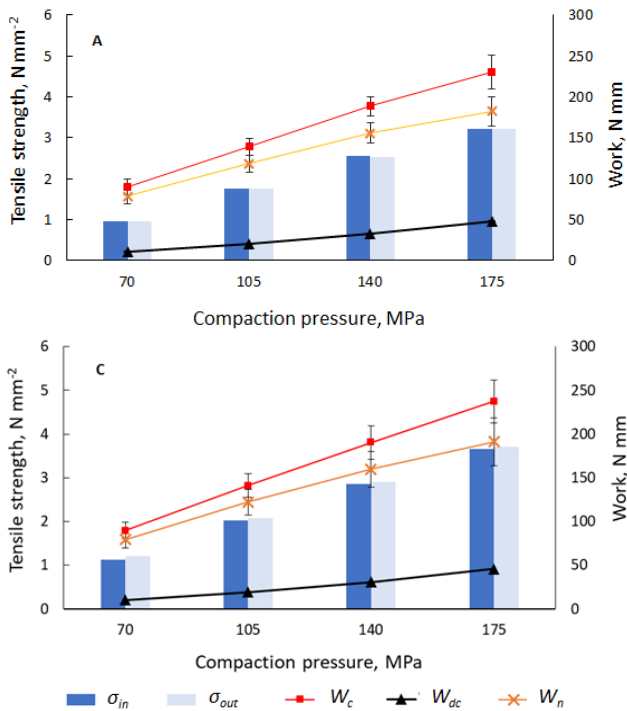


Figure 3. Comparison of the tablet tensile strength (in and out of the die), compaction, decompaction and net work with increasing the applied compaction pressure at: A) laboratory, B) pilot and C) commercial scale runs

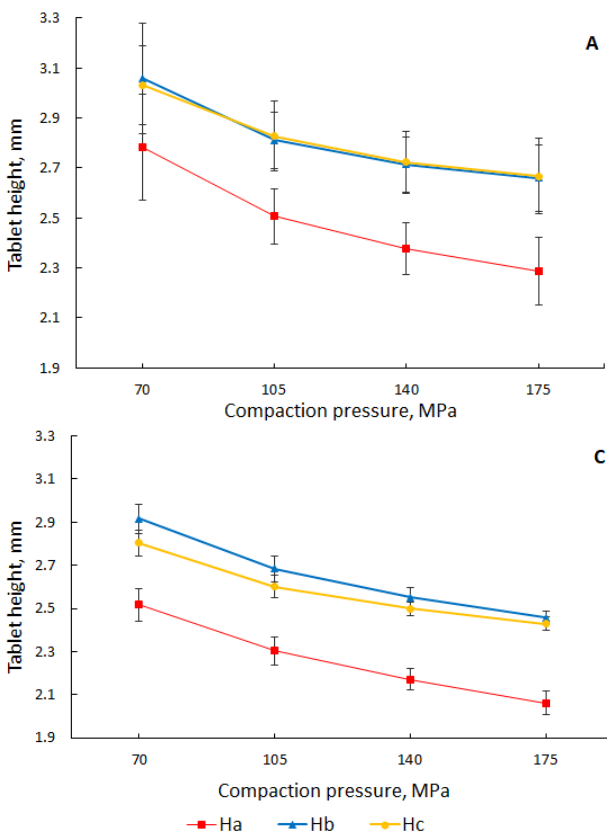


Figure 4. Comparison of  $H_a$ ,  $H_b$  and  $H_c$  at increasing the applied compaction pressure at: A) laboratory, B) pilot and C) commercial scale runs.

Figure 6 shows the increase of  $W_d$  and  $W_e$  with the increase in the compaction pressure. The increase of  $W_e$  is not significant while  $W_d$  increases up to 140 MPa, after which value of the compaction pressure it does not further increase significantly being the highest for pilot scale samples.

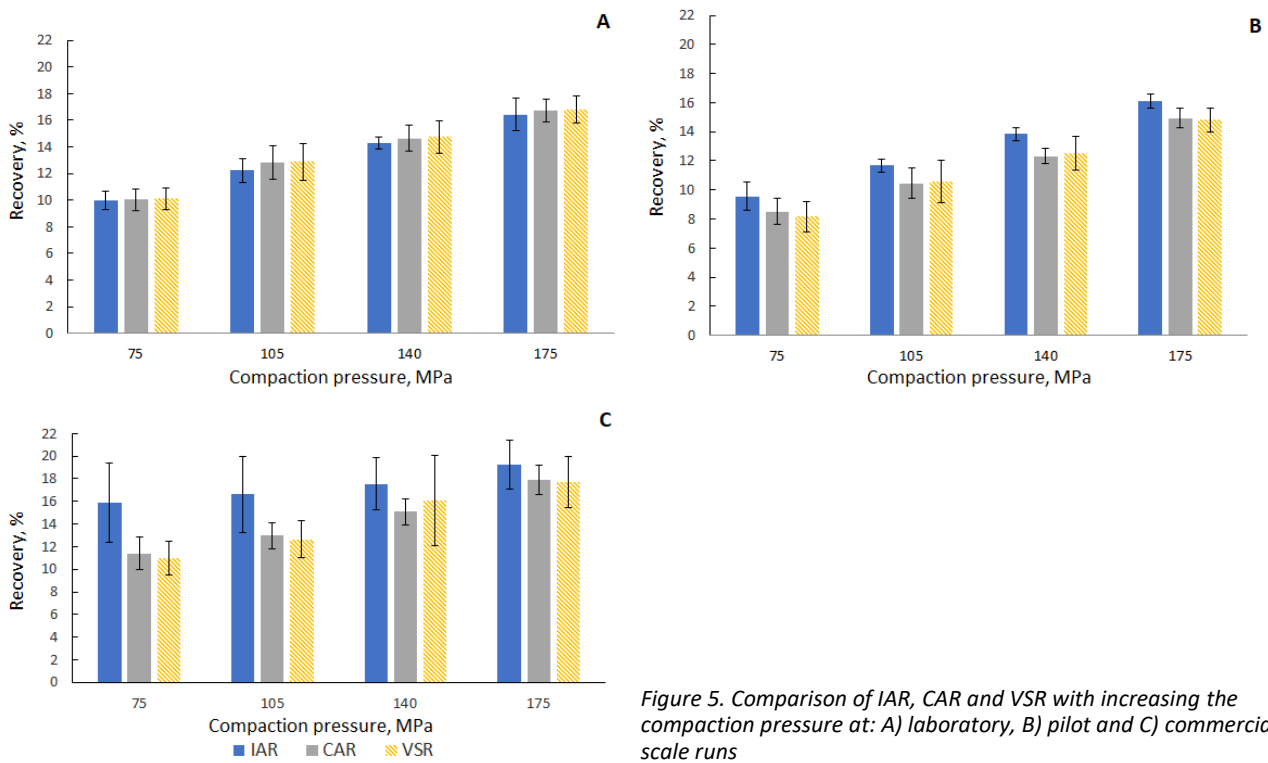


Figure 5. Comparison of IAR, CAR and VSR with increasing the compaction pressure at: A) laboratory, B) pilot and C) commercial scale runs

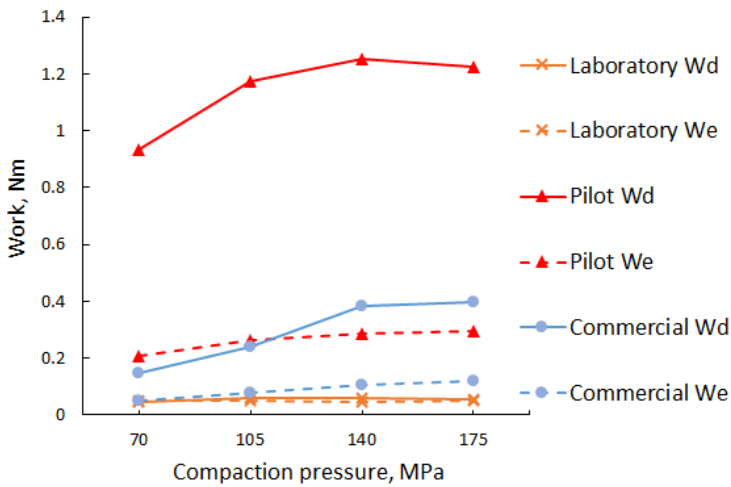


Figure 6. Comparison of detachment and ejection work with increasing the compaction pressure at laboratory, pilot and commercial scale runs

The obtained data were further analyzed through machine learning modeling. Firstly, the Shapiro-Wilk test was carried out (Fig. 7), with  $W$  values shown in Table 1. A regularization effect was applied to avoid overfitting of the models.

Further, we used a non-parametric approach – the Kruskal-Wallis rank sum test to find relation between input variables and responses (Table 2) using stepwise, ridge, lasso and elastic net regression models. The data are then divided into “buckets”, each representing a different scale of experimental runs.

The models are compared using R-squared and MSE values (Fig. 8). MSE values for responses  $W_c$ ,  $W_{dc}$ ,  $W_n$ ,  $H_a$ ,  $H_b$ , and  $H_c$  were minimal (0.0002-0.03, with the exception of 0.37 determined for the response  $W_c$  at the commercial scale). The other responses showed the highest MSE values using a stepwise regression model, with commercial scale runs showing the highest MSE and lowest R-squared values.



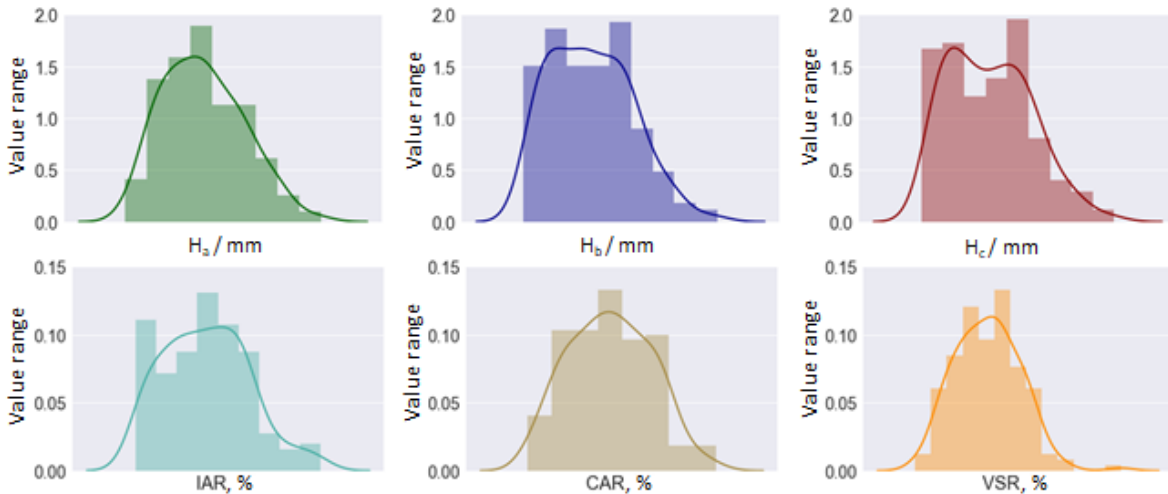


Figure 7. Data distribution analysis using the Shapiro-Wilk test

Table 1. The Shapiro-Wilk test for different responses with *W* and *p*-values

Response	<i>W</i>	<i>p</i> -value
$\sigma_{in}$	0.94	***
$W_c$	0.96	***
$W_{dc}$	0.90	***
$W_n$	0.97	**
$H_a$	0.98	***
$H_b$	0.97	***
$H_c$	0.96	***
IAR	0.97	**

\**p* < 0.05; \*\**p* < 0.01; \*\*\**p* < 0.001

Table 2. The Kruskal-Wallis rank sum test with Chi-squared and *p*-values

Response	Chi-squared	<i>p</i> -value
$\sigma_{in}$	22.189	***
$W_c$	7.1463	*
$W_{dc}$	43.769	***
$W_n$	11.857	**
$H_a$	23.322	***
$H_b$	19.575	***
$H_c$	37.083	***
IAR	5.8947	0.053

\**p* < 0.05; \*\**p* < 0.01; \*\*\**p* < 0.001

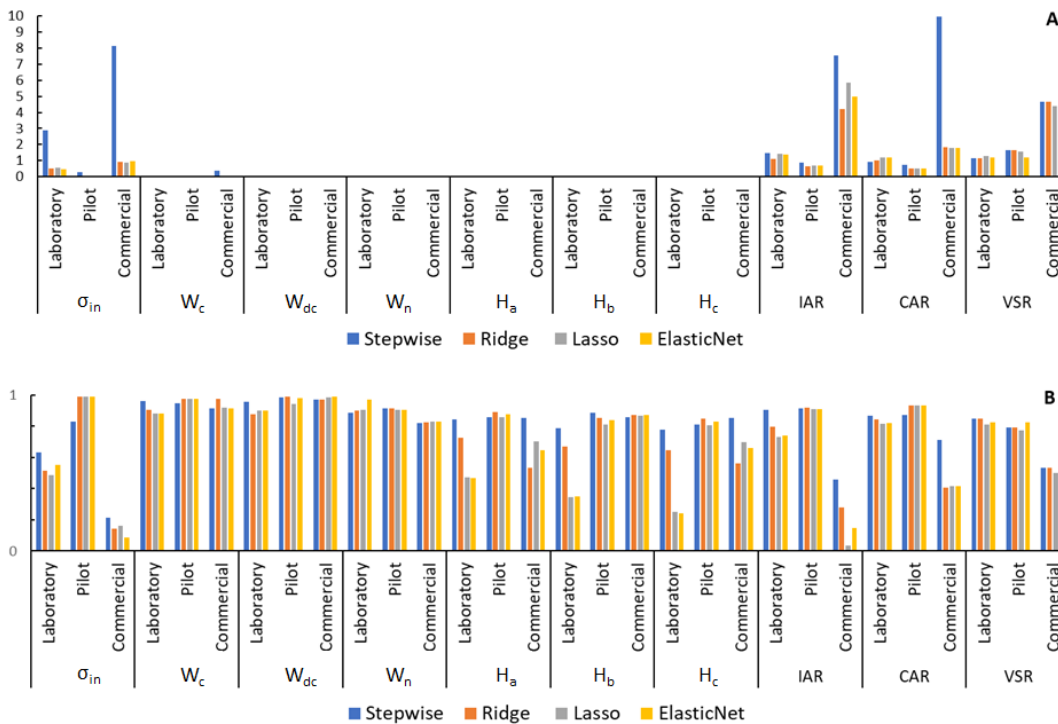


Figure 8. "Bucket" model analysis of data obtained from laboratory, pilot and commercial scale runs. Comparison of stepwise, ridge, lasso and elastic net regression models using: A) MSE and B) R-squared values.





Finally, laboratory scale runs were used for training while pilot and commercial scale runs were used for testing machine learning algorithms. Models were evaluated by comparing their RMSE values. RMSE train values were the highest for the response IAR (3.19-3.73), followed by responses  $\sigma_{in}$  and  $\sigma_{out}$  (0.14-1.07) with the ridge regression model having the highest and the stepwise regression model the lowest RMSE values. RMSE test values were the highest for responses  $\sigma_{in}$  and  $\sigma_{out}$  (0.93-4.30) followed by the response IAR (0.53-2.37). The model with the best fit of data for responses  $\sigma_{in}$ ,  $\sigma_{out}$  and IAR was the boosted regression trees (0.93, 0.93 and 0.53 for the RMSE test, respectively). Responses  $H_a$ ,  $H_b$ ,  $H_c$  and  $W_{dc}$  had the lowest values for both train and test RMSE for all algorithms applied. Despite the high RMSE train values, all responses had high R-squared values across all models applied (Fig. 9).

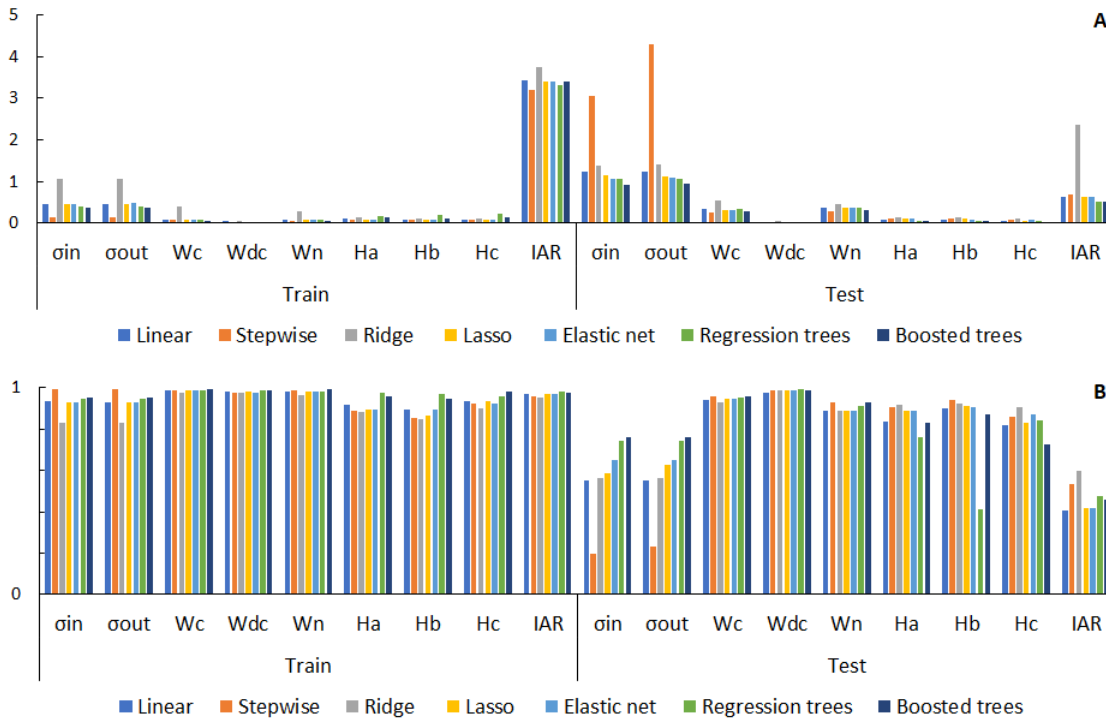


Figure 9. Comparison of train and test values: A) RMSE and B) R-squared. Laboratory scale runs were used for training the models while pilot and commercial scale runs used for testing the models

Table 3 shows significant individual variables and their estimated correlation orientations chosen by the stepwise regression model. Variables with positive correlations are marked with ‘+’ while those with negative correlations are marked with ‘-’ signs.

Table 3. Identification of significant variables and their estimated correlation orientations determined by using a stepwise regression model and selected responses

Significant Variables	Responses						
	$\sigma_{in}$	$W_c$	$W_{dc}$	$W_n$	$H_a$	$H_b$	$H_c$
Compaction force, N	+ ***	+ ***	- ***	+ ***	- ***	- ***	- ***
TCP, %	+ ***	- ***		- ***	- **	- **	- ***
SSG, %	- *	- ***		- ***			- ***
Screen shape (round)	- **						- **
Water concentration, %	- ***						- ***
Particle size > 500 $\mu m$		+ **		+ ***			
Particle size 250 - 500 $\mu m$		+ ***		+ ***			
Particle size 150 - 250 $\mu m$	+ ***						
Particle size 0 - 150 $\mu m$	+ ***						

\*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001



The extent of influence of individual variables is shown by the boosted regression trees model predictor importance analysis (Fig. 10). It is evident that the compaction force is the most influential variable for all responses.

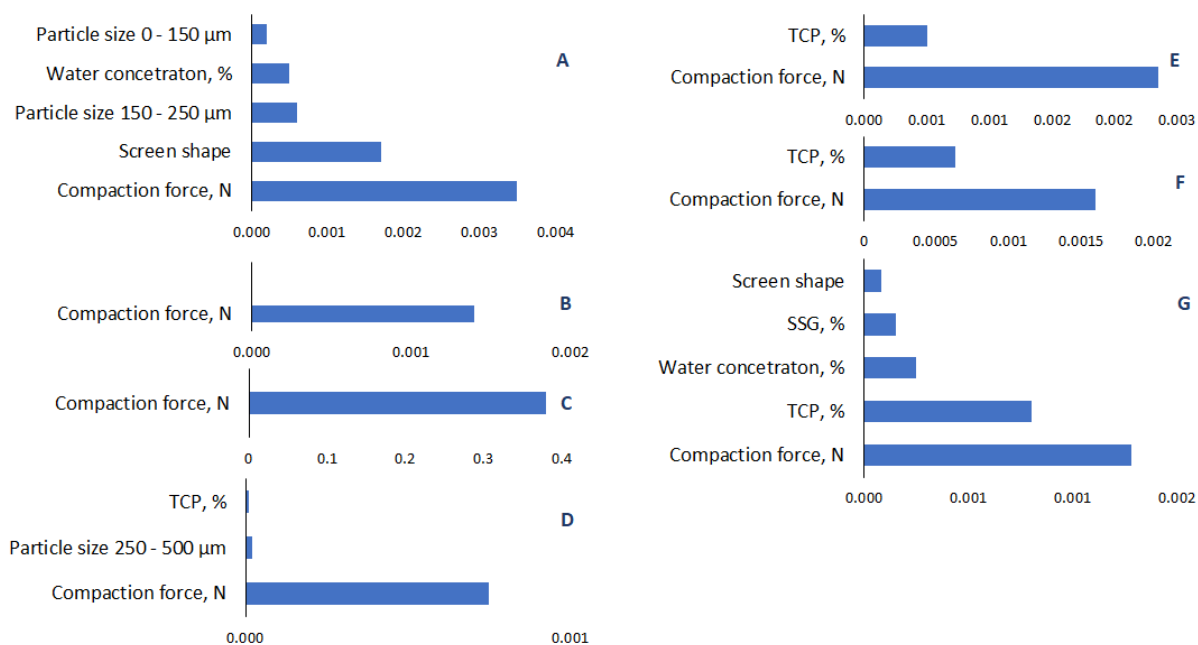


Figure 10. Boosted trees regression predictor importance of: A)  $\sigma_{in}$ , B)  $W_c$ , C)  $W_{d_c}$ , D)  $W_c$ , E)  $H_a$ , F)  $H_b$  and G)  $H_c$ .

#### 4. DISCUSSION

Compaction work is a measure of the forces applied in processes that are involved in compaction of a material (such as plastic deformation or fragmentation) [34,35]. Compactibility is characterized by the tablet tensile strength, while elastic recovery is used to describe compressibility of a powder blend [36]. Many issues in pharmaceutical manufacturing are direct consequences of tablet expansion, which is caused by elastic behavior of materials [37]. At the decompaction stage, once the upper punch starts to ascend, materials start to undergo a process of elastic deformation, which may continue after the tablet ejection from the die [38]. This tablet expansion is called time-dependent viscoelastic recovery [39]. It is well known that elastic changes in a tablet are negatively influencing compactibility of powders [40], which then influence coating and packaging processes as well as stability and storage.

Manufacturability is another term often used to describe a powder blend by using the tablet ejection stress. Detachment and ejection stresses correspond to forces applied on a compressed tablet residing in a die and are arising from residual die wall stresses along the axial and radial directions of a tablet [41]. Additional factors that influence the ejection stress are tablet dimensions, compact-die wall friction, compactibility of the powder, and its mechanism of compaction. High compaction pressure could increase the ejection force by increasing the residual die wall stress and wall friction. Neither of high compaction nor ejection forces are desirable since they expose tablets to high friction and ejection stresses, which may result in breakage of bonds between particles within a tablet [42], capping, lamination and punch sticking [43].

In our study, pilot scale samples have shown the highest tablet tensile strength and compaction work as well as the highest detachment and ejection work. Pilot scale samples have also shown the highest compactibility but the lowest manufacturability as the ejection stress is significantly higher as compared to samples from laboratory and commercial scales, at all compaction pressures.  $W_d$  is dramatically higher than  $W_e$ , due to the design of the compaction simulator and a significantly longer distance needed to detach the tablet from the die base, than to eject the tablet into the ejection cavity [44].

There were negligible differences found between  $H_b$  and  $H_c$ , which indicates that most of the tablet elastic recovery is axial relaxation occurring in the die. Furthermore, comparison of CAR and VCR shows that volumetric expansion of a

tablet out of the die is not significant. It can be also be noticed that  $H_c$  is often lower than  $H_b$ , which could be explained by densification of the solid structure [42], which is known to occur in calcium phosphate. The commercial scale samples showed the lowest tablet height in the die, which can indicate good compressibility and high tensile strength. Corresponding  $\sigma_{in}$  and  $\sigma_{out}$  results were not the highest as compared to the other experimental scale levels probably due to subsequent elastic recovery, consistent with higher IAR, CAR and VSR values determined for these samples.

The obtained scale-up data were further analyzed using the Shapiro-Wilk test. It was found that data do not exhibit normal distribution as all  $W$  values are below 1. Using the Kruskal-Wallis rank sum test it was found that each scale of experimental runs had different impacts on followed responses. High MSE values determined by using the stepwise regression model indicated that data analysis requires regularization, which was applied through the ridge, lasso and elastic net regression techniques. Also, high MSE values determined for responses IAR, CAR and VSR, indicate that prediction of these responses is not reliable on the commercial scale level.

For the final model development, different machine learning algorithms were applied, with the RMSE value used to evaluate models [45]. This parameter represents a measure of the absolute fit of the model to the experimental data or a measure of the average uncertainty that can be expected when predicting the performance of a new sample. Again, the tablet tensile strength and IAR had high RMSE values. The tablet tensile strength had lower RMSE train values but higher RMSE test values (most apparent in the stepwise regression model). This finding may indicate a possibility of overfitting, which can be resolved by using regularization methods (*e.g.* ridge, lasso and elastic net algorithms). For prediction of the tablet tensile strength, the boosted trees regression model was found to provide the best fit, with the lowest RMSE and highest R-squared values.

Compaction work, decompaction work, net work and tablet height were tablet parameters successfully predicted using all machine learning techniques. The employment of these models represents the application of QbD principles during the scale-up process, where prediction of compressibility of a material is crucial for successful industrial tablet production.

Stepwise regression was used as a model that separates significant from non-significant variables [46,47]. Compaction pressure is negatively correlated with  $W_{dc}$ , which is consistent with the expectation that a higher tensile strength will lead to a lower elastic recovery [48,49]. TCP concentration is negatively correlated with the tablet height. It is well known that calcium phosphates increase the tablet tensile strength [50], which will further result in lower height tablets. It has been reported that starches display significant elastic recovery [41], which is consistent with the obtained significance of SSG concentration in  $\sigma_{in}$  and  $H_c$  prediction. Furthermore, it was shown that higher concentrations of SSG caused a decrease in the tablet tensile strength [51]. Another finding from the stepwise regression model is that the concentration of water (binding solvent) is negatively correlated to  $\sigma_{in}$ . This is consistent with literature data, showing that the increase in solvent concentration, decreases the granule porosity together with the tablet tensile strength [48]. In addition, decreased concentration of a solvent provided more porous granules, better suitable for compaction by brittle deformation caused by TCP [52], which results in higher  $\sigma_{in}$ .

The extent of importance of significant variables was studied using the boosted regression trees model. A high value of the predictor importance indicates that the predictor is important for a given variable [53], and represents an estimation calculated as a sum of estimates or changes in the MSE due to splits in the regression tree model divided by the number of branch nodes [54]. In the present study, the variable with the highest predictor importance is the compaction force, followed by the TCP concentration. All variables found to have a statistical significance are also significant from the practical point of view in influencing CQAs [12]. This is important for selecting the most important variables for formulation development, optimization and scale-up modeling.

The results of this study are consistent with the machine learning models' theoretical scope. CQA such as  $\sigma_{in}$  is shown to be influenced by the milling screen hole shape, which is a categorical input variable. Models that had the lowest RMSE values for this CQA were models that can analyze categorical input variables, *e.g.* decision tree (regression tree) and ensemble (boosted regression trees) models. CQAs such as  $W_c$  and  $W_n$ , although shown to be influenced by formulation and particle size factors, were affected mostly by the compaction force as a variable with the highest magnitude of influence, hence all studied models had similar and low RMSE values.

This work demonstrates that force-displacement measurements can be used to examine a material's compactibility, compressibility and manufacturability in an easy and efficient way. Furthermore, obtaining data from laboratory, pilot and commercial scale provided an insight into the influences of multiple input variables on each CQA at a different scale level.

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**SAŽETAK****Modelovanje transfera tehnologije vlažne granulacije tehnikama mašinskog učenja korišćenjem parametara kompresibilnosti, kompaktilnosti i proizvodljivosti**Nada Millen<sup>1</sup>, Aleksandar Kovačević<sup>2</sup>, Lalit Khara<sup>3</sup>, Jelena Đuriš<sup>1</sup> i Svetlana Ibrić<sup>1</sup><sup>1</sup>*Institut za Farmaceutsku tehnologiju i kozmetologiju, Farmaceutski fakultet, Univerzitet u Beogradu, Beograd, Srbija*<sup>2</sup>*Fakultet tehničkih nauka, Univerzitet u Novom Sadu, Novi Sad, Srbija*<sup>3</sup>*Inhouse Remote Development, Seven N Consulting Pvt Ltd, Gurgaon, Haryana, Indija*

(Naučni rad)

Svrha ove opsežne studije je ispitivanje uloge principa dizajna kvaliteta i tehnika mašinskog učenja u uvećanju razmera procesa vlažne granulacije. Ova studija je istražila opseg uticaja promenljivih koje potiču od karakteristika formulacije i procesnih parametara. Pored toga, ispitivani odgovori su uključili oblasti kompresibilnosti, kompaktilnosti i proizvodljivosti mešavine praška. Na kraju su modeli koji su razvijeni pomoću laboratorijskih probi testirani na uzorcima sa pilot i komercijalnog nivoa proizvodnje. Odvajanje i izbacivanje tableta izračunato je pomoću merenja zavisnosti sila-pomerj. Značajne numeričke i kategoričke ulazne promenljive su identifikovane koristeći regresioni model "korak po korak" (engl. *stepwise*) i njihova važnost je procenjena korišćenjem modela regresionih stabala sa tehnikom "jačanja" (engl. *boosted*). Pilot probe su pokazale najveću zateznu čvrstoću i rad kompaktacije kao i najveći rad odvajanja i izbacivanja. Kritični atributi kvaliteta (KAK) koji su najuspešnije predviđeni su rad kompaktacije, rad dekompaktacije, neto rad i debljina tablete. Najvažnija ulazna varijabla koja utiče na sve KAK je sila kompaktacije. Regresiona stabla sa tehnikom "jačanja" je model sa najmanjom vrednosti sume kvadrata razlika za sve praćene odgovore. Ovaj rad pokazuje pouzdanost razvijenih modela i može se uspešno koristiti kao deo pristupa dizajna kvaliteta u transferu procesa vlažne granulacije.

*Ključne reči:* princip dizajn kvaliteta; veštačka inteligencija; rad kompaktacije; rad dekompaktacije; elastični oporavak