

# Utilization of Response Surface Methodology for Modeling and Optimization of Tablet Compression Process

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## ABSTRACT

**Rationale:** Table compression process has a profound effect on different quality attributes of table manufacturing process such as appearance, content uniformity, hardness, thickness, friability, Disintegration time and Dissolution time. Among all the table compression parameters, feeder speed, precompression, main compression forces and Turret speed have a substantial effect on tablet properties. **Aim:** Statistical modeling and optimization approach has been utilized to model and optimize Levocetirizine tablet formulation compression process using Response Surface Methodology. **Methods:** A 3-level Central Composite Design has been chosen by taking turret speed, pre & main compression forces and Feeder speed as input variables and tablet characteristics (hardness, thickness and disintegration time) as output variables. **Results:** Non-linear regression models have obtained with respective to output variables (hardness, thickness and disintegration time) with R<sup>2</sup> values of 99.26%, 98.01% and 99.84% for hardness, thickness and disintegration time, respectively. The effect of individual, square and interaction terms on the table hardness, thickness and disintegration has been summarized through the significance test and depicted through response surface plots. An optimized tablet characteristic of 15.3 kP hardness, 3.7 mm thickness and 226 sec disintegration time have been obtained using predicted tablet compression process variables

of 68 rpm Turret speed, pre and main compression forces of 2.05 and 7.95 kN respectively and Feeder speed of 27 rpm. **Conclusion:** The results demonstrated the reliability of the proposed statistical approach to model and optimized the compression studies of levocetirizine tablet formulation. The present study helps in scale-up studies of tablet compression during Levocetirizine tablet formulation.

**Key words:** Central Composite Design, Levocetirizine, Optimization, Statistical Modeling, Tablet Compression.

**Key message:** The present study showcasing the profound effect of tablet compression parameters on the quality characteristics of Levocetirizine tablets through a modeling coupled optimization approach.

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## INTRODUCTION

The pharmaceutical industry works thrive for developing, manufacturing and introducing new drugs to the market, by satisfying the regulatory requirements which comply to the drug safety, identity, strength, purity and quality standards.<sup>1</sup> Levocetirizine dihydrochloride is the R-enantiomer of Cetirizine. It is a second generation piperazine derivative with potent H1 selective, anti-histaminic or anti-allergic activities. It has a two-fold higher affinity for H1 receptors than cetirizine. The clinical efficacy of cetirizine and levocetirizine is comparable with a marginal advantage of better antipruritic effect of levocetirizine. The difference between these two drugs and traditional antihistamines such as Chlorphenamine (*chlorpheniramine*), is a less sedative effect on the central nervous system.<sup>2</sup> Impinging new approaches in drug development arena will be helpful in enhancing efficiency by providing regulatory relief, flexibility, and offer substantial business benefits throughout the product's lifecycle.<sup>3</sup> Tablet compression is the subject of substantial research in Tablet formulation studies. Understanding compression mechanisms, identifying critical process and material parameters are often crucial for process development.<sup>4</sup> FDA has reported a strategy as to how ANDA applicants can move towards implementation of Quality by Design approaches such as Response Surface methodology (RSM). Based on the desired quality attributes of the drug products, the inputs and process variables are stipulated. The product quality attributes that would be affected by compression include appearance, tablet weight, content uniformity, hardness, thickness, friability, Disintegration time and

Dissolution time. According to FDA's case study, it has found that feeder speed variation may cause over-lubrication or inconsistent die filling while improper pre-compression force may cause lamination/capping. Also, the suboptimal compression force may affect tablet hardness, friability and, ultimately, dissolution. Turret speed may cause inconsistent die filling which may then impact hardness and disintegration, dissolution, assay, content uniformity, friability, weight variability and appearance. Based on this risk assessment study it was found that feeder speed, precompression force, main compression force and Turret speed has a sound impact on tablet properties.<sup>5-8</sup>

Modeling and optimization of tablet compression parameters in pharmaceutical manufacturing and necessary supportive data, particularly in the present the industrial scenario is mainly dependent on Design of Experiments approach.<sup>9,10</sup> Response surface methodology (RSM) utilizes the combination of statistical and mathematical tools. It provides the individual and interactive effects of process variables (input variables) on the targeted output to model the process, usually by representation through non-linear regression equation. The effectiveness of modeling coupled optimization approach in pharmaceutical sector has been reported in several instances.<sup>11</sup> Various studies on effects of tablet formulation and process parameters on tablet properties were evaluated and quantified by multivariate analysis techniques; principal component analysis (PCA) and partial least square regression's (PLS).<sup>12-16</sup> The Design of Experiment (DOE) as an essential element of the RSM paradigm, has

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been widely adopted in studies for many applications including risk assessment, process robustness and product design to improve industrial production efficacy.<sup>17-23</sup> Hence, in the present study, we have utilized RSM approach to model and optimize the tablet compression step of Levocetirizine tablet formulation by taking turret speed, pre & main compression force and feeder speed as input variables and tablet characteristics (hardness, thickness and disintegration time) as output variables.

## MATERIALS AND METHODS

### Materials and equipment

Levocetirizine HCl was received as a gift sample from Symed lab Limited, Hyderabad, India. Magnesium stearate NF vegetable source (Ferro) was received as a gift sample from Biovams Pharmaceuticals Pvt. Ltd, Ahmedabad, India. Lactose monohydrate EP, Microcrystalline cellulose NF ph102 and Croscarmellose sodium NF were procured from SD fine chemicals Ltd, Mumbai. Colloidal silicon dioxide NFCAB-O-SIL M5 was procured from Cabot Sanmar Ltd, Mumbai, and all the other reagents were of analytical grade. Two high Speeds single rotatory European make compression machines were used for the present study.

### Methods

For screening and optimization purpose, a simple formulation was taken and used on two different high-speed rotary tablet presses. Parameters that are deemed insignificant at one machine may prove to be significant on the other machine. Similarly, operational limitation of the full-scale equipment must be considered when proposing the design space. The range of operating conditions and discontinuous configuration option makes it difficult to develop a tablet formulation that is sufficiently robust for all the various compression conditions because a solid formulation is not imparted by small process variation which is practically difficult to achieve.

### Tablet compression methodology

A dry granulation process was used to prepare a blend of raw materials (except magnesium stearate) were sifted through #60 ASTM (American Society for Testing and Materials) using a Vibro Sifter. Pre-blending for 10 minutes was done using an Octagonal blender 150 L. Pre-blend materials have been sifted through #40 ASTM followed by blending for 10 minutes. Magnesium stearate was sifted through #60 ASTM followed by lubrication of blend materials with sifted magnesium stearate for 05 minutes. The present study has been conducted using two single sided rotatory high-speed compression machines as a model to show how DOE helps in optimizing a robust formulation (tablet) as an approach for implementation of RSM which improves the production efficiency.<sup>24</sup> Tablets were compressed using 'B' tooling standard square shaped punch having diameter 8 millimeters.

### RSM based modelling and optimization approach

Modeling coupled optimization approach facilitates the understanding of the process along with the enhanced yield through a selection of the optimized process variables. RSM was one of the approach for modeling and optimization tasks of pharmaceutical processes. In the present study, we have adopted a RSM approach for compression studies of Levocetirizine tablets formulation through central composite design (CCD) of Response Surface Methodology (RSM) and executed through MINITAB 14 software.

### Selection of tablet compression parameters for central composite design

Tablet compression studies are mainly dependent on process variables namely Turret speed (RPM), Pre-compression force (kN), Main com-

pression force (kN) and Feeder speed (RPM). The finished tablets were examined regarding hardness, thickness and disintegration time. Based on the one variable at a time approach, experimental results coupled with the literature survey and prior experience in statistical modeling, in the present study CCD was utilized for RSM approach by taking four variables of compression studies at three levels. In the present study three-level, four factorial CCD design has been utilized by taking the tablet compression variables (Turret speed, Pre-compression force, Main compression force & Feeder speed) as input variables and Tablet Hardness, Tablet Thickness and Tablet Disintegration time as output variables. The range of four compression variables utilized for the present study was tabulated under Table 1. Based on the used range of input variables, the central composite design of RSM planned a design of experiment (DOE) set consists of 31 sets of experiments. The DOE set utilized in the present study shown in Table 2. The designed sets of experiments were executed through wet lab experiments and concerned output variables (Tablet hardness, Tablet thickness and Tablet disintegration time) were noted to each set.

### Statistical analysis

Non-linear regression analysis was carried out based on the data collected as per CCD (Table 2) planning for response, namely hardness, thickness and disintegration time of tablets using MINITAB 14 software which resulted in a second-order polynomial equation by giving the effect of linear, square and interaction terms of process variables on the response. The non-linear relationship between a response and input variables has been represented by a polynomial quadratic equation (Eqn. 1) to describe the functional relationship between the response, Y and the input variables  $x_1, x_2, \dots, x_k$

$$Y = \sum_{i=1}^k \beta_i x_i + \sum_{i=1}^k \beta_{ii} x_i^2 + \sum_{i < j}^k \beta_{ij} x_i x_j \quad (\text{Eq. 1})$$

The response include the linear terms  $x_1, x_2, \dots, x_k$ , square terms  $x_1^2, x_2^2, \dots, x_k^2$ , and interaction terms  $x_1 x_2, x_1 x_3, \dots, x_{k-1} x_k$ .

The coefficient of the non-linear regression model can be determined using the method of least squares. The effect of the parameters and their interaction terms on the response has been studied by conducting the significance tests, and Analysis of variance (ANOVA) has been carried out on each response to check the adequacy of the model.<sup>25</sup> The detailed analysis of the effect of parameters and their interactions on the response was also done through the surface plots using MINITAB 14 software.

## RESULTS AND DISCUSSION

Compression machine setting plays a major role in getting the desired tablet properties of tablet formulation process, which usually differs from formulation to formulation. In our experiment, we have considered four machine setting parameters namely, turret speed, Pre and main compression force and feeder speed. Usually, at higher turret speeds, tablet hardness will decrease due to the lesser dual time at the meantime if turret speed is low; tablet hardness will be higher, which will impact the dissolution of a tablet. Pre-compression and main compression force adjustment play an important role in controlling hardness and thickness of the tablet. Powder filling in die cavity depends on the speed and design of the feeder. If feeder speed is low it may lead to improper die filling which will be resulting in weight variation and variation in hardness and thickness. If feeder speed is high it will overflow the die cavity and it can lead to weight variation and variation in hardness and thickness. To get the desired tablet, a combination of machine setting parameters is essential; the trial and error method in machine setting parameters will consume more powder and time. In this type of instances, RSM

approach is a scientifically approved technique to model and optimize the process parameters.

The effect of tablet compression variables namely turret speed, pre & main compression forces and Feeder speed on tablet characteristics, i.e., hardness, thickness and disintegration time was investigated using RSM according to CCD.<sup>26</sup> The least squares technique has adopted for the development of second-order polynomial equation, which gives the effect of individual, square and interaction terms of the tablet compression variables on the responses (Tablet hardness, Tablet thickness, and Tablet disintegration time).

Prediction of responses namely hardness, thickness and disintegration time for the given values of turret speed, pre & main compression forces, and Feeder speed have depicted through Eq. (2) – Eq. (4) as follows:

The estimated non-linear Regression for Hardness (Kp) in un-coded-form is:

$$\begin{aligned} \text{Hardness (Kp)} = & 48.3016 - 0.679279X_1 - 15.0765X_2 - 0.278188X_3 + 0.238967X_4 \\ & + 0.00592000 X_1^2 - 1.40800X_2^2 + 0.354667X_3^2 \\ & + 0.00302041X_4^2 + 0.267500X_1X_2 - 0.0741667X_1X_3 \\ & - 0.00982143X_1X_4 + 0.558333X_2X_3 + 0.0946429X_2X_4 \\ & + 0.000595238X_3X_4 \end{aligned} \quad \text{Eq.(2)}$$

The estimated non-linear Regression for Thickness (mm) in un-coded form is:

$$\begin{aligned} \text{Thickness (mm)} = & 2.12178 + 0.0506520 X_1 - 0.276000X_2 \\ & + 0.0661627X_3 + 0.00892460X_4 - 4.66667E \\ & - 04X_1^2 + 0.0533333X_2^2 - 0.00962963X_3^2 - 2.38095E-04X_4^2 \\ & + 0.000250000X_1X_2 + 0.00108333X_1X_3 + 5.35714E \\ & - 05X_1X_4 - 0.00583333X_2X_3 + 0.00125000X_2X_4 \\ & - 7.73810E-04X_3X_4 \end{aligned} \quad \text{Eq.(3)}$$

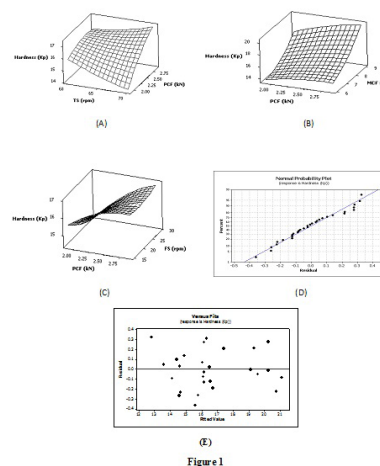
The estimated non-linear Regression for Disintegration time (sec) in un-coded form is:

$$\begin{aligned} \text{Disintegration time (sec)} = & 1835.33 - 66.1165X_1 + 41.7678X_2 + 67.4797X_3 \\ & + 17.9907X_4 + 0.531787X_1^2 - 30.8213X_2^2 - \\ & 1.86904X_3^2 - 0.218476X_4^2 + 1.15000X_1X_2 \\ & - 0.483333X_1X_3 - 0.128571X_1X_4 + 5.50000X_2X_3 \\ & + 0.285714X_2X_4 - 0.190476X_3X_4 \end{aligned} \quad \text{Eq.(4)}$$

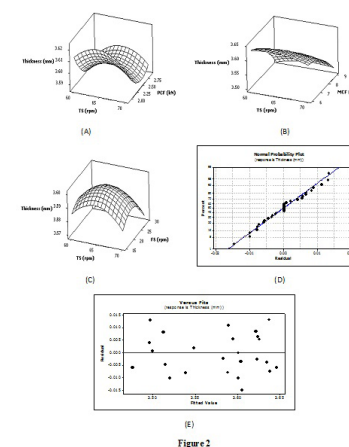
Where  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  represents turret speed, pre-compression force, main compression force and Feeder speed respectively.

The prediction accuracy of the proposed models seems in close agreement of predicted and experimental values of CCD experiments (done in triplicates) (Table 2). The significance of individual, square, interaction terms of compression variables ( $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$ ) on tablet hardness, thickness and disintegration time have also deduced from the P-values of the significance test (Table 3). The P- value remains less than 0.5 by considering 95 % as a level of confidence for all factors except  $X_1^2$  &  $X_4^2$  terms of tablet hardness and  $X_2$  &  $X_1X_4$  terms of tablet thickness. Furthermore, the significance effect of linear, square and interaction terms on tablet hardness, thickness and disintegration time has been demonstrated by the ANOVA results (Table 4), where P-values of these terms have seemed to be lesser than the significant value level ( $\alpha$  0.05) except  $X_1^2$  &  $X_4^2$  terms for tablet hardness and  $X_1$ ,  $X_1X_3$  &  $X_1X_4$  terms of tablet thickness. The fitness and adequacy of the proposed models are further demonstrated by the  $R^2$  and adjusted  $R^2$  values for tablet hardness ( $R^2= 99.26\%$ ; Adj.  $R^2=98.61\%$ ), tablet thickness ( $R^2= 98.01\%$ ; Adj.  $R^2= 96.27\%$ ) and tablet disintegration time ( $R^2= 99.84\%$ ; Adj.  $R^2=99.70\%$ ).

To understand the effect of the independent variables on the dependent variable, response surface plots of the quadratic polynomial model has generated by varying two of the independent variables within the experimental range while holding other variables kept constant at the central point.<sup>27</sup> Figure 1 (a) shows the effect of turret speed (rpm) and pre-compression force (kN) on hardness (Kp). It revealed that increase



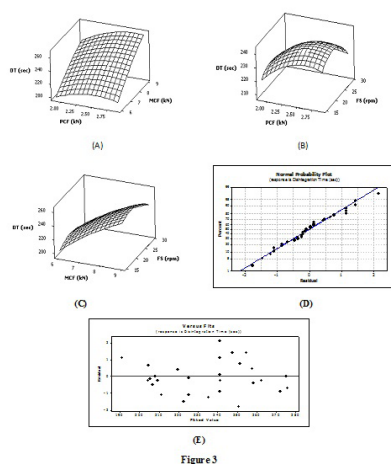
**Figure 1:** Surface plots of Hardness (Kp) with: (A) Turret speed (RPM) and Pre-compression force (kN), (B) Pre-compression force (kN) and Main-compression force (kN), (C) Pre-compression force (kN) and Feeder speed (RPM), (D) Normal % Probability and studentized residual plot for Hardness (E) The studentized residual and fitted response plot for hardness.



**Figure 2:** Surface plots of Thickness (mm) with: (A) Turret speed (RPM) and Pre-compression force (kN), (B) Turret speed (RPM) and Main-compression force (kN), (C) Turret speed (RPM) and Feeder speed (RPM) (D) Normal % Probability and studentized residual plot for Thickness (E) The studentized residual and fitted response plot for Thickness.

in (rpm turret speed) with pre-compression force (kN) resulted in progressive enhancement of hardness (Kp). Figure 1 (b) shows the effect of pre-compression force and main compression force on hardness (Kp). It demonstrated that maximum hardness (Kp) has obtained at the pre-compression force of 2.05 kN and main compression force of 7.95 kN. Figure 1 (c) showed the effect of pre-compression force and feeder speed on hardness (Kp). It showed maximum hardness (Kp) at the pre-compression force of 2.05 kN and feeder speed of 27 rpm.

The 3D response surface plots represent the regression equation. Figures 2 (a) - 2(c) represent the 3D response surface plots for the optimum conditions of tablet thickness (mm). Each figure represents the effect of two variables on thickness. Figure 2 (a) indicates that maximum thickness of 3.7 mm has obtained with a turret speed of 68 rpm and pre-compression force of 2.05 Kn. Figure 2(b) depicts that the maximum thickness has attained at using turret speed of 68 rpm and main compression



**Figure 3:** Surface plots of Disintegration Time (Sec) with: (A) Pre-compression force (kN) and Main-compression force (kN), (B) Pre-compression force (kN) and Feeder speed (RPM), (C) Main-compression force (kN) and Feeder speed (RPM) (D) Normal % Probability and studentized residual plot for Disintegration time (E) The student zed residual and fitted response plot for Disintegration time.

sion force of 7.95 kN. Figure 2 (c) similarly shows the effect of varying turret speed and feeder speed on thickness. Figures 3 (a) - 3 (c) represent the 3D response surface plots for the optimum conditions of disintegration time (sec). Each figure represents the effect of two variables on disintegration time (sec). Figure 3 (a) showed the effect of Pre-compression force (kN) and Main-compression force (kN), Fig 3 (b) showed the effect of Pre-compression force (kN) and Feeder speed (RPM) and Figure 3 (c) showed the effect of Main-compression force (kN) and Feeder speed (RPM) on disintegration time (sec). Response surface plot analysis showed maximum disintegration time (sec) was observed at the pre-compression force of 2.05 kN, the main compression force of 7.95 kN and feeder speed of 27 rpm. The predicted non-linear equation of fitted response surface has also checked through diagnostic plots of Normal % probability Vs studentized residuals and Studentized residual Vs fitted response, for tablet hardness, tablet thickness and tablet thickness, which have depicted in Figure 1(C) & 1(D), Figure 2(C) & 2(D) and Figure 3 (C) & 3(D), respectively. The normal % probability and studentized residuals plots, which have shown in Figure 1(C), Figure 2(C) and Figure 3 (C) for hardness, thickness and disintegration time of tablet, respectively. Usually, the studentized residuals measure the number of standard deviations separating the actual and predicted values. The residuals showed the how well the derived models satisfy the assumptions of analysis of variance (ANOVA). The studentized residuals and predicted tablet hardness, tablet thickness and tablet disintegration time have depicted in Figure 1(D), Figure 2(D) and Figure 3 (D). Random scattered these plots suggesting that the variance of original observations be constant for all values of the responses.<sup>28</sup>

Response surface optimizer function of MINITAB 14 has utilized for drawing the optimal responses with the predicted compression variables. An optimized tablet hardness of 15.2 Kp, tablet thickness of 3.57 mm and tablet disintegration time of 227 secs has proposed by utilizing the tablet compression variables of turret speed of 68 rpm, feeder speed of 27 rpm and Pre & main compression forces of 2.05 kN and 2.7 kN, respectively. The proposed set of tablet compression variables has chosen for experimental testing. The obtained tablet properties (15.3 Kp hardness, the thickness of 3.7 mm and 226 s of disintegration time) of triplicate experimental runs seemed to be in close agreement with the

predicted tablet properties. The enhanced results have reported through the usage of RSM approach in the case of extended-release drug delivery of cefpodoxime proxetil by taking the amount of hydroxypropyl methylcellulose (HPMC K4M), sodium alginate (SA) and microcrystalline cellulose (MCC) as the variables.<sup>29</sup> Bose *et al.*, (2013) reported the enhanced results for sustained release of Itopride HCl by utilizing response surface methodology.<sup>30</sup>

## CONCLUSION

In the present study, the compression process of Levocetirizine has been modeled and optimized through RSM approach using compression parameters as input variables and tablet characteristics (hardness, thickness and disintegration time) as output variables. The optimum compression variables have determined as 68 rpm Turret speed, Pre- & main compression force of 2.05kN, 7.950 kN respectively with Feeder speed of 27 rpm. Utilizing the optimum conditions, the compression process of Levocetirizine results in a tablet properties of 15.3 Kp hardness, 3.7 mm thickness and a disintegration time of 226S. The results obtained from this work clearly defined the baseline operating parameters that yield compatibility and reproducibility throughout production which is our first goal of this utilized RSM approach. Hence the outcome of this investigation of response optimization suggests it to be a valuable tool for similar processes. As compared to random experimentation, implementation of Design of Experiments with well designed statistical experiments improves the results.

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## CONFLICT OF INTEREST

The authors declared that they don't have any conflict of interests in publishing this article.

## ABBREVIATION USED

**ANDA:** Abbreviated New Drug Application; **ANOVA:** Analysis of Variance; **CCD:** Central Composite Design; **DOE:** Design of Experiments; **FDA:** Food and Drug Administration; **PCA:** Principal Component Analysis; **PLS:** Partial Least Squares; **RSM:** Response Surface Methodology.

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