Research Article

QbD Approach: Tablet Compression Process Optimization Using Design of Experiments

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ABSTRACT

Present study describes an approach to predict tablet properties by multivariate method. In this study, a quality by design approach has been applied to optimize tablet compression process. The effect of four process parameters on tablet compression process on two compression machines were characterized. Turret speed (two levels), Pre Compression force (two levels), Main compression force (two levels), and Feeder speed (two levels) represent the four parameters studied. Compression machine geometry and powder loading method were treated as constant parameters. Design of experiment (DOE) was used to assess the impact of each parameter on critical tablet properties like hardness, thickness, friability and disintegration time. 2^4 full factorial design were applied in this study. Minor change in main Compression Force impacts tablet properties significantly. Tablet Properties are not significantly affected by Turret Speed, Pre compression force and feeder speed given the range studied. Process parameters were reproducible having minimal impact on tablet properties in case the machine geometry is same.

Keywords: Quality by Design (QbD), Design of Experiment (DOE), Turret speed, feeder speed, Compression force.

INTRODUCTION

A Tablet must comply with safety, identity, strength, purity and quality standards as per regulatory requirements for its introduction into the market. Any new approach in the drug development process for tablets, could increase efficiency, provides regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle[1].

Tablet compression is a critical step in the process of tablet manufacturing hence it is important to identify critical process parameter during tablet compression[2]. In Pharmaceutical industry, the initial business goal is the creation of baseline operating parameters that would yield compatibility and reproducibility, and second part is the ability for rapid optimization of parameters under custom application environment which are subject to change over a certain period of timeline[3,4].

Present work is undertaken to explore optimization of parameters used for tablet compression in pharmaceutical manufacturing with range of its compatibility/reproducibility and requisite supportive data, particularly in the light of a industry's current movement toward submissions based on Design of Experiments (DOE) approach as a part of quality by design (QbD)[5].

Optimization of Tablet Formulation using 2^4 Full Factorial Design

Introduction & Optimization

Current approach of pharmaceutical industry is to develop an acceptable formulation within a short period of time with less man power and productivity costs. Traditional approach of optimization is one variable at a time which is a time consuming process, moreover ideal formulation development is difficult to achieve through this approach. Industrial experience has shown that process operating parameters significantly affect tableting quality and standards[12].

In many cases these effects are not strictly additive, process parameters can interact both synergistically as well as antagonistically. It is therefore very essential to understand complexity of pharmaceutical formulation by using established statistical tools such as factorial designs. DOE is helpful to improve limitation of study, interaction effects and give quick results. DOE is a multivariate approach and gives clear definition of variable effects. It can be used for three purposes:

i. batch progress monitored in real time allows for early fault detection

ii. Prediction - Built a correlative model from previous data that can predict the quality of current batch

iii. Control -adjust process conditions to control the batch quality in real time.

2^4 full factorial design was used to evaluate effect of selected independent variables on the response to characterize physical properties of the tablets and to optimize procedure[15].

The number of experiments required for these studies is completely dependant of number of independent variable selected. The response Y measured for each trial is denoted as below:

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_{12} x_1 x_2 + \beta_{23} x_2 x_3 + \beta_{13} x_1 x_3 + \beta_{14} x_1 x_4 + \beta_{24} x_2 x_4 + \beta_{34} x_3 x_4 + \beta_{123} x_1 x_2 x_3 + \beta_{234} x_2 x_3 x_4 + \beta_{134} x_1 x_3 x_4 + \beta_{1234} x_1 x_2 x_3 x_4$$

Y is dependent variables

Where β represents the unit changes in Y per unit changes in X.

β_0 = Y-intercept {a constant value} which is arithmetic means of 32 runs

Two way interaction terms ($x_1 x_2$), ($x_2 x_3$), ($x_3 x_4$), ($x_1 x_4$), ($x_1 x_4$), ($x_2 x_4$), ($x_3 x_4$): shows how the response changes when two factors are simultaneously changed.

Three way interaction terms ($x_1 x_2 x_3$), ($x_2 x_3 x_4$), ($x_1 x_3 x_4$): shows how the response changes when three factors are simultaneously changed. Four way interaction terms ($x_1 x_2 x_3 x_4$): shows how the response changes when four factors are simultaneously changed.

Experimental Design

Quality risk analysis has been performed to identify critical input variables (factors) which might have a significant impact on product quality attributes. Failure mode and effects analysis (FMEA) method has been adopted for assessment, It was identified that Feeder speed, Pre-Compression Force, Main-compression force and Turret speed might have significant impact on product quality attributes hardness, thickness, disintegration time (DT) and friability.

The design lay out is tabulated in Table-1

Table 1: Study Independent & Dependent variables with ranges and Level

Independent variable name	Ranges and Level	Response Variable Name	Desired response
Turret speed	14 to 25 RPM	Tablet Hardness	18 ± 3 kp
Pre Compression force	1.9 to 2.9 kN	Friability	NMT 0.5%
Main compression force	5.3 to 9.0 kN	Disintegration Time	500 sec
Feeder speed	18 to 30 RPM	Tablet Thickness	3.30-3.70 mm

RPM – Revolution Per Minute, kN- Kilo Newton, kp- Kilopascal, Sec – Seconds

MATERIALS AND METHODS

Materials

Anhydrous Lactose NF, Microcrystalline cellulose PH 102, Sunset yellow Aluminium lake 40% , Magnesium Stearate, Purified Talc all reagents are analytical grade.

Materials	% w/w Quantity (tablet)
Anhydrous Lactose NF	64.35
Microcrystalline cellulose (PH102)	34
Sunset Yellow Aluminium Lake 40%	0.15
Magnesium stearate	1.00
Purified Talc	0.5

Experimentation

Design expert 8 software is used for present study. A simple formulation is taken and used on two different rotary tablet presses for screening and optimization of process. Based on the Q8, Q10 ICH guidelines risk assessments was done to find out high risk factors to be studied. ANOVA and Pareto analysis are done to find out significant factors for both machines. Tablet process optimization done through design space and based on that optimized parameters tablets were compressed to confirm the study.

Our work outlines the activity performed to achieve a mechanistic understanding of the compression process on the effect of each input variable of product quality. There are two main experimental objectives for which DOE can be used; those are screening and optimization[6].

Screening is to identify main effects of key variables and to determine ranges within the parameters. Optimization is a follow up study to identify optimal operating conditions[7,8].

Sometimes the amount of work increases significantly as number of study variables increase. Therefore, Pareto type analysis was done to know how large number of process variables effect the tableting quality[13].

In a first step, the effect of different levels of each independent variable on the considered responses was studied i.e. in particular, four factors were studied at two levels. In this study four independent variables such as turret speed, pre compression force, main compression force and feeder speed in two levels (high and low) have been taken into consideration (Table-2)[14].

Two replications of 16 experiments were taken to minimize error. Optimization was done based on the priority of significant factors and production needs[16]. The generated models contain explaining nonlinear responses.

This design also resolves four factor interaction effects of individual terms.

Our full study addressed all four responses namely tablet hardness, thickness, disintegration time (DT), Friability (%).

The experimental plan and responses observed in a screening phase, were carried out in randomized order according to 16-run matrix provided for by the Factorial design strategy are illustrated in Table-2.

Preparation of blend for the study

Dry granulation process was used to prepare a blend, raw materials except magnesium stearate and Purified talc 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 sifted through #40 ASTM followed by blending for 10 minutes. Magnesium stearate and Purified Talc was sifted through #60 ASTM followed by lubrication of blend materials with sifted magnesium stearate for 05 minutes. The study was conducted using two single sided rotatory compression machines as a model to show how DOE helps in optimizing a robust formulation (tablet) which improves production efficiency. Tablets were compressed using 'B' tooling Size 6.5mm, round shaped standard convex tablets were used for the study.

Evaluation Parameters of Tablets

Hardness

Hardness of tablets was determined by using Schulinger Auto tester. The tablets must be hard enough to withstand mechanical stress during packaging, shipment, and handling by a consumer. The tablet hardness of about 15-21 Kp is considered adequate for mechanical stability. Determination was made in triplicate & mean value is considered.

Thickness

Thickness of tablets were determined using Schulinger Auto tester. Thickness is critical for packing especially in blister packs and a range of 3.5mm Average value of the ten tablets were taken into the consideration.

Disintegration Time

Drug absorption from the site of action is more important for which tablets have some pre-defined disintegration time to reach site of action. Disintegration test of tablets was determined using Electrolab Disintegration test apparatus subjecting the tablets to temperature batch 37±2 degree Celsius. 10 tablets were taken for the study and average value was taken into the consideration. (Insert expected DT range)

Friability

Resistance to abrasion and chipping during handling suggest to perform friability test. 6.5 grams of Tablets were taken for the test using Electrolab friabilator for 100 Revolutions.

Percentage of friability was calculated of the dedusted tablets from the loss of weight. Weight loss should not more than 0.5%. Determination was made in triplicate and mean value is considered.

Statistical Analysis

Statistical analysis of 2^4 full factorial design was performed by regression analysis. To evaluate the effect of each factor with different levels to the response , ANOVA was performed using Design expert 8.0(STAT-EASE) Demo version software to demonstrate influence of each factor graphically response surface plots were generated using Design expert 8.0(STAT-EASE) Demo version software.

Based on the effects of all critical independent variables mathematical models are determined for each response on each machine to see that all machines are giving similar results.

A full model is a model that is having all possible terms significant or not significant.

A reduced model is a model that does not include all the possible terms.

It becomes a reduced model by omitting terms. reduce of model done where terms are not significant.

Machine 1

Full Model

Hardness =16.5531 -0.921875 * A -0.253125 * B + 4.65313 * C + 1.07187 * D + 0.271875 * AB + 0.578125 * AC + 0.046875 * AD + 0.259375 * BC + 0.053125 * BD + 0.821875 * CD -0.140625 * ABC + 0.278125 * ABD + 0.471875 * ACD + 0.890625 * BCD -0.234375 * ABCD

Reduced Model

Hardness =+16.553-0.92188* A-0.25313*B+4.6531*C+1.0719*D

Machine 2

Full Model

Hardness =14.5359 -0.426562 * A -0.467188 * B + 4.61719 * C -0.148437 * D -0.0796875 * AB + 0.204688 * AC + 0.139063 * AD -0.335938 * BC + 0.242187 * BD + -0.317188 * CD + 0.326562 * ABC -0.0453125 * ABD + 0.295312 * ACD -0.326563 * BCD -0.314062 * ABCD

Reduced Model

Hardness =+14.536-0.42656*A-0.46719*B+4.6172*C -0.14844*D

Final Regression Equation in Terms of Coded Factors For Thickness

Machine 1

Full Model

Thickness= 3.54625 + 0.00875 * A -0.00625 * B -0.07875 * C -0.008125 * D -0.01375 * AB -0.00375 * AC -0.004375 * AD -0.0025 * BC + 0.006875 * BD + 0.009375 * CD + 0.005 * ABC -0.009375 * ABD + 0.000625 * ACD -0.001875 * BCD + 0.011875 * ABCD

Reduced Model

Thickness =+3.5463+0.0087500*A-0.0062500*B-0.078750*C-0.0081250*D

Machine 2

Full Model

Thickness =3.58656 + 0.0196875 * A + 0.0165625 * B - 0.0928125 * C + 0.0084375 * D + 0.0021875 * AB + 0.0015625 * AC + 0.0028125 * AD -0.0103125 * BC + -0.0078125 * BD + -0.0146875 * CD -0.0059375 * ABC -0.0109375 * ABD -0.0065625 * ACD + 0.0065625 * BCD + 0.0096875 * ABCD

Reduced Model

Thickness=+3.5866+0.019687*A+0.016562*B-0.092813*C+0.0084375*D

Final Regression Equation in Terms of Coded Factors For DT

Machine 1

Full Model

DT= 283.063 + -3.75 * A + 4.625 * B + 37.25 * C + 3.375 * D -0.0625 * AB -3.3125 * AC + 0.3125 * AD + 0.4375 * BC -0.6875 * BD + 1.0625 * CD + 2.25 * ABC + 2.625 * ABD -1.26084e-015 * ACD + -3.125 * BCD + 1.9375 * ABCD

Reduced Model

DT=+283.06-3.7500*A+4.6250*B+37.250*C+3.3750*D

Machine 2

Full Model

DT=229.187 + -2.0625 * A -11.75 * B + 36.0625 * C -3.875 * D -2.125 * AB -3.8125 * AC -5.875 * AD + 3 * BC + 2.4375 * BD + 2.5 * CD + 0.5 * ABC + 3.5625 * ABD + 3.625 * ACD -6.0625 * BCD -2.3125 * ABCD

Reduced Model

DT=+229.19 -2.06*A-11.75*B+36.06*C-3.88*D

Final Regression Equation in Terms of Coded Factors For Friability

Machine 1

Full Model

Friability =0.245625 -0.018125 * A -0.01625 * B -0.06875 * C -0.01125 * D -0.005 * AB -0.0075 * AC -0.005 * AD + 0.001875 * BC + 0.000625 * BD -0.000625 * CD + 0.005625 * ABC + -0.005625 * ABD -0.006875 * ACD + 0.00875 * BCD -0.0025 * ABCD

Reduced Model

Friability =+0.25-9.688E-003*A-4.688E-003*B-0.064*C-9.063E-003*D

Machine 2

Full Model

Friability =0.375 -0.00875 * A + 0.00625 * B -0.1275 * C -1.76586e-017 * D + 1.8573e-018 * AB + 0.0025 * AC -0.00375 * AD + 0.00375 * BC -0.01125 * BD -0.00375 * CD -0.01625 * ABC -0.005 * ABD -0.00625 * ACD + 0.0125 * BCD + 0.0075 * ABCD

Reduced Model

Friability =+0.37500-0.0087500*A+0.00625003*B-0.12750*C-7.3598E-018*D

Effect of Pre Compression force

16 batches had been prepared to study effect of pre compression force in both tablet presses is listed in the Table-3 and table 4. Lower precompression force of 1.9 kp and higher Pre Compression force of 2.9 kp are applied. With higher Pre Compression force hardness become higher than limit when feeder speed is high and after friability test chipping in tablets were observed (Run 25, Run 26 in machine 1). Similarly If higher precompression force(2.9 Kp) in combination with lower main compression force (5.3 Kp) applied resulted hardness become lower than the specified limit and lamination defects are observed during harness tests (Run 15 in machine 1 and Run 10 in machine 2). From this it was observed that precompression force does not have significant impact on hardness.

Effect of main Compression force

Higher the main compression force (include value) higher will be hardness (Run 14,28 in Machine 1 and Run 5 , 15 in Machine 2). Lower Main compression force (include value) results lower hardness than the specified limit (Run 1, 4 in Machine 1 and Run 9, 13 in machine 2.

Effect of turret Speed and feeder Speed

There is no impact on harness in change in turret speed or feeder speed. However higher feeder speed in conjuction with higher main compression force resulted higher hardness (run 1,25 in machine 1 and Run 5,20 in machine 2).

ANOVA analysis

Analysis of variance (ANOVA) (Table 2) indicated that the assumed regression model was significant and valid for each considered response. Main effects are having significant impact hence reduced model was taken into consideration for ANOVA analysis. Comparison of regression analysis with respect to full model and reduced model is demonstrated in Table-3. Among main effects the main compression force is having a significant impact on all response variable. Lack of Fit F value is more than 0.1000 in all model indicates that lack of Fit is not significant relative to pure error which is good for model. Prob > F value less than 0.0500 indicates that the all models are significant. Difference between the predicted R^2 and Adjusted R^2 value less than 0.2 shows a significant agreement.

Table 2: Calculation for testing the models in proportions

1) for Hardness

	MACHINE 1					MACHINE 2				
				F	p-value				F	p-value
Source	SSA	df	MS	Value	Prob > F	SSA	df	MS	Value	Prob > F
Model	758.86	4	189.72	32.92	< 0.0001 *	695.70	4	173.93	64.79	< 0.0001 *
A- Turret Speed	27.20	1	27.20	4.72	0.0388*	5.82	1	5.82	2.17	0.1524
B- Pre Compression Force	2.05	1	2.05	0.36	0.5559	6.98	1	6.98	2.60	0.1184
C- Main Compression Force	692.85	1	692.85	120.21	< 0.0001 *	682.19	1	682.19	254.13	< 0.0001 *
D- Feeder Speed	36.77	1	36.77	6.38	0.0177	0.71	1	0.71	0.26	0.6125
Residual	155.62	27	5.76			72.48	27	2.68		
Lack of Fit	74.36	11	6.76	1.33	0.2929**	23.71	11	2.16	0.71	0.7163
Pure Error	81.26	16	5.08			48.77	16	3.05		
Cor. Total	914.48	31				768.18	31			

2) for Thickness

	MACHINE 1					MACHINE 2				
				F	p-value				F	p-value
Source	SSA	df	MS	Value	Prob > F	SSA	df	MS	Value	Prob > F
Model	0.20426	4	0.051066	27.418	< 0.0001	0.299	4	0.0748	45.3	< 0.0001*
A-Turret Speed	0.0024500	1	0.0024500	1.3154	0.26148	0.0124	1	0.0124	7.51	0.0108
B-Pre Compression Force	0.0012500	1	0.0012500	0.67114	0.41983	0.00878	1	0.00878	5.31	0.0291
C- Main Compression Force	0.19845	1	0.19845	106.55	< 0.0001	0.276	1	0.276	167.	< 0.0001
D-Feeder Speed	0.0021125	1	0.0021125	1.1342	0.29631	0.00228	1	0.00228	1.38	0.251
Residual	0.050288	27	0.0018625			0.0446	27	0.00165		
Lack of Fit	0.019888	11	0.0018080	0.95156	0.52125	0.0235	11	0.00213	1.61	0.187**
Pure Error	0.030400	16	0.0019000			0.0212	16	0.00132		
Cor. Total	0.25455	31				0.344	31			

3) for DT

	MACHINE 1					MACHINE 2				
				F	p-value				F	p-value
Source	SSA	df	MS	Value	Prob > F	SSA	df	MS	Value	Prob > F
Model	45901.	4	11475.	36.166	< 0.0001	46650.75	4	11662.69	30.04	< 0.0001
A-Turret Speed	450.00	1	450.00	1.4183	0.24406	136.13	1	136.13	0.35	0.5587
B-Pre Compression Force	684.50	1	684.50	2.1573	0.15345	4418.00	1	4418.00	11.38	0.0023
C- Main Compression Force	44402.	1	44402.	139.94	< 0.0001	41616.13	1	41616.13	107.17	< 0.0001
D-Feeder Speed	364.50	1	364.50	1.1488	0.29329	480.50	1	480.50	1.24	0.2758
Residual	8566.9	27	317.29			10484.12	27	388.30		
Lack of Fit	1226.9	11	111.53	0.24313	0.98901	4574.12	11	415.83	1.13	0.4032
Pure Error	7340.0	16	458.75			5910.00	16	369.38		
Cor. Total	54468.	31				57134.88	31			

4) for Friability

	MACHINE 1					MACHINE 2				
Source	SSA	Df	MS	F Value	p-value Prob > F	SSA	df	MS	Value	p-value Prob > F
Model	0.17426	4	0.043566	32.742	< 0.0001	0.52390	4	0.13098	42.049	< 0.0001
A-Turret Speed	0.010513	1	0.010513	7.9008	0.0090862	0.0024500	1	0.0024500	0.78656	0.38297
B-Pre Compression Force	0.0084500	1	0.0084500	6.3507	0.017952	0.0012500	1	0.0012500	0.40131	0.53174
C- Main Compression Force	0.15125	1	0.15125	113.67	< 0.0001	0.52020	1	0.52020	167.01	< 0.0001
D-Feeder Speed	0.0040500	1	0.0040500	3.0438	0.092419	0.00000	1	0.00000	0.00000	1.0000
Residual	0.035925	27	0.0013306			0.084100	27	0.0031148		
Lack of Fit	0.0097250	11	0.00088409	0.53990	0.84846	0.022900	11	0.0020818	0.54427	0.84527
Pure Error	0.026200	16	0.0016375			0.061200	16	0.0038250		
Cor. Total	0.21019	31				0.60800	31			

SSA- Sum of Squares, df-Decrease of freedom, MS-Mean Squares,*Significant,**Non Significant

Pareto Analysis+

Graphic analysis of effects allowed different effect of factors level to be evaluated in the Figure-1. When multiple factors are anlysed the Bonferroni correction counteracts used to find out most real factors which are affecting the process. The Bonferroni correction counteracts is defined as division of individual significance level be divided by number of factors with 5 % error. The values of Bonferroni correction and t value are taken form ANOVA table, and comparison chart were prepared for better visibility for machine 1 and 2. We observed that for response hardness, main compression force is most important about 67-81%. The value of turret speed, pre-compression force and feeder speed below the t value which is less impact on the getting desired response of hardness. Similarly, for response thickness main compression force is highest that is more than 68%. Pre compression contributing rest of the factors are not as much of effect less than Bonferroni value. For response DT also we have observed Main compression force plays a very important role more than 60%, Pre-compression force contributing about 24% for machine 2. Rest of the factors are not much effect. For Friability it is for both the machines main compression force plays very important role for setting of machine more than 60 %. Rest of the parameters are less effect less than Bonferroni value.

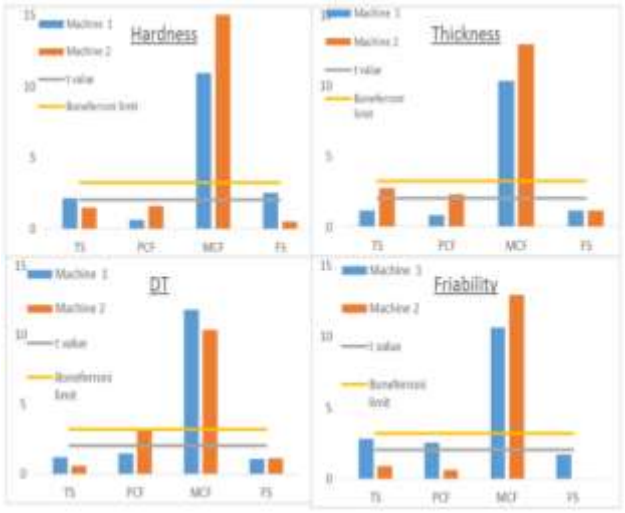

Figure 1: Pareto Chart

X-axis Factors→ TS- Turret Speed, PCF-Pre Compression Force, MCF-Main Compression Force & FS- Feeder Speed

Y- axis- t- value effect

t-value - 2.05183

Boneferroni value- 3.2194

3D Surface graphs

Omitted terms in terms of interaction effects does not contribute the prediction of each response like hardness, thickness, disintegration Time and friability. The results are shown in the form of response surface plots. (Figure 2-5)

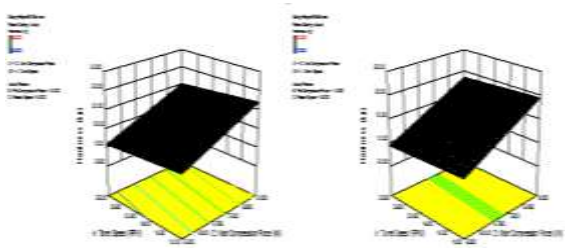

Figure 2: 3D Surface graph for Hardness machine 1 and 2

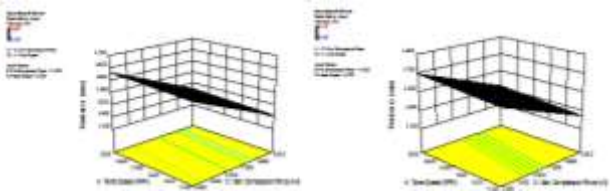

Figure -3: 3D graph for Thickness machine 1 and 2

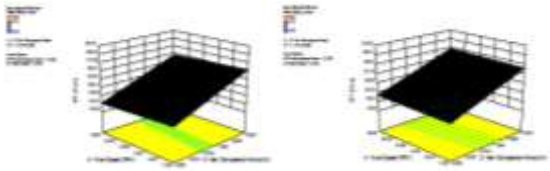

Figure -4: 3D graph for DT machine 1 and 2

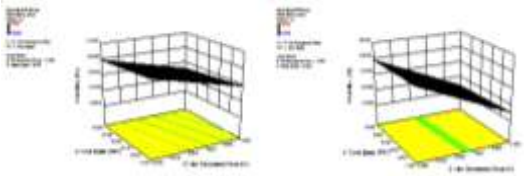

Figure 5: 3D graph for Friability machine 1 and 2

Hardness response

The summary of fit and analysis of variance results show that a very good model was obtained for hardness. Main-Compression force is the most important factor impacting tablet hardness, indicated by a high sum of squares value (Table no.2). Further it is evident from Pareto analysis (fig no. 1) for both machines it indicates that main-compression force are having significant effect. Both 3D plots support this analysis (fig no.2) from a practical perspective, Main compression force is the only factor that impacts hardness significantly. Minor increase in compression force increase hardness and vice versa.

Thickness response

The summary of fit and analysis of variance results show that a very good model was obtained for Thickness, High sum of squares from ANOVA(Table no-2) and Pareto Analysis (fig no.1) indicates that for both the machines main compression force plays a significant importance. 3D surface plot Fig no.3 support the analysis increase in Main-compression force decreases thickness and vice versa.

DT responses

A very good model was obtained for disintegration time as seen in the previous responses, main factor impacting

disintegration time is Main -compression force. Response Hardness analysis summaries that increase in Main compression force increase hardness harder tablet would expect higher Disintegration time and Vice versa. Refer table no. 2 for ANOVA analysis Figure no-1 for Pareto and Figure no. 4, 3D plot.

Friability responses

The summary of fit and analysis of variance results show that a very good model was obtained for Friability. Main Compression force is the most important factor impacting tablet Friability, indicated by a high sum of squares value (Table no.2). Further it is evident from Paroto analysis (fig no. 1) for both machines it indicates that main-compression force are significant effect . Both 3D plots support this analysis (fig no.5) from a practical perspective, Main compression force is the only factor that impacts Friability significantly.

Main Compression force was identified as a potential critical process parameter, because of its significant impact on the critical quality attribute responses studied. Pre-compression force turret speed and feeder speed are included in some of the models to get a better statistical fit, however their contributions are not significant within the ranges studied.

Based on the understanding of compression, appropriate process operating conditions will be determined to accommodate two of rotary tablet press.

Selection of Optimized condition in tablet compression

It is found that the best condition to optimize hardness, thickness and disintegration time correspond to the turret speed, Pre Compression force, Main Compression force and Feeder speed are tabulated below.

Variables	Unit of Measure	Machine-1	Machine-2
Turret Speed	RPM	25	25
Pre-Compression Force	kN	1.9	1.9
Main Compression Force	kN	9	9
Feeder Speed	RPM	18-30	18-30

This optimum point represents the predicted point. To validate the predictive ability of response surface model for each response between optimized conditions, the predicted and measured response has been checked and verified. Tablets have been prepared in simulation of optimized condition of the compression variables. The confidence level for each response at 95% confidence level was calculated.

The predicted values are inside the confidence interval of each observed response. Stratified samples collected and are subjected to content uniformity test for dye content (sunset yellow Aluminum Lake 40%) to conform the content uniformity well within the limit.[9-11]

Content uniformity test

Observed dye content value is minimum 92.0%, maximum 96.7% and Average 94.12% (limit 90-110%). Relative standard deviation (RSD) is found 1.80% (limit NMT-5%).

CONCLUSION

It was concluded that the appropriate statistical design and optimization techniques can be successfully used in the optimizing process parameters in tablet compression. If Geometry of tablet presses are same then similar process parameters can be reproducible in all machine with minimal impact on tablet properties in terms of hardness, thickness, disintegration time and friability. Similarly Minor change in main compression Force will have significant impacts on tablet properties. Other variables like Turret Speed, Pre compression force and feeder speed does not have significant Impact on tablet properties.

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