

## Optimization of Granulation and Compression process Variables of Atenolol Tablets using Box-Behnken Design

Tarak J. Mehta<sup>\*1</sup>, Mohan Mothilal<sup>2</sup>, Alpesh D. Patel<sup>1</sup>, Mukesh R. Patel<sup>1</sup>, Dr K.R.Patel  
Natvarlal M. Patel<sup>1</sup>

<sup>1</sup>Shri B. M. Shah College of Pharmaceutical Education and Research, Modasa, India

<sup>2</sup>SRM College of Pharmacy, Kattankulathur, Chennai

### Abstract

Pharmaceutical tablets represent the most popular drug delivery systems. Tablets are manufactured by compressing a powder formulation in a die. Following this process the tablets are subjected to a bulk handling and other operations during which the bioavailability (disintegration, dissolution) behaviour and mechanical integrity must be maintained. The final properties of the tablets depend on the choice of ingredients used in the powder formulation, the details of the mixing process and selection of process parameters applied by tableting equipment. The application of three or higher-level experimental design using the response surface methodology does not appear to have been reported in development and optimization of drug release methods until now. The relationship between one or more response variables and set a quantitative parameters can be examined well by using response surface models, such as central composite design or Box-Behnken design.

In this present work systemic analyses of the process parameters during compression process and explore their influence on the final properties of the tablets have been studied. Also illustrate how tablet properties are controlled by dependent variables of granulator and compression machine.

\*Corresponding author, Mailing address:

**Mr. Tarak J. Mehta**

Lecturer-Department of Pharmaceutical  
Technology,

Shri B. M. Shah College of Pharmaceutical  
Education and Research,

College Campus, Modasa-383315, Gujarat, India

Tel: +02774249587

Mobile- +919925074029

**E-mail: tarakjmehta@yahoo.com**

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## Introduction

Pharmaceutical tablets represent the most popular drug delivery systems. Tablets are manufactured by compressing a powder formulation in a die. Following this process the tablets are subjected to a bulk handling and other operations during which the bioavailability (disintegration, dissolution) behaviour and mechanical integrity must be maintained. The final properties of the tablets depend on the choice of ingredients used in the powder formulation, the details of the mixing process and selection of process parameters applied by tableting equipment<sup>1</sup>.

The application of three or higher-level experimental design using the response surface methodology does not appear to have been reported in development and optimization of drug release methods until now. The relationship between one or more response variables and set a quantitative parameters can be examined well by using response surface models, such as central composite design or Box-Behnken design.

In this present work a systemic analysis of the process parameters during compression process and explore their influence on the final properties of the tablets have been studied. Also illustrate how tablet properties are controlled by dependent variables of granulator and compression machine.

## Materials and Methods

### MATERIALS:

Atenolol was received by Ariane Org Chem. Ltd. (Hyderabad, India). Heavy magnesium carbonate and Gelatin was procured from Taurus chemicals (London, U.K.). Sodium Lauryl sulphate and maize starch were received from Cognis (Mumbai, India). Magnesium stearate was gift sample from Febro Ltd (London, U.K.). All chemicals used for this study were of analytical reagent grade. Freshly distilled water was used through out the work.

## EXPERIMENTAL DESIGN

### Manufacturing of Tablets

Atenolol, heavy magnesium carbonate, maize starch and sodium lauryl sulphate (60-80 mesh, 250-177  $\mu\text{m}$ ) were mixed in Rapid Mixer Granulator (Sainath boilers and pneumatics, India) for 10 mins at different impeller and chopper speed. Purified water (50%) was heat and add gelatin in heated water with constant stirring until dissolve. 3.57 % w/w maize starch paste (granulating agent) was prepared with boiling purified water. Add the gelatin solution to starch paste and mixed properly. Add the granulating agent to the material over a period of 2 min at different impeller and chopper speed followed by kneading for about 2 min to get a good granular mass. Wet granular mass was dried in fluidized bed dryer (Bectochem, India, 20kg) at an internal temperature of  $60 \pm 5^\circ\text{C}$ , outlet temperature  $40 \pm 5^\circ\text{C}$  till a loss on drying of 1.5–3.3 % was achieved on IR moisture balance in auto mode at  $105^\circ\text{C}$ .

Table 1: Composition of Tablet

Ingredients	Lot/Batch No	Quantity/Batch
Atenolol	AP148104	1.00 kg
Gelatin	RM2/00621/04	40.0 gm
Heavy magnesium carbonate	HMC0323/03	1.740 kg
Maize starch	101180	930.0 gm
Sodium lauryl sulphate	RM/0323/03	66.0 gm
Maize starch (for paste)	101180	24.0 gm
Purified water	-	1.392 kg
Magnesium stearate	100661	100.0 gm

Dried granules were sifted through 18 mesh on vibratory sifter (Bectochem, India) and mill the retentions of granules through 1 mm screen of multimill (bectochem, India) with knives forward direction at slow speed. The dried granules were blended with 1% magnesium stearate in Octagonal

In the presented study, granulation process was optimized by taking three different lots, in which dependent variables were impeller speed, binder addition time, chopper speed, impeller mixing time

blender (Bectochem, India) for 20 min. Tablets (390 mg) were compressed on a 16 station rotary tablet compression machine (Rimek, India) using a 9 mm standard flat-face punch. The prepared tablets were round and flat with an average diameter of  $9.0 \pm 0.1$  mm and a thickness of  $4.75 \pm 0.2$  mm.

and their effect on bulk density, true density, Carr's index, and hausner ratio (Table 2).

**Table 2:** Presentation of 3 experiments with variables for granulation process

Lot No	Impeller Speed	Binder addition Time (min)	Impeller Mixing time (min)	Amp. reading	Chopper Speed
1	Fast	1	12	3.7	Slow
2	Slow	2	8	3.9	Fast
3	Fast	2	6	3.9	Fast

**Table 3.** Compression process variables design and Response data of batches in the Box Behnken design (BB 1-BB 15)

Batch	X <sub>1</sub> (Ton)	X <sub>2</sub> (Ton)	X <sub>3</sub> (rpm)	Hardness (N)	Friability (%)	DT (sec)
BB1	-1	-1	0	28.34	1.8	122
BB2	-1	1	0	57.7	0.3	362
BB3	1	-1	0	35.39	0.8	128
BB4	1	1	0	70.3	0.08	96
BB5	-1	0	-1	42.36	0.23	215
BB6	-1	0	1	59.09	0.37	303
BB7	0	-1	1	25.9	1.9	138
BB8	1	0	-1	40.3	0.32	340
BB9	0	-1	-1	32.08	0.58	126
BB10	0	-1	1	40.3	0.73	132
BB11	0	1	-1	43.8	0.65	150
BB12	1	0	1	60.8	0.12	830
BB13	0	0	0	51.0	0.9	260
BB14	0	0	0	47.42	0.88	265
BB15	0	0	0	46.88	0.92	261
Variables	Level					
	Low (-1)	Medium (0)	High (1)			
(X <sub>1</sub> ) Precompression force (ton)	0	1	2			
(X <sub>2</sub> ) Compression force (ton)	2	4	6			
(X <sub>3</sub> ) Compression speed (rpm)	25	30	35			

For compression process three levels Factorial Box-Behnken experimental design was used to evaluate effect of selected independent variables on the responses, to characterize physical properties of tablets and to optimize the procedure. This design is suitable for exploration of quadratic response surface

and for construction of polynomial models, thus helping to optimize process by using a small number of experimental runs. For the three levels three factor Box and Behnken Experimental design, a total of 15 experimental runs, shown in Table 3, are needed. The generated models contain Quadratic term explaining

the non linear nature of responses This design also resolves the three factor interaction effect of individual terms and allow a mid level setting (0), for

The design consists of replicated center points and a set of points lying at the mid points of each edge of multidimensional cube that defines the region of interest .The model is of the following form:

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_4x_1x_2 + b_5x_2x_3 + b_6x_1x_3 + b_7x_1^2 + b_8x_2^2 + b_9x_3^2 + E$$

Where y is the selected response, b<sub>0</sub>-b<sub>9</sub> are the regression coefficients, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are the factors studied and E is an error term. The Box-Behnken experimental design is an orthogonal design.

the combination of the factors (montgomery,1991;Singh et al.,1995).

Therefore, the factor levels are evenly spaced and coded for low, medium and high settings; as -1, 0, +1 (Montgomery,1991; Singh et al.,1995;Karnachi and Khan ,1996). Factors studied in the Box and Behnken experimental design where: precompression force (X<sub>1</sub>), compression force (X<sub>2</sub>) and compression speed (X<sub>3</sub>). The factors levels are shown in Table 3. The selected responses were Hardness (Y<sub>1</sub>), friability (Y<sub>2</sub>) and Disintegration time (Y<sub>3</sub>). The responses studied and the constraints selected considering Atenolol Physical properties and regarding U.S.FDA guidelines, presented in Table 4.

**Table 4:** Responses selected and the constraints used in Box-Behnken design

Code	Parameter	Constraints
Y <sub>1</sub>	Hardness	35-40 N
Y <sub>2</sub>	Friability	NMT 0.5 % w/w
Y <sub>3</sub>	Disintegration time	NMT 10 minutes

### Evaluation of Tablets

#### Hardness

The hardness of the tablets was tested for 10 tablets by pharma hardness tester (Pharma Test, Germany) and average hardness (N) was being taken and compared with that of standard one.

#### Friability

Friability test was performed in accordance with USP (Electroleb friabilator, Mumbai) 5 tablets were selected randomly, their individual weight was taken and then kept in the friabilator and rotated for 4 min at a speed of 25 rpm the tablets were taken out and any loose dust from them was removed, the weight was registered and friability was calculated as a percentage weight loss.

#### Disintegration time

The disintegration of the tablets was tested in a disintegration tester (Pharma Test, Germany), six tablets were put in to a basket that was raised and lowered in a beaker containing preheated water at 37°C. The disintegration test was calculated as the mean value and as the range.

#### *In-vitro* dissolution studies

The release rate of atenolol from tablets (n=3) was determined according to British Pharmacopoeia (ref) using the Dissolution Testing Apparatus 2 (model TDT-60T, Electrolab, India) fitted with paddles. The dissolution test was performed using 900 mL of 0.1 N HCl, 37±0.5°C and 50 rpm. A 5 mL sample was withdrawn from the dissolution apparatus at predetermine time interval, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µm membrane filter and

diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solution was measured at 275 nm using UV/VIS spectrophotometer (Jasco V530, Japan). Cumulative drug release was calculated using the equation generated from Beer Lamber's calibration curve in the linearity range of  $\mu\text{g/mL}$ .

### Statistical analysis

Statistical analysis of the Box-Behnken design batches was performed by multiple regression analysis using Microsoft Excel. To evaluate the contribution of each factor with different levels to the response, the two-way analysis of variance (ANOVA) was performed using the DESIGN EXPERT 6.0.11 (STAT-EASE) demo version software. To graphically demonstrate the influence of each factor on the response, the response surface plots were generated using DESIGN EXPERT 6.0.11 (STAT-EASE) demo version software.

### Results and discussion

In the present investigation, combinations of three variables were studied using the Box-Behnken

experimental design. The mathematical models developed for all the dependent variables using statistical analysis software are shown in equations (1)-(3):

$$\begin{aligned} \text{Hardness} = & 48.43 + 11.92 X_1 + 5.60 X_2 - 0.37 X_3 + \\ & 1.38 X_1 X_2 - 0.58 X_1 X_3 + 2.19 X_2 X_3 - 1.41 X_1^2 + 0.91 \\ & X_2^2 - 5.10 X_3^2 \\ R^2 = & 0.6794 \end{aligned} \quad \text{----- (1)}$$

$$\begin{aligned} \text{Friability} = & 0.90 - 0.45 X_1 - 0.19 X_2 + 0.13 X_3 + 0.19 \\ & X_1 X_2 - 0.43 X_1 X_3 - 0.17 X_2 X_3 + 0.016 X_1^2 - 0.16 X_2^2 - \\ & 0.21 X_3^2 \\ R^2 = & 0.8202 \end{aligned} \quad \text{----- (2)}$$

$$\begin{aligned} \text{Disintegration Time} = & 262.00 + 62.25 X_1 + 53.25 \\ & X_2 + 85.25 X_3 - 68.00 X_1 X_2 + 28.50 X_1 X_3 + 168.50 X_2 \\ & X_3 - 72.75 X_1^2 - 12.25 X_2^2 + 59.75 X_3^2 \\ R^2 = & 0.6043 \end{aligned} \quad \text{----- (3)}$$

The hardness of all tablets was found to be below 61 N

**Table 5:** Box-Behnken Experimental Design

Batch	X <sub>1</sub> (Ton)	X <sub>2</sub> (Ton)	X <sub>3</sub> (rpm)	Hardness (N)	Friability (%)	DT (sec)
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Variables	Level					
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	(X <sub>2</sub> ) Compression force (ton)			2	4	6
(X <sub>3</sub> ) Compression speed (rpm)				25	30	35

**Table 6:** Analysis of variance for dependent variables from the Box-Behnken design

Source	SS	df	MS	F-value	Probability
<b>Hardness</b>					
Regression	1526.00	9	169.56	1.18	0.0045
Residual	720.21	5	144.04		
Total	2246.22	14			
<b>Friability</b>					
Regression	3.40	9	0.38	2.53	0.01591
Residual	0.74	5	0.15		
Total	4.14	14			
<b>Disintegration</b>					
Regression	2.830	9	31446.69	0.85	0.6097
Residual	1.853	5	37059.90		
Total	4.683	14	4.683		
SS - sum of squares, df - degree of freedom, MS - mean of square, F-Fischer's ratio					

**Table 7:** Granulation Optimization : Analysis data

<b>Batch No.: 1</b>					
Lot No.	Initial air drying time	Total Hot air drying Time	Inlet Temp (°C)	Outlet Temp. (°C)	LOD (% w/w)
Lot-1	10 minutes	50 minutes	50-60	44	1.50
Lot-2	10 minutes	60 minutes	60	44	1.80
Lot-3	10 minutes	70minutes	55-56	38	2.20

### Results and Discussion

In The Present investigation granulation and compression process were optimized.

#### Results and Discussion for Granulation Process :

In granulation process, impeller speed, binder addition time, chopper speed, impeller mixing time were studied by taking three different lots for dependent variables i.e. bulk density, true density, Carr's index, and hausner ratio (Table 2).

#### Effect of impeller and chopper speed

Various granulation batches prepared to study the effect of impeller and chopper speed are listed in table 1

#### Results and Discussion for Compression Process:

Combinations of three independent variables were studied using the Box Behnken design. The mathematical models developed for all the

dependent variables using design expert software are shown in equation (1)-(3)

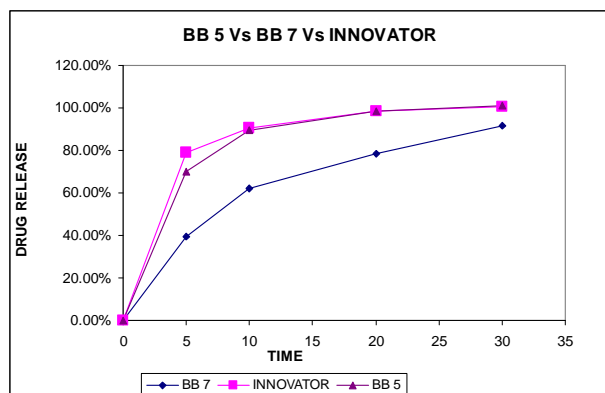
#### Effect of Pre Compression Force , Compression force and Compression speed :

15 batches had been prepared to study the effect of pre compression force is listed in table no 3. so, we took three different pre compression force -1 indicates there is no pre compression force, 0 indicates pre compression force is 1tonne, +1 indicates precompression force is 2 tonnes, after preparing all the batches results showed that ,after applying pre compression force hardness becomes higher than limit in combination with lower compression force and lower compression force showed cracking tableting defect (BB 4). So, result showed that Precompression force should not be given ,when we are applying higher compression force and ,and when Precompression force is not given and compression force is also lowered cause

lower hardness and friability problems with high compression speed.(BB 7)

All three independent variables also affects invitro dissolution studies ,if pre compression force is 2 tonnes and compression force 6 tonnes with lowe compression speed 25 rpm ,takes more time to dissolve and vice versa.

Dissolution profiles for two Optimized batches BB 5 and BB 7 were analysed and compared with innovator product and calculated for similarity factor showed result given in table no. 7

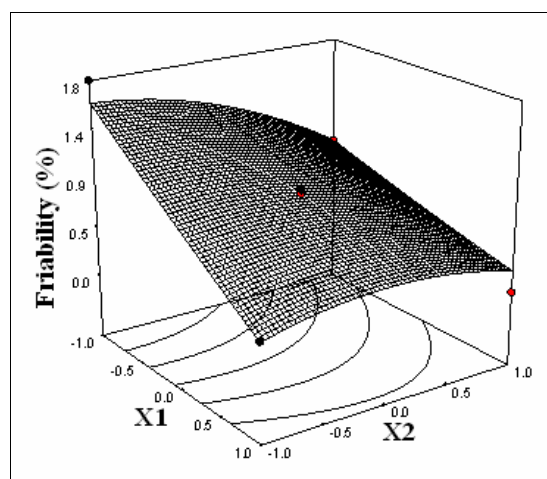
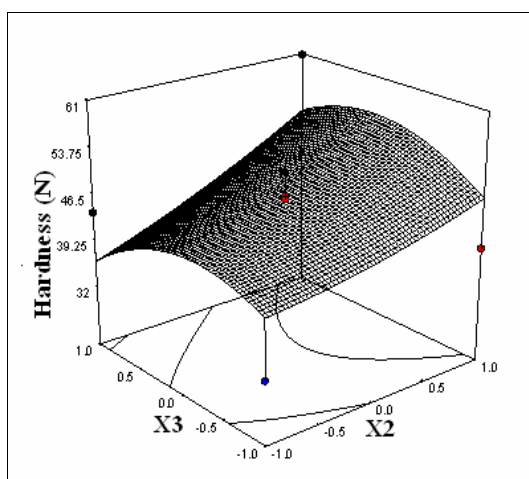
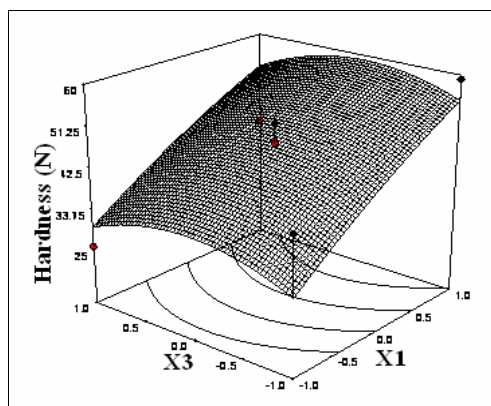


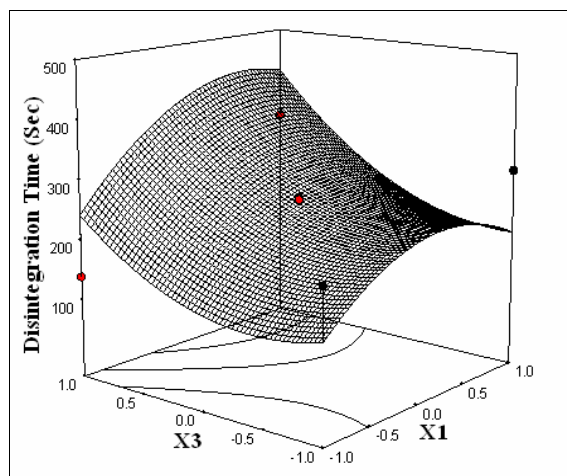
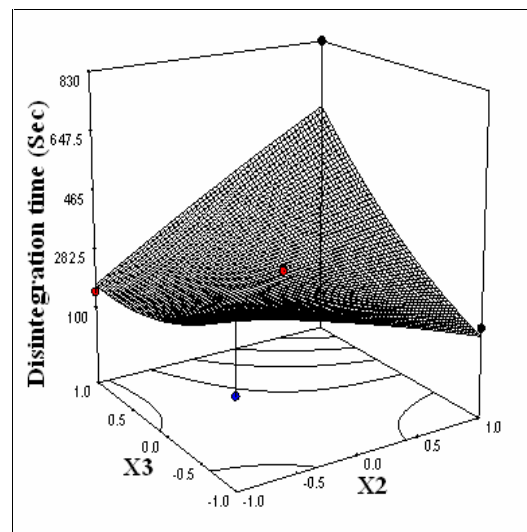
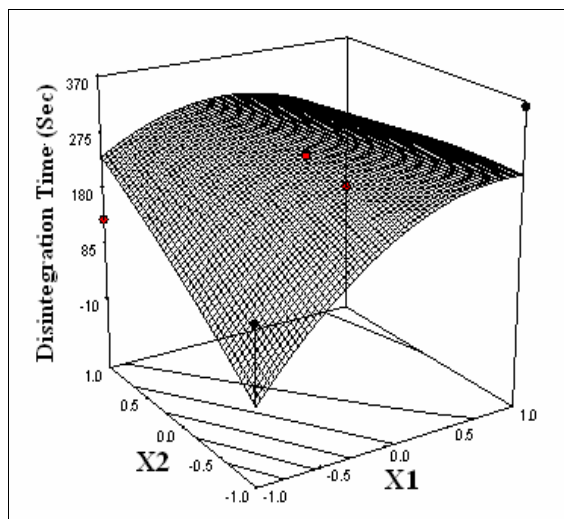
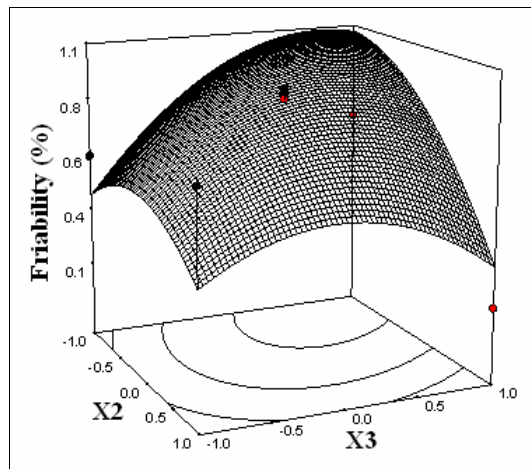
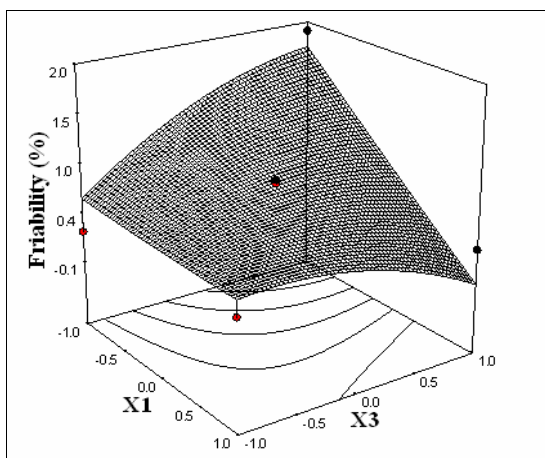
**Figure 1:** Comparison of Optimized Batch With innovator

**Table No 8**

Formulation	f2 (similarity factor)	f1(difference factor)
BB 5	67	03
BB 7	29	26

**Figure 2 :** Comparison data using Design Expert Software







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