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OPTIMISATION OF COMPRESSION FORCE AND LUBRICANT MIXING TIME FOR THE ORODISPERSIBLE TABLET BY DESIGN OF EXPERIMENT APPROACH

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ABSTRACT

A two factor, three level (3^2) face full factorial design was used to study the effects of compression force (CF) and lubricant mixing time on disintegration time (DT) and hardness of amlodepine-ramipril orodispersible tablets (ODTs). Orodispersible tablets were prepared by direct compression. Multiple linear regression analysis was used for generation of polynomial equation and optimization of formulation. Results of multiple linear regression analysis indicated that both the factor affect tablet properties. The optimized level of independent variables; compression force (138.54 MPa) and lubricant mixing time (2.59 min) provided a rapid disintegration (30.0 sec) with optimum hardness (3.5 kg/cm^2).

KEYWORDS: *Design of experiment, orodispersible, 3^2factorial design, process variables, optimization.*

INTRODUCTION

Dysphagia or difficulty in swallowing is common in patients, particularly paediatric and geriatric patients. To overcome this problem, Orodispersible technology has gained more attention over the last decade.[1] Orodispersible tablets (ODT) are dispersed rapidly upon contact with the saliva and release drugs without the need of water. Ideally ODT disintegrate rapidly with sufficient mechanical strength to allow for handling and shipment. Various technologies have used to prepare ODT, range from lyophilisation to tablet compression.

Depending on the technology used therefore, the resultant ODTs differ in their characteristics, disintegration time (DT) and mechanical strength. ODT formulated by lyophilisation, disintegrate rapidly (2–3 s) due to their high porosity; but have poor mechanical strength requiring specialised packaging.[2] Conventional compression process was used to formulate ODT with higher mechanical strength, but they show prolong disintegration time.[3]

The pharmaceutical technologist has devoted considerable effort, to formulate ODT with rapid DT and sufficient mechanical strength. Various strategies have been used such as addition of effervescent excipients, use of superdisintegrating excipient and low compression force, to lower the DT. To improve mechanical strength a number of post compaction treatments, moisture treatment; a solid-state transition of amorphous sugars (such as maltose) to its crystalline form have been used.[4]

Compression is one of the most important process variable in tablet manufacturing process. It is well known that a little change in compression force (CF) can significantly affect the tablet hardness and disintegration time.[5] In general, the greater the compression force applied, the harder the tablets and slower disintegration.[6] Shipar et al (2014) reported that change in CF from low to high showed twelve time increase in hardness from 2.30 to 25.24 kg/cm^2 and 3.0 fold increase in DT.[7] Lubricant, an excipient to reduce friction, is an essential ingredient of a tablet formulation. Magnesium stearate is one of the most frequently used lubricants and affects tablet properties.[8]

In the present study, the effect of compression force and lubricant mixing time on the disintegration time and hardness of ODT was evaluated by design of experiment (DOE) approach. Factorial design was used to optimize the compression force and lubricant mixing time. A two factor, three levels (3^2) full factorial design was used and nine experimental runs were performed. Statistical models with interaction terms were derived to investigate influence of compression force (X1) and lubricant mixing time (*X*2) on tablet disintegration (*Y*1) and hardness (*Y*2).

MATERIAL AND METHODS

Materials

Amlodepine and ramipril were obtained as a gift sample from Dr. Reddy's Laboratories Ltd. Baddi, India. Sodium starch glycolate was obtained as a gift sample from S.D.Fine Chem

Ltd, Mumbai, India. Microcrystalline cellulose and magnesium stearate were procured from Colorcon Asia Pvt.Ltd., Goa, India. Talc, Aerosil 200 and Aspartame were purchased from Loba Chemie Pvt. Ltd., Mumbai, India.

Experimental Design

A 3^2(two factor at three levels) full factorial design was used for optimization of orodispersible tablet containing amlodepine and ramipril. Design Expert 9.0.6 (Minneapolis, MN, USA) used for generation and evaluation of the empirical second order polynomial model. These models were used to analyse effect of independent variables on the responses. One-way ANOVA was used to determine the significance of the model ($P < 0.05$) and individual response. The amount of sodium starch glycolate and amount of magnesium stearate are the prime selected independent variables (factors), which were changed at three levels (-1. 0 and +1). Levels for two factors are presented in Table 1.

Table 1: Independent variables and critical quality attributes (response) of the 3^2 factorial design.

Independent variables	**Level**		
	-1	**0**	**+1**
X1 = Compression Force (MPa)	75	150	225
X2 = Lubricant mixing time (Min)	2.0	5.0	8.0
Critical quality attributes (response)			
Y1 = Disintegration time (Sec) Y1 = Hardness (kg/cm^2)			

The matrix of 3^2factorial design was shown in table 2. Nine trial batches of orodispersible tablets were prepared as suggested by 3^2 factorial designs. The disintegration time (*DT*, sec) and hardness (kg/cm2) were investigated as the critical quality attributes (responses).

Table 2: 3^2 Factorial design matrix

Run	**Independent variables (Factor)**		**Dependent variables (Response)**	
	X1	**X 2**	**Y1**	**Y2**
1	-1.000	-1.000	25.3	3.1
2	-1.000	0.000	27.4	2.94
3	-1.000	1.000	33.21	2.8
4	0.000	-1.000	27.5	3.64
5	0.000	0.000	43.67	3.4
6	0.000	1.000	62.31	3.06
7	1.000	-1.000	25.99	4.5
8	1.000	0.000	55.35	4.1
9	1.000	1.000	87.65	3.63

X1 = Compression force (MPa); X2= Lubricant mixing time (Min); Y1= Disintegration Time (Sec); Y2= Hardness (kg/cm2)

Preparation of orodispersible tablets

Table 3 presents composition of orodispersible tablet of amlodepine and ramipril. Orodispersible tablets were prepared by direct compression. The drugs and all the excipients were passed through a # 40 mesh screen. The blend was prepared by mixing drug and excipients except lubricant, manually in a polyethylene bag for 15 min. The lubricant was added to this blend and mixed properly again for 2/5/8 min and then compression of 200 mg powder into flat-faced tablets, with a diameter of 6 mm, was carried out on a mechanical hydraulic press (ESH Tablet Compaction Simulator, Huxley Bertram Engineering Ltd). Tablets were compressed under conditions where compression force varied from 75 to 225 MPa. Total nine formulations were prepared as per factorial design; changing the levels of the independent process variables, i.e. compression force (75, 150 and 225 MPa) and amount of magnesium stearate (2, 5 and 8 mg), as shown in table 2.

Table 3: Detailed composition of ramipril-amlodepine orodispersible tablet

S.no	Ingredients	Amount (mg)
1	Ramipril	2.5
2	Amlodipine besilate	5.0
3	Mannitol (SD 200)	40
4	Sodium Starch Glycolate	4.15
5	Aerosil 200	4
6	Aspartame	10
7	Talc	2
8	Magnesium Stearate	1.57
9	MCC (Avicel 112) qs	200 qs

Disintegration test

Orodispersible tablet is disintegrated in the mouth due to the action of saliva, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions.[9] A modified disintegrating apparatus method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium could be placed below the sieve. To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a

disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.[4, 10]

Hardness

Pfizer Hardness Tester was used to determine hardness of prepared orodispersible tablets. Hardness of the ten tablets of each trial batch was measured and mean value was determined.

Selection of optimized formulation

Optimized formulation was selected on the basis of rapid disintegration with optimum hardness.

Validation of experimental design

Polynomial equations for both responses were generated using Design expert software version 9.0.2 (Stat-Ease, Inc, USA). The model was validated by preparing three random formulations covering the entire range of independent variables. The observed and predicated values of the responses were quantitatively compared. The linear regression analysis between observed and predicted values of the response was also performed using Graph pad prism 5.00.

RESULT AND DISCUSSION

Average tablet weight (Fig.1) of experimental batches was found to be in a range of 206.2 ± 1.98 – 217.2 ±1.501 mg and complied with the pharmacopoeial limits. The tablet thickness (Fig2) was 1.97 ± 0.20 to 2.26 ± 0.25 mm and showed low variability related to the formulation flow and consistency of compression force. A decrease in tablet thickness was observed with increasing compression force (CF) at each lubricant mixing time studied, signifying an increase in tablet density. The low variability observed for both parameters support the reproducibility of orodispersible tablet.

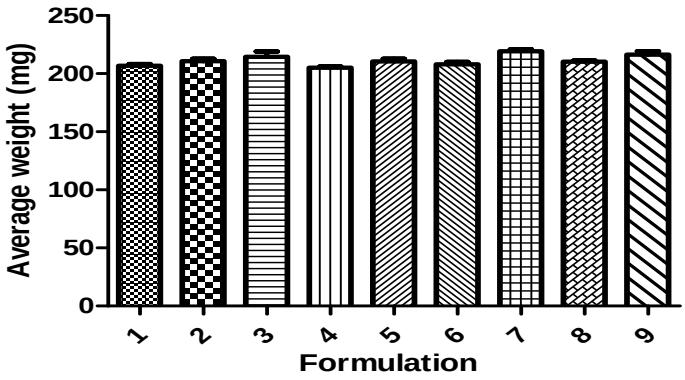

Figure 1: Average tablet weight of orodispersible formulations

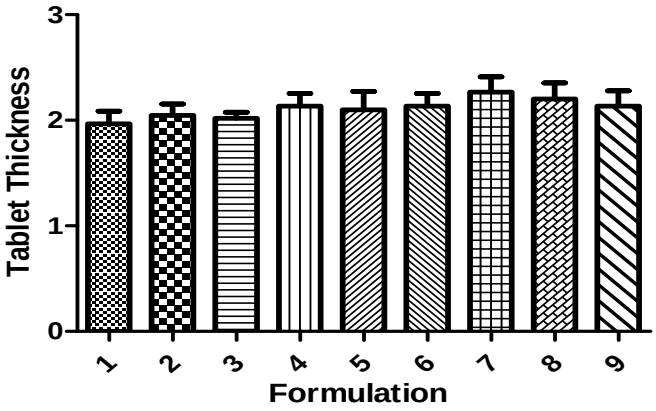

Figure 2: Tablet Thickness of orodispersible formulations

Experimental design, model fitting and analysis of data

The main aim of this work was to optimize process variables for orodispersible tablet of amlodepine-ramipril. A 3^2 factorial design was utilized to determine the effect of independent variables on critical quality attributes. The independent variables (factor) and critical quality attributes (response) are shown in table 1. The experimental run and respective observed values are shown in table 2.Ideally, the orodispersible tablet should rapidly disintegrate with sufficient mechanical strength to withstand handling, packaging, transport and more importantly should be easy to handle by the patient. Therefore disintegration time and hardness were selected as critical quality attributes in this study (response). Formulation showed disintegration time ranged from 25.3 to 87.65 sec and hardness ranged from 2.8 to 4.5 kg/cm^2.

The observed values of responses were analysed by design expert 9.0.6 (Minneapolis, MN, USA). All the response values were fitted to linear, 2 F1, quadratic and cubic. Selection of best fit model was based on the several statistical parameter comparisons which included R^2, *p* value, SD and PRESS value. The probability value (α) was fixed at 0.05 which indicates term would be significant if the p value is less than 0.05. Model summary statics and sequential model comparison was given in table 4.

As shown in table 4 linear, 2F1 and quadratic models were statically significant (p value < 0.05 for both, response Y1 and response Y2. For both responses Y 1 and Y2 , quadratic model had smaller standard deviation, larger R^2value, closer agreement between adjusted & predicated R^2 and smaller PRESS value than other statistically significant model, therefore it was selected as best fit model.

Table 4; Model summary statistics and Sequential model comparison for the disintegration time (Y1) and hardness (Y2).

Model	Sequential comparison		Model summary statistics				
	p Value		SD	R^2	Adjusted R^2	Predicated R^2	PRESS
	For the disintegration time (Y1)						
Linear	0.0078		11.07	0.8014	0.7352	0.3611	2364.66
2 F1	< 0.0001		1.60	0.9965	0.9945	0.9932	25.04
Quadratic	0.001		0.21	1.0000	0.9999	0.9997	1.21
Cubic	0.7879		0.28	1.0000	0.9998	0.9960	14.80
	For the hardness (Y2)						
Linear	0.0001		0.14	0.9507	0.9342	0.8602	0.36
2 F1	0.0295		0.094	0.9825	0.9720	0.9398	0.15
Quadratic	0.0050		0.021	0.9995	0.9986	0.9949	0.013
Cubic	0.6912		0.025	0.9998	0.9980	0.9554	0.11

SD indicates standard deviation; PRESS indicates predicated residual sum of squares

Result of analysis of variance (ANOVA) for both responses is shown in table 5. Larger F value and high R^2 value, which further illustrates the suitability of quadratic model.

Table 5: Analysis of variance (ANOVA) for the response Y1 and Y2

Source of Variation	Df	SS	MS	F	R^2	*p*-value
ResponseY1, Disintegration time (sec)						
Model	5	3701.21	740.24	16972.62	1.00	< 0.0001
Residual	3	0.13	0.044			
Total	8	3701.34				
ResponseY2, Hardness (kg/cm^2)						
Model	4	2.55	0.51	996.37	0.999	< 0.0001
Residual	4	2.56×10^{-3}	4.36×10^{-4}			
Total	8	2.55				

DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, fischer's ratio; R^2, regression coefficient..

The polynomial equations derived by multiple linear regression analysis for response Y 1 and Y 2 are as follows:

$$Y_1 = +43.48 + 13.85\,X_1 + 17.40\,X_2 + 13.44\,X_1X_2 - 2.01\,X_1^2 + 1.52\,X_2^2 \ldots\ldots\ldots\ldots (Eq.\,1)$$

$$Y_2 = +3.37 + 0.57X_1 - 0.29\,X_2 - 0.14\,X_1X_2 + 0.14X_1^2 - 0.025\,X_2^2 \ldots\ldots\ldots\ldots (Eq.\,2)$$

These equations shows the quantitative effects of process variables; X1 (compression force) and X2 (Lubricant mixing time) and their interactions on the responses; Y1 (disintegration time), Y2 (hardness). Coefficient of factors and corresponding p values are listed in table 6.

The term X_2^2 was found to be non significant for response Y2. Backward elimination method was used for model reduction. The equation for reduced model (RM) for the response Y2 is given below

$$Y_2 = +3.37 + 0.57X_1 - 0.29\,X_2 - 0.14\,X_1X_2 + 0.14\,X_1^2 \ldots\ldots\ldots (Eq.3)$$

Table 6: Coefficient and *p*-value of each factor, for response Y1 and Y2

Factor	Y1 Disintegration time (sec)		Y2 Hardness (kg/cm^2)	
	Coefficient	***p*-value**	**Coefficient**	***p*-value**
X1	13.85	< 0.0001	0.57	< 0.0001
X2	+ 17.40	< 0.0001	- 0.29	< 0.0001
X1X2	+ 13.44	< 0.0001	- 0.14	0.0009
X_1^2	-2.01	0.0009	0.14	0.0022
X_2^2	+1.52	0.0020	-0.025	**0.1890**

Significant factor (p < 0.05).All bold values have p- value > 0.05, hence considered insignificant.

The effect of independent variables on response disintegration time (Y1) is schematically represented in figure 3 as response surface plot. Compression force had a positive effect on disintegration time. Increase in disintegration time with an increase in compression force could be assigned due to formation of more condensed compacts with increasing the compression force. This increase in tablet density hampered the rate and extent of solvent uptake and penetration into the tablets, therefore tablets disintegrate slowly. Lubrication mixing time had also positive effect on disintegration time. As lubricant mixing time increases, disintegration time increases. The interaction of compression force (X1) and lubricant mixing time (X2) had a positive impact on the disintegration time (Y1).

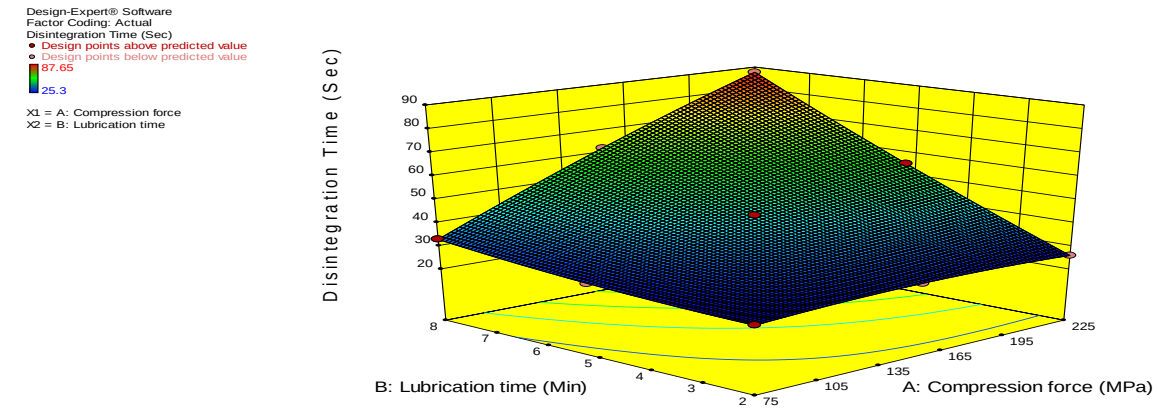

Figure 3: Response surface plot, the influence of X1(compression force) and X2 (lubricant mixing time) on response Y1 (disintegration time).

The response surface plot for the effect of compression force (X1) and lubricant mixing time (X2) and their interaction effects on the response hardness (Y2) of is depicted in figure 4. Compression force had positive effect on the hardness of the orodispersible tablet formulation. However, Hardness decreased with the increased lubricant mixing time (*X*2). This decrease in hardness is due to more uniform mixing of lubricant on the surface of powder particle and prohibited inter-particulate forces.

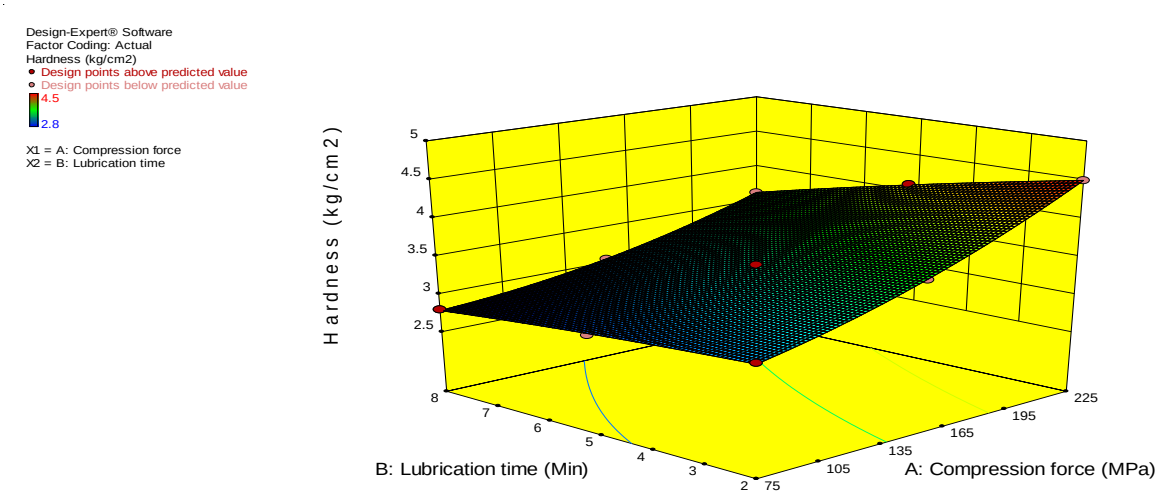

Figure 4: Response surface plot, the influence of X1(compression force) and X2 (lubricant mixing time) on response Y2 (hardness).

Optimisation of orodispersible tablet

The numerical optimisation based on desirability approach was carried out to obtain the optimum level of compression force (X1) and lubrication mixing time (X2) to formulate tablets with disintegration time (Y1) below 30 sec and hardness (Y2) equal or more than 3.5 kg/cm^2. The constraints, optimized level of factors and predicated responses are shown in table 7. The optimum level for compression force (X1) and lubricant mixing time (X2) was found to be 138.54 MPa and 2.59 minute respectively.The predicated value of response disintegration time (Y1) and hardness (Y2) were 30.0 sec and 3.5 kg/cm^2 respectively.

Table 7: Constraints, level of independent variables and predicated responses for optimization of orodispersible tablets.

Constraints			
Name	**Goal**	**Lower limit**	**Upper Limit**
Compression force (MPa)	In range	75	225
Lubricant mixing time	In range	2	8

(Min)			
Disintegration time (sec)	Target < 30	25.3	87.65
Hardness (kg/cm^2)	Target ≥ 3.5	2.8	4.5

SOLUTION				
Compression force (MPa)	**Lubricant mixing time (Min)**	**Disintegration time (sec)**	**Hardness (kg/cm^2)**	**Desirability**
138.54	2.59	30.0	3.5	1.00

Figure 5 was illustrated a close agreement between predicated and observed value of responses.

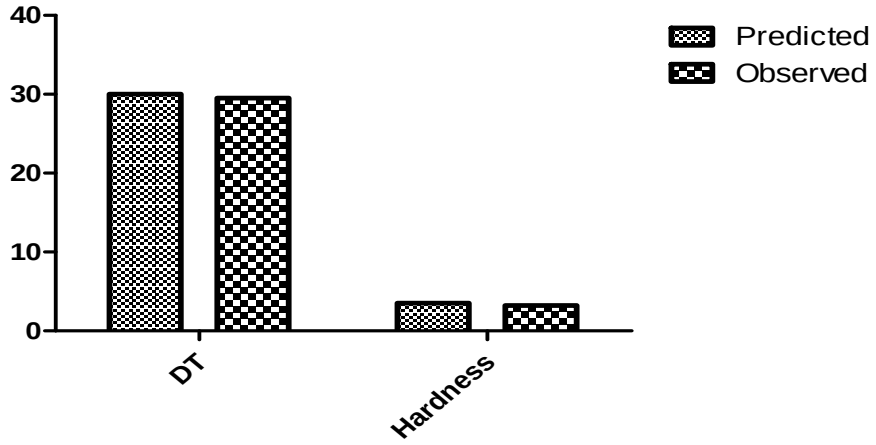

Figure 5: Comparison between predicted and observed value of responses for optimized orodispersible tablet

Validation of experimental design

To validate the polynomial mathematical model, dissolution of optimized formulation and three random formulations covering the entire range of independent variables were performed. For each of these formulations, value of X1 and X2 were substituted to estimate response Y1 and Y2. Table 8 shows the experimental condition of random formulations, predication and observed value of responses along with percentage prediction error.

Table 8: Comparison between observed and predicated value for response Y1 (Disintegration time) and Y 2 (Hardness) for different check points.

S.no	Experimental trial Factors (Coded)		Response	Observed value	Predicated value	Percent predication error
	X1	X2				
1	0.8	-0.6	Y 1 Y 2	35.98 4.43	36.93 4.52	- 2.64 - 2.03
2	- 0.55	0.46	Y 1	39.28	40.17	- 2.26

			Y 2	3.06	3.0	1.96
3	0.44	-0.9	Y 1 Y 2	28.06 3.93	27.39 4.0	2.38 -1.78

Percent predication error was calculated by using formula $\frac{(observed\ value - predicated\ value)}{Observed\ value} x\ 100$

Linear correlation curve (fig.6) between observed and predicated responses, establish a close agreement ($r^2 > 0.98$). Robustness of mathematical model is demonstrated by significant value of r^2 and lower value of percentage predication error.

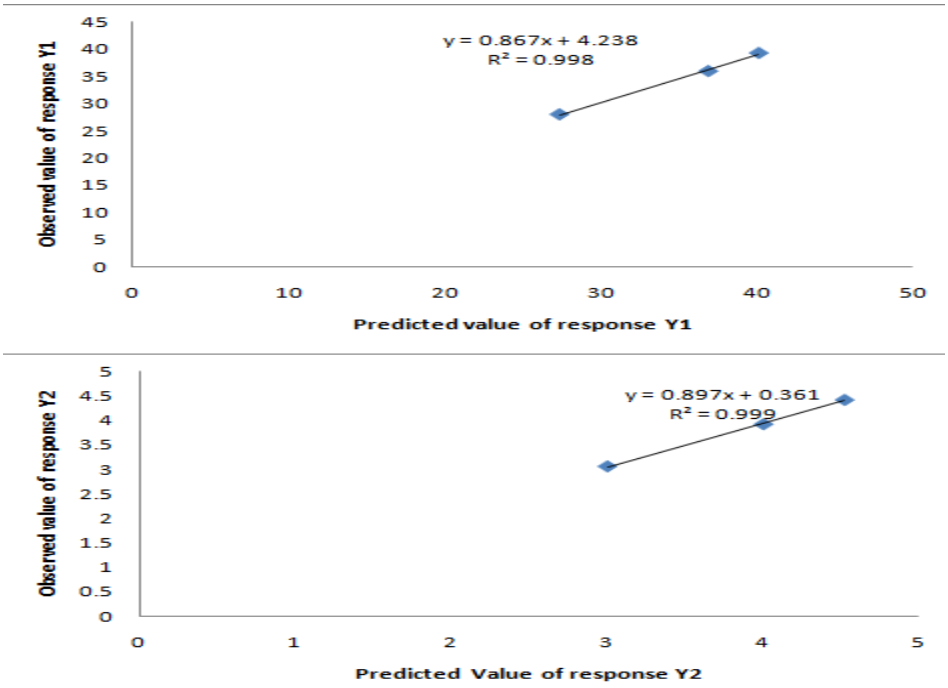

Figure 6: Validation of experimental model, linear correlation between predicted and actual value of random formulations

CONCLUSION

In this study design of experiment approach was used to evaluate effect of compression force and lubricant mixing time on an orodispersible tablet of amlodepine and ramipril. The study showed compression force and lubricant mixing time were critical process variables for the formulation of orodispersible tablets. From the experimental design compression force (138.54 MPa) and lubricant mixing time (2.59 min) was found optimum to provide rapid disintegration with optimum hardness. A close agreement was found between predicated and observed value of optimised formulation. Thus the design of experiment can be a reliable approach for optimization of orodispersible tablet.

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