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Optimization of Tetrabenazine Tablet Formulation to Improve Dissolution Shift

Santanu Roy^{1*}, K.Kannan², Jitendra Baweja³, Amol Choulwar⁴

1. Glenmark Pharmaceutical Limited, Mumbai, India

2. Department of Pharmacy, Annamalai University, Chidambaram, India

3. Colorcon India Pvt. Limited, Verna, GoA, India

4. Sanofi-Aventis India Pvt. Ltd., Mumbai, India

ABSTRACT

A two level four factor partial factorial design was adopted, composite of experiment design was applied to optimize a tablet formulation of Tetrabenazine (TBZ) Tablets 25mg containing high percentage of Lactose Anhydrous, Sodium starch Glycolate, Magnesium Stearate and Starch/Lactose Ratio. The particle size distribution of Lactose Anhydrous is used as dependent variable and Sodium starch Glycolate, Magnesium Stearate and Starch/Lactose Ratio were used as independent variables for optimizing some tablets response parameters. Responses parameters for final TBZ Tablets were percentage of TBZ dissolve at thirty minutes. Design of Experiments (DOE) is an organized approach to determine the relationship between independent process variables and their effect on the response variable.²⁴ partial factorial design were applied in this research work. The models were validated for accurate prediction of response characteristics and use to identify the optimum formulation. The results that an optimum TBZ 25mg tablets having a volume similar to commercial products can be produced by dry granulation process utilizing Lactose Anhydrous.

Keywords: Tetrabenazine (TBZ), Design of Experiment (DOE), Critical Quality Attributes (CQA), Content Uniformity (CU), Acceptance Value (AV).

*Corresponding Author Email: santanu_2k1@rediffmail.com

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INTRODUCTION

To determine the shelf life of a drug product, long term stability studies are to be carried out. For a stability study, a random sample of tablets is taken from several batches. The tablets are stored under ambient conditions (25°C/65% RH). Being an end product testing Quality Control tool, the dissolution testing has often been used for evaluating challenges encountered during development of formulation and process and Tetrabenazine tablet 25 mg stability to establish. During interpretation of long term stability study data of Tetrabenazine Tablet 25mg found that the tablet dissolution shift (slow down) upon stability at different time interval and different lots (batch to batch). The use of experimental design, optimization and multi variate technique to investigate root cause of tablet dissolution shift.

Dissolution shift (slow down) upon stability and develop control strategies for a drug product during formulation and process development. An experimental design was carried out to evaluate the interaction and effects of the design factors on critical quality attributes (CQA) of dissolution upon stability. The design space was studied by design of experiment (DOE) and multivariate analysis to ensure desire dissolution profile and minimal dissolution shift upon stability.

Further the level of two or more processing parameters may interact to produce an unanticipated result. This is sometimes referred to as synergism or potentiation, in which the effect of supposedly independent factors is many folds the sum of effects of the factors taken separately. Thus, some factors may be discovered to be interdependent. Utilizing the tool of optimization for redeveloped and marketed a tablet formulation containing 25mg of TBZ. This made possible the manufacture of a tablet of palatable dimension and acceptable dissolution performance.

MATERIALS AND METHOD

Materials:

Anhydrous Lactose/Lactose Anhydrous, Pre-gelatinized Starch, Sodium Starch Glycolate, Iron oxide yellow, Talc, Colloidal silicon dioxide, Magnesium Sterate all selected ingredients are pharmaceopial grade.

Experimentation:

Tetrabenazine (TBZ), Lactose anhydrous, corn starch and sodium strach glycolate were sifted through sieve 40 and blended in Octagonal blender (Bectochem,India) for 45 minutes. Iron oxide yellow along with purified talc were sifted through sieve100 and colloidal silicon dioxide was sifted through sieve 40. These sifted excipient were added to the previously blend and blending was continued for 15minutes in octagonal blender. Magnesium sterate was sifted through sieve 60

and transferred to blender and Lubricated for 5 minutes. The slug was prepared from the blend by using roll compactor (Alexanderwerk AG, Germany) to get the granules. Slugs was milled and passed through 10.0 mm S.S Screen, slow speed, knives forward using comminuting mill (M/s Ganson Ltd., India).

Talc was sifted through sieve 60 and mixed with the above granules in octagonal blender for 10minutes. Magnesium sterate was sifted through sieve 60 and lubricated in the same blender for 5minutes. Finally lubricated blend was compressed in single roratory compression machine (Cadmac, India).

Evaluation of Tablets

Content Uniformity:

Uniformity of Dosage the content uniformity test was carried out by using analytical grade reagent, by HPLC (Water make), C18 column, flow rate 2.0 min, and gradient method at 275nm used UV detector.

Dissolution studies:

The release rate of TBZ 25mg was determined according to USFDA web site, dissolution data base (ref) using the Dissolution testing Apparatus II (model TDT-60T,Electrolab,India) fitted with paddles. The dissolution test was performed by using 900ml of 0.1N HCL kept at $37\pm 0.5^{\circ}\text{C}$ and 50 rpm. A 5ml sample was withdrawn from the dissolution apparatus at predetermine time interval (30 minutes). The samples were filtered through a $0.45\mu\text{m}$ membrane filter and dilute to a suitable concentration with 0.1N HCl. Absorbance of these solution was measured at 275nm using UV spectrophotometer (JascoV350, Japan). Drug release was calculated using the equation of Beer Lambert's calibration curve.

Experimental Design

The selected independent variables are:

1. Lactose Anhydrous
2. Sodium Starch Glycolate (Type A, pH 5.5-7.5)
3. Magnesium Stearate
4. Starch/Lactose Ratio

The ranges selected for dry granulation process are summarized in Table 1. The weight of tablets was kept constant at 125mg, by adjusting the quantity of Lactose Anhydrous. Require particle size distribution of Lactose Anhydrous were generated by sieving in Table 2.

Table 1: Selected levels of excipients

Excipient	Low level	High level
Lactose Anhydrous	Coarse	Fine
Sodium Starch Glycolate (TypeA, pH 5.5-7.5)	2.60%	4.60%
Magnesium Stearate	1.15%	1.65%
Strach/Lactose Ratio	2.83:97.17	10.83:89.17

Table 2: Particle size Distribution of Lactose Anhydrous

Pariticle size	Specification	Level 1(+1) (Fine grade)	Level 2(-1) (coarse grade)
% Below 45 micron	0 to 20	18	2
% Below 150 micron	40 to 65	64	42
% Below 250 micron	80 to 100	96	82

All other processing and formulation variables were kept constant throughout the study. As shown in Table 3, the eight experiments represent a design for four factors at two levels, these are represented by +1 and -1, analogous to the any two level partial factorial design.

Table 4, summarizes the value of response parameters obtained from the studies. These parameters are percentage of drug dissolved at thirty minutes sampling point, content uniformity, weight variation, disintegration time and hardness.

The experimental plan and responses observed in a screening phase were carried out in randomized order according to eight run matrix provided for by the Factorial design strategy. Our full study addressed all response namely granules characteristics are illustrated in Table 5.

Mathematical model was developed correlating the selected process variables and the response, content uniformity and dissolution are given in Table 7 & 8.

Table 3: Design matrix for formula of optimization

Experimental Runs				
Batch No.	PSD of Lactose Anhydrous	Sodium strach Gluconate	Magnesium Stearate	Starch/Lactose ratio
SR-T-001(Batch Size: 1000 tablets)	Coarse	2.6	1.150	2.83:97.17
SR-T-002(Batch Size: 1000 tablets)	Fine	2.6	1.150	10.83:89.17
SR-T-003(Batch Size: 1000 tablets)	Coarse	4.6	1.150	10.83:89.17
SR-T-004(Batch Size: 1000 tablets)	Fine	4.6	1.650	10.83:89.17
SR-T-005(Batch Size: 1000 tablets)	Coarse	2.6	1.650	10.83:89.17
SR-T-006(Batch Size: 1000 tablets)	Fine	2.6	1.650	2.83:97.17
SR-T-007(Batch Size: 1000 tablets)	Coarse	4.6	1.650	2.83:97.17
SR-T-008(Batch Size: 5000 tablets)	Fine	4.6	1.150	2.83:97.17

Table 4: Summary of response studies

Batch No.	Response studies						
	Physical Appearance	Maximum Individual % Weight Variation from Target (125.00 mg)	Maximum Difference of Thickness (mm)from Target	Maximum Difference of Hardness (kP)from Target	Disintegration Time (min)	% Friability	% Drug Dissolution
SR-T-001	Free of any defect	2.800	0.060	0.700	3 min 45 sec	0.3	100
SR-T-002		3.100	0.120	0.900	4 min 15 sec	0.38	99
SR-T-003		1.200	0.080	1.300	3 min 30 sec	0.38	104
SR-T-004		1.800	0.050	1.000	4 min 10 sec	0.35	100
SR-T-005		3.000	0.080	0.900	3 min 50 sec	0.2	98
SR-T-006		2.500	0.120	0.700	5 min 45 sec	0.4	100
SR-T-007		3.100	0.110	0.900	4 min 45 sec	0.28	97
SR-T-008		1.600	0.110	0.900	3 min 20 sec	0.31	93
Acceptance Criteria	Acceptable free of any defect	125.00±5%	2.5±0.3	4.5±2.5	NMT 15 minutes	NMT 1%: No Breakage of Tablets	In 30 min NLT 80% (Q)

Table 5: Granules Characteristic

Batch No.	Bulk Density (g/cc)	Tap Density (g/cc)	Response studies					Pass through# 100 (%)
			Retention on # 20(%)	Retention on # 40 (%)	Retention on # 60(%)	Retention on # 80% (%)	Retention on # 100 (%)	
SR-T-001	0.661	0.957	1.152	13.461	9.834	8.844	8.342	52.851
SR-T-002	0.634	0.962	0.381	5.362	11.153	12.180	9.161	52.323
SR-T-003	0.658	0.967	0.360	7.254	8.732	6.527	7.842	60.325
SR-T-004	0.606	0.963	0.422	8.743	12.127	10.612	8.246	48.501
SR-T-005	0.656	0.961	0.380	12.241	10.242	9.513	10.614	62.012
SR-T-006	0.643	0.973	0.252	1.243	11.876	11.435	9.400	43.003
SR-T-007	0.632	0.972	0.663	11.801	11.212	8.137	11.313	51.802
SR-T-008	0.658	0.982	0.001	11.207	11.344	7.501	8.934	55.764

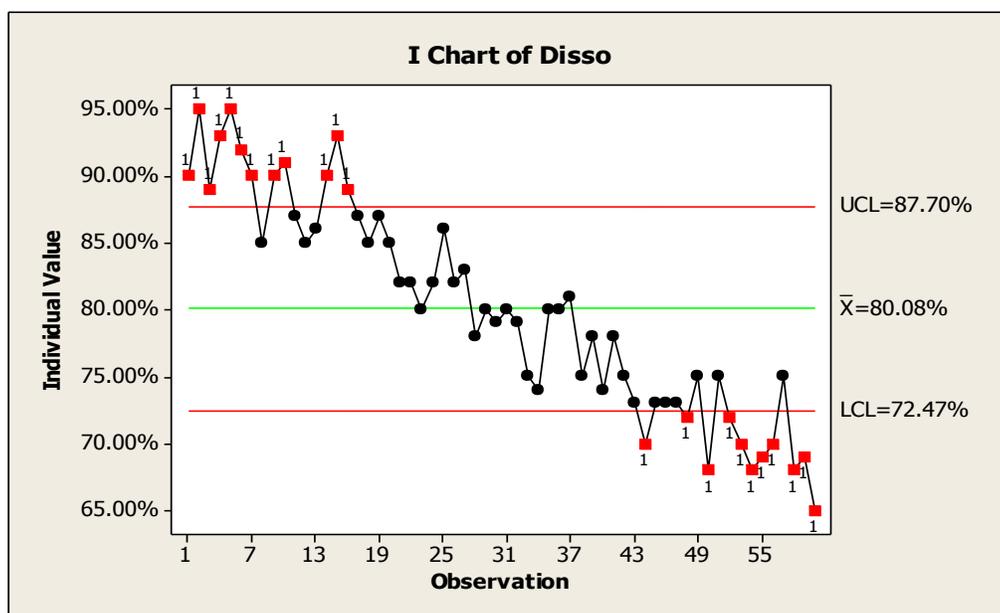
RESULTS AND DISCUSSION

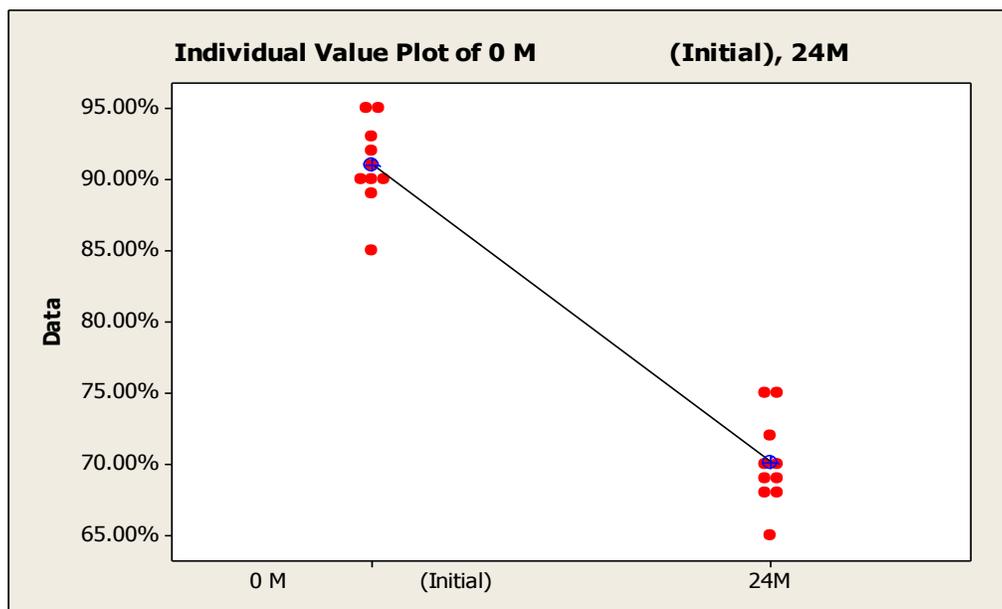
Trend data of ten commercial batches (dissolution shift upon stability)

Table 6: Long term stability of Tetrabenazine Tablets 25 mg at ambient condition (25°C/65% RH)

Batch #	Stability Frequency	Dissolution Data (%)						
		0 month (Initial)	3 months	6 months	9 months	12 months	18 months	24months
JKKTT001		90%	87%	85%	82%	80%	78%	75%
JKKTT002		95%	85%	83%	82%	79%	75%	72%
JKKTT003		89%	86%	85%	80%	75%	73%	70%
JKKTT004		93%	90%	89%	82%	74%	70%	68%
JKKTT005		95%	93%	91%	86%	80%	73%	69%
JKKTT006		92%	89%	83%	82%	80%	73%	70%
JKKTT007		90%	87%	85%	83%	81%	73%	75%
JKKTT008		85%	85%	80%	78%	75%	72%	68%
JKKTT009		90%	87%	85%	80%	78%	75%	69%
JKKTT010		91%	85%	83%	79%	74%	68%	65%

Graphical representation of dissolution shift upon stability





Statistical Analysis of Data

All the statistical and regression analysis procedure on the response parameters were performed using the DOE methodology. The sets of data obtaining from the statistical analysis were then subjected to computerized regression models including an intercept and main effect terms of each independent variable. Two way interaction terms and a stepwise regression procedure was used to assess all main effects, some two way interactions and quadratic terms for usefulness in the model to obtain a more adequate regression model for each response parameter. A full model is a model that is having all possible terms Table-7, figure-1.

Table 7: Model Evaluation

Response	Terms included in reduced model	Co-efficient	P-Value	R-square	Justification for inclusion
Tablet Content Uniformity (AV Value)	Constant	6.643	0.013	98.41%	R-square value is acceptable P-value for all the term is greater than 0.05
	Conc of Sodium Starch Glycolate	1.391	0.074		
	Conc of Lubricant	-0.931	0.111		
	Ratio of Starch to Lactose	0.738	0.144		
	PSD of Lactose	0.280	0.338		
	Conc of Sodium Starch Glycolate	-0.832	0.126		
	*Ratio of starch to lactose				
	Conc of Sodium Starch Glycolate	-1.103	0.098		
	*PSD of Lactose				

Predication Equation:

$$\text{Tablet Content Uniformity (AV value)} = 6.643 + 1.391(A) - 0.931(B) + 0.738(C) + 0.280(D) - 0.832(AC) - 1.103(AD)$$

The p-value for all the formulation variables is greater than 0.05 indicates there is no significant impact in content uniformity. The tablet content uniformity Acceptance value (AV) is less than

10.0 at studied range of variables observed. Hence, the range selected will not have any impact on critical quality attribute of drug product.

Table 8: Model Evaluation

Response	Terms included in reduced model	Co-efficient	P-Value	R-square	Justification for inclusion
Tablet %	Constant	97.631	0.0001	97.72%	R-square value is acceptable P-value for all the term is greater than 0.05
Dissolution at 30 minutes	Conc of Sodium Starch Glycolate	0.5012	0.283		
	Conc of Lubricant	-1.0000	0.535		
	Ratio of Starch to Lactose	0.23000	0.102		
	PSD of Lactose	-5.23000	0.068		
	Conc of Lubricant*PSD of Lactose	3.00000	0.157		

Predication Equation:

$$\text{Tablet \% Dissolution at 30 minutes} = 97.631 + 0.50012(A) - 1.0000(B) + 0.23000(C) - 5.23000(D) + 3.0000 (BD)$$

The p-value for all the formulation variables is greater than 0.05 indicates insignificant for tablet % Dissolution at 30 minutes. The % Dissolution at 30 minutes greater than 95.0 at studied range of variables observed. Hence, the range selected will not have any impact on critical quality attribute of drug product.

The optimum values obtained from the contour plots for the independent variables in order to obtain the best values for each of the four response variables are given in Table 8. In vitro dissolution data may provide an indication of in-vivo bioavailability, therefore the percentage of drug dissolve at 30 minutes was identified as the response parameter. The optimized formulation satisfied all constraints simultaneously.

Statistical Analysis of Design of Experiments:

(1) Effect of Variables:

A Pareto chart showing the effect of core tablet formulation process variables on Tablet Content Uniformity (%) and % dissolution at 30 minutes Pereto Chart of Formulation variables on Tablets Content Uniformity and % Dissolution at 30 minutes. The estimated effect for each individual terms are presented in table 7 & 8 and figure-1.

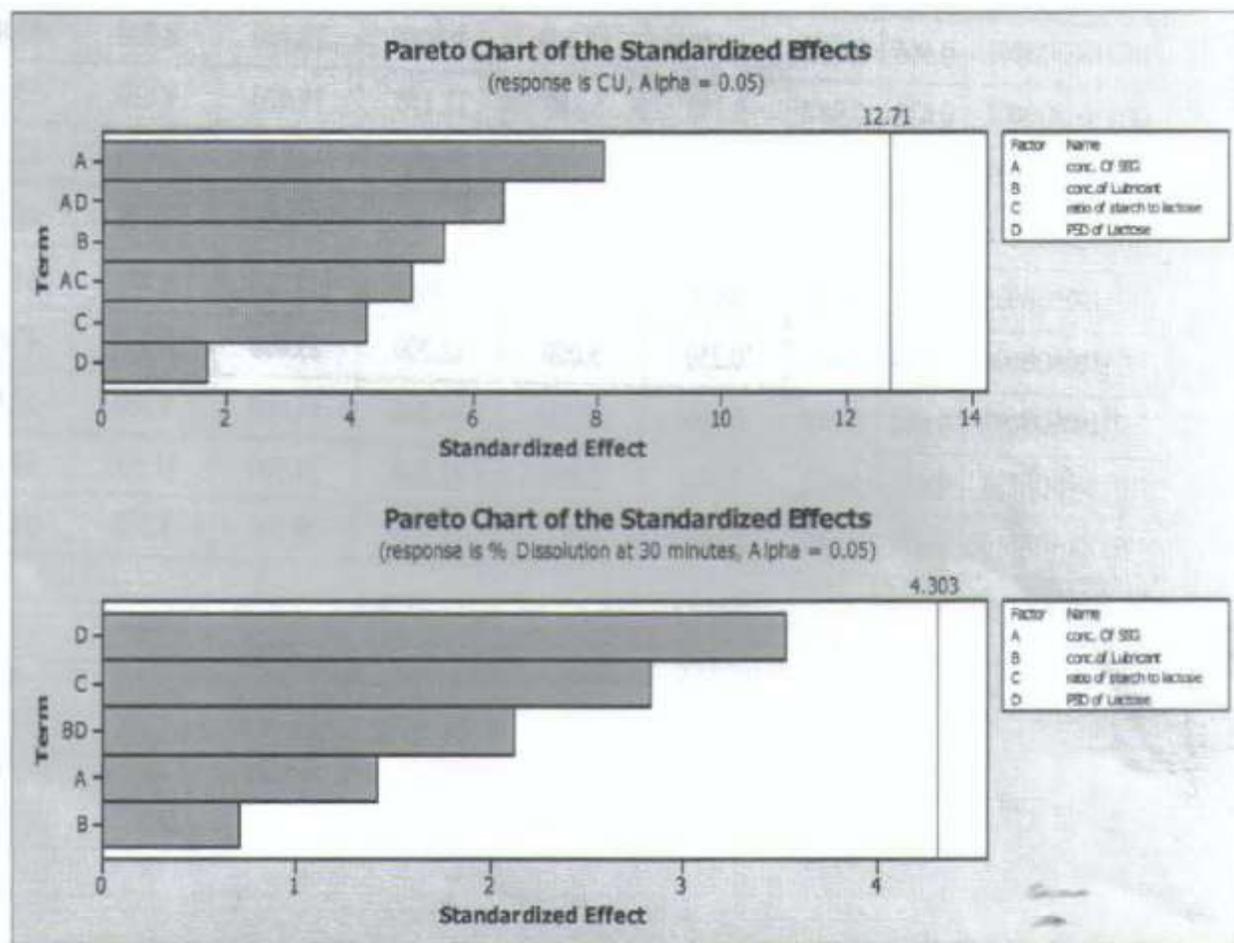
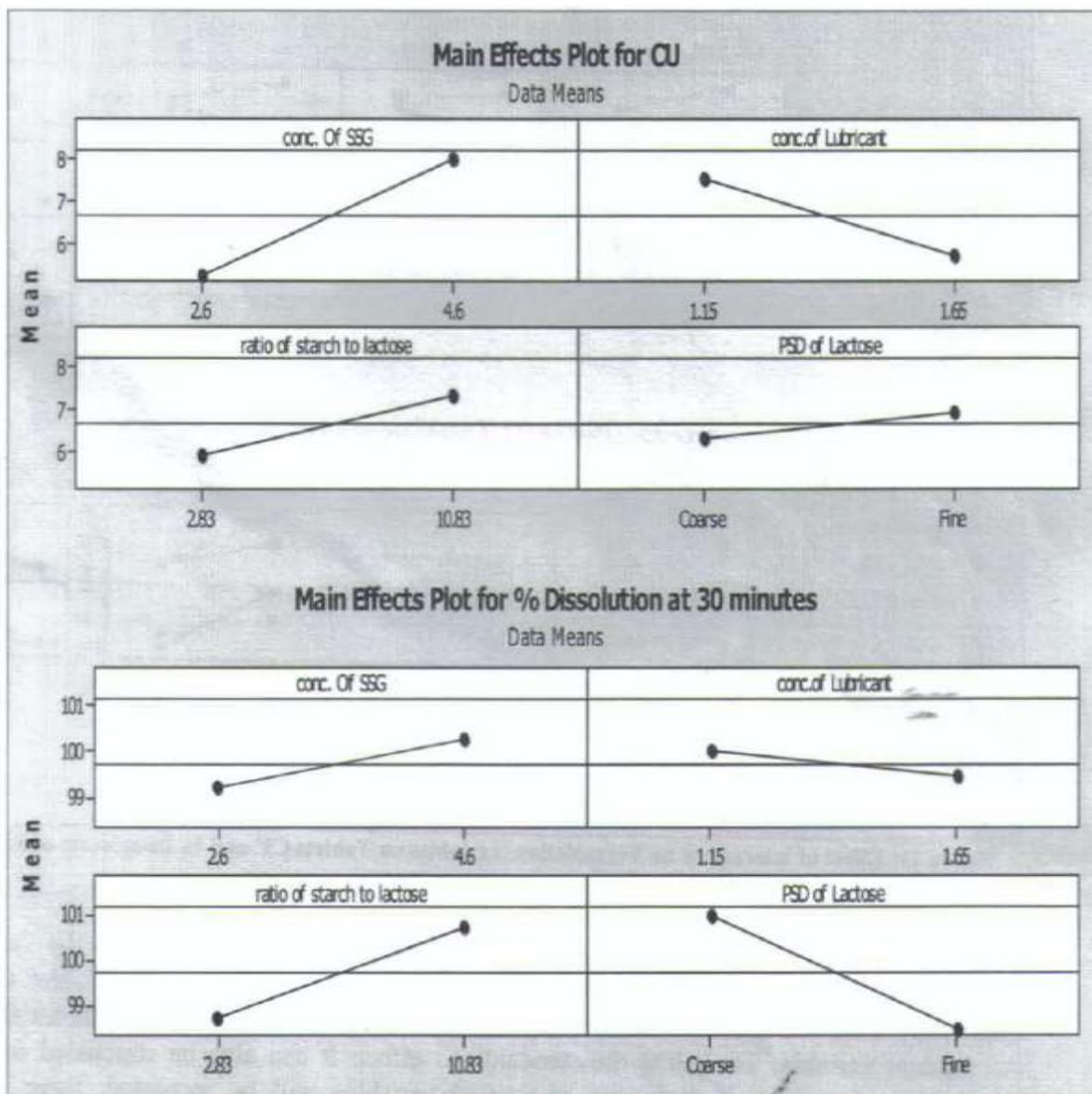


Table 9 summarizes the response tablets properties obtained from the eight formulations in experimental design. The concentration of excipient information about whether the impact of the variable on response is positive or negative.

Table 9: Effects of Formulation Variables

Formulation Variable	Effects	
	Content Uniformity(%)	% Dissolution at 30 min
Main Effect		
Conc of Sodium Starch Glycolate	2.773	1.000
Conc of Lubricant	-1.881	-0.500
Ratio of Starch to Lactose	1.461	2.500
PSD of Lactose	0.572	-2.500
Concentration of SSG* Ratio of Starch to Lactose	-1.613	
Concentration of SSG* PSD of Lactose	-2.211	
Concentration of Lubricant*PSD of Lactose		1.000
Standardized Effect	12.71	4.303



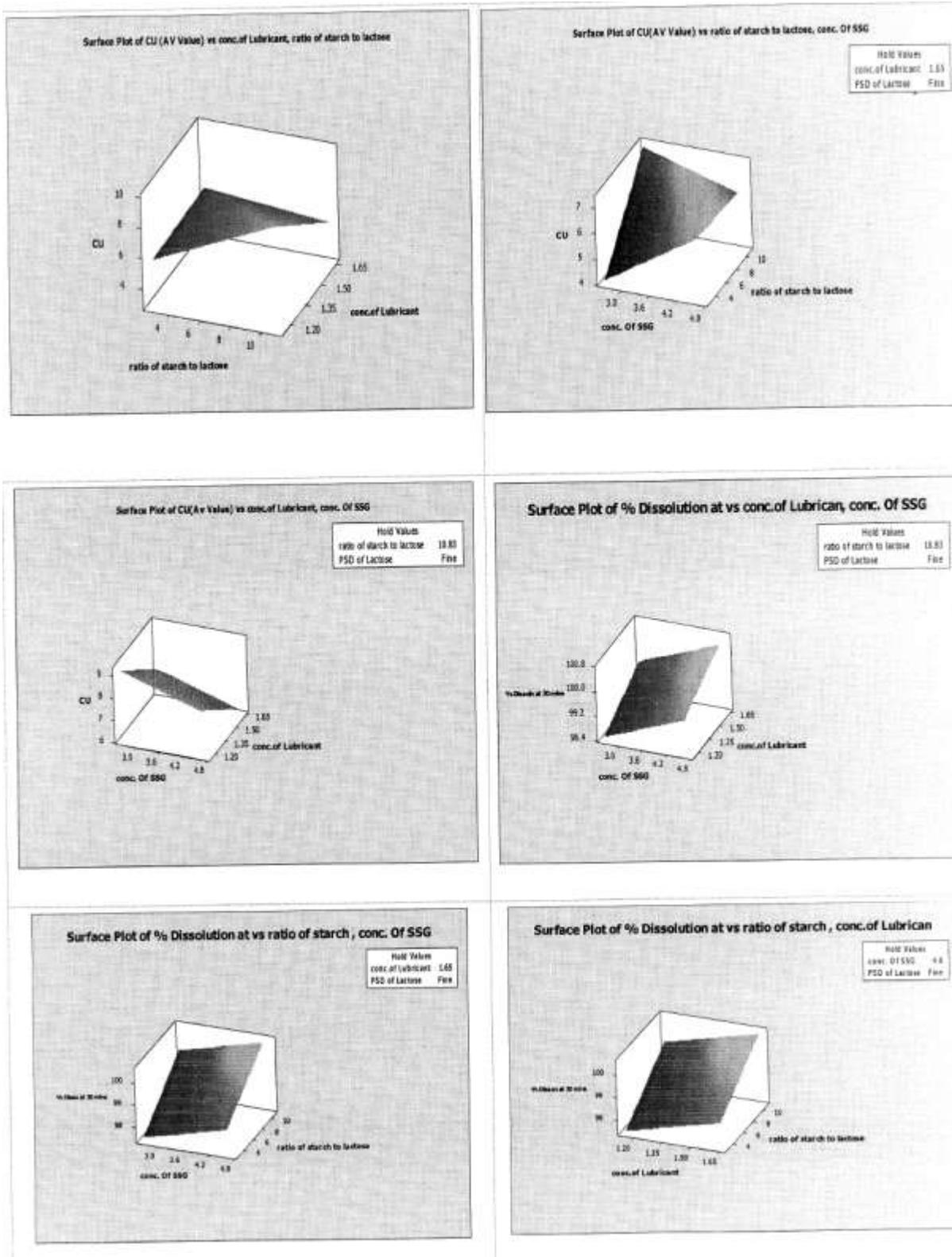
Main Effect:

The main effect plot showing impact of formulation variables within studied range on Tablets Content uniformity and % Dissolution at 30 minutes is given figure-2.

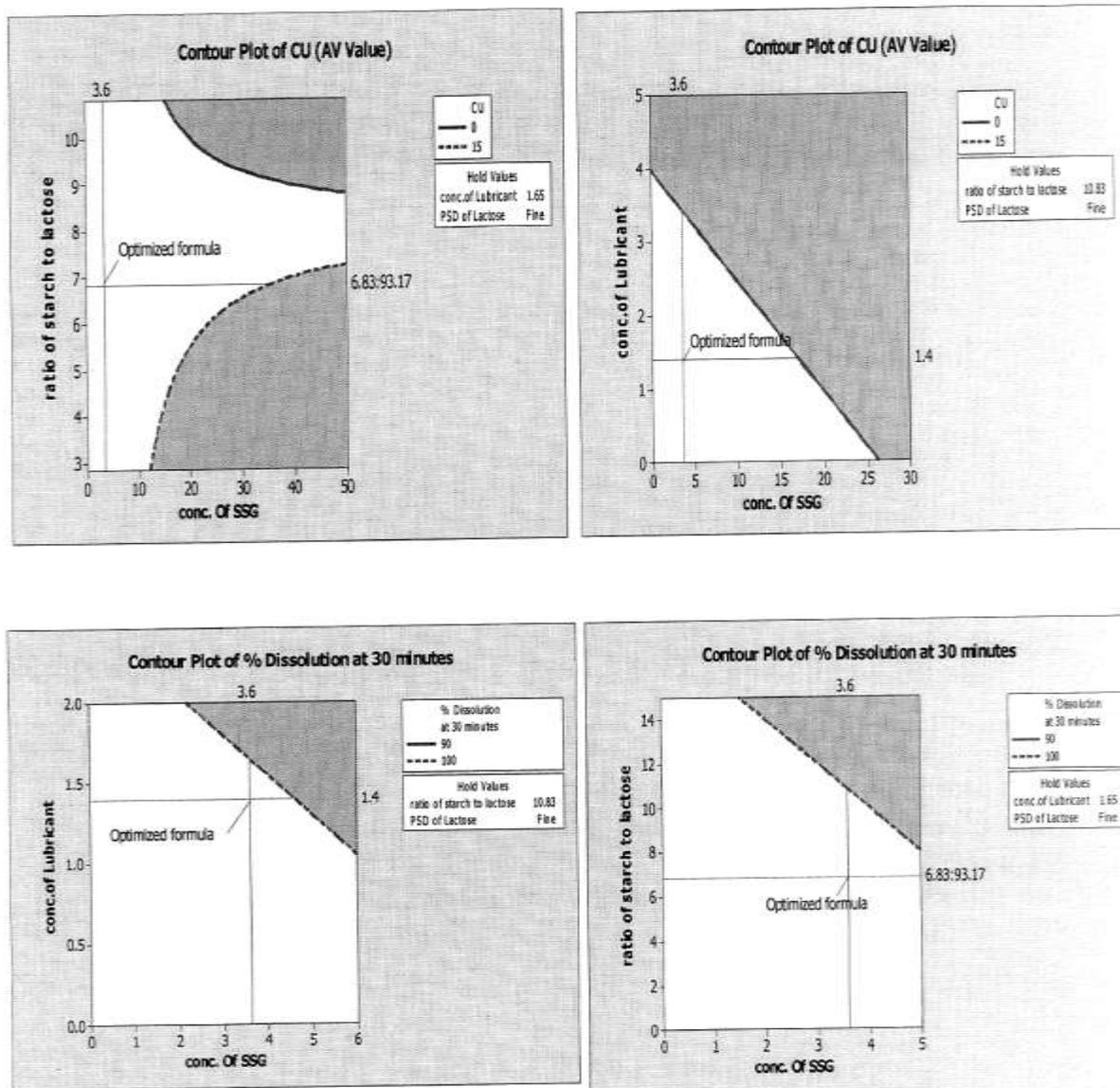
Main effect of Formulation process variables on Tablets CU and (%) Dissolution at 30 minutes

The absolute effect of selected variables within studied range are less than the standardized effect and the Tablet Content Uniformity Acceptance value (AV) is less than 10.0 and % Dissolution at 30 minutes is more than 95.0%. Hence, it can be concluded that there is no significant impact of selected variables within the studied range on Tablet Content Uniformity and % Dissolution at 30 minutes.

(3) Surface Plot: Surface Plot of Formulation variables on Tablets Content Uniformity and % Dissolution at 30 minutes



(4) Design Space: Design space for formulation variables on Tablet CU and % Dissolution



The white area shown overlaid contour plot is the formulation design space. Any of the combination of variables within the formulation design space will show acceptable CU and %Dissolution of the drug product. The intersecting straight line indicates that the optimized formula is within the formulation design space.

The data of Design of Experiment studies revealed that experimental run within selected range of all the independent variables did not show any impact on Critical Quality Attributes (CQA) and other in process test results. Hence, the selected range can be considered as a design space in which any change will not have any impact on CQA of drug product.

The formulation composition was finalized based on formulation optimization. In the formulation optimization studies, impact of Lactose anhydrous PSD, level of sodium starch glycolate ranges

for these excipients selected did not have any impact on the in-vitro dissolution.

Table 8 Composition of Tetrabenazine Tablets

Sr. No.	Ingradient	Mg/tablet
Stage A Dry mixing		
1	Tetrabenazine	25.000
2	Anhydrous Lactose/Lactose Anhydrous	85.300
3	Pregelatinised Starch	6.250
4	Sodium Starch Glycolate	4.500
Stage B Blending-I		
1	Iron oxide yellow	0.200
2	Talc	0.750
3	Colloidal silicon dioxide	0.500
Stage C Lubrication-I		
1	Magenesium Sterate	1.000
Stage D Blending-II		
1	Talc	0.750
Stage E Lubrication-II		
1	Magenesium Sterate	0.750
Net weight of Core Tablet (mg)		125.000

Stability Data of scale up Batch (optimize formulation):

Product Name: Tetrabenazine Tablet		Mfg Date: 30/10/15
Strength: 25 mg		Stability initiation date: 05/11/14
Batch No.: SR-T-008		Pack: 112 tablets in 60 cc White HDPE Bottle with
Batch Size: 5000 Tablets		33mm CRC cap with seal, one 2gm silica gel canister
Condition	Station (Months)	Dissolution at 30 min
Initial	0	97%
40°C/75%RH	1	94%
	2	96%
	3	95%
	6	97%
30°C/65%RH	1	94%
	2	95%
	3	97%
	6	98%
25°C/60%RH	3	96%
	6	95%
	9	96%
	12	96%

CONCLUSION

In this TBZ tablet formulation development, computer assisted regression analysis and mathematics model can be utilized to produce accurate representation of the relationship between the independent variables and tablets response properties and optimize a suitable tablet

formulation. The optimization technique can help us to further define and control the whole system. The dry granulation process selection as well as proportion of excipient could be optimized successfully. By implementation of eight experiments the effect of two level four factors and their interactions were determined. Not significant factors were identified and eliminated early. A Design space which guaranties a product having specified quality attributes has been found. Design of Experiments (DOE) is an applicable method for optimization of pharmaceutical processes and improves the dissolution slow down upon stability.

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