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OPTIMIZATION OF TETRABENAZINE TABLET FORMULATION TO MEET THE REQUIRED DISSOLUTION PROFILE AND CONTENT UNIFORMITY

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Keywords:

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

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ABSTRACT: An approach to determine the relationship between independent process variables and their 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. Response parameters for final TBZ Tablets were percentage of TBZ dissolve at thirty minutes. Design of Experiments (DOE) is an organized effect on the response variable. 2^4 partial factorial designs 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.

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 25mg 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).

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The use of experimental design, optimization and multi variate technique to investigate root cause of tablet dissolution shift [2, 5, 7, 11]. 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 [2, 7]. 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 inter-dependent. 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 METHODS:

Materials: Anhydrous Lactose / Lactose Anhydrous, Pre-gelatinised Starch, Sodium Starch Glycolate, Iron oxide yellow, Talc, Colloidal silicon dioxide, Magenesium 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 sieve 100 and colloidal silicon dioxide was sifted through sieve 40. These sifted excipient were added to the previously blend and blending was continued for 15 minutes in octagonal blender. Magnesium stearate 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 10 minutes. Magnesium stearate was sifted through sieve 60 and lubricated in the same blender for 5 minutes. Finally lubricated blend was compressed in single rotatory 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, Electro lab, India) fitted with paddles. The dissolution test was performed by using 900ml of 0.1N HCL kept at 37 ± 0.5 °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 0.45µm membrane filter and dilute to a suitable concentration with 0.1N HCl. Absorbance of these soultion was measured at 275nm using UV spectrophotometer (JascoV350, Japan). Drug release was calculated using the equation of Beer Lamber'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. Strach/Lactose Ratio.

All other processing and formulation variables were kept constant throughout the study. 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 designs [2, 7, 6, 12]. 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.

RESULTS AND DISCUSSION: All the statistical and regression analysis procedure on the response parameters were performed using the DOE methodology [2, 9, 12]. 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. 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. 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 optimumized formulation satisfied all constraints simultaneously. 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.

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 within 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 1: SELECTED LEVELS OF EXCIPIENTS

Excipient	Low level	High level
Lactose Anhydrous	Coarse	Fine
Sodium Starch Glycolate (Type A, 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

The ranges selected for dry granulation process are summarized.

TABLE 2: PARTICLE SIZE DISTRIBUTION OF LACTOSE ANHYDROUS

Particles 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

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.

TABLE 3: DESIGN MATRIX FOR FORMULA OF OPTIMIZATION

Experimental Runs				
Batch No.	**PSD of Lactose Anhydrous**	**Sodium trach Glucolate**	**Magnesim 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

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: 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	CU (AV Value)
SR-T-001		2.800	0.060	0.700	3 min 45 sec	0.3	100	3.05
SR-T-002		3.100	0.120	0.900	4 min 15 sec	0.38	99	9.05
SR-T-003		1.200	0.080	1.300	3 min 30 sec	0.38	104	9.75
SR-T-004	Free of any	1.800	0.050	1.000	4 min 10 sec	0.35	100	5.98
SR-T-005	defect	3.000	0.080	0.900	3 min 50 sec	0.2	98	4.65
SR-T-006		2.500	0.120	0.700	5 min 45 sec	0.4	100	4.5
SR-T-007		3.100	0.110	0.900	4 min 45 sec	0.28	97	8.46
SR-T-008		1.600	0.110	0.900	3 min 20 sec	0.31	93	5.96
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)	NMT 15

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.

TABLE 5: GRANULES CHARACTERISTIC

Batch No.	Bulk Density (g/cc)	Tap Density (g/cc)	Response studies					
			Retension on # 20(%)	Retension on # 40 (%)	Retension on # 60(%)	Retension on # 80% (%)	Retension on # 100 (%)	Pass through # 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

Surface Plot of Formulation variables on Tablets Content Uniformity and % Dissolution at 30 minutes. 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.

TABLE 6: LONG TERM STABILITY OF TETRABENAZINE TABLETS 25mg 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%

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

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 *Ratio of starch to lactose	-0.832	0.126		
	Conc of Sodium Starch Glycolate *PSD of Lactose	-1.103	0.098		
Predication Equation: 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)					

All the statistical and regression analysis procedure on the response parameters were performed using the DOE methodology [2, 9, 12]. 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.

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 % Dissolution at 30 minutes	Constant	97.631	0.0001	97.72%	R-square value is acceptable; P-value for all the term is greater than 0.05
	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: 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 optimumized formulation satisfied all constraints simultaneously.

TABLE 9: EFFECTS OF FORMULATION VARIABLES

Formulation Variable	Effects	
	Content Uniformity (%)	% Dissolution at 30 minutes
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 Starchto 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

Summarizes the response tablets properties obtained from the eight formulations in experimental design. The concentration of excipient information and the impact of the variable on response are either positive or negative.

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 within 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.

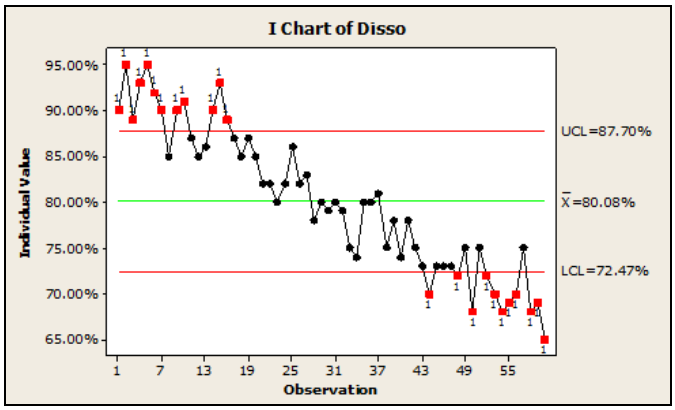
TABLE 10: COMPOSITION OF TETRABENAZINE TABLETS

Sr. No.	Ingredient	Mg/tablet
	Stage A Dry mixing	
1	Tetrabenzine	25.000
2	Anhydrous Lactose/Lactose Anhydrous	85.300
3	Pre-gelatinised 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	Magnesium Stearate	1.000
	Stage D Blending-II	
1	Talc	0.750
	Stage E Lubrication-II	
1	Magnesium Sterate	0.750
	Net weight of Core Tablet (mg)	125.000

TABLE 11: STABILITY DATA OF SCALE UP BATCH (*IN VITRO* DISSOLUTION)

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 33mm**
Batch Size: 5000 Tablets	**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%

Stability Data of scale up batch and *in vitro* dissolution data.



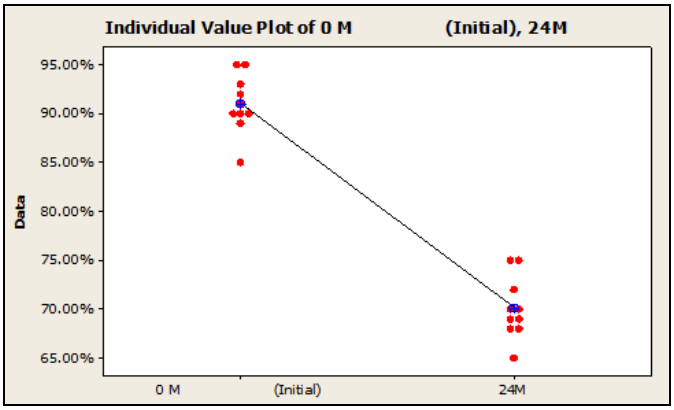


FIG. 1 AND 2: GRAPHICAL REPRESENTATION OF DISSOLUTION SHIFT UPON STABILITY

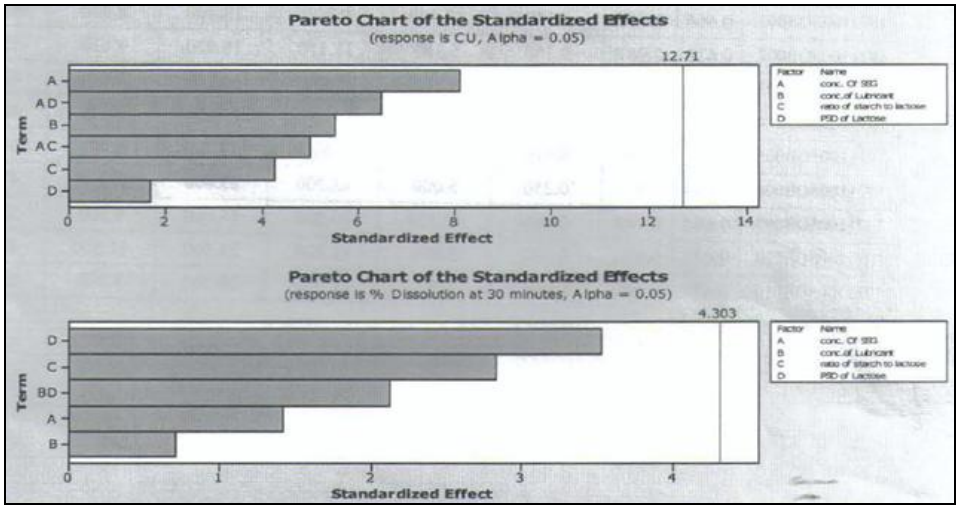


FIG. 3: EFFECT OF VARIABLES

The main effect plot showing impact of formulation variables with in studied range on Tablets Content uniformity and % Dissolution at 30 minutes. Main effect of Formulation process variables on Tables 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.

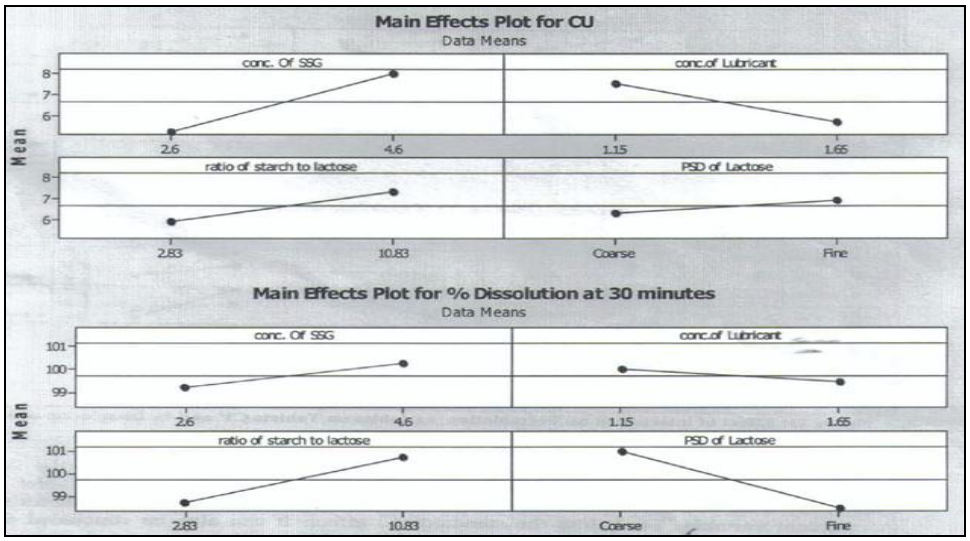


FIG. 4: MAIN EFFECT

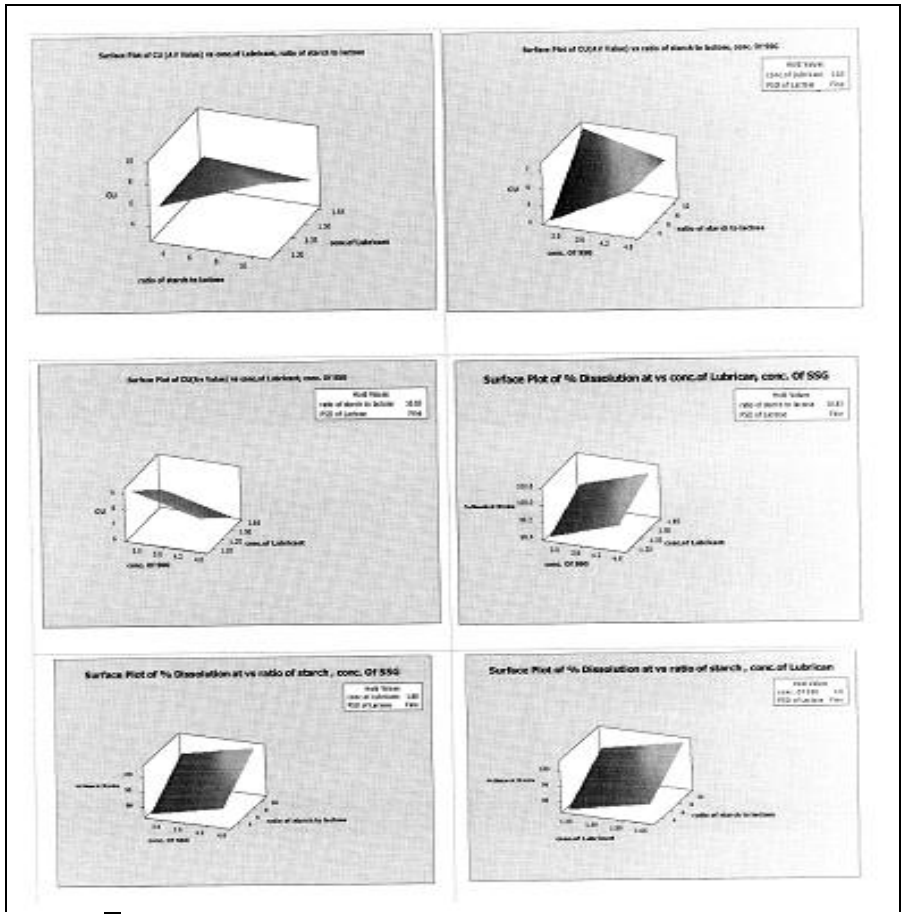


FIG. 5: SURFACE PLOT: SURFACE PLOT OF FORMULATION VARIABLES ON TABLETS CONTENT UNIFORMITY AND % DISSOLUTION AT 30 MINUTES

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.

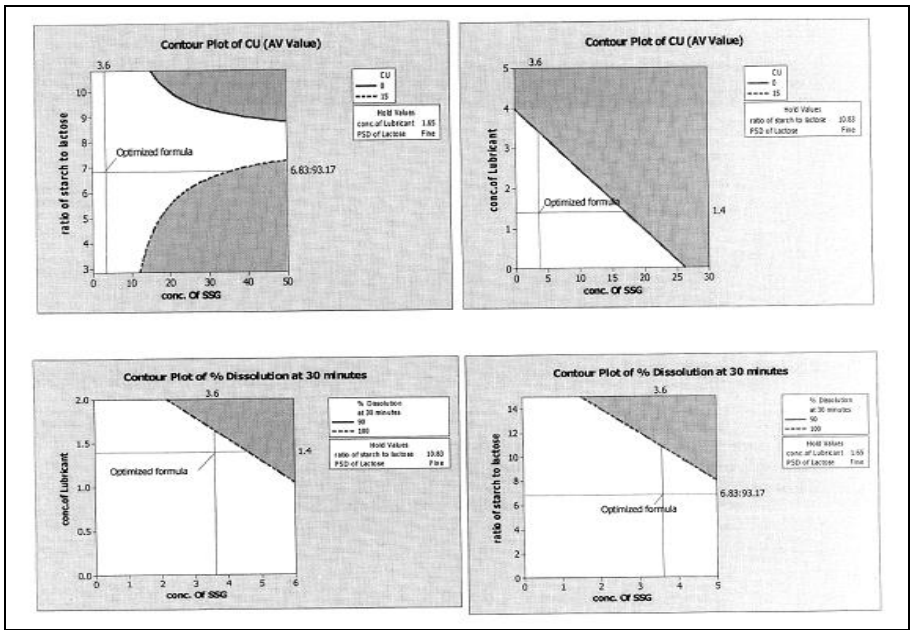


FIG. 6: DESIGN SPACE: DESIGN SPACE FOR FORMULATION VARIABLES ON TABLET CU AND % DISSOLUTION

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 within which any change will not have any impact on CQA of drug product.

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. Factorial design applications are used to optimizing the formulation as well as to overcome the dissolution shift.

CONFLICT OF INTEREST: All authors have none to declare.

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