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Research Article

APPLICATION OF FACTORIAL DESIGN FOR ENHANCEMENT OF DISSOLUTION OF BCS CLASS IV DRUGS

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A R T I C L E I N F O

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A B S T R A C T

A two level four factor partial factorial design was adopted for enhancement of the Dissolution of a Biopharmaceutics Classification (BCS) Class IV drug [1,2,5,8,12,13,14,17]. Design of experiment (DOE) was applied to optimize a tablet formulation of Tetrabenazine (TBZ) Tablets 25mg containing high percentage of Lactose Anhydrous, Sodium starch Glycolate, Magnesium Stearate and Strach/Lactose Ratio.The particle size distribution of Lactose Anhydrous is used as dependent variable and Sodium starch Glycolate, Magnesium Stearate and Strach/Lactose Ratio were used as independent variables for optimizing some tablets response parameters [1,2,8,12,13]. Response parameters for final TBZ Tablets were percentage of TBZ dissolve at thirty minutes.The data were analyzed by means of Pareto chart, interaction of variables and quadratic response surface model. Response surfaces were generated for tablet percentage of dissolution and content uniformity required disintegration time and frability as a function of independent variables.The models were validated for accurate prediction of response characteristics and used to used 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 [1,2,3,9,12,13,15].

INTRODUCTION

The absolute aqueous solubility for the Tetrabenazine (TBZ) in water is approximately 0.025mg/ml. The aqueous solubility of TBZ was found low and having impact on the in-vitro dissolution. Dissolution slow down upon stability and develop control strategies for a drug product during formulation and process development. A partial factorial 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 [1,2,9,12,13,15].

Further the level of two or more processing parameters may interact to produce an unanticipated result. This is sometimes refered to as synergism or potentiation, in which the effect of supposedly independent factors is many fold the sum of effects of the factors taken separately. Thus, some factors may be discovered to be interdependent.Utilizing the tool of factorial design for redeveloped and marketed a tablet formulation containing 25mg of TBZ.

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This made possible the manufacture of a tablet of acceptable dissolution performance [1,2,5,8,12,13,14,17].

MATERIALS AND METHOD

Drug Substance
Chemical Names: Tetrabenzine
IUPAC name: (SS,RR)-3-Isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-pyrido [2,1-a]isoquinolin-2-one
Molecular Formula: $C_{19} H_{27} NO_3$
Molecular Weight: 317.42258g/mol
Chirality: Racemic mixture
Clinical data
Route of administration: Oral (tablets, 25mg)

Pharmacokinetic data
Bioavailability: Low, extensive first pass effect
Protein binding: 82%-85%
Metabolism: Hepatic
Excretion: Renal (~75%) and fecal (7-16%)

Pharmacology

The precise mechanism of action of Tetrabenazine is unknown. Its anti-chorea effect is believed to be due to a reversibile depletion of monoamines such as dopamines, serotonin, norepinephrine and histamine from nerve terminals. Tetrabenazine reversibly inhibits vesicular monoamine transporter 2, resulting in decreased uptake of monoamines into synaptic vesicles, as well as depletion of monoamine storage.

Therapeutic of use

A drug formerly used as an antipsychotic but now used primarily in the symptomatic treatment of various hyperkinetic disorders. It is a monoamine depletor and used as symptomatic treatment of chorea associated with Huntington's disease.

Aqueous Solubility as Function of pH

The solubility of Tetrabenazine in aqueous media as a function of pH was measured and is presented in Table 1. The calculated dose solubility volume of Tetrabenazine is less than 250ml at pH 1.2 to 4.5 and graeter than 250 ml at pH 6.0 to 7.8. Tetrabenazine is considered as Biopharmaceutical Classification System (BCS) Class IV drug (Low Soluble and low Permeable).

Table 1 Quantitative solubility of Tetrabenazine at different pH aqueous system

Solvent Media	Tetrabenazine (Batch No: SH-7-48876)	
	Quantitative solubility (mg/ml)	Dose Solubility Volume (Calculated at 37ºC) Maximum Dose (25mg)
0.1 N HCL, pH 1.2	28.41	0.73
0.01N HCL , pH 2.1	3.3	4.15
Acetate buffer , pH 2.8	41.27	0.44
Acetate buffer , pH 4.5	0.49	32.33
Phsphate buffer, pH 6.0	0.03	400
Phsphate buffer, pH 6.8	0.03	723.31
Phsphate buffer, pH 7.2	0.02	731.34
Phsphate buffer, pH 7.8	0.02	821.34
Purified Water	0.02	845.32

Dose solubility volume for Tetrabenazine at pH 1.2-7.8

Dose solubility volume for Tetrabenazine at pH 1.2-7.8 demonstrated that Tetrabenazine were soluble at low pH and solubility decreased significantly between pH 2.8-4.5. The solubility remained relatively constant between pH 6.0-7.8 (Poorly Soluble). The absolute aqueous solubility for the Tetrabenazine in water is approximately 0.02mg/ml and was having impact on the in-vitro dissolution.

Density (Bulk and Tapped) and Flowability

The bulk, tapped and true density as well as the flowability of Tetrabenazine (SH-7-48876) were measured.
Bulk density: 0.416g/cc
Tapped density: 0.675g/cc
The observed compressibility index and Hausner ratio was 33.231 and 1.634 respectively. Compressibility index>37 and Hausner ratio> 1.50 indicates very poor flow characteristics.

Materials

Anhydrous Lactose/Lactose Anhydrous, Pregelatinised Starch, Sodium Starch Glycolate, Iron oxide yellow, Talc, Colloidal silicon dioxide, Magenesium Sterate all slected ingradients 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 trasferred 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 (Bultmann JM *et al*., 2002). 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±0.5ºC and 50 rpm. A 5ml sample was withdrawn from the dissolution apparatus at predetermine time interval, and the dissolution media was replaced with fresh dissolution medium.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.

The selected independent variables are:

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

The ranges selected for dry granulation process are summarized in Table 2. 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 3.

Table 2 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 3 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 4, the eight experiments represent a design for four factors at two levels, these are represented by +1 and -1 and two level partial factorial design.

Table 4 Design matrix for formula of optimization

Batch No.	Experimental Runs			
	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

Table 5 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.

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

RESULT AND DISCUSSION

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-3.

The p-value for all the formulation varibles is greater than 0.05 indicates insignificant for tablet 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 varibles is greater than 0.05 indicates insignificant for tablet % Dissolution at 30 minutes.

Table 5 Summary of response studies

Batch No.	Response studies							
	Physical Appearance	Maximum Individual % weight Variation from Target (125.00 mg)	Maximum Differance of Thickness (mm) from Target	Maximum Differance of Hardness (kP) from Target	Disintegration Time (min)	% Friability	% Drug Dissolution	CU (AV Value)
SR-T-001	Free of any defect	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		1.800	0.050	1.000	4 min 10 sec	0.35	100	5.98
SR-T-005		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

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 6.

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.

Table 6 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

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 indentified as the response parameter. The optimumized formulation satisfied all constraints simultaneously.

Statistical Analysis of Design of Experiments

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 figre-3.

The impact of concentration of excipient information was the variable on response is positive or negative. The main effect plot showing impact of formulation variables with in studied range on Tablets Content uniformity and % Dissolution at 30 minutes is given figure-4.

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% at studied range of variables. Hence, it can be concluded that there is no siginificant impact of selected variables within the studied range on Tablet Content Uniformity and % dissolution at 30 minutes.

Table 7 Model Evaluation

Response	Terms included in reduced model	Co- efficient	P-Value	R-squre	Justification for inclusion
Tablet Content Uniformity (AV Value)	Constant	6.643	0.013	98.41%	R-square value is acceptable
	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		P-value for all the term is greater than 0.05
	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)

Table 8 Model Evaluation

Response	Terms included in reduced model	Co- efficient	P-Value	R-squre	Justification for inclusion
Tablet % Dissolution at 30 minutes	Constant	97.631	0.0001	97.72%	R-square value is acceptable
	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		P-value for all the term is greater than 0.05

Predication Equation:
Tablet % Dissolution at 30 minutes = 97.631+0.50012(A)-1.0000(B)+0.23000(C)-5.23000(D) +3.0000 (BD)

Table 9 summarizes the response tablets properties obtained from the eight formulations in experimental degisn.

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

3D Conformer

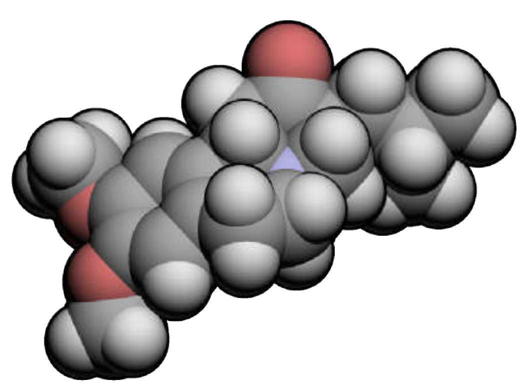

Figure 1

Mechanism of action

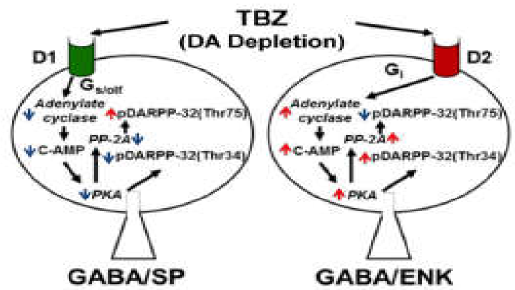

Figure 2

Effect of Variables

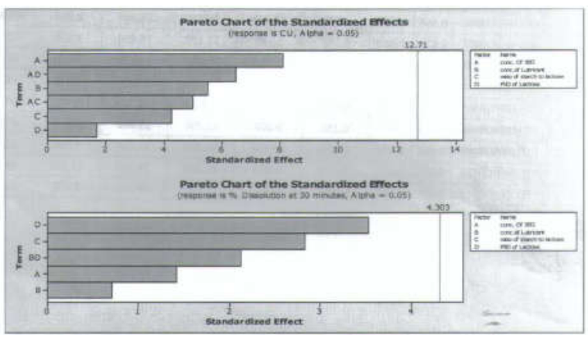

Figure 3

Main Effect

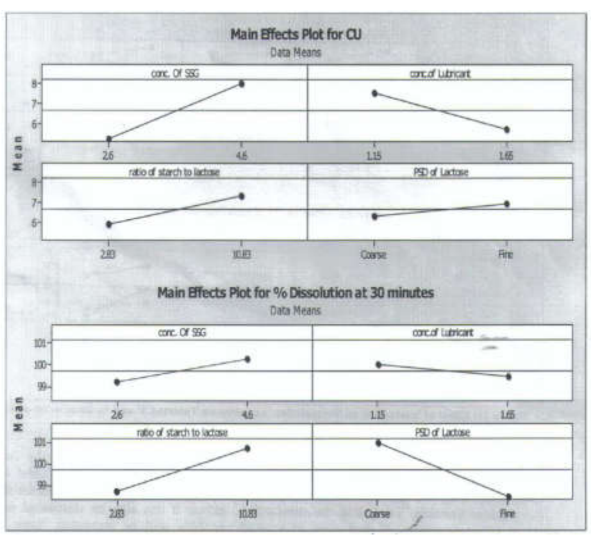

Figure 4

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

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 consideredas a design space with in which any change will not have any impact on CQA of drug product.

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

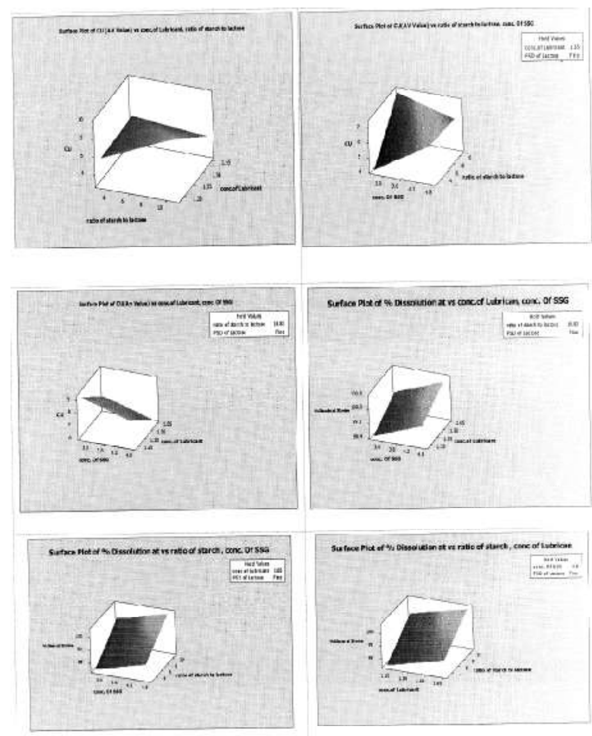

Figure 5

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

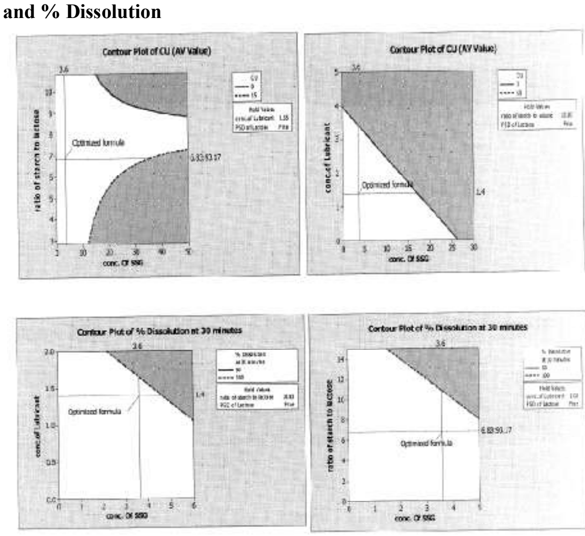

Figure 6

The formulation composition was finalized based on formulation optimization. In the formulation optimization studies, impact of Lactose anhydrous PSD, level of sodium strach glycolate ranges for these excipients selected did not have any impact on the invitro dissolution. Final composition of Tetrabenazine Tablets are given in Table 10.

Table 10 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

CONCLUSIONS

In this TBZ tablet formulation was optimized using 2^4 partial factorial designs. Mathematical model can be utilized to produce accurate representation of the relationship between the independent variables and optimised 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 propotion of excipient could be optimised succesfully. By implementation of eight experiments the effect of two level four factors and their interactions were determined. A Design space which guaranties a product having specified quality attributes has been found. Design of Experiments (DOE) is an applicable method for optimisation of BCS class IV drug.

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