IJPSR (2014), Vol. 5, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 October, 2013; received in revised form, 28 February, 2014; accepted, 26 March, 2014; published 01 April, 2014

A STUDY ON FEASIBILITY OF OPTIMIZATION TECHNIQUE IN FORMULATION OF DISPERSIBLE TABLETS BY FACTORIAL DESIGN

R.E. Ugandar*, Kiran C. Nilugal, Nagarajan Srinivasan and Nagashekhara Molugulu

Faculty of Pharmacy, Asia Metropolitan University, G-8, Jalan Kemacahaya, Taman Kemacahaya, Batu 9, Cheras- 43200, Selangor, Malaysia

Keywords:

Optimization, Simplex-design, Desirability, variables, Dispersible tablets, Super-disintegrants

Correspondence to Author:

R.E. Ugandar

Lecturer, Faculty of Pharmacy, Asia Metropolitan University, G-8, Jalan Kemacahaya, Taman Kemacahaya, Batu 9, Cheras- 43200, Selangor, Malaysia

E-mail: rajan@masterskill.edu.my

ABSTRACT: In the present research work an attempt was made to study the effect of formulation variables in the development of dispersible tablet by using various super disintegrants. Instead of normal trial and error method an optimization technique was adapted. Amount of Crosscarmellose sodium, SSG and MCC were included as independent variables and hardness, percentage friability, disintegration time and wetting time were considered as dependent variables. The study was conducted separately for Starch and CPVP as binders. The post compression parameters like hardness, percentage friability, disintegration time and wetting time were found to be within the permissible limits of IP. The results were fitted to quadratic and linear model and were found to be significant. For the selection of optimized formulation a numerical optimization by desirability function was performed with desired constraints. The optimized tablet formulations contained 10.79mg of Crosscarmellose sodium and 1.21mg of MCC for starch as binder and 3.38mg of SSG with 8.62mg of MCC for CPVP as binder. Observed results were in close accord with the predicted values of the optimized formulations, and consequently demonstrate the feasibility of the optimization procedure in the development of dispersible tablets.

INTRODUCTION:

Optimization [1, 2, 3]: In today's industrialized society almost every product that eventually reaches the market has a long lineage of testing and modification to its design before it sees the light of day. So "success is the most difficult commodity" to come out, especially with the time frame imposed, which is structured by a customer need or by a competitive threat.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(4).1208-27

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(4).1208-27

This leads to experimenters or researchers to find the most efficient schemes of formulating, testing and apply such schemes to as broad a gamut of application required to make a successful product. The word optimize is defined as, to make as perfect, effective or functional as possible.

Optimization may be interpreted as to find out the value of controllable independent variable, that gives the most desired value of dependent variables. The application of formulation optimization techniques is relatively essential to the practice of pharmaceutical formulation, when used intelligently, with the common sense; these "statistical" methods will broaden the perspective of the formulation process. During any experiment at the pre-formulation stage, certain problems will

be experienced. They are often not known before in hand. These variables will significantly influence the response or responses. By using screening designs and ANOVA one can solve these problems. A second serious complication may arise with new excipients and new process factors, for which qualitative or quantitative effects are not known and nor are they predictable. Before choosing the design, following question must be answered. Which part of the factor space should be chosen for experiments, are these constraints to be put on the levels of the variables.

The third complication is that formulated products, in particular dosage form has to confirm to several requirements, very often competing. The formulator has to trade off objectives and choose a compromise. A fourth problem is the lack of insight in the balance between the required prior knowledge to perform an adequate optimization study and the gain in knowledge obtained by the study. It should be emphasized that in the performance of an optimization study, the development scientist can also be a factor. Reliable prior experience and knowledge are prerequisites.

Terms used in optimization [4]

Variables: These are the measurements, values, which are characteristics of the data. There are two types of variables; Dependent variables and independent variables. Independent variable is the variable that is manipulated in an experiment. This variable remains unchanged (or "independent") between conditions being observed in an experiment. It is the "presumed cause. "Independent variables are the variables, which are not dependent on any other values e.g., Lubricants concentration, drug to polymer ratio, etc. Dependent variable values are dependent on the concentration of independent variables used.

Factor: Factor is an assigned variable such as concentration, temperature, lubricant, drug to polymer ratio, polymer to polymer ratio or polymer grade. A factor can be qualitative or quantitative. A quantitative factor has a numerical value to it (concentration 1%, 2%… so on), drug to polymer ratio (1:1, 1:2…etc). Qualitative factors are the factors, which are not numerical (polymer grade, humidity condition, type of equipment, etc) these are discrete in nature.

Levels: The levels of a factor are the values or designation assigned to the factor. That is when concentration is considered as a factor, 1 % will be one level, while 2% will be another level. Two different plasticizers are levels for grade factor. Usually levels are indicated as low, middle or high. Normally for ease of calculation the numeric and discrete levels are converted to –1 (low level) and +1 (high level). The general formula for this conversion is;

Level = X - the average of the two level / Half the difference of the level

Where 'X' is the numeric value

Response: Response is mostly interpreted as the outcome of an experiment. It is the effect, which we are going to evaluate i.e. Disintegration time, duration of buoyancy, etc.

Effect: The effect of a factor is the change in response caused by varying the levels of the factor. This describes the relationship between various factors and levels.

Interaction: It is also similar to effect, which gives the overall effect of two or more variables (factors) on a response. For example, the combined effect of lubricant and glidant on hardness (response) of a tablet. In the trial and error method, a lot of formulations have to be prepared to get a conclusion, which involves lot of money, time and energy. These can be minimized by the use of optimization technique.

Optimization process: Based on the previous knowledge or experience or from literature, the independent variables are determined and set in the beginning. Selection of a suitable model, based on the results of the factor screening is done. The experiments are designed and are conducted. The responses are analyzed by ANOVA, test on lack of fit, to get an empirical mathematical model for each individual response. The responses are screened, by using multiple criteria to get the values of independent variables.

Experimental design: Experimental design is a statistical design that prescribes or advises a set of combination of variables. The number and layout of these design points within the experimental region depends on the number of effects that must

be estimated. Depending on the number of factors, their levels, possible interactions and order of the model, various experimental designs are chosen. Each experiment can be represented as a point within the experimental domain, the point being defined by its coordinate (the value given to the variables) in the space.

Factorial design: It is an experimental design, which uses dimensional factor space at the corner of the design space. Factorial designs are used in experiments where the effects of different factors or conditions on experimental results are to be elucidated. These are the designs of choice for simultaneous determination of the effect of several factors and their interaction. The simplest factorial design is the two-factorial design where two factors are considered each at the two levels, leads to the four experiments, which are situated in two dimensional factor spaces at the corners of a rectangle.

If there are three factors, each at two levels, eight experiments are necessary which are situated at the corners of an orthogonal cube in a 3-dimensional space. The number of experiments is given by 2n, where 'n' is the number of factors. If the number of factors and levels are large, then the number of experiments needed to complete a factorial design is large. To reduce the number of experiments, fractional factorial design can be used (½ or ¼ of the original number of experiments with full factorial design).The fitting of an empirical polynomial equation to the experimental result facilitates the optimization procedure.

The general polynomial equation is as follows:

$$Y = B0 + B1X1 + B2X2 + B3X3 + \ldots + B12\ X1\ X2 + B13X1X3 + B23X2X3 + \ldots + B123X1X2X3.$$

Where, Y is the response, X1, X2, X3 are the levels (concentration) of the 1, 2, 3 factors, B1, B2, B3, B12, B13, B23, B123 are the polynomial coefficients. B0 is the intercept (which represents the response when the level of all factors is low).

Validation of the Model: The model is validated using ANOVA calculation, and then the estimation of pure measurement error is done. The variance of these observations pooled over all to get an estimate of pure error of variance.

The F-test on regression and lack of fit will be useful for judging descriptive properties of a model and the significance of model terms.

Predictions using the selected model: Once a model is selected and validated, the brute force method is applied for the prediction of response. With the help of 3D-response surface or a 2D contour diagram, the prediction is done using these graphs either by grid search or feasibility search methods.

MATERIALS AND METHODS:

Excipients: Crosscarmellose sodium and Sodium starch gylcolate and microcrystalline cellulose was received as gift samples from M/S Apotex India Research ltd, Bangalore. Starch was obtained as a gift sample from M/S Eros Pharma Pvt Ltd. Peenya, Bangalore. Cross Povidone was obtained as a gift sample from M/S Ce-Chem Laboratories, Peenya, Bangalore. Aspartame was obtained as a gift sample from M/S Strides Arco Lab, Bangalore. Isopropyl alcohol and Colloidal silicon dioxide were received as gift samples from M/S Strides Arco Lab, Bangalore.

Instruments:

Analytical balance: Sartorius Single Pan Balance.

Tablet punching machine: Rimek RSB-4, minipress, Karnavati (10 stations)

Pfizer Hardness Tester: Praveen Enterprises. Bangalore

Friability Testing Apparatus: Indian Equipment Corporation. Mumbai

Method:

Formulation design for fast dissolving tablets [5]: Independent variables were determined and the experiments were designed by using simplex design. Calculated quantities of ingredients were weighed and sifted through appropriate sieves and mixed in the ascending order. The mixture of ingredients was used to prepare granules by Wet granulation with appropriate binding agents with Isopropyl alcohol as solvent. Prepared granules were sieved through sieve number 8 and dried in oven for 30 min.

Dried granules were sieved through 22/44 sieves and mixed with 15% w/w fines, lubricants and disintegrants and subjected for punching by compression. Prepared formulations were subjected for post compression parameters such as hardness, friability (F in %), disintegration time (DT in Sec.) and wetting time (WT in Sec.). The values obtained were used to optimize the formulations to obtain OF1 and OF2 by using the factorial simplex design, calculated statistical parameters and design expert software version 6.05. List of ingredients used in milligrams as per simplex design for prepared formulations with starch and CPVP as binders are represented in **Table 1 and 2** respectively.

RESULTS:

TABLE 1: LIST OF INGREDIENTS IN MILLIGRAMS AS PER SIMPLEX DESIGN FOR FORMULATIONS WITH STARCH AS BINDER

Ingredients in mg.	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
Drug (Diluent)	50	50	50	50	50	50	50	50
Starch	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Aerosil	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Mg stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
MCC	77.95	77.95	77.95	77.95	77.95	77.95	77.95	77.95
CCNa	12.0	0.0	0.0	6.0	6.0	0.0	4.0	12.0
SSG	0.0	12.0	0.0	6.0	0.0	6.0	4.0	0.0
MCC	0.0	0.0	12.0	0.0	6.0	6.0	4.0	0.0
Total	150	150	150	150	150	150	150	150

TABLE 2: LIST OF INGREDIENTS IN MILLIGRAMS AS PER SIMPLEX DESIGN FOR FORMULATIONS WITH CPVP AS BINDER

Ingredients in mg.	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
Drug (Diluent)	50	50	50	50	50	50	50	50
PVP k30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Aerosil	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Mg stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
MCC	77.95	77.95	77.95	77.95	77.95	77.95	77.95	77.95
CCNa	12.0	0.0	0.0	6.0	6.0	0.0	4.0	12.0
SSG	0.0	12.0	0.0	6.0	0.0	6.0	4.0	0.0
MCC	0.0	0.0	12.0	0.0	6.0	6.0	4.0	0.0
Total	150	150	150	150	150	150	150	150

Evaluation of prepared Tablets [6]:

Hardness (H in Kg/cm^2): The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in Kg/cm^2.

Friability (F in %) [7]: The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four min. The tablets were weighed again (W_{final}).The percentage friability was then calculated by:

$$F = (W_{initial} - W_{final} / W_{final}) \times 100$$

Disintegration time (DT in sec) [8]: The *in-vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Wetting time (WT in sec) [9]: A piece of tissue paper folded twice was placed in a small Petri plate (internal diameter = 6.5 cm) containing 10 ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^{o}C.

Optimization [10]: The runs or formulations were designed based on Simplex design and are evaluated for the response variables. The response values are subjected to multiple regression analysis to find out the relationship between the factors used and the response values obtained. The response values subjected for this analysis are Hardness (Kg/cm^2), Friability (%),Disintegration time (DT) in seconds, Wetting time (WT) in seconds, The wetting time and disintegration time were chosen for analysis of effect of amount of Sodium starch glycolate, effect of amount of Cross Carmellose sodium and the combined effect of Sodium starch glycolate and Cross Carmellose sodium.

Statistical Analysis: The effect of formulation variables on the response variables were statistically evaluated by applying one way ANOVA at 0.05 level using a commercially available software package design of experiments® 6.05 (Stat Ease, USA). The design was evaluated by quadratic model, which bears the following equation.

$$\mathbf{Y= b_0 + b_1 X_1+ b_2 X_2 + b_3 X_1 X_2 + b_4 X_{12} + b_5 X_{22}}$$

Where y is the response variable, b_0 the constant and b_1, b_2, $b_3 \ldots b_5$ are the regression coefficients. X_1 and X_2 stand for the main effect; X_1X_2 are the interaction terms, show how response changes when two factors are simultaneously changed. X_{12}, X_{22} are quadratic terms of the independent variables to evaluate the non-linearity.

Using the regression coefficient of the factors, the polynomial equation for the response is constructed. Significantly contributing factors are only considered for the equation generation.

Desirability Details: The method makes use of an objective function, D (X), called the desirability function. It reflects the desirable ranges for each response (di).The desirable ranges are from zero to one (least to most desirable respectively).The simultaneous objective function is a geometric mean of all transformed responses. If any of the responses or factors falls outside their desirability range, the overall function becomes zero. For simultaneous optimization each response must have a low and high value assigned to each goal.

Maximum: di = 0 if response < low value , 0 < di < 1 as response varies from low to high and di = 1 if response > high value.

Minimum: di = 1 if response < low value, 1 <di < 0 as response varies from low to high and di = 0 if response > high value.

Target: di = 0 if response < low value, 0 < di < 1 as response varies from low to target, 1 < di < 0 as response varies from target to high and di = 0 if response > high value.

Range: di = 0 if response < low value, di = 1 as response varies from low to high and di = 0 if response > high value.

TABLE 3: POST COMPRESSION PARAMETERS OF FORMULATIONS CONTAINING (STARCH AS BINDER)

Parameters*	Run1	Run2	Run3	Run4	Run5	Run6	Run7	Run8
Hardness (Kg/cm^2)	5.28 ± 0.33	5.25 ± 0.17	4.20 ± 0.17	3.88±0.29	4.16±0.17	4.55 ± 0.17	4.50±0.60	3.16±0.48
Friability (%)	0.27 ± 0.01	0.25 ± 0.01	0.12 ± 0.02	0.13±0.01	0.18±0.01	0.07±0.02	0.61±0.01	0.35±0.01
DT (Sec)	18.33 ± 1.45	20.04 ± 0.19	20.33±0.33	18.00±1.67	16.13±0.18	25.50±1.67	32.50±0.33	22.50±0.10
Wetting in (Sec)	27.00 ± 0.58	25.67 ± 0.58	23.67±0.88	10.50 ± 1.20	12.50±1.20	8.50±0.73	25.67±0.88	5.33±0.67

*N = 3

TABLE 4: DESIGN AND SUMMARY RESPONSE DATA (STARCH AS BINDER)

Run	Type	Factors (mg)			Responses			
		A	B	C	Hardness (Kg/cm^2)	DT (Sec)	F %	WT (Sec)
1	Vertex	12	0	0	5.28	18.33	0.27	27.00
2	Vertex	12	0	0	5.25	20.04	0.25	25.67
3	Center Edge	6	6	0	4.20	20.33	0.12	23.67
4	Center	4	4	4	3.88	18.00	0.13	10.50
5	Vertex	0	12	0	4.16	16.13	0.18	12.50
6	Center Edge	6	0	6	4.55	25.50	0.07	8.50
7	Vertex	0	0	12	4.50	32.50	0.61	25.67
8	Center Edge	0	6	6	3.16	22.50	0.35	5.33

TABLE 5: ANOVA FOR MIXTURE QUADRATIC MODEL FOR HARDNESS (STARCH AS BINDER)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	3.417458	5	0.683492	118.9507	0.0084*
Linear Mixture	2.262172	2	1.131086	196.8473	0.0051*
AB	0.182759	1	0.182759	31.80623	0.0300*
AC	0.06939	1	0.06939	12.07623	0.0738
BC	0.964806	1	0.964806	167.909	0.0059*
Residual	0.011492	2	0.005746	-	-
Lack of Fit	0.011042	1	0.011042	24.53781	0.1268
Pure Error	0.00045	1	0.00045	-	-
Cor Total	3.42895	7	-	-	-

*Statistically significant at $\alpha < 0.05$

TABLE 6: STATISTICAL PARAMETERS (STARCH AS BINDER)

Std. Dev.	0.075802	R-Squared	0.996649
Mean	4.3725	Adj R-Squared	0.98827
C.V.	1.733617	Pred R-Squared	0.067883
PRESS	3.196184	Adeq Precision	31.43738

TABLE 7: ESTIMATED REGRESSION COEFFICIENTS FOR HARDNESS (STARCH AS BINDER)

Factor	Coefficient Estimate	DF	Std error
A	5.260418	1	0.053498
B	4.150837	1	0.075514
C	4.490837	1	0.075514
AB	-1.87589	1	0.332623
AC	-1.15589	1	0.332623
BC	-4.49673	1	0.347024

TABLE 8: ANOVA FOR MIXTURE LINEAR MODEL FOR DISINTEGRATION TIME (STARCH AS BINDER)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	163.6497	2	81.82486	14.22276	0.0086*
Linear Mixture	163.6497	2	81.82486	14.22276	0.0086*
Residual	28.76546	5	5.753093	-	-
Lack of Fit	27.30341	4	6.825853	4.668687	0.3324
Pure Error	1.46205	1	1.46205	-	-
Cor Total	192.4152	7	-	-	-

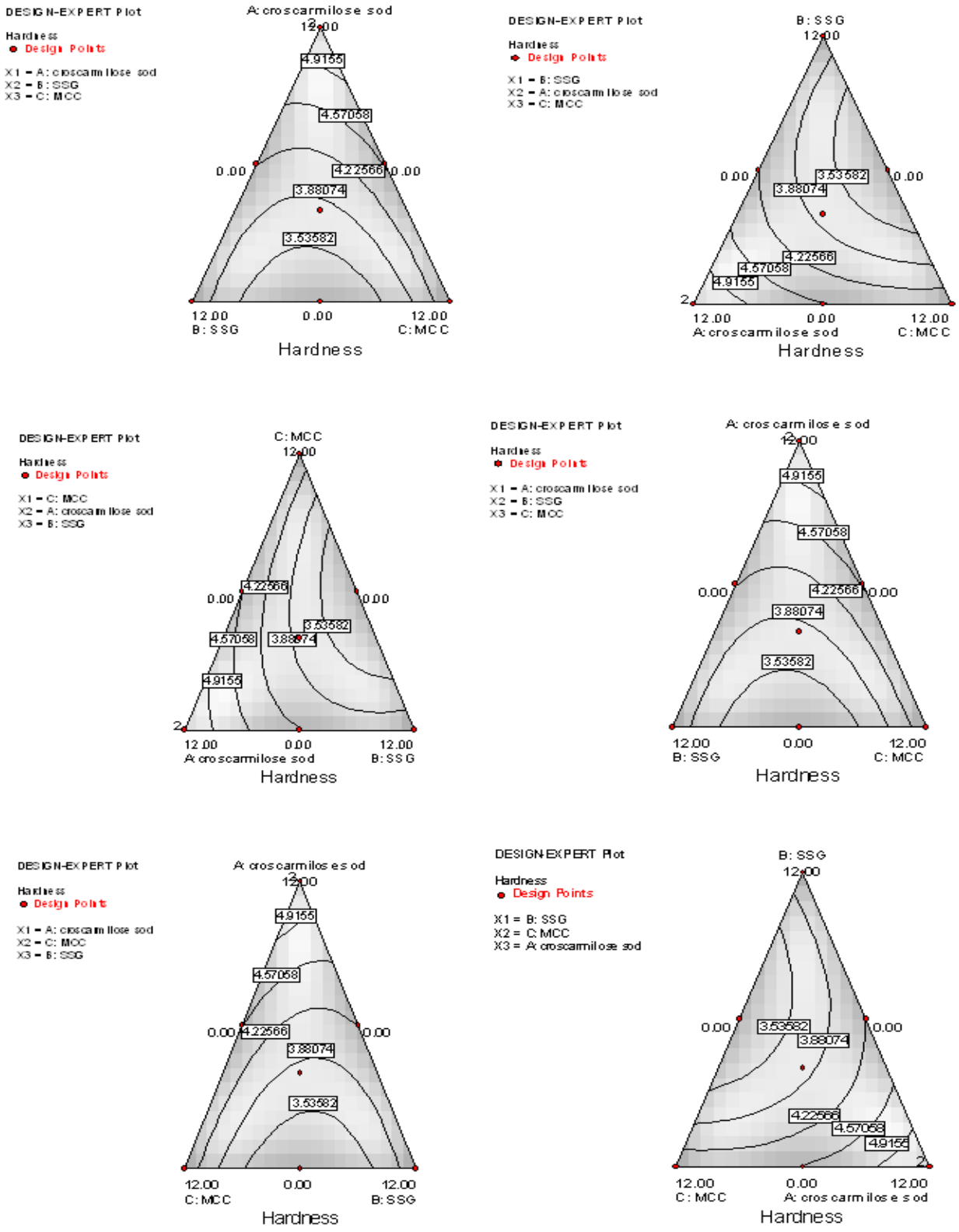
*Statistically significant at $\alpha < 0.05$

TABLE 9: STATISTICAL PARAMETERS DISINTEGRATION TIME (STARCH AS BINDER)

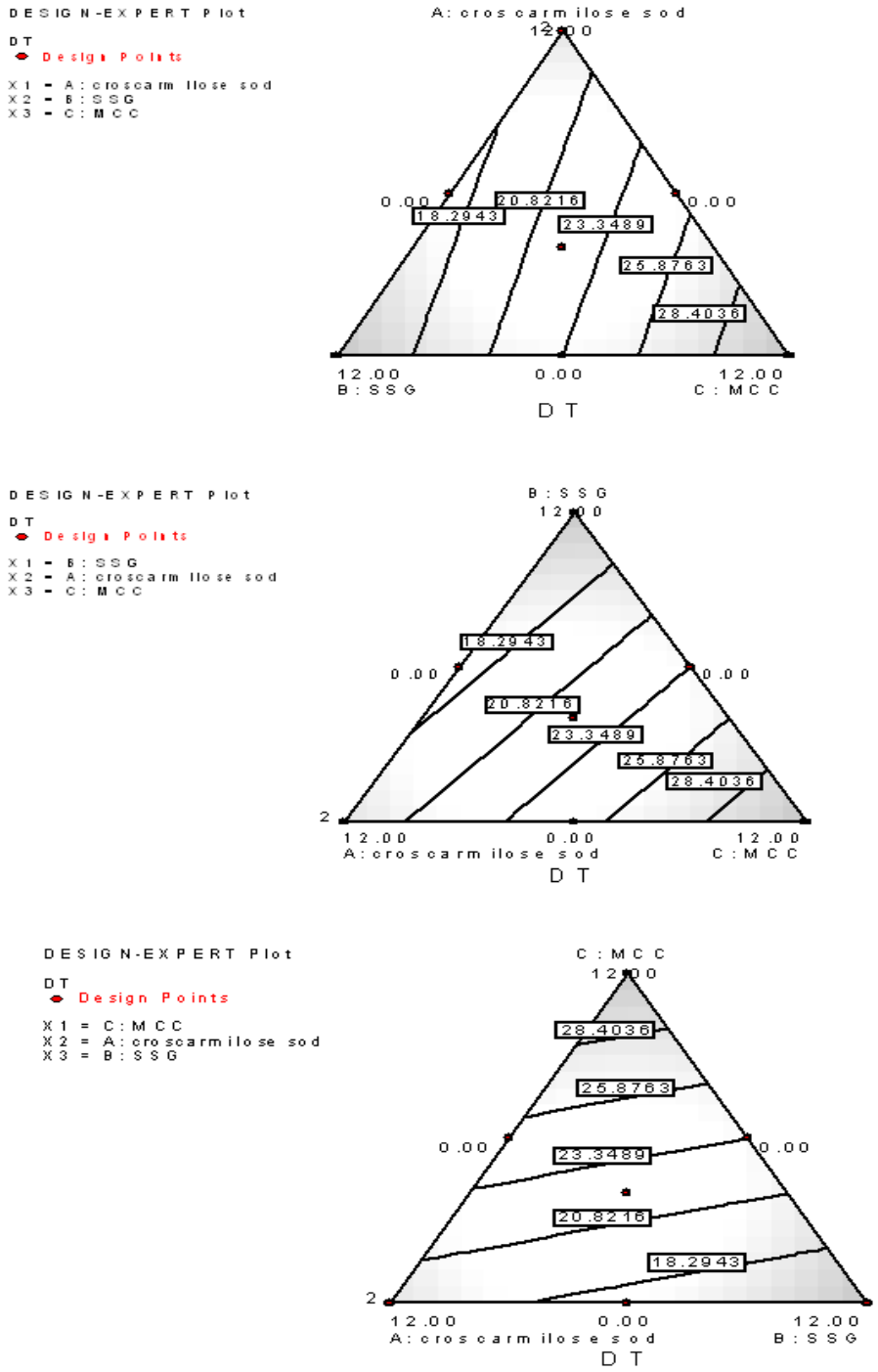
Std. Dev.	2.398561	R-Squared	0.850503
Mean	21.66625	Adj R-Squared	0.790704
C.V.	11.07049	Pred R-Squared	0.669754
PRESS	63.54429	Adeq Precision	10.32399

TABLE 10: ESTIMATED REGRESSION COEFFICIENTS FOR DISINTEGRATION TIME (STARCH AS BINDER)

Factor	Coefficient Estimate	DF	Std error
A	-4.03841	1	2.16958
B	-9.3538	1	2.520824
C	13.3922	1	2.520824



GRAPH 1: DESIGN-EXPERT PLOTS FOR HARDNESS (STARCH AS BINDER)



GRAPH 2: DESIGN-EXPERT PLOTS FOR DISINTEGRATION TIME (STARCH AS BINDER)

TABLE 11: ANOVA FOR MIXTURE QUADRATIC MODEL FOR FRIABILITY (STARCH AS BINDER)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	0.212525	5	0.042505	336.2605	0.0030*
Linear Mixture	0.089103	2	0.044551	352.4498	0.0028*
AB	0.007817	1	0.007817	61.84027	0.0158*
AC	0.112934	1	0.112934	893.4342	0.0011*
BC	0.001444	1	0.001444	11.4273	0.0775
Residual	0.000253	2	0.000126	-	-
Lack of Fit	5.28E-05	1	5.28E-05	0.264047	0.6978
Pure Error	0.0002	1	0.0002	-	-
Cor Total	0.212777	7	-	-	-

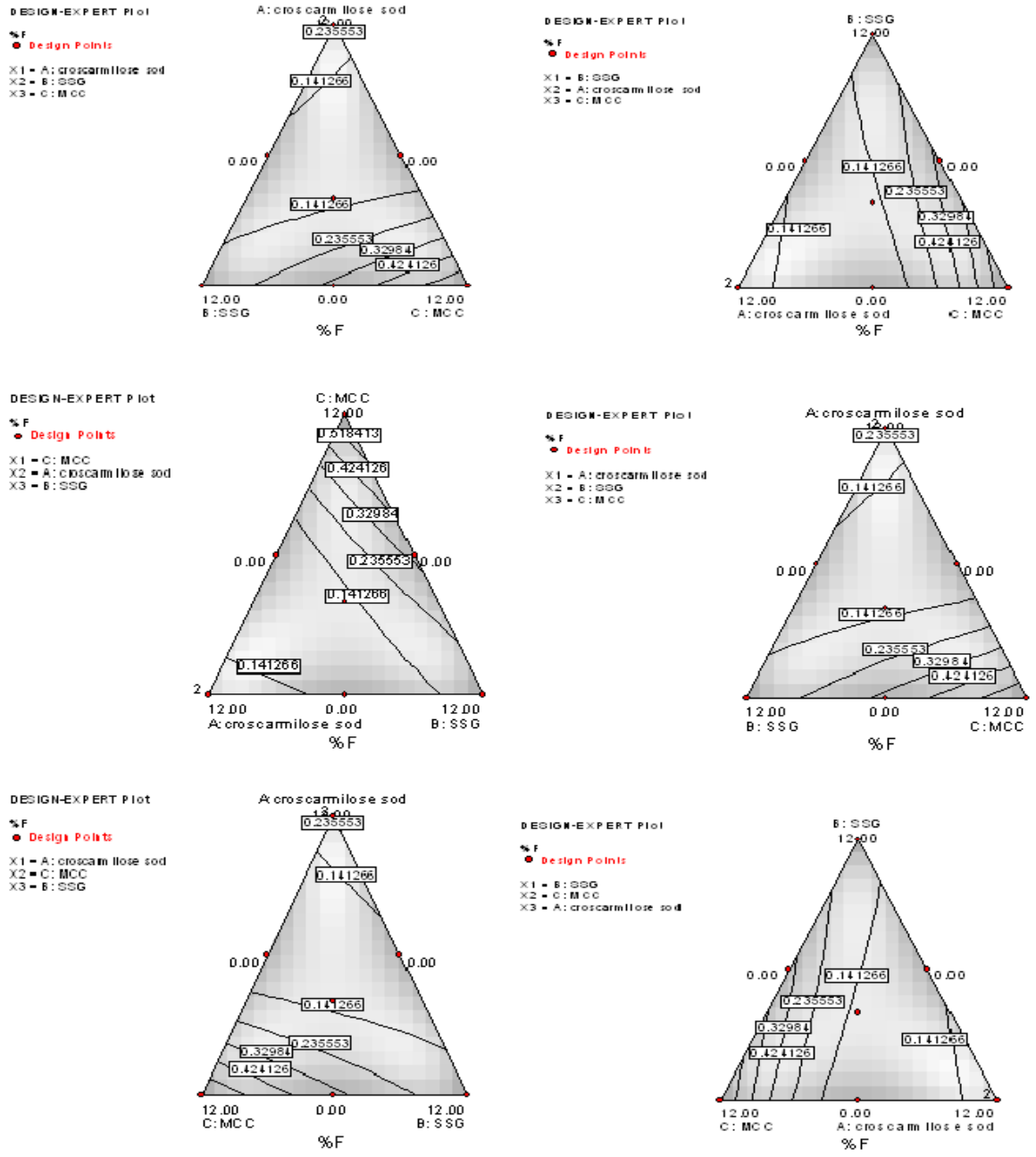
*Statistically significant at $\alpha < 0.05$

TABLE 12: STATISTICAL PARAMETERS

Std. Dev.	0.011243	R-Squared	0.998812
Mean	0.247292	Adj R-Squared	0.995842
C.V.	4.546448	Pred R-Squared	0.924468
PRESS	0.016071	Adeq Precision	55.99065

TABLE 13: ESTIMATED REGRESSION COEFFICIENTS FOR FRIABILITY (STARCH AS BINDER)

Factor	Coefficient Estimate	DF	Std. error
A	0.259683	1	0.007935
B	0.179366	1	0.0112
C	0.6127	1	0.0112
AB	-0.38796	1	0.049334
AC	-1.47463	1	0.049334
BC	-0.17399	1	0.051471



GRAPH 3: DESIGN-EXPERT PLOTS FOR % FRIABILITY (STARCH AS BINDER)

TABLE 14: ANOVA FOR MIXTURE QUADRATIC MODEL FOR WETTING TIME (STARCH AS BINDER)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	563.0988	5	112.6198	149.4994	0.0067*
Linear Mixture	182.2263	2	91.11314	120.95	0.0082*
AB	17.39713	1	17.39713	23.09418	0.0407*
AC	245.1021	1	245.1021	325.3659	0.0031*
BC	137.2981	1	137.2981	182.2592	0.0054*
Residual	1.506624	2	0.753312		
Lack of Fit	0.61778	1	0.61778	0.695037	0.5576
Pure Error	0.888844	1	0.888844		
Cor Total	564.6054	7			

*Statistically significant at $\alpha < 0.05$

TABLE 15: STATISTICAL PARAMETERS FOR WETTING TIME (STARCH AS BINDER)

Std. Dev.	0.867936	R-Squared	0.997332
Mean	17.35376	Adj. R-Squared	0.99066
C.V.	5.001427	Pred. R-Squared	0.67721
PRESS	182.249	Adeq. Precision	27.53249

TABLE 16: ESTIMATED REGRESSION COEFFICIENTS FOR WETTING TIME (STARCH AS BINDER)

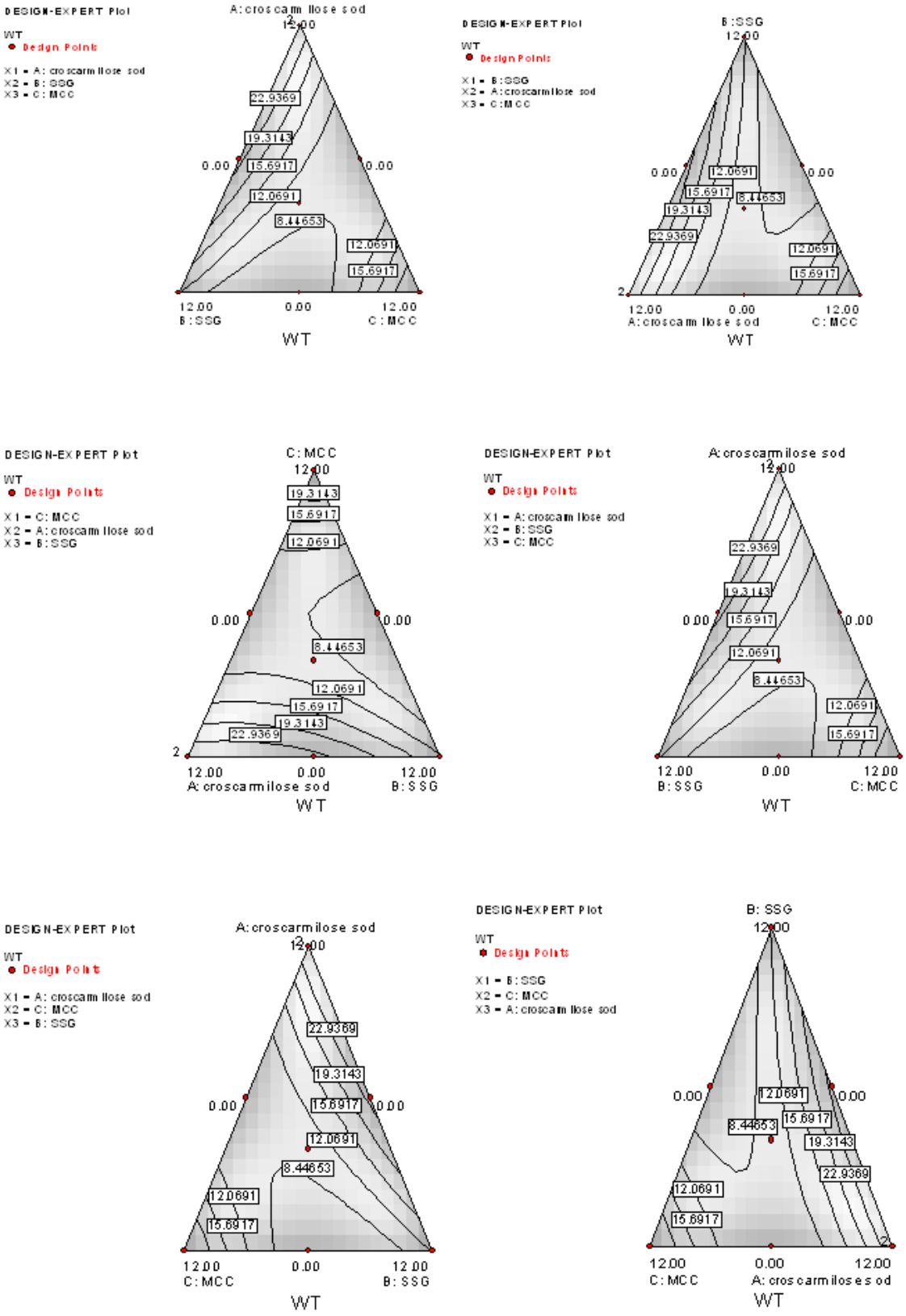
Factor	Coefficient Estimate	DF	Std error
A	26.29908	1	0.612555
B	12.43146	1	0.864629
C	25.59813	1	0.864629
AB	18.30239	1	3.808522
AC	-68.6977	1	3.808522
BC	-53.6425	1	3.973418

TABLE 17: CONSTRAINED TABLE

Constraints	Goal	Lower Limit	Upper Limit
CCNa	is in range	0	12
SSG	is in range	0	12
MCC	is in range	0	12
Hardness	is target = 5.28	3.16	5.28
DT	is target = 20	16.13	25
%F	is in range	0.065	0.61
WT	is in range	5.33	20

TABLE 18: PREDICTED SOLUTIONS FOR TABLETS CONTAINING STARCH AS BINDER

Number	CCNa	SSG	MCC	Hardness	DT	%F	WT	Desirability
1	10.79	0.00	1.21	5.07802	20.4822	0.161582	20	0.904289



GRAPH 4: DESIGN-EXPERT PLOTS FOR WETTING TIME (STARCH AS BINDER)

By utilizing **DESIGN- EXPERT 6.05 VERSION,** we obtained one solution as optimized formulation. The coded values for the factors were converted into the actual quantities in milligrams.

The formulation code given for optimized formulation was **OF-1** (Optimized-formulation-1) and is represented in Table 19.

TABLE 19: OPTIMIZED FORMULATION WITH STARCH AS BINDER (OF-1) AND INGREDIENTS USED

Ingredients	OF-1	(mg)
Lactose		50
Starch		7.5
Aerosil		0.3
Mg stearate		0.75
Aspartame		1.5
MCC		77.95
Crosscarmellose sodium		10.79
Sodium Starch Glycolate		0.0
Microcrystalline cellulose		1.21
Total		150

TABLE 20: POST COMPRESSION PARAMETERS OF FORMULATIONS CONTAINING CPVP AS BINDER

Parameters *	Run1	Run2	Run3	Run4	Run5	Run6	Run7	Run8
Hardness (Kg/cm^2)	4.20 ± 0.06	4.17 ± 0.29	3.17 ± 0.03	2.17 ± 0.17	5.50 ± 0.29	5.50 ± 0.10	4.57 ± 0.44	4.10 ± 0.17
Friability (%)	0.45 ± 0.02	0.43 ± 0.03	0.10 ± 0.02	0.52 ± 0.05	0.19 ± 0.02	0.13 ± 0.05	0.24 ± 0.04	0.33 ±0.02
DT (Sec)	79.48 ± 5.89	65.33 ± 1.67	41.67 ± 1.67	28.33 ± 1.67	43.33 ± 1.45	34.67 ± 4.48	23.33 ± 8.21	82.67 ± 1.76
Wetting in (Sec)	42.67 ± 0.44	81.67 ± 2.89	66.67 ± 4.91	16.67 ± 2.33	115.00 ± 2.89	25.00 ± 2.33	51.67 ± 1.67	39.66 ± 8.82

TABLE 21: DESIGN AND SUMMARY RESPONSE DATA (CPVP AS BINDER)

Run	Type	Factors (mg)			Responses			
		A	B	C	Hardness (Kg/cm^2)	DT (Sec)	F %	WT (Sec)
1	Vertex	12	0	0	4.20	79.48	0.45	42.67
2	Vertex	12	0	0	4.17	65.33	0.43	81.67
3	Center Edge	6	6	0	3.17	41.67	0.10	66.67
4	Center	4	4	4	2.17	28.33	0.52	16.67
5	Vertex	0	12	0	.50	43.33	0.19	115.00
6	Center Edge	6	0	6	5.50	34.67	0.13	25.00
7	Vertex	0	0	12	4.57	23.33	0.24	51.67
8	Center Edge	0	6	6	4.10	82.67	0.33	39.66

TABLE 22: ANOVA FOR MIXTURE QUADRATIC MODEL FOR HARDNESS (CPVP AS BINDER)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	8.715922	5	1.743184	689.9914	0.0014*
Linear Mixture	0.043435	2	0.021718	8.596362	0.1042
AB	3.306181	1	3.306181	1308.66	0.0008*
AC	2.809207	1	2.809207	1111.947	0.0009*
BC	2.557098	1	2.557098	1012.157	0.0010*
Residual	0.005053	2	0.002526	-	-
Lack of Fit	5.28E-05	1	5.28E-05	0.010554	0.9348
Pure Error	0.005	1	0.005	-	-
Cor Total	8.720975	7	-	-	-

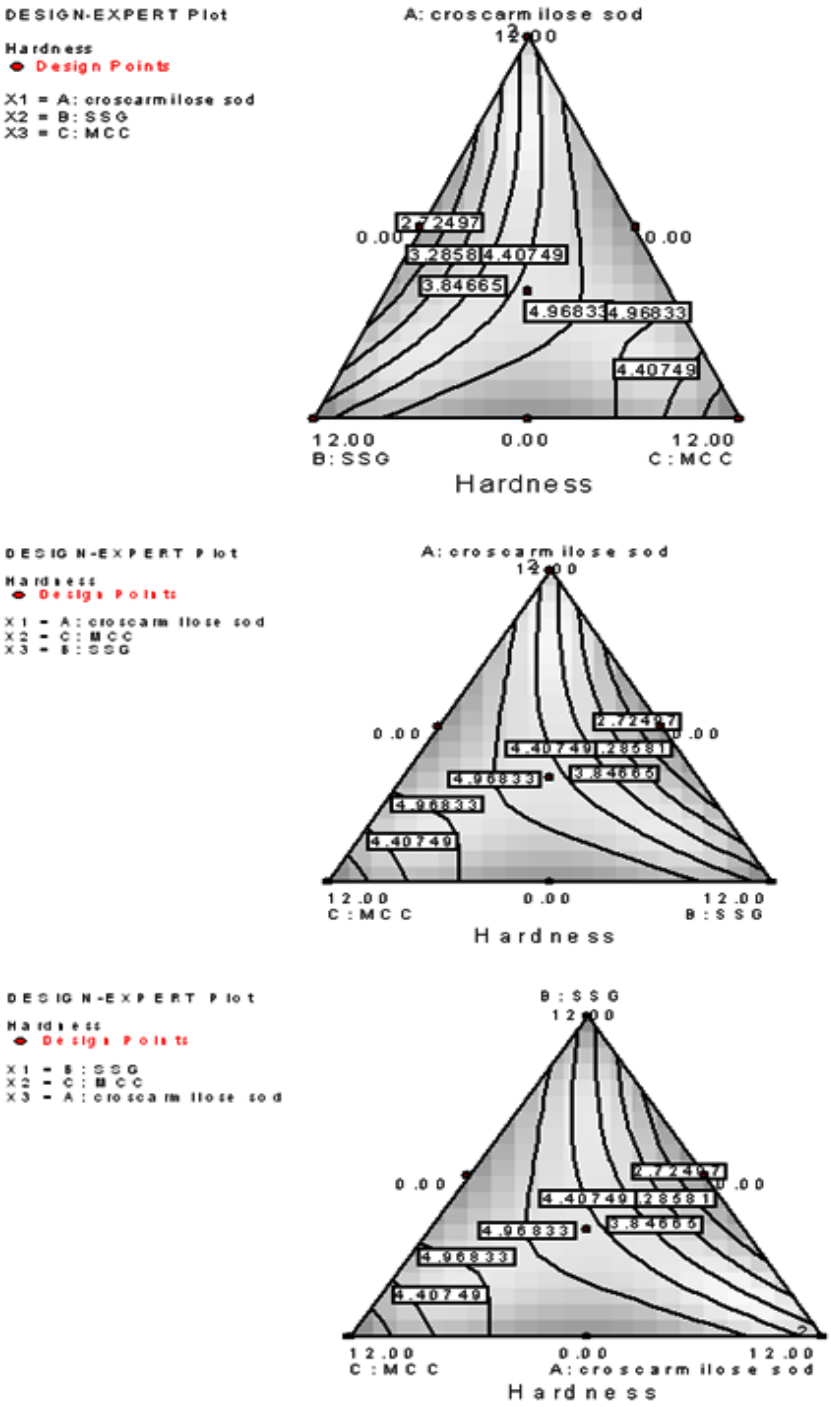
*Statistically significant at $\alpha < 0.05$

TABLE 23: STATISTICAL PARAMETERS OF RESPONSE HARDNESS (CPVP AS BINDER)

Std. Dev.	0.050263	R-Squared	0.999421
Mean	4.170834	Adj R-Squared	0.997972
C.V.	1.205111	Pred R-Squared	0.995973
PRESS	0.035115	Adeq Precision	76.57699

TABLE 24: ESTIMATED REGRESSION COEFFICIENTS FOR HARDNESS IN KG/CM^2 (CPVP AS BINDER)

Factor	Coefficient Estimate	DF	Std.error
A	4.150317	1	0.035474
B	4.1673	1	0.050072
C	3.1673	1	0.050072
AB	-7.9787	1	0.220556
AC	7.35463	1	0.220556
BC	7.320664	1	0.230105



GRAPH 5: DESIGN EXPERT PLOTS FOR HARDNESS (CPVP AS BINDER)

TABLE 25: ANOVA FOR MIXTURE QUADRATIC MODEL FOR DISINTEGRATION TIME (CPVP AS BINDER)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	8.715922	5	1.743184	689.9914	0.0014*
Linear Mixture	0.043435	2	0.021718	8.596362	0.1042
AB	3.306181	1	3.306181	1308.66	0.0008*
AC	2.809207	1	2.809207	1111.947	0.0009*
BC	2.557098	1	2.557098	1012.157	0.0010*
Residual	0.005053	2	0.002526	-	-
Lack of Fit	5.28E-05	1	5.28E-05	0.010554	0.9348
Pure Error	0.005	1	0.005	-	-
Cor Total	8.720975	7	-	-	-

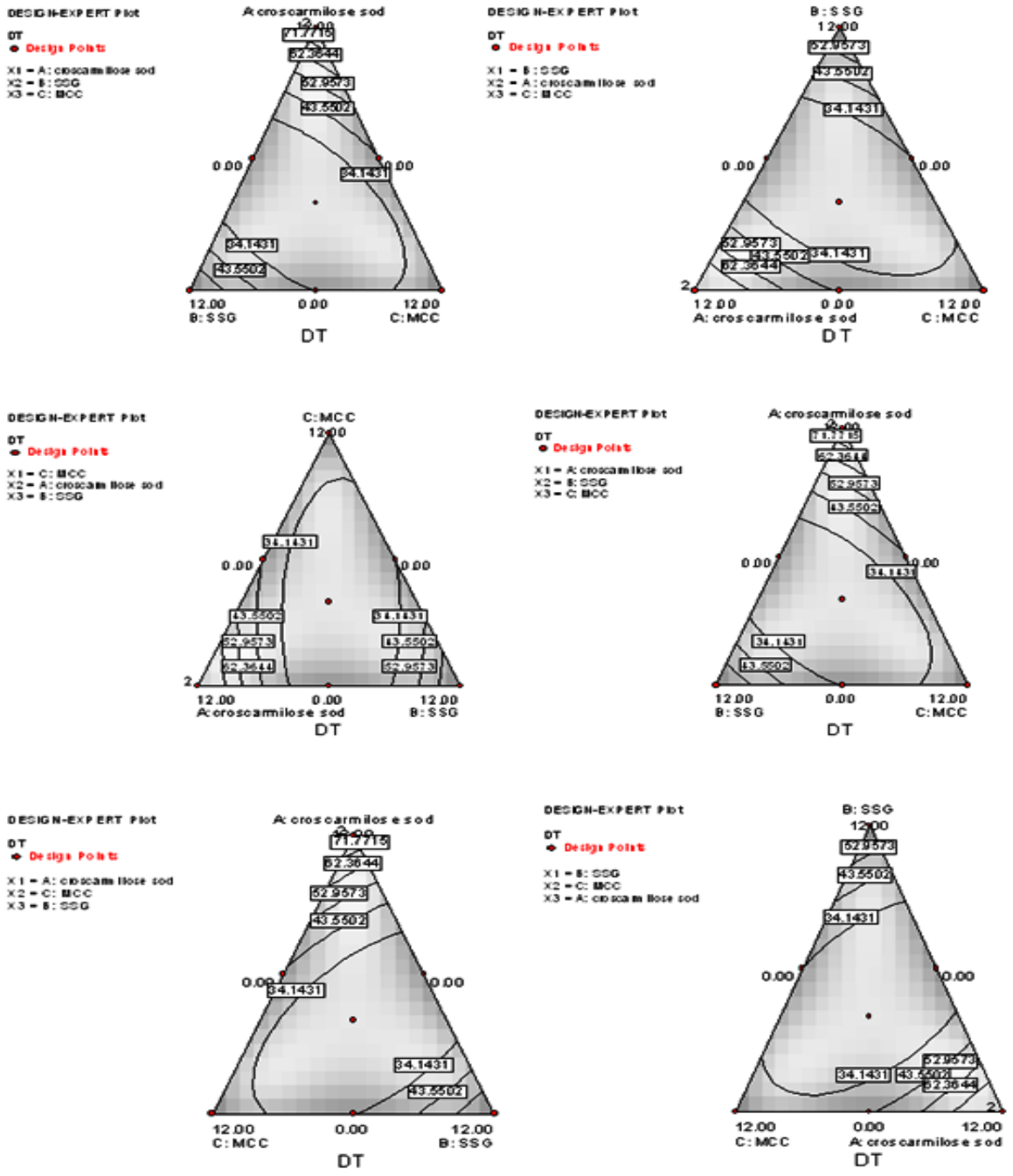
*Statistically significant at $\alpha < 0.05$

TABLE 26: STATISTICAL PARAMETERS OF DISINTEGRATION TIME (CPVP AS BINDER)

Std. Dev.	0.050263	R-Squared	0.999421
Mean	4.170834	Adj R-Squared	0.997972
C.V.	1.205111	Pred R-Squared	0.995973
PRESS	0.035115	Adeq Precision	76.57699

TABLE 27: ESTIMATED REGRESSION COEFFICIENTS OF DISINTEGRATION TIME(CPVP AS BINDER)

Factor	Coefficient Estimate	DF	Std error
A	4.150317	1	0.035474
B	4.1673	1	0.050072
C	3.1673	1	0.050072
AB	-7.9787	1	0.220556
AC	7.35463	1	0.220556
BC	7.320664	1	0.230105



GRAPH 6: DESIGN-EXPERT PLOTS FOR DISINTEGRATION TIME (CPVP AS BINDER)

TABLE 28: ANOVA FOR LINEAR MODEL FOR FRIABILITY (CPVP AS BINDER)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	3690.15	5	738.0301	137.7277	0.0072*
Linear Mixture	1340.783	2	670.3913	125.1053	0.0079*
AB	1747.285	1	1747.285	326.0701	0.0031*
AC	300.6764	1	300.6764	56.11081	0.0174*
BC	301.4063	1	301.4063	56.24702	0.0173*
Residual	10.71724	2	5.358618	-	-
Lack of Fit	5.650324	1	5.650324	1.115142	0.4827
Pure Error	5.066912	1	5.066912	-	-
Cor Total	3700.868	7	-	-	-

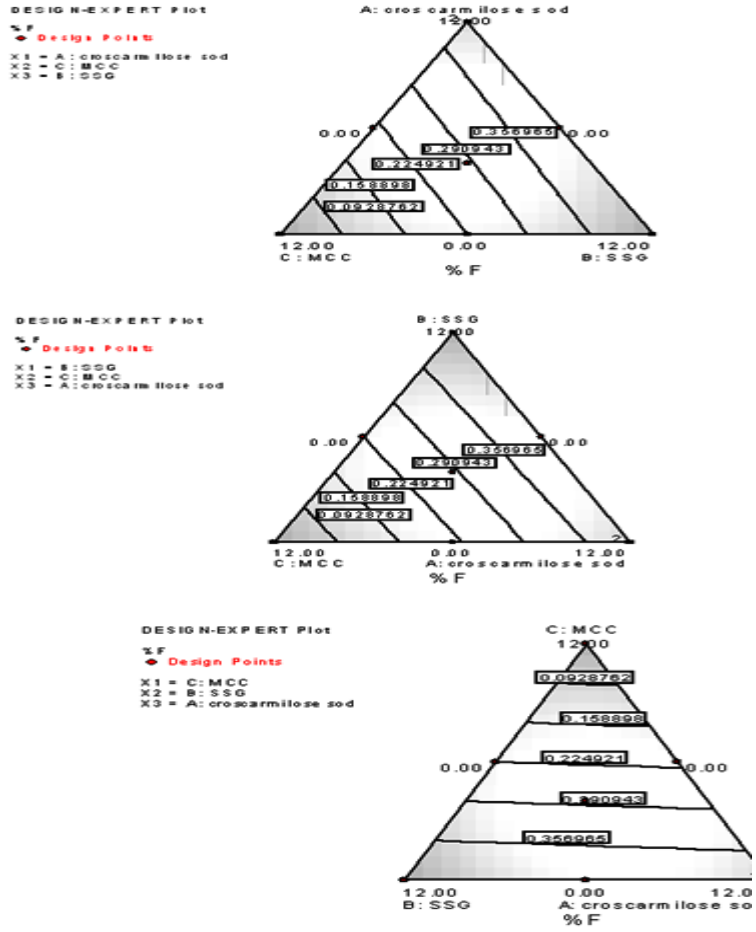
*Statistically significant at $\alpha < 0.05$

TABLE 29: STATISTICAL PARAMETERS FOR DT

Std. Dev.	2.314869	R-Squared	0.997104
Mean	49.85208	Adj R-Squared	0.989864
C.V.	4.643475	Pred R-Squared	0.552882
PRESS	1654.724	Adeq Precision	27.92374

TABLE 30: ESTIMATED REGRESSION COEFFICIENTS FOR FRIABILITY (CPVP AS BINDER)

Factor	Coefficient Estimate	DF	Std error
A	81.17863	1	1.633745
B	65.54062	1	2.30605
C	41.87395	1	2.30605
AB	-183.422	1	10.1577
AC	-76.0884	1	10.1577
BC	-79.4791	1	10.59749



GRAPH 7: DESIGN-EXPERT PLOTS FOR FRIABILITY (CPVP AS BINDER)

TABLE 31: ANOVA FOR MIXTURE QUADRATIC MODEL FOR WETTING TIME (CPVP AS BINDER)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F α
Model	7209.107	5	1441.821	265.2535	0.0038*
Linear Mixture	647.2928	2	323.6464	59.5416	0.0165*
AB	1587.332	1	1587.332	292.0232	0.0034*
AC	3207.357	1	3207.357	590.0611	0.0017*
BC	1767.125	1	1767.125	325.1001	0.0031*
Residual	10.87127	2	5.435635	-	-
Lack of Fit	5.856326	1	5.856326	1.167775	0.4753
Pure Error	5.014945	1	5.014945	-	-
Cor Total	7219.978	7	-	-	-

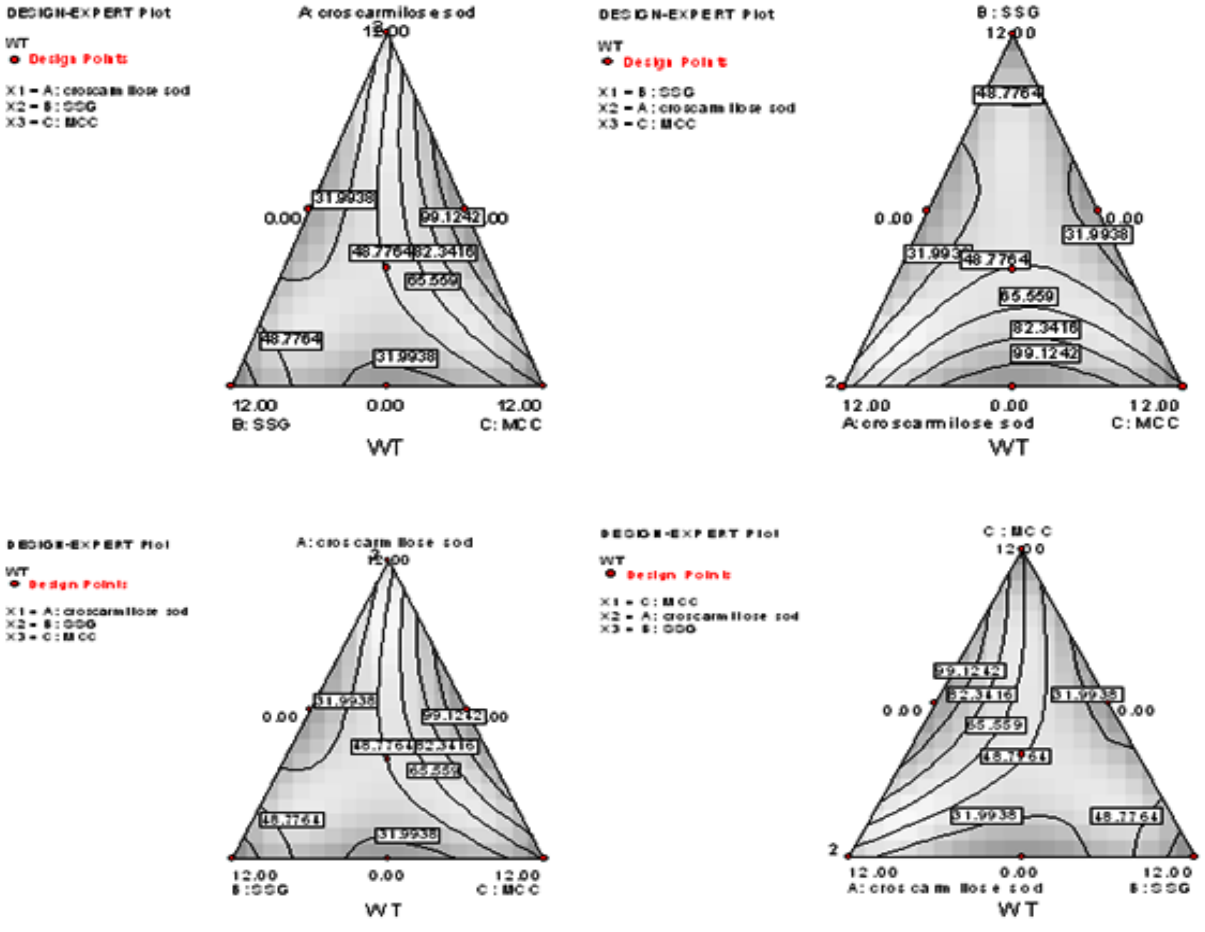
*Statistically significant at α < 0.05

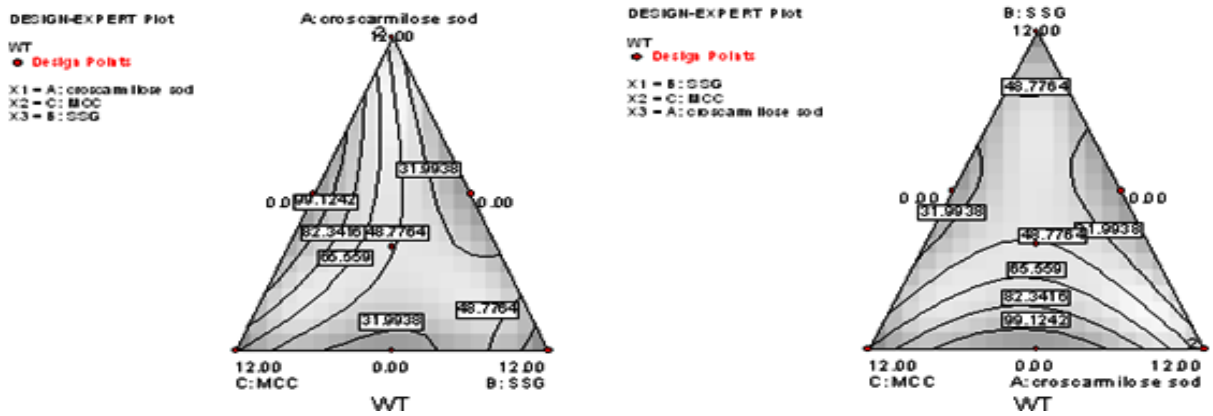
TABLE 32: STATISTICAL PARAMETERS FOR WETTING TIME (CPVP AS BINDER)

Std. Dev.	2.331445	R-Squared	0.998494
Mean	54.85425	Adj R-Squared	0.99473
C.V.	4.250254	Pred R-Squared	0.762588
PRESS	1714.113	Adeq Precision	48.7018

TABLE 33: ESTIMATED REGRESSION COEFFICIENTS FOR WETTING TIME (CPVP AS BINDER)

Factor	Coefficient Estimate	DF	Std error
A	40.97798	1	1.645443
B	81.45597	1	2.322563
C	66.45563	1	2.322563
AB	-174.825	1	10.23044
AC	248.5093	1	10.23044
BC	-192.447	1	10.67338





GRAPH 8: DESIGN-EXPERT PLOTS FOR WETTING TIME (CPVP AS BINDER)

TABLE 35: CONSTRAINED TABLE

Constraints	Goal	Lower Limit	Upper Limit
CCNa	is in range	0	12
SSG	is in range	0	12
MCC	is in range	0	12
Hardness	is in range	3.5	5.5
DT	minimize	23.333	82.666
%F	minimize	0.102	0.516
WT	minimize	16.666	115

By utilizing DESIGN EXPERT 6.05 VERSION, we got one solution as optimized formulation. The coded values for the factors were converted into the actual quantities in milligrams. The formulation code given for optimized formulation was **OF 2 (Optimized-formulation-2).**

TABLE 36: PREDICTED SOLUTIONS FOR TABLETS CONTAINING CPVP AS BINDER

Number	CCNa	SSG	MCC	Hardness	DT	%F	WT	Desirability
1	0.00	3.38	8.62	4.92937	32.4611	0.138357	31.7559	0.868263

Table 37: Optimized formulation (OF2) and ingredients used

Ingredients	OF-2	(mg)
Lactose		50
CPVP		7.5
Aerosil		0.3
Mg stearate		0.75
Aspartame		1.5
MCC		77.95
Crosscarmellose sodium		0.0
Sodium Starch Glycolate		3.38
Microcrystalline cellulose		8.62
Total		150

TABLE 38: COMPARATIVE POST COMPRESSION PARAMETERS OF OPTIMIZED FORMULATIONS (OF1 & OF2)

Formulation	OF1 (Starch as binder)		OF2 (PVP as binder)	
	Predicted	Actual	Predicted	Actual
Hardness(Kg/cm^2)	5.07	4.92 ± 1.25	4.92	4.82 ± 1.32
DT (Sec)	20.48	22.50 ± 4.58	32.46	34.68 ± 2.34
Friability (%)	0.1615	0.19 ± 0.05	0.1383	0.15 ± 0.09
WT (Sec)	20	24 ± 2.5	31.755	34.53 ± 3.4

DISCUSSION: To achieve the objective, the present study was focused in the development of placebo dispersible tablets by wet granulation technique. Instead of normal trial and error approach, a standard statistical design of experiment (DOE), a simplex design was adapted. The formulation variables like, amount of SSG, Cross Carmellose sodium and MCC were included to study their effect on dependent variables such as hardness, % friability, WT and DT. Formulations were prepared randomly following simplex design, the materials used and compositions were presented in **Table 1 and 2**, for starch and CPVP as binders respectively. Wet granulation technique was adapted for making tablets using Starch and CPVP as binding agents. Drug was replaced with lactose to make placebo tablets. Crosscarmellose sodium (CCNa), SSG and Micro Crystalline Cellulose (MCC) were used as super-disintegrants. Aspartame was included as a sweetening agent; Aerosil and Magnesium stearate were used as glidant and lubricating agent respectively.

Effect of formulation variables on Hardness (H) of the tablets with starch as binder: The determined H values were represented in **Table 3** and the design and summary response data was shown in **Table 4**. The design-expert plots of hardness were shown in **Graph 1**. The ANOVA for mixture quadratic model was represented in **Table 5**. The model terms were found to be significant with a probability value of 0.0084 which was shown in Table 5 and a high R^2 value of 0.996649 indicates the adequate fitting of the quadratic model and shown in **Table 6**. In this model, factor A, B, C, and their interaction factors AB, AC, and BC were found to be significantly affecting the hardness of the tablet which are shown in **Table 7**. From the correlation coefficient values it was observed that factor A that is the amount of CCNa was significantly influencing the hardness of the tablet when compared to other factors. Interaction factor between AC exhibited least effect on the hardness of the tablet.

Effect of formulation variables on Disintegration time (DT) of the tablets with starch binder: The determined DT values were represented in Table 3. The model terms for the DT were found to be significant with an F value of 14.22 which was shown in **Table 8** and R^2 value of 0.8505 indicating the adequate fitting of the linear model which was shown in **Table 9**. In this case, only Factor A, B and C were found to be significantly affecting the DT of the tablets. Among the studied variables factor C i.e. when the amount of MCC was increased the DT also found increased, but in case of increased amount of SSG, the DT of the tablet was found decreased. Hence an appropriate amount of combination of super-disintegrants makes the tablet to disintegrate in short time. ANOVA for Mixture Quadratic Model is shown in Table 8. Statistical Parameters and estimated regression coefficients for DT were shown in Table 9 and **Table 10** respectively and the design-expert plots for DT were shown in **Graph 2**.

Effect of formulation variables on Friability (F) of tablets with starch as binder: The determined F values were represented in Table 3. The model terms were found to be significant with a probability value of 0.0030 shown in **Table 11** and a high R^2 value of 0.99812 shown in **Table 12** which indicates the adequate fitting of the quadratic model. In this model, factor A, B, C and its interaction factors AB and AC were found to be significantly affecting the percentage friability of the tablets and are shown in **Table 13**. Linear mixture of the model showed a positive influence whereas the interaction terms showed negative influence and the values are shown in **Table 14**. The statistical parameters were shown in **Table 15**. The design- expert plots for DT were shown in **Graph 3**. From design and summary response data, Table 4, it can be concluded that all the formulations passes the test for friability, since conventional compressed tablets that loose less than 1% of their weight are generally considered acceptable.

Effect of formulation variables on Wetting time (WT) of tablets with starch as binder: The determined WT values were represented in Table 3. ANOVA for Mixture Quadratic Model is shown in Table 14. Statistical Parameters and estimated regression coefficients for wetting time were shown in **Table 15 and 16** respectively. The design-expert plots for WT were shown in **Graph 4**. In this case also, factor A, B, C, and their interaction factors AB, AC, and BC were found to be significantly affecting the percentage WT of the tablets. As the amount of all the 3 super-disintegrants were increased, the wetting time also found increased, but the effects due to factor B were found to be

minimal. The interaction factor between A and C had a dominating negative influence on the WT and found decreased. The constrained table and predicted solutions for tablets containing starch as binder were shown in **Table 17 and 18** respectively. From the discussed results the formula for dispersed tablets by using starch as binder was optimized and the ingredients with quantities of optimized formulation **(OF-1)** were shown in **Table 19**.

Effect of formulation variables on Hardness (H) of tablets with CPVP as binder: The determined H values were represented in **Table 20**. Design and Summary Response Data was represented in **Table 21**. ANOVA for mixture quadratic model was shown in **Table 22**. Statistical Parameters and estimated regression coefficients for Hardness were shown in **Table 23 and 24** respectively. The design-expert plots were shown in **Graph 5**. The model terms were found to be significant with a probability value of 0.0014 which is shown in Table 22, a high R^2 value of 0.9994 indicates the adequate fitting of the quadratic model which is shown in Table 23. In this model from Table 24, the interaction factors AB, AC, and BC were found to be significantly affecting the hardness of the tablet. It may also be incurred that interaction factor due to AB had a negative influence and whereas the same of AC and BC had a positive influence on the hardness of the tablet, suggesting an appropriate amount of all the 3 superdisintegrants yield a tablet with good hardness which can withstand the abrasions during transportation and storage.

Effect of formulation variables on Disintegration time (DT) of tablets with CPVP as binder: The determined DT values were represented in Table 20. ANOVA for Mixture Quadratic Model was shown in **Table 25**. Statistical Parameters and estimated regression coefficients for DT were shown in **Table 26 and 27** respectively. The design-expert plots were shown in **Graph 6**. The model terms for the DT were found to be significant with an F value of 137.72 which is shown in Table 25and R^2 value of 0.9971which is shown in Table 26 indicating the adequate fitting of the quadratic model. In this case, factor A, B, C, and its interaction factors AB, AC, and BC were found to be significantly affecting the DT of the tablets and are represented in Table 27.

Linear mixture showed a positive influence where as its interaction terms showed a negative influence on the DT of the tablet which are shown in **Table 27**. To our surprise as the amount of CCNa was increased the DT of the tablet also increased, which may be due to increased strength of the tablet contributed by CCNa along with CPVP.

Effect of formulation variables on Friability (F) of tablets with CPVP as binder: The determined friability values (F) were represented in Table 20. ANOVA for Mixture Quadratic Model is shown in **Table 28**. Statistical Parameters and estimated regression coefficients for F were shown in **Table 29 and 30** respectively. The design-expert plots were shown in **Graph 7**. The model terms for F were found to be significant indicating the adequate fitting of the linear model.

In this case, only Factor A, B and C were found to be significantly affecting the % friability of the tablets which is shown in Table 30. Among the studied variable factor C, that is as the amount of MCC was increased the % friability was decreased. From the design and summary response data Table 21 it can be concluded that all the formulation passes the test for friability, since conventional compressed tablets that loose less than 1% of their weight are generally considered acceptable.

Effect of formulation variables on Wetting time (WT) of tablets with CPVP as binder: The determined WT values were represented in Table 20. ANOVA for Mixture Quadratic Model is shown in **Table 31**. Statistical Parameters and estimated regression coefficients for Hardness were shown in **Table 32 and 33** respectively. The design-expert plots were shown in **Graph 8**. The constrained table was shown as **Table 34**. Predicted solution for tablets containing CPVP as binder was shown in **Table 35**. The quadratic model was found to be significant. In this case also, factor A, B, C, and its interaction factors AB, AC, and BC were found to be significantly affecting the percentage friability of the tablets.

As the amount of all the 3 super-disintegrants were increased, the WT time also increased, but the effects due to factor A were found to be minimal. The interaction factor between A and C had a dominating positive influence on WT as it was found increased.

A numerical optimization technique by the desirability approach was used to generate the optimum setting for the formulation OF-2 with CPVP as binder. The ingredients with quantities of optimized formulation were mentioned in **Table 36** and the formulations were evaluated for the various responses and the predicted values were compared with actual values and shown in **Table 37**. The comparative post compression parameters of Optimized Formulations (OF1 & OF2) are represented in Table 38.

CONCLUSION: In the present work, an attempt was made to develop dispersible tablets using various super disintegrants. To get a desired product, optimization techniques were adopted. Designs of formulation were run by simplex design by taking Crosscarmellose sodium, Sodium starch glycolate and MCC as independent variables and hardness, percentage friability, DT and WT as dependent variables by applying the computer optimization technique.

The results revealed that, SSG may not be a suitable super-disintegrant if starch was used as binding agent and whereas Crosscarmellose sodium may not be suitable in case of CPVP as binding agent, observed responses were in close accord with the predicted values of the optimized formulations, and consequently demonstrate the feasibility of the optimization procedure in the development of dispersible tablets.

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How to cite this article:
Ugandar RE, Nilugal KC, Srinivasan N. and Molugulu N.: A study on feasibility of optimization technique in formulation of dispersible Tablets by Factorial design. *Int J Pharm Sci Res* 2014; 5(4): 1208-27.doi: 10.13040/IJPSR.0975-8232.5(4).1208-27