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Research Article

Optimization of Cyclodextrin Loaded Lornoxicam Fast Dissolving Tablets Using Box-Behnken Design

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Abstract: The present investigation was undertaken in the design and evaluation of fast dissolving tablets of the Non-Steroidal anti-inflammatory drug Lornoxicam. Lornoxicam is an orally bio available oxicam derivative with anti inflammatory, antipyretic and analgesic properties upon oral administration. The main aim of this study is to prepare mouth dissolving tablets of hydroxyl propyl ß cyclodextrin loaded lornoxicam by Box-Behnken design. The main objective is to enhance the solubility, palatability of Lornoxicam by using cyclodextrin as a complexing agent and optimize the formulation by using Box-Behnken design.The inclusion complexes of Lornoxicam were prepared by physical mixture and solvent evaporation method by using drug and HP ß cyclodextrin in various ratios (1:1 and 1:2). Dissolution study was carried out for the 2 ratios of kneading method and solvent evaporation method. 1:1 ratio of solvent evaporation method was selected for the optimization by Box-Behnken design. The selected inclusion complexes were then utilized for the preparation of tablets by direct compression. The independent variables are lactose, sodium starch glycolate and crospovidone. The dependent factors studied were wetting time, in vitro disintegration, in vivo disintegration and in vitro dissolution. Optimized Formulae were prepared and evaluated for in vitro dissolution characteristics, in vitro disintegration time, wetting time, and their physico-mechanical properties. The predicted formula formulated with the Box-Behnken statistical design consisted of lactose, sodium starchglycolate and crospovidone at the optimum levels of 30, 20 and 20 mg respectively which is considered as the best optimized formulation with good dissolution profile. The bioavailability has been increased from the optimized formulation. The formulation was evaluated for stability.From the research a taste masked mouth dissolving tablet formulation is selected to increase patient compliance with enhanced solubility, dissolution and stability.

Keywords: Lornoxicam, HPβ Cyclodextrin, Box- Behnken factorial design, Dependent variables, Independent variables.

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1. INTRODUCTION

The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. USFDA has defined FDTs tablets as "A solid dosage form containing medical substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue".1Fast dissolving tablets promotes Rapid drug therapy intervention and First pass metabolism is reduced hence improving the bioavailability. Lornoxicam, an orally bioavailable oxicam derivative, is a nonsteroidal anti-inflammatory derivative (NSAID) with analgesic, anti-inflammatory, antipyretic properties 2Lornoxicam's anti-inflammatory and analgesic activity is related to its inhibitory action on prostaglandin and thromboxane synthesis through the inhibition of both COX-1 and COX-2 upon oral administration. It is used for the treatment of various types of pain, especially resulting from inflammatory diseases of the joints, Pain and swelling of joints, surgery, sciatica, and other inflammations. It is used in muscular skeletal and joint disorders such as osteoarthritis and rheumatoid arthritis severe joint disease. Lornoxicam is used in the treatment of ankylosing spondylitis. Lornoxicam differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains particularly the pronounced efficacy of the drug. It ismetabolized by cytochrome 2C9, 5'-hydroxy-lornoxicam and eliminated through liver and kidney with a half life of 3-5hrs. The bioavailability of lornoxicam drug is 90–100% (absorbed from GI Tract)2. A computer-aided optimization design -Box - Behnken factorial design predicts the levels of independent variables (lactose, sodium starch glycolate, crospovidone) those affect the dependent variables (wetting time, in vitro disintegration, in vivo disintegration and in vitro dissolution). The test (experimental) design, in general, is used to simultaneously study the effects of multiple independent variables (factors) on response variability; therefore, it is a multivariate analysis method. A large number of objects can be learned by performing a small number of tests in a simple test design where the important object can be easily identified using a full factorial design.3 The Box-Behnken design is a rotatable second-order design based on a three-level incomplete factorial design. Box–Behnken designs of experiments provide modeling of the response surface. Design points are positioned at the middle of the subareas of the dimension k-1. In the case of three factors, for instance, the points are located in the middle of the edges of the experimental domain. Goals of Box- Behnken design:

☐ The design can be sufficient to fit a quadratic model, which includes square effects and interaction effects between factors.
☐ Each factor, or independent variable, is placed at one of three equally spaced values. For conducting experiments at least three levels are required.
☐ The ratio of the number of experimental points to the number of coefficients in the quadratic model should be reasonable..

Multivariate analysis with a small number of experiments can be easily done with Box-Behnken design (BBD) face response surface methodology (RSM) and D-optimal design. The model-equation is produced by BBD to understand the relationship between variable (independent) and quality (dependent) responses. BBD is an independent quadratic design in which the treatment combination is centered at the edges of the process area and in the center. BBD designs are rotatable (or close to rotating) and require three levels of each factor The present study includes the preparation of Lornoxicam fast dissolving tablets by complexing with beta cyclodextrins to enhance solubility and bioavailabilitywith optimization based evaluation by direct compression method.4,5.

2. MATERIALS AND METHODS

2.1. Materials

Lornoxicam,Hydroxypropylβ beta cyclodextrin (HPβCD), Lactose, Sodium Starch Glycolate (SSG),Crospovidone,Microcrystalline cellulose (MCC), Magnesium stearate, talc,Aerosol6and rotary compression machine.

2.2. Preparation and formulation of Lornoxicamcyclodextrin Complex

The required quantities of the drug and HPβ-Cyclodextrin were weighed accurately in a molar ratio of 1:1,1:27-10 A homogenous paste of cyclodextrin was prepared in a mortar by adding water: methanol mixture (3:2) in small quantities, then the drug was added with continuous kneading it was triturated for 1 hour, an appropriate quantity of water: methanol (3:2).11-13 mixture was added further to maintain the consistency of the paste. 14 Then the paste was dried in a hot air oven at 55℃ for 24 hours. Then the dried complexes were then pulverized and passed through sieve no 120 and then stored.15 According to the batch size all the ingredients are weighed, mixed and compressed by direct compression method on a rotary compression machine using 7mm flat round punch constant for all tablets. Compression force must be kept constant in all the formulations.

2.3. Construction of Calibration Curve for Lornoxicam

2.3.1. *Preparation of stock and working standard solution*

Accurately weighed quantity of 100 mg of Lornoxicam was taken into a 100 mL volumetric flask. It was dissolved in 100 mL of 50:50 ratios of pH 6.5 phosphate buffer and methanol solution to get a strength of 1000 µg/mL. Working standard solution (100 µg/mL) was prepared by diluting 10 mL of stock solution to 100 mL with 50:50 ratios of pH 6.5 phosphate buffer and methanol solution. 16

2.3.1. Estimation of Lornoxicamin pharmaceutical dosage form

To measure the Lornoxicam content of a marketed tablet (label claim 8mg of Lornoxicam per tablet) 20 tablets were taken and crushed in mortar and pestle to obtain fine powder. Weight of the powder equivalentto 8mg of Lornoxicam was transferred to a 100 mL volumetric flask containing 50mL of methanol and phosphate buffer (1000 µg/mL), the mixture was sonicated for 15minutes. The solution was filtered and 1mL of the filtered solution was diluted tenfold to obtain a concentration of 100µg/mL stock solution. The assay was performed by finding out the absorbance value of the sample solution and the percentage assay was calculated with reference to the standard solution.17

$$\%\text{Assay}= \frac{\text{Sample absorbance}}{\text{standard absorbance}} \times \frac{\text{Standard concentration}}{\text{test concentration}} \times 100$$

The linearity was determined by analyzing six independent levels of calibration curve in the range of 0-60µg/mL. Absorbance of each solution against blank was recorded, a curve of absorbance vs. concentration was plotted and correlation coefficient and regression line equation for Lornoxicam were determined.

2.3.4. Construction of calibration curve for Lornoxicam

The calibration curve for Lornoxicam was constructed in the 1:1 ratio of methanol and phosphate buffer pH 6.5 solution.

2.3.5. Preparation of stock solution

Lornoxicam (50mg) was weighed accurately and dissolved in 50 mL of 1:1 ratio of methanol and phosphate buffer solution to get a concentration of 1mg/mL in the volumetric flask.[18]

2.3.6. Preparation of phosphate buffer solution pH 6.5±0.05

Phosphate buffer solution was prepared by mixing 17.8 grams of sodium dihydrogen orthophosphate dissolved in 250 mL of distilled water and volume is made up to 500 mL distilled water in volumetric flask.[19] Freshly prepared 0.2 M NaOH (58 mL) is added to it and the volume made up 500 mL with distilled water. The pH of the buffer was adjusted to 6.5 using the pH meter.

2.3.7. Preparation of working standard solutions

From the stock solution, 1, 2, 3, 4, 5 and 6 mL of the solutions were taken from 100 mL volumetric flasks and were made up to the volume using water, to get solutions of 10, 20, 30, 40, 50 and 60µg/mL concentrations respectively. The absorbance of the above dilutions was determined, at 339nm, using UV spectrophotometer Phosphate buffer solution of pH 6.5±0.05 and methanol (50:50) solution as the blank. [20,21,22]. Data for the standard lornoxicam plot was tabulated in table-1. Calibration plot for lornoxicam was shown in figure -1. A calibration curve (Figure 2) was constructed by plotting the absorbance against the concentration; [23] of Lornoxicam. A regression equation was derived from the plot, which was used for the estimation of Lornoxicam in Phosphate buffer solution of pH 6.5±0.05. The method obeyed Beer's law in the concentration range of 10-60µg/mL and the value was found to be 0.998 indicating a positive correlation; 24 between the concentration of Lornoxicam and the corresponding absorbance values. The regression line describing the relation between concentration and absorbance was as follows.[25]

$$Y = 0.0166X-0.0228$$

Where, Y is the absorbance at 339 nm and X is the concentration of Lornoxicam in µg/mL.

Table 1: Data for standard Lornoxicam plot

Concentration (µg/mL)	Absorbance
0	0.000±0.00
10	0.154±0.21
20	0.287±0.45
30	0.454±0.25
40	0.609±0.45
50	0.820±0.31
60	0.995±0.31

(All the values are expressed as mean ± SD, n=3)

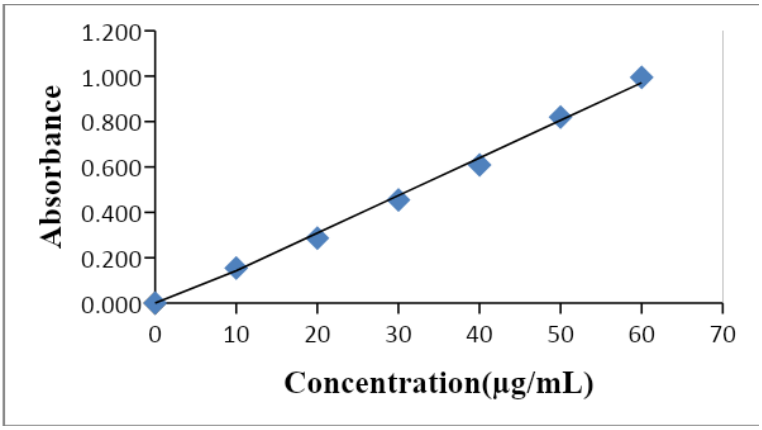


Fig 1: Calibration plot for Lornoxicam

3. RESULTS AND DISCUSSION

3.1 Drug - excipients compatibility study

3.1.1. FTIR Spectroscopy

Fourier transform infrared spectroscopy (FTIR) is a simple technique for the detection of changes within excipients – drug mixture. Disappearance of an absorption peak or reduction of the peak intensity combined with the appearance of new peaks gives clear evidence of interactions between the drug and the excipients. The sample (pure or drug plus excipients) was ground gently with anhydrous KBr and was compressed to form a pellet. This pellet was taken up for FTIR spectroscopy. The scanning range was 400 cm-1 to 4000 cm-1 and the results were shown in Figure 2-4.

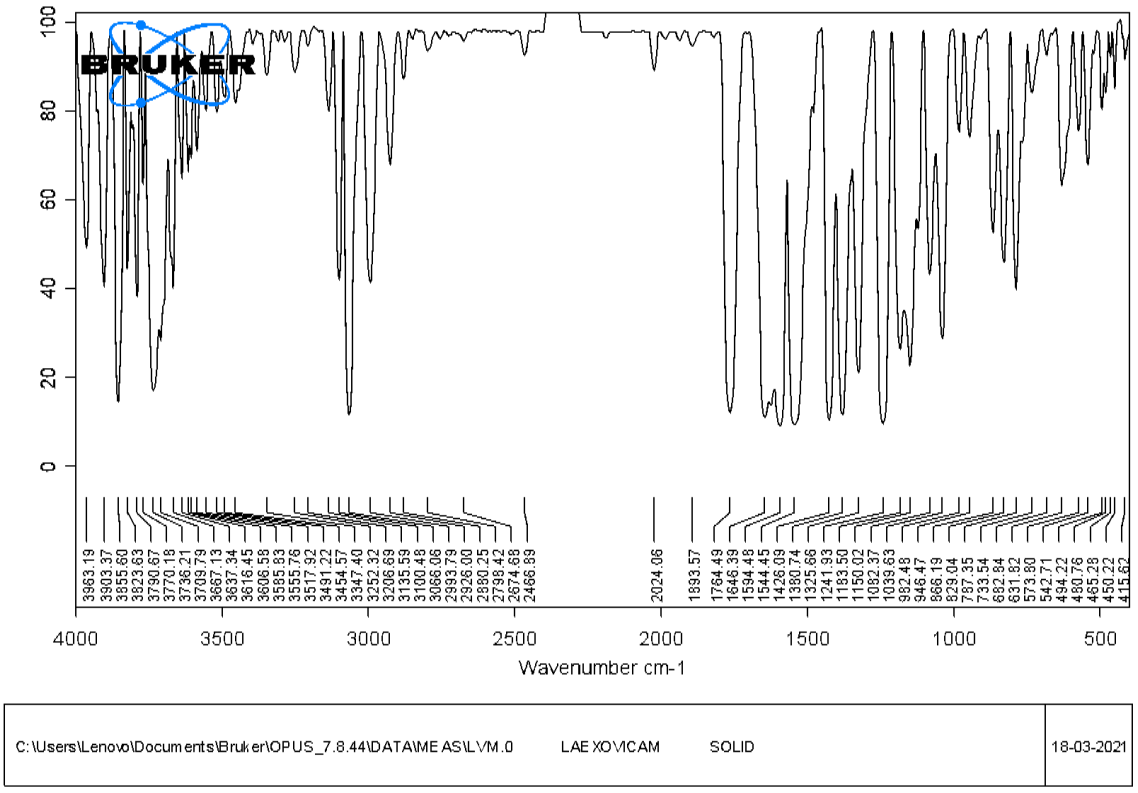


Fig 2: FTIR – lornoxicam pure drug

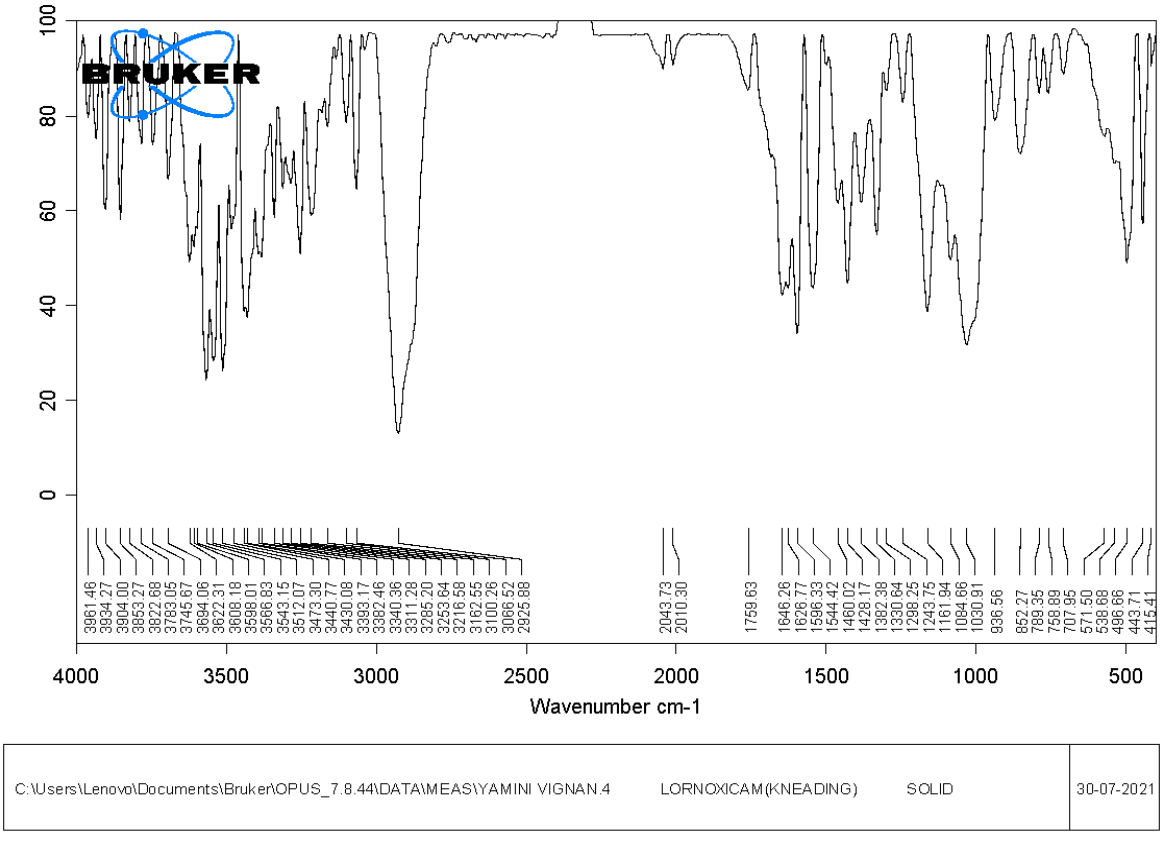


Fig 3: FTIR – lornoxicam kneading method

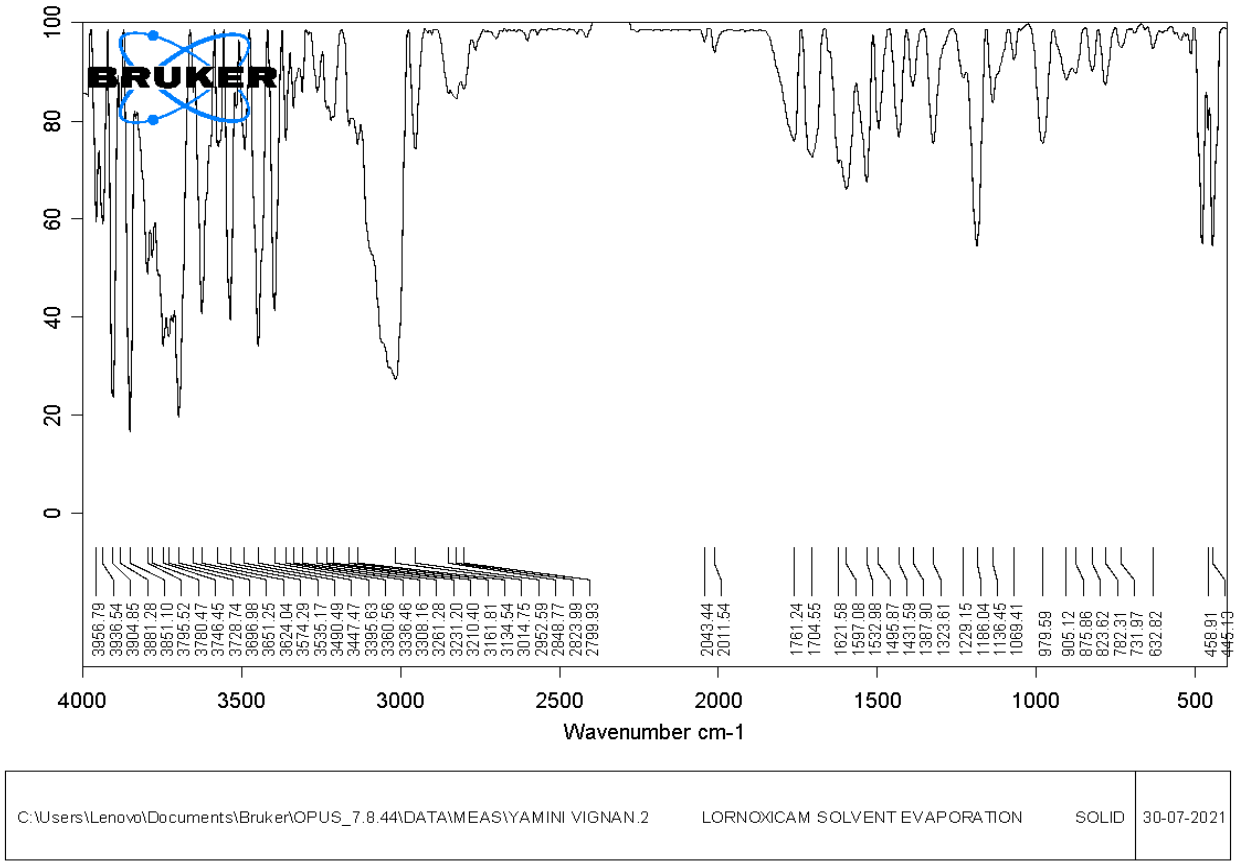


Fig 4: FTIR- Lornoxicam solvent evaporation method

3.2. DSC (differential scanning calorimetry)

Differential scanning calorimetry (DSC) is one of the well-developed techniques used in detection of incompatibilities in drug/ drug and drug/excipient interactions. Both the sample and reference are maintained at nearly the same temperature throughout the experiment.The temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned. Differential scanning calorimetry can be used to measure a number of characteristic properties of a sample. Sample 5.1 mg was weighed in aluminium pans and hermetically sealed using a crimping device. An empty aluminium pan was used as a reference standard on the other side. Generally nitrogen was used as a purge gas during the analysis at a flow rate of 100ml/min. Samples were held 30˚C and 350˚C For 10 min then heated 10˚C/min. DSC thermo gram of Lornoxicam pure drug showed a characteristic endothermic peak at 165.85˚C and the results were shown in figure 5. DSC thermo gram of Lornoxicam (solvent evaporation method) showed a characteristic endothermic peak at 166.4˚C and the results were shown in Figure 6. Hence there is no such difference between the endothermic peaks of pure drug and solventevaporation method.

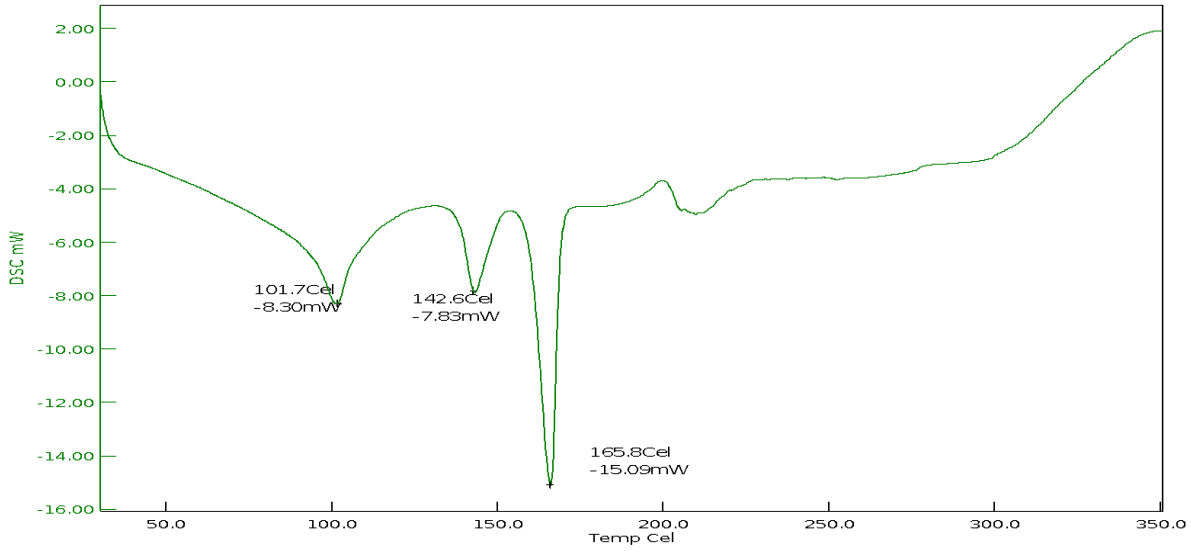


Fig 5: DSC- lornoxicam pure drug

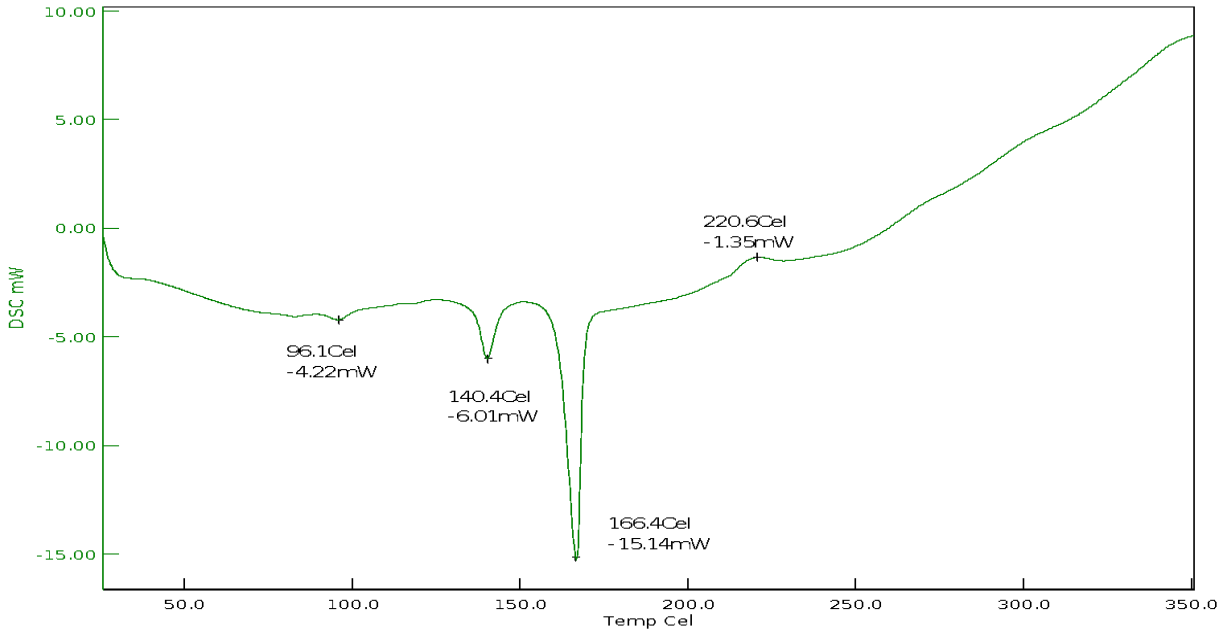


Fig 6: DSC- lornoxicam solvent evaporation method

3.3. Experimental design

Box-Behnken experimental design is used to optimize the formulation of cyclodextrin loaded fast dissolving tablets of Lornoxicam by physical mixture method and solvent evaporation method. The prepared tablets were evaluated for all the evaluation parameters.[26]Box-Behnken design produced various formulations containing specified amounts of the independent variables (Lactose, SSG, Crospovidone) and the dependent factors studied were wetting time, in vitro disintegration, *invivo* disintegration and in *vitro* dissolution. Hence the better formulation of the cyclodextrin loaded lornoxicam fast dissolving tablets were with optimization-based evaluation thereby the promising tablets showed greatest drug dissolution satisfactory wetting time, *in vitro disintegration* time, *in vitro* disintegration time and *in vivo* dissolution time and physico-mechanical properties that are suitable for fast dissolving tablets.[27]Box-Behnken design includes three factors and three levels.

$$Y==bo+b1X1+b2X2+b3X3+b12X1X2+b13X1X3+b23X2X3+b11X12+b22X22+b33X32$$

y = measured response associated with each factor level combination b0 = intercept, b1– b33 = regression coefficients. X1,X2,X3 = factors studied, XiXi Xi2 (i=1, 2 or 3) represent interaction and quadratic terms The goodness of fit of the model was determined using determination coefficient (R2) with amount of variability in the observed response values based on the experimental factors and interactions. The value exists between 0-1. R2 value which lies close to 1 implies better response with a good stronger model. The number of terms in the model and sample size are determined by the adjusted determination coefficient value and various response surfaces were constructed to present the effect of formulation variables on drug release.[28]According to the suggested experimental design, 17 formulations (including 3 center points) tabulated in table 2 were prepared experimentally in triplicate. The obtained data were fitted to the appropriate models (linear, 2-FI and quadratic) and analyzed by the one-way analysis of variance (ANOVA) and the results were shown in table 4. The models were explained by polynomial equations and their related three-dimensional (3D) response surface plots were created by design-expert® software. The interacting and quadratic effects of independent variables selected are AB, AC, BC, A^2, B^2 and C^2 respectively. one-way analysis of variance (ANOVA) was performed on the suggested model for the responses Y1, Y2, Y3,Y4 to identify significant effect.

Table 2: Ranges and constraints of independent and dependent variables

Independent variables	Symbols	Levels lowest	Central	Highest
Lactose	A	1	2	3
SSG	B	1	2	3
Crospovidone	C	1	2	3
	Y1	Minimize		
	Y2	Minimize		
	Y3	Minimize		
	Y4	Minimize		

Table 3: Modeling of the response in the experimental design

		Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3	Response 4
Std	Run	A:lactose	B:SSG	C:crospovidone	wetting time	in vitro disintegration time	*invivo* disintegration time	In vitro dissolution
		Mg	Mg	Mg	Sec	Sec	Sec	%
2	1	50	6	13	13.5	28.9	33.5	96.9
15	2	30	13	13	13.5	19.5	40.6	93.7
12	3	30	20	20	9.5	15	28	99.6
9	4	30	6	6	26.5	30	46.5	89.9
1	5	10	6	13	15.2	28.9	41.2	93.7
16	6	30	13	13	12.9	19.6	39.2	94.2
5	7	10	13	6	26.4	24.6	46.9	90.5
14	8	30	13	13	14.6	19.3	38.2	94.8
11	9	30	6	20	8.5	26.5	29.5	98.7
13	10	30	13	13	12.6	19.4	37.4	94.6
4	11	50	20	13	12.6	10	32.5	96.4
6	12	50	13	6	25.3	25.3	45.3	91.2
7	13	10	13	20	9.5	12	28.5	98.4
17	14	30	13	13	14.6	19.6	36.5	95.4
3	15	10	20	13	14.9	10	39.6	93.5
10	16	30	20	6	24.3	17.5	44.5	90.6
8	17	50	13	20	8	12.5	30	98.6

Y1=wetting time, Y2=in vitro disintegration time, Y3=in vivo disintegration time, Y4=in vitro dissolution

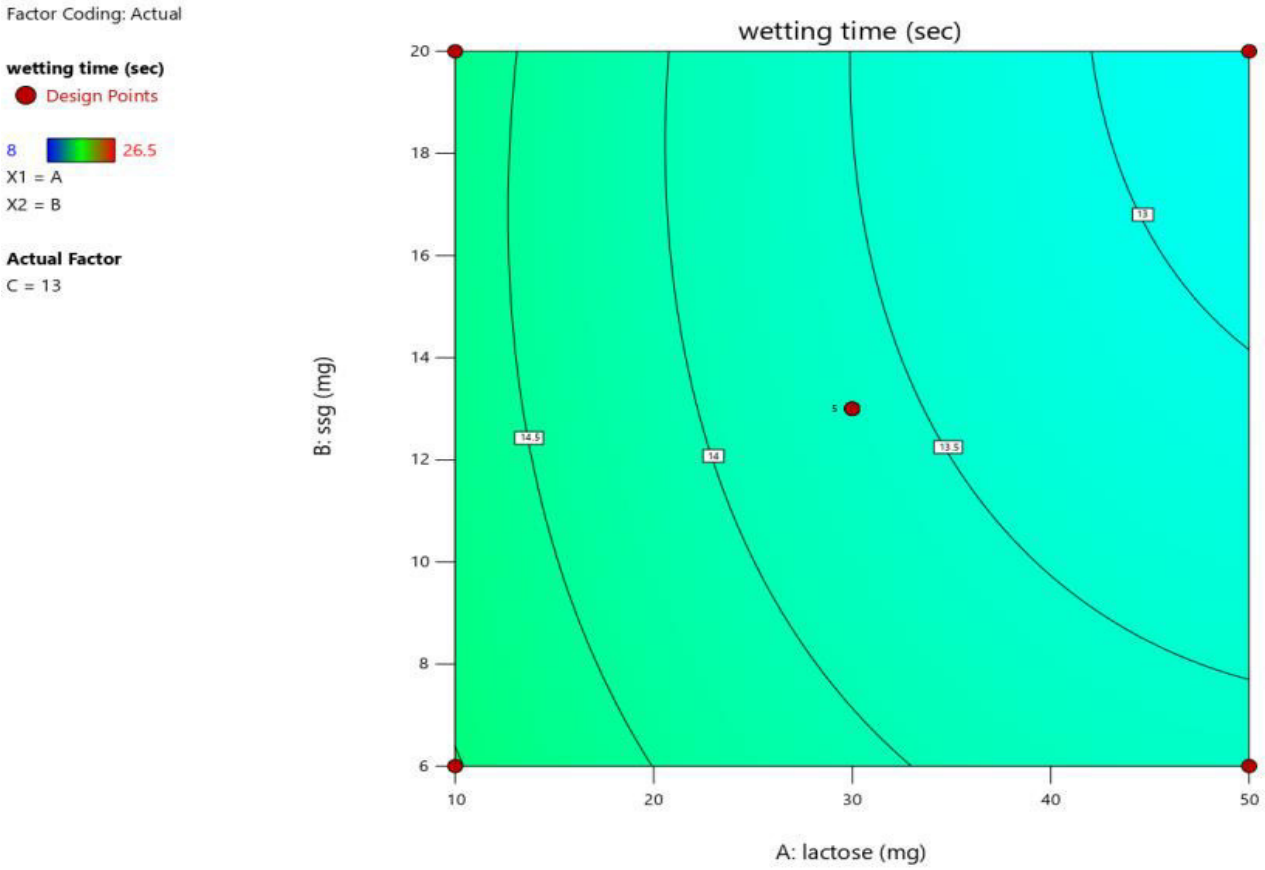
Table 4: box behnken design: model characteristics

Dependent variables	P value	Best fitted model	Lack of fit	Adequate precision	Predicted R2	Adjusted R2	R2
Y1	0.0002	Quadratic	In significant (p>0.05)	32.2837	0.9854	0.9787	0.9936
Y2	< 0.0001	Linear	Significant	17.1572	0.8215	0.6979	0.8550
Y3	< 0.0001	Linear	In significant (p>0.05)	19.235	0.9103	0.8681	0.9271
Y4	< 0.0001	Linear	Insignificant(p>0.05)	26.347	0.9398	0.9094	0.9545

In the present study, ANOVA was applied at 95 % confidence level to evaluate the model significance. The model p-values observed for Y1, Y2, Y3 and Y4 responses were 0.0002,<0.0001,<0.0001 and <0.0001. The independent variables manifested significant effects on the tested responses away from experimental errors or chances.[29,30,31,32,33]The efficiency of the model was inspected using lack of fit values based on their p-values where non-significant values of lack of fit were good and fitted the satisfactory model. Effect of the independent variables on wetting time(Y1), *in vitro* disintegration time(Y2), *in vivo* disintegration time(Y3), *in vitro* dissolution(Y4).[34,35,36,37] The results were mentioned in Table 3 and the various effects of independent variables on wetting time, *in vitro* disintegration time, *invivo* disintegration and *in vitro* dissolution along with linear correlation between predicted and actual response, 3D response surface graphs were shown in the Figure 7-13.The matrix of seventeen experimental formulations was constructed. Standard error graph was satisfactory to obtain relatively minimum values of standard error close to 1or lower across the area of interest. The box-behnken design model characteristics were shown in table-4. The models generated were used to construct response surface (3D) plots for Y1, Y2, Y3 and Y4 responses of formulations to understand the main and interaction effects of the 3 factors. The 2D Plots and the 3D plots explained the influence of various independent variables on the dependent variables.Response surface plots were also generated to establish the effect on response factors. The effect of independent variables on the dependent variables were shown in figure 7-13 (wetting time, *in vitro* disintegration time, *in vivo* disintegration time and *in vitro* dissolution time, all the responses were obtained from the dependent variables used as shown in the figure 7-13).

3.4 In vitro dissolution study

From the dissolution profile of all the formulations, it was found that the cumulative percentage drug release increased with increase in concentration of Sodium Starch Glycolate, crospovidone and lactose in varying ratios. 1:2 Ratio of physical trituration method 1:1 Ratio of solvent evaporation method showed the best drug release profile.[38]


Factor Coding: Actual
wetting time (sec)
Design Points
8
26.5
X1 = A
X2 = B
Actual Factor
C = 13
wetting time (sec)
B: ssg (mg)
A: lactose (mg)
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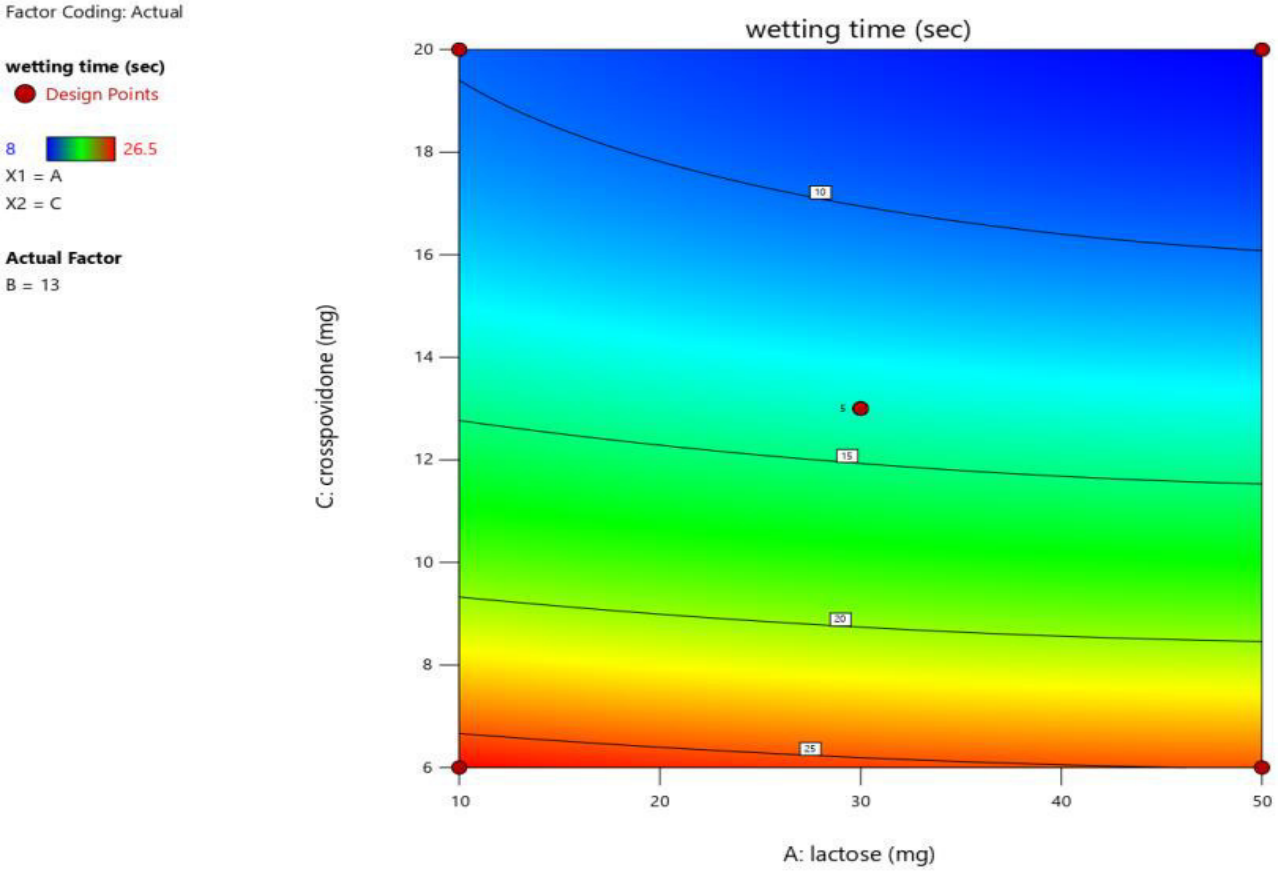
Factor Coding: Actual
wetting time (sec)
Design Points
8
26.5
X1 = A
X2 = C
Actual Factor
B = 13
wetting time (sec)
C: crosspovidone (mg)
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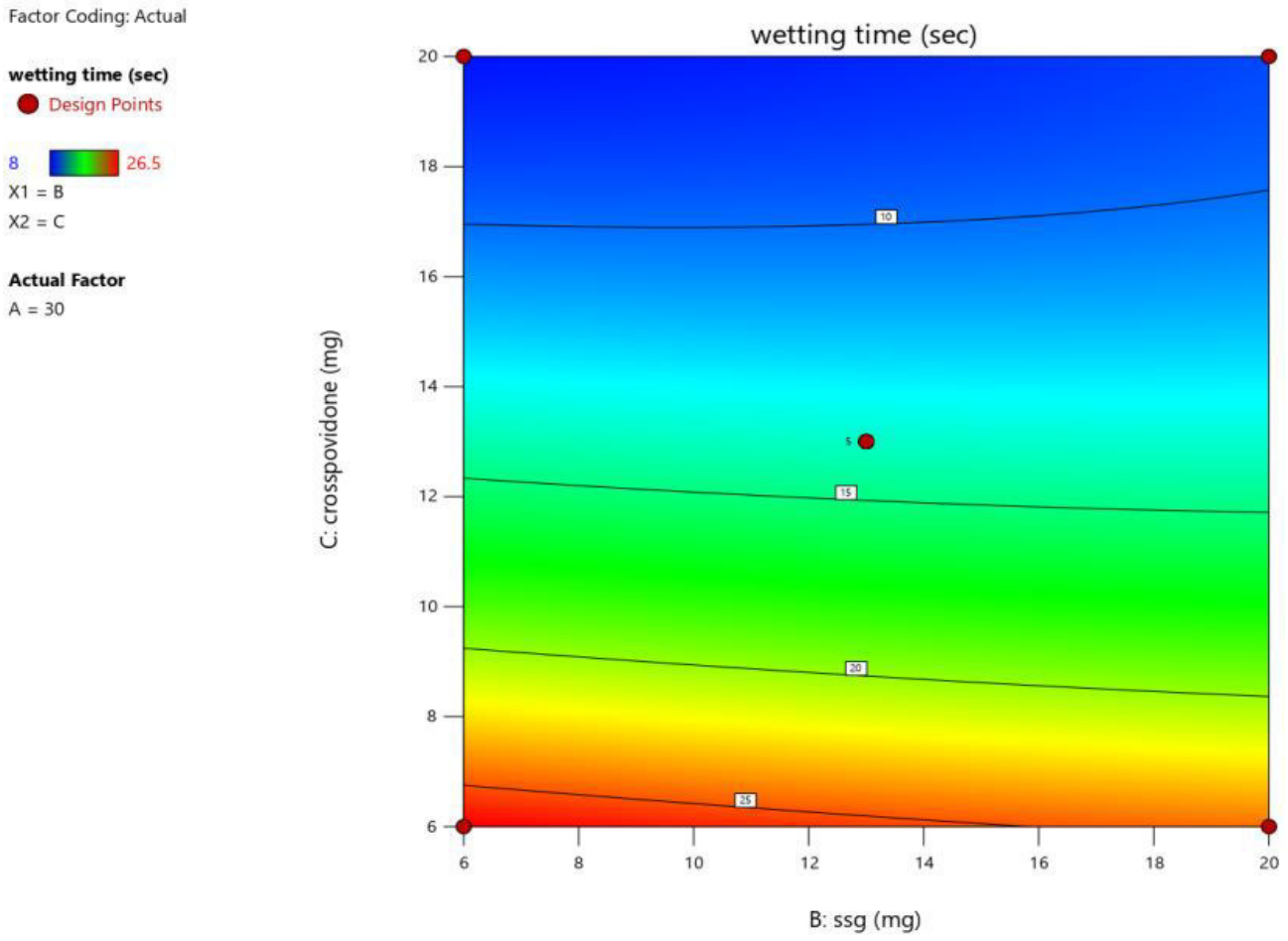


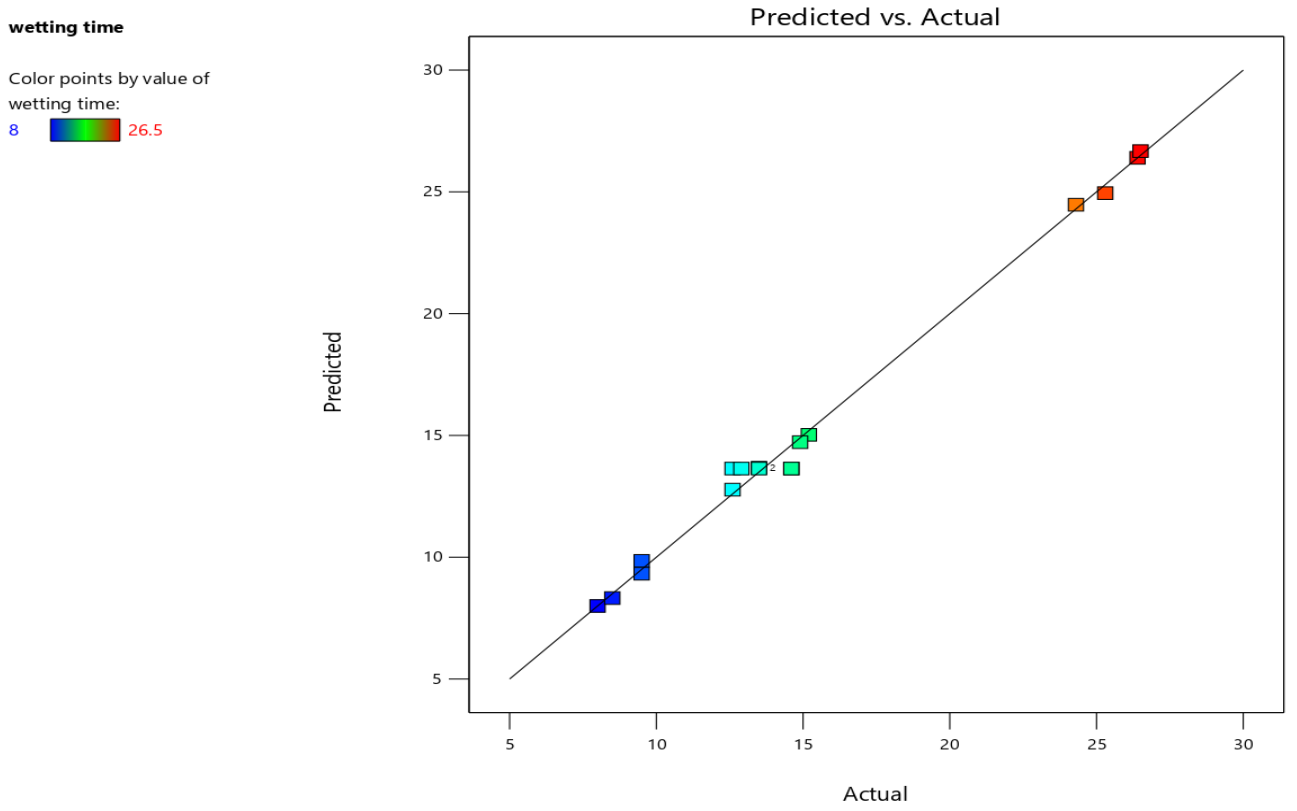
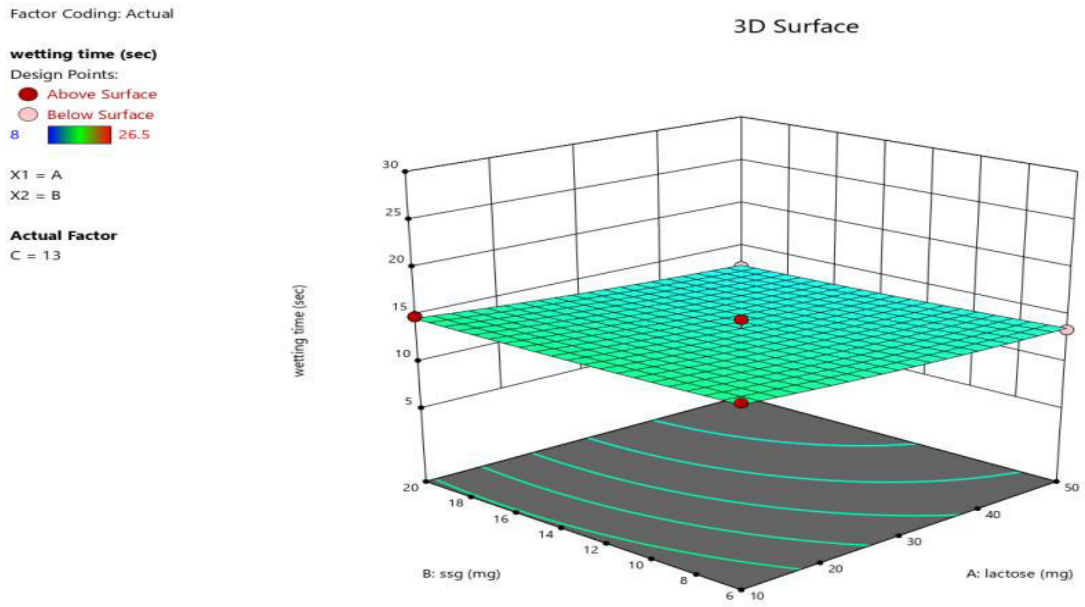
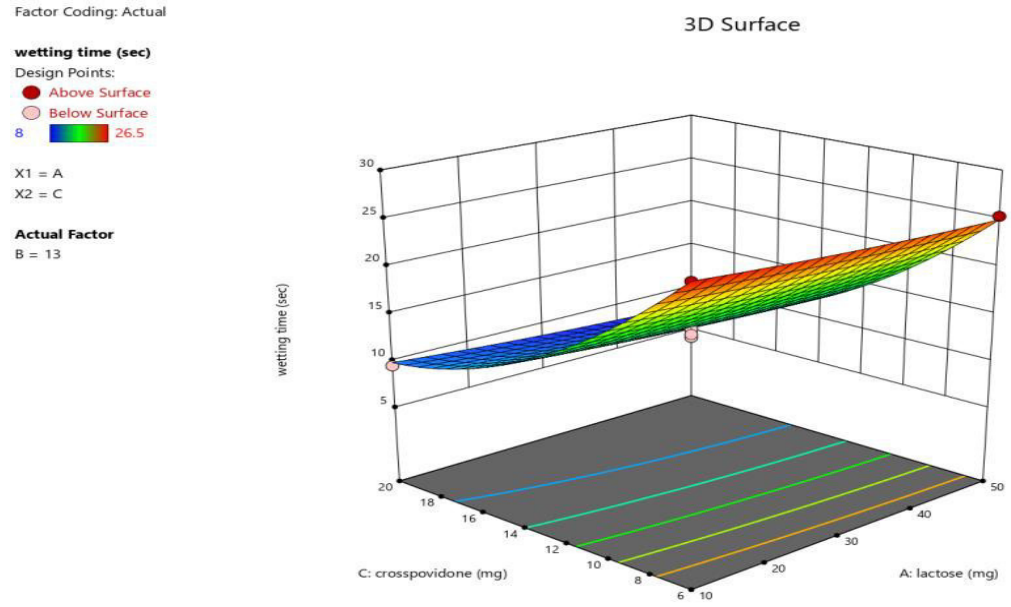


Fig 7: Effect of independent variables on wetting time of fast dissolving tablets





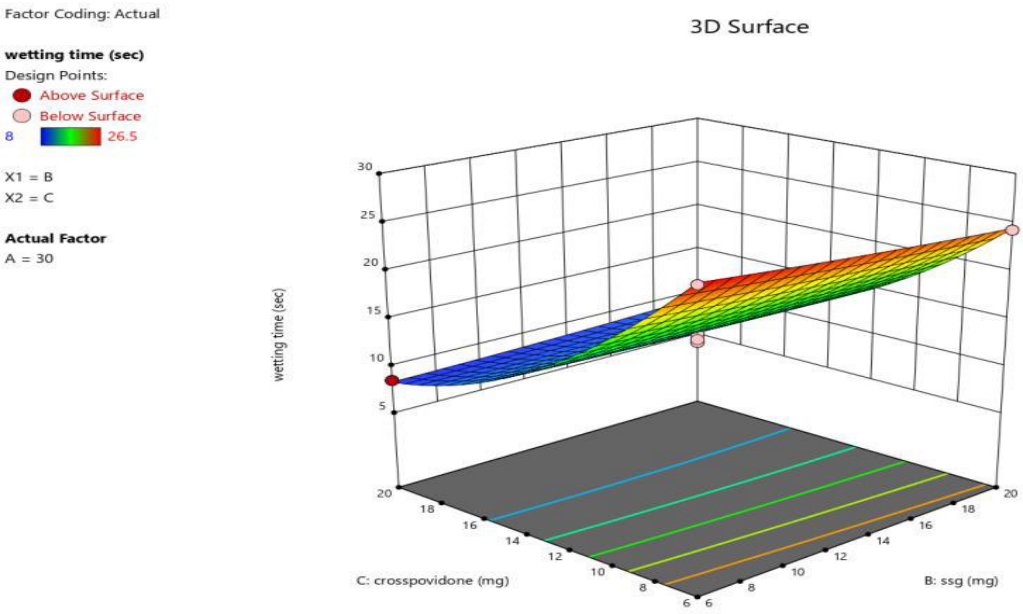


Fig 8: 3D response surface graphs of influence of AB, AC, BC on wetting time (Y1)

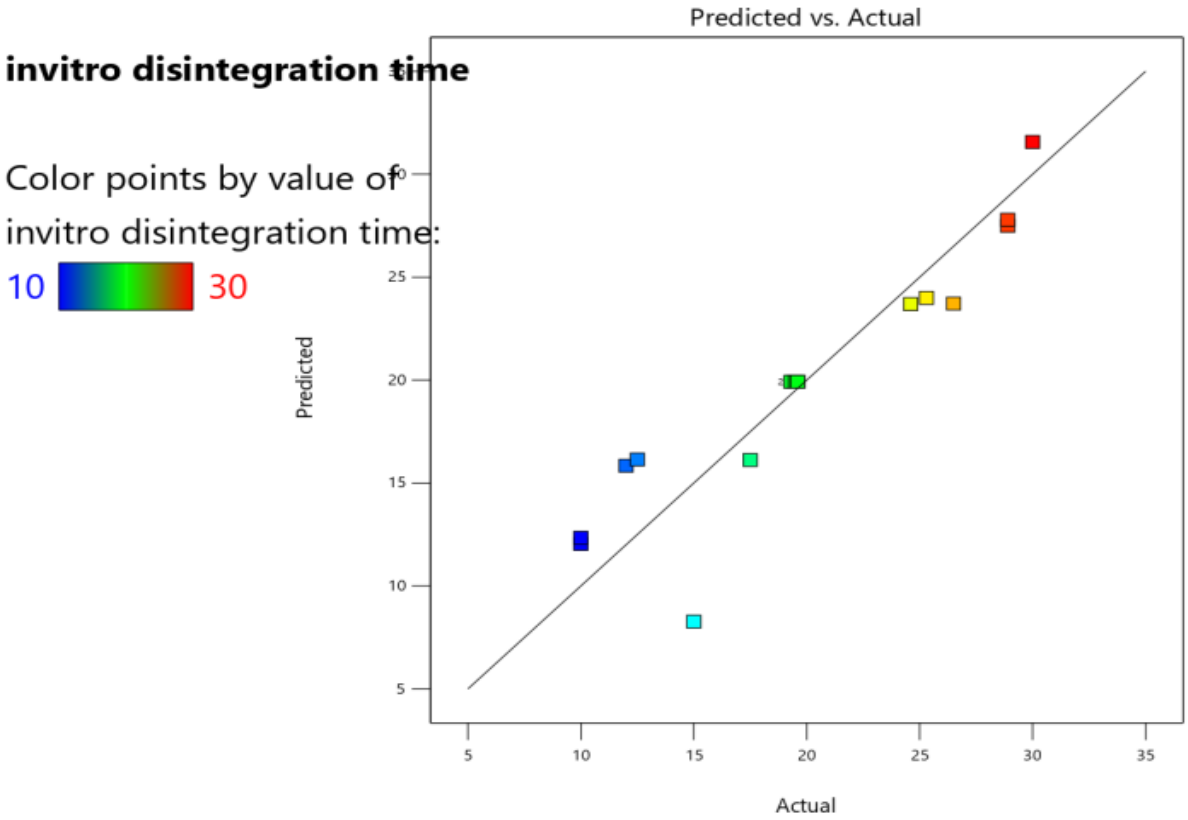


Fig 9: Effect of independent variables on *in vitro* disintegration time of fast dissolving tablets

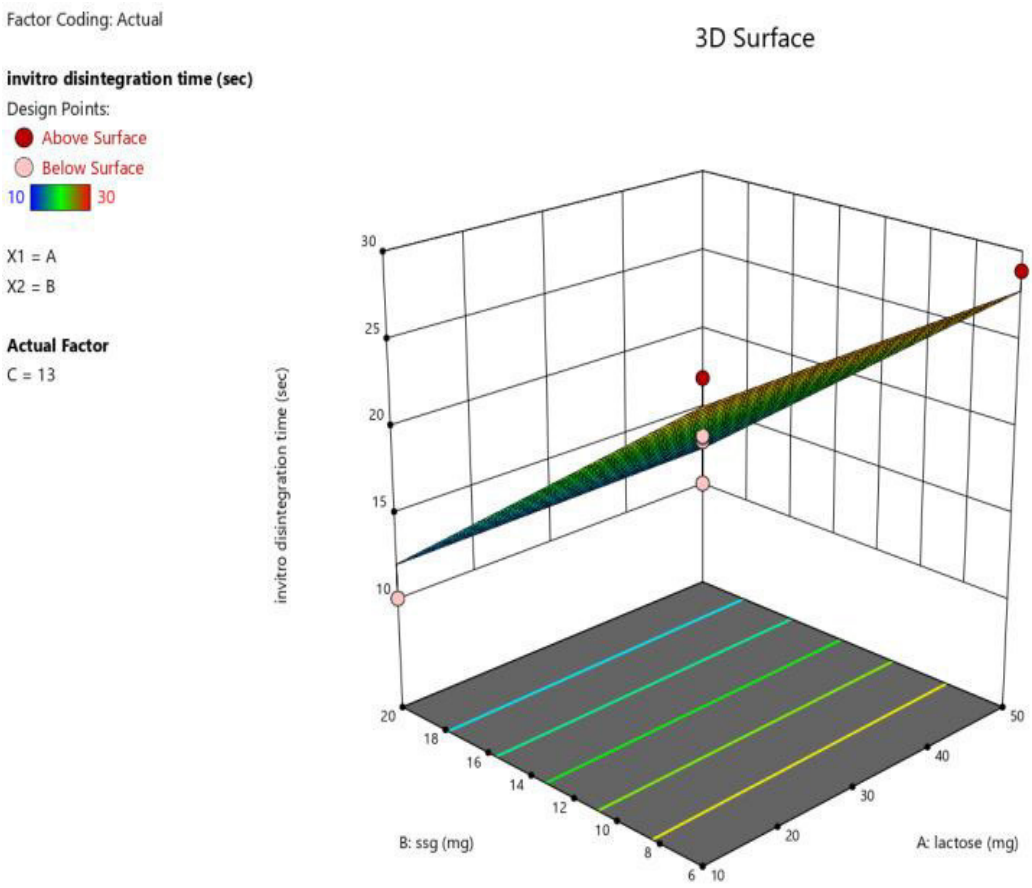


Fig 10: 3D response surface graphs of influence of BA on *in vitro* disintegration time (Y2)

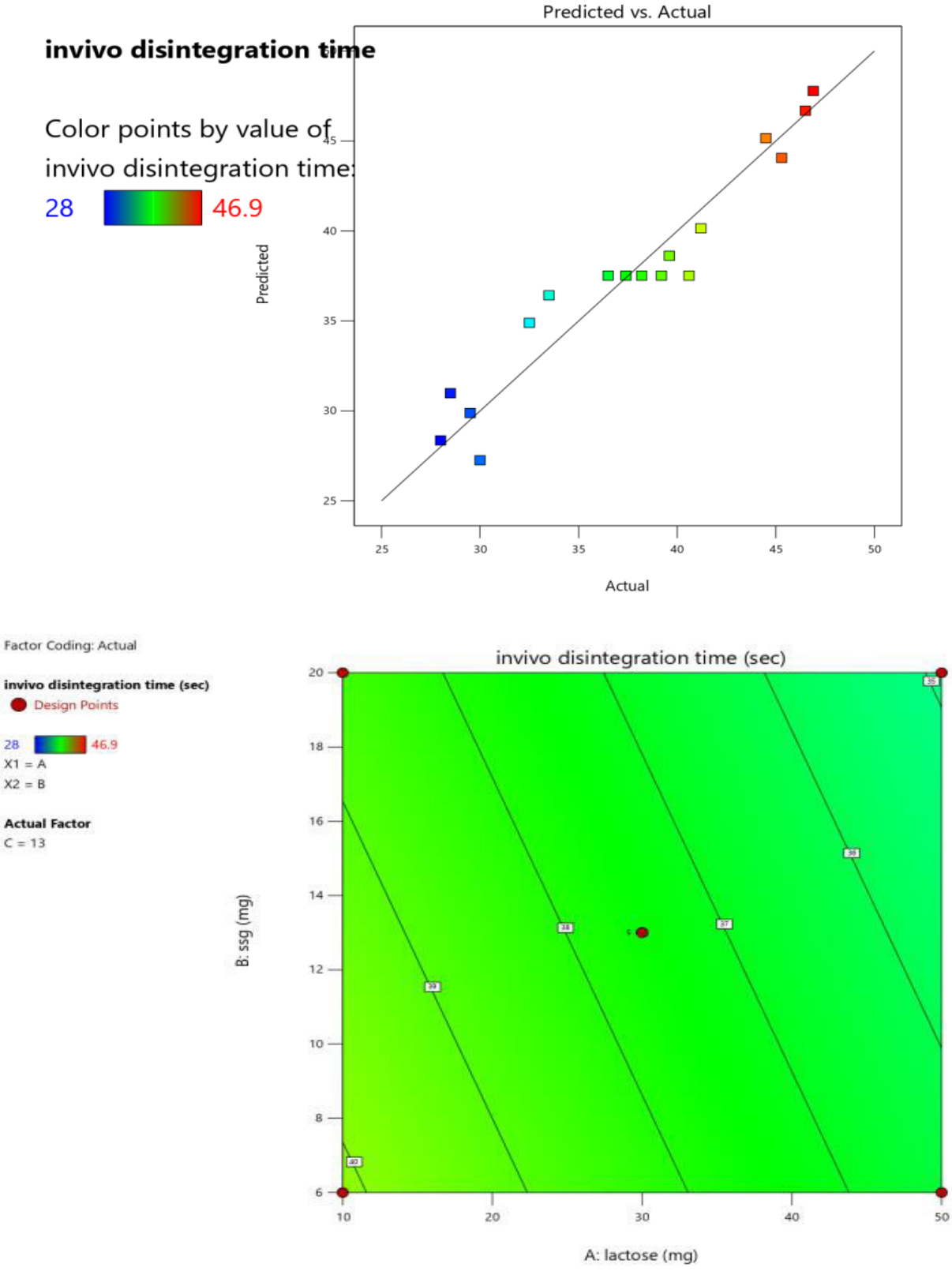
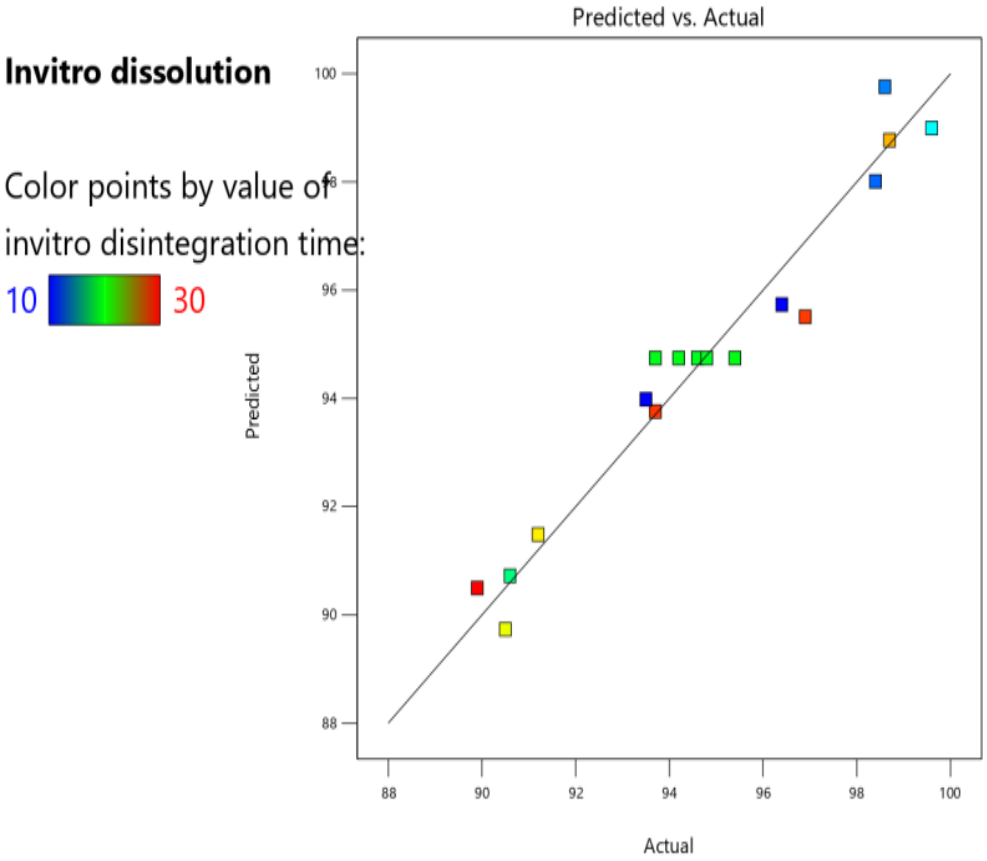
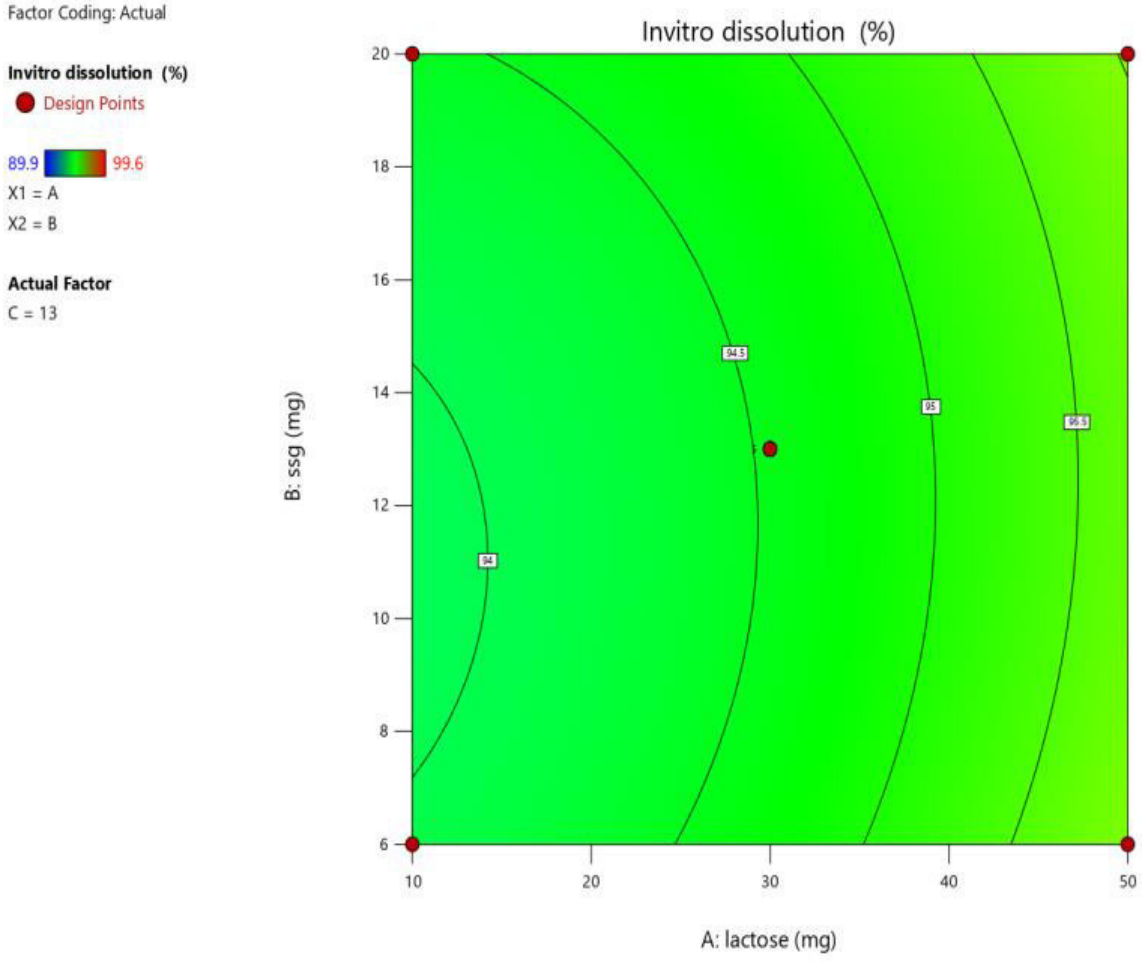


Fig 11: Effect of independent variables on *in vivo* disintegration time of fast dissolving tablets


Invitro dissolution
Color points by value of invitro disintegration time:
10
30
Predicted vs. Actual
Predicted
Actual
100
96
94
92
90
88
88
90
92
94
96
98
100


Factor Coding: Actual
Invitro dissolution (%)
Design Points
89.9
99.6
X1 = A
X2 = B
Actual Factor
C = 13
Invitro dissolution (%)
B: ssg (mg)
A: lactose (mg)
20
18
16
14
12
10
8
6
10
20
30
40
50
94
94.5
95
95.5

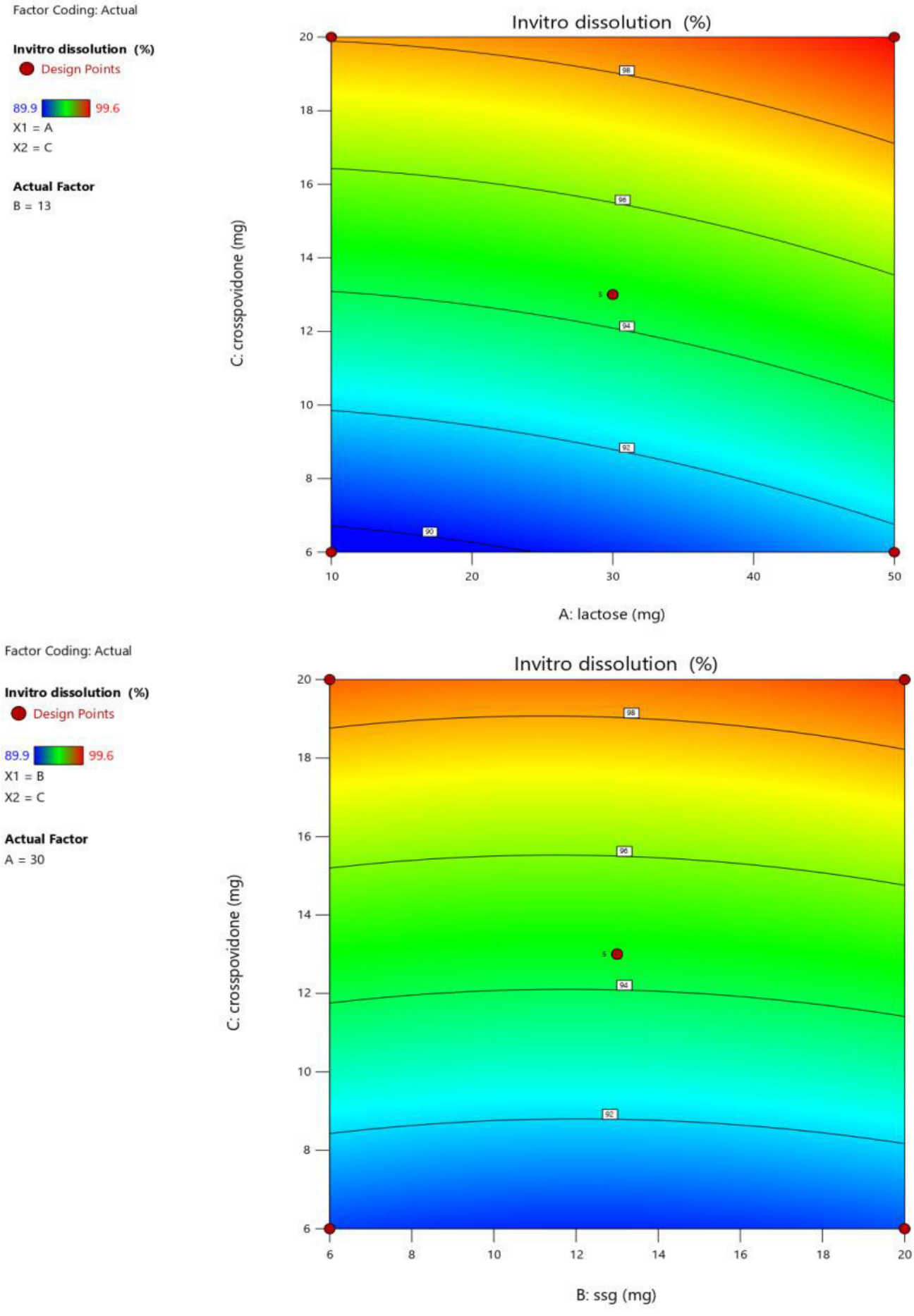


Fig 12: Effect of independent variables on *in vitro* dissolution time (Y4) of fast dissolving tablets

Factor Coding: Actual

Invitro dissolution (%)

Design Points:

Above Surface

Below Surface

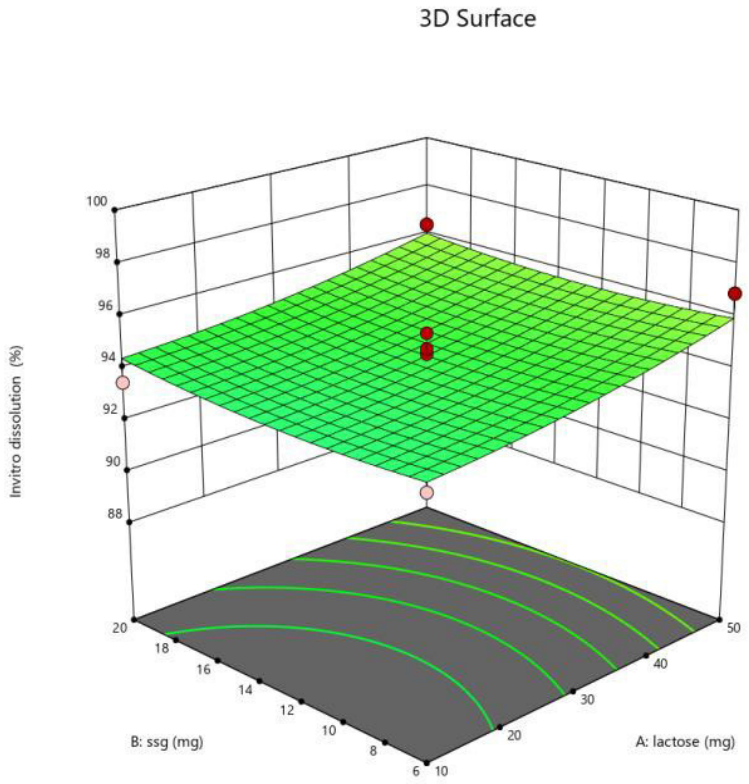
89.9 99.6

X1 = A

X2 = B

Actual Factor

C = 13



Factor Coding: Actual

Invitro dissolution (%)

Design Points:

Above Surface

Below Surface

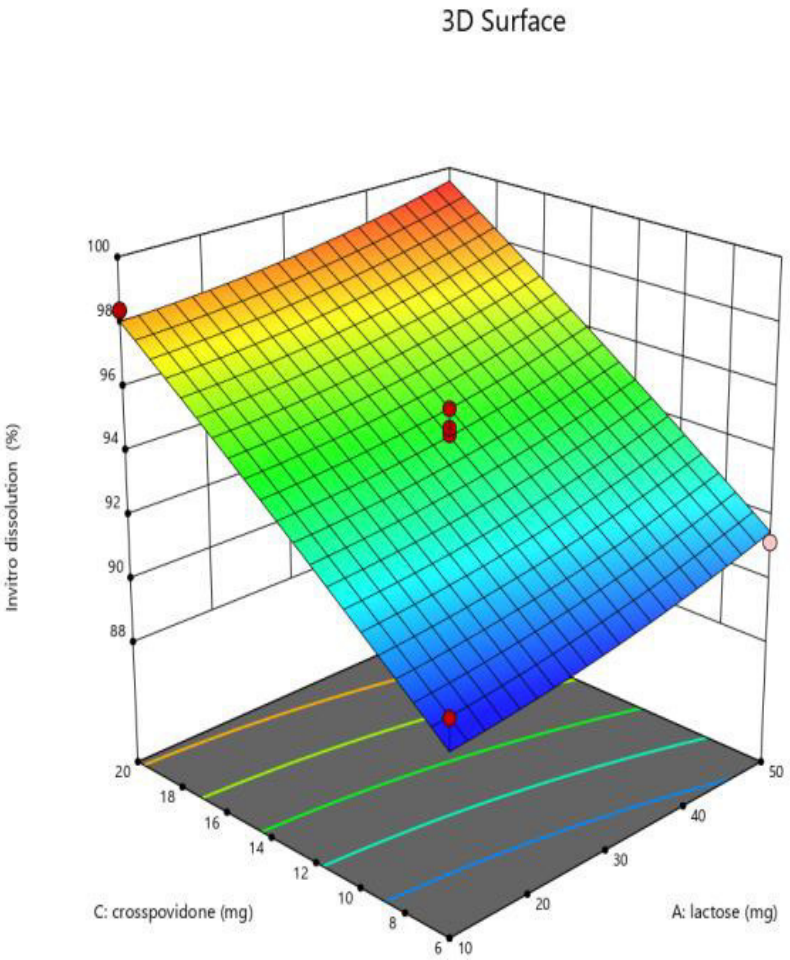
89.9 99.6

X1 = A

X2 = C

Actual Factor

B = 13



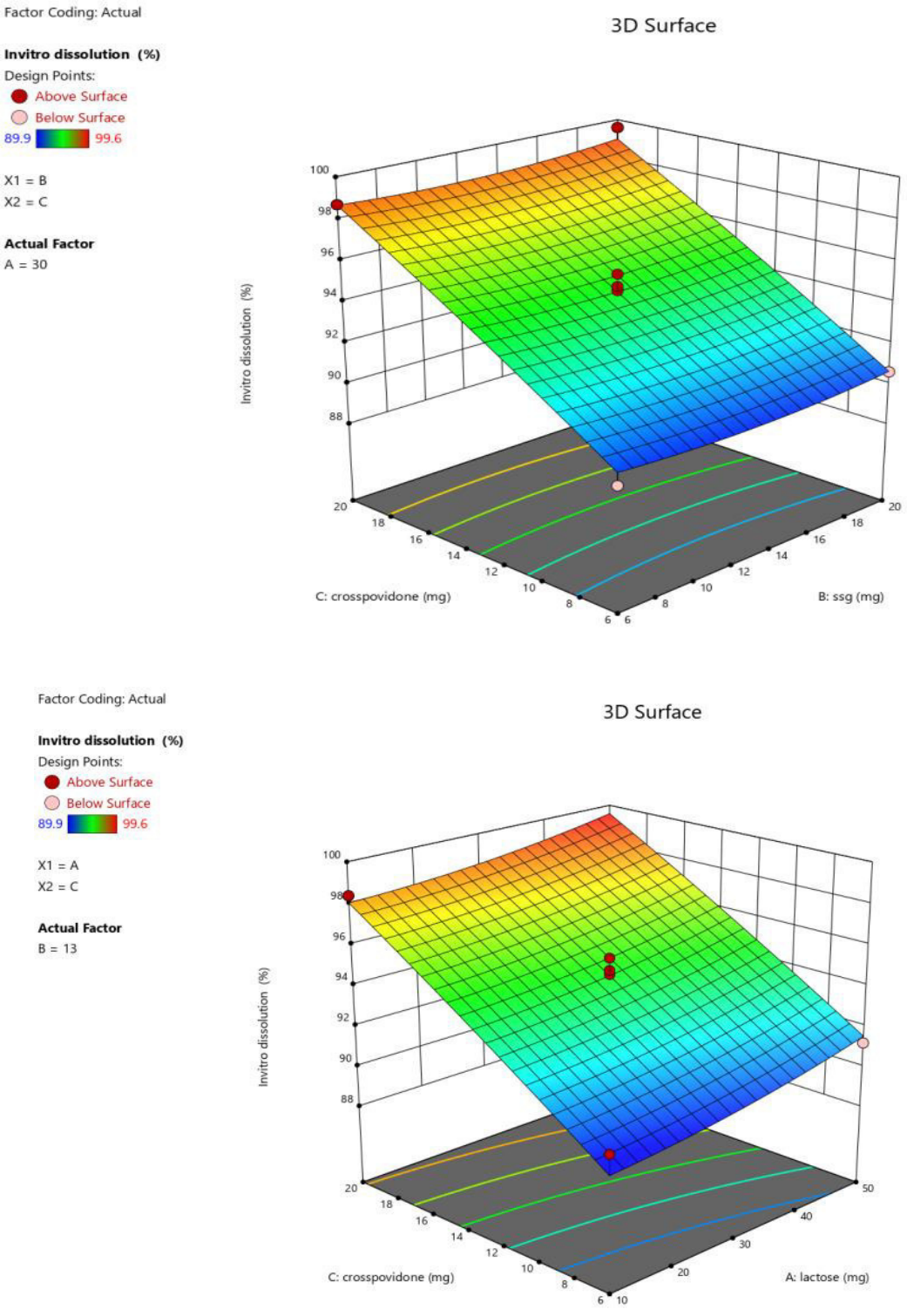


Fig 13: 3D response surface graphs of influence of BA on *in vitro* dissolution time (Y4)

Evaluation studies

Table 5 -Stability studies	
Time in Months	**%Drug Content in Tablets**
0	**98.24**
1month	**98.69**
2 months	**98.82**
3 months	**99.63**

The optimized formulation of the fast dissolving tablets is subjected to stability study as per ICH guidelines to assess their stability with respect to their physical appearance and release characteristics as mentioned in table 5. Stability studies proved that the formulation is quite stable and no change was observed

4. CONCLUSION

Drugrelease profile has shown an increase of dissolution profile in 1:1 ratio of solvent evaporation method. A set of 17 trails were done resulting in 17formulations (including 3 center points). Dissolution of the optimized batch with a percentage of 99.6% was selected as the optimized formulation with lactose, SSG and crospovidone(30mg, 20mg and 20mg) respectively. From the study the optimized formulation has been selected and the stability studies were conducted and the percentage drug content was found within limits in the entire study. From this research studythe dissolution and the bioavailability was increased with optimized formulation. Stability of the formulation was found to be within limits.Lornoxicam fast dissolving tablets increased patient compliance compared to other dosage forms.hence, based on the optimized formula the solubility, dissolution and stability data were found to be more effective which further helps in formulating the best dosage forms with best dissolution profile and stability.

5. AUTHOR CONTRIBUTION STATEMENT

DrTrinadha Rao conceptualized and designed the study, research done by M.Yamini and Ch.V.S. Phanindra, Data analysis and interpretation by P.N.Mallikarjun, Critical revision by DrPV.KamalaKumari and final review by Prof. Y.Srinivasa Rao.

6. CONFLICTS OF INTEREST

Conflict of interest declared none

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