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Research Article

Design, Development and Optimization of Pulsatile Core in Cup Tablets of Naproxen

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ABSTRACT
The aim of the present study to prepare Pulsatile release tablet of naproxen for the treatment of rheumatoid arthritis. The drug delivery system was designed to deliver the drug at a time when it could be most needful for the patient. Drug excipient compatibility studies were carried out using DSC and found to be compatible with each other. Pulsatile tablet was prepared by direct compression method using different type and amount of superdisintegrants and coating polymers and evaluated for pre and post compression parameters. Box Behnken design was applied to optimize responses. Concentrations of Sodium starch glycolate (SSG) (X_1), Ethyl cellulose (EC) (X_2), and HPMC K100M (X_3) were selected as independent variables while Lag time (Y_1) and % drug release at 8 hrs (Y_2) were selected as dependent variables. The prepared tablets were evaluated for post compression parameters and results indicated that concentration of SSG has major effect on *in vitro* drug release while concentration of EC and HPMC K100M has major effect on Lag time. Batch BE13 prepared with SSG 35mg, EC 175mg, and HPMC K100M 75 mg was found to be best batch as it achieves predetermined lag time of 5 hr 02 min and 99.32% of drug release. There was no significant variation in formulation at the end of six month accelerated stability study.

Keywords: Pulsatile Tablets, Naproxen, Superdisintegrant, Coating polymers, Box-Behnken design.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates[1].

The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. But there are certain conditions which demand release of drug after a lag time[2]. It is required that the drug should not be released during the initial phase of dosage form administration such type of release pattern is known as pulsatile release.

Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner and diseases with established oscillatory rhythm in their pathogenesis includes asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases acts as a push for the development of "Pulsatile Drug Delivery Systems"[3]. Pulsatile system is gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drug delivery system, thus providing special and temporal delivery[4].

This system are designed according to circardian rhythm of the body[5]. Human circardian rhythm is based on biological sleep activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period)[6]. Biological rhythms not only impact the function of physiology, but the pathophysiology of diseases[7].

If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration[8]. For example, in an asthmatic patient circadian changes are seen in normal lung function, and in cardiovascular diseases, several functions (e.g. Blood pressure, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms where pulsatile drug delivery system can be useful.

Naproxen is a member of propionic acid derivative related to the arylacetic acid group of non steroidal anti-inflammatory (NSAIDS) drugs, cyclooxygenase inhibitor, used to treat inflammation, pain and joint stiffness in patients suffering from rheumatoid arthritis.

Naproxen is found to be effective in both experimental and clinical pain in rheumatoid arthritis. It is rapidly absorbed from GI tract following oral administration.

The mean oral bioavailability of naproxen from the tablet is 95% relative to oral solution and half-life of about 12 hrs[9]. Thus, the aim of present investigation is to formulate and evaluate press coated naproxen tablet for the treatment of rheumatoid arthritis using suitable experimental design.

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Table 1: Selection of Levels for Independent Variables and Coding of Variable.

Levels	Coded value	Independent variables		
		Concentration of Sodium starch glycolate (mg) X_1	Concentration of Ethyl cellulose (mg) X_2	Concentration of HPMC K100M (mg)X_3
Low	-1	30	170	70
Intermediate	0	35	175	75
High	+1	40	180	80

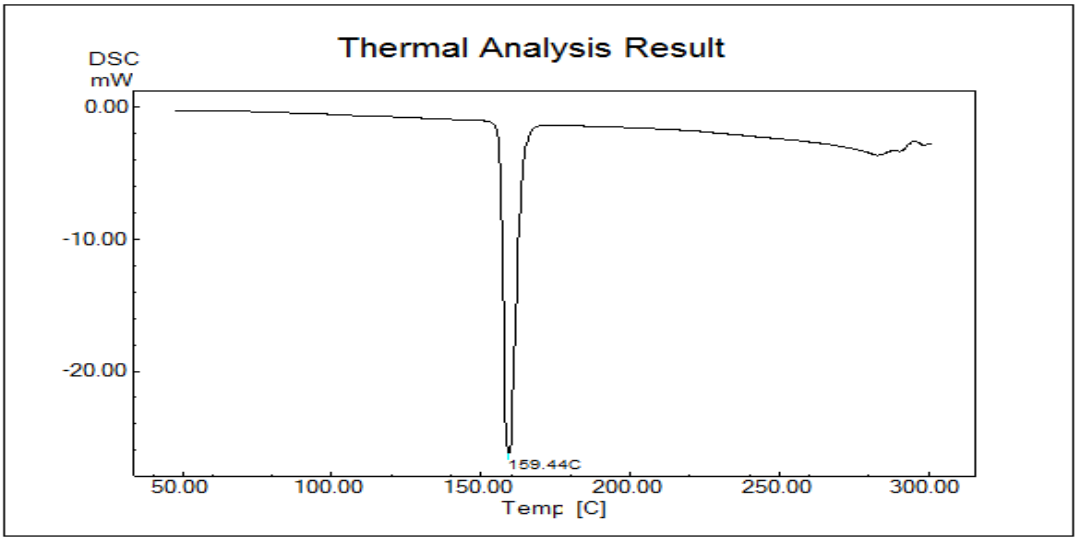


Figure 1: DSC Thermogram of Naproxen.

Table 2: Composition of Compression Coated Pulsatile Tablets.

Type of Layer	Ingredients (mg)	BE1	BE2	BE3	BE4	BE5	BE6	BE7	BE8	BE9	BE 10	BE 11	BE 12	BE 13	BE 14	BE 15
Core Layer	Naproxen	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
	Sodium Starch Glycolate	30	40	30	40	30	40	30	40	35	35	35	35	35	35	35
	Avicel	54.5	54.5	44.5	64.5	54.5	54.5	44.5	64.5	54.5	54.5	54.5	54.5	54.5	54.5	54.5
	Mg. Stearate	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Coat Layer	Ethyl Cellulose	170	180	180	175	175	175	175	175	170	170	180	180	175	175	175
	HPMC K100M	75	75	75	70	70	80	80	80	70	80	70	80	75	75	75
Total (mg/ tablet)		600	600	600	600	600	600	600	600	600	600	600	600	600	600	600

MATERIALS AND METHODS

Naproxen was obtained as a complimentary sample by Intas Pharmaceuticals Pvt. Ltd., Ahmedabad; HPMC K100M was received from Colorcon Asia Pvt. Ltd., Goa; Sodium Starch glycolate was gifted from Zhaveri Pharma Chemicals, Maharashtra; Ethyl cellulose was received from Dows Chemicals, Chennai. Magnesium stearate and talc was purchased from S.D. fine chemicals, Mumbai.

Drug-Excipients Compatibility Study by DSC[10]

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyser and operating software. The samples (drug and excipients) were heated in sealed aluminium pans under nitrogen flow (30 ml/min) at a scanning rate of 5^0C/min from 50 to 300^0C. Empty aluminium pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

Box-Behnken Design[11,12]

A 3-factor 3-level Box-Behnken statistical design was used for the formulation of Pulsatile release tablet. This design is suitable for exploring quadratic response surface and constructing second order polynomial models. It is applied to study the influence of the effect of independent variables i.e. Concentration of Sodium starch glycolate (X_1), Ethyl cellulose (X_2), and HPMC K100M (X_3) on the dependent variable i.e. Lag time (Y_1) and %CDR at 8hr (Y_2). A design matrix comprising 15 experimental run was

Table 3: Post-Compression Evaluations of Core tablets of Batches BE1 to BE15.

Batch	Thickness (mm) (n=3)	Diameter (mm) (n=3)	Hardness (Kg/cm^2) (n=3)	Friability (%) (n=5)	Weight variation (mg) (n=20)	Drug Content (n=10)	Disintegration Time (Sec) (n=3)
BE1	3.02 ± 0.08	9.00 ± 0.016	2.52 ± 0.19	0.63 ± 0.015	Pass	99.73 ± 0.11	115 ± 0.90
BE2	3.75 ± 0.02	8.97 ± 0.012	3.19 ± 0.20	0.68 ± 0.024	Pass	98.24 ± 0.16	25 ± 1.25
BE3	3.26 ± 0.05	8.82 ± 0.010	3.23 ± 0.12	0.65 ± 0.020	Pass	98.39 ± 0.15	110 ± 1.10
BE4	3.35 ± 0.07	9.00 ± 0.025	2.72 ± 0.26	0.62 ± 0.010	Pass	99.42 ± 0.15	24 ± 1.43
BE5	3.20 ± 0.06	8.92 ± 0.020	2.89 ± 0.14	0.74 ± 0.026	Pass	97.71 ± 0.20	112 ± 1.51
BE6	3.60 ± 0.05	8.80 ± 0.032	2.79 ± 0.21	0.60 ± 0.022	Pass	96.43 ± 0.10	28 ± 0.90
BE7	3.52 ± 0.07	8.92 ± 0.019	3.12 ± 0.22	0.61 ± 0.011	Pass	99.32 ± 0.18	115 ± 1.16
BE8	3.82 ± 0.09	8.79 ± 0.024	2.60 ± 0.16	0.69 ± 0.023	Pass	98.55 ± 0.16	32 ± 1.18
BE9	3.72 ± 0.01	9.00 ± 0.052	2.54 ± 0.12	0.64 ± 0.028	Pass	97.26 ± 0.21	30 ± 1.26
BE10	3.49 ± 0.05	8.82 ± 0.045	3.12 ± 0.28	0.62 ± 0.011	Pass	97.81 ± 0.14	35 ± 0.78
BE11	3.31 ± 0.07	8.98 ± 0.011	2.98 ± 0.19	0.66 ± 0.029	Pass	98.24 ± 0.30	32 ± 1.26
BE12	3.12 ± 0.06	9.00 ± 0.024	3.00 ± 0.10	0.67 ± 0.015	Pass	98.65 ± 0.12	31 ± 1.42
BE13	3.29 ± 0.07	8.96 ± 0.032	3.02 ± 0.18	0.75 ± 0.010	Pass	99.45 ± 0.10	30 ± 1.20
BE14	3.54 ± 0.03	8.99 ± 0.040	3.5 ± 0.12	0.69 ± 0.021	Pass	99.24 ± 0.20	31 ± 1.34
BE15	3.46 ± 0.01	8.97 ± 0.023	3.01 ± 0.12	0.70 ± 0.022	Pass	98.98 ± 0.19	30 ± 1.20

All values are expressed as mean ± standard deviation

Table 4: Post-Compression Evaluation Parameters of Coated Tablets of Batches BE1 to BE15.

Batch	Thickness (mm) (n=3)	Diameter (mm) (n=3)	Hardness (Kg/mg^2) (n=3)	Friability (%) (n=5)	Drug Content (n=10)	Lag time(hrs) (n=3)
BE1	6.18 ± 0.010	12.00 ± 0.017	5.1 ± 0.014	0.52 ± 0.058	99.5 ± 1.29	4.50 ± 0.16
BE2	5.88 ± 0.022	11.96 ± 0.019	5.6 ± 0.060	0.45 ± 0.093	97.3 ± 1.67	4.45 ± 0.07
BE3	6.05 ± 0.021	11.99 ± 0.030	5.5 ± 0.040	0.49 ± 0.110	98.5 ± 1.38	5.10 ± 0.11
BE4	6.08 ± 0.020	11.95 ± 0.025	5.3 ± 0.031	0.45 ± 0.128	99.6 ± 1.75	5.12 ± 0.21
BE5	6.02 ± 0.018	11.94 ± 0.010	5.2 ± 0.016	0.50 ± 0.098	95.5 ± 1.51	4.50 ± 0.26
BE6	5.94 ± 0.016	11.98 ± 0.030	5.1 ± 0.022	0.53 ± 0.059	97.9 ± 1.36	4.42 ± 0.15
BE7	6.04 ± 0.021	12.00 ± 0.012	5.4 ± 0.010	0.45 ± 0.123	96.8 ± 1.80	5.25 ± 0.30
BE8	6.06 ± 0.025	11.98 ± 0.021	5.5 ± 0.038	0.47 ± 0.150	98.2 ± 1.28	5.20 ± 0.10
BE9	6.02 ± 0.032	11.96 ± 0.018	5.9 ± 0.011	0.42 ± 0.123	97.9 ± 1.62	4.25 ± 0.24
BE10	6.03 ± 0.020	11.97 ± 0.019	5.5 ± 0.018	0.49 ± 0.059	99.5 ± 0.99	4.30 ± 0.05
BE11	5.95 ± 0.027	12.00 ± 0.020	5.2 ± 0.090	0.53 ± 0.072	97.1 ± 0.89	4.50 ± 0.15
BE12	6.04 ± 0.017	12.00 ± 0.051	5.5 ± 0.026	0.48 ± 0.057	99.8 ± 1.42	5.25 ± 0.29
BE13	6.09 ± 0.027	11.98 ± 0.029	5.6 ± 0.014	0.42 ± 0.085	99.2 ± 1.53	5.01 ± 0.19
BE14	6.08 ± 0.032	11.92 ± 0.022	5.5 ± 0.025	0.46 ± 0.098	98.8 ± 1.40	5.03 ± 0.16
BE15	6.06 ± 0.030	11.95 ± 0.020	5.5 ± 0.022	0.44 ± 0.096	99.2 ± 1.23	5.05 ± 0.10

All values are expressed as mean ± standard deviation

constructed. The design consists of replicated center points and the set of points lying at the midpoint of the multidimensional cube that defines the region of interest. The nonlinear quadratic model generated by the design in the form:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{11} X^2 + \beta_{22} X^2 + \beta_{33} X^2 + E$$

Where, Y is the measure response associated with each factor level combination, β_0 is constant, β_1 - β_3 are linear coefficients, β_{12}, β_{13} **and** β_{23} are the interaction coefficients between two factors and computed from the observed experimental value of Y from the experimental runs and X_1, X_2 and X_3 are the coded levels of independent variables. The terms X_1X_2 **(i= 1, 2 and 3)** represent the interaction effect and X_1^2, X_2^2 and X_3^2 represent the curvature effects. The concentration range of independent variables under study is shown in table 1 along with their low and high levels, which were selected based on the results from preliminary experimentation. The composition of batches BE1 to BE15 according to Box-Behnken statistical design was given in table 2.

Table 5: Summary of Response Y_1.

Std. dev.	0.094	R- Squared	0.9781
Mean	4.79	Adj R-squared	0.9388
C.V. %	1.95	Pred R-squared	0.6591
PRESS	0.68	Adeq R-squared	15.713

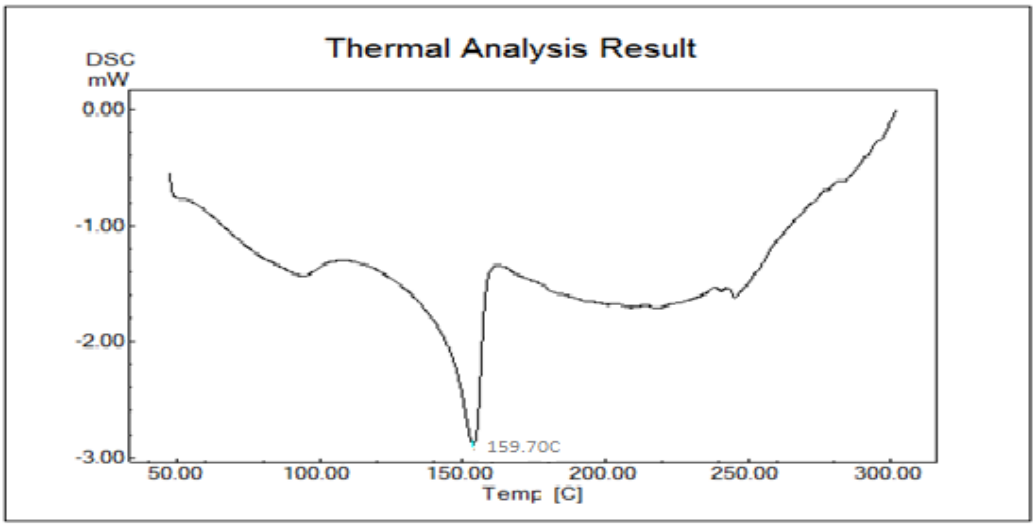


Figure 2: DSC Thermogram of Naproxen, SSG, Avicel, Mg. stearate, Talc, Ethyl cellulose, and HPMC K100M Mixture.

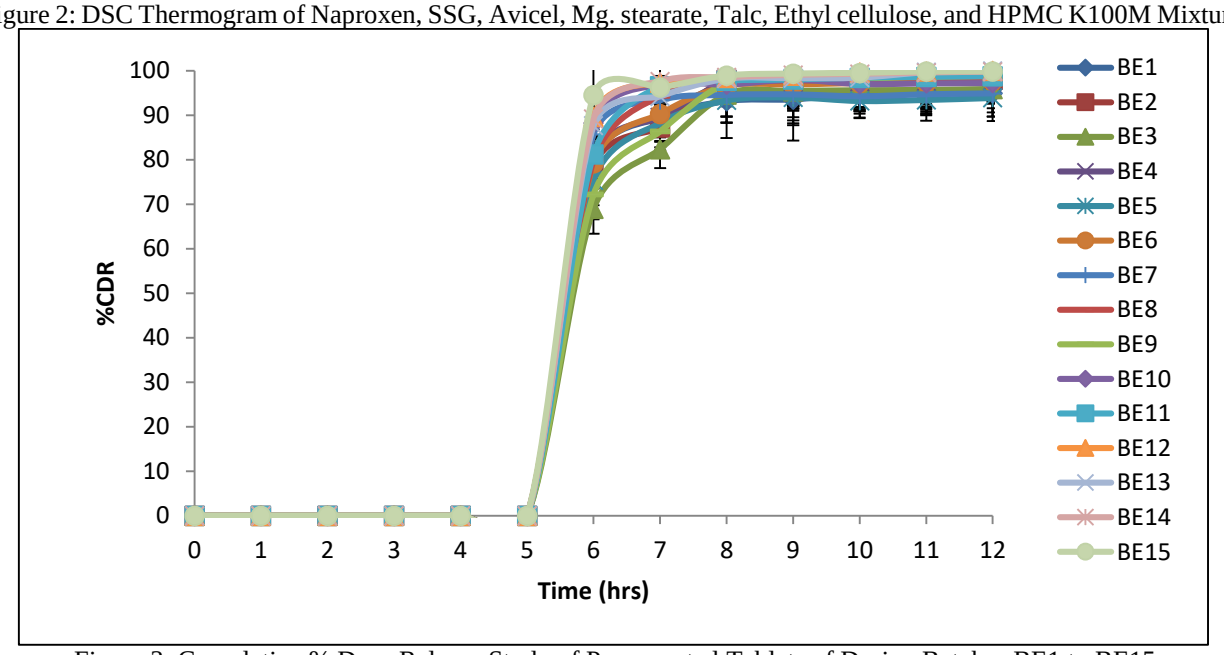


Figure 3: Cumulative % Drug Release Study of Press coated Tablets of Design Batches BE1 to BE15

Table 6: ANOVA Response Surface Quadratic Model for Y_1.

Source	Sum of Square	DF	Mean Square	F Value	p-value prob > F
Model	1.96	9	0.22	24.87	0.0012
X_1	0.00032	1	0.00032	0.37	0.5717
X_2	0.54	1	0.54	61.22	0.0005
X_3	0.93	1	0.93	106.49	0.0001
X_1X_2	0.0001225	1	0.000122	0.14	0.7236
X_1X_3	0.0000225	1	0.0000225	0.026	0.8789
X_2X_3	0.12	1	0.12	14.00	0.0134
X_1^2	0.000102	1	0.000102	0.12	0.7460
X_2^2	0.23	1	0.23	26.55	0.0036
X_3^2	0.15	1	0.15	17.02	0.0091
Residual	0.044	5	0.000874	-	-
Cor Total	2.00	14	-	-	-

The core tablets of Naproxen were prepared by direct compression technique. Naproxen and all other excipients were passed through 40# sieve, weighed accurately and mixed thoroughly except talc and magnesium stearate. Than the above powder mixture was lubricated with talc and magnesium stearate. Core tablets were prepared by

compressing the entire ingredients using 9mm punch and die cavity on a rotary tablet press. The core tablets were compression coated with different weight ratios (w/w) of HPMC K100M, and Ethyl cellulose. Half of the total quantity of coating powder blend was filled in die cavity to make a powder bed at the bottom. The previously compressed tablet using 9 mm punch placed manually in the centre on the above powder blend. The remaining equivalent powder was filled in the die, and the content was compressed using a flat faced punch, 12 mm in diameter in rotary tablet punching machine (Karnavati Engineering).

Evaluation Parameters for Core Tablet[13,14]

Thickness and Diameter

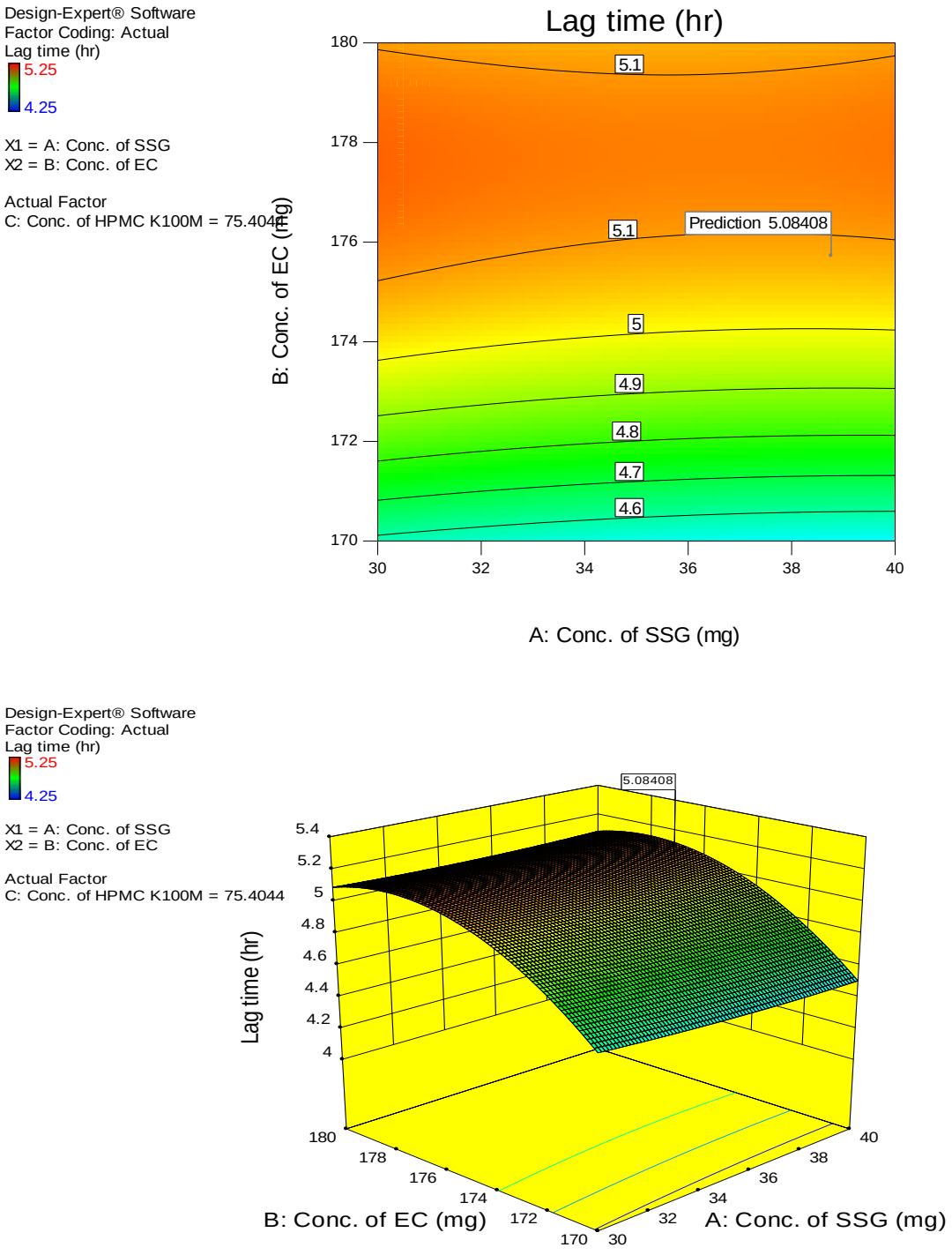


Figure 4: 2D and 3DContour Curve Showing effect of SSG (X_1) and EC (X_2) on Lag time(Y_1).]

Thickness and diameter of tablets were measured using vernier calipers. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked from each batch and analysed for hardness. The mean and standard deviation were also calculated.

Friability

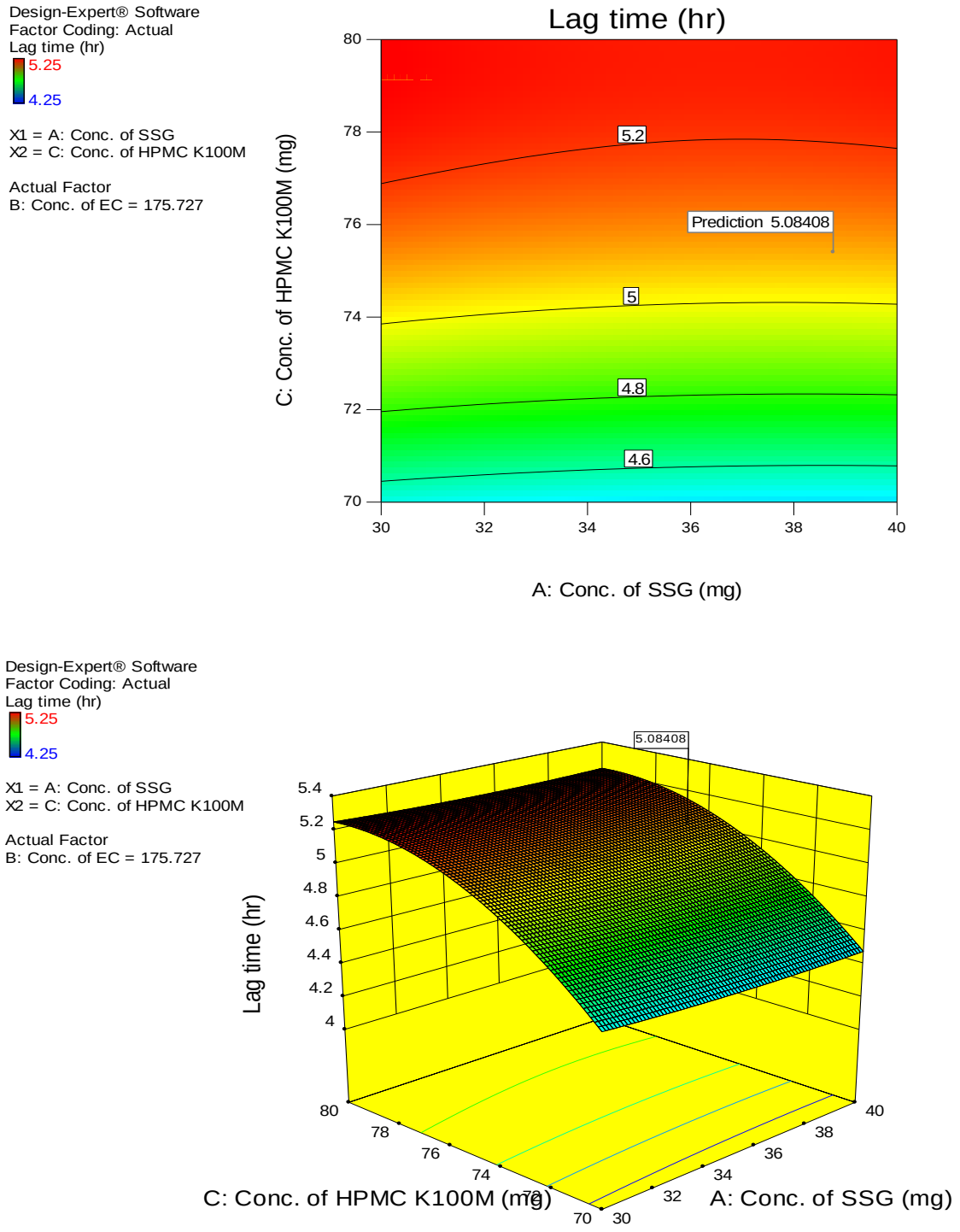


Figure 5: 2D and 3D Contour Curve Showing effect of SSG (X_1) and HPMC K100M (X_3) on Lag time(Y_1)

Friability of tablets was determined using the Roche friabilator. Ten tablets were weighed together and placed in friabilator for 100 revolutions.

The % friability was calculated by,

$$F = \frac{Winitial - Wfinal}{Winitial} X\ 100$$

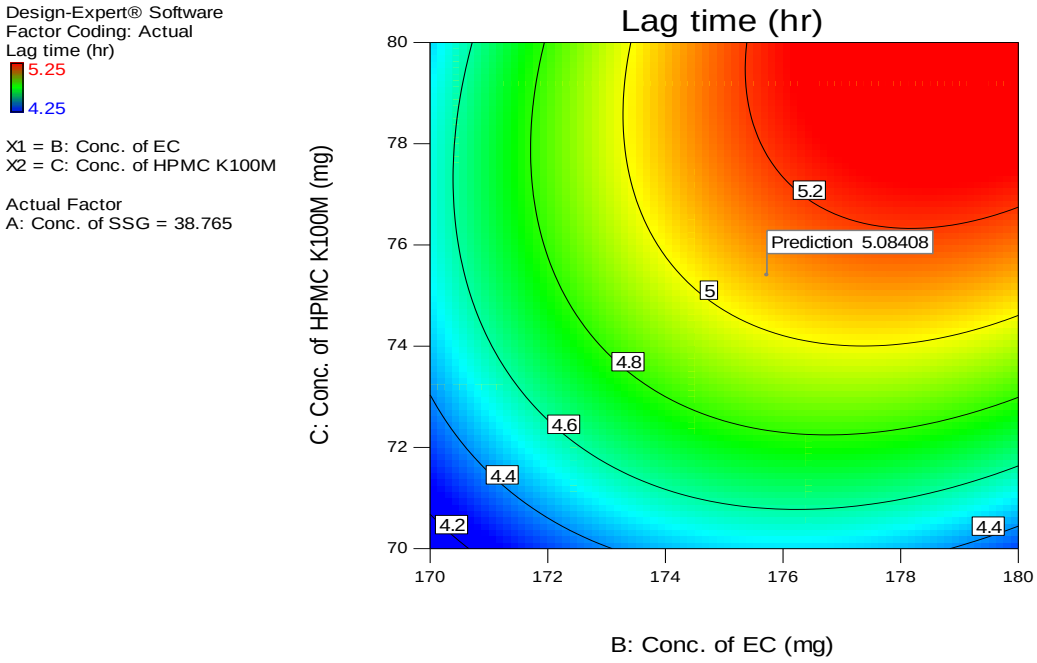
Weight Variation Test

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations were determined and recorded[11].

$$Percentage\ Deviation = \frac{Individual\ Weight - Average\ Weight}{Individual\ Weight}$$

Disintegration Time

The *in vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each



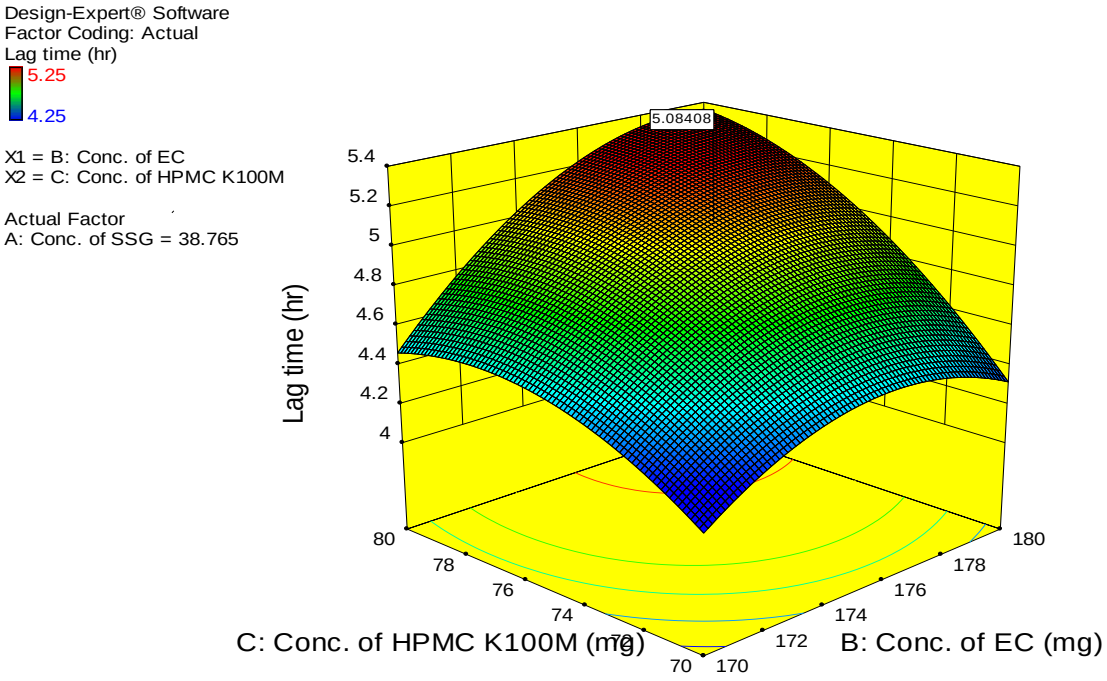


Figure 6: 2D and 3D Contour Curve Showing effect of EC (X_2) and HPMC K100M (X_3) on Lag time(Y_1)

Table 8: ANOVA Response Surface Quadratic Model for Y_2.

Source	Sum of Square	DF	Mean Square	F Value	p-value prob > F
Model	51.02	9	5.67	41.64	0.0004
X_1	26.75	1	26.75	196.51	< 0.0001
X_2	0.35	1	0.35	2.59	0.1684
X_3	0.60	1	0.60	4.40	0.0899
X_1X_2	2.54	1	2.54	18.69	0.0076
X_1X_3	0.26	1	0.26	1.91	0.2255
X_2X_3	0.21	1	0.21	1.52	0.2723
X_1^2	18.10	1	18.10	132.96	< 0.0001
X_2^2	2.17	1	2.17	15.94	0.0104
X_3^2	1.80	1	1.80	13.26	0.0149
Residual	0.68	5	0.14	-	-
Cor Total	51.70	14	-	-	-

of the six tubes of the apparatus with lid on upper side and the time(seconds) taken for complete disintegration of the tablet in phosphate buffer pH 7.4 (since dosage form is designed to release drug after the lag time) at 37±0.5ºC with no palatable mass remaining in the apparatus was measured.

Drug Content

The drug content was carried out by weighing ten tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which was equivalent to specified weight of Naproxen and dissolved in 100 ml volumetric flask containing 100 ml of phosphate buffer pH 7.4 and volume was made to 100 ml with buffer. The volumetric flask was shaken using sonicator for 1 hr and after suitable dilution with Phosphate buffer pH 7.4, the drug content was determined using UV-Visible Spectrophotometer at 331 nm.

Evaluation of Coated Tablet[13,14]

The press coated tablets were evaluated for post compression parameters such as thickness, diameter, weight variation and hardness as per procedure mentioned in evaluation parameter for core tablets.

Rupture Test (Lag time determination)

The Rupture test was carried out using USP paddle apparatus. Here all other Parameters were same as *In-Vitro* Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time. This was determined by Rupture test.

In vitro Dissolution Study

In vitro dissolution study was carried out using USP Type II (paddle method) apparatus. The prepared tablets were subjected to dissolution using dissolution medium of 0.1 HCl for 2 hours and the same tablets were placed in 900ml of phosphate buffer pH 7.4 for further release of the drug. The study was carried out for 12 hour at 50 rpm. At definite time intervals, 5ml of the sample was withdrawn; filtered and replaced with fresh buffer media. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 331nm.

Statistical Analysis[11,12]

Table 7: Summary of Response Y_2.

Std. dev.	0.37	R- Squared	0.9868
Mean	97.06	Adj R-squared	0.9631
C.V. %	0.38	Pred R-squared	0.8013
PRESS	10.27	Adeq R-squared	19.308

Statistical Analysis of the Box-Behnken design batches was performed by multiple regression analysis using Microsoft excel. In this design 3 factors are evaluated, each at 3 levels, and experimental trials are performed at all 15 possible combinations. To evaluate the contribution of each factor with different levels to the response, the two-way analysis of variance (ANOVA) was performed using the Design Expert 10 (STAT – EASE) demo version software. To graphically demonstrate the influence of each factor on the response, the response surface plots, Normal plot of residual, Two- Dimensional counter plot, 3-D graph, and overlay plot, were generated using the Design Expert 10 (STAT – EASE) demo version software.

Checkpoint Analysis[11,12]

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points and the theoretical values of lag time and %CDR at 8hr were calculated by substituting the values in the polynomial equation.

Optimization of Formulation[11,12]

The computation for optimized formulation was carried using Design Expert 10.0.6.0 (STAT – EASE) software. The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). The models were evaluated in terms of statistically significant coefficients and R^2 values. Various feasibility and grid searches were conducted to find the optimum parameters. Various 3-D response surface graphs were provided by the Design Expert software. The optimized formulation factors were evaluated for various response properties.

Kinetics of Drug Release[15]

In order to describe the kinetics of drug release from sustained release formulation, various mathematical equations have been proposed namely, Zero order rate, First order equation, Higuchi model and Hixson–Crowell cube root law. To authenticate the release model, dissolution data can further be analyzed by Korsmeyer Peppas equation. The criteria for the selection of most suitable model were value of regression coefficient (R^2) nearer to 1, smallest values of Residual sum of squares (SSR) and Akaike Information Criteria (AIC).

Stability Study[16,17]

Stability studies of the optimized formulation was carried out to determine the effect of presence of formulation additives on the stability of the drug under accelerated storage conditions as per ICH guidelines. The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40 ± 2°C/ 75 ± 5 % RH for time period of 6 Month.

RESULTS AND DISCUSSION

Drug Excipients Compatibility Study by DSC

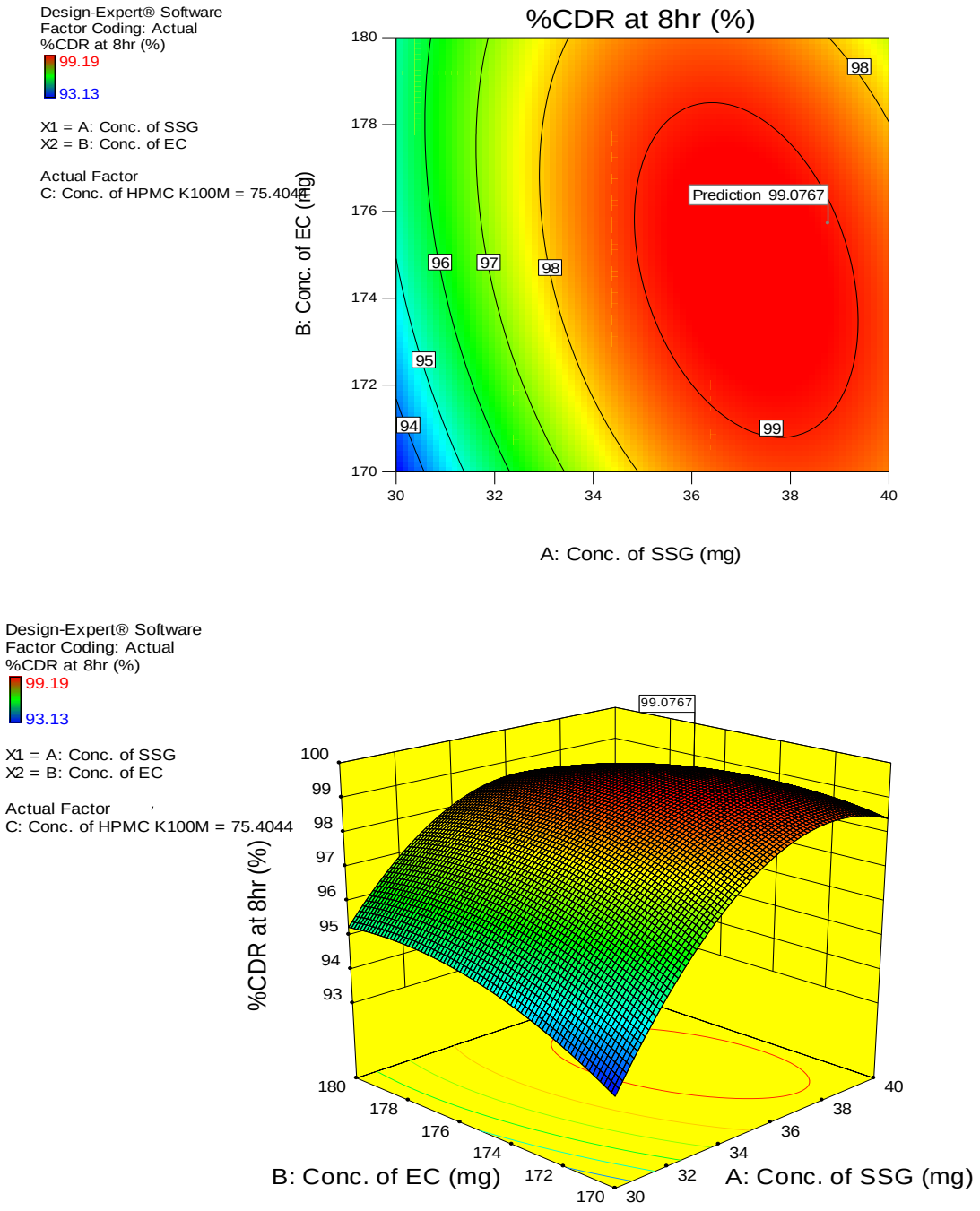


Figure 7: 2D and 3D Counter Plot Showing the effect of of SSG(X_1) and of EC(X_2) on %CDR at 8 hrs(Y_2).

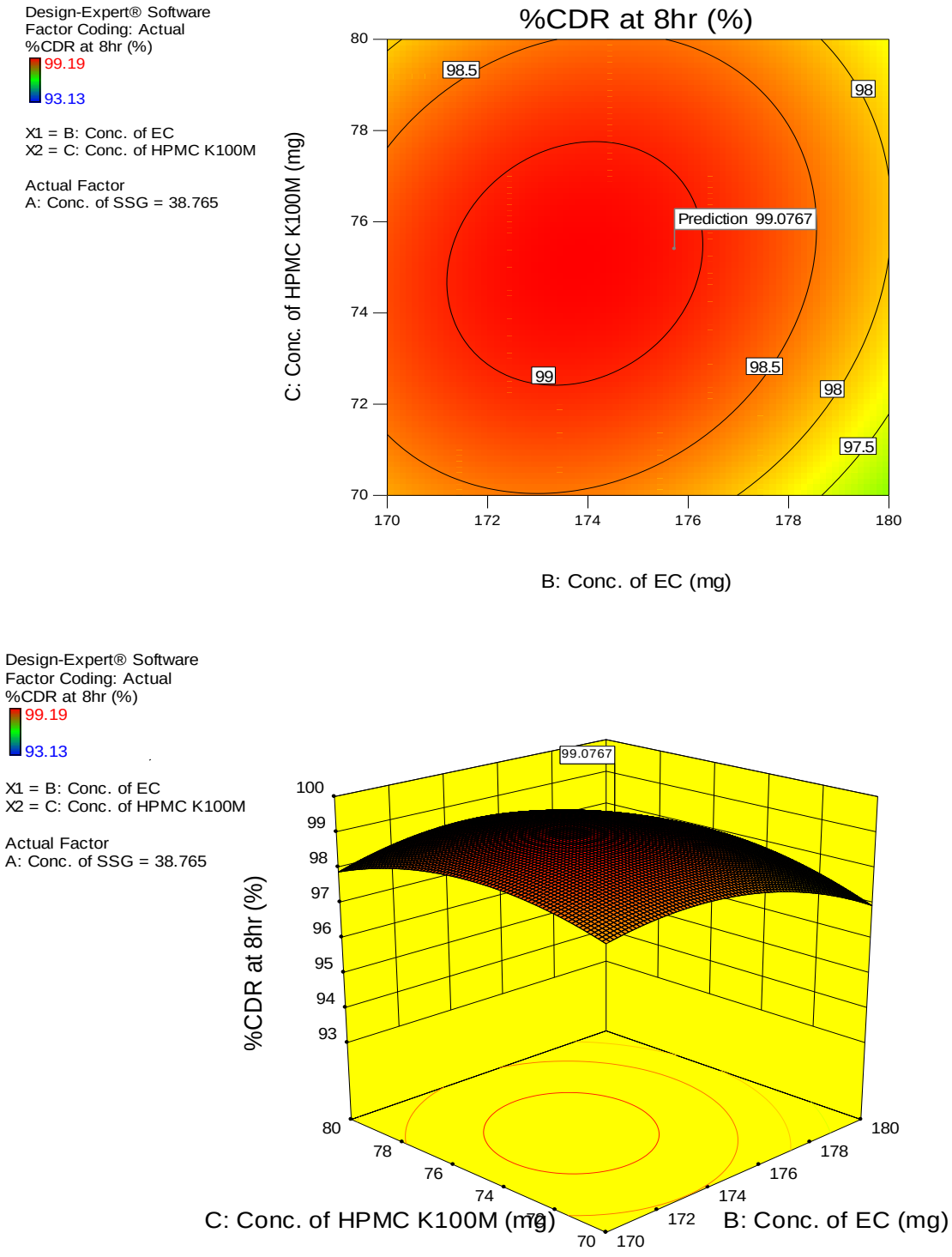


Figure 8: 2D and 3D Contour Curve Showing effect of EC (X_2) and HPMC K100M (X_3) on % CDR at 8 hrs(Y_2)

DSC thermogram of Naproxen and mixture of Naproxen with other excipients were shown in figure 1 and 2. DSC thermogram of drug with excipients exhibits sharp peak at 159.70˚ which was identical to the DSC of drug. The thermal analysis study of Naproxen and excipients suggest that there is no interaction of the drug with other excipients.

Evaluation Parameters for Core Tablets All the prepared tablets were evaluated for various physical parameters. Table 3 includes the results (mean ± SD) of weight variation, hardness, thickness, diameter, friability, % drug content and disintegration time of batches BE1 to BE15 which were prepared using different combinations of

functional excipients. All the prepared (BE1 to BE15) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. Thickness and diameter of all tablets was in the range between 3.02 ± 0.08 to 3.82 ± 0.09 mm and 8.79 ± 0.024 to 9.00 ± 0.052mm. Hardness of tablets was in range between 2.52 ± 0.19 to 3.5 ± 0.12 kg/cm^2. Friability was in range between 0.60 ± 0.022 to 0.75 ± 0.010 %. Friability values of all the tablets were less than 1 % in all cases shows good mechanical strength at the time of handling and transports. Drug content was in the range between 96.43 ± 0.10 to 99.73 ± 0.011%, and Disintegration time ranges from 24 ± 1.43 to 115 ± 1.16 sec. Thus, all the physical parameters of the manually compressed tablets were quite within control.

Evaluation Parameters for Coated Tablets

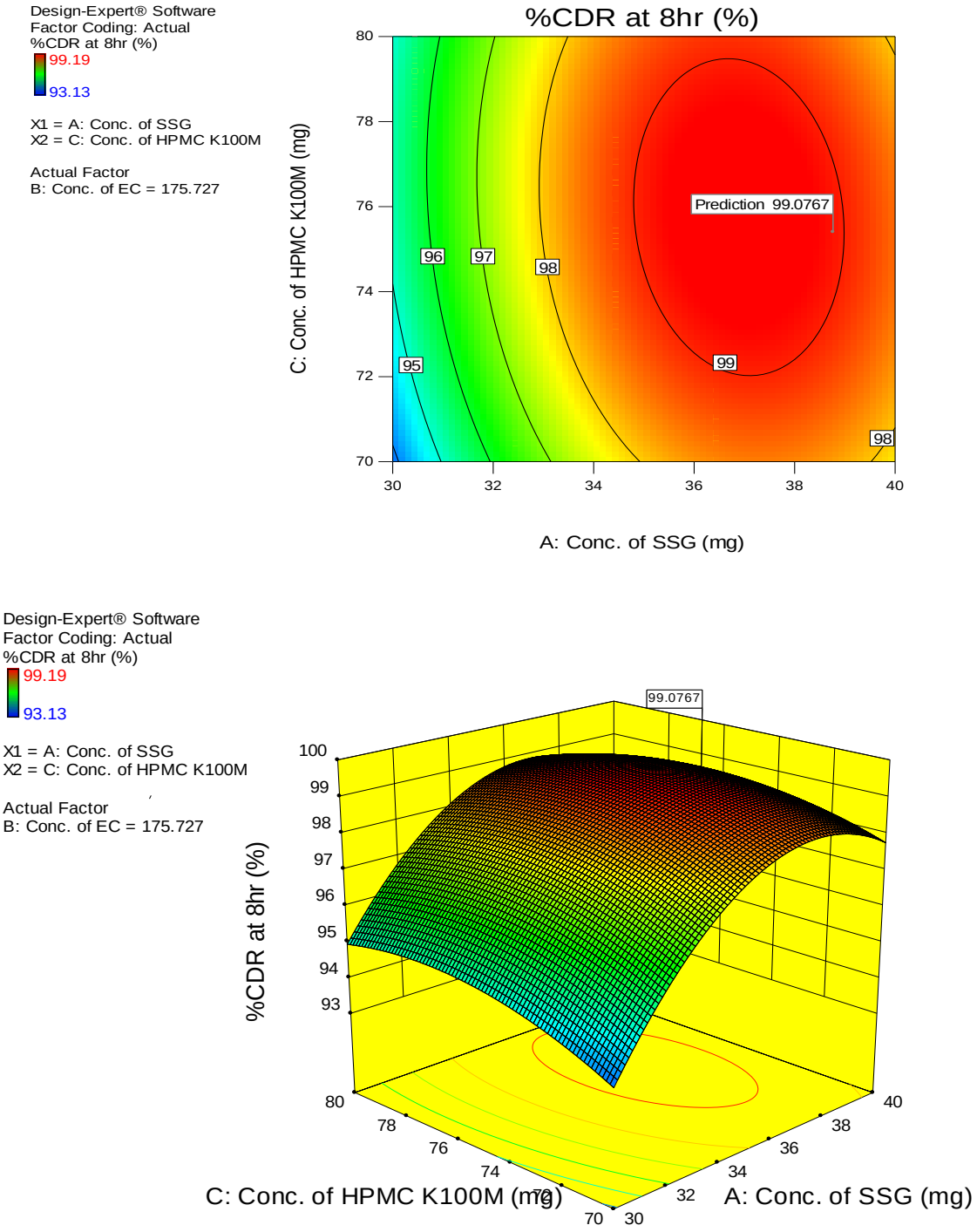


Figure 9: 2D and 3D Contour Curve Showing effect of SSG (X_1) and HPMC K100M (X_3) on % CDR at 8 hrs(Y_2)

Table 9: Checkpoint Batches with Predicted and Measured value of Lag time and %CDR at 8hr.

Batch Code	X_1	X_2	X_3	Lag Time		%CDR at 8hr	
				Measured	Predicted	Measured	Predicted
BE16	0	0.5	-0.5	4.81	4.83	98.50	98.56
BE17	-0.5	0	0.5	5.02	5.16	97.45	97.57
BE18	0.5	-0.5	0	4.79	4.83	99.01	99.08

Table 10: Fitting of Release Profile of Optimized Formulation to Kinetic Models.

Batch	Model	Parameters Used				
		R^2	R	K	SSR	AIC
BE13	Zero-order	0.7084	0.8803	8.508	8786.0980	120.052
	First-order	0.5773	0.8315	0.124	12734.2382	124.8766
	Higuchi	0.4965	0.7923	22.844	15169.8844	127.1519
	Korsemeyer –Peppas	0.7845	0.8898	1.894 n=1.679	6493.5152	118.1213
	Hixson Crowell	0.6183	0.8496	0.037	11498.1366	123.5492

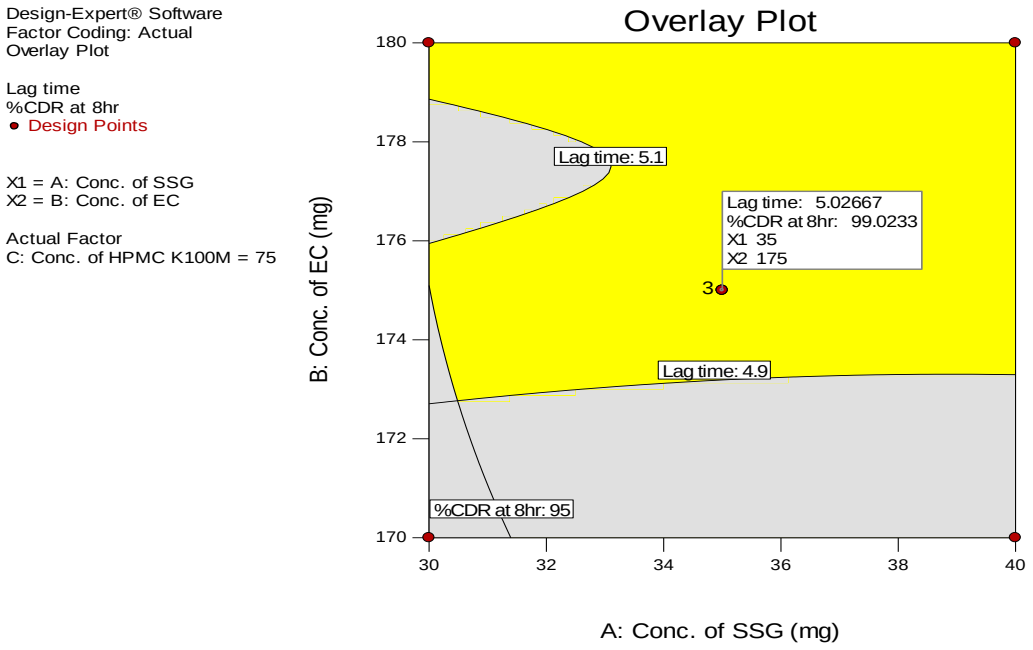


Figure 10: Overlay Plot of Batch BE13.

All the coated tablets of design batches BE1 to BE15 were evaluated for their various physical parameters which shows in Table 4 that includes the values of weight variation, hardness, thickness, diameter, friability, % drug content and lag time. Weight variation data of all the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. Thickness and diameter of all the tablets was in the range of 5.88 ± 0.022 to 6.18 ± 0.010 mm and 11.92 ± 0.022 to 12.00 ± 0.051 mm respectively. Hardness of the prepared tablets was observed within the range of 5.1 ± 0.014 to 5.9 ± 0.011 kg/cm^2. Friability of all the tablets were found to be less than 1 %. The drug content of all the batches of naproxen tablets was in the range of 95.5 ± 1.51 to 99.8 ± 1.42% and that is within the pharmacopoeial range. Lag time of all the prepared batches was found between 4.25 ± 0.24 to 5.25 ± 0.30 hrs. Batch BE13 shows predetermined lag time of 5.01 ± 0.19 hrs. Thus, all the physical parameters of the manually compressed tablets were quite within control.

In Vitro Dissolution Study

All Pulsatile tablets of Naproxen (Batch BE1 to BE15) were prepared using different concentration of sodium starch glycolate as superdisintegrant and also different concentration of hydrophobic polymer Ethyl cellulose and hydrophilic polymer HPMC K100M. Figure 3 shows the dissolution profile of the press coated tablets. HPMC K100M and Ethyl cellulose retains drug release property due to its gelling property. From the figure, it was evident that lag time and % CDR was dependent on the concentration of SSG, EC and HPMC K100M. It was observed that as the concentration of Ethyl cellulose and HPMC K100M increases, lag time increases. Among all these batches, batch BE13 containing optimum

concentration of ingredients has shown better lag time (5hr) and %CDR (98%) compared to all other batches. So, it was considered as optimized batch for pulsatile drug release of naproxen.

Statistical Analysis

A 3 level and 3 factor design with 2 independent variable at 3 different level are used to study the effect on dependent variable. Various models, such as linear, 2FI, quadratic and cubic, were fitted to the data for these responses simultaneously using Design Expert software and adequacy and good fit of the model was tested using analysis of variance (ANOVA). The multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS) provided by Design-Expert software were used as factors for selection of adequate models and listed in table 5 and 7 for response Y_1 and Y_2 respectively. Results of ANOVA for response lag time (Y_1) and % CDR at 8hr (Y_2) are listed in table 6 and 8 respectively.

Full Model Equation in Terms of Coded Factors

$$\mathbf{Y_1 = 5.03 - 0.020\ X_1 + 0.26\ X_2 + 0.34\ X_3 + 0.018\ X_1X_2 + 0.00075\ X_1X_3 + 0.17\ X_2X_3 + 0.017\ X_1^2 - 0.25\ X_2^2 - 0.20\ X_3^2,\ R^2 = 0.9781}$$

Positive sign infront of terms indicate synergistic effect while negative sign indicate antagonistic effect upon responses. From the equation, it may be concluded that positive sign of level X_2, X_3, X_1X_2, X_1X_3, X_2X_3, X_1^2 had positive effect on response while negative sign of X_1, $X_2^2$and X_3^2 had negative effect on response.

Reduced Model Equation

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X_2, X_3, X_2X_3, X_2^2, X_3^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

$$\mathbf{Y_1 = 5.03 + 0.26X_2 + 0.34X_3 + 0.17\ X_2X_3 - 0.25\ X_2^2 - 0.20\ X_3^2}$$

Above 2D counter plot and surface 3D plots shows the effect of concentration of Sodium starch glycolate (X_1), concentration of Ethyl cellulose (X_2) and concentration of HPMC K100M (X_3) on Lag time (Y_1). From the above graph it can be concluded that the coefficients X_2 and X_3 has more prominent effect on Lag time(Y_1) than coefficient X_1. It indicated that as the concentration of Ethyl cellulose and HPMC K100M increases, Lag time decreases.

Full Model Equation

$$\mathbf{Y_2 = 99.02 + 1.83\ X_1 + 0.21\ X_2 + 0.27\ X_3 - 0.80\ X_1X_2 - 0.25\ X_1X_3 + 0.23\ X_2X_3 - 2.21\ X_1^2 - 0.77\ X_2^2 - 0.70\ X_3^2,\ R^2 = 0.9868}$$

Positive sign infront of terms indicate synergistic effect while negative sign indicate antagonistic effect upon responses. From the equation it may be concluded that positive sign of level X_1, X_2, X_3, X_2X_3 had positive effect of on response while negative sign of X_1X_2, X_1X_3, X_1^2, X_2^2, X_3^2 had negative effect on response.

Reduced Model Equation

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X_1, X_1X_2, X_1^2, X_2^2, X_3^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Table 11: Stability Study of Optimized Formulation (BE13).

No. of Months	Lag time (n=3)	% Drug release in 8 hrs (n=3)
0	5 hr 02 min	98.90 ± 3.5
6	5 hr 01 min	98.79 ± 2.72

All values are expressed as mean ± standard deviation, n=3.

$$\mathbf{Y_2 = 99.02 + 1.83\ X_1 - 0.80\ X_1X_2 - 2.21\ X_1^2 - 0.77\ X_2^2 - 0.70\ X_3^2}$$

This 2D and 3D contour plots shows the effect of concentration of Sodium starch glycolate (X_1), Ethyl Cellulose (X_2) and HPMC K100M (X_3) on %CDR at 8hr (Y_2). Above 2D counter plots and surface 3D plot indicated that Concentration of SSG (X_1) has more prominent effect on % drug release than coefficients X_2 and X_3. As the concentration of SSG increases, % drug release also increases.

Check Point Analysis

Three check point batches were prepared & evaluated for Lag time & %CDR at 8 hrs, as shown in table 9. When measured % CDR values were compared with predicted % CDR, the differences were found to be not significant. Thus, it can be concluded that the obtained mathematical equation is valid for predicted values.

Optimization of Formulation

The overlay plot of responses generates an optimized area as per desired criteria. This was the most important part of the response surface methodology. The formulation of the drug which released the drug in controlled and complete manner was selected for optimum formulation. After studying the effect of the independent variables on the responses, the levels of these variables that give the optimum response were determined. The optimum formulation was selected based on the criteria of attaining complete and controlled drug release as well as lag time. Batch BE13 having 35 mg of SSG, 175 mg of EC and 75mg of HPMC K100M fulfilled maximum requisites of an optimum formulation because of better regulation of release rate. The said formulation have lag time of 5.02 hrs and 99.02% drug release in 8 hr.

Drug Release Kinetic Study

In order to examine the kinetic of drug release from prepared Pulsatile tablets, the dissolution data of optimized formulation BE13 was fitted into different kinetic models i.e. Zero order, First order, Higuchi model, Hixson-Crowell and Korsemeyer-Peppas model. The criteria for the selection of most suitable model were value of regression coefficient (R^2) nearer to 1, smallest values of Residual sum of squares (SSR) and Akaike Information Criteria (AIC). Table 10 shows the data obtained. The optimized formulation fitted well into Korsemeyer-Peppas, it was confirming the desired release profile. The calculated R^2 value for Korsemeyer-Peppas were 0.7845. According to Korsemeyer-Peppas equation, the release exponent "n" value is > 0.5, which indicates that drug release is non-fickian diffusion type.

Stability Study

Stability study of pulsatile tablet of naproxen was carried out for 6 Months at specified condition. The stability studies of the optimized formulation (BE13) shown no significant changes in the physical parameters, Lag time and % drug release in 8 hr when stored at 40 ± 2ºC/ 75 ± 5% RH. So, it was considered that formulation having good stability.

CONCLUSION

Naproxen Pulsatile release tablet was successfully formulated by direct compression method by using various superdisintegrants and coating polymers at different concentrations. Results of preformulation study of drug and excipients indicate that, it has good flow property and compressibility. Pulsatile release tablet of naproxen develops to satisfactory level in terms of predetermined lag time of 5 hrs and *in vitro* drug release. From the results of preliminary batches, further formulations as per Box Behnken design were prepared using different concentration of superdisintegrant and coating polymers at different concentrations. Amongst all the batches formulated, batch BE13 that contains 10% sodium starch glycolate as a superdisintegrant, 175 mg of ethyl cellulose and 75 mg of HPMC K100M which were used as a coating polymers shows predetermined lag time of 5 hrs and 99.32% of drug release. Accelarated stability studies proved that the formulation BE13 found to be stable after a period of 6 month of stability study. From this study, it was concluded that pulsatile tablet of Naproxen is taken at bed time and expected to release the drug in early morning hours during rheumatoid attacks.

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