

Optimization of Perindopril Erbumine Controlled Release Floating Tablet Using 3^2 Central Composite Design

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Abstract

The aim of present investigation was to develop efficient controlled release floating tablet (CRFT) of Perindopril Erbumine. Floating dosage form for gastric retention has potential to use as controlled-release drug delivery systems which providing opportunity for both local and systemic drug action. The tablets were prepared by using wet granulation techniques using PVP K 30, SFG and Acrypol 934. A 3^2 full factorial design (CCD) was applied to optimize two independent variables at three different levels by varied response variables. Two independent variables i.e. amount of SFG (i.e., polymer X_1) and amount of Acrypol 934 (i.e., polymer X_2) were varied at three different levels that was coded for low, medium and high (-1, 0, 1 respectively). The response variables T_6 (cumulative % amount of drug released in 6 hr) (Y_1), T_{12} (cumulative % amount of drug released in 12 hr) (Y_2), Q_{50} (time in minutes required to 50 % of drug released) (Y_3), FLT (Y_4), TFT (Y_5), and Swelling Index after 12 hr (Y_6) were selected for present study. ANOVA study was also employed to optimize for best fitted quadratic model. Compressed matrices exhibited Super case-II transport drug release kinetics approaching zero-order, as the value of release rate exponent (n) varied between 0.9430 and 1.0133. Formulation A4 was the optimized best formulation from the response surface plot and contour plot of all the formulation.

Key Words:

Acrypol 934, ANOVA, CCD, FLT, SFG, TFT.

INTRODUCTION

For the present study, the aim was to develop controlled release floating dosage form to increase the gastric residence time for the drug which leads to increase the bioavailability of drug. Many literatures were suggested that the most convenient method of controlled delivery of drug is undoubtedly oral, but oral controlled release of the drug for an extended period of time that exhibits more absorption in stomach and upper small intestine, has not been successful with conventional approaches. So, it has been decided to develop the controlled release floating dosage form as a novel approach for the drug delivery and the tablet is well known as most convenient dosage form among all oral drug delivery. Finally it was decided to develop a controlled release floating tablets (CRFT). [1, 2] Perindopril Erbumine is a novel antihypertensive agent, widely absorbed from the stomach and upper part of the small intestine. It has shorter elimination half life (0.8hr to 1hr), so necessity to frequent administration and bioavailability can be improved by making the drug completely absorbed in the stomach and upper part of the small intestine. CRFT of Perindopril Erbumine was developed using sterculia foetida gum (SFG) and Acrypol 934. [3, 4]

SFG is a natural gum and it is obtained from gummy extrudes from stem bark of sterculia foetida belongs to the family of sterculiaceae. It is freely soluble in water via hydration and practically insoluble in absolute ethanol. It is

used as suspending agent, viscosity enhancer and rate controlling polymer in controlled release dosage. [5, 6]

Acrypol 934 is a synthetic high molecular weight cross linked water soluble polymer of acrylic acid, which is known as "Carbomer". It is freely soluble in water and alcohol. It is used as cross linking agent for controlled release matrix as a rate controlling polymer, stabilizing agent in emulsion, thickening and viscosity modifying agent.

Optimization study was done to determine the appropriate concentration of SFG and Acrypol 934 in combination as a controlled release polymer and aim was to predict individual effect of both polymers (SFG and Acrypol 934) at different concentration level. A 3^2 full factorial design was selected to optimize two independent variable at three different levels by varied response variables. Experimental trials were performed at all nine possible combinations. Two independent variables i.e. amount of SFG (polymer X_1) and amount of Acrypol 934 (polymer X_2) were varied at three different levels that was coded for low, medium and high (-1, 0, 1 respectively). The response variables were measured by a multiple factorial regression analysis using the best fitted quadratic model for each trial and it was carried out in MS EXCEL 2007. Various computations required for current study using response surface plot and contour plot were carried out by employing software Design Expert version 8.0.7.1 A

statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses. [7, 8]

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1 . The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. ⁹

MATERIALS

Perindopril Erbumine was obtained as a gift sample from Zydus Cadila Healthcare limited, Ahmedabad. *Sterculia Foetida* Gum (SFG) was obtained as a gift sample by Medicinal natural products research laboratory, University Institute of Chemical Technology, Mumbai. PVP K 30 obtained as a gift sample from Alembic limited, Vadodara. Acrypol 934 was obtained as gift sample from Corel Pharma Chem, Ahmedabad. NaHCO_3 , Lactose, Talc, Mg. Stearate and IPA used in the present study were provided by K. J. College of pharmacy, Vadasma, Gujarat. India.

METHODS

Preparation of Perindopril Erbumine Controlled Release Floating Tablet

Perindopril Erbumine controlled release floating tablets were prepared by wet granulation techniques using different concentrations of various polymers. To prepare tablet, weighed all ingredients except talc and magnesium stearate and shifted through sieve no 40 then blend uniformly in glass mortar with pestle. After sufficient mixing, the blend was wetted by adding sufficient quantity of isopropyl alcohol as a granulating agent. Prepared wet mass was granulated by passing through sieve no 18. Prepared granules were dried at $50^\circ\text{C} - 60^\circ\text{C}$ for 20 min in hot air oven. After drying, dried granules were lubricated by adding sufficient quantity of magnesium stearate and talc for 5 min. The tablets were compressed using 6 mm punch on 8 station rotary punching machine.

Experimental Design [7, 8, 9]

A central composite design (CCD) was employed for the optimization of Perindopril Erbumine controlled release floating tablets. A 3^2 full factorial design was selected to optimize two independent variables at three different levels by varied response variables. Experimental trials were performed at all nine possible combinations. Two independent variables i.e. amount of SFG (polymer X_1) and amount of Acrypol 934 (polymer X_2) were varied at three different levels that was coded for low, medium and high (-1, 0, 1 respectively). The response variables T_6 (cumulative % amount of drug released in 6 hr) (Y_1), T_{12} (cumulative % amount of drug released in 12 hr) (Y_2), Q_{50} (time in minutes required to 50 % of drug released) (Y_3), FLT (Y_4), TFT (Y_5), and Swelling Index after 12 hr (Y_6) were selected for present study. The experimental design with corresponding formulations is outlined in **Table 1**.

Floating Properties [10]

To measure the floating properties, five tablets from each formulation were selected randomly and placed in beaker containing 250 ml of 0.1 N HCL (pH 1.2). The temperature

was maintained at $37 \pm 0.5^\circ\text{C}$. The time by which the tablet started to float on the surface of medium for FLT and entire duration of time by which the tablet constantly remained on the surface of the medium for TFT was noted. The Floating lag time (FLT) and Total Floating Time (TFT) of tablet of each formulation is shown in **Table 2**.

Swelling Study [10]

The extent of swelling can be measured in terms of percentage weight gain by the tablet. Five tablets from each formulation were selected randomly for the swelling study. Each tablet individually weighed (W_0) and separately placed in beaker containing 100 ml of 0.1N HCL (pH 1.2). The tablet was removed from each beaker after 1 hour of time interval and excess surface solvent from the tablet was wiped out carefully with filter paper. Each swollen tablet was reweighed (W_t) and the swelling index (SI) is calculated using the following formula,

$$\text{Swelling index (SI)} = [(W_t - W_0) / W_0] \times 100$$

Where, W_t = Final weight of tablet at time t (mg), W_0 = Initial weight of tablet (mg)

The value of swelling index for the tablet of each formulation is given in **Table 2**.

In Vitro Dissolution Study [11]

The *In-vitro* dissolution study for the tablet of each formulation was conducted as per United States Pharmacopoeia type II apparatus. The rotating paddle method was used to study the drug release from the tablets. Dissolution medium 900 ml of 0.1 N HCl (pH 1.2) was placed in dissolution vessel. The release was performed at $37^\circ\text{C} \pm 0.5^\circ\text{C}$ and at a rotational speed of paddle about 50 rpm. Tablets were placed in each dissolution vessel. The 5 ml samples were withdrawn at the time interval of one hour for 16 hrs. The collected samples were filtered through Whatman filter paper No. 40 and analyzed for drug content by UV Spectrophotometer. The absorbance for each sample was measured at 207 nm and the concentration of drug present was calculated using calibration plot of Perindopril Erbumine. Then, the cumulative percentage amount of drug released after each time interval was calculated using the formula,

$$\text{Cumulative Amount of Drug Release} = C \times DF \times DM$$

Where, C = Concentration of drug ($\mu\text{g/ml}$), DF = Dilution Factor is 1, DM = Dissolution Medium (900 ml)

Statistical analysis [12]

Statistical optimization of perindopril erbumine tablet was done by design expert software, Version 8.0.7.1. the study type was response surface, 9 runs were applied to the design type central composite and design model was selected as quadratic. The quadratic model is best fitted for the results to determine the effect of independent variable on response variables. There was considerable difference observed in minimum and maximum values of each response variable with respect to the independent variables. By applying two sided ANOVA with 95 % confidence level, their predicted values were found for each response variables. The value of $P < 0.05$ was considered to be significant. To demonstrate graphically the influence of each factor on responses, the response surface plots and Contour plots were generated.

RESULTS AND DISCUSSION

From the preliminary study, it was found that SFG and Acrypol 934 were efficient polymer to achieve controlled drug releasing property by forming swellable matrix with the drug. Therefore, optimization study was applied to find best possible concentration of both polymer for the present investigation. The formulations were designed by 3^2 full factorial design which is shown in **Table 1**. Amount of SFG and amount of acrypol 934 were selected as independent variables and it was coded as X_1 and X_2 respectively. Both variable optimized by varied at three different level.

The matrix tablets of designed formulation were prepared by wet granulation method. Developed tablets were evaluated for various response variables. The response variables T_6 (cumulative % amount of drug released in 6 hr) (Y_1), T_{12} (cumulative % amount of drug released in 12 hr) (Y_2), Q_{50} (time in minutes required to 50 % of drug released) (Y_3), FLT (Y_4), TFT (Y_5), and Swelling Index after 12 hr (Y_6) were selected for present investigation. The results of all response variables are shown in **Table 2**.

The values of T_6 was varied from 30.89% to 43.39%, T_{12} was varied from 57.93% to 84.19%, Q_{50} was varied from 408 min to 612 min, FLT was varied from 76 seconds to 95 seconds, TFT varied from 16 hrs to 22 hrs, SWI was varied from 96% to 130%. The quadratic model is best fitted to determine the effect of independent variable on response variables. There was considerable difference observed in minimum and maximum values of each response variable with respect to the independent variables. By applying two sided ANOVA with 95 % confidence level, their predicted values were found for each response variables and it was shown in **Table 3**.

Drug release profile from all the developed formulation was applied for model dependent kinetics by providing the kinetic treatment and it was exhibited Super case-II transport drug release kinetics approaching zero-order, as the value of release rate exponent (n) varied between 0.9430 and 1.0133. The kinetic treatment of drug release profile for all the formulation A_1 to A_9 was shown in **Table 4**.

Table 1: Selected Factor Combinations as per 3^2 full factorial design

CODE	CODED LEVEL		ACTUAL VALUES (mg)	
	X_1	X_2	X_1	X_2
A ₁	-1	-1	10	6
A ₂	-1	0	10	8
A ₃	-1	1	10	10
A ₄	0	-1	14	6
A ₅	0	0	14	8
A ₆	0	1	14	10
A ₇	1	-1	18	6
A ₈	1	0	18	8
A ₉	1	1	28	10

Table 2: The results of each response variables as per 3^2 full factorial design

Code	Code X_1	Code X_2	T_6 (%)	T_{12} (%)	Q_{50} min	FLT Sec	TFT hrs	SWI (%)
A1	-1	-1	43.39	84.19	408	80	16	96.89
A2	-1	0	37.48	73.89	462	79	17	104.2
A3	-1	1	37.68	73.27	474	76	19	113.7
A4	0	-1	40.09	80.12	450	83	18	102.5
A5	0	0	38.41	76.27	456	82	20	110.9
A6	0	1	34.41	69.18	522	79	21	123.7
A7	1	-1	40.88	74.76	453	95	19	106.9
A8	1	0	34.48	66.39	534	90	20	126.7
A9	1	1	30.89	57.93	612	87	22	130.3

Table 3: Significant level and predicted values of each response variables

Response	Name	Units	Obs	Analysis	P-value	Predicted Value
Y_1	T_6	%	9	Polynomial	0.0497	039.93
Y_2	T_{12}	%	9	Polynomial	0.0241	078.48
Y_3	Q_{50}	min	9	Polynomial	0.0346	451.33
Y_4	FLT	Sec	9	Polynomial	0.0036	081.56
Y_5	TFT	hr	9	Polynomial	0.0064	018.56
Y_6	SWI	%	9	Polynomial	0.0257	103.43

Table 4: Kinetic treatments to dissolution profile for each formulation A1 to A9

Code	Zero Order		Hixon Crowell		Korsmeyer Peppas			Higuchi Plot	
	(R ²)	K ₀	(R ²)	K _H	(R ²)	n	K _k	(R ²)	Kp
A1	0.9996	6.9659	0.9564	0.6225	0.9996	0.9670	0.9534	0.9654	0.0342
A2	0.9979	6.2374	0.9592	0.5961	0.9966	1.0133	0.7602	0.9626	0.0381
A3	0.9984	6.1665	0.9576	0.5898	0.9974	0.9987	0.7834	0.9640	0.0386
A4	0.9999	6.6667	0.9591	0.6106	0.9993	0.9795	0.8786	0.9628	0.0357
A5	0.9991	6.3956	0.9606	0.6020	0.9975	0.9983	0.8014	0.9619	0.0371
A6	0.9992	5.7928	0.9638	0.5748	0.9941	1.006	0.7019	0.9585	0.0409
A7	0.9973	6.2349	0.9509	0.5891	0.9985	0.9760	0.8559	0.9696	0.0383
A8	0.9995	5.4715	0.9535	0.5484	0.9978	0.9452	0.7954	0.9675	0.0437
A9	0.9991	4.8097	0.9534	0.5147	0.9940	0.9430	0.7014	0.9678	0.0497

Response Y₁

$$T_6 = + 56.065 + 1.03 * X_1 - 3.953 * X_2 - 0.143 * X_1 * X_2 - 0.014 * X_1^2 + 0.26 * X_2^2$$

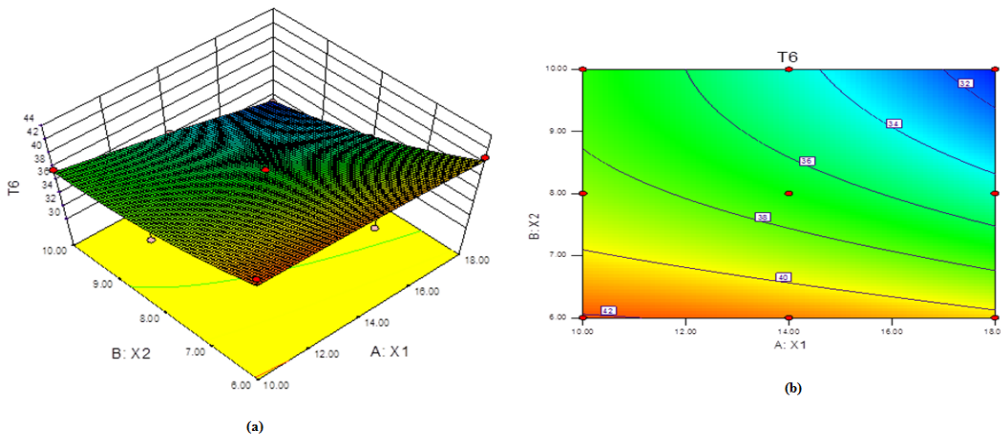
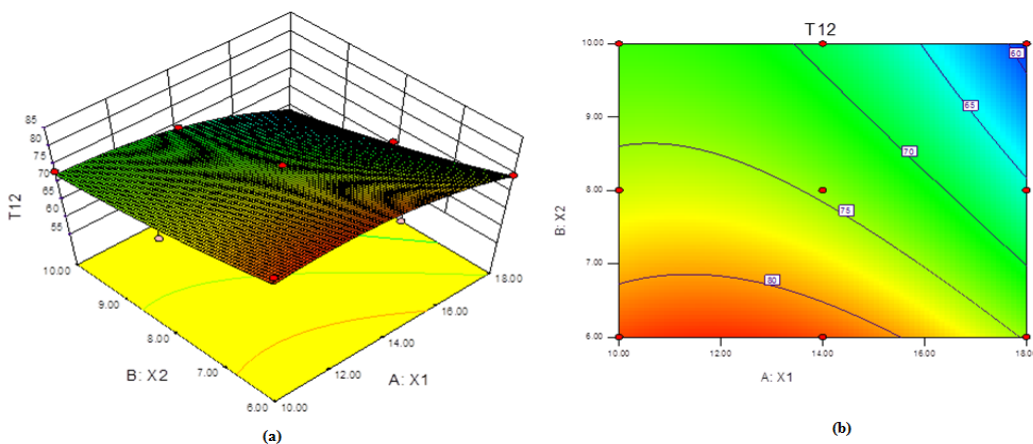
The regression co efficient was found from the ANOVA study and it was found that the negative effect of X₂ coefficient while positive of X₁ coefficient at low level on the response variable but at high level opposite results were found. It was ment that the concentration of Acrypol 934 was not created much impact on drug release rate when it compared with the concentration of SFG at low level in the formulations. Negative coefficient was found in combination of both variables and it was suggested that when the concentration of polymer to drug was increased, the drug release from the dosage was decreased. When the concentration of SFG was increases, the drug release rate

was significantly reduced. It was found from the response surface plot and contour plot shown in **Figure 1**.

Response Y₂

$$T_{12} = +73.068 + 6.17 * X_1 - 4.87 * X_2 - 0.185 * X_1 * X_2 - 0.22 * X_1^2 + 0.27 * X_2^2$$

The regression equation was suggested that the effect of variable X₁ and X₂ on response Y₂. From the **Figure 2**, it was found that at the low level the effect of variable X₁ on the drug release was more considerable than the variable X₂. But at high level both are equally significant on the response variable. The negative coefficient was found for the combination of X₁ and X₂ suggesting that the cumulative percentages of drug release was significantly reduced by increasing the concentration of independent variables in combination.

**Figure 1:** (a) Response surface plot and (b) Contour plot for response Y₁**Figure 2:** (a) Response surface plot and (b) Contour plot for response Y₂

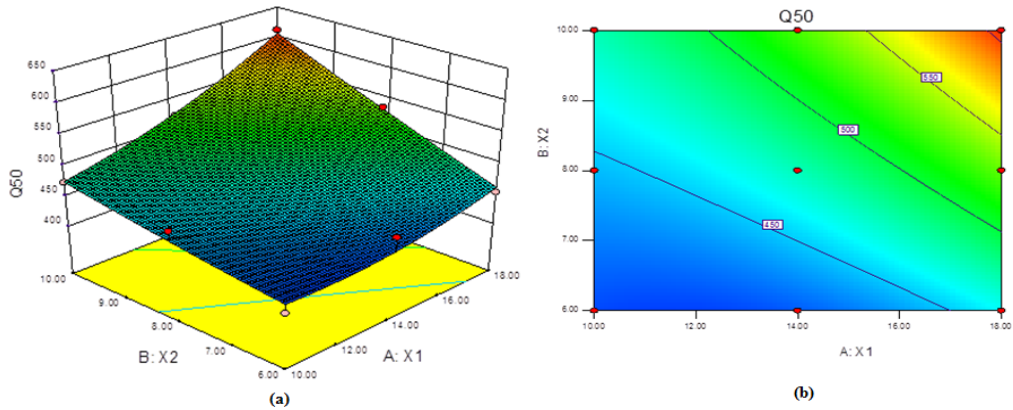


Figure 3: (a) Response surface plot and (b) Contour plot for response Y_3

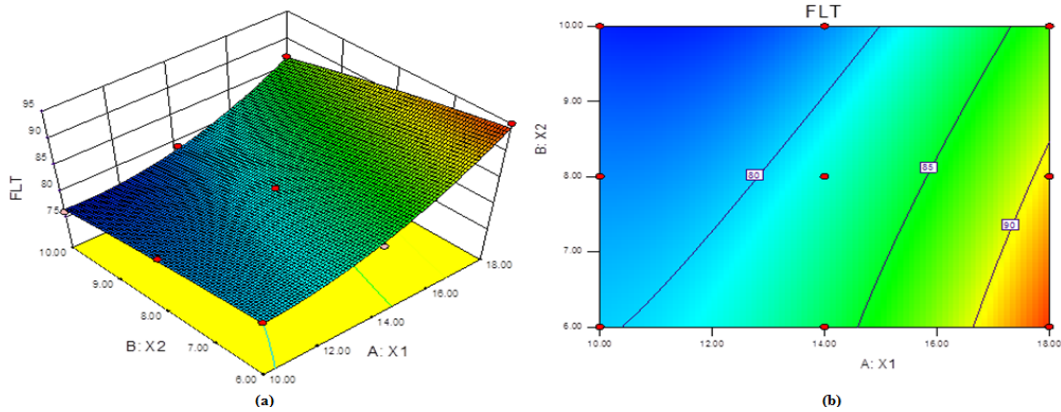


Figure 4: (a) Response surface plot and (b) Contour plot for response Y_4

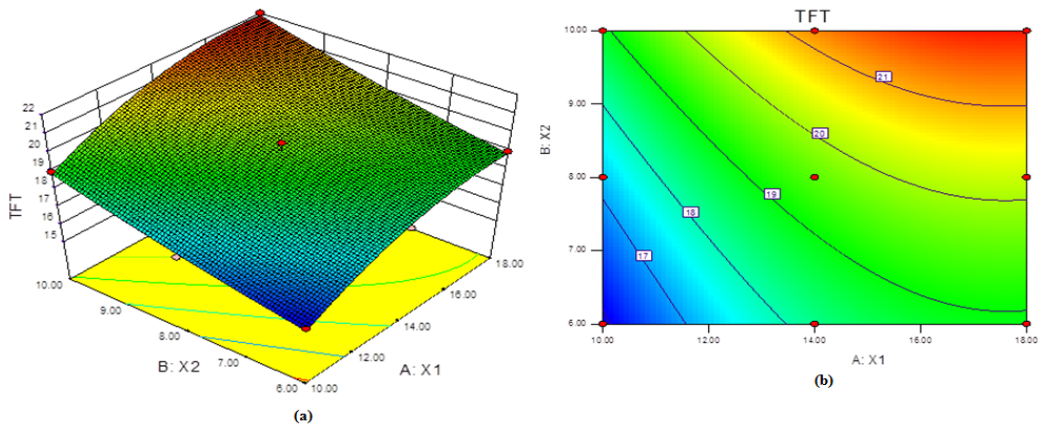


Figure 5: (a) Response surface plot and (b) Contour plot for response Y_5

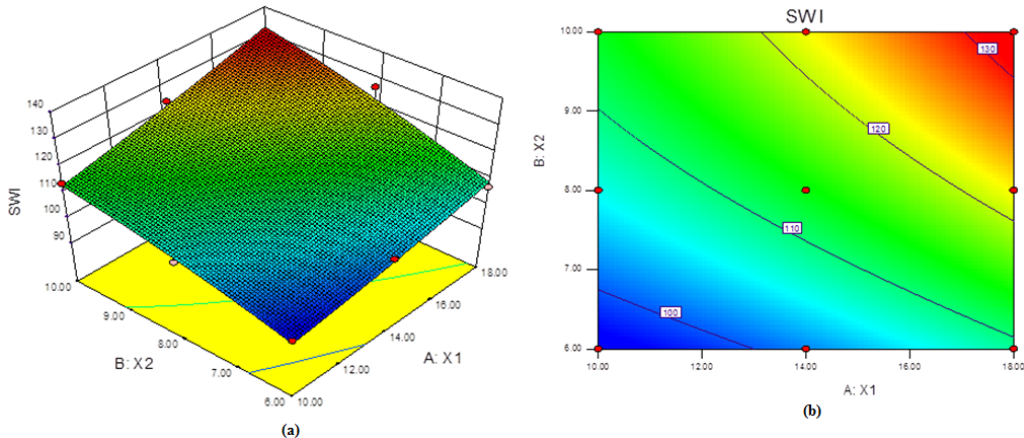


Figure 6: (a) Response surface plot and (b) Contour plot for response Y_6

Response Y₃

$$Q_{50} = +670.71 - 38.0 * X_1 - 25.94 * X_2 + 2.91 * X_1 * X_2 + 0.91 * X_1^2 + 0.6 * X_2^2$$

The regression equation was suggested that the effect of variable X₁ and X₂ on response Y₃ was found negative. It might be indicated that the effect of selected variable on response (Y₃) was not significant individually at low level. But the positive coefficients in the equation were indicated that the significant effect observed when the selected variables were used at high level as well as in combination. From the **Figure 3**, it was found that at the low level the individual effect of variables X₁ and X₂ on the response Y₃ were not considerable significant. But at high level both are equally significant on the response variable. And in combination also significant response was found. Hence, this results might be revealed that the time required for 50 % drug release was enhanced with the concentration of polymer (SFG and Acrypol 934) to drug in the dosage increasing.

Response Y₄

$$FLT = + 90.10 - 3.0 * X_1 + 1.75 * X_2 - 0.13 * X_1 * X_2 + 0.198 * X_1^2 - 0.08 * X_2^2$$

The regression equation was suggested that the variable X₂ was more significant than the variable X₁ because negative coefficient was found for variable X₁ by ANOVA. It was suggested that FLT was enhanced when the level of SFG in the formulations was enhanced. And, opposite effect was found by X₂ variable because the value of its coefficient was positive. It was indicated that the value of FLT was reduced when the level of X₂ variable enhance. From the **Figure 4**, it was revealed that the level of X₂ variable more significant because the FLT value lower towards the direction of higher level of X₂ variable than X₁ variable.

Response Y₅

$$TFT = + 0.76 + 1.83 * X_1 + 0.083 * X_2 + 2.67 * X_1 * X_2 - 0.052 * X_1^2 + 0.042 * X_2^2$$

The coefficient for both variables was found to be positive at low level, high level and in combination. It was suggested that there was linear relationship observed on response variable by the selected X₁ and X₂ variable. From the **Figure 5**, it was found that gradually rises the value of TFT as the concentration of both polymer SFG and Acrypol 934 increases. But, it was also indicated that the level of X₂ variable was more predominant than the value of X₁ variable. Because the response direction move towards the higher level of X₂ variable than X₁ variable.

Response Y₆

$$SWI = +50.45 - 0.91 * X_1 + 8.64 * X_2 + 0.21 * X_1 * X_2 + 0.047 * X_1^2 - 0.40 * X_2^2$$

The coefficient of X₂ variable was found to be positive at low level but X₁ variable coefficient was negative. It was suggested that X₁ variable move towards the predicted value positively with the concentration of Acrypol 934 while negatively observed with the concentration of SFG at low level but at high level vice versa results were obtained. Both variable might be affecting SWI significantly but the effect of X₂ variable was more predominant than X₁ variable. From the **Figure 6**, it was found that the response value was increased by increasing the level of both variable (X₁ and X₂).

CONCLUSION

Controlled release floating tablets of Perindopril Erbumine with SFG and Acrypol 934 were prepared and optimized using central composite experimental design (3² Full Factorial Design) and multiple response optimizations. The quantitative effect of these factors on the release rate could be predicted by using polynomial equations. The model was found to be satisfactory for describing the relationships between formulation variables and individual response variables. The experimental values of each response variables obtain from the optimized formulation were very close to the predicted values. The developed tablets were found desirable drug release kinetics and found to be zero order. Formulation A₄ was found to be best optimized formulation because of its desirable drug release kinetics and other response variables.

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