FACTOR INFLUENCE STUDY OF IVABRADINE HCL OSMOTIC PUSH PULL TABLETS USING FRACTIONAL FACTORIAL DESIGN

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ABSTRACT

A push pull osmotic tablets of Ivabdradine was formulated and different factors affecting the release profile were studied with the help of design of experiments. A fractional factorial design was used for the factor influence study. Various core and coating factors were selected for the study. The responses selected were lag time, Zero order rate constant, PCUR at 24 hrs. ANOVA and regression analysis were used for the identification of significant factors and constructing the polynomial equation representing the responses. A 5 % SL (p< 0.05) was chosen for the study. Various plots like Half normal plot, Normal plot, Pareto chart were also studied. The factors which were affecting the PCUR at 24 hrs were identified as Propylene glycol > weight gain> Nacl in the DL. The significant factors which were affecting the R^2 were Nacl DL> Nacl PL. The lag time for the drug release was greatly affected by PEG > Weight gain > Nacl in the DL. The simultaneous effect of two factors were represented and studied with the help of contour plots and response surface plots.

Keyword: Design of experiments, PCUR, Contour plot, Response surface plot, Factor influence study.

INTRODUCTION

Design of experiments is nowadays widely used for the pharmaceutical product development and optimization. One has to be very conscious while choosing the right design for any study. As the statistical designs are based on assumptions, a wise selection of design is mandatory for the success of the research. Plenty of designs are available for designing the experiments during the product development. The following flow chart will be showing the basic steps for the systematic approach followed while applying the DoE in product development. With the help of the designed experiments, the effects of multiple variables on the responses can be studied. When sufficient literatures are available about the different factors affecting the product as well as process, the first step, ie, the screening study can be omitted. Out of many trivial factors the vital factors were identified and can proceed with the factor influence study. Factor influence study will be helpful for identifying and quantifying the significant factors. So final optimization can only include the significant factors identified after factor influence study. This step will minimize the number of factors included in the optimization study thus drastically reducing the experimental trials.

Fractional factorial designs are reduced factorial designs which can be used when many vital factors are to be included in a factor influence study. In the present study, push pull osmotic tablets of ivabradine Hcl were developed with the help of fractional factorial design. Numbers of factors were identified as vital after screening study. So before optimization a factor influence study was performed to quantify the effect of the vital factors. This would be helpful for the optimization of the formulation where we can only concentrate on the highly significant factors obtained after factor influence study.

Thus the number of experimental trials can be further minimized and better design can be selected for the optimization. Ivabradine Hcl, A heart rate lowering agent used for the treatment of Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm. The formulation is available in the market as immediate release dosage form to be taken twice daily. A once daily Osmotic drug delivery system of Ivabradine Hcl was developed with an intention of more patient compliance. A zero order release, which reduces the fluctuations in the plasma concentration, is only expected in the case of osmotically controlled systems.

MATERIALS AND METHODS

Materials

The Ivabradine Hcl was received as gift sample from Alembic Pharmaceuticals Limited; Butylated hydroxyl toluene, Sodium lauryl sulfate, Sodium chloride was received from Merck; Polyethylene Oxide and cellulose acetate was received from signet; Dibasic calcium phosphate from Innophos; Magnesium stearate from Ferro; iron oxide and Propylene glycol from Alembic Limited. Other regents were of analytical grade.

Methods

I. Formulation and evaluations of Push pull osmotic tablets of Ropinirole Hcl [2]

A fractional factorial design with 8 selected factors **2 [8-4]**(ie 1/32 fraction) with **Resolution IV** was selected for the study. 16 trials with 4 centre points were planned for the study. The selected factors with levels chosen are given in the Table 1. The responses selected for the study were given in the Table: 2. The formula table showing all the ingredients taken in each trial is explained in the Table: 3 and 4.

The prepared granules of both the pull layer and push layer of trial 1- 20 were weighed separately in sachets. First drug layer was compressed using rotary tablet compression machine and made thin tablet and then push layer was added by setting the dye cavity and in the upper pull layer tablet was put as a plug and final sharp compression was carried out. By this bilayer tablets were made. Hardness was adjusted while compressing the granules. 5.0 mm biconcave punch was used in preparation of bi layer tablets.

Coating and drilling of core tablet.[3,4]

The prepared bi layer tablets were then coated with coating solution (Acetone :water 90:10) Coating of core tablet was done by conventional coating method in coating pan. 10 tablets were removed at an interval of 30min and increase of weight was noted down until it was observed sufficient %wt gain. Coated tablets were allowed to dry completely in a hot air oven at $60\,^{0}C$ and finished by standard polishing procedure. The drug delivery orifice having diameter of 0.6 mm was made on the surface of one side of the tablets(above the drug layer) by using Micro drill. High speed stainless steel drill bits were used for drilling.

Flow chart of the proceedings using DoE [1]

The systematic steps of the product optimization using DoE is shown in the flow chart given in figure.1
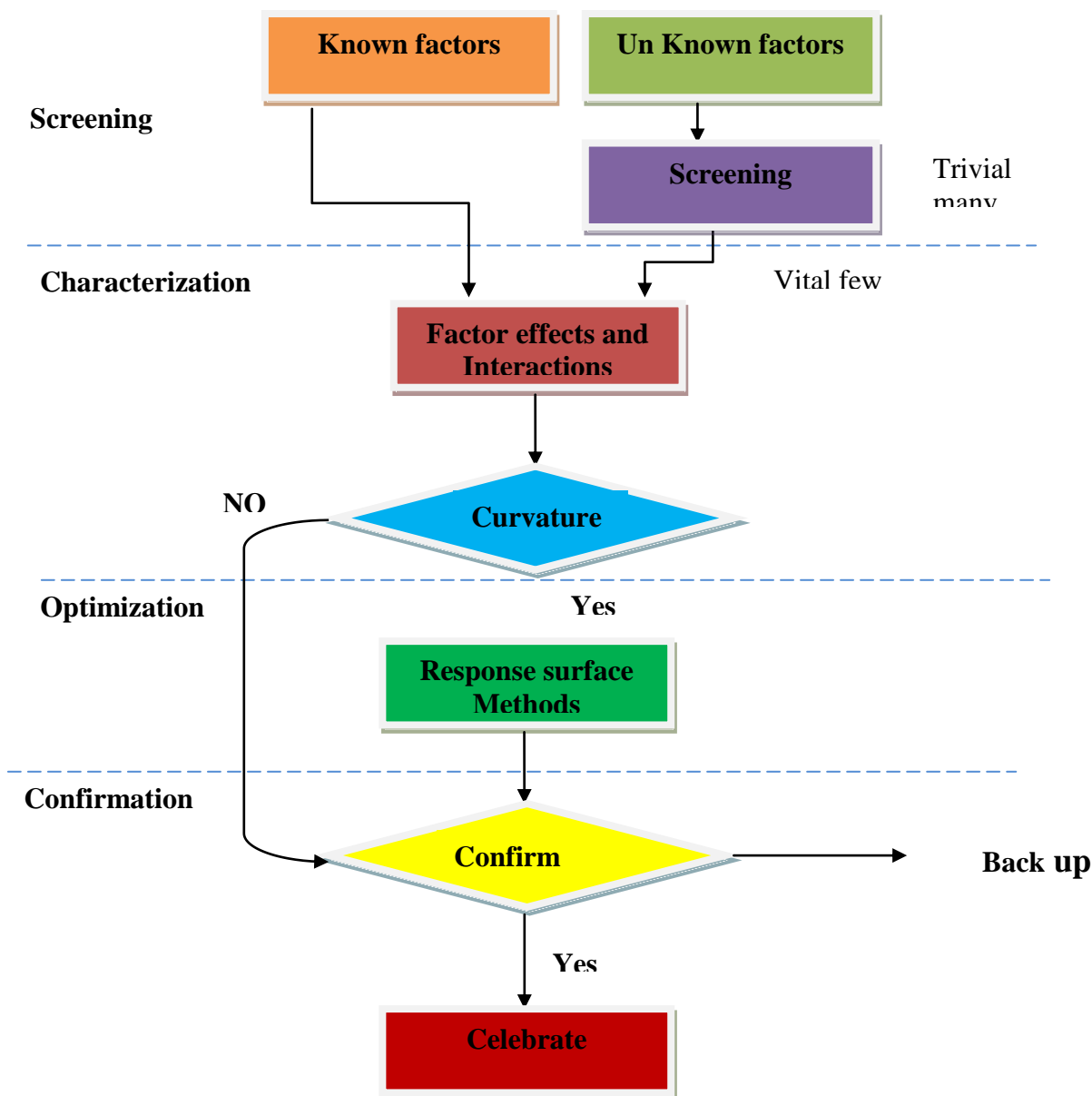
Fig. 1: It shows systematic steps of the product optimization using DoE

Table 1: It shows the selected Factors with levels affecting osmotic push pull delivery system for the factor influence study

Factors		Levels	
		Min(-)	Max(+)
1	PEO in the drug layer (% w/w of the API)	10	100
2	Nacl concentration in drug layer(% w/w core tablet)	1	10
3	SLS in the drug layer (%w/w of the drug layer)	1	5
4	PEO (coagulant) in the push layer (% w/w of the drug layer)	5	50
5	Sodium chloride in the Push layer (% w/w % of the extender)	5	50
6	SLS in the Push layer(%w/w of the push layer)	1	5
7	Propylene Glycol (% w/w of the coating weight)	1	10
8	Weight gain (%)	10	20

Table 2: It shows the selected response for the factor influence study

Response	Unit	Weightage
Cumulative release at 24 Hrs	%	+++++
R^2	----	++++
Lag time	Hrs	+++

Table 3: It shows the contents of the formulation IB 1-10

	Ingredients	IB 1	IB2	IB3	IB4	IB5	IB6	IB7	IB8	IB9	IB 10
1	ivabradine hydrochloride	10.91	10.91	10.91	10.91	10.91	10.91	10.91	10.91	10.91	10.91
2	Dibasic calcium phosphate	36.49	26.67	31.99	22.17	34.49	24.67	29.99	20.17	36.47	26.65
3	PEO 400 K	1.09	10.91	1.09	10.91	1.09	10.91	1.09	10.91	1.09	10.91
4	Sodium chloride	0.50	0.50	5.00	5.00	0.50	0.50	5.00	5.00	0.50	0.50
5	BHT	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.025	0.025
6	SLS	0.50	0.50	0.50	0.50	2.50	2.50	2.50	2.50	0.50	0.50
7	IPA										
8	Magnsium stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
9	PEO 7000 K (WSR 302)	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	25.00	25.00
10	Sodium chloride	0.13	1.25	1.25	0.13	1.25	0.13	0.13	1.25	1.25	12.50
11	Dibasic calcium phosphate	39.62	38.50	36.70	37.82	36.70	37.82	39.62	38.50	14.18	2.93
12	BHT	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.03
13	SLS	0.45	0.45	2.25	2.25	2.25	2.25	0.45	0.45	2.25	2.25
14	Iron oxide Red	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
15	IPA										
16	Magnsium stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
15	Cellulose acetate	9.3	18.1	18.9	7.6	8.6	18.8	17.1	9.4	18.1	9.3
16	Acetone	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
18	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
19	Propylene Glycol	0.19	0.95	0.10	1.90	0.95	0.19	1.90	0.10	0.95	0.19
	Total Weight of Coating	9.5	19.0	19.0	9.5	9.5	19.0	19.0	9.5	19.0	9.5
	Total tablet weight	104.5	114.0	114.0	104.5	104.5	114.0	114.0	104.5	114.0	104.5

Table 4: it shows the contents of the formulation IB 11-20

	ingredients	IB11	IB 12	IB 13	IB 14	IB15	IB16	IB17	IB18	IB19	IB20
1	ivabradine hydrochloride	10.91	10.91	10.91	10.91	10.91	10.91	10.91	10.91	10.91	10.91
2	Dibasic calcium phosphate	31.97	22.15	34.47	24.65	29.97	20.15	28.32	28.32	28.32	28.32
3	PEO 400 K	1.09	10.91	1.09	10.91	1.09	10.91	6.00	6.00	6.00	6.00
4	Sodium chloride	5.00	5.00	0.50	0.50	5.00	5.00	2.75	2.75	2.75	2.75
5	BHT	0.025	0.025	0.025	0.025	0.025	0.025	0.014	0.014	0.014	0.014
6	SLS	0.50	0.50	2.50	2.50	2.50	2.50	1.50	1.50	1.50	1.500
7	IPA										
8	Magnsium stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
9	PEO 7000 K (WSR 302)	25.00	25.00	25.00	25.00	25.00	25.00	13.75	13.75	13.75	13.75
10	Sodium chloride	12.50	1.25	12.50	1.25	1.25	12.50	3.78	3.78	3.78	3.78
11	Dibasic calcium phosphate	4.73	15.98	4.73	15.98	14.18	2.93	23.81	23.81	23.81	23.81
12	BHT	0.03	0.03	0.03	0.03	0.03	0.03	0.01	0.01	0.01	0.01
13	SLS	0.45	0.45	0.45	0.45	2.25	2.25	1.35	1.35	1.35	1.35
14	Iron oxide Red	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
15	IPA										
16	Magnsium stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
15	Cellulose acetate	8.6	18.9	18.8	8.6	9.4	17.1	13.5	13.5	13.5	13.5
16	Acetone	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
18	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
19	Propylene Glycol	0.95	0.10	0.19	0.95	0.10	1.90	0.78	0.78	0.78	0.78
	Total weight of coating	9.5	19.0	19.0	9.5	9.5	19.0	14.3	14.3	14.3	14.3
	Total tablet weight	104.5	114.0	114.0	104.5	104.5	114.0	109.3	109.3	109.3	109.3

In vitro dissolution study [5]

Dissolution test was performed using USP II paddle apparatus (DS-8000, Lab India, Analytical instrument pvt ltd, Navi Mumbai, India.) at 37˚C± 0.5˚C in 900 ml of phosphate buffer 6.8. Paddle speed was kept at 50 rpm. Samples were withdrawn after predetermined. time intervals of 1,2,3,4,6,8,12,16,20,24 hrs and the drug content was measured using an UV spectrophotometer at the 286 nm. Samples were suitably diluted and absorbance was measured. Cumulative percentage drug released was calculated for each batch. The study was performed in triplicate and the average was reported. The data of % cumulative release from each trial batch were subjected to kinetic release studies to assess the fit into the zero-order release kinetics. The R^2 value was found out to determine the best fit zero order release kinetics.

Analysis of responses [6,7]

For all the batches, the Push pull osmotic tablets were formulated as per the procedure explained in the methods. All the batches were subjected to in vitro dissolution using USP II (paddle) Apparatus up to 24 hour. The samples were withdrawn at an interval of 1hr and analyzed using UV Spectrophotometer (Shimadzu1800) at 286 nm. From graph of %cumulative drug release verses time, lag time ($t_{10\%}$) T90 and R^2 values were determined.

ANOVA and regression analysis

The results obtained for the study design was analysed with the help of design expert software and significance of factors were found out by ANOVA analysis. The hypothesis were tested with a level of significance 5 % ($p < 0.05$)

Polynomial equation

From the regression analysis of the responses the mathematical equation can be constructed which can be used for the prediction of the responses at any selected levels of the factors. If the suggested model for the optimization is linear, the following linear model would be used,

$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 \ldots\ldots\ldots + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{123} X_1 X_2 X_3 + error$

Half Normal plot and normal plot

For 2-level factorial designs, this plot can be used to choose significant effects.

Normal plot

For 2-level factorial designs, this plot can be used to choose significant effects. They show up as outliers on the normal probability plot.

Pareto chart

Pareto chart is bar graph for the clear identification of the significant factors.

Contour plots and response surfaces plots

Contour plot is a 2D graphical representation of the effect of less than 3 factors on a single response. Response surface plots are the 3D version of the contour plot. A better understanding will be possible with the help of response surface plots.

RESULT AND DISCUSSION

Factor influence study of the Ivabdadine Hcl push pull osmotic tablets was done with the help of 2_{IV} [8-4] fractional factorial designs. Twenty trials were formulated as per the procedure given in the materials and methods.

The invitro dissolution of each trial was performed as per the procedure given in the materials and methods. The PCUR at 24 hrs, R^2, and the lag time was recorded and analysed with the help of design expert software 8.0.7.1 version. The result of the invitro dissolution profile was given in the Table.5.

Analysis of responses – PCUR at 24 hrs

With the help of the half normal plot, normal plot and pareto chart the significant factors affecting the PCUR was determined. The plots are given in the figures 2, 3 and 4. From the graph it was evident that the factor which are affecting the cumulative release up to 24 hrs are B (Nacl in the DL), G (Propylene glycol) H (the weight gain). The Shapiro-Wilk Normality Test indicates the non significance of the non selected factors. From the pareto chart also it was clearly

evident that the factors B, G, H are the significantly affecting the cumulative response at 24 hrs. All the factors cross the t limit and G and H crosses the Bonferroni limit. The magnitude of the effect can be written as Propylene glycol > weight gain > sodium chloride in the drug layer.

Table 5: It shows the result of the dissolution study

Trial NO	CUR at 24 hr	R^2	Lag time
IB1	70.1	0.952	4.1
IB2	52.3	0.8489	3.5
IB3	70.4	0.9315	4
IB4	100	0.997	3
IB5	82.2	0.8713	3.5
IB6	35.3	0.9531	4.5
IB7	84.2	0.9993	3.6
IB8	100	0.9549	3
IB9	82.5	0.9598	4.2
IB10	76	0.8582	4.1
IB11	100	0.9689	2.9
IB12	55.1	0.9982	4.7
IB13	50	0.8573	5
IB14	90.2	0.8614	3.5
IB15	78.5	0.9978	3.5
IB16	100	0.9781	3.1
IB17	80.5	0.9263	4
IB18	79.2	0.9455	3.4
IB19	80.2	0.9331	4
IB20	79	0.9229	3.6

The significance level selected for the study was 5 % and the p value was 0.05. Values of "Prob > F" less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant. In this case **B (p =*0.0062*), G (p =*0.0018*), and H (p =*0.0024*)** are significant model terms. The Model F-value of 12.29 implies the model is significant. There is only a 0.02% chance that a "Model F-Value" this large could occur due to noise. The "Lack of Fit F-value" of 5.00 implies the Lack of Fit is not significant relative to the pure error.

Fig. 2: It shows the Half Normal plot of the effect of the factors on PCUR at 24 hrs
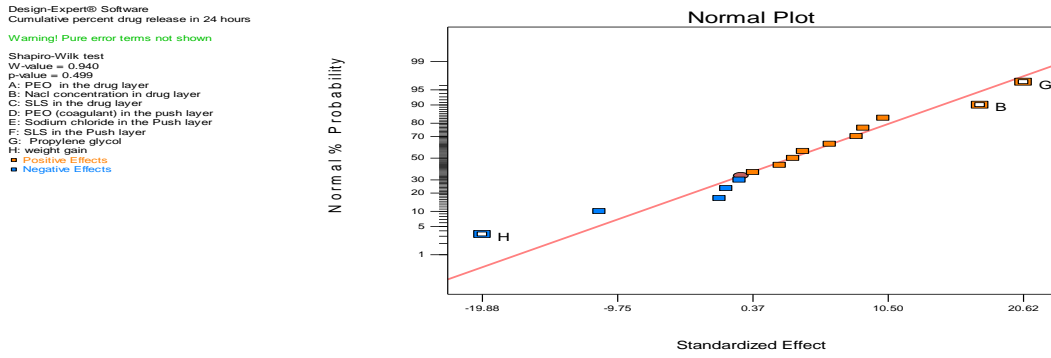
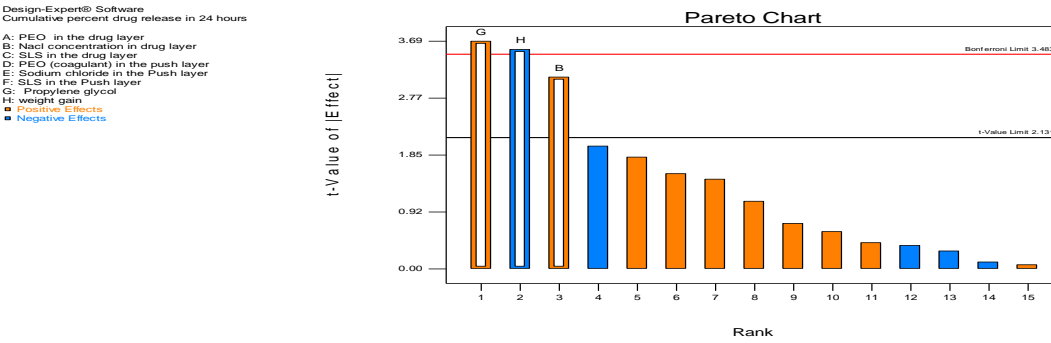**Fig. 3: It shows the Normal plot of the effect of the factors on PCUR at 24 hrs**

Fig. 4: It shows the Pareto chart of effect of the factors on PCUR at 24 hrs

The polynomial equation representing the PCUR at 24 hrs was given as,

Cumulative percent drug release in 24 hours = +84.64028+1.93056 * Nacl in drug layer +2.29167 * Propylene glycol -1.98750 * weight gain

Figure 5 shows the contour plot and response surface plot of the simultaneous effect of Nacl DL and Propylene glycol on the PCUR at 24 hrs at a time. At lower concentration of propylene glycol Nacl DL had little effect. High PCUR at 24 hrs would be expected at high levels of both the factors.
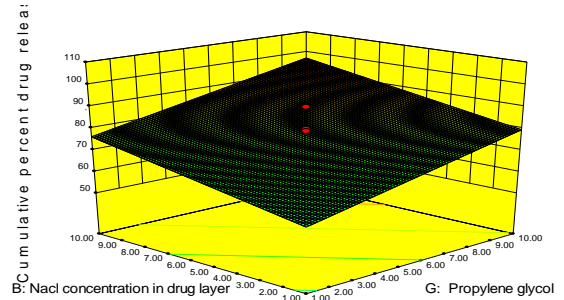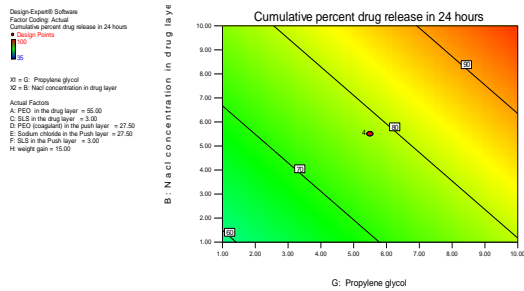
Fig. 5: It shows the Contour plot and RS Plot – Effect of Nacl DL and Propylene Glycol on PCUR at 24 hrs
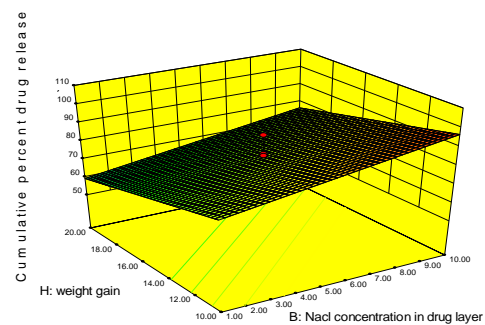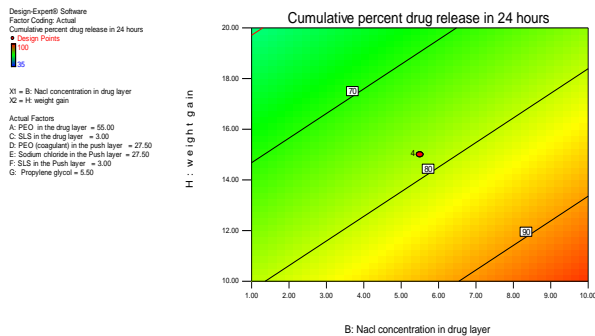
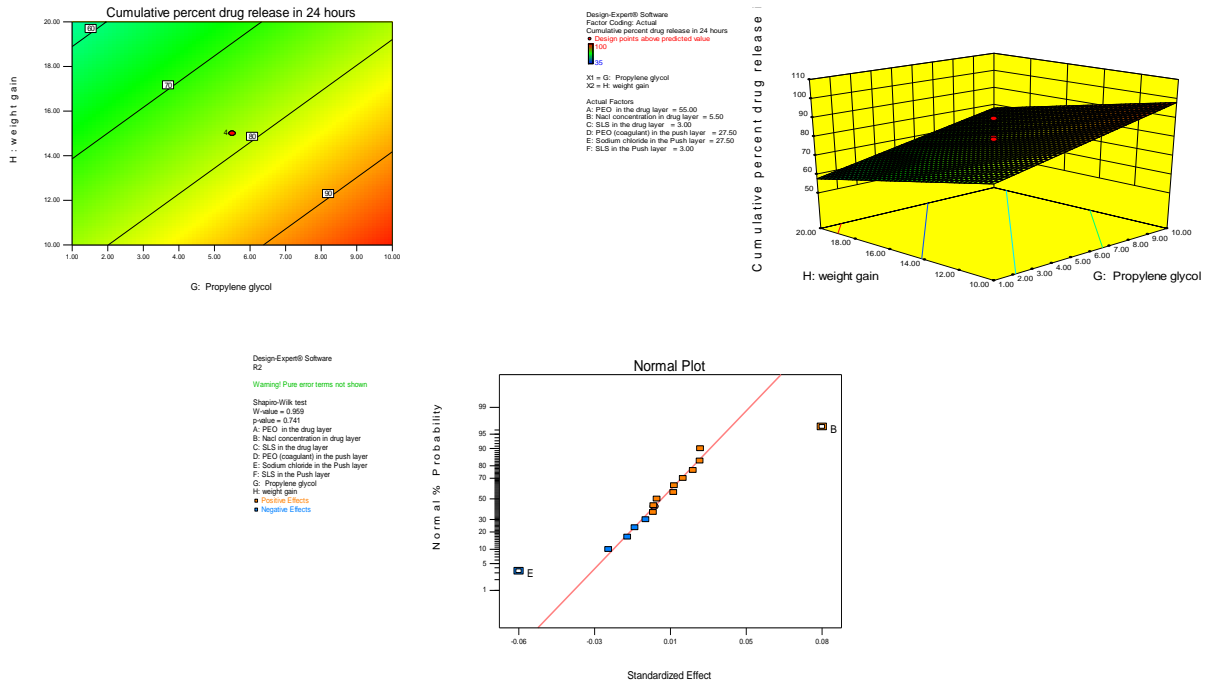**Fig. 6: It shows the Contour plot and RS Plot – Effect of Nacl DL and weight gain on PCUR at 24 hrs**

Fig. 7(1): It shows the Half Normal plot of the effect of the factors on R^2

Fig. 7: It shows the Contour plot and RS Plot – Effect of Nacl DL and weight gain on PCUR at 24 hrs

Figure.6 shows the Contour plot and Rs plot, showing the change in PCUR at24hr with the change in weight gain and Nacl.Nacl DL had a positive effect and Weight gain had an opposite effect on the response. At the low levels of weight gain the Nacl had a prominent effect.

Figure.7 shows the contour plot and RS plot showing the simultaneous effect of weight gain and propylene glycol on the PCUR at 24hrs. At 10 % of the weight gain the response is more prone to slight changes propylene glycol. But at a higher weight gain even a 10% of propylene glycol is not sufficient to achieve 80% release at 24hrs.

Analysis of responses - Rate constant(R^2)

With the help of the half normal plot and normal plot shown in figure 7 and 8, the significant factors affecting the $R^2$was determined. The plots are given in the figures and. From the graph it was evident that the factor which are affecting the release rate constant (R^2)were B (Nacl in the DL) and E(Nacl in the push layer). The Shapiro-Wilk Normality Test displayed the non significance of the non selected factors.
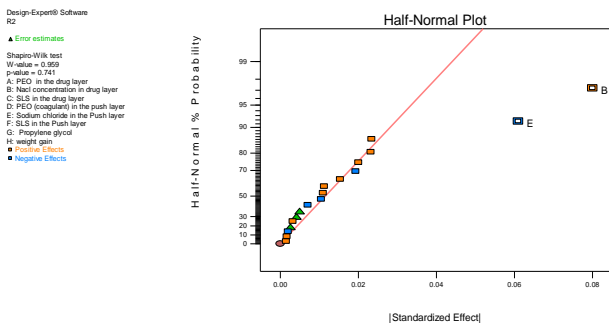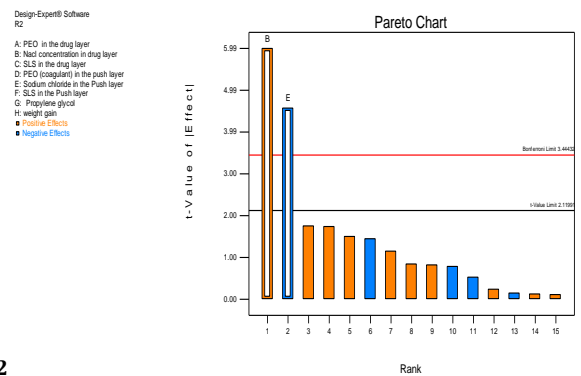

Fig. 8: It shows the half Normal plot of the effect of the factors

onR2

Fig.9: It shows the Pareto chart of effect of the factors on R^2

The Pareto chart shown in figure.9 represents the significant effect of B and E on the zero order rate constant. Both the factors crosses the t and Bonferroni limit confirm the obvious effect of these factors on the zero order rate constant. The magnitude of the effect can be written as Nacl in the drug layer > Nacl in the push layer. The F-value from the ANOVA analysis 29.11 implies the model is significant. Factors **B (p =< *0.0001)*, E(***0.0002)* are significant model terms.. The "Lack of Fit F-value" of 0.3706 implies the Lack of Fit is not significant relative to the pure error. The polynomial equation representing R^2 can be written,

R^2 =+0.91727+9.10833E-003* Nacl concentration in drug layer - 1.38833E-003* Sodium chloride in the Push layer. The Figure.10 shows the Contour plot and response surface plot for the simultaneous effect of factor B and E at a time. From the plot it is obvious that the factor B had a positive effect and E had a negative effect. High levels of Nacl in the DL and low levels of Nacl in the PL yields a better R^2 value. The change in concentration of Nacl in the DL is more evident at low level of Nacl in the PL.
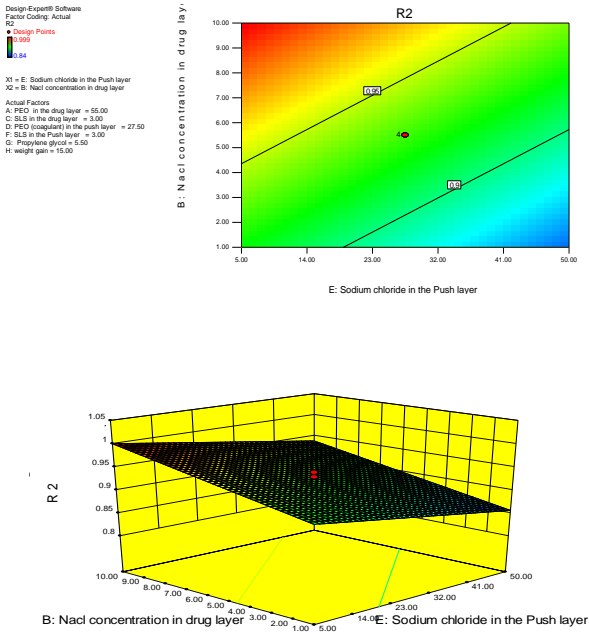
Design-Expert® Software
Factor Coding: Actual
R2
● Design Points
0.999

0.84

X1 = E: Sodium chloride in the Push layer
X2 = B: Nacl concentration in drug layer

Actual Factors
A: PEO in the drug layer = 55.00
C: SLS in the drug layer = 3.00
D: PEO (coagulant) in the push layer = 27.50
F: SLS in the push layer = 3.00
G: Propylene glycol = 5.50
H: weight gain = 15.00

Fig. 10: It shows the Contour plot and RS Plot – Effect of Nacl DL and Nacl in PL on R²

Analysis of responses – lag time

Figures 11, 12 show the half normal plot and normal plot of the effect of factors on the R². The significant factor affecting the lag time was identified as B (Nacl in the DL) G (propylene Glycol), H (the weight gain) The Shapiro-Wilk Normality Test displayed the non significance of the non selected factors. So no other factors except B, G, and H are affecting the lag time.
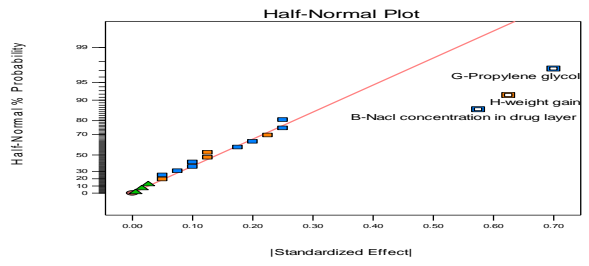

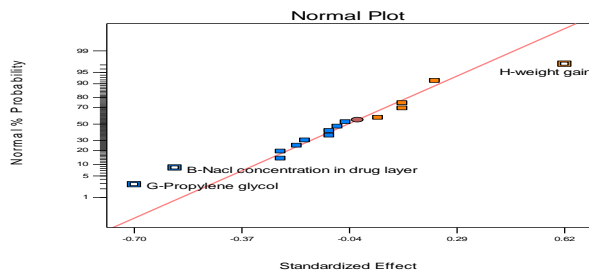**Fig. 11 : It shows the Half Normal plot of the effect of the factors on lag time**

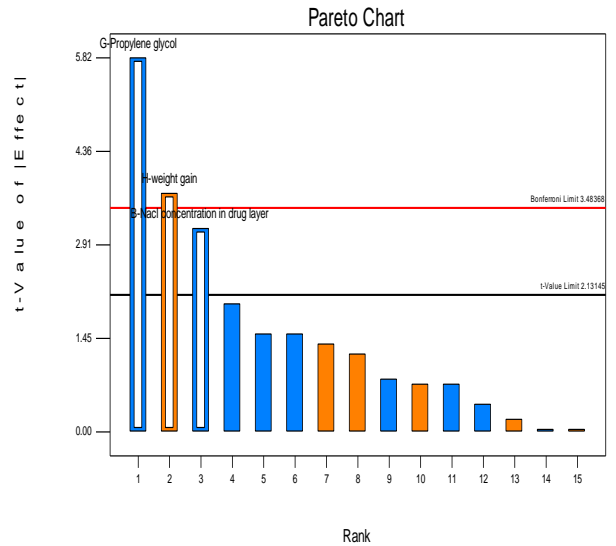**Fig. 12: It shows the Normal plot of the effect of the factors on lag time**

Fig. 13: It shows the Pareto chart of the effect of the factors on lag time

Figure 13 shows the Pareto chart of effect of factors on the lag time in terms of T value. The factors significantly affecting the lag time were G, H and B accordingly. G and B had a negative effect and H had a positive effect. Propylene glycol had greater effect on the lag time. The magnitude of the effect of significant factors on the lag time can be written as G > H> B. No other factors or interaction terms were significant as they does not crosses the t limit.

The significance level selected for the study was 5 % and the p value was 0.05. The Model F-value of 23.8514 implies the model selected is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Factors **B (**$3.292E^-[04]$**)**, **G(**$9.855E^-[05]$**)** *and H (*$1.467E^-[04]$*)*were the significant model terms affecting the lag time. The "Lack of Fit F-value" of 2.7202,implies that the Lack of Fit is not significant relative to the pure error. this means that the polynomial model is fitting all of the design points well. The polynomial equation representing the lag time was written as,

lag time =3.5211- 0.0639* Nacl DL- 0.0722 * PG + 0.0625 * weight gain (Actual terms)

Figure 14 shows the contour plot of the simultaneous effect of factor B and the G at a time. At low levels of Propylene glycol even 10% of Nacl in the level was not sufficient to produce the desired lag time. But at high level of Propylene glycol 1% or less Nacl can sufficient for the desired effect. Nacl had seldom effect at the high level of propylene glycol. Response surface clearly represents the chief effect of factor G.

The Figure 15 shows the Contour plot and Rs plot, of the simultaneous effect of factor B and the H at a time. Nacl had a negative effect on the lag time ie, as the concentration changes from low to high the lag time decreases. But the weight gain had an opposite effect. At low weight gain and high concentration of Nacl in the DL produces the desired effect. Nacl had a prominent effect at low weight gain. Figure 16 shows the contour plot and response plot of the combined effect of propylene glycol and weight gain at a time. Weight gain had a positive effect on the lag time and propylene glycol had a reverse effect. Effect of propylene glycol was more pronounced at low weight gain. From the RS plot the greater effect of the propylene glycol is well understood.
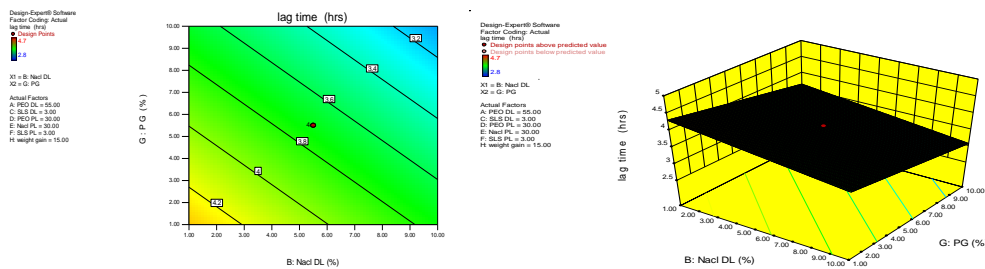
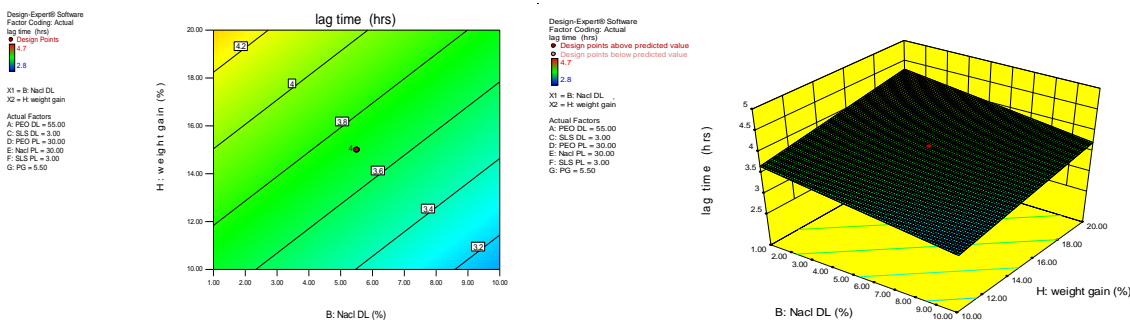**Fig. 14: It shows the Contour plot and RS Plot – Effect of Nacl DL and Propylene Glycol on lag time**

Fig. 15: It shows the Contour plot and RS Plot – Effect of Nacl DL and weight gain on lag time
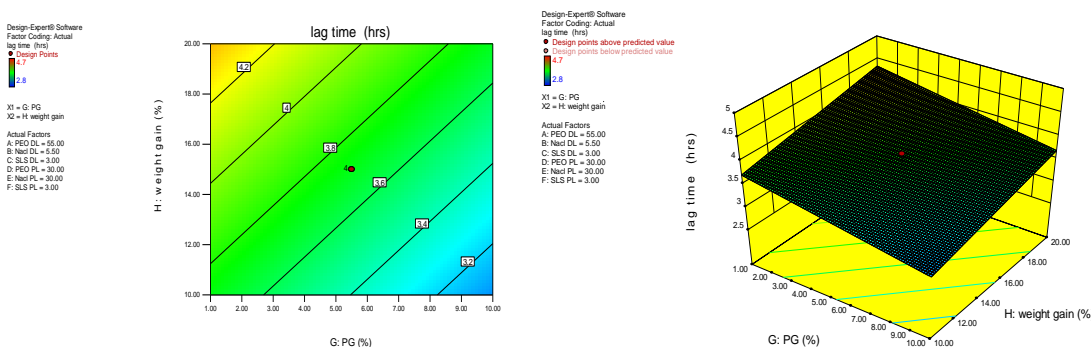

Fig. 16: It shows the Contour plot and RS Plot – Effect of Weight gain and Propylene Glycol on lag time

CONCLUSION

The factor influence study of the ivabradine Hcl push pull osmotic tablets was done with the help of 2 $_{IV}$ [8-4] fractional factorial design. Core factors and coating factors are combainly selected for the factor influence study. The effect of the factors on the responses like PCUR at 24 hrs, Zero order rate constant and lag time were studied. It was found from the study that the most significant factors which affecting the responses were Propylene glycol (plasticizer), weight gain and the Nacl in the DL. Researchers can concentrate more on the coating parameters and Nacl DL for the optimization of Ivabradine Hcl Push pull osmotic tablets. A better chance of variation with in the design space without affecting the desired profile can be possible with change in coating parameters for the formulation of a push pull osmotic tablets ivabradine Hcl.

Conflict of Interest: None

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