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CONTROLLED POROSITY OSMOTIC PUMP TABLET OF ATENOLOL - CONSTRUCTION OF 2^2 FACTORIAL DESIGN, CALCULATING INTERACTION OF FACTORS & PREDICTION BY MATHEMATICAL MODEL AND ANALYZING BY SOFTWARE

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ABSTRACT

The objective of present investigation is to construct and evaluate the formulations of controlled porosity osmotic pump tablet of Atenolol by applying 2^2 factorial design. A selected two levels two factors experimental design was developed and evaluated to find out the significance of combined effects of the factors on percentage drug release to obtain the optimized combination to achieve the desired controlled release dosage form. The factorial design calculations were done by hand and the drug release is predicted by using mathematical equation. The cube and contour plots were plotted. The curvature lines indicated interaction, which was calculated and predicted using mathematical models for both the factors. This was further analysed and confirmed by using Stat- Ease Design Expert version 11. The effects of two factors i.e osmotic agent and pore former on drug release were established. The construction of a factorial design involves the selection of parameters and the choice of responses. It was concluded that effect of pore former and osmotic agent in the formulation had significant effect on drug release. The optimized formulation OF4 with high concentration of both these factors showed 97% drug release and they had significant effect on each other which was confirmed by manual calculation and also by software.

INTRODUCTION:

Controlled drug delivery systems is designed to achieve better selectivity and longer duration of action and to decrease dose frequency, it shows customized delivery profiles. Conventional formulations have many limitations so control release formulation are preferred to maintain uniform dosing and increase safety margins for high potency drugs. Controlled porosity osmotic pump is based on the principle of

osmosis which provides better release of drug that is independent of pH and agitation intensity. It is the most promising strategy based delivery system and most reliable as oral drug delivery system. The CPOP delivers the drug in sustained manner and it is a significant milestone in osmotic drug delivery system. Beta blockers continue to be first choice of drugs recommended by JNC VI & WHO-ISH. The beta blockers are useful in treating conditions that may coexist with hypertension such as supra ventricular tachyarrhythmia, previous myocardial infarction, angina pectoris, glaucoma (applied topically) and migraine headache. Optimization is done by systematic Design of Experiment (DOE), to improve the outcomes. It is necessary to optimize as it reduces the cost, time, reproducibility, safety and efficacy. There are different types of experimental designs. One of the experimental designs is Factorial Design. Construction and calculation of factorials by hand is easy and the experiment can be run and analysed without any hinderance with perfect accuracy and prediction of the outcomes. The aim of the research is to compare the factorial design obtained, interaction plots with software generated plots and results to confirm the interaction of the factors which affects the drug release.

MATERIALS & METHODS:

Atenolol (API) and Mannitol was procured from SD Fine Chemicals Mumbai. Starch, Magnesium stearate, Colloidal silicon dioxide, Tartrazine yellow was purchased from Yarrow Chem Products, Mumbai. Eudragit RLPO, Sodium Chloride, Ethanol, Acetone and PEG 400 were obtained from Dr. Reddy's Laboratories, Hyderabad. All the chemicals and solvents were of analytical grade. The tablets were prepared by wet granulation technique, the core tablets contains osmotic agent (mannitol), coating solution contains the pore former (sodium chloride) and the (Eudragit RLPO) acts as semi permeable membrane. Ethanol and acetone are used as solvents in coating composition. PEG 400 acts as a plasticizer and starch is used as binding agent in core tablets.

METHOD:

(a). Construction of 2^2 factorial design:

The 2^2 factorial design is constructed manually and the procedure is provided below. The base 2 indicates the levels and the power (superscript) indicates the factors. In this work two factors are considered and the factors should have 2 values each as there are two levels. The two levels indicates two values for each factor. 2 x 2 =4, hence four experiments are performed.

Step 1: Depending on the factors this 2^2 factorial design is chosen.

Step 2: Considering the factors and levels desired. The two factors selected are: 1. Pore former 2. Osmotic agent. The two levels are represented as **'+'** and **'_'**. The positive sign indicates the high or maximum value and the negative sign indicates the low or minimum value.

Step 3: The two levels for pore former (concentrations) are [2 % (Min) & 9% (Max)], the two levels for osmotic agent (concentrations) are [3% (Min) & 40% (Max)].

Step 4: Cube plots are drawn which shows the effect of each factor. The 70, 76, 85 & 97% represents the drug release of four formulations as shown in Figure 1.

Step 5: (a) Calculating the effect of pore former (Factor A), it is shown in the Figure 2. **(b).** Calculating the effect of osmotic

agent (Factor B) as shown in the below Figure 3.

Step 6: The maximum and minimum values are not taken, i.e (97 and 70 %) are not considered as shown in Figure 4.

Inference from Contour plot: As the lines are not parallel it indicates interaction in Figure 5, and curvature lines signifies interaction between factors selected. Contour plot showing the direction to run the experiment is shown in Figure 6.

Step 7: Interaction plots are drawn to know and confirm whether the factors are depending on each other or not. It is provided in Figure 7.

Inference: By analyzing the Interaction plots it is considered that as the lines are not parallel there is interaction between both the two factors selected. The contour plots non linearity and interaction plots can also be confirmed by using the software.

(b). Prediction by mathematical models:

$$y = 82 + 4.5\ X_A + 9\ X_B \qquad \text{Equation (1)}$$

The above equation is obtained by the prediction from mathematical model, and following the simple steps by which the percentage release of drug can be calculated. Here **"y"** represents Prediction. The base line or intercept obtained is 82 it is easily calculated by adding all the four values of drug release and taking its average. It is provided in Figure 8. Calculating the effect of pore former (Factor A) and osmotic agent (Factor B) from high to low as shown in Figures 9 and 10 respectively.

There is 9% increase in drug release when we move from 2 to 9% concentration of pore former, but for our convention only report the half of 9 as 4.5% drug release.The reason to consider only the half is because when there is 9 unit increase it jumps from two units -1 to +1 i.e leap of 2 units. But the jump should be -1 to 0 & then 0 to +1, so half of 9 i.e 4.5 is considered as shown in Figure 11.

Report the half of 18 as 9% as shown in the Figure 12**.**

- So the equation obtained is $y = 82 + 4.5\ X_A + 9\ X_B$ Equation (1)
- The X_A & X_B are "**Coded Variables**" which means "**To Represent**".
- $X_A = -1$ (This represents the Minimum level of Factor A i.e 2).
- $X_A = +1$ (This represents the Maximum level of Factor A i.e 9)
- $X_B = -1$ (This represents the Minimum level of Factor B i.e 3).
- $X_B = +1$ (This represents the Maximum level of Factor B i.e 40).
- X_A, X_B are the Coded units.

Predicting the drug release: If the concentration of osmotic agent is 3% and pore former is 9%, substitute $X_A = +1$ and $X_B = -1$ in the above mathematical equation (1). The +1 represents maximum concentration of pore former-Factor A (9%) and -1 represents minimum concentration of osmotic agent-Factor B (3%). Thus +1 & -1 by default are considered maximum and minimum values.

$$y = 82 + 4.5(+1) + 9(-1) = 82 + 4.5 - 9 = 77.5\ \%$$

The 77.5% represents the output i.e the predicted drug release at maximum concentration of pore former and minimum concentration of osmotic agent. But to predict the drug release if the concentration of osmotic agent is 3% and if pore former is 5 or 6% by mathematical equation it is described below. The numbers 5 and 6 represents **"Real World Values"**.

- As $X_A = -1$ for 2% concentration of pore former

- So $X_A = 0$ represents the 5% concentration of pore Former.
- $X_A = 0.5$ represents the 6% concentration of pore Former.
- 0 & 0.5 represents coded units and 5% & 6% are real world values.

Considering the cube plot again it is used to mark the concentration of 5%. It lies in between 2 to 9%, the X_A lies in between and thus it is coded as X_A as 0 as shown in Figure 13. Substitute $X_A = 0$ and $X_B = -1$ in equation (1) to predict the drug release if concentration of pore former is 5% and osmotic agent is 3%.

$$Y = 82 + 4.5(0) + 9(-1) = 82 + 0 - 9 = 73\ \%$$

The drug release is 73% when the concentration of osmotic agent is 3% and pore former is 5%. Similarly the drug release can be predicted when the concentration is varying, by simple mathematical equations and calculations. This prediction is reasonable and justified as 73 lies midway in between 70 and 76 % as shown in Figure 14.

(c). Prediction of Interaction of factors & its calculations:

Main effect describes the effects of a factor on the outcome. Curvature is an evidence of interaction in the system. The main effect is due to pore former and osmotic agent. Mathematically interaction is defined as the half the difference and subtract the low values from high values.

Calculating Interaction of main effect A (Pore former): For osmotic agent at maximum concentration subtract 97-85 = 12

For osmotic agent at minimum concentration subtract 76 -70 = 6

Average =18 / 2 = 9

Report half of 9 as 4.5 as discussed previously, as it is main effect of A, it is represented as $4.5X_A$.

Calculating Interaction of main effect B (Osmotic agent):

For pore former at maximum concentration subtract 97- 76 = 21. For pore former at minimum concentration subtract 85 -70 = 15 Average = 36 / 2 =18

Report half of 18 as 9 as discussed previously, as it is main effect of B, it is represented as $9X_B$.

Interaction of AB effect: For osmotic agent at maximum concentration subtract 97- 85 = 12

For osmotic agent at minimum concentration subtract 76 -70 = 6

Interaction =12 - 6 = 6/2 =3

Report the half of 3 as 1.5, it is $1.5\ X_AX_B$ as interaction is "half the difference".

Interaction of BA effect: For pore former at maximum concentration subtract 97- 76 = 21. For pore former at minimum concentration subtract 85-70 = 15.

Interaction =21 - 15 = 6/2 =3

Report the half of 3 as 1.5; it is $1.5\ X_BX_A$ as interaction is "half the difference".

Applying prediction Model:

- y = baseline which is calculated previously as 82.
- Main effect of A factor= $4.5X_A$
- Main effect of B factor = $9X_B$
- Interaction Effect of AB factors = $1.5X_AX_B$.
- Interaction Effect of BA factors = $1.5X_BX_A$. The both interactions of AB and BA are symmetrical.

Predicting the effect of interaction: Considering the concentration of pore former is minimum and concentration of osmotic agent is maximum, it is calculated below as:

- Coding units for X_A = -1, as it is low.
- Coding units for X_B= +1, as it is high.
- The equation is $y = 82 + 4.5X_A + 9X_B + 1.5\ X_AX_B$ Equation (2), substitute the coded unit values in this equation.

$$y = 82 + 4.5(-1) + 9(+1) + 1.5(-1)\ (+1)$$

y = 82 - 4.5 + 9 - 1.5 = 85% drug release, (- 4.5 indicates the pore former contribution, +9 indicates osmotic agent contribution which is positive and it improves the drug release and -1.5 indicates the interaction of factors). Predicting the effect of interaction when the concentration of pore former and osmotic agent is maximum, it is calculated below as:

- Coding units for X_A = +1, as it is high.
- Coding units for X_B = +1, as it is high.

Substitute the coded unit values in the equation (2).

$$y= 82 + 4.5(+1) + 9(+1) + 1.5(+1)\ (+1)$$

y = 82+4.5+9+1.5 = 97% drug release, (+ 4.5 indicates the pore former contribution, +9 indicates osmotic agent contribution both are positive which increases the drug release and +1.5 indicates the interaction of factors which works in favour of drug release).

Inference: The system exhibits interaction as the last term is not zero it is $1.5X_AX_B$ and $1.5X_BX_A$. The effect of one factor (A) is depending on the value of another factor (B). Interactions are symmetrical. The same equation is also obtained from Design Expert and it confirms the interaction of both factors.

(d). Analyzing by Software Stat –Ease (Design Expert Version 11.0.1.0)

By utilising the Factorial study type - Model type and D- Optimal Design the factors are analysed to obtain the relationship between them i.e pore former and osmotic agent. The design model is 2FI. The sub type is - Randomized and the number of runs is 9. The results of Standard Error, VIF, R_i, Matrix measures and Leverages by Stat Ease Design Expert Version 11 are provided in Tables 4, 5, 6 and Figures 15, 16, 17. The optimized formulation selected by factorial design is provided in Table 3.

Inference after analyzing the results obtained from Software:

- The low Standard Errors are better and it should be similar to each other in a balanced design.
- The Ideal VIF (Variation Inflation Factor) Value is 1.0, VIF > 10 is a cause for concern, VIF >100 is a cause for alaram indicating coefficients are poorly estimated due to multi collinearity. It measures how much variance of the models is inflated by lack of orthogonality in the design.
- Ideal R_i^2 (Multiple Correlation Coefficient) is 0.0, high values means terms are correlated with each other leading to poor models.
- Smaller scaled D-Optimally criterion is better and Determinant of $(X^1X)^{-1}$,Trace of $(X^1X)^{-1}$ values should be small which is acceptable.
- Leverage close to 1. Consider replicating these points or make sure they are run very carefully. It is the potential for a design point to

influence the fit of the model coefficient based on its position in the design space.

Final equation obtained from software in terms of coded factors:

R1= 82.00+4.50+9.00+1.50(4.50 is A Factor, 9.00 is B Factor, 1.50 is AB Interaction Factor). The equation in terms of coded factor can be used to make predictions about the responses for given levels of each factor. By default the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation was useful for identifying the relative impact of the factors by comparing the factor coefficients.

Table 1: 2^2 Factorial design construction

Formulation	Standard Order	Factor A (%Pore Former)	Factor B (%Osmotic Agent)	Output (% Drug release)
OF1	1	_	_	70%
OF2	2	+	_	76%
OF3	3	_	+	85%
OF4	4	+	+	97%

Table 2: Coefficient in terms of coded factors by Stat Ease

Factors	Coefficient Estimate
Intercept	82.00
A-Pore former(factor A)	4.50
B-Osmotic agent (factor B)	9.00
AB	1.50

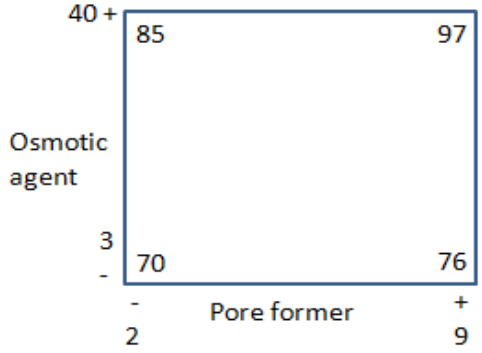


Figure 1: Cube plot

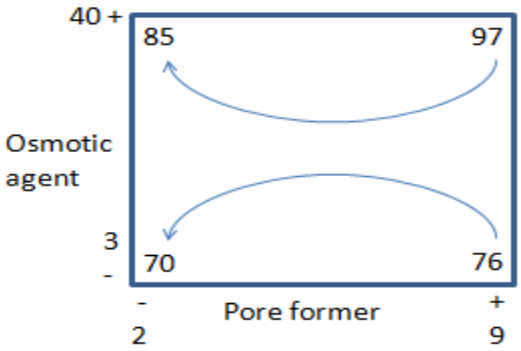


Figure 2: Cube plot for Factor A

Subtracting: 97 - 85 = 12, 76 - 70 = 6. Calculate the average 18/2, Average = 9

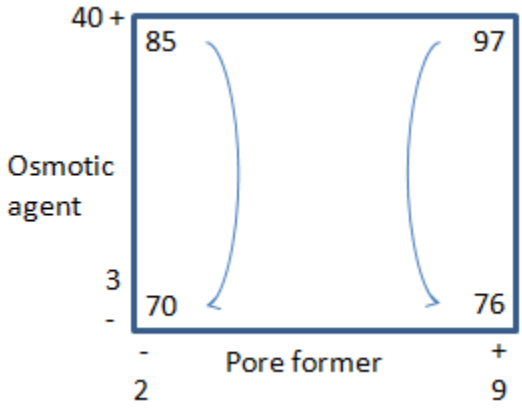


Figure 3: Cube plot for Factor B

Subtracting: 97 - 76 = 21, 85 - 70 = 15. Calculate the average 36/2, Average =18.

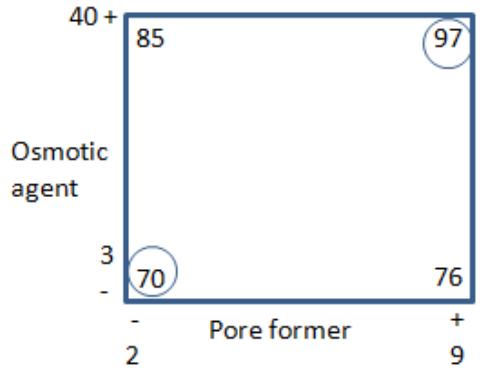


Figure 4: Cube plot

An intermediate value i.e 85% is considered and the lines are drawn on opposite side as seen in Figure 5.

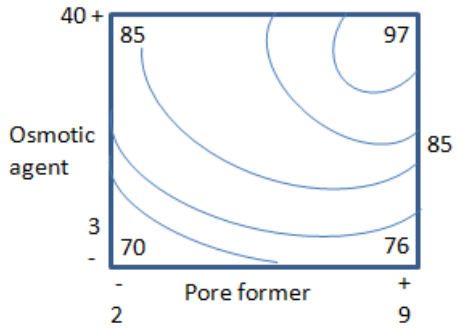


Figure 5: Contour plot

- The lines are not parallel but curvature lines are obtained as seen in Figure 5.
- To maximise the drug release the experiment is run in the direction shown below in Figure 6.

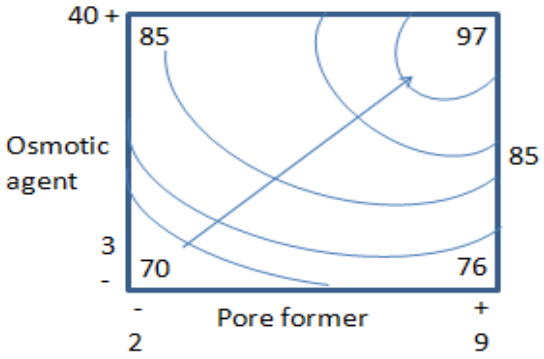
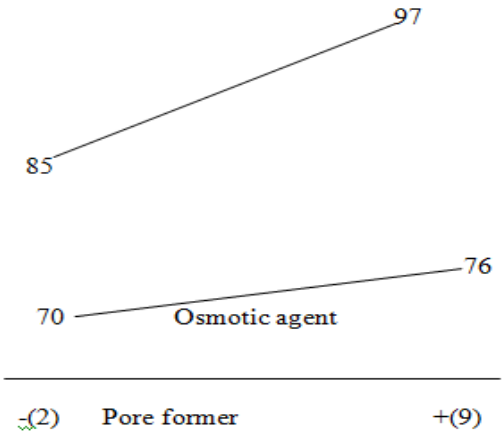


Figure 6: Contour plot showing the direction to run the experiment.



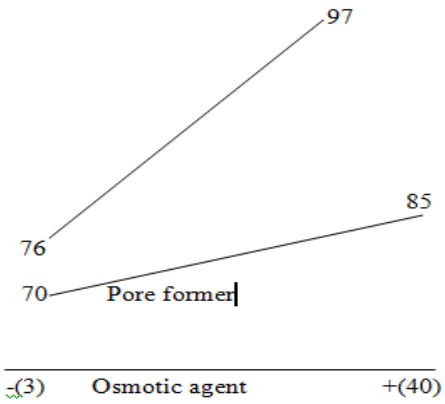


Figure 7: Interaction plots

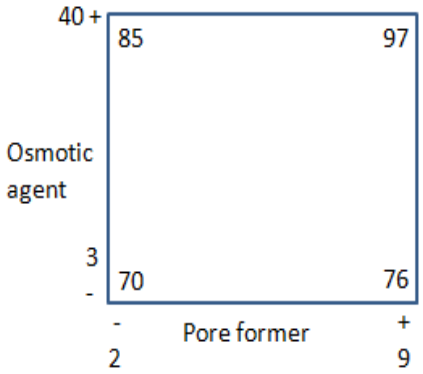
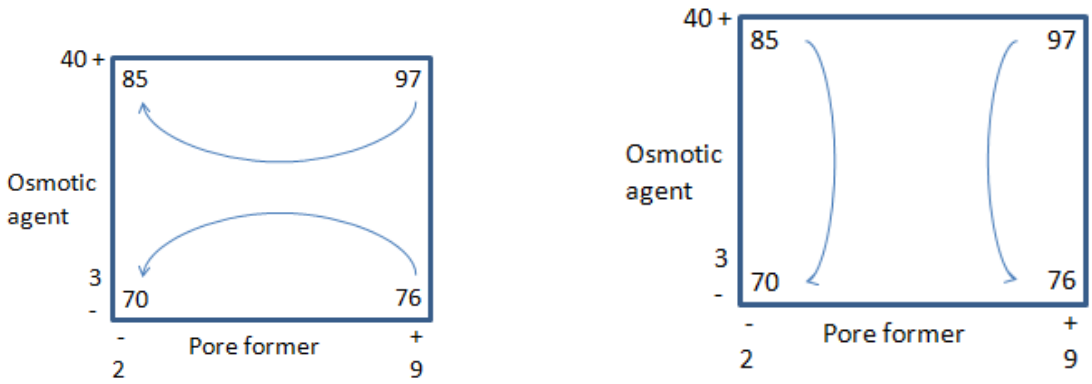


Figure 8: Cube plot

STEP 1: Base line = 70+76+85+97/4= 82



Figures 9 & 10: Cube plots for calculating the effects of pore former and osmotic agent

Subtracting: 97-85 = 12 (For osmotic agent at high concentration)

76-70 = 6. (For osmotic agent at low concentration), Average is 18/2 =9

97- 76 = 21(For high concentration of pore former)

85- 70 =15 (For low concentration of pore former), Average is 36/2 = 18

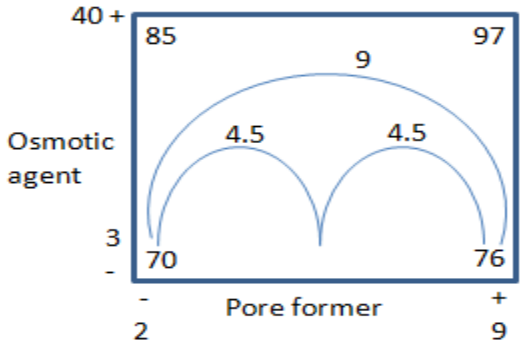


Figure 11: Cube plot showing the leap of units

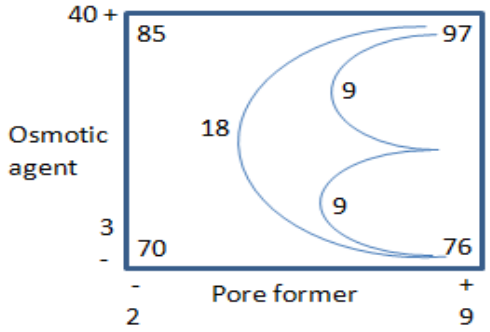


Figure 12: Cube plot showing leap of units

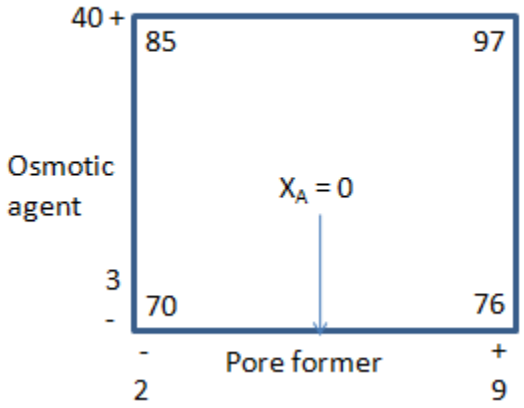


Figure 13: Cube plot showing 5% concentration at which $X_A = 0$.

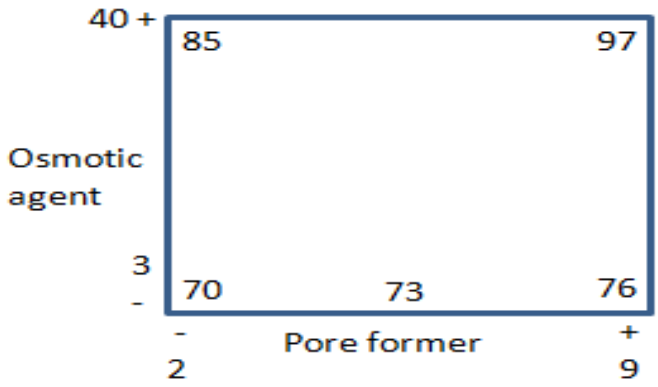


Figure 14: Cube plot showing 73% drug release as predicted by mathematical equation.

RESULTS & DISCUSSION:

Table 3: Composition of optimized formulation OF4

S.NO	OF4 Optimized Formulation Ingredients (core tablet-mg)	Quantity
1.	Atenolol	100 mg
2.	Mannitol (Osmotic agent)	40% of total weight=27 mg
3.	Starch	1.5
4.	Magnesium stearate	1
5.	Colloidal silicon- di-oxide	0.5
6.	Tartrazine yellow	q.s
	Total Weight	130

	Coating	
7.	Eudragit (RLPO)	2.5 g
8.	Sodium Chloride	9 % of total weight of core tablet = 6.9 mg
9.	PEG 400	2
10.	Acetone	10 ml
11.	Ethanol	80 ml
% Total weight gain (w/w)		5

Table 4: Results of Standard Error, VIF & R_i^2

TERM	**STANDARD ERROR**	**VIF**	**R_i^2**
A	0.3385	1.01852	0.0182
B	0.3385	1.01852	0.0182
AB	0.3385	1.01852	0.0182
Result	**Acceptable**	**Acceptable**	**Acceptable**

Table 5: Results of Matrix Measures

Matrix Measures	**Value**
Condition no. of Coefficient Matrix	1.33
Maximum Variance Mean	0.500
Average Variance Mean	0.4586
Minimum Variance Mean	0.333
G Efficiency	88.89
Scaled D-Optimality Criterion	1.02
Determinant of $(X^1X)^{-1}$	1.6276E-4
Trace of $(X^1X)^{-1}$	0.4583
I	0.4583
Bal	1
Ideal bal	1

Table 6: Results of Leverage

RUN	**LEVERAGE**	**SPACE TYPE**	**BUILD TYPE**
1	0.5000	Factorial	Model
2	0.3333	Factorial	Model
3	0.3333	Factorial	Model
4	0.3333	Factorial	Model
5	0.5000	Factorial	Model
6	0.5000	Factorial	Model
7	0.5000	Factorial	Model
8	0.5000	Factorial	Model
9	0.5000	Factorial	Model
AVERAGE	**0.4444**		

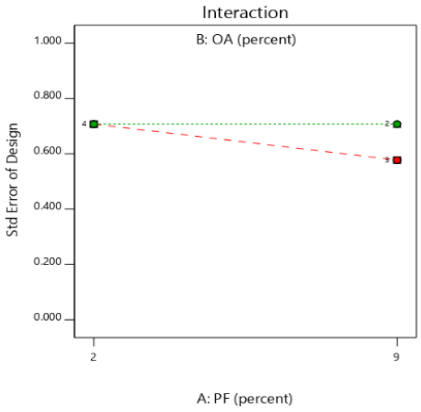


Figure 15: Interaction plot by Stat Ease design

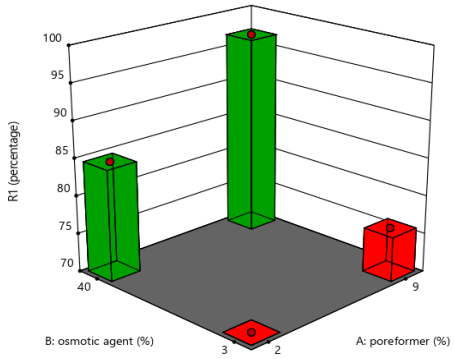


Figure 16: 3D Surface plot of factors and% drug release by Stat Ease

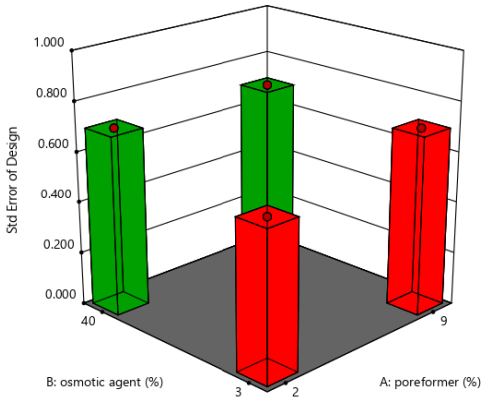


Figure 17: 3D Surface plot of factors and standard error of design by Stat -Ease

The same equation is obtained by calculating by hand and also by software, hence the construction of factorial design and prediction by mathematical models by hand was as accurate as software.

Inference: The coefficient estimate represents the expected change in response

"y" per unit change in "x" when all remaining factors are held constant. The intercept in an orthogonal design is overall average resposes of all runs. The coefficients are adjustments around the average based on the factor settings, when the factors are orthogonal the VIF's are 1.VIF <1 are tolerable.

Inference after analyzing the results obtained from Software:

The low Standard Errors are better and it should be similar to each other in a balanced design. The Ideal VIF (Variation Inflation Factor) Value is 1.0, VIF > 10 is a cause for concern, VIF >100 is a cause for alaram indicating coefficients are poorly estimated due to multi collinearity. It measures how much variance of the models is inflated by lack of orthogonality in the design.

- Ideal R_i^2 (Multiple Correlation Coefficient) is 0.0, high values means terms are correlated with each other leading to poor models.
- Smaller scaled D-Optimally criterion is better and Determinant of $(X^1X)^{-1}$,Trace of $(X^1X)^{-1}$ values should be small which is acceptable. Smaller scaled D-Optimally criterion is better and Determinant of $(X^1X)^{-1}$, Trace of $(X^1X)^{-1}$ values are small which is acceptable.

Inference: Leverage close to 1. It is the potential for a design point to influence the fit of the model coefficient based on its position in the design space.

CONCLUSION:

The construction of factorial designs by hand, predicting the drug release by mathematical models, calculating the interaction of factors and analysing by Stat – Ease Design Expert Version 11 helps to confirm the responses accurately with perfect prediction which helps to select the optimized formulation. The contour plots and interaction plots for 2^2 Factorial design confirmed interaction of factors which were further analysed by Design Expert. The formulation OF4 is optimized as the drug release is 97% which contains 9% of pore former and 40% of osmotic agent. It is deduced that more the amount of osmogen and more the amount of pore former it has significant effect on drug release. The prediction of interactions was as accurate as software. It is very easy and precise to calculate by hand and run the experiment to analyse it at any point of time. The results of VIF were 1.01852, Ri^2 was 0.0182, and standard error of 0.3385 is acceptable as they are within the specified limits. It was observed that smaller scale D-optimally criterion had small values which again are acceptable. The final coded factors equation derived was same by both calculation and by Stat- Ease Design Expert software.

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