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Factorial design used in optimization immediate release solid dosage sirolimus

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ABSTRACT

The aims of this study were to develop a predictive immediate release tablet formulation system for soluble drugs. sirolimus was evaluated for powder properties. The effects of binder and disintegrant were investigated. Factorial design was applied to optimize the drug release profile. Sirolimus batch F11 yielded the best fit formulation. This research indicates that the proper amount of binder and disintegrant can produce drug dissolution profiles comparable to their brands.

Keywords: Sirolimus; Factorial Design; Immediate Release.

1. INTRODUCTION

The majority of the pharmaceutical companies use the expression "state of the art" referent a drug design. However, the design of a drug is a science. Experimental design is planned structure interference in the natural order of events. Its strength lies in the fact that much of the substantial gain in knowledge in all science has come from actively or deliberately manipulating or interfering with the stream of events. A physical model must be constructed and in the basis of either empirical data or experimental values. Various mathematical formulas are investigated with the objective of obtaining a most suitable formula which will form the basis of linking the variables of the process. The formulas include dissolution profiles of all batches, which can be fitted to zero order, first order [1,2], Higuchi , Hixson Crowell, Korsemeyer and Peppas , and Weibull models to ascertain the kinetic modeling of drug release.

The aims of this study were to develop a predictive immediate release tablet formulation for soluble drugs. In this experiment, sirolimus hydrochloride was chosen as an active product due to its highly soluble in water and its low permeability. In order to obtain the most favorable sirolimus tablet formulation, the effect of binder and disintegrant levels were examined which may interact with each other in an experiment and have an effect on responses [3-8]. Several designs are available; however, factorial design is a major interest. Factorial design has been used to establish the extent of the main effects and the extent and significance or non significance of interaction effects.

2. MATERIALS AND METHODS

Sirolimus (purity 99.4%) and all other additives used were purchased from Sigma-Aldrich, India.

2.1. Preparation of batches with doe (Full factorial design)

Full factorial design allows studying the effect of each factor on the response variable, as well as the effects of interactions between factors on the response variable.

2.2. Optimization of batches using doe

Batches were prepared namely F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 with composition as mentioned. The tablets prepared with composition achieved utilizing Stat-ease which is software for Design of experiment. Three critical factors were selected which influence the percentage drug release at 120 mins. They were poloxamer 188, which enhances the solubility of the drug, second was Kollidon CL which was the superdisintegrant. Third factor was the Magnesium stearate which apart from its lubrication functionality if percentage quantity changes then may impart hydrophobicity.

2.3. Weight variation, Hardness, Friability and Disintegration of tablets

Tablets were evaluated to predict the effect of 3 formulation factors on the overall characteristics of the finished product.

Table - 1: Variables for optimization and their upper and lower levels

Independent variables		Levels	
		Low	High
Variable	**Unit**	-1	+1
Poloxamer 188	%	1	4
Kollidon CL	%	4.5	10.50
Magnesium stearate	%	0.5	1.5

As indicated by the appended data the disintegration of tablets prepared with high concentration of Kollidon CL showed faster disintegration as compared with batches having low concentration of Kollidon CL.

2.4. *In Vitro* drug release

The result of in vitro drug release studies of batches was observed in 500 ml of 0.4% SLS at 120 mins which is our response.

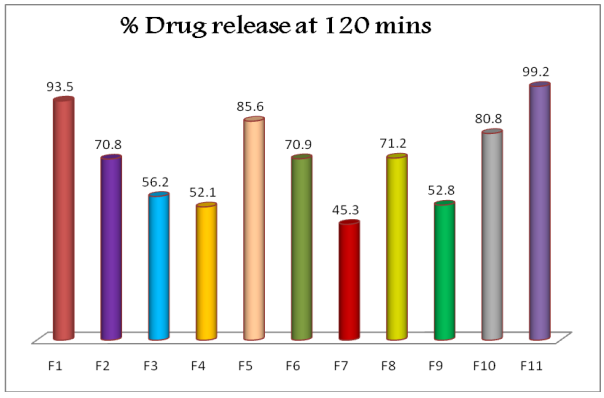

Figure - 1: Percentage Drug release at 120mins

Table - 2: Variable Optimization Using DOE matrix generated by Stat- Ease software

Std	Run	Batch	Factor 1	Factor 2	Factor 3
			A-Poloxamer 188 (%)	B-Kollidon CL (%)	C-Magnesium Stearate (%)
2	1	F1	4	4.5	0.5
11	2	F2	2.5	7.5	1
3	3	F3	1	10.5	0.5
7	4	F4	1	10.5	1.5
8	5	F5	4	10.5	1.5
10	6	F6	2.5	7.5	1
5	7	F7	1	4.5	1.5
9	8	F8	2.5	7.5	1
1	9	F9	1	4.5	0.5
6	10	F10	4	4.5	1.5
4	11	F11	4	10.5	0.5

Table - 3: Hardness, Friability and disintegration of tablets

Batch No	Hardness (N)	Disintegration time (sec)	Friability (%)	Avg. Weight (gm.)
F1	68	158	0.12	1.548
F2	60	128	0.14	1.542
F3	43	92	0.25	1.551
F4	45	94	0.22	1.553
F5	44	90	0.29	1.557
F6	54	125	0.20	1.549
F7	66	154	0.16	1.554
F8	58	130	0.18	1.549
F9	64	150	0.10	1.542
F10	69	155	0.10	1.552
F11	48	90	0.22	1.554

Table - 4: *In vitro* drug release profile	
Batch No.	**% Drug release at 120 mins**
F1	93.5
F2	70.8
F3	56.2
F4	52.1
F5	85.6
F6	70.9
F7	45.3
F8	71.2
F9	52.8
F10	80.8
F11	99.2

3. RESULTS AND DISCUSSION

3.1. Analysis of results by doe

observed values of responses i.e. percentage drug release at 120 min, was then entered in the matrix to evaluate the final results.

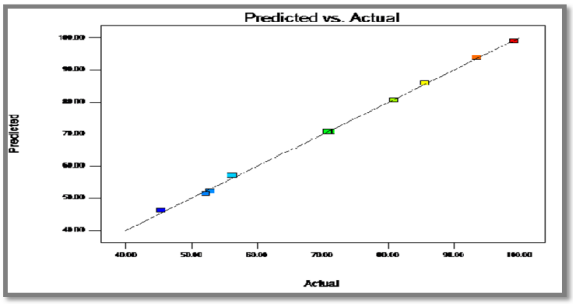

Figure - 2: Actual Vs Predicted Plot

The Model F-value of 1417.12 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In this case A, B, C, AC is significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The "Lack of Fit F-value" of 18.89 implies there is a 5.09% chance that a "Lack of Fit F-value" this large could occur due to noise.

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If the R^2 value is 1 it accounts for perfect linear relationship. An R^2 of 0 indicates that the fit serves no better as a prediction model than the overall response mean. The "Pred R-Squared" of 0.9940 is in reasonable agreement with the "Adj R-Squared" of 0.9982 "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 104.695 indicates an adequate signal. This model can be used to navigate the design space.

Table - 5: Responses entered in matrix created by Stat-Ease software

Runs	Std	FACTOR 1 A-Poloxamer 188	Factor 2 B-Kollidon CL	Factor 3 C-Magnesium stearate	Response % Drug release AT 120 Mins
2	1	4	4.5	0.5	93.5
11	2	2.5	7.5	1	70.8
3	3	1	10.5	0.5	56.2
7	4	1	10.5	1.5	52.1
8	5	4	10.5	1.5	85.6
10	6	2.5	7.5	1	70.9
5	7	1	4.5	1.5	45.3
9	8	2.5	7.5	1	71.2
1	9	1	4.5	0.5	52.8
6	10	4	4.5	1.5	80.8
4	11	4	10.5	0.5	99.2

Table - 6: ANOVA summary 1

	Adjusted F-value	Model p-value	Unadjusted F-value	Model p-value
Model	1243.88	< 0.0001	1417.12	<0.0001
Curvature	0.27	0.6277	-	-
Lack of Fit	23.87	0.0405	18.89	0.0509

Table - 7: ANOVA summary 2

Source	Sum of squares	Df	Mean square	F Value	p-value Prob > F	
Model	3174.78	4	793.7	1417.12	< 0.0001	Significant
A-Poloxamer	2914.66	1	2914.66	5204.05	< 0.0001	
B-Kollidon CL	53.56	1	53.56	95.63	< 0.0001	
C-Magnesium stearate	179.55	1	179.55	320.58	< 0.0001	
AC	27.01	1	27.01	0.0004		
Residual	3.36	6	0.56			
Lack of fit	3.27	4	0.82	18.89	0.0509	Not significant
Pure Error	0.087	2	0.043			

Table - 8: ANOVA summary 3

Std. Dev.	0.75	R-Squared	0.9989
Mean	70.76	Adj R-Squared	0.9982
C.V. %	1.06	Pred R-Squared	0.994
PRESS	19.08	Adeq Precision	104.695

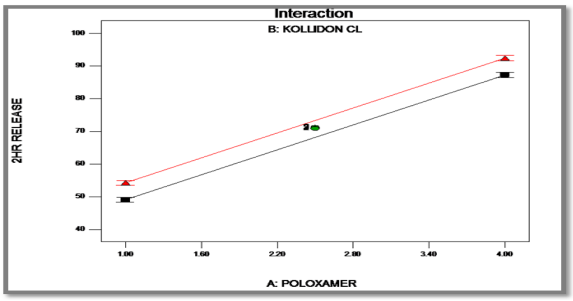

Figure - 3: Interaction plots for Poloxamer and Kollidon CL.

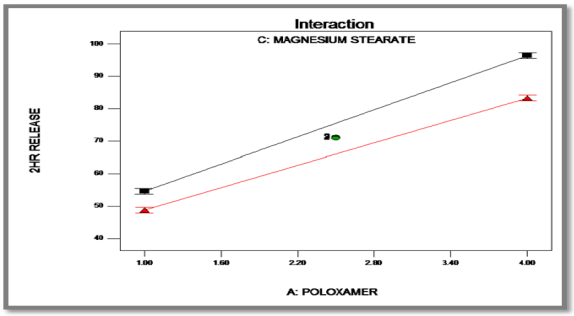

Figure - 4: Interaction plots for Poloxamer and Magnesium stearate.

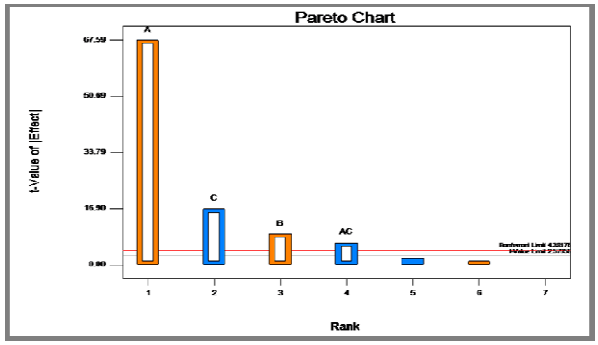

Figure - 5: Pareto chart

An interaction occurs when the response is different depending on the settings of two factors. Plots make it easy to interpret two factor interactions. They will appear with two non-parallel lines, indicating that the effect of one factor depends on the level of the other.

The "I beam" range symbols on the interaction plots are the result of least significant difference (LSD) calculations. If the plotted points fall outside the range, the differences are unlikely to be caused by error alone and can be attributed

to the factor effects. If the I beams overlap there is not a significant difference (95% confidence is default) between the two points. You can then choose the most economical or convenient level for that factor.

In the pareto chart the values above the the orange line which is called Bonferroni limit are almost certainly significant. The values between the orange and black lines (t values) are having possibility of being significant. Values below the t lines are of not significance. This gave us an idea that poloxamer 188 and kollidon CL are having positive effect. It also gave us an idea about negative effect of magnesium stearate.

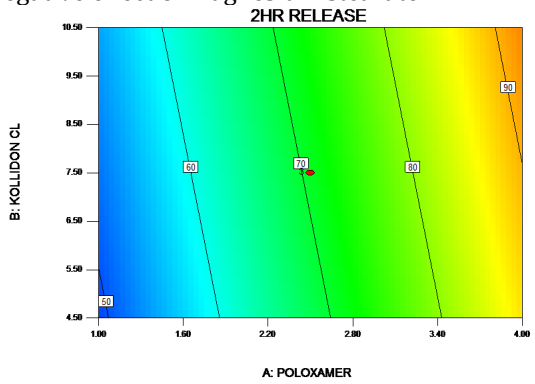

Figure - 6: Contour plot.

The contour plot is a two-dimensional representation of the response across the select factors. The predicted value of the response is shown by default. This is useful for optimizing response surfaces graphically.

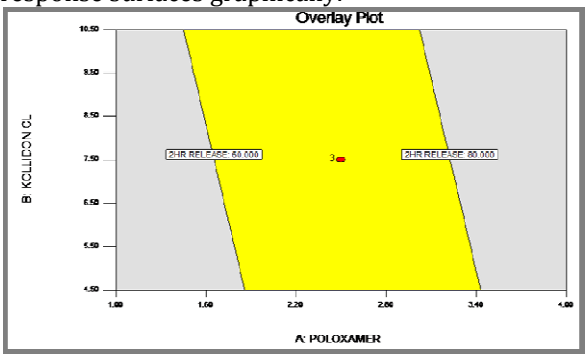

Figure - 7: Overlay plot.

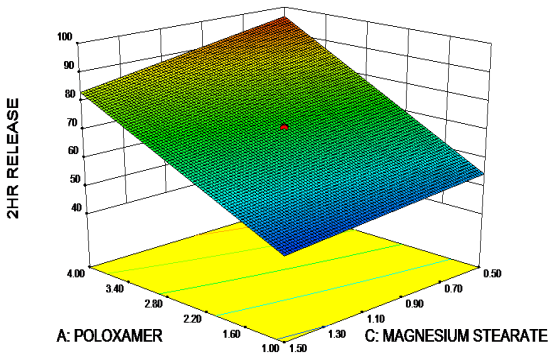

Figure - 7: 3D Surface.

When the corners of square are eliminated, the standard (catolog) design no longer fill the remaining space. Rather than shrinking a COD or BB design ti fit in the middle part of the space we used optimal design to build a custom design that fills the space.

3 D Surface gives us an idea about effect of factors at 2 hour release. It gives design points above predicted value. It shows us both positive impact and negative impact of the poloxamer 188 and magnesium stearate respectively.

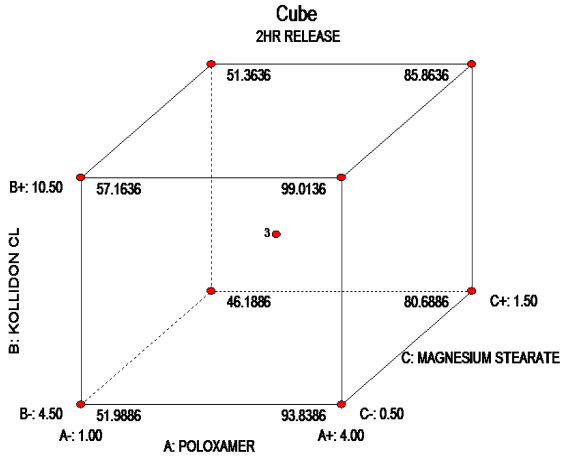

Figure - 8: Cube.

For our three factors factorial cube reduces to a two dimensional equilateral triangle of all combinations of three components. By application of all low and high levels for factors we are getting the percentage drug release.

4. CONCLUSION

A factorial experiment is an experiment consisting of combinations of all factors at all selected levels. The purpose is to derive the nature of a relationship between independent factors and dependent variables. High order interactions are possible in that one factor may depend on the presence or absence of two other factors, termed a second-order interaction. The study of factorial designs represented that batch F11 provided the closest similarity to the reference drug.

5. REFERENCES

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