RESEARCH ARTICLE

Formulation and Optimization of Immediate Release Tablets Using 3^2 Factorial Design

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ABSTRACT

The present study focuses on the formulation and optimization of immediate release tablets using a 3^2 factorial design to enhance drug dissolution and bioavailability. The formulation was prepared using the wet granulation method, incorporating superdisintegrants at varying concentrations to evaluate their impact on disintegration and dissolution. The selected independent variables were X1 and X2 where X1 is the amount of disintegrant and X2 is the amount of binder and three levels for each factor were selected (−1, 0, +1) indicating low, centre, and high values.

Nine formulation batches of tablets were prepared and evaluated for pre-compression and post-compression parameters. The response variables included flow property. Evaluation parameters such as tablet hardness, friability, weight variation, drug content, in-vitro disintegration, and dissolution studies were performed.

The obtained F value exceeds the crucial F value, indicating that the result is significant at the specified probability threshold ($p<0.05$). The complete model was deemed significant; hence, it has been utilized for forecasts. Impact of independent variables on t90% drug release.

Keywords: Immediate release tablets, factorial design, superdisintegrants, wet granulation, optimization, dissolution enhancement.

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Conflict of interest: None

INTRODUCTION

Oral drug delivery is the most preferred route of administration due to its convenience, cost-effectiveness, and patient compliance. Among oral dosage forms, immediate-release (IR) tablets are widely used because they ensure rapid onset of action by allowing quick disintegration and dissolution in the digestive system [1]. These tablets are formulated without any special modifications to delay or extend drug release, making them ideal for conditions requiring prompt therapeutic effects. The formulation of IR tablets involves a careful selection of excipients such as diluents, binders, disintegrants, and lubricants to achieve optimal drug performance. Advances in pharmaceutical technology have improved the manufacturing processes of IR tablets, ensuring better bioavailability, stability, and uniformity. [2,3]

Antipsychotic drugs are widely prescribed for the treatment of psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder. These medications help regulate neurotransmitter activity in the brain, reducing symptoms like hallucinations, delusions, and mood instability. Immediate-release (IR) tablets are preferred for their ability to deliver rapid therapeutic effects, ensuring better patient adherence and symptom control. Developing an optimized IR formulation requires selecting appropriate excipients, balancing disintegration and dissolution rates, and ensuring stability. Critical factors such as drug solubility, bioavailability, and pharmacokinetics influence the formulation process. [4,5]

The main focus of present research was Formulation development, optimization and evaluation of immediate release tablets of an antipsychotic Drug Risperidone that is bioequivalent to the reference product marketed in Japan by Janssen Pharmaceutical K.K.

Risperidone a benzisoxazole derivative, is an atypical antipsychotic drug with high affinity for 5-hydrotryptamine (5-HT) and dopamine D2 receptors. It is used primarily in the management of schizophrenia, inappropriate behavior in severe dementia and manic episodes associated with bipolar I disorder. [6]

METHODOLOGY

Table 1: Characteristics of Uncoated Tablet

Time (min.) Units	D.T. (min:sec)
F003	5:10
F004	4:50
F005	3:45
F006	3:30
F007	4:25
F008	2:30
F009	4:15

Table no 1 contains the disintegration time of all the preparation.

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Table 2: *In-Vitro* Dissolution Study in pH 6.8

Time (min.)	0	5	10	15	20	30	45	60	F_2 Value
F003	0.0	27.4	56.4	69.6	70.2	74.8	74.9	74.9	46.57
F004	0.0	24.6	57.3	70.3	71.7	76.2	76.9	77.4	49.37
F005	0.0	37.9	69.4	89.8	91.2	95.8	95.9	95.9	51.28
F006	0.0	31.5	67.8	87.2	90.6	94.4	94.6	94.7	55.96
F007	0.0	30.4	62.7	72.5	78.9	84.4	84.5	84.5	67.76
F008	0.0	37.4	69.7	89.3	90.8	95.4	95.4	95.5	52.38
F009	0.0	30.2	60.4	75.1	82.4	89.1	89.2	89.3	81.07

Table 2 contains *In-Vitro* dissolution study of all the formulations

Table 3: Design Layout of 3^2 Factorial Designs.

Batches	X1 : Corn Starch	X2:- HPMC 15Cps	X1 : Corn Starch (mg)	X2:- HPMC 15Cps (mg)
F9-A	−1	−1	5	1
F9-B	0	−1	7	2
F9-C	+1	−1	9	3
F9-D	−1	0	5	1
F9-E	0	0	7	2
F9-F	+1	0	9	3
F9-G	−1	+1	5	1
F9-H	0	+1	7	2
F9-I	+1	+1	9	3

Where 1 is the high value, −1 is the low value, and 0 is the centre value for the factors X_1 & X_2

Y1 : Disintegration Time (5 Min)

Y2 : $t_{90\%}$ (Percentage Release after 45 min)

For disintegration test of tablet put it in to the apparatus and note the time at which it completely disintegrate.

- Sample : 6 Tablets.
- Medium : Purified Water.
- Temperature : 37ºC ± 0.5ºC

Method for *In vitro* dissolution study

Dissolution Parameters

- Dissolution Medium : Water
- Volume of Medium : 900 ml
- Apparatus Used : Paddle (JP apparatus II)
- Revolution Per Minute : 50
- Sample drawn : 10 ml
- Detection : By HPLC
- Wave length : At 280 nm.
- Temperature : 37^0 C ± 0.5^0 C

Procedure

Inject separately mobile phase, blank preparation, standard and sample preparation into the chromatograph, record the chromatograms and measure the responses for analyte peak. Calculate the quantity in percentage of Drug X dissolved by using following formula.

= Ws x (P/100) x (At/As) x (1/C) x (9/5)

Where,

A_t = Peak Area of the Drug X in the Test solution

A_s = Peak Area of the Drug X in the Standard solution

Table 4: Coefficients

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	5.1389	0.0517	99.36	0.000	
x1	-0.3333	0.0283	-11.77	0.001	1.00
x2	-0.3833	0.0283	-13.53	0.001	1.00
x1x2	-0.6500	0.0347	-18.73	0.000	1.00
x1sq	0.6667	0.0491	13.59	0.001	1.00
x2sq	-0.3833	0.0491	-7.81	0.004	1.00

Table 5: Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.0693889	99.67%	99.13%	96.06%

Table 6: Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	5	4.42111	0.88422	183.65	0.001
x1	1	0.66667	0.66667	138.46	0.001
x2	1	0.88167	0.88167	183.12	0.001
x1x2	1	1.69000	1.69000	351.00	0.000
x1sq	1	0.88889	0.88889	184.62	0.001
x2sq	1	0.29389	0.29389	61.04	0.004
Error	3	0.01444	0.00481		
Total	8	4.43556			

Coefficients of Regression Analysis for Disintegration Time , model summary, analysis of variance are given in table 4,5,6

W_s = Precise quantity taken of the Drug X Reference Standard (mg)

C = Labeled amount of Drug X

P = % Assay of Drug X Reference Standard

RESULTS AND DISCUSSION

Optimization of Tablet By Factorial Design

Tablets of Risperidone were prepared by wet granulation method. All ingredients were mixed step by step then passed thorough sieve (number 100) and mixed with drug for 15 min in poly bag. Lubricants such as talc and magnesium Stearate were added in this powder mixture at last and again mixed for 5 min. The active blends were compressed into tablets (127 mg) using Cadmach 'B' tooling machine. On the basis of results of preliminary batches, selected F-9 formulation batches were prepared by using 3^2 factorial design using two independent variables X_1 and X_2 where X_1 is the amount of disintegrant and X_2 is the amount of binder. Three levels for each

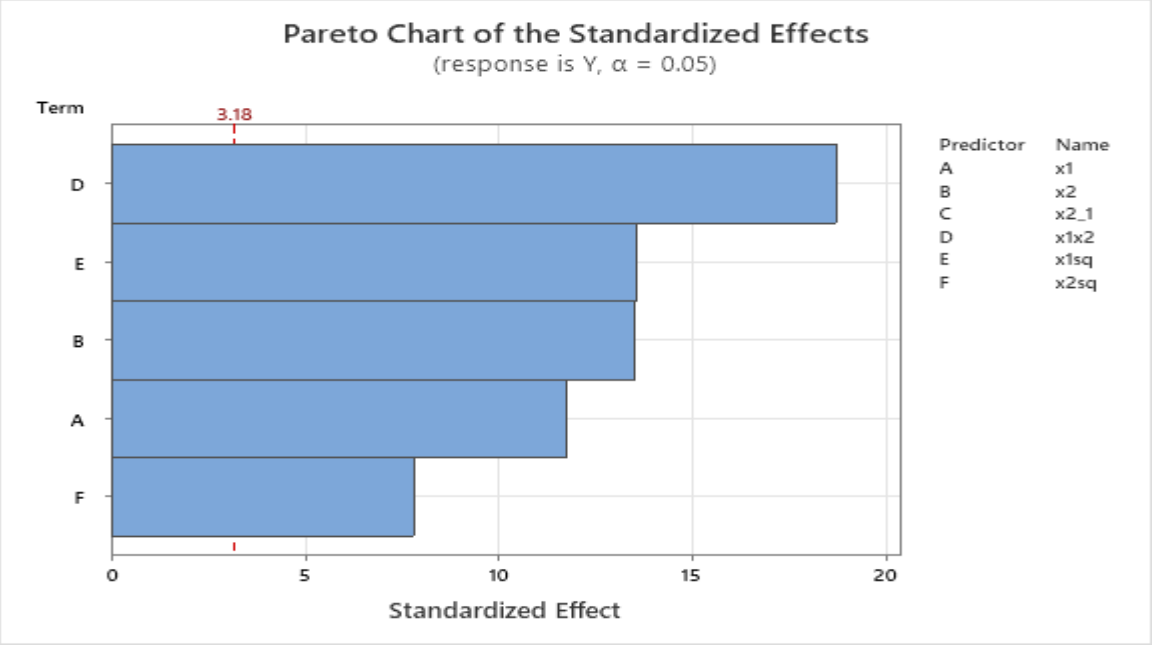

Figure 1: Pareto chart to shows standaridizes effects of disintegrates (X1)

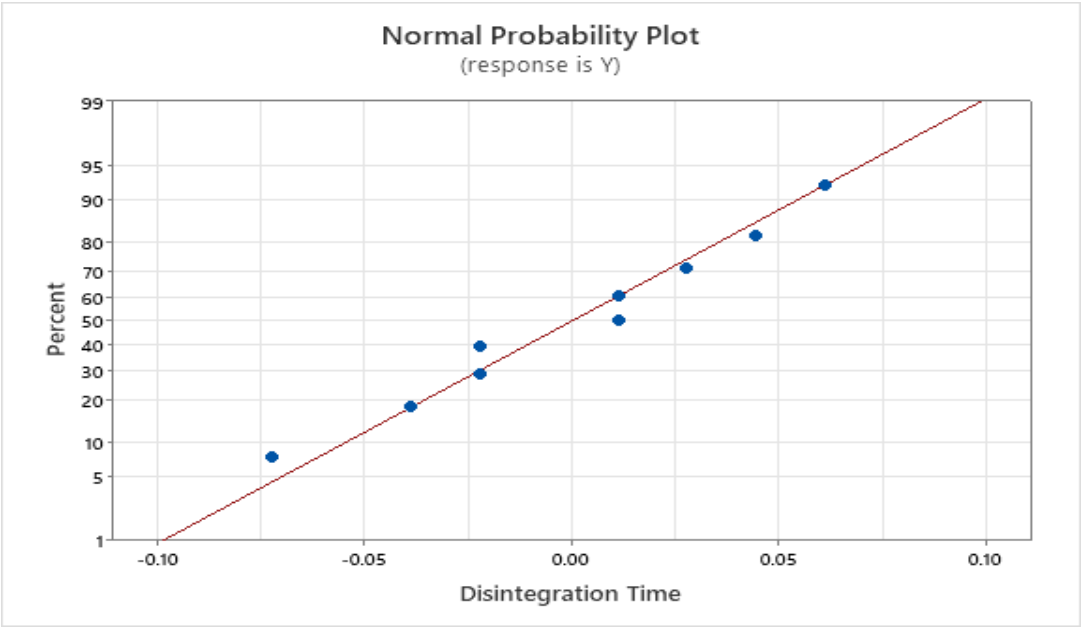

Figure 2: Normal Probability plot shows response Y1 (Disintegration Time).

Table 7: Coefficients

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	90.03	1.05	85.93	0.000	
x1	-3.632	0.574	-6.33	0.008	1.00
x2	6.375	0.574	11.11	0.002	1.00
x1x2	3.403	0.703	4.84	0.017	1.00
x1sq	3.015	0.994	3.03	0.056	1.00
x2sq	-5.115	0.994	-5.15	0.014	1.00

Table 8: Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
1.40574	98.67%	96.45%	89.06%

Table 9: Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	5	439.793	87.959	44.51	0.005
x1	1	79.134	79.134	40.05	0.008
x2	1	243.844	243.844	123.40	0.002
x1x2	1	46.308	46.308	23.43	0.017
x1sq	1	18.180	18.180	9.20	0.056
x2sq	1	52.326	52.326	26.48	0.014
Error	3	5.928	1.976		
Total	8	445.721			

Coefficients of regression analysis for % drug release, model summary and analysis of variance are mentioned in table 7,8 and 9.

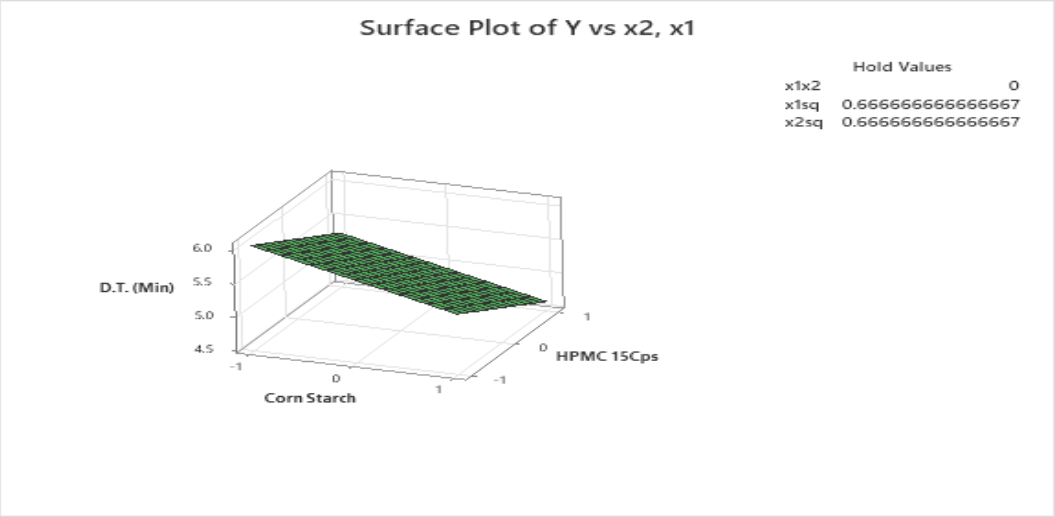

Figure 3: Shows 3D response surface plots for the effect of disintegrates (X1) on the response Y1 (Disintegration Time).

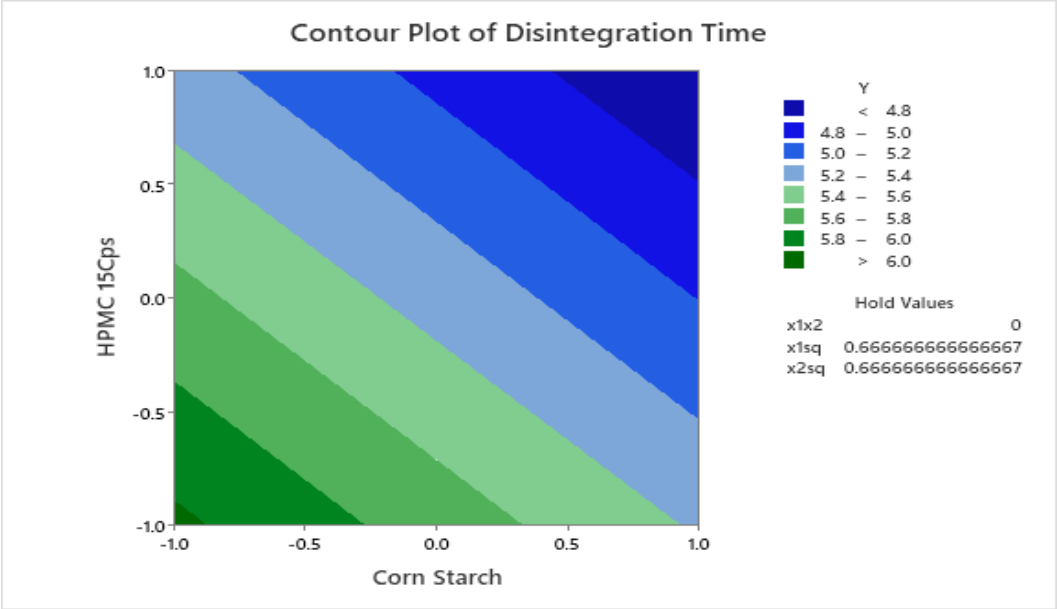

Figure 4: Contour plots for the effect of disintegrates (X1) on the response Y1 (Disintegration Time)

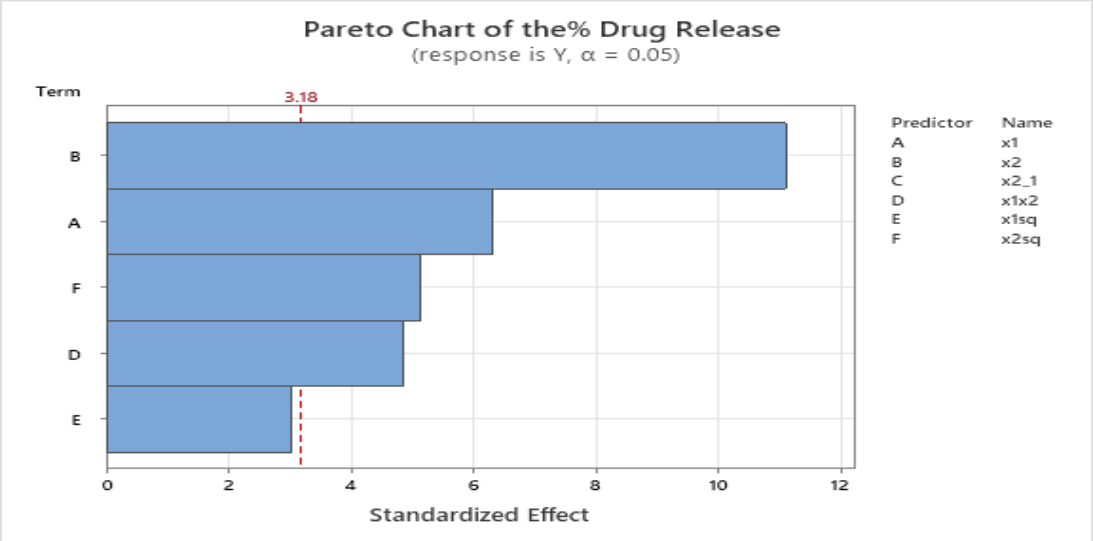

Figure 5: Pareto chart to shows standardized effects of % drug release (X2)

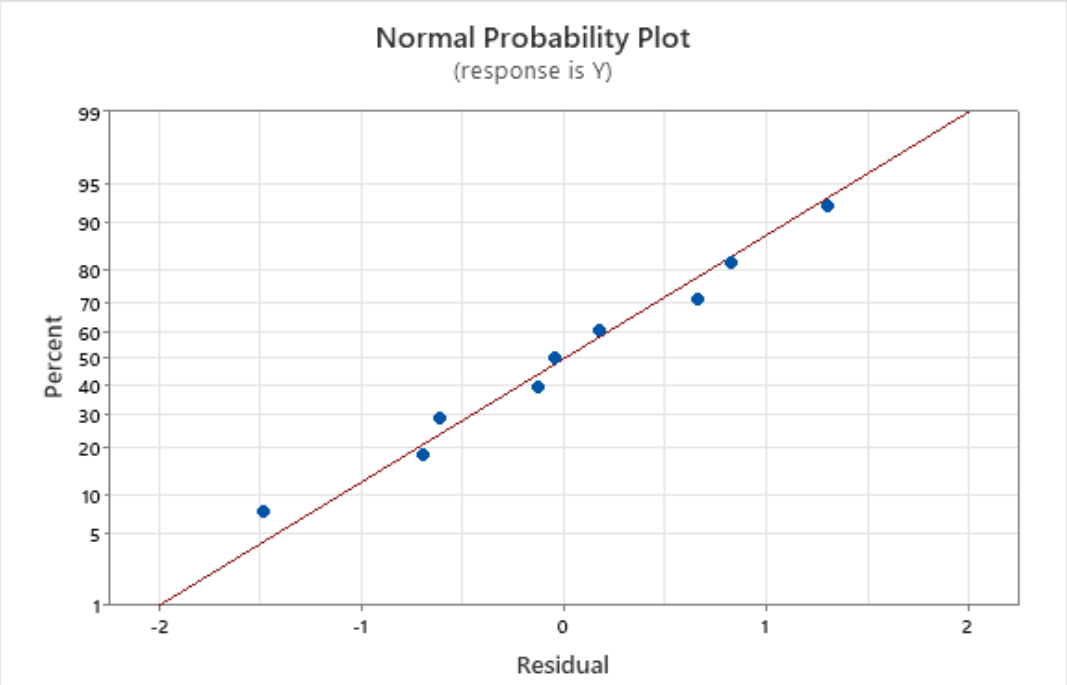

Figure 6: Normal Probability plot shows response Y2 (t90%).

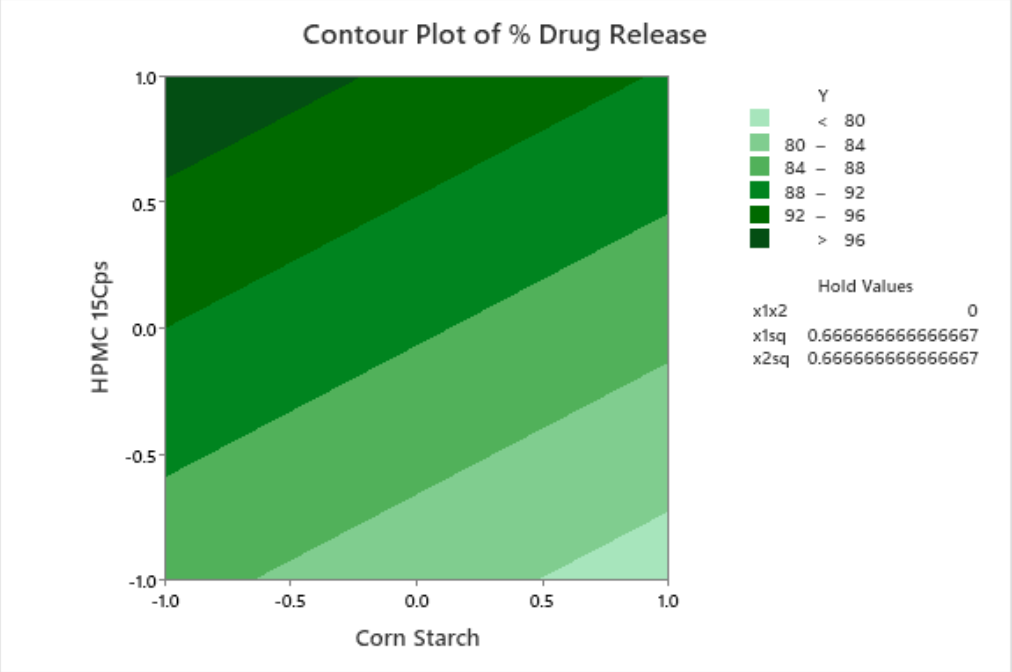

Figure 7: Contour plots for the effect of variable X2 on the response Y2 (t90%)

Table 10: Characteristics of prepared granules of F09-A-F09-I formulations

Time (min.)	Bulk Volume	Bulk density	Tapped Volume	Tapped density	Carr's index (%)	Hausner's ratio	Angle of repose	Moisture Content	Content Uniformity	Assay
Units	(mL)	(g/cm^3)	(mL)	(g/cm^3)	(%)	-	(^{o})	(%)	(%)	(%)
F09-A	81.45	0.61	72.45	0.69	11.04	1.12	20.57	1.36	99.88	99.87

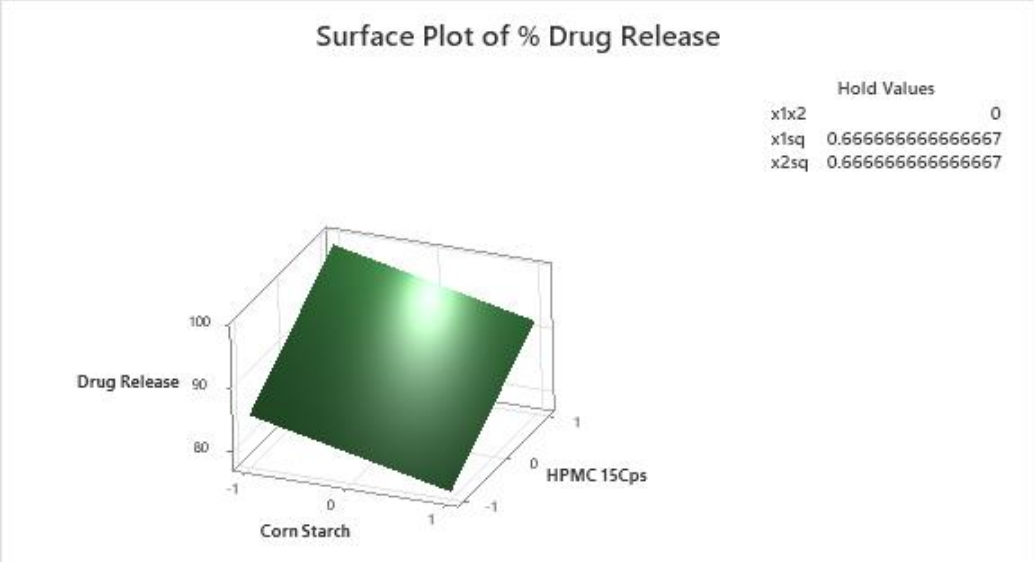

Figure 8: Shows 3D response surface plots for the effect of variable X2 on the response Y2 (t90%).

Table 11: Characteristics of Uncoated Tablet

Time (min.)	Colour	Shape	Weight	Hardness	Thickness	Diameter
Units	-	-	(mg)	(Kp)	(mm)	(mm)
F09-A	White	Round	126.8	5.4	3.76	7.17

Table 12: Characteristics of Uncoated Tablet

Time (min.)	Friability	D.T.	Content Uniformity	Assay
Units	(%)	(min:sec)	(%)	(%)
F09-A	0.18	3:50	99.95	99.95

Table 13: Optimized Formula

Sr. No.	Quantity	mg/tablet
Intragranular		
1	Drug X	2.00
2	Lactose Monohydrate	53.20
3	Lactose Monohydrate	53.20
4	Corn Starch	7.40
5	HPMC 15 Cps	2.20
6	Purified Water	q.s.
Extragranular		
7	Corn Starch	--
8	MCC (Comprecel 102)	7.00
9	Aerosil	0.50
10	Sodium Lauryl Sulphate	0.50
11	Magnesium Stearate	1.00
	Total	127.00

Characteristics of prepared granules for formulation F09-A to F09-I are displayed in table 10. Different characteristics of Uncoated Tablet and there results are given in table 11 and 12. The optimized formula after the optimization through factorial design is given in table 13.

factor were selected (−1, 0, +1) indicating low, centre, and high values. Nine formulation batches of tablets were prepared and evaluated for pre-compression and post-compression parameters. The design layout and composition of 3^2 factorial designs of Risperidone tablet formulation are given in Tables 3. [6,7]

Optimized Formulations

The resulting data were fitted into MS Excel and Minitab 21.2 (Trial Version) and analyzed statistically using analysis of variance (ANOVA). The data were also

subjected to 3-D response surface methodology to determine the influence of Corn Starch and HPMC 15Cps on dependent variable t90%. [8,9]

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response

$$Y= b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11}X_1^2 + b_{22} X_2^2$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and bi (b_1 , b_2 , b_{12}, b_{11}, and b_{22}) is the estimated coefficients for the factor Xi (X_1 , X_2 , $X_1 X_2$, X_{12}, and X_{22}). The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction term ($X_1 X_2$) shows how the response changes when two factors change simultaneously. The polynomial terms (X_{12}, X_{22}) are included to investigate nonlinearity. [10,11,12]

The application of a grid point search methodology was employed as an optimization tool. This methodology involves splitting the design space into a grid and thereafter searching for the values of the disintegration time and t90%. [13,14]

Preparation and Characterization of Optimized formulation

A full factorial design was employed to examine the influence of two components; the impacts of independent variables on responses were modeled using a polynomial equation for disintegration time and t90% drug release. The regression equations derive conclusions based on the coefficient's magnitude, where a positive sign in the polynomial equation signifies an increase in response with an increase in value, while a negative sign indicates a decrease in response with an increase in value. The interaction terms demonstrated the alteration in reaction when two factors were modified concurrently.

Regression Analysis for Disintegration Time

Effect of independent factors on disintegration time:

Regression Equation

Y1 = 5.1389 - 0.3333 x1 - 0.3833 x2 - 0.6500 x1x2 + 0.6667 x1sq - 0.3833 x2sq

Standaridizes effects of disintegrates (X1) is shown via pareto chart in the figure 1 and Normal Probability plot showing response Y1 (Disintegration Time) is shown in figure 2. The Contour plots for the effect of disintegrates (X1) on the response Y1 (Disintegration Time) has been displayed in figure 4.

Regression Analysis for % Drug Release

Regression Equation

Y2 = 90.03 - 3.632 x1 + 6.375 x2 + 3.403 x1x2 + 3.015 x1sq - 5.115 x2sq

Figure 3 displays the contour plots and 3D surface model of the independent variables X1 and X2, with the dependent variables Y1 (Disintegration Time) and Y2 (t90%).

The obtained F value exceeds the crucial F value, indicating that the result is significant at the specified probability threshold ($p<0.05$). The complete model was deemed significant; hence, it has been utilized for forecasts. Impact of independent variables on t90% drug release.

Standardized effects of % drug release (x2) through pareto chart if shown in figure 5. figure 6 contains the normal probability plot showing response y2 (t90%). Contour plots for the effect of variable x2 on the response y2 (t90%) has been given in figure 7 and figure 8 contains the 3d response surface plots for the effect of variable x2 on the response y2 (t90%).

The application of a grid point search methodology was employed as an optimization tool. This methodology involves splitting the design space into a grid and thereafter searching for the values of the disintegration time and t90%

CONCLUSION

The study successfully developed and optimized immediate-release tablets using a 3^2 factorial design. In conclusion, the future scope of such a study could involve cutting-edge scientific advancements in pharmacology, patient-centric formulation strategies, and innovative drug delivery systems. Ultimately, the goal would be to improve patient outcomes, reduce side effects, and provide more accessible, effective treatment options for mental health disorders.

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