RESEARCH ARTICLE

Optimization of Natural Polymer-Based Eperisone Hydrochloride Sustained Release Tablets using 3^2 Factorial Design

Ashutosh Sharma*, Pankaj Arora

Faculty of Pharmacy, Lords University Alwar, Rajasthan, India

Received: 5th Oct, 2024 ; Revised: 22th Oct, 2024; Accepted: 10th Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT

Eperisone Hydrochloride is a centrally acting muscle relaxant used to treat spasticity and musculoskeletal disorders. However, its short half-life necessitates frequent dosing, leading to reduced patient compliance. This study aims to develop and optimize sustained-release (SR) matrix tablets of Eperisone Hydrochloride using a 3^2 factorial design and natural polymers. The effect of polymer concentration and type on drug release was analyzed to achieve an optimal formulation. The matrix tablets were prepared using the wet granulation method with natural polymers such as Mimosa Pudica mucilage, Psidium guajava mucilage. Evaluation parameters included hardness, friability, swelling index, drug content, and in-vitro drug release. The optimized formulation exhibited a prolonged drug release profile, making it a promising alternative to conventional formulations.

Keywords: Eperisone Hydrochloride, Sustained Release, Matrix Tablets, 3^2 Factorial Design, Natural Polymers, Drug Release Optimization

How to cite this article: Ashutosh Sharma, Pankaj Arora. Optimization of Natural Polymer-Based Eperisone Hydrochloride Sustained Release Tablets using 3^2 Factorial Design. International Journal of Pharmaceutical Quality Assurance. 2024;15(4):2640-47. doi: 10.25258/ijpqa.15.4.68

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Eperisone Hydrochloride is widely prescribed for the treatment of muscle spasms and neurological disorders. Despite its efficacy, the drug's short half-life (1.6–2.5 hours) requires multiple daily doses, leading to fluctuations in plasma drug levels and reduced patient compliance.[1] Sustained release (SR) matrix tablets can address this limitation by maintaining a steady drug concentration over an extended period, minimizing dosing frequency.[2]

Natural polymers such as Mimosa Pudica mucilage, Psidium guajava mucilage have gained attention in pharmaceutical formulations due to their biocompatibility, biodegradability, and ability to form gel-like matrices that modulate drug release.[3,4] These polymers can enhance drug retention, providing prolonged therapeutic effects while reducing side effects. The present study focuses on developing and optimizing sustained release matrix tablets of Eperisone Hydrochloride using natural polymers and evaluating their physicochemical and drug release characteristics.[5,6]

In the present work, an attempt was made to develop sustained-release matrix tablets of Eperisone Hydrochloride, with the use of natural polymers for their sustaining effect. Wet granulation technique is used for tablet formulation along with the addition of suitable additives along with natural polymer as a release retarding polymer.[7,8]

METHODOLOGY

Granules for Eperisone HCl matrix tablets were prepared by wet granulation technique using various percentages of extracted polymer mucilage powder of *Mimosa pudica* L and extracted polymer mucilage powder of *Psidium guajava* L and PVP K 30 as release retardant polymers. All the powders passed through sieve No.80. The required quantity of drug, various polymers and other ingredients were mixed thoroughly and a sufficient volume of granulating agent (isopropyl alcoholic solution of polyvinyl pyrrolidone) was added slowly. After enough cohesiveness was obtained, the wet mass was sieved through sieve No.60. The granules were dried at 35°C for 30 minutes and then the dried granules were passed through sieve No.100. MCC and magnesium stearate were finally added as a glidant and lubricant respectively. Formula is shown in table 1.

Hardness

Hardness of tablets is the amount of force needed to split them. Monsanto hardness tester were used to determine the hardness of the formulated tablets. Tablets placed between the avanils and pressure applied. The hardness was calculated as kg/cm^2. Three tablets from each formulation were taken and average was calculated.[9,10]

In-vitro Dissolution Study

Dissolution studies of matrix tablets are performed to ensure sustained release of the drug (Eperisone HCl) for longer duration. Dissolution studies of prepared matrix tablets was performed in two steps. Initially, Acid buffer pH 1.2 (corresponding to gastric environment) was used as dissolution media for initial two hours. Then, the dissolution media was replaced with Phosphate buffer pH 6.8 (corresponding to intestinal environment) as dissolution media for next ten hours. Paddle apparatus was used for dissolution studies at 50 RPM and $37^0 \pm 0.5^0$C.[11,12]

**Author for Correspondence: ashutoshs896@gmail.com*

Table 1: Formulation of Eperisone HCl sustained release matrix tablets

Ingredients (mg)	ET1	ET2	ET3	ET4	ET5	ET6	ET7	ET8	ET9
Eperisone HCl	150	150	150	150	150	150	150	150	150
Mimosa Pudica mucilage	70	75	80	70	75	80	70	75	80
Psidium guajava mucilage	10	10	10	15	15	15	20	20	20
Lactose	128	123	118	123	118	113	118	113	108
PVP K-30	10	10	10	10	10	10	10	10	10
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Micro crystalline cellulose (MCC)	20	20	20	20	20	20	20	20	20
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	8	8	8	8	8	8	8	8	8
Total weight	400	400	400	400	400	400	400	400	400

RESULTS AND DISCUSSION

Hardness

The hardness of prepared ET tablets was found to be in the range of 6.2±0.3 kg/cm3 to 7.2±0.3 kg/cm3. This indicates good tablet strength. The mean hardness (in kg/cm³) of the preparations ranges from 6.2 to 7.2 with minor differences reflected in the ± values. The minimum hardness is that of batch ET1 at 6.2±0.3 and the maximum that of ET9 at 7.2±0.3. The other batches have intermediate hardness as ET2 at 6.3±0.2, ET3 at 6.9±0.3, ET4 at 6.4±0.2, ET5 at 6.8±0.3, ET6 at 7.1±0.3, ET7 at 6.7±0.3, and ET8 at 7.0±0.2. The hardness is generally the same with minor differences between the batches. Overall, the hardness is relatively consistent, with minor variations across the batches. Results of hardness are shown in table 2.

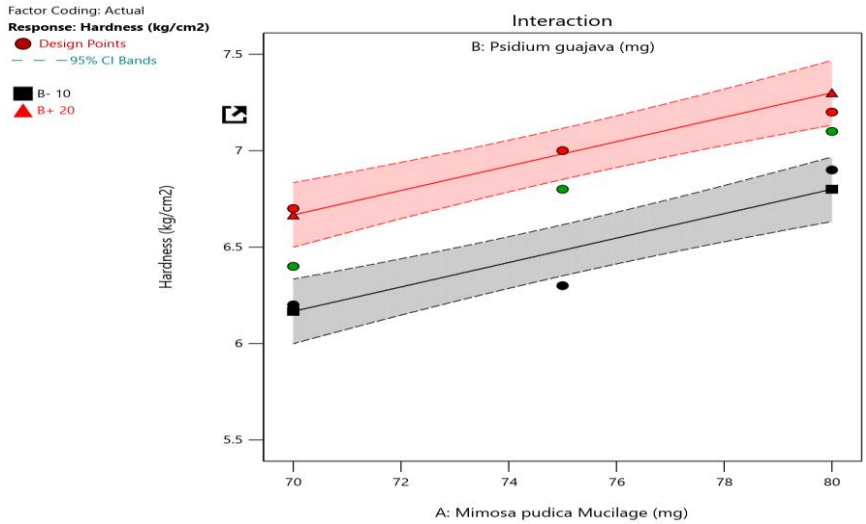

Figure 1: Interaction plot for the effect of concentration of Mimosa pudica mucilage(MPM) and Psidium guajava mucilage(PGM) extracted polymers on the Hardness

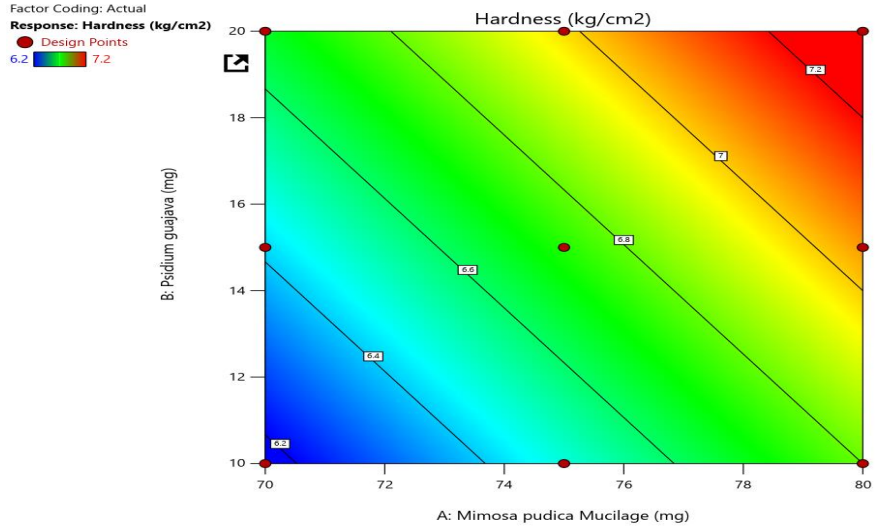

Figure 2: Contour plot for effect of concentration of Mimosa pudica mucilage(MPM) and Psidium guajava mucilage(PGM) extracted polymers on the Hardness

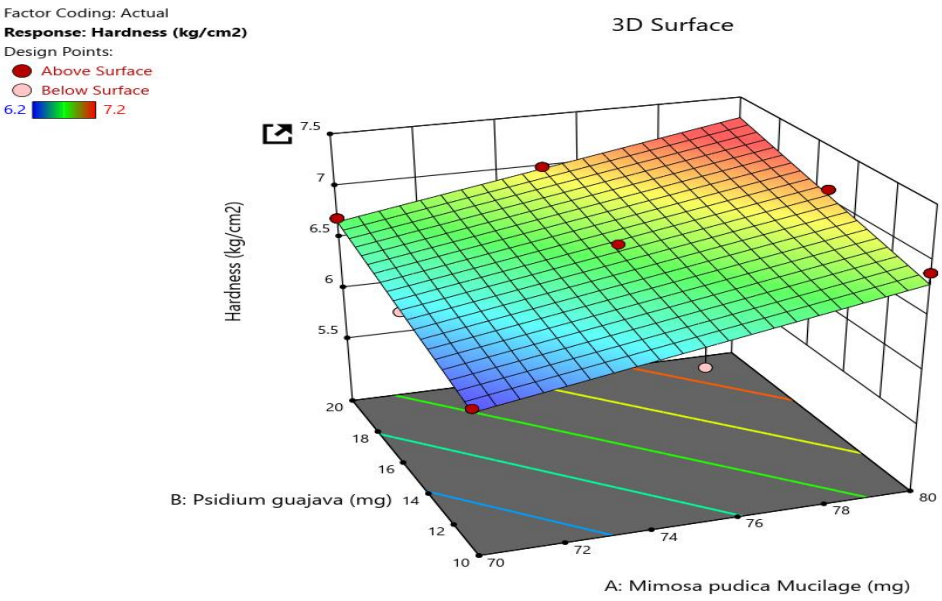

Figure 3: Contour plot 3D Surface graph for effect of concentration of Mimosa pudica mucilage(MPM) and Psidium guajava mucilage(PGM) extracted polymers on the Hardness

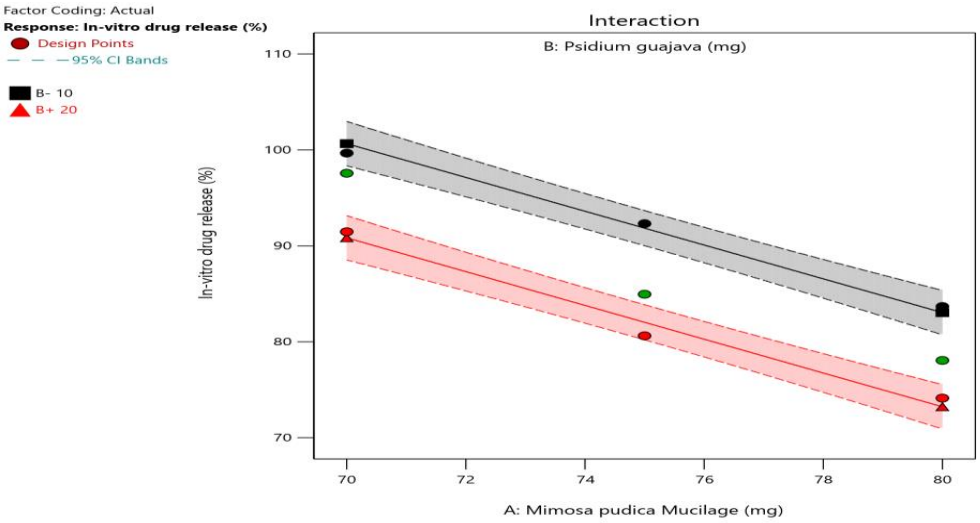

Figure 4: Interaction plot for the effect of concentration of Mimosa pudica mucilage(MPM) and Psidium guajava mucilage(PGM) extracted polymers on In-vitro drug release

***In-vitro* Dissolution Study**

Based on the data, here is the minimum and maximum release over the 12-hour period for the different formulations. The minimum release occurs with ET9, which starts at 0.00 at 0 hours and reaches a value of 74.13 at 12 hours, showing the lowest values across all time points. The maximum release occurs with ET1, which starts at 0.00 at 0 hours and reaches a value of 99.67 at 12 hours, consistently showing the highest values at every time point throughout the observation period. Results of dissolution profile is shown in table 3.

Table 2: Average Hardness of prepared tablets

Formula Batch No.	Average Hardness (kg/cm^3)
ET1	6.2±0.3
ET2	6.3±0.2
ET3	6.9±0.3
ET4	6.4±0.2
ET5	6.8±0.3
ET6	7.1±0.3
ET7	6.7±0.3
ET8	7.0±0.2
ET9	7.2±0.3

Optimization of the Formulation

The factorial design, a commonly used statistical approach for planning and optimization of experimental series, was used. The used design comprises a 3^2 full factorial design. The experimental runs, with independent variables and the measured responses were determined. After applying optimization (numerical) by Design expert software, predicted process variables and response variables were obtained. The optimal settings of the formulation variables (factors) as predicted by the Design expert software as numerical were as follows:

3^2 Full Factorial Design was employed, using the amount of extracted polymer mucilage powder of *Mimosa pudica*

Table 3: Dissolution profile of Eperisone HCl tablet formulations

Time (Hrs.)	Formulations Batch No.								
	ET1	ET2	ET3	ET4	ET5	ET6	ET7	ET8	ET9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	8.14	6.86	7.29	9.86	6.43	5.57	8.14	5.57	4.29
2	17.58	12.44	13.29	22.73	11.15	13.29	14.15	8.58	9.00
3	28.31	23.16	23.17	29.61	23.16	21.02	26.6	15.87	16.30
4	40.35	35.62	28.33	41.64	29.19	24.9	37.77	22.75	19.75
5	48.53	42.94	38.22	55.4	36.93	31.79	45.95	31.77	24.48
6	57.16	51.99	44.69	64.46	43.83	37.82	54.15	37.81	31.37
7	64.94	61.05	52.03	69.68	52.02	49.01	61.92	48.99	38.26
8	73.58	67.97	58.94	77.47	59.8	54.63	67.13	57.19	46.02
9	81.8	74.48	65.01	84.41	66.29	61.12	72.35	61.97	54.21
10	90.38	80.48	71.44	91.7	72.72	67.98	77.06	68.82	60.21
11	96.57	88.79	78.45	94.89	78.44	73.69	84.94	72.4	67.19
12	99.67	92.32	83.68	97.57	84.96	78.06	91.47	80.62	74.13

Table 4: 3^2 Full Factorial Design Layout

Formula Batch No.	Independent Variable			
	Coded value	Amount of *Mimosa Pudica* mucilage (MPM)	Coded value	Amount of *Psidium guajava* mucilage (PGM)
ET1	-1	70	-1	10
ET2	0	75	-1	10
ET3	1	80	-1	10
ET4	-1	70	0	15
ET5	0	75	0	15
ET6	1	80	0	15
ET7	-1	70	1	20
ET8	0	75	1	20
ET9	1	80	1	20

(MPM) and extracted polymer mucilage powder of *Psidium guajava* (PGM) in mg as independent variables. Hardness (kg/cm^2) and % cumulative drug release at 12 hrs were dependent variables. Where Y is the dependent variable, X1 and X2 are the independent variables. Table 4 contains the full factorial layout. Table 4 contains the 3^2 Full Factorial Design Layout. Independent and dependent variables of formulation is shown in table 5.

Table 5: Independent and dependent variables of formulation

Independent Variable	Level	Amount of *Mimosa Pudica* mucilage (MPM) (mg) (X1)	Amount of *Psidium guajava* mucilage (PGM) (mg) (X2)
	Low	70	10
	Medium	75	15
	High	80	20
Dependent Variable	Hardness (kg/cm^2)		
	% Cumulative Drug Release at 12 Hrs		

Table 6: 3^2 factorial experimental design's experimental trials, independent variables and observed responses

Formula Batch No.	X_1	X_2	Observed Responses	
			R_1	R_2
ET1	70	10	6.2	99.67
ET2	75	10	6.3	92.32
ET3	80	10	6.9	83.68
ET4	70	15	6.4	97.57
ET5	75	15	6.8	84.96
ET6	80	15	7.1	78.06
ET7	70	20	6.7	91.47
ET8	75	20	7	80.62
ET9	80	20	7.2	74.13

RESULTS AND DISCUSSION

Optimization of the Formulation

3^2 factorial experimental design's experimental trials, independent variables & observed responses along with their responses are given in table 6,7.

Responses

Factor coding is Coded.

Sum of squares is Type III - Partial

The Model F-value of 46.26 implies the model is significant. There is only a 0.02% chance that an F-value this large could occur due to noise (table 9).

P-values less than 0.0500 indicate model terms are significant. In this case A, B are 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. Table 8 contains Model suggestion for Hardness response and table 9 contains ANOVA for Linear model (Hardness).

The Predicted R^2 of 0.8578 is in reasonable agreement with the Adjusted R^2 of 0.9188; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 19.106 indicates an

Table 7: Responses Details

Responses	Name	Units	Observations	Min.	Maxi.	Mean	Std. Dev.	Ratio
R1	Hardness	kg/cm^3	9	6.2	7.2	6.73	0.3606	1.16
R2	*In-vitro* drug release	%	9	74.13	99.67	86.9	8.82	1.34

Table 8: Model suggestion for Hardness response

Source	Sequential p-value	Adjusted R^2	Predicted R^2	
Linear	0.0002	0.9188	0.8578	Suggested
2FI	0.3774	0.9179	0.8011	
Quadratic	0.7324	0.8889	0.5377	
Cubic	0.4804	0.9231	-0.7524	Aliased

Table 9: ANOVA for Linear model (Hardness)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.9767	2	0.4883	46.26	0.0002	significant
A-Mimosa pudica Mucilage	0.6017	1	0.6017	57	0.0003	
B-Psidium guajava	0.375	1	0.375	35.53	0.001	
Residual	0.0633	6	0.0106			
Cor Total	1.04	8				

Fit Statistics			
Std. Dev.	0.1027	R^2	0.9391
Mean	6.73	Adjusted R^2	0.9188
C.V. %	1.53	Predicted R^2	0.8578
		Adeq Precision	19.1064

adequate signal. This model can be used to navigate the design space.

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors.

As a rough rule, VIFs less than 10 are tolerable, results are displayed in fig 1,2,3. Coefficients in Terms of Coded Factors(Hardness) is shown in table 10.

Factor coding is Coded.

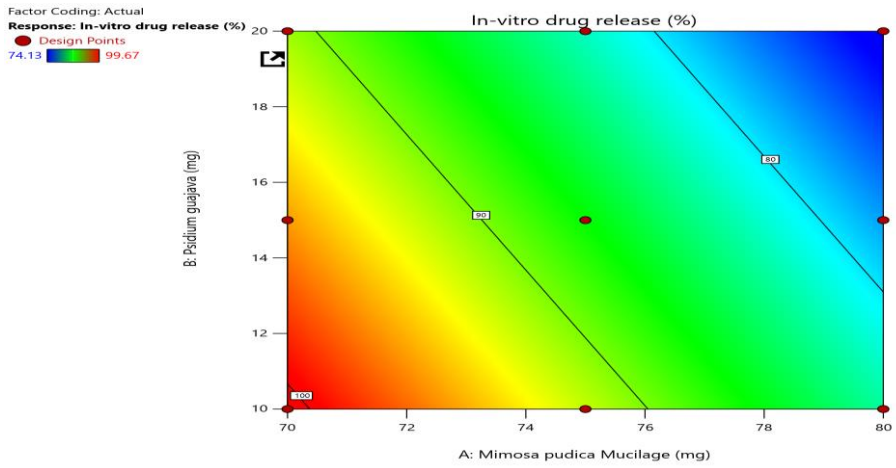

Figure 5: Contour plot for the effect of concentration of Mimosa pudica mucilage (MPM) and Psidium guajava mucilage(PGM) extracted polymers on In-vitro drug release%

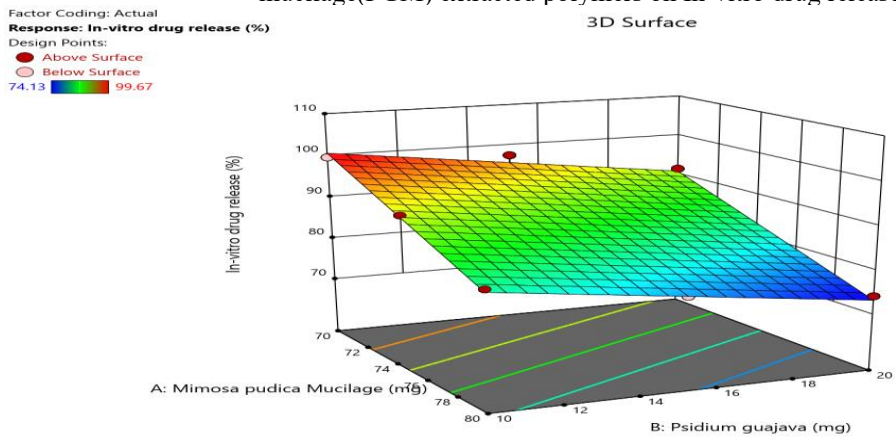

Figure 6: Contour plot 3D surface for the effect of concentration of Mimosa pudica mucilage (MPM) and Psidium guajava mucilage (PGM) extracted polymers on In-vitro drug release%

Table 10: Coefficients in Terms of Coded Factors(Hardness)

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	6.73	1	0.0342	6.65	6.82	
A-Mimosa pudica Mucilage	0.3167	1	0.0419	0.214	0.4193	1
B-Psidium guajava	0.25	1	0.0419	0.1474	0.3526	1

Table 11: Model suggestion for In-vitro drug release response

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001		0.9741	0.9614	Suggested
2FI	0.6762		0.9701	0.9382	
Quadratic	0.4983		0.9687	0.8718	
Cubic	0.5153		0.9751	0.4325	Aliased

Table 12: ANOVA for Linear model In-vitro drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	609.89	2	304.95	151.7	< 0.0001	significant
A-Mimosa pudica Mucilage	465.34	1	465.34	231.49	< 0.0001	
B-Psidium guajava	144.55	1	144.55	71.91	0.0001	
Residual	12.06	6	2.01			
Cor Total	621.96	8				

Sum of squares is Type III - Partial

The Model F-value of 151.70 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are 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. Results are tabulated in table 11,12.

Fit Statistics			
Std. Dev.	1.42	R^2	0.9806
Mean	86.94	Adjusted R^2	0.9741
C.V. %	1.63	Predicted R^2	0.9614
		Adeq Precision	33.5093

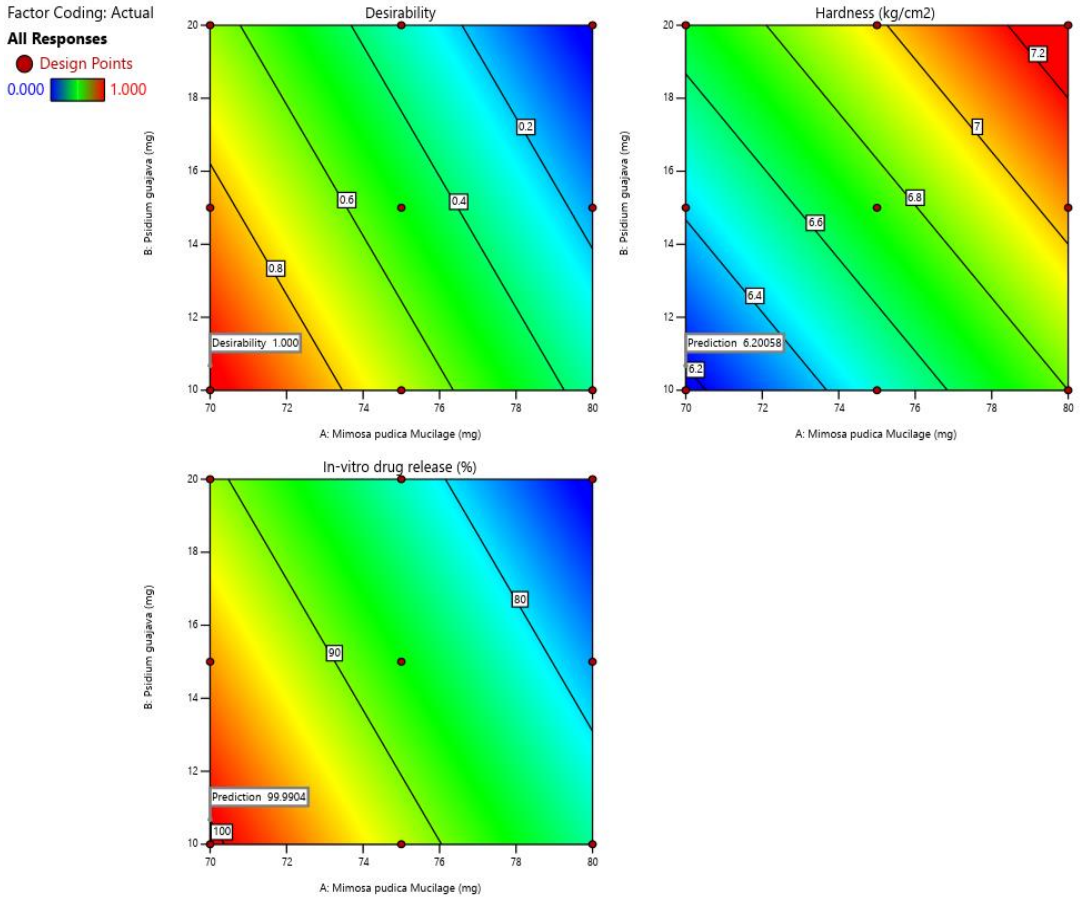

Figure 7: Contour plot for optimization of all responses

Table 13: Coefficients in Terms of Coded Factors for In-vitro release

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	86.94	1	0.4726	85.79	88.1	
A-Mimosa pudica Mucilage	-8.81	1	0.5788	-10.22	-7.39	1
B-Psidium guajava	-4.91	1	0.5788	-6.32	-3.49	1

Table 14: Optimized formulation process and response variables

Code	Solution					Error	Desirability
	Process Variables		Response Variables				
	X1	X2		Predicted Value	Observed Value		
OET1	70.002	10.676	R1	6.200	6.2	0.0	1
			R2	99.99	99.67	0.36	

The Predicted R^2 of 0.9614 is in reasonable agreement with the Adjusted R^2 of 0.9741; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 33.509 indicates an adequate signal. This model can be used to navigate the design space.

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant (shown in table 13). The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

By creating a contour plot using design expert software, the standardised influence of the independent variables and interaction between them on the dependent variables was examined. These were used to demonstrate the influence of independent variables as well as interaction between them with dependent variables (fig 4,5 & 6).

DISCUSSION

The overlay plot revealed that the area of interest is in the "yellow zone" of Figure Formulations having a concentration of concentration of Mimosa pudica mucilage (MPM)(X1)(70.002 mg) and Psidium guajava mucilage(PGM) (X2)(10.675 mg)extracted polymers with a hardness of 6.20 kg/cm3, and in the experimental area of the overlay plot, the %CDR is 99.99% showed the greater acceptability than other checkpoint batches. It was therefore chosen as batches OET1 (Table 14).

The checkpoint batch findings showed no significant difference between the results. As a result, in certain variable ranges, the equation obtained for specific responses is validated. The similarity between observed and expected response values was used to measure the robustness of prediction and these statistics show the

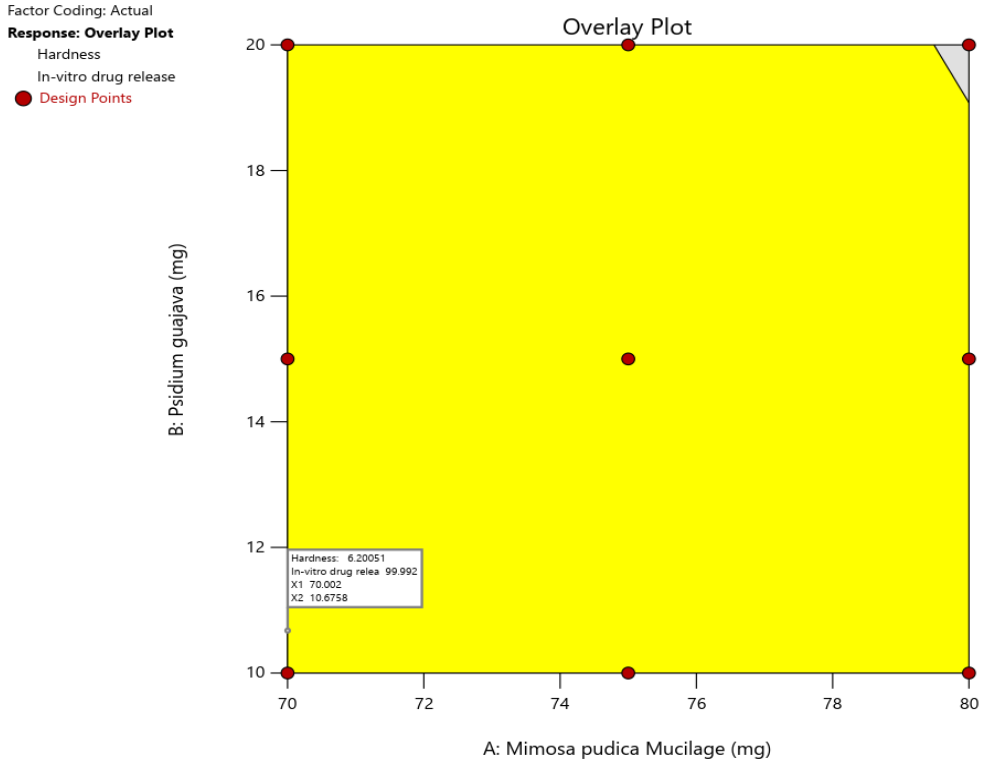

Figure 8: Overlay Plot showing combined effects of extracted polymers

validity of the produced model. Batch ET1 was selected as the optimized formulation.

CONCLUSION

The study successfully developed and optimized Eperisone Hydrochloride sustained-release matrix tablets using a 3^2 factorial design. The use of natural polymers demonstrated effective drug release modulation, providing an alternative to synthetic excipients. The optimized formulation offers potential benefits in enhancing patient compliance and therapeutic efficacy. Further in-vivo studies are recommended to validate these findings.

REFERENCES

1. Sharma, N, Sharma V, Ravindra N (2024). Formulation and Optimization of Ion Exchange Resin Beads of Tolperisone Hydrochloride Using 23 Factorial Design. International Journal of Health Advancement and Clinical Research (tz), 2(3), 8–14.
2. Ganesh, GNK, Kumar S, Jawahar N, Senthil V, Venkatesh DN, Srinivas MS, 2010. Preparation and evaluation of sustained release matrix tablet of diclofenac sodium using natural polymer. Journal of pharmaceutical sciences and research, 2(6), p.360.
3. Mondal N, The Role of Matrix Tablet in Drug Delivery System. International journal of Applied Pharmaceutics. 2018, 10,1-6.
4. Kabir ER, Syeara N, Khan TTS. Formulation design and optimization of sustained release tablet dosage form of Diacerein, European Polymer Journal, 2023; 189; 111982.
5. Bagde S, Mamidi HK, (2023). Nanostructured Lipid Carriers of Eperisone Hydrochloride using Quality by Design Approach. Journal of Drug Delivery and Therapeutics, 2023; 13(2): 37-46.
6. Sharma R, Bansal M, Garg A, Agarwal V, Sharma D, Formulation and Evaluation of Sustain Release Matrix Tablet of Aceclofenac, International Journal of Health Advancement and Clinical Research (tz), 2023; 1(1);06-11.
7. Bodea A, Leucuta SE, 1997. Optimization of propranolol hydrochloride sustained release pellets using a factorial design. International journal of pharmaceutics, 154(1), pp.49-57.
8. Kumar A, Kurmi BD, Singh D, 2023. Development and method validation of design of experiments-optimized tablet formulation for simultaneous detection of exemestane and everolimus. ASSAY and Drug Development Technologies, 21(6), pp.273-287.
9. Radhika PR, Pal TK, Sivakumar T, 2009. Formulation and Evaluation of Sustained Release Matrix Tablets of Glipizide: Sustained release matrix tablets of glipizide. Iranian Journal of Pharmaceutical Sciences, 5(4), pp.205-214.
10. Shanmugam S, Chakrahari R, Sundaramoorthy K, Ayyappan T, Vetrichelvan T, 2011. Formulation and evaluation of sustained release matrix tablets of Losartan potassium. International Journal of Pharm Tech Research, 3(1), pp.526-234.
11. Patra C, Kumar A, Pandit H, Singh S, and Devi M, 2007. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride. Acta Pharmaceutica, 57(4), p.479.
12. Ahmed V, Sharma S, Bhatt P, 2020. Formulation and evaluation of sustained release tablet of diltiazem hydrochloride. Int. J. Pharmaceut. Sci. Res, 11(5), pp.2193-2198.