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Design, Development and Optimization of Extended-Release Matrix Tablets of Losartan Potassium

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ABSTRACT: *Losartan potassium (LP), an orally active antihypertensive drug, has poor bioavailability (32–33%) and a short half-life (1.5–2 h) due to extensive first-pass metabolism. The present study aimed to design and optimize extended-release (ER) matrix tablets of LP to enhance patient compliance and therapeutic efficacy. Compatibility between the drug and polymers was confirmed by FTIR analysis. Formulations were optimized using HPMC K4M and ethyl cellulose (EC) as independent variables through Response Surface Methodology (RSM) employing a Central Composite Design (CCD). Design Expert® 13 generated 13 trial formulations, which were evaluated for precompression, postcompression, and in vitro dissolution parameters using USP type II apparatus in pH 6.8 buffer for 12 h. The selected responses were swelling index (SI, Y_1), time for 50% release (t_{50}, Y_2), and cumulative release at 12 h (Q_{12}, Y_3). Statistical analysis showed significant model terms ($p < 0.05$) with non-significant lack of fit and good correlation between predicted and adjusted R^2 values. The optimized formulation exhibited SI of 322, t_{50} of 7.3 h, and Q_{12} of 81.9%, closely matching predicted results. Drug release followed zero-order kinetics ($r = 0.9964$) with a super case-II transport mechanism ($n = 1.425$), indicating release governed by polymer swelling, relaxation, erosion, and diffusion. Stability studies confirmed formulation robustness. Overall, CCD proved to be an effective tool for optimizing LP ER matrix tablets, achieving sustained release suitable for once-daily antihypertensive therapy.*

Keywords: *Losartan Potassium, Extended Release, Central Composite Design, HPMC K4M, Ethyl Cellulose, ANOVA.*

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I. Introduction

Oral administration is the most favored route of administration owing to the convenience, non-invasiveness, and high compliance of the patient. Conventional formulations, however, need to be administered frequently in order to achieve therapeutic drug concentrations, thereby resulting in poor compliance and fluctuating plasma drug concentrations. Evidently, for such limitations, Extended Release (ER) formulations, specifically matrix tablets, have gained much prominence as a primary strategy for controlled and prolonged drug release over a period of time[1,2]. Controlled oral dosage forms are specifically designed to achieve a prolonged therapeutic effect through slow release of the drug over a prolonged time period following single dosing. It achieves steady and efficient plasma drug concentration *in vivo*. Modified release formulations are very good technologies for the optimization of drug bioavailability and for plasma concentration-time profile enhancement. Such formulations are in general classified as delayed release and extended (or prolonged) release systems **[1,2].** Extended Release (ER) matrix tablets are solid dosage forms that release the active pharmaceutical ingredient (API) at a predetermined rate, maintaining therapeutic levels for an extended period without repeated administration. These systems consist of a drug embedded within a hydrophilic or hydrophobic polymer matrix that regulates its diffusion and dissolution over time. ER formulations are crucial for drugs with short half-lives and those requiring sustained plasma concentrations for efficacy. The primary objective of sustained release formulations is to deliver the drug at a controlled, predetermined rate, thereby enhancing patient compliance by reducing the frequency of dosing. Additionally, sustained release minimizes fluctuations in plasma drug levels, avoiding undesirable peaks that could lead to local or systemic side effects. As a result, therapeutic drug concentrations are maintained within the desired range for an extended duration, ensuring effective and safer treatment **[3-5].**

Losartan potassium (LP) is an orally active angiotensin-II antagonist used to treat high blood pressure. It belongs to Biopharmaceutical Classification System (BCS) Class III with water solubility of 0.0216 mg/ml and a log P of 5.37[17]. Although the drug is highly soluble in water, its oral bioavailability is just 33%[18]. This has been attributed to its insufficient absorption from the lower gastrointestinal tract and it has plasma elimination half-life of 1.5 to 2 h[19]. Due to its short half-life and side effects like diarrhea, muscle cramps, dizziness, insomnia, nasal

congestion, persistent cough, it would be more desirable to administer losartan potassium in a prolonged or ER dosage form to maintain the plasma level of the drug for 8-12 h or to reduce its frequent administration **[6,7].** Hence**,** the present research work was planned to design, development and optimization of ER matrix tablets of LP to enhance patient compliance and improved therapeutic effects. Thus, development of ER matrix tablets of LP will enhance patient adherence and therapeutic outcomes by providing a more consistent plasma concentration of the drug. This eventually reduces dosing frequency and minimizing side effects compared to conventional formulations with regular dosing frequency. This goal is accomplished by employing design of experiments (DoE) as a computational method to statistically validate the formulation through RSM.

II. Materials and Methods

Materials Used: Losartan potassium (LP) was kindly supplied by Hetero Drugs Ltd, Hyderabad. HPMC K4M and Ethyl cellulose was procured from Yarrow Chem Products, Mumbai. Anhydrous dibasic calcium phosphate (ADCP), mannitol, magnesium stearate and talc were procured from SD fine chemicals.

FTIR Studies: FTIR spectral analysis of drug, and combination of drug and polymers and optimized compression coated tablets were recorded to investigate the changes in chemical composition of the drug after combining with excipients. Spectra were obtained using a Shimadzu FTIR-1700 spectrophotometer. The powder was compressed to form potassium bromide discs for scanning, with a range from 4000 cm^{-1} to 400 cm^{-1}

Construction of Calibration Curve for Estimation of the Drug: 25 mg of LP was transferred into a 25 ml volumetric flask containing 15ml of Methanol solution. The mixture is sonicated for 10 min to dissolve the drug completely, and volume was made up to 25 ml (1000 µg/ml solution). Next, 2.5 ml solution was transferred into another 25 ml volumetric flask and volume was made up to 25 ml with pH 6.8 buffer solution to get 100 µg/ml solution which is considered as working standard solutions. Series of dilutions were made in the concentration range of 2-10 µg/ml solution. A standard curve was prepared using λ max 225 nm in pH 6.8 buffer solution, The absorbance of the resulting solutions was measured keeping dissolution medium as a blank. Concentration versus optical density values is plotted and displayed table and shown in (Figure 1) the concentration range of 2-10 µg/ml. The method obeyed Beer-Lambert's law and both solutions were stable for 24 h.

Table 1: Calibration curve data of LP

Concentration (µg/ml)	Absorbance Mean± SD(n=3)
2	0.095 ± 0.0005
4	0.190 ± 0.0011
6	0.285 ± 0.0010
8	0.380 ± 0.0015
10	0.475 ± 0.0010

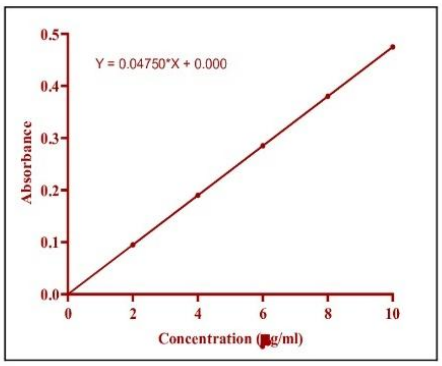

Figure 1: Calibration curve of LP

Designing of ER Matrix Tablets of LP using Design of Experiment (DoE): In the present study, ER matrix tablets of LP tablets were designed, developed and characterized by QbD concept using (DoE **[8-10].** In this design, 2 independent factors HPMC K4M (X1) and EC (X2) were evaluated each at 2 levels viz., Low and High coded as -1 and +1, respectively as shown in table 2. Total 13 batches of ER matrix tablets were generated at all 13 possible combinations using HPMC K4M and EC. And 13 experimental trials generated with 5 center points were performed at all combinations. Design Expert® (Trial Version 13) was used to generate CCD (α = 1) and the regression analysis was used to optimize the concentration of X1 and X2.

Table 2: Factors and Responses as per CCD

Variables	Levels used, Actual (coded)	
Independent Variables (mg)	**Low (-1)**	**High (+1)**
X1- HPMC K4M	150	200
X2- EC	50	75
Dependent Variables (Responses)		
Y1- SI, Swelling index		

Y2- $t_{50\%}$, the time in which 50 % of the drug released.
Y3- Q_{12}, Cumulative amount of drug released after 12 h

Table 3: Formulae of ER matrix tablets of LP generated as per CCD

Trial batches	Ingredients (mg)					
	HPMC K4M	EC	LP	ADCP	Mannitol	Total weight
F1	150	62.5	50	50	87.5	400
F2	175	62.5	50	50	62.5	400
F3	175	75	50	50	50	400
F4	200	62.5	50	50	37.5	400
F5	200	50	50	50	50	400
F6	175	62.5	50	50	62.5	400
F7	175	50	50	50	75	400
F8	150	50	50	50	100	400
F9	175	62.5	50	50	62.5	400
F10	175	62.5	50	50	62.5	400
F11	150	75	50	50	75	400
F12	200	75	50	50	25	400
F13	175	62.5	50	50	62.5	400

Pre-Compression Parameters: Before compression, the powder bed was subjected for various pre-compression parameters including angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The angle of repose was assessed using the funnel method, while digital bulk density apparatus was employed for determining both bulk and tapped density. Then Carr's compressibility index and the Hausner's ratio was calculated.

Method of Formulation of ER Matrix Tablets of LP: Each tablet weighing 400 mg (containing 50 mg of drug) were prepared by direct compression method. This method involves the compression of tablets directly from powder bed of active ingredient and excipients. All ingredients (Table 3) were passed through #100 mesh separately and weighed accurately, mixed in geometrical order including the lubricant and blended properly for few minutes. The powder was individually filled in the die cavity (10 mm diameter), and constant pressure was applied. Then, tablets were compressed by direct compression method.

Post-Compression Evaluation Parameters: The thickness, hardness, uniformity of weight, drug content uniformity, and friability of the ER tablets were carried out according to the standard methodology using relevant equipment.

Swelling Index (SI): Swelling property of ER matrix tablets of LP was determined by placing it in the dissolution 100 ml beaker, in 90 ml of pH 6.8 Buffer at 37±0.5°C. The weight and volume reached by ER matrix tablets of LP over time was determined by withdrawing the tablets periodically from dissolution medium. The tablets were weighed on an analytical balance after slight blotting with tissue paper to remove the excess liquid. The volume of the tablets was obtained by measuring the thickness and diameter, considering a right circular cylinder form. The determined weight and volume were used to calculate the ER matrix tablets of LP density over the dissolution study. Swelling characteristics were expressed in terms of percentage swelling index according to the following equation.

$$\mathrm{SI} = \frac{(\text{Weight of swollen tablet} - \text{Initial weight of tablet})}{\text{Initial weight of tablet}} \times 100$$

***In vitro* Dissolution Studies:** *In vitro* drug release studies of all ER matrix tablets of LP of drug were carried out using USP XXII dissolution apparatus type II (paddle method) at 50 rpm. The dissolution test was carried out in 900 ml of pH 6.8 Buffer, maintained at 37 ± 0.5^0C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at every hour over a period of 12 h. The samples were replaced with fresh dissolution medium to maintain sink conditions. Then samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with pH 6.8 Buffer. Absorbance of these solutions was measured at 225 nm using a double beam UV spectrophotometer. The percentage drug release was plotted against time to determine the drug release profile. The study was conducted in triplicate.

Optimization: After completion of all evaluation parameters, selected responses viz., Y1 (SI), Y2 ($t_{50\%}$) and Y3 (Q_{12}) were studied and evaluated. The data obtained were treated using design software to generate possible statistical parameters. The data was analyzed statically using analysis of variance (ANOVA) to explain the influence of independent variables on dependent variables. The data were also subjected to 3-D and 2-D response surface methodology to study the interaction of X1 and X2. Further, numerical point prediction method was used to generate optimized formula by keeping all factors in range, conformation was done to generate predicted response values as per Design space. The optimized ER matrix tablets of LP was formulated and evaluated

experimentally and data was compared with predicted response values. The predicted and experimental data was validated within the DoE space to ratify the results.

Kinetic Modeling: In order to describe the kinetics of the release process of drug in the different formulations, different kinetic models were fitted to the obtain dissolution data of formulations using linear regression analysis.

III. Results and Discussion

Hydrophilic polymers such as HPMC K4M are extensively used for modifying drug release from extended-release dosage forms. However, hydrophilic matrices are unable to achieve constant drug release throughout the intended duration **[11].** Few studies have shown that polymer swelling and erosion behavior can be modified by using a combination of polymers **[12, 13].** It is also reported that combining hydrophilic polymers with hydrophobic ones has been shown to effectively modulate swelling and erosion behavior, leading to more consistent release kinetics **[14].** Some researchers reported that using ethyl cellulose (EC) derivatives in matrix tablets led to nearly zero-order release extending up to 24 h **[16].** Therefore, in the present study, ethyl cellulose (EC), a hydrophobic polymer, was incorporated alongside HPMC K4M to achieve the desired drug release profile from the polymer matrix system.

Drug-Polymer Interaction Studies: The FTIR spectrum of LP, and physical mixture of drug with HPMC K4M and EC are shown in figure 2. The pure LP's FTIR spectra showed principal peaks at various wave numbers, such as O–H stretching at 3179 cm^{-1}, C–H stretching at aromatic at 3005 cm^{-1}, C–H stretching aliphatic at 2934 cm^{-1}, N=N stretching at 1626 cm^{-1}, C=C stretching at 1458 cm^{-1}, C–N stretching at 1260 cm^{-1}, and C–Cl stretching at 762 cm^{-1}. In the spectrum of all PMs, the drug under study have retained its identity without changing in its characteristic's peaks. This indicated that no chemical interaction between the drug and polymers used in formulations.

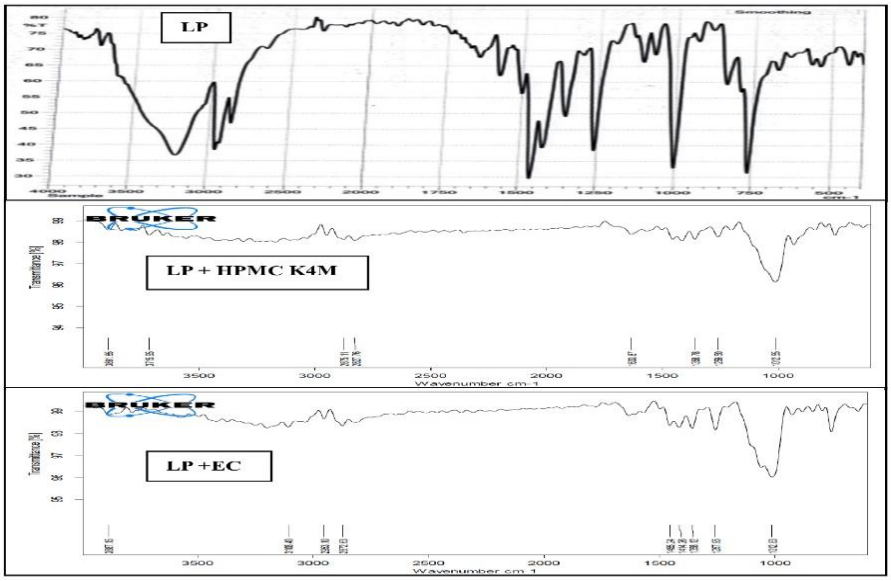

Figure 2: FTIR spectra of Formulation of LP, LP+ HPMC K4M and LP + EC

Precompressional Characteristics of Powder Bed: Bulk density and tapped density were found in the range of 0.405 to 0.587 and 0.522 to 0.692 respectively. The compressibility index and Hausner's ratio of all batches of powder blends was found in the range of 16.57 to 27.97 and 1.198 to 1.388 respectively. The angle of repose of all batches of powder blend was 30.55 to 38.69. The results of all precompressional characteristics of powder blend demonstrated good flow characteristics. Thus, powder bed could able to subject for direct compression without any manufacturing issues.

Postcompression Evaluation of ER tablets of LP: All tablets were visually observed for their physical appearance. They were off-white colored, round shaped, uncoated with plain surface on both sides and also were found to be good without chipping, capping and sticking. The post compression evaluation results are expressed as mean ± SD as shown in table 13. All batches of tablets were found uniform in their thickness and exhibited in the range of 4.003 to 4.053 mm. Hardness was found in the range 11.43 to 13.23Kg/cm^2. This indicated that, manufactured ER matrix tablets of LP were sufficiently hard to resist breaking during normal handling, packaging and transportation. Also, a high degree of compaction resulting in high hardness is a primary way to control and slow the drug release. The results of friability below 1% revealed that manufactured tablets have sufficient mechanical strength to withstand rupture and erosion during handling. The drug content of all batches of ER

matrix tablets was found in the range of 96.18% to 99.13% of LP. Low standard deviation (SD) values in the drug content indicated uniform drug distribution in all batches of table. Also, maximum allowed percentage weight variation for tablets weighing 400 mg or less weight of tablet is ± 5% according to IP. In our study, no formulations were exceeding this limit and thus all batches of ER matrix tablets are tablets passed weight variation test**.**

Table 4: Post compression evaluation for ER matrix tablets of LP

Trial Batches	Thickness (mm)	Weight Variation (mg)	Hardness (kg/m^2)	Swelling Index (%)	Friability ± SD	% Drug content ± SD
F1	4.00 ± 0.01	399.0 ± 1.00	11.43 ± 0.05	292 ± 1.00	0.75 ± 0.02	96.18 ± 1.12
F2	4.03 ± 0.02	400.0 ± 1.00	12.27 ± 0.05	320 ± 1.00	0.63 ± 0.01	97.20 ± 0.97
F3	4.00 ± 0.0	399.0 ± 1.00	11.57 ± 0.15	310 ± 2.51	0.69 ± 0.01	98.44 ± 0.79
F4	4.01 ± 0.02	400.0 ± 1.00	12.43 ± 0.05	364 ± 1.52	0.70 ± 0.06	97.32 ± 0.93
F5	4.01 ± 0.01	400.0 ± 1.00	12.27 ± 0.05	375 ± 2.64	0.68 ± 0.01	96.33 ± 0.95
F6	4.03 ± 0.02	400.0 ± 1.00	11.83 ± 0.05	321 ± 2.64	0.72 ± 0.01	98.36 ± 1.07
F7	4.04 ± 0.02	399.0 ± 1.00	12.57 ± 0.05	328 ± 2.00	0.71 ± 0.09	96.21 ± 1.09
F8	4.01 ± 0.01	399.7 ± 0.57	12.63 ± 0.11	300 ± 2.00	0.67 ± 0.01	97.47 ± 1.16
F9	4.05 ± 0.02	399.7 ± 1.52	11.87 ± 0.05	322 ± 3.51	0.71 ± 0.08	97.25 ± 1.05
F10	4.03 ± 0.03	400.0 ± 1.00	13.13 ± 0.05	320 ± 3.51	0.72 ± 0.04	97.18 ± 0.95
F11	4.03 ± 0.0	400.0 ± 1.00	12.37 ± 0.05	280 ± 2.08	0.78 ± 0.04	98.15 ± 0.94
F12	4.04 ± 0.020	399.7 ± 0.57	12.77 ± 0.057	350 ± 3.05	0.72 ± 0.02	98.26 ± 1.16
F13	4.05 ± 0.020	399.0 ± 1.00	13.23 ± 0.057	322 ± 2.08	0.69 ± 0.04	99.13 ± 0.31

Swelling Studies by Weight Method: Swelling of the polymeric matrix is a critical parameter since it directly influences the drug release profile from matrix-based drug delivery systems. The swelling study revealed a clear influence of polymer composition on the hydration behavior of ER tablets. Formulations containing higher proportions of HPMC K4M exhibited greater swelling indices due to the rapid hydration and gel layer formation **[17].** Equally, formulations with higher levels of EC demonstrated comparatively lower swelling indices. This might be due to the hydrophobic nature of the polymer. And it functioned primarily as an inert, insoluble matrix former that restricted excessive fluid penetration and also helped to maintain matrix integrity throughout the dissolution period. Overall, a balanced swelling profile was achieved with the combination of HPMC K4M and EC provided. Excessive swelling due to hydrophilic polymer HPMC K4M, which could lead to faster erosion and uncontrolled drug release, was effectively modulated by EC. All the formulations (F1–F13) maintained swelling for more than 6 h, ensuring their suitability for extended-release applications.

***In vitro* Dissolution Studies:** The *in vitro* dissolution profiles of trial batches (F1–F13) are depicted in figure 3. The results revealed that drug release from all batches was extended over the 12 h period while maintaining good matrix integrity. The selected response variables were Swelling Index, SI (Y1); time for 50% drug release, $t_{50\%}$, (Y2); and cumulative drug release at 12 h, Q_{12}, (Y3). The observed values of SI, $t_{50\%}$ and Q_{12} were subjected to multiple regression analysis to establish the relationship between the formulation factors and the corresponding responses. SI (Y1) was found to vary within the range of 280 to 375; $t_{50\%}$ (Y2) ranged from 6.0 to 8.3 h; and Q_{12} (Y3) varied from 72.4% to 99.2% across the formulations (F1–F13). The response data were entered into Design Expert software to generate statistical outputs of one-way ANOVA at the 0.05 level of significance, model fit statistics, polynomial equations, interaction plots, normality plots, 2D contour plots, and 3D surface plots **[18-21].** All these analyses were used to interpret the influence of formulation factors on the selected responses, and the results were further optimized to obtain the final optimized formulation.

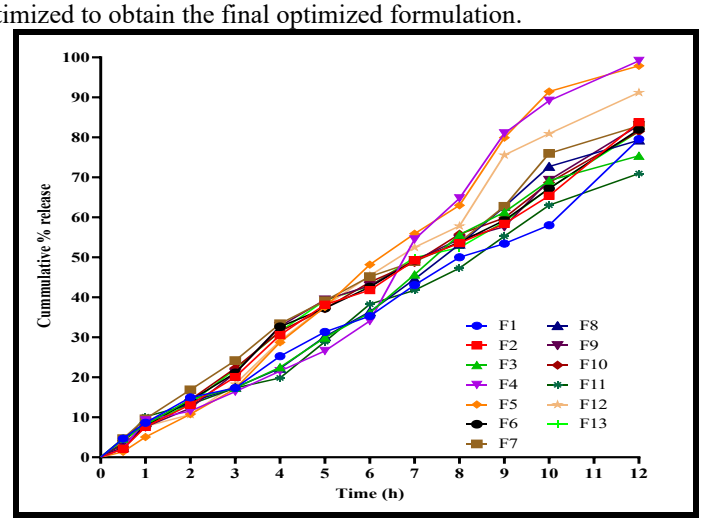

Figure 3: Comparative *in vitro* dissolution profile of trial ER matrix tablets of LP (F1 to F13)

Optimizations of Formulation using DoE: The relationships between independent variables with dependent responses were assessed by the CCD. Response data of Y1, Y2 and Y3 were experimentally made and substituted in Design Expert Software and possible statistical data were generated. The data indicated that X1 (HPMC K4M), and X2 (EC) influenced the selected responses. The p-value was below 0.05 clarifies that, the models generated were statistically significant to describe the interrelationship among the independent factors and the dependent responses and hence further reduced model was not generated.

Table 5: Trial runs as per CCD and their response data

Trial Runs	Factors (mg)		Responses		
	X1 (HPMC K4M)	X2 (EC)	Y1 (SI)	Y2 $t_{50\%}$ (h)	Y3 Q_{12} (%)
1	150	62.5	292	8.1	74.4
2	175	62.5	320	7.3	82
3	175	75	310	7.6	78.5
4	200	62.5	364	6.3	95.6
5	200	50	375	6	99.2
6	175	62.5	321	7.4	82
7	175	50	328	6.9	86.4
8	150	50	300	7.5	80
9	175	62.5	322	7.3	83
10	175	62.5	320	7.4	81.5
11	150	75	280	8.3	72.4
12	200	75	350	6.5	92.5
13	175	62.5	322	7.3	81.5

Study of Effect of Independent Variables on Y1, Y2 and Y3: The *p*-value of the regression model at each time point was obtained using analysis of variance (ANOVA). It was less than 0.05 confirming the validity of the regression equation model for Y1, Y2 and Y3 as shown in the following table 6.

Response Y1: The swelling behavior of ER tablets (Y1) strongly correlated with the type and proportion of polymers used. ANOVA results confirmed that HPMC K4M (factor A) had the most significant effect on swelling index, followed by ethyl cellulose (factor B). Higher levels of HPMC K4M led to increased swelling due to rapid hydration and gel formation, which in turn prolonged the diffusion pathway and delayed drug release (higher $t_{50\%}$ values). Conversely, EC, being hydrophobic, reduced excessive swelling and acted as a structural matrix former, ensuring consistent release.

The polynomial equation was generated for actual factors. The following quadratic polynomial equation suggests significant model terms HPMC K4M and EC on the swelling index with positive intercept.

Y1 (SI) = 378.48 -2.29092 *HPMC K4M + 1.36345 * EC -0.004 *HPMC K4M *EC +
0.0113931 *HPMC $K4M^2$ -0.0120276 * EC^2

Each term in the above equation represents a interaction between factors that affects the response variable (SI). And the coefficients signify the strength and direction of these influences.

The negative linear coefficient of HPMC K4M (−2.29092) indicates that increasing HPMC tends to reduce SI, whereas the positive linear coefficient of EC (+1.36345) suggests SI initially increases as EC increases (other factors held constant). Both polymers show significant quadratic curvature. This means responses are not purely linear. The interaction term (−0.004 *HPMC K4M *EC) is slightly negative, showing that using both polymers at higher levels together depresses SI more than their individual effects alone.

Table 6: ANOVA data of Y1. Y2, Y3.

Response Y1 (SI)					
Quadratic Model	**Sum of Squares**	**Df**	**Mean Square**	**F-value**	**p-value**
Significant	8658.20	5	1731.64	1114.47	< 0.0001
A- HPMC K4M	7848.17	1	7848.17	5051.03	< 0.0001
B- EC	661.50	1	661.50	425.74	< 0.0001
AB	6.25	1	6.25	4.02	0.0849
A^2	140.04	1	140.04	90.13	< 0.0001
B^2	9.75	1	9.75	6.28	0.0407
Residual	10.88	7	1.55	-------	------
Lack of Fit **Not Significant**	6.88	3	2.29	2.29	0.2200
Pure Error	4.00	4	1.00	-------	-------
Cor Total	8669.08	12	-------	-------	-------
Response Y2 ($t_{50\%}$)					
Quadratic Model	**Sum of Squares**	**Df**	**Mean Square**	**F-value**	**p-value**
Significant	5.18	5	1.04	342.55	< 0.0001
A-HPMC K4M	4.34	1	4.34	1432.84	< 0.0001
B- EC	0.6667	1	0.6667	220.35	< 0.0001
AB	0.0225	1	0.0225	7.44	0.0295
A2	0.0680	1	0.0680	22.47	0.0021
B2	0.0316	1	0.0316	10.43	0.0145
Residual	0.0212	7	0.0030	-------	-------
Lack of Fit **Not Significant**	0.0092	3	0.0031	1.02	0.4722
Pure Error	0.0120	4	0.0030	-------	-------
Cor Total	5.20	12	-------	-------	-------
Response Y3 (Q_{12})					
Quadratic Model	**Sum of Squares**	**Df**	**Mean Square**	**F-value**	**p-value**
Significant	734.67	5	146.93	378.65	< 0.0001
A- HPMC K4M	610.04	1	610.04	1572.07	< 0.0001
B- EC	82.14	1	82.14	211.67	< 0.0001
AB	0.2025	1	0.2025	0.5218	0.4935
A^2	29.67	1	29.67	76.46	< 0.0001
B^2	1.46	1	1.46	3.77	0.0934
Residual	2.72	7	0.3881	-------	-------
Lack of Fit **Not Significant**	1.22	3	0.4055	1.08	0.4522
Pure Error	1.50	4	0.3750	-------	-------
Cor Total	737.39	12	-------	-------	-------

Response Y2: The response Y2 ($t_{50\%}$) was influenced by the combined effects of swelling and gel integrity. Formulations with optimal HPMC K4M levels exhibited controlled hydration, achieving the target $t_{50\%}$ range of 6 to 8 h. Excessive HPMC caused thicker gel layers and slower release, whereas higher EC concentrations-maintained matrix integrity but reduced swelling, slightly lowering $t_{50\%}$. The following quadratic actual equation with negative intercept suggests significant model terms HPMC K4M and EC on the Y2, i.e., the time taken for 50% drug release.

Y2 ($t_{50\%}$) = -1.35718+0.0688621 *HPMC K4M+0.154184 *EC-0.00024 *HPMC K4M*EC –
0.000251034 * HPMC $K4M^2$-0.000684138 * EC^2

The positive coefficient suggests that increasing HPMC increases $t_{50\%}$ (slows drug release) due to gel formation and swelling, which creates a diffusion barrier. In the main effect of *EC (+0.154184), larger positive coefficient than HPMC suggests that EC has a stronger effect in prolonging $t_{50\%}$. This might be attributed to its hydrophobic matrix-forming property that reduces water penetration and drug diffusion. The interaction term (-0.00024 AB) has negative coefficient suggests that when both HPMC and EC are used together at higher levels, their combined effect slightly reduces $t_{50\%}$ compared to the sum of their individual effects. Whereas, quadratic terms are negative, indicating curvature in the response surface. This means after a certain concentration of HPMC or EC, further increases do not continue to prolong release; instead, $t_{50\%}$ may plateau or even decrease slightly. EC's quadratic effect (-0.000684138) is stronger than HPMC's, confirming that excessively high EC levels may hinder proper hydration and destabilize release kinetics.

Response Y3: For Y3 (Q_{12}), the cumulative release after 12 h varied from 70.94% to 99.13%, reflecting the balance between diffusion (governed by HPMC swelling) and erosion/barrier control (mediated by EC). Formulations with moderate levels of both polymers achieved the desired release within the therapeutic window, demonstrating that a synergistic combination of hydrophilic (HPMC K4M) and hydrophobic (EC) polymers is

critical for predictable extended release. Thus, CCD-based statistical analysis validated the experimental findings: HPMC K4M controls swelling and diffusion, EC modulates release by reducing excessive hydration, and their interaction determines the overall release kinetics. The optimized formulation achieved a swelling index of 322, t50 of 7.3 h, and Q_{12} of 81.9%, closely matching predicted values, thereby confirming the robustness of the QbD approach.

The following polynomial equation was generated for actual factors.

Y3 (Q_{12}) = 216.504 -1.47711 *HPMC K4M -1.00407 *EC + 0.00072 *HPMC K4M*EC +
0.00524414 *HPMC $K4M^2$ + 0.00465655 *EC^2

The above equation is a mathematical representation of the relationship between the factors (HPMC K100M and EC) and the response (cumulative drug released after 12 h). The negative coefficient of *HPMC K4M (-1.47711) suggests that as the amount of HPMC K100M increases, the Q_{12} decreases. This is attributed to the higher swelling and gel strength of HPMC K4M retarding the drug release. EC also has a negative effect on the cumulative amount of drug release. Increasing EC also decreases Q_{12}, due to its hydrophobic nature and diffusion-retardant effect. The small interaction effect (-0.00024 AB) suggests that the polymers act mostly independently, with limited synergism. The positive quadratic terms of both polymers indicate that their effects are not indefinitely linear; beyond a certain level, further increases in polymer concentration do not proportionally reduce Q_{12}.

Comparative Analysis of Response Surface Plots (Y1, Y2, Y3): For Y1 (SI), an increase in HPMC K4M markedly enhanced swelling due to its hydrophilic and gel-forming nature. Whereas, EC being hydrophobic, reduced the extent of swelling when used at higher concentrations. For Y2 ($t_{50\%}$), both polymers exhibited a synergistic effect in prolonging drug release. For Y3 (Q_{12}), the contour plot demonstrated that higher levels of HPMC K4M and EC together maintained controlled release up to 12 h, achieving a maximum drug release of ~99%. Overall, HPMC K4M governed the swelling and matrix integrity, while EC acted as a release-retarding agent. Their combined optimization ensured a balance between swelling, drug diffusion, and sustained release, enabling the desired extended-release profile.

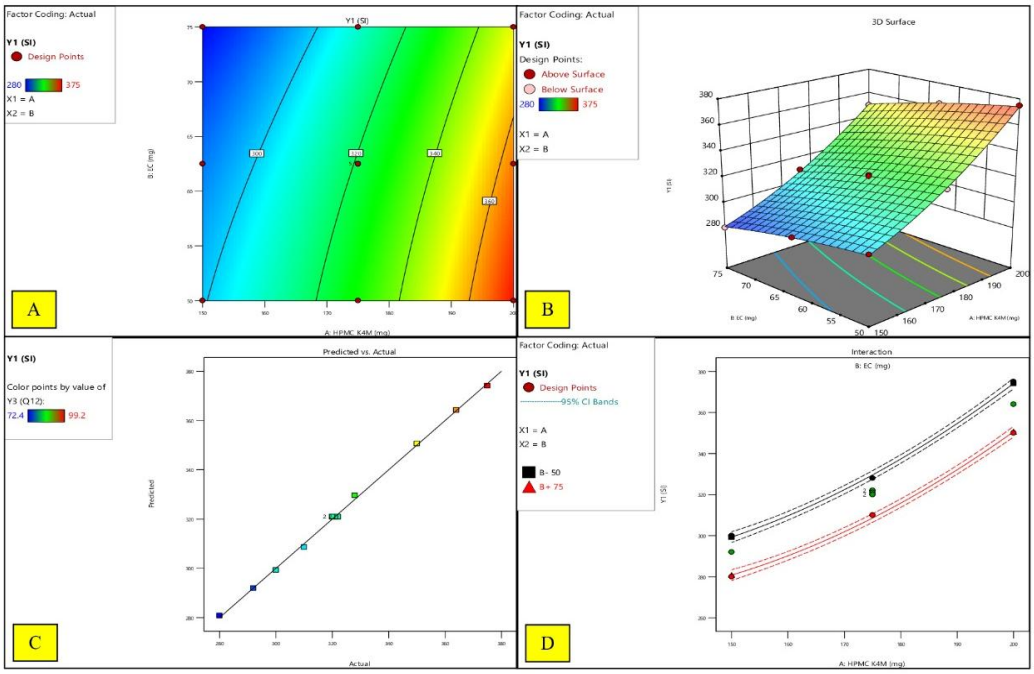

Figure 4: (A) 2D Response counter plot **(B)** 3D Response counter plot **(C)** Predicted vs. Actual Plot, and **(D)** Interaction plot of **Y1**

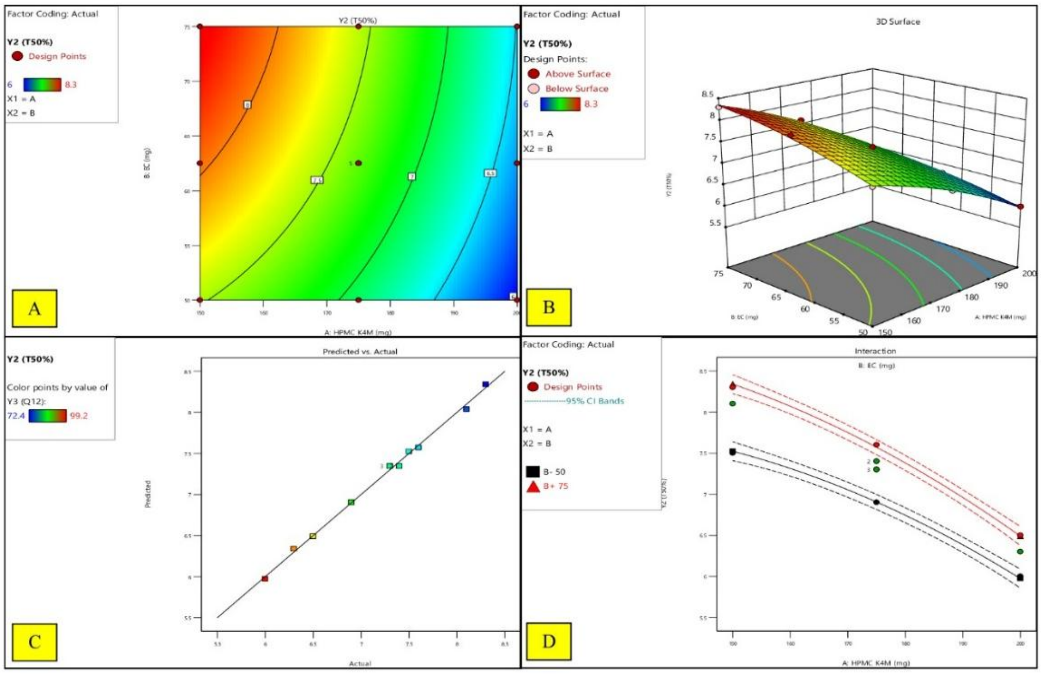

Figure 5: (A) 2D Response counter plot **(B)** 3D Response counter plot **(C)** Predicted vs. Actual Plot, and **(D)** Interaction plot of **Y2**

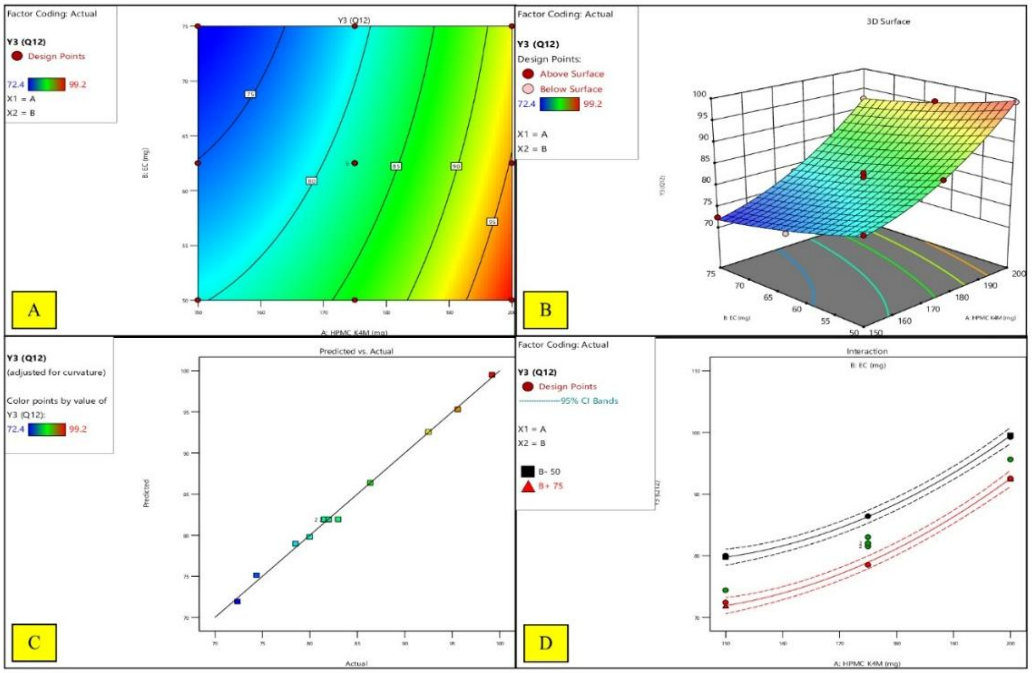

Figure 6: (A) 2D Response counter plot **(B)** 3D Response counter plot **(C)** Predicted vs. Actual Plot, and **(D)** Interaction plot of **Y3**

Development of Optimized Formulation by Numerical Optimization: Numerical optimization using the desirability approach was applied to identify the optimized formulation. Independent variables, HPMC K4M (X1) and EC (X2) concentrations, and dependent responses, Y1 (SI), Y2 ($t_{50\%}$) and Y3 (Q12), were set within the desired ranges. The point prediction method confirmed the optimized concentrations of HPMC K4M and EC (Table 24), while the predicted responses were in close agreement with experimental values, as validated at a 95% confidence interval (Table 25). The desirability function plot (Figure 25) along with the overlay plot (Figure 26) illustrate the optimized formulation, clearly indicating the batch that achieves the optimum response values.

Table 7: Optimized formula by point prediction method as per CCD

Factor	Polymer	Level	Response	Predicted Response
X1	HPMC K4M	175.00	Y1 (SI)	320.966
X2	EC	62.50	Y2 ($t_{50\%}$)	7.34483
			Y3 (Q_{12})	81.9207

Table 8: Predicted mean responses and confidence intervals for optimized batch

Point prediction: Two-sided, confidence = 95%, Population = 99%						
Analysis of responses	**Predicted Mean**	**Std Dev**	**n**	**SE Mean**	**95% CI Low for Mean**	**95% CI High for Mean**
Y1 (SI)	320.966	1.24	1	0.517583	319.742	322.189
Y2 ($t_{50\%}$)	7.34483	0.05	1	0.022839	7.29082	7.39883
Y3 (Q_{12})	81.9207	0.62	1	0.25866	81.3091	82.5323

The optimization study identified HPMC K4M (175 mg) and EC (62.5 mg) as the most suitable polymer concentrations for achieving the desired responses. The predicted swelling index (Y1) was 320.97, indicates a strong gel layer, ensuring matrix integrity and $t_{50\%}$ (Y2) was 7.34 h, suggests that half of the drug is released in 7.4 h, reflecting sustained release. Similarly, at 12 h (Q_{12}), nearly 82% drug release is predicted, showing near-complete release within the target time frame. The CI of 81.30 to 82.53 again confirms reproducibility. The point prediction analysis established these responses with narrow confidence intervals (95%), indicating high precision and reproducibility. The results indicated that HPMC K4M provided matrix swelling and integrity, while EC contributed to sustained drug release up to 12 h, with no evidence of dose dumping. Overall, the statistical validation underscores the robustness of the model and reliability of the optimized formulation capable achieving the desired release parameters.

Table 9: Optimized formulae of ER matrix tablet of LP as per CCD

Ingredients	Quantity (mg)
LP	50
HPMC K4M	175
EC	62.5
ADCP	50
Mannitol	62.5
Total weight (mg)	400

Preparation and evaluation of optimized formulation: The ER matrix tablets of LP as per CCD were identified by numerical optimization and desirability function by "trading off" of various response variables for attaining the desired goals, minimization of response variables. The optimized ER tablet comprising HPMC K4M and EC generated as per CCD was prepared and validated for the predicted response. The optimized formula as per CCD as well as experimental values with possible percentage error is given in the following table 10.

Table 10: Predicted vs. experimental response values of optimized batch

Response	Predicted	Experimental	% Relative Error
Y1 (SI)	320.966	322	1.034
Y2 ($t_{50\%}$)	7.34483	7.3	0.123
Y3 (Q_{12})	81.9207	81.9	0.0207

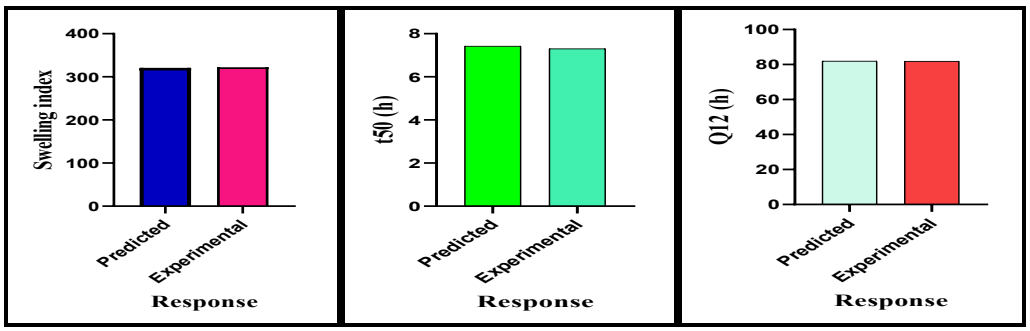

Figure 7: Comparative profiles of predicted and experimental response for optimized ER matrix tablet of LP.

No significant difference was observed for Y1 (SI), Y2 ($t_{50\%}$) and Y3 (Q_{12}) parameters when experimental values are compared with the predicted values as shown in the figure 7. Hence the experimental results of optimized formulation were in accordance with the predicted values, which show the practicability and reproducibility of the model. Validation of the predicted values of responses was performed experimentally and comparing the data, which indicated high degree closeness between the predicted and observed values of the responses. This confirmed excellent prognostic ability of the employed mathematical model. For most pharmaceutical applications, a percentage error of less than 10% is generally considered acceptable for the predicted response compared to the experimental response. The obtained percentage error in our study design is < 5%. This ensures that the model developed through the CCD is able to accurately predict the behavior of the system within the experimental design space.

Precompressional evaluation: The optimized tablet blend exhibited a bulk density of 0.4113 ± 0.00152 g/cm³ and a tapped density of 0.5237 ± 0.00115 g/cm³, indicating good packing ability of the powder. The calculated Carr's index (21.45 ± 0.3651%) and Hausner's ratio (1.273 ± 0.00585) were within acceptable limits, suggesting fair flow properties. The angle of repose (32.93 ± 0.4193°) further confirmed that the powder blend possessed satisfactory flowability, suitable for direct compression.

Postcompressional evaluation: The optimized tablets showed a uniform thickness (4.004 ± 0.00010 mm) and diameter (10 ± 0.00 mm), indicating consistent tablet dimensions. The hardness was found to be 12.30 ± 0.2646 kg/cm², confirming adequate mechanical strength to withstand handling. The average tablet weight was 399.7 ± 0.5774 mg, with minimal variation, complying with pharmacopeial standards. The friability value of 0.68 ± 0.011% was well below 1%, demonstrating good resistance to mechanical abrasion. The drug content was 96.89 ± 1.628%, confirming uniformity of drug distribution within the tablets. A high swelling index of 322 ± 2.00% suggested excellent swelling behavior, and gel layer acts as a barrier to drug release, controlling both diffusion and erosion contributing to sustained release. This directly correlate with the drug release kinetics, highlighting the complementary roles of HPMC K4M (hydrophilic swelling/gel-forming) and EC (hydrophobic release-retarding) in achieving controlled release of LP from the matrix tablets.

***In vitro* drug release studies:** The *in vitro* dissolution studies for optimized ER matrix tablets of LP as per CCD was studied and results were computed and analyzed by dissolution software PCP Disso V3. The *in vitro* dissolution study results are given table 11 and its corresponding dissolution profile is shown in figure 8. The optimized batch shows a gradual and sustained release of drug, reaching about 82% release at 12 h. In the early phase (first 2 to 3 h), the release is relatively slow, indicating effective control over burst release. From 4 to 8 h, the release rate is nearly linear, suggesting that combination of diffusion and erosion-controlled release due to the gel-forming nature of HPMC K4M and providing nearly consistent zero-order release. Whereas, EC acts as a hydrophobic matrix former that slows medium penetration, reduces burst effect and sustains release over 12 h.

Table 11: *In vitro* dissolution data of optimized ER matrix tablet of LP

Time (h)	% Drug release
1	7.590 ± 0.02
2	13.82 ± 0.02
3	21.22 ± 0.01
4	32.08 ± 0.02
5	38.45 ± 0.04
6	42.32 ± 0.05
7	46.21 ± 0.01
8	53.67 ± 0.01
9	59.27 ± 0.02
10	67.67 ± 0.01
12	81.30 ± 0.05

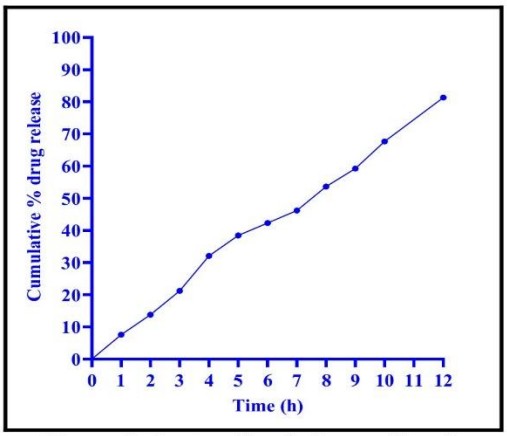

Figure 8: *In vitro* dissolution profile of optimized ER matrix tablet of LP

Mechanism of drug release: The *in vitro* drug release data of the optimized ER matrix tablets were fitted into various kinetic models to elucidate the release mechanism. The data obtained were also put in Korsemeyer-Peppas model in order to find out '*n'* value, which describes the drug release mechanism **[22].** The correlation coefficient 'r' values, release rate constants (K values) and 'n' values of Korsemeyer-Peppas model are summarized in table 12.

The results revealed that the drug release followed zero-order kinetics (r = 0.9964, K = 6.8265), which exhibited the highest correlation coefficient among the tested models. This indicates that the release rate remained constant and independent of drug concentration, a characteristic highly desirable for extended-release formulations. The Korsmeyer–Peppas model (r = 0.9910) further supported the release behavior, with an exponent value of n = 1.425, indicating a super case-II transport mechanism. This suggests that the drug release was governed by a combination of polymer swelling, chain relaxation, and erosion along with diffusion.

The key phenomena governing gel-layer formation and thereby drug release rate, include water penetration, polymer swelling, drug dissolution, diffusion and matrix erosion. In hydrophilic matrices such as those containing HPMC, the polymer swells upon hydration to form a gel layer, which controls drug release by diffusion through the hydrated matrix. Over time, the gel may erode, further influencing release kinetics. In contrast, EC being a hydrophobic polymers slow water penetration and reduce erosion, thereby sustaining drug release by acting as a diffusion barrier **[23].** In the present investigation, by combining hydrophilic and hydrophobic polymers, a balance between swelling, gel strength, and matrix erosion were achieved, leading to a more controlled and predictable release profile.

Table 12: Mathematical modelling and comparative kinetic values of optimized ER matrix tablet of LP

Kinetic models	Constant values	
Zero order, K_0 (%mg/h)	r	0.9964
	K_0	6.8265
First order, $K_1 \times 10^2$ (min^{-1})	r	0.9634
	K_1	-0.1103
Higuchi, K_h (%mg)	r	0.9390
	K_h	18.7657
Peppas	r	0.9910
	n	1.4250
Best fit model: Zero order		

Where, r = Coefficient of correlation; K_0, K_1, K_h, = release rate constants for Zero order, First order and Higuchi kinetic model respectively; and n = release rate exponent of Korsemeyer´s Peppas model.

Conclusion: The present study successfully developed and optimized ER matrix tablets of LP using a DoE approach. The optimized formulation, containing HPMC K4M and EC, demonstrated desirable swelling, mechanical strength, and a sustained drug release of ~81% over 12 h, with a high desirability value of 0.96. The results confirmed the ability of the matrix system to maintain consistent drug release, reduce dosing frequency, and improve patient compliance while reducing the risks associated with conventional release formulations. Stability studies further validated the robustness of the optimized formulation. This formulation approach can also be extended to other drugs requiring extended-release therapy.

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Conflict of Interest: The Authors declare no conflict of interest.

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