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Formulation and Optimization of Extended Release Matrix Tablets of Losartan Potassium Using Response Surface Methodology (RSM)

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Authors' contributions

This work was carried out in collaboration between all authors. Author YDR designed the formulation and RSM. Authors CMC and KRK supervised the evaluation of designed formulations. Author DD proposed the plan and supervised all the work. All authors read and approved the final manuscript.

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ABSTRACT

The aim of this research work was to formulate and systematically evaluate *in vitro* performance of extended release matrix tablets of Losartan potassium. Tablets were prepared by direct compression method, applying Response Surface Methodology (RSM) by incorporating a 3-factor, 2-level Box-Behnken statistical design. Independent variables are the release retardant polymers such as HPMC K4M (X1), ethyl cellulose (X2), and sodium carboxy methyl cellulose(X3) and dependent variables are the percentage drug release in 0.1N HCL for 2 hours (Y1) and in 6.8 Phosphate buffer up to 24 hours (Y2) were studied. The Validation and optimization of study with 17 confirmatory runs indicated high degree of prophetic ability of response surface methodology with mean percentage error (± SD) as 1.54 ± 2.87% and 2.27 ± 1.36% drug release in 0.1N HCL

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and buffer. The physical evaluation and *in vitro* release studies were performed on all the formulations and the data were fitted to different release kinetic equations. The optimized formulation depicted a release of 16.98% and 96.26% from 0.1N HCL and buffer solutions at 24 hours. Point prediction tool of design expert software (version 8.0.1), RSM, shows 17.71% and 95.72% validity of the predicted model for drug release from 0.1N HCL and buffer solutions respectively. The optimized formulation follows Higuchi model and first order release kinetics which shows non-fickian type of release. Applying RSM, with few runs, effective extended release formulation of Losartan potassium was developed.

Keywords: HPMC K4M; ethyl cellulose; sustained release; response surface methodology; Box-Behnken design; variables; responses.

1. INTRODUCTION

The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/ or targeting the delivery of thedrug to a tissue [1]. Such dosage form not only increase patient compliance due to reduction in frequency of dosing, but they also reduce the severity and frequency of side effects, as they maintain substantially constant blood levels and avoid fluctuations associated with the conventional immediate release formulations [1]. One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively, drug and retardant blend may be granulated prior to compression. Selection of the proper method depends on the properties of the drug, polymer and other ingredients. Among the different strategies to prolong the drug action, formulation of matrix tablet has gained immense popularity now a days because it has the advantage of simple processing and a low cost of fabrication [2].

Losartan potassium is a potent, highly specific angiotensin-II type 1 receptor antagonist with antihypertensive activity. It is the first of a new class of drug to be introduced for clinical use in “hypertension” due to selective blockade of AT-1 receptors and consequent reduced pressure effect of angiotensin II [3]. It belongs to class III, is soluble in acidic pH. Losartan potassium is having a narrow therapeutic index, poor bio availability (25 to 35%) and short biological half-life (1.5 – 2 hrs) [4,5] Administration of Losartan potassium in a delayed release system would be more desirable for antihypertensive effects by maintaining the Losartan plasma concentration well above the minimum effective concentration. Developing a delayed release drug delivery system of Losartan potassium is desirable for an effective treatment of hypertension and is useful to reduce the dosage frequency to improve patient compliance [6].

Response surface methodology (RSM) is one of the popular methods in the development and optimization of drug delivery systems. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimum formulation [7,8,9]. Box-Behnken statistical design is one type of RSM design that is an independent, rotatable or nearly rotatable, quadratic design having the treatment combinations at the midpoints of the edges of the process space and at the center [10,11,12]. Independent variables are the release retardant polymers such as HPMC K4M (X1), ethyl cellulose (X2), and Sodium carboxy methyl cellulose (X3) and dependent variables are the percentage drug release in 0.1N HCL for 2 hours (Y1) and in 6.8 phosphate buffer for 24 hours (Y2) were studied. Additionally, it requires few experimental runs and less time and thus provides a far more effective and cost-effective technique than the conventional processes of formulating and optimization of dosage forms.

2. MATERIALS AND METHODS

2.1 Materials Used in the Preparation Losartan Potassium Matrix Tablets

Losartan potassium (LP) a gift from Hetero drugs, Hyderabad (India). HPMC K4M and ethyl cellulose (EC) are provided by Colorcon Ltd, Mumbai. (India). Sodium carboxy methyl cellulose (SCMC) is a gift from Simla industries, Mumbai (India). Lactose purchased from Himedia Mumbai (India). Magnesium stearate

and Talc bought from SD fine chemicals Ahmadabad (India).

2.2 Methods

2.2.1 Computer aided optimization design

A computer aided response surface methodology using Box-Behnken statistical design with 3 factors, 2 levels were employed in optimization study. This design is suitable for exploration of second order polynomial model, quadratic response surfaces, thus helping in optimizing a process using a small number of experimental runs (17 runs) with Design expert (version 8.0.1), RSM, to study the effect of the amounts of various polymer blends used as three independent variables (factors), on the property of Losartan potassium sustained release matrix tablets.

This cubic design is characterized by a set of points lying at the midpoint of each edge of a multi-dimensional cube and center points replicates (n=5). The polynomial equations for different models are given below,

Linear model;

$$Y = A1\ X1 + A2\ X2 + A3\ X3$$

Quadratic model;

$$Y = A_0 + A_1 X_1 + A_2 X_2 + A_3 X_3 + A_{12} X_1 X_2 + A_{13} X_1 X_3 + A_{23} X_2 X_3 + A_{11} X_1^2 + A_{22} X_2^2 + A_{33} X_3^2$$

Second order;

$$Y = A_1 X_1 + A_2 X_2 + A_3 X_3 + A_{12} X_1 X_3$$

The *Y* is the measured response associated with each factor level combination; A_0 is an intercept; A_1 to A_{33} are regression coefficients computed from the observed experimental values of *Y*; and X_1, X_2 and X_3 are the coded levels of independent variables. The terms $X_1 X_2$ and X^2n (n = 1, 2 or 3) represent the interaction and quadratic terms, respectivel [13]. The preliminary studies provided a setting of the levels for each formulation. Three variables and two responses were involved in this optimization design.

2.2.2 Experimental design of sustained release matrix tablets of Losartan potassium

In the present investigation two independent formulation variables evaluated were X1: Polymeric concentrations and dependent variables investigated were Y1: Percentage drug release in 0.1N HCL at the end of 2 hours, Y2: % drug release in 6.8 Phosphate buffer at the end of 24 hours. 17 different batch formulations of matrix tablets were evaluated to determine the potential effect of those independent variables on the dependent variables. Critical formulation factors, design summary, summary type and sub-type are shown in Table 1.

The minimum and maximum specifications of these variables are entered into the software (Design Expert) to obtain a suitable design to optimize the critical formulation variable to show a better response. Optimized formula in formulation development has been developed based on the developed design model and they are analyzed for their dissolution response. The data thus obtained is entered into the design model for the optimization.

2.2.3 FTIR (Fourier transform infrared spectroscopy) studies

Infrared IR spectrum with high quality is acquired by the FTIR method, has its application in studies of drug – excipients interaction, contaminant analysis, etc. Fourier transformation mathematical operation can resolve the signal captured by detector as a

Table 1. Design summary and level of independent variables

Factor	Name	Unit	Minimum	Maximum	Mean	Std. Dev	Design summary	
A	HPMC K4M	mg	80.00	160.00	120.0	27.44	**Study type**	Response Surface
B	EC	mg	6.00	40.00	23.00	11.66	**Design type**	Box-Behnken
C	SCMC	mg	2.00	12.00	7.00	3.43	**Design Model**	Quadratic
File version	8.0.71				**Runs**	17		

Summation of all these cosine signals and in connection with the contribution of each wavelength. IR spectrum with high quality is acquired by KBr (pellet) method. Samples were prepared in KBr disk (2 mg sample in 200 mg KBr) with a hydrostatic press at a force of 40psi for 4min.The scanning range was 400-4000 $cm^{-1}$and spectrum was obtained. The mixture spectra were compared with that of the original spectra.

2.2.4 DSC (Differential Scanning Calorimetry) studies

For thermal analysis and drug–excipient mixtures, a differential scanning calorimeter was used. Samples (3-7 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10℃/min over the temperature range of 0-500℃.

2.2.5 Micromeritic properties of drug-excipients blend

The micromeritic properties of drug-excipients blend which should be evaluated to ensure the proper formulation of the tablet dosage form is an important aspect in matrix tablet formulation. Angle of repose, apparent bulk density, tapped density, compressibility index and Hausner's ratio were evaluated [14,15].

2.2.6 Preparation of tablets

The drug and the excipients used were all passed through 80-mesh sieve. The active ingredient LP and each single polymer (HPMC K4M, EC, SodCMC) and diluent (Lactose), lubricant (Magnesium stearate), glidant (Talc) were blended together by dry mixing in a laboratory mixer for 10 minutes. The mixture was compressed by using eight station tablet punching machine (Elite scientific and equipment) with an 8 mm standard flat round punch and die set at compression force 4-6 ton. Hardness of all tablets was adjusted to 6.5 to 7.5 Kg/cm^2. Total tablet mass was around 250 mg [16].

2.2.7 Assay of tablets

At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg of the drug was weighed accurately and dissolved in 100 ml of phosphate buffer of pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.1 filter paper. Then transfer 1mL of the above solution into 100 mL volumetric flask and make up the volume with phosphate buffer of pH 6.8. The absorbance of the diluted solutions was measured at 205 nm. The concentration of the drug was computed from the standard curve of the Losartan potassium in phosphate buffer of pH 6.8.

2.2.8 Physical properties of sustained release tablets

The tablets were characterized immediately after the formulation. The weight variation of the 20 tablets was accomplished according to guidelines mentioned in IP 2010 using an electronic balance. Friability of 10 tablets was evaluated by Roche type friabilator for 4 min at the rate of 25 rpm. For each formulation the hardness of 10 tablets was evaluated using Monsanto hardness tester (chambell electronics, India). The thickness of the 10 tablets was measured by Vernier calipers. As the formulations one sustained release matrix tablet so there is no scope of disintegration test.

2.2.9 *In vitro* dissolution studies

In-vitro dissolution study of Losartan potassium was carried using Electrolab TDT-06P (USP type-II) dissolution test apparatus. For the first 2 hours, 900 ml of 0.1NHCL media was used in the dissolution vessels followed by 900ml of pH 6.8 buffer media for the rest 22 hours at 37 ± 0.5℃ with 50 rpm. Samples withdrawn (10 ml) were replaced with an equal amount of fresh dissolution medium at particular time intervals, samples were immediately filtered through 0.45µ membrane filter and diluted with dissolution media. The samples were analyzed spectrophotometrically at λ_{max} at 205 nm using Shimadzu UV-Visible Spectrophotometer. The amount of drug present in the samples was calculated using the calibration curve constructed from reference standards. Cumulative % drug release was plotted against time was calculated [17,18].

2.2.10 Drug release kinetics

The Formulations were subjected to kinetic analysis by fitting the release data to different kinetic models to explain the release kinetics of Losartan potassium from tablets. These kinetic data were estimated using different kinetic orders. Zero order as cumulative amount versus time (Equation 1), first order as log cumulative

amount of drug remaining versus time (Equation 2) and Higuchi's model as cumulative percentage of drug released versus square root of time (Equation 3) [19].

$$Q = Q_0 + K_0 t \quad (1)$$

$$\text{Log } C = \text{Log } C_o - kt / 2.303 \quad (2)$$

$$Q = K_t^{1/2} \quad (3)$$

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs time [20,21].

$$Mt / M\alpha = Ktn$$

$$\text{Log } Mt / M\alpha = \log K + n \log t$$

Where, Mt/Mα-fraction of drug released at time t
t – Release time
K – Kinetic constant (incorporating structural and geometric characteristics of (Preparation)
n – Diffusion exponent indicative of the mechanism drug release.

3. RESULTS AND DISCUSSION

Losartan potassium tablets were prepared by direct compression method. The ideal process for a capital and operational cost basis is direct compression. This is, at most, a two-step process involving screening and/or milling and final mixing. An effective excipient binder is needed and should have good compression and consolidation properties as a dry additive, even at low concentrations (< 30%) in the formulation. Good adhesive properties in the dry form are a combination of a rough and porous surface combined with a Vander Waal's and/or a hydrophilic bonding mechanism to attach the active ingredient(s) to the excipient. This feature is needed to assure good mixing of drug and excipients and to prevent segregation.

3.1 FTIR Studies

FTIR spectra of Losartan potassium and with excipients are shown in Fig. 1. FTIR spectrum of Losartan potassium has shown characteristic peaks C-O (primary alcohol), C-N stretching and C = C stretching at 1074, 1340 and 1580 cm^{-1} respectively. The spectra obtained from the physical mixture of pure drug with HPMCK4, Ethyl cellulose and sodium CMC respectively indicated the presence of the characteristic bands of the drug almost at the same wave numbers.

3.2 DSC Studies

When DSC studies were carried out under atmospheric condition, no significant change in thermal behavior was noted. (Fig. 2). The DSC thermo gram of Losartan potassium gave endothermic peak corresponding to the temperature 189.32℃, which indicates its sharp melting point. The DSC thermo gram of the drug with excipent physical mixture shows drug peak at 189.69℃, which is almost similar to that of pure drug. The results of FTIR and DSC studies confirmed the absence of any interaction between drug and excipients

3.3 Pre Compression Parameters

The Compressibility Index (%) of all the formulations [F1-F17] developed in the formulation development phase was found to be excellent to passable i.e. 8.51 to 18.75% shown in the table 24. The Hausner's Ratio of all the formulations [F1-F17] developed in the formulation development phase was found to be excellent to good i.e. 1.09 to 1.23 shown The Angle of repose of all the formulations [F1-F17] developed in the formulation development phase was found to be good to passable i.e. 25°.78 ' to 31°.58 '. All the results are shown in the Table 2.

3.4 Physicochemical Characteristics and Assay of Tablets

All the formulated tablets containing the active drugs were evaluated to find the physical properties like hardness, thickness, friability and drug contents (Table 3). In a weight variation test, the Pharmacopeial limit of percentage deviation for tablets whose weight is more than 250 mg is ±5%. Due to formulation requirement, two formulations F5 and F13 were prepared for weights of 270 and 260 respectively and both the formulations were also found to be in limits. The average percentage deviation of all the tablets was found within the limit which was less than 1%. Hardness of the tablets was found acceptable and uniform from batch to batch variation. The drug content was also found uniform and within the prescribed limit.

3.5 *In vitro* Studies

Mean cumulative % release of Losartan potassium at different time intervals is shown in

Fig. 3. Among all formulations releases, formulation with 120 mg of HPMC K4 shown maximum CDR by the end of 24 hrs. Formulation F2 and F9 has 120 mg HPMC K4M. And having lower concentrations of EC has shown maximum CDR by the end of 24 hrs. The formulated with 120 mg HPMC K4 but higher concentrations of EC, viz., F1, F3, F4, F6, F7, F8, F15 and F17 has shown lower CDR at the end of 24 hrs. At the same instance, the concentration of Sod CMC has shown little influence on the CDR.

Formulations with higher amount of HPMC K4 (160 mg), has shown very lower CDR except in the formulation F12, where it has shown 86% CDR. The higher CDR in this formulation may be due lesser amount of EC and SodCMC.

Formulations with lower amount of HPMC K4 (80mg) has shown better CDR in all formulation. The CDR at the end of 24 hrs was ranged between 86 to 92%.

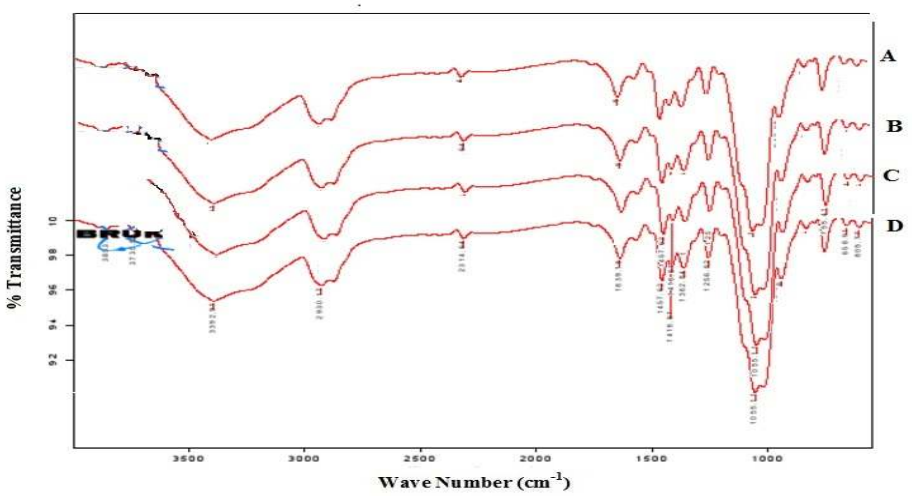

Fig. 1. FTIR spectra of Losartan potassium (A) Pure drug (B) with HPMC K4M (C) with Ethyl cellulose (D) with Sodium CMC

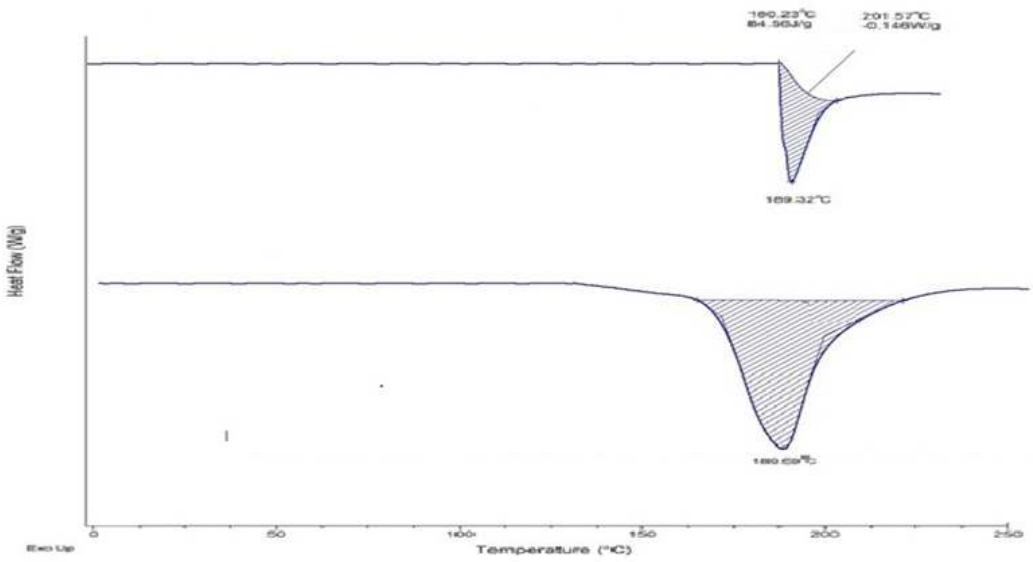

Fig. 2. DSC of Losartan potassium pure drug and with physical mixture of excipients

Table 2. Pre-compression evaluation parameters

Form. code	Bulk density (g/cc) Avg±SD (n=3)	Tapped density (g/cc) Avg±SD (n=3)	Compressibility index (%) Avg±SD (n=3)	Hausner's ratio Avg±SD (n=3)	Angle of repose Avg±SD (n=3)
F-1	0.242± 0.006	0.269± 0.007	10.06± 5.630	1.114± 0 .067	27.82± 0.542
F-2	0.230± 0.006	0.267±0.008	15.19 ±0.329	1.178 ±0. 004	30.75± 1.22
F-3	0.242± 0.006	0.269 ±0.007	10.06 ±5.630	1.114 ±0.067	27.82 ±0.542
F-4	0.246± 0.006	0.272 ±0.008	8.683 ±5.596	1.097 ±0 .682	26.65 ±0.510
F-5	0.22 ±0.005	0.239 ±0.006	8.51 ±4.082	1.094±0.04 85	26.06± 1.053
F-6	0.242 ±0.006	0.269 ±0.007	10.06± 5.630	1.114± 0 .067	27.82± 0.542
F-7	0.242 ±0.006	0.272 ±0.008	11.246± 3.713	1.127 ±0.046	25.78 ±0.684
F-8	0.242 ±0.006	0.269 ±0.007	10.06 ±5.630	1.114 ±0 .067	27.82 ±0.542
F-9	0.235 ±0.004	0.272 ±0.008	13.716 ±1.893	1.158 ±0.024	27.75 ±1.414
F-10	0.230 ±0.006	0.274 ±0.004	17.276 ±2.136	1.209 ±0.031	30.53 ±0.425
F-11	0.230 ±0.006	0.255 ±0.025	16.183 ±4.029	1.194 ±0.056	30.67 ±0.490
F-12	0.246 ±0.006	0.267 ±0.008	7.59 ±3.848	1.083 ±0 .045	26.88 ±0.869
F-13	0.255 ±0.007	0.283 ±0.008	8.726 ±4.954	1.093 ±0.065	26.67 ±0.830
F-14	0.223 ±0.005	0.272 ±0.008	18.75 ±0.415	1.230 ±0.006	30.70± 0.689
F-15	0.242 ±0.006	0.269 ±0.007	10.06 ±5.630	1.114 ±0.067	27.82 ±0.542
F-16	0.230 ±0.006	0.267 ±0.008	15.14 ±3.496	1.179 ±0.048	31.58 ±0.693
F-17	0.230 ±0.006	0.254 ±0.007	11.843 ±0.271	1.134± 0.003	26.23 ±0.970

(All the values are calculated as (Mean ±SD)

Table 3. Physicochemical characteristics of tablets

Form. code	Weight variation Avg±SD (n=20)	Hardness (Kg/cm^2) Avg ± SD (n=5)	Friability (%)	Thickness (mm)	Drug content Avg ± SD (n=3)
F-1	250 ± 7.071	7.06 ± 0.094 66 ± 0.094	0.079±0.011	3.06 ±0.057	98.63 ±0.305
F-2	248 ± 6.782	6.9 ± 0.374	0.1941±0.01	3.4± 0.2	9 7.908 ±0.195
F-3	250 ± 7.071	7.06 ± 0.094	0.079±0.011	3.06 ±0.05 7	98.63 ±0.305
F-4	249 ± 4.358	6.7 ± 0.081	0.115±0.03	3.26 ±0.115	97.74 ±0.47
F-5	271 ± 7	7.66 ± 0.188	0.131±0.016	3.76 ±0.057	101.67±0.827
F-6	250 ± 7.071	7.06 ± 0.094	0.079±0.011	3.06 ±0.05 7	98.633 ±0.305
F-7	250 ± 7.071	6.7 ± 0.355	0.026±0.011	3.53 ±0.05 7	98.93 ±0.351
F-8	250 ± 7.071	7.06 ± 0.094	0.079±0.011	3.06 ±0.05 7	98.633 ±0.305
F-9	250.5 ± 6.689	6.7 ± 0.081	0.1502±0.03	3.16 ±0. 152	98.628 ±1.03
F-10	250 ± 7.071	6.7 ± 0.294	0.341±0.019	3.3 ±0.17 3	98.533 ±0.802
F-11	252 ± 6	6.9 ± 0.216	0.238±0.045	3.43 ±0.057	98.513 ±1.359
F-12	252 ± 6	6.56± 0.0471	0.434±0.028	3.36 ±0.115	98.948 ±0.611
F-13	263 ± 4.582	6.66 ± 0.169	0.182±0.012	3.53 ±0.0 57	100.60±0.740
F-14	245.5 ± 5.894	6.96 ± 0.124	0.225±0.033	3.53 ±0 .057	97.117 ±0.355
F-15	250 ± 7.071	7.06 ± 0.094	0.079±0.011	3.06 ±0.0 57	98.633 ±0.305
F-16	252 ± 7.483	7.06 ± 0.205	0.1783±0.01	3.36 ±0.0 57	98.948 ±0.611
F-17	249 ± 4.358	6.63 ± 0.309	0.279±0.013	3.23 ±0.2 08	97.740 ±0.470

(All the values are calculated as (Mean ±SD)

To understand the drug release kinetics from the polymeric matrices, release data were analyzed according to Zero-order, First-order, Higuchi models and Korsmeyer-Peppas model the parameters are listed in Table 4. Firstly, no formulation fits the Zero-order kinetics model, meaning that it is very difficult to get Zero-order release profile from water soluble drug containing matrix tablets. In contrast, the R^2 values calculated from the Higuchi model ($Mt/M\infty < 0.6$) suggested best fit. On the other hand, all the formulations fit First-order model, R^2 values calculated are in the range of 0.938 to 0.976. Using Korsmeyer-Peppas model, value of exponent n was calculated. Except for the formulation F9, the value of n was in the range of

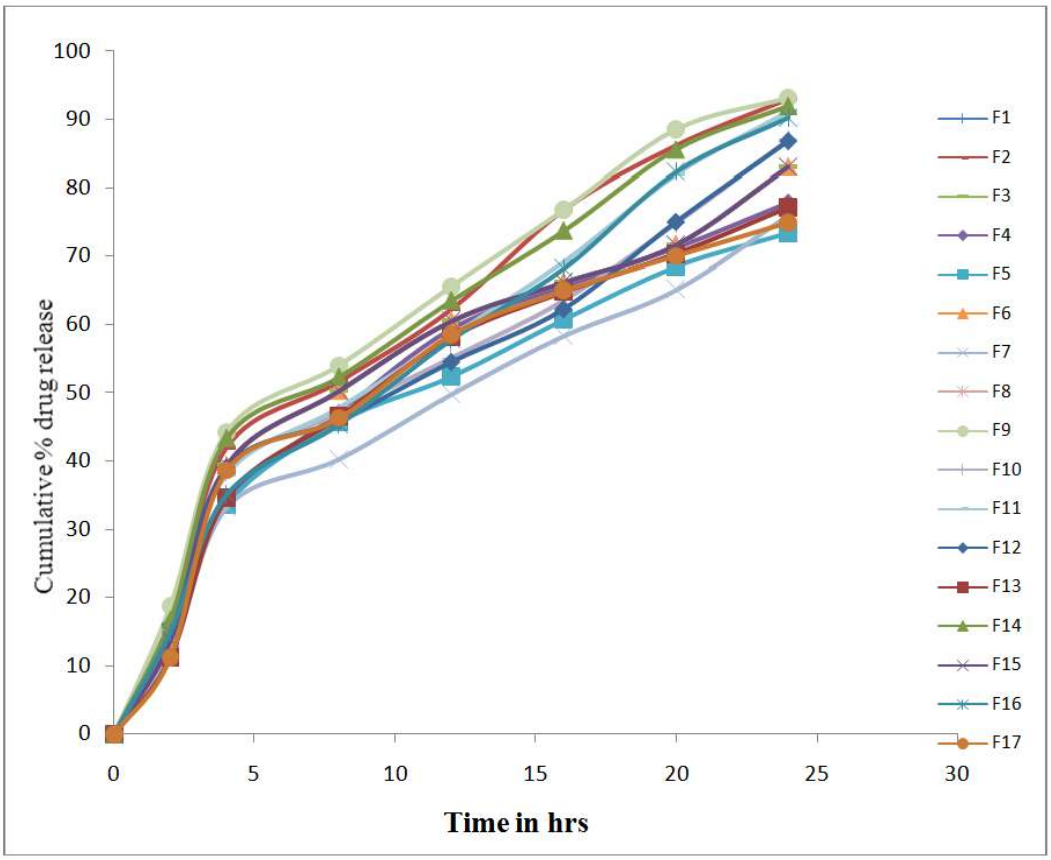

Fig. 3. Graphical representation of *in vitro* drug release of all formulations

0.211 to 0.218. This is an indication that the dominant drug transport mechanism appears to be Fickian diffusion (n < 0.45). Formulation F9 the drug transport mechanism revealed anomalous transport Figs. 4 & 5 (n value 0.45-0.89) with the value of n 0.590, which may be due to the lower concentrations of EC and SodCMC.

3.6 RSM Optimization Results of Losartan Potassium

Three-dimensional (3D) response surface plots and two dimensional (2-D) contour plots were constructed based on the model polynomial functions using Design Expert software. These plots are very useful to see interaction effects of the factors on the responses.

3.6.1 Response surface analysis (release in 0.1N HCl)

Represent the contour plot and three dimensional response surface graph for the studied response properties % CDR release in 2 hrs in 0.1N HCl medium. It is evident from the contour plot and three dimensional analysis that the high concentration of the polymers shown low release of the drug. With lowest concentrations of the polymers, release of drug was shown to be greater.

3.6.2 Response surface analysis (release in pH 6.8 phosphate buffer)

Figs. 6 & 7 represent the contour plot and three dimensional response surface graph for the studied response properties % CDR release up to 24 hrs in pH 6.8 phosphate buffer medium. From the contour plot it can be concluded that release in 24 hrs decreases with increase in the amounts of all polymers. The response changes the variables in a linear and descending manner.

The responses obtained, subjected to the analysis in Design Expert software to point prediction for optimized formulation. The details

are given in Table 7. The critical formulation factors that affect the desired response of the formulation were found to be different concentrations of the HPMC K4, EC and SCMC which are 100 mg, 6 mg and 12 mg respectively. Using the predicted values, optimized formulation has been developed and various pre and post compression parameters were determined. The values for pre and post compression parameters were found to be in limits. The tablets produced with the predicted values of variable factors showed 96.26% drug release in 24 hrs. The dissolution profile of optimized formulation follows Higuchi model and first order release kinetics which shows non-fickian type of release. Both erosion and diffusion mechanisms are responsible for sustaining the release of Losartan potassium from formulating matrix tablets. The Percentage prediction error of the optimized formulation was calculated and given in Table 8. The values shown to be within the range as predicted values.

Table 4. *In-vitro* drug release kinetics of all formulations

Form. code	Zero order		First order		Higuchi		Korsmeyer-Peppas		Drug release mechanism
	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent (n)	
F-1	0.775	3.974	0.957	-0.031	0.972	16.77	0.646	0.211	Fickian transport
F-2	0.841	4.480	0.972	-0.043	0.981	18.79	0.653	0.217	Fickian transport
F-3	0.775	3.974	0.957	-0.031	0.972	16.77	0.646	0.211	Fickian transport
F-4	0.806	3.828	0.970	-0.028	0.978	16.12	0.664	0.213	Fickian transport
F-5	0.790	3.602	0.959	-0.025	0.985	15.19	0.646	0.205	Fickian transport
F-6	0.775	3.974	0.957	-0.031	0.972	16.77	0.646	0.211	Fickian transport
F-7	0.852	3.519	0.970	-0.024	0.976	14.73	0.678	0.210	Fickian transport
F-8	0.775	3.974	0.957	-0.031	0.972	16.77	0.646	0.211	Fickian transport
F-9	0.803	4.567	0.976	-0.045	0.985	19.24	0.947	0.590	Non-Fickian transport
F-10	0.839	3.991	0.950	-0.032	0.978	16.73	0.649	0.210	Fickian transport
F-11	0.871	4.248	0.956	-0.038	0.982	17.75	0.660	0.214	Fickian transport
F-12	0.839	3.968	0.928	-0.032	0.975	16.63	0.648	0.209	Fickian transport
F-13	0.807	3.788	0.953	-0.027	0.973	15.94	0.673	0.215	Fickian transport
F-14	0.817	4.447	0.972	-0.042	0.981	18.70	0.643	0.215	Fickian transport
F-15	0.775	3.974	0.957	-0.031	0.972	16.77	0.646	0.211	Fickian transport
F-16	0.901	4.200	0.962	-0.037	0.977	17.48	0.682	0.218	Fickian transport
F-17	0.754	3.760	0.938	-0.027	0.962	15.90	0.656	0.212	Fickian transport

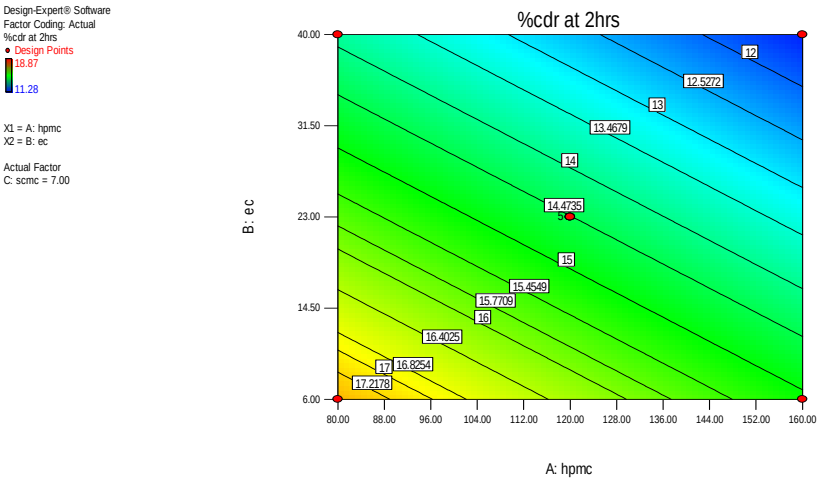

Fig. 4. Response 1 contour graph (%CDR in 0.1N HCl)

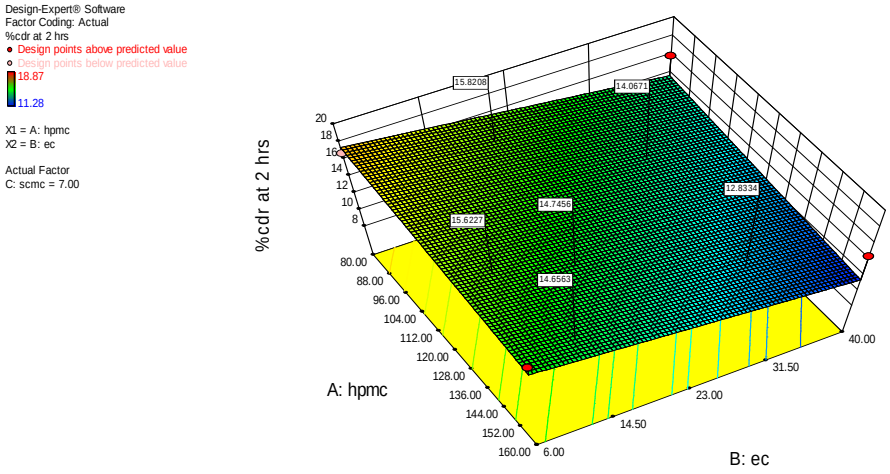

Fig. 5. Response 1 - 3D surface graph (%CDR in 0.1N HCl)

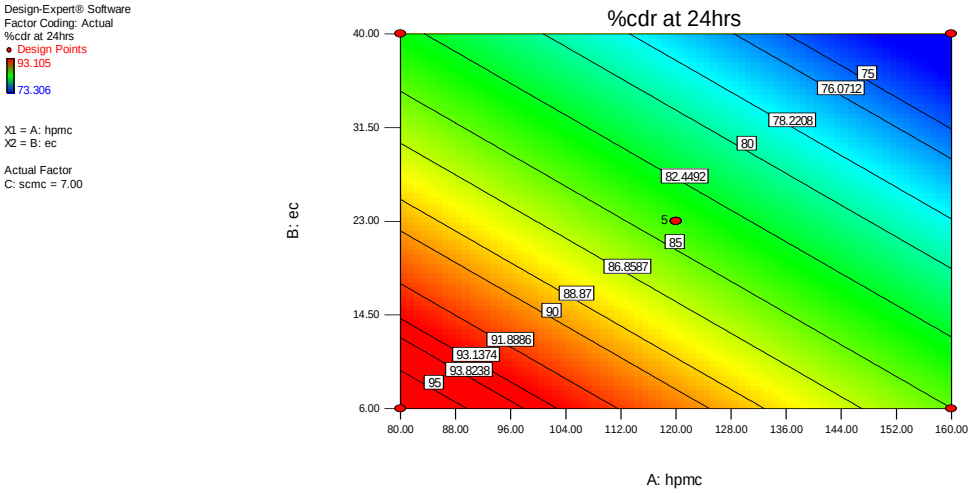

Fig. 6. Response 2 contour graph (%CDR in pH 6.8 phosphate buffer medium)

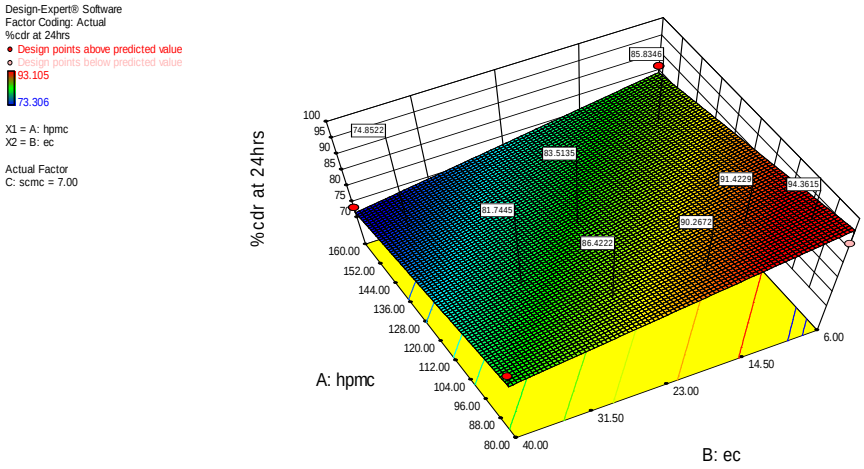

Fig. 7. Response 2- 3D Surface graph (%CDR in pH 6.8 phosphate buffer medium)

Table 5. Percentage prediction error of the optimized formulation

Response	Predicted value	Experimental value	Percentage prediction error
% cdr in 0.1N HCL	17.71	16.98	-4.299
%cdr in 6.8 Buffer	95.72	96.26	0.56

4. CONCLUSION

The extended release matrix tablets of Losartan potassium formulation system include the drug delivery system that achieves slow and extended release of the drug over an extended period of time. The response variables of the formulation are optimized by the Response surface methodology. The *in vitro* dissolution release kinetics of the matrix tablet analyzed indicated the successful extended release of the matrix tablet for several hours.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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