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FORMULATION AND OPTIMIZATION OF LOSARTAN POTASSIUM SUSTAINED RELEASE TABLETS BY STATISTICAL EXPERIMENTAL DESIGN

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Abstract:
The objective of the present study was to develop hydrophilic polymer and hydrophobic polymer based matrix Losartan potassium sustained release tablets which can release the drug up to time of 12 hrs in predetermined rate using 3^2 factorial design. The SR (sustained release) tablets of Losartan potassium were prepared employing different concentrations of HPMCK100 and ethyl cellulose in different combinations as rate retardants by Direct Compression technique. The quantity/ concentration of Polymers, HPMCK100 and ethyl cellulose required to achieve the desired drug release was selected as independent variables, X1 and X2 respectively whereas, drug release for 2hr (Y1), 12 hr (Y2) and time required for 50% (t50%) of drug dissolution (Y3) were selected as dependent variables which were restricted to 20-30%, NLT 80% and NLT 3 hrs respectively. Statistical elucidations of polynomials were established for all the responses. The formulations were evaluated for pre compression and post compression parameters. Contour plots and 3D surface plots revealed that desired drug release can be achieved (target) by maintaining factor X1 at high level and factor X2 at low level. From the kinetic and mathematical results, the drug release follows first order and Higuchis Fickian diffusion kinetics. The results demonstrated the effectiveness of the proposed design for development of Losartan potassium sustained release tablets with optimized properties.

Keywords: *Losartan potassium, DoE, HPMCK100, Ethyl cellulose Sustain release, Contour plots*

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INTRODUCTION:

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Sustained release preparations are helpful to reduce the dosage frequency and side effects of drugs and improve patient's convenience [1]. Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials. The most commonly used method of modulating the drug release is to include it in a matrix system [2, 3].

Losartan potassium is a potent, highly specific angiotensin II type 1 receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 hours [4]. Administration of Losartan Potassium in a sustained release dosage form with dual release characteristics i.e., burst release followed by an extended release over 12 hours, would be more desirable as these characteristics would allow a rapid onset followed by protracted anti-hypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration [5, 6]. Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical area for its ease, compliance, faster production, avoids hydrolytic or oxidative reactions occurred during processing of dosage forms [5, 6].

In the present study, a sustained release dosage form of losartan potassium has been developed that makes less frequent administration of drug [5, 6].

Development of dosage form depends on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism and the *in vivo* environment. It is an important issue to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs [7] have been recognized as useful techniques to optimize the process variables which reduce the number of trials and experiments. Normal method for the manufacturing of sustained release tablets may involve several formula by trial and error method for optimization which may impose high cost on the final product. An experimental statistical technique involves selection of variables that affect the formulation. The levels of the variables should be chosen by referring the Hand book of pharmaceutical experiments, USFDA-IIG limits or based on the literature. Application of these variables with levels to the design softwares gives few combinations; hence optimizing the formula by establishing contour plots reduces the number of trials. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating sustained release dosage forms [8].

Hence an attempt was made in this research work to formulate Sustained release (SR) tablets of Losartan potassium using HPMC K100 LV (100 cps) and EC (45 cps). Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of independent variables on dependent variables. Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The SR tablets formulation by direct compression method is most acceptable in large scale production.

A 3^2factorial design was employed to systematically study the drug release profile. A 3^2 factorial design was employed to investigate the effect of two independent variables (factors), i.e. the amounts of HPMC and EC on the dependent variables, i.e. 2hr, 12hr, t50% (time taken to release 50%).

MATERIALS AND METHODS

Materials

Losartan potassium, obtained as a gift sample from Connexios Life sciences, Banglore. MCC, HPMCK15, Aerosol, Magnesium stearate, Talc were purchased from SD fine chemicals, Mumbai.

Methods

Differential Scanning Calorimeter (DSC)

The drug and excipients were passed through the #60 sieve and mixed. Accurately transferred 5 mg of drug alone, a mixture of drug and excipients into the pierced DSC aluminum pan and scanned at the temperature range of 25-290°C heating rate of 10°C/min. The thermograms obtained were compared for any interaction between the drug and excipients with that of thermogram of drug alone.

Formulation and development of losartan potassium sustained release tablets

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses. A selected three level, two factor experimental design (3^2 factorial design) describe the proportion in which the independent variables HPMC K100 and EC were used in formulation of losartan potassium sustained release (SR) tablets. The time required for 2hr, 12hr, t50% drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for final Equations [1].

The three levels of factor X_1 (HPMCK100) at a concentration of three levels of factor X_2(EC) at a concentration of 20%, 30%, 40% (% with respect to total tablet weight) was taken as the rationale for the design of the Losartan potassium SR tablet formulation. Totally nine losartan potassium sustained release tablet formulations were prepared employing selected combinations of the two factors i.e. X_1, X_2 as per 3^2 factorial and evaluated to find out the significance of combined effects of X_1, X_2 to select the best combination and the concentration required to achieve the desired prolonged/ sustained release of drug from the dosage form [9].

Experimental Design

Experimental design (Montgomery DC et al., 2004) utilized in present investigation for the optimization of polymer concentration such as, concentration of HPMCK100 was taken as $X_1$and concentration of EC was taken as X_2. Experimental design was given in the Table 1. Three levels for the Concentration of HPMCK100 were selected and coded as -1= 20%, 0 =30%, +1=40%. Three levels for the Concentration of EC were selected and coded as -1= 20%, 0=30%, +1=40%.

Table 1: Experimental Design Layout

Formulation code	X1	X2
F1	-1	-1
F2	0	-1
F3	1	-1
F4	-1	0
F5	0	0
F6	1	0
F7	-1	1
F8	0	1
F9	1	1

Preparation of Losartan potassium Sustained Release Tablets

All ingredients were collected and weighed accurately according to the formula given in Table 2. Losartan potassium was sifted with Microcrystalline Cellulose and polymers through sieve no. 44# and then sieved with remaining excipients. Colloidal silicon dioxide (Aerosil-200) and magnesium stearate were sifted separately, through sieve no. 60#. All the ingredients (except lubricant- magnesium stearate) were blended in double cone blender for 15 minutes. Magnesium stearate was added finally and then again blended for 5-6 minutes.

Table 2: Formulation of Losartan potassium sustained release tablets

Ingredients	Quantity of ingredients per each formulation								
	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Losartan potassium	50	50	50	50	50	50	50	50	50
MCC	193	168	143	168	143	118	143	118	93
HPMCK15M	50	75	100	50	75	100	50	75	100
Ethyl cellulose	50	50	50	75	75	75	100	100	100
Aerosil	2	2	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Total weight	350	350	350	350	350	350	350	350	350

Evaluation of Pre compression parameters

Bulk density (BD)

The bulk density was determined by transferring the accurately weighed blend sample into the 100 ml graduated cylinder by keeping it in a slanting position. The initial volume and weight were noted. The ratio of weight of the sample to the volume it occupied was calculated [10].

Tapped density (TD)

Tapped density was determined by transferring the accurately weighed blend sample into 100 ml measuring cylinder which was placed in Electrolab Tapped Density Apparatus (method USP-I). Initial volume (V_0) of the cylinder was noted and then the cylinder was tapped for 10 times and the volume was measured. Further additional 500 tapings were made and the volume was noted. Continue the tapings to 1250 if the difference between the volume measured after 10 and 500 tapings was more than 2ml [10].

Compressibility index (CI)

Compressibility index (CI) is a measure of the propensity of a powder to be compressed. It is a direct measurement of potential powder arch or the bridge strength and stability. It was calculated according to the equation given below [10].

$$CI = \left(TD - \frac{BD}{TD}\right) * 100$$

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula [10].

Hausner ratio = Tapped density / Bulk density

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of repose

The angle of repose (**θ**) was determined using funnel method. The blend was poured through a funnel that can be raised vertically to a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated [10].

$$\theta = \tan^{-1} (h/r)$$

Evaluation of Post compression parameters

Weight variation

20 randomly selected tablets were weighed individually; the average weight and the standard deviation were calculated (Prajapati BG et al., 2010).

Tablet thickness

Twenty tablets were taken and their thickness was recorded using Vernier caliper scale [11].

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured [11].

Friability

Friability of the tablets was determined using Roche friabilator at 25 rpm/min for 4 min. 20 tablets were weighed and loss in weight (%) was calculated [11].

$$\text{Friability} = (W1 - W2) / W1 \times 100$$

Weight of 20 Tablets = W1,
Weight of 20 Tablets after friability = W2

Drug content of Losartan potassium

Content uniformity was determined by accurately weighing 20 tablets and crushing them in mortar, an accurately weighed quantity of powder equivalent to 20 mg of drug was transferred to a 100ml volumetric flask. Few ml of water was added and shaken for 15 min. Volume was made up to 100 ml with distilled water. The solution was filtered through Whatmann filter paper (No.41). 5 ml of the filtrate was diluted to 100 ml with 0.1N HCl. Then absorbance of the resulting 10 mg/ml solution was recorded at 205.5nm. Content uniformity was calculated using formula [12].

$$\% \text{ Purity} = 10\ C\ (Au / As)$$

Where,
C - Concentration, Au and As - Absorbance's obtained from standard preparation and assay preparation respectively.

***In vitro* Dissolution Study**

The *In-vitro* dissolution study for the Losartan potassium sustained release tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 6.8 Phosphate buffer as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analysed for drug release by measuring the absorbance at 250 nm using UV Visible spectrophotometer after suitable dilutions [13].

Release kinetics

To study the release kinetics of *in-vitro* drug release, data was applied to kinetic models such as Zero order, First order, Higuchi and Korsmeyer-Peppas. The kinetics of drug release was calculated by using PCP disso V3 software.

Statistical analysis and Optimization

Data obtained from all sustained release tablet formulations were analyzed using design expert software (version 10) to generate the study design. The best-fit model was selected based on comparisons of several statistical parameters, provided by design expert software. In addition, analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The relationship between the dependent and independent variables was further elucidated using contour plots. Subsequently, a graphical optimization technique using contour plots were used to generate new formulations with the desired responses. Dissolution studies were carried out on the prepared optimized formulation to verify the theoretical prediction. The relative errors (%) between the predicted and experimental values for each response were calculated [14].

Stability studies

Stability studies at 40° C ±2°C /75% ± 5% RH was carried out for 3 months for an optimized formulation which was filled in HDPE containers. The optimized formulation was evaluated for *in vitro* drug release after 3 months respectively [15].

RESULTS & DISCUSSIONS:

DSC thermographs revealed that the melting point of the pure drug is 279.18ºC and that of the drug in the formulation is 289.91ºC. As there was no shift of melting point in the formulation as compared to the pure drug, it indicated that there is no chemical and physical interaction which is likely to affect the pharmacotechnical properties of the formulation. DSC thermograms of pure drug and optimized formulation were depicted in Fig 1.

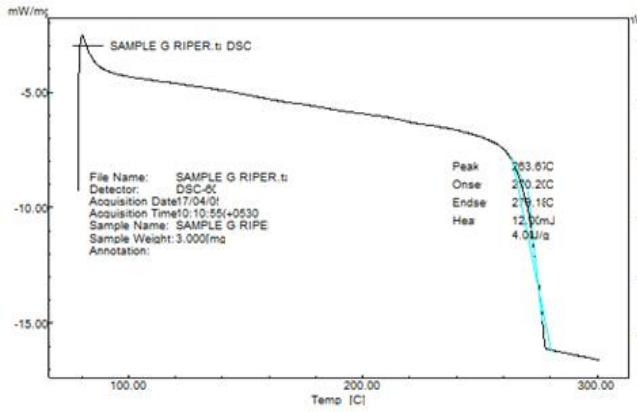

Fig. 1A: DSC thermogram of Losartan potassium

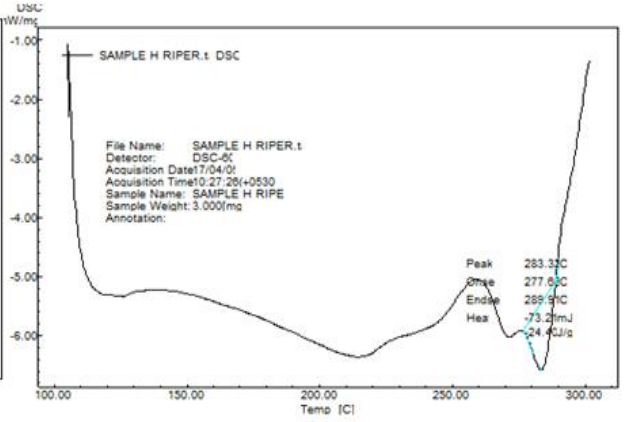

Fig. 1B: DSC thermogram of Optimized formulation

Pre compression and Post parameters of powder blend

Bulk and tapped density differences between the formulations were negligible and the density values of formulations were well within limits, indicating that the prepared dry blend were non-aggregated and indicated good free flowing property. The value of compressibility index was in the range of 15.98 % to 19.23 % and HR was in the range of 1.15 to 1.59. Pre compression and post parameters of powder blend were tabulated in Table 3 & 4.

Tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications. The thickness of tablets was found to be 4.11 to 4.16 mm which shows uniform thickness due to uniform die fill. Hardness of the tablets was found to be 5.38-5.81 kg/cm^2. In all the formulations, the friability values were less than 1% and meet the Indian pharmacopoeia (I.P) limits. The percentage of drug content for F1 to F9 was found to be in between 99.6 to 101.2 of Losartan potassium, it complies with official specifications.

Table 3: Evaluation of pre compression parameters of powder blend

Powder blend	Angle of repose	Bulk density	Tapped density	Carr's index (%)	Hausner's ratio
F1	23.2±0.21	0.422± 0.24	0.581± 0.14	19.23	1.21
F2	21.5± 0.45	0.412± 0.19	0.544± 0.27	23.52	1.33
F3	25.3± 0.33	0.432± 0.09	0.548± 0.09	20.12	1.59
F4	22.0± 0.07	0.452± 0.17	0.588± 0.17	15.98	1.20
F5	24.6± 0.17	0.425± 0.08	0.499± 0.18	19.21	1.16
F6	23.6± 0.27	0.432± 0.14	0.511± 0.08	21.31	1.19
F7	24.2± 0.09	0.452± 0.09	0.541± 0.09	23.13	1.15
F8	24.5± 0.08	0.413± 0.18	0.564± 0.14	22.1	1.18
F9	22.5± 0.34	0.461± 0.19	0.587± 0.18	19.91	1.23

All results were average of n=3 observation

Table 4: Evaluation of post compression parameters

Formulation code	Hardness Kg/cm^2**	Friability (%)*	Weight variation (%)*	Drug content (%w/w)*	Thickness (mm)*
F1	5.68±0.408	0.284±1.1	351.0±1.48	100±1.3	4.14±0.11
F2	5.81±0.418	0.451±1.4	350.0±0.99	99.6±1.3	4.16±0.12
F3	5.49±0.443	0.228±0.9	350.0±1.2	99.8±1.4	4.12±0.11
F4	5.38±0.452	0.369±0.5	350.5±1.3	99.9±1.5	4.12±0.11
F5	5.91±0.360	0.554±0.8	350.6±1.1	101.2±1.9	4.11±0.13
F6	5.47±0.402	0.411±1.7	351.0±0.32	99.80±1.2	4.13±0.11
F7	5.52±0.376	0.322±1.9	349.9±0.29	100.3±1.1	4.15±0.13
F8	5.52±0.379	0.399±1.4	350.3±1.0	100.2±1.6	4.18±0.11
F9	5.68±0.390	0.401±0.9	350.0±1.3	100. 1±1.1	4.11±0.12
Standards	4-8	<1	± 5%	90-110	-

All values are expressed as mean ± SD, *n = 20, **n=5

***Invitro* Drug release study**

From the *invitro* data it was concluded that all formulations were able to extend the drug release for duration of 12 hours. But the formulations with high concentration of ethyl cellulose (F1, F7 and F9) were not able to control the burst release (30% release in 2 hours). Formulations with high concentration of HPMC K100 and with low concentration of Ethyl cellulose met the extended release criteria i.e., NMT 30% release in 2 hours, NLT 80% release in 12 hours. The regression coefficient values obtained revealed that all formulations follow the first order release with Higuchi diffusion (r^2 near to 0.99) and follows Fickian diffusion (n value $\leq$ 0.5). HPMC K100 due to quick hydration of polymer matrix and ethyl cellulose due to slow hydration of matrix and its property to form a thick gel layer, which retarded the drug release from the tablet. *Invitro* drug release of Losartan potassium from formulations F1 to F9 was depicted in the figure 2.

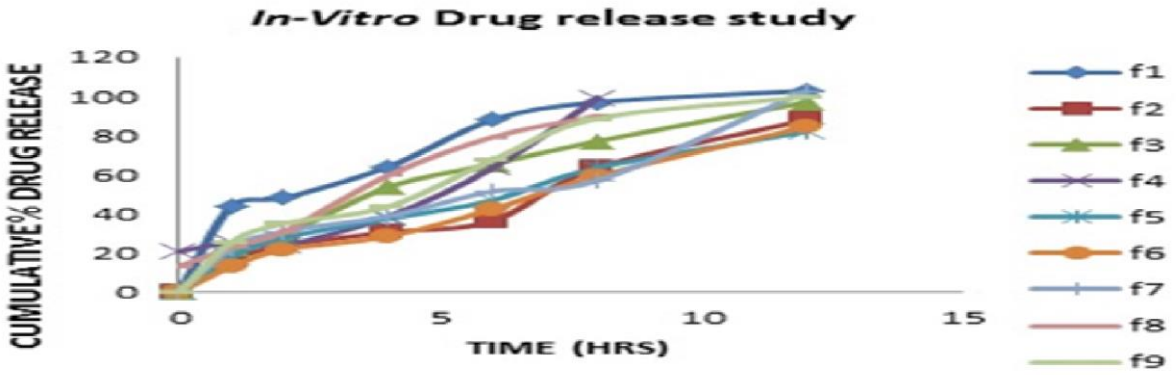

Fig. 2: *In vitro* drug release of Losartan potassium

Multiple Regression analysis

Multiple regression analysis technique was used to generate the best fit models for the analyzed responses. The final equations of reduced model contain only the significant factor terms corresponding to the response analyzed.

Reduced model equations for responses are as follows:

Drug release at 2 hrs (Y_1) = 29.31 + 3.03 X_1 – 2.00 X_2 +5.70 X_1X_2

From the ANOVA results (Table 5) it was found that the major factors affecting the drug release at 2 hrs was factor X_1, X_2 & X_1 X_2. The first one had positive effect and latter one had negative effect. By increasing the concentration of HPMC K100 drug release increased and increasing the concentration of Ethyl cellulose the drug release decreased and F1, F7 had shown burst release whereas interaction between the factors increased the drug release. Contour plots and 3D response plots has showed that inorder to maintain burst release i.e, NMT 30% in 2 h. HPMC should be maintained at high levels and EC should be maintained at low levels. From the figure 3 & 4 it is clearly shown that by maintaining the concentrations of HPMC and EC at drug release at 63.5-92.5 mg and 61.5-80mg respectively the controlled drug release (88%, 90%) can be achieved to the desired target level (Drug release at 2 h NMT 30%). Contour plots (Figure 3) and 3D surface plots (Figure 4) showed the effect of factor X_1 and X_2 on response Y_1. It was observed that in order to control the drug release i.e., 30%, the concentrations of factor X_1 and factorX_2 were kept at high level and low level respectively.

Table 5: ANOVA table for the response Y1 (drug release at 2 hr)

ANOVA for Response Surface Quadratic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	Model
Model	26.58	5	5.52	8.79	0.0447	significant
A-HPMC K100	6.657	1	6.657	0.011	0.0244	
B-EC	3.29	1	3.29	5.41	0.0326	
AB	2.12	1	2.12	3.86	0.0413	
Residual	1.88	3	0.63			
Cor Total	29.46	8				

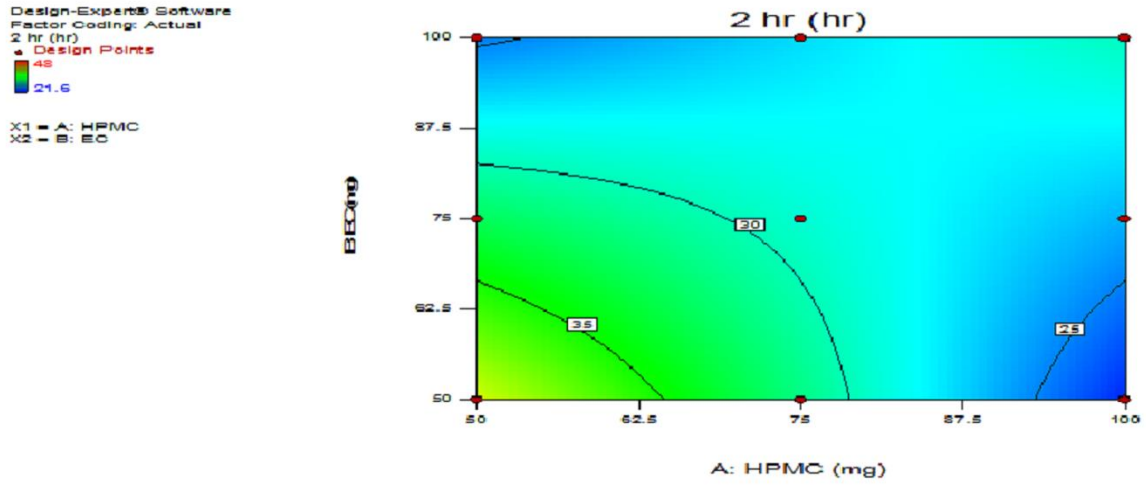

Fig. 3: Contour plot showing the effect of X1 and X2 on drug release at 2 hrs

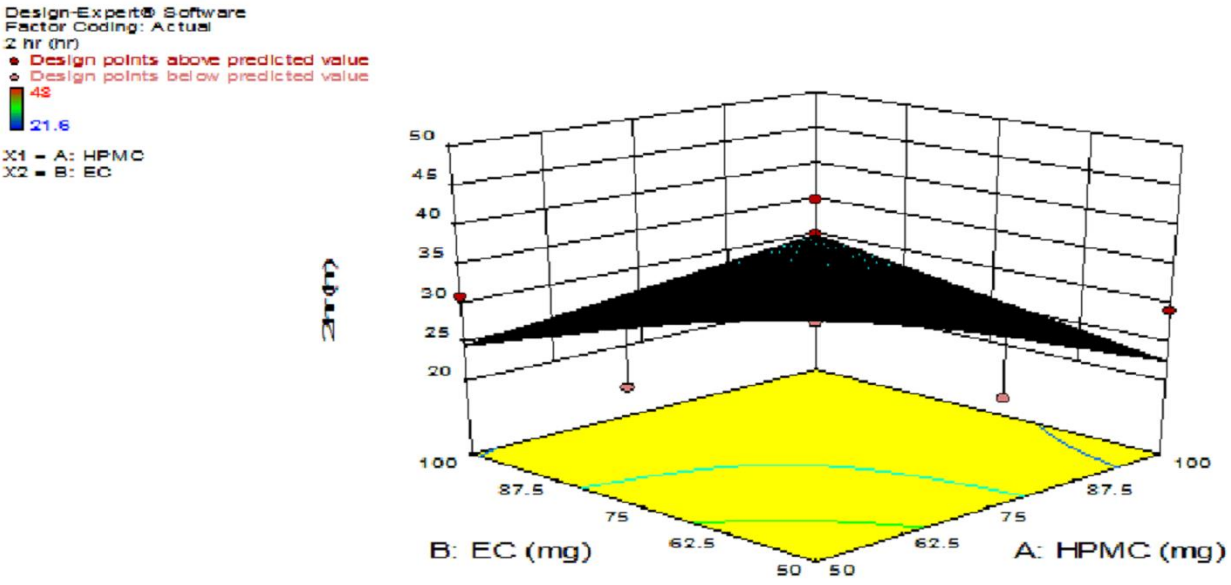

Fig. 4: 3D response plot showing the effect of X1 and X2 on drug release at 2 hrs

Drug release at 12 hrs (Y_2) = 93.07 + 3.84 X_1 + 2.04 X_2 +0.84 X_1X_2

From the ANOVA results (Table 6) it was found that the major factors affecting the drug release at 12 hrs was factor X_1, X_2 & X_1 X_2. All the factors showed positive effect. By increasing the concentration of HPMC K100 and Ethyl cellulose drug release increased and all the formulations showed sustained effect whereas interaction between the factors increased the drug release. Contour plots and 3D response plots has showed that inorder to maintain sustained release i.e, NLT 80% in 12 h. HPMC should be maintained at high levels and EC should be maintained at low levels. From the figure 5 & 6 it is clearly shown that by maintaining the concentrations of HPMC and EC at 60-95 mg and 55-80mg respectively the controlled drug release (88%, 90%) can be achieved to the desired target level (Drug release at 12 h NLT 80%).

Contour plots (Figure 5) and 3D surface plots (Figure 6) showed the effect of factor X_1 and X_2 on response Y_2 (drug release at 12 hrs) the required criteria is the drug release from the dosage form is not less than 80%. In this scenario design space is selected with more drug release and by maintaining factor X_1 at high level and factor X_2 at low level all criteria will meet [10].

Table 6: ANOVA table for the response Y2 (drug release at 12 hr)

ANOVA for Response Surface Quadratic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	Model
Model	158.44	5	29.79	9.36	0.0345	significant
A-HPMC K 100	26.69	1	26.69	8.73	0.0598	
B-EC	17.58	1	17.58	6.18	0.0889	
AB	3.79	1	3.79	1.13	0.3653	
Residual	9.51	3	3.17			
Cor Total	157.95	8				

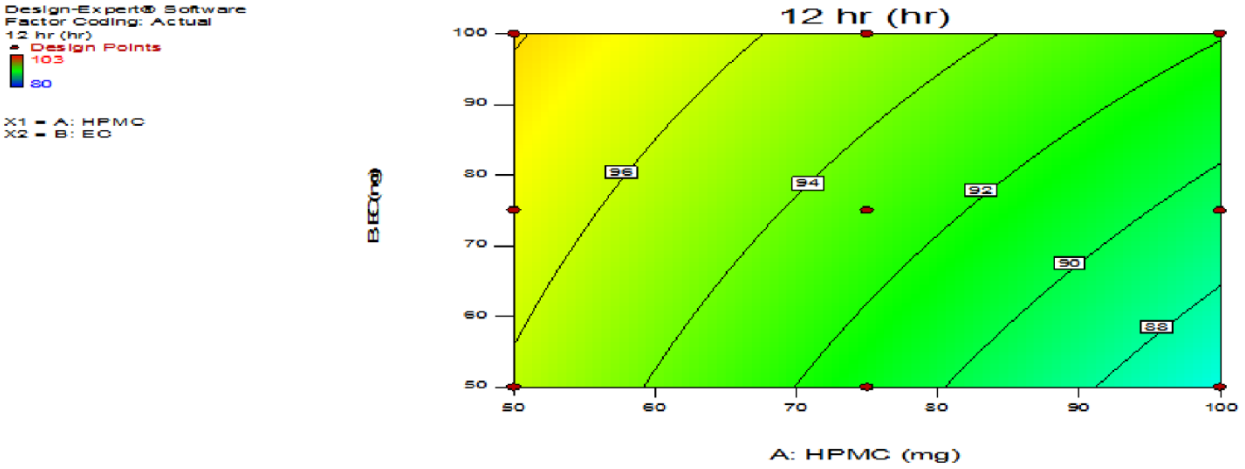

Fig. 5: Contour plot showing the effect of X1 and X2 on drug release at 12 hrs

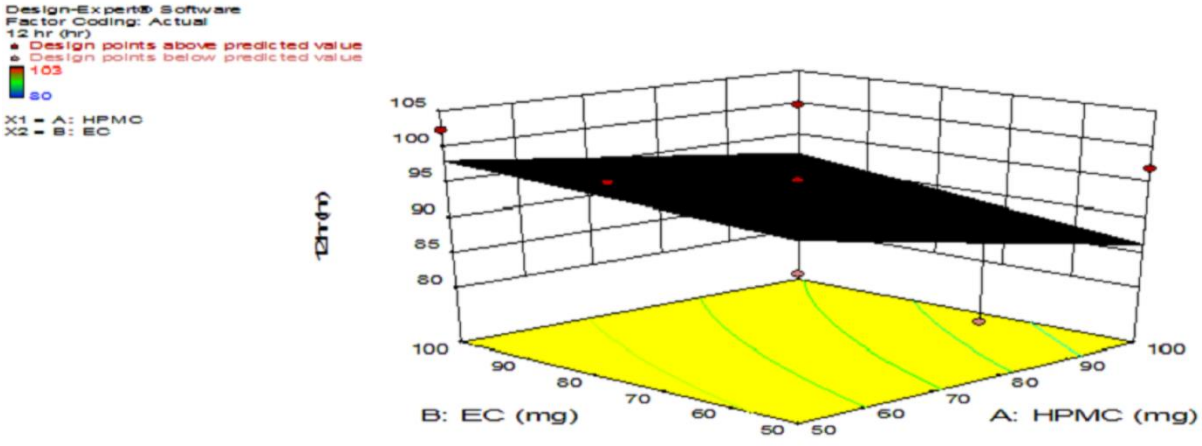

Fig. 6: 3D response plot showing the effect of X1 and X2 on drug release at 12 hrs

Time taken to release 50% drug (Y_3) = 5.36 + 0.75 X_1 + 0.30 X_2 – 1.20 X_1X_2

From the ANOVA results (Table 7) it was found that the major factors affecting the t50% was factor X_1, X_2 & X_1 X_2. Contour plots (Figure 7) and 3D surface plots (Figure 8) showed the effect of factor X_1 andX_2 on response Y_3. Contour plots and 3D response plots has showed that inorder to maintain t 50 %. From the figure 7 & 8 it is clearly shown that by maintaining the concentrations of HPMC and EC at 62-88 mg and 65-80mg respectively the controlled drug release (5h, 6h) can be achieved to the desired target level (t 50% in NLT 3h).

Table 7: ANOVA table for the response Y3 (t 50%)

ANOVA for Response Surface Linear model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	Model
Model	1.08	2	0.54	18.87	0.0026	significant
A-HPMC K 100	0.78	1	0.78	30.72	0.0015	
B-EC	0.15	1	0.15	7.03	0.048	
Residual	0.17	6	0.029			
Cor Total	1.26	8				

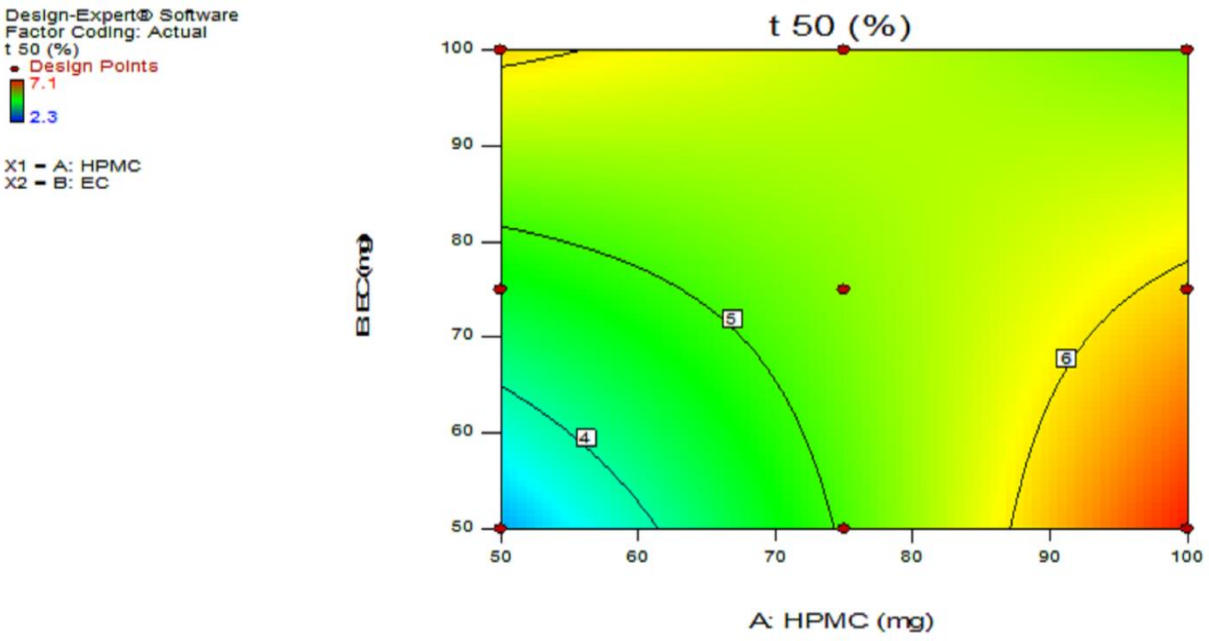

Fig. 7: Contour plot showing the effect of X1 and X2 on t 50 (hrs)

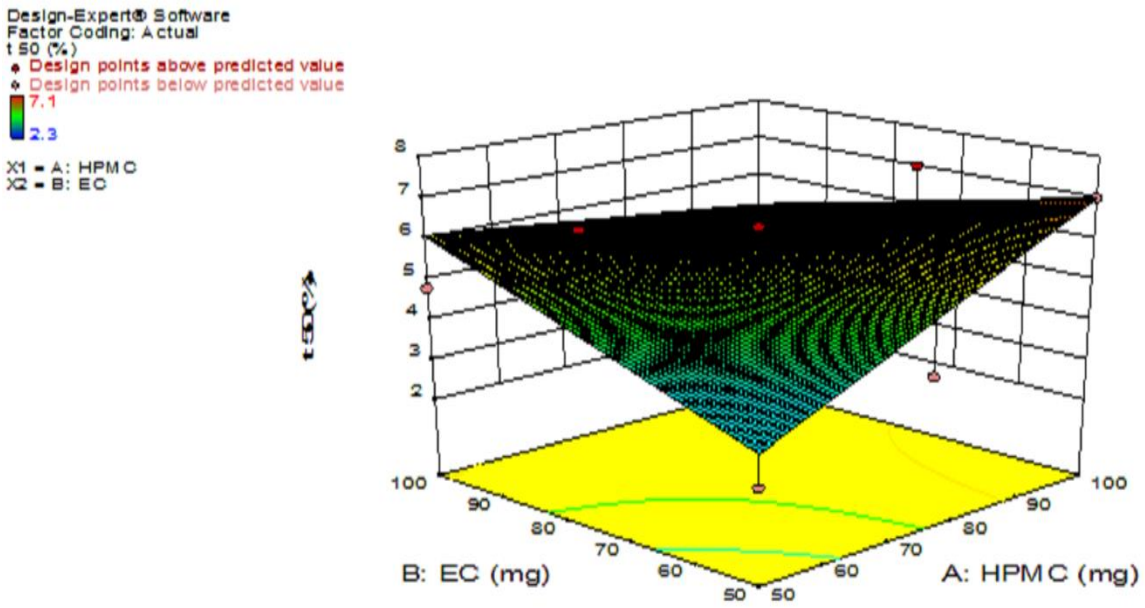

Fig. 8: 3D response plot showing the effect of X1 and X2 on t 50 (hrs)

To optimize all the responses with different targets, a multi criteria decision approach like a numerical optimization technique by the desirability function and graphical optimization technique by the overlay plot were used (Figure 9). The optimized results gave solution with theoretical target profile characteristics and which were shown in Table 8. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within 1.08 %. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model. Losartan potassium marketed tablets of Conventional dosage form of Czar 50mg (Aurobindo Pharma Ltd) was purchased to study drug release shown in table 9.

Table 8: Comparison of experimental results with predicted responses of Losartan potassium sustained release tablets formulation

Ingredient	Composition (mg/tab)	Response	Predicted value	Experimental value	Standard error
HPMC K100	79.3	Y1	29.76	29.1	0.33%
		Y2	90.23	92.4	1.08%
EC	50.2	Y3	5.39	5.2	0.09%

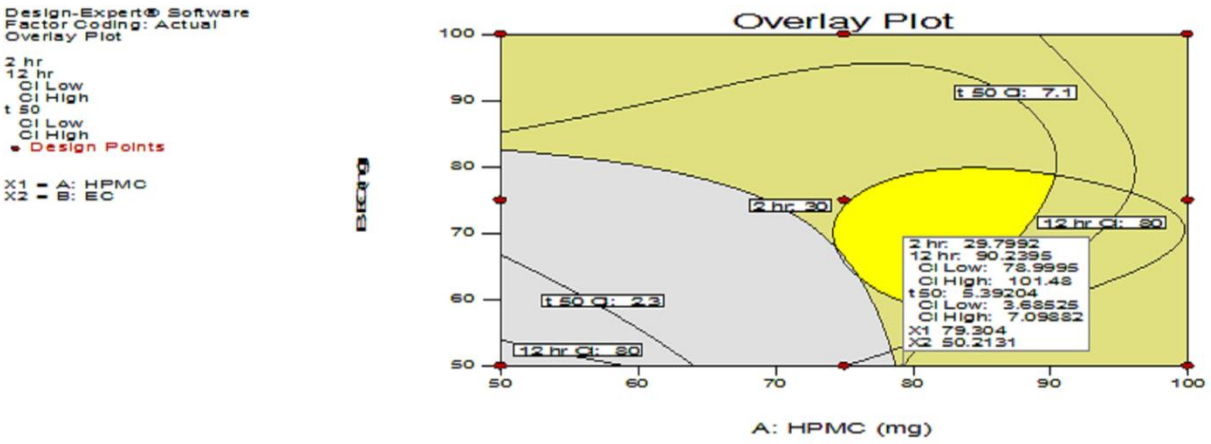

Fig. 9 Overlay plot of Optimized formulation

Table 9: Drug release from Marketed Losartan potassium conventional tablet of Czar 50 mg

Time (min)	% cumulative drug release
10	20.8 ± 2.4
20	39.4 ± 2.1
30	50.6 ± 1.8
40	64.2 ± 1.5
50	84.8 ± 2.4
60	96.8 ± 2.7

All values are expressed as mean ± SD, n = 6

The optimized formulation showed no significant changes in *In vitro* drug release after 3 months and the results were tabulated in the table 10.

Table 10: Stability studies of optimized formulation after 3 months

Parameter	**Result**
Tablet weight (mg)	352 mg
Thickness	4.12 mm
Hardness (Kg/cm^2)	5.8 Kg/cm^2
Friability	0.42%
Drug release (%)	90.5 % Cumulative % drug release at the end of 12 h

CONCLUSION:

Hydrophilic matrix of HPMC alone could not control the Losartan potassium release effectively for 12 hours. It is evident from the results that a matrix tablet prepared with hydrophilic polymer and hydrophobic polymer is a better system for sustained release of a highly water-soluble drug like Losartan potassium and 3^2 factorial design (DoE) could be successfully applied for the development of Losartan potassium sustained release tablets with fewer numbers of trials and better quality attributes.

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