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Development and Evaluation of Losartan Potassium Sustained Release Tablet Formulations

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Abstract

Objective: The purpose of the present research study was to develop sustained release (SR) tablet formulations for Losartan Potassium using HPMCK100M as a release retardant.

Methods: Losartan Potassium is an antihypertensive agent angiotensin-II receptor blocker belongs to BCS class-II agent. SR tablets for Losartan Potassium were formulated using variable quantities of HPMCK100M and Xanthan Gum by direct compression method. quantities of polymers was chosen as independent variables, X_1 and X_2 respectively whereas, time required for dissolution 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) of drug from formulation were chosen as dependent variables. 9 formulations were prepared and evaluated for various pharmacopoeial tests.

Results: The results reveals that all formulations were found to be within the acceptable limits and release rate profiles of all formulations were fitted to kinetic models. The statistical parameters were determined. Polynomial equations were developed for dependent variables. Validity of them was checked by countercheck formulations (C_1, C_2). According to SUPAC guidelines, formulation (F_4) containing mixture of 10% HPMCK100M and 14% Xanthan gum, was found to be identical formulation (dissimilarity factor f_1= 1.765, similarity factor f_2= 86.735) to marketed product (**COZAAR**).

Conclusion: Formulation F_4 follows First order kinetics, Non-Fickian Diffusion Anomalous Transport. (n= 0.825).

Key Words: Losartan Potassium, 3^2 Factorial Design, Sustained delivery, HPMCK100M, Xanthan gum, First order kinetics, Anomalous transport.

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INTRODUCTION

Oral route is the extensively used mode of administration for both conventional delivery systems and novel drug delivery systems. Tablets are the most famous solid dosage forms sold in the market. For chronic Therapy, immediate release formulations are required to be administered in repetitive mode results patient non-compliance[1]. However, oral administration of majority of drugs facilitates hepatic first pass metabolism, results low systemic availability of active ingredient, shorter action and development of non-active or toxic metabolites[2].

The aim of developing SR formulations is to maintain sink conditions (C_{SS} levels for prolonged period). Systems such as modified release / timed release also similar to sustained drug delivery [3-5].

SR formulations shows reduction in frequency of administration in comparison with prompt release dosage forms [6]. SR formulations offers advantage over immediate release formulations by optimising characteristics of active ingredients.

Polymers plays a key role in the release of drug from formulations. Polymers from natural sources are widely used in product development due to numerous advantages. Gums such as guar, xanthan, tragacanth, alginates, pectin etc. celluloss such as HPMC,HPC, CMC, SCMC extensively used for retarding property [7].

Formulations processed by Direct Compression (DC) technique, a simple approach because of Easer, rapid production, No degradative effects occurred during manufacturing, compliance.[6] The suitability of drug candidates for sustained release system based on biopharmaceutical, pharmacokinetic and pharmacodynamic properties of it [8].

Drug Profile and Rationality for Experimental Design

The aim of present research work, to develop SR tablet formulation for Losartan Potassium to decrease the dosing frequency and patient compliance by improving the bioavailability. Losartan Potassium, antihypertensive agent, angiotensin-II receptor blocker, belongs to BCS Class-II agent.

It is used for the management of myocardial Infarction, congestive heart failure. it was absorbed readily from GI tract and having low bioavailability (33%), shorter $t_{1/2}$(1.5-2.5 hr). hence there is need to select proper release retardant to achieve C_{SS} and to produce desired improved clinical response (conventional tablets should be taken 2-3 times a day to attain C_{SS}). Administration of Losartan Potassium in a sustained release formulation would be more beneficial for the management of hypertension. Hence, to reduce dosing frequency, improve therapeutic efficacy, patient compliance once daily sustained release Losartan Potassium is desirable [9-13].

Formulating a dosage form for obtaining a desirable drug release with minimum heuristics is essential. RSM with polynomial equation based concept has been efficiently utilised for optimization process [14].

Hence an attempt is made in current work to design SR tablet formulations of Losartan Potassium using HPMCK100M and Xanthan gum by using 3^2 Factorial design technique. The significant variables such as quantity of HPMCK100M and Xanthan gum and dependent variables, i.e. $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (Time taken for dissolution 10%,50%,75%,90% of drug respectively).

MATERIALS AND METHODS

Materials used in research work were procured from the various sources. Losartan Potassium was a gift sample from Seeko Medicare Pvt Ltd, Hyderabad, India. HPMCK100M, Xanthan gum, MCC and Lactose were procured from Loba Chemie Pvt.Ltd, Mumbai. Other excipients such as magnesium stearate, Talc were procured from S.D. Fine Chem. Ltd., Mumbai.

Design, Development of Losartan Potassium Sustained Release Tablet Formulations

3^2 factorial design, describe the proportion in which the independent variables amounts of HPMCK100M and Xanthan gum were used in current proposal The time required for 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) dissolution were opted as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for resultant equations. Polynomial equations were developed for dependent variables in accordance with Linear step-wise backward Regression Analysis Technique.

The 3 levels of both factor **X_1** (HPMCK100M) and **X_2** (Xanthan gum) at 6%, 10%, 14% concentrations (% with respect to 250 mg). nine formulations were designed and prepared using trail run combinations of the two factors i.e **X_1, X_2** as per experimental design and evaluated to check the significance of combined effects of **X_1, X_2** to select the best combination and to optimise.

Manufacture of Losartan Potassium Sustained Release Tablet Fomulations

Losartan Potassium SR Tablets were obtained by utilising Direct Compression method. Composition of each Tablet was shown in Table 2. All ingredients required for formulation were collected and weighed accurately and passed through sieve no 40. They were subjected to polybag mixing for 10-15 min to obtain a uniform powder blend. magnesium stearate was added to the powder blend and then again mix for 4-5 min, Blend was subjected to compression by using tablet Minipress (8 mm round punches and same hardness used for required number of tablets). Compressed tablets were evaluated as per official standards and unofficial tests. Tablets were packaged in air tight, light resistance and moisture proof containers.

Experimental Design

Experimental design used in experimentation for the optimization of release rate modifiers concentration such as, quantity of HPMCK100M was labeled as X_1 and quantity of Xanthan gum was labeled as X_2. Formulation design was summarized in Table 1. 3 levels for the quantity of HPMCK100M were selected and coded as -1= 6%, 0=10%, +1=14%. Three levels for the quantity of Xanthan gum were selected and coded as -1= 6%, 0=10%, +1=14% [15]. Formulae for all the factorial batches were given in Table 2.

Table 1: Experimental Design Layout

Formulation Code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	-1
F_4	0	1
F_5	0	0
F_6	0	-1
F_7	-1	1
F_8	-1	0
F_9	-1	-1
C_1	-0.5	-0.5
C_2	+0.5	+0.5

Table 2: Formulae for the Preparation of Losartan Potassium Sustained Release Tablets

Name of Ingredients	Quantity of ingredients per each tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Losartan Potassium	100	100	100	100	100	100	100	100	100
Lactose	56	66	76	66	76	86	76	86	96
Microcrystalline Cellulose	20	20	20	20	20	20	20	20	20
HPMC K 100M	35	35	35	25	25	25	15	15	15
Xanthan Gum	35	25	15	35	25	15	35	25	15
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total Weight	250	250	250	250	250	250	250	250	250

Evaluation of Losartan Potassium SR tablet formulations

Mechanical Strength

The Mechanical strength of the tablets was determined by diametric breakdown of tablet with the help of Monsanto/ Pfizer's Hardness Tester, results expressed in terms of kg/cm^2.

Friability

This test was executed by using Roche friabilator. A sample of 20 tablets are taken weighed (W) and dedusted in a drum for 4 minutes at a speed of 25 rpm or 100 free

falls and weighed (W_1) again. % friability was determined by using following formula. % weight loss should not be more than 0.8.

Friability (%) = [(W- W_1) / W)] x 100

Content Uniformity

A sample of 20 tablets was chosen randomly & the % drug content was determined, the tablets content should be in the range of 100±15% of the labelled amount can be considered as the test was passed.

Assay

A sample of 20 tablets collected and subjected to pulverisation. Powder equivalent to 80 mg was dissolved in 1dL of phosphate buffer pH 6.8, subjected to agitation to get more solubilisation. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of final solution was measured by using UV-Visible Spectrophotometer at 205 nm by employing phosphate buffer pH 6.8 as blank.

Thickness

This test was performed by using vernier calipers by placing the tablet between two arms of the vernier calipers. Final result was recorded

In-vitro Drug Release Study

The In vitro drug release study was performed by using USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium for initial 2 hours followed by phosphate buffer pH 6.8 at 50 rpm and temperature 37±0.5°C as standard set of conditions specified by monograph for SR Formulations. 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 analyzed for the absorbance at 205 nm using UV Visible spectrophotometer after appropriate dilutions. The determinations were performed in triplicate (n=3).

Kinetic modeling of drug release:

The dissolution profile of formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to know the pattern, order of drug release and mechanism [5,16-18].

RESULTS AND DISCUSSION

SR Tablet formulations of Losartan Potassium were prepared and optimized by 3^2 factorial design in order to screen the best combination of different drug release rate modifiers, HPMCK100M, Xanthan gum and also to achieve objective of present research work. The 2 factorial variables utilized in the development of formulations are, quantities of HPMCK100M & Xanthan gum were opted as independent variables (X_1, X_2), and In vitro dissolution characteristics such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ & $t_{90\%}$ considered as dependent variables. 9 formulations were designed and formulated utilizing 3^2 factorial design and all the formulations containing 100 mg of Losartan Potassium as dose.

All the tablets were subjected to various official tests such as mean hardness, friability, drug content, mean thickness and results are summarised in Table 3. The hardness of tablets was found to be **4.526±0.44-5.07±0.43 Kg/cm².** % Weight loss in for formulations < **0.45**. Drug content factorial formulations was found to be within **acceptable range only**. In vitro drug release studies were done for factorial batches using 0.1 N HCl for initial 2 hours followed by phosphate buffer pH 6.8 as a dissolution media at 50 rpm and 37±0.5°C. The In vitro dissolution profiles of tablets were shown in Fig.1-4 (Kinetic Plots) and the Statistical values for kinetic models were tabulated in Table 4. % Cumulative Drug release for trial batches F_1-F_9 at 12Hr were found to be **89.35-96.331%**. From the result it reveals that the rate of drug release was higher for batches containing Low level of X_1 compared with others, due to High quantity of polymer results drug may have entrapped within a polymer matrix causing a decrease in release rate. Therefore, predicted release of drug can be resulted by manipulating the quantities of X_1,X_2.

Formulation F_4 containing 25 mg of HPMCK100M, 35 mg of Xanthan gum exhibited promising kinetic values (**$t_{10\%}$= 0.380 h, $t_{50\%}$ = 2.520 h, $t_{75\%}$ = 5.040 h, $t_{90\%}$ = 8.382 h**). The variation in initial rapid release of drug is due to difference in the viscosity of the polymeric mixtures. As we know that viscosity of polymer is inversely proportional to the rate of drug release, variation in the viscosity is due the formation of thicker gel layer in formulation [19].

The In vitro drug release profile of Losartan Potassium trail runs was subjected to goodness of fit test by linear backward step-wise regression analysis according to kinetic/ mathematical models to know the drug release mechanism. Kinetic plots shown in fig.1,2,3,4. It was known that from the above results dissolution profile of most of batches follows First order kinetics with co-efficient of determination (R^2) values above **0.974 (0.974-0.982)**. The values of r of factorial batches for Higuchi's kinetics was found to be **0.956-0.965**, which confers that the data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values **0.671- 0.901** that proves Non-Fickian diffusion mechanism (anomalous drug transport). Polynomial equations were derived for dependent variables by backward stepwise linear regression analysis with the help of **PCP Disso** software and kinetic plots were constructed by using **SIGMAPLOT V13** software. Response surface morphology plots were shown in Fig.5-8 for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ using X_1 and X_2 on both the axes respectively. The Kinetic parameters for factorial formulations F_1 to F_9 were shown in Table 5.

Polynomial equation for 3^2 full factorial designs was explained as follows

$$Y= b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11} X_1^2+b_{22} X_2^2\ldots$$

Where, Y is dependent variable, b_0 is average response of 9 trails, b_1 is estimated co-efficient for X_1. The main effects (X_1 and X_2) shows the mean result/ impact of changing one factor at a time from proximities of low to high value. The interaction term/ compatibility (X_1X_2) represents

how the response varies when two factors/variables are simultaneously changed. X_1^2 and X_2^2 are useful for evaluating non-linearity. Validity of developed equations was scrutinised by designing 2 check point formulations of intermediate concentration (C_1, C_2).

The polynomial equations for dependant variables developed as follows,

$$Y_1 = 0.376+0.054X_1+0.0220X_2-0.005X_1X_2+0.0405\ X_1^2+0.0252X_2^2 \textbf{ (for } t_{10\%})$$

$$Y_2 = 2.491+0.355X_1+0.143X_2-0.027\ X_1X_2+0.270\ X_1^2+0.172\ X_2^2 \textbf{ (for } t_{50\%})$$

$$Y_3 = 4.982+0.722X_1+0.288X_2-0.050\ X_1X_2+0.541\ X_1^2-0.332\ X_2^2 \textbf{ (for } t_{75\%})$$

$$Y_4 = 8.270+1.192X_1+0.484X_2-0.082\ X_1X_2+0.898\ X_1^2+0.554\ X_2^2 \textbf{ (for } t_{90\%})$$

Table 3: Post-Compression Parameters

S. No	Formulation Code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	% Weight Variation	Drug Content (%)
1	F_1	4.526±0.44	3.30±0.01	0.263±0.07	249.47±1.4	97.88±1.2
2	F_2	4.74±0.46	3.32±0.13	0.357±0.025	249.88±1.32	99.05±1.5
3	F_3	4.83±0.47	3.44±0.12	0.398±0.46	251.76±1.31	99.97±1.6
4	F_4	5.06±0.44	3.52±0.18	0.44±0.007	252.23±1.45	99.93±1.5
5	F_5	4.98±0.2	3.57±0.14	0.362±0.02	251.98±1.5	99.89±1.4
6	F_6	4.96±0.04	3.55±0.12	0.44±0.005	253.8±1.5	101.18±1.5
7	F_7	5.07±0.43	3.53±0.05	0.44±0.04	249.39±1.42	100.02±1.45
8	F_8	4.96±0.04	3.58±0.12	0.363±0.06	252.86±1.4	100.9±1.36
9	F_9	4.95±0.05	3.54±0.11	0.444±0.02	248.8±1.2	101.18±1.44

Table 4: Statistical Parameters

S.No	Formulation Code	Kinetic Parameters											
		Zero Order			First Order			Higuchi			Korsmeyer-Peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F_1	1.065	9.166	0.972	2.099	0.097	0.979	23.237	33.837	0.956	0.671	1.346	0.992
2	F_2	0.310	9.339	0.973	2.108	0.107	0.982	22.744	34.710	0.961	0.720	1.317	0.990
3	F_3	0.526	9.290	0.971	2.101	0.104	0.982	22.506	34.575	0.961	0.721	1.326	0.989
4	F_4	0.467	9.554	0.971	2.129	0.119	0.975	22.954	35.426	0.958	0.825	1.196	0.992
5	F_5	1.735	9.714	0.970	2.156	0.137	0.975	22.476	36.220	0.962	0.870	1.164	0.991
6	F_6	1.897	9.707	0.970	2.153	0.136	0.974	22.338	36.213	0.962	0.888	1.145	0.991
7	F_7	1.820	9.574	0.968	2.125	0.124	0.976	22.183	35.770	0.962	0.846	1.190	0.988
8	F_8	3.091	9.735	0.965	2.154	0.143	0.976	21.705	36.564	0.965	0.889	1.160	0.986
9	F_9	3.250	9.727	0.965	2.152	0.142	0.975	21.567	36.557	0.965	0.901	1.143	0.986

F_1 to F_9 are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope

Table 5: Dissolution Parameters of Losartan Potassium SR Tablets

S.No	Formulation Code	Kinetic Parameters			
		$t_{10\%}$ (Hrs)	$t_{50\%}$ (Hrs)	$t_{75\%}$ (Hrs)	$t_{90\%}$ (Hrs)
1	**F_1**	**0.475**	**3.106**	**6.215**	**10.324**
2	**F_2**	**0.430**	**2.819**	**5.637**	**9.364**
3	**F_3**	**0.439**	**2.880**	**5.765**	**9.580**
4	**F_4**	**0.380**	**2.520**	**5.040**	**8.382**
5	**F_5**	**0.340**	**2.204**	**4.405**	**7.322**
6	**F_6**	**0.334**	**2.204**	**4.411**	**7.329**
7	**F_7**	**0.371**	**2.437**	**4.871**	**8.090**
8	**F_8**	**0.322**	**2.111**	**4.222**	**7.010**
9	**F_9**	**0.323**	**2.114**	**4.228**	**7.023**

Table 6: Dissolution Parameters for predicted and observed values for Check Point Formulations

Formulation Code	Predicted Value				Actual Observed Value			
	$t_{10\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h))	$t_{90\%}$ (h)	$t_{10\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h))	$t_{90\%}$ (h)
C_1	0.355	2.330	4.680	7.777	0.354	2.333	4.689	7.766
C_2	0.435	2.848	5.689	9.448	0.430	2.839	5.674	9.432

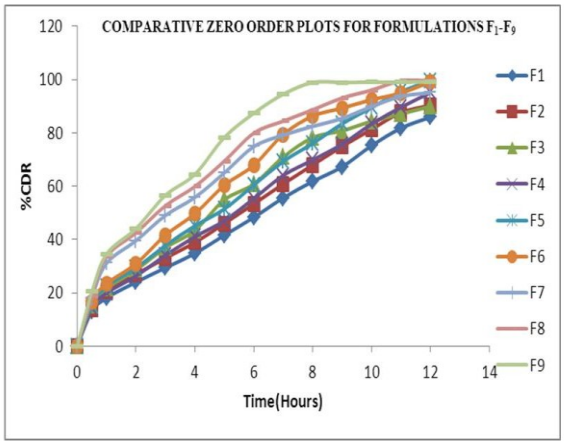

Figure 1: Comparative Zero Order Plots for F_1-F_9

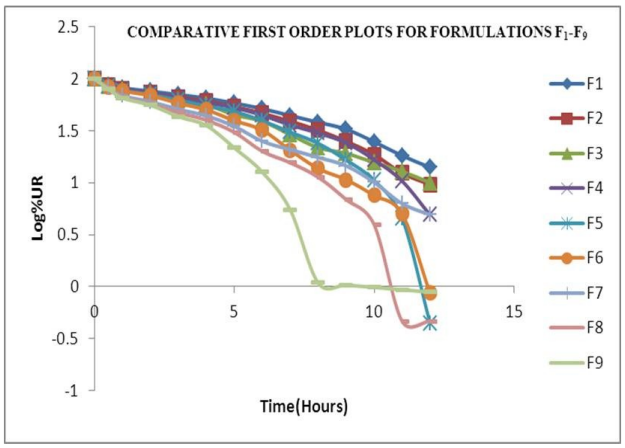

Figure 2: Comparative First Order Plots for F_1-F_9

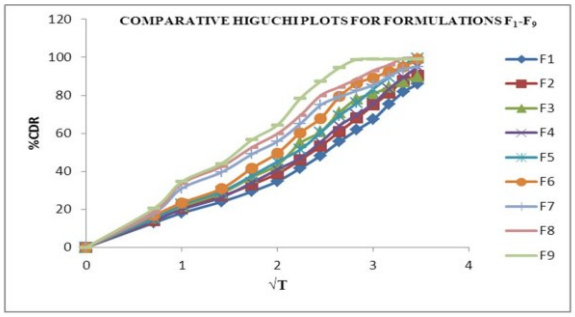

Figure 3: Comparative Higuchi Plots for F_1-F_9

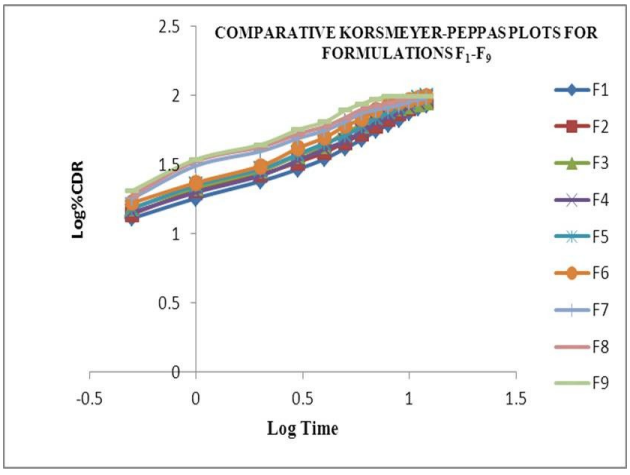

Figure 4: Comparative Korsmeyer-Peppas Plots for F_1-F_9

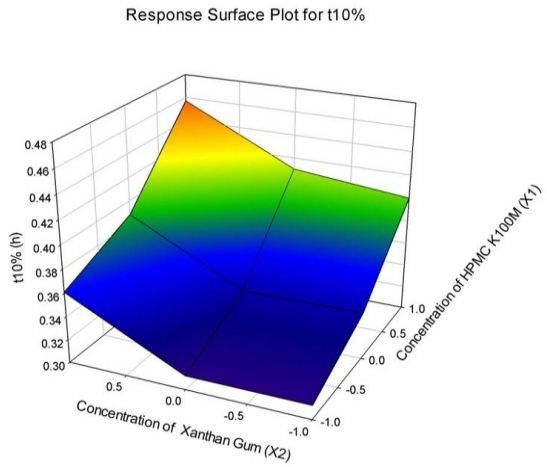

Figure 5: Response surface plots for $t_{10\%}$

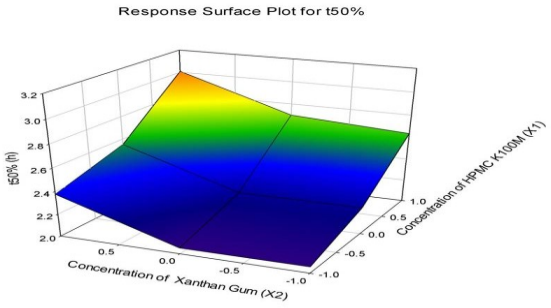

Figure 6: Response surface plots for $t_{50\%}$

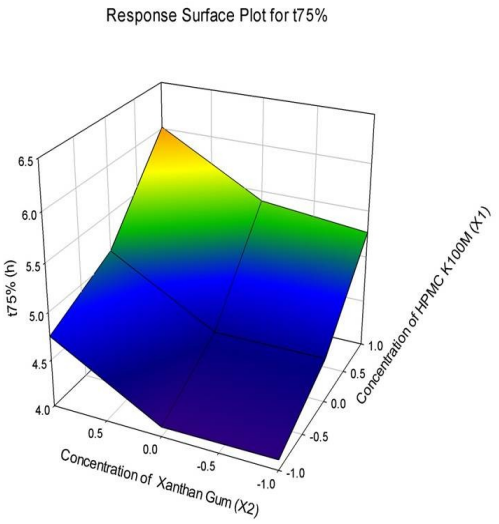

Figure 7: Response surface plots for $t_{75\%}$

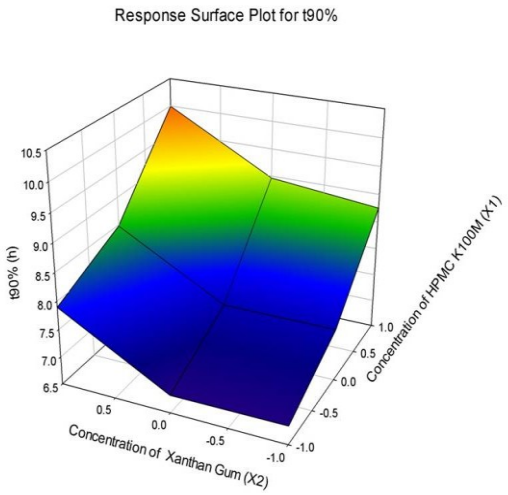

Figure 8: Response surface plots for $t_{90\%}$

The $+^{ve}$ sign for co-efficient of X_1 in Y_1, Y_2, Y_3 and Y_4 polynomials denotes that, as the quantity of of HPMCK100M increases, Y value also increases. In other hand, the represents that both independent variables shows significant impact on dependent variables. From the results it can be concluded that, as the increase in quantity of the retardants leads to decrease in drug release rate and drug release pattern may be changed by appropriate chosen of independent variables. The Drug release kinetic parameters for predicted from the developed polynomial equations and those actual observed from experimental results are presented in Table 6.

The closeness of both values for dependant variables indicates validity of developed equations. The response surface plots were constructed to show the impact of independent variables on dependant variables. F_4 is compared with marketed product (**COZAAR**) shows similarity factor (f_2) 86.7348, difference factor (f_1) 1.76497 (There is no significant difference in drug release because t_{cal} is<0.05).

CONCLUSION

The current research theme envisions the use of release retardants, HPMCK100M and Xanthan gum in the formulation development of sustained release tablets of Losartan Potassium with the help of 3^2 factorial techniques. From the results it clears that the amount of polymer is inversely proportional to the rate of drug release. Combination of retardants used since there is no incompatibility with the drug which may be more favourable for obtaining desired prolonged release of the drug. F_4 obeys Higuchi's square root law , drug release pattern mechanism was found to be Non-Fickian Diffusion (Anomalous Transport), First order release type. On the basis of kinetic parameters, the optimized formulation **F_4** may be used for the effective management of hypertension and to reduce the risk of Low ventricular Dysfunction, cardiovascular disease, Herat attack, stroke. This may

improve the patient compliance by reducing the dosing frequency. We could be able to minimize the per oral cost of the Formulation.

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