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DEVELOPMENT, OPTIMIZATION AND EVALUATION OF GASTRORETENTIVE TABLETS CONTAINING LOSARTAN POTASSIUM BY USING 3^2 FULL FACTORIAL DESIGN

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Keywords:

Gastroretentive floating tablets, HPMC K15 M, Losartan potassium, MCC, 3^2 full factorial design

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ABSTRACT: Background: The present investigation was aimed at developing, optimize and evaluate gastroretentive floating tablets containing Losartan potassium to retain in the stomach for prolong and predictable period of time for hypertensive patients. In the present study, the effect of HPMC K15M showed prolong release of drug in gastric pH environment. **Results:** These formulations were evaluated for the parameters like drug excipient compatibility study, thickness, hardness, tablet density, floating lag time, total floating time, weight variation test, % friability, drug content, % swelling index and accelerated stability studies. On the basis of preliminary results, the amount of HPMC K15M (X_1) and the amount of MCC (X_2) were chosen as independent variables in 3^2 full factorial design while % Friability (%F) and Cumulative % drug release at 12 hrs (Q_{12}) were taken as dependent variables. Multiple linear regression analysis, ANOVA and graphical representation of the influence of factors by contour plots were performed using Design Expert. *In-vitro* release data were fitted to various models to ascertain kinetic of drug release. The release profile of the optimized batch was found to follow Higuchi model (r^2=0.993). Check point batch was prepared to validate the evolved model. **Conclusion:** Batch F_7 was selected as an optimized batch because it showed friability less than 1 (0.80) and more % cumulative drug release (95.94) at 12 hrs. The optimized formulation was subjected to accelerated stability study and it was found to be stable.

INTRODUCTION: Oral route of drug delivery system is the most preferable, desired, and convenient method of administration. About 90% of all drugs used to produce systemic effect are administrated by oral route due to its ease of administration, low cost of therapy and patient compliance.

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Oral route of administration has received more attention in the field of pharmaceutical due to flexibility in the designing of dosage form than the other routes. Main prerequisite for the oral performance of the drug delivery system is that drug should have good absorption throughout the gastrointestinal tract (GIT) [1, 2].

Gastro retentive drug delivery system (GRDDS) ensures that whole drug delivery system remains within the gastric region for longer duration of time. This improves gastric retention time for such drug in comparison to conventional dosage form and further minimum effective concentration of drug remains maintained in systemic circulation for

longer duration. This also improves the solubility of drugs which are less soluble at alkaline pH of intestine and wastage of drug during the absorption process is reduced remarkably. GRDDS also provide higher concentrations of drug the gastric diseases like ulcer, gastritis, oesophagitis *etc* [3, 4]. The three aspects Gastrointestinal Physiology, Physicochemical properties of the drug and Dosage form characteristics help us to develop a successful oral sustained release matrix drug delivery dosage form [5, 6]. The need for gastro-retentive dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. Several techniques of GRDDS are Floating i.e. Low-density form of the dosage form that buoyant in gastric fluid, high density dosage form that retained in the bottom of stomach, bio-adhesion to stomach mucosa and expansion by swelling or unfolding to a large size which the system through the pyloric sphincher [7]. Based on the buoyancy mechanism, floating systems are classified as non-effervescent system and effervescent system [8, 9].

Losartan potassium is widely used for hypertensive patients [10, 11]. In the present study, it was tried as a model drug to develop a gastroretentive floating tablets to achieve prolong release of drug in gastric pH environment for 12 hrs. Thus, the present investigation was carried out for improving floating time as well as prolong the release of Losartan potassium by exploring statistical experimental design.

MATERIALS AND METHODS:

Materials and Reagents: Losartan potassium was received as a generous gift sample from Mepro Pharmaceutical Pvt. Ltd., Wadhwan, Gujarat. HPMC K4M, HPMC 15M were obtained from Colorcon, Goa. Camphor, MCC, NaCMC and PVP K30 were purchased from SAVA fine chemical, Mumbai. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Formulation of Gastroretentive Tablets: Tablets were prepared by wet granulation method. Required quantity of Losartan potassium, MCC, HPMC K4M, HPMC K15M and NaCMC weighed accurately and mixed properly. Mixture was granulated with binder and solvent (PVP K-30 in IPA) and the resultant cohesive mass screened through sieve 20#. It was dried with the help of a tray dryer and then dried granules passed through 20 # sieve. Later on weighed quantity of camphor, magnesium stearate and talc were mixed with granules. Finally, the granules were compressed with the help of 8 stations tablet compression machine. The prepared tablets were placed in tray dryer to sublime the camphor which was added during formulation [12].

Preliminary Screening of Gastroretentive Polymers: Preliminary study of different polymers was carried out to check the effect of release profile of gastroretentive formulation. Composition of Preliminary Trial Batches L_1 to L_6 were shown in **Table 1.**

TABLE 1: COMPOSITION OF PRELIMINARY TRIAL BATCHES OF LOSARTAN POTASSIUM OF GASTRORETENTIVE TABLETS

Ingredients	L_1	L_2	L_3	L_4	L_5	L_6
Losartan potassium	50	50	50	50	50	50
HPMC K4M	20	40	-	-	-	-
HPMC K15M	-	-	20	40	-	-
Na CMC	-	-	-	-	20	40
Camphor	30	30	30	30	30	30
MCC	115	95	115	95	115	95
PVP K30	6	6	6	6	6	6
Magnesium stearate	3	3	3	3	3	3
Talc	6	6	6	6	6	6
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Weight before sublimation	230	230	230	230	230	230
Weight after sublimation	200	200	200	200	200	200

*All weights in mg, HPMC K4M = Hydroxy propyl methyl cellulose K4M, HPMC K15M = Hydroxy propyl methyl cellulose K15M, NaCMC = Sodium carboxy methyl cellulose, MCC = Microcrystalline cellulose, PVP K 30= Polyvinyl Pyrrolidone K 30

Optimization of Variables Using Full Factorial Design: A 3^2 full factorial design [13] was used in the present study. On the basis of preliminary results, the amount of HPMC K15M (X_1) and MCC (X_2)

were chosen as independent variables in 3^2 full factorial design while Q_{12} and % Friability was taken as dependent variables. Multiple linear regression analysis and ANOVA and graphical representation of the influence of factors by contour plots were performed using Demo version of Design Expert 7.1.5. The experimental runs and measured responses of 3^2 full factorial design batches of Escitalopram oxalate was depleted in **Table 2.**

Drug-Excipients Compatibility Study: Drug-Excipients interaction plays a vital role to achieve better stability of drug in dosage form. Fourier transform infrared spectroscopy (FTIR) was used to study the physical and chemical interactions between drug and excipients. FTIR spectra of Escitalopram oxalate, HPMC K15M and their mixture were recorded using KBr mixing method on FTIR instrument [14, 15].

Evaluation Parameters of Gastroretentive Tablets: Thickness, Hardness, Tablet density, Floating lag time, Total floating time, Weight variation test, % Friability, Drug content and % Swelling Index of the formulations were measured as described by Tack-Oon Oh *et al* [16], Melinda Kakuk *et al.*[17], Schneider F *et al* [18].

Floating Lag Time: The time taken by the tablet emerges onto the surface of dissolution medium, at pH 1.2, temperature 37±0.5°C, paddle rotation at 50 rpm and 900ml as volume, it was measured using stopwatch [19].

***In-vitro* Dissolution Study:** Dissolution test was carried out using rotating paddle method. The stirring rate 50 rpm. 0.1 N HCl use as dissolution medium 900 ml and maintained at 37±0.5°C. Samples of 5ml were withdrawn at predetermined time up to 12 hrs and replace with 5ml of fresh dissolution medium. The collected samples was suitably diluted with dissolution fluid and analyzed for the Losartan potassium at 254nm by using a double beam UV spectrophotometer [20].

Kinetic Modeling of Dissolution: The dissolution profile was fitted to various models such as zero order, first order, Higuchi, Korsemeyer and Peppas, to ascertain the kinetic of drug release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release [21, 22].

Zero-order Model:

$$Q_t = Q_0 + Kt_0$$

Where, Q is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution (most times, Q_0= 0) and K_0 is the zero order release constant expressed in units of concentration/time.

First Order Model:

$$\log Q_t = \log Q_0 - K_t / 2.303$$

Where, Q_t is the amount of drug dissolved in time t, Q is the initial concentration of drug, K is the first order rate constant and t is the time.

Higuchi Model:

$$Q_t = KH\ t_{1/2}$$

Q_t is the amount of drug dissolved in time t, KH is the Higuchi dissolution constant and t is the time.

Korsmeyer Peppas Model:

$$Mt / M\infty = Ktn$$

Where, Mt / M∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent.

Short term Stress Stability Study: The optimized tablets were wrapped in aluminium foil and stored at 60±0.5°C and 75% RH for peroid of two months [23].

After two months, tablets were tested for drug content and *in-vitro* release profile. The dissolution profile of product was compared using f_2 which is calculated from the following formula.

$$f_2 = 50 \times \log " (1+ 1/n \sum (t=1)^n w_t\ (R_t-T_t)^2 ^(-0.5) \times 100)$$

Where log is logarithm to the base 10, n is the number of time points, ∑ is summation over all time points, R_t is the mean dissolution value of the reference profile at time t and T_t is the mean dissolution value of the test profile at the same time point.

The US FDA draft guidance document contains more information on similarity factor (f_2). The value of similarity factor (f_2) between 50 and 100

suggests that the two dissolution profiles are similar [24].

RESULTS AND DISCUSSION:

Preliminary Study: All the batches of gastroretentive tablets showed hardness in the range from 5.0 to 5.4 kg/cm^2. All the batches of gastroretentive tablets showed density in the range from 0.821 to 0.845 g/cm^3. All the batches of gastroretentive tablets showed % Friability in the range from 0.821 to 0.895. All the batches of gastroretentive tablets showed % Cumulative drug release in the range from 86.91 to 98.78. Batch L_1 and L_2 showed rapid release of drug within 8 hours compared to L_3, L_4, L_5 and L_6. *In-vitro* dissolution study of Batch L_3 and L_4 showed better result compared to L_5 and L_6. The result of preliminary study revealed that HPMC K15M or MCC alone was not sufficient to achieve desired release profile. Hence further trials were done using combination of HPMC K15M and MCC in order to understand their effect and to optimize concentration of both for desired release profile. The batches were evaluated for hardness, density, % friability, % cumulative drug release at 12 hrs, duration of floating and the result were shown in **Table 2.**

TABLE 2: EVALUATION OF PRELIMINARY TRIAL BATCHES OF LOSARTAN POTASSIUM OF GASTRORETENTIVE TABLETS

Ingredients	Hardness	Density	% Friability	% CDR at 12 hrs	Duration of floating
L_1	5.0	0.821	1.08	98.78	<12
L_2	5.2	0.828	0.98	96.20	<12
L_3	5.2	0.829	0.76	96.61	>12
L_4	5.3	0.865	0.57	84.90	>12
L_5	5.2	0.826	0.88	88.83	>12
L_6	5.4	0.895	0.79	86.91	>12

Drug-Excipients Compatibility Study: All the peaks which were present in pure drug (Losartan potassium) also present in drug polymer mixture, it was concluded that there was no interaction between drug and polymer during FTIR study. This confirmed that the presence of other excipients did not affect the drug stability. The Spectrograph of Losartan potassium, HPMC K15 M and mixture of Losartan potassium and HPMC K15M were shown in **Fig. 1, Fig. 2** and **Fig. 3** respectively.

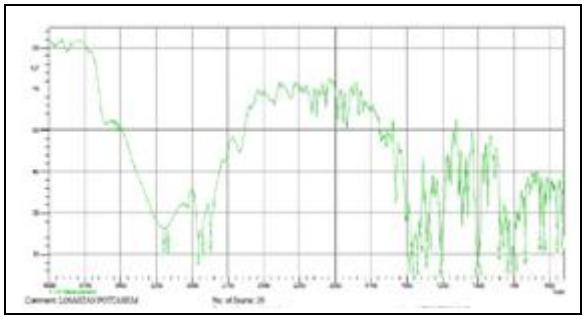

FIG. 1: FTIR SPECTRUM OF LOSARTAN POTASSIUM

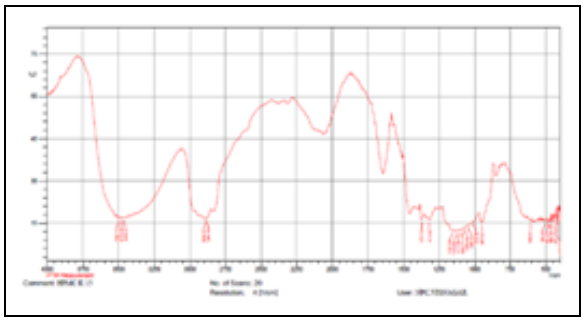

FIG. 2: FTIR SPECTRUM OF HPMC K15M

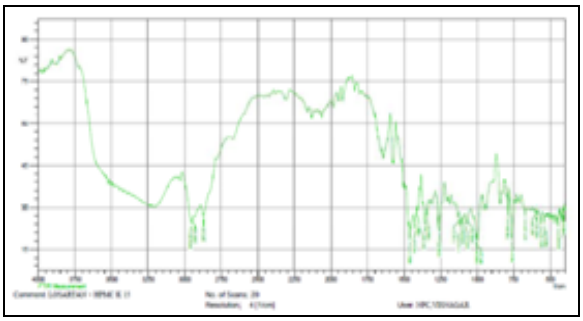

FIG. 3: FTIR SPECTRUM OF LOSARTAN POTASSIUM AND HPMC K15 M

Full Factorial Design Batches: A 3^2 full factorial design was used in the present study. In this design 2 factors were evaluated, each at 3 levels and experimental trials were performed for all 9 possible combinations. HPMC K15M forms stronger and thick matrix at higher concentration Thus drug entrapped in it, takes more time to release and MCC was used to bind tablets as well as to achieve the desired drug release. An optimized combination of these two may be able to achieve a tablet showing slow release of drug on the surface of gastric pH 1.2 at 12 hours. Hence, amount of HPMC K15M and MCC were assumed as independent variable in a 3^2 full factorial design. The amount of HPMC K15M was taken as 25 mg, 30 mg and 35 mg while MCC was taken as 95 mg, 105 mg and 115 mg which response as -1, 0,+1 levels respectively. The factorial batches were evaluated for Thickness, Hardness, Tablet density, Floating lag time, Total floating time, Weight variation test, % Friability, Drug content and Swelling Index were shown in **Table 3** and **4(A), 4(B)** respectivey. % Friability and % Cumulative drug release (%CDR) at 12 hrs were taken as dependent variables. The swelling index and % *in-vitro* drug release of Losartan potassium gastro-retentive tablets were shown in **Fig. 4** and **Fig. 5** respectively.

TABLE 3: RUNS AND MEASURED RESPONSES OF 3^2 FULL FACTORIAL DESIGN OF LOSARTAN POTASSIUM GASTRO-RETENTIVE TABLETS

Batch Code	(Amount of HPMC K15M) X_1	(Amount of MCC) X_2	% Friability Y_1	%CDR at 12 hrs (Q_{12}) Y_2
F1	-1	-1	0.48	94.30
F2	0	-1	0.50	91.11
F3	1	-1	0.47	87.14
F4	-1	0	0.65	95.56
F5	0	0	0.63	93.68
F6	1	0	0.59	88.09
F7	-1	1	0.80	95.94
F8	0	1	0.88	94.14
F9	1	1	0.81	89.13

Factors and the levels in the design

Independent variables	Levels		
	Low (-1)	Medium (0)	High (1)
Amount of HPMC K15M(X_1), mg	25	30	35
Amount of MCC (X_2), mg	95	105	115

TABLE 4(A): RESULTS OF EVALUATION PARAMETERS OF FACTORIAL BATCHES

Batch Code	Thickness (mm)	Hardness (kg/cm^2)	Density (g/cm^3)	Floating lag time (sec)	Duration of floating (hrs)
F1	3.13±0.14	6.0±0.13	0.81±0.04	0	>12
F2	3.10±0.30	5.2±0.21	0.82±0.01	0	>12
F3	2.98±0.10	6.1±0.42	0.85±0.02	0	>12
F4	3.20±0.13	5.1±0.11	0.80±0.01	0	>12
F5	3.24±0.21	5.4±0.18	0.79±0.04	0	>12
F6	3.21±0.32	5.3±0.14	0.79±0.08	0	>12
F7	3.15±0.15	6.1±0.15	0.80±0.01	0	>12
F8	2.99±0.27	5.8±0.23	0.87±0.02	0	>12
F9	3.30±0.24	5.7±0.12	0.76±0.01	0	>12

*Data expressed (±SD); n=3

TABLE 4(B): RESULTS OF EVALUATION PARAMETERS OF FACTORIAL BATCHES

Batch Code	Weight Variation (Avg.)		Friability (%)	Drug content (%)	Swelling Index (%)
	Before Sublimation (mg)	After Sublimation (mg)			
F1	224.66±0.12	201.46±0.50	0.48	97.86	289
F2	231.25±0.01	200.66±0.57	0.5	99.25	334
F3	236.54±0.19	200.35±1.13	0.47	96.92	391
F4	225.33±0.57	201.20±0.76	0.65	97.15	280
F5	229.66±0.55	201.46±1.50	0.63	98.57	331

F6	234.33±0.58	201.33±0.57	0.59	95.53	388
F7	225.00±1.73	200.23±0.68	0.80	97.63	276
F8	230.66±1.52	202.13±1.20	0.88	98.74	337
F9	235.33±1.15	201.03±0.05	0.81	95.83	392

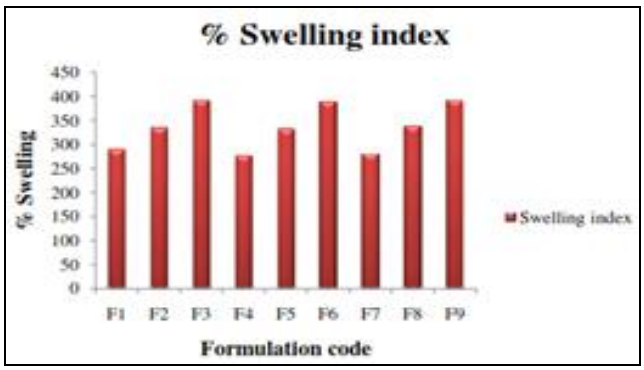

FIG. 4: SWELLING INDEX OF BATCHES F1-F9

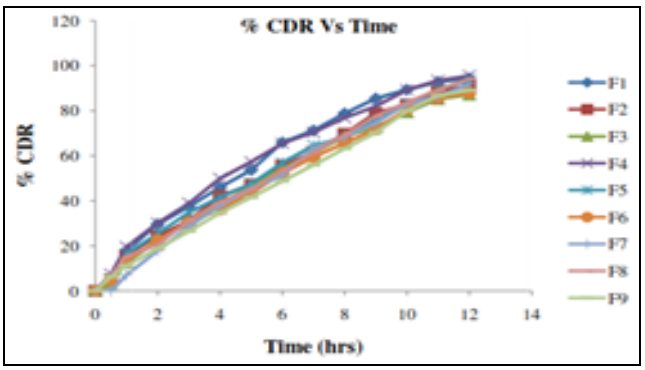

FIG. 5: *IN-VITRO* DRUG RELEASE OF BATCHES F1-F9

3^2 Full Factorial Design Model Evaluation: A statistical model [25] incorporating interactive and polynomial terms was used to evaluate the responses:

$$Y=b_0 +b_1X_1 +b_2X_2 +b_{12}X_1X_2 +b_{11}X_1^2+b_{22}X_2^2$$

where, Y is the dependent variable, b_o is the arithmetic mean response of the 9 runs and any bi is the estimated coefficients for the related factor Xi. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term "X_1X_2" shows how the response changes when the two factors change simultaneously. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The fitted equations (full model) relating the responses, that is, % Friability and % cumulative percentage drug release (% CDR) to the transformed factor were shown in **Table 5.** The polynomial equation can be used to draw conclusion after considering the magnitude of co-efficient and the mathematical sign it carries (i.e. positive or negative). The results of ANOVA suggested that F values calculated for % Friability and % CDR were 45.75 and 58.53 respectively **Table 6**. Tabulated F value was found to be 9.01 at $\alpha = 0.05$. Calculated F values were greater than tabulated value for all the dependent variables therefore all selected factors showed significant effect. R^2 value of % Friability and % cumulative percentage drug release (% CDR) were 0.9897 and 0.9899 respectively, indicating good correlation between dependent and independent variables. The reduced models were developed for response variables by omitting the insignificant terms with $P > 0.05$. The terms with $P < 0.05$ were considered statistically significance and retained in the reduced model. The coefficients for full and reduced models for response variables were shown in **Table 5**. From the results of multiple regression analysis, it was found that both factors had statistically significant influence on all dependent variables as $P<0.05$ **Table 6.**

TABLE 5: SUMMARY OF REGRESSION OUTPUT OF FACTORS FOR MEASURED RESPONSES

Coefficients	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
% Friability	0.62	-0.023	0.17	-0.015	3.33	0.033	0.989
Q_{12} (hrs)	93.30	3.57	1.11	0.087	-1.28	-0.48	0.989

TABLE 6: RESULTS OF THE ANOVA FOR DEPENDENT VARIABLES

		Q_{12}			
Source of variation	DF	SS	MS	F	P
Regression	5	87.80	17.56	58.53	0.0034
Residual	3	0.90	0.30		
Total	8	88.70			
		% Friability			
Source of variation	DF	SS	MS	F	P
Regression	5	0.1866	0.0366	45.75	0.005

Residual	3	0.0019	0.0008
Total	8	0.1885	

Full and Reduced Model for % Friability: The results of statistical analysis were revealed that a corresponding increase in the % Friability of tablet was observed with increase in concentrations of MCC. MCC was used in formulation to help the polymer for retarding the release of drug. From the contour plot graph **Fig. 7** and the regression coeffecient values of factors it was concluded that the concentration of MCC had negligible effect on % cumulative drug release at 12 hours compared to HPMC K15M. For % Friability, the significance levels of the coefficients b_1, b_{12}, b_1^2 and b_2^2 found to be P =0.14, 0.37, 0.76 and 0.22 respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_1 and b_2 were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model for friability was predicted as:

$$\% \text{ Friability} = 0.62 + (0.17^* X_2)$$

Full and Reduced Model for Q_{12} (%CDR at 12 Hours): The result of % cumulative drug release at 12 hours revealed that a corresponding decrease in drug release from tablet was observed with increase in concentration of HPMC K15 M polymer. It was due to higher concentration of HPMC K15 M which formed stronger matrix and drug entrapped in it took more time to release. From the contour plot graph **Fig. 6** and the regression coeffecient values of factors it was concluded that the concentration of MCC had negligible effect on % cumulative drug release at 12 hours compared to HPMC K15M. MCC had less significant effect on % CDR at 12 hours. For % Cumulative drug release at 12 hours, the significance levels of the coefficients b_{12} and b_2^2 were found to be P = 0.77 and 0.30 respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_1, b_2 and b_1^2 were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model for % Cumulative drug release at 12 hours (Q_{12}) was predicted as:

$$Q_{12} = 93.30 + (3.57^* X_1) + (1.11^* X_2) - (0.087^* X_1^2)$$

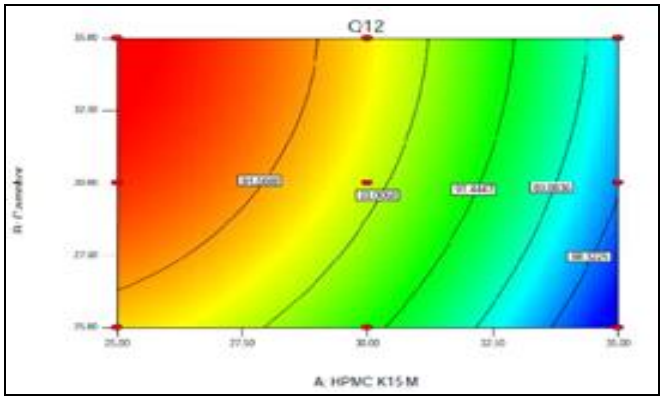

FIG. 6: CONTOUR PLOT SHOWING %CDR AT 12 HRS AT DIFFERENT COMBINATION OF X_1 AND X_2 (Q_{12})

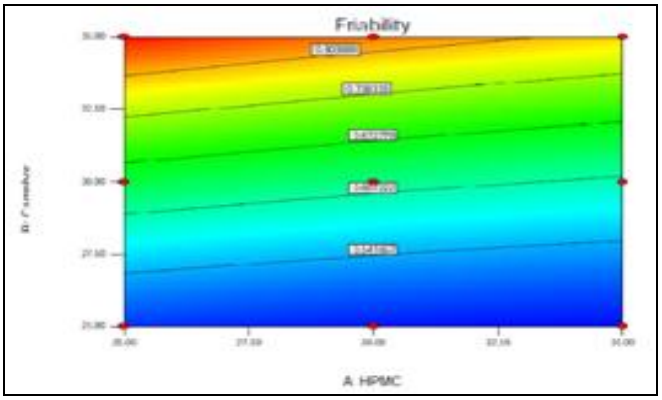

FIG. 7: CONTOUR PLOT SHOWING % FRIABILITY AT DIFFERENT COMBINATION OF X_1 AND X_2

Formulation of Check Point Batch: To validate the evolved mathematical models, check point batch CP1 was prepared and evaluated. The observed and predicted values were shown in **Table 8.** Good correlation was found between observed and predicted values. Hence, it was concluded that the evolved models may be used for theoretical prediction of responses within the factor space.

TABLE 7: FORMULATION OF CHECK POINT BATCH

Batch Code	Variable Level			
	Coded Value		Actual Value	
	X_1	X_2	X_1(mg)	X_2(mg)
CP1	-0.5	-0.5	27.5	32.5

TABLE 8: EVALUATION OF CHECK POINT BATCHES AND COMPARISON WITH PREDICTED VALUE

Batch Code	Actual value	Predicted value
	X_1& X_2 = -0.5	X_1& X_2 = -0.5
% Friability	0.64	0.71
Q_{12}	92.21	90.94

Selection of Optimize Batch in Factorial Design Study: In the present study, the following constraints were arbitrarily used for the selection of an optimized batch: Friability < 1 and % CDR > 95 and %. Batches F_4 and F_7 met the selection criteria. In the present study, Batch F_7 was selected as an optimized batch because it showed highest % cumulative drug release at 12 hrs (95.94) and % Friability (0.80). Thus, the best selected formulation was subjected to Kinetic study model and accelerated stability study.

Kinetic Modeling of Dissolution Data of Factorial Batches: The dissolution profile of selected factorial batch F_7 fitted to Kinetic models such as zero order, first order, Higuchi, Korsemeyer and Peppas, to ascertain the kinetic of drug release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release. The diffusion exponent n is the indicative of mechanism of drug release from the formulation. The n value is used to characterize different release mechanisms, concluding for values for a slab, of n < 0.5 for Fickian diffusion mechanism, 0. 5 < n < 1.0 to non-Fickian transport, values of n = 1 Case-II transport and n > 1.0 to super case II transport. All selected batches showed n value between 0.5 and 1.0, so drug released by non-fickian transport mechanism. Data analysis of factorial batch F_7 was described by using different models which was shown in **Table 9.** Drug release may follow Higuchi model as it was evident by correlation coefficient of 0.993 which indicate that drug diffusion takes place only in one dimension (edge effect must be negligible) and perfect sink condition was observed.

TABLE 9: DATA ANALYSIS OF FACTORIAL BATCH F_7 BY USING DIFFERENT MODELS

Model	Zero order	First order	Higuchi	Korsemeyer Pepas
Linearity (r^2)	0.981	0.784	0.993	0.969

Short Term Stress Stability Study: Batch F_7 was kept for stability study. The *in-vitro* release profile at initial and after two months was compared using f_2 value which was 79.26.

There is less difference in the f_2 value which indicate that the prepared formulation was stable as shown in **Table 10** and **Fig. 8.**

TABLE 10: EVALUATION OF OPTIMIZED BATCH F_7 FOR STABILITY STUDY

Parameters	Initial	After two months
Thickness(mm)	3.15	3.2
Hardness (kg/cm^2)	6.1	5.9
Density (g/cm^3)	0.80	0.76
% Friability	0.80	0.74
Drug Content	97.63	96.51
% Swelling Index	276	268

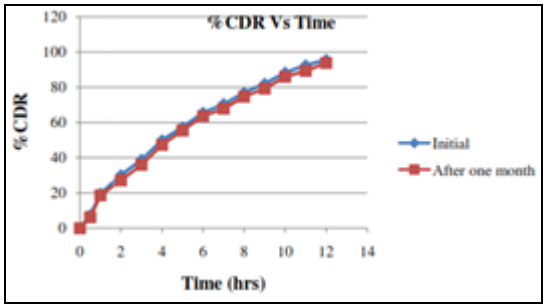

FIG. 8: *IN-VITRO* DRUG RELEASE OF F_7 BATCH AFTER SHORT TERM STABILITY STUDY

CONCLUSION: In present study gastroretentive floating tablets of Losartan potassium were successfully formulated using HPMC K15M as polymer, MCC as binder and camphor as a pore forming during sublimation method. Also it was observed that the present study was able to develop a gastroretentive floating tablet with slow release of Losartan potassium in gastric fluid environment. A

3^2 full factorial design was employed using two independent variables i.e. amount of HPMC K15M and MCC as X_1 and X_2 at 3-levels. The result of factorial design were analyzed stastitically and check point batch was prepared to validate the factorial analysis. The release profile of the optimize batch F_7 was found to follow Higuchi model (r^2=0.993). Optimize batch F_7 was found to be stable in the stability evaluation.

The formulation containing Losartan potassium as a drug with polymer HPMC K15M and MCC as binder to prepare gastro-retentive tablets by sublimation method was convenient for oral administration and it may be helpful to improve patient compliance by reducing dose frequency.

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