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DESIGN, DEVELOPMENT AND EVALUATION OF LABETALOL HCl GASTRO RETENTIVE FLOATING TABLETS

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ABSTRACT:
The main aim of present research study is to formulate the floating tablets of Labetalol HCl using 3^2 factorial design. Labetalol HCl, non selective **α, β**- adreno receptor antagonist, Indicated for treatment of Hypertension/moderate Heart Failure. The Floating tablets of Labetalol HCl were prepared employing different concentrations of HPMCK4M and sodium bicarbonate in different combinations by Direct Compression technique. The concentration of HPMCK4M and sodium bicarbonate required to achieve desired drug release was selected as independent variables, X_1 and X_2 respectively whereas, time required for 10% of drug dissolution ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) were selected as dependent variables. 9 formulations were designed and are evaluated for hardness, friability, thickness, % drug content, Floating Lag time, *In-vitro* drug release. From the Results concluded that all the formulation were found to be within the Pharmacopoeial limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept, slope & regression coefficient were calculated. Polynomial equations were developed for $\mathbf{t_{10\%}, t_{50\%}, t_{75\%}, t_{90\%}}$. Validity of developed polynomial equations were verified by designing 2 check point formulations. According to SUPAC guidelines the formulation (F_8) containing combination of 20% HPMCK4M and 3.75% sodium bicarbonate, is the most identical formulation which meets the objective of work. The selected formulation (F_8) follows Higuchi's kinetics, and the mechanism of drug release was found to be Non-Fickian Diffusion (n= 1.033, Super Case-II transport).

Keywords: Labetalol HCl, 3^2 Factorial Design, Gastro retentive Floating Tablet, HPMCK4M, sodium bicarbonate, Floating Lag Time.

1. INTRODUCTION

Enteral route is the most comfortable, extensively used route of administration for both prompt delivery systems and new drug delivery systems. Tablets are the most famous solid formulations available in the market and are preferred by patients and physicians alike. In case of treatment of chronic disease conditions, conventional release formulations are required to be administered in frequent manner and therefore shows patient non-adherence to prescription.[1] However, ingestion of majority of drugs shows first pass effect and/or first pass hepatic metabolism presystemic elimination by gastrointestinal degradation as a result of which low systemic bioavailability and shorter duration of action

and development of non-active or toxic transformed products.[2]

Rapid gastrointestinal transit can result in incomplete drug release from a Dosage form above the absorption zone, leading to diminished efficacy of the administered dose. Therefore, different approaches have been postulated to reside the formulation in the gasric environment, reduces the wastage of drug and improves systemic availability of drug. These include bioadhesive systems, swelling, altered density systems and expanding systems. Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits gastric emptying even when the pyloric sphincter is in an uncontracted state.[3]

The utilization of macromolecules like polymers in modulating the rate of drug release has turn to an essential tool in the product development of pharmaceutical formulations. Numerous reports over many years reveals that they play key role in the release of drugs from dosage form for various drugs.[4]

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 arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms.[5-6]

In the present research work, a Gastro retentive floating dosage form of Labetalol HCl has been developed that makes less frequent administering of drug also to improve Bioavailability.

Labetalol hydrochloride, 2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)-amino] ethyl]-benzamide, a non-selective α, β-adrenoceptor antagonist which is used in the treatment of hypertension. It is appreciably soluble in lower and higher pH solutions, with minimum solubility between pH 6 to 10. The drug shows variable bioavailability ranging from 10-80% which may be attributed to its instability in alkaline pH and poor absorption due to precipitation. It is administered in doses ranging from 50-200 mg twice a day due to its shorter half life of 3-6 hrs suggesting the need for sustained release formulation.

The major objective of the present investigation was to develop a gastro retentive drug delivery system containing Labetalol Hydrochloride using 3^2 Factorial design as an optimization technique. The present study involved the design of Labetalol Hydrochloride gastric floating matrix tablets by combining HPMCK4M, Sodium bicarbonate and investigation of the combined effect of these Formulation variables on the floating behavior and *in vitro* release pattern of the drug.[7-13]

Hence an attempt is made in the current research study to formulate Floating Tablets of Labetalol HCl using HPMCK4M and sodium bicarbonate. Instead of heuristic method, a standard statistical tool design of experiments is employed to study the effect

of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The Floating tablets formulation by direct compression method is most acceptable in large scale production.

A **3^2** full factorial design was employed to systematically study the drug release profile. A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of HPMCK4M and Sodium bicarbonate on the dependent variables, i.e. $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (Time taken to release 10%,50%, 75%,90% respectively)

2. MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Labetalol HCl was a gift sample from Aurobindo Pharma Pvt Ltd, Hyderabad, India. HPMCK4M from colorcon, sodium bicarbonate, Micro crystalline cellulose were procured from Loba Chemie Pvt. Ltd, Mumbai. Other excipients such as stearic acid, citric acid, Aerosil and talc were procured from S.D. Fine Chem. Ltd., Mumbai.

Formulation Development of Labetalol HCl Gastroretentive 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 .[14-16]

A selected three level, two factor experimental design (3^2 factorial design) describe the proportion in which the independent variables HPMCK4M and sodium bicarbonate were used in formulation of Labetalol HCl Floating Tablets. The time required for 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for Final Equations. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (step-wise backward Linear Regression Analysis).

The three levels of factor X_1 (HPMCK4M) at a concentration of 10%, 15%, 20%. Three levels of factor X_2 (sodium bicarbonate) at a concentration of 3.75%, 7.5%, 11.25% (% with respect to total Tablet weight) was taken as the rationale for the design of the Labetalol HCl floating tablet formulation. Nine Labetalol HCl floating 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 release of drug (by providing gastro retentivity) from the dosage form.

Preparation of Labetalol HCl Floating Tablets:

All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and HPMCK4M were blended geometrically in a mortar and pestle for 15 minutes then

sodium bicarbonate, talc and aerosil were mixed one by one. After mixing these ingredients, the powder blend was passed through # 44 mesh. Powder blend was subjected to compression by using rotary tablet punching machine (RIMEK), Ahmedabad). Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

Experimental Design:

Experimental design utilized in present investigation for the optimization of excipients quantities such as, amount of HPMCK4M was taken as X_1 and amount of Sodium bicarbonate was taken as X_2. Experimental design was given in the Table 1. Three levels for the Concentration of HPMCK4M were selected and coded as -1= 10%, 0=15%, +1=20%. Three levels for the Concentration of Sodium bicarbonate were selected and coded as -1= 3.75%, 0=7.5%, +1=11.25%. Formulae for all the experimental batches were given in Table 2.

EVALUATION OF LABETALOL HCl SUSTAINED RELEASE TABLETS:

Hardness

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm² is considered adequate for mechanical stability.

Friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.[18]

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Content Uniformity

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.

Assay

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was dissolved in 100ml of 0.1N Hydrochloric acid by sonication for 30 min. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 302 nm using 0.1 N Hydrochloric acid as blank.[7,12]

Thickness

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

In-Vitro Buoyancy Studies

The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.[15]

In-Vitro Dissolution Study

The *In-vitro* dissolution study for the Labetalol HCl Floating tablets were carried out in USP XXXIX type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl 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 analyzed for the presence of the drug release by measuring the absorbance at 302 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).[12]

Kinetic modeling of drug release

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release.[17-19]

3. RESULTS AND DISCUSSION:

Gastro Retentive Floating tablets of Labetalol HCl were prepared and optimized by 3^2 factorial design in order to select the best combination of different release rate modifiers, HPMCK4M, sodium bicarbonate and also to obtain the desired retention drug at gastric environment). The 2 factorial parameters involved in the development of formulations are, amount of HPMCK4M & sodium bicarbonate as independent variables (X_1, X_2), and *In vitro* dissolution parameters such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ & $t_{90\%}$ as dependent variables. Nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 200 mg of Labetalol HCl were prepared as a floating tablet dosage form by Direct Compression technique as per the formulae given in Table 2.

All the final trails were evaluated for various pharmacopoeial tests such as drug content, mean hardness, friability, mean thickness, mean diameter, Floating lag time and results are summarised in Table 3. The hardness of tablets was in the range of **4.41-4.68 Kg/cm².** Weight loss in the friability test was not more than **0.67%**. Drug content of prepared tablets was within **acceptance range only**. Results for all Post-compression parameters were tabulated or shown in Table 3. *In-vitro* Dissolution studies were performed for prepared tablets using 0.1 N HCl as a dissolution media at 50 rpm and temperature 37±0.5°C. The *In-vitro* dissolution profiles of tablets are shown in Fig.1 and the dissolution parameters are given in Table 4. Cumulative % Drug release of Factorial Design Formulations F_1-F_9 at 10 Hr were found to be in the range of **72.98-100.05 %**. From the result it reveals that, as the quantity of HPMCK4M increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release

increases and at the same time floating lag time decreases.

Therefore, required release of drug can be obtained by manipulating the composition of HPMCK4M and sodium bicarbonate.

Much variation was observed in the $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ due to formulation variables. Formulation F_8 containing 40 mg of HPMCK4M, 30 mg of sodium bicarbonate showed promising dissolution parameter (**$t_{10\%}$= 0.415 h, $t_{50\%}$ = 2.749 h, $t_{75\%}$ = 5.495 h, $t_{90\%}$ = 9.125 h**) which meets the objective of work by providing more gastric retentivity and maximum drug release. The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. Dortunc and Gunal have reported that increased viscosity resulted in a corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation.[20]

The *In-Vitro* dissolution data of Labetalol HCl Floating formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and plots shown in fig.1,2,3,4. It was observed from the above that dissolution of all the tablets followed first order kinetics with co-efficient of determination (R^2) values in the range of **0.872-0.998**. The values of r of factorial formulations for Higuchi's equation was found to be in the range of **0.931-0.997**, which shows 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 ranges from **0.901- 1.301** that shows Non-Fickian diffusion mechanism (Super Case-II Transport). Polynomial equations were derived for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ values by backward stepwise linear regression analysis. The dissolution data (Kinetic parameters) of factorial formulations F_1 to F_9 are shown in Table 5.

Polynomial equation for 3^2 full factorial designs is given in Equation

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

Where, Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated co-efficient for factor X_1. 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 two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check point Formulations of Intermediate concentration (C_1, C_2).

The equations for $t_{10\%}$, $t_{50\%}$ $t_{75\%}$ and $t_{90\%}$ developed as follows,

$$Y_1= 0.580+0.169X_1-0.079X_2+0.003X_1X_2-0.0911\ X_1^2-0.053X_2^2 \textbf{ (for } \mathbf{t_{10\%}})$$

$$Y_2= 3.822+1.111X_1-0.551X_2+0.017X_1X_2-0.601\ X_1^2-0.340X_2^2 \textbf{ (for } \mathbf{t_{50\%}})$$

$$Y_3 = 7.631+2.224X_1-1.12X_2+0.027X_1X_2-1.200X_1^2-0.682X_2^2$$ **(for $t_{75\%}$)**

$$Y_4 = 12.682+3.701X_1-1.820X_2+0.04X_1X_2-1.984X_1^2-1.135X_2^2$$ **(for $t_{90\%}$)**

The positive sign for co-efficient of X_1 in Y_1, Y_2, Y_3 and Y_4 equations indicates that, as the concentration of HPMCK4M increases, $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ value increases. In other words the data demonstrate that both X_1 (quantity of HPMCK4M) and X_2 (quantity of sodium bicarbonate) affect the time required for drug release ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$). From the results it can be concluded that, as the amount of HPMCK4M in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release increases, drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. The Dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarized in Table 6. The closeness of predicted and observed values for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ indicates validity of derived equations for dependent variables. From the results, the formulation (F_8) is considered as best formulations which meets the primary objectives of research work.

4. CONCLUSION

The present research study envisages the applicability of drug release rate modifier and Gas generating agent such as HPMCK4M and sodium bicarbonate respectively in the design and development of Gastro Retentive Floating tablet formulations of Labetalol HCl utilizing the 3^2 factorial design. From the results it was clearly understand that as the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release increases and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired floating delivery of the drug for longer periods. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be Non-Fickian Diffusion (Super Case-II Transport), First order release type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation **F_8** may be used once a day administration in the management of **Hypertension, Angina Pectoris and moderate Heart Failure.**

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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 Labetalol HCl floating 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
Labetalol HCl	200	200	200	200	200	200	200	200	200
HPMCK4M	80	80	80	60	60	60	40	40	40
Sodium bicarbonate	45	30	15	45	30	15	45	30	15
Micro crystalline cellulose	17	32	47	37	52	67	57	72	87
Stearic acid	40	40	40	40	40	40	40	40	40
Citric acid	10	10	10	10	10	10	10	10	10
Aerosil	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total Weight	400	400	400	400	400	400	400	400	400

Table 3: Post-compression parameters for the formulations

S.No.	Formulation Code	Hardness (kg/cm^2)	Floating lag time (min)	Diameter (mm)	Thickness (mm)	Friability (%)	Weight Variation	Drug Content (%)
1	F_1	4.63	1.11	9.98	4.66	0.61	400.07	95.65
2	F_2	4.68	3.52	9.95	4.67	0.62	400.32	95.77
3	F_3	4.66	4.34	9.99	4.68	0.55	400.05	95.58
4	F_4	4.51	0.91	9.99	4.51	0.67	400.60	93.07
5	F_5	4.60	3.22	9.98	4.59	0.66	400.45	95.60
6	F_6	4.65	4.15	10.02	4.62	0.55	400.90	97.35
7	F_7	4.41	0.31	10.00	4.42	0.67	400.23	94.66
8	F_8	4.51	2.92	10.01	4.49	0.63	400.66	97.09
9	F_9	4.53	3.85	10.00	4.54	0.57	400.03	96.88

Table 4: Regression analysis data of 3^2 factorial design formulations

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	12.137	7.732	0.969	1.993	0.071	0.996	5.282	27.408	0.991	0.959	1.056	0.938
2	F_2	10.575	7.335	0.975	1.990	0.063	0.998	5.717	25.920	0.992	0.938	1.050	0.941
3	F_3	9.408	7.169	0.978	1.993	0.058	0.998	6.303	25.234	0.991	0.911	1.059	0.949
4	F_4	14.528	8.269	0.961	2.005	0.090	0.994	4.642	29.625	0.991	0.999	1.062	0.919
5	F_5	12.929	7.410	0.959	1.977	0.066	0.994	4.2999	26.553	0.990	0.965	1.043	0.914
6	F_6	10.522	7.487	0.965	1.997	0.064	0.994	6.387	26.596	0.986	0.901	1.104	0.924
7	F_7	42.212	6.712	0.808	1.959	0.159	0.872	20.917	26.853	0.931	1.301	0.809	0.822
8	F_8	18.613	8.403	0.952	2.027	0.110	0.984	1.685	30.512	0.995	1.033	1.032	0.890
9	F_9	16.337	8.467	0.964	2.025	0.105	0.986	3.463	30.413	0.997	1.032	1.044	0.910

F_1 to F_9 are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope and MP-Marketed Product.

Table 5: Dissolution parameters for factorial design batches

S.No	Formulation Code	Kinetic Parameters			
		$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)}$)	$t_{90\%\ (h)}$
1	F_1	0.642	4.217	8.432	14.002
2	F_2	0.732	4.815	9.624	15.988
3	F_3	0.787	5.158	10.315	17.135
4	F_4	0.510	3.363	6.723	11.166
5	F_5	0.696	4.568	9.135	15.178
6	F_6	0.718	4.712	9.419	15.652
7	F_7	0.288	1.887	3.776	6.258
8	F_8	0.415	2.749	5.495	9.125
9	F_9	0.439	2.877	5.752	9.554

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	0.505	3.3079	6.615	10.974	0.503	3.3068	6.611	10.977
C_2	0.583	3.875	7.733	12.855	0.585	3.872	7.731	12.852

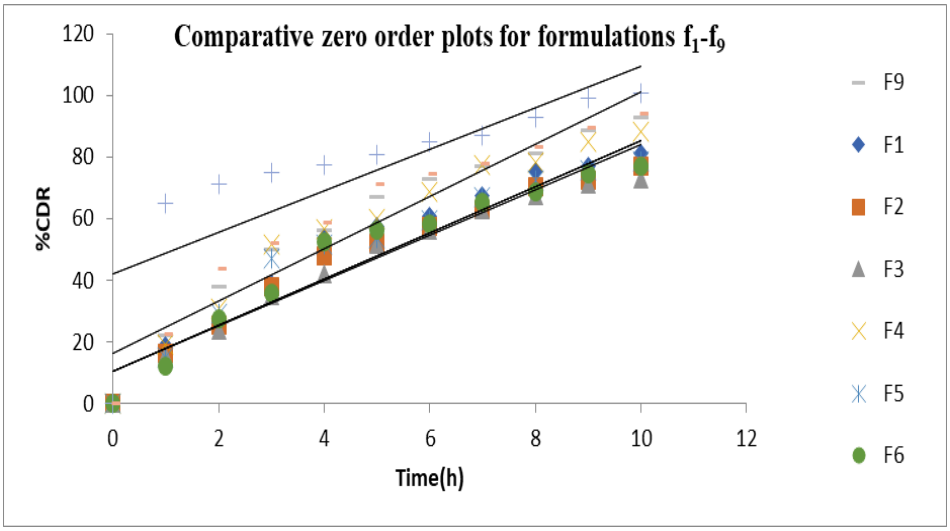

Fig. 1 Comparative Zero order plots

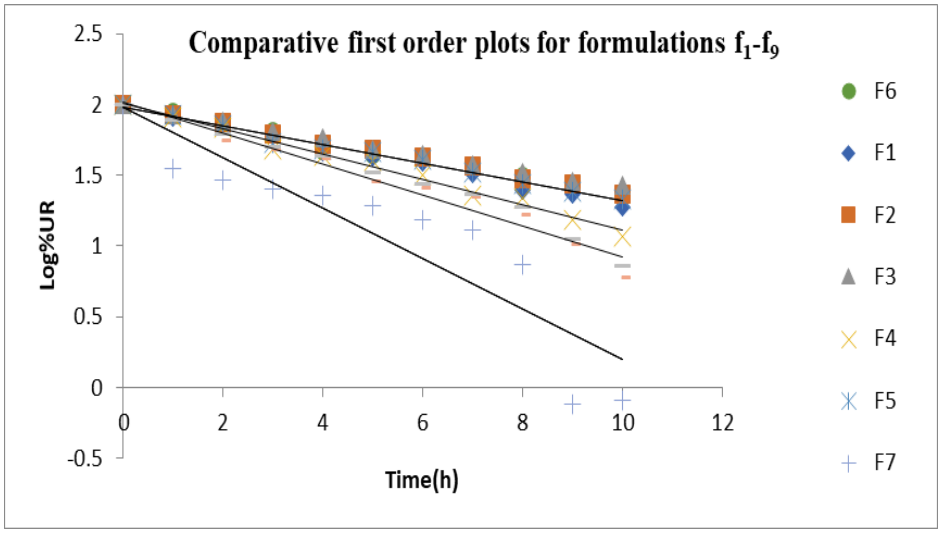

Fig. 2 Comparative First order plots

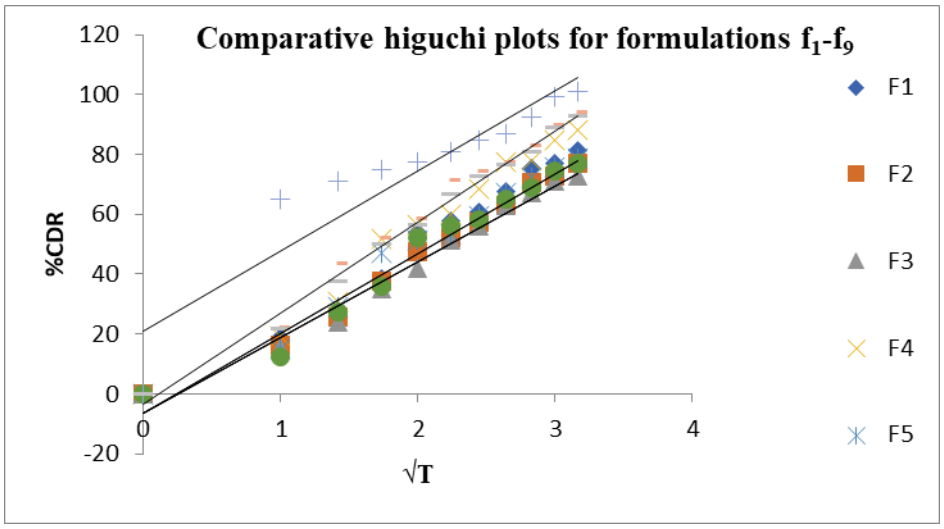

Fig. 3 Comparative Higuchi plots

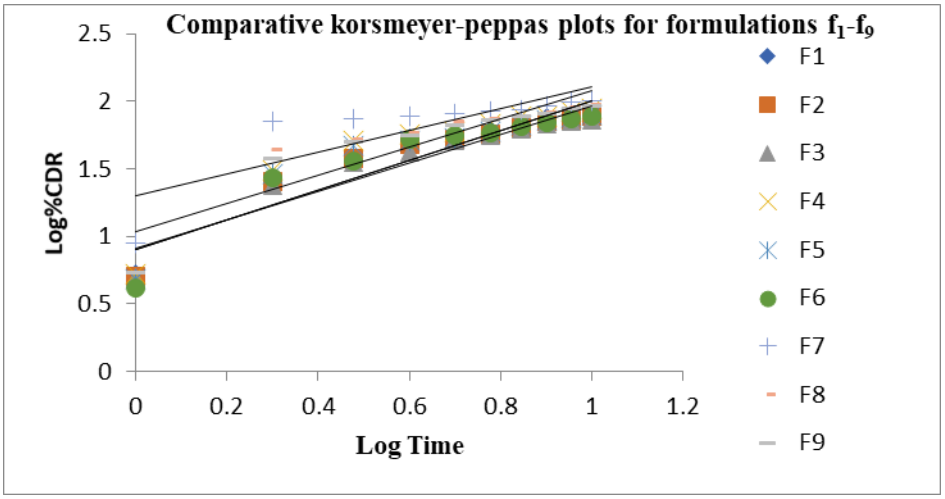

Fig. 4 Comparative Korsmeyer Peppas plots

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