STATISTICAL OPTIMIZATION OF GASTRIC FLOATING SYSTEM FOR ORAL CONTROLLED DELIVERY OF CLARITHROMYCIN

S.R.Shahi[*1], N.V.Shinde[1], G.R.Agrawal[1], S.A.Shaikh[2], S.S.Shaikh[3], V.G.Somani[1], M.A.Kale[1], P.B.Shamkuwar[1], A.N. Padalkar[4]

[*1]Goverment College of Pharmacy, Vedant Road, Aurangabad, M.S. 431005
[2]Jeevanjyoti Herbaceuticals, Beed-by-pass Road, Aurangabad, M.S.-431002
[3]Kamla Nehru College of Pharmacy, Rauza Baugh, Aurangabad, M.S. 431001
[4]Concept Pharmaceuticals Ltd, Chikalthana, Aurangabad M.S. 431005
E-mail: sadhanashahi@yahoo.com

ABSTRACT

The development of an optimized gastric floating drug delivery system is described. Statistical experimental design and data analysis using response surface methodology is also illustrated. A 3^2 factorial design for the controlled release of clarithromycin was used with two formulation variables: X1 (HPMC K4M) and X2 (citric acid). Nine formulations were prepared and dissolution studies and floating characteristics were performed on these formulations. The dissolution data obtained were then fitted to the PCP disso version 2.08 software. Linear regression analysis and model fitting depicted that the formulations followed Hixon Crowell model. The two formulation variables were found to be significant for the release properties (P < 0.05), while citric acid loading was found to be significant for floating lag time. The quadratic mathematical model developed could be used to further predict formulations with desirable release and floating properties.

Key words: *Clarithromycin, floating tablet, wet granulation, factorial design, $t_{50\%}$, $t_{85\%}$,, Floating lag time (FLT), response surface plot.*

INTRODUCTION

Oral drug delivery system has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via various pharmaceutical dosage forms. All the pharmaceutical products for systemic delivery via oral route of administration irrespective of mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid, dispersion or liquid) must be developed within the intrinsic characteristic of GIT physiology. A rational approach to enhance the bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area i.e. in the stomach and to release the drug in controlled manner. Another group of drugs that could benefit from retention and controlled release in the stomach are those meant for the treatment of pathologies located in the stomach, duodenum or the small intestine[1, 2, 3].

Gastroretentive drug delivery system can improve the controlled delivery of drugs that have an absorption window, by continuously releasing the drug for prolonged period of time before it reaches to its absorption site. Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability of the drug that are having site specific absorption from the stomach or upper part of small intestine. Therefore, different approaches have been proposed to retain the dosage form in the stomach including bioadhesive

systems, swelling and expanding system, floating systems and delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [4, 5].

Helicobacter pylori is a prevalent human specific pathogen, which is now believed to be the causative bacterium for chronic gastritis, peptic ulcer and adenocarcinoma, one of the most common forms of cancer in humans and its eradication requires high concentration of drug within the gastric mucosa for long duration[6]. Thus, floating oral delivery system is expected to remain buoyant in a lasting way upon the gastric contents and enhance bioavailability of all drugs which are well absorbed from the GI tract [7].

Clarithromycin is an advanced generation macrolide antibiotic used in treatment of *H. pylori* and respiratory infection. In controlled release formulation, if the concentration of antibiotic is maintained above MIC, drug resistance can be reduced. To achieve the desired therapeutic profile with maximum drug utilization and improve the patient compliance present study was applied to develop the gastroretentive drug delivery system for Clarithromycin [8].

EXPERIMENTAL

Clarithromycin was received as gift sample from IPCA Laboratories, Ratlam, HPMC K4M, sodium bicarbonate, citric acid, PVPK30 and magnesium stearate were received as gift sample from Concept Pharmaceuticals, Aurangabad. Folin Ciocalteu Phenol Reagent was purchased from Qualigens chemicals, Mumbai. All other chemicals were of analytical grade.

1. Preparation of Clarithromycin floating tablets

Different tablet formulations were prepared by wet granulation method. Clarithromycin (250mg) was mixed with varying concentration of HPMC K4M, to obtain different formulations of tablet. Other excipients added to this mixture were PVP K30 (binding agent), sodium bicarbonate (gas generating agent), citric acid (solubilizing agent), magnesium stearate (lubricating agent). Isopropyl alcohol was used as granulating agent. The granules were prepared by passing the wet mass through sieve # 16 and then dried at 50ºC for 1hr. These dried granules were then lubricated with magnesium stearate and passed through sieve # 22. The granules were then compressed using Labpress Rotary Tablet Machine using 12mm flat faced punches to obtain the tablets.

2. Evaluation of formulation

A. Physical characterization

The fabricated tablets were characterized for weight variation test (n=20), hardness (n=5), (Monsanto hardness tester), thickness (n=5) using a vernier caliper and friability (Roche Friabilator).

B. Assay of tablets

Five tablets were weighed individually, crushed to fine powder and about 100 mg of drug was dissolved in 0.1N HCl, the solution was filtered through 0.45µ membrane filter. The absorbance was measured at 760 nm after suitable dilution using F. C. Phenol reagent as a colour forming agent [9].

3. Factorial design

A 3^2 factorial design was used in this study and 2 factors were evaluated, each at 3 levels; experimental trials were performed at all 9 possible combinations [10]. The percentage of HPMC

K4M and citric acid were selected as independent variables. The floating lag time and the time required for 50% and 85% of drug release were selected as dependent variables. Tablet weight was not constant because that would require the use of diluents for weight adjustment, which in turn may have caused variation in release profile. Thus we did not alter the amount of diluents in the formulation to nullify any effect due to change in the proportion of diluents.

4. In vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time, as per the method described by Rosa et al [11]. The tablets were placed in 100 ml beaker containing 0.1N HCl and the time required for the tablets to rise to the surface and float was determined as the floating lag time.

5. In vitro dissolution studies

The release rate of Clarithromycin from floating matrix tablet (n=3) was determined using USP dissolution test apparatus Type II (paddle method). The dissolution test was performed using 900 ml of 0.1NHCl at 37 ± 0.5ºC and 50 rpm. This study was done for 24 hrs. A sample of 5 ml were withdrawn at an interval of 15min,30min,1hr,2hr,4hr,8hr,12hr,16hr,20hr and 24hr respectively. The samples were replaced with fresh dissolution medium each time. The samples were filtered through 0.45µm membrane filter. Samples were suitably diluted with 2ml of F. C. Phenol Reagent (diluted to 1:2 with distilled water) and 2ml of 20 % sodium carbonate solution and the volume made up to 10 ml with dissolution media. The resultant samples were analyzed at 760 nm against reagent blank.

6. Kinetic modeling of drug release

The dissolution data of all the batches was fitted to zero order, first order, Higuchi model[12], Krosmeyer Peppas[13] and Hixon-Crowel model[14] to ascertain the kinetic modeling of drug release by using PCP Disso Version 2.08 software, and the model with highest correlation coefficient was considered to be the best model.[15]

RESULT AND DISCUSSION

The tablets of different formulations were evaluated for the weight variation test, thickness and hardness. The results are shown in table 3. The weight variation, thickness and hardness values showed no significant difference from the average value. The friability was also within the specified limits.

The drug content in all the batches of Clarithromycin floating tablets was in the range of 95 to 105%. This ensured good uniformity of the drug content in the tablets.

The desired floating characteristics were achieved by using sodium bicarbonate as gas generating agent. The sodium bicarbonate produces CO_2 gas in the presence of acidic media such as gastric fluid. The gas generated is trapped and protected within the gel formed by polymer, thus decreasing the density of tablet below 1gm/cm^3, and the tablet becomes buoyant. To study the effect of sodium bicarbonate on floating time initially the concentration was varied from 12 to 18%. The optimized concentration i.e. 18% was sufficient to produce the tablet with floating time more than 24hrs and was selected for further study. The effect of citric acid concentration on the floating lag time was also studied. It was observed that with the increase in concentration of citric acid, floating lag time was decreased (table no.2).

The primary objective of the study was to design a floating tablet of the Clarithromycin with release profile sufficient to maintain high local/systemic concentration. Before the application of

3^2 factorial designs, preliminary trials were carried out to obtain the optimized concentration of polymer. The second variable citric acid was chosen because of its significant effect on the FLT and the drug release profile. All the nine batches showed variable release profile (figure.4). The polymer concentration being constant and an increase in the concentration of citric acid the dissolution profile was improved significantly.
The 3^2 full factorial design was selected to study the effect of independent variables HPMC K4M (X_1) and Citric Acid (X_2) on dependent variables $t_{50\%}$, $t_{85\%}$ and floating lag time. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y=b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11}X_1^2+b_{22}X_2^2 \quad (1)$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i(b_1,b_2,,b_{12},b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value[16,17]. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The t_{50}, t_{85} and floating lag time for the nine batches (F1-F9) showed a wide variation (i.e., 450.4-627.9 minutes, 1023.1-1426.4 minutes and 7.40-32.71 seconds, respectively). The responses of the formulations prepared by 3^2 factorial design batches are indicated in table 2. The data clearly indicate that the t_{50}, t_{85} and floating lag time values are strongly dependent on the selected independent variables. The fitted equations relating the responses t_{50}, t_{85} and floating lag time are shown in the following equations, respectively.
Final Equations in Terms of Coded Factors:

$$t_{50}=547.66+42.78X_1-42.36X_2-4.07X_1X_2-13.62\ X_1^2+1.92\ X_2^2 \quad (2)$$

Final equations in Terms of Actual Factors:
t_{50}=221.49+31.67HPMC K4M-16.87 Citric Acid-0.40 HPMC K4M Citric Acid -0.53 HPMC

$$K4M^2+0.48\ \text{Citric Acid}^2 \quad (3)$$

Final Equations in Terms of Coded Factors:

$$t_{85}=1240.71+97.21X_1-96.25X_2-9.25X_1X_2-28.47\ X_1^2+6.42\ X_2^2 \quad (4)$$

Final equations in Terms of Actual Factors:
t_{85}=540.37+68.70HPMC K4M-42.46 Citric Acid-0.92 HPMC K4M Citric Acid -1.13 HPMC

$$K4M^2+1.60\ \text{Citric Acid}^2 \quad (5)$$

Final Equations in Terms of Coded Factors:

$$FLT=19.18+6.14X_1-5.49X_2-2.99X_1X_2-3.73\ X_1^2+1.59\ X_2^2 \quad (6)$$

Final equations in Terms of Actual Factors:
FLT=-71.70+8.39 HPMC K4M+0.051 Citric Acid-0.29 HPMC K4M Citric Acid -0.14 HPMC

$$K4M^2+0.39\ \text{Citric Acid}^2 \quad (7)$$

Table 3 shows ANOVA for the dependent variables t_{50}, t_{85} and FLT. Only significant terms of the model are retained in the tables. The coefficients of X_1 and X_2 were found to be significant at $p<0.05$, hence they were retained in the reduced model. Increasing the concentration of the HPMC K4M resulted in the decrease in the release of Clarithromycin and increase in FLT of the tablet. However, the increase in concentration of the citric acid resulted in decrease in FLT and increase in drug release. Overall both the variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 7.1.4 trial software. The response surface plot of the percentage of HPMC K4M (X_1) and citric acid (X_2) Vs t_{50}, t_{85} and FLT are shown in figure 1, 2, and 3. The response plot showed that there is significant effect of both factors on the t_{50}, t_{85} and FLT. Increased HPMC K4M concentration caused decrease in drug release from the tablet but increased in the floating lag time. However, both the variables favor the preparation of controlled release floating tablets of Clarithromycin.The release profile of Clarithromycin from the 3^2 factorial design batches are shown in figure.4. All the batches showed good in vitro buoyancy and increase in citric acid concentration caused decrease in FLT as shown in the figure.5.

Linear regression analysis and model fitting showed that all the formulations followed Hixon Crowell Model, which had a higher value of correlation coefficient as shown in table 5. The model can be best described by the equation,

$$W_0^{1/3}-W_t^{1/3}=K_S T \qquad (8)$$

Where, W_0 is the initial amount of drug in pharmaceutical dosage form, Wt is the remaining amount of drug in pharmaceutical dosage form at time t and K_S is a constant incorporating the surface volume relationship. When this model is used, it is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix. The value of n i.e. diffusional release exponent was >5 represents anomalous transport or non-fickian diffusion, table 5.

Thus, the present work focuses on the formulation and evaluation of gastroretentive drug delivery system based on floating mechanism. The effervescent based floating drug delivery system is a promising approach to achieve in vitro buoyancy. The addition of matrix forming polymer HPMC K4M allows controlled release of Clarithromycin over an extended period of time which is essential to improve the bioavailability and patient compliance. A systemic study using the 3^2 factorial designs revealed that the amount of HPMC K4M and citric acid had a significant effect on the drug release profile and floating lag time. Therefore, the desired dissolution profile and floating characteristics can be achieved by suitable composition of polymer and acid.

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Table 1. Amount of Variables in 3^2 Factorial Design

Coded Values	Actual Values (%)	
	X_1	X_2
-1	15	2
0	20	4
+1	25	6

Table 2. Formulation and Dissolution Characteristics of 3^2 Factorial Design Batches

Formulation Code*	Coded Values		Response time t_{50} (min) ± SD	Response time t_{85} (min) ± SD	Floating Lag Time (sec) ± SD	Total Weight of Tablet (mg)	Floating Time (hours)	Tablet Integrity
	X_1	X_2						
F1	-1	-1	526.6±5.21	1196.2±11.60	14±0.60	531	24	+
F2	-1	0	501.2±10.71	1138.6±24.53	9.73±0.46	536	24	+
F3	-1	+1	450.4±20.05	1023.1±6.69	7.40±0.43	541	24	+
F4	0	-1	594.5±8.26	1350.6±19.00	24.67±0.50	561	24	+
F5	0	0	545.5±6.86	1239.4±15.04	18.7±0.55	566	24	+
F6	0	+1	509.0±3.18	1156.3±28.79	16.22±0.90	571	24	+
F7	+1	-1	627.9±10.21	1426.4±23.19	32.71±1.01	591	24	+
F8	+1	0	571.6±5.47	1298.5±12.37	21.15±0.75	596	24	+
F9	+1	+1	535.4±5.05	1216.3±11.44	14.62±0.59	601	24	+

*All batches contained 250mg of Clarithromycin, 18% of sodium bicarbonate, 12% PVPK30, 1% of Magnesium stearate, X_1 and X_2 are the percentage of HPMCK4M and citric acid, respectively.

Table 3. Analysis of Variance

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	P Value	Model Significant/Nonsignificant Relative to Noise
For t_{50}						
Model	22239.51	5	4447.90	86.47	0.0004	Significant
X_1	10982.48	1	10982.48	213.51	0.0001	Significant
X_2	10769.61	1	10769.61	209.37	0.0001	Significant
Residual	205.75	4	51.43	-	-	-
Core Total	22445.26	9	-	-	-	-
For t_{85}						
Model	114532.2	5	22906.45	77.91	0.0004	Significant
X_1	56706.48	1	56706.48	192.88	0.0002	Significant
X_2	55584.38	1	55584.38	189.07	0.0002	Significant
Residual	1175.93	4	293.98		-	-
Core Total	115708.2	9	-	-	-	-
For FLT						
Model	478.44	5	95.68	46.53	0.0012	Significant
X_1	226.32	1	226.32	110.07	0.0005	Significant
X_2	181.39	1	181.39	88.22	0.0007	Significant
Residual	8.22	4	2.05	-	-	-
Core Total	486.66	9	-	-	-	-

Table 4.Properties of compressed Clarithromycin floating tablets

Formulation Code	Weight (mg)±SD(n=20)	Hardness kg/cm^2±SD (n=5)	Thickness (mm)±SD(n=5)	Friability	Drug Content (%)±SD(n=3)
F1	530.4(1.4)	6.9(0.21)	3.26(0.04)	0.33	99.60(1.19)
F2	535.7(1.3)	7.2(0.35)	3.28(0.02)	0.40	98.37(0.95)
F3	542.1(1.7)	7.5(0.69)	3.30(0.01)	0.18	101.80(1.13)
F4	562.3(1.2)	7.4(0.40)	3.32(0.02)	0.13	99.50(0.86)
F5	566.5(1.3)	7.7(0.37)	3.34(0.06)	0.22	99.90(1.12)
F6	573.2(1.1)	7.9(0.27)	3.36(0.04)	0.31	102.70(1.10)
F7	590.4(1.5)	7.8(0.59)	3.40(0.03)	0.18	103.20(1.23)
F8	596.4(1.5)	7.9(0.35)	3.42(0.08)	0.27	97.30(0.90)
F9	600.8(1.2)	8.1(0.40)	3.44(0.03)	0.21	98.50(0.78)

Table 5.Model Fitting Data of Floating Controlled Release Tablets of Clarithromycin

Sr.no	Formulation	Models	r	n	K
1	F1	Zero Order	0.9798	0.570	1.3150
		First Order	0.9751		
		Matrix	0.9805		
		Korsemeyer Peppas	0.9822		
		Hixon Crowell	0.9943		
2	F2	Zero Order	0.9762	0.569	1.3690
		First Order	0.9691		
		Matrix	0.9839		
		Korsemeyer Peppas	0.9850		
		Hixon Crowell	0.9936		
3	F3	Zero Order	0.9704	0.559	1.5395
		First Order	0.9392		
		Matrix	0.9858		
		Korsemeyer Peppas	0.9825		
		Hixon Crowell	0.9884		
4	F4	Zero Order	0.9849	0.596	1.0207
		First Order	0.9836		
		Matrix	0.9697		
		Korsemeyer Peppas	0.9828		
		Hixon Crowell	0.9939		
5	F5	Zero Order	0.9857	0.628	0.8637
		First Order	0.9784		
		Matrix	0.9684		
		Korsemeyer Peppas	0.9851		
		Hixon Crowell	0.9919		
6	F6	Zero Order	0.9714	0.574	1.3509
		First Order	0.9784		
		Matrix	0.9860		
		Korsemeyer Peppas	0.9935		
		Hixon Crowell	0.9936		
7	F7	Zero Order	0.9874	0.631	0.7695
		First Order	0.9863		
		Matrix	0.9625		
		Korsemeyer Peppas	0.9799		
		Hixon Crowell	0.9937		
8	F8	Zero Order	0.9872	0.627	0.8378
		First Order	0.9819		
		Matrix	0.9650		
		Korsemeyer Peppas	0.9827		
		Hixon Crowell	0.9932		
9	F9	Zero Order	0.9824	0.613	0.9861
		First Order	0.9825		
		Matrix	0.9767		
		Korsemeyer Peppas	0.9880		
		Hixon Crowell	0.9956		

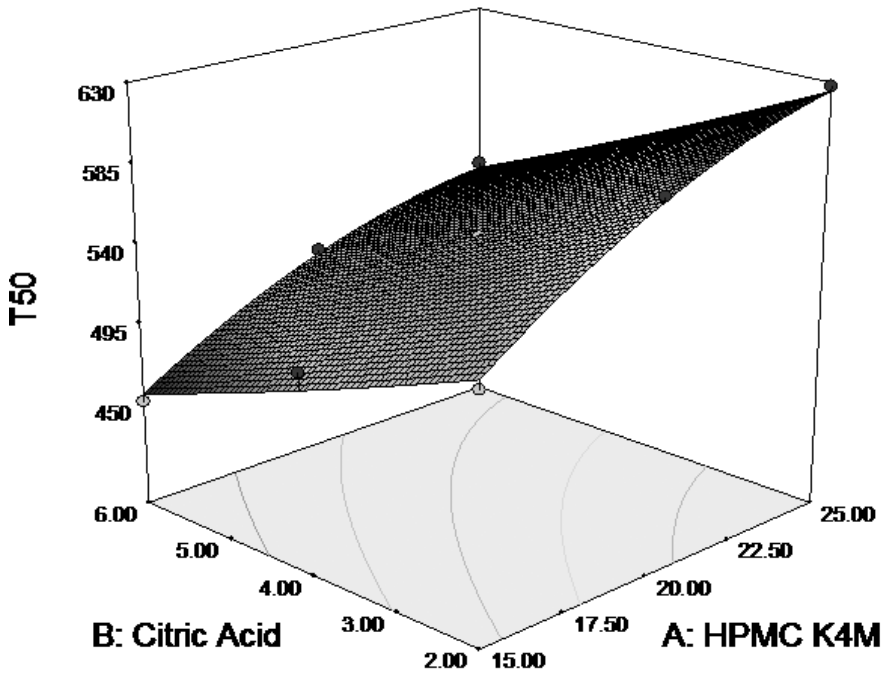

Fig.1.Response Surface Plot of t50

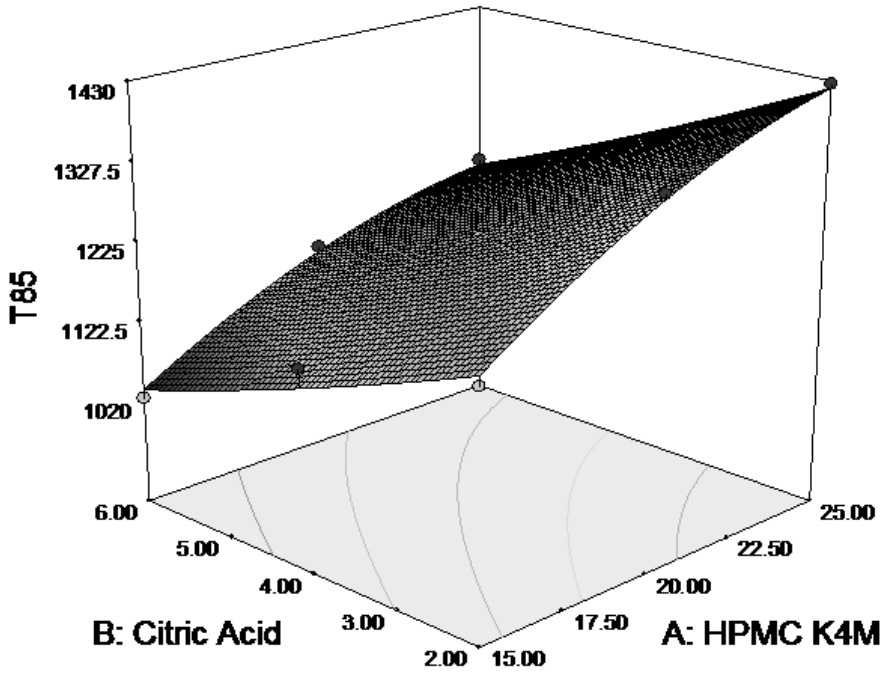

Fig.2.Response Surface Plot of t_{85}

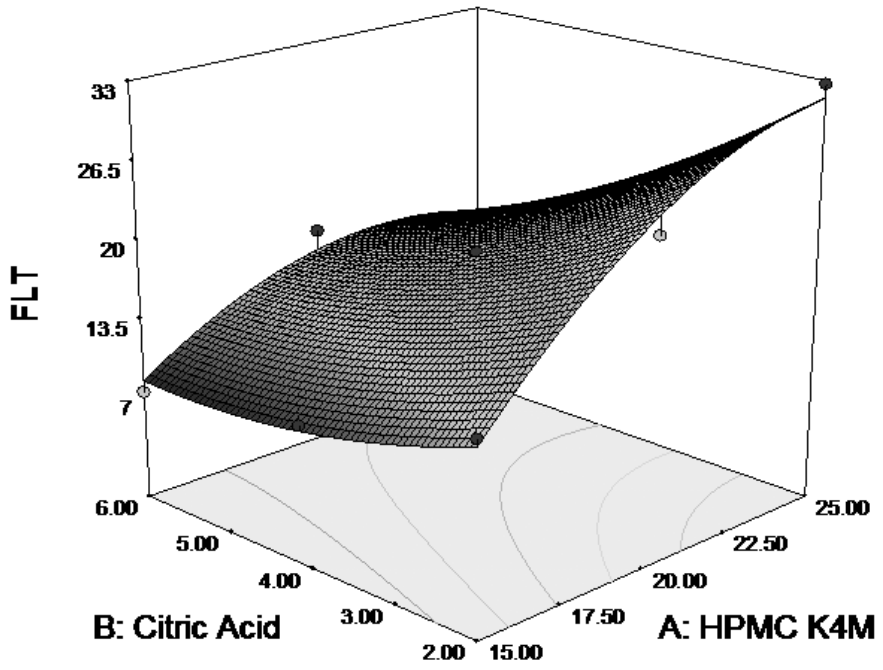

Fig.3 Response Surface Plot of FLT (Floating Lag Time)

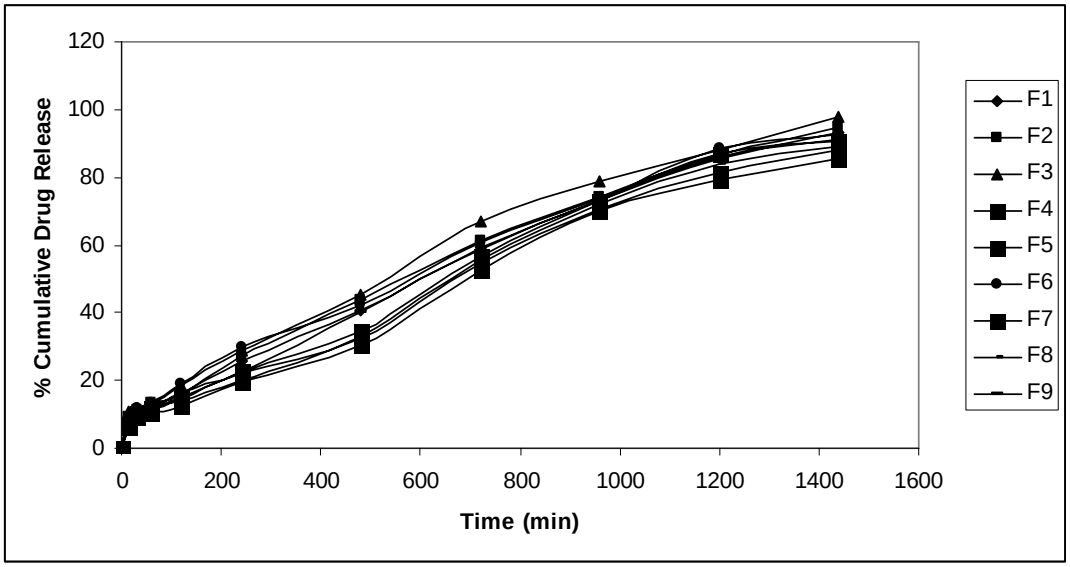

Fig4. Release Profile of Clarithromycin from 3^2 Factorial Design Batches

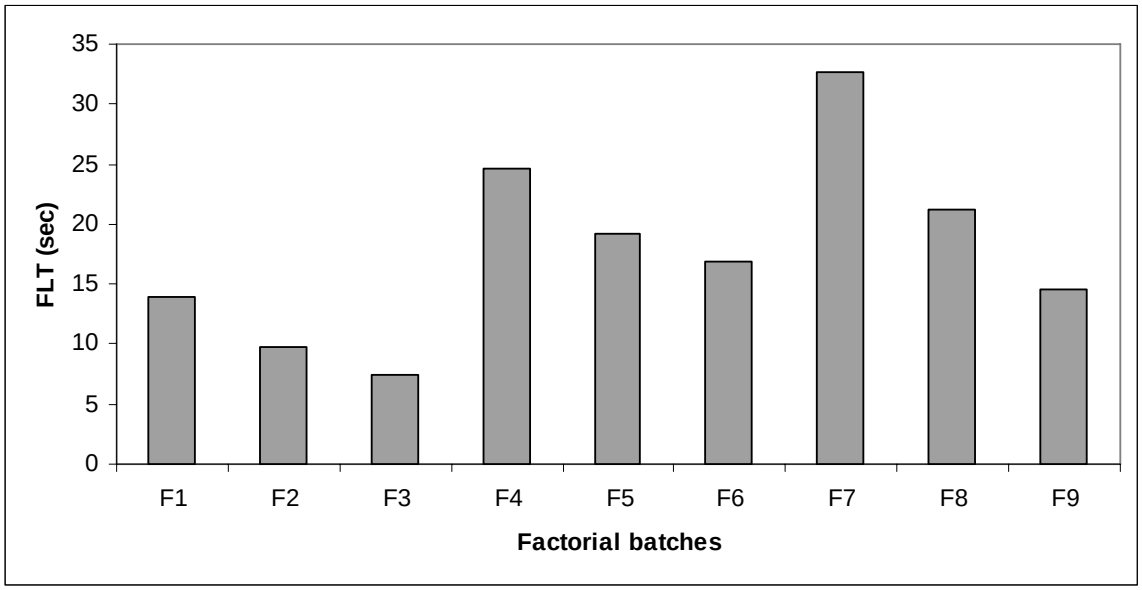

Fig 5.Floating Lag Time of 3^2Factorial Design Batches

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