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Development of Gastro Retentive Drug Delivery System of Cephalexin by using Factorial Design

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ABSTRACT

The objective of this research work was to formulate and optimize the floating drug delivery system containing cephalexin using 2^3 factorial design. Floating tablets were prepared by direct compression method incorporating HPMC K4M, xanthan gum, guar gum, sodium bicarbonate and tartaric acid as gas generating agent. The influence of independent variables like, polymer: polymer ratio, polymer type and tartaric acid on floating lag time and cephalexin release profile were studied. The diffusion exponent (n) of Krosmeyer Peppas for optimized formulation was found to be 0.635 which indicates the mechanism of drug release was anomalous transport. Floating lag time of optimized formulation was 1.50 min and remained buoyant for 24 hrs. Optimized formulation was checked for stability at 40ºC / 75% RH which was found to be stable. Scanning electron microscopy study revealed gel formation. FT-IR studies revealed that there was no chemical interaction between cephalexin and other excipients.

KEYWORDS: Floating drug delivery systems (FDDS), 2^3 factorial design, cephalexin (CFL), Fourier Transform Infrared Spectroscopy (FT-IR) and Scanning electron microscopy (SEM).

INTRODUCTION

The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems[1]. Prolonging the gastric residence of a dosage form may be of therapeutic value. Amongst the methods available to achieve this, floating dosage forms show considerable promise[2].

The basic idea behind the development of such a system is to maintain a constant level of drug in the blood plasma in spite of the fact that the drug does not undergo disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood[3].

Several approaches are used for the formulation of gastroretentive systems such as mucoadhesion[4, 5], flotation[6], sedimentation[7, 8], expansion[9, 10] and modified shape systems[11, 12]. Both single-unit systems (tablets or capsules) and multiple-unit systems (multiparticulate systems) have been reported in the literature[13]. Among these, FDDS offer the most effective and rational protection against early and random gastric emptying compared to the other methods proposed for prolonging the gastric residence time (GRT) of solid dosage forms[14].

Extended-release dosage forms with prolonged residence time in the stomach are also highly desirable

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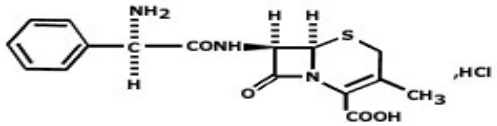
for drugs that are locally active in the stomach and those are unstable in the intestinal or colonic environment or which have low solubility at higher pH values[15]. FDDS has a lower density than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time[16].

Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. Effervescent floating dosage forms prepared with the help of swellable polymers such as methylcellulose and various effervescent compounds such as sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms[17].

The objective of present work was to develop gastro retentive formulation, which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract[18].

Cephalexin (CFL) is chemically 7-[(amino-phenyl acetyl) amino]-3-methyl-8- oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, belongs to the first generation cephalosporins, intended for oral administration. With the brand names of Ceporex (or Keflex) in the US, Novolexin in Canada, and many others outside North America, cephalexin is one of the top 20 drugs used in prescriptions worldwide. The first-generation cephalosporins have the highest activity against gram-positive and gram-negative bacterias.[19, 20]

Figure 1: Structure of Cephalexin



Mechanism of action of CFL is same as that of beta-lactam antibiotics (such as penicillins). It acts by binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall and inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that it interferes with an autolysin inhibitor[21]. CFL inhibits mucopeptide synthesis in bacterial cell wall, causing cell death[22].

Oral therapy with CFL results in peak concentration in plasma of 16 µg/ml after a dose of 0.5 gm, this is adequate for the inhibition of many gm + ve and gm – ve pathogens. It is well absorbed from the GI tract. The drug is not metabolized and 70-100% is excreted in the urine[23].

CFL is chosen as the model drug in this study because it has a very short half life 0.9 ± 0.18 hour and peak concentration of 28±6.4 mg/ml.[3] And also degrading rapidly in basic media and remaining stable under mild acidic conditions makes CFL as suitable candidate for formulation into floating dosage form in order to prolong the GRT. No loss in its activity occurred in 72 hours at 25^0 C in the pH range of 3 to 5. The rate of degradation found at pH 6-7 (25^0C) was approximately 3% and 18% per day, respectively. In U.S.P hydrochloric acid buffer (pH 1.2), CFL lost 5% activity in 24 hours at 37^0 C as compared to 45% loss in phosphate buffer at pH 6.5 [24].

1. Materials and Methods

1.1 Materials

Cephalexin was obtained as a gift sample from Karnataka antibiotics and pharmaceuticals limited (KAPL), Bangalore, India. Polymers like HPMCK4M, xanthan gum, guar gum, tartaric acid were obtained as gift samples from Karnataka antibiotics and pharmaceuticals limited, Bangalore. All other chemicals used in the study were of analytical grade.

1.2 Experimental design

Factorial design is an experimental design technique, from which the factor involved and its relative importance can be assessed. In the present study a 2^3 factorial design was employed, containing 3 factors evaluated at 2 levels (Table 1). The experimental trials were performed at all 8 possible combinations and the three independent formulation variables evaluated were:

A = Polymer: polymer ratio

B = Polymer type (xanthan gum/guar gum)

C = Tartaric acid

The response variables tested were:

R1 = Floating lag time

R2 = First hour drug release

R3 = % Drug release at 12hr and

R4 = Diffusion exponent (n)

Table 1: Level of formulation variables

Coded values	Independent variables		
	Polymer: Polymer ratio (A) HPMC K4M: xanthan/guar gum	Polymer type (B)	Tartaric acid (C)
1	4:1	Xanthan gum	20
-1	1:1	Guar gum	0

*HPMC indicates hydroxyl propyl methyl cellulose

1.3 Preparation of floating tablet:

Floating tablets of CFL were prepared using HPMC K4M as swellable polymer, natural gums like xanthan gum/guar gum, sodium bicarbonate ($NaHCO_3$) and tartaric acid as gas generating agent and dicalcium phosphate (DCP) as diluent, magnesium stearate as lubricant and talc as glidant.

The drug and excipients were passed through sieve no. 44 (mesh aperture size 355 ± 13µm) prior to the preparation of the dosage form .The entire ingredients were weighed separately and mixed thoroughly for 10 minutes to ensure uniform mixing in geometrical ratio. The tablets were prepared by direct compression technique using 13 mm punch in 16-station rotary machine; Elit Jemkay engineers Pvt Ltd, Ahmedabad.

1.4 Sample Analysis:

CFL was analyzed by ultraviolet (UV) spectrophotometric method at λ_{max} 263 nm. The content of CFL in the formulation analyzed by dissolving in distilled water and was suitably diluted to give final concentrations of 5 to 50 µg/ml. The absorbance of sample was measured at 263 nm against distilled water as a blank.[25]

2 EVALUATION PARAMETERS

2.1 Flow properties

The tablet blend were evaluated for their bulk density, tapped density, compressibility index and flow properties. The tapping method was used to determine the bulk density, tapped density and percent compressibility index.

Compressibility index = $[\rho_t - \rho_b / \rho_t] \times 100$

Where ρ_t = tapped density

ρ_b = initial bulk density of tablet blend.

Angle of repose θ of the tablet blend measures the resistance to particle flow and was determined by fixed funnel method.

2.2 Thickness and diameter:

Control of physical dimensions of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured in mm using Vernier Calipers.

2.3 Hardness:

The Monsanto hardness tester was used to determine the tablet hardness .The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet which was expressed in kg/cm^2.

2.4 Friability:

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets. The % friability was then calculated by: -

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

2.5 Weight variation:

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. IP limit for weight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

$$PD = (W_{avg}) - (W_{initial}) / (W_{avg}) \times 100$$

Where PD= Percentage deviation,

W_{avg} =Average weight of tablet,

$W_{initial}$ =Individual weight of tablet.

2.6 *In vitro* buoyancy study:

The *in vitro* buoyancy was characterized by floating lag time and floating duration. The test was performed using USP type II paddle type apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37 ± 0.5^0. The floating lag time (time period between placing the tablet in the dissolution medium and tablet floating) and floating duration of the tablets were determined by visual observation.

2.7 *In vitro* release testing:

In vitro drug release of the formulation was carried out by USP type II basket type apparatus with rotating speed of 50 rpm and at temperature of 37 ± 0.5^0 C. The dissolution medium used was 0.1N HCl (pH 1.2). The samples were withdrawn at predetermined time intervals for period of 12 hrs and replaced with the fresh medium, suitably diluted and were analyzed using UV/Visible spectrophotometer (Shimadzu Corporation, UV-1601, Japan). The test was performed in triplicate.

2.8 Statistical analysis:

The effect of formulation variables on the response variables were statically evaluated by applying one-way ANOVA at 0.05 level, using the commercially available software package Design-Expert®, version 7.1.5 (Stat- Ease, Inc.). The design was evaluated using a linear model, which bears following equation.

$R = b_0 + b_1 A + b_2 B + b_3 C$

Where R is the response variable, b_0 the constant and b_1, b_2, b_3 is the regression coefficient. A, B and C represent the main effect

2.9 Fourier Transform Infrared Spectroscopy:

IR spectroscopy was carried out for the following a) pure drug CFL, b) CFL with HPMC K4M, c) CFL with xanthan gum, d) CFL with $NaHCO_3$, e) CFL with tartaric acid, f) CFL with DCP, g) CFL with talc and h) CFL with magnesium stearate using Shimadzu FTIR model 8300 by taking KBr disc.

2.10 Scanning electron microscopy (SEM):

The surface morphology of tablet membrane film of optimized formulation was examined before and after dissolution using scanning electron microscope. The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were taken at excitation voltage of 20 KV. JSM-840A scanning Microscope; Jeol-Japan with JFC-1100E ion sputtering device was used.

2.11 Stability Studies

Accelerated stability studies were carried out as per ICH guidelines. The tablets were stored at different storage conditions at elevated temperature 40^0C/±/2^0C/75%± /5% RH for 6 months. The samples were withdrawn at monthly intervals and checked for physical appearance, drug content, floating properties and *in vitro* drug release studies.

3 RESULTS AND DISCUSSION

3.1 Design of experiment Formulation development:

The formulations were designed using 2^3 level Factorial design, the materials and compositions used

are presented in (Table 2). In this study, the effect of formulation variables- polymer: polymer ratio, polymer type and tartaric acid were chosen as independent variables. The dependent (response) variables included were floating lag time, first hour drug release, % drug release at 12 hr and diffusion exponent (n) (Table 3). For the generation of factorial models, only coefficients found to be significant ($p<0.05$) were used.

Table 2: Material and Composition of floating tablets

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8
cephalexin	250	250	250	250	250	250	250	250
HPMC K4M	125	200	200	200	125	125	200	125
Xanthan gum	125	50	50	-	-	-	-	125
Guar gum	-	-	-	50	125	125	50	-
Tartaric acid	0	0	20	0	20	0	20	20

Note: All the quantities are expressed in terms of milligrams. Each formulation contains 40 mg of sodium bicarbonate, 1% of magnesium stearate, 1% of talc and quantity sufficient to 600 mg of di-calcium phosphate.

Table 3: 2^3 factorial design with corresponding responses for floating lag time, dissolution characteristics and diffusion exponent.

Formulation code	R1 Floating lag time (min)	R2 First hour drug release (%)	R3 % drug release at 12 hour	R4 Diffusion exponent (n)
F1	7	18.22	91.71	0.62
F2	5.12	19.6	93.75	0.6
F3	2.62	18.4	96.75	0.64
F4	22	15.98	82.6	0.65
F5	55	13.88	83.31	0.68
F6	56	14.46	80.7	0.69
F7	20	16.28	84.68	0.63
F8	6.2	17.61	91.85	0.63

3.2 Flow property:

The bulk density of the powder formulation was in the range of 0.27-0.34 gm/cc; the tapped density was in the range of 0.34-0.41 gm/cc, which indicates that the powder was not bulky. The angle of repose of the drug powder was in the range of 33.2^0-38.9^0, which indicate satisfactory flow of the powder, the Carr's index was found to be in the range of 16-20, indicating compressibility of the tablet blend is fairly passable (Table 4).

Table 4: Data for blend evaluation

Formulation code	Evaluation parameters			
	Bulk density	Tapped density	Angle of	Carr's Index
F1	0.345	0.416	36.8	17.06
F2	0.3106	0.3803	37.4	18.32
F3	0.3064	0.3698	33.9	17.14
F4	0.302	0.3684	35.7	18.02
F5	0.2756	0.3408	36.4	19.13
F6	0.3117	0.3887	38.9	19.80
F7	0.3219	0.3909	35.4	17.65
F8	0.3255	0.4012	34.6	18.86

3.3 Tablet thickness and diameter:

The thickness of the tablet indicates that die fill was uniform. It depends upon the size of the punch (13 mm) and the weight of the tablet (600 mg). The thickness of the tablet was found to be 3.8-3.9 mm with diameter of 13± 0.1 mm.

3.4 Hardness: Hardness was found to be 3.3-4.5 kg/cm^2 which have good mechanical strength.

3.5 Friability: friability was found to be within the limits and was reported to be 0.5%.

3.6 Weight variation: The average percentage deviation of 20 tablets of each formula was less than ± 5 %, which provided good uniformity. (Table 5)

Table 5: Data for tablet evaluation

Formulation code	Evaluation parameters			
	Thickness ±S.D. (mm)	Hardness± S.D.(kg/cm^2)	Friability (%)	Average weight variation
F1	3.85 ± 0.043	3.5 ± 0.4	0.321	0.603 ± 0.011
F2	3.7 ± 0.055	4.16 ± 0.2	0.233	0.600 ± 0.009
F3	3.78 ± 0.085	4.23± 0.2	0.199	0.602 ± 0.010
F4	3.75 ± 0.067	4.23± 0.1	0.352	0.601 ± 0.135
F5	3.82 ± 0.054	3.93 ± 0.6	0.452	0.602 ± 0.008
F6	3.79 ± 0.048	4.4 ± 0.3	0.244	0.601 ± 0.010
F7	3.85 ± 0.028	3.6 ± 0.2	0.498	0.602 ± 0.008
F8	3.88 ± 0.039	3.3 ± 0.3	0.545	0.599 ± 0.008

3.7 Optimization results: Optimized formula

Optimized formula is drug 250 mg, HPMC K4M 200 mg, Xanthan gum 50 mg, Tartaric acid 19.68 mg, Sodium bicarbonate 40 mg, DCP 28.32 mg, Magnesium stearate 1% and talc 1%. A numerical optimization technique by the desirability (0.9) approach was used to generate the optimum setting for the formulation. The optimized formulation was prepared and evaluated for the various responses. And the analysis of variance (ANOVA) information is shown in (Table 6). *In vitro* release profile was compared with USP limits as shown in the (Table 7).

Table.6 Analysis of Variance for Dependent Variables from Factorial Design*

Source	Sum of Squares	df	Mean square	F value	Probability
Floating lag time			**R^2= 0.8506**		
Model	2877.98	3	959.33	7.59	0.0397
A-A	693.04	1	693.04	5.48	0.0793
B-B	2179.98	1	2179.98	17.24	0.0142
C-C	4.96	1	4.96	0.039	0.8526
Residual	505.65	4	126.41		
Cor Total	3383.63	7			
First hour drug release			**R^2=0.9659**		
Model	27.06	3	9.02	37.74	0.0022
A-A	4.64	1	4.64	19.40	0.0117
B-B	21.88	1	21.88	91.54	0.0007
C-C	0.55	1	0.55	2.28	0.2052
Residual	0.96	4	0.24		
Cor Total	28.02	7			
% drug release at 12hr			**R^2=0.9838**		
Model	249.35	3	83.12	81.11	0.0005
A-A	13.03	1	13.03	12.72	0.0235
B-B	228.66	1	228.66	7.48	0.0001
C-C	7.66	1	7.66	223.13	0.0522
Residual	4.10	4	1.02		
Cor Total	253.45	7			
Diffusion exponent (n)			**R^2=0.7087**		
Model	4.500E-003	3	1.500E-003	3.24	0.1427
A-A	1.250E-003	1	1.250E-003	2.70	0.1755

B-B	3.200E-003	1	3.200E-003	6.92	0.0582
C-C	6.350E-003	1	5.000E-005	0.11	0.7588
Residual	1.850E-003	4	4.625E-004		
Cor Total	5.000E-005	7			

*Probability less than 0.05 indicate model terms are significant.

Table 7: Comparison of release profile of controlled release tablets labeled for dosing every 12 hours with optimized formulation:

Time (hours)	Amount dissolved (USP	Release profile of
1	5 - 15	15.35
2	12 - 30	27.85
4	25 – 50	44.79
8	55 - 75	67.12
12	90 -100	97.14

3.7.1 Floating lag time (R1)

Among all the formulations, F2 and F3 formulations showed good floating properties with floating lag time of 5.12 min and 2.62 min respectively. This might be due to the presence of swellable polymer HPMC K4M and xanthan gum in 4:1 ratio and also due to the presence of gas generating agent. The gelling capacity of polymers also helps to float tablet by entrapping carbon dioxide gas. However the floating lag time of F5 and F6 formulation were found to be more (55 min) which might be due to the low levels of HPMC K4M and highly viscous guar gum. The floating lag time of optimized formulation was found to be 1.50 min and remained buoyant for 24hrs.

$$R1= 38.04250-6.20500*A-16.50750*B-0.078750*C$$

The linear model for R1 (floating lag time) found to be significant with F-value of 7.59 and P value 0.0397. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case, B is significant model term with P value of 0.0142. The factors A, B and C have an antagonistic effect on floating lag time. The effect of polymer: polymer ratio and polymer type on the floating lag time was found to be significant. Figure 5 represents the observed response values compared to that of predicted values. The effect of factors A, B and C can be further elucidated with the help of response surface plot (Figure 6). As the amount of HPMC K4M increased the floating lag time is decreased and it is lower in case of tablets prepared from xanthan gum than those prepared from guar gum. Results indicate that xanthan gum is superior to guar gum.

Table 8: Comparison of experimented and predicted values of optimized formulation

Optimized formulation	Dependable variables			
	Floating lag time R1	First hour drug release R2	% drug release at 12hr R3	Diffusion exponent R4
Pred.	2.6 min	18.5%	96.7%	0.630
Exp.	1.50 min	15.35%	97.14%	0.635

3.7.2 First hour drug release R2:

$$R2= +15.79625+0.50750*A+1.65375*B-0.026125*C$$

When the HPMC K4M content is more, as the factor A increases from 1:1 to 4:1 the first hour drug release increases which is desirable for an extended release formulation. In case of factor B (polymer type) xanthan gum shows synergistic effect than guargum.

The linear model for R2 (first hour release) found to be significant with F-value of 37.74 and P value 0.0022. In this case, A and B are significant model terms with P value of 0.0117and 0.0007 respectively. The effect of factors A, B and C can be further elucidated with the help of response surface plot (Figure 7). In case of figure 7(a) high level of factor B (xanthan gum) gave high value of R2 at all levels of factor A and in case of figure 7(b) high level of factor A gave high value of R2 at all the levels of factor C which indicates that the factor A, polymer: polymer ratio and factor B (xanthan gum) have significant positive effect on first hour drug release.

Figure 2: Dissolution profiles of the formulations

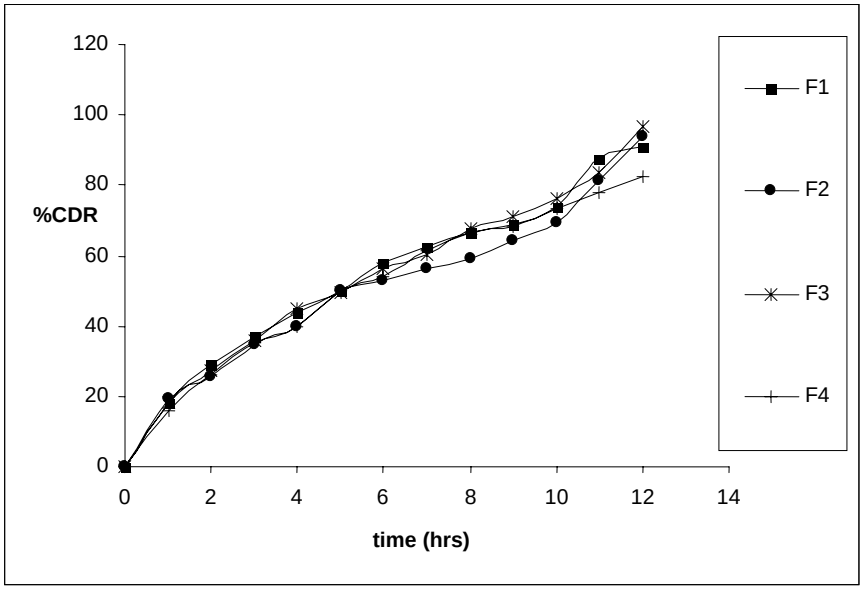
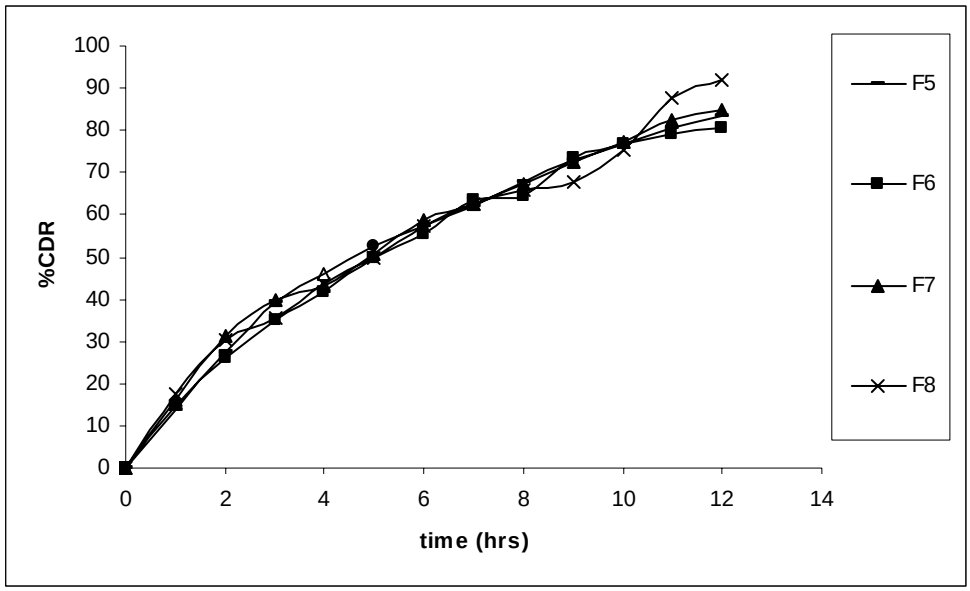


Figure 3: Dissolution profiles of the formulations



3.7.3 % drug release at 12 hr R3:

In this case, when the levels of all the 3 factors increases the percentage of durg release also increases i.e., the polymer:polymer ratio of 4:1, polymer type (xanthan gum) and high level of tartaric acid shows complete release of drug. The drug release profiles of all the formulations are given in the figure 2 and 3.

$$R3= +85.06292+0.85083* A+5.34625* B+0.097875* C$$

The linear model for R3 (% drug release at 12 hr) found to be significant with F-value of 81.11 and P value 0.0022. In this case A, B are significant model terms with P value of 0.0235 and 0.0001 respectively. Figure 8 represents the observed response values compared to that of predicted values. The effect of factors A, B and C can be further elucidated with the help of response surface plot (Figure 9). The high level of factor B gave high value of R3 at all the levels of factor A where in case of figure 9(b), high level of factor B gave high value of R3 at all the levels of factor C which indicates that the factors A and B have significant positive effect on 12 hr drug release. Similar effect was observed in case R2. The factor B showed higher value indicating xanthan gum releases the drug at faster rate than guar gum.

3.7.4 Diffusion exponent (n) R4:

$$R4= +0.66083-8.33333E-003 * A-0.020000* B+2.50000E-004* C$$

The "Model F-value" of 3.24 implies the model is not significant. Data was analyzed by Krosmeyer Peppas plot. The ‘n’ value of optimized formulation was found to be 0.635 which was in the range of $0.45<n<0.89$ and K value 18.17. The diffusion exponent values indicate that the drug release follows non fickian transport.

3.8 FT-IR spectroscopy

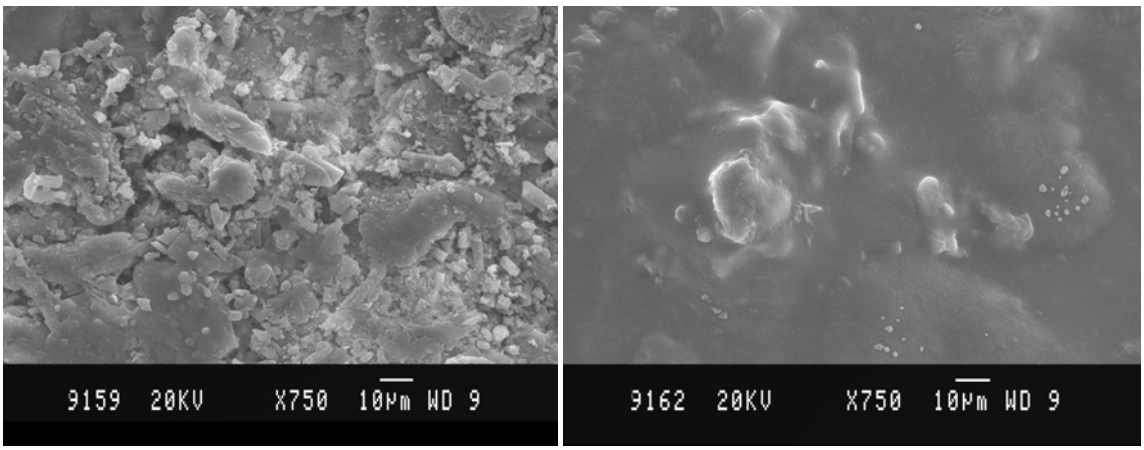
The FT-IR studies revealed that CFL is compatible with the excipients used in the formulation. There were no extra peaks observed in the IR spectrum. The IR absorption band in cm^{-1} of the drug and excipients was found to be similar. This established that the drug CFL and all the excipients used in the study showed no interaction and indicated that they were compatible with each other (Table 9).

Table 9: FTIR studies of Cephalexin alone and with excipients

FUNCTIONAL	α- NH_2	β – lactam	Amide	-COOH	-COOH
Standard CFL	2612.4	1759.9	1689.5	1592.1	1398.3
CFL +HPMC K4M	2616	1758	1689.5	1594	1398.3
CFL +Xanthan gum	2613	1759	1689.5	1596	1399.3
CFL + $NaHCO_3$	2609.5	1759.9	1689.5	1596	1398.3
CFL + Tartaric acid	2613.4	1760.9	1689.5	1592.1	1397.3
CFL + DCP	2610	1758	1689.5	1594	1395.4
CFL + Talc	2612.4	1759.9	1689.5	1592.1	1397.3
CFL +Magnesium stearate	2612	1757	1689.5	1595	1399.3

3.9 Scanning Electron Microscopy: SEM of the optimized formulation showed a well-uniformed gel structure which might be due to polymer relaxation upon absorption of water (Figure 4).

Figure 4: Scanning electron microphotographs of optimized formulation: (A) –tablet at dry state, (B) – tablet after 8 hr swelling.



(A) **(B)**

3.10 Stability Studies: Stability studies were carried out as per ICH guidelines. The optimized formulation was found to be stable in terms of physical appearance, drug content, floating properties and *in vitro* drug release.

Figure 5: correlation between actual and predicted values for floating lag time (R1)
R1= FLOATING LAG TIME

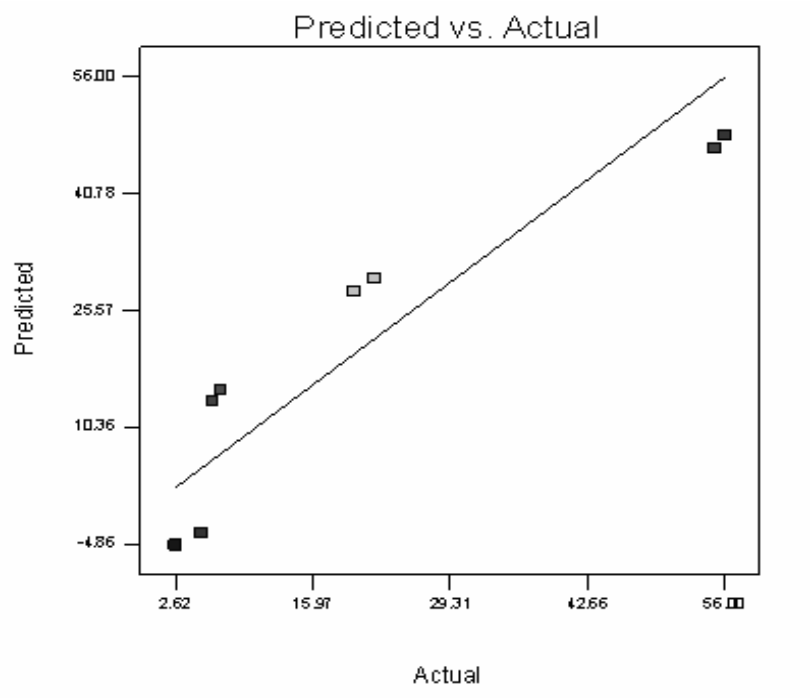
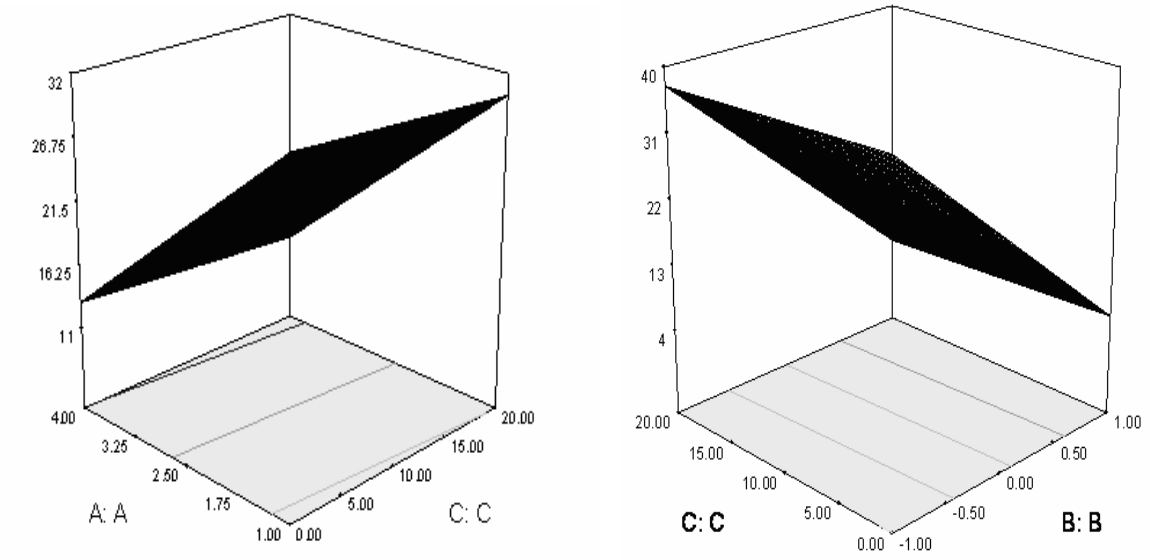


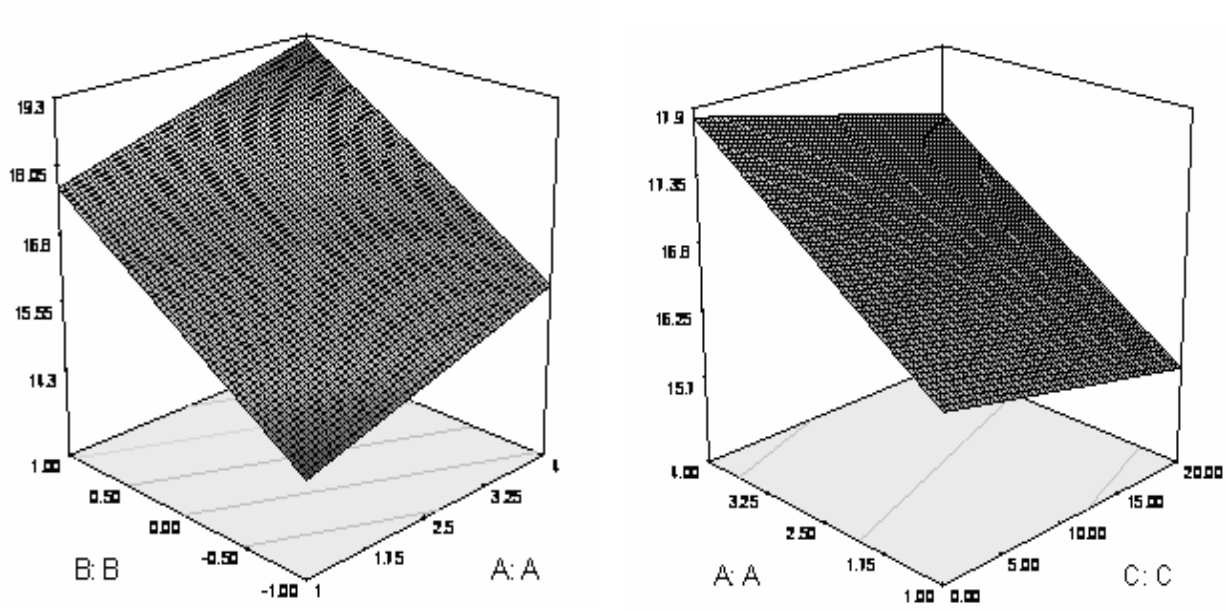
Figure 6: Response surface plots showing the effect of polymers and tartaric acid on floating lag time R2= FIRST HOUR DRUG RELEASE



(a) (b)

Figure 7: Response surface plots showing the effect of polymers and tartaric acid on first hour drug release.

R3= % DRUG RELEASE AT 12 HOUR



(a) (b)

Figure 8: correlation between actual and predicted values for % drug release at 12 hour (R3)

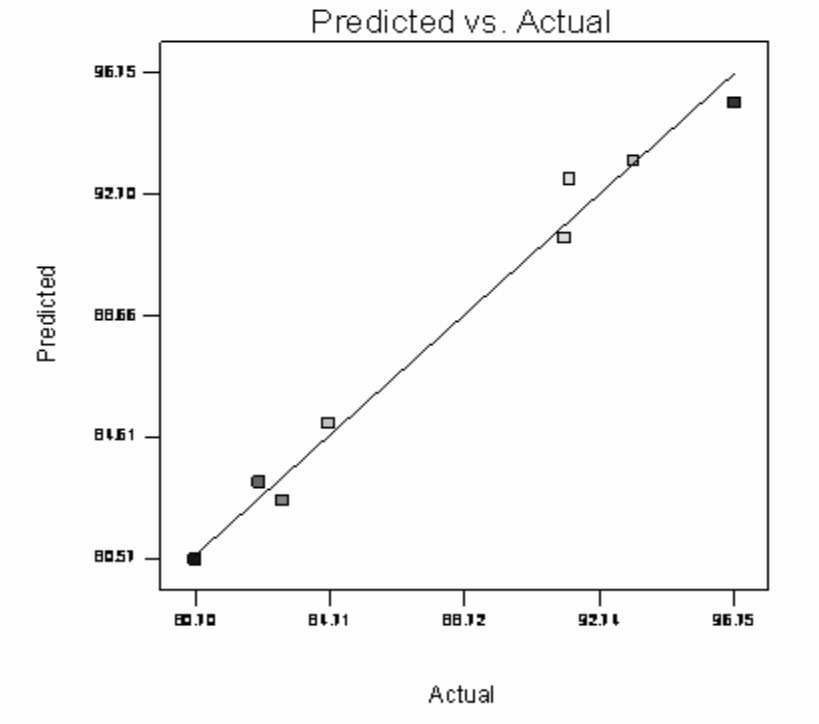
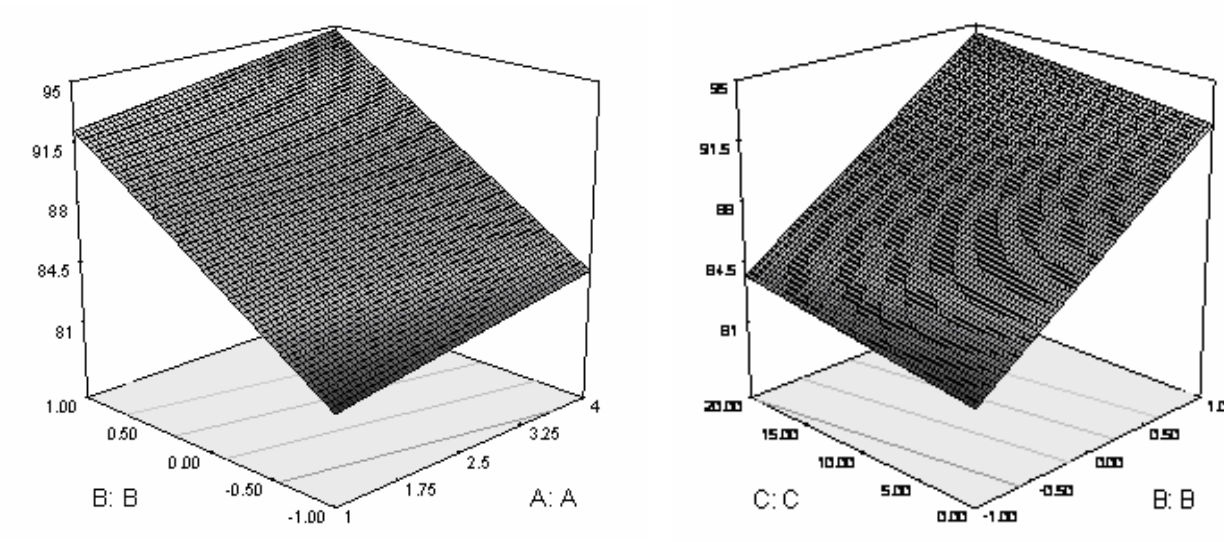


Figure 9: Response surface plots showing the effect of polymers and tartaric acid on % drug release at 12 hour.



(a) (b)

4. CONCLUSION

Gastro-retentive drug delivery system was successfully prepared by using factorial design. It was found that sodium bicarbonate and tartaric acid have predominant effect on the floating lag time and is decreased with the increase in the ratio of HPMC K4M and xanthan gum and also xanthan gum showed increased drug release where as guar gum has retardant effect.

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