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FORMULATION AND EVALUATION GSTRORETENTIVE STUDIES OF CEFDINIR FLOATING TABLET USING FACTORIAL DESIGN

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ABSTRACT

This study aimed to develop controlled release gastroretentive drug delivery system of Cefdinir and conducting its *in vitro* evaluations. Effervescent floating gastroretentive drug delivery system of Cefdinir was prepared utilizing Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA) statistical design with 3 factors, 2 levels and 15 experimental trials. Formulation optimization was done by setting targets on selected responses. Optimized formulation showed satisfactory controlled *in vitro* drug release for more than 12 h with excellent buoyancy properties (floating lag time <1 min, floating duration >12 h). The statistically optimized formulation released drug according to zero order kinetics with a non-fickian diffusion mechanism. Better therapeutic effect can be expected since Cefdinir exhibits concentration dependent killing. Hence, gastro retention can be a promising approach to enhance bioavailability of Cefdinir with narrow absorption window in upper GIT.

Key Words:- Cefdinir, Floating tablets, Gastroretentive, Bioavailability, Optimization.

INTRODUCTION

Oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake. However, oral administration has only limited use for important drugs, from various pharmacological categories, that have poor oral bioavailability due to incomplete absorption and/or degradation in the gastrointestinal (GI) tract. Some of these drugs are characterized by a narrow absorption window (NAW) at the upper part of the gastrointestinal tract. This is because of proximal part of the small intestine exhibits extended absorption properties (including larger gaps between the tight junctions, and dense active transporters). Despite the extensive absorption properties of the duodenum and jejunum, the extent of absorption at these sites is limited because the passage through this region is rapid. Enhancing the gastric residence time (GRT) of a NAW the drug may significantly improve the net extent of its absorption (Alexander *et al*., 2006).

Floating drug delivery systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. .

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain

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buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

Cefdinir is an expanded-spectrum, oral, third-generation cephlosporin antimicrobial agent active against Gram-positive and Gram-negative bacteria (Pooja Mathur *et al*., 2010; Desai *et al*., 1993). It is used in the treatment of acute chronic bronchitis, rhinosinusitis, and pharyngitis and uncomplicated skin and skin-structure infections in adults and adolescents; it is indicated for acute otitis media, acute sinusitis, and community-acquired pneumonia (Wilson *et al*., 2001; Rubinstein *et al*., 1988). Cefdinir requires controlled release because of its short biological half-life of ~1.5 h (Shaha SH *et al*., 2009).

MATERIALS AND METHODS

Cefdinir was a gift sample from (Aurobindo Pharmaceuticals Limited, Hyderabad, India). HPMC K4 and HPMC K100 were obtained from Hetro Pharmaceuticals, Hyderabad, India). Gum Karaya obtained from local market. Sodium bicarbonate, Citric acid, Magnesium stearate was procured from Loba chemie Private Ltd. All other chemicals and reagents were analytical grade and used as received.

Experimental Design

2^3 (three factor and two level) factorial design was employed for optimization of the floating tablets containing Cefdinir. Amount of HPMCK100 (X1, mg), Surelease (X2, mg) and Gum Karaya (X3, mg) were selected as independent variables, which were varied at two levels (low and high). The cumulative drug release after 8h (R8h, %) in simulated gastric fluid, pH 1.2 used as dependent variable (response). Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA) was used for generation and evaluation of statistical experimental design. The matrix of the design including investigated factors and responses are shown in Table 1.

For optimization, effects of various independent variables upon measured responses were modeled using the following mathematical equation involving independent variables and their interactions for various measured responses generated by 2^3 factorial design as follows,

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_1X_3 + b_6X_2X_3$$

Where, Y is the dependent variable, while b_0 is the intercept, b_1, b_2, b_3, b_4, b_5 and b_5 are regression coefficients; X_1, X_2 and X_3 are undependable variables; X_1X_2, X_2X_3 and X_1X_3 are interaction between variables. One-way ANOVA was applied to estimate the significance of the model ($p<0.05$) and individual response parameters.

Formulation of Cefdinir floating tablets

Floating granules were prepared by wet granulation technique (Prajapati *et al*., 2009; Anilkumar *et al*., 2010). The active ingredient and excipients such as citric acid, sodium bicarbonate and polymer were weighed accurately and mixed homogeneously according to geometric proportions as per the formulation Table 2. 2%w/v alcoholic solution of respective polymer was used as a granulating agent for each formulation. The coherent mass was sieved through mesh no. 16 and then dried in hot air oven at 60ºC for 45 min. The dried granules were passed through sieve no. 22 to get uniform granules. The granules were blended with 2% Magnesium stearate and Talc for 2-3 minutes and which were used as a lubricant and glidant respectively to improve flow property. Citric acid and sodium bicarbonate were incorporated as a stabilizing and gas-generating agent respectively. The granules were subjected for evaluation studies followed by compressed into floating tablets weighing about 550mg containing 300mg of Cefdinir using 6.8 mm shallow biconcave punches in Cadmach rotary tablet punching machine to a hardness of 4-6 kg/cm^2.

All ingredients were taken in mg, 2% respective polymer solution was used as granulating agent, 2% of Magnesium stearate and Talc were used as lubricant and glidant respectively in all formulations

Evaluation of Floating Tablet

In vitro buoyancy study

The *In vitro* buoyancy studies were performed for two parameters such as floating lag time (FLT) and total floating time (TFT). These parameters were determined for all the formulations of Cefdinir. The randomly selected tablets from each formulation were kept in a 100mL beaker containing pH 1.2 simulated gastric fluids. The time taken for each tablets to rise on the surface and float was taken as floating lag time (FLT).

The total floating time of all tablets were performed by using dissolution test apparatus USP type II paddle method with a stirring speed of 50 rpm at 37°C ± 0.5°C in 900 mL of pH 1.2 simulated gastric fluids for 12 hours. The duration of time the floating tablets constantly remain on surface of medium is taken as total floating time (TFT) (Jaimini *et al*., 2007; Ferdous Khan *et al*., 2008)

In vitro dissolution study

Dissolution characteristics of the formulated floating tablets of Cefdinir were carried out using USP Type II (paddle) dissolution test apparatus model EDT-08Lx 8 Station Electro labs dissolution tester (Mukesh *et al*., 2004)

Method

900 mL of enzyme free simulated gastric fluid pH 1.2 was filled in dissolution vessel and temperature of the medium was set at 37°C ± 0.5°C. One tablet of different batch was placed in each dissolution vessel and the rotational speed of paddle was set at 50rpm. 5mL of sample was withdrawn at predetermined time interval of every one hour for up to 12 hours and same volume of fresh medium was replaced immediately. The 2.5mL from withdrawn sample was diluted to 25mL in volumetric flask and filtered through 0.45µ membrane filter. The resultant samples were analyzed for drug content against enzyme free simulated gastric fluid as a blank at 390nm using UV-Visible spectrophotometer. The content of drug was calculated using the following equation (1). The percentage cumulative drug release was also calculated using the following equation (2).

$$Amount\ of\ drug = \frac{Absorbance\ of\ sample}{Absorbance\ of\ standard} X \frac{Amount\ of\ drug\ taken\ in\ mg}{200} X \frac{10}{100} X \frac{900}{1} X \frac{10}{5} X 1 X \frac{\%\ purity\ of\ standard}{100} X \frac{100}{25} ----(1)$$

$$Cumulative\ percentage\ drug\ release \frac{Amount\ of\ drug\ released}{Amount\ of\ drug\ loaded} X 100 -(2)$$

Treatment of dissolution data with different kinetic model

The quantity of drug released from floating tablets was analyzed as a function of the square root of time, which is typical for systems where drug release is governed by diffusion. However, the use of this relationship in swellable matrix system is not justified completely as such system can be erodible and the contribution of the relaxation of polymeric chains to drug transport has to be taken into account. Therefore, analysis of drug release from swellable matrix must be performed with a flexible model that can identify the contribution to overall kinetics, an equation proposed by Ritger and Peppas (Ritger *et al*., 1987). For finding out the mechanism of drug release from floating tablets, the dissolution data obtained from the above experiments were treated with the following different release kinetic models.

Zero order release (Cumulative percent drug released Vs time) equation

$$Q = K_0 t \text{ ---------- (1)}$$

Higuchi's (Cumulative percent drug released Vs square root of time) equation

$$Q = K_H t^{½} \text{ ---------- (2)}$$

Korsmeyer and Peppas (Log cumulative percent drug released versus log time) equation

$$F = (M_t/M) = K_m t^n \text{ ---------- (3)}$$

Stability study

The ICH guidelines for evaluation of stability data describe when and how extrapolation should be considered while proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by available data from the stability under the log-term storage condition. The data of multiple batches were analyzed using linear regression, pool ability tests and ANCOVA statistical modeling these were amenable to analysis for quantitative attributes with upper acceptance criteria of 110% and lower acceptance criteria of 90% of label claim. The relationship between residuals and time is assumed to be linear. Two-sided 95 % confidence intervals of the regression line for residuals (% relative to the original amount) of a drug product intersect with upper and lower acceptance criteria of label claimed. Then, the shortest one was the shelf life. Analysis of covariance (ANCOVA) was employed to test the difference in slopes and intercepts of the regression lines (Carstensen *et al*., 1977).

Method

Accelerated stability study was carried out as per ICH guideline 'Q1E Evaluation for stability Data'(ICH June 2004) using Ostwald stability chamber for F14 formulations were selected as an optimum formulations and the stability study was carried out at room temperature as well as different accelerated temperature and humidity conditions for a period of twelve months. The conditions were modified as 25°C/60%RH, 40°C/70%RH, 50°C/75%RH, 60°C/80%RH for every three months i.e. 3rd, 6th, 9th and 12th month respectively.

Ten tablets were individually wrapped using aluminum foil and packed in amber colored screw cap bottle and kept at above specified conditions in stability chamber for twelve months. Tablet samples were evaluated after 1st, 3rd, 5th, 6th, 9th, and 12th month for drug content as well as subjected for the *In vitro* drug release study. All the parameters have not shown any much variation when compared to the initial data. The *In vitro* dissolution was carried out for twelve months at the interval of four months.

The method adopted and remaining parameters were same as described in dissolution study. The dissolution profiles were analyzed with the aid of dissolution similarity factor f2 and time point analysis. The drug release profiles were not affected by exposing to different temperature with specified humidity conditions.

RESULTS AND DISCUSSION

Statistical analysis

Statistical optimization was performed using Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA). All measured data are expressed as mean±standard deviation (S.D.). Each measurement was done in triplicate (n = 3). Based on the selected responses of two variables (X_1, X_2), the ratio of matrix forming polymers and (X_3) diluents were optimized and total 15 formulations were set to prepared. The compositions of drug, polymer and other additives of all formulations were presented in the Table 3.

Evaluation of optimized formulations

The optimized formulations were identified based on constrains used in the experiment. The optimized formulations were compressed into tablets according to the method given in Table 3. and evaluated for time to get T50% in vitro drug release, results were presented in Table.

In vitro buoyancy study

From the results of floating lag time it was found that as the concentration of gas generating agent and citric acid significantly influenced on floating lag time. The floating ability was due to presence of $NaHCO_3$ and citric acid. Another aspect of results of these studies clears that the level as well as viscosity of the polymer has a great impact over the floating lag time and total floating time, as the level and viscosity of the polymer were reduced the floating lag time get shorten. It was also observed that total floating time was greater when the viscosity of the polymer used was greater, which was supported by Li and co-workers who reported that higher viscosity grade generally exhibited greater floating capability. MCC used in all formulation of floating tablets was found to have significant influence over the density of the tablets which provide low density for the tablets when compared to other conventional lubricants. Total Floating Time for all formulations showed greater than 12 hours are presented in Picture 4.

Buoyancy of the floating tablets was governed by both swelling of hydrocolloid particles on surface when it contacts the gastric fluid and presence of void space or porosity in the dry center of the tablet.

In vitro dissolution study

Linearity was obtained from the standard curve of Cefdinir in simulated gastric fluid, it indicates that the drug obeys Beer-Lambert's law in concentration range of 5.0–30µg/mL.

In vitro drug release study revealed that the tablets of F14 has shown highest percentage of cumulative drug release at the end of 12^{th} hour this might be due to presence of Gum Karaya while the drug releases were not satisfactory in other formulations with HPMC K100 and HPMC K4. The most probable fact behind these observations with all formulations other than F14 was the concentration of polymer used in those formulations was not effectively influenced on the rate of drug release.

In vitro drug release study was carried out over the floating tablets of Cefdinir containing different proportion of HPMC K100, HPMC K4 and Gum Karaya, the effect of polymer was observed on drug release. From the observation it was found that F2 has shown drug release range of 26.95 – 95.34% among its proportions, F7 has shown drug release range of 17.66 – 87.43% among its proportions, F14 has shown drug release range of 30.92 – 98.25% among its proportions this was the highest drug release among all floating tablets of Cefdinir. The dissolution data are given in Table from 5-11 and the drug release pattern with kinetics treatment were depicted as Picture from 5-14.

Treatment of dissolution data with kinetic model

Dissolution data of all floating tablets were subjected to the treatment of different kinetic equations, it was found to be that the drug release pattern were best fitted with zero order release equation and involves combination of polymer relation and consequently swelling. The n value obtained with the application of Koresmeyer and Peppa's equation was found to be 0.5801 for F14. This value indicates a non-Fickian release mechanism that may be attributed to swelling and dissolution of the polymeric matrix. 'n' values obtained for best formulations are given in Table 5-11 the dissolution and kinetic data are given in Table 11 and graphs are shown from 5 to14.

From the dissolution profile of each formulation initial burst effect was observed to some extent this might be due to inherent characteristics of polymer matrix.

Stability study

Overall observations from different evaluation studies such as drug-polymer interactions, evaluation of granules, physicochemical parameters, swelling index, *In vitro* buoyancy and *In vitro* dissolution were carried out on all floating tablets of Cefdinir, the F14 has shown

optimum results. Based on the obtained results this formulation was subjected for further stability study. The study was conducted as per ICH guidelines for the period of twelve months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH, 60°C/80%RH.

The data of multiple batches were analyzed using linear regression, poolability tests and ANCOVA statistical modeling these were amenable to analysis for quantitative attributes with upper acceptance criteria of 110% and lower acceptance criteria of 90% of label claim. There was a significant difference in intercepts (Y=100.31, 101.46, 101.32) but no significant difference in slope (-0.3252x) among the batches. The predicted shelf life of F14 was found to be 26.35 months and percentage drug releases were 96.79, 95.84 and 93.25% after 4^{th}, 8^{th} and 12^{th} months respectively. It was observed that there was no substantial change in dissolution profile after twelve months. The stability study revealed that the floating tablets of F14 may be stable for the period of two years. The observed and calculated values are given in Table 12-13. The residuals obtained from the calculated values are shown in Picture 15-17.

Table 1. Levels of independent variables

Level	HPMCK100 (mg) X1	Surelease (mg) X2	Gum Karaya (mg) X3
Low (-1)	60	60	20
High (+1)	180	180	120

Table 2. Formulation of floating tablets of Cefdinir

F. Code	Drug	HPMC K100	HPMC K4	Gum Karaya	$NaHCO_3$	Citric acid	Total
F1	300	180	--	--	90	20	550
F2	300	150	--	--	90	20	550
F3	300	120	--	--	90	20	550
F4	300	90	--	--	90	20	550
F5	300	60	--	--	90	20	550
F6	300	--	180	--	90	20	550
F7	300	--	150	--	90	20	550
F8	300	--	120	--	90	20	550
F9	300	--	90	--	90	20	550
F10	300	--	60	--	90	20	550
F11	300	--	--	180	90	20	550
F12	300	--	--	150	90	20	550
F13	300	--	--	120	90	20	550
F14	300	--	--	90	90	20	550
F15	300	--	--	60	90	20	550

Table 3. Factorial design of the formulation with results and constraints

Run No.	Variable			Response
	HPMCK100 (mg) X1	Su release (mg) X2	Gum Karaya (mg) X3	% of drug release after 8 hours
1	60	60	20	67.34
2	180	180	120	77.38
3	60	60	120	76.59
4	180	60	120	75.24
5	60	180	20	55.29
6	60	60	20	58.59
7	60	180	120	76.37
8	180	60	20	69.58
9	60	180	20	68.36

10	60	180	120	74.27
11	180	180	120	78.58
12	180	180	20	66.16
13	60	60	120	77.48
14	180	60	120	79.16
15	180	60	20	67.54
16	180	180	20	65.26

Table 4. Kinetic treatment to dissolution data of tablets of best formulation

Kinetic model	F14		
	R^2 value	Slope	Intercept
Zero order	0.9347	7.2109	20.4593
Higuchi's	0.9942	28.7339	-0.9244
Korsemeyer Peppas	0.5801	1.0756	0.9558

Table 5. *In vitro* drug release and Higuchi data for F1-F5

Time (hrs)	Square root time	Cumulative % drug released				
		F1	F2	F3	F4	F5
1	1.00	12.72	15.47	17.47	14.87	11.96
2	1.41	17.14	22.14	25.09	20.35	16.34
3	1.73	23.28	29.96	33.12	24.72	19.32
4	2.00	29.43	34.52	40.65	31.94	24.45
5	2.24	37.85	41.26	47.53	36.78	28.74
6	2.45	44.67	48.92	51.49	41.43	33.47
7	2.65	51.26	55.94	56.56	47.71	40.85
8	2.83	57.24	62.65	62.86	52.75	43.37
9	3.00	61.18	67.24	65.82	55.84	48.83
10	3.16	65.12	74.16	70.35	61.45	53.44
11	3.32	68.77	79.57	74.87	67.95	59.15
12	3.46	71.47	84.56	78.94	69.97	62.57

Table 6. Peppa's data for F1-F5

Log time	Log cumulative % drug released				
	F1	F2	F3	F4	F5
0.00	1.10	1.19	1.24	1.17	1.08
0.30	1.23	1.35	1.40	1.31	1.21
0.48	1.37	1.48	1.52	1.39	1.29
0.60	1.47	1.54	1.61	1.50	1.39
0.70	1.58	1.62	1.68	1.57	1.46
0.78	1.65	1.69	1.71	1.62	1.52
0.85	1.71	1.75	1.75	1.68	1.61
0.90	1.76	1.80	1.80	1.72	1.64
0.95	1.79	1.83	1.82	1.75	1.69
1.00	1.81	1.87	1.85	1.79	1.73
1.04	1.84	1.90	1.87	1.83	1.77
1.08	1.85	1.93	1.90	1.84	1.80

Table 7. *In vitro* drug release and Higuchi data for F6-F10

Time (hrs)	Square root time	Cumulative % drug released				
		F6	F7	F8	F9	F10
1	1.00	14.37	17.66	14.36	8.07	10.26
2	1.41	23.72	25.93	27.75	14.82	15.47
3	1.73	28.78	33.26	32.25	21.49	20.46
4	2.00	35.46	38.68	34.98	26.23	26.85
5	2.24	41.13	47.12	42.62	32.19	29.97
6	2.45	47.75	52.37	48.74	37.89	35.62
7	2.65	52.95	59.66	54.55	44.65	42.44
8	2.83	56.75	65.82	60.96	48.95	46.63
9	3.00	59.15	74.26	65.38	53.07	51.64
10	3.16	65.72	79.67	68.62	57.72	55.43
11	3.32	72.82	85.29	72.81	63.07	60.84
12	3.46	73.84	87.43	76.27	67.63	65.87

Table 8. Peppa's data for F6-F10

Log time	Log cumulative % drug released				
	F6	F7	F8	F9	F10
0.00	1.16	1.25	1.16	0.91	1.01
0.30	1.38	1.41	1.44	1.17	1.19
0.48	1.46	1.52	1.51	1.33	1.31
0.60	1.55	1.59	1.54	1.42	1.43
0.70	1.61	1.67	1.63	1.51	1.48
0.78	1.68	1.72	1.69	1.58	1.55
0.85	1.72	1.78	1.74	1.65	1.63
0.90	1.75	1.82	1.79	1.69	1.67
0.95	1.77	1.87	1.82	1.72	1.71
1.00	1.82	1.90	1.84	1.76	1.74
1.04	1.86	1.93	1.86	1.80	1.78
1.08	1.87	1.94	1.88	1.83	1.82

Table 9. *In vitro* drug release and Higuchi data for F11-F15

Time (hrs)	Square root time	Cumulative % drug released				
		F11	F12	F13	F14	F15
1	1.00	20.67	15.63	26.95	30.92	13.51
2	1.41	30.85	30.47	34.13	39.34	22.57
3	1.73	38.62	38.94	42.78	48.33	30.95
4	2.00	44.67	47.56	49.16	53.37	40.52
5	2.24	52.14	57.42	54.85	58.68	50.56
6	2.45	57.89	63.68	62.68	67.24	56.23
7	2.65	66.46	68.53	70.51	76.18	62.64
8	2.83	72.83	73.26	79.44	82.24	68.77
9	3.00	79.25	79.91	85.24	86.67	75.79
10	3.16	85.12	86.58	89.93	91.42	82.19
11	3.32	90.18	90.96	93.36	95.78	87.63
12	3.46	92.34	93.25	95.34	98.25	89.65

Table 10. Peppa's data for F11-F15

Log time	Log cumulative % drug released				
	F11	F12	F13	F14	F15
0.00	1.32	1.19	1.43	1.49	1.13
0.30	1.49	1.48	1.53	1.59	1.35
0.48	1.59	1.59	1.63	1.68	1.49
0.60	1.65	1.68	1.69	1.73	1.61
0.70	1.72	1.76	1.74	1.77	1.70
0.78	1.76	1.80	1.80	1.83	1.75
0.85	1.82	1.84	1.85	1.88	1.80
0.90	1.86	1.86	1.90	1.92	1.84
0.95	1.90	1.90	1.93	1.94	1.88
1.00	1.93	1.94	1.95	1.96	1.91
1.04	1.96	1.96	1.97	1.98	1.94
1.08	1.97	1.97	1.98	1.99	1.95

Table 11. *In vitro* drug release and Higuchi data for best formulation F14

Time (hrs)	Square root time	Cumulative % drug released	Log time	Log cumulative % drug released
1	1.00	30.92	0.00	1.49
2	1.41	39.34	0.30	1.59
3	1.73	48.33	0.48	1.68
4	2.00	53.37	0.60	1.73
5	2.24	58.68	0.70	1.77
6	2.45	67.24	0.78	1.83
7	2.65	76.18	0.85	1.88
8	2.83	82.24	0.90	1.92
9	3.00	86.67	0.95	1.94
10	3.16	91.42	1.00	1.96
11	3.32	95.78	1.04	1.98
12	3.46	98.25	1.08	1.99

Table 12. Comparison of observed with calculated assay of best formulations subjected to stability study

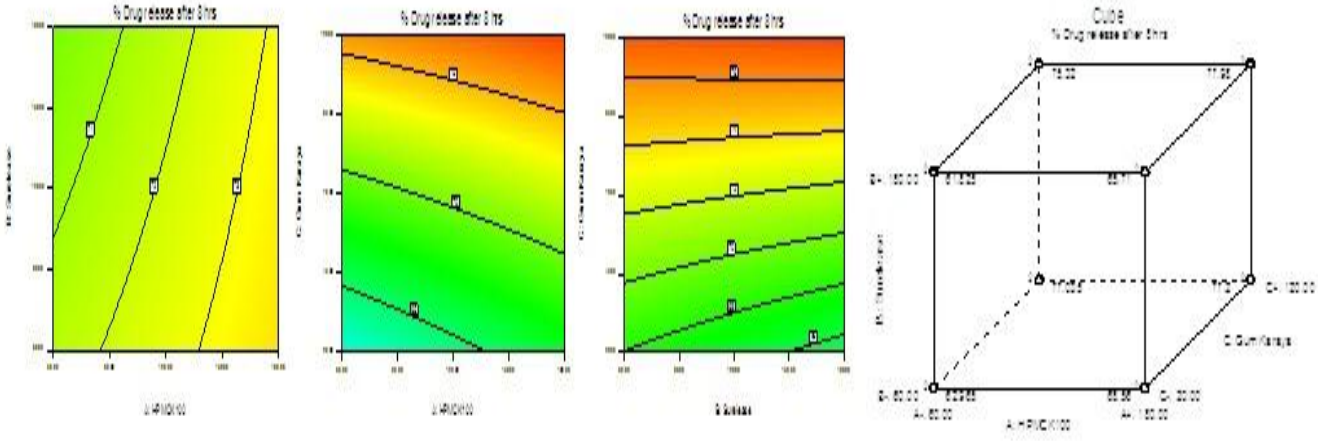
Time in months	F14	
	Observed Assay (%) Mean ± SD	Calculated Assay (%) Mean ± SD
1	101.12 ± 0.48	100.82 ± 0.71
2	100.18 ± 1.03	100.49 ± 0.71
4	99.82 ± 1.13	99.84 ± 0.71
6	98.98 ± 1.05	98.86 ± 0.71
8	98.10 ± 0.49	97.89 ± 0.71
10	97.13 ± 0.78	96.91 ± 0.71
12	101.12 ± 0.48	100.82 ± 0.71

Each value represents the mean ± standard deviation (n=3)

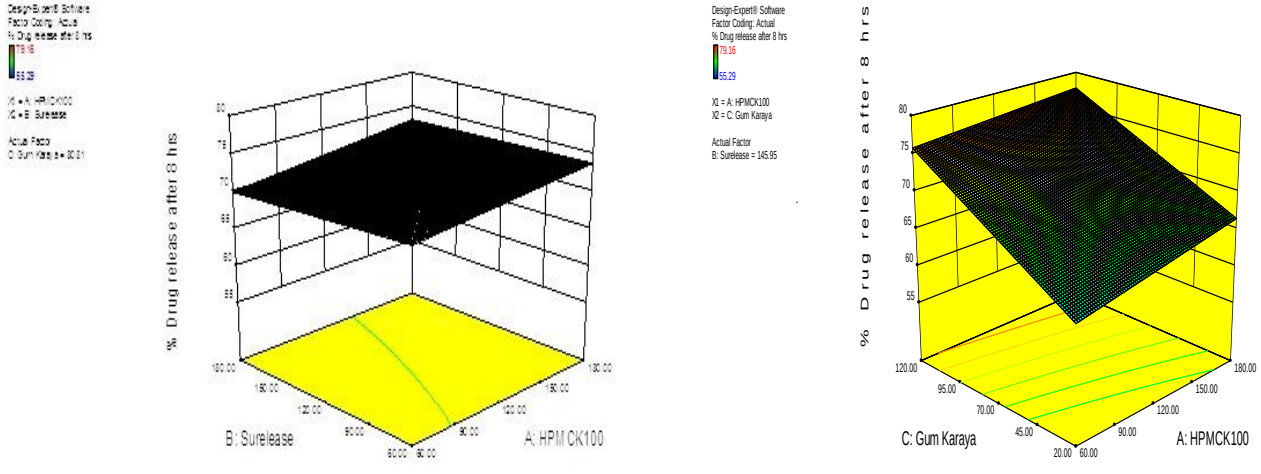
Table 13. Comparison of dissolution data of best formulation subjected to stability study with standard release

Time in hrs	Cumulative % drug release of F14			
	Standard	After 4 month	After 8 months	After 12 months
1	30.92	29.35	24.72	25.65
2	39.34	37.43	34.35	32.22
3	48.33	45.76	40.46	37.44
4	53.37	50.74	47.44	46.53
5	58.68	56.94	53.52	51.94
6	67.24	65.61	63.45	61.51
7	76.18	73.76	71.34	67.65
8	82.24	80.62	78.15	75.75
9	86.67	85.45	81.54	78.52
10	91.42	89.62	86.72	82.26
11	95.78	93.38	90.75	89.84
12	98.25	96.79	95.84	93.25

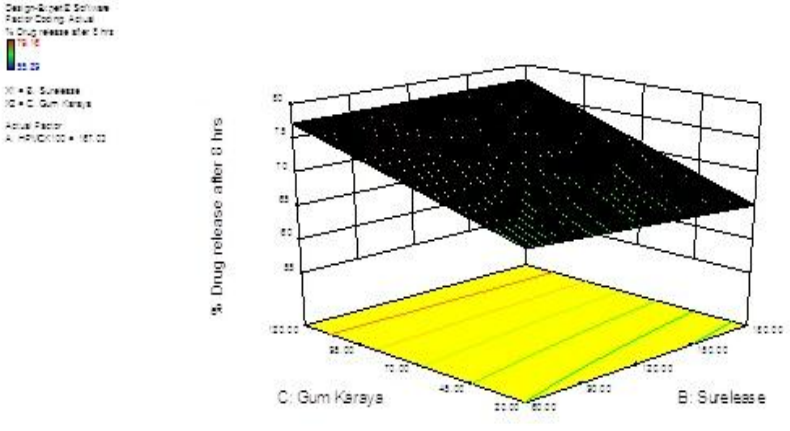
Picture 1. Contour plot showing the effect of polymers concentration on % drug release after 8 hours



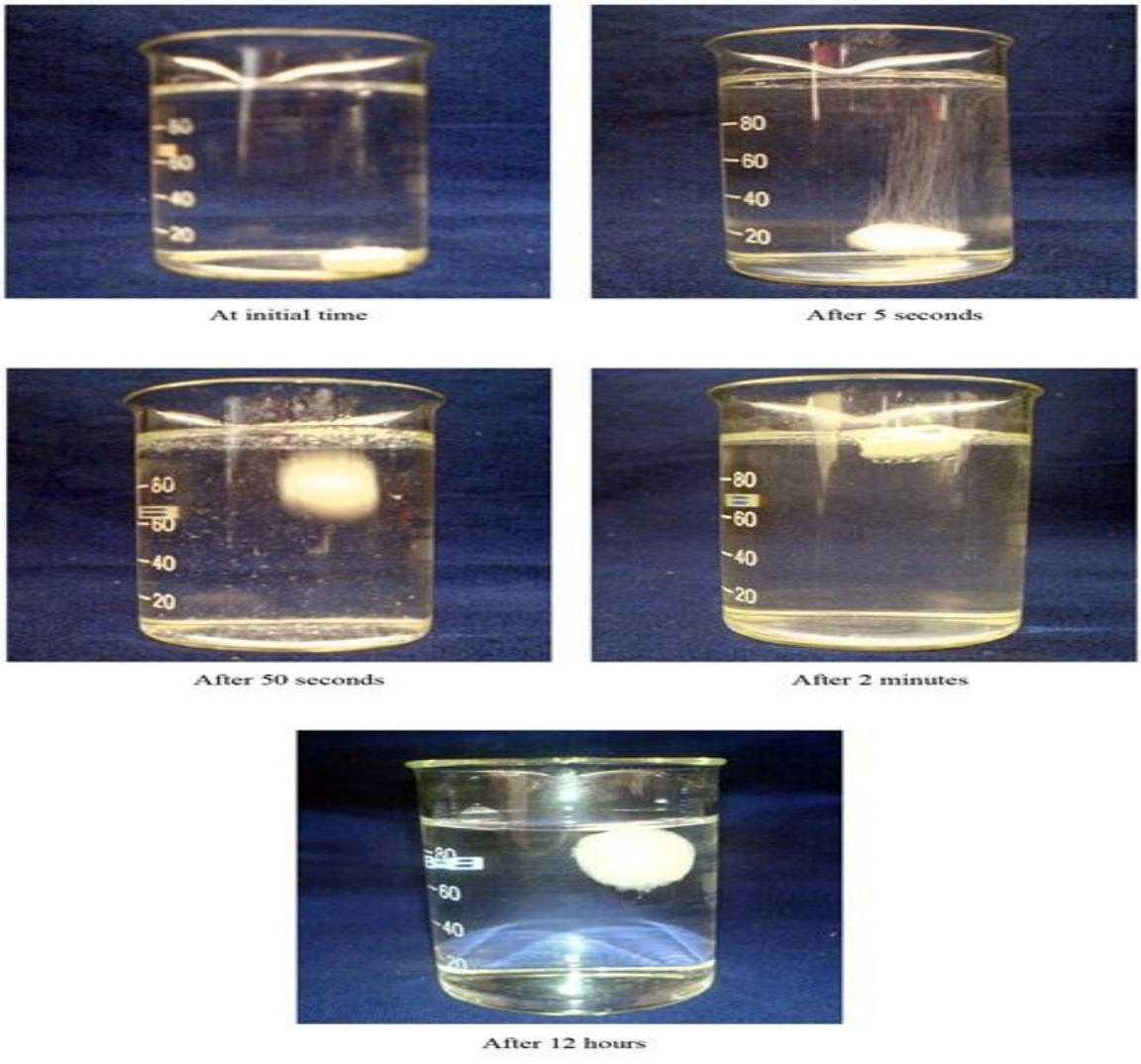
Picture 2. Cube plot showing the effect of polymers concentration on % drug release after 8 hours



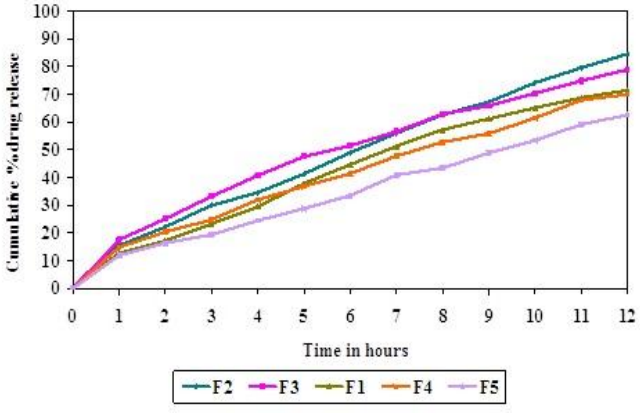
Picture 3. 3D surface plot showing the effect of polymers concentration on % drug release after 8 hours



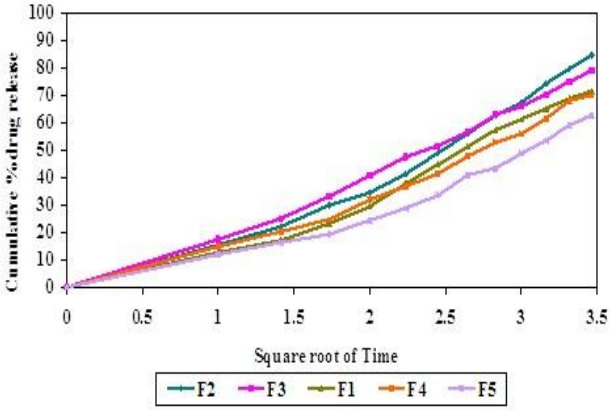
Picture 4. *In vitro* Buoyancy Study of F14



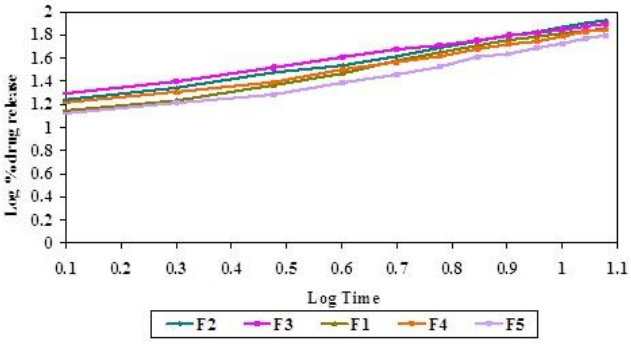
Picture 5. *In vitro* drug release plot of F1-F5



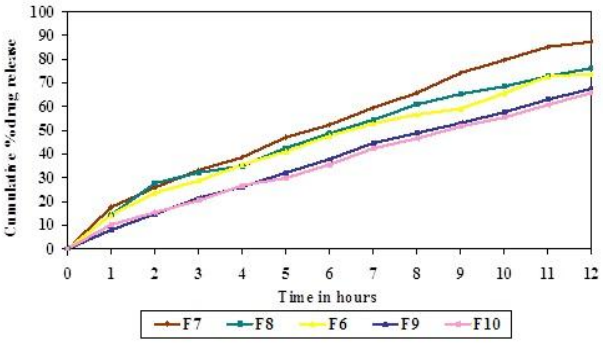
Picture 6. Higuchi's plot of F1-F5



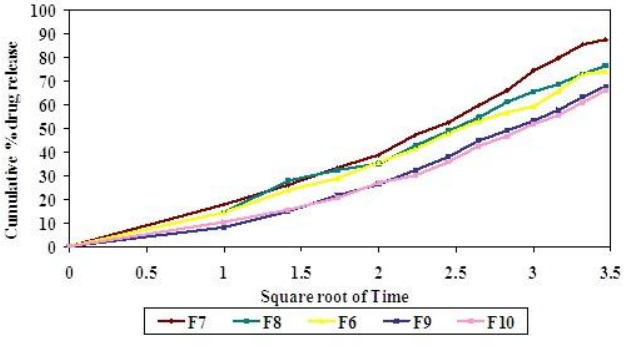
Picture 7. Peppa's plot of F1-F5



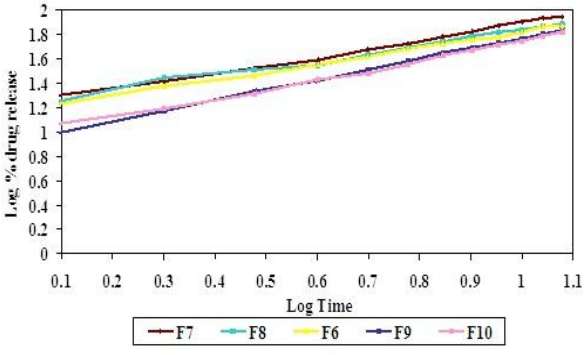
Picture 8. *In vitro* drug release plot of F6-F10



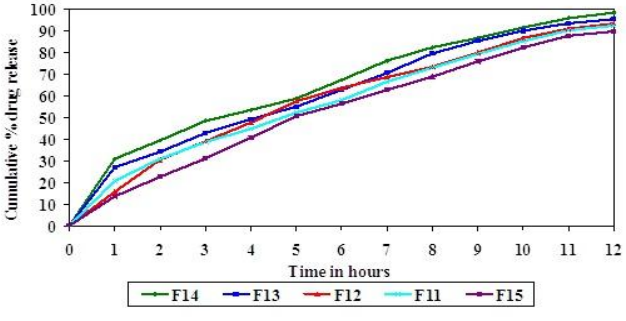
Picture 9. Higuchi's plot of F6-F10



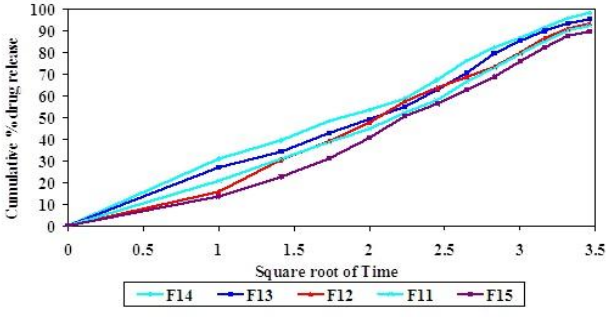
Picture 10. Peppa's plot of F6-F10



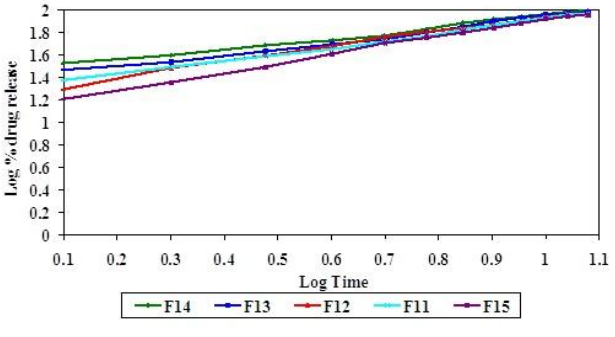
Picture 11. *In vitro* drug release plot of F11-F15



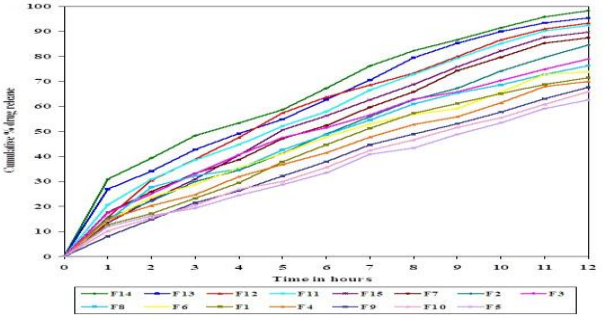
Picture 12. Higuchi's plot of F11-F15



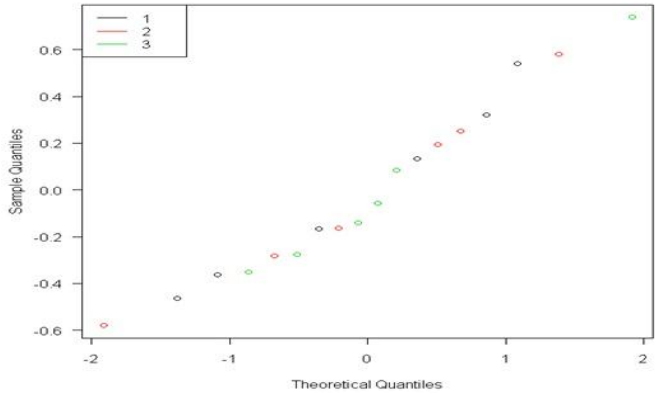
Picture 13. Peppa's plot of F11-F15



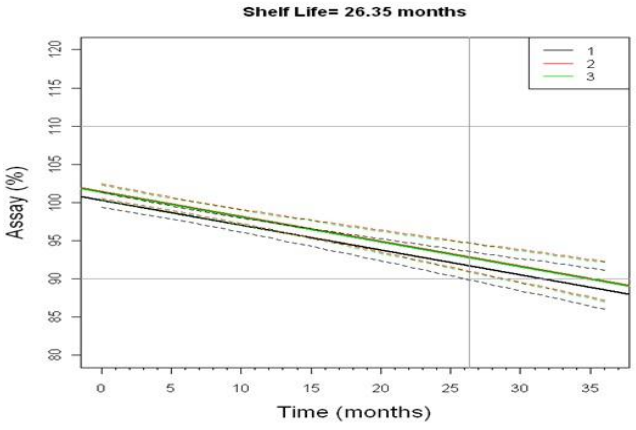
Picture 14. Comparison of drug release pattern of all floating tablets of Cefdinir with rank order



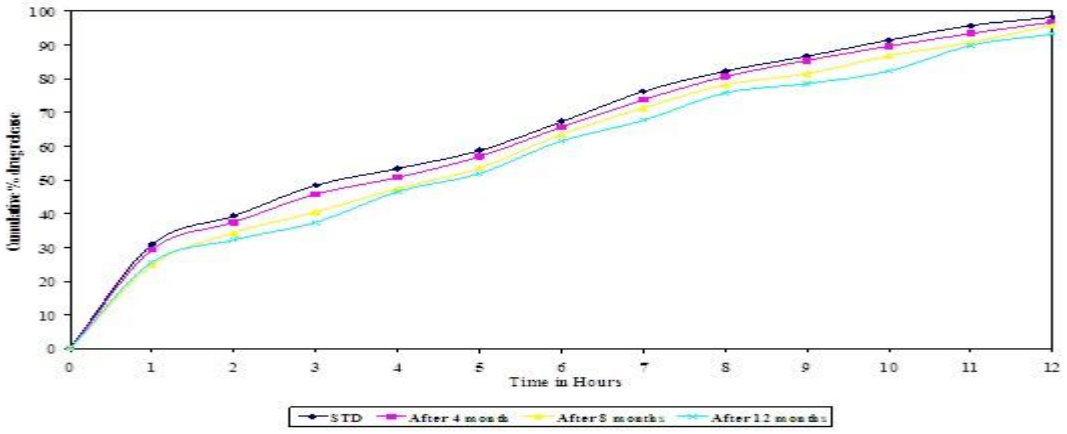
Picture 15. Normal Q-Q plot of residuals obtained from calculated values of F14 batches subjected for stability study



Picture 16. Graph showing predicted shelf life of F14



Picture 17. Drug release pattern of F14 during stability study for every 4 months up to 12 months



CONCLUSION

The approach of the present study was to develop floating tablets of Cefdinir using natural polymer modified from commercially available Gum Karaya having desirable properties such as floating, swelling, biocompatible and biodegradable and proper utilization of natural polymer with minimized quantity. Hence, evaluated the release profiles of floating formulations.

The results obtained in this study leads to the following conclusions.

- Formulation F14 containing 60mg of Gum Karaya was found to release a maximum of 98.25% at the 12th hour.
- The drug release from F14 was found to follow zero order kinetics. It was also found linear in Higuchi's plot, which confirms that diffusion is one of the mechanisms of drug release.
- The FTIR analysis reveals that there was a weak intermolecular interaction between drugs and excipients and these was no significant chemical interaction between drug and polymers.
- Comparison of synthetic polymer with modified Gum Karaya, the floating tablets prepared by using Gum Karaya have shown optimized drug release.
- This revealed the fact that modified Gum Karaya with Cefdinir floating tablets has shown comparable floating and drug release characteristics, thus it may have fair clinical efficacy.
- Hence, the formulation F14 has met the objectives of the present study.
- It was concluded that F14 formulation hold promise for further *In vivo* studies, which can be extrapolated for the development of floating drug delivery system.

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