Formulation development and In-Vitro evaluation of floating tablets of Cefixime

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ABSTRACT

Objective: Cefixime is a third generation cephalosporin antibiotic having bactericidal activity by inhibition of cell wall synthesis and is used in the treatment of uncomplicated UTI, pharyngitis and tonsillitis, acute bronchitis and acute exacerbation of chronic bronchitis, uncomplicated gonorrhoea etc. The concept of formulating floating tablets containing Cefixime offers a suitable and practical approach in serving desired objective of retaining the drug in the stomach to increase the its bioavailability.

Methods: The tablets were prepared by direct compression method and total of 12 formulations are developed employing HPMC K100M and HPMC K15M as polymers for sustaining the drug release and sodium bicarbonate as the gas generating agent.

Results: Various polymers have been selected and subjected to IR-spectroscopic studies and found that there were no drug–excipient interactions. The powder blends of all the formulations have shown good flow properties. Other parameters such as hardness, friability, drug content uniformity, Floating lag time and *in-vitro* dissolution studies were performed and the results were satisfactory.

Conclusion: Formulation F 12 was found to be best in all aspects and was considered as optimized formulation, it has a low floating lag time of 2mins and has shown a maximum drug release of 99% at the end of 24 hours and drug release was by diffusion through the polymer matrix.

Keywords: Cefixime, Cephalosporin, Bioavailability, Floating lag time, Diffusion.

INTRODUCTION

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups.[1] One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF or GRDS). [2]

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. [3]

In the present work Cefixime floating tablets are prepared by using combination of Hydrophilic polymers and gas generating agents such as citric acid and sodium bi carbonate. By using different types of polymers and excipients the formulation could be retained for longer periods of time in the stomach and provided controlled release of the drug. Cefixime a third generation cephalosporin antibiotic having bactericidal activity by inhibition of cell wall synthesis and is used in the treatment of uncomplicated UTI, otitis media, pharyngitis and tonsillitis, acute bronchitis and acute exacerbation of chronic bronchitis, uncomplicated gonorrhea. [4]

Cefixime is a very poorly soluble in water after its oral administration, it is slowly and incompletely absorbed from the gastrointestinal tract, which resulting into the poor bioavailability i.e., 40-50%. [5, 6] So, in order to improve the therapeutic effect of the drug by increasing its bioavailability it was formulated as floating drug delivery system for controlled release with increased gastric retention.

MATERIALS AND METHODS

Materials: Cefixime was obtained as a gift sample from Hetero drugs Pvt .Ltd, Hyd. HPMC K15 and HPMC K 100M were purchased from Merk

specialities Pvt Limited, Mumbai. PVP K30 was purchased from SDFCL Fine chem. Ltd. Magnesium Stearate and citric acid were purchased from Hi media laboratories Pvt. Ltd, Mumbai. India. Aerosil and Sodium bicarbonate were procured from Sigachi Chloro Chemicals Pvt. Ltd. Hyderabad.

Methods:

Drug excipient compatability studies by FT-IR:

Excipients are integral components of almost all pharmaceutical dosage forms. To investigate any possible interaction between the drug and the utilized polymers HPMC K100M, HPMCK15M, PEO. IR spectrum of pure drug cefixime and its physical mixture was carried out by using FTIR in the range of 400 cm^{-l} to 4000cm^{-1}

Formulation of Cefixime Gastro Retentive Drug Delivery Systems:

Cefixime floating tablets were formulated using direct compression technique [7] in this method all the ingredients are weighed properly and passed through sieve no 40 except Aerosil and magnesium stearate. Weighed Aerosil and magnesium stearate are passed through sieve no 60 and blended uniformly and compressed using a tablet compression machine in 9 mm punch.

Table. 1: Formulation of Cefixime Gastro Retentive floating tablets

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cefixime	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K 15 M	100	150	200	250	300	350	-	-	-	-	-	-
HPMC K 100 M	-	-	-	-	-	-	100	150	200	250	300	350
PEO	50	50	50	50	50	50	50	50	50	50	50	50
Mg. stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
PVP K 30	25	25	25	25	25	25	25	25	25	25	25	25
Aerosil	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Sodium bicarbonate	100	100	100	100	100	100	100	100	100	100	100	100
Citric acid	100	100	100	100	100	100	100	100	100	100	100	100
MCC	310	260	210	160	110	60	310	260	210	160	110	60
Total weight (mg)	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200

EVALUATION OF DRUG AND EXCIPIENT BLENDS

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. [8, 9]

Bulk density (D_b): It is the ratio of total mass of powder to the bulk volume of powder.

It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder

Tapped density (D_t):

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$D_t = \frac{M}{V_1}$$

Where, M is the mass of powder, V_t is the tapped volume of the powder

Carr's index (%):

The bulk density is the measurement of weight to the volume of the sample. Tapped density is

determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = 100 \times \frac{\text{Tappeddensity} - \text{Bulk density}}{\text{Tappeddensity}}$$

Hausner's ratio:

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Angle of repose (θ): It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$\tan\theta = \tan^{-1}$ (h/r)

Where, θ is the angle of repose ; h is the height; r is the radius

Method: The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface.

The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. A value for angle of repose $\geq 40^{o}$ suggests a poorly flowing material.

EVALUATION PARAMETERS AND PROCEDURES

Thickness: This is only dimensional variable which is press dependant. It depends on volume of die fill and compression force. A±5% variation is allowed. The tablet thickness is measured in mm by mean of callipers as thickness gauge and micrometer.[9,10]

Hardness: It is the measure of the resistance of a tablet to chipping, abrasion or breakage under conditions of storage, transport, packing and handling before use. The tablet hardness is defined as the force required to break a tablet in a diametric compression test. The hardness was measured in terms of Kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 tablets was recorded.[9,10]

Weight variation: Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.[11]

Friability: Friability of the tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.[11]

Content uniformity test: Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of Cefixime was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The Cefixime content was determined by measuring the absorbance at 287.5 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.[12]

In vitro buoyancy properties: The tablets (n = 3) were placed in a 100 ml beaker containing 0.1 N HCl. The time taken for tablet to emerge on surface of medium and the duration it remained on the surface of the medium is floating lag time and total floating time respectively.[13, 14]

***In-vitro* drug release study [15]**

The *in-vitro* dissolution study of Cefixime tablets were determined using USP XXIII type II (paddle) dissolution apparatus. The paddle rotation speed of 100 r/min and temperature of 37 ± 0.5˚C was maintained. Aliquots (5 ml) of the solution were collected at predetermined time intervals from the dissolution apparatus and samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 287.5 nm using UV-visible double-beam spectrophotometer (Systronics 2202, Hyd). Cumulative percentage drug release was calculated using equation(y = 0.036 x + 0.019) generated from standard calibration curve (R2 = 0.998).

Kinetic analysis of dissolution data [16]

To analyze the *in-vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3).

$$C = K_0 t \quad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - K_1 t / 2.303 \quad (2)$$

where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

where, K_H is the constant reflecting the design variables of the system.

The following plots were made using the in-vitro drug release data:

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time (First order kinetic model);

Cumulative % drug release vs. square root of time (Higuchi model);

Mechanism of drug release

Korsmeyer has derived a simple relationship which described drug release from a polymeric system Eq. (4). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \quad (4)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

RESULTS AND DISCUSSION

Drug excipient compatability studies:

Compatibility studies of pure drug with excipients were carried out prior to the preparation of floating tablets. IR spectra of pure drug and combination of drug and excipients were obtained and shown in the figures 1 to 5. All the characteristics indicate compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

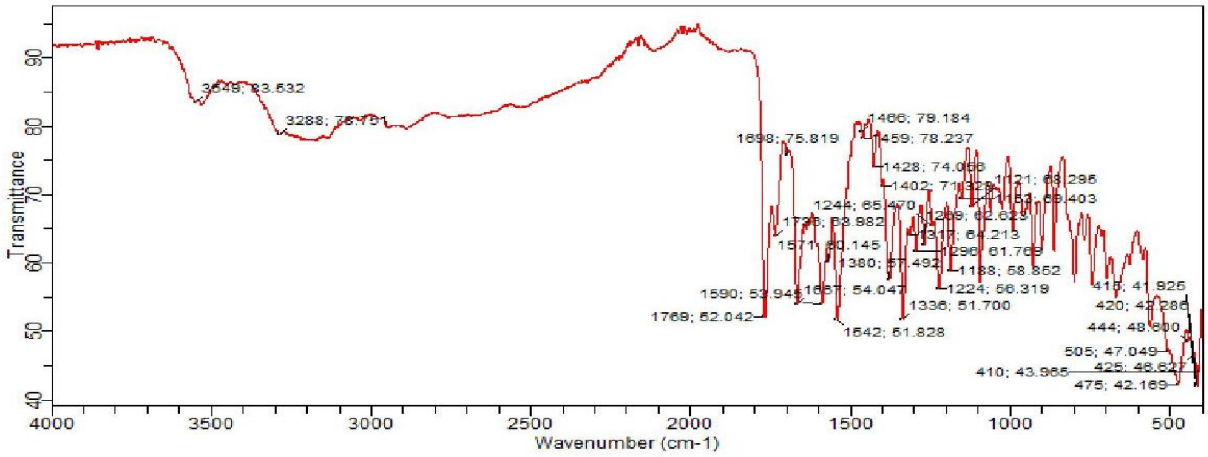

Fig No.1: FTIR spectrum of Cefixime

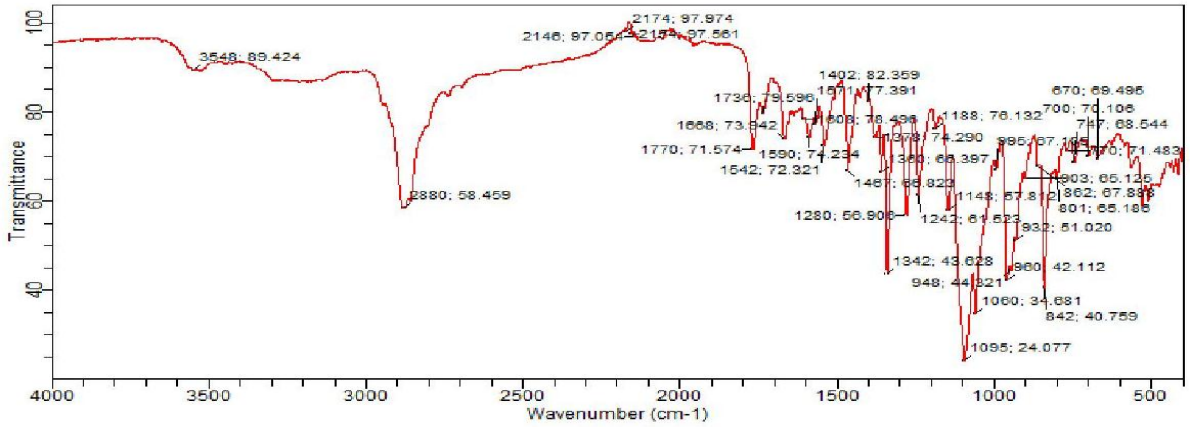

Fig No.2: FTIR spectrum of Cefixime + PEO

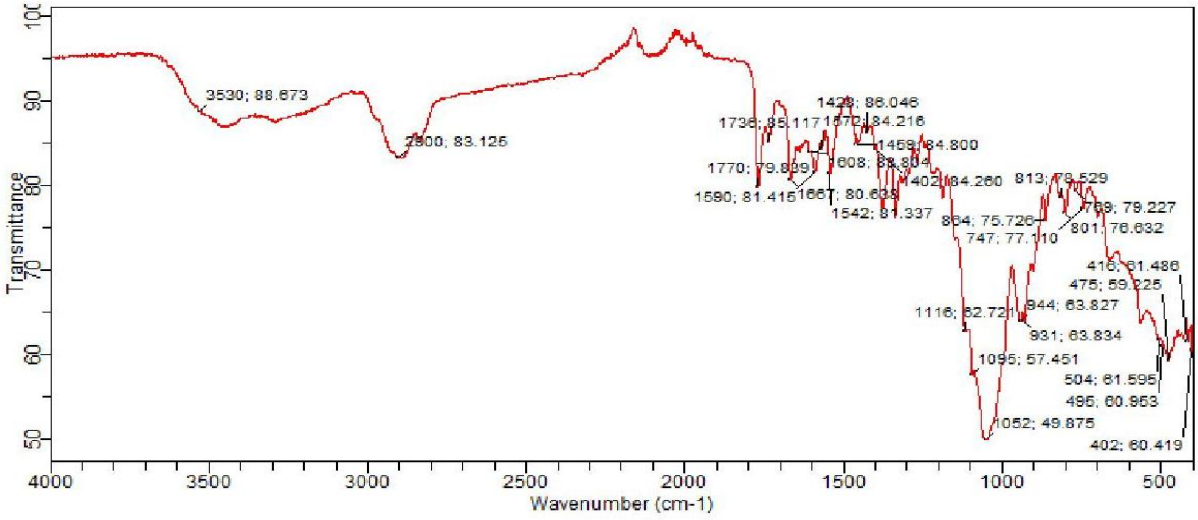

Fig No.3: FTIR spectrum of Cefixime + HPMC K 15M

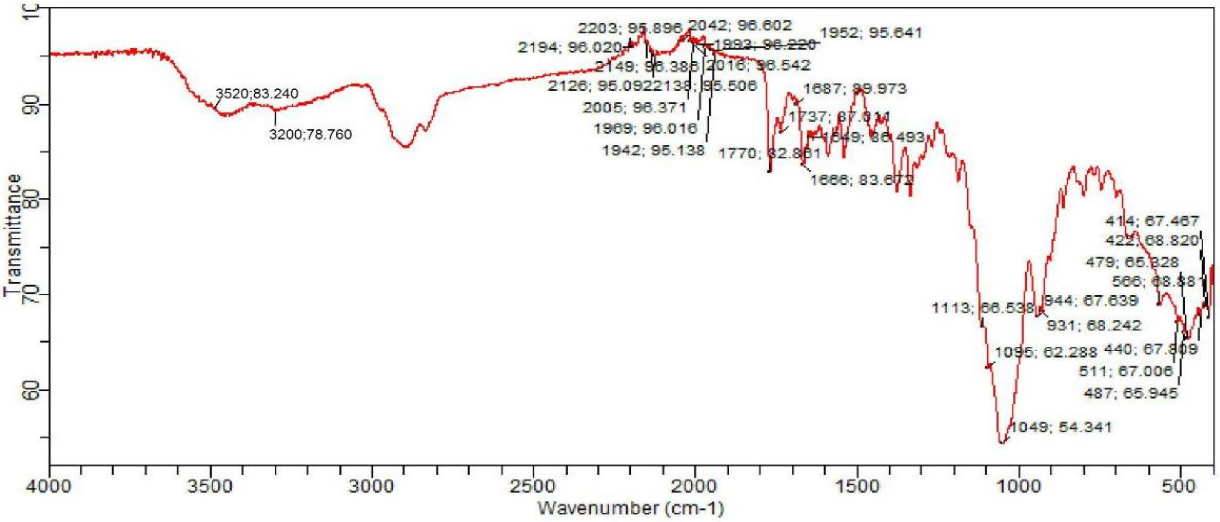

Fig No.4: FTIR spectrum of Cefixime + HPMC K 100M

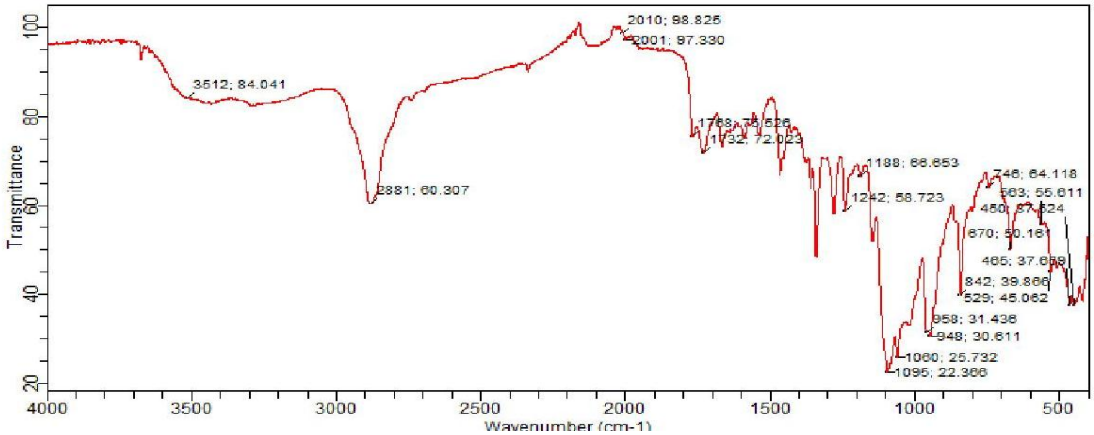

Fig No.5: FTIR spectrums of Cefixime + Optimized Formulation

Pre compression studies of Cefixime:

The results of precompression studies are given in the table-2.

Angle Repose: The values for angle of repose for the formulations are in the range of 22.15 to 28.82. All the formulations showed angle of repose below 30^0 which indicates a good flow property.

Bulk Density: The bulk density values for the formulations are in the range of 0.39 to 0.59 g/cc respectively. The values obtained lies within the acceptable range and not a large difference exists between the bulk density values.

Tapped Density: The Tapped density values for the formulations are in the range of 0.44 to 0.68 gm/cc respectively. The values obtained lies within the acceptable range and not a large difference exists between the Tapped density values.

Carr's index: The values for the formulations were in the range of 11.36 to 21.8% which indicates good flow property.

Hausner's: The values for the formulations are in the range of 1.12 to 1.25 which indicates good flow property.

Table. 2: Results of Pre-compression parameters of Cefixime powder blend

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr's index(%)	Hausner's ratio
F1	0.462±0.002	0.591±0.001	26.06±0.030	21.8±0.010	1.25±0.020
F2	0.469±0.002	0.561±0.001	25.42±0.025	16.39±0.98	1.19±0.050
F3	0.46±0.002	0.55±0.001	26.62±0.030	16.36±0.17	1.19±0.050
F4	0.59±0.001	0.68±0.002	29.19±0.025	13.04±0.14	1.15±0.040
F5	0.530±0.001	0.618±0.001	28.72±0.014	14.23±0.53	1.16±0.040
F6	0.50±0.001	0.58±0.001	27.02±0.010	13.79±0.85	1.16±0.040
F7	0.49±0.001	0.56±0.002	25.51±0.090	12.50±1.56	1.14±0.020
F8	0.47±0.002	0.54±0.001	28.68±0.120	12.96±0.77	1.14±0.020
F9	0.46±0.002	0.53±0.001	25.32±0.140	13.20±0.04	1.15±0.040
F10	0.39±0.060	0.44±0.030	22.15±0.030	11.36±0.03	1.12±0.030
F11	0.47±0.002	0.54±0.001	27.68±0.140	12.96±0.77	1.15±0.040
F12	0.46±0.002	0.53±0.001	28.82±0.120	13.20±0.04	1.15±0.040

Post Formulation Studies: The results of post formulation studies of cefixime floating tablets are represented in table-3.

Hardness: Hardness of the tablet formulations was found to be in the range of 4.4 to 4.6 kg/cm^2. The hardness of all the formulations was almost uniform and possesses good mechanical strength with sufficient hardness.

Friability: Friability values were found to be in the range of 0.119 to 0.61% which was found to be below 1% indicate that the tablets of all the formulations are having good compactness and strength to withstand the force without breaking.

Uniformity of weight: All the prepared Floating tablets of Cefixime were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed limits.

Uniformity of drug content: The value indicates uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 98.34 to 100.34%.

Floating lag time: The floating lag time is the time taken for the formulation to start floating in the dissolution vessel. All the 12 formulations showed the floating lag time within 2 to 14 min and remained floating for more than 6 hrs thus ensuring sustained floating of the formulations.

Table.3: Post Formulation Studies of Cefixime floating tablets

Formulation code/Parameter	Hardness Kg/cm^2	Friability %	Content uniformity %	Floating lag time	Total floating time
F1	4.5±0.02	0.23±0.02	99.65±0.15	14 min	6 hrs
F2	4.5±0.02	0.54±0.02	99.34±0.14	12 min	13 hrs
F3	4.6±0.07	0.61±0.01	98.34±0.14	8 min	15 hrs
F4	4.6±0.07	0.27±0.23	99.21±0.18	10 min	13 hrs
F5	4.4±0.03	0.12±0.40	100.34±0.10	11 min	12 hrs
F6	4.4±0.03	0.51±0.02	99.96±0.12	3 min	18 hrs
F7	4.4±0.03	0.29±0.23	98.45±0.11	5 min	8 hrs
F8	4.4±0.03	0.21±0.40	99.35±0.20	5 min	12 hrs
F9	4.5±0.02	0.119±0.40	99.78±0.12	6 min	15 hrs
F10	4.5±0.02	0.24±0.19	100.2±0.10	5 min	16 hrs
F11	4.5±0.02	o.49±0.01	99.26±0.16	6 min	19 hrs
F12	4.5±0.02	0.36±0.17	99.51±0.20	2 min	24 hrs

***In-vitro* Drug Release:** The dissolution studies for the cefixime floating tablets were performed and the results obtained are given in the table 4 and 5 and represented in figures 6 to 8. All the formulations showed good floating capacity, but better sustainability of drug release was seen in F12 formulation which sustained the drug release to 99% for 24 hrs.

Table No: 4. *In-vitro* Drug Release studies of Cefixime floating tablets (F1-F6)

Time (Hrs)	Cumulative % drug release					
	F1	F2	F3	F4	F5	F6
1	47±0.09	44±0.15	42±0.36	33±0.80	31±0.09	32±0.96
2	58±0.23	58±0.23	56±0.29	43±0.21	43±0.21	38±0.09
4	68±0.66	66±0.72	61±0.12	57±2.9	55±1.48	46±0.92
6	77±0.04	72±1.10	68±0.66	65±0.32	68±0.66	52±0.55
8	93±0.76	86±0.42	75±0.12	72±3.1	73±0.47	58±0.36
10	98±1.50	95±1.50	86±0.42	83±0.26	84±0.28	66±0.72
12	-	98±1.50	93±0.14	89±0.54	87±0.42	72±0.29
14	-	98±1.50	96±0.29	94±0.20	92±0.44	83±0.26
16	-	-	98±1.50	98±1.50	94±0.20	88±0.18
18	-	-	-	-	98±1.50	92±0.44
20	-	-	-	-	-	96±0.29
22	-	-	-	-	-	99±0.28

Table No: 5. *In-vitro* Drug Release studies of Cefixime floating tablets (F7-F12)

Time (Hrs)	Cumulative % drug release					
	F7	F8	F9	F10	F11	F12
1	43±0.21	44±0.15	38±0.12	36±0.26	28±4.5	20±2.10
2	55±1.48	55±0.48	44±0.15	41±3.5	38±0.12	28±1.50
4	66±0.72	62±0.10	53±0.2	51±0.18	46±0.92	41±3.50
6	73±0.47	68±0.66	65±0.32	63±0.74	52±0.02	51±0.18
8	87±0.42	77±0.04	68±0.66	69±0.57	64±0.05	58±0.36
10	93±0.14	85±1.36	83±0.26	82±0.09	76±0.13	66±0.72
12	97±0.38	94±0.20	89±0.54	89±0.54	83±0.26	72±0.29
14	-	98±1.50	93±0.14	93±0.14	88±0.18	77±0.04
16	-	-	98±1.50	95±0.47	92±0.44	82±0.09
18	-	-	-	97±0.38	95±0.47	88±0.18
20	-	-	-	-	98±1.50	93±2.50
22	-	-	-	-	-	97±0.38
24	-	-	-	-	-	99±0.74

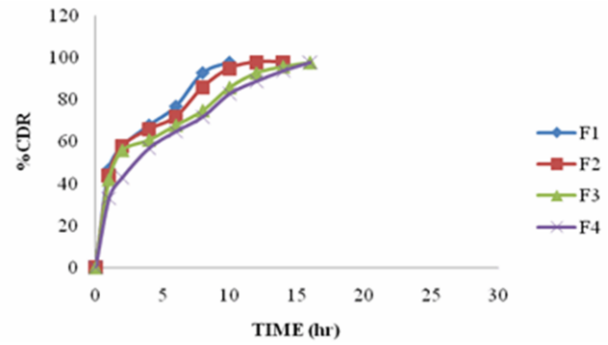

Fig No.6: *In-vitro* dissolution profile of F1 - F4 formulations

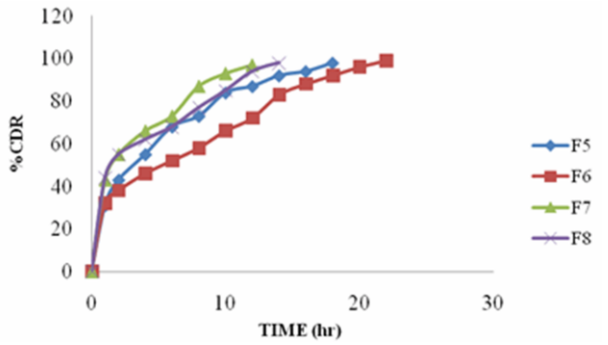

Fig No.7: *In-vitro* dissolution profile of F5 – F8 formulations

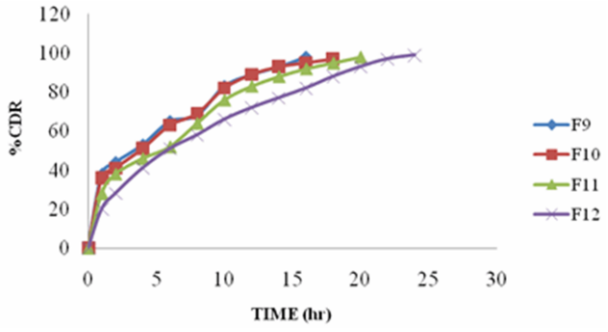

Fig No.8: *In-vitro* dissolution profile of F9-F12 formulations

Kinetic release studies of Cefixime:

To understand the mechanism and limits of drug release, the drug release data of the in-vitro dissolution studies were analyzed with various kinetic model like zero order ,First order, Korsemeyer Peppas Model, Higuchi model and the values of slope, intercept and R^2 were calculated in each case on the basis of kinetic analysis and reported in the table-6 and represented in figure 9-12. The best linearity was found in Higuchi equation plot R^2=0.999 indicates the release of drug from matrix as a square root of time dependent process based in Fickian diffusion.

Table No: 06 - Kinetic release studies of Cefixime

Formulation code/Parameter	Zero Order	First Order	Korsemeyer Peppas Model		Higuchi	Best fit model
	R^2	R^2	n	R^2	R^2	
F1	0.981	0.960	0.313	0.978	0.983	Higuchi
F2	0.934	0.896	0.309	0.975	0.972	Peppas

F3	0.959	0.916	0.302	0.976	0.980	Higuchi
F4	0.964	0.895	0.397	0.997	0.996	Peppas
F5	0.922	0.835	0.397	0.995	0.984	Peppas
F6	0.986	0.946	0.386	0.967	0.983	Zero Order
F7	0.964	0.919	0.321	0.990	0.989	Peppas
F8	0.983	0.951	0.292	0.970	0.985	Higuchi
F9	0.978	0.943	0.358	0.976	0.985	Higuchi
F10	0.952	0.907	0.375	0.977	0.983	Higuchi
F11	0.957	0.891	0.437	0.984	0.985	Higuchi
F12	0.960	0.850	0.508	0.998	0.999	Higuchi

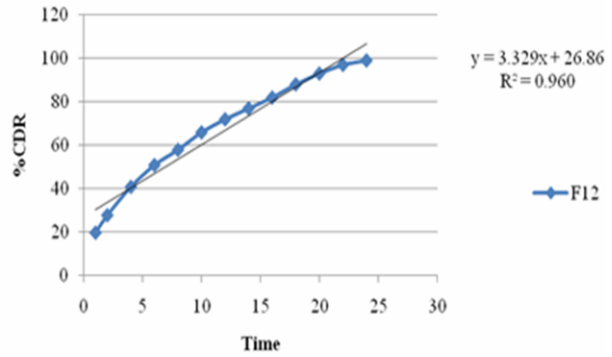

Fig No.9: Zero order kinetic model for optimized formulation

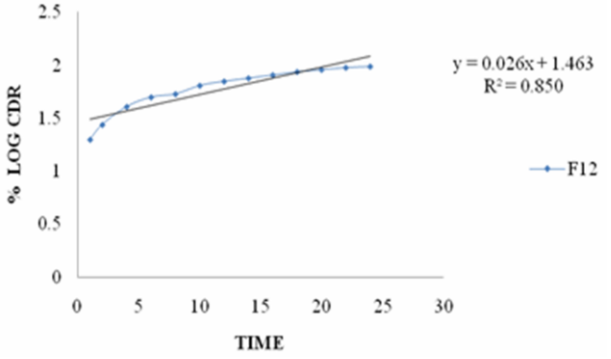

Fig No.10: First order kinetic model for optimized formulation

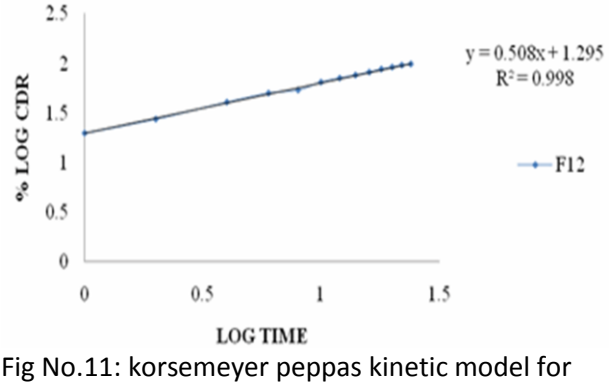

Fig No.11: korsemeyer peppas kinetic model for optimized formulation

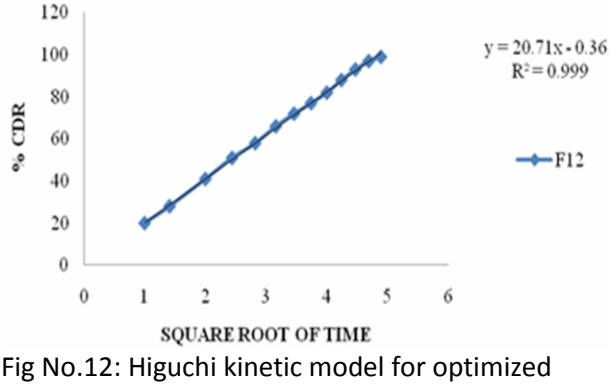

Fig No.12: Higuchi kinetic model for optimized formulation

CONCLUSION

Cefexime is absorbed throughout the GIT but it shows better absorption in the stomach when compared to other parts of the GIT. In the present work, Floating matrix tablets of Cefexime were designed with a view to enhance the absorption and bioavailability of the drug. Different batches of formulations were prepared using hydrophilic polymer (ie) HPMCK15M and HPMC K 100M in combination with Poly ethylene oxide. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, Floating lag time and in-vitro dissolution. Among all the formulations, the formulation F12 with 350mg of HPMC K100m in combination with 50 mg of PEO emerged as the overall best formulation based on drug release characteristics, which showed a sustained release of the drug from the hydrophilic matrix (i.e) 99% release of drug in 24 hrs when compared to F6 formulation which contained equal amount of HPMC K 15M which showed a sustained release only up to 22 hrs. From the kinetic analysis it was found that the drug release from the formulation is by higuchi model ie., by diffusion.

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