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Formulation, *In-Vitro* Evaluation and Release Kinetics of Cephalexin Matrix Tablets using HPMC K4M, HPMC K15M, HPMC K100M and Ethyl Cellulose

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ABSTRACT

The purpose of the study was to develop cephalexin matrix tablets as controlled release dosage form having short half-life and to establish good drug release rate at low proportion of polymers mixture. Tablets were compressed by incorporating the release retardant polymer in a matrix form along with drug which prolong the drug release. Drug and polymer interactions were established by Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimeter (DSC) studies. Twelve formulations were prepared by mixing ethyl cellulose (EC) and different viscosity grades of hydroxypropyl methylcellulose (HPMC) i.e. K4M, K15M and K100M, in various proportions. F-1 to F-4 formulations were prepared with K4M and EC in 100:5:5, 100:10:5, 100:15:5 and 100:20:5; similarly, F-5 to F-8 were prepared with K15M; and F-9 to F-12 were prepared with K100M using wet granulation process. The FTIR and DSC spectrum confirmed absence of chemical interaction between drug and polymers. All the pre compression and post compression parameters were found to be in limits. From the dissolution testing, F-4 showed 100.34 % medicament release in 12 h. The design signifies the drug release rate of matrix tablets were influenced by polymers mixture i.e., EC:HPMC K4M in 5 mg: 20 mg proportion, and the formulation controlled 100 % medicament release up to 12 h effectively. It was found that K4M grade showed good control over drug release than K100M and K15M viscosity grades.

KEY WORDS: Controlled release, Matrix tablets, Polymers mixture, Release Kinetics.

1. INTRODUCTION

In developing countries, people are infected very often. Generally, disease causing agents are both gram positive and gram negative bacteria, thus proper treatment should be taken with medicaments, which have efficient action to neutralize the activity of these microorganisms. All cephalosporin possesses a wide range of bactericidal activity. Cephalexin is a first generation cephalosporin, and it is orally active drug. It inhibits cell wall synthesis of gram-positive bacteria. Actually, controlled release systems are used to decrease dosage regimen and maintain steady-state levels and therefore better control over acute diseases, with maximum utilization of drug by enabling reduction in total amount of dose administered and leads patient compliance. In this work, a series of trial were made to design, formulate and evaluate *in vitro* release of cephalexin matrix tablets up to 12 h, as previously the work was done for 6 h release matrix tablets. The formation of matrix system with release retardant polymer effects the drug release for an extended period of time with complete utilization of the drug. Wet granulation process was implemented for tablet compressing. The cephalexin matrix tablets were designed by using ethyl cellulose and hydroxypropyl methylcellulose in different proportion such as 5 mg:5 mg, 5 mg:10 mg, 5 mg:15 mg and 5 mg:20 mg (EC:HPMC K4M / KM15M / KM100M). In all formulations, 5 mg of EC (fixed quantity); and HPMC grades in a range of 5 mg to 20 mg were used to prepare polymers mixture. Twelve formulations were prepared and evaluated for their pre-compression and post-compression parameters. Low proportions of the polymers mixture were used i.e., in a range of 2.85 % to 7.14 % of the tablet weight, to establish the *in vitro* release of the drug up to 12 h and they were supported by evaluated parameters such as drug release rate, cumulative % drug released and drug released mechanism. The significance of the study was to establish suitable polymers combination ratio over the drug release rate from the dosage form up to 12 h.

2. MATERIALS AND METHODS

Cephalexin was gift sample from Ranbaxy Lab, Gudgaon, HPMC K4M, HPMC K15M, HPMC K100M, EC, Dibasic calcium phosphate, Magnesium stearate and Talc used are of analytical grade.

Fourier Transform Infrared (FTIR) spectroscopy: FTIR study were carried out on pure drug, individual polymers and optimized formulation. Equal weight of sample and potassium bromide (about 1 mg each) were mixed and compressed to form a pellet and then scanned them from 400 to 4000 cm^{-1}.

Differential Scanning Calorimetry (DSC): DSC study was carried out between drug and excipients to establish chemical interactions. Basically, the thermal attributes of a physical mixture are the sum of the thermal properties of individual components.

Formulation of controlled release matrix tablets: Required quantities of drug and all excipients were passed through the sieve 44 # and weighed accurately and then blended them properly (except lubricant and glidant) as per the formula (Table.1). The wet damp mass was formed by slowly adding granulating liquid as distilled water q.s. (quantity sufficient). The cohesive material was sieved through 12 # to form wet granules. Then they were dried at 50ºC for 2 h in a hot air oven (Universal Hot Air Oven) and then passed through 22 # mesh to collect uniform size of granules; and then talc and magnesium stearate were added to lubricate and then compressed them with the help of a single punch-tableting machine (Shakti) with tablets hardness maintained in the range of 4 to 6.02 kg / cm^2.

Table.1. Composition of tablet formulations

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
Cephalexin	100	100	100	100	100	100	100	100	100	100	100	100
Ethyl cellulose	5	5	5	5	5	5	5	5	5	5	5	5
HPMC K4M	5	10	15	20	--	--	--	--	--	--	--	--
HPMC K15M	--	--	--	--	5	10	15	20	--	--	--	--
HPMC K100M	--	---	--	--	--	--	--	--	5	10	15	20
DCP*	230	225	220	215	230	225	220	215	230	225	220	215
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Distilled water (in ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight of tablet (in mg)	350	350	350	350	350	350	350	350	350	350	350	350

* DCP is Dicalcium phosphate

Pre-compression evaluation parameters: Teknik Bulk Density Apparatus was used to measure bulk density. Presieved granules were placed in to a graduated measuring cylinder and then calculated the bulk density by measuring the weight and volume. It was repeated for three times. For tapped density measurement, granules were filled in graduated measuring cylinder of tap density tester, and operates for certain number of taps until the granules volume reaches a minimum. It was repeated for three times. Hausner's ratio and Carr's index were calculated. They were repeated for three times. Repose angle (θ) was calculated by pouring the weighed granules into the glass funnel which was firmed to a stand at 3 cm height. The granules were passed through the funnel on to the surface of a graph paper and form a cone. Then measured the height (h) and diameter (d) of the cone and calculated the repose angle. Three trials were carried out. The repose angle can be measured using the formula,

$$\theta = \tan^{-1}\left(\frac{2h}{d}\right)$$

Post-compression evaluation for formulated matrix tablets: Monsanto hardness tester was used to determine the hardness of the tablet, and six tablets were used for hardness measurement. Based on European Pharmacopoeia (EP), twenty tablets were randomly taken for the calculation of weight variation test and determined their average weight. Individual tablets weight were compared with the average weight. Three tablets were randomly selected for the measurement of thickness and the tablet was placed between two arms of the vernier calipers and thickness was measured. 10 tablets were selected randomly and put inside the Roche friability test apparatus (Teknik) for the determination of friability. Initially weighted 10 tablets and then revolved them in a drum for four minutes. Then dedusted and reweighed the tablets and calculated the lost quantity and then expressed into percentage value.

Randomly ten tablets were taken, weighed the total weight and calculated the average weight of them. Then they were grinded individually to fine powder. Powder equivalent to 355.6 mg of cephalexin was transferred into a volumetric flask (100 ml capacity), added 80 ml of 0.1 N HCl buffer to dissolve completely and then made up to 100 ml with the buffer solution. Then the solution was filtered through a Whatman filter paper. Then placed small quantity of filtrate in a cuvette and noted down the absorbance using UV-Vis Spectrophotometer (Systronic 2203) and quantity of the drug in the sample was calculated. Similarly, the drug solution prepared in phosphate buffer of pH 6.8 and quantity of the drug in the sample was calculated.

In vitro dissolution of controlled release tablets of cephalexin was studied in USP XXIII dissolution apparatus (Electrolab) rotated at 100 rpm. 900 ml of 0.1 N HCl buffer for 2 h, then in phosphate buffer of pH 6.8 up to 12 h. The dissolution media used for the test maintained at 37ºC ± 0.5ºC temperature throughout the experiment and one tablet was used in each test. At predetermined time intervals, each time 5 ml of samples were pulled out from dissolution medium using a syringe fitted with a pre-filter and immediately 5 ml of pure quantity of dissolution media was replaced after each withdrawn of samples. Then the samples were analyzed for their absorbance at 262 nm for calculating the drug content. The dissolution studies were carried out for three determinations. Calculated the cumulative percent drug released from the dissolution data and plotted the dissolution graph by placing time on X-axis and cumulative percent drug released on Y-axis.

Zero and first order rate of reaction were calculated by incorporating dissolution data obtained from 12 formulations. Cumulative amount of drug released to time graph, represents zero order release and the equation is expressed as, $C = K_0 t$, where K_0 is the zero order rate constant and t is the time (in h). Log cumulative % of drug remained vs. time graph, represents first order release, and equation is, $\text{Log } C = \text{Log } C_0 - (Kt / 2.303)$, where C_0 is the concentration of drug at zero time, K is the first-order constant and t is the time.

Cumulative % drug released vs. square root of time graph, denotes Higuchi model and the equation is, $Q = K t^{1/2}$, where K is the constant expresses the design variables of the system and t is the time in h. The equation signifies drug release rate is inversely depends on the square root of time. Korsmeyer Peppas (KP) equation were used to determine drug release mechanism from the dosage form. 12 h dissolutions data of drug release were plotted using the KP equation i.e., log cumulative % drug released vs. log time, and then exponent 'n' was calculated. $M_t/M_\infty = K t^n$, where M_t / M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and 'n' is an exponent that characterize the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent $n = 0.45$, it is Fickian diffusion; if $0.45 < n < 0.89$, it is non Fickian or anomalous diffusion; and if $n=0.89$, it expresses Case-II Transport or typical Zero order release.

3. RESULTS AND DISCUSSION

IR spectrum of pure drug, polymers and power mixtures of drug, excipients & the polymers were taken. The characteristics peaks of cephalexin are obtained at 3273.31 cm^{-1}, 3056.31 cm^{-1}, 2884.64 cm^{-1}, 1759.14 cm^{-1}, 1693.56 cm^{-1}, 1396.51 cm^{-1}, 1281.74 cm^{-1}, 1196.87 cm^{-1}, 1071.49 cm^{-1}, 986.62 cm^{-1}, 818.81 cm^{-1}, 696.33 cm^{-1} and 581.56 cm^{-1}. The obtained IR spectra indicate good compatibility in between drug and excipients. All the spectra are shown in the Fig.1 to Fig.4. In DSC test, drug peak was obtained at 199.1ºC in drug-polymer mixture whereas the pure drug showed an endothermic peak at 191.34°C. It indicates there was no phase transformation in between drug and polymers (Fig.5 to Fig.6).

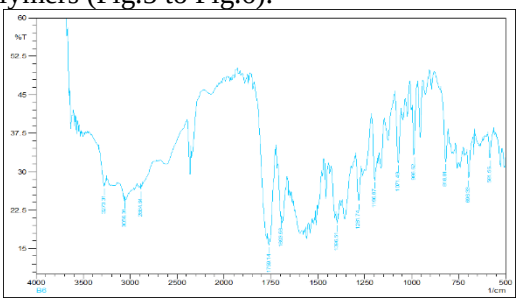

Figure.1. IR Spectrum of cephalexin alone

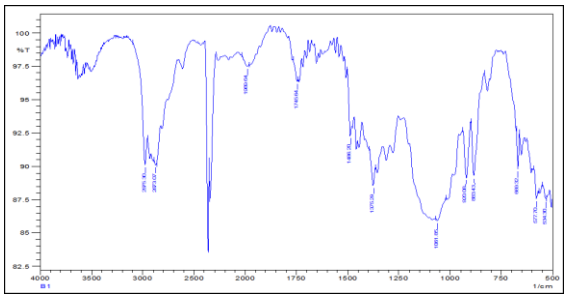

Figure.2. IR Spectrum of ethyl cellulose alone

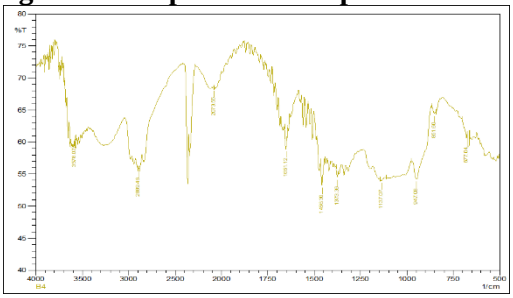

Figure.3. IR Spectrum of HPMC K4M alone

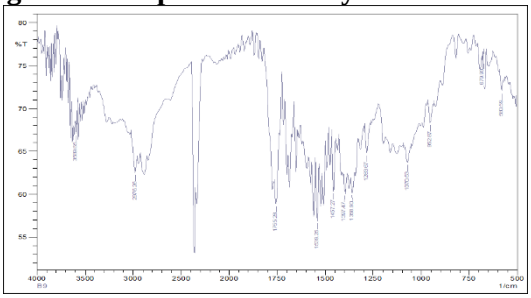

Figure.4. IR Spectrum of cephalexin, with excipients and polymers

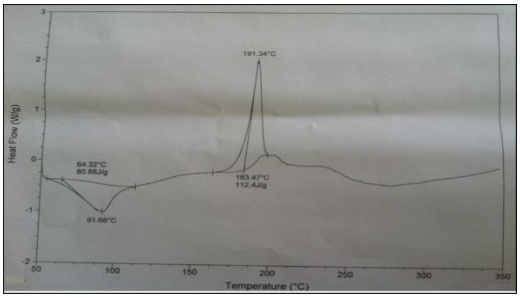

Figure.5. Thermogram of pure drug

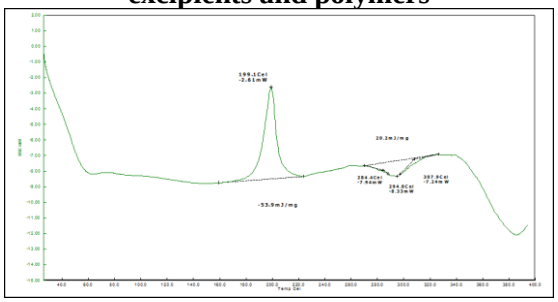

Figure.6. Thermogram of drug and polymers

Bulk densities and tapped densities of the granules of all formulations were calculated and they were ranged from 0.365 to 0.394 g / ml and from 0.420 to 0.461 g / ml respectively (Table.2). Lower values of bulk and tapped densities indicated that granules were in good packing with spherical shape and small size. The Hausner's ratio values ranged from 1.114 to 1.197. Evaluated values were less than 1.25 indicating good flow of granules and it was

observed to be within pharmacopoeial limits. The Carr's index values ranged from 12.18 % to 14.53 %. Carr's index values between 5-15 indicate excellent flow. The results obtained indicate that the granules flow properties were within the pharmacopoeia limit (Table.2). Angle of repose values ranged from 23.24° to 25.63°, indicate good flow properties of granules and uniform size of distribution, and it was observed to be within the official standard limits (Table.2).

Table.2. Precompression parameters of the granules

Formulation Code	Bulk Density (g / ml)	Tapped Density (g / ml)	Carr's Index (%)	Hausner's ratio ± SD	Angle of repose
F-1	0.384	0.441	12.92	1.148±0.03	25.41°
F-2	0.379	0.434	12.67	1.145±0.04	23.24°
F-3	0.394	0.461	14.53	1.170±0.03	24.32°
F-4	0.370	0.422	12.32	1.140±0.04	25.63°
F-5	0.369	0.428	12.18	1.149±0.06	24.21°
F-6	0.365	0.437	14.47	1.197±0.01	24.74°
F-7	0.372	0.428	13.08	1.150±0.03	25.62°
F-8	0.384	0.420	12.28	1.114±0.03	24.37°
F-9	0.370	0.422	12.32	1.140±0.06	23.38°
F-10	0.375	0.421	12.32	1.135±0.01	24.34°
F-11	0.380	0.432	12.23	1.142±0.03	25.12°
F-12	0.371	0.425	13.26	1.190±0.04	25.10°

All values are mean ± standard deviation (SD) for n=3 determination

The hardness of the tablets were ranged from 5.52 to 6.02 kg / cm^2, and the thickness were ranged from 2.30 to 2.35 mm. The tablet mean thickness was almost uniform in all the formulations (Table 3); and more than 5.52 kg / cm^2 hardness indicates strong compactness of the tablets which increases disintegration and drug dissolution time. The weights of the tablets were between 1.71 % to 2.30 %, as the actual weight of the tablet is 350 mg. The Pharmacopoeial specification for weight variation limit is ± 5 % for uncoated tablets weighing more than 324 mg. Hence all the formulations were passed the weight variation test (Table.3). Friability of all the formulations was determined, and the values were ranged from 0.32 to 0.82 %. Friability of the formulated tablets was found to be below 1 %, which indicates good mechanical resistance of the tablets. Hence all the formulations were within the Pharmacopoeial limits (Table.3). Percent drug content of the drug in all the formulated tablets was found to be within limit. Percent drug content of cephalexin was within 98.48 % to 99.30 % for all formulations. The results were within the range indicate uniformity of mixing (Table.3).

Table.3. Evaluation parameters of the compressed tablets

Formulation Code	Thickness (mm) ± SD	Weight variation (%)	Hardness (kg/cm^2) ± SD	Friability (%) ± SD	Drug Content (%) ± SD
F-1	2.30±0.35	1.93	5.22±0.01	0.32±0.01	99.25±0.40
F-2	2.32±0.45	1.82	5.72±0.36	0.76±0.01	99.13±0.25
F-3	2.35±0.37	1.71	6.02±0.01	0.82±0.01	99.15±0.16
F-4	2.30±0.39	1.85	5.53±0.36	0.66±0.01	99.30±0.41
F-5	2.35±0.44	2.19	5.55±0.35	0.42±0.01	98.48±0.41
F-6	2.33±0.43	1.83	5.76±0.36	0.49±0.01	99.10±0.49
F-7	2.35±0.38	2.30	5.88±0.33	0.61±0.01	98.58±0.52
F-8	2.32±0.29	1.98	5.55±0.32	0.45±0.01	99.30±0.44
F-9	2.31±0.55	1.76	5.52±0.36	0.59±0.01	98.64±0.06
F-10	2.35±0.52	1.86	5.78±0.33	0.60±0.01	98.56±0.56
F-11	2.32±0.56	2.10	5.58±0.32	0.49±0.01	98.81±0.58
F-12	2.31±0.33	1.94	5.54±0.36	0.55±0.01	99.11±0.44

All values are mean ± standard deviation (SD) for n=3 determination

In vitro drug release studies were carried out for 12 h (Table.4). The data indicated that formulations F-1 to F-12, released 92.34 %, 93.89 %, 94.36 %, 100.34 %, 89.91 %, 90.6 %, 91.63 %, 92.5 %, 92.48 %, 95.41 %, 95.48 % and 97.47 % of cephalexin respectively at the end of 12 h. From the *in vitro* release data profile, It was observed that when HPMC polymer concentration increases in the formulations it increases % drug release from the dosage form i.e., F-1 < F-2 < F-3 < F-4 (K4M used formulations), F-5 < F-6 < F-7 < F-8 (K15M used formulations), and F-9 < F-10 < F-11 < F-12 (K100M used formulations). Based on % of drug release, F-1, F-2, F-3, F-5, F-6, F-7, F-8, F-9, F-10 and F-11 formulations could not able to release more than 90 % and 95.48 % of the drug at 10 h and

12 h respectively i.e., they hardly released approximately 5.48 % drug in last two hours in comparison to F-4 and F-12 formulations, which was not complied to the intended study design; and it was found that their polymers combination were not in appropriate ratio to control the drug release, whereas formulations F-4 and F-12 were released the drug in controlled and efficient manner up to 12 h, and their % released were 100.34 % and 97.47 % respectively. From the data obtained from different formulations, it was concluded that the formulation F-4 (EC:HPMC K4M in 5 mg:20 mg ratio) released 100.34 % of cephalexin in 12 h could be optimized as the best formulation as it prevailed cent percentage release of the drug.

Table.4. *In vitro* dissolution profile for formulations F-1 to F-12 (± SD)

Time (h)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
1	18.66 ±0.19	16.08 ±0.15	21.11 ±0.14	15.48 ±0.16	25.11 ±0.15	26.7 ±0.21	25.24 ±0.13	21.03 ±0.13	18.59 ±0.12	20.25 ±0.19	20.60 ±0.16	15.09 ±0.13
2	29.33 ±0.12	26.19 ±0.19	27.18 ±0.18	25.33 ±0.24	28.21 ±0.26	28.9 ±0.16	28.47 ±0.16	26.75 ±0.18	24.55 ±0.15	24.34 ±0.12	26.10 ±0.13	23.48 ±0.15
3	56.02 ±0.26	43.25 ±0.22	45.55 ±0.15	39.05 ±0.16	49.65 ±0.21	49.61 ±0.12	50.78 ±0.12	52.74 ±0.15	50.21 ±0.19	50.44 ±0.13	50.24 ±0.18	50.84 ±0.13
4	57.48 ±0.18	54.63 ±0.20	53.29 ±0.12	40.26 ±0.18	51.98 ±0.12	55.01 ±0.18	56.06 ±0.18	57.84 ±0.12	55.40 ±0.12	55.79 ±0.18	56.19 ±0.15	55.68 ±0.12
5	59.37 ±0.20	60.46 ±0.25	60.73 ±0.16	56.89 ±0.12	57.23 ±0.18	57.19 ±0.16	59.47 ±0.14	60.73 ±0.20	58.94 ±0.16	60.84 ±0.14	60.35 ±0.14	60.78 ±0.14
6	60.54 ±0.23	64.4 ±0.22	69.33 ±0.13	65.84 ±0.13	60.00 ±0.15	59.53 ±0.13	59.89 ±0.16	66.30 ±0.15	60.13 ±0.13	63.57 ±0.26	63.71 ±0.25	65.42 ±0.13
7	65.79 ±0.21	69.8 ±0.18	75.17 ±0.13	73.96 ±0.13	60.59 ±0.14	63.05 ±0.18	54.16 ±0.21	67.22 ±0.16	63.82 ±0.24	69.46 ±0.16	69.58 ±0.20	70.96 ±0.18
8	69.44 ±0.20	72.57 ±0.21	75.46 ±0.18	79.16 ±0.17	65.26 ±0.19	67.99 ±0.12	69.88 ±0.15	69.87 ±0.13	67.39 ±0.19	73.45 ±0.13	76.15 ±0.26	78.49 ±0.14
9	71.92 ±0.18	74.61 ±0.12	77.65 ±0.26	82.95 ±0.12	70.22 ±0.22	71.63 ±0.23	79.37 ±0.13	71.93 ±0.12	73.68 ±0.14	78.35 ±0.17	85.13 ±0.19	88.26 ±0.12
10	78.19 ±0.24	79.27 ±0.21	79.98 ±0.18	91.65 ±0.21	73.28 ±0.13	78.78 ±0.16	85.06 ±0.17	77.53 ±0.24	75.87 ±0.25	82.89 ±0.15	88.29 ±0.24	92.84 ±0.14
11	86.07 ±0.21	85.42 ±0.16	88.48 ±0.17	96.47 ±0.16	83.78 ±0.12	84.47 ±0.13	87.25 ±0.20	88.86 ±0.26	80.99 ±0.16	88.43 ±0.13	92.66 ±0.22	94.26 ±0.16
12	92.34 ±0.18	93.89 ±0.18	94.36 ±0.15	100.34 ±0.14	89.91 ±0.13	90.60 ±0.18	91.63 ±0.12	92.50 ±0.20	92.48 ±0.13	95.41 ±0.13	95.48 ±0.20	97.47 ±0.13

All values are mean ± standard deviation (SD) for n=3 determination

Data of *in vitro* release were fitted to different equation and kinetic models to explain the release kinetics of cephalexin from the controlled release matrix tablet. Estimated data were plotted according to the zero order equation and first order equation, the formulations showed with regression values between 0.9548 and 0.9899 in zero-order, & 0.9460 and 0.9747 in first order (Table.5). All formulations following a zero order release pattern as the zero order regression was greater than first order regression.

Table.5. Release kinetics of formulated matrix tablets

Formulation Code	Correlation Coefficient	
	Zero order	First order
F-1	0.9548	0.9524
F-2	0.9670	0.9627
F-3	0.9693	0.9683
F-4	0.9899	0.9545
F-5	0.9730	0.9535
F-6	0.9784	0.9641
F-7	0.9688	0.9613
F-8	0.9559	0.9538
F-9	0.9596	0.9460
F-10	0.9701	0.9569
F-11	0.9763	0.9747
F-12	0.9711	0.9679

The *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity with R^2 values between 0.9753 and 0.9914, and it indicating that diffusion mechanism involved in the release of the drug from the tablets. To confirm the diffusion mechanism, the data were fit into Korsmeyer Peppas equation to calculate the slope 'n', and the values were ranging from 0.4655 to 0.7382. As the slope was less than 0.89, the diffusion mechanism involved in formulations F-1 to F-12 was considered to be non-Fickian (Table.6).

Table.6. Diffusion characteristics of formulated matrix tablets

Formulation code	Kinetic models		
	Higuchi	Peppas model	
	R^2	R^2	n
F-1	0.9774	0.9768	0.5633
F-2	0.9914	0.9906	0.7074
F-3	0.9893	0.9843	0.5939
F-4	0.9943	0.9968	0.7473
F-5	0.9834	0.9823	0.4879
F-6	0.9860	0.9784	0.4655
F-7	0.9753	0.9752	0.5053
F-8	0.9795	0.9802	0.5781
F-9	0.9797	0.9749	0.5955
F-10	0.9878	0.9800	0.6105
F-11	0.9909	0.9842	0.6162
F-12	0.9890	0.9811	0.7382

4. CONCLUSION

Successfully designed controlled release cephalexin matrix tablets using EC and different viscosity grades of HPMC such as K4M, K15M and K100M in different proportions. The polymers mixture were used in a range of 2.85 % to 7.14 % of a tablet weight. In all 12 formulations a constant quantity of EC used i.e., 5 mg, along with HPMC grades to formulate matrix tablets. F-1 to F-4 formulations were prepared taking EC with K4M in the ratios of 1:1, 1:2, 1:3 and 1:4, similarly F-5 to F-8 were prepared with K15M and F-9 to F-12 prepared with K100M. Results obtained from FTIR spectra, there were no interaction in between polymers and drug. Tablets were evaluated for weight variations, drug content, *in vitro* dissolution. Formulations which prepared by polymer mixture at 1:1, 1:2, 1:3 ratio were not produced more than 96 % drug release. Whereas F-4, F-8 and F-12 were released 100.34 %, 92.50 and 97.47 % of drug respectively, which were prepared in a ratio of 1: 4. As per dissolution profile of all formulations, F-4 (EC:HPMC K4M in 5mg:20 mg ratio) released 100.34 % of drug in 12 h was selected as the best fit formulation. It concluded that K4M (low viscosity) grade of HPMC at 7 % concentration extended the drug release up to 12 h thereby increasing patient compliance. The work is to be continued for *in vivo* study support to establish its clinical significance.

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