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FORMULATION DESIGN AND EVALUATION OF CEPHALEXIN CONTROLLED RELEASE MATRIX TABLETS

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ABSTRACT

The aim of the present work was to design controlled release matrix tablets of Cephalexin by incorporating the drug in a matrix made up of using combination of low concentration of hydrophobic polymer and hydrophobic polymers, to study their release pattern and release mechanism of the drug from matrix tablets upto 12 hours. Hydrophobic polymer is the rate retardant material, but different combinations with hydrophilic polymer increase the release rate to establish intended drug release up to 12 hours. Matrix tablets were formulated with the combination of hydrophobic to hydrophilic polymers in the ratios of 1:1, 1:2, 1:3 and 1:4. F1 to F4 formulation were prepared with ethylcellulose (EC) and hydroxypropyl methyl cellulose (HPMC K4M), F5 to F8 were prepared with EC and HPMC K15M and F9 to F12 were prepared with EC and HPMC K100M. Designed matrix tablets were evaluated for various pre-compression and post-compression parameters. F4 is the optimized formulation, showed 100.34% release at the end of 12 hours as it showed good release rate profile compared to all formulations. Drug released pattern followed zero order with non-Fickian diffusion method.

KEYWORDS: Matrix former, Controlled release tablet, Release Kinetics, HPMC, Ethyl cellulose.

INTRODUCTION

In developing countries, infectious diseases are very often. The infectious diseases are precipitated by both gram positive and gram negative bacteria hence, the treatment is necessary with broad spectrum of activity. All cephalosporin posses a wide range of bactericidal activity. Cephalexin is an orally active first generation cephalosporin, which has high activity against gram-positive bacteria, these act by inhibiting bacterial cell wall synthesis.[1][2] Controlled release dosage forms have number of advantages over conventional dosage forms, such as improved patience compliance due to decrease in dosing frequencies, reduction in fluctuation in steady-state levels and therefore better control of disease, maximum utilization of drug enabling reduction in total amount of dose administered.[3][4] In the present work, an attempt has been made to design, formulate and evaluate *in-vitro* release of cephalexin matrix tablets. As the effect of controlled release dosage form is relatively more, incorporating the drug in the matrix tablet will prolong the drug release. These are prepared by wet granulation method. The matrix tablets of cephalexin designed using polymers such as ethylcellulose with hydroxypropyl methylcellulose (HPMC) K4M, HPMC K15M, HPMC 100M in different proportions and evaluated for various precompression and post compression parameters.[5][6] The effect of combination of polymers EC, HPMC K4M, K15M, K100M, on response parameters such as drug release pattern, cumulative percent release of the drug and drug release mechanism were studied.

MATERIALS AND METHODS

Cephalexin was a gift sample from Ranbaxy Pharma Ltd., Gurgaon, India., HPMC K4, HPMC K15, HPMC K100, Ethyl cellulose, Dibasic calcium phosphate (DCP), Magnesium stearate, Talc and all other ingredients used are of analytical grade.

Formulation of tablets

Required quantities of drug and all excipients were passed through the Sieve 44# and then accurately weighed and blended properly (except lubricant and glidant) as per the formula given in the 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. The wet granules were dried at 50ºC for 2 hr in a hot air oven (Universal Hot Air Oven) and then passed through 22# mesh to get granules of uniform size; and then talc and magnesium stearate are added to lubricate and then compressed using a single punch-

tableting machine (Shakti) with hardness of the tablets maintained between 5-6 kg/cm^2.[7][8][9][10]

Table-1: Formulation of cephalexin Controlled Release Matrix Tablet.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
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	180	175	170	165	180	175	170	165	180	175	170	165
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)	300	300	300	300	300	300	300	300	300	300	300	300

RESULTS AND DISCUSSION

Calibration curve by UV spectral analysis

A series of standard solutions of cephalexin (2-10µg/ml) in 0.1N HCl were prepared and their absorbance were measured at 262 nm against 0.1N HCl as reagent blank (Figure 1).

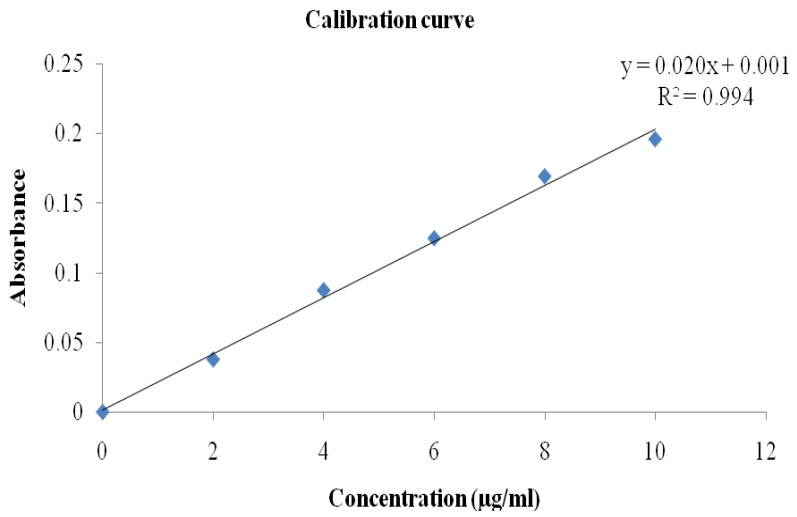

Figure 1 : Calibration curve of cephalexin.

Drug Excipient compatibility studies

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the

polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Fourier Transform Infrared (FTIR) spectroscopy

Pure drug, individual polymers and optimized formulation were subjected to FTIR study. About 1-2mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr pellet. The samples were scanned from 500 to 4000cm^{-1} (Figure 2-5).

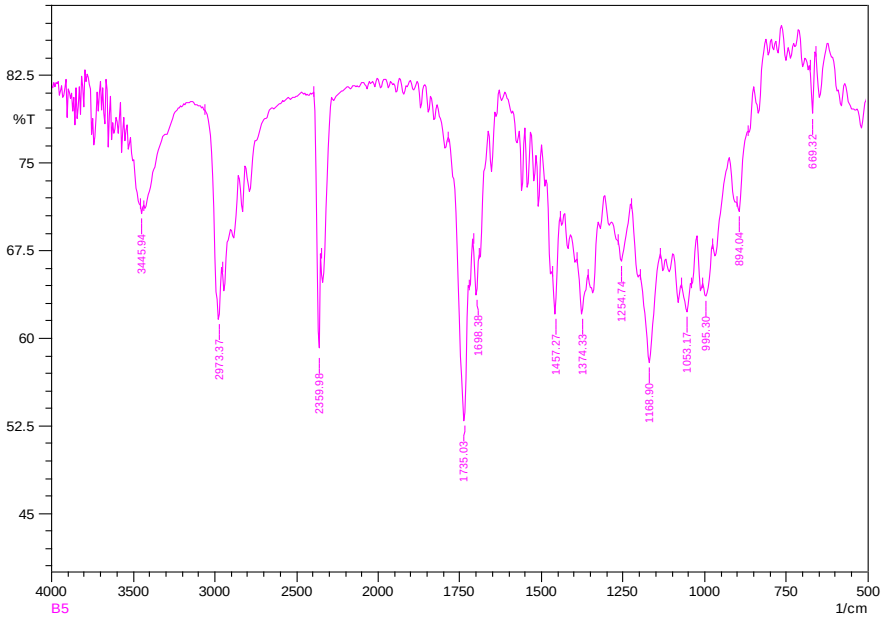

Figure 2: FTIR Spectrum of pure cephalexin.

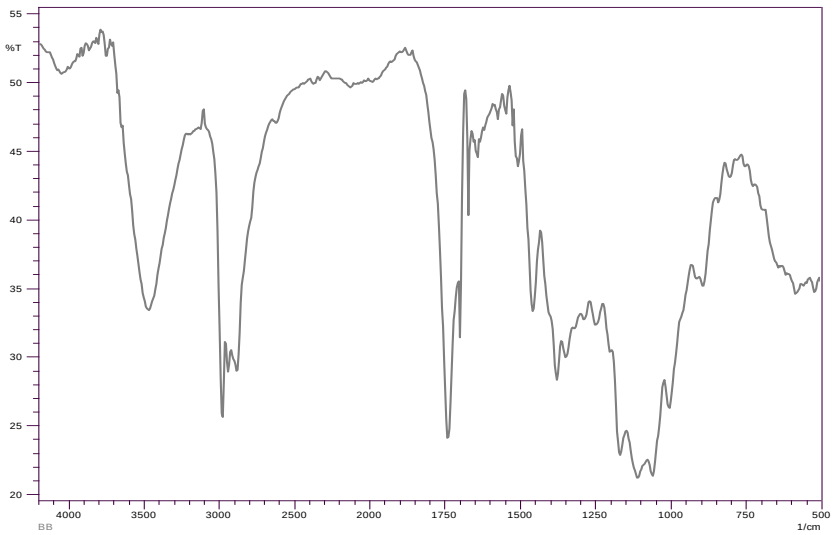

Figure 3: FTIR Spectrum of pure cephalexin, EC and HPMC K4M.

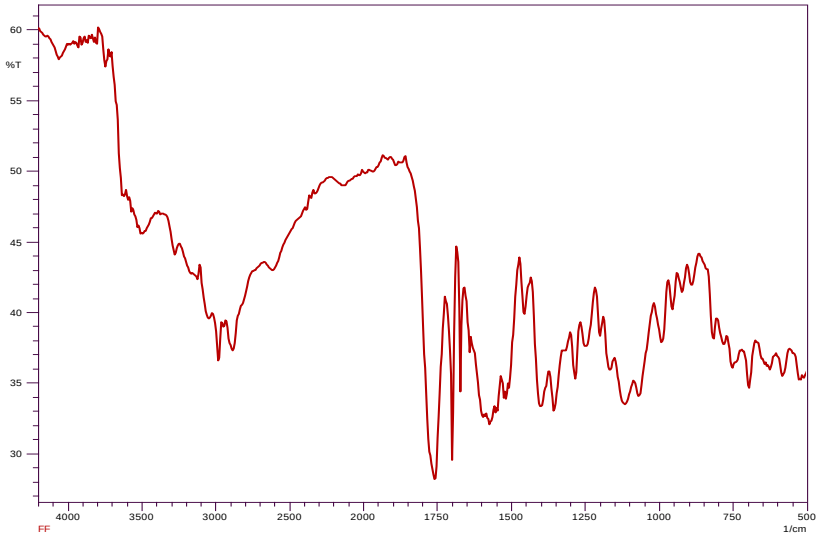

Figure 4: FTIR Spectrum of pure cephalexin, EC and HPMC K15M.

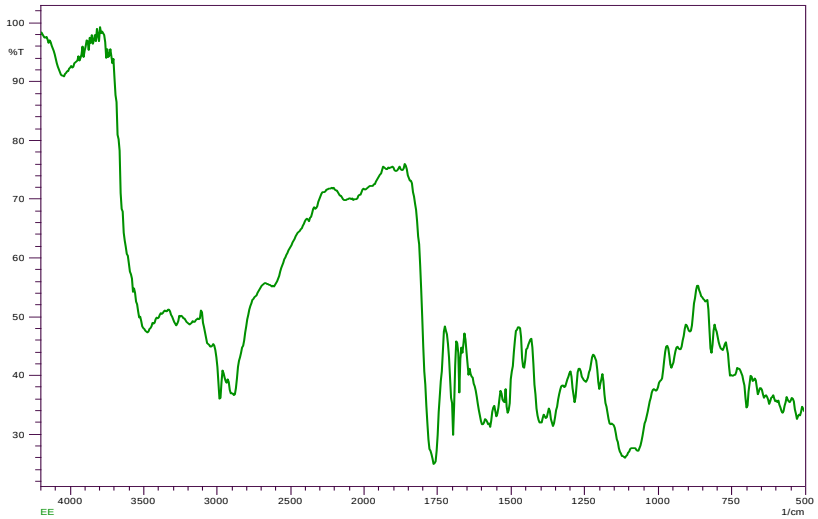

Figure 5: FTIR Spectrum of pure cephalexin, EC and HPMC K100M.

Evaluation of tablet blend

Bulk Density

Apparent bulk density is determined by placing pre-sieved drug excipients blend in to a graduated cylinder and measuring the volume and weight as it is.[11]

Tapped Density

Tapped density is determined by USP method II Tablet blend was filled in 100 ml graduated cylinder of tap density tester which operates for fixed number of taps until the powder bed volume reaches a minimum, thus is calculated using formula[12];

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

where, M =Weight of powder taken; V_t =tapped volume.

Angle of Repose

Angle of repose 'θ' is determined by using funnel method. Tablet blend is poured from funnel that can be raised vertically until a maximum cone height 'h' is obtained. Diameter heap D, was measured. The angle of repose is calculated by formula;

$$\theta = \tan^{-1}\frac{2h}{D}$$

Compressibility Index and Hausner Ratio

This is measured for the property of a powder to be compressed; as such they are measured for relative importance of interparticulate interactions. Compressibility index is calculated by following equation;

$$\text{Compressibility Index} = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

where, ρ_t =tapped density; ρ_b =bulk density;

Hausner ratio is calculated by following equation[13];

$$\text{Hausner Ratio} = \rho_t / \rho_b$$

where, ρ_t =tapped density and ρ_b =bulk density

Table 2: Bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio of the granules of cephalexin formulation.

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose
F1	0.379	0.434	12.67	1.145±0.04	23.24°
F2	0.394	0.461	14.53	1.170±0.03	24.32°
F3	0.370	0.422	12.32	1.140±0.04	25.63°
F4	0.369	0.428	12.18	1.149±0.06	24.21°
F5	0.377	0.424	12.57	1.143±0.04	24.24°
F6	0.392	0.452	14.63	1.168±0.03	24.32°
F7	0.373	0.422	12.32	1.142±0.04	25.63°
F8	0.368	0.428	12.18	1.149±0.06	25.21°
F9	0.379	0.435	12.66	1.155±0.04	23.74°
F10	0.394	0.460	14.57	1.170±0.03	24.62°
F11	0.370	0.422	12.38	1.140±0.04	24.63°
F12	0.369	0.428	12.18	1.149±0.06	24.21°

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

Evaluation of tablet

Weight Variation

Twenty tablets are randomly selected from each batch individually weighed; the average weight and standard deviation of 20 tablets are calculated.[14]

Thickness

The thickness of the tablet is measured by using digital vernier callipers, twenty tablets from each batch are randomly selected and thickness are measured.[15]

Hardness

Hardness is measured using Pfizer hardness tester, for each batch three tablets are tested.[16]

Friability

Twenty tablets are weighed and placed in the Roche Friabilator and apparatus is rotated at 25 rpm for 4 min. After revolution the tablets are dusted weight.[17]

Drug Content Uniformity

Twenty tablets of each type of formulation are weighed and crushed in mortar and powder equivalent to 100 mg of cephalexin is weighed and dissolved in 100 ml of 0.1N HCl. From the stock solution 1 ml sample is withdrawn and diluted to 10 ml with 0.1N HCl. The absorbance is measured at wavelength 262 nm using double beam UV-Visible spectrophotometer.

Table 3: Hardness, friability and drug content of matrix tablets of cephalexin formulations.

Formulation	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
F1	5.62±0.36	0.77±0.01	99.18±0.25
F2	5.02±0.01	0.72±0.01	99.15±0.16
F3	5.53±0.36	0.66±0.01	99.30±0.41
F4	5.55±0.35	0.42±0.01	98.48±0.41
F5	5.52±0.36	0.59±0.01	98.64±0.06
F6	5.78±0.33	0.60±0.01	98.56±0.56
F7	5.58±0.32	0.49±0.01	98.81±0.58
F8	5.54±0.36	0.55±0.01	99.11±0.44
F9	5.54±0.36	0.61±0.01	99.11±0.44
F10	5.76±0.36	0.45±0.01	98.48±0.41
F11	5.88±0.33	0.59±0.01	99.10±0.49
F12	5.55±0.32	0.60±0.01	98.58±0.52

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

In-Vitro Dissolution Study

The study is carried out using 0.1N HCl for first 2 hours and in phosphate buffer pH 6.8 upto 12 hours using the USP apparatus types II, the dissolution medium 900 ml maintained at 37ºC ±0.5ºC, The absorbance was measured at 262 nm, the dissolution study are carried out for 12 hrs.[18]

Table 4: Comparative dissolution profile for formulations F1 – F12.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	16.68	10.06	16.9	10.35	19.31	22.15	19.74	15.65	15.65	15.74	16.04	12
1	18.66	16.08	21.11	15.48	25.11	26.7	25.24	21.03	20.77	20.25	20.6	15.09
1.5	26.32	20.98	22.7	22.02	27.82	28.64	27.74	24.94	23.01	22.79	23.01	17.93
2	29.33	26.19	27.18	25.33	28.21	28.9	28.47	26.75	24.55	24.34	26.1	20
3	56.02	43.25	45.55	39.05	49.65	49.61	54.87	56.94	52.41	52.41	54.25	60.11
4	57.48	54.63	53.29	40.26	51.98	55.01	59.24	66.13	59.26	58.61	63.44	70.47
5	59.37	60.46	60.73	56.89	57.23	57.19	63.47	70.05	62.76	63.14	70.29	76.45
6	60.54	64.4	69.33	65.84	60	59.53	68.87	76.05	63.49	63.57	76.13	83.45
7	65.79	69.8	75.17	73.96	60.59	63.05	71.64	78.38	65.39	64.45	77.73	86.63
8	69.44	72.57	75.46	79.16	65.26	67.99	74.85	81.74	65.68	64.6	78.61	89.87
9	71.92	74.61	77.65	82.95	70.22	71.63	79.37	83.49	63.2	65.18	78.75	90.3
10	78.19	79.27	79.98	91.65	73.28	78.78	85.06	85.13	66.7	66.35	79.19	90.89
11	86.07	83.95	82.9	96.47	83.78	84.47	87.25	86.84	65.83	66.49	79.48	91.33
12	89.72	89.2	89.75	100.34	89.91	90.6	91.63	89.32	70.06	67.37	80.21	91.62

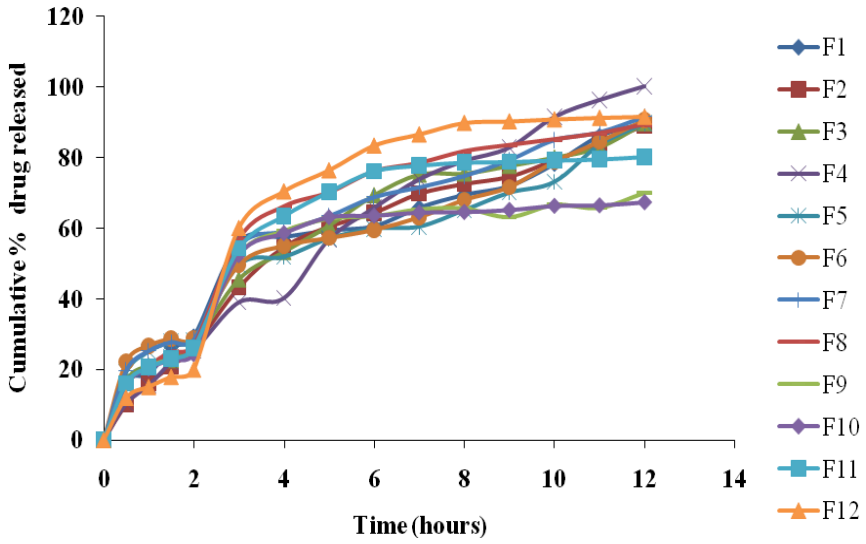

Figure 6: Comparative dissolution profile for formulation F1-F12.

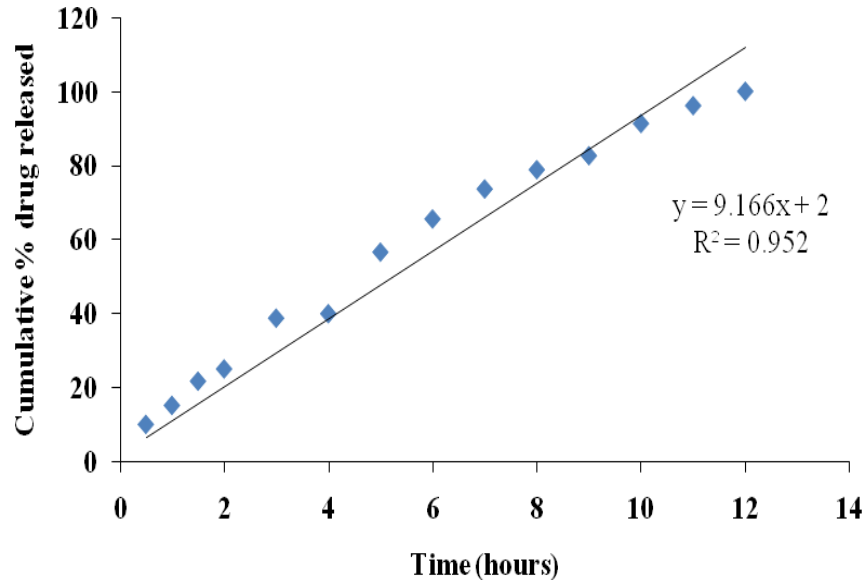

Figure 7: Dissolution plot for optimized formulation F-4.

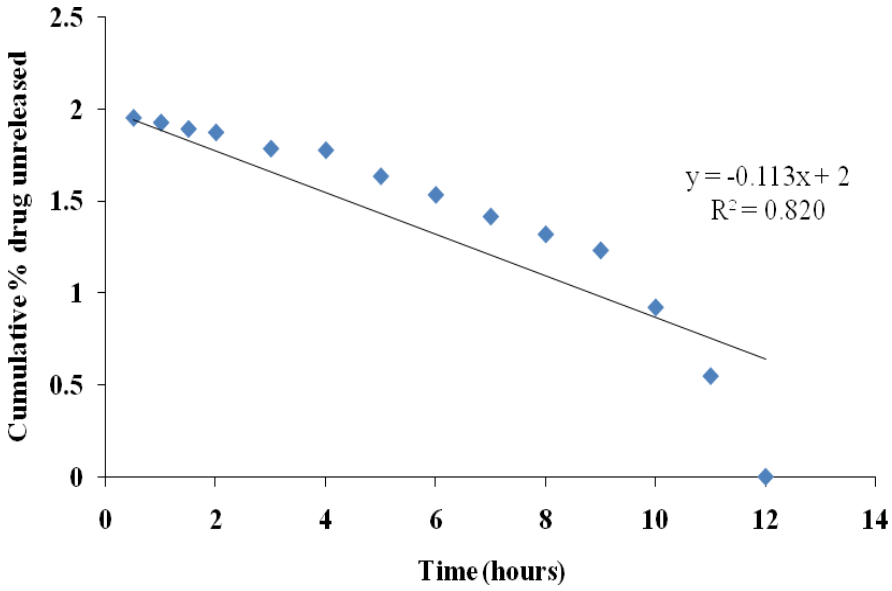

Figure 8: First order plot for optimized formulation F-4.

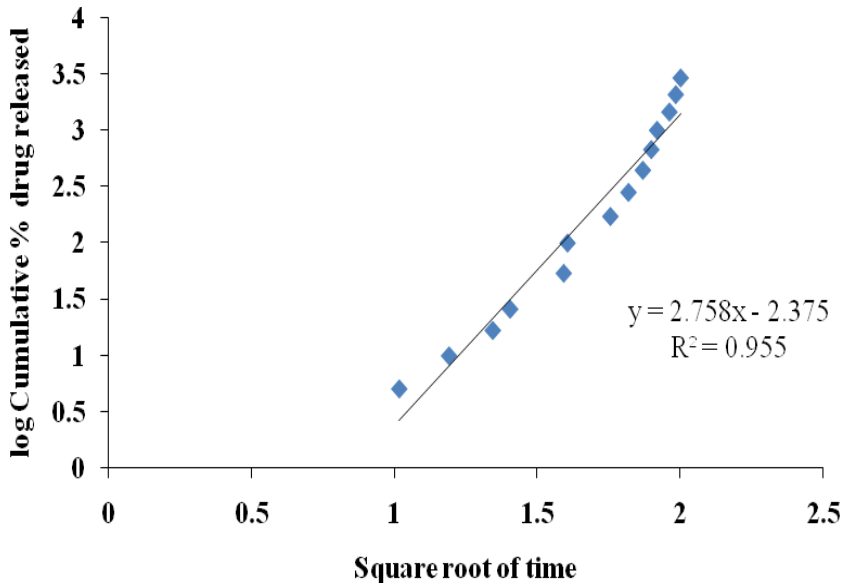

Figure 9: Higuchi plot for optimized formulation F-4.

Table 5: Application of kinetics for dissolution profile of formulation F-4.

Time (hrs)	%CDR	Log %CDR	Log %drug unreleased	Square root time	Log time	Slope 'n'
0.5	10.35	1.0149	1.9526	0.7071	-0.3010	0.7473
1	15.48	1.1898	1.9270	1.0000	0.0000	
1.5	22.02	1.3428	1.8920	1.2247	0.1761	
2	25.33	1.4036	1.8731	1.4142	0.3010	
3	39.05	1.5916	1.7850	1.7321	0.4771	
4	40.26	1.6049	1.7763	2.0000	0.6021	
5	56.89	1.7550	1.6346	2.2361	0.6990	
6	65.84	1.8185	1.5335	2.4495	0.7782	
7	73.96	1.8690	1.4156	2.6458	0.8451	
8	79.16	1.8985	1.3189	2.8284	0.9031	
9	82.95	1.9188	1.2317	3.0000	0.9542	
10	91.65	1.9621	0.9217	3.1623	1.0000	
11	96.47	1.9844	0.5478	3.3166	1.0414	
12	100.34	2.0015	--	3.4641	1.0792	

CDR: Cumulative drug release.

Inference

As per the above table the zero order regression value (0.9899) is more than first order regression(-0.9545), it concluded the drug release follows zero order release mechanism. As per Korsmeyer slope equation, slope value of F4 i.e., 0.7473 indicated drug release follows non-Fickian diffusion mechanism.

Stability studies

The accelerated stability study for the formulation at 40°C ± 2°C and 75% RH ± 5% RH was conducted for the 3 months, which includes the testing of parameters like identification of physical characters, identified by FTIR studies, dissolution profile and assay throughout period.

The stability studies on optimized formulation of cephalexin matrix tablets were conducted according to the ICH guidelines.

Table 6: Stability study of optimized formulation at 40°C ± 2°C and 75% RH ± 5% RH.

Time (months)	Physical change	Percentage of drug in the formulation
1	No	98.75
2	No	99.25
3	No	98.50

CONCLUSION

The market for drug delivery system has come a long way and will continue to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into a new delivery system, thus providing numerous therapeutic and commercial advantages. Matrix tablet drug delivery systems provide several all the advantages including greater flexibility and adaptability. It is evident from the results the that matrix tablets prepared from HPMC along with ethyl cellulose a better system for twice-daily controlled release matrix tablet of cephalexin. Formulation F-4 exhibited satisfactory drug release in the initial hours and the total release pattern was very close to the 100% release profile. So, F-4 was the most successful, cost-effective and optimized formulation.

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