JOURNAL OF DRUG DELIVERY RESEARCH

eISSN 2319-1074

# RESEARCH ARTICLE

# FORMULATION AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLET OF CEPHALEXIN: INFLUENCE OF COMBINATION OF HYDROPHOBIC AND HYDROPHILIC MATRIX FORMER.

**Reddy B.B.K.*[,1], Nagoji K.E.V[2], Sahoo S[3], Shoney M[4] , Prasanthi P[5]**

[1,4,5]**Srinivasarao College of Pharmacy, P.M.Palem, Visakhapatnam-530041, Andhra Pradesh, India.**
[2]**Sri Venkateswara College of Pharmacy, Etcherla, Srikakulam-532410, Andhra Pradesh, India.**
[3]**P.G. Department of Chemistry, Berhampur University, Bhanja Bihar, Berhampur-760007, Odisha, India.**

**Corresponding author: B. Basanta Kumar Reddy**

## 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 hydrophilic and hydrophobic polymers, which prolong drug release to provide patient convenience. Hydrophilic and hydrophobic polymers such as hydroxypropyl methylcellulose of different grades and ethyl cellulose respectively, as carriers in various concentrations were used to study their release pattern and release mechanism of the drug from matrix tablets upto 12 hours. Matrix tablets were formulated with 1:1, 1:2, 1:3 and 1:4 hydrophobic to hydrophilic polymer ratio. F1 to F4 formulation were prepared with ethylcellulose and HPMC K4M in 1:1, 1:2, 1:3, 1:4, 2:1, 2:2, 2:3, 2:4, 3:1, 3:2, 3:3 and 3:4. Similarly, F5 to F8 were prepared with ethylcellulose and HPMC K15M and, and F9 to F12 were prepared with ethylcellulose and HPMC K100M and by dry granulation technique. Designed matrix tablets were evaluated for various pre-compression and post-compression parameters. F4 is the best formulation, showed 100.34% release at the end of 12 h as it showed good similarity factor as compared with theoretical release rate profile. Drug released pattern followed zero order with non-Fickian diffusion method.

**KEY WORDS: M**atrix former, **C**ontrolled release tablet, **R**elease Kinetics, **H**PMC, **E**thyl 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

eISSN 2319-1074

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 proportion such as 1:1, 1:2, 1:3, 1:4, 2:1, 2:2, 2:3, 2:4, 3:1, 3:2, 3:3 and 3:4 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, drug release mechanism, similarity factor, were studied.

## MATERIALS AND METHODS

Cephalexin, HPMC K4, HPMC K15, HPMC K100, Ethyl cellulose, Dibasic calcium phosphate, Magnesium stearate, Talc and all other ingredients used are of analytical grade.

**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 4000$cm^{-1}$ (Figure 1).

**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 2. 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 4-5 kg/$cm^2$ [7[[8][9][10].

**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];

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

where, M =Weight of powder taken; $V_b$ =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;

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

eISSN 2319-1074

where, $\rho_t$ =tapped density; $\rho_b$ =bulk density;

Hausner ratio is calculated by following equation[13];

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

where, $\rho_t$ =tapped density and $\rho_b$ =bulk density

**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.

**In-Vitro Dissolution Study:**

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

## RESULTS AND DISCUSSION

In the present work, matrix tablets of cephalexin have been formulated by using ethyl cellulose and HPMC grade polymers in different proportions such as 1:1, 1:2, 1:3, 1:4, 2:1, 2:2, 2:3, 2:4, 3:1, 3:2, 3:3, 3:4, to study the release of drug up to desired time by fixing the quantity of drug in each formulation (Table 1). The matrix tablets so prepared by wet granulation method are evaluated for their angle of repose, carr's index, hardness, friability, drug content and drug release characteristics (Table 2 and Table 3). The optimized formulation (F-4) prepared with polymers EC: HPMC K4M in the ratio 5 mg: 20 mg (1:4) show 100.34 % drug release in 12 hours, it could be optimized as the best formulation which is comparable. As ethyl cellulose is hydrophobic and HPMC grades are hydrophilic in nature, these polymers are used in the formulation of controlled release formulations. Prepared matrix tablets was slow and spread over a period of 12 hours and released from the matrix tablets was diffusion controlled and kinetic results reveal that all formulations followed zero order kinetics (Table 4 and Figure 2, 3, 4 & 5). The calculated “n” values from power law equation for drug release profiles are between 0.4655 - 0.7473 with a correlation coefficient > 0.93, suggesting that drug release mechanism from matrix tablets followed non-fickian diffusion transport mechanism.

eISSN 2319-1074

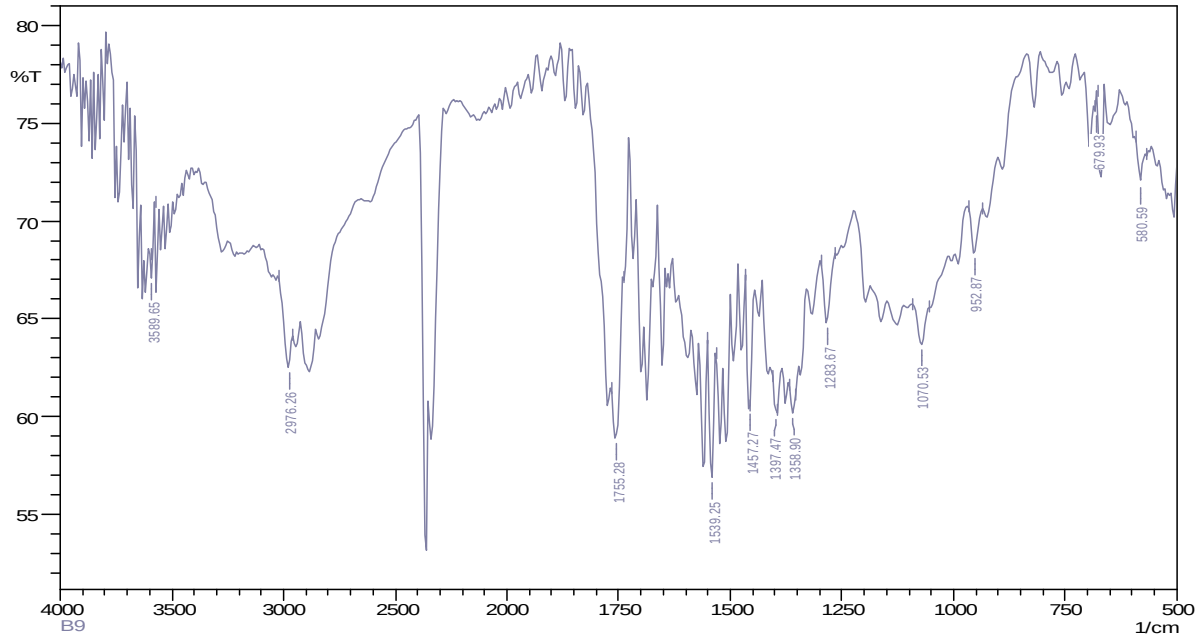


**Figure 1: Spectra of cephalexin, with excipients and polymers.**

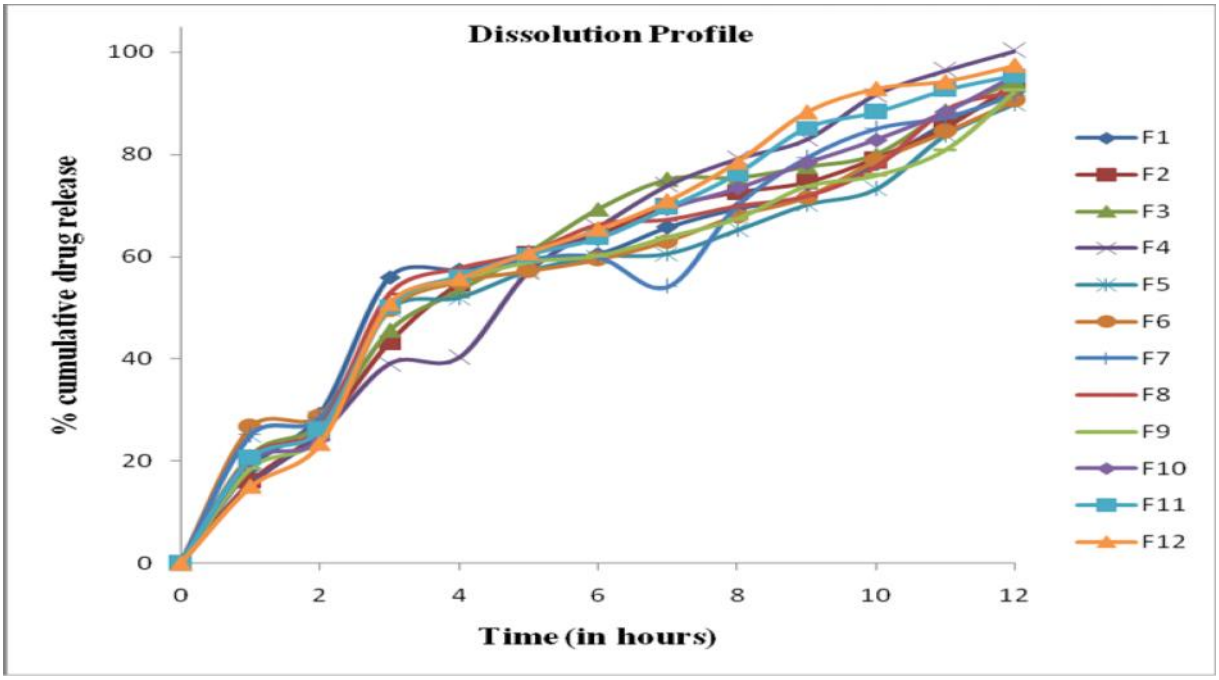


**Figure-2: Release Profile Plot of Matrix Tablets (F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12).**

eISSN 2319-1074

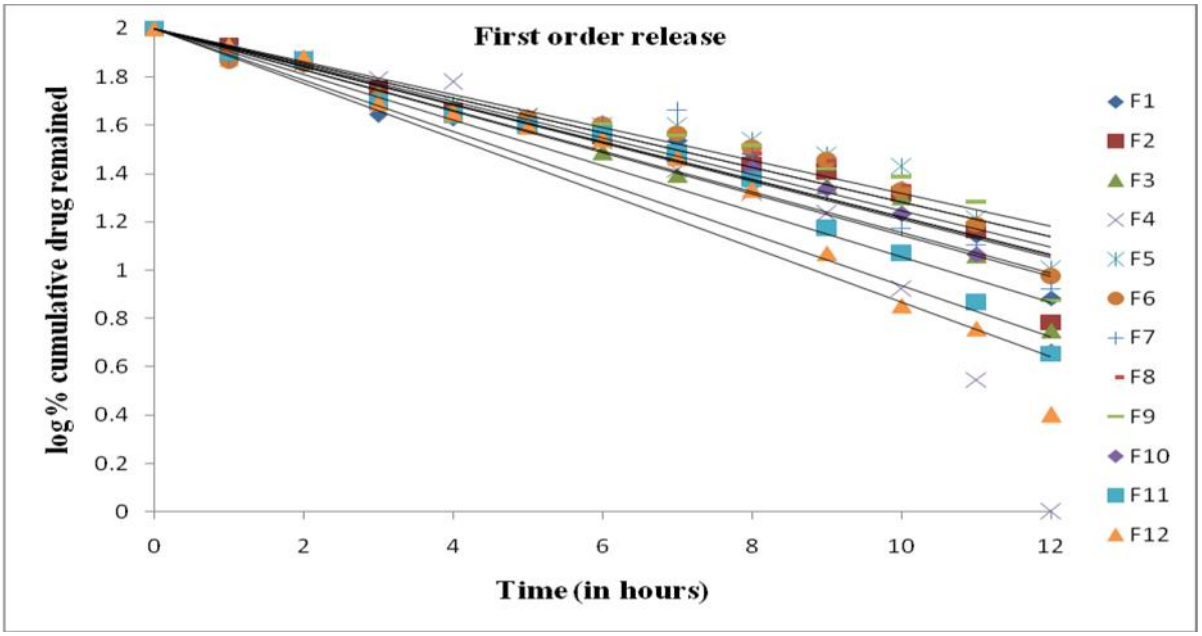


**Figure-3: First order released Plot of the matrix tablets (F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12).**

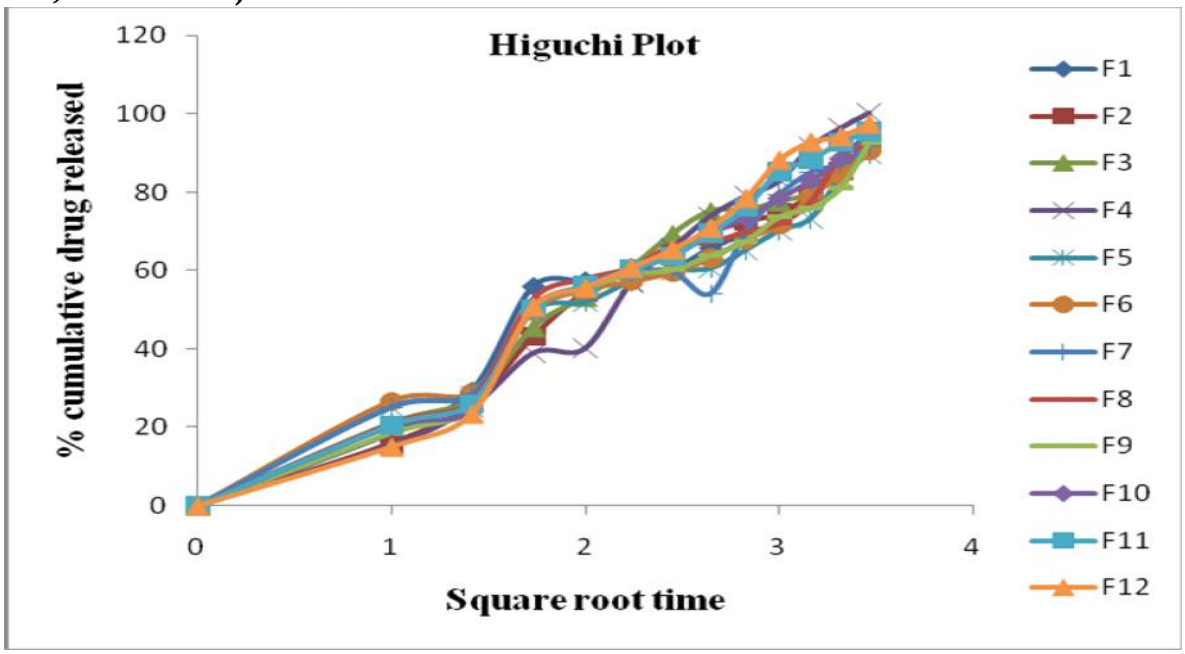


**Figure-4: Square Root Time Vs Percent Released Plot of Matrix Tablets (F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12).**

eISSN 2319-1074

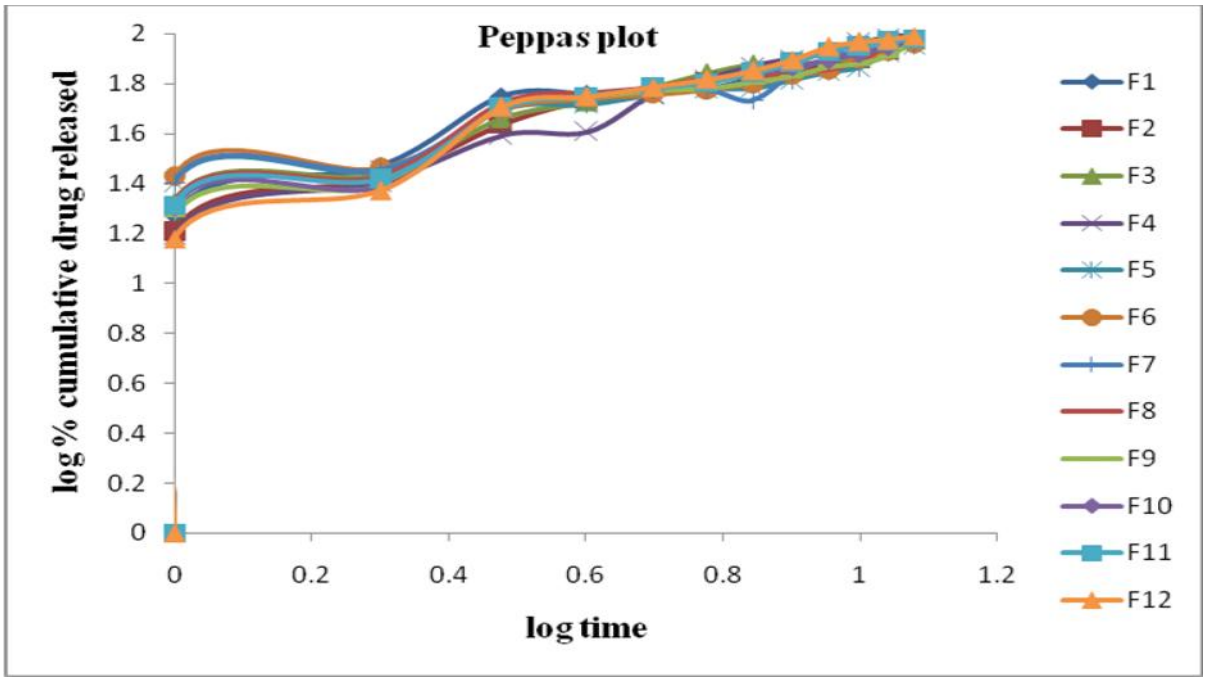


**Figure-5: Log Time Vs. Log Percent cumulative Drug Released plot of Matrix Tablets (F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12).**

**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 | 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 |

eISSN 2319-1074

**Table-2: Pre-compression Evaluation Tests.**

| Formulation Code | Bulk Density (gm/ml) | Tapped Density (g/ml) | Carr's Index (%) | Hausner's ratio | Angle of repose |
|---|---|---|---|---|---|
| F1 | 0.384 | 0.441 | 12.92 | 1.148±0.03 | 25.41° |
| F2 | 0.379 | 0.434 | 12.67 | 1.145±0.04 | 23.24° |
| F3 | 0.394 | 0.461 | 14.53 | 1.170±0.03 | 24.32° |
| F4 | 0.370 | 0.422 | 12.32 | 1.140±0.04 | 25.63° |
| F5 | 0.369 | 0.428 | 12.18 | 1.149±0.06 | 24.21° |
| F6 | 0.365 | 0.437 | 14.47 | 1.197±0.01 | 24.74° |
| F7 | 0.372 | 0.428 | 13.08 | 1.150±0.03 | 25.62° |
| F8 | 0.384 | 0.420 | 12.28 | 1.114±0.03 | 24.37° |
| F9 | 0.370 | 0.422 | 12.32 | 1.140±0.06 | 23.38° |
| F10 | 0.375 | 0.421 | 12.32 | 1.135±0.01 | 24.34° |
| F11 | 0.380 | 0.432 | 12.23 | 1.142±0.03 | 25.12° |
| F12 | 0.371 | 0.425 | 13.26 | 1.190±0.04 | 25.10 |

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

**Table-3: Post-compression Evaluation Data of Hardness, Friability, Drug Content and Thickness of Cephalexin Matrix Tablets Prepared by Wet Granulation Method.**

| Formulation Code | Thickness (mm) | Weight variation (%) | Hardness (kg/cm$^2$) | Friability (%) | Drug Content (%) |
|---|---|---|---|---|---|
| F1 | 2.30±0.35 | 1.93 | 5.22±0.01 | 0.32±0.01 | 99.25±0.40 |
| F2 | 2.32±0.45 | 1.82 | 5.72±0.36 | 0.76±0.01 | 99.13±0.25 |
| F3 | 2.35±0.37 | 1.71 | 6.02±0.01 | 0.82±0.01 | 99.15±0.16 |
| F4 | 2.30±0.39 | 1.85 | 5.53±0.36 | 0.66±0.01 | 99.30±0.41 |
| F5 | 2.35±0.44 | 2.19 | 5.55±0.35 | 0.42±0.01 | 98.48±0.41 |
| F6 | 2.33±0.43 | 1.83 | 5.76±0.36 | 0.49±0.01 | 99.10±0.49 |
| F7 | 2.35±0.38 | 2.30 | 5.88±0.33 | 0.61±0.01 | 98.58±0.52 |
| F8 | 2.32±0.29 | 1.98 | 5.55±0.32 | 0.45±0.01 | 99.30±0.44 |
| F9 | 2.31±0.55 | 1.76 | 5.52±0.36 | 0.59±0.01 | 98.64±0.06 |
| F10 | 2.35±0.52 | 1.86 | 5.78±0.33 | 0.60±0.01 | 98.56±0.56 |
| F11 | 2.32±0.56 | 2.10 | 5.58±0.32 | 0.49±0.01 | 98.81±0.58 |
| F12 | 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

eISSN 2319-1074

**Table- 4: Correlation Coefficient Values in the Analysis of Release Data of the Pure Drug Matrix Tablets Prepared as per Zero order, First order, Higuchi and Peppas Equation Models.**

| Formulation | $R^2$ Values | | | |
|---|---|---|---|---|
| | Zero order | First order | Higuchi | Peppas |
| F1 | 0.9548 | 0.9524 | 0.9774 | 0.9768 |
| F2 | 0.9670 | 0.9627 | 0.9914 | 0.9906 |
| F3 | 0.9693 | 0.9683 | 0.9893 | 0.9843 |
| F4 | 0.9899 | 0.9545 | 0.9943 | 0.9968 |
| F5 | 0.9730 | 0.9535 | 0.9834 | 0.9823 |
| F6 | 0.9784 | 0.9641 | 0.9860 | 0.9784 |
| F7 | 0.9688 | 0.9613 | 0.9753 | 0.9752 |
| F8 | 0.9559 | 0.9538 | 0.9795 | 0.9802 |
| F9 | 0.9596 | 0.9460 | 0.9797 | 0.9749 |
| F10 | 0.9701 | 0.9569 | 0.9456 | 0.9514 |
| F11 | 0.9763 | 0.9747 | 0.9612 | 0.9715 |
| F12 | 0.9711 | 0.9679 | 0.9756 | 0.9791 |

## 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. The hydrophilic matrix of HPMC alone could not control the drug release effectively for 12 hrs. 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.

**FINANCIAL SUPPORT AND SPONSORSHIP:**

Nil

## REFERENCES

1. Tripathi KD. Essential of Medical Pharmacology. 7th ed. New Delhi: Jayee Brothers Medical Publishers; 2013.
2. Satoskar RS, Bhandarkar SD, Ainapure SS. Pharmacology and Pharmacotherapeutics. 16th ed. Mumbai: Popular Prakashan; 1999.
3. Chugh I, Seth N, Rana AC, Gupta S. Oral sustained release drug delivery systems: an over view. Int Res J Pharm. 2012;3:57-62.

4. Gennaro AR, Remington: The Science and Practice of Pharmacy. 20th ed. Easton PA, USA: Mac Publishing Company; 2001.
5. Chien YW. Novel Drug Delivery Systems. 2nd ed. New York: Marcel Dekker Inc; 1992.
6. Bhalla HL, Raj PC. Release controlling polymers. Indian Drugs 1991;28:519-522.
7. Rezal MD, Qadir MA, Haider SS. Comparative evaluation of polymers as matrix for controlled release drug delivery. J Pharm Pharmaceutical Sci. 2003; 6: 274-291.
8. Andreopopulas AG, Tarantilli PA. Xanthan gum as a carrier for controlled release of drug. J. Biomater. App. 2001; 16: 35-38.
9. Parikh DM. Handbook of Pharmaceutical Granulation Technology. 2nd ed. Synthon Pharmaceuticals Inc. North Carolina, USA; 2005: p.191-192.
10. Reddy BBK, Nagoji KEV, Patnaik C. Studies on controlled release formulations of a macrolide antibiotic drug: Influence of HPMC of different grades as matrix former. World J Pharm Sci. 2015; 3: 2058-2068.
11. Basak SC, Shrinivasa R, Manavalan R, Rao P. Controlled release HPMC matrix tablet of propranolol HCl. Indian J Pharm Sci. 2004; 66(6): 827-833.
12. Shabaraya AR, Narayanacharyulu R. Design and evaluation of chitason matrix of metoprolol tartrate for sustained release. J Pharm Pharmaceutical Sci. 2008; 8(1): 231-236.
13. Shirwaikar AA, Jacob S, Grover V. Formulation and evaluation of sustained release tablets using an insoluble rosin matrix system. Indian J Pharm Sci. 2005; 67 (1): 80-83.
14. Krishanaiah YS, Lath K, Nageshwara L, Karthikeyan RS, Satyanarayana VBP. Development of colon target oral guar gum matrix tablet of Albendazole for the treatment of Helminthiasis. Indian J Pharm Sci. 2003; 65 (4): 378-385.
15. The British Pharmacopoeia, department of health/by stationary office on behalf of the medicine and health care product regulatory agency, crown copy right, 5thED, 2005: 1303-1304, 2588-2589, A133.
16. The United State of Pharmacopoeia 24/ NF19 Asian Edition. The official compendia of standard United States pharmacopoeial convection Inc. Rockville; 1995: 1015,1016, 1791.
17. Chaudhari PD. Formulation and Evaluation of fast dissolving tablet of famotidine. Indian Drug. 2005; 42(10): 641-649.
18. Raparla DV, Murthy TE. Formulation and evaluation of oral controlled release Glimepiride matrix tablets. Adv Phamacol Toxical. 2007; 8(2): 59-62.