ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF SUSTAINED RELEASE TABLETS OF CEFIXIME TRIHYDRATE

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Received on 13-04-2014 *Accepted on 02-05-2014*

Abstract:

The objective of present investigation was to formulate and evaluate hydrophilic matrix tablets of cefixime trihydrate to achieve sustained drug release with reduced frequency of drug administration, reduced side effects and patient compliance. Matrix tablets of cefixime trihydrate were prepared by using polymers like hydroxypropylmethylcellulose (HPMC K100, and HMC K4), and different diluents like microcrystalline cellulose, Ethyl cellulose, magnesium stearate, and talc as glidant. Cefixime is orally active third generation cephalosporin antibiotic. Cefixime is well absrobed from the Gut. The oral bioavailability is 40-50%. Cefixime sustained release tablets were prepared by direct compression method. The powder blend was subjected for pre-compressional parameters such as tapped density, bulk density,angle of repose, compressibilty index and hausner ratio. The prepared tablets are evaluated to post-compressional parameters such as hardness, friability, average weight, uniformity of weight and invitro dissolution studies. Drug compatability with excipients was checked FTIR studies. The values of pre-compressional parameters evaluated were within prescribed limits and indicated good free flowing property. The values of post- compressional parametres evaluated were within acceptable limits. The dissolution profiles of all the formulations were evaluated. Amongst all the formulations, the release profile of formula F7 gave optimum results. , It was concluded that for Cefixime trihydrate sustained release matrix Tablets, F7 is successful formulation and can be manufactured with reproducible characteristics from batch to batch.

Key words:

Cefixime trihydrate, Hydroxy Propyl Methyl Cellulose, Sustained Release, Matrix tablets.

1. Introduction:

The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutical, Pharmacokinetic and Pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route [1]. Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of drugs [2].

The sustained release oral dosage forms have been demonstrated to improve therapeutic efficacy by maintaining steady state drug plasma concentration. Various types of modified release formulations have been developed to improve the patient compliance and also clinical efficacy of the drug. Hydroxypropyl methyl cellulose (Hypromellose, HPMC) polymers have been widely studied for their application in oral sustained release formulations. Such hydrophilic polymers are most popular because of their flexibility to get a desirable drug release profile, cost effectiveness and broad regulatory acceptance [3]. HPMC has always been a first choice for formulation of hydrophilic matrix systems, because of providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods. HPMC most widely used as the gel forming agent in the formulations of solid, liquid, semisolid and controlled release dosage forms. The adjustment of the polymer concentration, the viscosity grades and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rates. The other advantages of sustained release dosage forms are patient compliance, reduction of local and systemic side effects, minimization of peaks and valleys in drug blood levels [4].

Cefixime Trihydrate is a relatively new broad spectrum third-generation cephalosporin, has very good in vitro activity against Streptococcus pneumonia. Conventional-release dosage form of Cefixime is administered, the peak plasma concentration achieved is 1.2 mg/L, and this concentration slowly declines below minimum effective concentration (MEC) within 12 hours.

2) Materials and Methods:

2.1) Materials: Cefixime trihydrate was obtained from Aurobindo Pharma Ltd, Hyderabad. HPMC grades were received from yarrow chem products, Mumbai. Other materials were purchased from Signet Chem, Mumbai, India.

2.2.1) Preformulation Studies:

2.2.1.1) Standardization Cefixime trihydrateof by UV-Visible spectrophotometry:

a) In 0.1 N Hcl Solution:

i) Preparation of stock solution: Stock solution 100µg/ml of Cefixime trihydrate was prepared in 0.1N Hcl solution. This solution was approximately diluted with 0.1N Hcl to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200- 400nm using Perkin Elmer Lambda-40 UV/VIS spectrophotometer.

ii) Standard calibration of Cefixime trihydrate in 0.1N Hcl:

100mg of was Cefixime trihydrate accurately weighed and dissolved in100ml of 0.1N Hcl to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with 0.1 N HCl to give concentrations in range of 5µg/ml to 25µg/ml respectively, absorbance was measured at 275nm.

a) In pH 7.2 Buffer:

i) Preparation of Stock solution

100mg of the drug (cefixime trihydrate) was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in methanol in sufficient quantity of pH 7.2 phosphate buffer and volume was made up to the mark with pH 7.2 phosphate buffers to get a 1000 µg/ml solution. One ml of the above solution was then further diluted to 100 ml with pH 7.2 phosphate buffer to get a stock solution of 10 (µg/ml).

ii) Preparation of the calibration curve

An accurately weighed quantity of Cefixime trihydrate (100mg) was dissolved in 100ml of 7.2 phosphate buffer to generate a stock solution having concentration of 1mg/ml.1ml of stock solution was further diluted to 100ml to produce standard solution having a concentration of 10mcg/ml, from this 2, 4, 6, 8 and 10ml were taken and were diluted to 10ml. It gives various concentrations of 2, 4, 6, and 10mcg/ml respectively. The absorbances of the solutions were measured at 288nm against blank (7.2 phosphate buffer) using UV-visible spectrophotometer.

2.2.1.2) Angle of repose

The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured.

The angle of repose was calculated using the following equation.

$$\text{Tan } \Theta = h/r$$

Where 'h' and 'r' are the height and radius respectively of the powder cone

2.2.1.3) Carr's compressibility index:

The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of blend from each formulation, filled into a 10mL of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5cm. The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume.

Carr's compressibility index was calculated by using following formula:

Carr's compressibility index (%) = [(Tapped density-Bulk density) X100]/Tapped density

2.2.1.4) Bulk Density (BD):

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The bulk densities (BD) of powder blends were determined using the following formula.

Bulk density = Total weight of powder / Total volume of powder

2.2.1.5) Tapped bulk density (TBD):

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities (TBD) of powder blends were determined using the following formula.

TBD= Total weight of powder / Total volume of tapped powder

2.3) Preparation of tablets: Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests. In all formulations, the amount of the active ingredient is equivalent to 200mg of Cefixime trihydrate[5-11].

Table 1: Formulations containing HPMC K4M:

INGREDIENTS	F1	F2	F3	F4	F5
Cefixime trihydrate	200	200	200	200	200
HPMC K4M	40	45	47.5	48.5	50
Micro crystalline cellulose	150	145	142.5	141.5	140
Magnesium stearate	4	4	4	4	4
Talc	6	6	6	6	6
Total tablet weight	400	400	400	400	400

All are expressed in mg.

Table 2: Formulations containing HPMC K100M, Ethyl cellulose, combination of HPMC K4M & HPMC K100M:

INGREDIENTS	F6	F7	F8	F9	F10
Cefixime trihydrate	200	200	200	200	200
HPMC K100M	100	95	---	190	240
HPMC K4M	---	---	50	190	120
Ethyl cellulose	---	---	50	---	---
Micro crystalline cellulose	95	90	50	---	---
Magnesium stearate	4	4	44	8	8
Talc	6	6	6	12	12
Total tablet weight	400	400	400	800	800

All are expressed in mg.

2.4) Evaluation of tablets:

The weight of tablets was evaluated on 20 tablets using an electronic balance. Friability was determined using 6 tablets in Roche friability tester at 25rpm. Hardness of the tablets was evaluated using an Monsanto hardness tester. The hardness of all the formulation was between 4-6kg/cm^2.

2.5) In vitro dissolution studies:

In vitro drug release studies from the prepared matrix tablets were conducted using USP type II apparatus at 37°C at 50rpm. Dissolution mediums used were 900mL of 0.1N HCl and phosphate buffer of pH 7.2. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for 2h and changed to phosphate buffer (pH 7.2) for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were

replaced with fresh dissolution media of respective pH. The samples were analyzed byPerkin Elmer Lambda-40 UV/VIS Spectrophotometer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time curve.

2.6) Data Analysis (Curve Fitting Analysis):

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:

1. Cumulative percentage drug released Vs Time (*In-vitro* drug release plots)
2. Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
3. Log cumulative percentage drug remaining Vs Time (First order plots)
4. Log percentage drug released Vs Log time (Peppas plots)

Zero order:

$$C = K_0 t$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time

t -is the time in hrs.

First order:

$$LogC = LogC_0 - Kt / 2.303$$

Where C_0 - is the initial concentration of drug,

K - is the first order constant

t - is the time in hrs.

Higuchi:

$$Qt = Kt^{1/2}$$

Where Q_t - is the amount of the release drug in time t,

K- is the kinetic constant and

t- is time in hrs

Korsmeyer Peppas:

$$Mt/ M\infty = Kt\, n$$

Where M_t - represents amount of the released drug at time t,

M_∞ is the overall amount of the drug (whole dose) released after 12 hrs

K- is the diffusional characteristic of drug/ polymer system constant

n- is a diffusional exponent that characterizes the mechanism of release of drug.

The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickian diffusion. If n < 0.5 the mechanism is quasi-Fickian diffusion, and 0.5 < n < 1.0, then it is non-Fickian or anomalous diffusion and when n = 1.0 mechanism is non Fickian case II diffusion, n> 1.0 mechanism is non Fickian super case II [12].

3. RESULTS AND DISCUSSION:

3.1 Preformulation characteristics:

The drug Cefixime trihydrate was standardized by UV method in 0.1N Hcl and pH 7.2 Buffer separately. The lamba max were 275nm and 288 nm in 0.1N Hcl and pH 7.2 buffer respectively and the linearity range was 5-25 mcg/ml and 2-10 mcg/mlin both the media.

Figure 1: Lambda Max of Cefixime trihydrate in 0.1 N HCl (275nm).

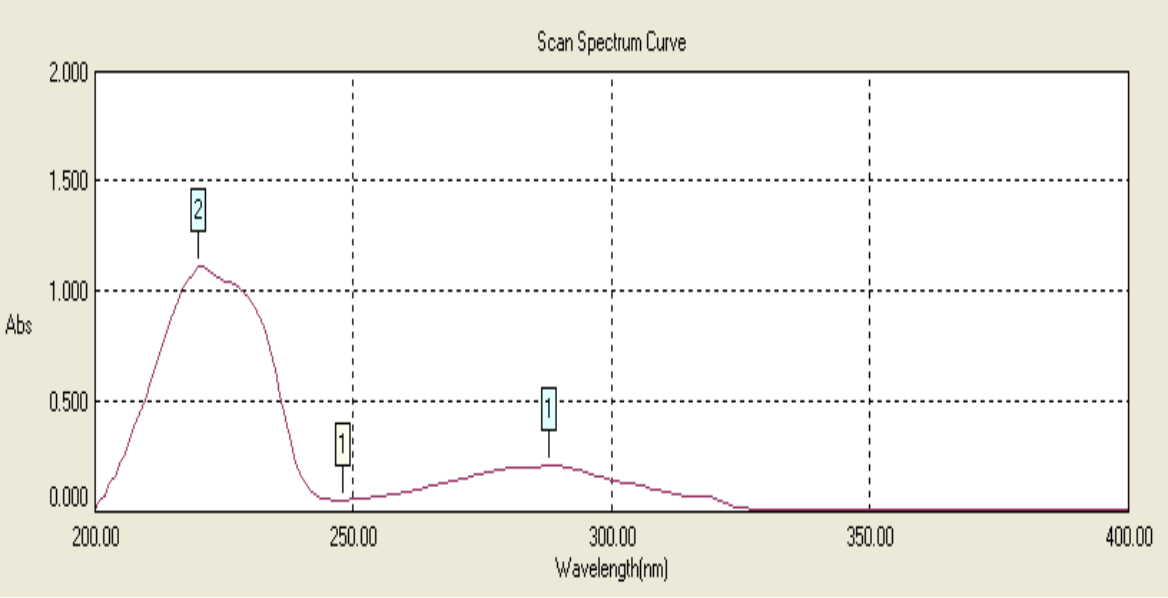
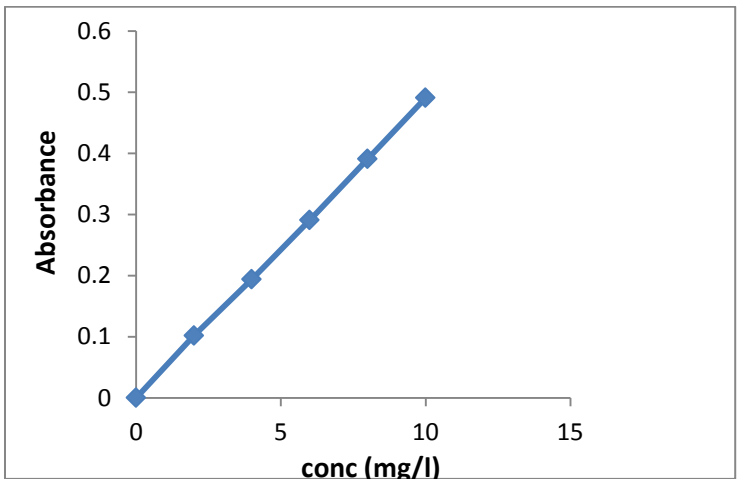


Table-3: Absorbances ofCefixime trihydrate in 0.1N HCL.

Concentration	Absorbance
0	0
5	0.212
10	0.340
15	0.431
20	0.576
25	0.694

Figure 2: Calibration curve ofCefixime trihydrate in 0.1N HCL.



Lambda Max ofCefixime trihydratein pH 7.2 Buffer (288nm).

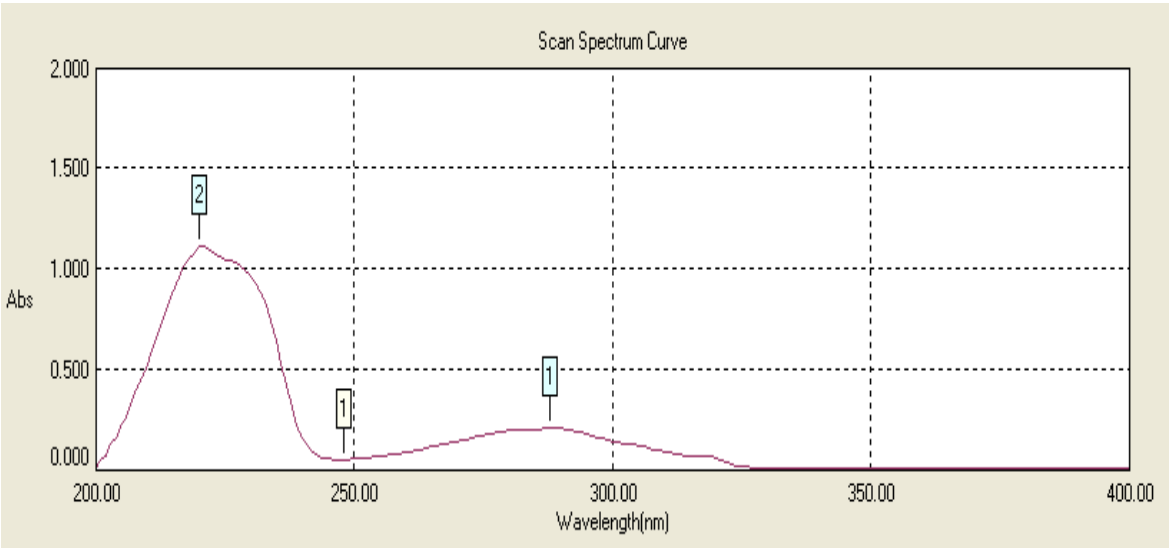
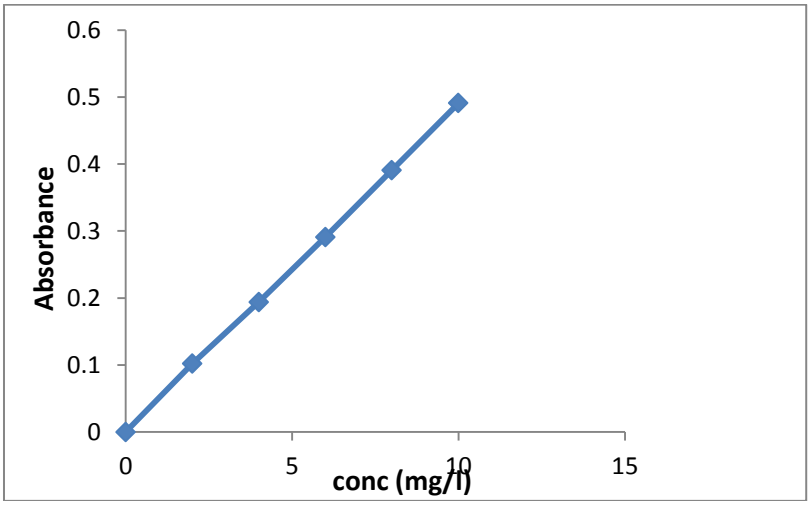


Table-4:Absorbances ofCefixime trihydrate in 7.2 Buffer.

Concentration	Absorbance
0	0
2	0.102
4	0.194
6	0.291
8	0.391
10	0.491

Figure 3: Calibration curve ofCefixime trihydrate in 7.2 Buffer.



3.2 Drug: Excipient Compatibility studies- FTIR: Drug-Excipient compatibility studies by FTIR revealed no interaction between drug and the polymers used in the formulation thus showing compatibility

Figure 4: FTIR spectra of pure Drug.

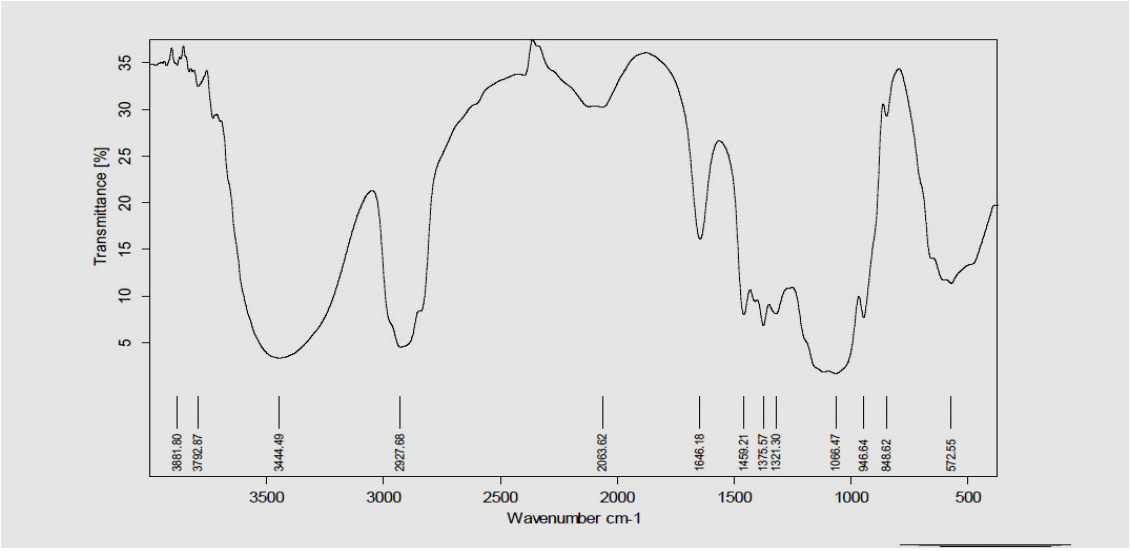
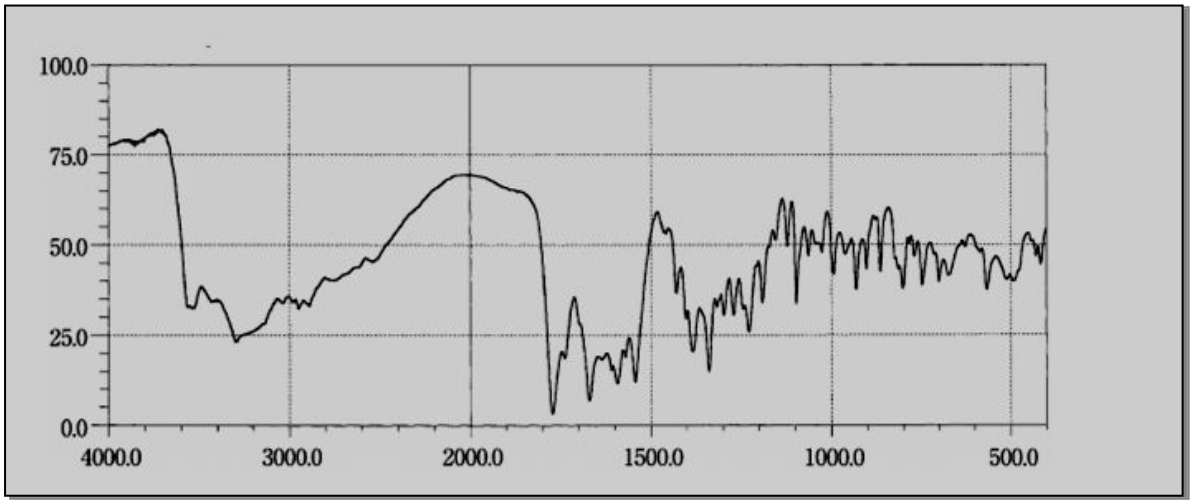


Figure 5: FTIR spectra of pure Drug, polymer.



3.3 Physical characteristics of blends and tablets:

The blends of different formulations were evaluated for angle of repose, Carr's compressibility index etc., the results of Angle of repose and Carr's compressibility Index (%) ranged from 16-28 and 14-16, respectively which showed that blends from all the formulations having good flow property. The hardness and percentage friability ranged from 4-5kg/cm2 and 0.18-0.35% respectively.

Table 5: Precompression parameters:

Powder blend	Angle of Repose (°)	bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio
F1	26	0.57	0.725	21.37	1.27
F2	27.5	0.576	0.733	21.41	1.27
F3	25.5	0.526	0.689	23.65	1.29
F4	29.2	0.562	0.743	24.36	1.32
F5	27.3	0.597	0.786	24.04	1.31
F6	28.4	0.516	0.651	20.73	1.26
F7	26.6	0.527	0.660	20.15	1.25
F8	29.1	0.532	0.645	17.13	1.21
F9	28.4	0.498	0.601	17.77	1.20
F10	27.4	0.518	0.630	20.9	1.21

Table 6: Postcompression parameters.

Formulations	Average Weight (mg)	Friability (%)	Uniformity of dosage units (%)	Hardness (Kg/cm2)	Thickness (mm)
F1	401±1.193	0.18	101.2	6±0.3	5.6±0.045
F2	403±2.143	0.39	101.5	5±0.4	5.3±0.023
F3	400±1.183	0.15	100.5	6±0.6	5.6±0.052
F4	399±1.193	0.76	99.5	4.5±0.4	5.4±0.045
F5	405±1.152	0.23	99.8	5.5±0.8	5.7±0.029
F6	404±1.195	0.18	100.3	6.5±0.4	5.7±0.041
F7	401±1.126	0.26	99.9	6.5±0.6	5.8±0.028

F8	399±2.193	0.17	99.5	6±0.8	5.4±0.062
F9	802±2.193	0.21	100.9	5.5±0.3	5.5±0.058
F10	801±2.186	0.32	98.9	6±0.4	5.3±0.092

c) In vitro drug release/dissolution studies:

Formulations F1, F2, F3, F4, F5, were made by using increasing concentrations of HPMCK4M with 200mg of Cefixime trihydrate. Drug release after 12hours was found to be:

F1-99.53%, F2-99.33%,F3-99.46%, F4-86.95%, F5-74.40%.

Formulations F6, F7contains HPMCK100 with 200mg of Cefixime trihydrate. Drug release after 12hours was found to be: F6-87.19%, F7-94.72%.

Formulations F8 containHPMCK4M and Ethyl cellulose with 200mg of Cefixime trihydrate. Drug release after 12hours was found to be: F8-90.39%.

Formulations F9, F10made by using increasing concentrations of HPMCK100 and HPMCK4M with 400mg of Cefixime trihydrate. Drug release after 12hours was found to be:

F9-93.63,F10-85.64%.

Table 7: Cumulative percentage drug release of F1, F2, F3, F4&F5 formulations:

Time (hrs)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	43.83	39.50	20.85	17.95	6.21
2	58.91	53.81	31.26	26.25	17.49
3	75.49	72.23	61.58	40.36	28.36
4	83.57	77.07	73.94	49.75	34.99
5	87.81	82.60	83.71	57.05	43.11
6	95.41	90.20	87.08	61.57	45.98
7	99.53	93.79	89.91	66.00	52.99
8	---	96.07	92.94	71.82	56.78
9	---	97.91	97.18	75.88	62.32
10	---	99.33	97.83	78.10	69.15
11	---	---	----	81.25	72.25
12	---	---	---	86.95	74.41

Figure 6: Dissolution graphs of F1, F2, F3, F4& F5 Formulations.

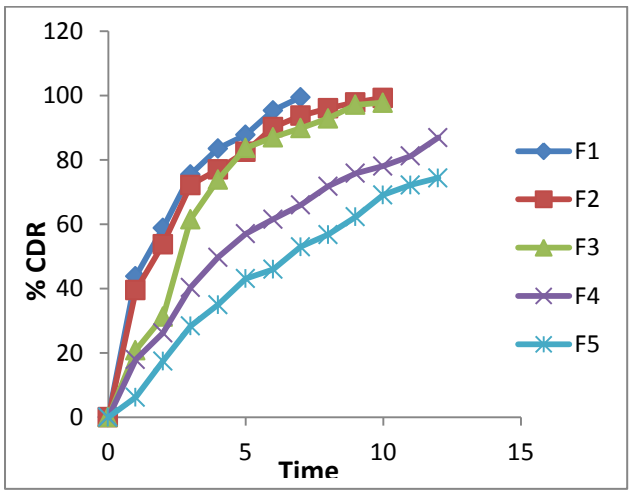
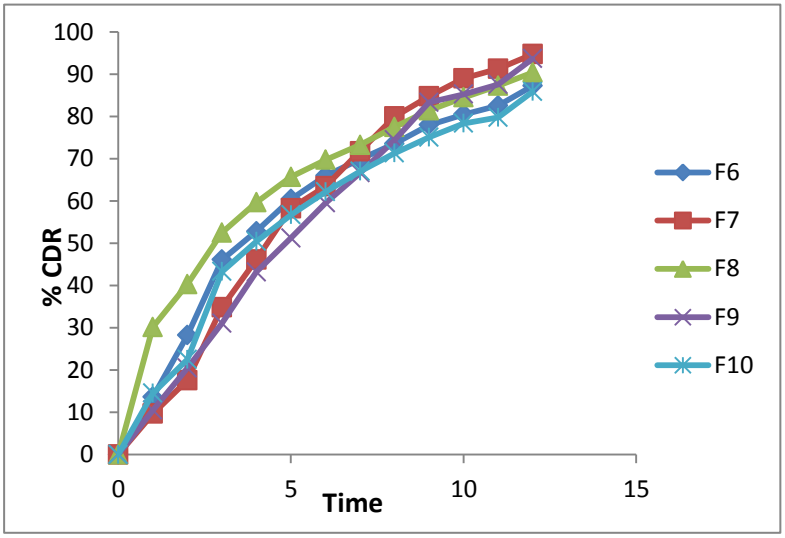


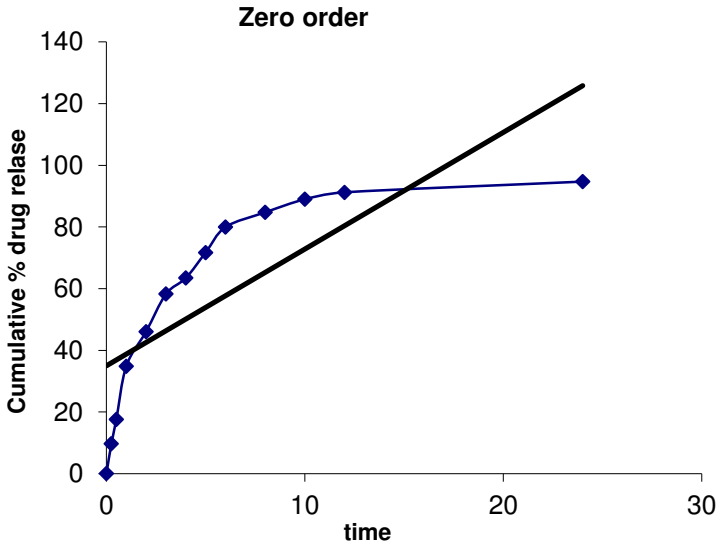
Table 8: Cumulative percentage drug release of F6, F7, F8, F9 &F10 formulations:

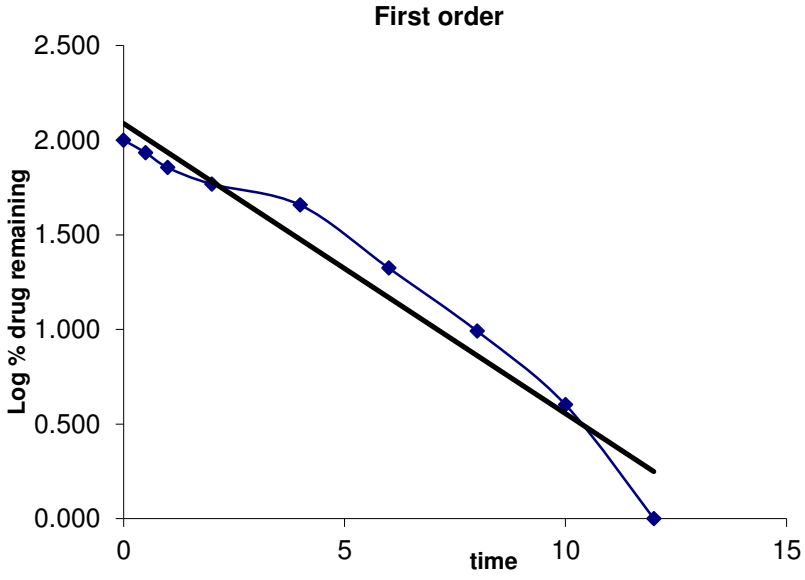
Time (hrs)	F6	F7	F8	F9	F10
0	0	**0**	0	0	0
1	13.58	**9.65**	30.15	10.5	14.48
2	28.22	**17.58**	40.29	20.43	22.5
3	46.07	**34.82**	52.48	31.05	43.29
4	52.78	**46.07**	59.64	43.18	50.41
5	60.38	**58.25**	65.64	51.21	56.70
6	65.92	**63.43**	69.71	59.47	62.14
7	69.82	**71.73**	73.22	66.60	66.98
8	73.52	**79.95**	77.46	74.39	71.29
9	77.97	**84.75**	81.43	83.30	75.05
10	80.46	**89.00**	84.48	85.25	78.35
11	82.56	**91.25**	87.25	87.53	79.74
12	87.19	**94.72**	90.39	93.63	85.84

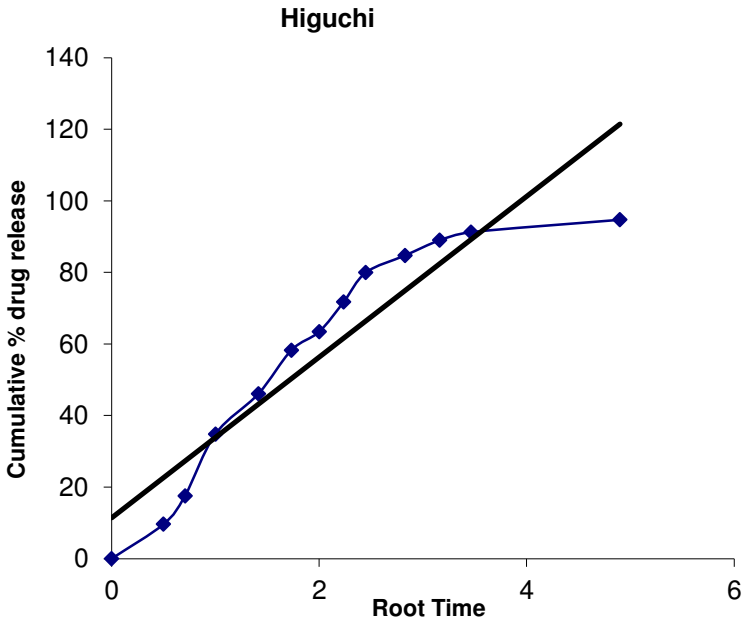
Figure 7: Dissolution graphs of F6, F7, F8, F9& F10 Formulations.

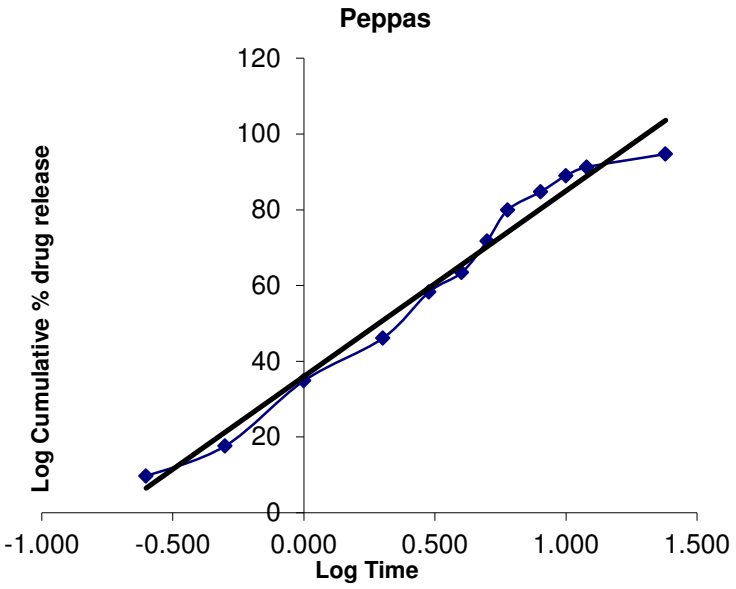


3.4 Release Kinetics of optimized formulation F7:









Conclusion:

Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutics effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. Regulated drug release in zero order kinetics attained with this formulation. From the above observations we can conclude that the better sustained release formulation is F7. (Increased concentration of HPMCK100) since initially % of drug is released is 10.53% at first hour and 94.72% after 12 hours of time was at good sustained release rate in comparison with other formulations (F1, F2, F3, F4, F5, F6, F8, F9,F10).

Acknowledgement:

The authors are thankful for the management of Aurobindo Pharma Ltd, Hyderabad, Bright Labs, Hyderabad for the gift samples of drug and polymers used in the work,I also thankful for the management of Vikas College of Pharmacy, Shameerpet, Jangaon, Warangal, A.P, India, Jayamukhi College of Pharmacy, Narsampet, Warangal, A.P, India.

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