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Research Article

Formulation and *In-Vitro* Evaluation of Cefixime Trihydrate Sustained Release Matrix Tablets

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ABSTRACT

The objective of present investigation was to formulate and evaluate hydrophilic matrix tablets of cefixime trihydrate to achieve a controlled and 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 K15, HPMC K100, and HMC K4), gum xanthan, polymethacrylate. and different diluents like microcrystalline cellulose, Ethyl cellulose, sodium starch glycollate, 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 polymer interaction was checked by comparing the IR spectra of the physical mixture of drug with excipients used the IR spectrum of pure drug. Drug compatability with excipients was checked by DSC and FTIR studies. The values of pre-compressional parameters evaluated were with in prescribed limits and indicated good free flowing property. The values of post- compressional parametres evaluated were with in acceptable limits. The dissolution profiles of all the formulations were evaluated. Amongst all the formulations, the release profile of formula F16 andF20 gave optimum results. , It was concluded that for Cefixime trihydrate sustained release matrix Tablets, F16 and F20 is successful formulation and can be manufactured with reproducible characteristics from batch to batch.

Key words: cefixime trihydrate, hydroxypropylmethylcellulose, sustained release, matrix tablets.

INTRODUCTION

The main goal of pharmaceutical formulation is to achieve better therapeutic activity by using smallest quantity of drug administered by the most suitable route. Oral route of drug administration has wide acceptable and of the drugs administered orally in solid dosage forms represents the preferred class of products. The reasons are as follows: “Tablets and Capsules represent unit dosage forms in which one usual dose of drug has been accurately placed”. Solid dosage forms of tablets and capsules are more commonly employed, the tablets have advantages

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than capsules in that they are tamper resistant and any adulterant of the tablet after its manufacture is almost certain to be observed. The adulteration can be easily found if it is done in either liquid form or solid form since deformation takes place, if it is done in liquid form and powders cannot be added to the tablet if once they are formed. The major disadvantage of capsules over tablet is their higher cost. The capsules either hard capsule or soft capsule they are susceptible to breakage if they were not stored properly. Today, most time-release drugs are formulated so that the active ingredient is embedded in a matrix of insoluble substance(s) (various: some acrylics, even chitin; these substances are often patented) such that the dissolving drug must find its way out through the holes in the matrix. Some drugs are enclosed in polymer-based tablets with a laser-drilled hole on one side and a porous membrane on the other side. Stomach acids push through the porous membrane, thereby pushing the drug out through the laser-drilled hole. In time, the entire drug dose releases into the system while the polymer container remains intact, to be later excreted through normal digestion. In some SR formulations, the drug dissolves into the matrix, and the matrix physically swells to form a gel, allowing the drug to exit through the gel's outer surface. Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutic, 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.The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose. Cefixime trihydrate sustained release matrix tablets were prepared by using different concentarations of different polymers like HPMC K4M, XANTHAN GUM, EUDRGIT- RL. In present research work cefixime is used. It is third generation cephalosporin antibiotic having bactericidal activity and used in the treatment of uncomplicated UTI, otitis media, pharyngitis, and acute excerbation of chronic bronchitis, uncomplicated gonorrhea. Cefixime with p^{Ka} value of 2.5 a weak acid which will remain unionized at acidic p^{H} thus increases absorption in the stomach region. Cefixime trihydrate inhibit mucopeptide synthesis in the bacterial cell wall, rendering it defective and osmotically unstable. These drugs are usually bactericidal, depending on the dose, tissue concentrations, organism susceptibility, and the rate at which organisms are multiplying. They are more effective against rapidly growing organisms while forming cell walls. Cefixime is not in soluble in water after its oral administration. It is slowly and incompletely absorbed from the GIT, which resulting into the poor bioavailability around 40-50%, so, inorder to improve the therapuetic effect of the drug by incresing its bioavalibilty, safe and effective levels are maintained for a long time. Cefixime trihydrate sustained release matrix tsblets were repared by direct compression method using different

concentrations of different hydrophilc polymers. The composiotions of sustained release tablets are given in **Table 1.**

MATERIALS AND METHODS

Materials: Cefixime trihydrate is a gift sample from darwin pharmaceuticals, HPMC K4M, HPMC K100 was obtained from colorcon asia pvt.ltd,goa. S.S.G, magnesium stearate, M.C, talc was obtained from sd fine chemicals ltd, mumbai. All other excipients and chemical used were of Analytical grade.

Methods: Preparation of sustained release matrix tablets: Sustained release tablets were prepared by direct compression method. All the ingredients were accurately weighed. Cefixime drug is mix to all the ingredients. Then the ingrdients were sifted through 20# mesh and the blend was mixed with magnesium stearate and talc and triturated for 1 minute. The final blend was compressed into tablets using 12mm punch. Compression force was adjusted to obtain tablets of hardness 6-9 kg/cm^2 with 4mm tablet thickness.

FORMULATION DEVELOPMENT

Sustained release tablets of Cefixime trihydrate were prepared and evaluated to increase its release time and bioavailability. In the present study 23 formulations with variable concentrations of different polymers were prepared and evaluated for physico-chemical parameters, drug-excipients compatibility studies and in-vitro release studies. The formula of these formulations were given in table

Formulation Of 200mg Cefixime Trihydrate Sustained Release Matrix Tablets: Tablets containing 200 mg of Cefixime trihydrate were prepared with a total tablet weight of 400 mg considering the Preformulation studies and the literature survey the excipients were selected and an attempt to produce sustained release matrix tablets maintaining the basic tablet properties.

Selection of Binders: Polymers are selected according to their drug release capacity for the sustained release tablets. HPMC, Ethyl cellulose, Eudragit-RL, is used as a tablet binder, in film coating and as a matrix for use in extended- release tablet formulations. Concentrations between 2%-5% w/w are used as binder in either in wet or dry granulation process. High viscosity grades may used to retard the release of drugs from matrix at levels of 10-80% w/w in tablets and capsules. PVP-K30 is used as a binder in 3% , Micro Crystalline Cellulose (20-90%) is widely used as a binder/diluent in both wet granulation and direct compression method, also it has some lubricant and disintegrant properties that make it useful in tableting.

Selection of diluents: Since direct compression method was followed the choice of directly compressible diluent was important. Microcrystalline cellulose was selected as the filler or diluent owing to its multiple functionality as binder,disintegrant, compressibility and flowability. The various grades available the granular form Avicel PH102 and PH101was selected as it had been already reported to provide lower crushing strengths and shorter disintegration times.

Selection of polymers: HPMC K4M, Xanthan gum, HPMC K100, Eudragit-RL and it's combinations were used in preparation of sustained release matrix tablets**.**

Selection of other ingredients: The flow property of the pure drug was found to be moderate (Hausner ratio ~ 1.3) thus to still improve the flow of the blend, Talc (1.0-10.0%) is used as glidant and lubricant, 5.0-30% used as tablet diluent and Magnesium stearate (0.5%) as lubricant were incorporated.

Formulation of 400mg cefixime trihydrate sustained release matrix tablets Formulation planning: Tablets containing 400 mg of Cefixime trihydrate were prepared with a total tablet weight of 800 mg. Considering the Preformulation studies and the literature survey the excipients were selected and an attempt was made to produce sustained release matrix tablets maintaining the basic tablet properties.

Selection of Binders: Polymers are selected according to their drug release capacity for the sustained release tablets. HPMC K4M, HPMC K100, Xanthan gum, Ethyl cellulose, is used as a tablet binder, in film-coating and as a matrix for use in extended-release tablet formulations. Concentrations between 2%-5% w/w are used as binder in either in wet or direct compression process. High viscosity grades may be used to retard the release of drugs from matrix at levels of 10-80% w/w in tablets and capsules. PVP-K30 is used as a binder in 3%, Micro Crystalline Cellulose (20-90%) is widely used as a binder/diluent in both wet granulation and direct compression method. It has some lubricant and disintegrant properties that make it useful in tableting.

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Evaluation of tablet blends and tablets: Physical evaluation of blend Micromeritic properties (bulk density and tapped density) The bulk density and tapped density of the tablet blend were calculated as per the method described.

Flow properties (Angle of repose, Compressibility index, Hausner ratio)

The powder flow properties of the tablet blend were estimated as per the method described.

EVALUATION OF TABLETS

Hardness: Five tablets from each batch were selected and hardness was measured using Electrolab Digital hardness tester to find the average tablet hardness or crushing strength.

Friability (%F): 20 tablets from each batch were selected randomLy and weighed. These preweighed tablets were subjected to friability testing using Roche friabilator for 100 revolutions. The tablets were subjected to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the % Friability.

$$\%F = 1-(\text{loss in weight}/\text{ initial weight})\ 100$$

Weight variation: Weight variation was calculated as per method descried in USP. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of the tablets differ by more than the percentage listed inbelow table and no tablets differ in weight by more than double that percentage.

Weight variation allowed as USPXX- NF XV.

Average weight of tablet (mg)	Percentage difference allowed
≤130	10
130-324	7.5
>324	5

Tablet thickness: Variation in the tablet thickness may cause problems in counting and packaging in addition to weight variation beyond the permissible limits. Tablet thickness should be controlled within a ± 5% of a standard value. Tablet thickness was measured by Vernier caliper

Content uniformity: Five tablets were selected randomly and powdered. 10 mg of tablet powder was dissolved in 100 mL of 7.2 phosphate buffer stirred for 60 min and filtered. 1 mL of the filtrate was diluted to 10 mL with 7.2 phosphate buffer. Absorbance of this solution was measured at 288 nm using 7.2 phosphate buffer as blank and content of Cefixime trihydrate was estimated.

In vitro drug release/dissolution studies: The tablet samples were subjected to in-vitro dissolution studies using USP Type- I dissolution apparatus at 37±2°C and 100 rpm speed. As per the official recommendation of USFDA, 900 mL of 0.1 N HCl (first 2hrs) and 7.2 Phosphate buffer (next 10hrs) was used as dissolution medium. Aliquot equal to 5 mL was withdrawn at specific time intervals and the dissolution media volume was complimented with fresh and equal volume of blank media (0.1 N HCl). The aliquots were filtered and scanned with appropriate dilution and amount of Cefixime trihydrate released from the tablet samples was determined spectrophotometrically at a wavelength of 288 nm by comparing with the standard calibration curve.

Parameters of in-vitro drug release/dissolution studies

Drug Name	Dosage Form	USP Apparatus	Speed (RPM)	Medium	Volume (mL)	Recommended Sampling Times (hrs)
Cefixime trihydrate	Tablets	I (Basket)	100	0.1 N HCl and 7.2P^{H} Phosphate buffer	900	0.5,1,2, 3,4,5,6,7,8, 9,10,12

Mathematical model fitting of obtained drug release data: The sustained release of drugs can be achieved by incorporating solutes, either in dissolved or in dispersed form, in polymers. During the design stage of these formulations, it is desirable to develop and use simple yet sophisticated mathematical models to describe release kinetics. From a mathematical point of view, controlled-release systems can be classified according to the physical mechanisms of the release of incorporated solute. Mathematical modeling of the release kinetics of specific classes of controlled-release systems may be used to predict solute release rates form and solute diffusion behavior through polymers and to elucidate the physical mechanisms of solute transport by simply comparing the release data to mathematical models.

The mechanism of drug release from the formulations during the dissolution in pH 7.2 phosphate buffer was determined by using

- Zero order

- First order
- Korsmeyer peppas plot
- Hixon-crowell equation
- Higuchi equation

PREFORMULATON STUDIES OF DRUG AND EXCIPIENTS

Description/Appearance: Cefixime trihydrate is a white to light yellow crystalline powder.

Determination of melting point: Melting point of Cefixime trihydrate was determined by capillary method and complied with USP standards, indicate purity of the drug.

Solubility: Cefixime trihydrate was soluble in methanol, acetone and glycerol.

Drug- Excipients compatibility studies by Infrared spectroscopy

Fig 01: IR Spectra of Cefixime trihydrate (pure drug)

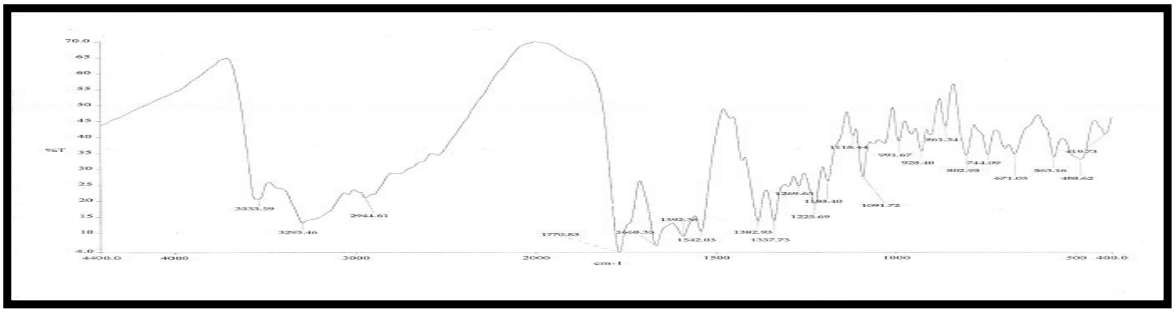


Fig 02: IR Spectra of F16

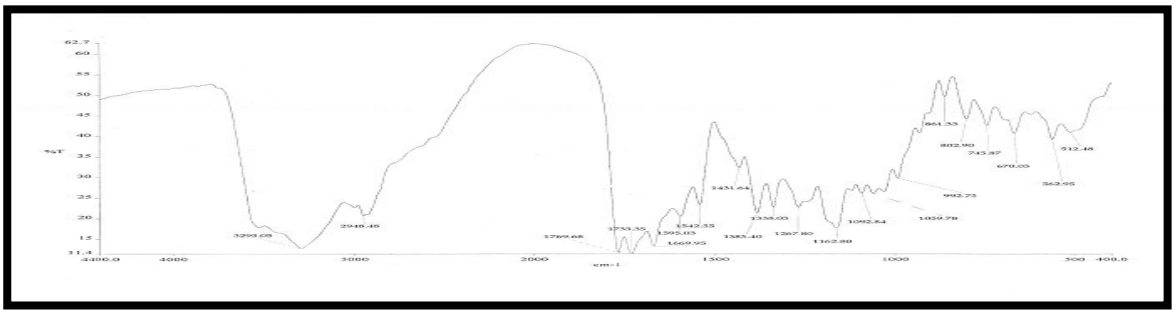
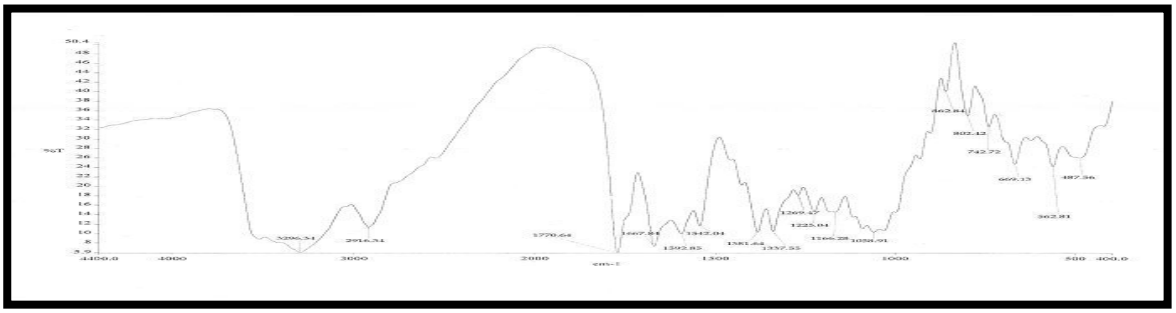


Fig 03: IR Spectra of F20



From IR Spectra's it was found that there was no drug-excipients interaction.

RESULTS AND DISCUSSION:

The present investigation was undertaken to formulate Cefixime trihydrate sustained release matrix Tablets for

Formulation Of Cefixime Trihydrate Matrix Tablets With Hpmc K4m

Table 1: Prototype formula taken for tablets (Weight in mg)

Formula	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Cefixime trihydrate	200	200	200	200	200
HPMC K4M	40 (10%)	45 (11.25%)	47.5 (11.87%)	48.5 (12.12%)	50 (12.5%)
Microcrystalline cellulose	150	145	142.5	141.5	140
Magnesium stearate	4	4	4	4	4
Talc	6	6	6	6	6
Total weight	400	400	400	400	400

formulation of cefixime trihydrate matrix tablets with xanthan gum

Table 2: Prototype formula taken for tablets (Weight in mg)

Formula	F_6 (mg)	F_7 (mg)	F_8 (mg)	F_9 (mg)
Cefixime trihydrate	200	200	200	200
Xanthan gum	50 (12.5%)	75 (18.75%)	80 (20%)	100 (25%)
Microcrystalline cellulose	140	115	110	90
Magnesium stearate	4	4	4	4
Talc	6	6	6	6
Total weight	400	400	400	400

formulation of cefixime trihydrate matrix tablets with hpmc k100

Table 3: Prototype formula taken for tablets (Weight in mg)

Formula	F10 (mg)	F11 (mg)
Cefixime trihydrate	200	200
HPMC K100	100 (25%)	95 (23.7%)
Microcrystalline cellulose	95	90
Magnesium stearate	4	4
Talc	6	6
Total weight	400	400

the treatment of respiratory tract infections, urinary tract infections and otitis media. All the experimental batches have been exposed to various evaluations like Angle of Repose, Bulk density, compressibility index, and Average weight, Thickness, Hardness, Friability, Assay, and In-vitro Dissolution.The primary applications for rate controlling polymers are for decreasing dissolution rate and extend the release of water-soluble drug. Successful drug design with polymers depends largely on understanding the physical, chemical and

formulation of cefixime trihydrate matrix tablets with eudragit-rl

Table 4: Prototype formula taken for tablets (Weight in mg)

Formula	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)	F16 (mg)	F17 (mg)
Cefixime trihydrate	200	200	200	200	200	200
Eudragit-RL	50	100	100	100	100	100
Microcrystalline cellulose	140	90	86	84	82	80
Sodium starch glycolate	-	-	4 (1%)	6 (1.5%)	8 (2%)	10 (2.5%)
Magnesium stearate	4	4	4	4	4	4
Talc	6	6	6	6	6	6
Total weight	400	400	400	400	400	400

formulation of 200mg cefixime trihydrate sustained release matrix tablets of f18, f19

Table 5: Prototype formula taken for tablets (Weight in mg)

Formula	F18 (mg)	F19 (mg)
Cefixime trihydrate	200	200
HPMC K4M	50 (12.5%)	20 (5%)
Ethyl cellulose (18cps)	50 (12.5%)	-
Xanthan gum	-	30 (7.5%)
Microcrystalline cellulose	90	140
Magnesium stearate	4	4
Talc	6	6
Total weight	400	400

formulation of 400mg cefixime trihydrate sustained release matrix tablets of f20, f21, f23,f24

Table 06: Prototype formula taken for tablets (Weight in mg)

Formula	F20(mg)	F21(mg)	F23(mg)	F24(mg)
Cefixime trihydrate	400	400	400	400
HPMC K100	190 (23.75%)	-	-	-
HPMC K4M	-	89 (11.13%)	98 (12.25%)	38 (4.75%)
Xanthan gum	-	-	-	57 (7.125%)
Ethyl cellulose (18cps)	-	-	98(12.25%)	-
Microcrystalline cellulose	190	291	184	285
Magnesium stearate	8	8	8	8
Talc	12	12	12	12
Total Weight	800	800	800	800

physiological factors to promote bioavailability. The linearity of Cefixime trihydrate standard curve was checked in the 7.2 phosphate buffer. It was found to be linear in the range of 2 mcg/mL to 10 mcg/mL. Formulations F1, F2, F3, F4, F5, were made by using increasing concentrations of HPMC K4M with 200mg of Cefixime trihydrate. The details of the formulae were given in Table no: 1.The formula mixtures were evaluated for tests such as bulk density, tapped density, compressibility index and Hausner ratio. The results

Table 07: Pre-compression parameters:

Powder blend	Angle of Repose (°)	Loose bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner ratio
F1	26	0.525	0.65	19.22	1.18
F2	27.5	0.528	0.645	18.1	1.22
F3	25	0.530	0.648	18.2	1.22
F4	29	0.571	0.660	15.58	1.16
F5	27.3	0.540	0.652	17.17	1.20
F6	31	0.482	0.582	17.18	1.21
F7	30	0.512	0.614	16.61	1.19
F8	31.5	0.554	0.685	19.12	1.23
F9	29	0.531	0.662	19.78	1.24
F10	28	0.516	0.651	20.73	1.26
F11	26.6	0.527	0.66	20.15	1.25
F12	26	0.533	0.651	18.12	1.22
F13	29	0.543	0.649	16.33	1.19
F14	27.9	0.541	0.652	17.02	1.20
F15	26	0.531	0.642	17.28	1.21
F16	28	0.523	0.637	17.81	1.21
F17	25.7	0.548	0.674	18.65	1.22
F18	29.1	0.532	0.645	17.51	1.21
F19	32.5	0.51	0.623	18.13	1.22
F20	28	0.498	0.601	17.13	1.20
F21	27	0.518	0.63	17.77	1.21
F22	30	0.525	0.628	16.40	1.19
F23	26.6	0.542	0.682	20.52	1.25

were shown in the Table no: 7. The compressed Tablets were tested for weight variation, thickness, hardness, friability, and uniformity of dosage units, the results were shown in the Table no: 8. Drug release profiles of formulations F1, F2, F3, F4 and F5 were conducted for about 12hrs. The results were shown in Table no: 9 and Figure no: 4. Zero order, First order, Peppas plots were shown in Figure no: 10,16, and 22

Formulations F6, F7, F8, F9, were made by using increasing concentrations of Xanthan Gum with 200mg of Cefixime trihydrate. The details of the formulae were given in Table no: 2, the formula mixtures were evaluated for tests such as bulk density, tapped density, compressibility index and Hausner ratio. The results were shown in the Table no: 7. The compressed Tablets were tested for weight variation, thickness, hardness, friability, and uniformity of dosage units The results were shown in the Table no:8.The Drug release profiles of formulations F6, F7, F8, F9 were conducted for about 12hrs.The results were shown in Table no: 10 and Figure no: 5. Zero order, First order, Peppas plots were shown in Figure no: 11, 17, and 23

Formulations F10, F11 was made by using different concentrations of HPMC K100 with 200mg of Cefixime trihydrate. The details of the formulae were given in Table no: 3.The formula mixtures were evaluated for tests such as bulk density, tapped density, compressibility index and Hausner ratio. The results were shown in the

Table 08: Post-compression parameters:

Formulations	Average Weight (mg)	Friability (%)	Uniformity of dosage units (%)	Hardness (Kg/cm^2)	Thickness (mm)
F1	401	0.18	101.2	6	3.2
F2	403	0.39	101.5	5	3.2
F3	400	0.15	100.5	6	3.3
F4	399	0.76	99.5	4.5	3.1
F5	405	0.23	99.8	5.5	3.3
F6	402	0.11	100.1	5.5	3.0
F7	400	0.36	103.2	5.5	3.1
F8	398	0.39	102.2	5	3.2
F9	400	0.45	101.4	5.5	3.2
F10	404	0.18	100.3	6.5	3.2
F11	401	0.26	99.9	5	3.3
F12	403	0.19	99.7	6	3.3
F13	402	0.55	100.5	5	3.2
F14	399	0.34	100.1	5.5	3.1
F15	400	0.21	99.8	6	3.1
F16	402	0.15	101.5	6.5	3.2
F17	400	0.40	100	5.5	3.2
F18	399	0.17	99.5	6	3.2
F19	405	0.24	98.7	6	3.3
F20	802	0.21	100.9	5.5	6.4
F21	801	0.32	98.9	6	6.5
F22	800	0.15	100.9	6.5	6.5
F23	803	0.29	102.1	6	6.5

Table no: 7. The compressed Tablets were tested for weight variation, thickness, hardness, friability, and uniformity of dosage units. The results were shown in the Table no: 8. The Drug release profiles of formulations F1, F2, F3, F4, and F5 were conducted for about 12hrs. The results were shown in Table no: 11and Figure no: 6. Zero order, First order, Higuchi, Peppas plots were shown in Figure no: 12,18, and 24.

Formulations F12, F13 F14, F15, F16, F17 was made by using different concentrations of Eudragit-RL and sodium starch glycolate with 200mg of Cefixime trihydrate. The details of the formulae were given in Table no: 4. The formula mixtures were evaluated for tests such as bulk density, tapped density, compressibility index and Hausner ratio. The results were shown in the Table no: 7. The compressed Tablets were tested for weight variation, thickness, hardness, friability, and uniformity of dosage units. The results were shown in the Table no:8. The Drug release profiles of formulations F1, F2, F3, F4, and F5 were conducted for about 12hrs.The results were shown in Table no: 12 and Figure no: 7. Zero order, First order, Peppas plots were shown in Figure no: 13,19, and 25.

The formulas of F18, F19 were given in Table no: 5. The results of tests such as bulk density, tapped density,

Table 09: Drug release profiles of formulations F1, F2, F3, F4, and F5

Time (hrs)	% Drug released (mean ± s.d., n=3)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	43.83±0.21	39.50±0.53	20.85±0.34	17.95±0.25	6.21±0.45
2	58.91±0.18	53.81±0.22	31.26±0.51	26.25±0.14	17.49±0.74
3	75.49±0.39	72.23±0.29	61.58±0.68	40.36±.26	28.36±0.36
4	83.57±0.25	77.07±0.35	73.94±0.30	49.75±0.55	34.99±0.45
5	87.81±0.30	82.60±0.16	83.71±0.11	57.05± 0.60	43.11±0.19
6	95.41±0.28	90.20±0.63	87.08±0.53	61.57±0.42	45.98±0.64
7	99.53±0.18	93.79±0.32	89.91±0.59	66.00±0.65	52.99±0.55
8	-	96.07±0.29	92.94±0.24	71.82±0.54	56.78±0.64
9	-	97.91±0.25	97.18±0.64	75.88±0.27	62.32±0.38
10	-	99.33±0.12	97.83±0.19	78.10±0.46	69.15±0.57
12	-	-	-	86.95±0.39	74.41±0.29

Formulations F1, F2, F3, F4, F5, were made by using increasing concentrations of HPMC K4M (Table: 7), among all these formulations F4 shows highest % drug release about 86.95 within 12 hrs.

Table 10: Drug release profiles of formulations F6, F7, F8, and F9

	% Drug released (mean ± s.d., n=3)			
Time (hrs)	F6	F7	F8	F9
0	0	0	0	0
1	21.27±0.56	21.71±0.28	19.70±0.25	6.56±0.31
2	35.38±0.34	35.70±0.30	36.027±0.54	11.22±0.20
3	83.16±0.19	62.34±0.27	52.36±0.18	16.46±0.34
4	85.11±0.53	68.84±0.36	56.85±0.46	22.54±0.51
5	89.72±0.28	82.40±0.29	62.02±0.58	28.81±0.24
6	93.41±0.76	92.71±0.21	67.56±0.41	35.28±0.67
7	97.93±0.38	98.26±0.12	70.89±0.32	40.08±0.28
8	-	99.89±0.05	74.49±0.57	49.86±0.26
9	-	-	78.92±0.62	55.68±0.57
10	-	-	80.86±0.25	61.68±0.12
12	-	-	86.58±0.31	74.41±0.45`

Formulations F6, F7, F8, F9, were made by using increasing concentrations of Xanthan Gum , among all these formulations F8 shows highest % drug release about 86.58 within 12 hrs.

compressibility index and Hausner ratio was shown in the Table no: 7 and the results of tests like weight variation, thickness, hardness, friability, and uniformity of dosage units was shown in the Table no:18. The drug release profile of F18 was shown in Table no: 13 and Figure no: 8 The formulas of F20, F21, F22, and F23 were given in Table no: 06. The pre-compression parameters was shown in Table no: 7 and post-compression parameters was shown in Table no: 8. The drug release profile of F20, F21, F22, F23 was shown in Table no: 14 and Figure no: 9. Zero order, First order, Peppas plots were shown in Figure no: 14,20, and 26

Table 11: Drug release profiles of formulations F10, F11

Time (hrs)	% Drug released (mean ± s.d., n=3)	
	F10	F11
0	0	0
1	13.58±0.35	9.65±0.19
2	28.22±0.61	17.58±0.24
3	46.07±0.47	34.82±0.61
4	52.78±0.28	46.07±0.34
5	60.38±0.34	58.25±0.40
6	65.92±0.56	63.43±0.42
7	69.82±0.25	71.73±0.21
8	73.52±0.54	79.95±0.27
9	77.97±0.15	84.75±0.37
10	80.46±0.34	89.00±0.29
12	87.19±0.27	94.72±0.53

Formulations F10, F11 was made by using different concentrations of HPMC K100 (Table: 9), among all these formulations F11 shows highest % drug release about 94.72 within 12 hrs.

Table 12: Drug release profiles of formulations F12, F13, F14, F15, F16, and F17

Time (hrs)	% Drug released (mean ± s.d., n=3)					
	F12	F13	F14	F15	F16	F17
0	0	0	0	0	0	0
1	9.18±0.35	4.53±0.54	9.10±0.34	10.65±0.30	10.87±0.29	2.090±0.58
2	13.80±0.56	7.14±0.28	13.43±0.35	15.32±0.44	14.12±0.50	38.60±0.71
3	22.92±0.95	14.27±0.34	25.77±0.63	25.67±0.28	34.67±0.24	57.25±0.25
4	29.73±0.31	18.83±0.69	36.29±0.68	32.06±0.61	49.20±0.64	74.38±0.34
5	35.83±0.58	26.03±0.55	49.21±0.26	39.22±0.53	64.51±0.59	81.31±0.57
6	40.08±0.61	30.28±0.25	62.96±0.59	49.21±0.37	70.81±0.43	85.47±0.66
7	43.59±0.24	33.88±0.81	69.52±0.68	60.39±0.59	79.93±0.57	89.35±0.52
8	48.75±0.36	38.40±0.64	71.74±0.29	63.76±0.42	84.71±0.46	95.16±0.47
9	53.09±0.2	46.15±0.92	77.19±0.32	71.35±0.81	90.68±0.55	-
10	57.89±0.57	52.98±0.39	80.97±0.43	77.00±0.49	95.24±0.21	-
12	63.71±0.35	60.46±0.81	84.48±0.51	89.48±0.36	99.37±0.38	-

Formulations F12, F13, F14, F15, F16, F17 was made by using different concentrations of Eudragit-RL and sodium starch glycolate (Table: 10), among all these formulations F16 shows highest % drug release about 99.37 within 12 hrs.

Table 13: Drug release profiles of F18, F19

Time (hrs)	% Drug released (mean ± s.d., n=3)	
	F18	F19
0	0	0
1	30.15±0.56	14.26±0.85
2	40.29±0.25	18.23±0.62
3	52.48±0.32	38.41±0.54
4	59.6 ±0.24	47.27±0.38
5	65.64±0.32	53.36±0.55
6	69.71±0.86	58.44±0.69
7	73.24±0.47	63.06±0.38
8	77.46±0.65	67.58±0.85
9	81.43±0.68	69.06±0.94
10	84.48±0.91	74.78±0.57
12	90.39±0.77	80.23±0.95

Formulation F18 was made by HPMC K4M and Ethyl cellulose (Table: 11); it shows 90.39% drug release within 12 hrs. Formulation F19 was made by HPMC K4M and Xanthan gum (Table: 11); it shows 80.23% drug release within 12 hrs.

Table 14: Drug release profiles of F20, F21, F22, and F23

	% Drug released (mean ± s.d., n=3)			
Time (hrs)	F20	F21	F22	F23
0	0	0	0	0
1	10.5±0.35	14.48 ±0.22	14.67 ±0.28	14.15 ±0.2
2	20.43±0.44	22.5 ±0.32	20.76 ±0.55	20.20 ±0.54
3	31.05±0.21	43.29 ±0.65	41.53 ±0.74	40.52 ±0.27
4	43.18±0.56	50.41 ±0.45	48.02 ±0.85	48.77 ±0.51
5	51.21 ±014	56.70 ±0.36	54.96 ±0.45	56.51 ±0.29
6	59.47 ±0.36	62.14 ±0.85	61.72 ±0.61	63.97 ±0.51
7	66.60 ±0.61	66.98 ±0.27	67.68 ±0.48	69.93 ±0.48
8	74.39 ±0.18	71.29 ±0.32	73.31 ±0.23	75.57 ±0.19
9	83.30 ±0.28	75.05 ±0.28	78.48 ±0.16	80.26 ±0.61
10	87.53 ±0.65	79.74 ±0.29	83.17 ±0.45	84.01 ±0.28
12	93.63 ±0.14	85.84 ±0.31	89.74 ±0.28	91.05 ±.24

Formulation F20 was made by using HPMC K100 (Table: 12); it shows 93.63% drug release within 12 hrs. Formulation F21 was made by using HPMC K4M (Table: 12); it shows 85.84% drug release within 12 hrs. Formulation F22 was made by using HPMC K4M and Ethyl cellulose (Table: 12); it shows 89.74% drug release within 12 hrs. Formulation F23 was made by using HPMC K4M and Xanthan gum (Table: 12); it shows 91.05% drug release within 12 hrs.

The formulas of *F20, F21, F22, and F23* were given in Table no: 12. The pre-compression parameters was shown in Table no: 7 and post-compression parameters was shown in Table no: 8. the drug release profile of *F20, F21, F22, F23* was shown in Table no: 14 and Figure no: 9. Zero order, First order, Higuchi, Peppas plots

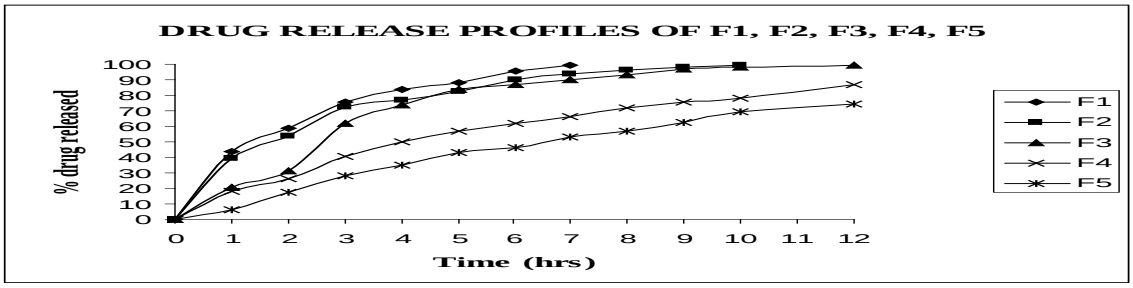


Fig 4: Drug release profile of F1,F2,F3,F4,F5

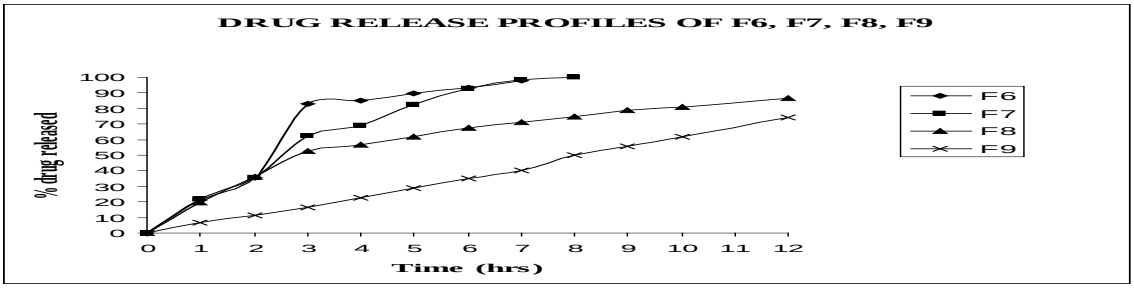


Fig 5: Drug release profile of F6,F7,F8,F9

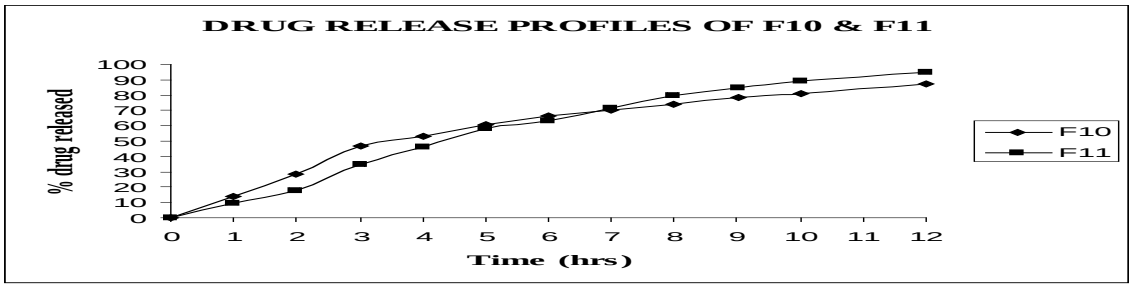


Fig 6: Drug release profile of F10,F11

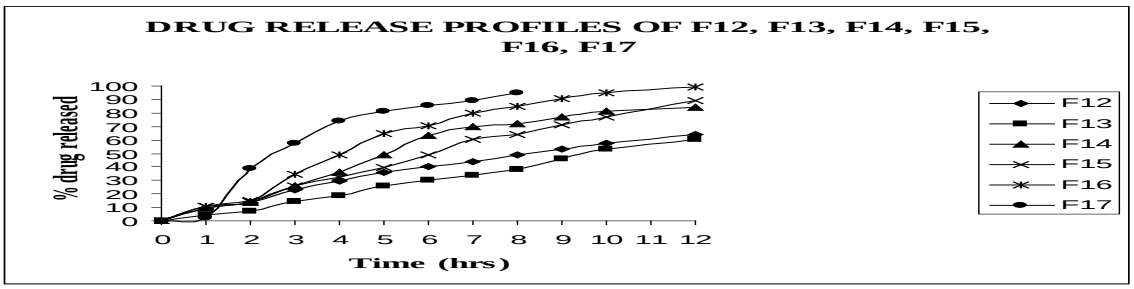


Fig 7: Drug release profile of F13,F14,F15,F16,F17

were shown in Figure no: 15, 21, and 27. The K_o, K_1, n values of all formulations were tabulated in Table no: 15.

SUMMARY AND CONCLUSION:

In this study, an attempt has been made to develop a formulation of 200 mg and 400 mg Cefixime trihydrate sustained release matrix Tablets, to attain sustained release system, matrix polymers like HPMC K4M, HPMC K100, Xanthan gum, Eudragit-RL, Ethyl cellulose were used. The formulations prepared were subjected to

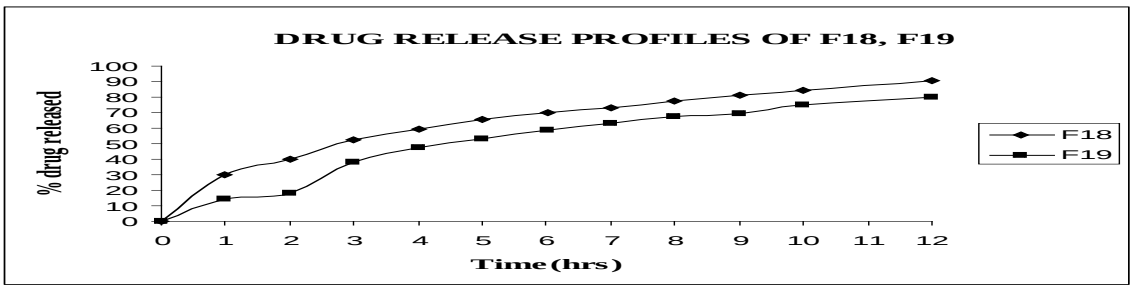


Fig 08: Drug release profile of F18,F19

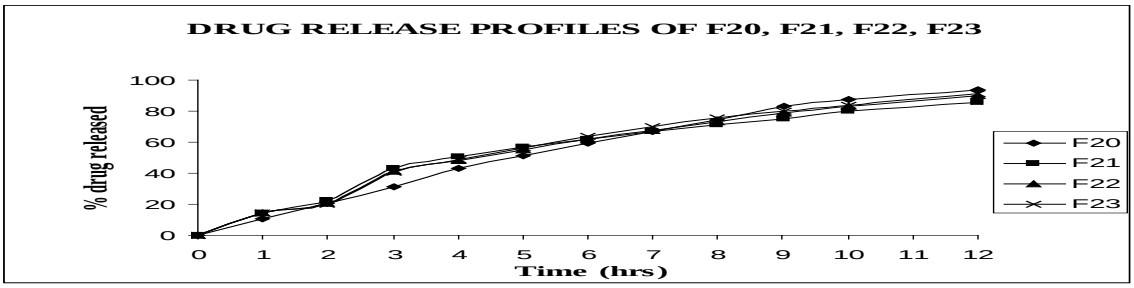


Fig 09: Drug release profile of F20,F21,F22,F23

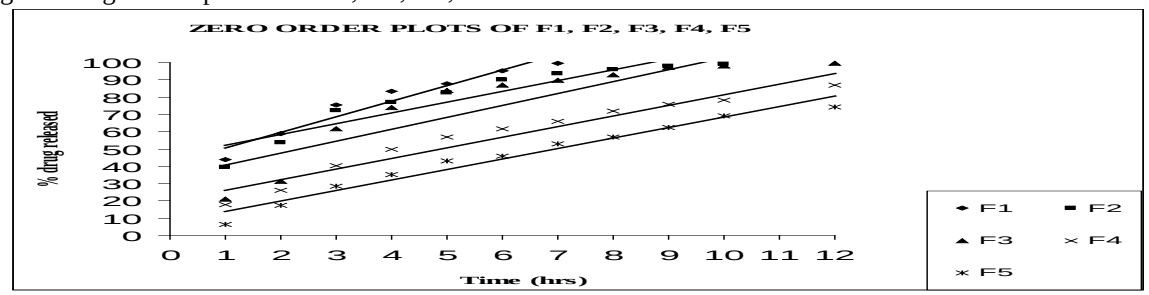


Fig 10: Zero order plot of F1,F2,F3,F4,F5

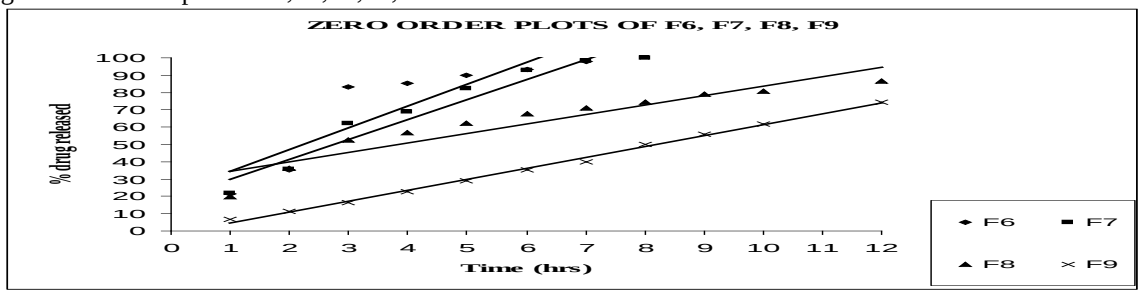


Fig 11: Zero order plot of F6,F7,F8,F9
physicochemical and in vitro dissolution studies.

The conclusion of the study is as follows:

- The linearity of Cefixime trihydrate standard curve was checked in the dissolution medium i.e., 7.2 phosphate buffer .It was found to be linear in the range of 2 mcg/mL to 10 mcg/mL.
- Preformulation studies were done initially and the results directed the further course of formulation. With the data from literature review, formulation trails were started using direct compression. The details of the
- formulas were given in Table no: 1,2,3,4,5, and 6. The powder blends was evaluated for tests such as bulk density, tapped density, compressibility index and Hausner ratio before punched into Tablets. The results
- were shown in the Table no: 7 and fulfilled the official requirements for compression Tablets through direct compression method.

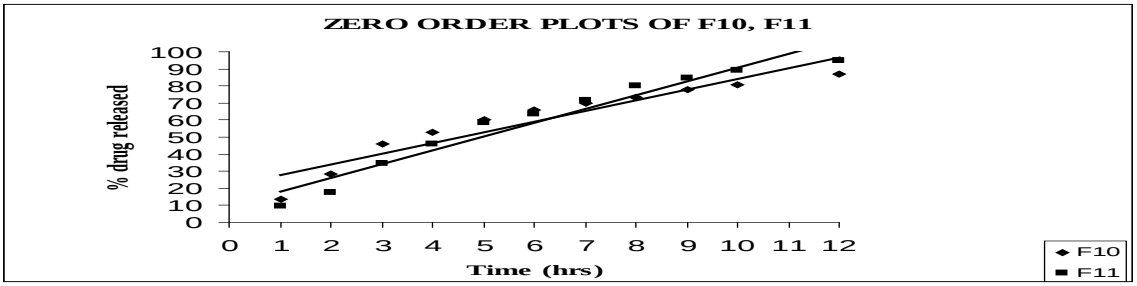


Fig 12: Zero order plot of F10,F11

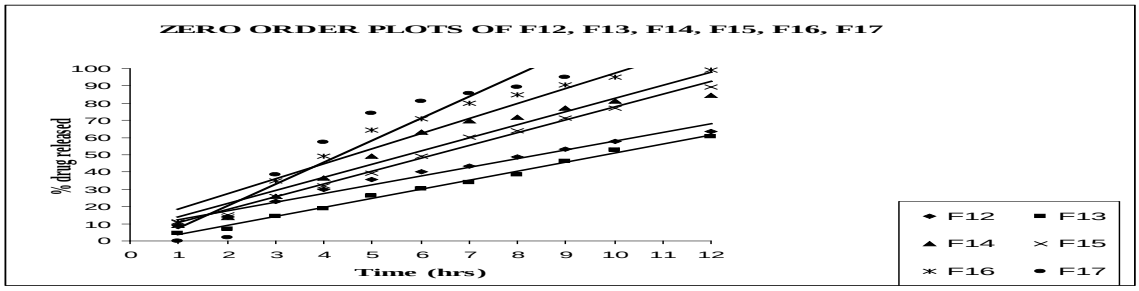


Fig 13: Zero order plot of F12,F13,F14,F15,F16,F17

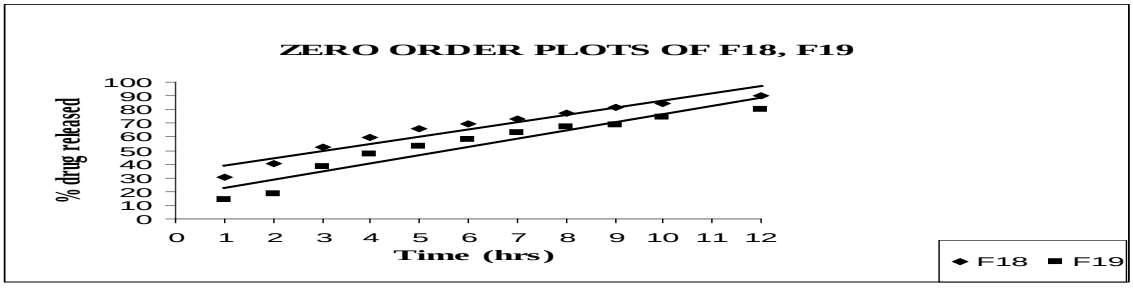


Fig 14: Zero order plot of F18,F19

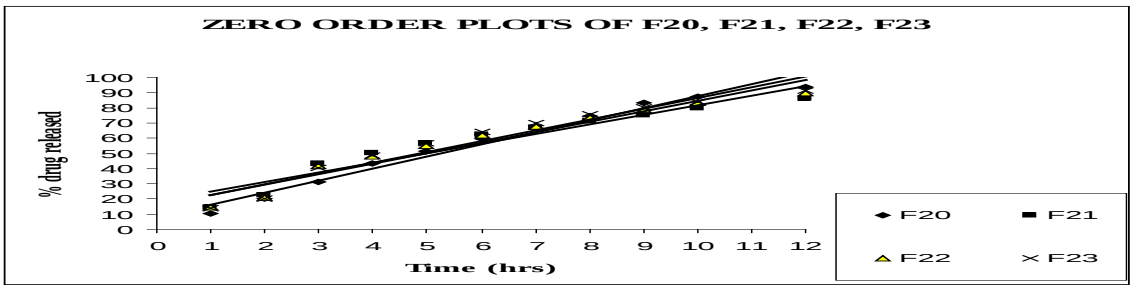


Fig 15: Zero order plot Of F20,F21,F23

- The compressed Tablets were tested for weight variation, thickness, hardness, friability, content uniformity. The results were shown in the Table no: 8 and all the Tablets fulfilled the official requirements of the compressed Tablets.
- The dissolution profiles of all the formulations were evaluated. The results were given in Table no: 9, 10, 11, 12, 13, and 14, amongst all the formulations, the release profile of the formula F16 (for 400 mg Tablet) and F20 (for 800 mg Tablet) gave optimum results.
- The formulations F16 and F20 were optimized considering the drug release profile and drug-excipients compatibility studies.

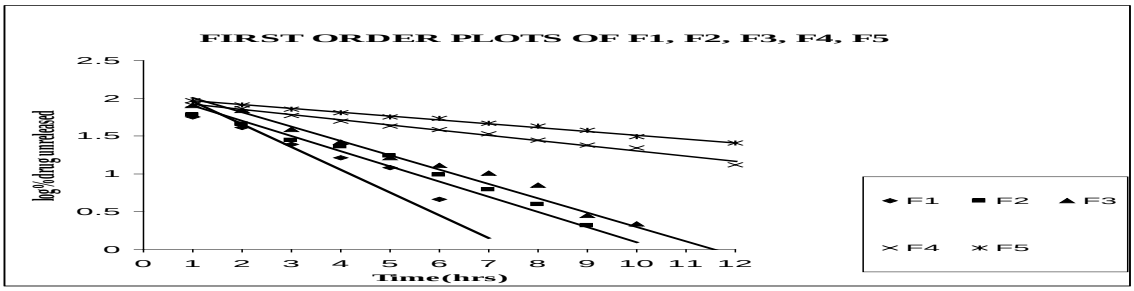


Fig 16:First order plot of F1,F2,F3,F4,F5

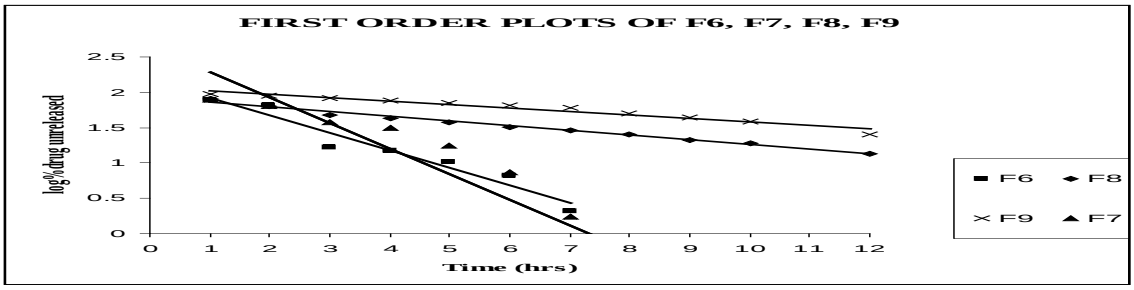


Fig 17:First order plot of F6,F7,F8,F9

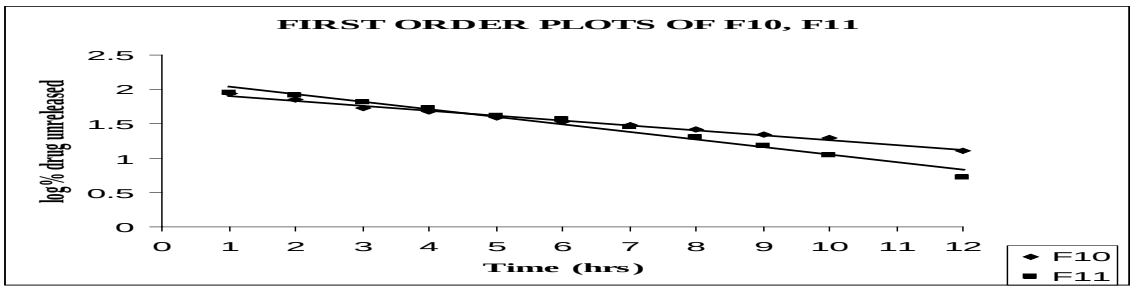


Fig 18:First order plot of F10,F11

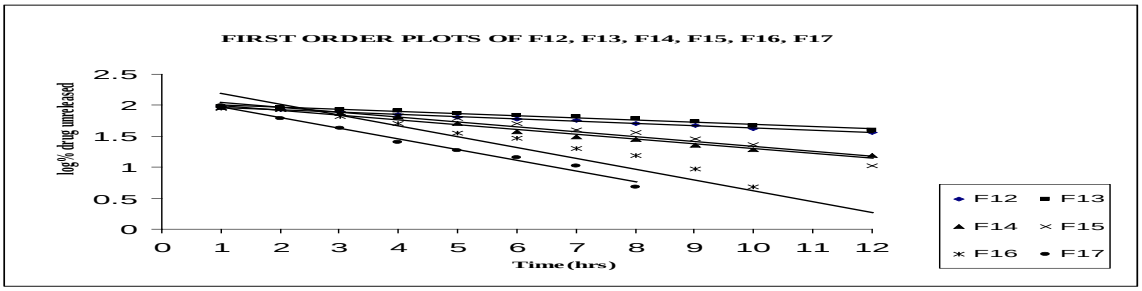


Fig 19: First order plot of F12,F13,F14,F15,F16,F17

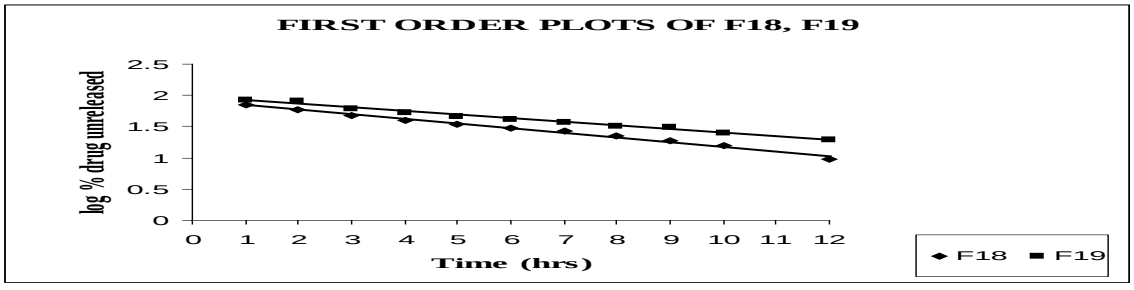


Fig 20: First order plot of F18,F19

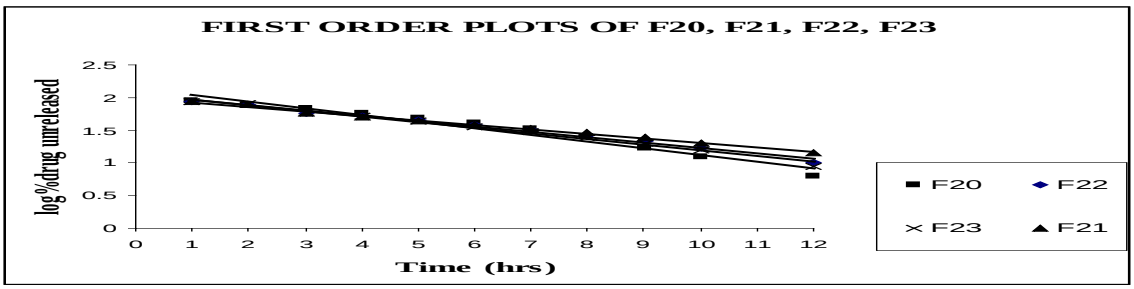


Fig 21: First order plot of F 20,F21,F22,F23

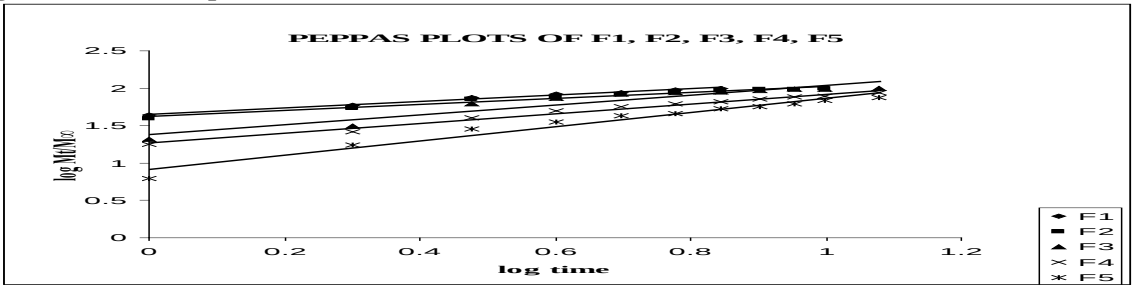


Fig 22: Peppas plot of F1,F2,F3,F4,F5

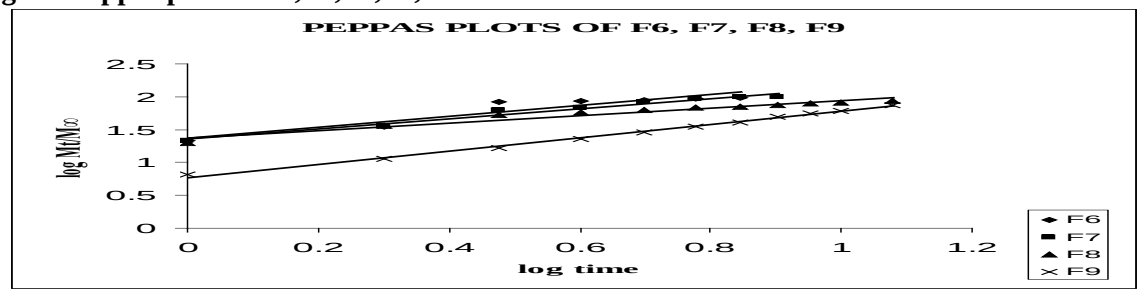


Fig 23: Peppas plot of F6,F7,F8,F9

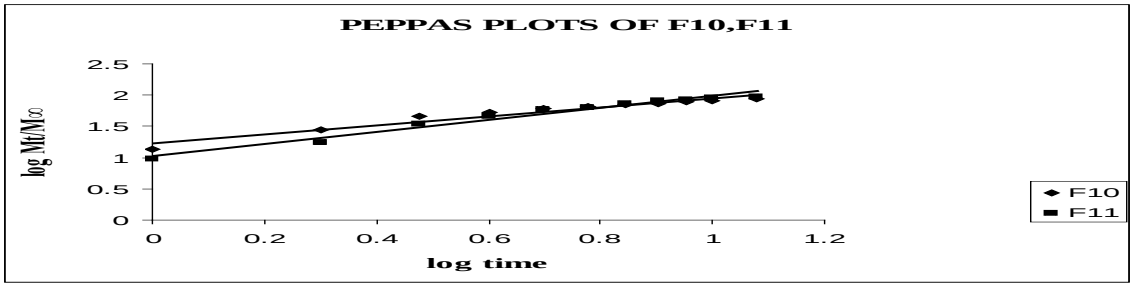


Fig 24; Peppas plot of F10,F11

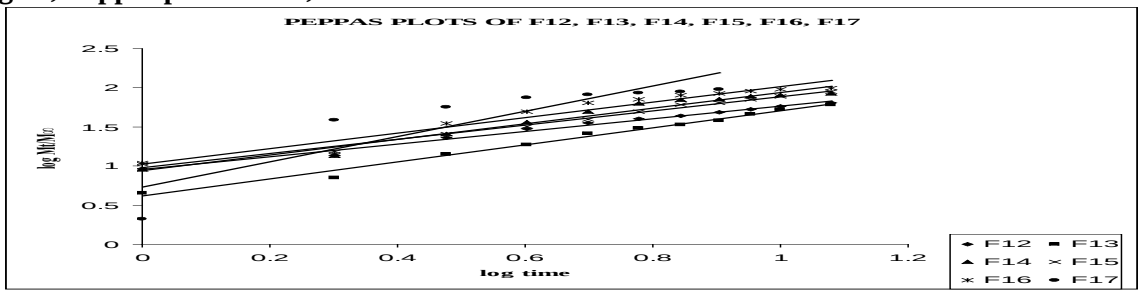


Fig 25; Peppas plot of F12,F13,F14,F15,F16,F17

- The formulae F16 follows first order release kinetics and super case-II transport.
- The formulae F20 follows zero order release kinetics and super case-II transport.

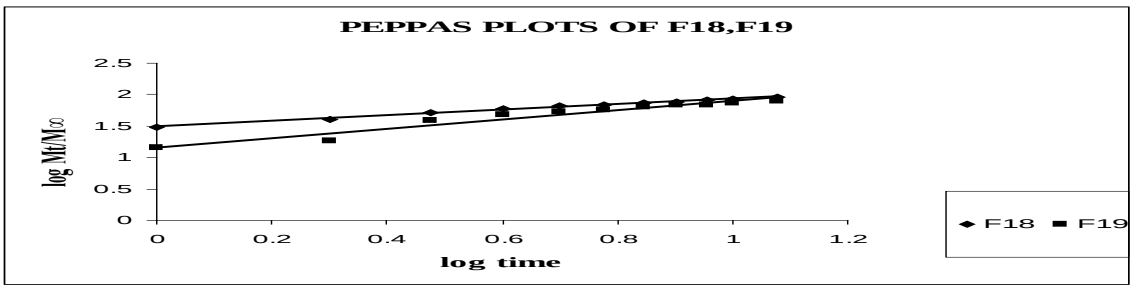


Fig 26 Peppas plot of F18andF19

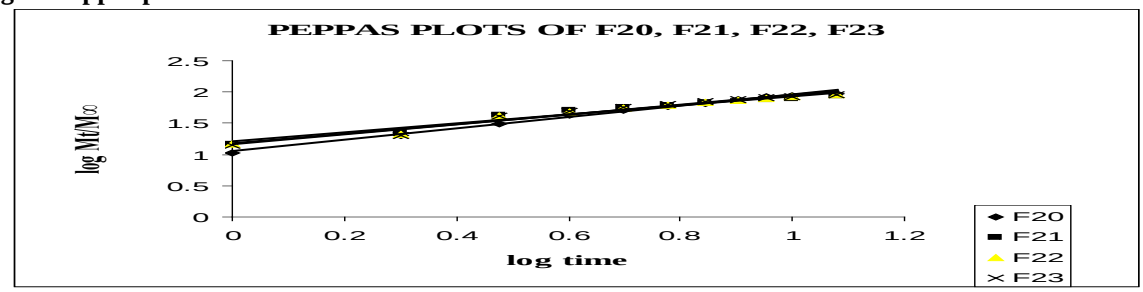


Fig 27: peppas Plot of F20, F21,F22,F23,F24,F25

- From this study, it may be concluded that for Cefixime trihydrate sustained release matrix Tablets, F16 and F20 is successful formulation and can be manufactured with reproducible characteristics from batch to batch.

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