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Research Article

PREPARATION AND EVALUATION OF MATRIX TABLET OF A THIRD GENERATION CEPHALOSPORIN DRUG

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ABSTRACT

Cefixime Trihydrate (CFT) is an orally active third generation cephalosporin. It has plasma half-life of 3-4 hrs. It is active against Gram+ve as well as Gram-ve bacteria. CFT is a third generation oral cephalosporin antibiotic that inhibits wide variety of gram-positive and gram-negative bacteria, especially most members of the family Enterobacteriaceae, including strains producing the common plasmid-mediated β-lactamases. It is well tolerated and one of the best 3rd generation cephalosporin to be available in oral form. CFT has widely been used in the treatment of respiratory and urinary tract infections. The objective of the present work is to design sustained release matrix tablets of CFT by incorporating drug in a matrix made up of release retardant polymers, which prolong drug release leading to minimization of the peak and valley effect in the plasma and provide patient convenience. The effect of combination of polymers on parameters like release pattern, release mechanism of the drug were studied. Since no report or literature is available regarding matrix based once a day formulation of CFT using polymers Eugragit RS 100, Eugragit RL 100 HPMC and PVP K30 to improve patient compliance with better efficacy and negligible side effects.

Keywords: Cefixime Trihydrate, Eugragit RS 100, Eugragit RL 100 HPMC and PVP K30.

INTRODUCTION

The infectious diseases are most common in developing countries. The infectious bacterial classes are both *Gram+ve* and *Gram-ve*. Hence, the treatment is necessary with an agent, which have broad spectrum of activity. Cefixime Trihydrate is an orally active third generation cephalosporin. Its biological half life is 3-4 hrs and bioavailability of 47%.

Sustained release dosage forms have number of advantages over conventional dosage forms viz, improved patient convenience due to less frequent dosing, 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.

The objectives of the present work are to design, formulate and evaluate matrix tablets of Cefixime Trihydrate for sustained release dosage form. As the effect of sustained release dosage form is relatively more, incorporating the drug in the matrix tablet will prolong the drug release.[1-3]

Spectrophotometric Method for Estimation of cefixime trihydrate

The standard calibration curve for Cefixime Trihydrate was prepared in Simulated Intestinal Fluid (SIF) Ph 7.2.

Standard Solution

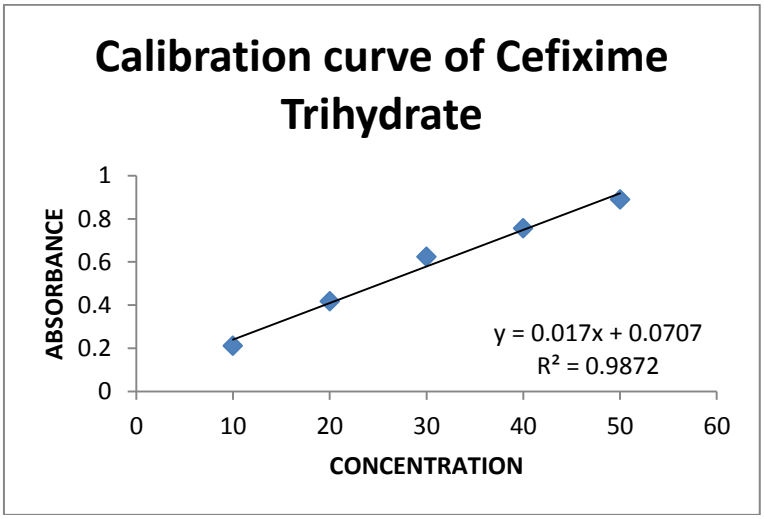
Accurately weighed 25 mg. of Cefixime Trihydrate was dissolved in 25 ml. of pH 7.2 buffer to give a concentration of 1 mg/ml.

Stock Solution

From the standard solution a stock solution was prepared to give a concentration of 10 mcg/ml. Aliquots of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 ml of stock solution was pipetted out into 10 ml volumetric flask. The volume was made upto the mark with the solvent. The absorbance of prepared solutions of Cefixime Trihydrate was measured at 288 nm against appropriate blank.[2-6]

Table 1: Standard Calibration Curve for Cefixime Trihydrate

S.NO.	Concentration	Absorbance
1	10	0.211
2	20	0.417
3	30	0.623
4	40	0.756
5	50	0.889



Preparation of granules

Cefixime Trihydrate (Third Generation Cephalosporin Drug) granules for tabletting were prepared by wet granulation method. Specified quantity of Cefixime Trihydrate, and other ingredients (except Mag.stearate. talc and PVP K30) were weighed according to the formula and transferred in a mortar and pestle and mixed thoroughly. The powder mass was mixed with PVP K30 and isopropyl alcohol (1ml) to obtain a sluggy mass and this was passed through sieve no 12 to obtain the granules. The granules prepared were dried at 50°C for 4 h. The dried granules were screened through sieve no 22 and stored for further studies. The specified quantity of magnesium stearate and talc were finally added and mixed for the compression of tablets.[7-10]

Preparation of Cefixime Trihydrate tablets

An ideal mixture of granules were directly punched into tablets weighing about 650 mg containing 280 mg of Cefixime Trihydrate, using rotary tablet compression machine , using 12 mm diameter concave punches. The different batches of Cefixime Trihydrate tablets were collected and stored in air tight containers.[11-15]

Table 2: Formulation of Matrix Tablet

S.NO.	INGREDIENTS (gm)	FORMULATION CODE								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	CEFIXIME TRIHYDRATE	200	200	200	200	200	200	200	200	200
2	HPMC K4M	150	180	120	150	180	120	-	-	-
3	EUDRAGIT RL100	-	-	-	70	40	100	70	40	100
4	EUDRAGIT RS 100	70	40	100	-	-	-	150	180	120
5	PVP K30	40	40	40	40	40	40	40	40	40
6	LACTOSE	180	180	180	180	180	180	180	180	180
7	MAG.STEARATE	5	5	5	5	5	5	5	5	5
8	TALC	5	5	5	5	5	5	5	5	5
	TOTAL	650	650	650	650	650	650	650	650	650

EVALUATION

A). Pre-compression Parameters

i). Angle of repose

Improper flow of powder is due to frictional forces between the particles. The frictional force in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The lower the angle of repose, better the flow property.

Procedure: The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.[10-13]

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

ii). Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 gm of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was observed. LBD and TBD were calculated using the following formula[14-17]:

$$LBD = \frac{\text{Weight of the Powder}}{\text{Volume of the packing}}$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}}$$

iii). Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index[14-17].

$$\text{Carr's index} = \frac{\text{Tapped Density} - \text{Fluff Density}}{\text{Tapped Density}} \times 100$$

2). Post-Compression Parameters

i). Color and Shape of Tablets

Matrix tablets were examined under lens for the shape and color of the tablets.

ii). Thickness and Diameter of Tablets

Thickness and diameter test permits accurate measurement and provides information on the variation between tablets. Ten tablets were taken and the thickness and diameter was measured using a dial-caliper. The tablet thickness and diameter should be controlled within the ± 5% variation of a standard value.[10-12]

iii). Weight Variation Test

Ten tablets were selected randomly from each formulation and weighed individually to check for weight variation. A little variation is allowed in the weight of a tablet by the U.S. Pharmacopoeia. According to Indian Pharmacopoeia ± 5% difference is allowed.[13-16]

iv). Hardness Test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets were determined using Monsanto hardness tester. It is expressed in kg/cm2. Ten tablets were randomly selected from each formulation and the mean and standard deviation values were calculated. [14-17]

v). **Friability Test**

The friability was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for run upto 100 revolutions. The tablets were weighed again. The % friability was then calculated by the formula [15-18],

$$F = \frac{\text{Initial weight of Tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

% friability of tablets less than 1% is considered acceptable.

vi). Drug Content Uniformity

All the ten formulations were tested for their drug content. Procedure: Ten Tablets were selected accurately, weighed and average weight per tablet calculated. Tablets were ground individually to fine powder. Accurately weighed tablet powder, equivalent to 200 mg of Cefixime Trihydrate was transferred to 100 ml volumetric flask. Powder was dissolved in 80 ml of pH 7.2 buffer and dissolved completely. Then the volume was made upto 100 ml with buffer. This solution was filtered by whatman filter paper. From this 1 ml of solution was withdrawn and volume made upto 100 ml using buffer. Absorbance of the sample solution was measured at 288 nm, and concentration of the drug in the sample was calculated.[12-16]

vii). *In-vitro* Dissolution Studies

In-vitro release studies were carried out using dissolution test apparatus USP XXIII. Procedure: The *in-vitro* dissolution studies of sustained release tablet formulations of Cefixime Trihydrate as a dosage form were carried out using dissolution test apparatus USP XXIII. The dissolution medium consists of 900 ml of standard buffer of pH 1.2 for two hours, followed by pH 7.2 for the next 10 hours. The temperature of the medium was maintained at 37 ± 50C. The speed of rotation of the basket was kept at 100 rpm. Aliquots of 5 ml were withdrawn after every 1 hr for the entire period of time. The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at different time intervals from the dosage form is measured by UV spectrophotometer, by measuring the absorbance for the sample solutions at 288 nm for Cefixime Trihydrate. The dissolution characteristics of each ormulation were studied, after accounting for the loss in the initial concentration of drug Cefixime

Trihydrate, while changing the buffer. The release studies for each formulation were conducted in 1.2 pH and 7.2 pH, indicating the reproducibility of the results.[17-20]

B) EVLUATION OF TABLETS

I). Pre-Compression parameters

1). Angle of Repose

Granules of formulations F-1, F-2, F-3, F-6, F-8, F-9 are considered as having good flow property while a granule of formulations F-4, F-5 and F-7 are considered as having fair flow property. The granules of different formulations were evaluated for Loose Bulk Density (LBD), Tapped Bulk Density (TBD) and Compressibility index (%) and the results are recorded in the Table 3.

Table 3: Pre-Compression parameters

S.NO.	Formulation code	Angle of Repose	Loose Bulk Density (g/ml) Mean ± S.D.(n = 5)	Tapped Bulk Density (g/ml) Mean ± S.D.(n = 5)	Compressibility Index (%) Mean ± S.D. (n = 5)
1	F1	32.5^0	0.284 ± 0.001	0.328 ± 0.002	7.64 ± 0.01
2	F2	33.9^0	0.263 ± 0.002	0.312 ± 0.001	6.84 ± 0.02
3	F3	32.5^0	0.245 ± 0.001	0.284 ± 0.003	6.66 ± 0.02
4	F4	36.8^0	0.294 ± 0.002	0.337 ± 0.004	9.37 ± 0.04
5	F5	37.8^0	0.292 ± 0.001	0.350 ± 0.001	10.4 ± 0.02
6	F6	35.4^0	0.262 ± 0.001	0.298 ± 0.003	5.76 ± 0.03
7	F7	38.7^0	0.323 ± 0.002	0.355 ± 0.002	9.37 ± 0.01
8	F8	33.8^0	0.404 ± 0.001	0.463 ± 0.001	10.2 ± 0.03
9	F9	34.2^0	0.295 ± 0.002	0.336 ± 0.004	6.52 ± 0.02

II). Post- Compression parameters

1). Color and shape of tablets

Randomly selected tablets from each batch examined under lens showed circular shape and yellowish-white color for all the formulations.

2). Thickness and Diameter Test

Tablet mean thickness (n=10) were almost uniform in all the ten formulations.

3). Weight Variation test

The weight variations for all the formulations are shown in Table. All the tablets passed weight variation test as the average % weight variation was within the I.P. limits of 5%.

4). Hardness Test

The hardness of all the tablets was maintained within 8-11 kg/cm2. The mean hardness values (n=10) was measured for all the formulations using Monsanto hardness tester.

5). Friability Test

Another measure of tablet strength is friability. The values of friability test are given in Table. The percent friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits.

Table 4: Post-Compression parameters

S.NO.	Formulation code	Thickness (mm) Mean ± S.D. (n=10)	Diameter (mm) Mean ± S.D. (n=10)	Weight Variation (mg) Mean ± S.D. (n=10)	Hardness (kg/cm2) Mean ± S.D. (n=10)	Friability (n=10) (%)
1	F1	2.88 ± 0.04	11.20 ± 0.02	597.20 ± 3.47	09.42 ± 0.05	0.43
2	F2	2.90 ± 0.08	11..22 ± 0.04	594.10 ± 4.15	10.38 ± 0.10	0.48
3	F3	2.96 ± 0.02	11.23 ± 0.03	595.10 ± 4.34	10.28 ± 0.05	0.52
4	F4	2.91 ± 0.06	11.20 ± 0.08	594.20 ± 5.20	09.30 ± 0.05	0.41
5	F5	2.91 ± 0.02	11.21 ± 0.09	595.90 ± 4.39	10.27 ± 0.04	0.38
6	F6	2.92 ± 0.04	11.14 ± 0.06	596.33 ± 3.23	11.27 ± 0.03	0.49
7	F7	2.96 ± 0.03	11.22 ± 0.02	594.10 ± 4.64	09.30 ± 0.05	0.57
8	F8	2.98 ± 0.02	11.23 ± 0.03	594.20 ± 4.14	10.30 ± 0.02	0.48
9	F9	2.97 ± 0.02	11.18 ± 0.06	594.10 ± 3.63	9.29 ± 0.04	0.47

6). Drug Content Uniformity

The percentage drug content of both the drugs in all the formulated tablets was found to be within limit.

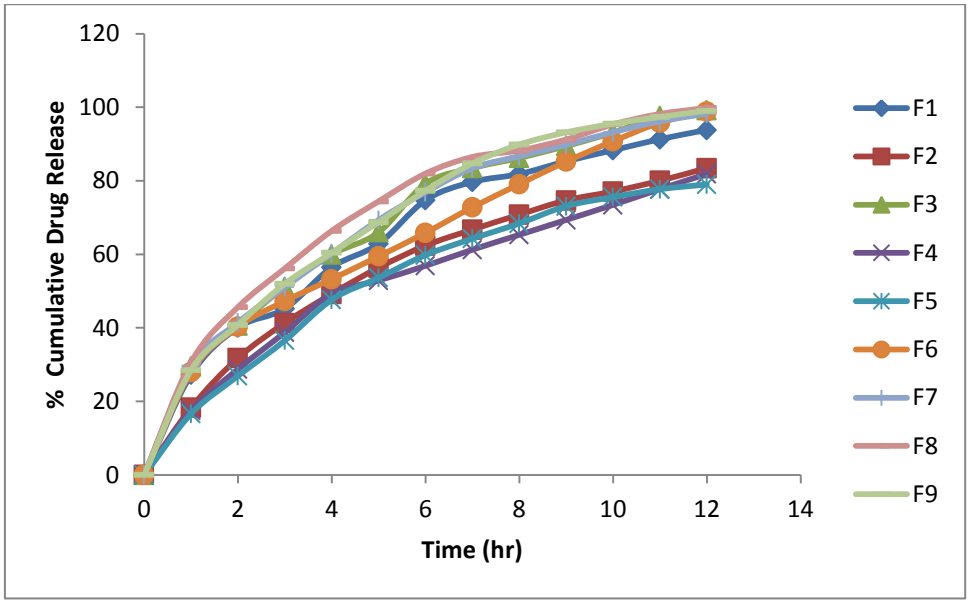
Table 5: Drug Content Uniformity

S.NO.	Formulation code	Percentage drug Content Mean ± S.D. (n=5)
1	F1	98.18 ± 0.04
2	F2	99.18 ± 0.05
3	F3	98.28 ± 0.05
4	F4	98.58 ± 0.06
5	F5	99.08 ± 0.03
6	F6	98.88 ± 0.08
7	F7	99.28 ± 0.07
8	F8	99.17 ± 0.06
9	F9	98.38 ± 0.06

In –vitro drug release study

The *in-vitro* dissolution studies of sustained release tablets of Cefixime Trihydrate as a dosage form were carried out using dissolution test apparatus USP XXIII. The dissolution medium consists of 900 ml of standard buffer of pH 1.2 for two hours, followed by pH 7.2 for the next 10 hours. The temperature of the medium was maintained at 37 ± 50C. The speed of rotation of the basket was kept at 100 rpm. Aliquots of 5 ml were withdrawn after every 1 hr for the entire period of time. The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at different time intervals from the dosage form is measured by UV spectrophotometer, by measuring the absorbance for the sample solutions at 288 nm for Cefixime Trihydrate. The concentration values of Cefixime Trihydrate were calculated. Percentage Cumulative drug release values were calculated based on drug content uniformity. The results obtained in the *in-vitro* drug release for different formulations are shown in Table.

Time (h)	% Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	27.26	18.27	29.46	17.52	16.64	28.01	29.73	30.67	28.52
2	40.10	31.77	40.62	28.75	26.91	40.30	41.43	45.64	40.81
3	45.23	41.32	51.16	38.80	36.56	47.27	51.09	56.16	51.99
4	56.47	49.24	59.95	49.26	47.65	53.26	60.28	66.38	60.41
5	62.87	56.38	65.98	52.88	53.62	59.45	69.35	74.41	68.75
6	74.72	62.37	79.21	56.88	59.79	65.85	76.89	81.96	77.30
7	79.69	66.73	83.45	61.26	64.26	72.78	83.43	86.48	84.72
8	81.82	70.78	86.23	65.30	68.41	79.07	86.68	88.23	89.85
9	85.31	74.68	89.45	69.36	73.10	85.23	89.77	91.22	93.18
10	88.30	77.09	93.12	73.45	75.57	90.75	93.22	95.34	95.51
11	91.31	80.01	97.61	77.73	77.71	95.79	96.17	98.17	97.36
12	93.83	83.46	99.21	81.85	78.99	98.84	98.25	99.82	99.04



CONCLUSION

The objective of the present work was to design, formulate and evaluate Cefixime Trihydrate sustained release dosage form by incorporating it in a sustained release matrix made up of release retardant polymers. (Hydrophilic and hydrophobic), which will prolong the drug release leading to minimize the peak and valley effect in the plasma and provide patient convenience.

The granules were subjected to pre-compression evaluation such as angle of repose, loose bulk density, tapped bulk density and compressibility index. It was concluded that granules exhibited good compressibility and flow property.

The tablets were subjected to various evaluation parameters such as thickness and diameter tests, weight variation test, hardness test, friability test, drug content uniformity test and in-vitro drug release study. The results for all above evaluation parameters indicate that the values are within the range.

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