Research Article
CODEN (USA): IJPLCP

ISSN: 0976-7126
Garg & Singh, 11(12):7117-7125, 2020

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Development Formulation and Evaluation of Sustained Release Matrix Tablets of Cefixime

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Article info

Received: 01/11/2020

Revised: 25/11/2020

Accepted: 28/12/2020

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Abstract

The objective of present work was to design sustained release 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 were prepared by using polymers like hydroxypropylmethylcellulose, Na CMC, Lactose monohydrate and different diluents. 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, compressibility index and hausner ratio. The drug polymer interaction was checked by comparing the IR spectra of the physical mixture of drug and IR spectrum of pure drug. The prepared tablets were evaluated to post compressional parameters such as hardness, friability, average weight, uniformity of weight and *in-vivo* dissolution study. Amongst all formulations, the release profile of F2 gave optimum results. It was concluded that all formulations followed zero order with non-fickian diffusion method.

Keywords: Cefixime, hydroxypropylmethylcellulose, sustained drug release, matrix tablets

Introduction

From the past few years research into the field of dosage formulation has been concentrated on the search for such systems that delay the release of drugs after their administration. Oral administration is the very important way of delivering sustained release drugs to the systemic circulation, owing to easy delivery, a better adjustment of the doses administered, better acceptance by patients and cost-effective manufacturing.[1] Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. Drug release rate from the dosage form is controlled mainly by the different types and proportion of polymers used in the tablet. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, greater attention on development of sustained release or controlled release drug delivery system has came to focus Sustained-release dosage forms have also made significant progress in terms of clinical efficacy and patient compliance.[2]

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Preparation of drug-embedded matrix tablet that involves the direct compression and wet granulation of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing sustained release dosage forms because it gives an easy way of manufacturing.[3] However, drug release from conventional matrix systems is based on porous diffusion of the active ingredient and is thus proportional to the square root of time, where mostly a constant drug delivery rate (zero-order release) is desired during the extended period. In order to obtain zero-order release, solvent-activated, matrix-type, controlled release devices have been developed. The drug is incorporated into a glassy polymer, which passes the glass transition temperature when brought in contact with water and swells. Depending on the swelling characteristics a constant drug release may be obtained.[4] Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e.[5] Hydrophobic matrix (such as wax, polyethylene, polypropylene, and ethyl cellulose) or hydrophilic matrix (such as hydroxypropylcellulose, hydroxypropyl-methylcellulose, methylcellulose, sodium carboxymethylcellulose, alginates and scleroglucan). Cefixime trihydrate inhibits mucopeptide synthesis in the bacterial cell wall, rendering it defective and osmotically unstable. They are more effective against rapidly growing organisms while forming cell walls. Cefixime is not soluble in water after its oral administration. Hence the aim of the present work was to develop, formulate and evaluate sustained release tablets of Cefixime using various polymers.

Material and Methods

Materials

All materials used in the present research were commercial samples. Pure drug cefixime trihydrate was obtained from Martina Bio Genesis PVT. LTD, polymers HPMC, EC, Na CMC, Magnesium Stearate, Talc, and di-potassium hydrogen phosphate were obtained from SD Fine Chem Ltd. Mumbai, EC, and Na CMC were obtained from Corel Pharma Chem., Ahemadabad.

METHODS

Preformulation studies

Identification of drug sample by using FTIR

This was carried out for the identification of the drug sample. For this, 10mg of drug sample and 400 mg of KBr were taken in mortar and triturated. A small amount of the triturated sample was taken and kept onto the sample holder and scanned from 4000cm-1 to 667cm-1 in FTIR. Spectrophotometer. The spectra obtained were interpreted for the functional group.

Determination of melting point

The melting point of Cefixime was determined by using melting point apparatus. For this, take a small amount of drug sample in capillary tube which was one sided closed and placed in a melting point apparatus and the temperature at which drug melted was noted.

Solubility

A semi quantitative determination of the solubility was made by adding solvent into small incremental amount to a test tube containing fixed quantity of solute or vice-versa. After each addition, the system is vigorously shaken and examined visually for any undissolved solute particles.

pH

The pH will be determined by the pH meter. The pH meter will be first calibrated by buffer tablets and pH will be checked. Suspend 0.5 g of pure cefixime drug in carbon dioxide-free water and dilute to 10 ml with the same solvent.

All the results of preformulation study has given in the table

Drug excipients interaction by FTIR

Infrared (IR) spectroscopy was conducted by using a FTIR Spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 400 cm 1. The procedure consists of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressing into discs to form pellet. The pellet will place in the light path and the spectrum was obtained.

Determination of absorption spectrum using spectrometric method

Determine the absorption spectrum of a solution of cefixime in 0.1 mol/L pH 7.2 phosphate buffer.

Preparation of standard calibration curve using spectrometric method

An accurately weighted amount of Cefixime equivalent to 100mg was dissolved in small amount of pH 7.2 Phosphate Buffer in 100ml volumetric flask and volume made up to 100ml with the same pH 7.2 Phosphate Buffer. From this stock's solution 1ml solution withdrawn and diluted up to 10ml with the pH 7.2 Phosphate Buffer in 10ml volumetric flask to get different concentration of 1µg, 2µg, 3µg, 4µg, 5µg, 6µg, 7µg, 8µg, 9µg and 10µg respectively (Table No-3). The absorbance of each solution was measured by UV-Visible Spectrophotometer at 288nm using pH 7.2 Phosphate Buffer as blank. A graph was plotted by taking concentration verses absorbance. The slope and regression values will be calculated from the graph. Graph has given in figure no 1.

Preparation of matrix tablet by wet granulation method Formulation chart for the preparation of Cefixime matrix tablet.

Table No.1: Formulation table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefixime	100	100	100	100	100	100	100	100	100
HPMC	200	300	400	-	-	-	200	100	300
Na CMC	-	-	-	200	300	400	200	300	100
Lactose monohydrate	200	100	-	200	100	-	-	-	-
Ethanolic solution of EC (4%)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Method of Preparation of Granules[7]

Granules of Cefixime were prepared by wet granulation method. All the corresponding powders mentioned in formulation table (Cefixime, HPMC and Na CMC) were weighed and grinded to fineness in a mortar and pestle. The powder was than kneaded with a clean and dry pestle using 4% ethanolic solution of EC as granulating fluid. The wet mass was then passed through a mesh no.16. The prepared granules were allowed to dry for 15-20 min. in an oven at 50˚C. The dried granules were then passed through a mesh no.22. Talc and Magnesium Stearate was added as lubricant and anti-adherent. This granule was then used for further processing.

Evaluation of pre-compression characteristics of granule blend[8-9]

Granules prepared by wet granulation method were evaluated for various rheological properties like bulk density, tapped density, compressibility index, angle of repose by using standard procedure. All these properties were carried out in triplicate (n=3) and average values were reported.

Bulk density

Bulk density was determined by placing the granules blend in a measuring cylinder and the total volume is noted. The weight of granule bed is determined by using digital weighing balance. Bulk density is calculated by using the following formula.

Tapped density

Tapped density was determined by taking the dried granules in a measuring cylinder and measures the volume of granules after 100 tapping's.

Compressibility index

Compressibility index was determined by placing the granules in a measuring cylinder and the volume (V0) was noted before tapping. After 100 tapings again volume was noticed.

Angle of repose

Angle of repose was determined by measuring the height and radius of the heap of the granule bed. A funnel was placed on the graph paper. Granules are placed in the funnel and slowly removed vertically. With the help of scale the height and radius of the heap are measured and noted.

Compression of granules into Tablets

After adding Lubricant (talc) and Anti-adherent (magnesium stearate) to the dry granules bed and after subsequent blending of granules were compressed into tablets on a tablet.

Evaluation of compression characteristics matrix tablet of Cefixime

The tablets were evaluated for in process and finished product quality control tests i.e.

appearance, thickness, weight variation, hardness, friability, swelling index, dissolution study.

Appearance

The appearance of tablet must be either a uniformly texture or a structure. The colour was checked by visual inspection. There should be no oily drops and no pin holes on the surface.

Thickness test

The tablets were evaluated for their thickness using a venirer calliper measured in terms of micrometer. Averages of three readings were taken and the results tabulated.

Hardness test

Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The force was measured in kilograms. The hardness was tested using Monsanto tester.

Friability test

Roche friabilator was used for testing the friability of the tablets. For this test, 20 tablets were weighted accurately and placed in the friabilator chamber and rotated at 25rpm for a period of 4min. Tablets were again weighted and the percentage weight loss was determining by using formula given below.

Weight variation test

20 tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet is determined from the collective weight. Note more than 2 of the individual weights may deviate from the average weight by more than the percentage deviation given in the monographs and none should deviate by more than twice that percentage given in the monographs.

Swelling index

The swelling behaviour of were studied. One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 7.2. At the end of 2 hr, the tablet was withdrawn, kept on tissue paper and weighed. The weighing was continued for every 2 hr, till the end of 12 hr. The % weight gain by the tablet was calculated by formula.

***In vitro* dissolution**

This dissolution test was performed for dissolution study of a drug under in-vitro condition in this dissolution apparatus, in required proper medium at 37ºC ± 0.5%. Dissolution study of sustained release cefixime matrix tablet was carried out in pH 7.2 phosphate buffer by using basket type dissolution apparatus at 50rpm. One tablet was placed at 900ml pH 7.2 phosphate buffer in basket type dissolution apparatus and set speed 50 rpm. Temperature should be 37ºC ± 0.5%. Then sample were withdrawn, at a time internal and replace by same quantity of freshly prepared pH 7.2 phosphate buffer. The procedure is repeated up to 12 hrs. The sample was analyses for drug content or percentage of drug release against pH 7.2 phosphate buffer as blank solution at the 288 nm. The percentage drug release was plotted against time to determine the release profile.

Kinetic model for drug release

All the formulation of prepared tablets were subjected to invitro release studies these studies were carried out using dissolution apparatus and pH 7.2 phosphate buffer was taken as the dissolution medium, obtained was plotted in different model of data treatment as follows:

Cumulative percent drug released vs. time (zero order rate kinetics)

Log cumulative percent drug retained vs. time (First Order rate Kinetics)

Log cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)

Log of cumulative % release Vs log time (Peppas Exponential Equation)

Korsmeyer and Peppas Model

The release rates from controlled release polymeric matrices can be described by the equation proposed by Korsmeyer et al. Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism.

For Fickian release, less than n=0.45 while for anomalous (Non-Fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, more than n = 0.89.

Results and Discussion

FTIR Study:

FT-IR Spectroscopy study was carried out for the identification of pure drug. The spectra obtained from the FT-IR studied at wavelength from

4000cm^{-1} to 400cm^{-1} and the characteristics peaks obtained.

Melting Point:

As per pharmacopoeia range of melting point of cefixime trihydrate is given between 218˚-255˚C.Melting point of pure drug was found in between 218˚- 220˚C.

pH:

The pH of the suspension was found to be in 3.8. This lies between actual pH ranges of cefixime. The absorption spectrum of a solution of cefixime in 0.1 mol/L phosphate buffer solutions, pH 7.2 and compare the spectrum with the reference spectrum, both the spectra exhibit similar intensities of absorption at the same wavelengths.

UV- Spectrophotometric study:

The absorbencies of these drug solutions were estimated at λmax 288 nm. The data were given in above Table No-3. A calibration curve was constructed as shown in Figure 1. The value of R^2 was found to be 0.9993 at 288 nm which is nearly to 1, which signifies linearity.

The Pre-compression evaluations of prepared granules were shown below. The granules were evaluated for bulk density, tapped density, carr's index and angle of repose and consistency in data obtained as indicated by their standard deviation value. The angle of repose of all formulation batches was found to be in good and excellent range. Angle of repose determines was in the range of 29.8 ± 0.79 to 32.8 ± 0.88. The value of angle of repose (Ɵ) showed that F4, F6, F7 had excellent flow properties while other were had good flow properties.

The evaluations of prepared sustained release matrix tablet were shown below. The tablets were evaluated for appearance, thickness, hardness, weight variation, friability, swelling index, dissolution study and consistency in data obtained. All prepared batches of tablets were well in appearance and were checked by visual inspection. The appearance of tablet had uniformly texture and structure. There were no oily drops and no pin holes on the surface. There were small variations in between thickness of all formulation but in a particular formulation there was no variation. The thickness of all formulation was ranged in between 3.2 ± 0 to 3.9 ± 0 mm. The hardness of the compressed tablets was determined by using hardness tester (Monsanto) indicate that the tablets are of adequate strength. Hardness of tablet of all formulation ranged from 5.6 ± 0.57 kg/cm2 and 8.8 ± 0.28 kg/cm2. The hardness of all formulation showed variation because of formulation combination and powder properties. The friability of all formulation was in the range of 0.1% to .99%. All formulation were comes under in standard limit i.e. less than 1%, hence passed the test for friability.

Friability:

The friability of F4 was very near to the standard limit.

Weight Variation:

The weight variation of all formulation was in the range of ± 5.1 to ± 4.8. The weight variation test was performed according to the procedure in the pharmacopoeia. In the weight variation test, pharmacopoeial limit is 5%. The individual deviation of all the tablets formulation was found to be within the limit and hence passed the test for uniformity of weight.

***In-vitro* release study:**

Dissolution study of all formulation performed. The sampling point of the drug was at the 1 hr time interval for 12 hr for dissolution study. A plot of % cumulative drug release versus time for sustained release matrix cefixime tablet of all formulation was shown in fig 4.4. Formulation F1, F2, F3 prepared tablets of cefixime using HPMC alone in increased ratio, in which drug was constant. As per result observation F1, F2, F3 gives drug release 14.36%, 15.47%, and 12.81%. In the later stage the release was found to be slower and controlled in the tablet with increased ratio of the polymer, gives drug release F1-98.61% in 6 hr, F2- 99.8 in 12 hr and F3-86.94% in 12 hr. Similarly in formulation F4, F5, F6 Na CMC used in increased ratio give drug release in 1 hr13.92%, 14.36%, 18.13% and in later drug release found to be 99.2% in 9 hr, 90.08% in 12 hr, and 97.89% in 12 hr. In formulation F7, F8, F9 combination of both polymer HPMC and NaCMC was used in different ratio 2:2, 3:1and 1:3. In first hour gives 12.62%, 12.67% and 16.35% drug release and later 89.86% and 81.21% in hour 99.43% after10 hr. Formulation F1, F4, and F9 shown 99.8% drug release before 12 hour. Based on experimental dissolution study formulation F2 and F6 was shown satisfactory release profile. Results of *In-vitro* study have given in table no 4.

Kinetic model of drug release:

Data obtained from the in-vitro release studies of tablets of Cefixime formulations were fitted to various Kinetics equations such as zero order, first order, Higuchi model and crossmeyer-peppas model. The model that gives high 'r2' value is considered as the best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r2) was determined. The release rate kinetic data for all the other equation can be seen in table no 5. When the data were plotted according to the zero order equation, the formulation F2 showed a fair linearity, with regression values 0.9902, indicate that the concentration was closely independent of drug release. From table 4.7 it was found that the in vitro release of F2 was best fitted in korsmeyer peppas model (r2=0.9988). The release exponent was 0.7327.

Conclusion

Release matrix tablet of cefixime trihydrate were successfully prepared using HPMC, and 4% ethanolic solution of EC by wet granulation method. The physical properties of tablet and its release kinetics indicate that wet granulation method is an acceptable method for designing of sustained release matrix tablet of Cefixime Trihydrate. The rate of release of drug from the tablet was observed to decrease as proportion of HPMC increases. From the results it was found that the *in vitro* release of F2 was best, following zero order (r2=0.9902) and korsmeyer peppas model (r2=0.9988). Kinetic model indicate non-fickian release character. Non-fickian kinetics found indicates that the release of the drug depends simultaneously on the matrix swelling and diffusion phenomena.

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ISSN: 0976-7126
Garg & Singh, 11(12):7117-7125, 2020

Table 1: Absorbance for standard curve of Cefixime trihydrate

Concentration (µg/ml)	Absorbance at 288
0	0
1	0.051
2	0.083
3	0.122
4	0.166
5	0.211
6	0.248
7	0.291
8	0.332
9	0.367
10	0.406

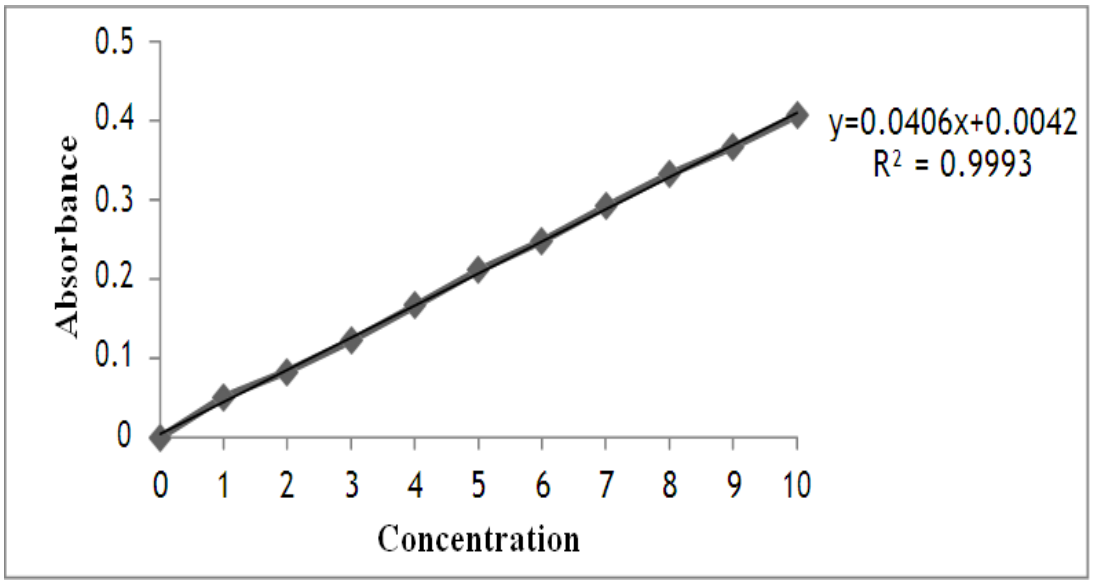

Fig. 1: Calibration Curve of Cefixime trihydrate

ISSN: 0976-7126
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Table 2: Results of Preformulation study

Formulation No.	Thickness (mm)	Hardness (Kg/cm^2)	Weight Variation (%)	Friability (%)	Swelling Index
F1	3.9±0	5.6±0.57	±0.81	0.27	88.4
F2	3.7±0	6.8±0.57	±1.01	0.23	98.1
F3	3.9±0	5.6±0.28	±0.76	0.44	137
F4	3.9±0	6.6±0.57	±1.34	0.99	211.5
F5	3.2±0	6.8±0.28	±1.03	0.36	240.5
F6	3.3±0	5.8±0.28	±0.78	0.39	160.8
F7	3.5±0	8.8±0.28	±0.83	0.38	278.5
F8	3.9±0	6.1±0.28	±1	0.2	148.4
F9	3.2±0	5.6±0.57	±0.87	0.1	190

Table 4: Cumulative drug release study of prepared formulations

Time (hr)	Cumulative drug release (% CDR)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	14.36	15.47	12.81	13.92	14.36	18.13	12.62	12.67	16.35
2	31.44	26.34	21.9	32.54	26.12	30.55	22.72	21.88	31.44
3	52.51	35.0	27.9	46.31	36.11	43.65	32.76.	30.23	42.54
4	70.5	43.66	37.23	56.75	45.21	53.43	44.47	37.67	51.87
5	93.59	51.22	45.89	75.4	53.89	62.99	51.68	44.25	55.01
6	98.61	59.45	50.35	89.85	61.12	70.78	58.61	50.49	63.24
7	__	65.92	66.78	92.79	68.8	84.12	64.84	64.15	75.69
8	__	73.05	70.15	95.28	73.05	87.27	72.29	70.14	88.36
9	__	75.75	72.18	99.2	78.19	86.88	76.53	73.65	95.51
10	__	83.1	79.5	__	83.11	93.8	78.78	80.24	99.43
11	__	88.91	84.01	__	84.04	95.18	83.25	80.64	__
12	__	99.8	86.94	__	90.08	97.89	89.86	81.21	__

Table 5: kinetic value obtained from different model of formulation

Formulation No.	Zero order	First order	Higuchi model	Korsmeyer Peppas model	
	r^2	r^2	r^2	n	r^2
F1	0.9957	0.8536	0.9838	1.1369	0.998
F2	0.9902	0.5802	0.9914	0.7327	0.9988
F3	0.9771	0.9772	0.9837	0.8011	0.9929
F4	0.9556	0.9591	0.9846	0.9109	0.9798
F5	0.9605	0.9869	0.9952	0.7344	0.9906
F6	0.9297	0.9586	0.9798	0.6923	0.9833
F7	0.967	0.9772	0.9959	0.7869	0.9903
F8	0.9652	0.9779	0.9818	0.784	0.9929
F9	0.9869	0.8478	0.9524	0.7321	0.9802

Cite this article as:
Garg P. and Singh G. (2020). Development Formulation and Evaluation of Sustained Release Matrix Tablets of Cefixime, *Int. J. of Pharm. & Life Sci*., 11(12): 7117-7125.
Source of Support: Nil
Conflict of Interest: Not declared
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