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Formulation and Evaluation of Controlled Release Matrix Tablets of Cefixime Trihydrate

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ABSTRACT: The main objective of the present work was to develop sustained release matrix tablets of Cefixime Trihydrate were prepared by direct compression techniques and evaluates the effect of formulation variables such as lubricant, binder, polymer content and viscosity grades of HPMC on the behavior of Cefixime Trihydrate release. The prepared tablets were evaluated for various physico-chemical parameters. *In vitro* release profile was check to evaluate the sustained release matrix tablet of Cefixime Trihydrate. The drug release from the optimized formulation was found to follow zero order kinetics. Thus the phenomenon of drug release showed that the release of optimized formulation is controlled by diffusion. Administration of Cefixime Trihydrate in a sustained release dosage would be more desirable for bacterial infections effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration. From *In vitro* dissolution profile, Formulation S3 was prepared with Hydroxypropyl methylcellulose (K15M) combination where drug release was about 99.14% at the end of 24 hrs and followed zero order with non-Fickian diffusion method. It is selected as the best formulation.

Keywords: Matrix tablets, direct compression, Release behavior, Cefixime Trihydrate.

RESEARCH PAPER

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INTRODUCTION

Matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms[1]. Among the different strategies to prolong the drug action, formulation of matrix tablet has gained immense popularity now a days because it has the advantage of simple processing and a low cost of fabrication Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form, and ease of scale-up and process validation. This is reflected by the large number of patents filed each year and by the commercial success of a number of novel drug delivery systems based on matrix technologies [2]. In matrix devices, the drug is homogeneously dispersed in either a hydrophobic or hydrophilic polymer matrix. The release rate from matrix systems remains unaffected by thin spots, pinholes, and other similar defects, which can be a serious problem with reservoir systems [3].

The design of sustained release delivery system is subject to several variables of considerable importance. Among these, route of drug delivery, the type of delivery system, the disease being treated, the patient, length of therapy and the properties of the drug. The drug should be stable in the gastro-intestinal tract as the sustained release systems release their contents over entire length of gastrointestinal tract. Therefore, drugs degraded by the acid environment of the stomach or degraded by the basic environment of intestine are unsuitable for formulation into sustained release dosage forms.

Sustained release matrix tablet can be prepared in two ways, one is direct compression of the powder blend containing the drug, polymer and other additives, and another one involves granulation prior to compression. Selection of the proper method depends on the properties of the drug, polymer and other ingredients. The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It required fewer unit operations, less machinery, reduced number of personnel and processing time, increased product stability and production rate [4]. HPMC, a semi synthetic derivative of cellulose, is a swellable and hydrophilic polymer.

Some research groups have worked on the usage of swellable HPMC as the retarding polymer to sustain the release of different drugs [5, 6]. It is very suitable to use as a retardant material in controlled release matrix tablets, as it is nontoxic and easy to handle [7]. Matrix tablets prepared using HPMC on contact with aqueous fluids gets hydrated to form a viscous gel layer through which drug will be released bydiffusion and/or by erosion of the matrix [8].

Almost in every developing country, infectious diseases are more common; among them bacteria are most responsible pathogenic microorganism [9]. Cefixime Trihydrate is a broad spectrum oral third generation cephalosporin antibiotic. It is well tolerated and is one of the third generation cephalosporins to be available in oral form. Cefixime Trihydrate is bactericidal and acts by inhibition of bacterial synthesis. It passes through ion channels in the bacterial cell wall and binds to the penicillin binding proteins (PBP) in the cell membrane causing acylation of membrane bound transpeptidase enzymes; this prevents cross linkage of peptidoglycan chains, which is necessary for bacterial cell wall strength and rigidity. This leads to reduced synthesis of peptidoglycans and result in damage to cell wall. Cefixime Trihydrate is stable in the presence of beta-lactamase enzymes [10, 11]. Cefixime is effective on infections of the middle ear (otitis media), tonsillitis, throat infections (pharyngitis), laryngitis, bronchitis, and pneumonia caused by susceptible bacteria. It is also used for treating urinary tract infections and gonorrhea as well as acute bacterial bronchitis in patients with chronic obstructive pulmonary disease.

MATERIALS AND METHODS

Materials

Cefixime Trihydrate was obtained as gift sample from Alkem Pharma Ltd., Hydroxypropyl methylcellulose (HPMC K4M HPMC K15M and HPMC K100M) was a gift sample received from Colorcon Asia Pvt. Ltd., Microcrystalline Cellulose (Avicel PH 102) and Lactose were gift sample from Signet Chemical Corporation. All chemicals and reagents used were of analytical grade.

Experimental Design

A number of preliminary experiments were conducted to determine the formulation and parameters by which the process resulted in sustained released tablet. Design expert software® (Design Expert trial version 8.0.1; State-Ease Inc., Minneapolis, MN, USA) was used in our study for to optimize the concentration of Hydroxypropyl methylcellulose (HPMC K4M HPMC K15M and HPMC K100M), Microcrystalline Cellulose and Lactose [12]. A two-factor, three-level, full factorial design was employed for the optimization procedure. Whereas experimental formulations are listed in Table 1.

Methods

Preparation of Tablets

Tablets were prepared by direct compression process. The composition of each tablet is shown in Table 1. Different batches of tablets, S1 to S9 were prepared by varying the concentration of Hydroxypropyl methylcellulose HPMC K4M HPMC K15M and HPMC K100M), Microcrystalline Cellulose and Lactose. The drug was passed through 40# sieve. Hydroxypropyl methylcellulose (K15M), Microcrystalline Cellulose and Dibasic Calcium Phosphate were passed through 30# sieve. All other ingredients were mixed for 15-20 min. After mixing, blending total mass was taken in a laboratory designed small drum blender machine for about 30 min. Particular attention was given to ensure thorough mixing and phase homogenization. Compression was done on Rimiek type 10-station compression machine, Germany, using 12 mm punch.

Table-1: Composition of sustained release matrix tablets of Cefixime Trihydrate

Ingredients	**Formulation code**								
(mgs)	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**
Cefixime Trihydrate	200	200	200	200	200	200	200	200	200
HPMC K15M	50	100	150	-	-	-	-	-	-
HPMC K4M	-	-	-	50	100	150	-	-	-
HPMC K100M	-	-	-	-	-	-	50	100	150
Microcrystalline Cellulose	195	145	95	195	145	95	195	145	95
Lactose	50	50	50	50	50	50	50	50	50
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total weight (mg)	500	500	500	500	500	500	500	500	500

Evaluation of Granules

Granules were evaluated for the flow parameters such as angle of repose Tap density, Hausner ratio and Carr's index as given Table 2.

Angle of repose

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [13, 14].

$\tan\theta = h/r$

Therefore $\theta = \tan h/r$

Where θ = angle of repose, h = height of the pile, r = radius of the pile base

Bulk density/Tapped density

Both bulk density (BD) and tapped density (TD) were determined. A suitable amount of powder blend from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 100 mL measuring cylinder. After observing its initial volume, the cylinder in the density tapper instrument and density is measured according to USP method II. The tapping was continued until no further change in volume was noted [13,14]. Volume of packing after tapping was noted. BD and TD were calculated using the following equation.

BD = weight of the powder / volume of the packing
TD = weight of the powder / tapped volume of the packing

Compressibility index

Compressibility index of the powder was determined by Carr's compressibility index [15] as using the following equation

Carr's index (%) = [(TD – BD) x 100] / TD

It helps in measuring the force required to break the friction between the particles and the hopper.

Hausner's ratio

It is the ratio of tapped to bulk density [15] and was calculated by using the following equation.

Hausner's ratio = TD/BD

Evaluation of tablets

Uniformity of weight

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight [16].

Thickness

The thickness of the tablet was measured by using digital venire caliper, twenty tablets from each batch were randomly selected and thickness was measured [16].

Hardness

Hardness was determined by taking six tablets from each formulation, using a Monsanto Hardness Tester [16].

Friability

The friability of sample of six tablets ware measured using a Roche Fribilator. Six pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fine's using 60 mesh screens and the percentage of weight loss was calculated [16].

% Friability = (Loss in weight / Initial weight) × 100

Drug content uniformity

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 100 mg of Cefixime Trihydrate was dissolved in 100 ml of pH 7.2 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 287 nm using UV-Visible spectrophotometer (UV 1601- Shimadzu, Japan) [16].

DISSOLUTION STUDIES

In vitro drug release studies for the prepared matrix tablets were conducted for a period of 24 hrs using USP XXII apparatus-I 37±0.5^{o}C and at 50 rpm speed; the in vitro release study was performed in 0.1 N HCL pH 1.2 for 2 hrs and in phosphate buffer pH 7.2 up to 24 hrs. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 287 nm for Cefixime Trihydrate by a UV-Visible spectrophotometer [16].

Release kinetics

Different kinetic models (zero-order, first-order, Higuchi's, Korsmeyer's and Hixson Crowell) were applied to interpret the release profile (the order and mechanism of Cefixime Trihydrate release) from matrix system. To study the mechanism of drug release

from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equation. However, two factors diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential equation (Korsmeyer equation), Eq. (1), which is often used to describe the drug release behavior from polymeric systems.

$$\text{Log } (Mt/Mf) = \text{Log } k + n \text{ Log } t \text{ ---------- (1)}$$

Where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release. Applied this equation to evaluate the drug release mechanism [17]. To clarify the release exponent for different batches of matrix tablets, the log value of percentage drug dissolved was plotted against log time for each batch according to the equation 1. A value of n = 0.45 indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non- Fickian) refers to a combination of both diffusion and erosion controlled-drug release [18].

The Hixson - Crowell cube root equation is:

$$M1/3 = Mo^{1/3} - Kct \text{ ---------- (2)}$$

Where, Kc is the cube root dissolution rate constant. Cube roots of percent releases (Cube root of initial drug load minus cube root of % drug remaining) are plotted against time (hour) to demonstrate the Hixson Crowell plot. Mean dissolution time (MDT) was calculated from dissolution data using the following equation [18].

$$MDT = (n / n+1) K^{-1/n} \text{ ---------- (3).}$$

STATISTICAL ANALYSIS

A one way analysis of variance (ANOVA) was used to analyze the dissolution data obtained for each batch of formulation to compare the drug release rate and comparison of mean dissolution time (MDT) of all formulations. A confidence limit of $P<0.05$ was fixed and the theoretical calculated values of *F (Fcrit and Fcal)* were compared for the interpretation of results. ANOVA was determined using SPSS software (Version 12, SPSS Inc., USA).

RESULTS AND DISCUSSION

Cefixime Trihydrate with all evident advantages proved to be a suitable candidate for development of a sustained-release dosage form. In present study Hydroxypropyl methylcellulose (K4M, K15M and K100M), Microcrystalline Cellulose and Lactose, which were used in hydrophilic matrix drug delivery systems, have been employed to formulate sustained-release tablets of Cefixime Trihydrate but alone it was not gives a good result so it was used in combination with hydrophobic polymer like Microcrystalline Cellulose.

The Pre formulation studies or Micromeritic Characterization of powder blend evaluated were found to be Angle of repose range from 26.11 ±1.44 to 28.69 ±0.16, Bulk density range from 0.31±0.04 to 0.34±0.04, Tapped density 0.39±0.02 to 0.42±0.01 and Carr's index range from 17.04±1.67 to 19.51±1.15 respectively, which indicate good flow property are shown in (Table 2).

The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, friability, drug content and *In vitro* drug dissolution studies. All the studies were performed in triplicate, and results are expressed as mean ±SD are shown in (Table 3).

The Avg. wt of the tablets were ranged from 500.1±2.2 mg to 501.0±1.2 mg, Thickness were ranged from 3.11±0.17 mm to 3.20±0.21 mm, Hardness were ranged from 3.59±0.21 kg/cm^2 to 3.89±0.11 kg/cm^2, The percentage friability were ranged from 0.01±0.21 % to 0.09±0.02 % and drug content of different batches ranged from 98.44±0.41 %to 99.89±0.31 % respectively, which is in acceptable criteria in tablet formulation.

In-Vitro dissolution studies

The result of the dissolution study indicating that S1, S2 and S3 released 24.54, 22.33, and 12.19 of Cefixime Trihydrate at the end of 2hrs and 87.88, 92.42 and 99.15 at end of 24hrs respectively. Formulation S4, S5 and S6 released 33.36, 26.21 and 25.19 at the end of 2hrs and 88.65, 93.16 and 94.17 at the end of 24hrs. Formulation S7, S8 and S9 released 34.16, 30.45 and 28.91 at the end of 2hrs and 87.56, 86.12 and 90.86 at the end of 24hrs. The released rate of Cefixime Trihydrate in formulation S3 was comparatively higher than other formulations the concentration of polymers Hydroxypropyl methylcellulose (K15M) in S3. This polymer concentration has been well known to retard the drug release by swelling in aqueous media. A polymer's ability to retard the drug release rate is related to its viscosity. The hydration rate of Hydroxypropyl methylcellulose (K15M) depends on the

nature of the substituents like hydroxypropyl group content. Hence, Hydroxypropyl methylcellulose (K15M) was used because it forms a strong viscous gel in contact with aqueous media, which may be useful in controlled delivery of drug [19]. The effect of polymer concentrations on drug release from matrix tablets is shown in Figure 1. It can be seen that by increase the polymer concentration combination, the rate of drug release from the matrix tablet decreases dramatically. The formulations containing relatively higher polymer content shows less initial drug release due to the unavailability of drug molecules at the surface of matrix tablets. Further, by increasing the concentration of polymer in the tablets formulation, a point will be reached where the pores or channels formed by the drug particles within the polymer matrix were diminished. i.e., the diffusion of drug molecules from the channels of the matrix was disturbed by the increased concentration of polymer.

Release kinetics

The data obtained from in vitro dissolution studies were fitted in different models viz. zero order, first order, Higuchi and Korsemeyer- Peppas equation, the results were shown in Table 3. It was also observed that highest correlation was found for Zero order profile (R2 > 0.99), which indicates the drug release via diffusion mechanism from hydrophilic matrices. To confirm the exact mechanism of drug release from these tablets, the data were fitted according to Korsemeyer-Peppas equation. A value of n for all matrices studied here was ranged between 0.97 to 0.99, indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism.

Table-2: Micromeritic properties of sustained release matrix tablets of Cefixime Trihydrate

Formulation Code	Angle of repose θ±SD	Bulk density (gm/ml) ±SD	Tapped density (gm/ml) ±SD	Carr's index (%) ±SD
S1	28.45 ±0.35	0.32±0.02	0.41±0.02	17.95 ±1.21
S2	28.11 ±0.19	0.31±0.04	0.42±0.01	18.42 ±1.41
S3	27.94 ±0.24	0.33±0.04	0.41±0.04	19.51 ±1.15
S4	28.69 ±0.16	0.33±0.02	0.41±0.03	19.51 ±1.15
S5	28.40 ±0.33	0.32±0.05	0.39±0.02	17.95 ±1.34
S6	26.11 ±1.44	0.33±0.04	0.40±0.02	17.50 ±1.39
S7	28.18 ±1.77	0.32±0.02	0.40±0.02	17.95 ±0.71
S8	26.48 ±0.51	0.34±0.04	0.41±0.03	17.04 ±1.67
S9	28.31 ±1.24	0.33±0.03	0.40±0.03	17.50 ±0.59

Table-3: Post compressional parameters of sustained release matrix tablets of Cefixime Trihydrate

Formulation Code	Avg. wt (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
S1	500.3±1.2	3.20±0.21	3.87±0.12	0.08±0.01	99.71±0.11
S2	500.1±2.2	3.16±0.14	3.81±0.35	0.08±0.02	99.17±0.52
S3	500.3±1.1	3.17±0.11	3.74±0.21	0.07±0.04	99.89±0.31
S4	500.2±1.6	3.14±0.26	3.89±0.11	0.06±0.02	98.49±0.23
S5	500.3±1.4	3.13±0.26	3.66±0.10	0.07±0.22	99.74±0.34
S6	500.2±1.1	3.12±0.13	3.60±0.19	0.08±0.01	98.67±0.41
S7	500.2±2.3	3.11±0.17	3.78±0.22	0.05±0.02	98.91±0.14
S8	501.0±1.2	3.19±0.06	3.80±0.24	0.08±0.03	99.50±0.16
S9	500.0±1.4	3.18±0.03	3.59±0.21	0.09±0.02	98.44±0.41

Table-4: Correlation coefficients according to different kinetic equations used for describing Cefixime Trihydrate release behavior

Formulation Code	Zero order		First order		Higuchi		Korsmeyer		Hixson Crowell	
	R^2	K_0(% h^{-1})	R^2	K_1(% h^{-1})	R^2	K_h (% $h^{-0.5}$)	R^2	n	R^2	K_c (% h^{-1})
S1	0.891	9.321	0.979	-0.097	0.993	29.764	0.990	0.441	0.951	0.266
S2	0.911	8.111	0.942	-0.062	0.988	25.831	0.998	0.460	0.960	0.191
S3	0.868	9.199	0.981	-0.097	0.995	29.094	0.990	0.452	0.977	0.239
S4	0.934	7.369	0.959	-0.070	0.991	23.431	0.971	0.474	0.951	0.181
S5	0.910	7.969	0.971	-0.056	0.984	25.521	0.984	0.484	0.961	0.208
S6	0.923	8.156	0.944	-0.077	0.991	22.547	0.987	0.544	0.958	0.189
S7	0.941	7.434	0.970	-0.063	0.987	23.463	0.971	0.486	0.954	0.199
S8	0.922	7.474	0.969	-0.069	0.984	25.688	0.984	0.531	0.961	0.171
S9	0.921	7.381	0.966	-0.064	0.986	23.374	0.979	0.489	0.967	0.194

R2-Correlation coefficients, K_0, K_1, K_h, K_c Release rate constant for zero order, first order, Higuchi, and Hixson Crowell release equation, respectively, n, diffusional exponent, indicative of release mechanism in Korsmeyer equation. All formulations except S1 and S5, (Fickian release) followed Non-Fickian (Anomalous) release.

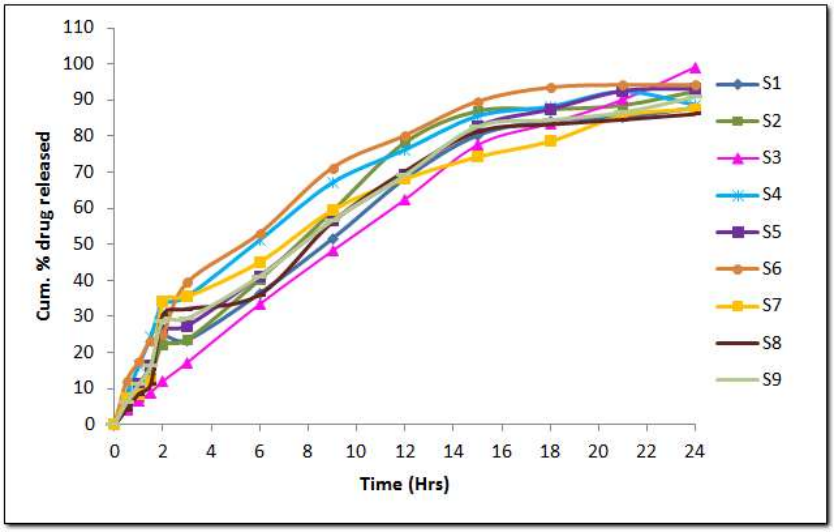

Fig-1: Comparative release profile of sustained release matrix tablets of Cefixime Trihydrate

CONCLUSIONS

From the study, it is possible to conclude that the proposed tablet formulations were suitable for direct compression method using and Hydroxypropyl methylcellulose (K15M), combination showed excellent time-delayed release of the drug. An optimal lag period in both acidic and basic environments, due to the initial swelling of polymers, followed by complete drug release in a controlled manner could be obtained owing mainly to diffusion through the swollen polymer and in part to the slow erosion. Thus, the delayed-onset extended-release system of Cefixime Trihydrate may be beneficial for bacterial infections diseases. The results are not only encouraging but they also promise effective management of such diseases through this novel approach after suitable trials in animal models and human beings.

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