Research Article

Preparation and Evaluation of Sustained Release Tablets of Cefixime Trihydrate using Natural Excipients

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ABSTRACT

Six batches of formulated sustained release matrix tablets of Cefixime Trihydrate were prepared by using different polymers like Tamarind Gum, Carnauba wax, HPMC, MCC, PVP K30 by wet granulation technique. The effects of prepared tablets by using natural polymers were evaluated for pre compression parameters, uniformity of content, assay and in vitro drug release. Influences of different parameters like pH, agitation intensity on drug release were also studied. Cefixime Trihydrate sustained release matrix tablets prepared using HPMC and carnauba wax was observed a better system for once-daily sustained release of a water-soluble drug like Cefixime Trihydrate which effectively release more than 100% for 12 hrs. All the prepared formulations (F01 to F06) were fitted in to zero order, first order, Higuchi's model and Korsemeyer-peppas model and the values of slope, intercept and r2 were calculated. The r2 values were found to be 0.9925(F05) and 0.9941(F06) for Higuchi's release model & 0.9792 for first order release model. The r2 values were found to be 0.9747(F04) for zero order release model. The formulations are following Higuchi's release model. Hence it is suggested that the drug was released by Fickian diffusion in all the cases.

Keywords: Carnauba wax, Tamarind gum, Matrix tablets, Cefixime Trihydrate, Higuchi's release model

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INTRODUCTION

CEFIXIME TRIHYDRATE is third generation oral cephalosporin, it has greatest onset against a wide range of sensitive gram positive, gram negative & anaerobic bacterial pathogens including beta-lactamase producing strains. It also attracted by the penicillin binding proteins at various site of activity [1]. It also interrupt bacterial cell-wall synthesis. It has 3 hours half-life, with slight variation over the typical therapeutic dosage range. The dose of Cefaxime trihydrate in healthy individual is 100- 300mg/day. The sustained release dosage form is required to improve the bioavailability of drug and the patient compliance by modifying the rate of drug absorption which reduces the frequency of dosing. The matrix system commonly used for manufacturing is sustained release tablet dosage form and it provides the minimum dosing frequency which decreases the threat of adverse effect and attain desired therapeutic action [2-4].

In present study the attempt was made to evaluate the release study of formulated tablet matrix by using natural binders. To attain this, melt granulation and wet granulation both the methods are used for different formulations. The formulation which includes water soluble substances are employed to wet granulation [5] and the formulation which consist of carnuba wax are subjected to melt granulation and this technique involves the formation of fatty wax matrix in which drug is embedded resulting in controlled release of the drug from the fatty matrix. The carnauba wax in various concentration mixtures are used to form the sustained release tablets. The fatty wax excipients have a higher melting range lies between 500-800^{0}C [6,7]. Hence attempts have been made to develop

extended release matrix tablets of Cefaxime trihydrate, using wax such as carnauba wax, Tamarind gum with the varying concentration of HPMC.

EXPERIMENTAL STUDIES

MATERIALS

Cefaxime trihydrate was a gift sample from Southshorn formulations Ltd, Vadodara. Carnauba wax procured from Sigma Aldrich, USA. Tamarind gum was prepared in laboratory. All other Chemicals were procured from Loba Chemicals Pvt. Ltd.

Preparation of Tamarind Gum

Preparation of tamarind kernel powder (TKP)

Raw seeds of Tamarind were dried in sun light for two days and the whole seed was broken into small pieces and ground into a fine powder. Distilled water was taken in a beaker and the required amount of fine powder of Tamarind seed was added to give a solution concentration of 4% (w/v). The solution was heated to 80-100°C with a constant stirring to avoid layer formation on the surface for 2 h, and subsequently filtered using glass wool to discard the un-dissolved fraction. The un-dissolved material contained approximately 25% of the dry weight substance. Then the dried materials are called Tamarind kernel powder (TKP).

Preparation of Matrix Tablets

Different matrix was prepared by wet granulation method [8] with the components as shown in (**Table 1**). All materials were mixed in a porcelain mortar by geometric dilution and then wetted with isopropyl alcohol in quantity sufficient to achieve the funicular state of agglomeration before passing through the sieve No. 20 mesh and drying in a hot air oven at 40ºC for 4 hours. The dried granules were rescreened through the sieve No. 20 mesh. The prepared granule. However, hydrophobic wax granules (formulation F3 and F6) were prepared by melting carnuba wax, and then Cefixime trihydrate was dispersed in molten carnuba wax. The mass was passed through a sieve No. 20 mesh to obtain the hydrophobic wax granules. These granules were mixed with HPMC and other diluents in a porcelain mortar by geometric dilution and then wetted with granulating liquid in quantity sufficient to achieve the funicular state of agglomeration. The wet mass was passed through a sieve No. 20 mesh and dried in a hot air oven at 40ºC for 4 hours, then left to cool down to room temperature. The dried granules were rescreened through the sieve No. 20 mesh then were compressed into tablets on a 16-station rotary compression machine.

Table 1: Composition of Matrix Tablets of Cefixime Trihydrate

Ingredients (mg)	F01	F02	F03	F04	F05	F06
Cefixime trihydrate	300	300	300	300	300	300
Tamarind Gum	75	115	150	-	-	-
Carnuba wax	-	-	-	75	115	150
MCC	150	150	150	150	150	150
HPMC	140	100	65	140	100	65
PVP K30	22.5	22.5	22.5	22.5	22.5	22.5
Mg Stearate	5	5	5	5	5	5
Talc	6	6	6	6	6	6
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5
Total Wt (mg)	700	700	700	700	700	700

EVALUATION PARAMETERS

Pre-compression Parameters

Angle of repose

The angle of repose was measured by using funnel method, which indicates the flow ability of the granules.

Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder/ volume of the packing. TBD = weight of the powder / tapped volume of the packing.

Compressibility index

Compressibility index of the granules was determined by using the formula:

CI (%) = [(TBD - LBD) / TBD] × 100

Post Compression Parameters

Appearance [9]

The tablet should be free from cracks, depressions, pinholes etc. The color and the polish of the tablet should be uniform on whole surface. The surface of the tablets should be smooth.

Tablet Dimensions [10]

The dimensions of the tablets are thickness and diameter. Thickness and diameter of a tablet were measured using vernier calipers.

Uniformity of weight [10]

According to the official test, twenty tablets from each batch were selected randomly & weighed individually using a highly sensitive electronic balance. Their mean weight was calculated for each batch. The percent deviation was calculated using the following formula.

$$\%\ Deviation = \frac{Individual\ weight - mean}{mean}$$

Tablet Hardness [10]

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness (diametric crushing strength). The hardness of 6 tablets of each formulation was measured by using Monsanto hardness tester.

Friability [10]

Friability is a measure of tablet strength. Roche friabilator was used to measure the friability by noticing initial weight of 10 tablets (W1) and placed in a friabilator for 4 min at a rate of 25 rpm dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and noted as (W2). The difference in the weight is noted and expressed as percentage. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$Friability = \frac{w1 - w2}{w2} \times 100$$

Drug Content [11]

Ten tablets were weighed and ground. The powder equivalent to 700 mg of drug was taken, dissolved in purified water. The absorbance of the resulting solution was measured at 233 nm. The amount of Cefixime Trihydrate was calculated & compared with standards stated in the monograph. All the batches should fall within the limit of 95 – 100 %.

Content Uniformity [11]

Twenty tablets were randomly selected & average weight was calculated. Tablets were crushed in a mortar individually and accurately weighed amount of tablet triturate from each blend was taken. Samples were transferred to twenty different volumetric flasks and were diluted up to the mark with purified water. The content was shaken well for some time and kept for 30 minutes for dissolving of drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 233 nm against blank reference and reported.

In vitro drug release [12]

In vitro drug release studies were carried out using USP – type II dissolution apparatus (paddle type) at 50 rpm. The dissolution medium consisted of 900 ml purified water maintained at 37 + 0.5 °C. Aliquots from the release medium were withdrawn & filtered, the concentrations of Cefixime Trihydrate were determined spectroscopically. The withdrawn samples were replaced with equal quantity of the media to maintain constant volumes. The cumulative percentage drug release was calculated.

Release Kinetics of the Optimized Formulation [13-16]

The dissolution profile of most satisfactory formulation was fitted to zero order & first order model to ascertain the kinetic modeling of the release. The methods were adopted for deciding the most appropriate model.

1. Zero order kinetic model (Cumulative % drug release v/s time)
2. First order kinetic model (log cumulative % drug remaining v/s time)

RESULTS & DISCUSSION

Angle of repose

The angles of repose (θ) for the blend of various formulations F01 to F06 were calculated and the value of θ for each formulation is shown in (**Table 2**). The angle of repose of pre-compressed blend of Cefixime trihydrate of formulations F1 to F6 was in the range 21.39º to 27.48º, indicating that the studied blends have excellent flow properties, because for a blend to have excellent flow properties, value of θ should be ≤ 25º **[12].**

Bulk density

The granules of different formulations were evaluated for Loose Bulk Density (LBD) and Tapped Bulk Density (TBD).The results are recorded in the (**Table 2**).

Compressibility %

The results of Compressibility index (%) ranged from 20.45 to 13.14. Carnauba wax and HPMC based granules have excellent compressibility index values ranging from 18.99 to 20.45. The results are recorded in the (**Table 2**). The Cefixime Trihydrate powder blends were free flowing as indicated by the values of bulk density (0.673 to 0.691 gm/cc), tapped density (0.846 to 0.853 gm/cc). Angle of repose ranged from 21.31 to 22.46. The values are given in (**Table 2**).

Table 2: Micromeritic properties of drug and powder blend

Drug & Formulation Blend	bulk density, gm/cc*	Tapped Density, gm/cc*	Angle of Repose, θ	Compressibility %*
Drug	0.76	0.875	27.48	13.14
F01	0.691	0.853	21.39	18.99
F02	0.683	0.849	22.13	19.55
F03	0.673	0.846	21.58	20.45
F04	0.694	0.851	21.31	18.45
F05	0.681	0.852	22.46	20.07
F06	0.678	0.842	21.63	19.48

Evaluation Parameters

The Cefixime Trihydrate matrix tablets were uniform in weight 700 mg of the tablets were uniform. The hardness of tablets was found to be between 7.5 to 8 kg/cm^2, while the friability of tablets was ranged between 0.14% to 0.4%. The tablets had enough hardness to withstand stress during transport & handling. The drug content in various formulations varied between 97.4 % to 100 % (**Table 3**).

Table 3: Post Compression Studies

Formulation	Uniformity of Weight (mg)*	Thickness, (mm)*	Hardness, (kg/cm^2)*	Friability (%)	Drug content (%w/w)
F01	700	5.7+0.15	7.5±0.2	0.31±0.02	98.3±0.2
F02	700	5.7+0.25	7.5±0.2	0.4±0.025	100.1±0.1
F03	700	5.7+0.2	7.5±0.2	0.4±0.015	98.7±0.5
F04	700	5.7+0.3	8 ±0.2	0.22±0.01	99.4±0.54
F05	700	5.7+0.2	8 ±0.2	0.27±0.01	98.1±0.1
F06	700	5.7+0.25	8 ±0.2	0.14±0.01	97.4±0.15

Compatibility Studies

Infrared spectroscopy studies

The characteristics peaks of Cefixime Trihydrate are obtained at 3530.64 cm^{-1}, 3297.06 cm^{-1}, 2927.30 cm^{-1}, 1771.84 cm^{-1}, 1669.85 cm^{-1}, 1592.10 cm^{-1}, 1542.37 cm^{-1}, 1383.41 cm^{-1}, 1337.31 cm^{-1}, 1225.82 cm^{-1}, 1188.94 cm^{-1}, 1094.90 cm^{-1}, 993.48 cm^{-1}, 862.80 cm^{-1}, 800.55 cm^{-1}, 745.77 cm^{-1}, 565.59 cm^{-1} All these peaks are also observed along with some additional peaks in the granules which clearly indicates the compatibility of drug and other excipients and there is no any chemical interaction observed in the granules.

Uniformity of Drug content

All the formulations exhibited uniformity of drug content.

In-vitro release study

From the results of in-vitro release of SR matrix tablet of Cefixime Trihydrate, The formulation F2 containing 115 mg tamarind gum and 100 mg HPMC has released the drug in 8 hrs whereas F6 (Carnuba wax 150 mg and HPMC 65 mg) has showed 100 % release in 12 hours (**Fig. 1**).

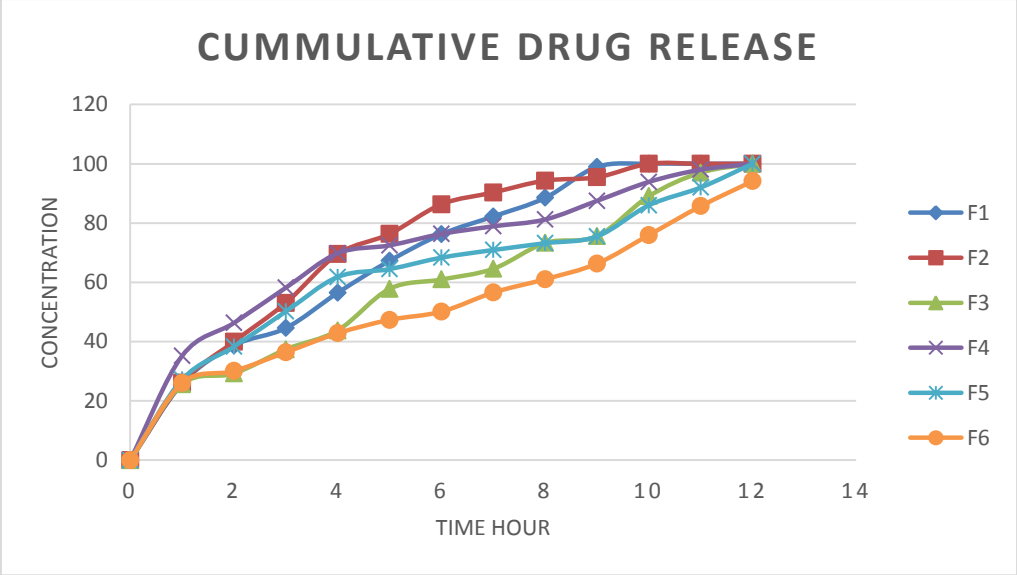

Figure 1: In-Vitro Release Study of Cefixime Trihydrate Matrix Tablets

It was also observed that as the amount of tamarind gum increases from 75mg to 150 mg in the formulation there was no apparent change in drug release rate. This may be due to the drug entrapped in hydro gel by forming hydrophilic polymers [6].

In case of Carnauba wax Gum, there was considerable difference between the release rates. But the drug release profile of Carnauba wax 150 mg showed lesser release compare to other formulation. As the concentration of Carnauba wax increased, the release rate of Cefixime Trihydrate was decreased. This again, is due to the drug entrapped in hydro gel by forming hydrophilic polymers around the matrix formulation and retarded drug release from the matrix.

Table 4: Kinetic Analysis of Dissolution Data

Formulation	Ist	Higuchi	Zero	Korsmeyer Peppas	
	R^2	R^2	R^2	R^2	n
F01	0.7496	0.7923	0.6817	0.88	0.296
F02	0.816	0.8892	0.782	0.933	0.31
F03	0.8494	0.8933	0.8027	0.9413	0.272
F04	0.9653	0.9835	0.9747	0.9804	0.332
F05	0.9792	0.9925	0.9661	0.9634	0.361
F06	0.9643	0.9941	0.9497	0.9686	0.382

The in vitro drug release data of all the six formulations (F01 to F06) were fitted in to zero order, first order, Higuchi's model [17] and Korsemeyer-peppas model and the values of slope, intercept and r^2 were calculated in each case. These values are shown in The R^2 values were found to be 0.9925(F05) and 0.9941(F06) for Huguchi's release model & 0.9792 for first order release model. The R^2 values were found to be 0.9747(F04) for zero order release model. On the basis of kinetic analysis it can be concluded that the drug release from the studied formulation followed Higuchi's release model as it has highest value of R^2. Hence it can be suggested that diffusion is the main mechanism of drug release from Cefixime trihydrate formulations and suggesting that the drug was released by Fickian diffusion in all the cases.

CONCLUSION

Matrix tablets of Cefixime Trihydrate were successfully prepared using tamarind gum and carnauba wax, HPMC, MCC as excipients by Wet granulation method. Of the several formulations investigated, the formulation F6 containing hydrophilic matrix of HPMC and carnauba wax was a better system for

once-daily sustained release of a water-soluble drug like Cefixime Trihydrate which effectively release more than 100% for 12 hrs. Cefixime Trihydrate release from the matrix tablet was inversely proportional to the agitation intensity of the dissolution medium, confirms hydrodynamic conditions of GIT is the major mechanism for drug release. Drug release from the developed formulation followed Higuchi kinetic model.

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