IJPSR (2013), Vol. 4, Issue 9 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 April, 2013; received in revised form, 25 June, 2013; accepted, 16 August, 2013; published 01 September, 2013

XANTHAN GUM BASED ONCE A DAY MATRIX TABLET OF CEFIXIME TRIHYDRATE: DEVELOPMENT AND EVALUATION

Nagendra Kumar [1], Rahul Tripathi [1], Gopal Nath [2] and Brahmeshwar Mishra*[1]

Department of Pharmaceutics, Indian Institute of Technology [1] (Banaras Hindu University) Varanasi-221005, Uttar Pradesh, India
Department of Microbiology, Institute of Medical Sciences [2] (Banaras Hindu University) Varanasi-221005, Uttar Pradesh, India

Keywords:

Antimicrobial, Cefixime trihydrate, erosion, *In vitro* release, Matrix tablet, Xanthan gum

Correspondence to Author:

Professor Brahmeshwar Mishra

Department of Pharmaceutics, Indian Institute of Technology, Banaras Hindu University, Varanasi – 221005, Uttar Pradesh, India

E-mail: bmishrabhu@rediffmail.com

ABSTRACT: The present study was an attempt to investigate the feasibility of the matrix based sustained release unit dosage formulation of cefixime trihydrate. Matrix tablets were prepared by using xanthan gum along with the other polymer combinations (Guar gum, sodium alginate and hydroxypropylmethyl cellulose). Effect of different formulation variables like polymer concentration, ratio of polymer combination and compression force was evaluated. The Fourier transform infrared spectroscopy, differential scanning calorimeter and X ray diffraction analysis were also carried out to evaluate physico-chemical compatibility between drug and excipients. *In vitro* release results suggested a 24 h controlled drug release from the prepared tablet of cefixime trihydrate. Swelling and erosion studies were performed to verify the release mechanisms involved in the formulation. *In vitro* antimicrobial study was also performed to check the synergistic efficacy of CFT with excipients. The formulations were found to be stable up to 3 months of stability testing at 40ºC/75% RH.

INTRODUCTION: Oral controlled release (CR) formulations have become very popular over conventional multidose therapy because of their uniform therapeutic efficacy, lesser or no side effects, and better patient compliance [1]. Matrix tablets are prevalent among the other oral controlled drug delivery formulations because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form, ease of scale-up and process validation [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(9).3390-99

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(9).3390-99

Hydrophilic polymers are being widely used in CR formulations for various drugs [3].

Xanthan gum (XG) is a hydrophilic polymer having high molecular weight heteroexo-polysaccharide gum produced by a pure culture fermentation of a carbohydrate with the microorganism *Xanthamonas campestris* [4]. Various reports are available for xanthan gum as a potential excipient for oral controlled release tablet dosage forms [5-9].

Sujja-Areevath *et al* observed that Fickian diffusion mechanism dominated during first half of dissolution period of diclofenac sodium mini-matrices prepared with XG of different ratios, while erosion mechanism during the latter half facilitated it zero-order release.

Naturally occurring XG has shown better release retardant and controlled delivery property than synthetically obtained hydroxypropylmethyl cellulose (HPMC) [10].

Cefixime trihydrate (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. Administering 200 mg of the conventional-release dosage form of CFT could achieve the peak plasma concentration at 2µg/ml, which has slowly declined below minimum effective concentration (MEC) within 12 h [11]. Once a day 400 mg of conventional CFT tablet if taken, the plasma concentration came down below MEC after 14 h for *Klebseilla pneumonia* [12] and may also potentiate the resistance to this bacterium which is a major pathogen for respiratory tract infection. Controlled release system not only maintains the plasma drug concentration above MEC throughout a day but also reduces dosing frequency and improves patient compliance.

Since no report or literature is available regarding matrix based once a day formulation of CFT using XG and other polymers therefore, we have made an effort to develop controlled release once a day matrix tablets of CFT using XG and other polymeric combination to improve patient compliance with better efficacy and negligible side effects.

MATERIALS AND METHODS:

Materials: CFT was kindly gifted from Alkem laboratories (Daman, India). XG was obtained as a gift sample from Lupin Pharm Pvt. Ltd (Pune, India). Agar and HPMC were purchased from Qualigen Fine Chemical (Mumbai, India). Microcrystalline cellulose (MCC), Polyvinyl alcohol (PVP), Sodium Alginate (NaAlg) and Guar Gum (GG) were purchased from Central Drug House (Delhi, India) and S.D. Fine chemicals (Mumbai, India), respectively. All other chemicals used were of analytical grade.

Methods:

Solubility study: Solubility studies in different aqueous media were carried out by *shake flask* method. Excess of CFT was placed in 20 ml amber vials with 10 ml of medium (buffers or distilled water) and vials were closed by lids. These vials were placed in the mechanical shaker equipped with thermostat for 24 h at 25°C to make the drug and solvent system in equilibrium. The saturated solutions were filtered through 0.45 membrane filters (Millipore, USA), suitably diluted assayed on UV Spectrophotometer (SHIMADZU® 1700, Japan) at 288 nm. Each experimental study was performed in triplicate.

Drug excipients compatibility study: Infra-red spectra were recorded on Fourier transform infrared (FT-IR) instrument (Shimadzu 8400, Japan) equipped with temperature controlled high sensitivity DLATGS detector. Samples were prepared and compressed with KBr on Minipress (Jasco, Japan) to form disc. The compressed discs were scanned over 400 to 4000 cm^{-1} and characteristic peaks were recorded and evaluated. Characteristic peaks were taken as criteria for interaction of drug and excipients.

Physical state of drug and excipients in the optimized formulation was determined by differential scanning calorimeter (DSC). Thermograms were measured with a differential scanning calorimeter (Shimadzu, DSC-50, Japan). The instrument was calibrated with 5 mg of Indium at a heating rate of 10°C/min (peak maximum: 124°C for CFT). The thermal behaviour was studied by heating 2-10 mg of the formulation at a rate of 10°C/min from 25°C to 250°C in a hermetically sealed pan under a nitrogen purge of 50 ml/min with an empty pan as reference [13-14].

Powder X-ray diffraction (PXRD) patterns of CFT and its physical mixture with excipients were collected in transmission using an X-ray diffractometer (Rigaku, Japan) with Cu-rotating anode (radiation; λ = 1.54 nm) generated at 18 kW. Powder diffractometer operating on Bragg-Brentano geometry was fitted with a curved crystal graphite monochromator in the diffraction beam from the range of 10–50º (2θ). The powder was packed into the rotating sample holder.

Preparation of matrix tablet: Tablets were prepared by direct compression using the formula listed as per **Table 1.** The ingredients were passed through #60 mesh sieve, further subjected for mixing in plastic bag for 10 min. This blended mixture was lubricated with talc and magnesium stearate (each passed through #60 mesh), and directly compressed into tablets using a single station tablet punching machine (Cadmach, India) fitted with 19×8.5 caplet standard concave punches (Table 1).

TABLE 1: DIFFERENT BATCHES OF MATRIX TABLET

Ingredients (mg)	Batch I	Batch II	Batch III	Batch IV	Batch V	Batch VI*	Batch VII	Batch VIII	Batch IX
CFT	450	450	450	450	450	450	450	450	450
XG	130	100	80	60	60	50	60	60	50
GG	---	---	---	---	20	20	---	---	20
NaAlg	---	---	---	---	---	---	20	---	---
HPMC 100 M	---	---	---	---	---	---	---	20	---
MCC 101	50	80	100	120	100	110	100	100	160
Mg. stearate	6	6	6	6	6	6	6	6	6
Talc	14	14	14	14	14	14	14	14	14
Final Tablet wt.	650	650	650	650	650	650	650	650	700

Evaluation of the Developed Formulations:

Evaluation of Powder Blend: The bulk and tap density of the powdered blend was determined using USP method I, and Compressibility index was calculated using formula;

$$\text{Compressibility index} = \frac{V_o - V}{V_o} \qquad (1)$$

$$\text{Hausner's Ratio} = \frac{V_o}{V} \qquad (2)$$

Where, V is the volume occupied by a mixture of a powder blend after being subjected to standardized tapping procedure and V_0 is the volume before tapping. Powder blend with compressibility index value up to15% show good flow property [15].

Evaluation of Tablets:

Determination of Hardness, Friability, Weight Variation, Thickness and the Total drug content: Hardness of tablets was determined using digital hardness tester (Campbell Electronics, India) using standard method [16]. Friability and weight variation were determined as per USP. Thickness of twenty randomly selected tablets was determined with digital Vernier calipers (Absolute Digimatic, MitutoyoCorp, Japan). Total drug content was determined as described in IP [17].

***In-vitro* release:** The matrix tablets were subjected to *in vitro* release studies using USP- XXIV dissolution apparatus type II at 50 rpm. Dissolution media used was phosphate buffer (pH 7.2, 900 ml) maintained at 37±0.5°C temperature. The aliquotes (5ml) were withdrawn at different time intervals and replaced with equivalent pre warmed (37± 0.5°C) volume of fresh medium. After filtration through 0.45 µm membrane filters, aliquots were diluted suitably and analyzed spectrophotometrically at 288 nm.

Effect of pH: To observe the effect of pH and to assure reliable performance of the developed matrix tablet, release studies of the optimized formulations were conducted according to pH change method (simulated gastric fluid (SGF, pH 1.2) for first 2 h, followed by phosphate buffer (pH 7.2) for remaining 24 h).

Determination of swelling and erosion behavior of matrix tablet: Matrix tablet was introduced into the dissolution apparatus under the standard set of conditions as specified for determination of *in vitro* drug release. The preweighed tablets were removed using a small wired basket and swollen weight of each tablet was determined. To examine matrix erosion, swollen tablets were placed in a vacuum oven at 40°C and after 48 hours tablets were removed and weighed. Swelling and erosion was calculated according to the following formula [18],

$$\text{Swelling index } (\%) = \frac{S-T}{T} \times 100 \qquad (3)$$

$$\text{Percentage erosion } (\%) = \frac{T-R}{T} \times 100 \qquad (4)$$

Where, S is the weight of the matrix after swelling; R is the weight of the eroded matrix; and T is the initial weight of the matrix.

Kinetics and statistical analyses of dissolution data:

Korsmeyer's - Peppas model:

$$\text{Log } (Qt) = \text{Log } (k) + n\text{Log } (t) \quad (5)$$

Where, Q(t) is percent drug release at time 't', K is a release rate constant representing incorporation structure and geometric characteristics, and n is the time exponent indicative of the mechanism of drug release [19].

Zero-order model: Drug release rate is independent of the concentration of the dissolved species. Zero-order equation can be given as:

$$F(t) = K_0 . t \quad (6)$$

Where F (t) is the fraction of drug dissolved in time t and K_0 is the apparent zero order release rate constant (CPR/h) and t is the time in h.

First-order model: Rate of drug dissolution is dependent on the concentration of the dissolving species.

$$\text{Log } Q_t = \text{Log } Q_0 + K_1.t/2.303 \quad (7)$$

Where Q_t is the amount of drug release at time t, Q_0 is the initial amount of drug in solution and K_1 indicate first order release rate constant (h^{-1}).

Higuchi model: Diffusion process is based on fick's first law of diffusion "percent of drug dissolved as a function of square root of time"

$$F(t) = K_H . t^{1/2} \quad (8)$$

Where K_H is the Higuchi dissolution constant and F(t) indicates the fraction of drug release at time 't'. Plot linearity (% CPR Vs square root of time) indicates that the release process is diffusion controlled and is applicable for matrix and transdermal formulation.

Statistical analysis: Release profiles of various batches were compared using model independent pair wise approach, which include the calculation of 'difference factor' *f1* and 'similarity factor' *f2* by using the following equations [20-21].

$$f_1 = \frac{\sum_{j=1}^{n} | R_j - T_j |}{\sum_{j=1}^{n} R_j} \times 100 \quad (9)$$

$$f_2 = 50 \times \log\left\{ \left[1 + (1/n) \sum_{j=1}^{n} w_j | R_j - T_j |^2 \right]^{-0.5} \times 100 \right\} \quad (10)$$

Where, n is the sampling number, R_i and T_i are the percent dissolved of the reference and test products at each time point j. The percent error is zero when the test and reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. The two release profiles were considered to be similar if f_1 value was lower than 15 (between 0 to15) and f_2 value was more than 50 (between 50 to100).

Antimicrobial activity of prepared tablets: A suspension of microbes (*Klebseilla pneumonia*) was prepared in 2% (w/v) sterilized saline water concentration adjusted to 10^6 CFU/ml by dilution with saline water and using UV visible optical density meter (Shimadzu 1601, Japan) at 600 nm. By sterilized swab stick 0.5 ml of this suspension was uniformly spread over agar plate. Then this plate was kept in hot air oven for 10 min for drying at 50 ^oC temperature.

Prepared disks imbibed with different samples (aliquots of dissolution media at different time interval) were placed in each quarter of plates. Then the cultured plates with disks were kept in incubator for 20 to 24 h. Swabbing and incorporation of disks were done in laminar flow stage under aseptic condition. Diameter of the zone of inhibition was measured by vernier calipers.

Accelerated stability study: Optimized formulation (Batch VI) was sealed in PVC bottle with aluminium foil. The packed formulations were stored in ICH certified stability chambers (NSW-175, Narang Scientific work, New Delhi, India) maintained at 40°C / 75% RH for 3 months. The samples were withdrawn and evaluated for drug content, hardness, burst strength and release studies.

RESULTS AND DISCUSSION:

Solubility study: Solubility of drug in different media was found to be 1.22±0.14 mg/ml (in trippled distilled water), 2.1±.011 mg/ml (in HCl buffer, pH 1.2), 6.53±0.23 mg/ml, 9.82±0.27 mg/ml and 10.76±0.34 mg/ml (in different phosphate buffer, pH 6.8, pH 7.2 and pH 7.4 respectively). CFT showed pH dependent solubility which increases with an increase in pH. The solubility in acidic pH was higher than water which demonstrated ionic strength dependent solubility.

Compatibility study: Fig. 1(A) showed the characteristic IR- band at wave number 3580(-OH), 1770 (lactam -C=O band), 1669 (amide carbonyl band -CO–NH), at 1591 (corresponding to two carboxylate groups) cm^{-1} of pure CFT. FT-IR studies revealed that characteristic peaks of drug were present in physical mixture of drug with excipients even after storing at 40 °C and 75% RH for 3 months, while absence of any new characteristic peaks indicated no interaction between the drug and excipients.

Fig. 1(B) represents a DSC thermograph of pure CFT (before storage) which show broad endothermic peaks at 127°C and 212°C of its trihydrate salt and melting point respectively. Thermographs of physical mixture of drug with excipients showed a shift in endothermic peak of its trihydrate due to moisture present in excipients and no any significant shift in endothermic peak of CFT melting point even after storage at 40°C and 75% RH for 3 months was observed.

Diffractograms of polymer, pure drug, freshly prepared physical mixture of both drug and polymer and physical mixture after 3 months storage are shown in **fig. 1(C).**The major peaks for CFT were seen at 15°, 19°, 20°, 22°, 23° and 27° angle of diffraction (2Θ) and remained same in physical mixture. There was no sign of formation of any new peak or shifting in original characteristic peak of CFT. The XRD data revealed crystalline nature of drug and physical compatibility between drug and excipients. Crystalline nature of drug was procured in the formulation even after 3 months of stability at 40°C/75% RH.

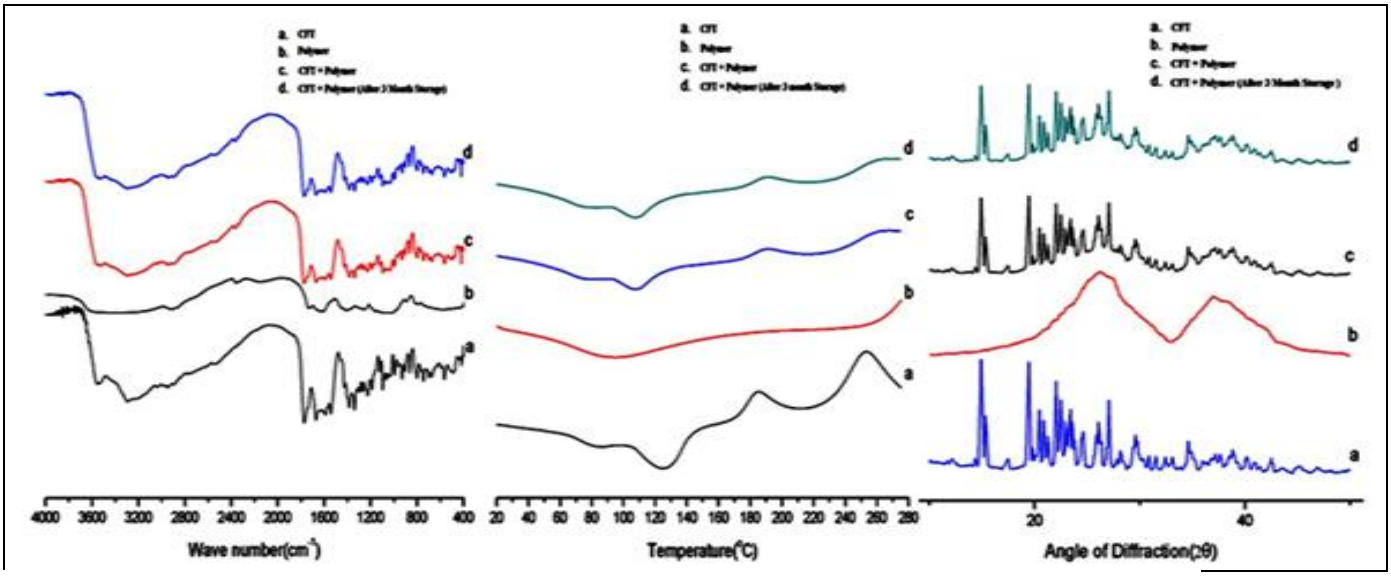


Fig. 1 (A) **Fig. 1 (B)** **Fig. 1 (C)**

FIG. 1 (A), (B) AND (C): FT-IR, DSC AND XRD PLOT OF (a) CFT, (b) POLYMER, (c) FRESHLY PREPARED PHYSICAL MIXTURE OF CFT AND THE POLYMER AND (d) PHYSICAL MIXTURE OF THE CFT AND POLYMER AFTER 3 MONTHS STORAGE AT 40°C/75%RH.

Tablet evaluation: The specifications for optimized batch are listed in **Table 2**. Compressibility index was calculated for all batches which were found to be less than 20%. Thickness of the tablet was also recorded. The hardness of the core tablets was in range of 5-7 kg/cm^2 and the friability did not exceed 1% in any of the batches. Drug content uniformity for all the batches was within the limit of ± 5% variation. The thickness of the prepared tablets was controlled within the acceptable ± 3% variation of predetermined value as par USP.

TABLE 2: PHYSICAL PARAMETERS OF BLEND POWDER AND TABLETS (BATCH-VI*)

Parameters	Mean ± SD
Bulk density (mg/cm^3)	546±12
Tapped density (mg/cm^3)	637±13
Compressibility index (%)	14.3±1.3%
Hausner's ratio	1.16±0.12
Tablet weight (mg, n=10)	648 ±12
Thickness of tablet (mm, n=10)	4.06±0.02
Hardness (kg/cm^2) Tablet	6.5±1.50
Friability (%)	0.35±0.17
Content uniformity (%, n=10)	99.37± 4.25

Effect of polymer XG concentration on CFT release: XG is widely used as swellable matrix polymer. The batches I, II, III and IV were prepared with XG only of 20, 13.84, 12.3 and 9.23% (w/w) polymer concentration. There were significant difference in rate and extent of drug release from batch I (D_{24} = 52%), II (D_{24} = 60%), III (D_{24} = 89%) and IV (D_{24} = 97%) at 24 h (**fig. 2**). Batch I and II showed almost zero order release profile with regression co-efficient R^2 = 0.995. Swellings of tablets of batches I and II were considerably more than other two batches III and IV due to high polymer content. Batch III (D_{24} = 89%) also showed almost zero order release. Batch IV released almost all the drug in 24 h thus optimized 9.23% concentration of polymer was used for further study. D_{24} represent % of drug release at the end of 24 h.

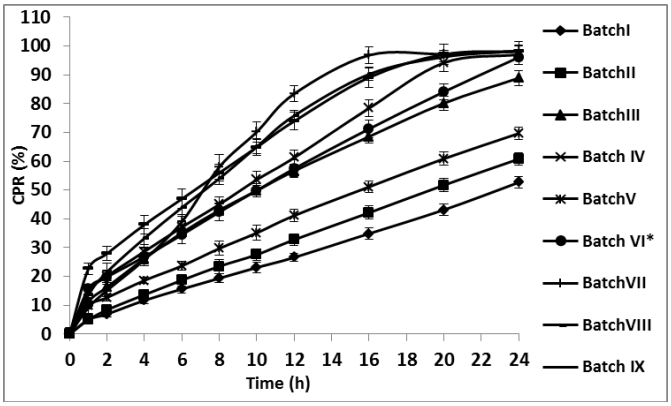


FIG. 2: DRUG RELEASE PROFILES OF BATCHES I-IX IN PHOSPHATE BUFFER 7.2 (VERTICAL BARS REPRESENT S D)

Effect of XG combination with different polymer: Different polymers (GG, HPMC & NaAlg) were incorporated in combination with XG for the preparation of matrix tablets to obtain controlled drug release. A fixed amount (20 mg) of other polymers was combined with 9.23 % w/w of XG.

Effect of GG, HPMC-100M and NaAlg: GG is a natural galactomannan obtained from the seed of *Cyamopsis tetragonolobus* (Family Leguminosae) [22]. Bresolin *et al* had showed that there is a synergistic effect in retardation of drug release when galactomannans was added with XG in aqueous medium [23-24]. The tablets of batch V was prepared using 3.1% w/w of GG (20 mg) with 9.23% w/w of XG (60 mg). The release of CFT from this batch was more retarded than the batch III which confirms the synergistic action of GG with XG in release retardation. Batch VI***** was formulated as 20mg of GG with 50 mg of XG. Batch VI***** showed well controlled release profile with initial burst release, with R^2 value 0.996 as shown in fig. 2 and Table 3.

HPMC is propylene glycol ether of methyl cellulose and a most important hydrophilic polymer used for the preparation of oral controlled drug delivery system [25]. HPMC has been found to be very versatile material for the formulation of soluble matrix tablets. In batch VIII 3.1% w/w of HPMC 100M was combined with 9.23% w/w of XG. Batch VIII showed higher drug release with zero order release kinetics after initial hour release (fig. 2). Here, HPMC being more water soluble resulted in formation of pores for water inlet in the matrix after getting dissolved causing higher drug release (75% of drug release was observed in 12 h).

Sodium alginate is a water-soluble salt of alginic acid, a naturally occurring, nontoxic polysaccharide found in all species of brown sea algae. Sodium alginate and XG are natural polymers, both of which have been employed as matrices for prolonged drug delivery systems [26-27]. Batch VII was formulated with 3.1% w/w of NaAlg and 9.23% w/w of XG. This batch showed considerably higher drug release with zero order release mechanism (fig. 2). Here 75% of drug was released within 12 h. After 4 h, the tablets started to float on media and showed higher release rate. More prominent pores were formed due to dissolution of sodium alginate in tablet matrix attributed to higher release rate.

Effect of amount of MCC 101: It is well known that MCC is hydrophilic diluents and is widely used. Fig. 2 shows the rate and extent of drug release from IX batch containing higher amount of

MCC was higher as compared with VI* batch due to hydrophilicity and disintegrating nature of MCC.

Effect of Compression Force: The effect of various compression forces on the release characteristics of CFT were studied by changing the hardness**.** Two hardness points 5 & 7 kg/cm^2 were selected for same batch VI* to observe the effect of hardness on drug release. However, no significant difference was found in release profile (**fig. 3**). However, it was important to note the compression force should be high enough to inhibit partial or total disintegration of the tablet, and from the industrial point of view, it is important to know the influence of this parameter [28].

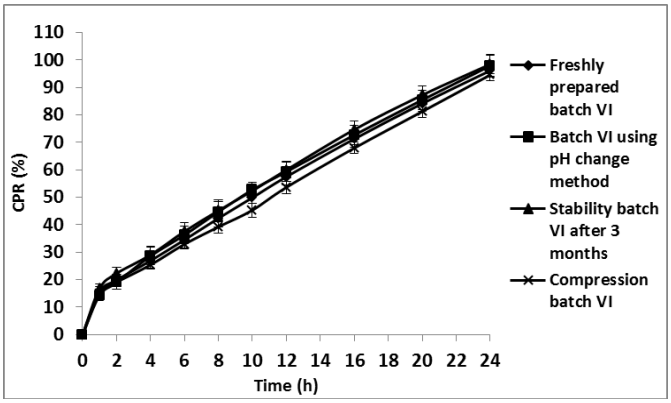


FIG. 3: DRUG RELEASE PROFILE OF BATCH VI UNDER VARIOUS CONDITIONS (VERTICAL BARS REPRESENT S D)

Effect of varying pH of dissolution media: Dissolution of batch VI* was studied in acidic pH (pH 1.2) for first two h and then acidic media was replaced by phosphate buffer (pH 7.2). There was no significant difference in release profile of batch VI* in phosphate buffer alone and in acidic buffer/phosphate buffer in buffer change method (fig. 3). So, release was independent of pH of the media. In both the cases there was almost 15% release of drug in respective buffer.

Swelling and Erosion Study: Swelling predominates in early hours, where tablet took 2 h to attain maximum swelling and became constant till 8th h after which swelling index declined slowly. The swelling index and erosion profile of batch VI* tablet is represented in **fig. 4**. The erosion behaviour complied with the zero order drug release from the tablet matrix. Cross-section and transverse-section view of matrix tablet (batch VI*) after 12 h dissolution are shown in **fig. 5**, which clearly depicted the eroding gel layer, rubbery matrix and glassy core of the tablet matrix.

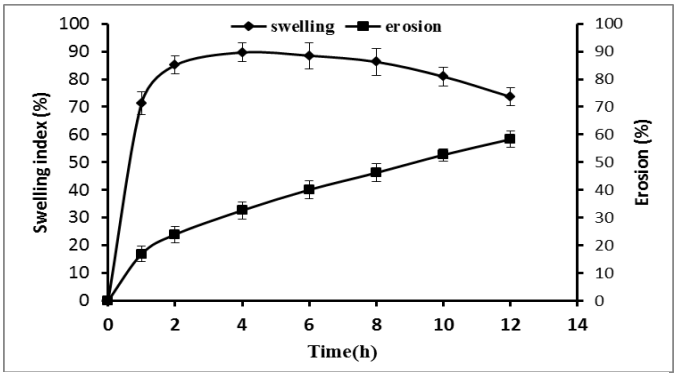
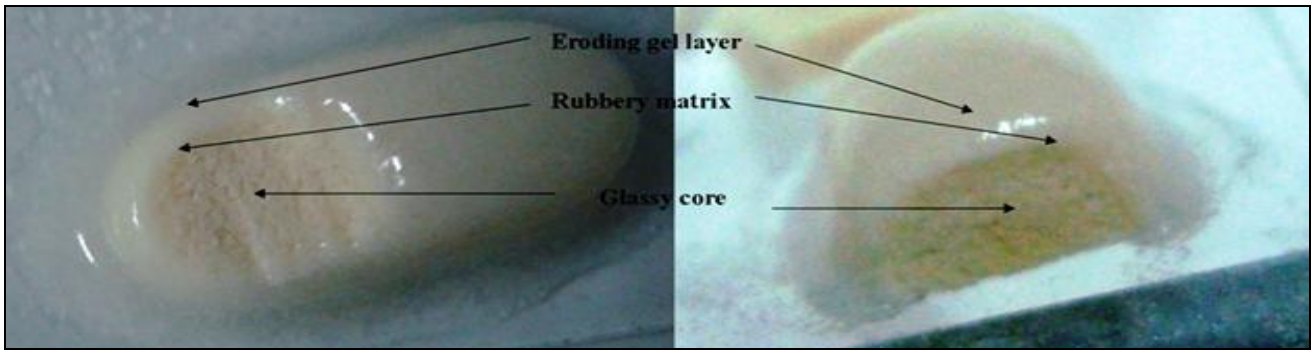


FIG. 4: SWELLING INDEX AND % EROSION PLOT OF BATCH VI TABLETS (VERTICAL BARS REPRESENT S D)



A **B**

FIG. 5: PHOTOGRAPHS OF SWOLLEN TABLETS OF BATCH VI (A) CROSS- SECTION (B) TRANSVERSE-SECTION VIEW AFTER 12 h

Mathematical modeling of *in vitro* release kinetics and statistical analyses: Data of *in-vitro* drug release was fitted to kinetic models and respective equations to explain the release kinetics of drug from tablet matrix (**Table 3**). The kinetic models used were zero-order equation, first order equation, Higuchi release and Korsmeyer's-Peppas models which are presented in **fig. 6**. The drug release profiles were subjected to different models of drug release kinetic and best-fit model was

selected on the basis of correlation coefficient (R) and the values of "n". The best fit with highest degree of correlation coefficient was shown by zero-order release rate model after an hour of burst effect for batches VI*.

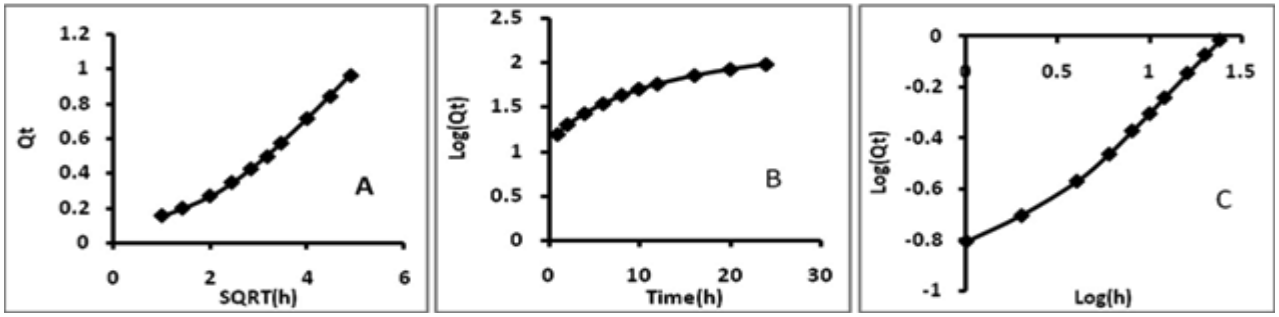


FIG. 6: MODEL FITTING TO INVESTIGATE EXPERIMENTALLY DETERMINED RELEASE OF CFT FROM BATCH VI (A) HIGUCHI, (B) FIRST ORDER KINETICS AND (C) KORSEMEYER-PEPPAS MODEL

TABLE 3: VARIOUS MATHEMATICAL KINETIC MODEL OF DRUG RELEASE OF BATCH VI*

Batch No.	Kinetic models							
	Zero order		First order		Higuchi model		Korsmeyer's-Peppas model	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	n
I	0.999	2.055	0.868	0.042	0.944	0.119	0.988	0.736
II	0.998	2.398	0.828	0.043	0.962	0.140	0.997	0.778
III	0.972	3.333	0.795	0.036	0.993	0.201	0.998	0.665
IV	0.983	3.605	0.847	0.034	0.983	0.215	0.989	0.603
V	0.991	2.635	0.860	0.036	0.976	0.156	0.984	0.632
VI*	**0.998**	**3.538**	**0.919**	**0.032**	**0.974**	**0.210**	**0.978**	**0.590**
VII	0.995	6.904	0.943	0.085	0.960	0.306	0.977	0.951
VIII	0.998	5.538	0.925	0.063	0.986	0.248	0.998	0.682
IX	0.996	4.300	0.967	0.042	0.979	0.192	0.980	0.443

Due to initial hour burst effect of batch VI*, it did not fit appropriately with Korsmeyer's-Peppas models. Hence it was concluded that optimized batch VI* will provide zero-order kinetic drug release after first hour burst release effect. Statistical parameters f_1 and f_2 of drug release were calculated by assuming batch VI as reference standard and results are shown in **Table 4**.

TABLE 4: STATISTICAL ANALYSES OF DRUG RELEASE PROFILE OF DIFFERENT BATCHES WITH OPTIMIZED BATCH VI*

Batch No.	I	II	III	IV	V	VI*	VII	VIII	IX
f_1	53.01	44.45	4.95	6.85	28.06	Reference	31.92	26.34	23.46
f_2	30.19	34.33	73.19	66.92	43.47	Reference	42.25	47.87	45.03
Results	NSR	NSR	SR	SR	NSR		NSR	NSR	NSR

NSR: No Similar Result, SR: Similar Result

Antimicrobial study: The known drug concentration (100, 200, 300 and 400µg/ml) were compared with the aliquots of test samples obtained at different time interval (2, 8, 16 and 20 h) of batch VI* by measuring zone of inhibition by disc plate method using *klebseilla pneumonia* micro-organism. Results are shown in **Table 5 and fig. 7**.

Test and standard sample showed very similar type of zone of inhibition. These results revealed that the drug in formulation has no any synergistic action with the formulation excipients as test samples drug concentrations are almost equal to that of standard sample drug concentration.

TABLE 5: ZONE OF INHIBITION OF TEST AND STANDARD DRUG SAMPLE

Test sample time (h)	Standard samples conc. (µg/ml)	Zone of inhibition (mm)	
		Standard (Mean ± SD)	Test (Mean ± SD)
2	100	22.2±1.3	22.0±1.0
8	200	24.3±1.0	24.0±1.5
16	300	25.8±1.2	25.5±2.0
20	400	28.2±0.8	27.8±1.7

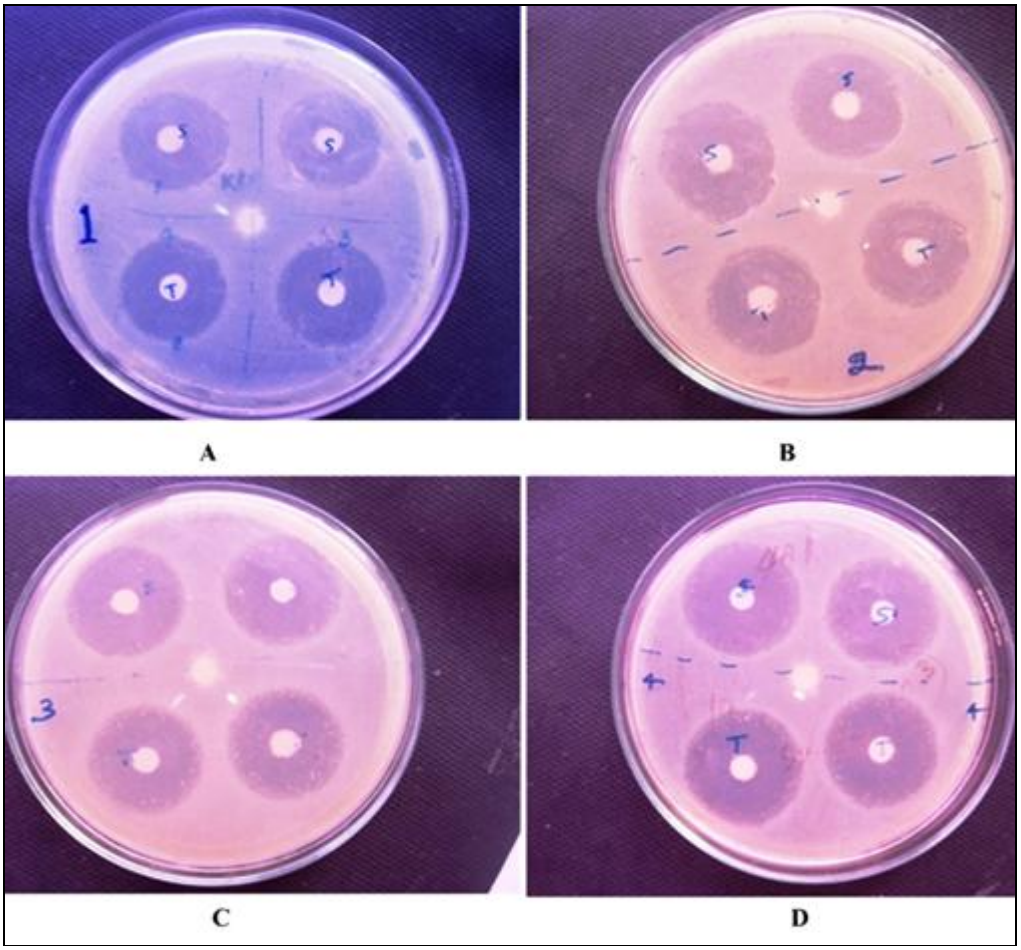


FIG. 7: ANTIMICROBIAL ACTIVITY OF STANDARD DRUG *VS* DRUG RELEASE FROM TABLET; 2 h CUMULATIVE DRUG RELEASE *VS* 100µg/ml, 8 h CUMULATIVE RELEASE *VS* 200µg/ml, 14 h CUMULATIVE RELEASE *VS* 300 µg/ml AND 20 h CUMULATIVE RELEASE *VS* 400 µg/ml. Upper half shows standard and lower half the test samples (S=standard, T=test samples, *Vs*=versus)

Accelerated stability study: The *in-vitro* release profiles indicate that the formulations were found to be stable as insignificant difference were observed in terms of drug content and release studies before and after storage (fig. 3). The f_1 (3.38) and f_2 (84.92) value of batch subjected to 3 months stability study showed the similar release profile as the fresh batch VI*.

CONCLUSION: The findings of this study demonstrate that direct compression of drug release retardant XG with other release retardant excipients effectively controls CFT release throughout the course of 24 h (Batch I - VI). Developed matrix tablet especially batch VI* showed good zero order release profile throughout 24 h. Various variables like content of XG, combination with other polymer (GG, NaAlg and HPMC), tablet hardness and effect of MCC PH 101 content have been investigated individually. Drug release from matrix system was found to be independent of release medium pH.

Mathematical modeling of drug release data suggested that matrix tablet followed zero order kinetics and provide required controlled release up to 24 h. Accelerated stability data confirmed that the developed optimized matrix formulation is stable and complied with reproducible release performance. GG showed synergistic retardant action with the XG (batch V and VI).

The optimized batch VI* showed first hour burst release effect which can be used as loading dose and controlled release for the rest of 24 h. Swelling and erosion study showed that the drug release mechanism was erosion controlled due to limited solubility of drug in dissolution media.

In vitro microbial study showed no any synergistic antimicrobial action of any excipient with CFT. Further, *in vivo* study is needed to prove the clinical usability of this once a day controlled release formulation.

ACKNOWLEDGEMENT: The first author acknowledges financial assistance from University Grants Commission (UGC), New Delhi, for carrying out this research work. All authors would like to acknowledge Department of Applied Physics and School of Material Science and Technology of IIT (BHU) for providing facility of XRD and DSC study respectively. We are also thankful to Alkem Laboratories and Lupin Pharma Labs for providing gift samples of drug and polymers.

REFERENCES:

1. Hiremath PS and Saha RN: Oral matrix tablet formulations for concomitant controlled release of anti-tubercular drugs: Design and *in vitro* evaluations. Int J Pharm 2008; 362(1-2):118-125.
2. Verma MVS, Kaushal AM, Garg A and Garg S: Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. Am J Drug Deliv 2004; 2(1):43-57.
3. Kuksal A, Tiwary AK, Jain NK and Jain S: Formulation and *in vitro, in vivo* evaluation of extended- release matrix tablet of zidovudine: influence of combination of hydrophilic and hydrophobic matrix formers. AAPS PharmSciTech 2006; 7(1):E1-E9.
4. Dhopeshwarkar Vand Zatz JL: Evaluation of xanthan gum in the preparation of sustained release matrix tablets. Drug Dev Ind Pharm 1993; 19(9):999-1017.
5. Cox PJ, Khan KA, Munday DL and Sujja-areevath J: Development and evaluation of a multiple-unit release dosage form for S(+)-ibuprofen: preparation and release kinetics. Int J Pharm 1999; 193(1): 73-84.
6. Sujja-areevath J, Munday DL, Cox PJ and Khan KA: Relationship between swelling, erosion and drug release in hydrophilic natural gum mini-matrix formulations. Eur J Pharm Sci 1998; 6(3):207-217.
7. Munday DL and Cox PJ: Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. Int J Pharm 2000; 203(1-2):179-192.
8. Talukdar MM and Kinget R: Comparative study on xanthan gum and hydroxypropyl methyl cellulose as matrices for controlled-release drug delivery: II drug diffusion in hydrated matrices. Int J Pharm 1997; 151(1):99-107.
9. Talukdar MM, Van den Mooter G, Augustijns P, Tjandra-Maga T, Verbeke N and Kinget R: *In vivo* evaluation of xanthan gum as a potential excipient for oral controlled-release matrix tablet formulation. Int J Pharm 1998; 169(1):105-113.
10. Talukdar MM, Michael A, Rombaut P and Kinget R: Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrix for controlled release drug delivery I - compaction and *in vitro* drug release behaviour. Int J Pharm 1996a; 129(9, suppl 1):233-241.
11. Dan M, Poch F, Edelman A, Asherov J, Hafely H and Atzmon Y: Serum bactericidal activity of newer oral cephalosporins in healthy volunteers. J Antimicro Chem 1998; 41(4):485-488.
12. Montay G, Masala F, Le RY, Le LA, Uhlrich J, Chassard D, et al. Comparative bioavailability study of cefixime administered as tablets or aqueous solution. Drugs 1991; 42 suppl 4:6-9:6-9.
13. Marshall MS, Isensee RK and Beck DJ: Thermospray mass spectrometer interface used as a flow reactor for *in situ* thermal degradation studies: applications to beta-lactam antibiotics. Anal Chem 1987; 59(7):989-995.
14. Rao RNG, Ram P and Bussetti SS: Formulation and evaluation of gas powered systems of cefixime tablets for controlled release. Int J Pharm Biosci 2010; 1(2):82-91.
15. United State Pharmacopoeia/National Formulary, 29th ed. Rockville, MD: United States Pharmacopoeial Convention; 2006.
16. Kumar P, Singh S and Mishra B: Gastroretentive drug delivery system of ranitidine hydrochloride based on osmotic Technology: development and evaluation. Curr Drug Deliv 2008; 5(4):332-342.
17. Indian Pharmacopoeia, Controller of Publication, Govt. of India, Ministry of Health and Family Welfare, New Delhi, 2010, Vol. II, 1013.
18. Roy DS and Rohera BD: Comparative evaluation of rate of hydration and erosion HRC and HPC and study of drug release from their matrices. Eur J Pharm Sci 2002; 16(3):193-199.
19. Korsmeyer RW and Peppas NA: Macromolecular and modeling aspects of swelling-controlled systems. In: Roseman TJ, Mansdorf SZ, editors. Controlled Release Delivery Systems. New York: Marcel Dekker; 1981. P. 77-90.
20. Costa P and Sousa LJM: Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 13(2):123-133.
21. Grassi M and Grassi G. Mathematical modelling and controlled drug delivery: matrix systems. Curr Drug Deliv 2005; 2(1):97-116.
22. Krishnaiah YSR, Satyanarayana S, Prasad YVR and Rao SN: Evaluation of guar gum as a compression coat for drug targeting to colon. J Int J Pharm 1998; 171(2):137-146.
23. Bresolin TMB, Sander PC, Reicher F, Sierakowski MR, Rinaudo M and Ganter JLMS: Viscometric studies on xanthan and galactomannan systems. Carbohydr Polym 1997; 33(2-3):131-138.
24. Bresolin TMB, Milas M, Rinaudo M, Reicher F and Ganter JLMS: Role of galactomannan composition on the binary gel formation with xanthan. Int J Biol Macromol 1999; 26(4):225-231.
25. Piriyaprasarth S and Sriamornsak P: Effect of source variation on drug release from HPMC tablets: Linear regression modeling for prediction of drug release. Int J Pharm 2011; 411(1-2):36-42.
26. Giunchedi P, Gavini E, Moretti MDL and Pirisino G: Evaluation of alginate compressed matrices as prolonged drug delivery systems. AAPS PharmSciTech 2000; 1(3):31-36.
27. Lu MF, Woodward L and Borodkin S: Xanthan gum and alginate based controlled release theophylline formulations. Drug Dev Ind Pharm 1991; 17(14):1987-2004.
28. Talukdar MM and Plaizier-vercammen J: Evaluation of xanthan gum as a hydrophilic matrix for controlled-release dosage form preparations. Drug Dev Ind Pharm 1993; 19(9):1037-1046.

How to cite this article:
Kumar N, Tripathi R, Nath G and Mishra B: Xanthan gum based once a day matrix tablet of Cefixime trihydrate: development and evaluation. *Int J Pharm Sci Res* 2013: 4(9); 3390-3399. doi: 10.13040/IJPSR. 0975-8232.4(9).3390-99