

DEVELOPMENT AND *IN VITRO* RELEASE KINETIC STUDIES OF EXTENDED RELEASE CEFUROXIME AXETIL MATRIX TABLETS BASED ON HYDROPHILIC POLYMERS

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Abstract

The purpose of this investigation was to design and develop extended release hydrophilic matrix tablets of cefuroxime axetil by using high viscosity grade hydroxypropyl methylcellulose (Methocel K4M CR) along with Methocel E5LV and E50LV in different concentrations. Nine different formulations (F1 - F9) were prepared by direct compression technique and tested for physicochemical evaluation and *in vitro* dissolution studies in different media. The dissolution data of optimized formulations (F5 - F9) were subjected to ANOVA-based model, model-independent and model dependent method and R Gui[®] applied for stability studies. Physical parameters were found to be within the acceptable range of USP36 / NF31. The formulation F9 (K4M CR 8% and E50LV 2%) exhibited the highest percentage of drug release and a mean dissolution time with considerable swelling index and low AIC values in all dissolution media studied was taken as reference formulation for Dunnett's t-test and *f1*, *f2* test. *In vitro* release kinetics results indicated a non-Fickian diffusion controlled drug release mechanism and was best fitted into Korsmeyer–Peppas equation ($R^2 = 0.937 - 0.999$). The rate of drug release was found to be increased as the fraction of the polymer decreased from 30% - 10%. For instance the matrix tablets containing 10% of K4M CR (F5) alone and in combination with E5LV and E50LV (F6 - F9) showed an extended release pattern up to 12 hrs. It appears that K4M CR (lower concentration) in combination with E5LV and E50LV can be effectively used for controlling the release rate of cefuroxime axetil.

Rezumat

Scopul acestui studiu a fost de a proiecta și dezvolta tablete cu eliberare prelungită cu matrice hidrofilă de cefuroximă, prin utilizarea de hidroxipropil metilceluloză cu grad de vâscozitate ridicat (Methocel K4M CR), împreună cu Methocel E5LV și E50LV, în diferite concentrații. Nouă formulări diferite (F1 - F9) au fost preparate prin tehnica de comprimare directă și testate pentru evaluarea fizico-chimică și studiile *in vitro* de dizolvare în medii diferite. Datele de dizolvare ale formulărilor optimizate (F5 - F9) au fost supuse diferitelor modele și s-au desfășurat studii de stabilitate. Parametrii fizici s-au dovedit a fi în intervalul acceptat de USP36 / NF31. Formularea F9 (K4M CR 8% și E50LV 2%) a prezentat cel mai mare procent de eliberare a medicamentului și timpul mediu de dizolvare cu indicii de gonflarea considerabil și valori scăzute AIC în toate mediile de dizolvare studiate, fiind luată ca formulare de referință pentru testul t, Dunnett *f1* și *f2*. Cinetica de eliberare testată *in vitro* a indicat un mecanism de cedare a medicamentului controlat prin difuzie non-Fickiană, fiind cel mai bine descris printr-o ecuație Korsmeyer-Peppas ($R^2 = 0,937 - 0,999$). Rata de eliberare a medicamentului a crescut concomitent cu scăderea fracțiunii de polimer de la 30% la 10%. De exemplu, tabletele matrice conținând 10% K4M CR (F5) singur și în asociere cu E5LV și E50LV (F6 - F9) au prezentat o eliberare prelungită până la 12 ore. Se pare că K4MCR (în concentrație mai mică), în combinație cu E5LV și E50LV poate fi utilizat în mod eficient pentru a controla viteza de eliberare a cefuroxim axetilului.

Keywords: cefuroxime axetil, extended release hydrophilic matrix, *in vitro* kinetics, stability studies

Introduction

During the past three decades, interest has been expressed by the researchers in optimizing drug therapy through delivery system design [1]. Hydrophilic matrix systems are one of the options for preparing extended release tablets which contain an intimate mixture of drug and release rate retarding polymers along with excipients in a defined proportion [2]. Hydroxypropyl methylcellulose (HPMC) has been identified as one of the

most suitable polymers for formulation of hydrophilic matrix system, due to its availability of different viscosity grades, nonionic nature, reproducible release profile and cost effectiveness [34]. Thus, this polymer has received considerable attention in the controlled release of pharmaceutical drugs [3]. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of HPMC, which forms the gel barrier through which

the drug diffuses [4]. For matrix tablets preparation, direct compression method still appears to be an efficient and cost effective technique and has many advantages over other methods, like fewer process validation steps, ease of fabrication and scaling up [5, 6]. However, in spite of the major advantages, pre-formulation studies are necessary to achieve the appropriate targeted drug release profile [7].

Cefuroxime axetil (CA) is the 1-acetoxyethyl ester of a β -lactamase cephalosporin, with a broad spectrum of activity against Gram-positive and Gram-negative microorganisms [8]. Cefuroxime axetil is acid stable and completely absorbed in the gastrointestinal tract and is rapidly hydrolysed by esterases in the intestinal mucosa and blood to cefuroxime. Absorption is increased by the presence of food [9]. It has a short biological half-life i.e. 1.2 hr and the peak plasma concentration is about 2 to 3 hr after oral dose [10, 11]. The bioavailability of cefuroxime axetil is variable and limited to 30% in fasted and 50% in fed state in humans [12, 13]. Therefore pharmacokinetic features of cefuroxime axetil make it a potential candidate for an extended release dosage form.

The aim of the present study was to develop extended release cefuroxime axetil 250 mg tablets using high viscosity grade HPMC (Methocel K4M CR) along with low viscosity grade Methocel E5LV and Methocel E50LV as a hydrophilic matrix to retard drug release. The *in vitro* release rate was studied in different pH media and different profiles comparison method was applied to the dissolution data to evaluate the release kinetics. The swelling, floating and buoyancy behavior of optimized formulations were investigated by using gel forming polymers and further analyzed on long term stability studies.

Materials and Methods

The following materials were used: Cefuroxime axetil USP (Nectar Life Sciences, Ltd. India), an almost white amorphous powder with the particle size range from 25 - 30 μ m. All the trial

formulations contained 300 mg of cefuroxime axetil per tablet equivalent to 250 mg of cefuroxime. Other excipients used were: Avicel PH 102[®] (FMC, USA), sodium lauryl sulphate, magnesium stearate (Fischer, UK). Starch 1500[®] (Pregelatinized starch) and HPMC polymers i.e. Methocel K4M CR[®], Methocel E5LV[®] and Methocel E50LV[®] were supplied by Colorcon Ltd., England. The software used were adds in programs DD solver[®], SPSS[®] 20.0 for Windows (IBM SPSS Statistics Inc., Chicago, USA) and Microsoft Excel 2010[®] for statistical analysis and dissolution profile comparison, while stability results were analysed by R Gui[®] 3.1.1 software.

FT-IR studies for drug-excipient compatibility

The infrared spectra of pure drug (Cefuroxime axetil), physical mixture of cefuroxime axetil pure drug with excipients (1:1) and optimized formulation (F9) were taken respectively and recorded on IR Prestige-21 (Shimadzu, Japan) using KBr discs. The scans were registered over the region of 4000-500 cm^{-1} .

Preparation of Matrix tablets

Nine different extended release cefuroxime axetil matrix tablet formulations (F1-F9) were prepared by direct compression method with different concentrations of hydroxypropyl methyl cellulose polymer (Methocel K4M CR, Methocel E5LV, Methocel E50LV) adjusted by avicel PH 102. Other excipients such as starch 1500, magnesium stearate and sodium lauryl sulphate were kept constant in all formulations (Table I). All the ingredients were accurately weighed as per weight for 100 tablets bulk quantity, sieved manually through a 40 mesh sieve and then mixed by tumbling action following a geometric dilution technique in a polyethylene bag for 15 minutes. The mixture was then blended with magnesium stearate for another 5 minutes to obtain a homogenous blend and compressed with manually operated single punch tablet machine (Korsch: Erweka, Germany) to produce oblong caplet shaped uncoated tablets each weighing 800 mg ($\pm$ 5%).

Table I

Composition of extended release cefuroxime axetil matrix tablet formulations

Ingredients	F1*	F2*	F3*	F4*	F5*	F6*	F7*	F8*	F9*
	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
Cefuroxime axetil*	300	300	300	300	300	300	300	300	300
Sodium lauryl sulphate	8	8	8	8	8	8	8	8	8
Starch 1500	40	40	40	40	40	40	40	40	40
Avicel PH 102	196	236	276	316	356	316	356	380	356
Magnesium stearate	16	16	16	16	16	16	16	16	16
HPMC K4M CR	240	200	160	120	80	80	64	40	64
HPMC E5LV	-	-	-	-	-	24	16	-	-
HPMC E50LV	-	-	-	-	-	16	-	16	16
Total compression weight (mg)	800	800	800	800	800	800	800	800	800

*Formulations code: F1 = Formulation 1, F2 = Formulation 2, F3 = Formulation 3, F4 = Formulation 4, F5 = Formulation 5, F6 = Formulation 6, F7 = Formulation 7, F8 = Formulation 8, F9 = Formulation 9

*All formulations contain 300 mg of cefuroxime axetil per tablet equivalent to 250 mg of cefuroxime.

Micromeritic properties of powder blends

Micromeritic properties i.e. bulk density (ρ_b), tapped density (ρ_t), compressibility index (CI), Hausner ratio (HR) and angle of repose (α) of the blended powder were determined by the following formulas under USP 36/ NF 31, 2013 guidelines [14].

$$\rho_b = M (\text{weight of the powder blend}) / V_b (\text{bulk volume}) \quad (1)$$

$$\rho_t = M (\text{weight of the powder blend}) / V_t (\text{tapped volume}) \quad (2)$$

$$CI = (\rho_t - \rho_b) / \rho_t \times 100 \quad (3)$$

$$HR = \rho_t / \rho_b \quad (4)$$

$$\alpha = \tan^{-1} (h (\text{cone height}) / r (\text{radius of the heap})) \quad (5)$$

Evaluation of Tablets

Tablets were subjected to various physical tests including weight (Analytical balance: Sartorius, Germany), thickness, length, width (Vernier caliper: CD-6, CSX, Mitutoyo, Japan), hardness variation (Hardness Tester: OSK Fujiwara, Ogawa Seiki Co. Ltd., Tokyo, Japan), and friability (Friabilator: H.jurgens GmbH & Co. D2800 Breman, Germany) according to the official pharmacopoeial [14] and unofficial methods.

Assay of Cefuroxime axetil Matrix Tablets

Assay of cefuroxime axetil was performed according to USP 36/ NF 31, 2013 guidelines using a HPLC system (LC-10AT VP, No.C20973806986 LP, Shimadzu Corporation, Kyoto, Japan) and the column Promosil® (Agela Technologies, USA) C-18, 4.6 x 250 mm containing 5 μ m packing, with injection volume about 10 μ L. The suitably filtered and degassed mixture of mobile phase was composed of 0.2 M monobasic ammonium phosphate and methanol (620:380) with a flow rate of 1.5 mL per minute. Randomly selected twenty tablets of each batch were pulverized and a quantity equivalent to 25 μ g/mL strength prepared in methanol and 0.2 M monobasic ammonium phosphate. The sonicated and filtered solution was then injected and peaks were detected at 278 nm. Each determination was carried out in triplicate.

In vitro drug release studies

The release of cefuroxime axetil was studied by USP Type II dissolution apparatus (Erweka DT, Heusenstamm, Germany) using 900 mL 0.07 N HCl (USP36 / NF31, official medium) as dissolution medium maintained at $37^\circ\text{C} \pm 0.5^\circ\text{C}$ with rotation speed of 100 rpm [14]. Aliquots of 10 mL were collected at pre-determined time intervals and were replenished with equivalent volume of fresh medium. The removed filtered test solution samples were suitably diluted with dissolution medium, in comparison with a standard solution having a known concentration of cefuroxime axetil,

equivalent to about 0.01 mg of cefuroxime per mL in the same dissolution medium. They were analysed by using an UV-Visible double beam spectrophotometer (1800: Shimadzu, Kyoto, Japan) at 278 nm.

The dissolution studies were also performed in different dissolution media like distilled water, 0.1 N HCl of pH 1.2 and phosphate buffers at pH 4.5 and 6.8. The mean for six tablets was used for analysis and the percentage of cumulative drug release was calculated.

Swelling and in vitro buoyancy studies

The optimized cefuroxime axetil matrix tablets (F5 - F9) were weighed individually (designated as W_1) and placed separately in a glass beaker containing 200 mL of 0.07 N HCl, maintained in a water bath at $37^\circ\text{C} \pm 0.5^\circ\text{C}$. At regular 0.5 hr time intervals until 12 hr, the tablets were removed from beaker, and the excess surface liquid was removed carefully using tissue paper [15, 16]. The swollen tablets were then re-weighed (W_2), and the percentage degree of swelling was calculated using the following formula:

$$\text{Percentage degree of swelling} = [(W_2 - W_1) / W_1] \times 100 \quad (6)$$

The *in vitro* buoyancy was determined by measuring floating lag times and duration of buoyancy according to the method described by Rosa et al. [17]. The tablets were placed in a beaker containing 200 mL 0.07 N HCl. The time required for the tablet to rise to the surface and float was taken as the floating lag time. The time for which tablets kept floating was termed as 'buoyancy time' of the tablets, which was determined for optimized formulations (F5 - F9).

*Applied methods to compare dissolution profiles and drug release kinetics**ANOVA-based models*

One-way ANOVA was employed for comparison of *in vitro* release profiles of optimized extended release 250mg cefuroxime axetil formulations. Then *post hoc* procedures for multiple comparison of dissolution profiles were performed by Dunnett's t-test (two-sided) using SPSS® 20.0 (IBM SPSS Statistics Inc., Chicago, USA) software [18].

Model-Independent methods

Similarity and dissimilarity factors f_2 and f_1 respectively were calculated by using the following formulas,

$$f_1 = \{[\sum_{i=1}^n |R_t - T_t|] / [\sum_{i=1}^n R_t]\} \times 100 \quad (7)$$

$$f_2 = 50 \times \log \{[1 + (1/n) \sum_{i=1}^n (R_t - T_t)^2]^{-0.5} \times 100\} \quad (8)$$

Where n is the number of samples, R_t and T_t represent the percentage dissolved of the reference and test product at each time point. The release profiles are significantly different if $f_1 > 15$ and $f_2 < 50$ [19].

Ratio-Test Approaches

Ratio tests are performed as ratios of percentage drug dissolved, area under the dissolution curve, and mean dissolution times of the reference formulation with those of a test formulation at the same sampling time [20]. The most common ratio test was the mean dissolution time (MDT) used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer, calculated by:

$$\text{MDT} = \frac{\sum_{i=1}^n \bar{t}_i \Delta M_i}{\sum_{i=1}^n \Delta M_i} \quad (9)$$

The area under the dissolution curve (AUC), variance of dissolution times (VDT), relative dispersion of dissolution times (RD) are estimated by:

$$\text{AUC} = \sum_{i=1}^n \frac{(t_i - t_{i-1})(y_{i-1} + y_i)}{2} \quad (10)$$

$$\text{VDT} = \frac{\sum_{i=1}^n (\bar{t}_i - \text{MDT})^2 \Delta M_i}{\sum_{i=1}^n \Delta M_i} \quad (11)$$

$$\text{RD} = \frac{\text{VDT}}{\text{MDT}^2} \quad (12)$$

Where i is the sample number; n number of sampling points; $\bar{t}_i$ time at the midpoint between i and $i-1$; ΔM_i additional amount of drug dissolved between i and $i-1$; t_i th time point; y_i percentage of drug dissolved at time t_i .

Model Dependent methods

Following are the formulas of some model dependent approaches:

Zero order release

$$Q_t = K_0 t \quad (13)$$

Where, Q_t is the amount of drug released in time t , K_0 is the release rate constant for zero-order, t is the time in hours [21].

First order release

$$\ln Q = \ln Q_0 - Kt \quad (14)$$

The drug release at time t is Q ; initial drug release is Q_0 at time t_0 and K is the first order rate constant [22].

Higuchi release kinetics

$$Q = K_H t^{1/2} \quad (15)$$

Where K_H is the release rate constant, t is the time and Q is the drug release [23].

Korsmeyer and Peppas model

$$Mt / M_\infty = Kt^n \quad (16)$$

Where, Mt/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, n is an exponent which characterizes the different release mechanisms [24].

Hixson-Crowell cube release model

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \quad (17)$$

Where Q_0 the initial amount of drug in the pharmaceutical dosage form. Q_t is the amount of drug release at time t and K_{HC} is constant showing surface to volume relation [25].

Weibull model

$$F(t) = F^\infty \cdot (1 - e^{-(t+T_0)/\alpha})^\beta \quad (18)$$

Where $F(t)$ is the amount of drug dissolved as a function of time t . F^∞ is total amount of drug released. T_0 is account for lag time measured as a result of the dissolution process. α denotes a scale parameter that describes the time dependence and β is shape parameter [26].

Stability studies

The stability studies of optimized extended release (F5 - F9) formulations were performed under the ICH guidelines at controlled room temperature ($25^\circ\text{C} \pm 0.5^\circ\text{C}$ at 75% relative humidity) for 12 months and accelerated ($40^\circ\text{C} \pm 0.5^\circ\text{C}$ at 75% relative humidity) temperature for six months [19, 27]. Analysis was performed at zero time and after specified time intervals. Samples were examined for hardness, friability, drug content and percentage of drug release according to the USP36 / NF31, 2013 guidelines, while shelf life was also calculated by using software R Gui[®].

Results and Discussion*FT-IR studies for drug-excipients compatibility*

Drug-excipients interaction plays a vital role in the drug release from any dosage form. Infrared spectra of cefuroxime axetil showed the characteristic absorption peaks at 1681.93, 1737.86, 1782.23 cm^{-1} indicating the presence of carbonyl C=O stretching. The strong absorption band at 3481.51 cm^{-1} represented the primary amine N-H stretching vibration and the characteristic band at 1215.15 cm^{-1} represented the C-H stretching. The IR spectra of physical mixture of drug with each excipient (1:1) and optimized F9 formulation also showed the above mentioned absorption peaks. It was concluded that there was no chemical interaction between the drug and excipients used in the present research.

The FT-IR spectra of cefuroxime axetil (CA), physical mixture (CA: polymer) and F9 formulation are shown in Figure 1. This is in agreement with the earlier work reported [28] where FT-IR studies concluded no interaction between cefuroxime axetil and excipients.

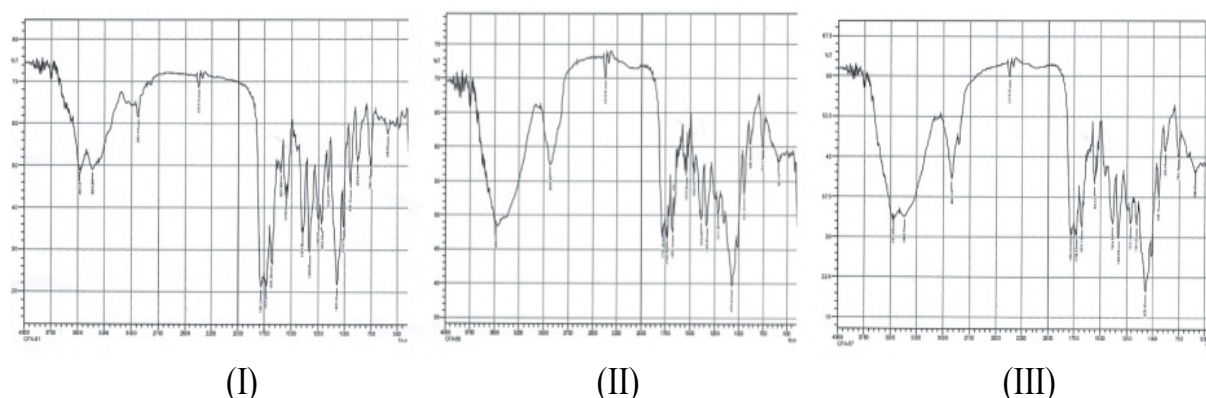


Figure 1.

FT-IR spectra of cefuroxime axetil and excipients. Pure drug cefuroxime axetil (I), physical mixture of drug and polymer K4M CR (II) and optimized formulation F9 (III)

Table II

Micromeritic properties of cefuroxime axetil extended release tablet formulation blends (N = 3)

Trial Formulation	Mass (g)	Bulk Volume (mL)	Tapped Volume (mL)	Bulk Density (g/mL)	Tapped Density (g/mL)	Angle of Repose (θ)	Compressibility Index (%)	Hausner Ratio
F1	7.96 ± 0.12	25.50 ± 0.15	21.50 ± 0.16	0.31 ± 0.13	0.37 ± 0.22	36.58 ± 0.14	15.69 ± 0.16	1.19 ± 0.37
F2	8.25 ± 0.10	27.40 ± 0.09	23.00 ± 0.13	0.30 ± 0.09	0.36 ± 0.06	36.62 ± 0.05	16.06 ± 0.12	1.19 ± 0.09
F3	10.12 ± 0.06	31.05 ± 0.14	27.25 ± 0.18	0.33 ± 0.26	0.37 ± 0.14	33.87 ± 0.09	12.24 ± 0.38	1.14 ± 0.27
F4	7.97 ± 0.10	25.00 ± 0.11	22.00 ± 0.13	0.32 ± 0.28	0.36 ± 0.52	31.26 ± 0.16	12.00 ± 0.16	1.14 ± 0.09
F5	7.92 ± 0.13	24.50 ± 0.15	21.00 ± 0.06	0.32 ± 0.08	0.38 ± 0.09	34.25 ± 0.12	14.29 ± 0.15	1.17 ± 0.07
F6	7.96 ± 0.09	29.50 ± 0.13	25.15 ± 0.17	0.27 ± 0.22	0.32 ± 0.38	34.52 ± 0.27	14.75 ± 0.15	1.17 ± 0.47
F7	8.03 ± 0.52	29.75 ± 0.24	25.80 ± 0.16	0.27 ± 0.34	0.31 ± 0.27	32.78 ± 0.13	13.28 ± 0.17	1.15 ± 0.08
F8	8.05 ± 0.07	30.10 ± 0.10	26.15 ± 0.11	0.27 ± 0.06	0.31 ± 0.07	32.00 ± 0.08	13.12 ± 0.07	1.15 ± 0.05
F9	7.95 ± 0.07	24.50 ± 0.17	21.00 ± 0.06	0.32 ± 0.15	0.38 ± 0.24	34.64 ± 0.37	14.29 ± 0.24	1.17 ± 0.28

Table III

Physicochemical properties of cefuroxime axetil extended release tablet formulations (N = 20)

Trial Formulation	Weight (mg)	Thickness (mm)	Length (mm)	Width (mm)	Hardness (kg)	Friability (%)	Assay (%)	Floating Lag time (min)	Buoyancy time (hr)
Pharmacopoeial Limits (USP 36)	±5%	±5%	-	-	> 5 kg	< 1%	90-110%	(min)	(hr)
F1	800.07 ± 5.21	6.11 ± 0.04	19.41 ± 0.01	9.42 ± 0.02	13.91 ± 1.17	0.84 ± 0.09	101.23 ± 0.72	N/P*	N/P
F2	802.25 ± 6.94	6.09 ± 0.04	19.40 ± 0.01	9.43 ± 0.02	12.89 ± 1.02	0.63 ± 0.09	100.40 ± 0.75	N/P	N/P
F3	800.44 ± 6.44	6.10 ± 0.03	19.43 ± 0.02	9.43 ± 0.02	11.59 ± 0.79	0.61 ± 0.11	100.43 ± 1.03	N/P	N/P
F4	801.40 ± 5.95	6.10 ± 0.05	19.41 ± 0.01	9.40 ± 0.01	10.09 ± 0.97	0.79 ± 0.09	100.47 ± 1.13	N/P	N/P
F5	800.31 ± 5.66	6.10 ± 0.05	19.43 ± 0.02	9.41 ± 0.01	9.33 ± 1.14	0.73 ± 0.18	101.34 ± 0.82	90	8
F6	800.77 ± 3.78	6.12 ± 0.04	19.42 ± 0.02	9.44 ± 0.02	11.36 ± 0.52	0.64 ± 0.11	98.46 ± 1.10	95	6.5
F7	799.82 ± 4.72	6.10 ± 0.05	19.41 ± 0.01	9.44 ± 0.01	12.04 ± 0.98	0.52 ± 0.15	97.01 ± 1.52	80	8
F8	799.97 ± 5.33	6.10 ± 0.03	19.42 ± 0.02	9.43 ± 0.02	11.79 ± 1.29	0.48 ± 0.19	102.67 ± 1.90	-	-
F9	802.06 ± 6.75	6.09 ± 0.04	19.41 ± 0.02	9.40 ± 0.01	13.24 ± 1.14	0.44 ± 0.17	101.85 ± 0.88	75	9.5

N/P* = Not performed

Table IV

Multiple dissolution comparison by Dunnett's t test (two-sided) of extended release cefuroxime axetil test products against reference product (F9) in USP dissolution medium 0.07 N HCl (N = 6)

Time (Hours)	(I) Formulation	(J) Formulation	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Boundary	Upper Boundary
0.5	F5	F9	-1.870	0.591	0.014	-3.411	-0.329
	F6	F9	-1.703	0.591	0.027	-3.244	-0.163
	F7	F9	2.435	0.591	0.001	0.894	3.976
	F8	F9	8.838	0.591	0.000	7.298	10.379
1.0	F5	F9	-2.927	0.845	0.007	-5.128	-0.725
	F6	F9	-2.245	0.845	0.045	-4.447	-0.043
	F7	F9	-0.820	0.845	0.733	-3.022	1.382
	F8	F9	10.247	0.845	0.000	8.045	12.448
2.0	F5	F9	-6.025	0.570	0.000	-7.512	-4.538
	F6	F9	-5.363	0.570	0.000	-6.850	-3.877
	F7	F9	2.638	0.570	0.000	1.152	4.125
	F8	F9	6.123	0.570	0.000	4.637	7.610
3.0	F5	F9	-15.803	0.718	0.000	-17.675	-13.932
	F6	F9	-17.570	0.718	0.000	-19.442	-15.698
	F7	F9	-10.675	0.718	0.000	-12.547	-8.803
	F8	F9	-2.950	0.718	0.001	-4.822	-1.078
4.0	F5	F9	-17.877	0.857	0.000	-20.110	-15.643
	F6	F9	-18.635	0.857	0.000	-20.869	-16.401
	F7	F9	-8.130	0.857	0.000	-10.364	-5.896
	F8	F9	-1.577	0.857	0.225	-3.810	0.657
6.0	F5	F9	-20.150	0.764	0.000	-22.141	-18.159
	F6	F9	-20.705	0.764	0.000	-22.696	-18.714
	F7	F9	-11.022	0.764	0.000	-13.013	-9.030
	F8	F9	-3.413	0.764	0.001	-5.405	-1.422
8.0	F5	F9	-21.322	0.654	0.000	-23.027	-19.617
	F6	F9	-18.498	0.654	0.000	-20.203	-16.793
	F7	F9	-8.568	0.654	0.000	-10.273	-6.863
	F8	F9	-5.895	0.654	0.000	-7.600	-4.190
10.0	F5	F9	-23.222	0.783	0.000	-25.263	-21.180
	F6	F9	-23.863	0.783	0.000	-25.905	-21.822
	F7	F9	-6.622	0.783	0.000	-8.663	-4.580
	F8	F9	-5.923	0.783	0.000	-7.965	-3.882
12.0	F5	F9	-17.817	0.568	0.000	-19.297	-16.336
	F6	F9	-10.657	0.568	0.000	-12.137	-9.176
	F7	F9	-5.872	0.568	0.000	-7.352	-4.391
	F8	F9	-1.808	0.568	0.013	-3.289	-0.328

Table V

Difference factor (f_1) and similarity factor (f_2) values of F9 (Reference) with optimized (F5 - F8) cefuroxime axetil extended release formulations in different pH dissolution media

Comparison	Factor	0.07 N HCl (USP D. M.)	Distilled water	pH 1.2 (0.01 N HCl)	pH 4.5 (Phosphate buffer)	pH 6.8 (Phosphate buffer)
F9 vs. F5	f_1	24.82	8.55	1.51	43.31	29.54
	f_2	39.60	53.73	44.87	30.45	38.13
F9 vs. F6	f_1	23.30	17.75	23.62	20.98	18.45
	f_2	40.51	53.57	40.46	46.25	49.20
F9 vs. F7	f_1	9.16	13.46	5.77	16.43	6.69
	f_2	56.97	57.60	61.09	50.78	64.93
F9 vs. F8	f_1	0.62	2.01	15.18	12.29	0.27
	f_2	61.29	77.81	47.23	55.10	84.73

D. M. = Dissolution Medium

Table VI

Ratio-test approaches in different dissolution media

Parameters	F5	F6	F7	F8	F9
0.07 N HCl (USP Dissolution medium)					
MDT/hour	4.11	3.45	3.79	3.50	4.72
AUC/mg/Lxh	561.76	760.97	682.84	741.40	570.54
VDt/h2	14.13	9.63	11.73	12.96	16.53
RD	0.84	0.81	0.82	1.06	0.74
0.1 N HCl (pH 1.2)					
MDT/hour	1.67	3.38	3.49	2.22	4.55
AUC/mg/Lxh	705.58	758.62	699.46	841.51	564.11
VDt/h2	7.08	12.38	14.52	9.60	18.72
RD	2.55	1.09	1.19	1.94	0.90
Distilled water					
MDT/hour	3.53	4.54	5.36	4.80	5.10
AUC/mg/Lxh	551.26	609.93	528.25	620.95	511.55
VDt/h2	10.35	11.66	14.36	12.18	11.11
RD	0.83	0.57	0.50	0.53	0.43
pH 4.5 phosphate buffer					
MDT/hour	4.52	3.80	4.75	4.60	4.32
AUC/mg/Lxh	411.52	715.25	601.67	636.34	566.97
VDt/h2	11.86	10.88	12.56	11.57	12.85
RD	0.58	0.75	0.56	0.55	0.69
pH 6.8 phosphate buffer					
MDT/hour	3.47	3.76	4.10	3.74	4.15
AUC/mg/Lxh	511.27	714.70	657.22	710.34	587.18
VDt/h2	10.09	11.40	14.16	11.74	12.61
RD	0.84	0.81	0.84	0.84	0.73

Table VII

In vitro release kinetics of optimized cefuroxime axetil extended release formulations in different dissolution media

Zero Order			First Order			Higuchi			Korsmeyer Peppas			Hixson-Crowell			Weibull model			
R ²	K	AIC	R ²	K	AIC	R ²	KH	AIC	R ²	K	n	AIC	R ²	K	AIC	R ²	β	AIC
0.07 N HCl (USP Dissolution medium)																		
0.509	6.932	66.963	0.830	0.118	57.423	0.992	20.386	44.932	0.995	21.784	0.466	37.091	0.752	0.033	60.814	0.992	0.765	33.922
0.630	7.179	65.830	0.865	0.123	56.747	0.979	20.958	40.052	0.979	20.802	0.504	42.037	0.812	0.035	59.712	0.977	1.180	44.691
0.513	8.381	70.396	0.901	0.171	56.039	0.991	24.647	34.375	0.994	26.239	0.468	32.635	0.831	0.046	60.872	0.991	0.968	38.112
-0.015	8.898	75.361	0.754	0.210	62.620	0.922	26.571	52.216	0.992	33.758	0.375	33.848	0.609	0.056	66.772	0.988	0.885	39.087
0.516	9.264	72.883	0.965	0.218	49.121	0.978	27.291	30.031	0.980	28.721	0.474	32.065	0.911	0.059	57.688	0.993	0.873	33.892
0.1 N HCl (pH 1.2)																		
-11.323	7.861	81.978	-5.384	0.196	76.058	-2.764	24.603	71.305	0.990	47.631	0.144	30.009	-7.054	0.049	78.150	0.990	0.279	33.872
0.099	6.958	70.229	0.534	0.120	64.309	0.884	20.649	51.822	0.933	25.648	0.384	48.851	0.418	0.034	66.297	0.958	2.469	46.635
-0.489	8.338	76.066	0.463	0.186	66.888	0.809	25.096	57.587	0.977	34.812	0.328	40.742	0.239	0.049	70.030	0.966	0.623	46.148
-3.739	9.558	83.170	-0.207	0.361	70.860	-0.119	29.513	70.177	0.977	50.498	0.213	37.409	-0.682	0.098	73.848	0.976	0.434	39.533
0.034	9.074	75.864	0.827	0.225	60.370	0.932	27.129	50.028	0.992	34.002	0.464	35.298	0.689	0.060	65.677	0.994	0.675	34.087
Distilled water																		
0.554	6.707	66.968	0.866	0.113	56.109	0.972	19.736	42.193	0.972	20.281	0.486	44.025	0.789	0.032	60.205	0.995	0.561	30.269
0.969	6.769	47.606	0.992	0.104	35.245	0.904	19.018	57.679	0.995	10.535	0.797	32.415	0.997	0.030	46.928	0.997	1.226	32.656
0.935	6.962	53.841	0.983	0.110	42.012	0.923	19.719	55.368	0.988	12.453	0.732	40.672	0.981	0.032	42.969	0.984	1.131	45.187
0.907	8.044	58.783	0.987	0.143	41.426	0.953	22.948	52.750	0.997	16.192	0.677	37.426	0.985	0.040	42.294	0.992	1.328	40.627
0.871	7.809	60.925	0.991	0.138	37.374	0.961	22.386	50.270	0.992	16.915	0.643	30.765	0.978	0.039	41.066	0.993	1.029	30.210
pH 4.5 phosphate buffer																		
0.866	5.249	54.159	0.965	0.074	42.121	0.962	15.059	42.845	0.992	11.479	0.638	30.459	0.941	0.022	46.785	0.997	0.752	34.329
0.765	7.127	63.726	0.959	0.122	47.955	0.976	20.667	43.364	0.985	18.071	0.569	41.022	0.919	0.034	54.132	0.994	0.716	34.100
0.891	7.751	59.232	0.988	0.135	39.059	0.963	22.175	49.515	0.999	16.348	0.655	29.581	0.980	0.038	43.871	0.996	1.230	34.585
0.893	8.166	60.160	0.992	0.148	44.986	0.958	23.347	51.756	0.997	16.990	0.662	30.766	0.988	0.041	40.486	0.996	1.260	34.022
0.653	8.813	70.006	0.979	0.188	37.295	0.985	25.776	41.960	0.985	24.946	0.517	23.557	0.935	0.051	39.957	0.996	0.835	32.780
pH 6.8 phosphate buffer																		
0.532	6.213	66.595	0.822	0.100	57.896	0.937	18.303	48.555	0.937	18.764	0.487	50.495	0.746	0.029	61.102	0.969	0.549	46.143
0.698	7.323	65.639	0.940	0.129	51.598	0.986	21.350	37.872	0.989	20.027	0.533	38.143	0.889	0.036	56.627	0.994	0.706	34.461
0.497	8.110	70.001	0.878	0.160	57.270	0.989	23.866	35.487	0.993	25.644	0.463	33.266	0.800	0.044	61.699	0.987	0.843	41.443
0.506	8.680	71.223	0.925	0.185	54.234	0.992	25.549	34.397	0.995	27.229	0.467	32.051	0.857	0.050	60.063	0.996	0.958	32.141
0.559	8.768	70.893	0.948	0.189	51.037	0.993	25.756	33.376	0.994	26.657	0.482	31.157	0.889	0.051	51.508	0.996	0.913	31.968

Evaluation of powder blends and tablets

In order to obtain optimum flow characteristics of powder, blends of each formulations (F1 - F9) were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose as shown in Table II. The results indicated that all powder blends showed fair to good flow characteristics according to USP36 / NF31; ranged from 31.26 ± 0.16 to 36.62 ± 0.05 degrees for angle

of repose, $12.00\% \pm 0.16$ – $16.06\% \pm 0.12$ for Carr's index, and 1.14 ± 0.09 – 1.19 ± 0.37 for Hausner's ratio. Singh and Kumar in 2012 studied the pre formulation characteristics for direct compression suitability of cefuroxime axetil and established the notion that blending poorly compressible drug with suitable excipients could be seen as a useful preformulation tool [29]. Extended release cefuroxime axetil matrix tablets were

prepared by direct compression method to avoid the unwanted swelling of HPMC, as heat and water are not implicated therefore product stability can also be improved [30]. The prepared tablets were subjected to pharmaceutical characterization such as weight, thickness, length, width, hardness variation, friability and drug content. The physical evaluation of the tablets revealed uniform weight, thickness, length and width for all the tablets (evident from low % RSD values). All formulations showed good hardness in the range of 9.33 ± 1.14 to 13.91 ± 1.17 kg, having a percentage friability of $< 1\%$ indicated that the tablets had sufficient mechanical strength.

The Assay method was linear over the range of 25 $\mu\text{g/mL}$ to 0.78 $\mu\text{g/mL}$ with R^2 value of 0.9994 and retention time between 10-14 minutes; the accuracy for LLOQ was 90% with CV % of 1.12% as precision and reproducibility. The assay results revealed that drug content between $97.01\% \pm 1.52$ to $102.67\% \pm 1.90$ is acceptable (Table III). Kostaova et al. and Ghosh and Barik, compared the various grades of HPMC polymer to develop matrix tablets and observed good physicochemical results [31, 32].

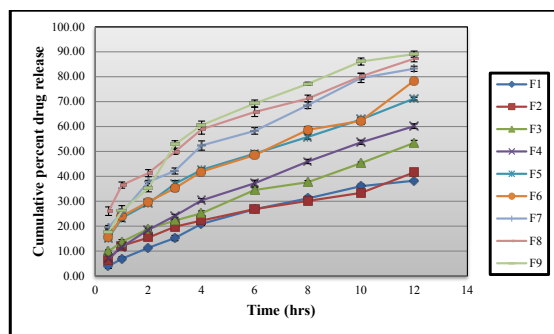


Figure 2.

Cefuroxime axetil percentage release from extended release formulations in 0.07 N HCl (USP dissolution medium) (N = 6)

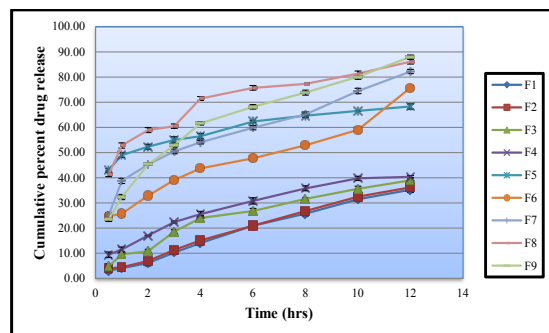


Figure 3.

Cefuroxime axetil percentage release from extended release formulations in 0.1 N HCl (pH = 1.2 medium) (N = 6)

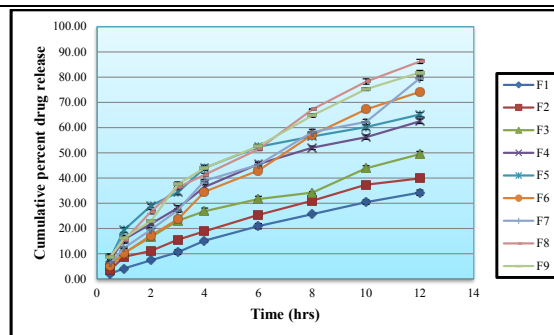


Figure 4.

Cefuroxime axetil percentage release from extended release formulations in distilled water (N = 6)

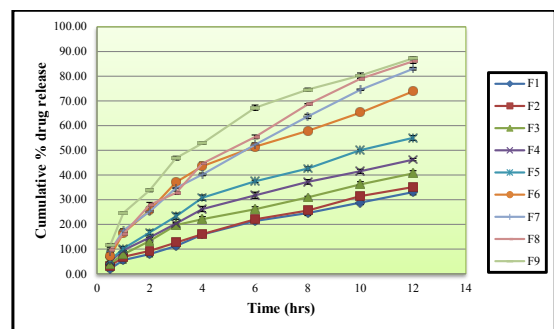


Figure 5.

Cefuroxime axetil percentage release from extended release formulations in pH = 4.5 phosphate buffer medium (N = 6)

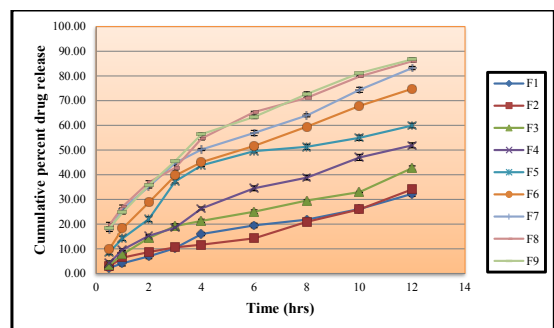


Figure 6.

Cefuroxime axetil percentage release from extended release formulations in pH = 6.8 phosphate buffer medium (N = 6)

In vitro drug release studies

According to Food and Drug Administration, USA, the dissolution profiles should be obtained for prescribed strengths in at least three dissolution media i.e. 1.2, 4.5 and 6.8 buffers. Water can be used as an additional medium [33]. In the current study, dissolution profiles of the developed extended release formulations were performed in different pH medium along with 0.07 N HCl (USP recommended dissolution medium) (Figures 2 - 6).. From the release profiles, it was observed that the variation in grades of polymers and its concentrations from F1 to F9 had variable effects

on drug release (Figures 2-6) and is in agreement with previous studies conducted on felodipine hydrophilic matrix tablets [34]. The formulation with 30% and 25% of K4MCR (i.e. F1 and F2) showed less than 40% of drug release at 12 hr in all dissolution media with minimum drug release in pH 6.8 medium i.e. $32.21\% \pm 0.97$ to $34.05\% \pm 0.78$ correspondingly. F3 and F4 with 20 and 15 percent of K4MCR had considerable drug release in 0.07 N HCl ($53.39\% \pm 1.01$ and $60.12\% \pm 0.92$ respectively) as compared to in 0.1 N HCl showed less than 40% drug release at 12 hr. Formulation F5 (10% K4M CR) was found to be more effective with a maximum drug release in 0.07 N HCl ($71.20\% \pm 0.55$) followed by 0.1 N HCl, distilled water, pH = 4.5 and 6.8 medium ($68.28\% \pm 1.02$, $65.12\% \pm 1.11$, $54.98\% \pm 1.61$, $59.91\% \pm 1.72$) within a period of 12 hr. Those formulations which contained HPMC K4M CR usually showed matrix diffusion type phenomenon [35]. It is widely known that high HPMC contents usually retard drug release [36, 37]. Asaduzzaman et al. revealed that the developed 16% Methocel K4MCR sustained release matrix was the best formulation [38]. Dhumal et al. developed bilayer floating tablets of cefuroxime axetil and reported that the formulation batch with the lowest K4MCR content (10.98%) showed the maximum drug release [39]. Similar conclusions were also drawn by earlier researchers who worked in the development of floating delivery systems of cefuroxime axetil [15, 28]. The extended release formulations with combined polymers compositions found to be more effective and showed maximum drug release [40]. Nighute and Bhise, in 2009 prepared microcrystals of cefuroxime axetil with HPMC E15LV which showed the highest solubility and dissolution rate of drug [41]. Comparable results were obtained with different concentrations of K4MCR with E50LV and E5LV. The formulation containing the mixed combination of 10% K4MCR, 2% E50LV and 3% E5LV (F6) presented less than 80% of drug release i.e. $78.36\% \pm 0.66$ in 0.07 N HCl, $75.73\% \pm 1.05$ in 0.1 N HCl, $74.76\% \pm 0.79$ in pH = 6.8, $74.16\% \pm 1.06$ in distilled water and $73.87\% \pm 0.86$ in pH = 4.5. Combination of 8% K4MCR with 2% E5LV (F7) also showed promising results i.e. more than 80% of drug release in all dissolution medium with maximum drug release ($83.18\% \pm 1.15$) in pH = 6.8 and minimum drug release ($79.56\% \pm 0.78$) in distilled water. Results of 2% E50LV with 5% and 8% of K4MCR (F8 & F9) were found to be very effective and showed best drug release profile in 0.07 N HCl i.e. $87.21\% \pm 1.23$ and $89.02\% \pm 1.24$ respectively. Danarao et al. successfully developed matrix tablets of cefixime trihydrate by using Methocel K4M (5%) and Methocel E50 LV (5%) as a rate retarding polymers [42]. In another study,

floating tablets of cefuroxime axetil containing combination of HPMC K4M and Eudragit RL100 provided a better control release action and improved bioavailability [43].

Cefuroxime axetil is a poorly water soluble drug with BCS class II characteristics [44]. Solubility of cefuroxime axetil was enhanced and optimized by the addition of 1% sodium lauryl sulphate and more than 80% drug released in dissolution medium of different pH [45]. In the present study, all the formulations (F1 - F9) were found to be more effective with maximum drug release in 0.07 N HCl followed by pH = 4.5, 0.1 N HCl, distilled water and pH = 6.8 within a period of 12 hrs.

Swelling and in vitro buoyancy studies

Swelling Index was calculated with respect to time showed increase in weight, indicating that the polymers employed in the present investigation were having a capacity to swell. The percent degree of swelling was slightly greater for F5 (148.68%) than F6 (142.31%), F7 (146.88%) and F9 (137.04%) up to 12 hr, while formulation F8 showed less percent swelling (68.54%) due to a less percentage of K4MCR and E50 i.e. 5% and 2% respectively and revealed that the high percentage of HPMC K4MCR imbibed more water and swollen to greater extent than formulations with a low percentage and increased with passage of time as shown in Figure 7. The gastro-retentive tablet approach for cefuroxime axetil, as reported by Gudigennavar et al. [46] showed similar results for the swelling studies. From the buoyancy studies, it was evident that all the optimized formulations (F5 - F7) showed variable buoyancy times (< 6 hr). The formulation F9 showed buoyancy times greater than 8 hr (Figure 8) without using gas generating agents due to which the lag time of all formulations exceeded 60 minutes.

Drug release kinetics

Three approaches have been extensively used for the comparison and ultimate selection of one best formulation based on the release pattern. Among the three approaches one is represented by statistical approaches which describe the analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA), second is represented by model dependent approaches and third are independent models like similarity factor (f_2) and differential factor (f_1) [33]. In the present study, F9 had more than 85% of drug release in all dissolution media, considered as a target formulation with R^2 adjusted value closest to 1 and a low value of AIC. It is also selected as a reference for Dunnett's t-test, f_1 and f_2 test. This technique was used in several other research studies for the comparison of drug release among dosage forms [18, 47].

The dissolution profile data of reference (F9) and test formulations (F5 - F8) were evaluated by one way ANOVA ($p = 0.05$) at each time point. Results inferred non-parallel and detected a significant difference ($p < 0.05$) between the reference and test formulations in each dissolution medium. As for *post hoc* procedure, the results of pair wise comparison of test products against reference product by Dunnett's t test in 0.07 N HCl are given in Table IV. It was found that the percent dissolved of formulation F7 at 1 hr and formulation F8 at 4 hr with reference to F9 were not statistically significant ($p > 0.05$). In other dissolution medium like 0.1 N HCl of pH = 1.2 revealed the same results of F7 and F8 at 2 and 10 hours respectively, while the release profiles of F8 in distilled water were not statistically significant at 0.5, 1, 3 and 6 hr time points. In pH = 6.8 phosphate buffer medium formulations F7 and F8 found to be non-significant ($p > 0.05$) at 0.5, 1, 3 and 6 hr time points, whereas a significant difference ($p < 0.05$) was observed in the release profile of all formulations in phosphate buffer of pH = 4.5.

Formulation F9 was taken as reference formulation and the dissolution profile was compared with other formulations using the f_1 differential and f_2 similarity test. The profile of F9 was observed to be similar with F7 in all dissolution media while all optimized formulations (F5 - F8) were found to be similar in distilled water (Table V). These findings are in line with previous studies in which this technique was used for the comparison of drug release among dosage forms [18, 48].

Ratio test parameters of mean dissolution time (MDT), area under the curve (AUC), variance of dissolution time (VDT), and relative dispersion of dissolution time (RD) for optimized formulations (F5 - F9) at different dissolution medium are shown in Table VI. The MDT values clearly show that MDT was considerably higher for F9 formulations as compared to other formulation whereas, all test formulations (F5 - F8) exhibited more AUC than F9. Higher MDT indicated a slower drug release. Thus, MDT was directly related to the polymer loading, polymer nature and physico-chemical property of the drug molecule [6]. The VDT and RD values of optimized formulations (F5 - F9) changed with the dissolution process, indicating the variations of the release mechanism.

The mechanism of drug release for the optimized formulations (F5 - F9) was determined by finding the R^2 value for each kinetic model: zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixon-Crowell and Weibull models, corresponding to the release data in each dissolution medium (Table VII). The zero order determinant coefficient (R^2) failed to fit all the formulations and similar poor correlation were observed in first order kinetic

model at each medium except in phosphate buffer pH = 4.5 ($R^2 = 0.959 - 0.992$). A non-linear relationship was obtained in 0.1 N HCl of pH = 1.2, when data applied to the Higuchi model as compared to other dissolution media, while the value of R^2 obtained from Hixson Crowell's equation of all formulations were best observed in phosphate buffer of pH = 4.5 ranged from 0.919 to 0.988 indicating change of surface area and diameter with the progressive dissolution of the matrix as a function of time. In the present study, Korsmeyer-Peppas and Weibull models are best fitted to each dissolution medium data of all formulation comprised R^2 value nearest to one. The 'n' values of Korsmeyer-Peppas model for the reference F9 formulation were in the range of 0.464 - 0.643 in all dissolution media. Therefore, the most probable mechanism of release was non-Fickian diffusion or anomalous diffusion. Mohapatra et al. reported "n" values within 0.49 - 0.59, showing anomalous transport for the cefuroxime axetil loaded gastroretentive floating tablets [40]. Rao et al. indicated non-Fickian diffusion controlled cefuroxime axetil release mechanism which best fitted the Korsmeyer-Peppas equation [28]. Talukdar et al. applied the same equation for evaluating the drug release mechanism from xanthan gum release matrix tablets [2].

Model Selection

The Akaike Information Criterion (AIC) is a measure of goodness of fit based on maximum likelihood. When comparing several models for a given data set, the model associated with the smallest value of AIC is regarded as giving the best fit out of that set of models [49]. As observed in Table VII, AIC values for zero order were found to be more than 50 and showed the failure of the model, similar results were obtained with first order release except in pH = 4.5 (37.29 - 47.95) and in distilled water (35.25 - 56.11). In order to obtain a clearer view of the release process, different release kinetics like Higuchi, Korsmeyer-Peppas, Hixon-Crowell and Weibull models were used. When comparing AIC values, Higuchi model was the best in the range of 30.03 - 52.22 in 0.07 N HCl dissolution medium. Hixon Crowell model also showed the highest values of AIC in all dissolution media with failure of the model. In Weibull model the lowest values of AIC were found in pH = 4.5 (32.78 - 34.59) followed by 0.07 N HCl (33.89 - 44.69).

Results revealed that the drug release from optimized formulations (F5 - F9) were best observed in 0.07 N HCl and pH = 4.5 phosphate buffer medium and Korsmeyer-Peppas model were found to be best with low values of AIC in pH = 4.5 (23.56 - 41.02) followed by 0.07 N HCl (32.06 - 42.03), distilled water (30.76 - 44.02), 0.1 N HCl

(30.01 - 48.85) and in pH = 6.8 phosphate buffer medium (31.16 - 50.49). Formulation F9 was found to be best optimized and showed low values of AIC of all models in almost all dissolution media (Table VII).

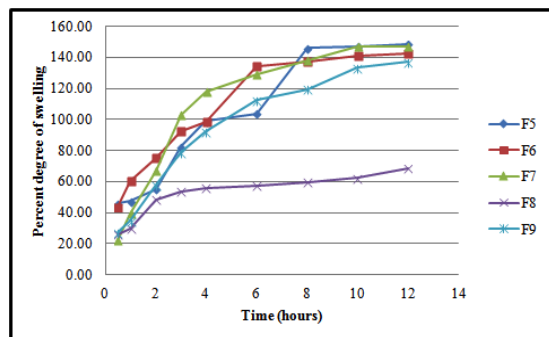


Figure 7.

Percentage degree of swelling of optimized cefuroxime axetil extended release formulations (F5 - F9)

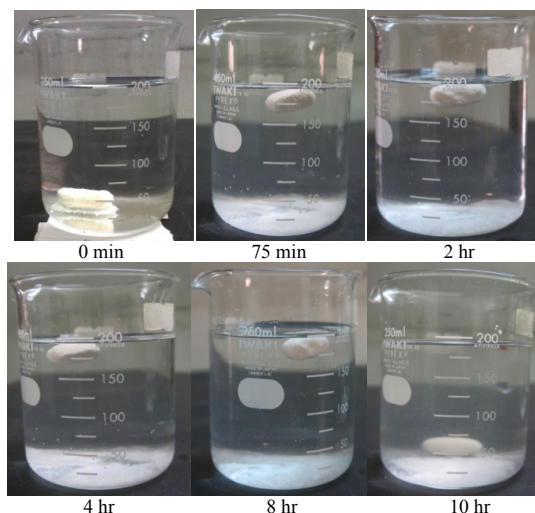


Figure 8.

In vitro buoyancy study of optimized cefuroxime axetil extended release formulation (F9)

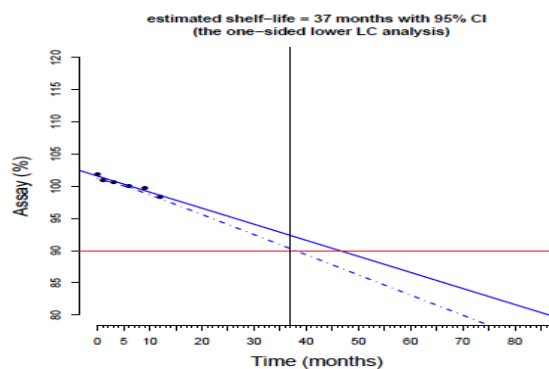


Figure 9.

Estimated shelf life of cefuroxime axetil extended release formulation (F9) at ambient temperature (25 ± 0.5°C)

Stability studies

The stability studies of optimized extended release (F5 - F9) formulations were performed for 12 months (ambient temp.) and 6 months (accelerated temp.) analysis. All the physicochemical tests like friability, hardness, weight variation, dissolution and assay were within the limits. The shelf life was estimated by R Gui[®] software and reference formulation F9 was found to be best optimized with a shelf life of 37 and 25 months at ambient and accelerated temperature respectively (Figure 9).

Conclusions

The present studies revealed that extended release matrix tablets of cefuroxime axetil containing low concentration of K4MCR in combination with ESLV and E50LV are an effective way in controlling the release rate of the drug (< 80%). Developed formulations (F1 - F9) gave satisfactory results for various physicochemical evaluations prepared by direct compression method and further optimized by ANOVA-based model, model dependent and model independent approaches. Formulations F5 to F9 gave better extended drug release results in comparison to other formulations and best fitted to Korsmeyer–Peppas model and Formulation F9 was found to be best optimized with low values of AIC for Higuchi, Korsmeyer–Peppas and Weibull models in all dissolution media.

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