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ASSESSMENT OF HYDROPHILIC MATRIX SYSTEM ON EXTENDED RELEASE DEVELOPED CEFUROXIME AXETIL TABLETS

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Exceptional qualities and consistency of hydrophilic matrix system (HPMC) has been presented a characteristics place for designing and development of drug delivery system. In view of this ten different extended release formulations of hydroxypropyl methylcellulose i.e. Methocel® K15M CR in combination with Methocel® E5LV and E50LV were designed with the addition of second generation cephalosporin drug cefuroxime axetil with 250 mg dose by direct compression method. Physicochemical properties of all formulated batches were examined by the reference pharmacopeial and non-pharmacopeial procedures. In vitro drug release characteristics were observed in different dissolution medium included phosphate buffers of pH 4.5 and 6.8, 0.1N HCl of pH 1.2, 0.07N HCl and distilled water. Four formulations i.e. F5, F8, F9 and F10 were selected as best optimized one and dissolution profile of these formulation were further analyzed by ANOVA-based model, model-independent and model dependent approaches and R Gumi® applied for stability evaluation. Results revealed a significant difference ($p < 0.05$) in drug release increased as a concentration of HPMC were reduced from high to low i.e. 30% - 10% concentration. In addition, up to twelve hours extended pattern (>85%) of drug release was observed in formulations containing 10% of K15M CR (F5) alone and in combination with E5LV and E50LV polymers (F8, F9 and F10). Evaluation of Korsmeyer–Peppas equation showed R^2 = 0.925 - 0.999 and best fitted in to the model of non-Fickian diffusion controlled release mechanism with n=0.478-0.879 indicates high viscosity grades polymers with low fractions displayed extended release patterns of drug

Key words: *Cefuroxime axetil; hydrophilic matrix system; in vitro release; non-Fickian diffusion*

INTRODUCTION

Therapeutic efficacy and safety of drugs, administered by conventional methods can be improved by more accurate spatial and temporal placement within the body, thereby reducing both the size and number of doses[1]. Conventional tablets containing drugs with short half-lives seem to be more challenging for patients due to less time interval between doses. Formulations with extended release have the advantage of reducing dose frequency and prepared by either reservoir or matrix system[2]. For this instance drugs can be incorporated into inert or erodible polymers that can be act as a platform for controlling the drug release profile. There are number of hydrophilic and hydrophobic polymers are used for this purpose[3].

Hydrophilic polymer matrix system is commonly employed in oral controlled drug delivery due to the cost effectiveness, acceptance by U.S Food and Drug administration and flexibility to get a desired drug release profile especially for water insoluble drugs[4-5]. Among different Hydrophilic polymer matrix system, HPMC (Hydroxypropyl methylcellulose) has been

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more frequently used due to its diffusion and erosion matrix release mechanism in different extended release formulations. In one study HPMC was applied as the matrix-forming polymer for the formulation of sustained release tablet of high dose hydrophobic drug (clarithromycin 500 mg) [6]. In another work hydroxypropyl methylcellulose and ethyl cellulose based novel expandable films were used for prolonged retention of Losartan Potassium in the stomach[7].

Cefuroxime axetil is a cephalosporin belongs to second generation, wide spectrum antibiotics effective against both Gram positive and Gram negative bacteria. Prodrug of cefuroxime is cefuroxime axetil that is administered orally. Chemically, cefuroxime axetil is the 1- (acetyloxy) ethyl ester of cefuroxime with molecular formula $C_{10}H_{13}N_2O_4S$ **(Fig. 1)** and it has a molecular weight of 510.48. According to Biopharmaceutical Classification System, cefuroxime axetil belongs to class II drugs that have low solubility and high permeability. The bioavailability of drug after oral administration is 37% which found increased from 37% - 52% taking after food and almost the entire drug is metabolized into active form and 50% can be recovered in urine[8-9].

In this study, different extended release formulations of cefuroxime axetil were developed by incorporation of high (Methocel® K15M CR) and low (Methocel® E5LV and Methocel® E50LV) viscosity grades of HPMC with directly compressible ingredients to evaluate the floating, buoyancy and swelling behavior of polymers on in vitro drug release in dissolution media of different pH . Previously the same extended release formulations of cefuroxime axetil were prepared by combination of different high (Methocel® K4M CR, K100M, K100M CR and K100LV CR) and low (Methocel® E5LV and E50LV) viscosity grades of HPMC and results revealed significant differences in drug release with variable concentration and grades of polymers[10-11]. In another work mucoadhesive minitablets cefuroxime axetil were developed with HPMC K100M and sodium carboxy methyl cellulose showed a desirable and promising drug release profile up to 24 hours[12].

MATERIALS AND METHODS

Materials

API: Cefuroxime axetil USP (Nectar Life Sciences, Ltd., Chandigarh, India).

Excipients: Magnesium stearate (Fischer scientific, Leicestershire, UK), Sodium lauryl sulphate (FMC, USA), Microcrystalline cellulose (Avicel PH 102®) (FMC Corporation, Philadelphia, USA), Methocel® K15M CR, Methocel® E5LV, and Methocel® E50LV (Colorcon Ltd., Dartford Kent, England), Starch 1500® (partly pregelatinized) (Colorcon Ltd., Dartford Kent, England). All chemicals are of analytical grades (Merck, Darmstadt, Germany).

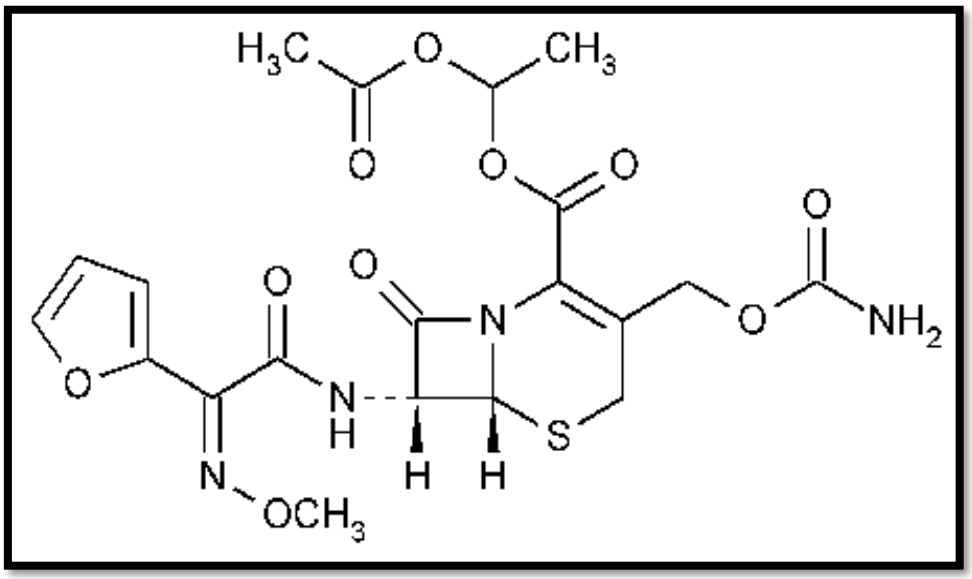


Fig. 1: Chemical structure of cefuroxime axetil ($C_{20}H_{22}N_4O_{10}S$) 1-acetyloxy ester of cefuroxime (Adapted from: USP 36, 2013).

Methods

Pre-formulation analysis

The purpose of the pre-formulation testing was to evaluate the physical properties of powder mixes prior to compression. Cefuroxime axetil USP is an amorphous powder that is practically white in color and has granular sizes between 25 and 30 μm. The micromeritics parameters of the blended powder from each formulation, including bulk density (BD), tapped density (TD), compressibility index (CI), Hausner ratio (HR), and angle of repose (α) were calculated using the methods under USP 36/NF 31, 2013 guidelines[13].

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

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

$CI = (TD - BD) / TD \times 100$ (3)

$HR = TD/BD$ (4)

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

Preparation of matrix tablets

Ten different batches of extended release cefuroxime axetil matrix tablet formulations (F1–F10) were prepared by using direct compression method with varying concentrations of hydroxypropyl methyl cellulose polymer (Methocel® K15M CR, Methocel® E5LV, Methocel® E50LV) which were then adjusted by Avicel® PH 102. Each tablet in the formulations had 300 mg of cefuroxime axetil, which is approximately 250 mg of cefuroxime. **Table 1 and Fig. 2** exhibit the formulations that all had the same other excipients, which included Starch 1500, magnesium stearate, and sodium lauryl sulphate.

Table 1 : Composition of extended release cefuroxime axetil 250mg matrix tablet formulations.

Name of ingredients	F1*	F2*	F3*	F4*	F5*	F6*	F7*	F8*	F9*	F10*
	mg/tab	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	300
Sodium lauryl sulphate	8	8	8	8	8	8	8	8	8	8
Starch 1500®	40	40	40	40	40	40	40	40	40	40
MCC (Avicel® PH 102)	196	236	276	316	356	356	356	380	372	364
Magnesium stearate	16	16	16	16	16	16	16	16	16	16
HPMC K15M CR	240	200	160	120	80	64	64	40	48	56
HPMC E5LV	_	_	_	_	_	_	16	_	_	_
HPMC E50LV	_	_	_	_	_	16	_	16	16	16
Total compression weight	800	800	800	800	800	800	800	800	800	800

* F1= Extended release formulation one (K15M CR 30%), F2= Extended release formulation two (K15M CR 25%), F3= Extended release formulation three (K15M CR 20%), F4= Extended release formulation four (K15M CR 15%), F5= Extended release formulation five (K15M CR 10%), F6= Extended release formulation six (K15M CR 5%, E50LV 2%), F7= Extended release formulation seven (K15M CR 6%, E50LV 2%), F8= Extended release formulation eight (K15M CR 7%, E50LV 2%), F9= Extended release formulation nine (K15M CR 8%, E50LV 2%), F10= Extended release formulation ten (K15M CR 8%, E5LV 2%).

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

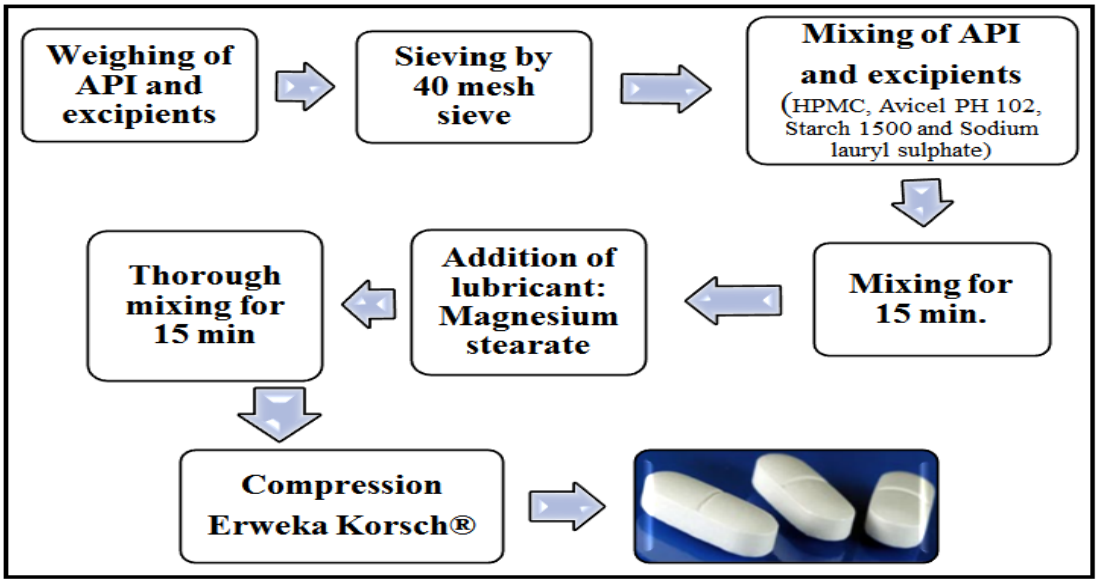


Fig. 2: Diagrammatic representation of the direct compression tablet manufacturing process.

FT-IR analysis

Infrared spectra of three different formulations—Cefuroxime axetil pure drug, Cefuroxime axetil pure drug in physical mixture with excipients (1:1), and the improved composition (F9) were measured on an IR Prestige-21 (Shimadzu, Japan) device by using KBr discs. The 4000-500 cm-1 area was the scan collection area[13].

Pharmaceutical assessment of tablets

Physical tests were performed on twenty tablets from each formulation using the official pharmacopoeial[13] and unofficial techniques. These tests consisted of weight (Analytical Balance: Sartorius, Germany), thickness, length, and width (Vernier caliper: CD-6, CSX, Mitutoyo, Japan), hardness variation (Hardness Tester: OSK Fujiwara, Ogawa Seiki Co. Ltd., Tokyo, Japan), and friability tests (Friabilator: H. Jurgens GmbH & Co. D2800 Bremann, Germany).

Analysis of cefuroxime axetil matrix tablets

Using HPLC (LC-10AT VP, No.C20973806986 LP, Shimadzu Corporation, Kyoto, Japan) and column Promosil® (Agela Technologies, USA) C-18, 4.6 x 250 mm, including 5µm packing with an injection volume of approximately 10µl, the assay of cefuroxime axetil was carried out in accordance with USP 36/NF 31, 2013 criteria [13]. The suitably filtered and degassed mixture of mobile phase composed of 0.2M monbasic ammonium phosphate and methanol (620:380) with a flow rate of 1.5 ml per minute. Twenty tablets from each batch were chosen at random and ground into a powder using a mixture of methanol and 0.2M monobasic ammonium phosphate, which produced a strength of 25µg/ml. Peaks at 278 nm were found after injecting a sonicated and filtered solution. Every assessment was made in triplicates.

In vitro drug release analysis

The study examined the release patterns of cefuroxime axetil by putting six tablets (N = 6) in a USP paddle type II dissolution apparatus (Erweka DT, Heusenstamm, Germany) that rotated at 100 rpm and contained 900 ml of dissolution medium at 37±0.5°C[11]. Various dissolution media were employed, including distilled water, 0.1N HCl with a pH of 1.2, 0.07N HCl (USP official medium), and phosphate buffers with pH values of 4.5 and 6.8. To maintain the sink condition, an aliquot of approximately, 10 milliliters of each medium was removed at various time intervals (0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours) and replaced with an equal volume of new dissolving medium. Dissolution medium was used to appropriately dilute the extracted, filtered test solution samples. The absorbance was measured at 278 nm using a UV/Vis double beam spectrophotometer (1800, Shimadzu, Japan), with a blank consisting of dissolving agent.

Swelling and In vitro buoyancy studies

The optimized cefuroxime axetil matrix tablets, identified as W1, were weighed individually and put into a glass beaker with 200 ml of 0.07 N HCl. The beaker was kept in a water bath at 37°C±0.5°C. The tablets were taken out of the beaker at regular intervals of 0.5 hours till 12 hours, and any surplus liquid on the surface was carefully cleaned using tissue paper[14, 15]. After reweighing the swelled tablets (W2), the following calculation was used to determine the percentage of swelling:

$$Percent\ Degree\ of\ Swelling = [(W_2/W_1)] \times 100 \quad (6)$$

By monitoring floating lag times and the buoyancy duration in accordance with the procedure wherein the tablets were put in a beaker with 200 ml of 0.07N HCl, the in vitro buoyancy was ascertained[16]. The floating lag time was measured as the amount of time it took for the tablet to rise to the surface and float. The phrase "buoyancy time" refers to the amount of time that tablets remained afloat. This value was established for tablets with improved formulas (F5, F8, F9, and F10).

Statistical analysis

ANOVA-based models

The in vitro release patterns of optimizesd extended-release 250 mg cefuroxime axetil formulations were compared using a one-way ANOVA. After that, post hoc procedures for multiple comparison of dissolution patterns were carried out applying SPSS® 20.0 (IBM SPSS Statistics Inc., Chicago, USA) software by Dunnett's t-test (two-sided)[17].

Model-Independent methods

The subsequent equations were used to determine the comparable and dissimilar factors, f_2 and f_1, accordingly:

$$f_1 = \left[\frac{\{\sum_{t=1}^{n}|R_t - T_t|\}}{\sum_{t=1}^{n} R_t}\right] \times 100 \quad (7)$$

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

Where n is the number of samples, R_t and T_t are the percent dissolved of the reference and test products at each time point. The release profiles are significantly different if f_1>15 and f_2<50[18].

Model dependent methods

Model dependent approaches are used in comparative studies of different formulation were calculated by DD solver® software. Following are few model dependent approaches which are extensively used for optimization process in previous literature [19].

a) Zero order reactions

$$\mathbf{Q_o = K_o t + Q_t} \quad (9)$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution. K_o is the zero order release constant expressed in units of concentration/time [17-19].

b) First order reactions

$$\mathbf{\ln Q = \ln Q_o - K_1 t} \quad (10)$$

Where Q_o is the initial concentration of drug and K_1 is first order rate constant and t is the time [17, 18, 19].

c) Higuchi release Kinetics

$$\mathbf{Q = K_H\ t^{1/2}} \quad (11)$$

K_H is the Higuchi dissolution constant, t is the time and Q is the drug release [17-19].

d) Korseemyer and Peppas kinetic model

$$\mathbf{M_t / M\infty = K_{KP}\ t^n} \quad (12)$$

$M_t / M\infty$ is a fraction of drug released at time t, K_{KP} is the release rate constant and n is the release exponent used to characterize different release for cylindrical shaped matrices [17- 19]

e) Hixson-Crowell release model

$$\mathbf{Q_o^{1/3} - Q_t^{1/3} = K_{HC}\ t} \quad (13)$$

Where Q_o is the initial concentration of drug in the tablets and the Q_t is the remaining concentration of drug in the dosage form at time t. K_{HC} is the Hixson–Crowell constant [17-19].

f) Weibull model

$$\mathbf{F(t) = F^{\infty}\ (1 - e^{((t + T_o)/\alpha)\beta)})} \quad (14)$$

Where F (t) is the amount of drug dissolved as a function of time t. F^{∞} is total amount of drug being released. T_o is account for lag time measured as a result of the dissolution process and α denotes a scale parameter that describes the time dependence and β is shape parameter which characterizes the curve [17- 19].

Stability studies

According to ICH recommendations[20], stability experiments of optimized extended release formulations (F5, F8, F9, and F10) packed in amber colored glass bottles were conducted at controlled room temperature

(25ºC±0.5°C at 75% relative humidity) for 12 months and accelerated temperature (40ºC±0.5°C at 75% relative humidity) for 6 months. At the beginning and end of the designated times the analysis were conducted as USP 36/NF 31, 2013 criteria and samples were assessed for hardness, friability, drug content, and percentage of drug release. Stability results of drug contents and percent drug release were analyzed with R-package "stab" of R Gui® 3.1.1 software (R Core Team, 2007-2012. CARN Packages) having a single-factor analysis, for single-batch based on ICH specification[20]. First order analysis was made at one sided lower control analysis at 90% confidence interval to calculate the shelf life of the optimized extended release formulations.

RESULTS AND DISCUSSION

Pre-formulation analysis

In order to investigate the impact of HPMC on in vitro release kinetics and drug release profile, ten (F1–F10) distinct batches of cefuroxime axetil 250 mg extended release tablets were created by varying the formulation parameters. In order to stop HPMC from ballooning unnecessarily, we used the direct compression technique[21]. Blends of each drug development were assessed for bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose in order to achieve the best flowbility of powders from bulk storage containers or hoppers into dies and to produce repeatable tablets with acceptable content uniformity, as indicated in **Table 2**.

According to USP 36/NF 31, the results showed that all powder blends had fair to good flow characteristics; the angles of repose ranged from 31.45±0.24 to 40.00±0.32 degrees, the Carr's index ranged from 11.93%±0.67 to 19.88%±0.17, and the Hausner's ratio was between 1.14±0.35 and 1.25±0.16. A bilayer tablet of cefuroxime axetil was examined for precompression properties by Parmar and Pednekar (2011), who noted good to exceptional powder flow[22]. MCC was used as a filler and binder in quickly disintegrating cefuroxime axetil tablet mixes in another investigation, where the flowability showed good to satisfactory results[23].

FT-IR analysis

Any active pharmaceutical ingredient's stability and efficacy in pharmaceutical dosage forms, both chemically and physically, mostly depend on how well it blends with the formulation's additives. The IR spectra of cefuroxime axetil in this investigation revealed the presence of carbonyl C=O stretching at 1681.93, 1737.86, and 1782.23 cm1, whereas the absorption peaks of N-H stretching at 3481.51 cm1 and C=H stretching at 1215.15 cm1 were clearly visible. These findings were in line with the typical N-H extending at 3481.51 cm1, C-H extending at 1215.15 cm1, and absorption peaks at 1681.93, 1737.86, and 1782.23 cm1. These outcomes were comparable to the medication and excipient physical mixture (1:1 w/w) and the optimal formulation (F9) that was chosen, which showed no evidence of a chemical liaison **(Fig. 3).**

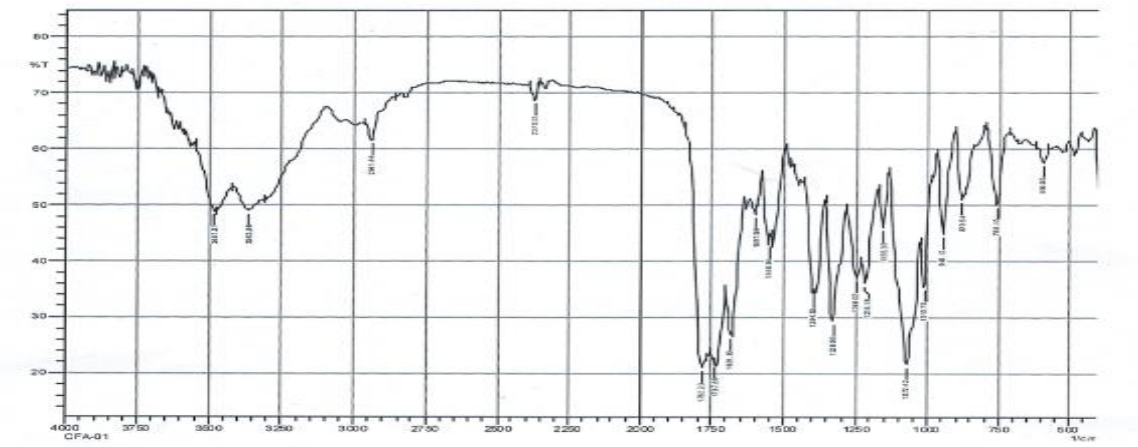
In a research article, Sruti et al. observed that cefuroxime axetil was compatible with excipients such as Sylysia 350 and Gelucire 50/13, which are used to improve the drug's tableting and dissolving qualities[24].

Pharmaceutical assessment of tablets

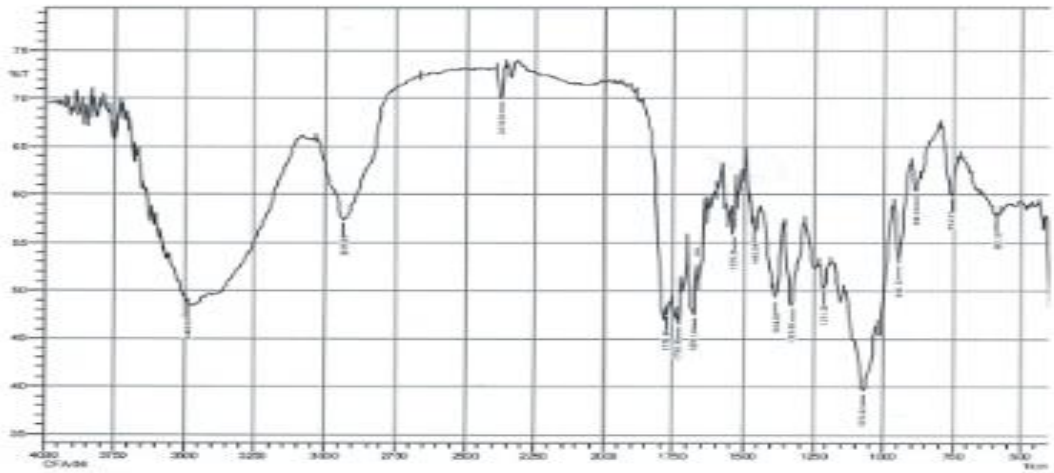
According to USP 36/NF 31, 2013 guidelines, the created formulations were assessed for response characteristics such as tablet weight variation, thickness, diameter, length, width, hardness, friability, and assay. Low RSD values in the results indicated homogeneous weight, thickness, length, and width. In the range of 9.70±1.15 to 13.78±1.23 kg, all formulations exhibited good hardness; a percentage friability of less than 1% meant that the tablets had adequate mechanical strength[13]. In 2012, Kostaova and Kostaova created a matrix system that demonstrated excellent mechanical qualities and minimal flexibility, based on Methocel® K15M combined with Avicel® PH 102[25]. To make sure the dosage form was homogeneous, a pharmaceutical assessment using high-performance liquid chromatography (HPLC) was carried out. The laboratory findings showed that, in accordance with the cefuroxime axetil tablet monograph, a drug concentration of 95.64%±1.33 to 103.70%±2.05 is acceptable **(Table 3)**. The outstanding pharmaceutical evaluation of tablets made with magnesium stearate, HPMC, and Avicel® PH 102 as excipients was documented by Mutalik et al. in 2007[26].

Table 2 : Micromeritic properties of cefuroxime axetil extended release tablet formulation blends (N=3).

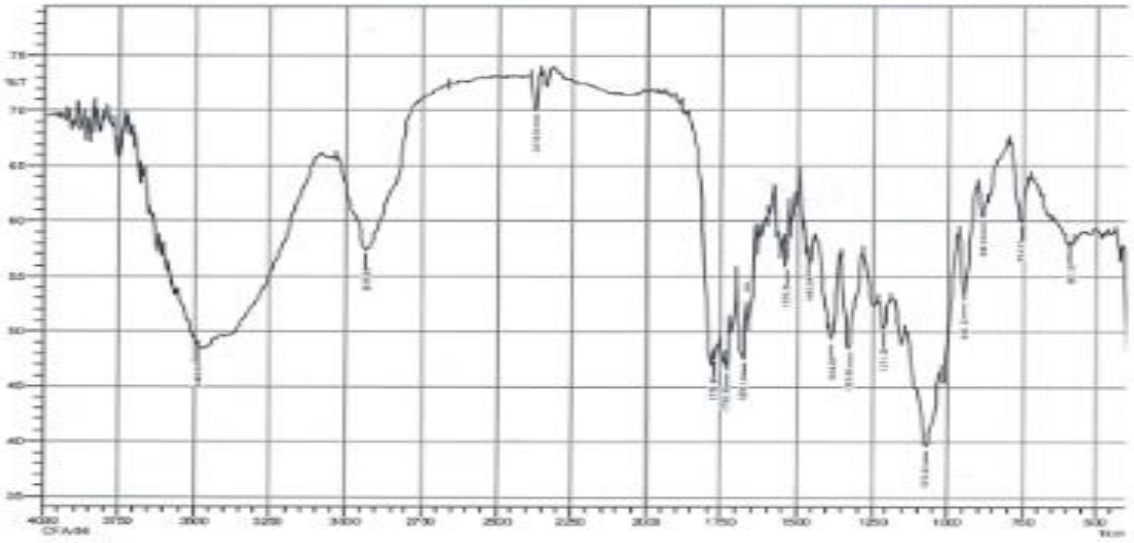
Formulation	Mass	Bulk volume	Tapped volume	Bulk density	Tapped density	Angle of Repose	Compressibility Index	Hausner Ratio
	(gm)	**(ml)**	**(ml)**	**(gm/ml)**	**(gm/ml)**	**(θ)**	**(%)**	**–**
F1	8.03±0.24	26.15±0.32	21.5±0.14	0.31±0.14	0.37±0.36	37.62±0.32	17.78±0.11	1.22±0.14
F2	8.15±0.35	27.00±0.11	22.00±0.29	0.30±0.24	0.37±0.27	38.92±0.11	18.52±0.32	1.23±0.09
F3	7.85±0.24	25.65±0.54	22.15±0.32	0.31±0.17	0.35±0.62	33.62±0.16	13.65±0.38	1.16±0.19
F4	10.05±0.32	29.20±0.16	25.10±0.15	0.34±0.25	0.40±0.09	34.80±0.34	14.04±0.24	1.16±0.06
F5	7.92±0.09	24.52±0.32	21.15±0.13	0.32±0.16	0.37±0.15	32.57±0.62	13.74±0.27	1.16±0.18
F6	7.92±0.13	24.50±0.11	21.00±0.15	0.32±0.24	0.38±0.34	34.26±0.11	14.29±0.29	1.17±0.42
F7	8.15±0.09	25.15±0.25	22.15±0.23	0.32±0.19	0.37±0.17	31.45±0.24	11.93±0.67	1.14±0.35
F8	7.93±0.13	25.15±0.19	20.15±0.31	0.32±0.67	0.39±0.09	40.00±0.32	19.88±0.17	1.25±0.16
F9	8.25±0.16	26.15±0.62	21.25±0.52	0.32±0.24	0.39±0.16	39.45±0.25	18.74±0.37	1.23±0.08
F10	10.32±0.54	29.60±0.15	25.35±0.15	0.35±0.24	0.41±0.09	34.23±0.67	14.36±0.29	1.17±0.13



a) Pure drug cefuroxime axetil**.**



b) Physical mixture of drug and HPMC K15M CR.



c) Optimized selected formulation F9.

Fig. 3 : FT-IR spectra of cefuroxime axetil and excipients.

Table 3 : Pharmaceutical properties of cefuroxime axetil extended release tablet formulations (N=20).

Trial Formulation	Weight (mg)	Thickness (mm)	Length (mm)	Width (mm)	Hardness (kg)	Friability (%)	Assay (%)
Pharmacopoeial Limits (USP 36)	**±5%**	**±5%**	**N/A**	**N/A**	**> 5 kg**	**< 1%**	**90-110%**
F1	799.93±3.26	6.13±0.04	19.43±0.02	9.42±0.02	13.78±1.23	0.73±0.11	103.7±2.05
F2	800.76±5.69	6.13±0.03	19.43±0.02	9.42±0.01	12.84±0.89	0.42±0.27	100.56±0.70
F3	801.40±6.36	6.07±0.04	19.42±0.02	9.42±0.01	11.13±0.88	0.79±0.09	96.97±0.66
F4	800.22±5.22	6.10±0.05	19.42±0.02	9.44±0.02	10.39±0.79	0.52±0.17	97.56±1.20
F5	800.76±3.60	6.10±0.04	19.43±0.02	9.44±0.01	9.70±1.15	0.71±0.14	99.97±0.44
F6	800.54±3.99	6.13±0.03	19.42±0.02	9.41±0.01	13.39±1.09	0.42±0.23	98.13±0.18
F7	799.96±3.03	6.13±0.03	19.43±0.02	9.42±0.01	13.03±0.86	0.68±0.15	96.48±1.98
F8	800.31±4.12	6.07±0.04	19.44±0.02	9.41±0.01	10.02±1.38	0.38±0.18	95.93±0.28
F9	800.34±4.43	6.09±0.05	19.41±0.02	9.41±0.01	10.37±0.85	0.43±0.27	95.77±1.33
F10	800.41±3.69	6.11±0.04	19.42±0.02	9.44±0.01	9.95±1.37	0.63±0.32	95.64±1.33

In vitro drug release studies

The dissolution profile of the developed cefuroxime axetil 250mg extended release formulations (F1-F10) were performed in five different dissolution medium i.e., 0.07N HCl (USP dissolution medium), 0.1N HCl of pH 1.2, phosphate buffers of pH 4.5 and pH 6.8 and distilled water. Previously dissolution properties of stearic acid coated cefuroxime axetil systems were investigated with a view to study the effects of the dissolution medium on both the release rate and the physical integrity of the microspheres[27] and the influence of buffer composition[28].

Formulations F1 and F2 exhibited the least quantity (<40%) of drug release in 0.07N HCl, according to the drug release profile. F3, F4, and F5 were among the other K15M CR formulations that shown good release in 0.07N HCl (46.80%±1.10, 68.90%±0.45, and 87.75%±0.87, respectively). However, in contrast to other dissolution media, distilled water showed a low release profile **(Fig. 4 and 5)**. In comparison to pH 6.8, 4.5, and distilled

water (68.12%±1.39, 68.12%±2.31, and 66.24%±1.02, respectively), F5 with a 10% polymer content showed an excellent release profile in 0.07N HCl and 0.1N HCl (87.75%±0.87 and 80.54%±1.78, respectively).

Singh et al. (2013) provided an explanation of how formulation release rates are affected by varying HPMC K15M concentrations. The release rate falls with a growing concentration[29]. Cefuroxime axetil gastroretentive tablets were made and the role of several polymers, such as Xanthan gum, HPMC K15M, and K4M, was investigated in a different study[30]. Combining 5% K15M CR (F6) and 6% K15M CR (F7) with 2% E50LV produced inconsistent outcomes in all of the dissolution mediums. In 0.07N HCl, the combination showed the highest (>75%) release rate and the lowest drug release, which were 50.63%±0.27 and 60.16%±0.66, respectively, in pH 6.8. In 0.07N HCl, F8 (7%) and F9 (8%) of K15M CR formulations with 2% E50LV demonstrated an improved release profile, 95.52%±1.65 and 96.21%±1.13, respectively, showing more than 85% of drug release in all dissolution mediums. In all dissolving media, the formulation F10 containing 2% E5LV and 8% K15M CR showed more than 80% drug release; in 0.07N HCl, the greatest release profile was 93.92%±0.62 **(Fig. 4 and 5)**. Rahman et al. (2011) used Eudragit L and various viscosity grades of HPMC, such as Methocel® E50LV and K15M CR, to develop sustain-release matrix tablets for ranolazine[31]. Based on HPMC K15M and E5LV polymers, Mohapatra et al. (2012) investigated the formulation development and in vitro evaluation of gastroretentive floating tablets containing cefuroxime axetil[32].

The findings demonstrated that Methocel® K15M CR (F5) at 10% in extended-release formulations exhibited maximal drug release in less than 12 hours. It was discovered that the mixed polymer composition extended-release formulations (F6–F10) were more efficacious and demonstrated the highest drug release across a range of dissolution media. 2009 saw the manufacturing of cefuroxime axetil microcrystals by Nighute and Bhise using HPMC E15LV, which demonstrated the drug's maximum solubility and dissolving rate[33].

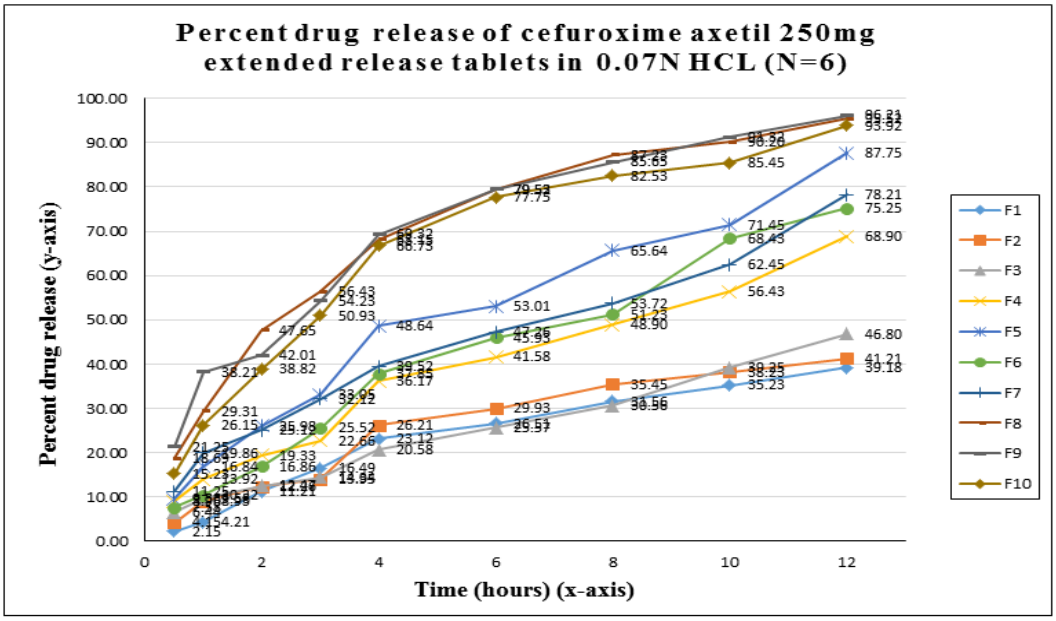


Fig. 4 : In vitro dissolution profile of extended release cefuroxime axetil formulations in 0.07N HCl (USP dissolution medium) (N=6)**.**

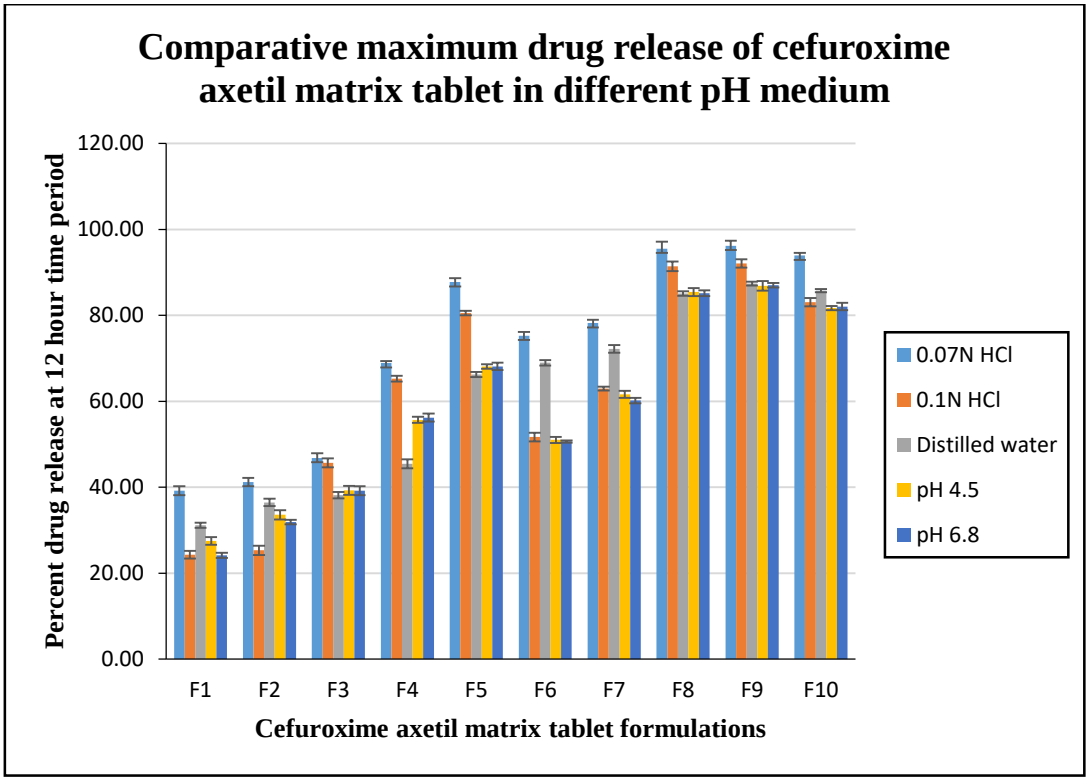
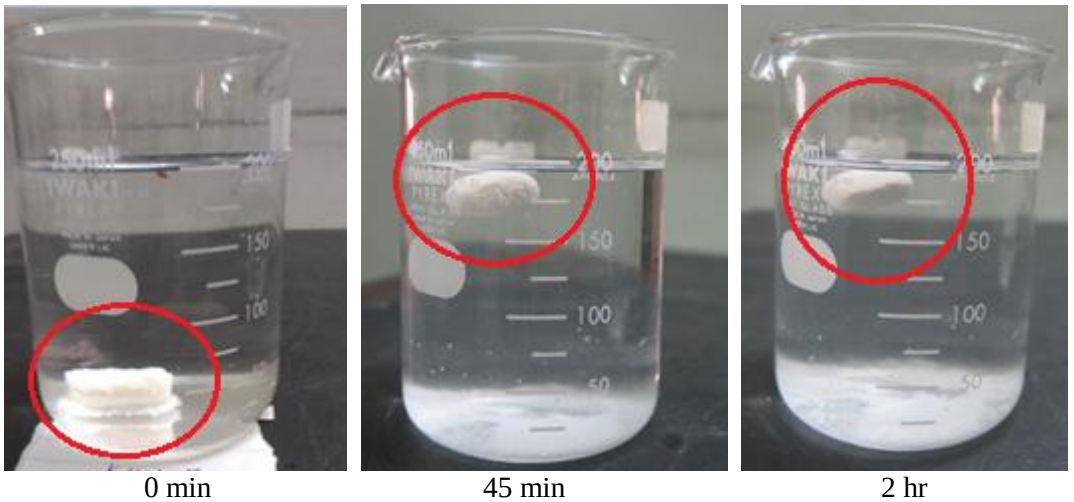


Fig. 5: Comparative maximum drug release of extended release cefuroxime axetil tablet formulations (N=6).

Swelling and In vitro buoyancy studies

In order to guarantee the matrix tablet's lightness and drug dispersion, tablet swelling is also essential[34]. In comparison to F8 (116.05%), F9 (155.0%), and F10 (145.12%) over a 12-hour period, the optimized extended-release formulations F5 with 10% of K15M CR and various combinations of K15M CR with E5LV and E50LV (F8, F9, and F10) demonstrated considerable swelling and strong tablet physical integrity. According to Rao et al. (2013), the gastro-retentive dosage form of cefuroxime axetil with varying K15M concentrations displayed a swelling index of greater than 150%[35]. According to tests on water absorption, formulations containing a high percentage of HPMC swelled more and absorbed more water than formulations containing a low percentage of HPMC. Bouncy studies revealed that formulation F9 showed maximum bouncy time up to 10 hours with floating lag time of 45 minutes without using gas generating agents **(Fig. 6)**. Matrix tablets comprising HPMC K4M and K15M had an improved swelling index with a short buoyant lag time and a total buoyancy time of more than 12 hours, according to Patel et al. in 2009[36].



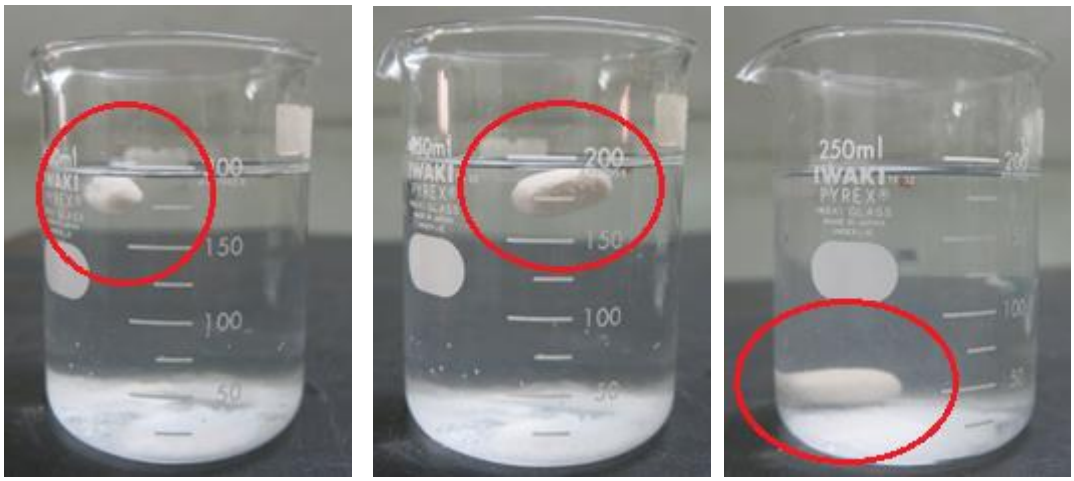


Fig. 6 : In vitro buoyancy study of optimized extended release formulation (F9).

Drug release kinetics

Analysis of variance (ANOVA), model-dependent, and model-independent techniques have been widely employed for the purpose of comparing and ultimately choosing the optimal formulation based on the release pattern. More than 85% of the drug was released in all dissolving media for Formulation F9, which was chosen as a reference for the Dunnett's t-test, f1 and f2 tests, with an adjusted R^2 value that was closest to one[17-19]. A one-way ANOVA ($p = 0.055$) was used to assess the dissolution profile data of the reference (F9) and test formulations (F5, F8, 8, and F10) at each timepoint. The results show no parallelity and a significant difference ($p<0.05$) was found in each dissolving substance. **Table S1** presents the outcomes of the pairwise comparison of test goods and reference products using Dunnett's t-test in 0.07N HCl, which is the post hoc approach. Findings showed that there was no significant difference ($p > 0.05$) between test F8's percent dissolved at 4, 6, 8, 10, and 12 hours and reference F9. Similarly, the release profiles of F8 in distilled water did not differ significantly at 0.5, 1, 3, or 6 hours, but the same results for F8 and F10 were found in other dissolving mediums, such as 0.1N HCl of pH 1.2, at 2 and 10 hours, respectively. The release profiles of all formulations in the pH 4.5 phosphate buffer medium showed a significant difference ($p<0.05$), but formulations F5 and F8 in the pH 6.8 phosphate buffer medium were determined to be non-significant ($p > 0.05$) at the 0.5, 1, 3, and 6 hour time intervals.

The current study found that while the profiles of F5 in 0.1N HCl and F8 in 0.07N HCl, distilled water, and phosphate buffers of pH 4.5 and 6.8, were similar to those of F9, the

extended-release formulations F10 passed both tests with average f1 and f2 values ranging from less than 15 to more than 50 in that order **(Table 4)** utilizing varying amounts of HPMC K4M and K100M polymers, Qazi et al. (2013) created sustained-release matrix tablets containing diltiazem HCl and conducted f1 and f2 tests, utilizing the optimized formulation as a reference formulation[37]. In the same vein, modeling of drug release from hydroxypropyl methyl cellulose drug delivery devices was also described by Siepmann and Peppas in 2001[38].

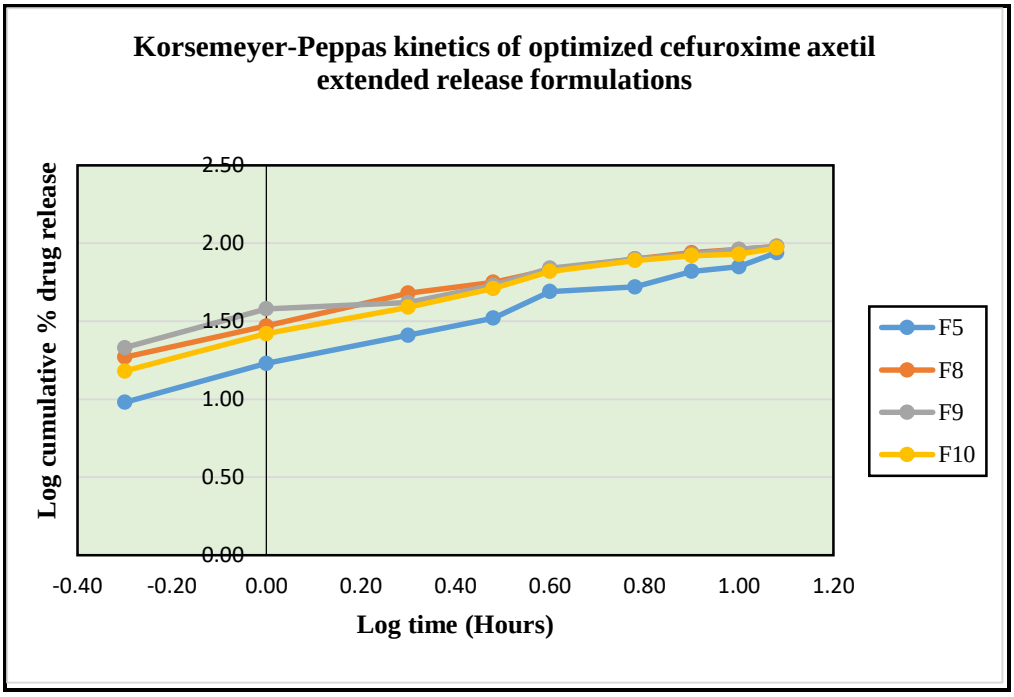
In all dissolving media, the extended release formulations (F1–F10) most closely matched the Higuchi model, the Korsmeyer-Pappas model, the Weibull model, and the closest comparable values to first-order release kinetics. The Weibull model's R2 values were as follows: 0.991-0.998 and 0.985-0.999 at phosphate buffers of pH 4.5 and 6.8, respectively; 0.987-0.999 in distilled water; and 0.971-0.999 and 0.947-0.998 at acidic dissolving mediums of 0.07N HCl and 0.1N HCl, respectively **(Fig. 8)**. Values of β that were closer to 1 or more than 1 had a parabolic curve with a higher beginning slope and a sigmoid-shaped curve. The Weibull model was utilized by Davit et al. (2009) to elucidate the dissolving characteristics of tablets[39]. Non-Fickian diffusion release was demonstrated by Korsmeyer and Pappas values of n that were more than 0.45 in all dissolving media (0.07N HCl n=0.478-0.644, 0.1N HCl n=0.487-0.501, distilled water n=0.510-0.542, phosphate buffer pH 4.5 n=0.584-0.758, phosphate buffer 6.8 medium n=0.493-0.879). In 0.07N HCl, R^2 varied from 0.964-0.987; in 0.1N HCl, 0.887-0.991; in distilled water, 0.972-0.999; and in phosphate buffer of pH 4.5 and 6.8 medium, 0.981-0.997 **(Fig. 7)**. For the cefuroxime-axetil-loaded gastroretentive floating tablets containing K15M and E5LV to optimize the drug release, Mohapatra et al. (2012) reported a n value within 0.49–0.59 that exhibited anomalous transit[32]. According to the Higuchi and Peppas model demonstrating Fickian diffusion, the polymer HPMC K15M had a sustaining impact on the release of cefuroxime axetil in a different investigation[28].

Stability studies

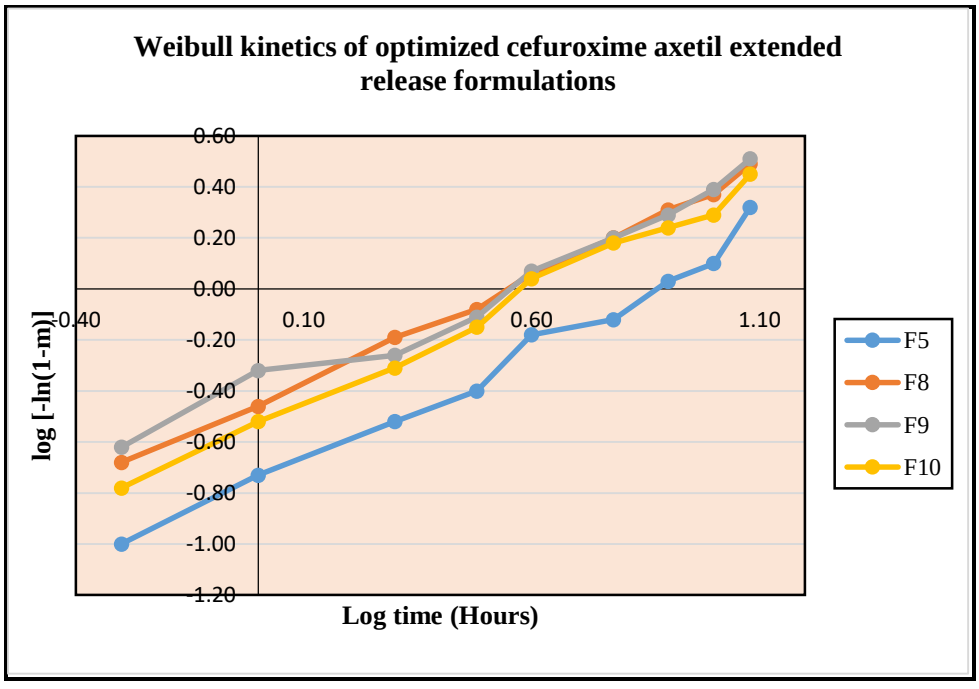
Following ICH recommendations[20], stability experiments were conducted on optimized extended release formulations (F5, F8, F9, and F10) for 12 (25 ºC±5°C) and 6 months (40 ºC±5°C at 75% relative humidity) time periods. Friability, hardness, weight variation, dissolving, and test physicochemical evaluations of adjusted formulations were found to be within pharmacopeial limits, and no changes in color or shape were noted. With a shelf life of 34 months at room temperature and 39 months at accelerated temperature, respectively, prolonged release formulations F9 were found to be the best optimized **(Fig. 8).** Shelf life was evaluated using R Gui® software. Cefuroxime axetil tablet stability was previously investigated using long-term (2 years), intermediate (1 year), and accelerated (6 months) stress stability tests. These tests showed that, in the presence of stress, cefuroxime axetil decomposes according to a first-order reversible autocatalytic reaction[40].

Table 4: In vitro therapeutic assessment of optimized cefuroxime axetil formulations with respect to similarity factor (f_2) and difference factor (f_1)**.**

Comparison	Factor	0.07 N HCl (D.M)	Distilled water	pH 1.2 (0.1N HCl)	pH 4.5 (Phosphate buffer)	pH 6.8 (Phosphate buffer)
F5 vs. F9	***f1***	28.70	18.98	15.29	32.58	39.84
	f2	35.87	43.44	49.53	37.66	33.53
F8 vs. F9	***f1***	0.87	4.79	29.05	3.05	7.22
	f2	70.44	74.29	36.04	78.95	67.08
F10 vs. F9	***f1***	6.96	3.74	3.92	7.47	12.32
	f2	63.03	72.08	49.17	70.12	56.80



(A)



(B)

Fig. 7 : Drug release kinetics of optimized cefuroxime axetil tablet formulations.
(A) Korsmeyer-Pappas Model (B) Weibull Model.

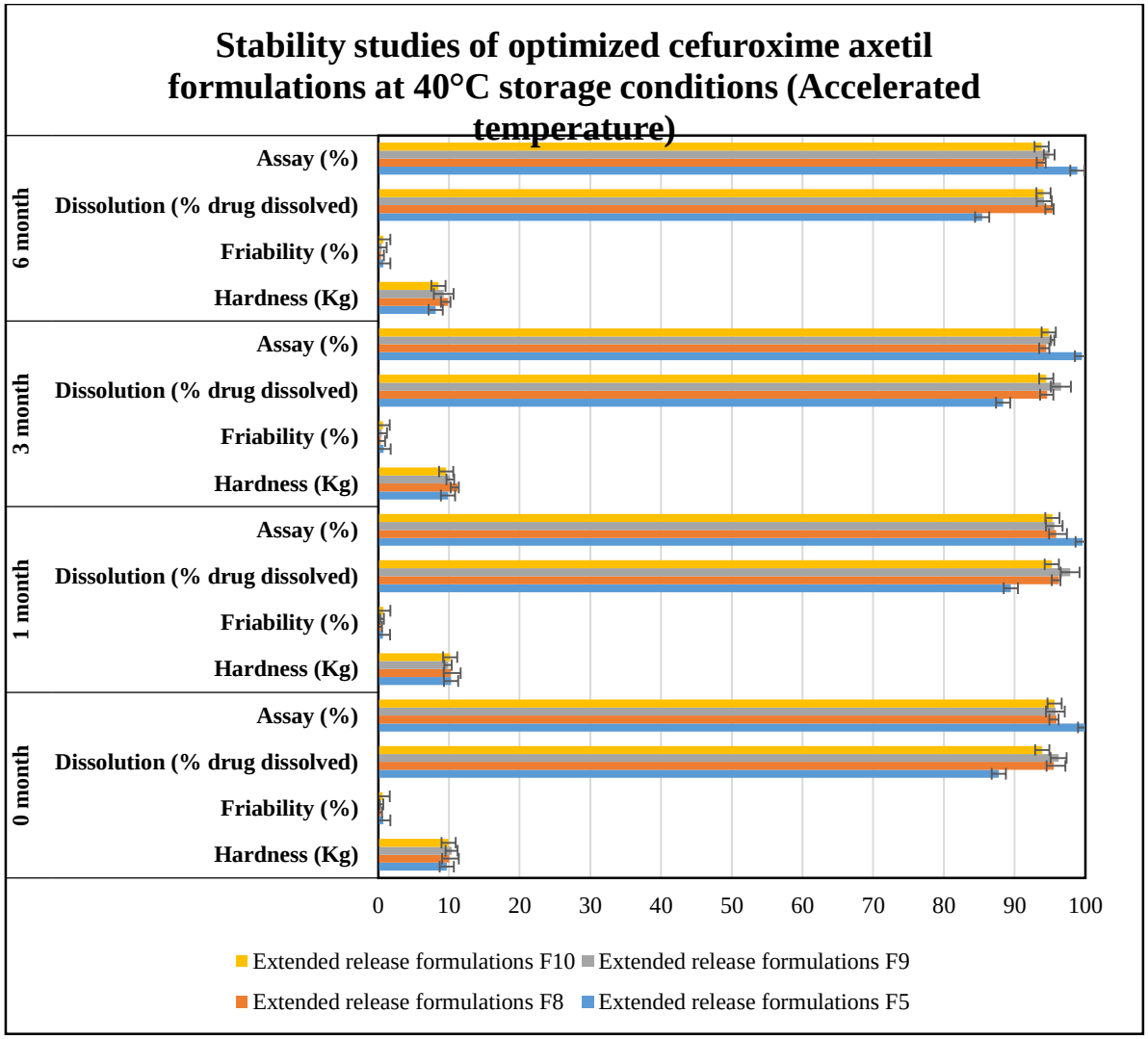


Fig. 8: Stability studies of optimized cefuroxime axetil formulations at 40°C storage conditions (Accelerated temperature).

Conclusion

A cost-effective and stable extended-release cefuroxime axetil tablet that is compatible with both drugs and excipients and has varying quantities of HPMC K15MCR (F1-F10) polymers manufactured via the direct compression method. It was discovered that the E5LV and E50LV combined polymer compositions (F8, F9, and F10), along with the extended-release formulation F5, were more effective. These formulations had maximal drug release (>80%) and a rate of drug release that increased as the polymer fraction decreased. While the generated extended-release formulations best fitted into the Korsmeyer-Peppas equation with the R^2 value closest to one indicated a non-Fickian diffusion mechanism, swelling and stability testing of the chosen optimized formulations produced excellent results.

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Table S1 : 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 0.07N HCl (N=6)**.**

Time (Hours)	(I) Formulations	(J) Formulation	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
0.5	Test 5	Ref 9	-11.685	0.647	0	-14.766	-8.604
	Test 8	Ref 9	-2.558	0.692	0.131	-5.656	0.539
	Test 10	Ref 9	-6.018	0.77	0.001	-9.303	-2.734
1	Test 5	Ref 9	-21.373	0.447	0	-23.294	-19.453
	Test 8	Ref 9	-8.903	0.71	0	-12.292	-5.514
	Test 10	Ref 9	-12.062	0.428	0	-13.887	-10.236
2	Test 5	Ref 9	-16.025	0.79	0	-19.494	-12.556
	Test 8	Ref 9	5.642	0.788	0.002	2.176	9.108
	Test 10	Ref 9	-3.185	0.75	0.071	-6.598	0.228
3	Test 5	Ref 9	-21.183	0.626	0	-23.897	-18.469
	Test 8	Ref 9	2.195	0.634	0.16	-0.541	4.931
	Test 10	Ref 9	-3.3	0.683	0.022	-6.194	-0.406
4	Test 5	Ref 9	-20.685	0.774	0	-24.283	-17.087
	Test 8	Ref 9	-0.173	0.933	1	-4.129	3.782
	Test 10	Ref 9	-2.595	0.797	0.231	-6.205	1.015
6	Test 5	Ref 9	-26.525	0.675	0	-29.554	-23.496
	Test 8	Ref 9	-0.015	0.961	1	-4.144	4.114
	Test 10	Ref 9	-1.782	0.659	0.434	-4.797	1.233
8	Test 5	Ref 9	-20.012	0.617	0	-23.058	-16.965
	Test 8	Ref 9	1.58	0.8	0.815	-1.804	4.964
	Test 10	Ref 9	-3.122	0.732	0.053	-6.275	0.032
10	Test 5	Ref 9	-19.87	0.614	0	-22.489	-17.251
	Test 8	Ref 9	-1.127	0.824	0.986	-4.88	2.627
	Test 10	Ref 9	-5.873	0.413	0	-7.899	-3.847
12	Test 5	Ref 9	-8.462	0.584	0	-10.968	-5.955
	Test 8	Ref 9	-0.692	0.818	1	-4.263	2.879
	Test 10	Ref 9	-2.293	0.528	0.063	-4.688	0.101

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تقييم نظام المصفوفة المحبة للماء على أقراص سيفوروكسيم أكسيتيل المطورة ذات الإطلاق الممتد

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تم في هذا البحث دراسة الصفات الاستثنائية واتساق نظام المصفوفة المحبة للماء (HPMC) كخصائص مميزة لتصميم وتطوير نظام توصيل دوائى . و في ضوء ذلك، تم تصميم عشر تركيبات مختلفة ذات إنطلاق ممتد عن طريق الكبس المباشر والمتكون من هيدروكسي بروبيل ميثيل سلولوز أي Methocel® K15M CR بالاشتراك مع Methocel® E5LV و E50LV مع إضافة عقار السيفالوسبورين الجيل الثاني سيفوروكسيم أكسيتيل بجرعة ٢٥٠ مجم.

وقد تم دراسة الخصائص الفيزيائية والكيميائية لجميع الصياغات المحضرة وذلك تبعا للدساتير والإجراءات المرجعية للأدوية وغير المرجعية. وتم دراسة خصائص إنطلاق الدواء في المختبر في أوساط إذابة مختلفة، شملت محاليل فوسفاتية عازلة بدرجة حموضة ٤,٥ و٦,٨، وحمض هيدروكلوريد ٠,١ نيوتن بدرجة حموضة ١,٢، وحمض هيدروكلوريد ٠,٠٧ نيوتن، وماء مقطر.

و تم اختيار أربع تركيبات، وهي F5 وF8 وF9 وF10، كأفضل تركيبات مُحسّنة، وحُلّلت أنماط ذوبان هذه التركيبات بشكل أعمق باستخدام نموذج قائم على تحليل التباين (ANOVA)، ومنهجيات مستقلة عن النموذج، ومعتمدة عليه، وطُبّقت مادة R Gumi® لتقييم الثبات. وأظهرت النتائج فرقًا كبيرًا ($p < ٠,٠٥$) في إنطلاق الدواء، حيث ازداد مع انخفاض تركيز HPMC من تركيز مرتفع إلى تركيز منخفض، أي من ٣٠% إلى ١٠%.

بالإضافة إلى ذلك، تم الحصول على نمط ممتد الأنطلاق يصل إلى اثنتي عشرة ساعة (<٨٥%) من إنطلاق الدواء في التركيبات التي تحتوي على ١٠% من K15M CR (F5) وحده وبالاشتراك مع بوليمرات E5LV (F8 وE50LV وF9 وF10).

و أظهر تطبيق معادلة كورسمير–بيباس أن R^2 = 0.925 - 0.999 وأفضل ملاءمة لنموذج آلية الإنطلاق المتحكم بها هو الانتشار غير المنتظم مع قيمة n = 0.478-0.879 وذلك يشير إلى درجات اللزوجة العالية للبوليمرات ذات الكسور المنخفضة التي تعرض أنماط إنطلاق ممتدة للدواء.