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RELEASE OF CEFUROXIME AXETIL FROM MATRIX TABLETS – EFFECT OF DIFFERENT HIGH VISCOSITY HYDROXYPROPYL METHYLCELLULOSE POLYMERS ON *IN VITRO* EXTENDED RELEASE

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Keywords:

Cefuroxime Axetil, Extended Release, Methocel®, *in vitro* Dissolution, Stability Studies

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ABSTRACT: Extended release hydrophilic matrix tablet formulations of cefuroxime axetil were developed and evaluated to observe the effect of different high viscosity hydroxypropyl methylcellulose (Methocel® K100M, K100M CR and K100LV CR) polymers on in vitro drug release. Fifteen different formulations (F1-F15) were prepared by direct compression. The results of the physical parameters and assay were found to be within the acceptable range of USP 36/NF 31. In vitro dissolution of each formulation, suitably compressed with 9.50±1.10 to 13.47±1.29 Kg hardness were performed in 0.07N HCl, distilled water, 0.1N HCl of pH 1.2 and phosphate buffers of pH 4.5 and 6.8 to observe the drug release. The drug release was higher with K100 LV CR polymer (F14, F15) as compare to K100M and K100M CR in 0.07N HCl (74.22%±0.69 for F14 and 83.57%±0.71 for F15) and in distilled water medium (65.19%±0.78 for F14 and 79.66%±1.05 for F15). The drug release rate from tablets containing K100LV CR was effectively controlled by decreasing the polymer concentration from 30-10%. Model-dependent method were used for data analysis and the best results were observed for F15 (K100LV CR 10%) in Higuchi (R^2=0.938-0.981), Korsmeyer–Peppas (R^2=0.941-0.982) and Weibull model (R^2=0.978-0.997) with non-Fickian release mechanism (n =0.436-0.553). R Gui® applied for stability studies shows the results of F15 formulation with shelf life 28 and 13 months at ambient and accelerated temperature respectively.

INTRODUCTION: Development of oral extended release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. Specifically, the interest awakened by matrix type delivery is completely justified in view of its biopharmaceutical and pharmacokinetic advantages over the conventional dosage forms [1].

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The drug release from hydrophilic systems involves diffusion, degradation, dissolution and swelling followed by diffusion [2]. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, do not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier which controls the drug release from and the liquid penetration into the center of the matrix system [3].

To achieve extended release through the use of water soluble polymer such as HPMC, the polymer must quickly hydrate on the tablet outer sheet to form a gelatinous layer (Dow, 2000). Hydroxypropyl methylcellulose (HPMC) has been widely used due to its rapid hydration good compression and gelling characteristics along with

its ease of use, availability and very low toxicity [4-6]. Methocel® K100M, Methocel® K100M CR and Methocel® K100LV CR are hydrophilic polymers that become hydrated, swollen and facilitates to diffuse the drug [7, 8]. Cefuroxime axetil is a second generation broad spectrum cephalosporin antibiotic that inhibits bacterial cell wall synthesis like other β–lactam antibiotics [9]. Cefuroxime axetil oral formulations are indicated for the treatment of upper and lower respiratory tract infections, in community acquired pneumonia and urinary tract infections [10, 11]. Short biological half-life i.e. 1.2 hrs and other pharmacokinetic features of cefuroxime axetil make it a potential candidate for extended release dosage form [12].

In the present work an attempt has been made to formulate cefuroxime axetil 250mg extended release matrix tablet with the addition of release retarding polymers Methocel® K100M, Methocel® K100M CR and Methocel® K100LV CR in different ratios. The effect of viscosity grade and polymer loading on drug release were recorded in different pH dissolution medium. Various kinetic models were also used to evaluate the release kinetics and best optimized formulation were further analyzed on long term stability and results were analyzed by freely available R Gui® software.

MATERIALS AND METHODS:

Materials: Cefuroxime axetil USP (Nectar Life Sciences, Ltd. India), 300mg of cefuroxime axetil equivalent to 250mg of cefuroxime. Starch 1500® (Partially pregelatinized starch) and HPMC polymers i.e. Methocel® K100M, Methocel® K100M CR and Methocel® K100LV CR were supplied by Colorcon Ltd., England. Microcrystalline cellulose or Avicel PH 102® (FMC, BioPolymer, Belgium), sodium lauryl sulphate (RdH, Germany) and magnesium stearate (Fischer, UK). All other chemicals used were of analytical grade (Merck, Darmstadt, Germany) and used without further purification. Software adds in program DD solver®, Microsoft Excel 2013® and R Gui® 3.1.3 (R Core Team, 2007-2012. CARN Packages)

Methods:

Preparation of matrix tablets: The amount of cefuroxime axetil, Starch 1500®, sodium lauryl sulphate and magnesium stearate in each matrix tablet were kept constant while the other excipients (HPMC and Avicel PH 102®) and their quantities used for trial formulations are given in **Table 1**. HPMC was used in concentrations ranging from 30-10%. Drug and pharmaceutical excipients accurately weighed as per weight for 100 tablets bulk quantity passed through 40 mesh sieve (ASTM E11, BS-410) and mixed thoroughly together by following geometric dilution method in a suitable size polyethylene bag for 15 minutes then blended with magnesium stearate for another 5 minutes to get a homogenous blend. The powders blend was then compressed directly by single punch compression machine (Korsch: Erweka, Germany) at target weights 800mg (±5) to produce oblong caplet shaped uncoated tablets. Following are the pre-formulation tests performed to assess the physical characteristics of powder blends before compression.

Micromeritic properties of powder blends: Micromeritics tests of blended powders i.e. bulk density (BD), tapped density (TD), angle of repose (α), carr's index (CI) and flow rate were performed by using simple apparatus i.e. measuring cylinder and funnel and determined by following formulas under USP 36/ NF 31, 2013 guidelines[13].

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

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

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

$$HR = TD/BD \quad (4)$$

$$\tan(\alpha) = \text{height} / 0.5 \times \text{base} \quad (5)$$

Pharmaceutical evaluation of tablets: The prepared tablets were evaluated for different parameters like weight variation (Analytical balance: Sartorius, Germany), thickness, length, width variation (Vernier caliper: CD-6, CSX, Mitutoyo, Japan), hardness (Hardness tester: OSK Fujiwara, Japan), friability (Friabilator: Hjurgens GmbH & Co. D2800, Germany) according to the pharmacopeial and non-pharmacopeial methods. Drug content (assay) of tablets was determined according to the standard procedure of USP 36/ NF 31, 2013 [13, 14].

***In vitro* dissolution studies:** Cefuroxime axetil releases patterns were carried out by placing tablets (N=6) in a USP paddle type II dissolution apparatus (Erweka DT, Heusenstamm, Germany) having 900 ml of dissolution medium at 37±0.5°C with rotating at 100 rpm. Different dissolution medium like 0.07N HCl (USP official medium) [13], distilled water, 0.1N HCl of pH 1.2 and phosphate buffers of pH 4.5 and 6.8 were used.

Approximately 10 ml aliquot of each medium was withdrawn at different time intervals compensated with same volume of fresh dissolution medium to maintain total volume. The removed filtered test solution samples were suitably diluted with dissolution medium. Absorbance were recorded using UV/Vis double beam spectrophotometer (1800, Shimadzu, Japan) at 278 nm and dissolution medium served as blank.

Drug release kinetics: The drug release kinetics was studied by plotting the data obtained from the in vitro drug release in various kinetic models like zero order, first order, Higuchi, Korsmeyer and peppas model, Hixson–Crowell model and Weibull model shown in **Table 2** and evaluated by DD solver® software [14, 15].

Stability studies: Stability studies for best selected formulation (F15) under the ICH guidelines [16] (ICH 2003) were performed at controlled room temperature (25ºC±0.5°C at 75% relative humidity) for 12 months and at accelerated (40ºC±0.5°C at 75% relative humidity) temperature in a stability chamber (NuAire, Plymouth, MN 55447, USA) for six months. During which the formulations were tested physically and chemically for quality attributes and the results were analyzed by using R Gui® Software. [17]

TABLE 1: COMPOSITION OF EXTENDED RELEASE CEFUROXIME AXETIL MATRIX TABLET FORMULATIONS

Name of Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	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	300	300	300	300	300
Sodium lauryl sulphate	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Starch 1500®	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Avicel® PH 102	196	236	276	316	356	196	236	276	316	356	196	236	276	316	356
Magnesium stearate	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16
Methocel® K100M	240	200	160	120	80	_	_	_	_	_	_	_	_	_	_
Methocel® K100M CR	_	_	_	_	_	240	200	160	120	80	_	_	_	_	_
Methocel®100LV CR	_	_	_	_	_	_	_	_	_	_	240	200	160	120	80
Total compression weight	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800

*F1= Extended release formulation one (K100M 30%), F2= Extended release formulation two (K100M 25%), F3= Extended release formulation three (K100M 20%), F4= Extended release formulation four (K100M 15%), F5= Extended release formulation five (K100M 10%), F6= Extended release formulation six (K100M CR 30%), F7= Extended release formulation seven (K100M CR 25%), F8= Extended release formulation eight (K100M CR 20%), F9= Extended release formulation nine (K100M CR 15%), F10= Extended release formulation ten (K100M CR 10%), F11= Extended release formulation eleven (K100LV CR 30%), F12= Extended release formulation twelve (K100LV CR 25%), F13= Extended release formulation thirteen (K100LV CR 20%), F14= Extended release formulation fourteen (K100LV CR15%), F15= Extended release formulation fifteen (K100LV CR 10%)

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

TABLE 2: KINETIC MODELS REQUIRED FOR DISSOLUTION PROFILE ANALYSIS

Models	Statistics	Parameters
Zero order*	% dissolved = K_o t	R^2, K_o
First order*	% dissolved = 100 (1 - $e^{-K_1 t}$)	R^2, K_1
Higuchi model*	% dissolved = K_H $t^{0.5}$	R^2, K_H
Korseemyer and Peppas*	% dissolved = K_{KP} t^n	R^2, K_{KP}, n
Hixson – Crowell*	% dissolved = 100 [1- (1- K_{HC} t)^3]	R^2, K_{HC}
Weibull model*	% dissolved = 100 [1 - $e^{(t - Ti)\beta / \alpha}$]	R^2,β

*In all models, % dissolved is fraction of drug released in time t
*K_o is the zero-order release constant
*R^2 is the Regression coefficient
*K_1 is the first-order release constant
*K_H is the Higuchi release constant
*K_{KP} is the release constant incorporating structural and geometric characteristics of the drug-dosage form; n is the diffusional exponent indicating the drug-release mechanism
*K_{HC} is the release constant in Hixson–Crowell model
*α is the scale parameter which defines the time scale of the process; β is the shape parameter which characterizes the curve

RESULTS AND DISCUSSION:

Micromeritics of tablet blends: The extended release tablets of cefuroxime axetil were prepared by direct compression technique. Several studies have shown that HPMC based oral extended release tablets were prepared by direct compression method along with different fillers and binders [18-20]. Blends of each trial formulation (F1-F15) were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose to obtain optimum flow and reproducible tablets with acceptable content uniformity. **Table 3** showed values of bulk densities ranged from 0.27±0.16 to 0.34±0.67 gm/ml, tapped densities 0.31±0.19 to 0.41±0.37 gm/ml, Hausner's ratio 1.13±0.16 to 1.27±0.47, compressibility index 11.54%±0.29 to 21.11%±0.37 and angle of repose 31.49°±0.09 to 41.85°±0.16. These parameters were found within the prescribed limits [13] (USP 36/ NF 31, 2013) and no significant difference was observed between the viscosity grades of HPMC (K100M, K100M CR and K100LV CR).

Similar results were also observed by Mohapatra et al in 2012 [21], who enlighten the effect of HPMC K100M polymer on cefuroxime axetil microbeads flowibility and Badshah et al in 2010 [22], studied the effect of Methocel® K100LV CR on flow properties and compressibility characteristics of olanzapine controlled release matrix tablets.

Pharmaceutical evaluation of tablets: All the batches of HPMC (K100M, K100M CR and K100LV CR) complied with the pharmacopoeial limits of weight, thickness, length and width (**Table 4**). The length and width variation results of developed cefuroxime axetil 250mg extended release formulations (F1-F15) showed a close resemblance (RSD<1%) which is directly related to weight (799.97±3.84 to 802.07±6.86 mg) and thickness (6.07±0.04 to 6.12±0.04 mm) of tablets. Crushing strength (9.50±1.10 to 13.47±1.29 Kg) and friability (<1%) of all the formulations were within acceptable limits indicating that the tablets had the capability to withstand shock and attrition during storage, transportation and consumption [13].

In the present study, the pharmaceutical assay was performed by HPLC (high performance liquid chromatography) to ensure uniformity of the dosage units. All the test formulations had assay and content uniformity within the acceptable limit (RSD<2%) as mentioned in monograph of cefuroxime axetil tablets [13]. This indicates that the blending time selected for test formulations was appropriate and resulted in a uniform random blend [14].

TABLE 3: 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	8.01±0.11	26.30±0.24	23.20±0.08	0.30±0.13	0.35±0.09	32.35±0.27	11.79±0.13	1.13±0.16
F2	8.12±0.09	27.00±0.58	23.00±0.01	0.30±0.11	0.35±0.07	34.15±0.52	14.81±0.17	1.17±0.06
F3	7.94±0.08	25.20±0.15	22.15±0.08	0.32±0.71	0.36±0.84	33.23±0.84	12.10±0.62	1.14±0.07
F4	7.98±0.25	25.00±0.57	21.00±0.27	0.32±0.54	0.38±0.11	36.16±0.32	16.00±0.19	1.19±0.18
F5	8.11±0.47	27.12±0.19	22.00±0.16	0.30±0.14	0.37±0.14	38.21±0.69	18.88±0.87	1.23±0.37
F6	7.92±0.57	24.50±0.24	21.00±0.54	0.32±0.17	0.38±0.23	34.25±0.62	14.29±0.37	1.17±0.24
F7	8.08±0.12	26.10±0.24	23.00±0.17	0.31±0.14	0.35±0.14	31.62±0.11	11.88±0.74	1.13±0.32
F8	10.12±0.24	30.15±0.09	26.00±0.16	0.34±0.67	0.39±0.57	33.52±0.07	13.76±0.23	1.16±0.74
F9	10.06±0.18	29.35±0.74	25.00±0.47	0.34±0.14	0.40±0.32	35.00±0.39	14.82±0.11	1.17±0.15
F10	7.92±0.08	26.00±0.11	23.00±0.17	0.30±0.12	0.34±0.37	31.49±0.09	11.54±0.29	1.13±0.54
F11	10.25±0.08	31.50±0.13	24.85±0.62	0.33±0.21	0.41±0.37	41.85±0.16	21.11±0.37	1.27±0.47
F12	9.50±0.032	30.25±0.62	25.15±0.34	0.31±0.19	0.38±0.16	36.65±0.13	16.86±0.18	1.20±0.37
F13	7.96±0.47	29.50±0.16	25.15±0.67	0.27±0.37	0.32±0.24	34.16±0.17	14.75±0.19	1.17±0.24
F14	8.01±0.12	29.75±0.67	25.80±0.37	0.27±0.16	0.31±0.19	32.45±0.11	13.28±0.27	1.15±0.21
F15	8.05±0.09	30.10±0.17	26.15±0.13	0.27±0.21	0.31±0.21	31.87±0.27	13.12±0.32	1.15±0.22

TABLE 4: PHARMACEUTICAL PROPERTIES OF CEFUROXIME AXETIL EXTENDED RELEASE TABLET FORMULATIONS (N=20)

Trial Formulation	Weight	Thickness	Length	Width	Hardness	Friability	Assay
	(mg)	(mm)	(mm)	(mm)	(kg)	(%)	(%)
Pharmacopoeial limits (USP 36)	**±5%**	**±5%**	**-**	**-**	**> 5 Kg**	**< 1%**	**90-110%**
F1	801.55±6.73	6.10±0.04	19.42±0.02	9.42±0.02	13.05±0.90	0.72±0.13	100.01±0.14
F2	799.80±3.84	6.08±0.04	19.41±0.02	9.44±0.01	12.93±1.01	0.70±0.12	99.18±0.82
F3	800.05±4.83	6.10±0.03	19.43±0.03	9.43±0.02	11.74±0.91	0.57±0.12	100.05±1.60

F4	800.36±5.58	6.08±0.05	19.40±0.01	9.40±0.01	10.14±0.97	0.62±0.19	100.41±1.26
F5	800.03±6.78	6.08±0.04	19.44±0.01	9.41±0.01	9.58±1.00	0.36±0.29	94.82±2.36
F6	801.73±6.14	6.12±0.04	19.43±0.02	9.41±0.01	13.47±1.29	0.84±0.13	102.85±1.95
F7	802.07±6.86	6.12±0.03	19.44±0.02	9.42±0.01	13.21±0.75	0.74±0.07	100.75±0.78
F8	800.21±5.22	6.07±0.04	19.43±0.02	9.42±0.01	10.31±0.72	0.57±0.12	100.69±1.20
F9	799.80±6.66	6.09±0.05	19.42±0.02	9.42±0.01	10.37±0.85	0.48±0.19	98.15±0.79
F10	800.80±5.70	6.10±0.04	19.43±0.02	9.44±0.01	9.95±1.37	0.31±0.07	105.34±3.82
F11	801.34±4.90	6.10±0.03	19.41±0.02	9.43±0.02	13.01±0.94	0.76±0.07	99.27±1.56
F12	799.97±3.84	6.08±0.04	19.41±0.01	9.44±0.01	12.92±1.10	0.84±0.17	101.25±0.87
F13	801.52±3.16	6.10±0.03	19.43±0.03	9.43±0.02	11.72±0.88	0.81±0.17	101.22±0.64
F14	799.80±3.84	6.08±0.05	19.41±0.02	9.40±0.01	10.14±0.97	0.60±0.08	99.77±0.55
F15	799.94±3.82	6.08±0.04	19.42±0.02	9.41±0.01	9.50±1.10	0.61±0.11	101.96±1.48

***In vitro* drug release studies:** An ideal extended release formulation releases the required quantity of drug with predetermined kinetics to maintain effective drug plasma concentration. In the present study dissolution profile of all the formulations in different pH medium gave an insight into the effect of polymer concentration, polymer grades and additives on release profile of the formulations. Cefuroxime axetil is a poorly water soluble drug [23], so that hydrophilic polymer (HPMC) was chosen to develop matrix tablets and extensively used in previous studies [24-26] . From the release profiles, it was observed that the variation in grade of polymer and its concentrations from F1 to F15 had variable effect on drug release.

Effect of HPMC K100M and K100M CR concentration: Formulations with HPMC K100M and K100M CR (F1-F10) showed no promising drug release in all medium (less than 40%) and only F5 with 10% K100M and F10 with 10% K100M CR gives 43.67%±0.95 and 45.21%±0.50 of maximum drug release in 0.07N HCl and 41.75±0.93 and 42.49±0.96 respectively in distilled water within 12 hrs of period (**Fig.1** and **2**). Similarly these formulations give least amount of drug release in 0.1N HCl (24.74±0.84 - 40.58±0.92).

This result indicates that the drug release rate is decreases with increasing the concentration of polymer and also the viscosity of HPMC had effects on tablet erosion and drug diffusion characteristics but high viscosity HPMC K100M and K100M CR had no promising effect on drug release and desired rate at the end of 12 hours is not achieved. Various researchers explained the effect of different concentration of HPMC K100M and K100M CR on drug release from matrix tablet respectively [27, 28]. Ferdous et al., in 2012 [29] reported the use of high to low amount of K100M CR in Gliclazide matrix tablets showed no improvement in drug release. In another study cefuroxime axetil microbeads were prepared by ion gelatin method using HPMC K100M polymer [21] .

Effect of HPMC K100LV CR concentration: Formulations with polymer K100LV CR showed more than 50% of drug release in all dissolution medium. Extended release formulations F11(30%) and F12(25%) with K100LV CR had maximum drug release profile in 0.1N HCl 69.89%±0.92 and 63.80%±0.79 but had low drug release profile in pH 6.8 i.e. 50.02%±0.79 and 50.64%±0.48 respectively. The 20% concentration of polymer in F13 formulation gives high cumulative percent drug release within 12 hrs (66.88%±1.05) in distilled water as compare to 0.07N HCl, 0.1N HCl, pH 6.8 and 4.5 medium (65.56%±1.02, 61.90%±0.84, 54.09%±0.29, 56.56%±1.01 in that order). The formulations containing 15% and 10% concentration of K100LV CR (F14 and F15) found to be more promising formulations as compare to previous one and had maximum drug release in 0.07N HCl i.e. 74.22%±0.69 (F14) and 83.57%±0.71 (F15). Both formulations had low drug release profile in 0.1N HCl i.e. 55.64%±1.01 and 50.20%±0.97 respectively but F15 also had good drug release (79.66%±1.05) in distilled water (**Fig. 1** and **2**).

Islam et al., in 2012 [30] examined the effect of K100LV CR as a single and in combination with Methocel® K15M CR and K4M CR in different percentages. In another analysis different grades of HPMC K100LV were used as extended release polymer to developed sustained release tablets of vildagliptin [31] .

By comparing three different grades of HPMC (K100M, K100M CR and K100LV CR), we concluded that low-viscosity grade and

concentration (15 and 10%) of HPMC K100LV CR provided better release characteristics in different pH medium and increase in molecular weight of HPMC hinder the drug release significantly (**Fig. 3**).

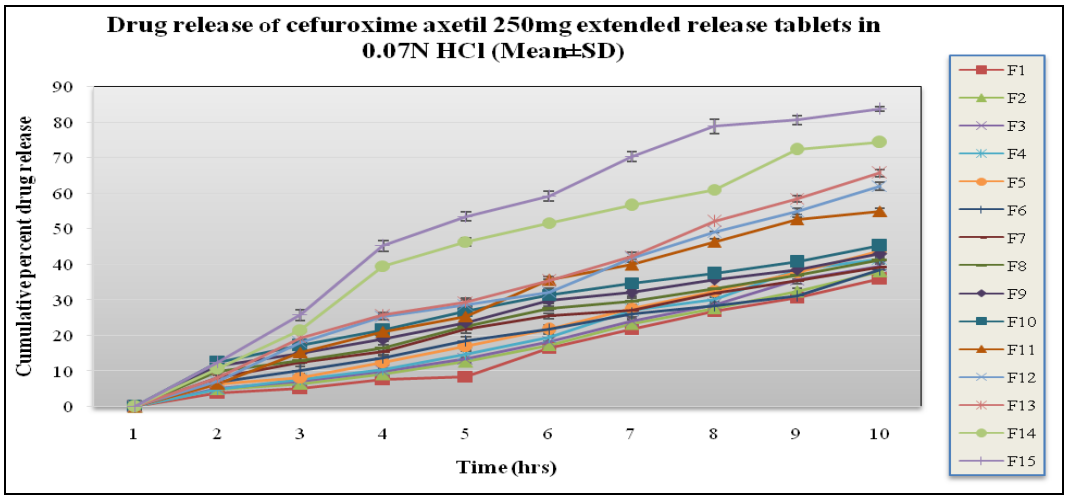

FIG. 1: *IN VITRO* DISSOLUTION PROFILE OF EXTENDED RELEASE CEFUROXIME AXETIL FORMULATIONS IN 0.07N HCl (USP DISSOLUTION MEDIUM) (N=6)

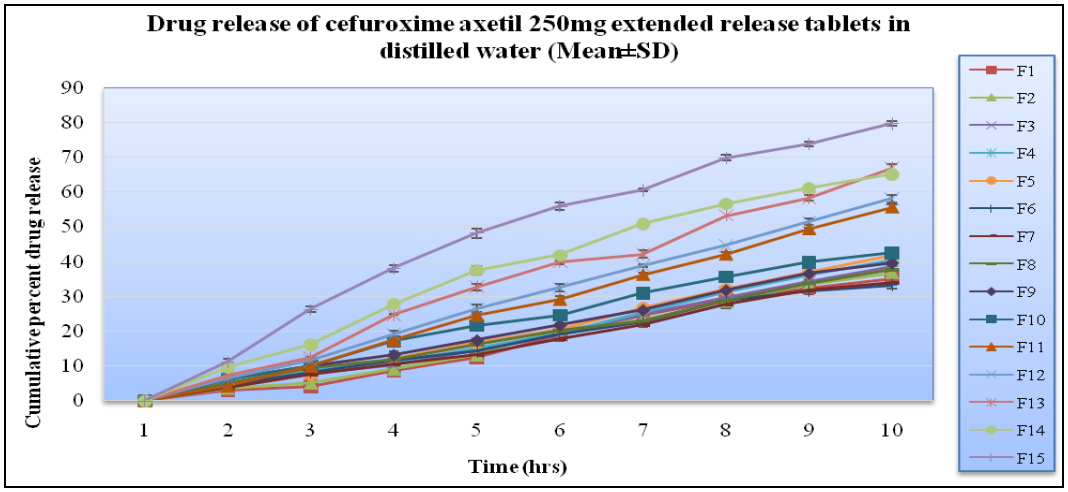

FIG. 2: *IN VITRO* DISSOLUTION PROFILE OF EXTENDED RELEASE CEFUROXIME AXETIL FORMULATIONS IN DISTILLED WATER (N=6)

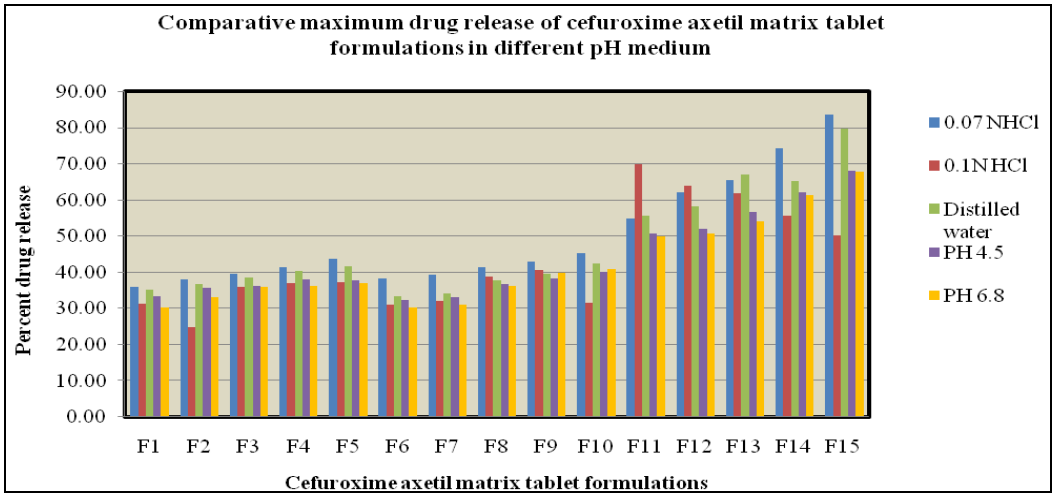

FIG. 3: COMPARATIVE MAXIMUM DRUG RELEASE OF EXTENDED RELEASE CEFUROXIME AXETIL TABLET FORMULATIONS AT 12 HOURS TIME PERIOD IN DIFFERENT PH MEDIUM (N=6)

Drug release kinetics: The dissolution profile data of all test formulations were subjected to statistical model at each time point and decision of the model was based on goodness of fit. The model with the highest determination coefficient i.e. R^2 was chosen as the best fit model [32-34]. Results revealed that regression values of zero order at all pH were more away as compare to first order kinetics.

The extended release formulations F1 to F10 containing different concentrations of K100M and K100MCR (30%-10%) followed Weibull model, Korsmeyer-Pappas model, Higuchi model and also nearest corresponding values to first order in all dissolution medium. The value of R^2 of Weibull model were ranged 0.986-0.998 and 0.967-0.997 in acidic dissolution medium 0.07N HCl and pH 1.2 of 0.1N HCl respectively, 0.993-0.999 and 0.965-0.998 at phosphate buffer of pH 4.5 and 6.8 correspondingly and 0.989-1.000 in distilled water. Values of β were nearest to 1 and sigmoid shape curve was observed. Korsmeyer-Pappas values of *n* were more than 0.45 at all dissolution medium showed non Fickian diffusion release had R^2 ranged 0.977-0.998 in 0.07N HCl, 0.945-0.995 in 0.1N HCl, 0.980-1.000 in distilled water, 0.989-0.996 and 0.968- 0.997 were calculated at phosphate buffer of pH 4.5 and 6.8 medium.

In the present work, value of R^2 of Higuchi model were ranged 0.887-0.985 in 0.07N HCl, 0.713-0.988 in 0.1N HCl, 0.949-0.987 and 0.891-0.980 in pH 4.5 and 6.8, 0.917-0.990 in distilled water. In one study, the in vitro drug release data were analyzed for zero order, first order, Higuchi and Korsmeyer Peppas models and good linear relationship was observed in the case of release retarding polymer HPMC K100M [35]. Ahsan et al in 2011 and Gambhire et al in 2007, studied the effect of Methocel® K100M CR on sustained release matrix tablets and explained the release mechanism with Higuchi and Korsmeyer equation [36, 37] .

Similar findings were observed with different K100LV CR (F11-F15) formulations showed first order, Higuchi, Korsmeyer Pappas, Weibull models. The R^2 values of Korsmeyer and Pappas model in the best optimized formulation of K100LV CR (F15) were found to be 0.952 and 0.982 in 0.07N and 0.1N HCl correspondingly, 0.980 in pH 4.5, 0.941 in pH 6.8 and 0.968 in distilled water. Values of *n* were more than 0.45 in 0.1N HCl, pH 4.5, 6.8 present non Fickian diffusion mechanism, while less than 0.45 at 0.07N HCl and distilled water showed Fickian diffusion release. R^2 values of Weibull model of F15 were 0.997, 0.985 at both acidic dissolution medium, 0.996 and 0.978 in phosphate buffer of pH 4.5 and pH 6.8 respectively, 0.996 in distilled water. In case of Higuchi model the R^2 values were 0.938 and 0.981 in 0.07N HCl and 0.1N HCl, 0.975 and 0.941in pH 4.5 and 6.8, 0.958 in distilled water (**Table 5**). Patel and Patel in 2006 [38] evaluate the contribution of HPMC K4M/ K100LV ratio and sodium lauryl sulfate on cefuroxime axetil release from HPMC matrices. Linear relationships were obtained between the amount of HPMC K100LV and diffusion exponent while dissolution profiles were fitted with the Korsmeyer and Peppas equation. Methocel® K100LV CR was also used to developed controlled release matrix tablets of olanzapine had release mechanism based on release exponent, *n* indicated zero order drug release [22] .

TABLE 5: *IN VITRO* RELEASE KINETICS OF OPTIMIZED CEFUROXIME AXETIL EXTENDED RELEASE FORMULATIONS IN DIFFERENT DISSOLUTION MEDIUM

Formulations	Zero Order		First Order		Higuchi		Korsmeyer Peppas			Hixson-Crowell		Weibull model	
	R^2	K_o (h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H($h^{-1/2}$)	R^2	K_{KP}(h^{-n})	n	R^2	K_{HC}($h^{-1/3}$)	R^2	β
0.07N HCl (USP Dissolution medium)													
F14	0.392	7.721	0.837	0.151	0.945	22.887	0.955	25.489	0.444	0.735	0.041	0.987	0.526
F15	0.343	9.025	0.932	0.219	0.938	26.831	0.952	30.368	0.436	0.843	0.059	0.997	0.609
0.1 N HCl (pH 1.2)													
F14	0.356	5.852	0.710	0.091	0.974	17.330	0.988	19.646	0.435	0.614	0.026	0.992	0.601
F15	0.547	5.170	0.780	0.074	0.981	15.186	0.982	15.736	0.482	0.716	0.022	0.985	0.649
Distilled water													
F14	0.596	6.708	0.888	0.113	0.979	19.694	0.979	19.753	0.498	0.817	0.032	0.998	0.599
F15	0.398	8.263	0.888	0.174	0.958	24.488	0.968	27.232	0.445	0.789	0.047	0.996	0.568
pH 4.5 phosphate buffer													
F14	0.836	5.977	0.965	0.090	0.968	17.213	0.990	13.776	0.614	0.935	0.026	0.997	0.739
F15	0.731	6.709	0.938	0.110	0.975	19.507	0.980	17.606	0.553	0.891	0.031	0.996	0.655
pH 6.8 phosphate buffer													
F14	0.737	6.083	0.922	0.094	0.967	17.680	0.974	15.760	0.559	0.876	0.027	0.991	0.643
F15	0.612	6.876	0.885	0.118	0.941	20.160	0.941	19.636	0.514	0.819	0.033	0.978	0.583

Stability studies: The stability studies of selected optimized extended release formulation F15 (K100LV CR 10%) were performed for 12 (Ambient temperature) and 6 months (Accelerated temperature) evaluation. All the physicochemical tests were within the limit and there was no color, shape, hardness and weight changes observed although drug content and dissolution results were also within pharmacopeial limits (**Table 6**). The stability studies data estimated by R Gui® software shows the shelf life of 28 months at ambient temperature (25ºC±0.5°C at 75% RH), whereas 13 months at accelerated temperature (40ºC±0.5°C at 75% RH).

TABLE 6: STABILITY STUDIES OF OPTIMIZED EXTENDED RELEASE CEFUROXIME AXETIL FORMULATION (F15) AT 25°C AND 40°C STORAGE CONDITIONS (AMBIENT AND ACCELERATED TEMPERATURES)

Stability studies of selected cefuroxime axetil formulation at 25°C storage condition (Room temp.)							
Study Period	**Drug content (%)**	**Weight variation (mg)**	**Hardness (Kg)**	**Friability (%)**	**Dissolution (% drug dissolved)**	**Appearance (color)**	**Shelf life (months)**
At 0 time (pre-storage)	101.96±1.48	799.94±3.82	9.50±1.10	0.61±0.11	83.57±0.71	Off white	28
After 1 month	100.54±0.74	799.14±4.12	10.21±0.27	0.57±0.39	85.19±0.28	Off white	
After 3 month	99.26±0.47	798.13±2.39	9.33±1.16	0.64±0.69	84.00±1.06	Off white	
After 6 month	99.11±0.63	797.85±3.53	8.47±0.17	0.69±0.57	83.69±0.28	Off white	
After 9 month	100.09±0.74	797.11±4.69	8.87±0.47	0.71±0.13	84.19±1.19	Off white	
After 12 month	99.09±1.72	796.52±2.85	8.16±1.29	0.57±0.24	82.16±0.29	Off white	
Stability studies of selected cefuroxime axetil formulation at 40°C storage condition (Accelerated temp.)							
Study Period	**Drug content (%)**	**Weight variation (mg)**	**Hardness (Kg)**	**Friability (%)**	**Dissolution (% drug dissolved)**	**Appearance (color)**	**Shelf life (months)**
At 0 time (pre-storage)	101.96±1.48	799.94±3.82	9.50±1.10	0.61±0.11	83.57±0.71	Off white	13
After 1 month	100.62±0.51	798.79±2.35	9.87±1.64	0.67±0.27	85.27±0.32	Off white	
After 3 month	99.47±0.54	796.84±3.03	9.12±0.42	0.70±0.57	84.29±1.26	Off white	
After 6 month	99.47±0.54	795.23±4.12	8.64±0.74	0.69±1.21	83.54±0.49	Off white	

CONCLUSION: From the data obtained, it can be concluded that the hydrophilic matrix of HPMC K100M and K100MCR tablets failed to control the cefuroxime axetil release effectively for 12 hours even at a low concentration of 10%. Formulated tablets (F1-F15) gave satisfactory results for various physicochemical evaluations like tablet dimensions, hardness, weight variation, friability and drug content. This study suggests that increase in concentration of polymers decreases the percent drug release and matrix tablets prepared with HPMC K100LV CR is better matrix system for extended release of cefuroxime axetil. Formulation F15 (10%) gave better extended drug release in comparison to other formulations in 0.07N HCl and distilled water dissolution medium (>80%) and best fitted to Higuchi (R^2=0.938-0.981), Weibull model (R^2=0.978-0.997) and Korsmeyer–Peppas model (R^2=0.941-0.982) with non-Fickian release mechanism (n=0.436-0.553) and satisfied stability results.

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REFERENCES:

1. Jyothshna DK, Kumar PB, Resddy VB, Sindhuri M, Madhavi P: Formulation and development of multilayer and monolithic extended release matrix tablets of alfuzosin HCl. Asian Journal of Pharmaceutical and Clinical Research. 2013;1(2): 76-79.
2. Keary CM, Sheskey PJ: Preliminary report of the discovery of a new pharmaceutical granulation process using foamed aqueous binders. Drug development and industrial pharmacy. 2004; 30(8): 831-845.
3. Rao N, Raj K, Nayak BS: Review on Matrix Tablet as Sustained Release. International Journal of Pharmaceutical Research & Allied Sciences. 2013; 2(3): 1-17.
4. Ravikumar K, Vinaya O, Santhikrishna U: Development of floating matrix tablets of salbutamol sulphate and study of drug release kinetics. Int J Res Pharm Biomed Sci. 2012; 3: 1346-1354.
5. Huang Y, Khanvilkar KH, Moore AD, Hilliard-Lott M: Effects of manufacturing process variables on in vitro dissolution characteristics of extended-release tablets formulated with hydroxypropyl methylcellulose. Drug development and industrial pharmacy. 2003; 29(1):79-88. doi: doi:10.1081/DDC-120016686
6. Fu XC, Wang GP, Liang WQ, Chow MSS: Prediction of drug release from HPMC matrices: effect of physicochemical properties of drug and polymer concentration. Journal of Controlled Release. 2004; 95(2): 209-216. doi: http://dx.doi.org/10.1016/j.jconrel.2003.11.0
7. McDermott J, Scholes P, Lin W, Connor A: Approaches to rapid in vivo optimization of hydrophilic matrix tablets. Hydrophilic Matrix Tablets for Oral Controlled Release: Springer; 2014. p. 205-232.

8. Sultana S, Halder S, Kabir A, Rouf A: Development and in vitro evaluation of once daily carbamazepine matrix tablet from hydrophilic polymers. International Journal of Pharmaceutical Sciences and Research. 2013; 4(3):1005-1012.
9. Lee YH, Kingston AW, Helmann JD: Glutamate dehydrogenase affects resistance to cell wall antibiotics in Bacillus subtilis. Journal of bacteriology. 2012;194(5): 993-1001.
10. PDR: Concise monograph of Ceftin®(cefuroxime axetil). GlaxoSmithKline . Research Triangle Park: NC 27709, 2014. web page: www.pdr.net
11. Wagenlehner FM, Wullt B, Perletti G: Antimicrobials in urogenital infections. International journal of antimicrobial agents. 2011; 38: 3-10.
12. Israr F, Mahmood ZA, Hassan F, Hasan SMF, Shoaib MH, Yousuf RI, Muhammad IN: Development and in vitro release kinetic studies of extended release cefuroxime axetil matrix tablets based on hydrophilic polymers. Farmacia. 2015; 63(5): 726-738.
13. USP36-NF31: The United States Pharmacopeia Convention, official December. 12601, Twinbrook Parkway, Rockville: MD 20852. 2013.
14. Israr F, Mahmood ZA, Hassan F, Hasan SMF, Jabeen S, Naz S, Bashir L: Formulation design and evaluation of cefuroxime axetil 125 mg immediate release tablets using different concentration of sodium lauryl sulphate as solubility enhancer. Brazilian Journal of Pharmaceutical Sciences. 2014; 50(4): 943-953.
15. Israr F, Mahmood Z, Hassan F, Hasan S: Pharmaceutical evaluation of cefuroxime axetil tablets available in drug market of Pakistan. Indian journal of pharmaceutical sciences. 2016; 78(1): 17-26.
16. ICH Guidelines: ICH Harmonized Tripartite Guideline: Stability testing of new drug substances and products Q1A(R2). International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use. 2003.
17. Khan A, Khan J, Sarwar HS, Hidayatullah K, Riaz A: Stability studies of the optimized oral controlled release verapamil hydrochloride tablet formulations. Int J Pharm, 2015; *5*(1): 80-86.
18. Dokala GK, Pallavi C: Direct compression-an overview. Int J Res Pharm Biomed Sci. 2013; 4(1):155-8.
19. Mirani AG, P Patankar S, S Borole V, S Pawar A, J Kadam V: Direct compression high functionality excipient using coprocessing technique: A brief review. Current drug delivery. 2011; 8(4):426-35.
20. Hashem FM, Shaker DS, Nasr M, Saad IE, Ragaey R: Guar gum and hydroxy propyl methylcellulose compressed coated tablets for colonic drug delivery: in vitro and in vivo evaluation in healthy human volunteers. Drug discoveries & therapeutics. 2011; 5(2): 90-95.
21. Mohapatra DK, Pattanayak D, Nandi S, Senapati P: Design and in vitro evaluation of cefuroxime axetil floating microbeads for the treatment of hospital acquired infection. Int. J.Pharm. Sci. and health care. 2012; 2(2): 36- 51.
22. Badshah A, Subhan F, Rauf, K: Controlled release matrix tablets of olanzapine: influence of polymers on the in vitro release and bioavailability. AAPS PharmSciTech. 2010; 11(3): 1397-1404.
23. Chen H, Khemtong C, Yang X, Chang X, Gao J: Nanonization strategies for poorly water-soluble drugs. Drug discovery today. 2011;16(7): 354-360.
24. Klančar U, Markun B, Baumgartner S, Legen I: A novel beads-based dissolution method for the in vitro evaluation of extended release HPMC matrix tablets and the correlation with the in vivo data. The AAPS journal. 2013;15(1): 267-277.
25. Viridén A, Abrahmsén-Alami S, Wittgren B, Larsson A: Release of theophylline and carbamazepine from matrix tablets – Consequences of HPMC chemical heterogeneity. European Journal of Pharmaceutics and Biopharmaceutics. 2011;78(3):470-9.
26. Tajarobi F, Larsson A, Matic H, Abrahmsén-Alami S: The influence of crystallization inhibition of HPMC and HPMCAS on model substance dissolution and release in swellable matrix tablets. European Journal of Pharmaceutics and Biopharmaceutics. 2011;78(1):125-33.
27. Shanmugam S, Chakrahari R, Sundaramoorthy, K, Ayyappan T, Vetrichelvan T: Formulation and evaluation of sustained release matrix tablets of Losartan potassium. J. Pharm. Tech. Res. 2011; 3: 226-234.
28. Juárezsoberanez D, Villafuerterobles L: Gelucire 39/01 as excipient for gastroretentive metronidazole sustained delivery. Int J Pharm Pharm Sci. 2011;3: 86-91.
29. Ferdous R, Anisuzzaman SM, Paul AK, Khan MS, Begum AA, Kundu SK: In vitro release kinetic study of gliclazide from Methocel K 100 MCR and Methocel K100 LVCR matrix tablets. Int.J. Pharm. Tech Res. 2012; 4(2): 883-888.
30. Islam A, Halder S, Bachar SC: Formulation and in vitro evaluation of betahistine dihydrochloride twice daily controlled release matrix tablet. Dhaka University Journal of Pharmaceutical Sciences. 2012; 10(2): 93-100.
31. Vishnu P, Chaitanya B, Naveenbabu K, Vijayavani CS: Formulation and evaluation of sustained release tablets of vildagliptin. International journal of pharmacy. 2013; 3(3): 587-593.
32. Jannesari M, Varshosaz J, Morshed M, Zamani M: Composite poly (vinyl alcohol)/poly (vinyl acetate) electrospun nanofibrous mats as a novel wound dressing matrix for controlled release of drugs. Int J Nanomedicine. 2011;6:993-1003.
33. Kaunisto E, Marucci M, Borgquist P, Axelsson A: Mechanistic modelling of drug release from polymer-coated and swelling and dissolving polymer matrix systems. International Journal of Pharmaceutics. 2011;418(1):54-77.
34. Costa P, Lobo JMS: Modeling and comparison of dissolution profiles. European journal of pharmaceutical sciences. 2001; 13(2): 123-133.
35. Ige PP, Gattani SG: In vivo radio imaging studies on designed swelling gastro retentive drug delivery system. African Journal of Pharmacy and Pharmacology. 2013; 7(43): 2846-2848.
36. Ahsan MQ, Rahman MM, Jha MK, Ahmed I, Moghal MMR, Rahman MH: Development and in-vitro evaluation of sustained release matrix tablets of salbutamol sulphate using methocel K100M CR polymer. International journal of pharmaceutical sciences and research. 2011; 2(03): 567-576.
37. Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR: Development and in vitro evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. AAPS PharmSciTech. 2007; 8(3): E166-E174.
38. Patel VF, Patel NM: Intragastric floating drug delivery system of cefuroxime axetil: in vitro evaluation. AAPS PharmSciTech. 2006; 7(1): E118-E124.

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