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Formulation and evaluation of bilayered floating tablets of cefuroxime axetil

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ABSTRACT

Study aims to design a Gastro retentive Drug Delivery System of Cefuroxime axetil (CA). CA is a broad spectrum beta lactam type of antibiotic. More specifically, it is a second-generation cephalosporin. CA has site specific absorption from upper gastro intestinal tract and in intestine it undergoes hydrolysis to cefuroxime having poor absorption. Unabsorbed drug causes high concentration of antibiotic entering into colon and contributes to side effects colitis. Therefore a gastro-retentive drug delivery system is required to ensure controlled drug delivery within drug absorbable region. Bilayer tablet, each layer containing half the dose of the drug was formulated with Immediate Release Layer (IRL) and Floating Matrix Layer (FML). The present research describes formulation of bilayered floating tablets of Cefuroxime axetil using HPMC polymers like HPMC K4M, HPMC K15M, HPMC K100M and Sodium alginate. All formulations showed acceptable specifications for weight variation, thickness, hardness and friability. The formulations containing HPMC K4M, HPMC K15M provides a better option for Controlled release than HPMC K100M and Sodium alginate.

Keywords: Cefuroxime axetil, HPMC K4M, HPMC K15M, HPMC K100M, Sodium alginate.

INTRODUCTION

Cefuroxime is a broad-spectrum/ beta lactamase stable, second generation antibiotic with proven record of efficacy and safety in the parenteral management of various infection including urinary tract infections [1]. Since cefuroxime is not absorbed orally, cefuroxime axetil (CA) (1-acetoxyethyl ester of a β-lactamase-stable cephalosporin), an orally absorbed pro-drug of cefuroxime is used in the treatment of common community acquired infections because of its in-vitro antibacterial activity against several gram-positive and gram-negative organisms [2**]**. Cefuroxime is a β-lactam type of antibiotic. More specifically, it is a second-generation cephalosporin [3, 4]. Cephalosporin's work the same way as penicillin's: they interfere with the peptidoglycan synthesis of the bacterial wall by inhibiting the final transpeptidation needed for the cross-links [5]. This effect is bactericidal. Cefuroxime is effective against the following organisms: Aerobic gram-positive microorganisms: *Staphylococcus aureus*, *Streptococcus pneumonia, and Streptococcus pyogenes*. Aerobic gram-negative microorganisms: *Escherichia coli*, *Haemophilus influenza*, *Haemophilus parainfluenzae*, *Klebsiella pneumonia*, *Moraxella c*, *Neisseria gonorrhoeae*, Spirochetes: *Borreliaburgdorferi* [6].

Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [7].

MATERIALS AND METHODS

Materials: The drug Cefuroxime axetil (CA) was received as a gift sample from Covalent Laboratories (Hyderabad, India). HPMC K4M, HPMC K15M, HPMC K100M, SODIUM ALGINATE(SA), Micro crystalline cellulose(MCC), Sodium Bicarbonate(SBC), Citric acid, Cross Carmellose sodium(CCS), Stearic acid were obtained from SD Fine chemicals Mumbai. Methanol and Conc.HCl is of analytical grade.

Standard curve for Cefuroxime axetil: 100 mg of Cefuroxime axetil was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in few ml of methanol (5 ml) and diluted to volume with 0.1 N Hcl to give stock solution 1000 µg/ml. From stock solution suitable dilutions were done, absorbance of solution were measured against 0.1N Hcl as blank at 278 nm using UVSpectrophotometer.

Preparation of Bilayer Tablets with Floating matrix layer: Bilayer tablets contain Floating matrix layer (FML) as a bottom and Immediate release layer as top layer (IRL). IRL contains CA, 150; CCS, 20; MCC, 80; Stearic acid, 5 mg. Ingredients of FML (Table 3) were weighed mixed homogenous and directly compressed [8] in a Rotary tablet machine (Cadmach, Ahmadabad , India) using a 13 mm standard flat face punches. IRL blend poured as top layer in the die containing initially compressed FML and then compressed to produce bilayer tablet.

Evaluation of Powder Blends: [9, 10, 11, 12]

Angle of repose: Angle of Repose of powder was determined by the funnel method. Accurately weigh powder blend were taken in the funnel. Height of the funnel was adjusted in such a way that tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan α= h/r

Bulk density and tapped density: An accurately weighed quantity of the blend **(W)**, was carefully poured into the measuring cylinder and the volume **(V0)** was measured. Then the cylinder was tapped for a fixed time. The minimum volume **(Vf)** occupied in the cylinder was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas

Bulk density = W/ V0

Tapped density = W/ Vf

Compressibility Index / Carr's Index (CI): It was obtained from bulk and tapped densities. It was calculated by using the following formula

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio: Hausner's ratio is a number that is correlated to the flowability of a powder. It is measured by ratio of tapped density to bulk density.

$$\text{Hausner's index} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of Tablets:

Thickness: Thickness of the tablets was determined using a digital vernier callipers.

Weight variation Test: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Drug content (assay): Drug content of the tablets was determined spectrophotometrically.

Hardness: Hardness of the tablets was determined using a Monsanto hardness tester. A tablet hardness of about 3 to 5 kg/cm2 is considered adequate for mechanical stability.

Friability: Friability of the tablets was measured in a friabilator (Roche). 20 tablets were accurately weighed (W0) and placed in friability test apparatus. They were observed for 100 rotations. After 100 rotations they were weighed again (W). The weight loss should not be more than 1% w/w.

$$\%\text{Friability} = (W0-W)/ W0 \times 100$$

Floating properties of tablets: The tablets were placed in a 100 ml glass beaker containing 0.1 N HCl and note Floating Lag Time: The time required for the tablet to rise to the surface of the medium and float was determined as floating lag time and Floating Duration Time: The time for which the tablet remained floating on the surface of medium was determined as floating duration time.

In vitro drug release study [13]**:** In vitro dissolution studies were designed to carry out in such a way that they simulate in vivo conditions. Dissolution was carried out in USP XXIII (Lab India, Mumbai) test apparatus using paddles. 900 ml of 0.1 N HCl was taken as dissolution medium. Dissolution was performed at 37 ± 0.5 ^{0}C with 100 rpm for 12 hours. A specified aliquot was withdrawn at specific intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours) and replaced with fresh dissolution medium of same quantity. Samples were diluted suitably, filtered 0.45µm filter paper and analyzed spectrophotometrically for drug content at 278 nm.

Kinetics of drug release [14]**:** Various models such as Zero order kinetics (cumulative percentage amount of drug release versus time), First order kinetics (log cumulative percentage of drug remaining to release versus time), Higuchi (fraction of drug release, Mt/Mi, versus square root of time) and KorsmeyerPeppas (log fraction of drug released, log Mt/Mi, versus log time) were applied to assess the kinetics of drug release from prepared tablets. Most suited model for drug release was predicted on the basis of regression coefficient i.e. nearer the value of regression coefficient towards 1, greater the suitability of best fitted release mechanism.

RESULTS AND DISCUSSIONS:

Table 1 illustrates the standard curve of Cefuroxime axetil. Table 2 illustrates the composition of Immediate Release Layer. Table 3 illustrates the composition of Floating Matrix Layer. Table 4.1 and 4.2 illustrates the Physical properties of powder blend of all formulations. The physical properties like Compressibility Index, Angle of repose and Hausner ratio were calculated and the values ranged as follows Cars index: 11.2-15.9, Hausner ratio :1.02-1.18, Angle of repose :<30° for all formulations. The results of the physical tests of many of the blends were in the limits and comply with the standards. Table 5 illustrates the physical properties of tablets of all formulations. The total Weight of each formulation was maintained constant ; the weight variation of the tablets were within the permissible limits of 5%, as specified for tablet weighing more than 325 mg . Weight of the tablet was fixed at 600 mg and the weight variation for every batch was tested and found within the acceptance limits. Hardness of the tablet was fixed 4kg/cm^2 and was maintained for all the batches in order to minimize the effect of hardness on the drug release because the effect of polymer concentration is the only area of interest. Tablet thickness was also used to assess the quality to tablets. Under uniform conditions of manufacture, the total weight of tablet and thickness were linearly related. The thickness of floating tablet ranged from 5.01 to 5.06 mm and linearly correlated with the weight of the tablet. Friability test of all the formulation was found satisfactory showing enough resistance to the mechanical shock and abrasion. Drug content uniformity in all formulations was calculated and the percent of active ingredient ranged from 95-98%. Table 6 illustrates the Floating properties of tablets that on immersion in 0.1N Hydrochloric acid media they remain buoyant for 12 h with lag time of 120 to 185 seconds. Sodium bicarbonate was added as a gas-generating agent. The optimized concentration of effervescent mixture utilized aided in the buoyancy of all tablets. This may be due to the fact that effervescent mixture in tablets produced Co2 that was trapped in swollen matrix, thus decreasing the density of the tablet below 1 making the tablets buoyant. Results are shown in table 6. All the batches showed good in vitro buoyancy. Table 7 illustrates the Cumulative percent drug release of formulations with HPMC K4M. In vitro dissolution study of formulations F1, F2, F3 and F4 were done in 0.1NHCL and the percent of drug release from formulations F2, F3and F4 was 97.96, 81.77, 79.05 in 12 h respectively, formulation F1 unable to sustain the drug release in desired period of time but in case of formulation F2, 97.96% of the drug was released in 12h, this was considered due to different polymer concentrations in all the four formulations. All these four formulations floated for 12 h, formulations F3 and F4 failed to drug release profile and floated with a lag time of 120 sec, for these reasons, it was considered as best formulation among all the four formulations. Table 8 illustrates the Cumulative percent drug release of formulations with HPMC K15M. In vitro dissolution study of formulations F5, F6, F7 and F8, prepared with HPMC K15M were done in 0.1N HCI and the percent of drug release from formulations F6, F7, and F8 was 97.65, 93.24 and 85.82 in 12 h respectively. Formulation F5 unable to sustain the drug release in desired period of time. This is because of change in polymer concentrations used in these formulations compared to K4M. Formulations F5, F7 and F8 failed to meet the desired drug release profile. Formulation F6 obtained the desired drug release profile and floated with a lag time of 136 sec, for these reasons it was considered as the best formulation among all the four formulations. Table 9 illustrates the Cumulative percent drug release of formulations with HPMC K100M. In vitro dissolution study of formulations F9 to F12 were also done in 0.1N HCL and the percent drug release was calculated. These four formulations prepared with K100M. The results indicated that higher viscosity grade of polymer concentrations drug release was retarded greatly. Comparing the three different grades of HPMC (K4M, K15M and K 100M), it was found that low-viscosity grade HPMC K4M provided better-sustained release characteristics with excellent drug release and floating lag time. Table 10 illustrates the Cumulative percent drug release of formulations with Sodium alginate. The formulations containing Sodium alginate F12 to F16 did not show promising results, however least lag time was optimized, but the drug release was poor, this is due to the conversion of sodium alginate to alginic acid in the acidic medium (pH 1.2) producing a tough and rubbery texture to the tablet. The drug release was further inhibited by sodium bicarbonate

in the alginate matrices. Table 11 illustrates the Release kinetics of optimized formulations. The mechanism of release for the optimized formulations was determined by finding the R2 value for kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations. For most of the formulations the R2 of Korsmeyer-Peppas and zero-order model is very near to 1 than the R2 value of other kinetic models. Thus it can be said that the drug release follows Korsmeyer-Peppas and zero-order model mechanism. The n values Korsmeyer-Peppas model of the best formulations are in between 0.55-0.85. Therefore the most porable mechanism that the release patterns of the formulations followed was non-fickian diffusion or anomalous diffusion. From this, best formulation from the each polymer (HPMC K4M, K15M) was found to be F2, F6 respectively.

CONCLUSION

Floating bilayered matrix tablets of cephalosporin antibacterial drug cefuroxime axetil was formulated consist of IRL (50% dose) for quick onset of action and FRL (50% dose) for gastro retentive controlled drug release in upper gastrointestinal tract, an approach to increase gastric residence time and thereby improve its bioavailability. Formulation F2, F6 gave better-controlled drug release in comparison to the other formulations. Among the polymers used to improve the gastric residence, cellulose polymers HPMC K4M, HPMC K15M showed control over drug release. The drug release pattern from the optimized formulation was best fitted to Korsmeyer-Peppas model and zero order kinetics.

Table 1: Standard curve of Cefuroxime axetil

Concentration(µg/ml)	Absorbance(nm)
0	0
4	0.182
8	0.326
12	0.466
16	0.622
20	0.793
24	0.940

Table 2: Composition of Immediate Release Layer (IRL)

INGREDIENTS	QUANTITY (mg)
CA	150
MCC	80
CCS	20
Stearic acid	5
	Total=255 mg

Table 3: Composition of Floating Matrix Layer(FML)

CODE	CA	SBC	CITRIC ACID	HPMC K4M	HPMC K15M	HPMC K100M	SA	MCC	STEARIC ACID
F1	150	60	10	65	-	-	-	55	5
F2	150	60	10	75	-	-	-	45	5
F3	150	60	10	85	-	-	-	35	5
F4	150	60	10	95	-	-	-	25	5
F5	150	60	10	-	35	-	-	85	5
F6	150	60	10	-	45	-	-	75	5
F7	150	60	10	-	55	-	-	65	5
F8	150	60	10	-	65	-	-	55	5
F9	150	60	10	-	-	34	-	85	5
F10	150	60	10	-	-	45	-	75	5
F11	150	60	10	-	-	55	-	65	5
F12	150	60	10	-	-	65	-	55	5
F13	150	60	10	-	-	-	40	80	5
F14	150	60	10	-	-	-	50	70	5
F15	150	60	10	-	-	-	60	60	5
F16	150	60	10	-	-	-	70	50	5

*Weight of each tablet equals 600mg.

Table 4.1: Physical properties of powder blend of formulations F1-F8

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Angle of repose	24	26	22	27	28	25	24	23
Compressibility index	11.3	12.6	13.5	14.1	12.5	11.4	12.6	14.4
Hausner's ratio	1.06	1.09	1.11	1.15	1.18	1.17	1.15	1.14

Table 4.2: Physical properties of powder blend of formulations F9-F16

Parameters	F9	F10	F11	F12	F13	F14	F15	F16
Angle of repose	25	26	28	29	25	24	23	22
Compressibility index	11.3	11.8	14.9	15.6	15.5	14.9	14.5	14.7
Hausner's ratio	1.04	1.09	1.14	1.15	1.17	1.14	1.13	1.10

Table 5: Physical properties of tablets of all formulations

Batches	Weight variation(mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content
F1	599.9±7.5	11±0.05	5.033±0.10	4.219±0.33	0.35	95.72±2.3
F2	601.8±7.6	11±0.05	5.028±0.09	4.179±0.34	0.36	98.92±2.6
F3	599.1±7.5	11±0.05	5.033±0.08	4.180±0.35	0.48	96.31.70±2.9
F4	599±7.3	11±0.05	5.045±0.07	4.25±0.32	0.29	96.03±1.4
F5	599.1±7.5	11±0.05	5.031±0.08	4.280±0.31	0.26	99.81±2.4
F6	602±7.4	11±0.05	5.039±0.09	4.282±0.33	0.23	99.63±2.1
F7	598±7.0	11±0.05	5.028±0.09	4.281±0.34	0.33	98.70±2.4
F8	598±7.6	11±0.05	5.023±0.08	4.178±0.35	0.41	98.05±2.4
F9	599±7.2	11±0.05	5.033±0.07	4.179±0.36	0.38	99.00±2.3
F10	598±7.5	11±0.05	5.038±0.08	4.27±0.34	0.41	95.70±2.4
F11	602±7.3	11±0.05	5.039±0.09	4.218±0.33	0.33	97.53±2.4
F12	599±7.4	11±0.05	5.045±0.08	4.223±0.32	0.53	98.09±2.3
F13	601±7.0	11±0.05	5.067±0.09	4.165±0.34	0.33	96.62±2.3
F14	599±7.2	11±0.05	5.032±0.07	4.178±0.34	0.35	98.10±2.2
F15	598±7.1	11±0.05	5.028±0.09	4.199±0.33	0.55	96.00±2.3
F16	597±7.2	11±0.05	5.031±0.09	4.24±0.35	0.38	98.39±2.4

Table 6: Floating properties of tablets

Formulation code	Floating lag time(sec)	Total floating time(hrs)
F1	126	>12
F2	120	>12
F3	130	>12
F4	136	>12
F5	124	>12
F6	136	>12
F7	146	>12
F8	159	>12
F9	161	>12
F10	172	>12
F11	174	>12
F12	180	>12
F13	145	>12
F14	169	>12
F15	179	>12
F16	185	>12

Table 7: Cumulative percent drug release of formulations with HPMC K4 M

Sampling time(hr)	F1	F2	F3	F4
0.5	30.47±1.8	29.28±2.4	30.78±1.2	32.44±2.4
1	36.01±1.3	31.53±2.0	34.67±1.4	33.41±2.4
2	43.86±1.4	35.69±2.2	39.04±1.6	38.33±2.6
3	49.63±1.8	39.2±2.3	44.55±1.7	42.41±2.5
4	55.90±1.6	45.09±2.4	46.29±1.3	45.01±2.4
5	62.60±1.2	49.50±2.5	52.94±1.7	47.63±2.9
6	67.13±1.4	52.20±2.8	58.28±1.6	52.70±2.8
7	71.68±1.4	54.03±2.9	63.49±1.9	55.36±2.4
8	75.54±1.2	66.34±1.9	68.57±1.2	57.23±2.9
9	80.05±1.9	68.62±2.3	72.65±1.6	59.12±2.5
10	98.64±1.8	75.90±2.6	77.22±1.2	65.99±2.7
11	-	90.28±2.4	79.85±1.5	72.89±2.5
12	-	97.96±2.3	81.77±1.6	79.05±2.9

Table 8: Cumulative percent drug release of formulations with HPMC K15 M

Sampling time(hr)	F5	F6	F7	F8
0.5	30.43±3.2	30.07±1.4	29.28±2.2	29.44±1.2
1	36.12±2.9	35.85±1.6	35.68±2.1	35.76±1.1
2	43.86±2.4	43.15±1.8	42.75±2.4	44.09±1.5
3	49.63±2.3	49.15±1.3	48.83±2.5	47.18±1.4
4	55.90±3.0	56.45±1.5	55.65±2.6	49.57±1.8
5	62.60±3.2	63.31±1.9	62.43±2.4	53.31±1.9
6	67.13±2.7	67.68±1.8	66.87±2.5	58.18±1.1
7	71.68±2.8	71.44±1.7	71.10±2.8	64.10±1.4
8	75.54±3.3	77.91±1.6	77.09±2.6	70.21±1.5
9	80.05±2.6	79.99±1.7	79.09±2.7	72.56±1.6
10	98.64±2.7	89.97±1.8	83.62±2.3	80.14±1.5
11	-	96.77±1.9	91.17±2.4	81.20±1.3
12	-	99.65±1.7	93.24±2.9	85.82±1.2

Table 9: Cumulative percent drug release of formulations with HPMC K100M

Sampling time(hr)	F9	F10	F11	F12
0.5	26.92±2.1	27.63±1.2	30±2.3	28.81±1.6
1	28.34±2.6	28.33±1.3	31.5±02.1	31.26±1.4
2	36.78±2.3	34.33±1.4	32.70±2.2	33.01±1.6
3	38.48±1.9	37.76±1.2	33.20±2.2	33.51±1.5
4	41.38±2.5	42.94±1.1	33.93±2.4	34.40±1.7
5	46.26±2.7	44.36±1.3	40.99±2.3	40.59±1.3
6	48.88±2.4	48.70±1.2	42.16±2.1	42.00±1.4
7	51.44±2.7	51.73±1.5	43.25±2.4	43.49±1.3
8	58.35±2.8	54.38±1.7	44.75±2.3	45.85±`1.7
9	59.53±2.4	60.59±1.4	45.78±2.2	46.41±1.5
10	66.88±2.3	63.76±1.5	47.92±2.1	48.08±1.6
11	71.26±2.2	66.00±1.7	56.00±2.3	51.34±1.7
12	73.46±2.6	67.53±1.6	60.08±2.2	52.40±1.4

Table 10: Cumulative percent drug release with Sodium alginate

Sampling time(hr)	F13	F14	F15	F16
0.5	29.91±1.2	29.44±1.2	31.42±2.1	31.02±1.3
1	30.95±1.4	33.18±1.09	33.17±2.2	35.77±1.4
2	32.93±1.6	36.76±1.4	35.25±2.4	38.02±1.2
3	36.90±1.2	41.46±1.2	37.97±2.3	40.13±1.1
4	44.84±1.2	45.16±1.3	41.49±2.2	41.93±1.3
5	49.98±1.1	48.96±1.2	44.72±2.4	46.10±1.2
6	53.33±1.4	52.70±1.1	47.72±2.3	48.25±1.3
7	54.81±1.5	56.93±1.2	50.51±2.1	51.51±1.4
8	58.50±1.6	60.55±1.3	53.78±2.0	55.34±1.3
9	65.13±1.7	64.59±1.2	57.39±2.2	56.98±1.2
10	69.43±1.1	68.02±1.1	60.14±2.4	59.33±1.3
11	71.14±1.3	71.02±1.4	63.78±2.3	62.02±1.4
12	74.13±1.2	72.86±1.2	67.51±2.2	62.59±1.1

Table 11: Release kinetics of optimized formulations

S.No.	Formulation	Zero Order	First Order	Higuchi	Korsmeyer & Peppas	Hixson crowell
1	F2	0.974	0.684	0.898	0.994	0.57
2	F6	0.962	0.503	0.931	0.915	0.75

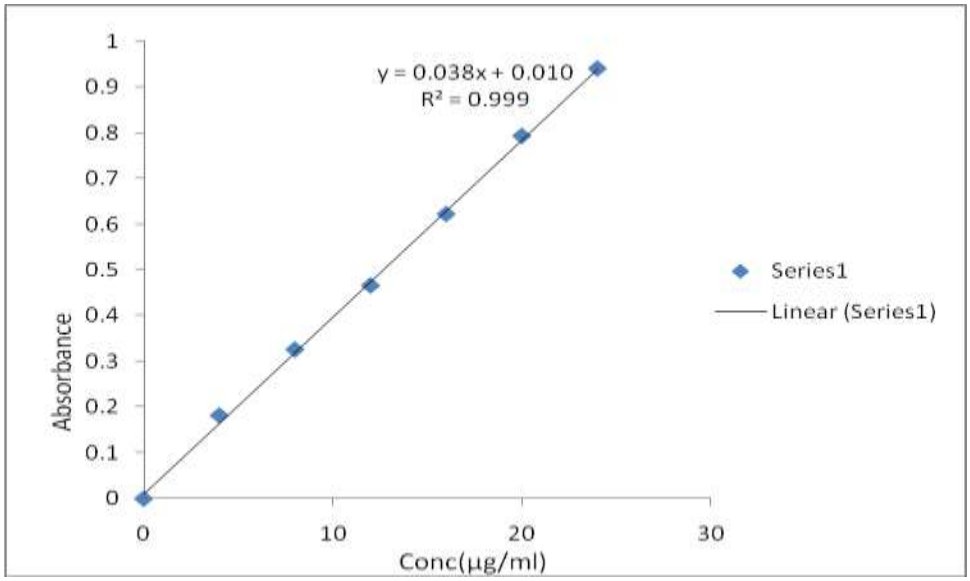

Figure 1: Standard curve of Cefuroxime axetil

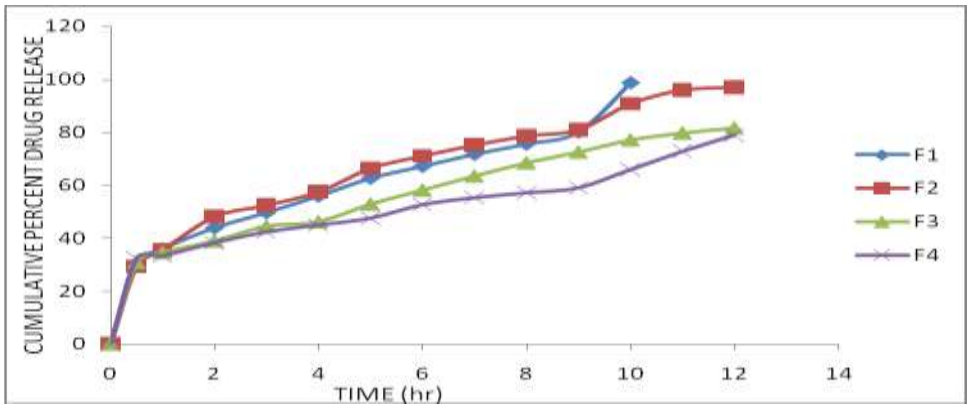

Figure 2: Cumulative percent drug release of HPMC K4M Vs time

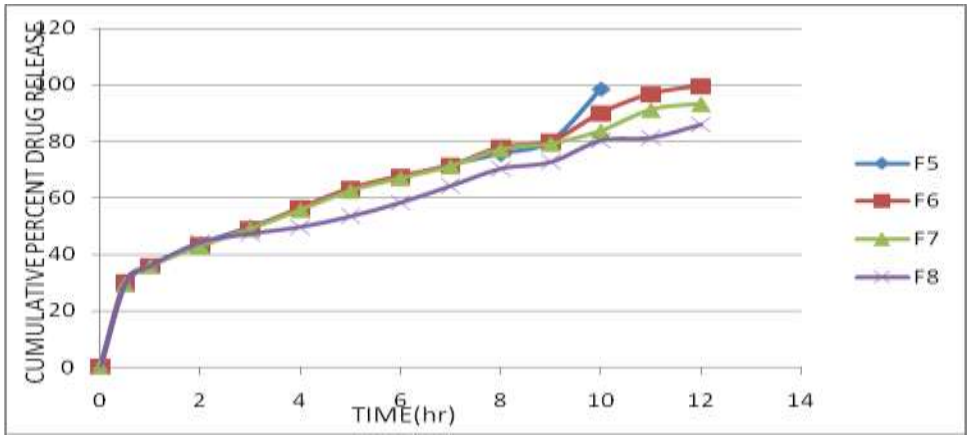

Figure 3: Cumulative percent drug release of HPMC K15M with time

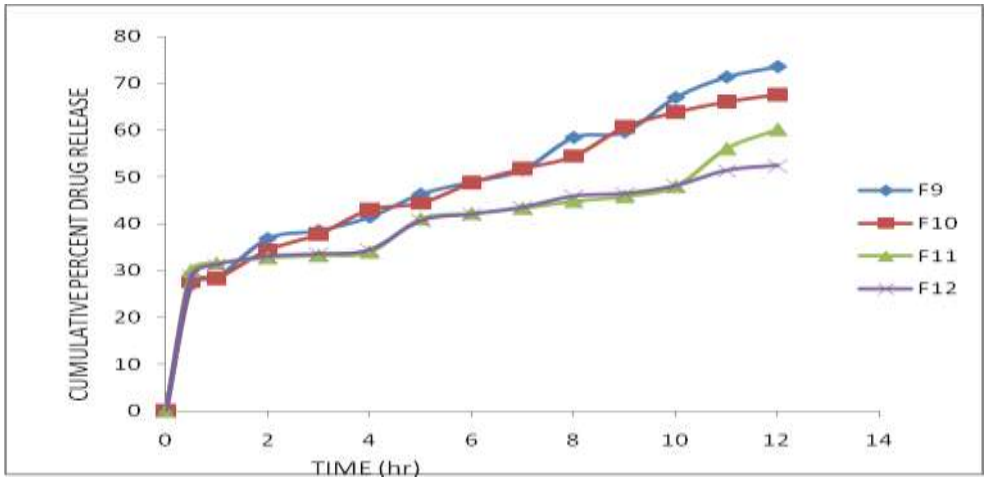

Figure 4: Cumulative percent drug release of HPMC K100M with time

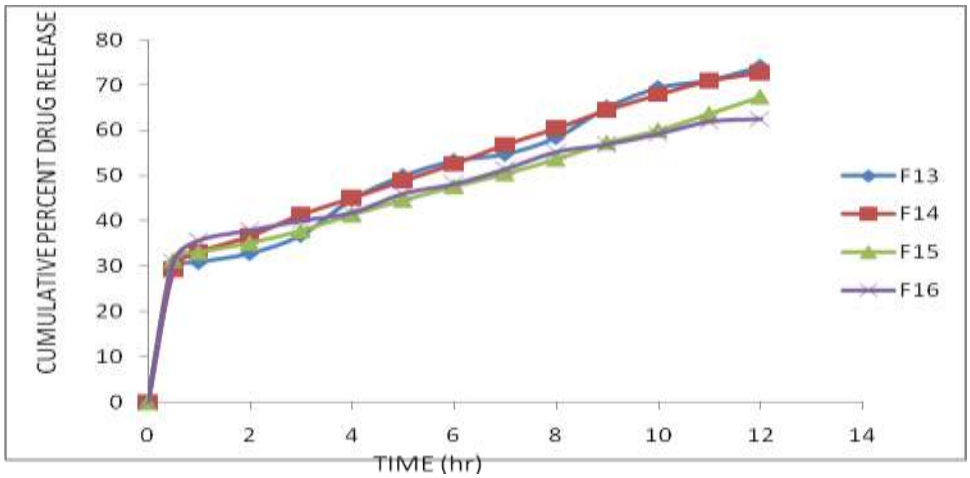

Figure 5: Cumulative percent drug release of Sodium alginate with time

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