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Research Article

DESIGN AND INVITRO ASSESSMENT OF GASTROSELECTIVE BUOYANT TABLETS OF CEFUROXIME AXETIL

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ABSTRACT

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS). GRDDS can improve controlled delivery of drugs with an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring optimal bioavailability. Drugs with a narrow absorption window are mostly associated with improved absorption at the jejunum and ileum due to the enhanced absorption properties of these sites (e.g. large surface area), or because of enhanced solubility in the stomach as opposed to the more distal parts of the GIT. Objective of the present work is to design and evaluate Gastroselective Buoyant Tablets of Cefuroxime axetil. Different formulae were developed by incorporating various polymers.All the developed formulations were subjected to *invitro* dissolution testing and the data was fitted to various exponential equations in order to assess the exact release mechanism. Compatibility among the drug and polymers was checked by subjecting the samples to FTIR and DSC characterization.

Keywords: Cefuroxime axetil, Controlled Release, Dissolution Testing, Floating Lag time.

1. INTRODUCTION

The controlled drug delivery system has been developed to alleviate the shortcomings of conventional formulations. There are many challenges and much excitement to come in the future of controlled DDS[1]. As our knowledge of biology (especially cell biology and DNA) increases, so will our ability to design nano-scale DDS that are serum stable and efficiently taken up by specific cells, then escape the endosome and target specific sites and pathways within the cells. With this increased ability to control the efficiency and specificity of the delivery process, along with increased ability to design potent biomolecular drugs with minimal side effects, the field of controlled DDS will become ever more biological and less material oriented in character. Further, as our understanding continues to increase of which DNA sequences encode for which diseases, and then which sequences in the same individual DNA may be used to predict precise therapeutic regimes for optimum treatment of those diseases in each individual. Such "personalized medicine" will place demands on the drug delivery scientist to be more biologically precise and accurate with our "controlled" delivery systems[2].

2. MATERIALS

Cefuroxime axetil was a generous gift from Dr. Reddy's labs India ltd. Hyderabad, Hydroxypropyl Methylcellulose K4M and Hydroxypropyl Methylcellulose K15M was obtained from ISP Hongkong Ltd as gift samples, Xanthane gum was procured from Dabur India Ltd, Delhi. Microcrystalline cellulose, Talc, Calcium carbonate and Magnesium stearate was purchased from S.D Fime Chem Ltd , India. All other solvents and reagents were of analytical grade.

3. PREFORMULATION STUDIES

During this study experiments were conducted to gather the physical and chemical properties of drug and excipients before going to the formulation development[3]. The following properties of the active ingredient specified are evaluated during preformulation study -a) Bulk Density, b) Tapped Density c) Measures of Powder Compressibility and d) Angle of Repose.

4. DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Cefuroxime axetil was mixed with different proportions with all excipients to be used in formulation in different ratios and kept at 40°c for four weeks**.** The physical properties (colour change) were monitored regularly[4]. The change in colour in any mixture was basis for discarding from study (Table 1).

5. STANDARD GRAPH OF CEFUROXIME AXETIL

The standard graph of Cefuroxime axetil in 0.1N HCl showed a good linearity with R^2 of 0.9997, in the concentration range of 0-30 µg/ml (Fig. 1 & Table 2).

Table 1: Different combinations of API and Excipients for Drug-Excipient compatibility study. (Exposed conditions 40°c)

Formula code	D:E	Initial observation	Week1	Week2	Week3	Week4
Drug alone	----	White powder	NC	NC	NC	NC
Drug +HPMCK15M	1:05	White powder	NC	NC	NC	NC
Drug+HPMCK4M	1:05	White powder	NC	NC	NC	NC
Drug+xanthan gum	1:0.5	White powder	NC	NC	NC	NC
Drug +magnesium stearate	50:01:00	White powder	NC	NC	NC	NC
All physical mixture with drug	----	White powder	NC	NC	NC	NC
Physical mixture with out drug	----	White powder	NC	NC	NC	NC

NC - No color change, **D: E-** Drug: Excipient

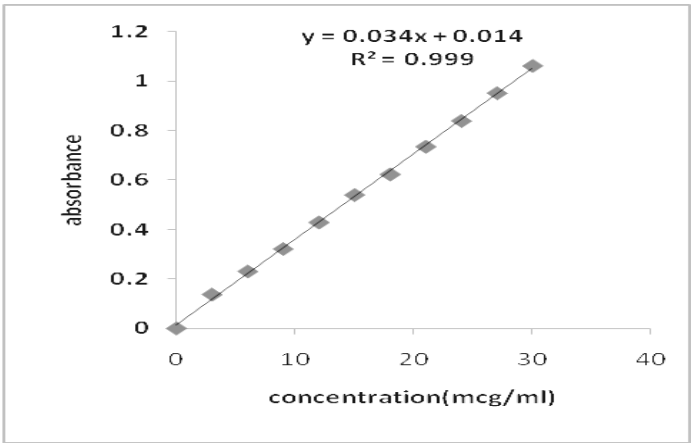

Fig. 1: Standard graph of Cefuroxime axetil in 0.1 N HCl

Table 2: Optical densities against different concentrations

Concentration in µg/ml	Absorbance at 278nm in 0.1N HCl
0	**0**
3	0.137
6	0.230
9	0.321
12	0.428
15	0.539
18	0.622
21	0.734
24	0.838
27	0.950
30	1.125

6. FORMULATION OF FLOATING MATRIX TABLETS OF CEFUROXIME AXETIL

6.1 Preparation of Floating Matrix Tablets of Cefuroxime axetil with HPMC K15M

Accurately weighed quantities of HPMC K15M, Lactose and calcium carbonate were taken in a mortar and mixed geometrically; to this mixture required quantity of cefuroxime axetil was added and mixed slightly with pestle. The powder is passed through sieve no 40 and the whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. This mixture was punched into tablets with caplet shaped punches. The drug and polymer ratio was varied to get Floating tablets of varying polymer concentration (Table 3).

6.2 Preparation of Floating Matrix Tablets of Cefuroxime axetil with HPMC K4M

Accurately weighed quantities of HPMC K4M, Lactose and calcium carbonate were taken in a mortar and mixed geometrically; to this mixture required quantity of cefuroxime axetil was added and mixed slightly with pestle. The powder is passed through sieve no 40 and the whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. This mixture was punched into tablets with caplet shaped punches (Table 4).

6.3 Preparation of Floating Matrix Tablets of Cefuroxime axetil with Xanthan gum

Accurately weighed quantities of xanthan gum, Lactose and calcium carbonate were taken in a mortar and mixed geometrically; to this mixture required quantity of cefuroxime axetil was added and mixed slightly with pestle. The powder is passed through sieve no 40 and the whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. This mixture was punched into tablets with caplet shaped punches (Table 5).

7. EVALUATION OF TABLETS

In addition to routine tests for general appearance, hardness, thickness, friability, drug content, weight variation, uniformity of content and drug release, floating lag time and floating duration time and the *in-vivo* gastro retentive time of GRDDS must be evaluated (Table 6).

Table 3: Composition of tablets formulated with HPMCK15M

Ingredients	Weight in milligrams								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefuroxime axetil	300	300	300	300	300	300	300	300	300
HPMC K 15M	150	75	75	75	75	75	50	40	30
Calcium carbonate	60	60	100	90	90	75	75	75	75
MCC	75	150	104	---	---	---	---	---	---
Lactose	---	---	---	120	108	185	210	220	230
Talc	7.5	7.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Magnesium stearate	7.5	7.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
SLS	---	---	6	---	12	---	---	---	---
Total Tablet Weight	600	600	600	600	600	650	650	650	650

Table 4: Composition of tablets formulated with HPMCK4M

Ingredients	Weight in milligrams						
	F10	F11	F12	F13	F14	F15	F16
Cefuroxime axetil	300	300	300	300	300	300	300
HPMC K4M	75	150	150	150	150	150	120
Calcium carbonate	90	70	75	75	75	75	75
MCC	120	65	55	45.25	---	---	---
Lactose	---	---	55	45.25	97	110	140
Talc	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Magnesiumstearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Sodiumlauryl sulfate	---	---		19.5	13	---	---
Total Tablet Weight	600	600	650	650	650	650	650

Table 5: Composition of tablets formulated with Xanthan Gum

Ingredients	F17	F18	F19	F20	F21	F22
Cefuroxime axetil	300	300	300	300	300	300
HPMC K4M	---	---	---	---	---	---
Xanthan gum	120	100	60	30	30	15
Calcium carbonate	100	75	100	100	100	100
MCC	---	---	---	---	---	---
Lactose	115	160	175	155	205	220
Talc	8.5	8.5	8.5	8.5	8.5	8.5
Magnesium stearate	6.5	6.5	6.5	6.5	6.5	6.5
Sodiumlauryl sulfate	---	---	---	---	---	---
Total tabletweight	650	650	650	600	650	650

Table 6: Physical properties of prepared powder blends

Formulation	CI	Angle of repose	Hausner ratio
F1	12.3	<30°	1.14
F2	15.9	<30°	1.18
F3	12.8	<30°	1.13
F4	15.7	<30°	1.18
F5	12.4	<30°	1.14
F6	11.2	<30°	1.13
F7	13.6	<30°	1.02
F8	12.5	<30°	1.16
F9	14.6	<30°	1.15
F10	12.6	<30°	1.17
F11	12.5	<30°	1.18
F12	11.3	<30°	1.14
F13	11.3	<30°	1.15
F14	15.9	<30°	1.16
F15	12.1	<30°	1.14
F16	15.7	<30°	1.15
F17	11.4	<30°	1.18
F18	11.9	<30°	1.16
F19	12.2	<30°	1.16
F20	12.4	<30°	1.16
F21	14.4	<30°	1.15
F22	12.4	<30°	1.17

All 22 formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacoepial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good. The results of the physical tests of many of the formulations were in the limits and comply with the standards (Table 7).

Floating Properties of Tablets

The *in vitro* buoyancy was determined by floating lag time as per the method described by Rosa et al., 1994. The tablets were placed in a 100 ml glass beaker containing 1.1 N HCl[6].

1. 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.
2. Floating Duration Time: The time for which the tablet remained floating on the surface of medium was determined as floating duration time (Table 8).

Table 7: Physical parameters of the prepared formulations

Formulation	Hardness	Weight Variation	Friability	Drug content
F1	5.0±0.5	605.22±1.21	0.22	98.23
F2	5.30±0.5	610.12±3.45	0.15.	99.65
F3	5.0±0.5	607.80±2.63	0.21	99.12
F4	5.31±0.5	596.09±2.43	0.25	98.44
F5	5.40±0.5	592.05±4.23	0.14	99.23
F6	5.50 ±0.5	652.37±3.45	0.11	98.63
F7	5.50±0.5	653.09±4.63	0.26	99.65
F8	5.50±0.5	663.65±2.12	0.24	98.65
F9	5.51±0.5	654.15±4.75	0.12	98.45
F10	5.54±0.5	664.50±2.52	0.16	99.64
F11	5.70±0.5	651.50±4.39	0.24	98.12
F12	5.60±0.5	655.50±4.35	0.26	99.72
F13	5.0±0.5	661.45±2.12	0.24	97.13
F14	5.50±0.5	658.33±1.45	0.23	99.12
F15	5.40±0.5	655.80±1.63	0.19	98.45
F16	5.60±0.5	665.09±2.43	0.21	98.65
F17	5.50±0.5	654.05±4.51	0.26	99.43
F18	5.55±0.5	652.37±3.89	0.24	97.67
F19	5.40±0.5	659.09±4.12	0.12	98.56
F20	5.40±0.5	645.65±4.20	0.14	99.51
F21	5.20±0.5	654.15±4.61	0.11	99.43
F22	5.55±0.5	643.50±4.39	0.13	98.62

Table 8: Floating properties of prepared formulations

Formulation	Floating Lag Time	Floating Time(Hrs)
F1	30 sec	>12
F2	35 sec	>12
F3	32 sec	>12
F4	45 sec	>12
F5	65 sec	>12
F6	20 sec	>12
F7	28 sec	>12
F8	68 sec	>12
F9	30 sec	>12
F10	44 sec	>12
F11	50 sec	>12
F12	35 sec	>12
F13	30 sec	>12
F14	36 sec	>12
F15	32 sec	>12
F16	55 sec	>12
F17	8 min	>12
F18	5min	>12
F19	10min	>12
F20	8min	>12
F21	5min	>12
F22	10min	>12

Formulations with HPMCK 4M, HPMC K15M were floated within 60 sec, whereas formulations with Xanthan gum were floated in 5-10 minutes.

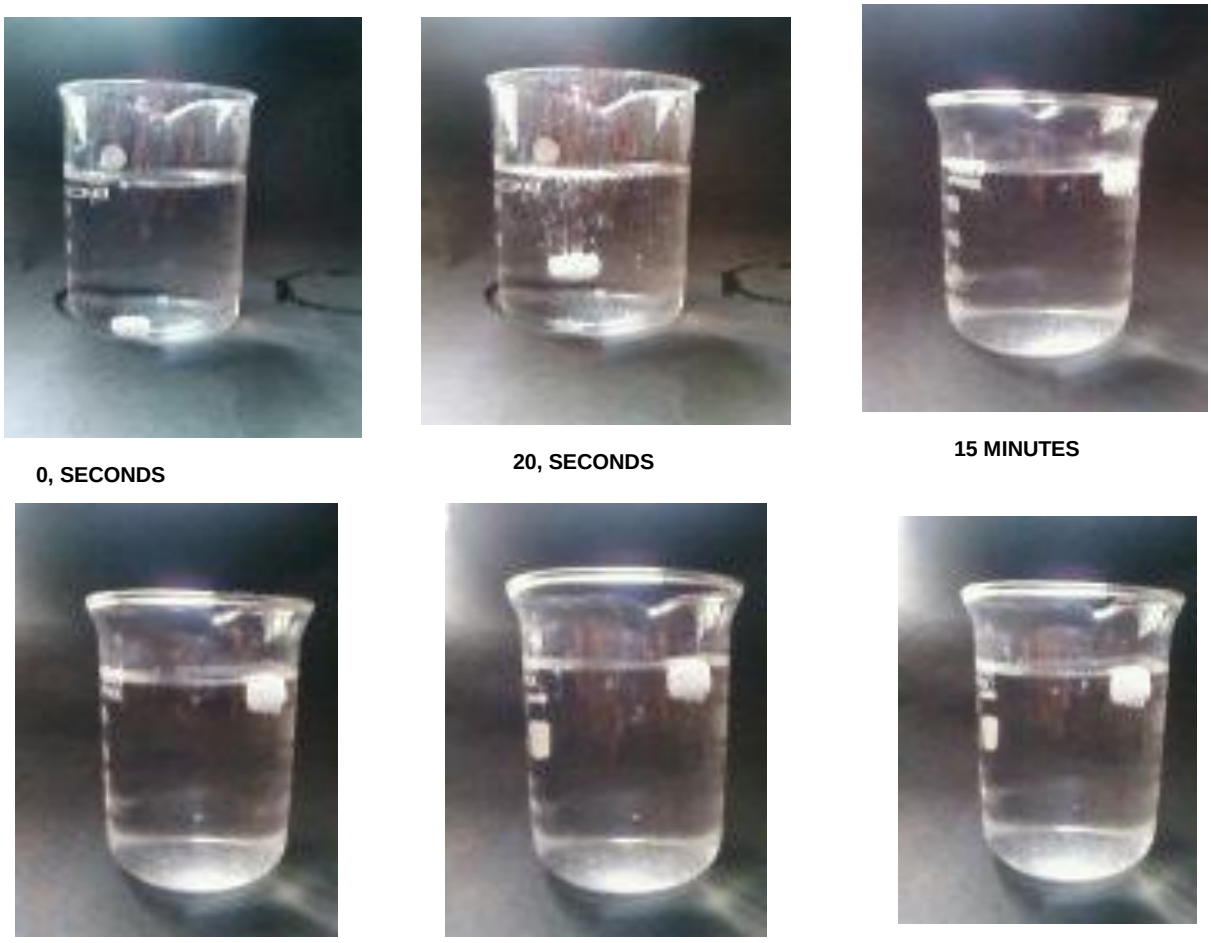

Fig. 2: *In Vitro* Buoyancy Study of Cefuroxime Axetil Floating Tablets

8. *IN – VITRO* DRUG RELEASE STUDIES:

The dissolution conditions used for studying the drug release from the matrix tablets of cefuroxime axetil are:

Apparatus : USP Type 2 (paddle)
Agitation speed (rpm) : 50
Medium : 1.2 pH HCL, 900ml
Temperature : 37.0 ± 0.5 C
Time : 0.5, 1, 2, 3, 4, 6, 8, 10, and 12hr
Wavelength : 278 nm

The samples were withdrawn at predetermined time points, diluted 10 times and were analyzed spectrophotometrically at 278 nm[9].

Table 9: Release Profile of Cefuroxime Axetil Tablets Prepared With HPMC K15 M

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	1.37	15.35	13.42	11.22	10.16	10.54	18.52	11.78	99.58
1	1.90	20.64	17.25	17.68	15.24	12.15	22.97	14.08	
2	4.65	23.08	22.02	19.16	18.31	17.34	27.63	21.07	
3	5.61	25.20	23.50	23.61	19.90	20.36	33.24	25.30	
4	6.14	27.10	26.78	27.63	22.12	25.12	37.69	38.22	
6	8.57	28.69	29.75	34.30	26.04	30.12	47.96	45.52	
8	16.20	36.21	32.92	41.08	28.48	38.45	56.32	62.68	
10	18.86	41.08	36.74	49.23	30.81	41.29	62.15	67.65	
12	21.81	41.61	41.08	57.81	35.15	47.36	73.27	75.17	

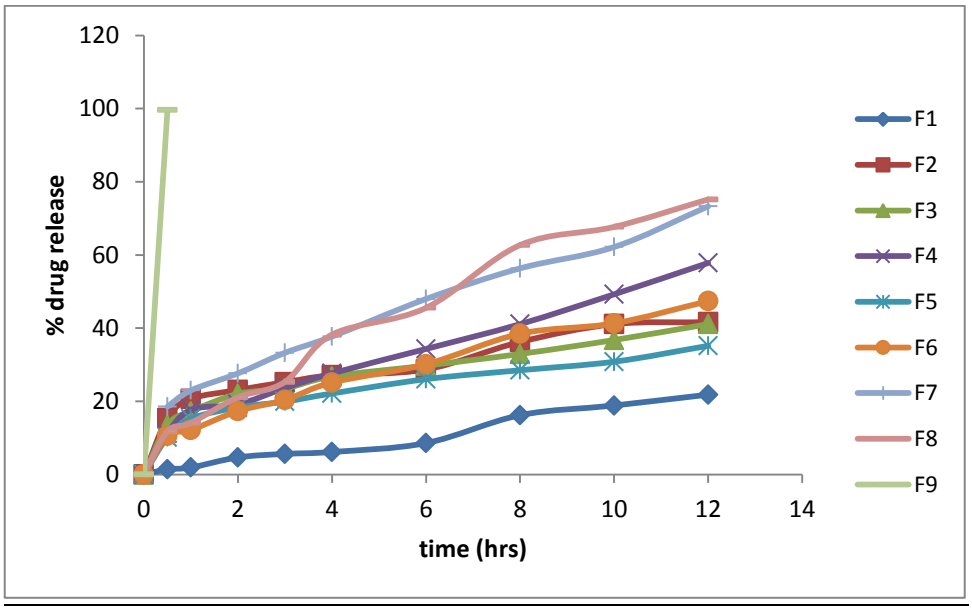

Fig. 3: Drug release profile of Cefuroxime axetil floating tablets with HPMC K15M polymer

Table 10: Drug Release Profile of Cefuroxime Axetil tablets Prepared with HPMCK4M

Time (hrs)	F10	F11	F12	F13	F14	F15	F16
0.5	31.55	24.56	36.84	39.91	31.34	40.44	38.45
1	54.95	31.44	42.35	44.25	39.70	48.81	42.86
2	67.02	36.56	49.76	48.62	48.64	53.04	48.70
3	78.35	42.45	54.10	52.94	53.78	57.38	57.28
4	91.27	45.74	60.24	56.43	56.43	61.62	63.42
6	99.10	51.14	65.64	61.25	63.42	65.22	70.09
8		57.81	70.72	67.55	68.82	78.45	78.56
10		64.27	76.23	73.90	72.10	80.25	91.05
12		72.95	81.52	83.75	80.04	85.44	98.68

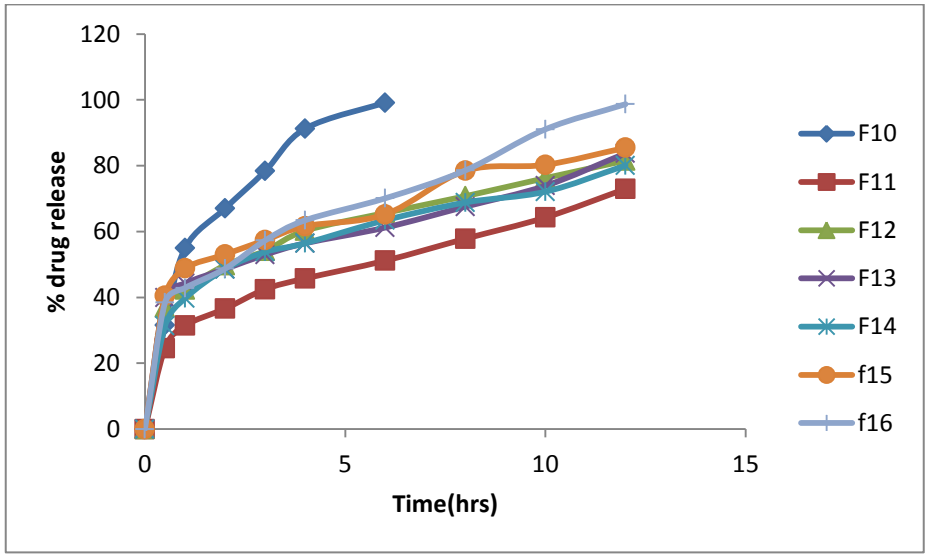

Fig. 4 Drug release profile of cefuroxime axetil floating tablets with HPMC K4M polymer

From the results, it is observed that though the polymer HPMC K4M has sustaining effect on the release of drug from the floating matrix tablets, but the increasing concentration of the same polymer in the formulation retards the release of cefuroxime axetil from the tablet. The formulationsF11, F12, F13, F14 had a release of drug less than 80% in 12 hrs. Whereas formulation F10 releases the drug 99% within 6 hrs only. Formulation F16 releases the 99% drug up to 12 hrs.

Table 11: Drug Release Profile of Cefuroxime Axetil Floating Tablets with Xanthan Gum Polymer

Time(hrs)	F17	F18	F19	F20	F21	F22
0.5	9.65	10.68	12.75	15.67	20.65	11.23
1	10.56	12.75	18.15	22.69	24.56	15.88
2	11.75	14.68	21.02	26.14	37.90	23.29
3	12.56	15.23	25.69	28.54	38.67	25.12
4	14.23	17.36	28.64	32.15	39.81	28.48
6	15.69	21.64	32.45	39.78	44.57	34.51
8	18.56	23.56	36.25	43.15	45.63	49.96
10	20.36	26.14	40.23	45.36	54.12	55.15
12	23.71	28.05	43.94	51.35	58.97	63.31

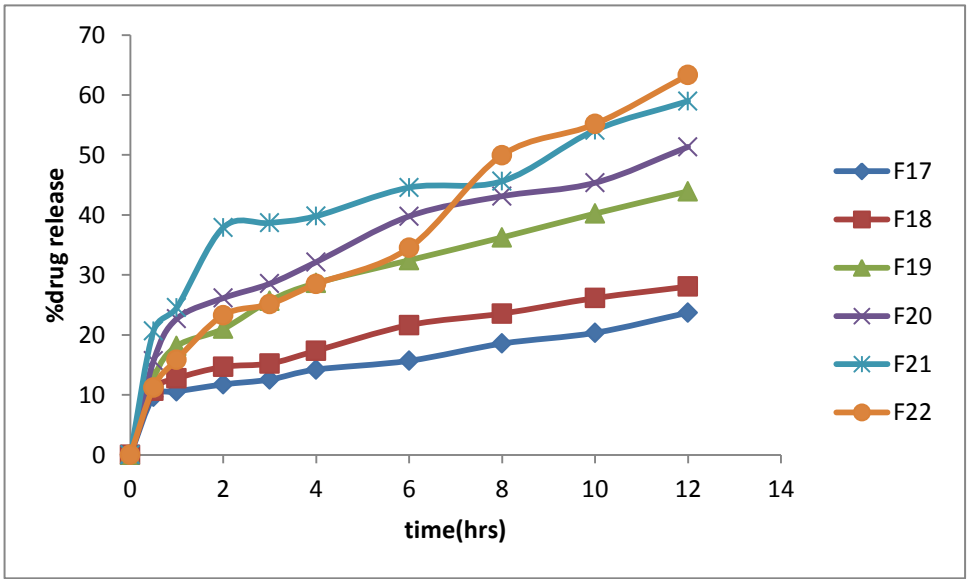

Fig. 5: Drug Release Profile of Cefuroxime Axetil Floating Tablets with Xanthan Gum Polymer

From the results tabulated, it is observed that though the polymer xanthan gum has sustaining effect on the release of drug from the floating matrix tablets, but the increasing concentration of the same polymer in the formulation retards the release of cefuroxime axetil from the tablet. The release of drug from the all formulations was less than 65% in 12 hrs

9. RELEASE KINETICS

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model dependent approach, the dissolution data was fitted to five popular release models such as Zero order, First order, Diffusion and exponential equations[10]. The order of drug release from matrix systems was described by using zero order or first order kinetics. The mechanism of drug release from matrix systems was studied by using higuchi, erosion equation and peppas-korsemeyer equation[11].

Table 12: Correlation coefficients (R^2) values of different kinetic models

Formulation	R^2 Values				Peppas (n) Value
	Zero order	First order	Higuchi	Erosion	
F1	0.975	0.89	0.933	0.968	0.952
F2	0.926	0.914	0.951	0.924	0.297
F3	0.962	0.877	0.989	0.985	0.333
F4	0.993	0.924	0.961	0.946	0.495
F5	0.95	0.841	0.99	0.981	0.329
F6	0.987	0.914	0.992	0.994	0.261
F7	0.995	0.971	0.981	0.977	0.464
F8	0.975	0.897	0.983	0.986	0.705
F9	0.985	0.845	0.986	0.987	0.367
F10	0.883	0.762	0.98	0.986	0.344
F11	0.976	0.909	0.984	0.975	0.332
F12	0.952	0.893	0.996	0.994	0.261
F13	0.988	0.968	0.969	0.945	0.245
F14	0.923	0.836	0.991	0.993	0.266
F15	0.958	0.914	0.974	0.949	0.234
F16	0.913	0.866	0.968	0.975	0.261
F17	0.994	0.98	0.959	0.933	0.32
F18	0.981	0.94	0.983	0.956	0.334
F19	0.955	0.854	0.996	0.989	0.362
F20	0.952	0.861	0.986	0.972	0.336
F21	0.866	0.764	0.906	0.909	0.287
F22	0.986	0.873	0.959	0.962	0.551

CONCLUSION

Gastroretentive floating matrix tablets of cefuroxime axetil were successfully prepared with hydrophilic polymers like HPMC K4M, HPMC K15M. From the in vitro dissolution analysis it was observed that the increasing concentration of polymers had a retarding effect on the drug release from the polymer matrices. The present study suggests possible *invivo* evaluation for assessment of various Pharmacokinetic parameters.

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REFERENCES

1. Garg R and Gupta GD. Progress in Controlled Gastroretentive Delivery Systems. TJPR. 2008;7(3):1055-1066.
2. Allan S. Hoffman. The Origins and Evolution of Controlled Drug Delivery Systems. Journal of Controlled Release. 2008;132:153-163.
3. Shweta Arora, Javed Ali, Alka Ahuja, Roop K Khar and Sanjula Baboota. Floating Drug Delivery Systems: A Review. AAPS Pharma SciTech. 2005;6(3):E372-E386.
4. Sungwon Kim, Jong Ho-Kim, Oju Jeon, Ick Chan Kwon and Kinam Park. Engineered Polymers for Advanced Drug Delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2009;71:420-422.
5. Dhumal Ravindra S, Rajmane Samit Kumar T, Dhumal Sanjay T and Pawar Atmaram P. Design and Evaluation of Bilayer Floating Tablets of Cefuroxime axetil for bimodal release. Journal of Scientific & Industrial Research. 2006:812-816.
6. Stanley. S. Davis. Formulation strategies for absorption windows. Drug Discovery Today. 2005;10(4):249-257.
7. Hwang. SJ, Park H and Park K. Gastric retentive drug delivery systems. Crit Rev Ther Drug Carrier Syst. 1998;15:243–284.
8. Mahesh. D. Chavanpatil, Paras jain, sachin chaudhari, Rajesh shear and Pradeep R. Vavia. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int J of Pharmaceutics. 2006;316:86-92.
9. Bardonnet PL. Faivre V, Pugh WJ, Piffaretti JC and Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. Journal of Controlled Release. 2006;111:1 – 18.
10. Basak SC et al. Development and invitro evaluation of an oral floating matrix tablet

formulation of ciprofloxacin. Indian J Pharm Sci. 2000;63(3):313-316.
11. Krogel I and Bodmeier R. Floating or pulsating drug delivery systems based on coated on effervescent cores. International Journal of Pharmaceutics. 1999;187:175-184.