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R E S E A R C H A R T I C L E

Formulation and *In-vitro* Evaluation of Floating Drug Delivery System for Flucloxacillin

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A B S T R A C T

In the present research work gastro retentive floating matrix formulation of Flucloxacillin by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various pre-formulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. The formulations prepared with Chitosanretarded the drug release up to 12 hours in the concentration of45 mg (F9).The formulations prepared with Guar gum were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

Keywords: Flucloxacillin, Guar gum and gastro retentive Floating tablets.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Flucloxacillinmagnesiumisanisoxazolylpenicillincontaining ß-lactam group of antibiotic which shows a bactericidal effect upon many gram positive organisms including ß-lactamase producing staphylococci and streptococci (1). Flucloxacillin magnesium is stable in acidic medium and not inactivated by staphylococcal ß-lactamases. The mechanism of action is by interfering with bacterial cell wall synthesis by targeting Penicillin Binding Protein (PBP). Flucloxacillin is effective in the treatment of infections caused by penicillin-resistant staphylococci, which is the sole indication for its use because other penicillins like benzyl penicillin are not resistant to staphylococci producing penicillinase or β-lactamases. Flucloxacillin is not inactivated by staphylococci-producing penicillinases and it is used for the treatment to skin and soft tissue infections and respiratory tract infections.

2. Materials and Methods

Flucloxacillin, Microcrystalline cellulose, Chitosan, Guar gum, Sodium CMC, Magnesium stearate, HPMC K4M, HPMC K15M , HPMC K 100M,Di sodium glycine carbonate, Talc all the chemicals were laboratory grade.

Formulation Development of Tablets:

All the formulations were prepared by direct compression. The compressions of different formulations are given in Table 1.The tablets were prepared as per the procedure given below and aim is to prolong the release of Flucloxacillin. Total weight of the tablet was considered as 300mg.

Procedure:

- Flucloxacillin and all other ingredients were individually passed through sieveno≠ 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using direct compression method.

Optimizations of Di Sodium Glycine Carbonate Concentration: Di sodium glycine carbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of Di sodium glycine carbonate were employed; floating lag time and floating duration were observed. Based on that the concentration of Di sodium glycine carbonate was finalized and preceded for further formulations.

Evaluation of post compression parameters for prepared Tablets:

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Table 1: Optimization Di Sodium Glycines Carbonate Concentration

S.No	Excipient Name	EF1	EF2	EF3
1	Flucloxacillin	125	125	125
2	Guar gum	30	30	30
4	Di sodium glycine carbonate	30	60	90
5	Mg.Stearate	5	5	5
5	Talc	5	5	5
7	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	300	300	300

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of Di sodium glycine carbonate was optimised.

Table 2: Formulation Composition for Floating Tablets

Formulation No.	Flucloxacillin	Sodium CMC	Chitosan	Guar gum	Di sodium glycine carbonate	Mag. Stearate	Talc	MCC pH102
F1	125	15	-----	-----	30	5	5	QS
F2	125	30	-----	-----	30	5	5	QS
F3	125	45	-----	-----	30	5	5	QS
F4	125	-----	15	-----	30	5	5	QS
F5	125	-----	30	-----	30	5	5	QS
F6	125	-----	45	-----	30	5	5	QS
F7	125	-----	-----	15	30	5	5	QS
F8	125	-----	-----	30	30	5	5	QS
F9	125	-----	-----	45	30	5	5	QS

All the quantities were in mg, Total weight is 300 mg.

Table 3: Formulation Composition for Floating Tablets

Formulation No.	Flucloxacillin	HPMC K4M	HPMC K15M	HPMC K100M	Di sodium glycine carbonate	Mag. Stearate	Talc	MCC pH102
F10	125	15	-----	-----	30	5	5	QS
F11	125	30	-----	-----	30	5	5	QS
F12	125	45	----	-----	30	5	5	QS
F13	125	-----	15	-----	30	5	5	QS
F14	125	-----	30	----	30	5	5	QS
F15	125	-----	45	-----	30	5	5	QS
F16	125	-----	-----	15	30	5	5	QS
F17	125	-----	-----	30	30	5	5	QS
F18	125	-----	-----	45	30	5	5	QS

All the quantities were in mg, total weight is 300 mg.

3. Results and Discussion

Present study was aimed to developing gastro retentive floating tablets of Flucloxacillin using various polymers. All the formulations were evaluated for physicochemical properties and in-vitro drug release studies.

Analytical Method: Graphs of Flucloxacillin were taken in Simulated Gastric fluid (pH 1.2) at 240 nm.

Table 4: Observations for Graph of Flucloxacillin in 0.1N HCl (240 nm)

Conc [µg/l]	Abs
0	0
1	0.245
2	0.467
3	0.698
4	0.913
5	1.131

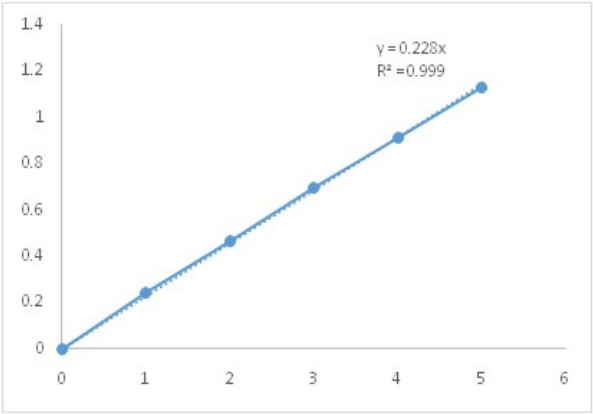

Figure 1: Standard Graph of Flucloxacillin in 0.1N HCl

Preformulation parameters of powder blend

Table 5: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.54	0.43	0.65	16.58	0.78
F2	26.48	0.42	0.66	16.45	0.87
F3	26.49	0.42	0.65	16.95	0.89
F4	27.54	0.49	0.64	18.54	1.24
F5	27.59	0.49	0.65	18.98	1.15
F6	27.55	0.48	0.64	18.64	1.19
F7	26.35	0.45	0.62	17.45	1.21
F8	26.33	0.46	0.61	17.54	1.22
F9	26.94	0.45	0.61	17.46	1.24
F10	27.84	0.42	0.62	14.56	1.35
F11	26.98	0.43	0.63	14.78	1.37
F12	27.45	0.43	0.62	14.85	1.36
F13	26.43	0.46	0.65	15.24	1.85
F14	26.55	0.46	0.66	15.36	1.89
F15	26.31	0.45	0.66	15.25	1.87
F16	28.48	0.47	0.67	14.95	1.54
F17	28.45	0.47	0.67	14.52	1.59
F18	28.14	0.46	0.66	14.64	1.56

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of0.42 to 0.49 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the

formulations was found to be in the range of0.61 to 0.0.67 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 14.52 to 18.98 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between0.78 to 1.89 indicating the powder has good flow properties.

Optimization of Sodium Bicarbonate Concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 50mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours

Quality Control Parameters For tablets: Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

Table 6: In-vitro quality control parameters for tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	301.2	2.3	0.52	2.31	99.45	2.65
F2	301.2	2.4	0.53	2.32	99.65	2.66
F3	301.7	2.5	0.53	2.32	99.35	2.67
F4	301.5	2.4	0.54	2.32	99.65	2.48
F5	301.8	2.3	0.56	2.31	99.45	2.49
F6	301.1	2.3	0.55	2.31	99.25	2.34
F7	302.1	2.4	0.58	2.32	99.24	2.36
F8	302.1	2.5	0.58	2.33	99.35	2.37
F9	303.4	2.3	0.59	2.34	99.63	2.84
F10	301.2	2.4	0.68	2.31	99.87	2.54
F11	301.1	2.3	0.68	2.32	99.84	2.59
F12	301.2	2.5	0.64	2.31	99.37	2.54
F13	301.3	2.3	0.41	2.32	99.38	2.48
F14	302.2	2.5	0.42	2.34	99.54	2.16
F15	303.1	2.3	0.42	2.33	99.35	2.48
F16	303.2	2.3	0.61	2.32	99.56	2.64
F17	302.4	2.5	0.62	2.33	99.65	2.34
F18	301.2	2.4	0.62	2.31	99.64	2.18

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In-Vitro Drug Release Studies

Table 7: Dissolution Data of Flucloxacillin Tablets Prepared With Sodium CMC in Different Concentrations

TIME (hr)	**F1**	**F2**	**F3**
0.5	10.26	8.59	7.54
1	26.48	15.68	13.45
2	38.59	22.34	19.65
3	52.64	29.84	23.64
4	69.58	36.48	28.61
5	85.48	48.15	37.41
6	99.49	56.48	42.15
7	101.78	67.42	49.13
8	-	72.48	57.64
9	-	79.16	66.34
10	-	83.26	74.86
11	-	89.46	81.46
12	-	93.45	91.48

Table 8: Dissolution Data of Flucloxacillin Tablets Prepared With Chitosan in Different Concentrations

TIME (hr)	F4	F5	F6
0.5	15.24	12.45	8.15
1	29.15	24.15	15.24
2	38.24	31.21	26.21
3	57.42	48.54	31.25
4	69.48	59.22	38.16
5	81.24	73.15	46.87

6	97.15	85.47	52.17
7	101.14	94.15	61.24
8	-	101.15	69.34
9	-	-	77.49
10	-	-	84.45
11	-	-	89.95
12			95.65

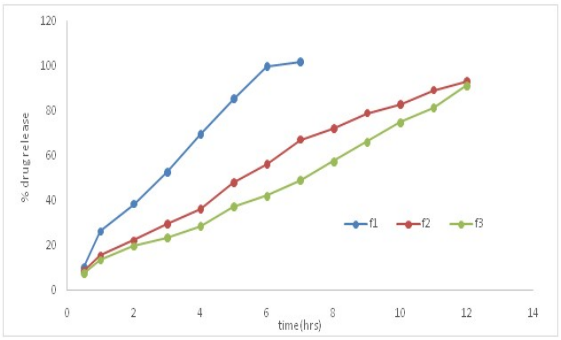

Fig 2: Dissolution profile of Flucloxacillin floating tablets (F1, F2, F3 formulations).

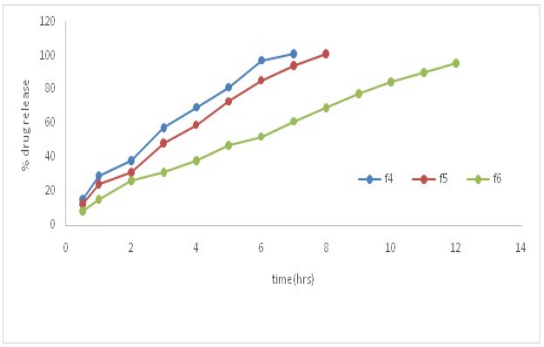

Fig 3: Dissolution profile of Flucloxacillin floating tablets (F4, F5, F6 formulations).

Table 9: Dissolution Data of Flucloxacillin Tablets Prepared with Guar gum In Different Concentrations

TIME (hr)	**F7**	**F8**	**F9**
0.5	21.16	15.64	14.54
1	37.24	24.35	22.16
2	48.15	36.67	29.64
3	57.16	43.16	37.16
4	67.59	58.16	48.15
5	78.54	66.11	54.64
6	86.34	72.14	66.95
7	93.49	79.84	74.18
8	101.24	83.46	79.97
9	-	91.49	87.49
10	-	98.16	91.34
11	-	101.06	94.16
12	-	-	99.75

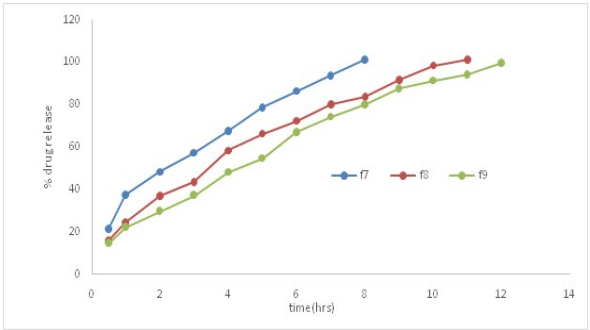

Fig 4: Dissolution profile of Flucloxacillin floating tablets (F7, F8, F9 formulations)

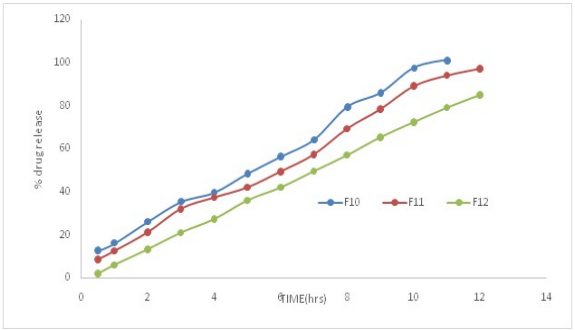

Fig 5: Dissolution profile of Flucloxacillin floating tablets (F10, F11, F12formulations).

Table 10: Dissolution Data of Flucloxacillin Tablets Prepared With HPMC K 4 M in Different Concentrations

TIME(hr)	F10	F11	F12
0.5	12.56	8.54	2.13
1	16.14	12.54	6.21
2	26.14	21.24	13.47
3	35.39	32.21	21.21
4	39.68	37.44	27.48

5	48.46	42.15	36.21
6	56.31	49.55	42.19
7	64.25	57.48	49.75
8	79.48	69.48	57.19
9	85.97	78.54	65.55
10	97.58	89.24	72.53
11	101.21	94.21	79.28
12	-	97.42	85.21

Table 11: Dissolution Data of Flucloxacillin Tablets Prepared With HPMC K15 MIn Different Concentrations

TIME (hr)	F13	F14	F15
0.5	12.34	16.53	6.48
1	25.14	19.24	12.12
2	53.17	27.54	21.16
3	67.25	39.15	28.47
4	84.21	48.16	34.65
5	95.16	57.22	42.16
6	101.20	69.34	53.18
7	-	75.16	61.24
8	-	87.49	69.23
9	-	97.46	76.46
10	-	101.33	83.45
11	-	-	89.48
12	-	-	94.27

Table 12: Dissolution Data of Flucloxacillin Tablets Prepared With HPMC K100M in Different Concentrations

TIME(hr)	F16	F17	F18
0.5	12.34	5.64	3.21
1	20.14	13.45	8.56
2	37.34	19.24	14.65
3	46.52	26.25	24.65
4	57.49	32.16	28.34
5	64.25	41.23	37.48
6	73.01	49.56	45.21
7	82.16	58.64	53.46
8	96.49	67.43	62.48
9	101.25	74.36	71.49
10	-	83.24	78.54
11	-	91.34	85.45
12	-	95.67	91.63

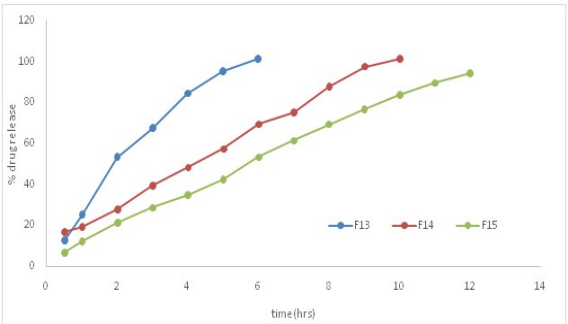

Fig 6: Dissolution profile of Flucloxacillin floating tablets (F13, F14, F15 formulations).

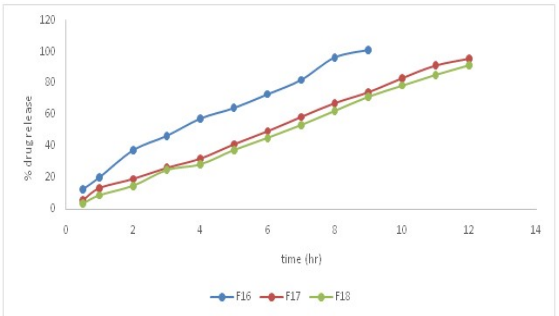

Fig 7: Dissolution profile of Flucloxacillin floating tablets (F16, F17, F18 formulations)

From the dissolution values it was evident that the formulations F11 & F15 were retarded the drug release up to 12 hours, they shown drug release of 97.42 and 94.27 % respectively. Formulations F10 –F12 contains HPMC K4M alone. As the concentration of HPMC K4M increases retardation nature was increased.F11 formulation containing 30 mg of HPMC K4M was show almost negligible amount of drug release in first 3 hours from the

5th hour onwards it shown drug release as the time proceeds slowly the polymer was undergone erosion and allowed the drug to come out from the dosage form. The formulation was retarded drug release up to 12 hours and it showed maximum drug release in 12 hours. Similarly the formulation F15 containing HPMC K15M in the concentration of 45 mg also showed similar drug release pattern.

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 13: Release kinetics data for optimised formulation (F9)

Time (T)	Root (T)	Cumulative (%) Release Q	Log (T)	Log (%) Release	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining
0.5	0.707107	14.54			1.932				85.46
1	1.000	22.16	0.000	1.346	1.891	22.160	0.0451	-0.654	77.84
2	1.414	29.64	0.301	1.472	1.847	14.820	0.0337	-0.528	70.36
3	1.732	37.16	0.477	1.570	1.798	12.387	0.0269	-0.430	62.84
4	2.000	48.15	0.602	1.683	1.715	12.038	0.0208	-0.317	51.85
5	2.236	54.64	0.699	1.738	1.657	10.928	0.0183	-0.262	45.36
6	2.449	66.95	0.778	1.826	1.519	11.158	0.0149	-0.174	33.05
7	2.646	74.18	0.845	1.870	1.412	10.597	0.0135	-0.130	25.82
8	2.828	79.97	0.903	1.903	1.302	9.996	0.0125	-0.097	20.03
9	3.000	87.49	0.954	1.942	1.097	9.721	0.0114	-0.058	12.51
10	3.162	91.34	1.000	1.961	0.938	9.134	0.0109	-0.039	8.66
11	3.317	94.16	1.041	1.974	0.766	8.560	0.0106	-0.026	5.84
12	3.464	99.75	1.079	1.999	-0.602	8.313	0.0100	-0.001	0.25

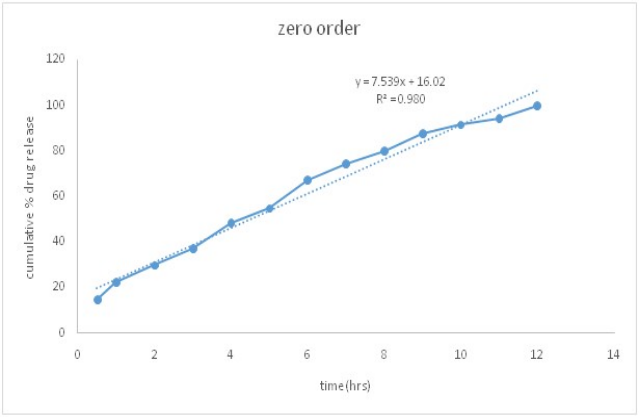

Fig 8 : Zero order release kinetics graph

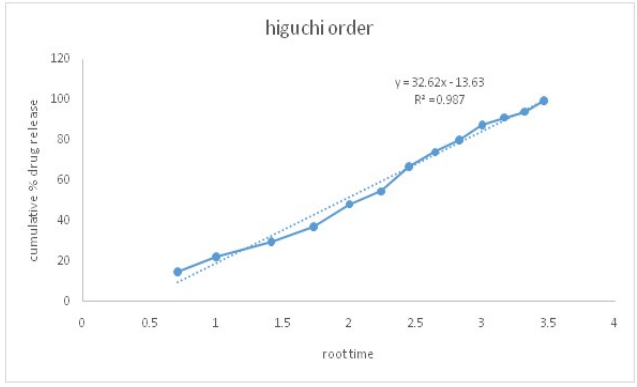

Fig 9 : Higuchi release kinetics graph

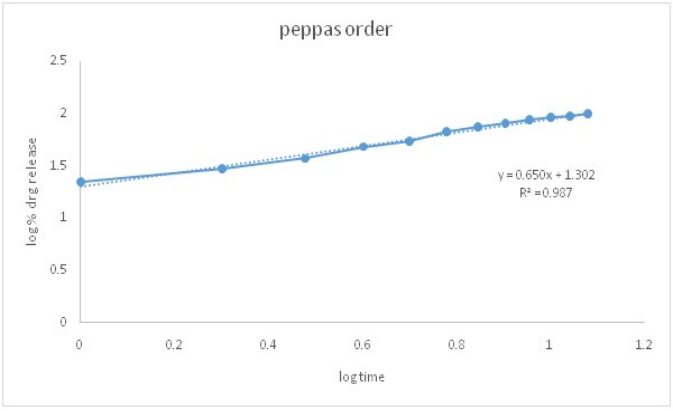

Fig 10: Kars mayer peppas graph

Fig 11: First order release kinetics graph

Table 14: Release kinetics Data for Optimised Formulation (F11)

TIME (T)	ROOT (T)	CUMULATIVE (%) RELEASE Q	LOG (T)	LOG (%) RELEASE	LOG (%) REMAIN	RELEASERATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining
0.5	0.707107	8.54	-0.301	0.931	1.961	17.080	0.1171	-1.069	91.46
1	1.000	12.54	0.000	1.098	1.942	12.540	0.0797	-0.902	87.46
2	1.414	21.24	0.301	1.327	1.896	10.620	0.0471	-0.673	78.76
3	1.732	32.21	0.477	1.508	1.831	10.737	0.0310	-0.492	67.79
4	2.000	37.44	0.602	1.573	1.796	9.360	0.0267	-0.427	62.56
5	2.236	42.15	0.699	1.625	1.762	8.430	0.0237	-0.375	57.85
6	2.449	49.55	0.778	1.695	1.703	8.258	0.0202	-0.305	50.45
7	2.646	57.48	0.845	1.760	1.629	8.211	0.0174	-0.240	42.52
8	2.828	69.48	0.903	1.842	1.485	8.685	0.0144	-0.158	30.52
9	3.000	78.54	0.954	1.895	1.332	8.727	0.0127	-0.105	21.46
10	3.162	89.24	1.000	1.951	1.032	8.924	0.0112	-0.049	10.76
11	3.317	94.21	1.041	1.974	0.763	8.565	0.0106	-0.026	5.79
12	3.464	97.42	1.079	1.989	0.412	8.118	0.0103	-0.011	2.58

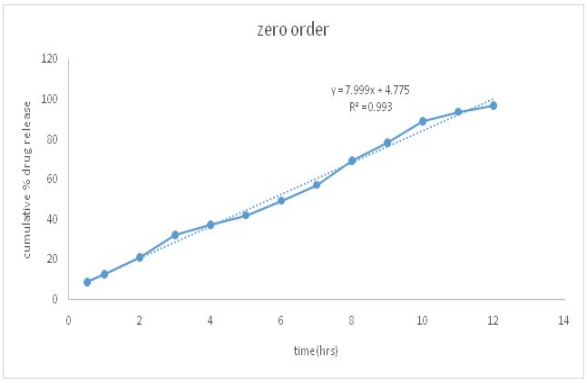

Fig 12 : Zero order release kinetics graph

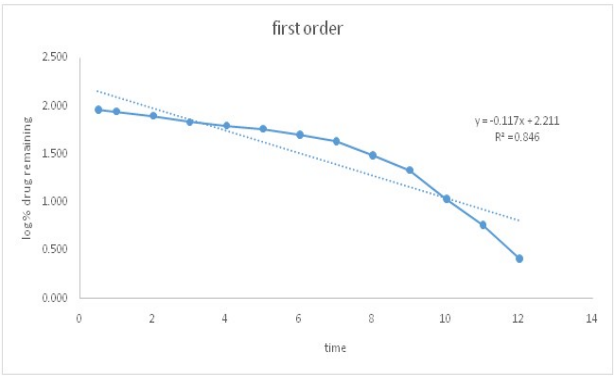

Fig 15: First order release kinetics graph

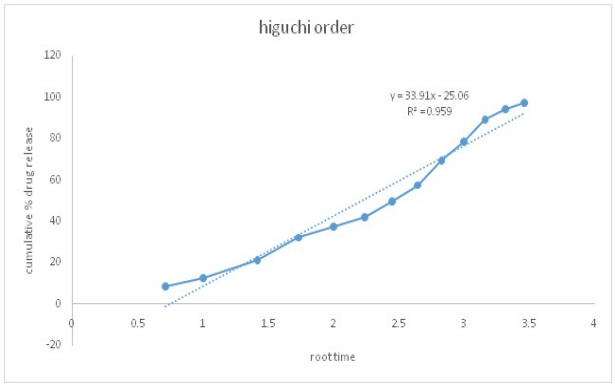

Fig 13 : Higuchi release kinetics graph

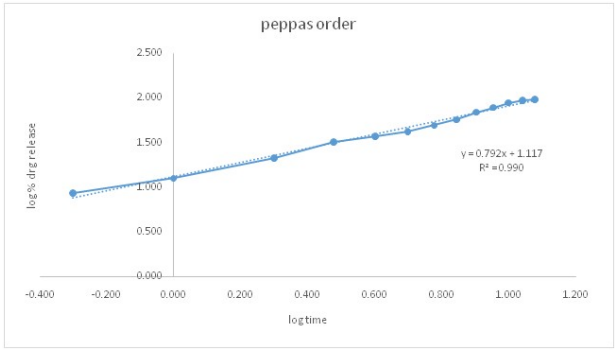

Fig 14: Kars mayerpeppas graph

4. Conclusion

In the present research work gastro retentive floating matrix formulation offlucloxacillin by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various pre-formulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared with Guar gum retarded the drug release up to 12 hours in the concentration of 45 mg (F9). Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Higchimechanism of drug release.

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