Research Article

Available Online at: www.ijpir.com

International Journal of Pharmacy and Industrial Research

ISSN Print 2231 – 3648
Online 2231 – 3656

Formulation and characterization of claritromycin floating tablets using various polymers

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ABSTRACT

The present study outlines a systematic approach for designing and development of Clarithromycin floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. Floating tablets of Clarithromycin have shown sustained release there by proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Different formulations were formulated by using direct compression technique. A floating drug delivery system (FDDS) was developed by using sodium bicarbonate as gas-forming agent and Chitosan, HPMC K4M and Ethyl cellulose as polymers. The prepared tablets were evaluated in terms of their physical characteristics, precompression parameters; *in vitro* release and buoyancy lag time the results of the *in vitro* release studies showed that the optimized formulation (C7) could sustain drug release for 12 hrs by using Ethyl cellulose in the concentration of 50 mg. The *in vitro* drug release followed Kors Mayer peppas release.

Key words: Clarithromycin, Chitosan, HPMC K4M, Ethyl cellulose, Floating lag time and Floating Tablets.

INTRODUCTION

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. Controlled drug delivery or modified drug delivery systems are divided into four categories.

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug (Figure 1). Controlled drug deliveries usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

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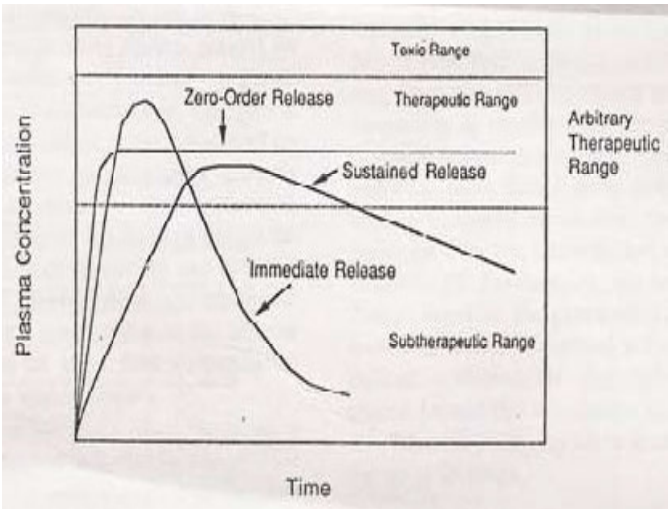

Figure 1: Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet

Biological aspects of gastric retention dosage forms

To comprehend the considerations taken in the design of gastric retention dosage forms and to evaluate their performance the relevant anatomy and physiology of the G.I tract must be fully understood. The extent of drug absorption in a segment of the G.I. tract depends generally on the rate of absorption as well as on the exposed surface area and time available for drug absorption. The G.I. Transit times of dosage forms in the various segments of the G.I. tract are listed in Table 1. The other factors influencing drug absorption are surface area, absorption mechanisms, pH values, enzymes and number of microorganisms.

Table 1: The Transit time of Different Dosage Forms across the Segments of GI Tract

Dosage form	Transit time (h)		
	Gastric	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Oral solution	0.3±0.07	4.1±0.5	4.4

It is well recognized that the stomach may be used as a depot for controlled release dosage forms. The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. The stomach is composed of the following parts. [9,10]

- Fundus
- Body
- Antrum

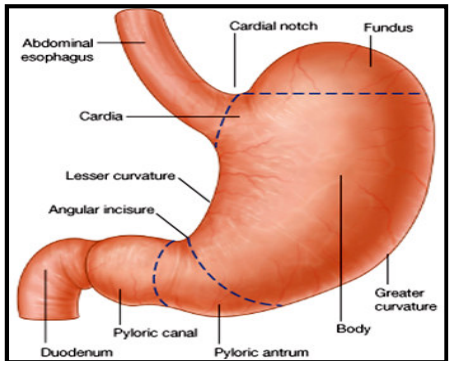

Figure 2: Anatomy of stomach

Floating drug Delivery Systems or Hydrodynamically Balanced Systems (HBS)

These systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the systems are floating in the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in plasma drug concentration. HBS system contains a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquires a bulk density of less than 1 thereby being buoyant on the gastric contents of stomach until all the drug was released.

HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsuleis developed, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1 thereby being buoyant on the gastric contents of stomach until all the drug was released (Figure 1.4).

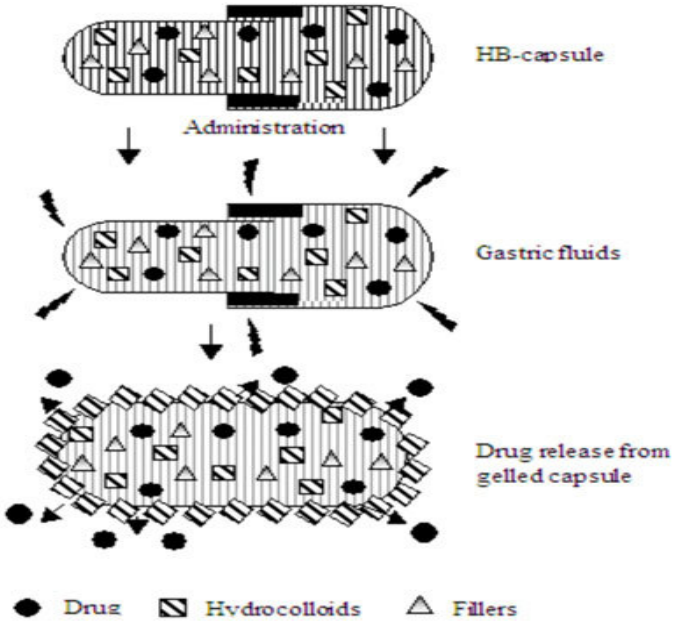

Figure 3: Working Principle of Hydrodynamically Balanced tablets

Advantages of GFDDS

- GFDDS remain in the stomach for several hours to increase GRT.
- Drugs that have poor Bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the Bioavailability
- **Fewer Doses:** Creating once daily formulations for improved patient compliance.
- **Improved plasma levels:** Both extends plasma concentration levels and provides a more linear release profile.
- **Better Bioavailability:** Delivers the drug in the upper G.I. tract for optimal absorption.
- **Less Irritation:** the polymer matrix acts as a buffer between harsh drug crystals and the stomach lining.
- **Fewer side effects:**keeps drugs out of the lower GI tract which can be harmful to intestinal flora. Lower peak concentrations can also reduce adverse pharmacological effects.

Limitations

- The major disadvantage of floating systems is requirement of a sufficiently high level of fluids in the stomach for the drug delivery i.e. up to 400ml of gastric fluids should be present for optimum buoyancy. However, this limitation can be overcome by coating the dosage form with bioadhesive polymers, which easily adhere to the mucosal lining of the stomach and retain. The dosage form can be administered with a glass full of water (200-250 ml) to provide the initial fluid for buoyancy.

- Floating system is not feasible for those drugs that have solubility or stability problems in gastric fluids.
- Drugs that are not stable at gastric pH are not suitable candidates to be as GFDDS.
- Drugs that irritate the mucosa are not suitable candidates and should be avoided to be formulated as GFDDS.
- The drugs, which have multiple absorption sites in the gastrointestinal tract and are absorbed throughout gastrointestinal tract, which under significant first pass metabolism, are not desirable candidates.

AIM &OBJECTIVE

The aim of the present work is to formulate & evaluate gastro retentive floating tablets of Clarithromycin using different types of polymers.
The Gastro Retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.

OBJECTIVES OF THE STUDY

1. Analytical method development for an Anti-bacterial agent.
2. To evaluate compatibility between drug-polymers and other excipients.
3. To carry out pre-formulation studies.
4. To develop and formulate controlled release floating delivery system.
5. To evaluate post compression parameters like weight variation, hardness, friability, content uniformity, floating lag time, etc.

Evaluation of developed formulation for *in-vitro* drug release studies.

Formulation development of floating Tablets

Procedure for direct compression method

1) Drug and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method by using 12 mm punch.

FORMULATION OF TABLETS

Table 2: Formulation composition for Floating tablets

INGREDIENTS (MG)	FORMULATION CODE								
	C1	C2	C3	C4	C5	C6	C7	C8	C9
Clarithromycin	250	250	250	250	250	250	250	250	250
Chitosan	50	100	150	-	-	-	-	-	-
HPMC K4M	-	-	-	50	100	150	-	-	-
Ethyl cellulose	-	-	-	-	-	-	50	100	150
$NaHCO_3$	20	20	20	20	20	20	20	20	20
Citric acid	15	15	15	15	15	15	15	15	15
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4
Lactose	156	106	56	156	106	56	156	106	56
Total weight	500	500	500	500	500	500	500	500	500

RESULTS AND DISCUSSION

Analytical Method

A. Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 210 nm.

B.Calibration curve

Graphs of Clarithromycinwas taken in 0.1N HCL (pH 1.2).

Table no 3: Observations for graph of Clarithromycin in 0.1N HCl

Conc [µg/mL]	Abs
0	0
2	0.137
4	0.261
6	0.378
8	0.497
10	0.613

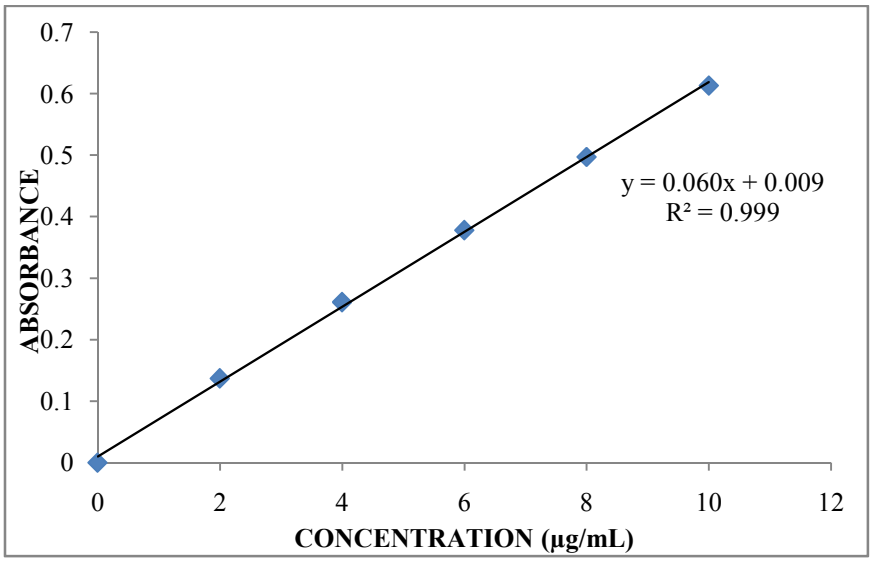

Fig 4: Standard graph of Clarithromycin in 0.1N HCL

Preformulation parameters of powder blend

Table 4: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
C1	22.44±0.2	0.58±0.01	0.66±0.01	11.81±2.2	1.13±0.02
C2	22.83±0.4	0.43±0.03	0.50±0.02	13.2±2.0	1.15±0.02
C3	23.31±0.3	0.47±0.02	0.55±0.03	14.23±2.0	1.16±0.23
C4	23.44±0.4	0.50±0.01	0.58±0.01	14.96±2.2	1.17±0.03
C5	22.16±0.2	0.48±0.02	0.55±0.01	12.14±4.9	0.65±0.23
C6	23.37±0.4	0.53±0.03	0.58±0.04	8.62±2.2	1.09±0.03
C7	23.53±0.5	0.55±0.02	0.61±0.03	9.84±2.0	1.11±0.03
C8	23.77±0.4	0.55±0.01	0.59±0.02	6.78±2.0	1.07±0.03
C9	23.04±0.3	0.54±0.01	0.57±0.01	5.26±2.0	1.06±0.02

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 of 0.43±0.03 to 0.58±0.01 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.50±0.02 to 0.66±0.01 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 14.96 which show that the powder has good flow properties.All the formulations has shown the hausners ratio ranging between 0.65 to 1.17indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

Table 5 : *In vitro* quality control parameters

Formulation codes	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (Sec)	Total floating time(Hrs)
C1	498.31	5.2	0.51	5.98	98.12	61	10
C2	497.68	5.9	0.46	5.31	96.35	50	11
C3	499.20	5.1	0.35	5.29	99.80	38	12
C4	498.18	5.0	0.72	5.73	98.14	42	9
C5	500.03	5.9	0.69	5.18	98.58	31	10
C6	499.10	6.3	0.31	5.27	97.21	25	12
C7	498.71	5.2	0.53	5.90	99.30	20	12
C8	496.38	5.7	0.42	5.14	98.14	31	12
C9	498.64	6.1	0.38	5.65	98.05	35	12

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

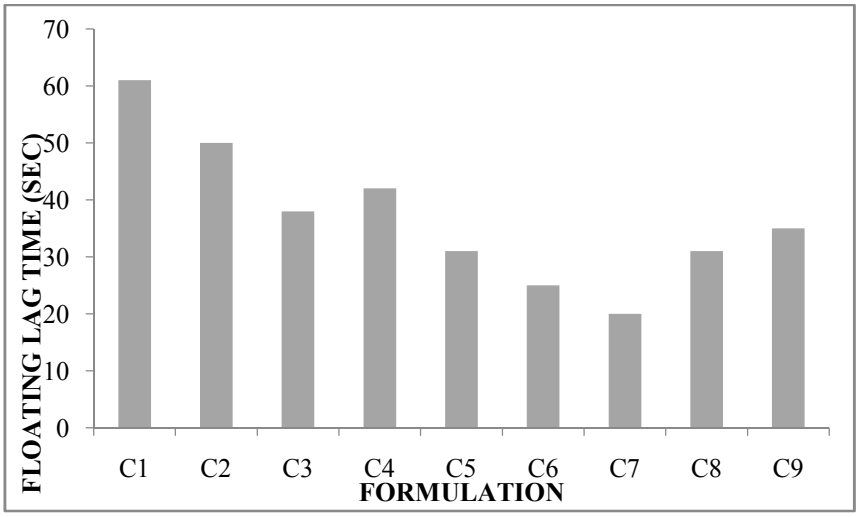

Figure 5: Floating lag time (Sec)

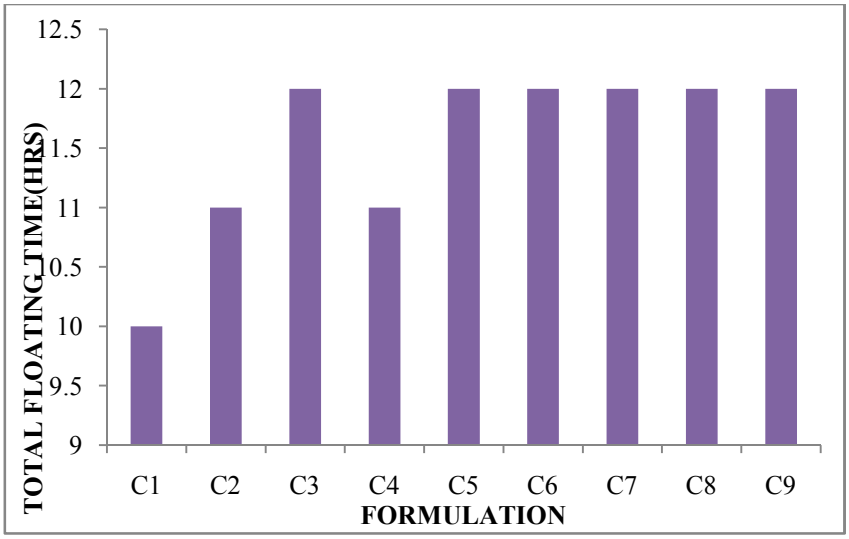

Figure 6: Total floating time (Hrs)

Buoyancy and total Flotation test:

From the results, it was observed that as the buoyancy lag time and the total floating time was studied for all the formulations. C1 to C9 total floating time were found to be respectively as shown in Table. The formulations with Chitosan polymer (C1, C2 and C3) showed high buoyancy lag time when compared to formulations with HPMC K4M polymer (C4, C5 and C6). For all the C5, C6, C7, C8 and C9 formulations showed more total floating time when compared to C1, C2, and C4.

Results revealed that as the concentration of the Chitosan and HPMC K4M polymer increases, the buoyancy lagging time decreases. The increase in the concentration of the Ethyl cellulose polymer resulted in the increase of the buoyancy lag time.

In vitro drug release studies

Table no 6: Dissolution data of floating tablets

TIME	% Cumulative drug release								
(HR)	C1	C2	C3	C4	C5	C6	C7	C8	C9
0	0	0	0	0	0	0	0	0	0
1	18.92	14.29	11.65	20.82	13.12	10.05	18.78	13.96	08.42
2	26.56	19.10	16.35	26.91	19.30	18.96	29.98	18.81	15.39
3	31.80	24.09	20.12	35.36	28.28	23.19	37.31	24.75	21.58
4	37.12	28.68	26.49	42.52	36.17	29.53	45.94	30.29	28.34
5	42.27	35.75	31.26	58.81	43.52	36.31	50.42	36.81	43.23
6	48.93	42.81	37.16	65.99	58.78	41.79	56.79	45.34	48.06
7	55.10	49.59	42.90	75.28	63.80	46.52	61.28	50.78	56.14
8	60.47	56.15	48.21	86.75	78.43	53.47	68.41	56.99	60.27
9	67.34	62.79	51.86	98.43	91.08	59.59	75.60	62.15	67.39
10	72.81	67.99	56.06		97.14	66.76	80.15	67.72	72.95
11	86.85	72.38	65.16			80.11	91.72	83.63	78.38
12	96.59	89.42	79.73			86.49	99.70	90.82	85.12

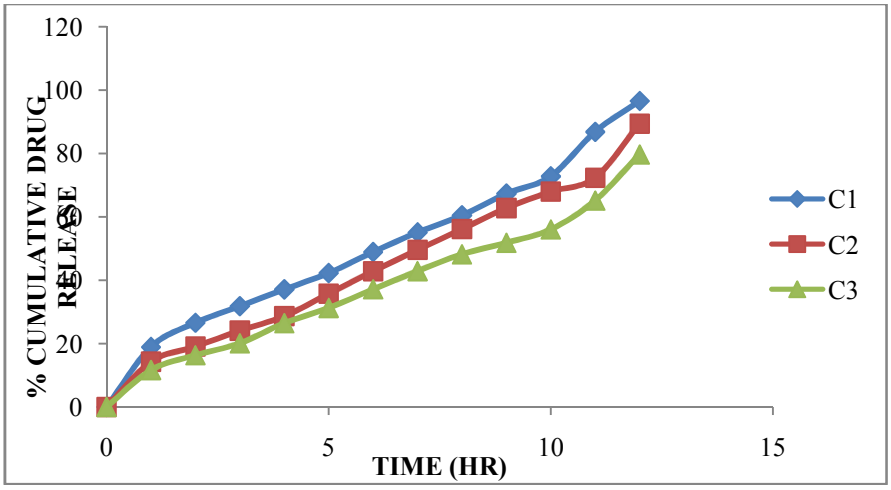

Fig 7: Dissolution data of Clarithromycin Floating tablets containing Chitosan

From the above figure 8.4 it can be observed that the polymer Chitosan has controlled effect on the release of drug from the floating tablet. The percentage of drug release from formulations C1, C2 and C3 was 96.59%, 89.42%, 79.73% respectively and difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. Formulations C1 release the drug within the desired time. Formulation C2 and C3 was showed low % of drug release from floating matrix tablets.

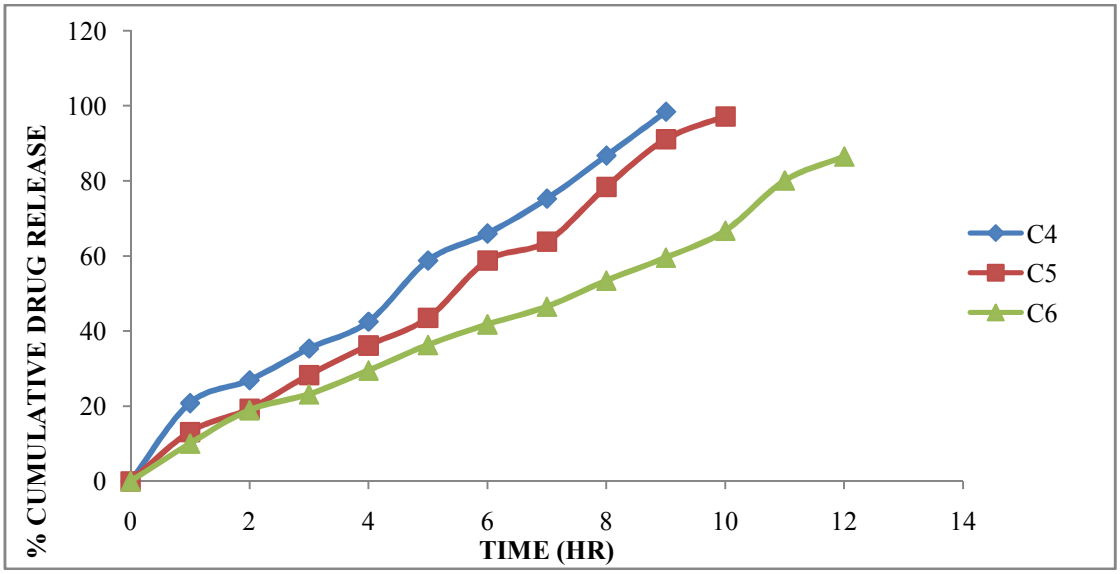

Fig: 8: Dissolution data of Clarithromycin Floating tablets containing HPMC K4M

From the above figure it can be observed that the polymer HPMC K4M has unable to controlled effect on the release of drug from the floating tablet. The percentage of drug release from formulations C4, C5, and C6 98.43% at the end of 9h, 97.14 % at the end of 10h and 86.49 % at the end of 12 h respectively. Formulations C4 and C5 failed to release the drug within the desired time. The difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. In that two formulations floated for 12h. Formulation C6 was showed good buoyancy properties (floating lag time: 25 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).

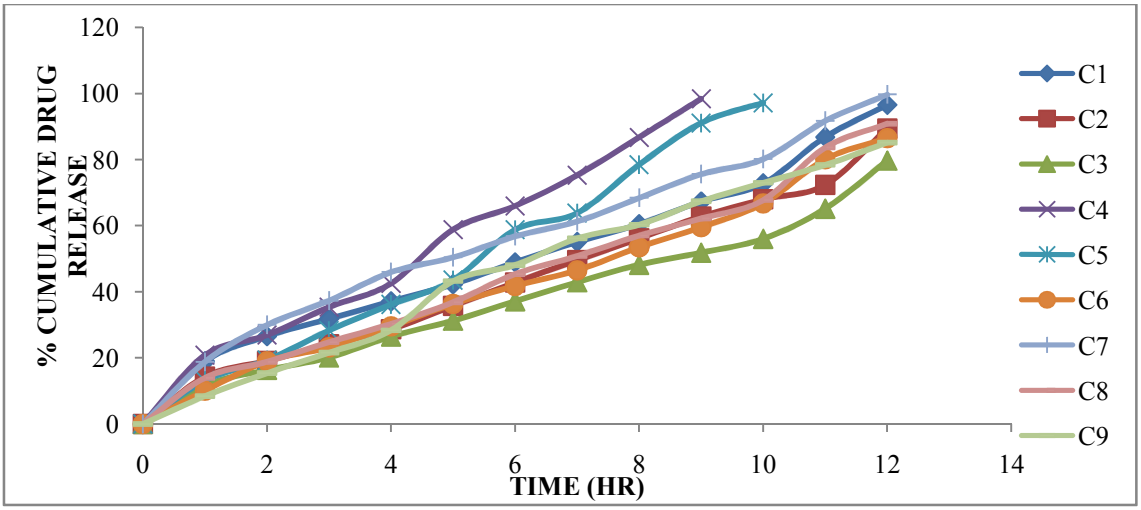

Fig: 9: Dissolution data of Clarithromycin Floating tablets containing all formulations (Chitosan, HPMC K4M and Ethyl cellulose)

The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in tables 8.4 respectively. Formulation C7 showed good drug release and buoyancy time than all other formulations. The formulation C7 showed a constant release in a controlled manner with 99.70%. Hence C7 was chosen for kinetics studies.

Application of Release Rate Kinetics to Dissolution Data for optimised formulation

Table No 7: Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
18.78	1	1.000	1.274	0.000	1.910	18.780	0.0532	-0.726	81.22	4.642	4.331	0.311
29.98	2	1.414	1.477	0.301	1.845	14.990	0.0334	-0.523	70.02	4.642	4.122	0.520
37.31	3	1.732	1.572	0.477	1.797	12.437	0.0268	-0.428	62.69	4.642	3.973	0.669
45.94	4	2.000	1.662	0.602	1.733	11.485	0.0218	-0.338	54.06	4.642	3.781	0.860
50.42	5	2.236	1.703	0.699	1.695	10.084	0.0198	-0.297	49.58	4.642	3.674	0.968
56.79	6	2.449	1.754	0.778	1.636	9.465	0.0176	-0.246	43.21	4.642	3.509	1.132
61.28	7	2.646	1.787	0.845	1.588	8.754	0.0163	-0.213	38.72	4.642	3.383	1.259
68.41	8	2.828	1.835	0.903	1.500	8.551	0.0146	-0.165	31.59	4.642	3.161	1.480
75.6	9	3.000	1.879	0.954	1.387	8.400	0.0132	-0.121	24.4	4.642	2.900	1.741
80.15	10	3.162	1.904	1.000	1.298	8.015	0.0125	-0.096	19.85	4.642	2.708	1.934
91.72	11	3.317	1.962	1.041	0.918	8.338	0.0109	-0.038	8.28	4.642	2.023	2.619
99.7	12	3.464	1.999	1.079	-0.523	8.308	0.0100	-0.001	0.3	4.642	0.669	3.972

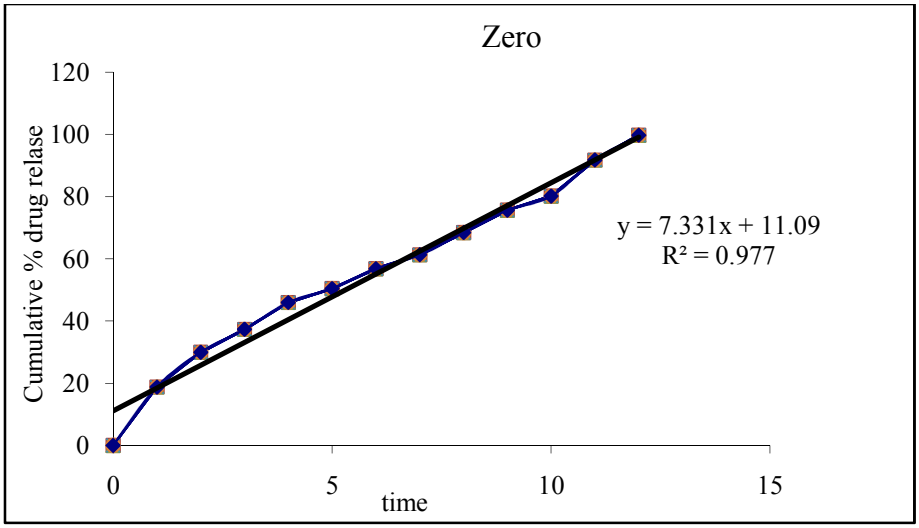

Fig no 10: Zero order release kinetics

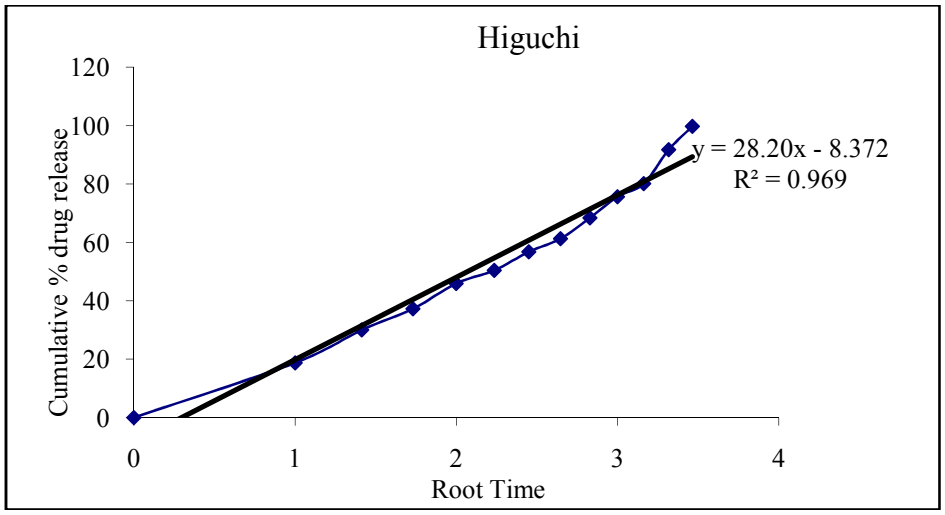

Fig no 11: Higuchi release kinetics

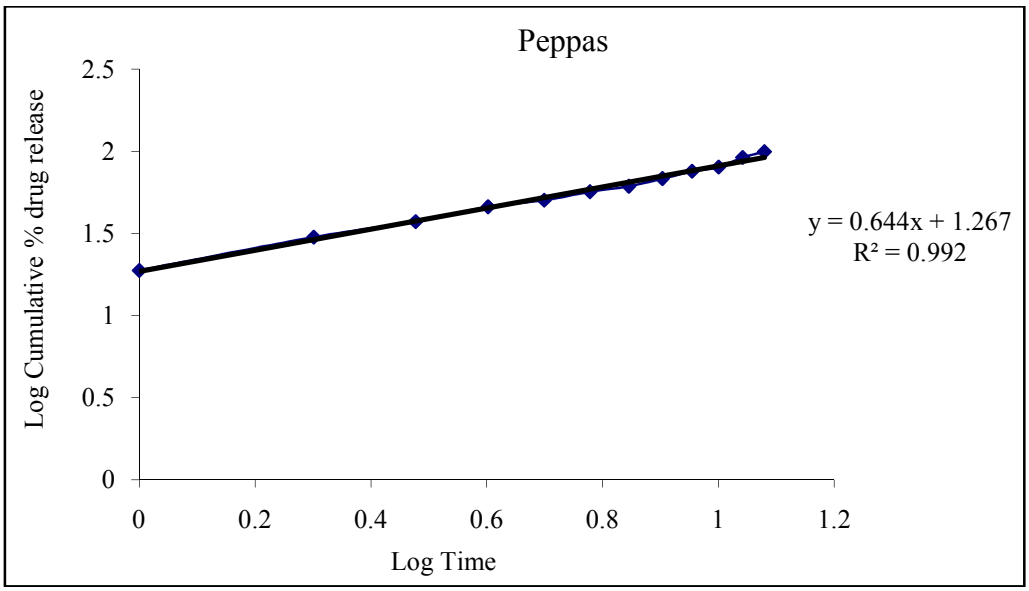

Fig 12: Kors mayer peppas release kinetics

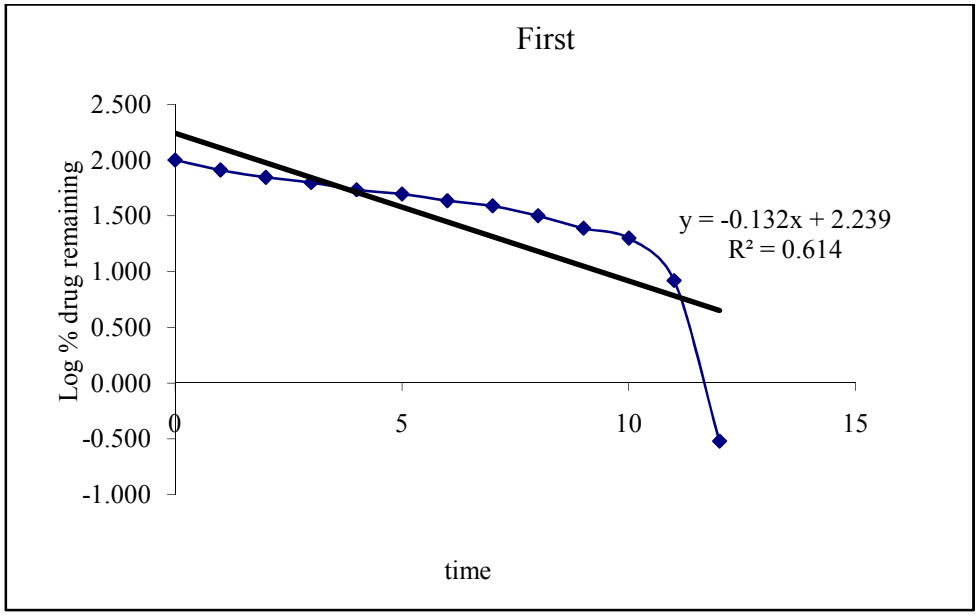

Fig 13: First order release kinetics

Optimised formulation C7 was kept for release kinetic studies. From the above graphs it was evident that the formulation C7 was followed Kors mayerpeppas release mechanism.

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy

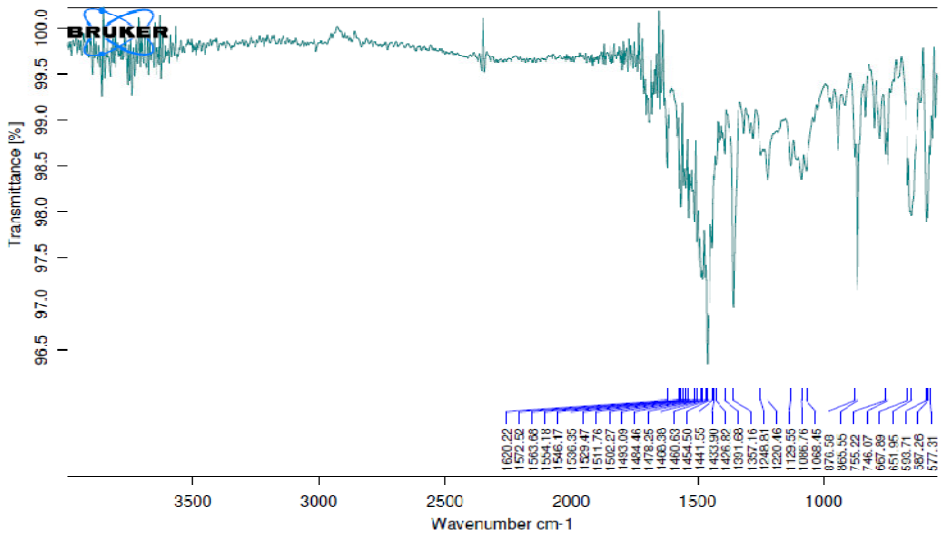

Figure 14: FTIR Spectrum of pure drug

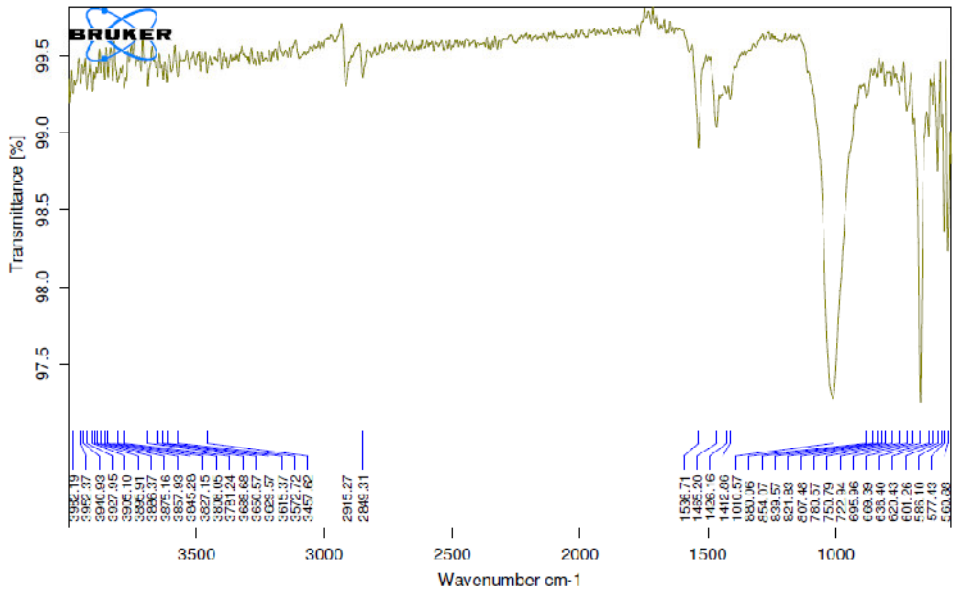

Fig 15: FTIR Spectrum of optimised formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions. Clarithromycin are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION

The preformulation parameters like angle of repose, bulk density, tapped density, Hausner's ratio; Carr's index of pure drug was evaluvated and complied with the pharmacopoeial specifications. FTIR studies showed there was no interaction between drug and polymer. Gastro retentive floating matrix tablets of Clarithromycin were successfully prepared with various polymers like Chitosan, HPMC K4M and Ethyl cellulose. The formulated batches were evaluated for physicochemical parameters, floating properties and dissolution profiles. From the evaluation results, it was observed that the tablets contain the higher viscosity Ethyl cellulose showed long floating lag time when compared to tablets prepared with other polymers. The physical properties like hardness, weight variation and friability of majority of the batches complied with the pharmacopoeial specifications. The drug content of all tablets was in the range of 96.35 – 99.80%. *In vitro* dissolution study of all the formulations was done in 0.1 N HCL. The tablets containing Ethyl cellulose (C7) showed satisfactory results with short floating lag time (20 sec) total buoyancy time more than 12 h, cumulative % drug release (99.70%) and controlled drug release up to 12 h. So C7 was taken for kinetic studies. The kinetic studies were carried for formulation C7 showed high regression value of 0.992 for Kors mayerpeppas release mechanism. Hence it was concluded that formulation C7 chosen as optimum formulation.

ACKNOWLEDGEMENT

The Authors are thankful to Sura Labs, Dilshukhnagar, Hyderabad for providing thenecessaryfacilities for theresearch work.

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