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Formulation research and development of floating matrix tablet of clarithromycin by using various synthetic natural polymers

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ABSTRACT

In the present research work Gastro retentive floating matrix formulation of Clarithromycin. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentration. gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentration of polymers of various grades of HPMC and guar gum as Polymeric substances. The formulation blend was subjected to various preformulation 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 HPMCK100M as polymer were retarded the drug release up to desired time period i.e., 12 hours in the concentration of 90 mg. Whereas in low concentration the polymer was unable to produce the desired action. (F5 formulation 97.36% drug release). The formulations prepared with HPMC K15M less retarded the drug release. 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 korsmeyar peppas order mechanism of drug release.

Keywords: Clarithromycin, HPMC, Guar gum polymers, Floating tablets.

INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient compliance and flexibility in formulation and cost effective manufacturing process (Leon Lachman). Many of the drug delivery systems, available in the market are oral drug delivery type systems Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1. Drugs with short half-life require frequent administration, which increases chances of

missing dose of drug leading to poor patient compliance.

2. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.
3. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the Css values fall or rise beyond the therapeutic range.
4. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs (Robinson Jr, Lee V.H.L,).

Gastric retention Systems

Is a device, which resides in the confines of the stomach over aprolonged period of time (prolonging the residence time of the drug delivery system) for the purpose of providing a platform for controlled release of biologically active agents. The system releases the active agent to be absorbed or released from the stomach to be absorbed in the upper parts of the small intestine. In particular it allows for less frequent dosing of the active agent than with immediate release formulations or sustained released formulations that are not gastric retentive dosage forms. In other applications the frequency of dosing may be the same, but the gastric retention dosage forms will beneficially alter the absorption profile of the active agent from that available with immediate release formulations. This may result in increased bioavailability of the active agent with reduced side effects. Over the last three decades, a various approaches have been pursued to prolong the residence time of a an oral dosage forms in the stomach, these methods include

- Floating systems
- Swelling and expanding systems
- Bio adhesive systems
- Modified- shape systems
- High density systems
- Other gastric emptying devices

Floating drug Delivery Systems or Hydro dynamically 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.

Hydrodynamically balanced sustained release tablets contains drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug is slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids (Hradman J.G, Limbrid, Goodman Gilman's,). Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form.

HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule is 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 4).

Swelling and expanding systems (Ichikawa M, Watanabe S, Miyake Y,)

One way to retain a dosage form in the stomach is by increasing its size. The stomach discharges its contents through the pylorus into the intestine. If the dosage form can attain a size larger than that of the pylorus, it can be retained in the stomach for a long time. Swelling type dosage forms are such that after swallowing, these products swell to a extent that prevents their exit from the stomach through the pylorus. As a result the dosage form is retained

in the stomach for a long period of time .These systems may be referred to as .plug type systems. Since they exhibit a tendency to remain lodged at the pyloric sphincter.

BIOADHESIVE SYSTEMS

(Abubakr et al., Rouge N, et al.,)**:** Bioadhesive drug delivery systems are usedto localize a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the G.I. tract. The proposed mechanism of bioadhesion is the formation of hydrogen and electrostatic bonding at the mucus-polymer junction. Rapid hydration in contact with the muco-epithelial surface appears top favour adhesion, particularly if water can be excluded at the reactive surfaces (Menon A, Wolfgang A.R, Saks A). These bioadhesive systems do not seem to be in a feasable solution as this bond formation is prevented by the acidic environment and thick mucus present in the stomach at the site .Some of the most promising excipients that have been used commonly in these mocoadhesive systems include polycarbophil, carbopol, lectins, chitosan, tragacanth, sodium alginate CMC, pectin, gelatin, etc.

Modified shape systems

(Ozdemir N et al.,)**:** Modified Shape Systems are no disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends, which extend the gastric retention time depending on size, shape and flexural modulus of the drug delivery device.

High-density systems

(Xu X, Sun M,)**:** The density of the pellets must exceed that of normal stomach contents (1.004 g/cm3). For preparing such formulations, drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder and zinc oxide. The weighed pellet can then be covered with a diffusion-controlled membrane.

Co-administration of gastric emptying delaying drugs

It involves simultaneous administration of a drug to delay gastric emptying together with a therapeutic drug. It involves feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release of these above mentioned approaches, floating drug delivery or Hydro dynamically balanced drug delivery systems are given much importance because of their ease of preparation and reliable and reproducible gastric retentive action.

Gastric floating drug delivery systems (GFDDS)

The various buoyant preparation s includes tablets, pills, granules, powders, capsules, hollow, Microspheres (micro balloons) and laminated films. Based on the mechanism of buoyancy, two distinctly different technologies i.e., non effervescent and effervescent systems have been utilized in the development of GFDDS.

Non-effervescent GFDDS

(Srivastava A.K, Wadwa S)**:** The approach involved in the formulation of floating dosage forms is intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier as shown in figure 7a. The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. Commonly used excipients, here are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.

Effervescent GFDDS

The floating drug delivery systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1 carbon dioxide is released, causing the beads to float in the stomach (wie j.p, huang.) The

matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gellyfied hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy as shown in figure 7b. The carbon dioxide generating components may be intimately mixed within the tablet matrix to produce a single-layered tablet or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for the sustained release effect (streubel a et al., wu.w,). This concept has also been exploited for floating capsule systems.

Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxyl propyl methyl cellulose (hpmc), and floating systems based on ion exchange resin technology, etc (nur o.a, zhang j.s),.

MATERIALS AND METHODOLOGY

Table: List of Materials Used

NAME OF THE MATERIAL	SOURCE
Clarithromycin	SURA LABS
Hydroxy Propyl Methyl Cellulose HPMC K15M, HPMC K100M)	Merck Specialities Pvt Ltd, Mumbai, India
Guar Gum	Merck Specialities Pvt Ltd, Mumbai, India
Sodium bicarbonate	Merck Specialities Pvt Ltd, Mumbai, India
Magnesium stearate	Merck Specialities Pvt Ltd, Mumbai, India
Micro crystalline cellulose	Merck Specialities Pvt Ltd, Mumbai, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India

ANALYTICAL METHOD DEVELOPMENT

Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve

100mg of clarithromycin pure drug was dissolved in 100ml of 0.1NHCL (stock solution) 10ml of solution was taken and make up with100ml of 0.1N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 2,4,6,8 and 10 µg/ml of clarithromycin per ml of solution. The absorbance of the above dilutions was measured at 274 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R2) which determined by least-square linear regression analysis.

In vitro drug release studies

Dissolution parameters

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCL
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c + 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

PROCEDURE

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCL was taken and process was continued from 0 to 12 hrs at 50 rpm.

At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 274 nm using UV-spectrophotometer.

RESULTS AND DISCUSSION

The present study was aimed to developing gastro retentive floating tablets of Clarithromycin using various HPMC polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

ANALYTICAL METHOD

Graph of clarithromycin was taken in Simulated Gastric fluid (pH 1.2) at 274 nm.

Table: Observations for graph of clarithromycin in 0.1N HCL (274nm)

CONCENTRATION (µG/ML)	ABSORBANCE
0	0
2	0.235
4	0.356
6	0.468
8	0.565
10	0.685

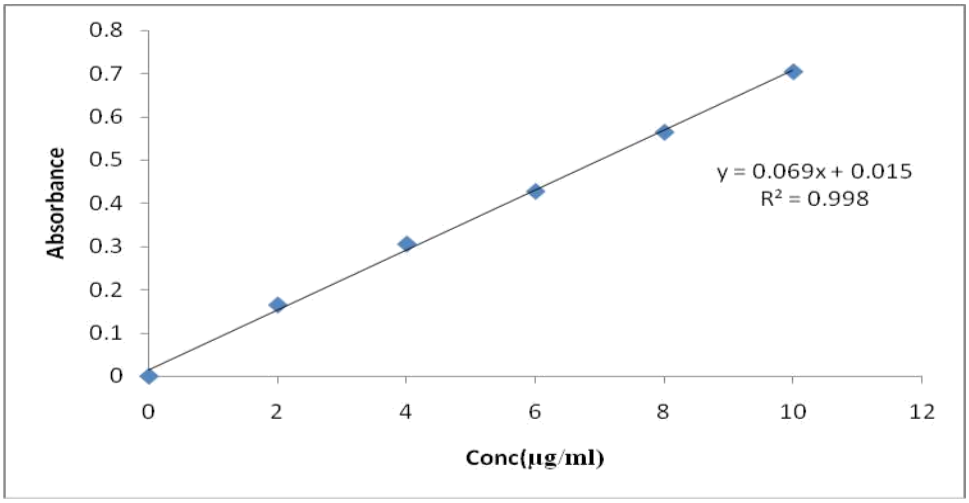
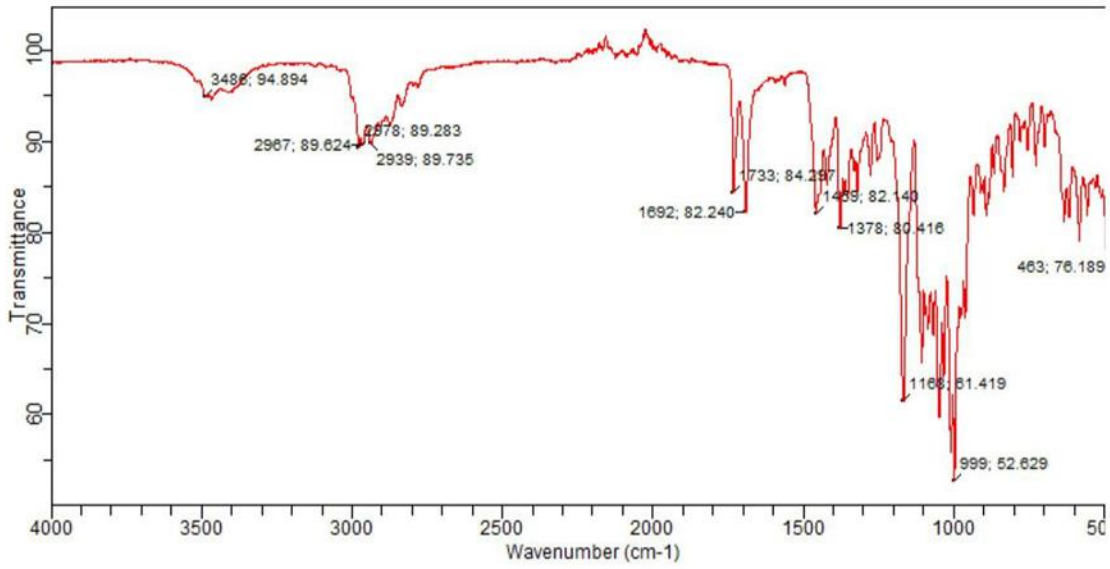


Figure**: Standard graph of clarithromycin in 0.1N Hcl.**

Drug – Excipient compatibility studies



Fourier transform-infrared spectroscopy

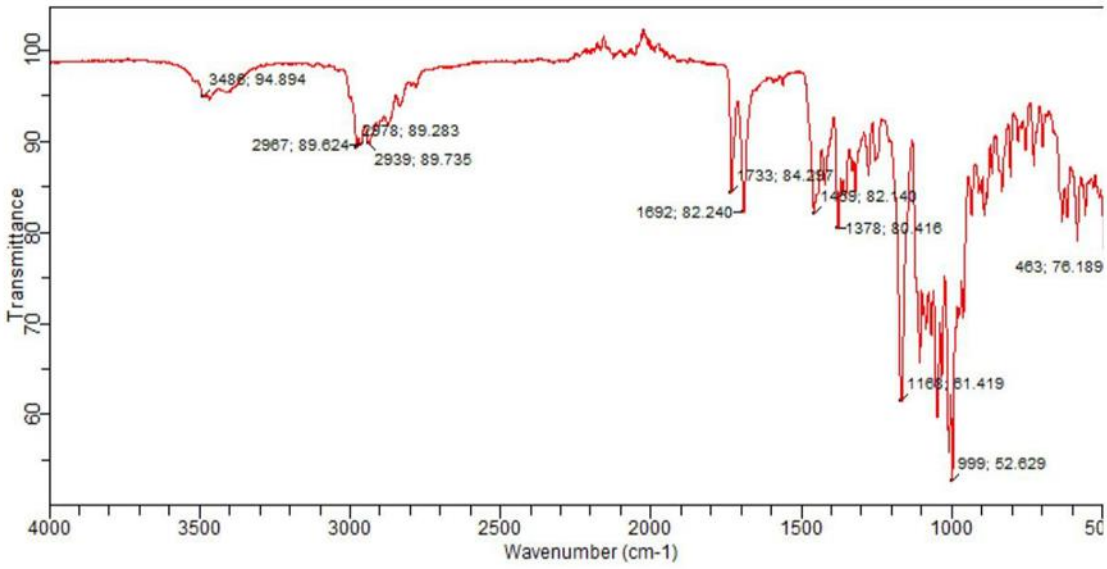


Figure: FT-TR Spectrum of clarithromycin pure drug.

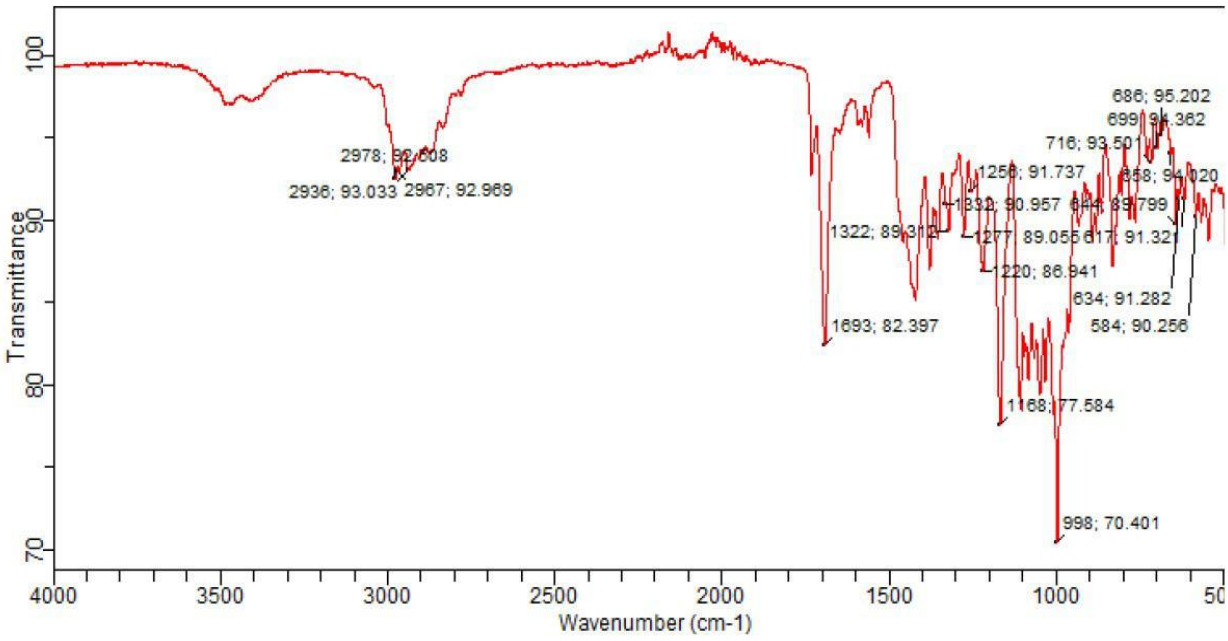


Figure: FT-IR Spectrum of Optimised Formulation

Preformulation parameters of powder blend

Table: 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	26.91	0.45	0.55	18.18	1.22
F2	25.23	0.47	0.55	14.54	1.17
F3	28.34	0.50	0.58	13.79	1.16
F4	27.71	0.46	0.55	16.36	1.19
F5	24.43	0.50	0.58	13.79	1.16
F6	25.32	0.47	0.55	14.54	1.17
F7	26.34	0.50	0.58	13.79	1.16
F8	28.86	0.41	0.50	18	1.21
F9	27.68	0.41	0.50	18	1.21

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 0.41 to 0.50 (gm/cm3) 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 to 0.58 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 13 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner's ratio ranging between 0 to 1.2 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 90 mg concentration showed less floating lag time of 5

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: 6.5.1. In vitro quality control parameters for tablets

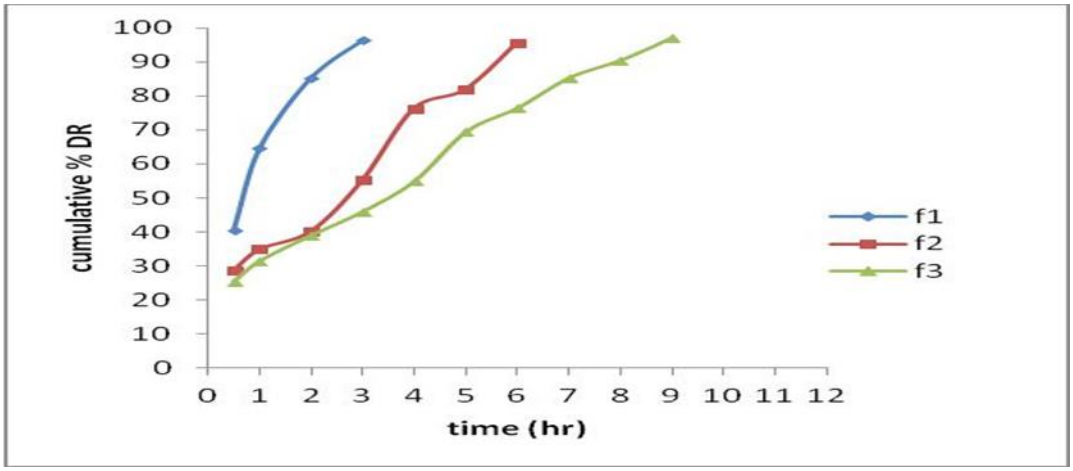
Formulation Code	Average Weight (mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	654.5	4.1	0.56	3.8	95.67	4.5
F2	650.4	4.0	0.64	3.9	98.54	5.1
F3	649.6	4.1	0.56	4.5	101.43	5.9
F4	641.6	4.3	0.55	4.0	100.78	5.6
F5	657.4	4.5	0.60	4.2	96.41	4.9
F6	650.7	4.1	0.58	3.5	98.65	5.4
F7	651.3	4.4	0.67	4.0	108.24	5.2
F8	646.2	4.0	0.53	3.7	102.56	4.6
F9	649.3	4.2	0.55	4.2	99.21	5.4

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 6.6.1: Dissolution Data of Clarithromycin Tablets Prepared with HPMC K 15 M in Different Concentrations.

TIME	CUMULATIVE PERCENT DRUG RELEASED		
(hr)	F1	F2	F3
0.5	40.56	28.77	25.45
1	64.54	34.89	31.45
2	85.32	40.24	38.98
3	96.36	55.23	45.99
4		76.25	54.91
5		81.90	69.46
6		95.56	76.47
7			85.32
8			90.49
9			97.12



Dissolution profile of clarithromycin floating tablets (F1, F2, F3 formulations)

Table: Dissolution Data of Clarithromycin Tablets Prepared with HPMC K 100M In Different Concentrations

TIME	CUMULATIVE PERCENT DRUG RELEASED		
(hr)	F4	F5	F6
0.5	23.57	11.98	9.98
1	32.12	19.67	15.67
2	42.45	26.35	22.35
3	53.10	31.34	27.34
4	69.66	39.68	31.68
5	76.33	46.31	35.31
6	84.01	50.76	47.76
7	96.77	57.72	50.72
8		65.33	58.33
9		71.90	60.90
10		80.20	65.20
11		88.22	70.22
12		97.36	79.36

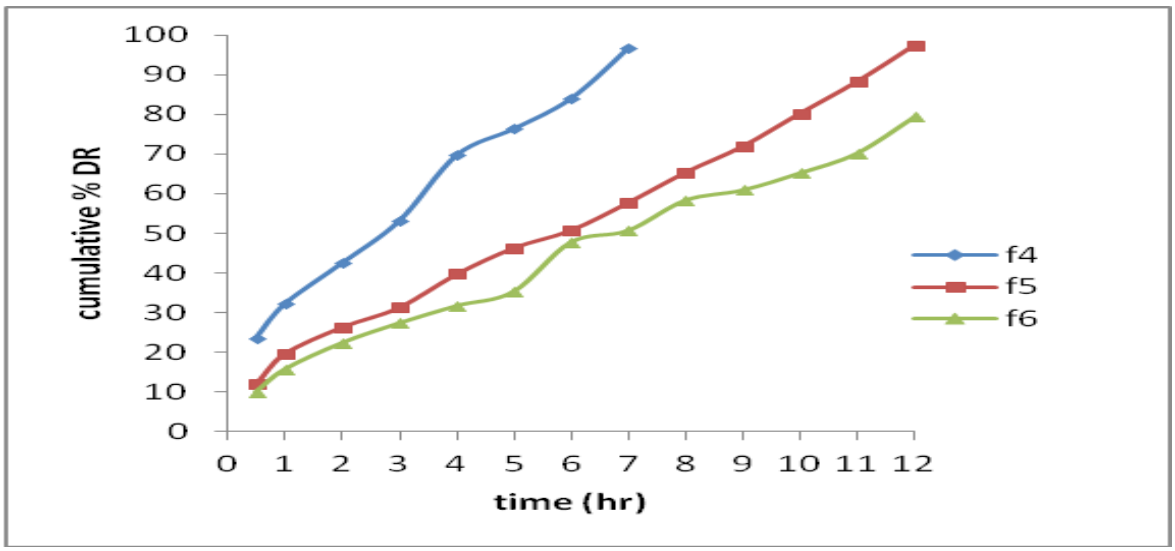


Fig: Dissolution profile of clarithromycin floating tablets (F4, F5, F6 formulations).

Table: Dissolution Data of Clarithromycin Tablets Prepared With Guar gum In Different Concentrations

TIME	CUMULATIVE PERCENT DRUG RELEASED		
(hr)	**F7**	**F8**	**F9**
0.5	46.23	35.14	20.77
1	68.42	49.81	33.91
2	75.90	55.34	45.23
3	83.56	60.52	59.13
4	99.54	78.53	61.1
5		83.64	70.97
6		96.54.	78.57
7			85.49
8			
9			93.67
10			
11			

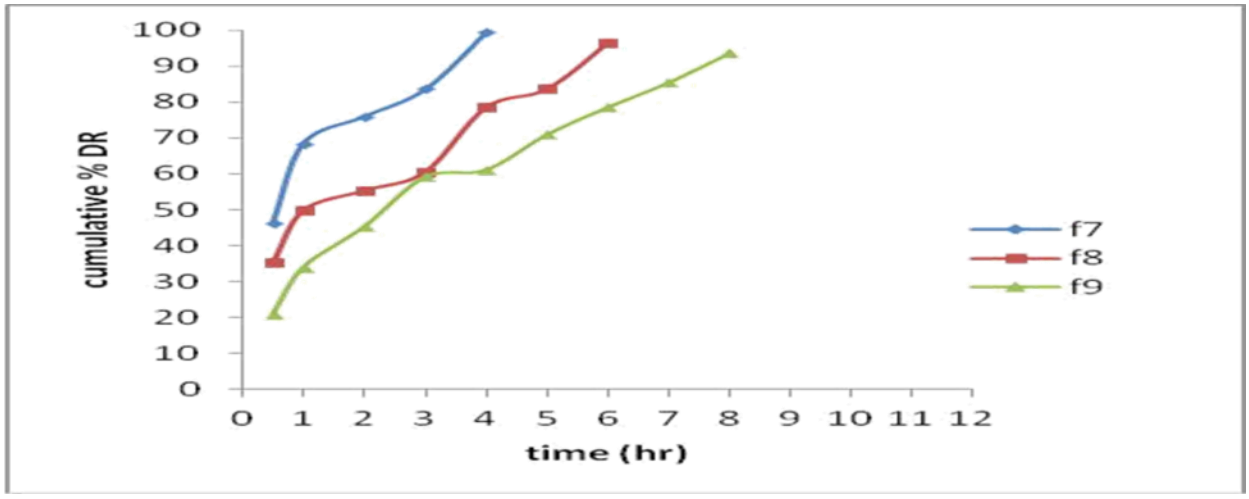


Fig: Dissolution profile of Clarithromycin floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with HPMC K100M as polymer were retarded the drug release up to desired time period i.e., 12 hours in the concentration of 90 mg. whereas in low concentrations the polymer was unable to produce the desired action. (F5 Formulation 97.366% Drug release) . The formulations prepared with higher concentration of HPMC K100M retarded the drug release in more than 12 hours. In lower

concentrations the polymer was unable to retard the drug release. The formulations prepared with HPMC K 15M and guar gum showed very less retardation capacity hence they were not considered.

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.

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
11.98	**0.5**	0.707	1.078	-.301	1.945	23.960	0.0835	-0.922	88.02	4.642	4.448	0.193
19.67	**1**	1.000	1.294	0.000	1.905	19.670	0.0508	-0.706	80.33	4.642	4.315	0.327
26.35	**2**	1.414	1.421	0.301	1.867	13.175	0.0380	-0.579	73.65	4.642	4.192	0.450
31.34	**3**	1.732	1.496	0.477	1.837	10.447	0.0319	-0.504	68.66	4.642	4.095	0.547
39.68	**4**	2.000	1.599	0.602	1.780	9.920	0.0252	-0.401	60.32	4.642	3.922	0.720
46.31	**5**	2.236	1.666	0.699	1.730	9.262	0.0216	-0.334	53.69	4.642	3.773	0.869
50.76	**6**	2.449	1.706	0.778	1.692	8.460	0.0197	-0.294	49.24	4.642	3.665	0.976
57.72	**7**	2.646	1.761	0.845	1.626	8.246	0.0173	-0.239	42.28	4.642	3.484	1.158
65.33	**8**	2.828	1.815	0.903	1.540	8.166	0.0153	-0.185	34.67	4.642	3.261	1.381
71.9	**9**	3.000	1.857	0.954	1.449	7.989	0.0139	-0.143	28.1	4.642	3.040	1.601
80.2	**10**	3.162	1.904	1.000	1.297	8.020	0.0125	-0.096	19.8	4.642	2.705	1.936
88.22	**11**	3.317	1.946	1.041	1.071	8.020	0.0113	-0.054	11.78	4.642	2.275	2.366
97.36	**12**	3.464	1.988	1.000	0.422	8.113	0.0103	-0.012	2.64	4.642	1.382	3.260

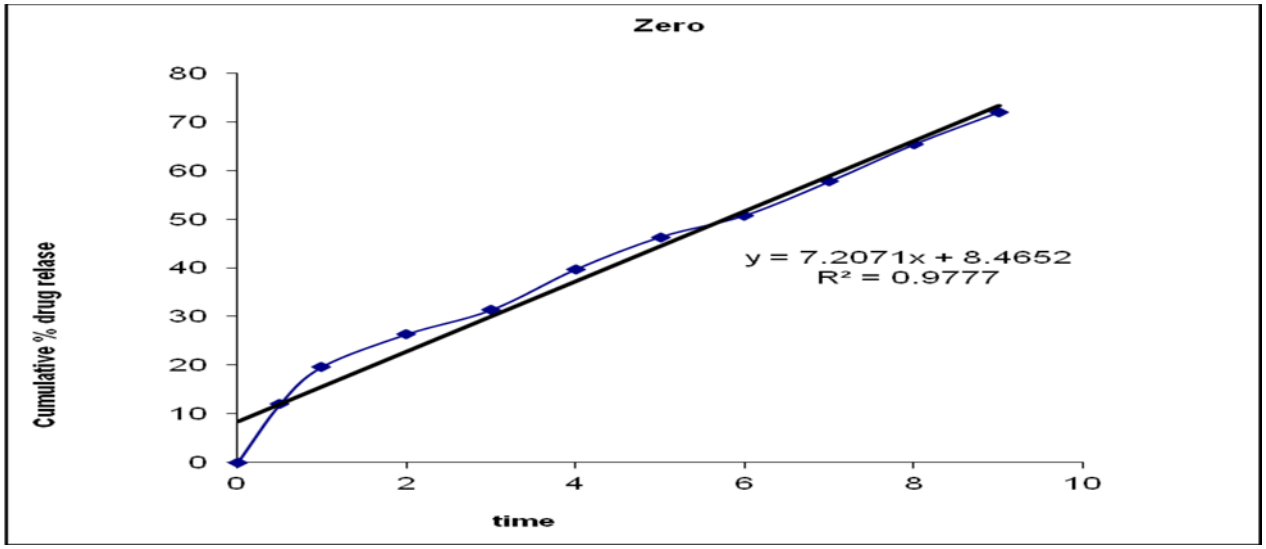
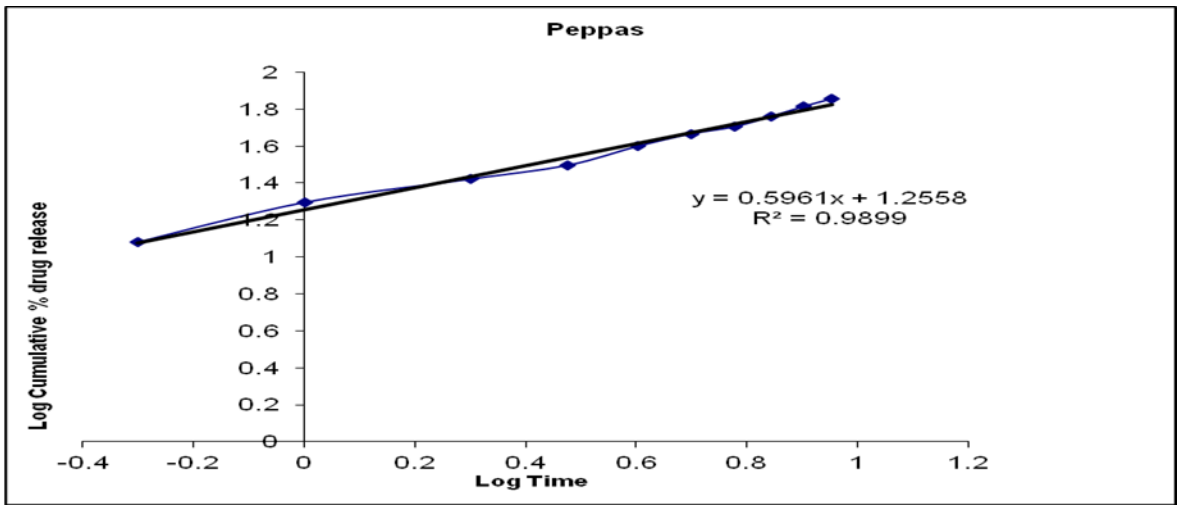


Fig 6.6.4 : Zero order release kinetics graph



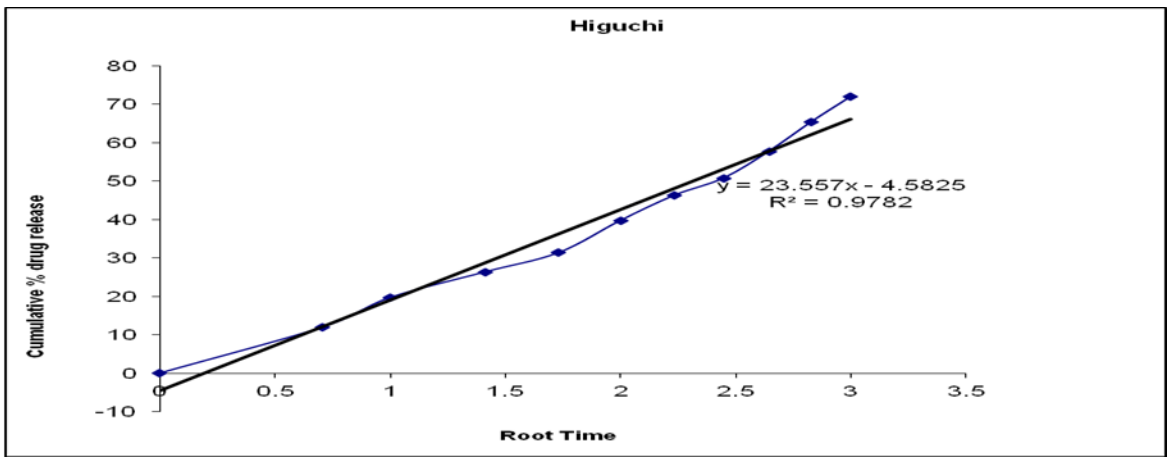


Fig 6.6.5: Higuchi release kinetics graph

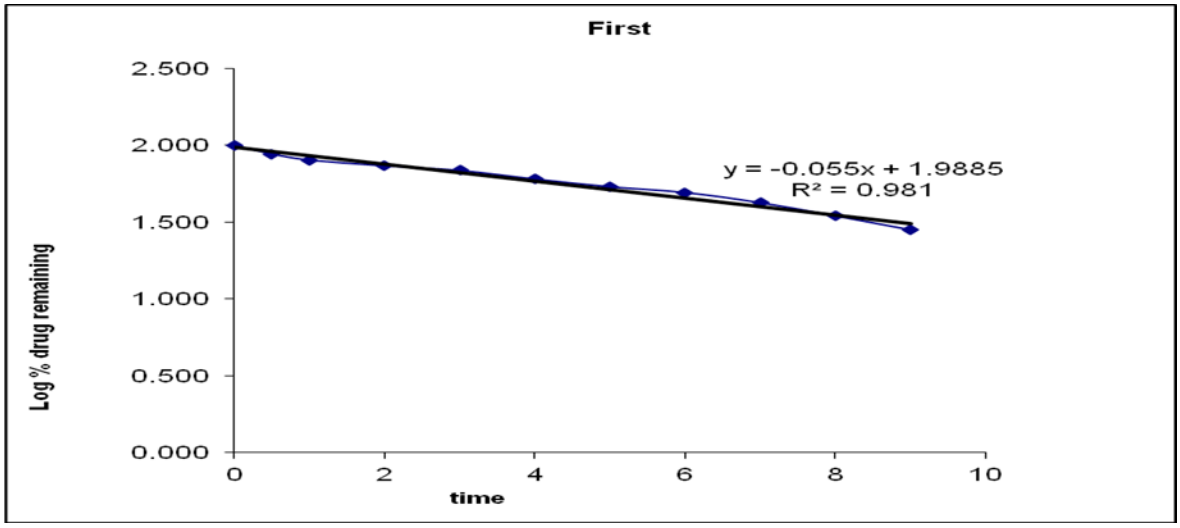


Fig 6.6.6: Kars mayer peppas graph

First order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed karsmayer peppas model release mechanism.

CONCLUSION

In the present research work gastro retentive floating matrix formulation of Clarithromycin by using various hydrophilic polymers were developed. 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 grades of HPMC and guar gum as polymeric substances. The formulation blend was subjected to various preformulation 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 HPMC K100M as polymer were retarded the drug release up to desired time period i.e., 12 hours in the concentration of 90 mg. whereas in low concentrations the polymer was unable to produce the desired action. (F5 Formulation, 97.36% Drug release). 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 peppas mechanism of drug release.

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