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DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM FOR THE MANAGEMENT OF PEPTIC ULCER

Minakshi S. Lothe., S.T.Thoke., U.T. Jadhao., D.A.Rathod. ,G.N.Dhembre., S.A.Wathore.
Department of Pharmaceutics, SVP College of Pharmacy, Hatta, Dist. Hingoli, Maharashtra

Abstract:
The aim of the study was the formulation of the floating matrix tablet of clarithromycin The floating tablet of Clarithromycin was prepared by wet-granulation method. The tablets were formulated using hydrophilic polymer HPMC K15M and HPMC K100M, along with an effervescent agent such as sodium bicarbonate. Preformulation compatibility studies indicate that there is no interaction between the excipient and the drug. Total eight batches were prepared and powder blends before compression was subjected for evaluation of flow properties. All the parameter was found to be within the limit showing good flow property. all batch was evaluated for thickness, hardness, friability, weight variation, drug content uniformity, swelling index, buoyancy studies, invitro release pattern. The thickness of tablet indicates that die fill was uniform in all the formulation and the formulation possessed sufficient hardness & friability indicating a good mechanical strength of the development formulation. The weight of the all the formulation were found to be with in pharmacopeial limit. The invitro dissolution profile of all the formulation of Clarithromycin was controlled over an extended period of time. The optimized formulation of F8 containing combination of HPMC K15M, HPMC K100M was consider as the best formulation with respect to its lower floating lag time, sustained in vitro drug release for 12 hrs, total floating time & improved bioavailability & site specific action. The developed formulation was found to be stable during the stability studies of 3 month indicating good stability of the tablets

Keywords: *Clarithromycin, H-pylori infection, floating time, stability studies.*

Corresponding Author:
Mr.Sandip T.Thoke,
Department of Pharmaceutics,
SVP College of Pharmacy, Hatta, Dist. Hingoli, Maharashtra
Mail-sandipthoke377@gmail.com

QR code

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INTRODUCTION:

The concept of floating drug delivery system was described in literature as early as1968. Floating dosage forms are oral dosage forms of tablets38, capsules, or micro beads and contain hydrocolloids that allow floating by swelling there by prolong the residence time of dosage form within gastro intestinal tract. Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.[1, 2]

A floating drug delivery system (FDDS) is a type of drug delivery system designed to prolong the residence time of drugs within the gastrointestinal (GI) tract, particularly the stomach. The primary objective of FDDS is to enhance the bioavailability and efficacy of drugs, particularly those with narrow absorption windows or those that degrade in the acidic environment of the stomach.In FDDS, the drug is typically incorporated into a formulation that possesses low density or contains gas-generating agents, allowing it to float on the gastric contents after ingestion. This buoyancy ensures that the drug remains in the stomach for an extended period, thereby prolonging its release and absorption. [3,4]

Effervescent system floating drug delivery system these are particular drug delivery system made up of matrix type and a swellable polymer such as methylcellulose and chitosan along with effervescent compounds *viz.* sodium bicarbonate, tartaric acid, citric acid. These are formulated in such a specific way as once it comes in contact with gastric juice; co_2 gets liberated with entrapment in swollen hydrocolloid to provide buoyancy for dosage form. The basis of the delivery system is on swellable asymmetric triple layer tablet approach design. Gas generating systems Low-density FDDS is based on the release of co_2 upon contact with gastric fluids after oral administration.[5] The materials are formulated in such a way that after entering in the stomach, co_2 is librated due to reaction with acidic gastric content and which get entrapped in the gel-based hydrocolloid. It produces an upward motion of the dosage form and maintains its buoyancy. Ultimately it causesa decrease in specific gravity of dosage form and hence resulting into a float on the chime. The co_2 generating components are mixed within the tablet matrix in a single layer or multi-layered form to produce gas generating mechanism in hydrocolloid layer,and the drug in the other layer results into a sustained release effect.[6]

Clarithromycin is a macrolide antibiotic that inhibits bacterial protein synthesis. It binds to the 50S ribosomal subunit of susceptible bacteria, blocking the translocation of peptides. This action prevents the bacteria from growing and replicating, making clarithromycin bacteriostatic. At higher concentrations, it can exhibit bactericidal activity against certain pathogens. Clarithromycin is rapidly absorbed from the gastrointestinal tract. The bioavailability is approximately 50% due to first-pass metabolism.

Materials and Method

Materials

Clarihtromycin was obtained as gift sample from Cipla Pharma pvt. Ltd., Mumbai, HPMC K4M & HPMC K100M were obtained from Colorcon Asia Pvt Ltd. All other chemicals are Analytical grades.

Method

Drug Excipients Compatibility Studies

Drug-excipient compatibility studies are an essential part of preformulation and formulation development processes in the pharmaceutical industry. These studies assess the compatibility of a drug substance with various excipients that are used to formulate the final dosage form. he primary purpose of drug-excipient compatibility studies is to evaluate potential interactions between the drug substance and excipients. These studies aim to identify any chemical, physical, or mechanical interactions that could affect the stability, efficacy, or safety of the final dosage form. By assessing compatibility early in the development process, formulation scientists can make informed decisions regarding excipient selection, formulation design, and process optimization. Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (Shimadzu, Japan). The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of the drug and other ingredients in the formulations were compared with that of the pure drug.[7]

Formulation of Clarithromycin Floating Tablets [8,9]

Clarithromycin floating tablets were prepared by wet granulation method using different concentrations of polymers with sodium bicarbonate as gas generating agent. All excipients expect talc and magnesium stearate were accurately weighted and passed through 40 mesh. Calculated the amount of drug, polymer, microcrystalline cellulose were mixed thoroughly in morter. A sufficient volume of the isopropyl alcohol as granulating agents were added slowly to achieve enough cohesive mass. The granules was prepared by passing the wet mass through a sieve no 16 #. The resultant granules were then dried in hot air oven at

60° for 30 min. The granules were collected and passed through 20 mesh. Finally dried granules were lubricated with magnesium stearate and talc my mixing properly in mortar. The lubricated granules were compressed using 9 mm round standard concave punches (Chamunda Press). The composition of different formulation of clarithromycin floating tablets is shown in the table 1.

Table 1: Composition of Floating Tablets of Clarithromycin

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Clarithromycin	500	500	500	500	500	500	500	500
HPMC K4M	100	125	150	-	-	-	75	50
HPMC K100M	-	-	-	100	125	150	75	100
PVP K30	40	40	40	40	40	40	40	40
Sodium Bicarbonate	30	30	30	30	30	30	30	30
Talc	2	2	2	2	2	2	2	2
Mg. stearate	2	2	2	2	2	2	2	2
Microcrystalline Cellulose	126	101	76	126	101	76	76	76
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Weight	800	800	800	800	800	800	800	800

Precompression Parameters

Flow properties of Physical mixture were determined by measurement of angle of repose, bulk density, and tapped density, compressibility index (CI) and hausner's ratio.[10,11]

Post compression Parameters

Weight Variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. The average weight per unit is then calculated by dividing the total weight by the number of units in the sample.[12]

Hardness

The hardness test is a crucial quality control measure in pharmaceutical manufacturing, particularly for solid oral dosage forms like tablets. Tablet hardness, often measured in terms of breaking force or resistance to crushing, provides an indication of the mechanical strength and robustness of the tablet. Hardness testing ensures that tablets can withstand handling, packaging, and transportation without breaking or crumbling, thereby maintaining their integrity and appearance throughout their shelf life. Hardness or tablet crushing strength ie the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.[13]

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.[14]

In Vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time method. The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).[15,16]

Content Uniformity

Ten tablets were randomly selected and tested for their drug content. Each tablet was powdered and quantity of powder equivalent to 100 mg of drug was taken and transfer it to 10 ml of 6.8 pH phosphate buffer. The resulting solution was then diluted appropriately and measured using a UV-Visible spectrophotometer at 210 nm.[17]

In-Vitro Dissolution Study

The in-vitro dissolution study was carried out in USP dissolution test apparatus type II (paddle) with a dissolution medium of 900 ml of 0.1N Hcl, at 50 rpm

(37±0.5°C). 5 ml aliquot was withdrawn at the specified time interval, filtered through whatman filter paper, and measured spectrophotometrically after suitable dilution at 210 nm using UV-Visible spectrophotometer. An equal volume of fresh medium, which was pre warmed at 37°C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. The results in the form of percent cumulative drug released was calculated.

Swelling Index

The swelling behaviour of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium as 0.1N HCl at 37 ± 0.5°C. After 1, 2, 3, 4, 5, and 6h, each dissolution basket containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point.[18]

Stability study

The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminum foil and was stored in stability chamber maintained at 40ºC and 75% RH for the period of 3 months. The Tablet were evaluated before and after 3 months for change in appearance, Hardness, disintegration time, drug content and in -vitro drug release.[19]

RESULT AND DISCUSSION:

Compatibility Studies (FT-IR)

Both the polymer and pure drug's infrared spectra are examined. It has been found in this investigation that there is no chemical interaction between the polymer and Clarithromycin. The major peak in the drug and polymer mixture's infrared spectra was found to remain unchanged, indicating that there was no physical interaction due to bond formation between the two substances.

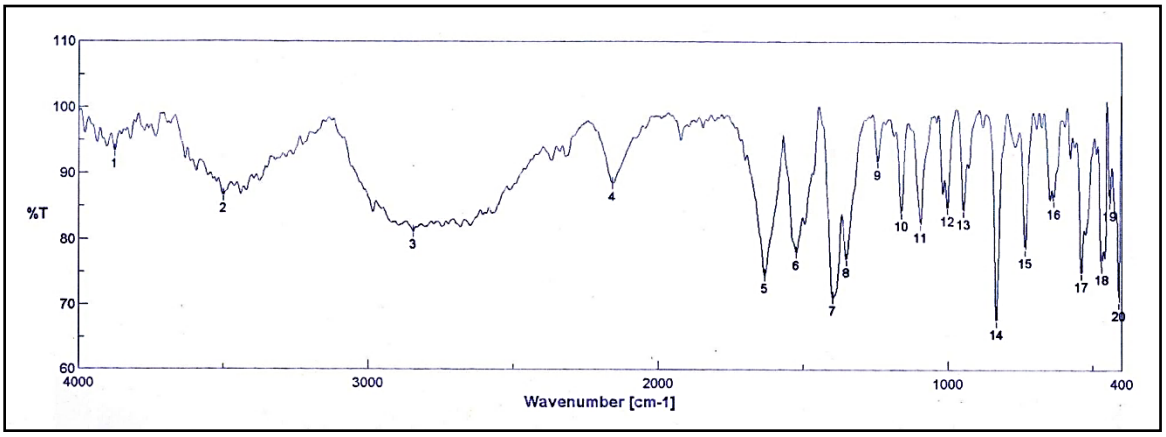

Figure 1 IR spectra of pure drug Clarithromycin

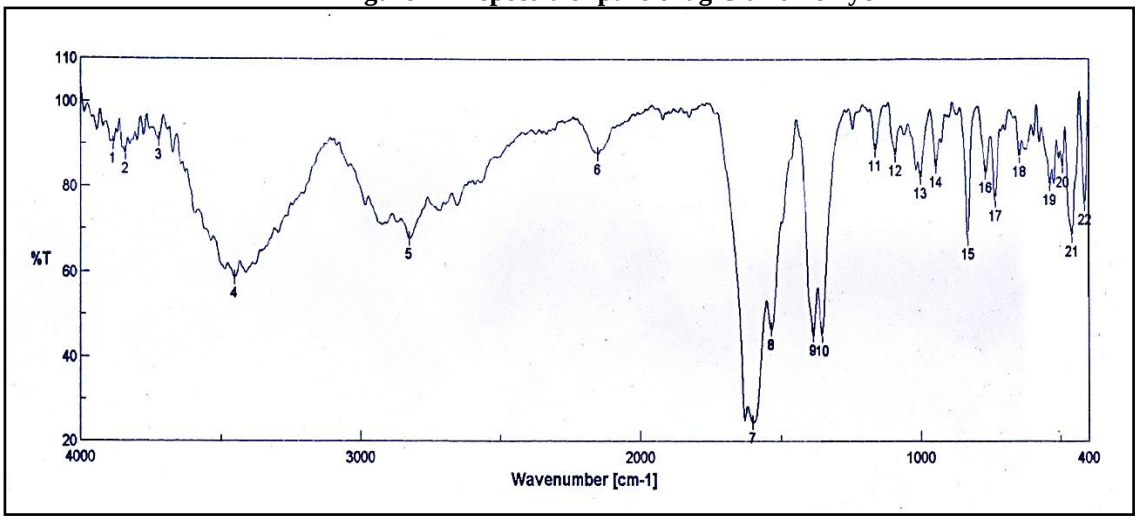

Figure 2 IR Spectra of Physical Mixture.

Pre compression Parameter

The results of micromeritic properties of powder blend were showed in table 8.2. Bulk density values for all batch powder blend was obtained in the range from 0.43 - 0.45 gm/cc and the tapped density values obtained in the range from 0.52 - 0.56 gm/cc. Angle of repose value for all the formulation ware found in the range between 25.12 – 28.32$^{\theta}$ showing good flow properties for all batch powder blends. The compressibility index and Hausner's ratio was further calculate to determine the flowability of powder blend. The % compressibility index value for all batch powder blends was found in the range of 15.38 to 20.37 indicating excellent to good flow properties for all batch. Hausner ratio for all batch powder blend was found below 1.25 showing excellent flow properties of powder blends of all batches. Thus from the micromeritics study it was found that all batch formulation exhibiting the good flow properties of the powder blend. Thus the powder showed better flow properties and were non aggregated.

Table 2: Micromeritics properties of powder blend (F1 to F8)

Batch	Angle of Repose (θ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility Index (%)	Hausner's Ratio
F1	27.60±0.12	0.45±0.16	0.55±0.56	18.18	1.22
F2	26.61±0.21	0.45±0.15	0.56±0.43	19.64	1.24
F3	26.16±0.16	0.43±0.33	0.54±0.31	20.37	1.25
F4	25.74±0.23	0.45±0.21	0.54±0.10	16.66	1.20
F5	28.32±0.31	0.44±0.24	0.55±0.16	20.00	1.25
F6	26.28±0.19	0.46±0.81	0.56±0.25	17.85	1.21
F7	27.46±0.25	0.45±0.42	0.54±0.27	16.66	1.20
F8	25.12±0.15	0.44±0.35	0.52±0.16	15.38	1.18

POST COMPRESSION PARAMETERS

Weight Variation:

The weight variation test for all tablets formulation (F1 to F8) was passed and found within pharmacopoeial standards. Passing the weight variation test ensures that each tablets was within a batch contains the specified amount of active pharmaceutical ingredient (API) and excipients. This ensures uniform dosing and therapeutic efficacy for patients consuming the medication.

Hardness

The hardness of tablets for all batch formulation (F1 to F8) was found in the range from 4.5 to 5 kg/cm2, which was found to be optimum and indicate tablets able to withstand mechanical shock.

Thickness

It was found from the range of 5.10 to 6.12 mm for formulation F1 to F8 is found to be optimum and indicated well distribution of pure drug. Tablet thickness directly influences the amount of active pharmaceutical ingredient (API) and excipients contained within each tablet. Consistent tablet thickness ensures uniformity of dosage across the batch, contributing to predictable and reliable therapeutic outcomes for patients.

Friability

The friability value of all tablets batch formulation F1 to F8 were found to be less than 1% indicating good mechanical strength of tablets. Passing the friability test ensures that tablets maintain their physical integrity and withstand mechanical stress under normal handling conditions.

Drug Content

Good uniformity of drug content was found within and among the different batches of tablet formulation. The values ranged from 95.26 to 99.80% which ware in pharmacopoeial limits.

Table 3: Post Compression parameters of Floating Tablets of Clarithromycin (F1 to F8)

Batch	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/Cm^2)	Friability (%)	Drug Content Uniformity (%)
F1	804.12±0.25	5.10±0.05	4.5±0.60	0.62±1.1	96.74±1.1
F2	805.34±1.10	5.96±0.07	4.5±0.55	0.60±0.9	98.82±1.2
F3	798.45±0.67	6.10±0.07	5.0±1.30	0.61±0.12	97.30±1.1
F4	802.26±0.54	5.21±1.8	4.5±0.80	0.56±0.18	96.08±1.1
F5	807.12±1.22	5.90±1.2	5.0±0.58	0.67±0.27	97.32±1.3
F6	804.63±1.24	6.12±1.2	4.5±0.85	0.60±0.16	95.26±0.4
F7	802.45±0.64	5.98±1.3	4.5±1.26	0.78±0.31	96.71±1.0
F8	802.16±0.52	5.90±1.4	4.5±1.16	0.54±0.24	99.80±0.9

(SD ± Mean of n=3)

In Vitro buoyancy studies

All the floating tablet formulation are prepared by effervescent approach. On immersion in to the 0.1N HCL all the floating effervescent tablet float immediately and remain buoyant more than 12hrs without disintegration. The tablet was induced by sodium bicarbonate without compromising the matrix integrity with the possible shortest bouncy lag time and buoyancy duration is up to 12hrs. It was observed that the gas generated was trapped in the tablet and protect within the gel formed by hydration of polymer, thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The total buoyancy time of all formulation was more than 12hrs. As concentration of the polymer increases the floating increase.

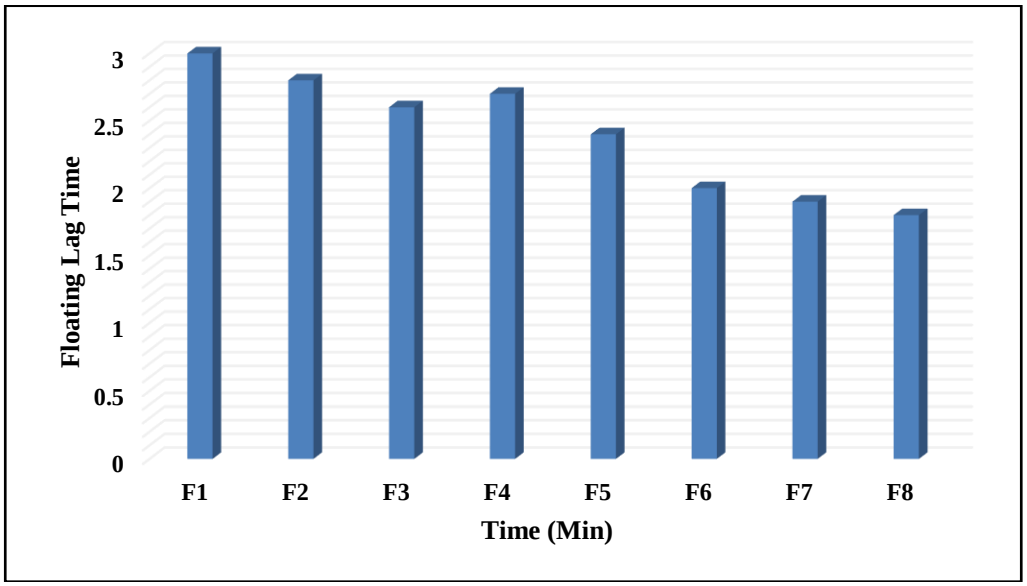

Figure 3: Floating Lag time of formulation (F1 to F8).

In-Vitro Dissolution Study

In vitro drug release study of prepared floating tablets of clarithromycin was determined in 0.1 N Hcl as dissolution medium. Formulations F1, F2 and F3 prepared with HPMC K4M showed 94.54, 96.47 and 96.98% drug release respectively in 7, 8 and 8 hrs respectively and fails to sustained the drug release up to 12 hrs. Formulation F4, F5, and F6 prepared with HPMC K100M showed 99.42%, 96.14% and 94.35 % drug release respectively in 10 hrs and again not able to sustained the drug release up to 12 hrs. While formulation F7 and F8 prepared with combination of both HPMC K4M and K100M as a rate control polymer was found to be effective in holding the drug in polymer matrix for longer duration. Batch F7 showed drug release of 93.42% in 12 hrs, while batch F8 showed drug release of 99.12% in 12 hrs. All the formulation showed sustaining the release of drug because of presence of hydrophilic two different grade of polymer. All batch formulation showed sustaining the drug release for extended period of time.

Among the different formulations, batch F8, prepared with combination of two grades of HPMC polymer, showed sustained release of drug for the periods of 12 hrs. From the results it was observed that, as the concentration of both grade of polymer increases, the drug release decreases.

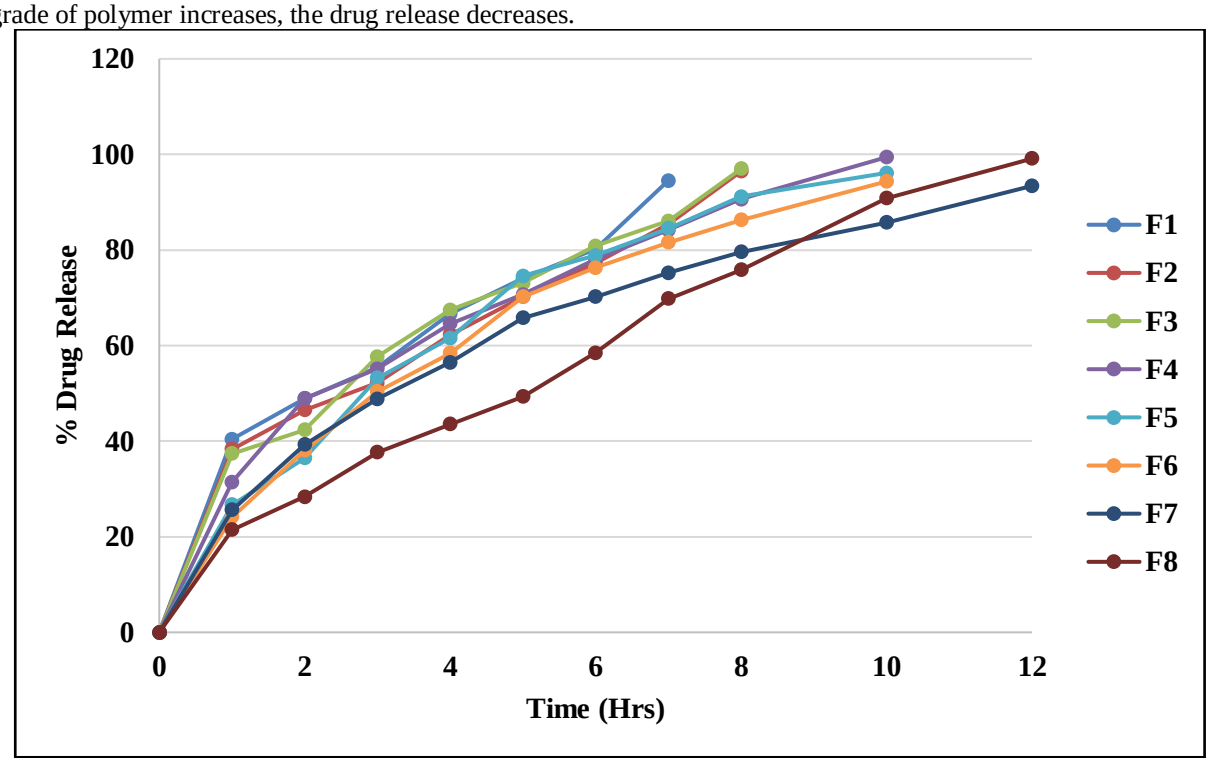

Figure 4: Comparative In vitro Dissolution Profile of formulation F1to F8

Swelling Index

Swelling study was performed on all the batches (F1 to F8) for 6 hr. The results of swelling index were shown in table 8.6, swelling index against time (hr) plotted in figure. 8.9. Swelling index study showed that the swelling increases with the time, because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. In the present study, the higher swelling index was found for tablets of batch F8 containing combination of polymer HPMC K4M and HPMC K100M. It was found that swelling index was higher for high viscosity grade polymer. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

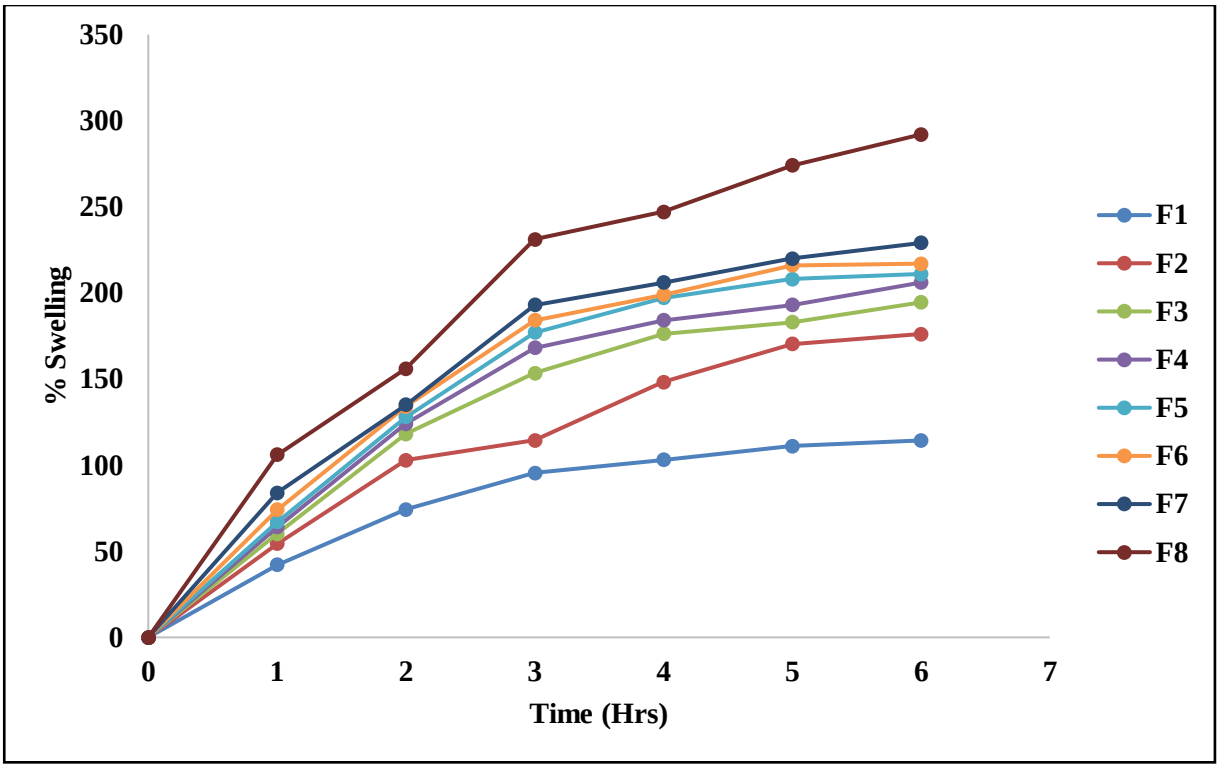

Figure 5: Swelling Index of Clarithromycin Floating Tablet.

Stability Study

Clarithromycin Floating tablets formulation showing promising results in term of lowest floating lag time and sustained drug release, was selected for stability studies. According to ICH guidelines, optimized formulations F8 were stored at 40^0C temperature and 75% relative humidity (RH) for a period of 3 months. Formulation was evaluated for appearance, Hardness, drug content, floating lag time, total floating time and In vitro drug release. At the end of 3 months no significant difference was observed in tested parameters. From the stability study it was concluded that clarithromycin Floating tablets formulation F8 was found to be stable. The results of stability data were shown in table 4.

Table 4: Stability data of Optimized formulation F8.

Formulation Code	Parameter	Before storage (0 month)	After storage (3 month)
F8	**Hardness (kg/cm2)**	4.5±1.16	4.5±0.58
	Drug Content (%)	99.00±0.90	98.76±0.42
	Floating lag Time (min)	1.8	2
	Total Floating Time (hr)	> 12 hrs	> 12 hrs
	% Drug Release	99.12 ±1.25	98.51±1.61

CONCLUSION:

From the present study following conclusion were observed The Floating tablet of clarithromycin can be prepared by wet-granulation method by using HPMC K15M, HPMC K100M, and sodium bicarbonate as a gas generating agent. All the prepared tablet was found to be good without capping and chipping. IR-spectroscopic studies indicate no drug-exicipent interaction in formulation. All batch formulations showed lower floating lag time and more than 12 hrs of total floating time.The in vitro dissolution profile of all the prepared floating tablets formulation of clarithromycin were found to extend the drug release over a period of 7 to 12 hrs.In vitro dissolution study showed that as the concentration of polymer increases the drug release decreases. Use of combination of polymer effectively controlled the release of drug over 12 hrs periods.Comparing all the formulation batch F8 was consider as the ideal formulation which exhibited (99.12%) drug release in 12 hrs and lower floating lag time of 1.8 min with a total floating time over

more than 12 hrs. Future details investigation is required to established in vivo efficiency of clarithromycin floating tablet and long term stability need to be confirm the stability of floating clarithromycin tablets.

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