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FORMULATION AND EVALUATION OF STOMACH SPECIFIC FLOATING *IN-SITU* GEL OF CLARITHROMYCIN

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Keywords:

Stomach specific floating drug delivery system, *In-situ* gel, Clarithromycin, Xanthan gum, Stomach ulcer

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ABSTRACT: Floating drug delivery system comes with the advantage of sustained release of drugs over a prolonged period of time thereby maximizing the oral absorption of drugs with narrow absorption window, it overcomes the challenges of conventional oral drug delivery system. The aim of the present work was to develop a novel floating *in-situ* gelling system for sustained drug delivery of Clarithromycin for stomach ulcer. *The in-situ* gelling system were prepared by dissolving different concentrations of gelling polymers like sodium alginate, gellan gum in deionized water at 70 °C. After cooling to 40 °C fixed amount of drug, $CaCO_3$ and released retardant polymer xanthan gum were dispersed with continuous stirring. All formulations showed pH in the range of 6.72 to 7.25, drug content was found to be in the range of 86.66% to 96.66%, floating lag time was <2 min, duration of floating was >12 h for all the formulations. It was observed that viscosity of solution increases with an increase in polymer concentration. *In-vitro* drug release was found to be in between 58.88% to 82.50% up to 12 h, and the maximum drug release was shown by formulation F1 (1.0%w/v sodium alginate). Drug release is inversely proportional to polymer concentration. The release kinetics of best formulation F7 (1.0%w/v sodium alginate and 0.25% w/v xanthan gum) followed first order with Higuchi diffusion mechanism. Hence, floating *in-situ* gelling system of Clarithromycin is a novel approach to increase patient compliance with reduced dosing frequency and increased residence time of drug in the stomach.

INTRODUCTION: Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation [1]. Oral drug delivery is the ideal and well preferable route of administration due to its simple and comfortable use and flexibility about different types of formulation [2].

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Drug absorption in the GIT is a highly variable process, and it depends on the factors like gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form, and site of absorption of drugs [3].

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract and maintain an effective drug

concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT [4]. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve prolong gastric residence time by the drug delivery [1].

Gastro-Retentive Drug Delivery System: GRDD is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper GIT for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the GRT of drugs [5]. This prolonged gastric retention enhances the bioavailability, decreases drug wastage, and improves solubility of drugs that are less soluble at high pH environment [6]. GRDDS provide support to reduce the frequent dosing of such drug by producing a controlled delivery within stomach for longer duration [7]. Gastro-retentive dosage forms are delivery systems that will provide the system to be able to control the gastric residence time or gastric transit time of the dosage form to achieve a prolonged and predictable drug delivery profile in the upper part of the GI-tract. Gastro-retentive systems can be based on the floating systems, bioadhesive or mucoadhesive systems and systems that have a size or will expand in the stomach to a size that is too large to pass the pyloric sphincter [2, 8].

In the *in-situ* type of drug delivery system, the preparation is in a solution form before administration in body, but it converts into a gel form after administration. An *in-situ* gel is made of polymer materials that have a solution or semisolid state that responds to external stimuli at the administration site. These gels also have conformations that can undergo reversible conversion to form a semisolid or solid preparation. Clarithromycin is a macrolide antibiotic hence it can be used to treat stomach ulcer. Clarithromycin is rapidly absorbed from GIT and undergoes first-pass metabolism and have shorter half-life and bioavailability thus they eliminated quickly from systemic circulation. To avoid this limitation, the development of oral sustained release floating *in-situ* gel of Clarithromycin is an attempt to release the drug slowly into the GIT specifically to stomach and maintain an effective drug concentration in the systemic circulation for long period of time [9-15].

The objective of the study is to formulate stomach specific floating *in-situ* gel of Clarithromycin using different polymers. Gastro retentive drug delivery of Clarithromycin in the form of oral *in-situ* gel will increase the residence time of the drug and also will release the drug for an extended period, thereby can reduce the frequency of dosing and also increase bioavailability. The prepared formulation is evaluated for appearance, pourability, viscosity, *in-vitro* gelling capacity, *in-vitro* floating studies, drug content, and *in-vitro* drug release.

MATERIALS AND METHODS:

Materials: Clarithromycin, xanthan gum, gellan gum (Yarrow chem. Products, Mumbai) sodium alginate (Chemvin Industries, Thrissur). All the other chemicals and reagents used in this study were of analytical grade.

Methods:

Preparation of Calibration Curve of Clarithromycin: The working standard solutions of clarithromycin (5-25 µg/ml) were scanned in the UV region and the absorbances were observed against 0.1 N HCl (pH 1.2) solution as blank at 273 nm. Finally, the calibration curve was plotted with concentration on X-axis and respective absorbances on Y-axis.

Drug Excipient Compatibility Studies: [16] Fourier-transform infrared (FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The pure drug was mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

Formulation of *in-situ* Gel of Clarithromycin: *In-situ* gels were prepared using gelling polymers like sodium alginate and release retardant polymer xanthan gum. Various concentrations of gelling polymer were dissolved in deionized water with weighed amount of trisodium citrate. The polymer solution is heated to 60-70 °C. A fixed quantity of drug, calcium carbonate and retardant polymer xanthan gum was added after cooling the solution below 40 °C with continuous stirring to form uniform dispersion. Required quantities of preservatives were added to the solution [17]. Finally, the volume was adjusted with the deionized water, and the resultant solution was stirred well and stored in amber-coloured bottle.

Appearance: Gel formulations were visually inspected for clarity, color and homogeneity.

Surface pH: The pH values of different formulations were measured using a calibrated digital pH meter at room temperature in triplicate.

Viscosity: [17] Viscosities of the formulations are determined with the help of Brookfield's digital Viscometer (DV-II) +Pro using S21 spindle at 50 rpm and measurement was for done for 6 times with fresh samples being used each time and average reading was taken.

***In-vitro* Floating Studies:** [18] Floating studies of *in-situ* gelling solution were carried out in 500 ml of 0.1N HCl (pH 1.2) in a beaker. 10 ml of solution was added to HCl with mild agitation. The parameters like the time taken for the system to float over the surface of the medium (floating lag time) and the time the formed gel constantly float over the surface of the dissolution medium (floating time) can be estimated.

***In-vitro* Gelling Capacity:** [19] To evaluate the formulations for their *in-vitro* gelling capacity by visual method, colored solutions of *in-situ* gel forming drug delivery system were prepared. The *in-vitro* gelling capacity of prepared formulations was measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37 ± 1 ºC temperature. One ml of colored formulation solution was added with the help of a pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into a stiff gel-like structure.

The gelling capacity of the solution was evaluated on the basis of stiffness of formed gel and time period for which the formed gel remains as such. The color was added to give visualized appearance to formed gel. The *in-vitro* gelling capacity was graded in three categories on the basis of gelation time and time period for which the formed gel remains. (+) Gels after few minutes dispersed rapidly (++) gelation immediate remains for 12 h (+++) gelation immediate remains for more than 12 h.

Determination of Drug Content: [20] 10 ml of *in-situ* gel was measured and transferred to 100 ml of the volumetric flask containing 0.1N HCl and stirred for 1 h on magnetic stirrer. The solution was filtered and suitably diluted with (0.1N HCl, pH 1.2 medium), and the drug concentration was determined by using a UV-visible spectrophotometer at 273 nm against a pH 1.2 medium as the blank solution.

***In-vitro* Drug Release Studies:** [21] The drug release study was carried out using USP Type II paddle-type apparatus at 37°C ± 0.5°C and at 50 rpm using 900 ml of a dissolution medium having 0.1N HCl (pH 1.2). *In-situ* gel equivalent to 100 mg of Clarithromycin was used for the test. 5 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µm membrane filter, dilute suitably, and analyzed by ultraviolet spectrophotometer at 273 nm. The same amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Each dissolution study was carried out for a period of 12 h.

Stability Studies: [22] The stability studies were carried out according to ICH and WHO guidelines to determine the physical and chemical stabilities of prepared formulations. The optimized formulation (F7) was kept in an airtight amber-colored bottle for a period of 6 months in room temperature (25 ºC ± 2 ºC at 65% RH ± 5% RH) and accelerated temperature (40 ºC ± 2 ºC at 75% RH ± 5% RH). The formulation was evaluated

visually and for its *in-vitro* gelling capacity, *in-vitro* floating ability, viscosity, drug content and *in-vitro* drug release.

RESULTS AND DISCUSSION:

Calibration Curve of Clarithromycin: Calibration curve of Clarithromycin was plotted by taking absorbance of solutions (5-25 µg/ml) at 273 nm using 0.1 N HCl (pH 1.2) as blank. The curve was drawn taking concentration on X-axis and corresponding absorbance on Y-axis. The curve was found to be linear and thus obeyed Beer Lambert's law in above concentration range. The standard graph of Clarithromycin is shown in following figure.

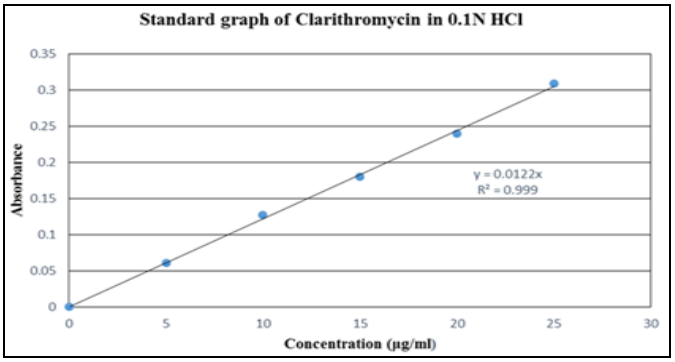

FIG. 1: CALIBRATION CURVE OF CLARITHROMYCIN

Drug Excipients Compatibility Studies: The compatibility of pure drug Clarithromycin with polymers used in the formulation, sodium alginate, gellan gum and xanthan gum were studied. The individual spectra are compared with the physical mixture of drug and polymer and no major differences were found in the absorption position of the peaks. Hence, there are no incompatibility problems with the drug and polymers. The table shows the absorption peaks of Clarithromycin that characterized the drug.

Appearance: All the formulations were visually inspected.The formulations were inspected visually for their appearance and for their pourability. All nine formulations were viscous free-flowing liquids and do not produce gelation at room temperature. The viscosity of formulation increases with increase in concentration of polymer. A formulation containing xanthan gum has more viscosity because of the viscosity enhancement property of xanthan gum.

Formulations F1 to F8 is easily pourable. F8 and F9 formulations are difficult to pour from the container due to high viscosity.

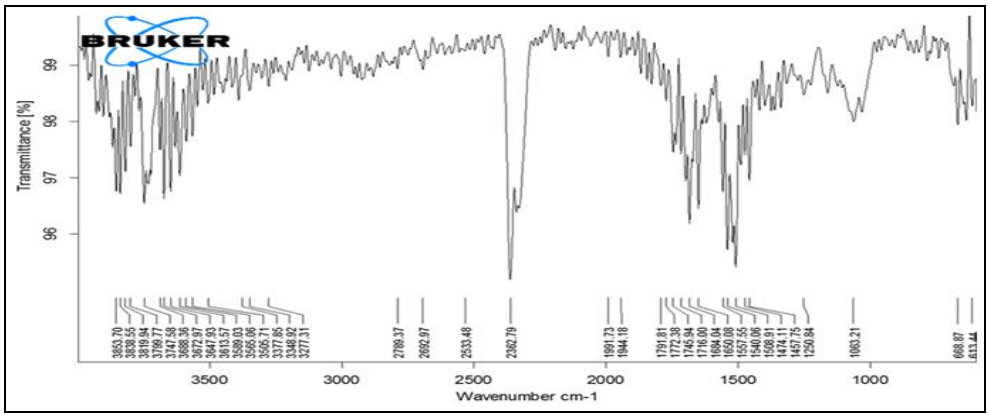

FIG. 2: FTIR SPECTRA OF CLARITHROMYCIN PURE DRUG

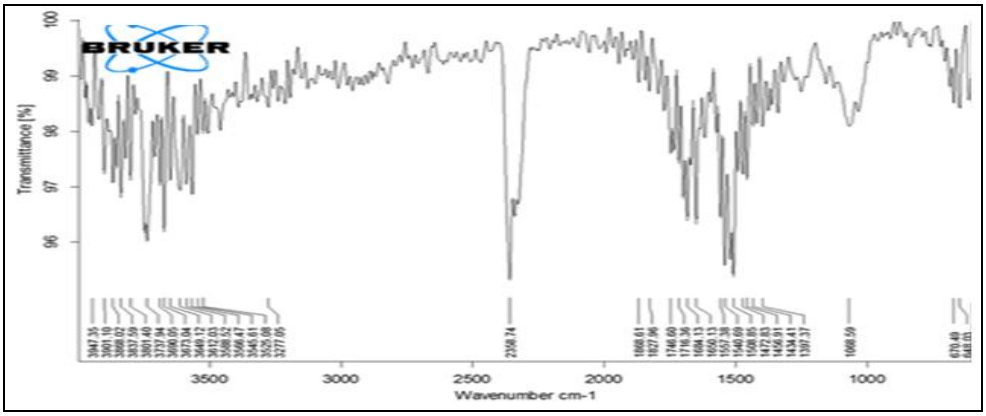

FIG. 3: FTIR SPECTRA OF PHYSICAL MIXTURE CLARITHROMYCIN AND XANTHAN GUM

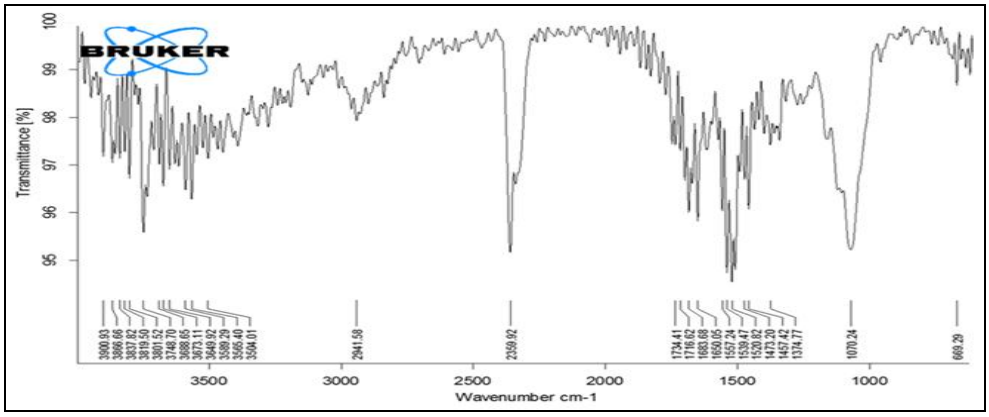

FIG. 4: FTIR SPECTRA OF PHYSICAL MIXTURE CLARITHROMYCIN AND SODIUM ALGINATE

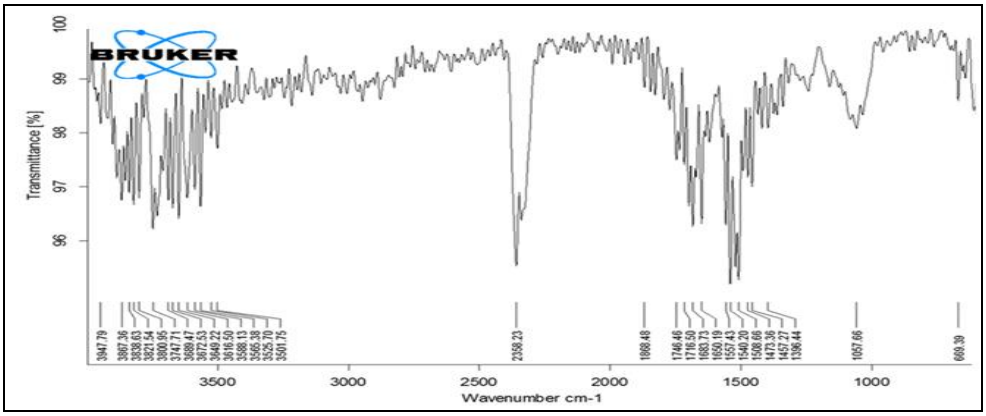

FIG. 5: FTIR SPECTRA OF PHYSICAL MIXTURE CLARITHROMYCIN AND GELLAN GUM

TABLE 1: COMPOSITION OF *IN-SITU* GEL

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clarithromycin (mg)	100	100	100	100	100	100	100	100	100
Sodium alginate (% w/v)	1.0	1.5	2.0	1.0	1.5	2.0	1.0	1.5	2.0
Gellan gum (% w/v)	-	-	-	0.75	0.75	0.75	-	-	-
Xanthan gum (% w/v)	-	-	-	-	-	-	0.25	0.25	0.25
Trisodium citrate (% w/v)	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Calcium carbonate (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methyl paraben	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Propyl paraben	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water (ml)	10	10	10	10	10	10	10	10	10

Surface pH: Measurement of pH is very important for oral preparations; otherwise it leads to irritation to the throat. The pH of formulation was found to be satisfactory and was in the range of 6.72- 7.25. The formulations were liquid at room temperature and the pH formulated. All the formulation has pH around neutral or slightly alkali. Maximum pH 7.25 was observed in F1 formulation, and minimum pH 6.72 was observed in F2 formulations. The pH of all the formulation was found to be satisfactory and within the orally acceptable range. Therefore, it will not cause any irritation to the administration of the formulations.

Viscosity: Different types of viscosity-enhancing polymers (gellan gum and xanthan gum) were added to sodium alginate solution in an attempt to improve viscosity and to obtain slower drug release than those formulations containing sodium alginate alone. The order of viscosity of the formulations from F1 to F9 is F9 > F8 > F7 > F6 > F5 > F4 > F3 > F2 > F1. The increase in viscosity of the formulations that were observed with the increase in the concentration of polymer can be related to the increasing crosslinking of the polymer.

Formulations containing xanthan gum have higher viscosities because of the viscosity enhancement property of xanthan gum. Formulations F8 and F9 were too viscous, making them difficult to pour from the container. The viscosity range was between 75.34 ± 0.45 -233.43 ± 0.32 cp.

***In-vitro* Floating Studies:** When the formulation comes in contact with the acidic environment, gelation as well as cross-linking of the calcium ions takes place providing a gel barrier on the surface of formulation. The carbon dioxide released is entrapped in the gel matrix giving buoyancy to the formulation. Then the polymeric network further restricts the diffusion of carbon dioxide as well as drug release. The floating ability of the formulations mainly depends on the concentration of the gelling polymer, carbon dioxide, and cation source. All the *in-situ* gel formulations had a floating lag time of <2 min, and all the formulations floated for more than 12 h. Therefore, the extended duration of floating was responsible for the sustained release of drug.

***In-vitro* Gelling Capacity:** Gelling capacity is the main pre-requisite of *in-situ* gel formulation. The *in-vitro* gelling capacity was determined using simulated gastric fluid in which the solution must undergo rapid transition to gel. All the formulations showed immediate gelation and remained for extended period of time when come in contact with simulated gastric fluid maintained at 37 ± 2 °C.

TABLE 2: *IN-VITRO* GELLING CAPACITY

Formulation code	*In-vitro* gelling capacity
F1	+++
F2	+++
F3	+++
F4	+++
F5	+++
F6	+++
F7	+++
F8	+++
F9	+++

(+++) gelation immediate remains for an extended period

Drug Content: Drug must be uniformly distributed throughout the sample. This is important in relation to batch to batch uniformity and thus efficacy of the preparation. If the drug is not distributed uniformly throughout the formulation, it could either lead to the availability of sub-therapeutic dose or toxic dose.

The percentage drug content of all prepared formulations was found to be in the range of 86.66 ± 0.09 – 96.66 ± 0.06%. The formulations exhibit fairly uniform drug content. Formulation F7 showed maximum drug content of 96.66%.

***In-vitro* Drug Release:** The *in-vitro* drug release profile of a drug predicts how a delivery system might function and gives valuable insight into its *in-vivo* behavior. The release studies of prepared *in-situ* gelling systems were carried out up to 12 hours using 0.1N HCl (pH 1.2) and the cumulative percentage drug released was calculated.

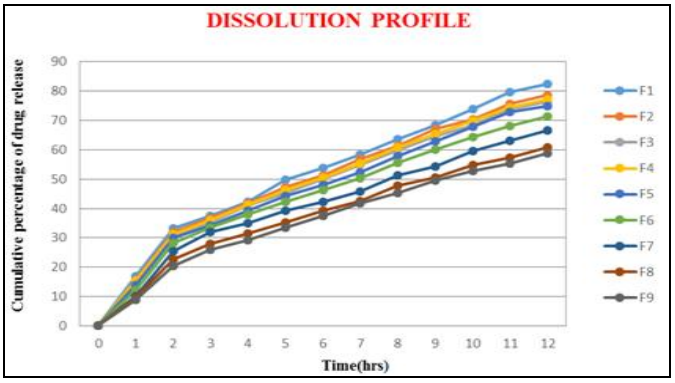

FIG. 6: *IN-VITRO* DRUG RELEASE PROFILE

The *in-vitro* drug release studies, it was observed that as the concentration of gelling agent increase, release of drug from the gastroprotective *in-situ* gel prepared decreases. Drug releasing pattern of different formulation contains a different concentration of gelling agent and drug release retardant polymers are given as follows: With sodium alginate: F1 > F2 > F3, with sodium alginate and gellan gum: F4 > F5 > F6 and with sodium alginate and xanthan gum: F7 > F8 > F9. The retarded release observed in formulations F4, F5, and F6 is because the gelation and aggregation of gellan gum occur through chemical bonding between calcium and carboxylic groups in the gellan chains. In the formulations F7, F8, and F9, there was a drastic decrease in the drug release due to the presence of xanthan gum which acts as a drug release retardant polymer as well as viscosity enhancing agents. Xanthan gum hydrates rapidly without lumping and increases the viscosity. Even at low concentrations, xanthan gum imparts high viscosity.

Due to high swelling nature of xanthan gum, it forms a thick gel structure which increased the diffusion path length of the drug; as a result there is delayed release of the drug from the formulation. As the concentration of sodium alginate, sodium alginate with gellan gum, and sodium alginate with xanthan gum increased, there was a decrease in the drug release. The result of this, the drug formulation F7, F8 and F9 were shown sustained release pattern.

Data Analysis: The linear regression coefficient of each kinetic model was calculated, and pattern of drug release from the dose was predicted. The drug release of F7 showed first-order kinetics with the Higuchi model drug release mechanism.

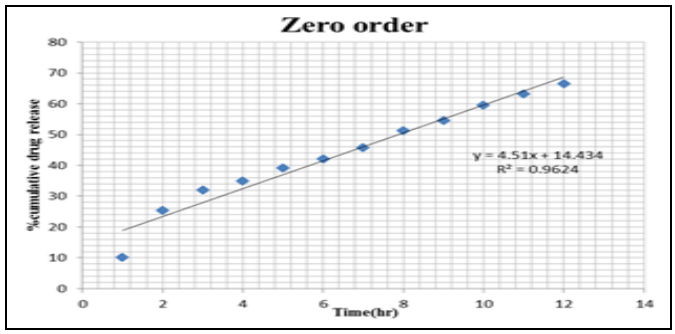

FIG. 7: ZERO ORDER RELEASE MODEL OF F7

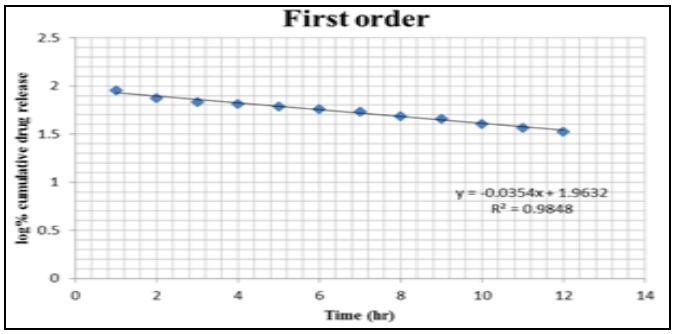

FIG. 8: FIRST ORDER RELEASE MODEL OF F7

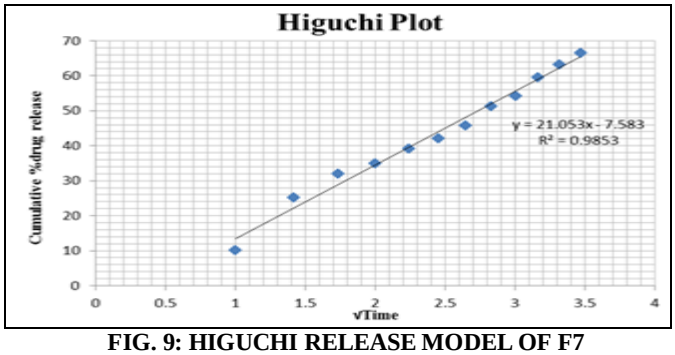

FIG. 9: HIGUCHI RELEASE MODEL OF F7

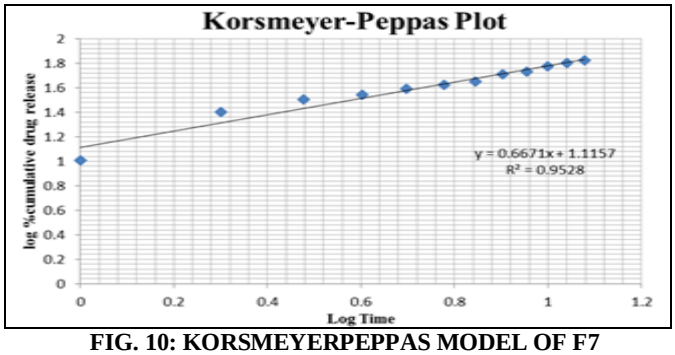

FIG. 10: KORSMEYERPEPPAS MODEL OF F7

Stability Studies: The optimized formulation F7 was selected for stability studies. The selected Formulation F7 were stored at 25 ºC ± 2 ºC/ 60% RH ± 5% RH and 40 ºC ± 2 ºC / 75% RH ± 5% RH for a period of 6 months. The parameters analyzed include appearance, *in-vitro* floating, *in-vitro* gelling capacity, viscosity, drug content and *in-vitro* drug release. From the stability study it was confirmed that the optimized formulation is stable at its storage temperature [23-29].

TABLE 3: STABILITY STUDY AT 40ºC ± 2ºC / 75% RH ± 5% RH

Parameter	Initial	After 3 months	After 6 months
Appearance	Viscous liquid	Viscous liquid	Viscous liquid
Viscosity (cp)	196.32	198.38	200.8
Floating lag time(sec)	55 ±1.23	57±0.10	58±0.52
Gelling capacity	+++	+++	+++
Drug content (%)	96.66	93.89	90.91
Cumulative percentage drug release (%)	66.50	64.00	61.45

TABLE 3: STABILITY STUDY AT 40ºC ± 2ºC / 75% RH ± 5% RH

Parameter	Initial	After 3 months	After 6 months
Appearance	Viscous liquid	Viscous liquid	Viscous liquid
Viscosity (cp)	196.32	198.38	200.8
Floating lag time(sec)	55±1.23	57±0.10	58±0.52
Gelling capacity	+++	+++	+++
Drug content (%)	96.66	93.89	90.91
Cumulative percentage drug release (%)	66.50	64.00	61.45

CONCLUSION: Stomach specific floating *in-situ* gel containing Clarithromycin was prepared using sodium alginate, gellan gum and release retardant polymer xanthan gum.

The prepared formulations were evaluated for visual inspection, surface pH, viscosity, *in-vitro* floating study, *in-vitro* gelling capacity, drug content, and *in-vitro* drug release. The formulation F7 was selected as the optimized formulation which has viscosity 233.43 ± 0.32 cp with drug content of 96.66 ± 0.06% and showed *in- vitro* drug release of 66.5% at the end of 12 h. It follows first-order release kinetics with Higuchi model release mechanism. The selected formulation was evaluated for stability. The formulation was stable

at room temperature and accelerated temperature over six months.

The present study has been a successful attempt to formulate gastro retentive *in-situ* gel of Clarithromycin, an orally administrated antiulcer drug with a view to improving its oral bioavailability and provide sustained release of the drug. The developed formulations met all prerequisites to become gastro retentive *in-situ* gel system that gelled and floated instantaneously in the pH conditions of the stomach. Hence, it can be concluded that stomach specific *in-situ* forming gel of Clarithromycin can be an effective formulation that shows improved efficacy, prolonged-release, patient compliance and cost-effective over conventional formulations.

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CONFLICTS OF INTEREST: None of the authors has any conflicts of interest in the context of this work.

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