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FORMULATION AND EVALUATION OF GASTRO RETENTIVE NOVEL FLOATING *IN-SITU* GELLING SYSTEM OF CURCUMIN

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ABSTRACT: The objective of the present study was to formulate and evaluate a gastro-retentive stomach specific novel floating *in-situ* gelling system of curcumin for potentially treating gastric ulcer, associated with Helicobacter pylori. The *in-situ* gel of curcumin was prepared by dissolving different concentrations of gelling polymer like sodium alginate in distilled water at 60 ºC. After cooling to 40 ºC, required quantities of sodium citrate and calcium carbonate were dispersed in it with continuous stirring followed by the addition of curcumin and sorbitol. Identification of drug was confirmed by DSC (melting point study), FTIR (functional groups study), and UV spectrophotometric analysis. Compatibility between drug and polymer were confirmed by DSC and FTIR studies. The micromeritic properties of curcumin were done, and all formulations showed pH in the range of 6.6 to 7.4, floating lag time was less than 1 min, duration of floating was more than 24 h for all the prepared formulations. Gelling capacity, gel strength, viscosity, and water uptake by the gel increased with the increase in sodium alginate concentration; the drug content was found to be in the range of 92.5 to 99.1%. Drug release was found to decrease with the increase in polymer concentration of gel. The release kinetics of all the formulations followed zero order mechanism.

INTRODUCTION: Floating oral *in-situ* gel forming system are widely explored for gastro retention purposes and 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. While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system.

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The gel formed from the *in-situ* gelling system, being lighter than gastric fluids, floats over the stomach contents and produces gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract [1]. *In-situ* forming gels are formulations, administered as a solution, which undergoes gelation when it reached to stomach due to physicochemical changes inherent to the biological fluids. In this way, the polymer which shows a sol-gel phase transition and plays an important role in drug delivery [3].

Sodium alginate (SA) is a widely used natural polymer in various drug delivery systems. It exhibits favorable biological properties such as

nontoxic, biocompatibility, biodegradability, and ulcer healing traits. Moreover, gelation of dilute solutions of SA occurs on the addition of di-and trivalent ions by a co-operative process. This generally leads to a reduction in the permeability of different solutes hindering the release of embodied drugs in the alginate gel matrices, allowing these systems to be used in controlling the drug release [1, 2]. Curcumin (diferuloylmethane) is a phenolic component extracted from the rhizome of turmeric.

As a bioactive compound, it has proven its medical efficacy in tumors like gastric cancers and gastric ulcer induced by *H. pylori*. However, its low water solubility and bioavailability limit its clinical uses via oral administration. Besides, curcumin in a buffer decomposes in a pH-dependent manner, and this degradation accelerates at neutral-basic conditions. Studies have suggested that curcumin could be well formulated to improve its solubility and bioavailability *via* a reliable controlled-or sustained-release system [4, 5].

Helicobacter pylori (*H. pylori*), one of the causative agents for bacterial infections in humans is responsible for several gastrointestinal diseases such as gastritis, gastric ulcer, and gastric cancer [7]. *H. pylori* infection can be treated with various combinations of antibiotics. Specifically, metronidazole is commonly used in conjunction with either amoxicillin or clarithromycin and an acid suppressor or an H_2-receptor antagonist to eradicate *H. pylori* infection. The above treatment has certain complication, like the adverse effect of drugs and increases resistance to microorganism. The objective of the present study was to develop curcumin floating in-situ gel that remains in the stomach, resulting in increased gastric residence time and thus increases the local concentration of the drug for complete eradication of *H. pylori* [6].

MATERIALS AND METHODS:

Preformulation Studies:

Identification of Drug by DSC Study: The melting point study was caring out with the help of Differential scanning calorimetry (DSC). The apparatus was calibrated, and Samples (2mg) were placed in a flat bottomed aluminum pan and heated at a constant rate of 10 °C/min in an atmosphere of nitrogen in a temperature range of 50-220 °C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples [8].

Identification of Drug by FTIR Study: Fourier-transform infrared (FT-IR) spectra were obtained using an FT-IR spectrometer (Bruker Alpha E, USA). The device was operated in the Attenuated Total Reflection (ATR) mode by placing the sample on the sample cell. The interpretation of the functional group was done in the scanning range of 500-4000 cm^{-1}. [9, 10]

Identification of Drug by Spectrometric Analysis: [11]

Determination of UV Absorption Maxima: Curcumin stock solution of (100 µg/ml) in 0.1N HCl (pH 1.2) was scanned in UV spectrophotometer in the range of 200-800 nm, and the λ max of the drug was determined.

Standard Calibration Curve: Standard stock solution Curcumin (10 mg) was accurately weighed and transferred to a 10 ml volumetric flask. DMSO was added to obtain a concentration of 1000 µg/ml (Stock-I). From Stock-I 1 ml of solution was withdrawn and transferred to a 10 ml volumetric flask and made up the volume with DMSO to obtain a concentration of 100 µg/ml (Stock-II). From the above stock solution-II aliquots of 1ml, 2 ml, 3 ml, 4 ml & 5 ml were withdrawn and transferred into 10 ml volumetric flasks and made up the volume with DMSO to obtain a concentration of 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml & 50 µg/ml respectively. The absorbances of all the aliquots were measured at 406 nm in triplicate and then a calibration curve was made.

Micromeritic Properties:

Bulk Density: An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into a graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml.

The volume measure was called as the bulk volume, and the bulk density is calculated by the following formula.

Bulk density = Weight of powder / Bulk volume

Tapped Density: It is the ratio of the total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times, and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times, and tapped volume was noted. The tapped density is calculated by the following formula.

Tapped density = Weight of powder / Tapped volume

Carr's Index [Compressibility Index]: It is one of the most important parameters to characterize the nature of powders and granules. It can be calculated from the following equation.

Carr's index = Tapped density - Bulk density / Tapped density × 100

TABLE 1: INTERPRETATION OF CARR'S INDEX FOR POWDER FLOW

CI (%)	Properties
5-12	Excellent
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Haussner's Ratio: Haussner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula

Haussner's ratio = Tapped density / Bulk density

TABLE 2: INTERPRETATION OF HAUSER'S RATIO FOR POWDER FLOW

Hausner ratio	Properties
1.00 – 1.11	Excellent
1.12 – 1.18	Good
1.19 – 1.25	Fair
1.26 – 1.34	Passable
1.35 –1.45	Poor
1.46 – 1.59	Very poor
> 1.60	Extremely poor

The angle of Repose: This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The angle of repose of granules was determined by the funnel method. The funnel was fixed at a particular height (2.5 cm) on a burette stand. The powder sample was passed through the funnel until it forms a heap. A circle was drawn across it without disturbing the pile. The radius and height of the heap were noted down. The same procedure was repeated for three times, and the average value was taken. The angle of repose was calculated using the following equation.

$$\tan\Theta = h / r$$

Where h and r are the height and radius of the powder cone, respectively.

TABLE 3: INTERPRETATION OF ANGLE OF REPOSE FOR POWDER FLOW

The angle of repose(θ)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Drug-Polymer Compatibility Study: [12]

DSC Spectra Study: The successful formulation of a stable and effective solid dosage form depends on the careful selection of the polymers, which are added to facilitate administration, to promote the consistent release and protect it from degradation. API and polymers were thoroughly mixed in a predetermined ratio given in below table and passed through the 40# sieve. The blend was to be filled in transparent glass vials and were closed with gray colored rubber stoppers and further sealed with aluminum seal and charged in to stress condition at below condition. Physical observation should be done every week up to 1 month, and DSC studies were carried out to determine the compatibility of excipients with the drug. DSC is one of the most powerful analytical techniques to determine the melting point of a drug. In the present study, the samples are kept under elevated temperature (between 50 ºC to 220 ºC). Chemical stability was confirmed by determining the melting point.

TABLE 4: DRUG AND POLYMER COMPATIBILITY STUDY

Drug + polymer	Ratio	40ºC ± 2°C 75% RH ± 5 % RH	40ºC ± 2°C 75% RH ± 5 % RH
API + Sodium Alginate	1:1	Obs in 2nd Weeks	Obs in 4th Weeks

FTIR Spectra Study: The presence of any possible drug-polymer interaction was studied by

FTIR spectroscopy. The physical mixture of drug and polymers were taken in a ratio of 1:1 and the IR spectra were recorded in a Fourier transform infrared (FTIR) spectrophotometer (Bruker, Alpha E, USA) within the scanning range of 500-4000 cm^{-1}.

Preparation of Formulations:

Preparation of Curcumin *in-situ* Gelling Solution: For the preparation of *in-situ* gel of curcumin, different concentration of sodium alginate was mixed with distilled water at 60 ºC and was stirred continuously until the formation of a homogeneous solution. After cooling to below 40 ºC sodium citrate and calcium carbonate of different concentration dispersed slowly in the resulting solution with continuous stirring by magnetic stirrer followed by the addition of sorbitol. Curcumin (200 mg) was then dissolved in 10 ml 0.1N HCl (pH 1.2) in a beaker slowly and added to the resulting solution with continuous stirring until a formation of clear solution. After that suspension was packed in ambered color bottle [13].

TABLE 5: FORMULATION OF *IN-SITU*-GEL WITH DIFFERENT CONCENTRATION

Formula code/Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Sodium Alginate (% w/v)	1	1.5	1.5	1.5	1.75	2	2	2	2.5	3	3	2.5
Sodium Citrate (% w/v)	0.2	0.2	0.225	0.225	0.25	0.25	0.25	0.25	0.5	0.5	0.5	0.25
Calcium Carbonate (% w/v)	0.25	0.26	0.27	0.3	0.35	0.4	0.5	0.6	0.625	0.65	0.625	0.625
Sorbitol (ml)	2	2	2	2	2	2	2	2	2	2	2	2
Curcumin (% w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
D.W.QS (ml)	100	100	100	100	100	100	100	100	100	100	100	100

Evaluation of Floating *in-situ* Gel Curcumin Solution (*in-vitro* gelation Study):

Gelation Time Determination: Gelation time was evaluated visually; it was measured by placing 5ml of 0.1 N HCl (pH 1.2) in a beaker and maintained at 37 ± 1 ºC. One ml of each formula was taken with the pipette and transferred slowly on the surface of the fluid, as the solution comes in contact with the gastric fluid solution; it was immediately converted into the gel-like structure. The gelation time was evaluated triplicate based on the period for which gel formed [14, 15].

Swelling Index: [14, 16] The percentage of the swelling index of *in-situ* gel of the formulations was determined. The *in-situ* gel formed by putting 5 ml of each formula in a petri dish and 40 ml of 0.1 N HCl (pH 1.2) was added. Then 0.1N HCl solution was completely removed from the gel, and the excess of 0.1N HCl solution was blotted out with tissue paper. The initial weight (Wo) of the gel was recorded, to this gel 10 ml of distilled water was added and after 60 min the water was decanted and the final weight (Wt) of the gel was recorded, this process was repeated for 5 h and the difference in the weight was calculated and reported. The % weight gain (swelling index) for formulations is calculated by the following equation (1):

$$\% \text{ Swelling index} = (W_t - W_0 / W_t) \times 100 \ldots\ldots\ldots (1)$$

Where, W_0 = Initial weight of the gel, W_t = weight gain by the gel.

Gel Strength Determination: Gel strength determination indicates the tensile strength of the gelled mass, which is the user parameter to evaluate whether it withstands in the peristaltic movement or not. The gel strength of the formulation is an important variable dependent on the type and concentration of the polymer, gas generating agent, and cation source ($CaCl_2$). The method to measure gel strength of gelled mass was modified; by using fabricated gel strength apparatus, and it was done triplicate. 25 ml of 0.1 N HCl (pH 1.2) was taken in the cylinder and to this solution (formulation) of 5 ml was added for gelation. After gelation, the HCl was drained off, leaving the formed gel mass, and then the device was rested on to the surface of the gel. At the free end of the device a lightweight pan (3 g) was attached to which the weights were added. The gel strength was reported in terms of weight required to pass the apparatus through the formed gel mass [17, 18].

Physical Appearance and pH Measurement: All the prepared sodium alginate based in situ solutions of curcumin were checked for their clarity and the pH of the solutions. The pH was also measured in each of the solution of sodium alginate based in

situ solutions of curcumin, using a calibrated digital pH meter at 25 ºC. The measurement of the pH of each data was in triplicate.

Density Measurement of Gel: For stomach, specific system density is an important parameter, and which must be less than the stomach fluid density (< 1.004) in case of floating in-situ gel. The Densities of all formulations were measured by forming a gel of 5 ml solutions were placed in measuring cylinder, and weight of this gel was noted by using the calibrated balance. Finally, the densities of different formulations were noted in triplicate [19].

***In-vitro* Buoyancy Study:** [20, 21] The *in-vitro* buoyancy study is characterized by floating lag time and duration of floating. *In-vitro* buoyancy study was carried out triplicate using USP dissolution apparatus type II using 900 ml medium of 0.1N HCl (pH 1.2). The medium temperature was kept at 37 ± 0.5 ºC. Accurately 10 ml of the prepared in-situ gel formulation was drawn up using a disposable syringe and placed carefully in the dissolution vessel. After the formation of in-situ gel, then the dissolution test apparatus was run at 50 rpm, this speed was slow enough to avoid breaking of gelled formulation and maintaining the mild agitation conditions believed to exist in vivo. The time the formulation took to emerge on to the medium surface (floating lag time) and the time over which the formulation constantly floated on the dissolution medium surface (duration of floating) were reported.

Drug Content Determination: [22] Accurately, 5 ml of liquid solution (containing 200 mg of the drug) from all formulations were taken and transferred to a 200 ml volumetric flask and to which 70 ml of 0.1N HCl was added. Shake the solution for 30 min, followed by 15 min sonication. The volume was to made 100 ml and was filtered using Whatman filter paper no.41. From this solution, 1 ml of sample was withdrawn and diluted to10 ml with 0.1N HCl. Contents of curcumin were determined spectrophotometrically at 406 nm using double beam UV-Visible spectrophotometer.

Viscosity Measurement of *in-situ* Gels: The viscosity of the prepared formulations were measured with Brookfield viscometer (Model no LVDVE 8557400) using a sample of 100 ml. Measurements were performed using suitable spindle number 62 and sheared at a rate of 10, 20, 30,40, 50, 60, 100 rpm, and the temperature was maintained at 37 ºC. The viscosity was read directly after 30 sec. All measurements were made in triplicate [23, 24].

***In-vitro* Drug Release Study:** The *in-vitro* release of curcumin from buoyant *in-situ* gel solutions was studied using USP type II (paddle type) dissolution test apparatus. 5 ml (containing 2% of curcumin) from each formulation was transferred using a disposable syringe, and then the syringe plunger depressed slowly to extrude 5 ml into a petri dish already containing 10 ml of 0.1N HCl. This petri dish containing formulation was placed on the surface of the medium and plunged into a dissolution vessel containing 900 ml of 0.1N HCl (pH 1.2) without much disturbance. The dissolution test apparatus was run at 50 rpm for maximum up to 6 hrs at a temperature 37± 0.5 ºC. 10 ml was withdrawn at regular intervals of time (30 min) and replenished with 10 ml of fresh medium. The dissolution test was carried out for 6 h.

Withdrawn samples were filtered using Whatman filter paper no. 41 and curcumin contents in the aliquots were determined spectrophotometrically using double beam UV-Visible spectrophotometer at a wavelength of 406 nm. The experiments were conducted in triplicate at each time interval, and the average was recorded [25, 26].

Kinetic Mathematical Modeling of Drug Release Profile: [26, 27] The cumulative amount of curcumin release from the prepared *in-situ* gel formulations at different time interval was fitted to zero order kinetics, first-order kinetics, Higuchi model and Korsmeyer-Peppas model to characterize the mechanism of drug release.

Zero Order Kinetic: It describes the system in which the drug release rate is independent on its concentration, as shown in equation (1):

$$Q_t = Q_0 + K_0 t \quad \text{……. (1)}$$

Where Q_t = the amount of drug dissolved in time t, Q_0 = the initial amount of drug in solution, K_o = the zero order release constant.

In this way, a graph of drug dissolved fraction versus time will be linear if the previously established condition were fulfilled.

First Order Kinetic: It describes the drug release from the systems in which the release rate is conc. dependent as described by equation (2):

$$\text{Log } Q_t = \log Q_0 - K_1 t/2.303 \text{ …….. (2)}$$

Where Q_t = the amount of drug released in time t, Q_0 = the initial amount of drug in the tablet and K1 is the first order release constant.

In this way, a graph of the decimal logarithm of the released amount of the drug versus time will be linear

Higuchi Model: It describes the release model in which the fraction of drug release from the matrix is proportional to the square root of time as shown in equation (3)

$$Q_t/Q_0 = K_H \sqrt{t} \text{……. (3)}$$

Where Q_t/Q_0 = cumulative amount of drug release at time t, K_H = the Higuchi dissolution constant reflecting formulation characteristics.

In this way, a graph of the cumulative percentage drug released versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to K_H.

Korsmeyer-Peppas Model: It is used for a better description of drug release behavior from a polymeric system as shown in equation (4)

$$\text{Log } (Q_t/Q_\infty) = \log K_{kp} + n \log t \text{ …… (4)}$$

Where Q_t/Q_∞ = the fraction of drug release at time t, Kkp =the constant incorporating structural and geometrical features of controlled release device and (n) = a diffusional release exponent indicative of the drug release mechanism for dissolution.

RESULTS AND DISCUSSION:

Preformulation Studies:

Identification of Drug by DSC Spectra: The DSC thermogram of curcumin analyses was conducted to explore the melting activities of the drug. DSC analysis showed a sharp endothermic peak at 172.01 ºC, which is an indication of the melting point of curcumin. The melting range of curcumin is 172-176 ºC as per the United States Pharmacopeia. So, it was found to be very close to an authentic range of official standards, as shown in **Fig. 1**.

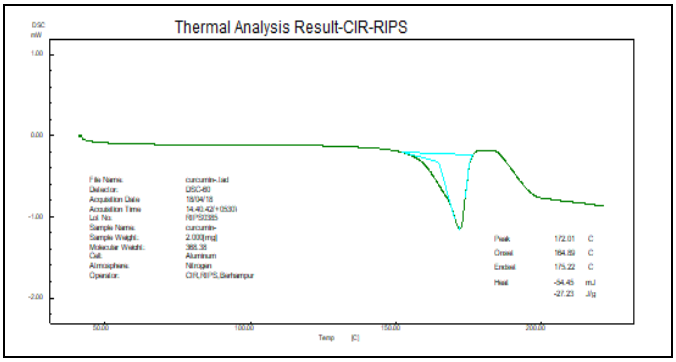


FIG. 1: DSC SPECTRA OF CURCUMIN

Identification of Drug by FTIR Spectroscopy Study: FTIR spectrum of curcumin showed its signature peak at 3505 cm^{-1} (phenolic O-H stretching vibration), 1627cm^{-1} (aromatic moiety C=C stretching), 1600 cm^{-1} (benzene ring stretching vibration), 1531cm^{-1} (C=O and C=C vibration), 1426cm^{-1} (olefinic C-H bending vibration), 1276 cm^{-1} (aromatic C-O stretching vibration), 1150 cm^{-1} (C-O-C stretching vibration).

The peaks obtained in the spectra of pure drug shown in **Fig. 2**, correlates with the peaks of the official spectrum of British Pharmacopeia which confirms the purity of the drug.

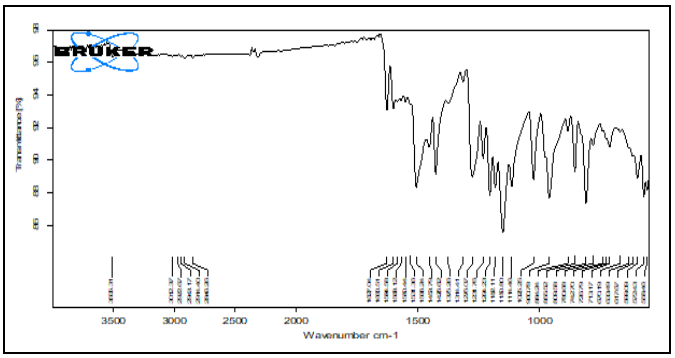


FIG. 2: FTIR ABSORPTION SPECTROSCOPY OF CURCUMIN

Identification of Drug by Spectrometric Analysis:

Determination of UV Absorption Maxima (λmax): Scanning curcumin stock solution by UV spectrophotometer at 200 - 800 nm gave the spectrum that has wavelength of maximum absorption (λ max) at 406 nm in gastric fluid solution 0.1N HCl (pH 1.2) as shown in the **Fig. 3**.

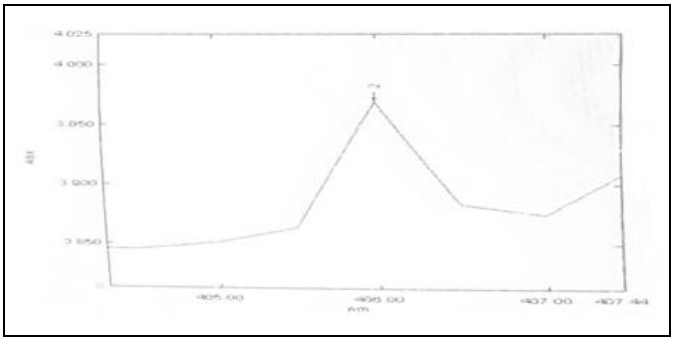


FIG. 3: UV SPECTRUM OF CURCUMIN

Determination of Calibration Curves of Curcumin: The calibration curves of curcumin in gastric fluid solution 0.1N HCl (pH 1.2) and was shown in **Fig. 4**.

A straight line was obtained by plotting the absorbance versus concentration with high regression coefficient; this indicates that the calibration curves obey Beer's law within the range of concentration used.

TABLE 6: LINEARITY TABLE OF CURCUMIN

Concentration (µg/ml)	Absorbance(nm)
10	0.197
20	0.388
30	0.569
40	0.758
50	0.926

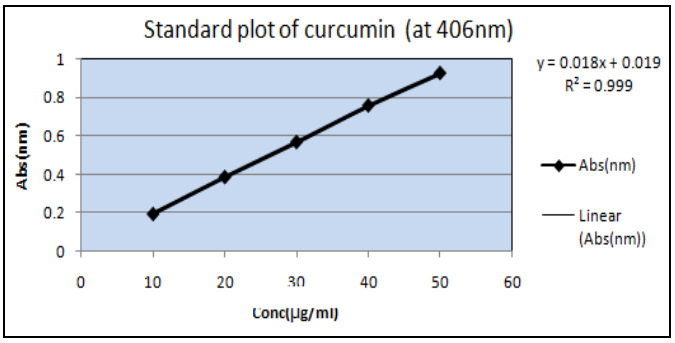


FIG. 4: STANDARD PLOT OF CURCUMIN

Micromeritic Properties Drug and Polymer: The micromeritic properties Drug and Polymer are reported in **Table 6**.

TABLE 7: MICROMERITIC PROPERTIES DRUG AND POLYMER

Ingredients	Parameters				
	Bulk Density gm/cm^3	Tapped Density gm/cm^3	Carr's Index (%)	Haussner's Ratio(H_R)	Angle of Repose (θ)
Curcumin	0.33	0.42	15.12	1.16	27.65
Sodium Alginate	0.41	0.47	14.51	1.17	25.02

Drug-Polymer Compatibility Study:

DSC Spectra Study: DSC of curcumin showed a sharp endothermic peak at 172.01 ºC (melting point). The physical mixture of curcumin with polymer (sodium alginate), there was no significant change observed in melting endotherm, *i.e.* is 163.19 ºC. Hence from DSC reports, it was concluded that the curcumin was found to be compatible with sodium alginate.

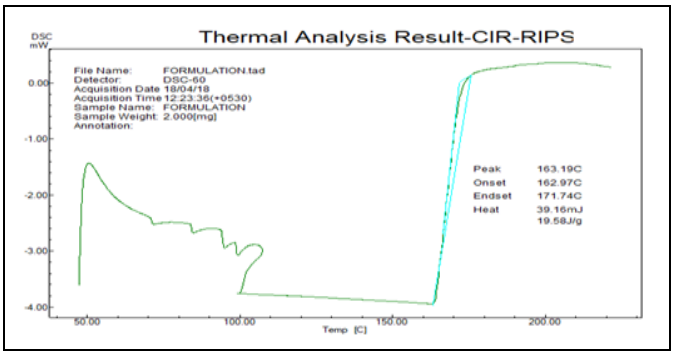


FIG. 5: DSC THERMOGRAM OF CURCUMIN +SODIUM ALGINATE

FTIR Absorption Spectroscopy Study: The compatibility of curcumin with the polymer was carried out using infrared spectroscopy in the scanning range of 500 to 4000 cm^{-1}. As there were no major changes in the peaks, indicates that there was no incompatibility of the drug with the polymers used in the formulations shown in **Fig. 7**.

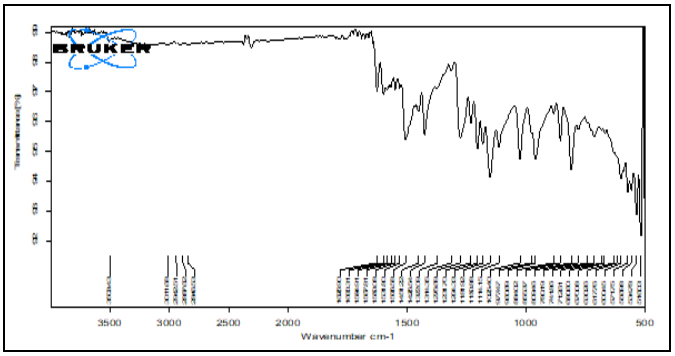


FIG. 6: FTIR SPECTRA OF CURCUMIN + SODIUM ALGINATE

Evaluation of Curcumin Floating *in-situ* Gel: All the formulations (F1-F12) prepared were evaluated for different parameters like gelation time, swelling index, gel strength, physical appearance pH measurement, density, floating lag time, duration of floating, and drug content the results are

summarized in **Table 8**. The entire evaluation test was done in compliance with Indian Pharmacopoeia (IP) and United State Pharmacopoeia (USP).

TABLE 8: EVALUATIONS OF CURUMIN FLOATING *IN-SITU* GEL

Formula Code / Parameters	F1	F2	F3	F4	F5	F6
Gelation Time (Sec)	10±0.1	9±0.3	5±0.1	3±0.2	8±0.4	3±0.1
Swelling Index (%)	9.3	9.8	11.1	11.4	12.8	15.2
Gel Strength (N/m^2)	6.5±0.2	6.9±0.8	7.3±0.6	7.6±0.1	8.1±0.3	8.5±0.9
Physical Appearance	clear	clear	clear	clear	clear	clear
pH	6.1	6.1	6.3	6.4	6.6	6.6
Density (gm/m^3)	0.4±0.01	0.5±0.01	0.5±0.05	0.5±0.06	0.5±0.09	0.6±0.01
FLT (sec)	92±0.01	78±0.05	75±0.08	73±0.01	68±0.03	54±0.09
DOF (hr)	8±0.01	10±0.03	10±0.09	12±0.05	14±0.08	17±0.01
Drug Content (%)	98.9	96.5	95.1	95.4	96.1	97.8
Formula Code / Parameters	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Gelation Time (Sec)	7±0.1	3±0.1	4±0,5	6±0.1	6±0.5	5±0.3
Swelling Index (%)	15.9	16.2	14.4	16.3	18.8	16.6
Gel Strength (N/m^2)	8.9±0.3	10±0.1	9.1±0.1	10±0.3	10±0.9	9.3±0.4
Physical Appearance	clear	clear	viscous	viscous	viscous	clear
pH	6.7	6.6	6.8	6.9	6.8	7.1
Density (gm/m^3)	0.6±0.07	0.8±0.01	0.7±0.05	0.9±0.06	0.8±0.09	0.7±0.08
FLT (sec)	41±0.01	38±0.06	31±0.07	28±0.01	27±0.09	32±0.01
DOF (hr)	20±0.05	24±0.01	25±0.09	20±0.01	21±0.08	23±0.09
Drug Content (%)	98.9	99.1	92.5	96.5	97.6	98.3

Values are expressed as mean ± SD of 3 readings (n=3). FLT = Floating Lag Time, DOF = Duration of Floating

Gelation Time Determination: Table 8 shows the different concentration of Na alginate in formulation F1to F12 has different gelation time. Formulation (F8-F12) showing that increase in $CaCO_3$ concentration which upon contact with 0.1N HCl (pH 1.2) the liquid polymeric solution should undergo a rapid sol-to-gel transition using ionic gelation. Formulas (F8, F10 & F11) showing that increase in the concentration of Na alginate causing gelation to undergo instantly and formed a good gel, this is due to internal ion tropic gelation effect of calcium on Na alginate, all these formulas (F1-F7) show a significant decrease in gelation time.

Swelling Index: The results in **Table 8** shows concentrations of polymers (Na alginate) play important role in swelling behavior of the in-situ gel. Increasing of Na alginate concentration in (F8-F12) shows a significant increase in swelling index. Increasing concentration of Na alginate leads to high percentages of hydration, and sodium-calcium ion exchange forming insoluble calcium alginate regions, followed by solvent penetration into the gel network and these result in ease of hydration and fast swelling of Na alginate.

Gel Strength Determination: Table 8 shows that the polymers Na alginate plays a vital role in the modulation of gel strength. As the concentration of Na alginate increases in (F8, F10, and F11), the gel strength increased significantly. This is due to the fact that Na alginate containing both carboxyl and hydroxyl groups in its structure, so increasing its concentrations resulting more carboxylic groups ready forcross-linking, thus triggering in an increase in electrostatic interaction in polymer matrix with the induction of the formation of strong bridges between polymer units by allowing the matrix to stretch further forming a rigid matrix and hence increasing the gel strength.

Physical Appearance and pH: Physical characterization parameters are reported in Table 8 to confirm that all formulation look clear except the formulation F9, F10 and F11 were viscous which is due to increase the concentration of polymer and $CaCO_3$. All the formulation had a pale yellow colored solution. They had pH in the range of 6.1-7.1, and these values reveal that all the formulations provide an acceptable pH according to USP.

Density Measurement: Density is an important parameter for gastro retentive drug delivery systems; these were estimated after forming the gel in 0.1N HCl. Densities of all formulated curcumin stomach specific in situ gels were in the range of

0.4 ± 0.01 to 0.9 ± 0.06 gm/cm^3 shown in **Table 8**. All formulations are having the densities values less the gastric fluid, which can be easily floated in the gastric contents.

Floating Lag Time: It was found that increasing the amount of calcium carbonate in (F1, F7 & F11), the floating lag time decreases significantly.Thus in (F1) containing 0.25% (w/v) $CaCo_3$ showed the highest floating lag time due to the generation of small amount of CO_2 gas, While (F7) containing 0.5% (w/v) $CaCO_3$ the amount of CO_2 was essential to achieve optimum *in-vitro* buoyancy since these formulations containing Na alginate and the calcium ions reacted with Na alginate to produce a cross-linking 3D gel network and swollen structure that may restrict further liberation of carbon dioxide and drug molecules, with intact formed gel. Further increase in the concentration of sodium bicarbonate in (F11) does not show any significant effect on floating behavior.

Duration of Floating: [22] Upon contact with an acidic medium, calcium carbonate effervesced, releasing carbon dioxide and calcium ions. Then, gelation and cross-linking by Ca^{++} ions took place to provide a gel barrier at the surface of the formulation. The released carbon dioxide was entrapped in the gel network producing a buoyant preparation, which resulted in extended floating. In formulations (F10 & F11) because of the increasing percentage of $CaCO_3$ as it is given in **Table 8**.

Drug Content Uniformity: The absorbance of the suitably diluted solutions was measured, and the formulations were evaluated for uniform distribution of curcumin. All the readings measured in triplicate and the average of the % drug content is determined by using standard calibration curve at 406 nm, and they found to be in the range of 95.3-99.1% as shown in **Table 8** indicating that curcumin was uniformly distributed within all the formulations [14].

Viscosity Measurements: The rheological properties of the solutions are of importance in the viewing of their proposed oral administration. The formulation should have an optimum viscosity that will allow easy swallowing as a liquid, which then undergoes a rapid sol-gel transition due to ionic interaction. **Table 9** and **Fig. 8, 9,** and **10** illustrate a significant increase in the viscosity of the formulations (F10, F11 & F12) as the concentration of Na alginate was increased with shear thinning behavior.

TABLE 9: EFFECT OF SHEAR STRESS ON VISCOSITY OF FORMULATIONS

SS (rpm) / For. no.	10	20	30	40	50	60	100
F1	580	530	496	460	410	380	270
F2	930	880	840	750	690	580	470
F3	932	883	842	754	691	582	471
F4	936	884	882	755	691	584	472
F5	1145	1115	1101	1090	1076	1023	1005
F6	1398	1368	1340	1305	1280	1269	1236
F7	1401	1369	1341	1306	1282	1270	1238
F8	1568	1535	1514	1501	1475	1446	1403
F9	1669	1635	1615	1603	1575	1547	1505
F10	1885	1867	1834	1812	1792	1774	1748
F11	1887	1867	1835	1814	1792	1776	1750
F12	1671	1639	1615	1603	1578	1551	1508

SS = Shear Stress, For no = Formulation no., Viscosity in Cps

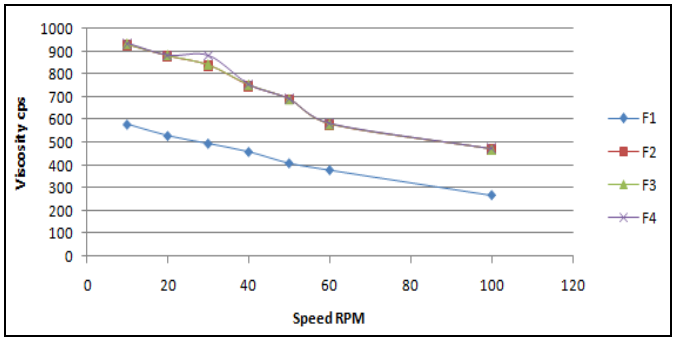


FIG. 7: RHEOLOGICAL PROPERTIES OF FORMULATION F1 TO F4

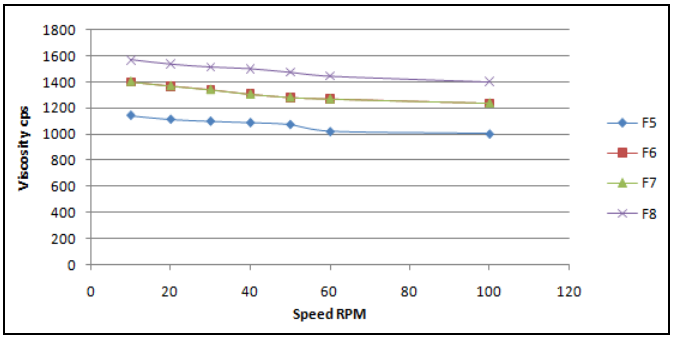


FIG. 8: RHEOLOGICAL PROPERTIES OF FORMULATION F5 TO F8

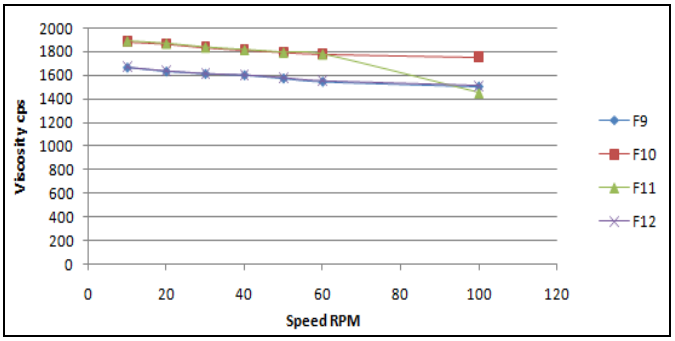


FIG. 9: RHEOLOGICAL PROPERTIES OF FORMULATION F9 TO F12

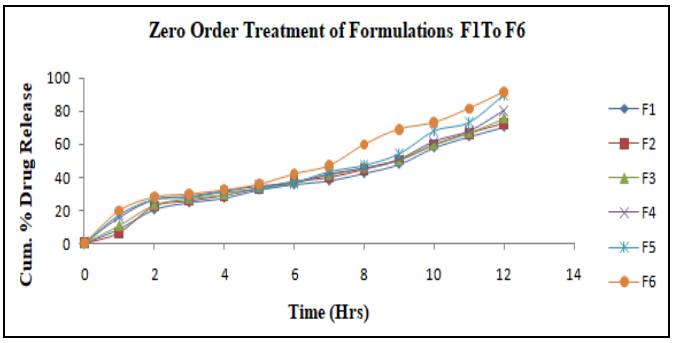
***In-vitro* Drug Release Study:** The prepared formulations were subjected for *in-vitro* dissolution study in 0.1N HCl to study the effect of different variables on the percentage of drug release. Effect of Na alginate in F11-F12 and its concentrations on *in-vitro* drug release from floating in-situ gels is shown in **Table 10**. A significant decrease in drug release was observed with increase in polymer concentration. The release of drug from these gels (F11-F12) was characterized by an initial phase of high release (burst effect) due to water penetration into the floating in situ gel matrix and then release of the drug *via* diffusion and dissolution.

The release profiles and the effect of the $CaCO_3$ (as ion cross-linking agent) amount on the formulations of curcumin were shown in **Fig. 11** & **12**. The results show that increasing concentration of $CaCO_3$ from F2 to F4 has a significant effect of retarding the release rate.

TABLE 10: *IN-VITRO* DRUG RELEASE OF CURCUMIN FLOATING *IN-SITU* GEL

F.C / Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	8.750	6.500	10.750	15.750	17.25	19.750
2	20.5097	22.5072	23.2619	26.5175	26.5192	28.0219
3	24.7727	25.7750	27.2758	28.5294	27.7794	29.7811
4	27.5275	29.0286	29.5302	31.7817	31.0308	32.2831
5	32.5305	33.2822	34.0327	34.7853	32.7844	35.7858
6	35.7861	37.5369	37.5377	36.5386	36.5364	42.0397
7	38.03972	39.7916	41.5416	42.0406	43.2906	47.0467
8	42.5422	44.7941	45.7961	45.5467	47.0481	59.8082
9	48.0472	50.2997	50.5508	51.0506	54.0522	69.0664
10	58.0533	59.8058	59.8061	61.8067	67.81	73.0767
11	64.8144	66.5663	67.0663	68.0686	73.0753	81.5811
12	70.5719	72.5738	75.8244	80.5756	89.8311	91.5906
F.C / Time (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	24.00	30.250	33.00	40.750	40.50	36.50
2	30.7767	32.2836	39.7867	41.2953	41.5450	46.5406
3	33.0342	42.0358	47.0442	42.0458	42.5461	58.8017
4	36.5367	48.5467	52.5522	43.2967	43.7972	67.5653
5	44.2906	58.5539	61.5583	45.5481	46.0486	73.0750
6	46.5492	69.3150	70.8183	49.0506	49.5511	76.5811
7	61.5517	75.5769	76.5786	51.0544	51.5550	80.5850
8	69.8183	81.5839	80.5850	54.3067	54.8072	83.8394
9	74.0775	87.3406	85.0894	55.5603	55.8108	87.5931
10	81.5882	91.5969	91.5944	58.8117	59.3119	92.3472
11	86.5906	93.1017	94.1017	60.5653	60.8158	95.6025
12	94.8461	99.1033	95.8544	63.0672	63.5675	97.1061

Drug Release Kinetics Studies: The drug release data of curcumin were fitted to models representing zero order, first order, Higuchi's and Korsmeyer Peppas equation kinetics to know the release mechanisms. The data were processed for regression analysis using Ms. Excel statistical function and release kinetics graphs were made. The results are shown in **Table 11**. It was found that the *in-vitro* drug release of formulation code 8 was best explained by zero order as the plots showed the highest linearity (R^2 = 0.997). The formulation code F8 followed the zero order.



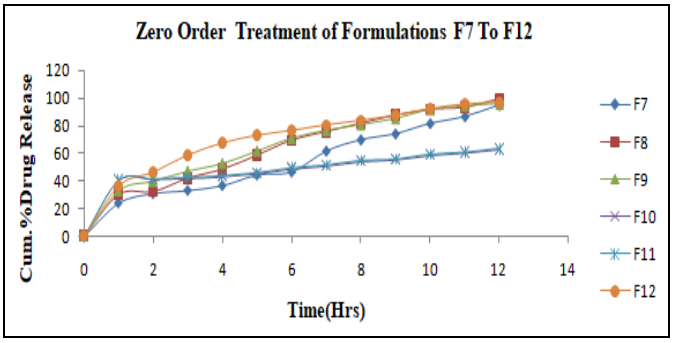
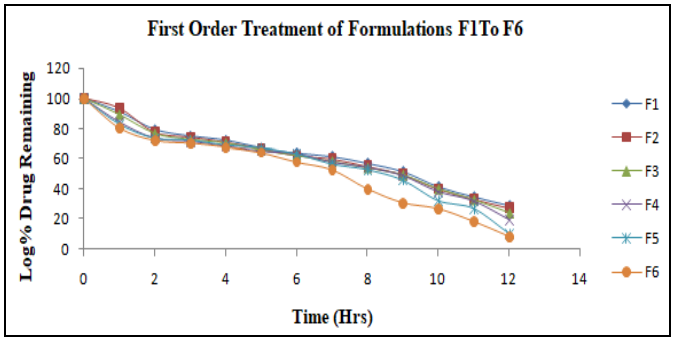


FIG. 10 AND 11: ZERO ORDER RELEASE KINETIC PLOT



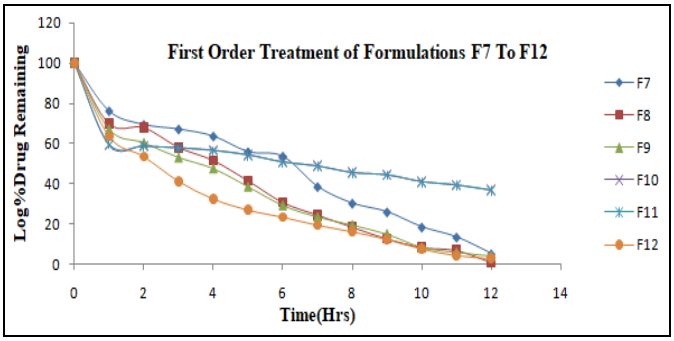
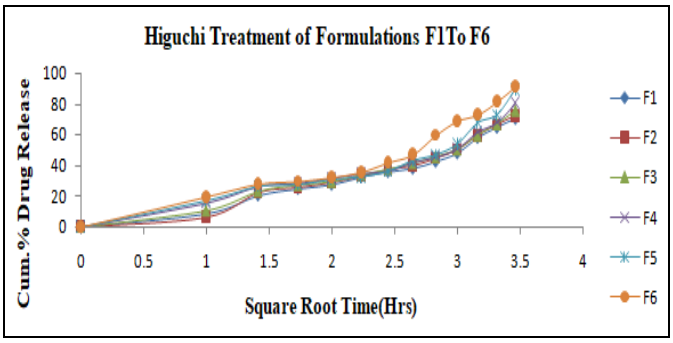


FIG. 12 AND 13: FIRST ORDER RELEASE KINETIC PLOT



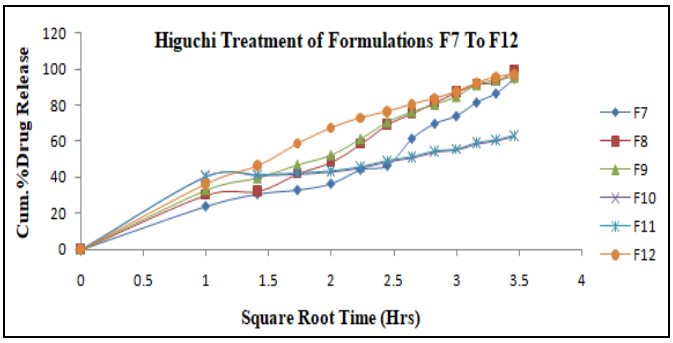
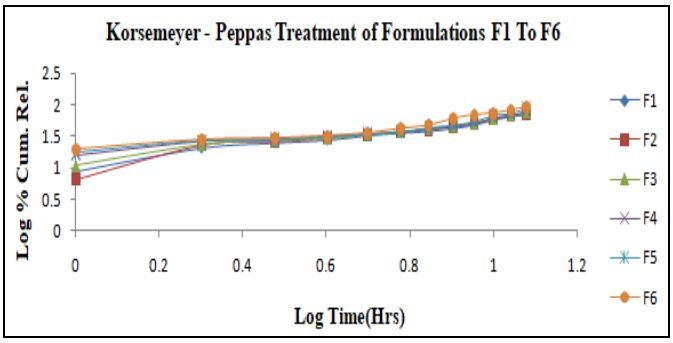


FIG. 14 AND 15: HIGUCHI RELEASE KINETIC PLOT



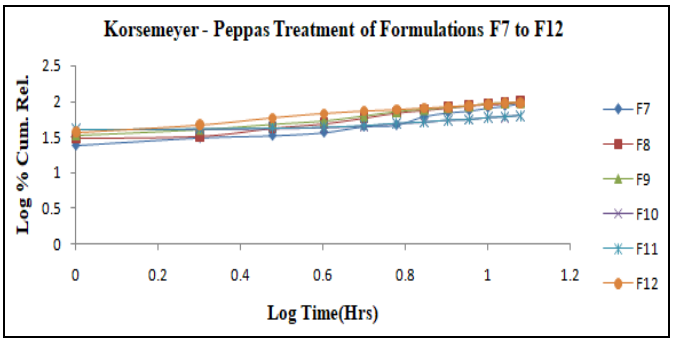


FIG. 16 AND 17: K-PEPPAS RELEASE KINETIC PLOT

TABLE 11: KINETIC MODELS STUDIES OF F1 TO F12 FORMULATIONS

Drug Release / Formula Code	Zero Order R^2	First Order R^2	Higuchi R^2	K. Peppas R^2
F1	0.974	0.304	0.969	0.963
F2	0.967	0.295	0.965	0.919
F3	0.973	0.298	0.966	0.965
F4	0.953	0.302	0.943	0.951
F5	0.949	0.281	0.945	0.916
F6	0.964	0.228	0.961	0.902
F7	0.985	0.173	0.968	0.909

F8	0.997	0.062	0.965	0.948
F9	0.959	0.077	0.939	0.975
F10	0.701	0.347	0.709	0.809
F11	0.705	0.345	0.713	0.836
F12	0.886	0.067	0.871	0.991

CONCLUSION: In the present research work, we successfully developed stomach specific *in-situ* gels of curcumin, which exhibit a unique combination of floatation and ionic gelation for prolonged residence in the stomach. The F8 formulation showed a satisfactory gel strength, density, physical appearance, drug content, and floating behaviors. It was revealed from the study that with the increase in the concentration of polymer, the viscosity and % of water uptake by gel also increased but the drug release from the in situ gel decreased. Thus, it can be concluded that the release of curcumin could be targeted to the stomach and sustain the drug release over some time. Hence by its liquid nature, *in-vivo* gelling capacity and gastric retention, the developed formulation could offer a variable alternative to conventional dosage forms, especially for the pediatric and geriatric patient.

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