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Formulation And Evaluation of Rebamipide Gastroretentive Floating *In-Situ* Gelling System for An Oral Controlled-Release Dosage Form

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Abstract

This study focuses on developing a novel floating *in-situ* gel system for the controlled delivery of Rebamipide (REB), a gastroprotective agent used to treat ulcers and gastritis. REB has a short half-life of 1.5 hours, requires 100 mg thrice daily, and shows low oral bioavailability (<10%) as a BCS class IV drug. To enhance gastric residence time and modulate drug release, a gastro-retentive floating *in-situ* gel was formulated. These polymeric systems remain in solution before administration and undergo gelation in the acidic stomach environment; sodium citrate was incorporated to prevent premature gelation. Thirteen formulations (F1-F13) were developed using varying concentrations of sodium alginate, gellan gum, HPMC K4M, and HPMC K100M. Among them, formulation F12 showed optimal performance, achieving 97.9% drug release over 5 hours and containing 1% w/v sodium alginate, 0.5% gellan gum and 1.5% w/v HPMC K4M. FTIR analysis confirmed the compatibility and interaction profile of the drug with the selected excipients. F12 was optimised based on drug release, gel strength, floating behaviour, buoyancy, density and swelling index, all of which showed satisfactory results. Dissolution data fitted the Korsmeyer-Peppas model (R^{2+}=0.982), with an n value of 0.765, indicating that the optimised formulation pattern of release was preceded by Fickian diffusion. Stability studies of F12 revealed no changes in appearance, viscosity, drug content or floating time throughout the storage period.

Keywords

Rebamipide (REB), Gastro Retentive, Floating *In-situ* gel, Sodium alginate, Gellan Gum.

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INTRODUCTION

Most of the drugs given via oral route are subjected to absorption throughout the gastrointestinal tract, with major absorption from stomach and intestine. [1,2]. After the drug release from dosage form, various processes occur which effect the absorption of the drugs, e.g. degradation of the drug enzymatic or microbial action, precipitation of drug etc. Drugs, which get absorbed more from the stomach or show local effect, should spend maximum time in stomach. Retention of dosage form in stomach for longer duration is difficult for conventional dosage forms like tablets and capsules, because of the gastric emptying.

Gastro Retentive Drug Delivery System are one of the approaches to ensure that a particular dosage form or drug remains within stomach for longer duration of time in stomach.[3]. The retention of oral dosage forms in the upper GIT causes prolonged contact time of the drug with the GI mucosa, leading to

higher bioavailability and hence therapeutic efficacy, with reduced dose size and time intervals for drug administration the patient compliance is improved. [4]. Floating drug delivery systems are the type of gastro retentive drug systems which float immediately upon contact with the gastric fluid. It is due to its property of low bulk density (< 1.00 g/cm3) and it provides sufficient buoyancy to remain float over gastric fluid for a prolonged period of time while the drug release at the desired rate at specific site. [5-7]. The Oral floating *In-situ* gelling system is a type of floating drug delivery system principally capable of releasing drug molecule in a sustained manner affording relatively consistent plasma profile.

Oral floating *In-situ* gel system are hydrogels which are liquid at room temperature and undergo gelation under ionic interaction or pH or temperature induced. It involves the use of gelling agent which can form a stable sol/suspension system contain the dispersed drug and other excipients.[8]. The gelling agents adopted are gellan gum or sodium alginate solution containing calcium chloride and sodium citrate, which involves the formation of the double helical junction zones followed by aggregation of the double helical segments to form a three dimensional network by complexation with free calcium ions and releases them in the acidic environment of stomach. [9,10].

drug, belongs to BCS class Ⅳ (low solubility, low permeability), possessing poor aqueous solubility and low oral bioavailability (less than 10%). It is usually act by cell preservation and tissue replacement and increases prostaglandin production (by stimulating COX-II) in the gastric mucosa, which improves the quality of ulcer healing. It also shields the gastric mucosa from noxious and ulcerogenic factors. It also inhibits specific inflammatory mechanisms, especially activation of neutrophils in the blood capillaries scavenging oxygen free radicals. [11,12]. Rebamipide is a weekly acidic drug showing pH-dependent solubility resulting in low solublity in the acidic gastric medium. It has both systemic and local action concentration of the drug in the stomach and prolonging its gastric retention would improve the therapeutic action of the drug not only locally but systemically as prolonged high concentration would augment local effect as well as systemic absorption.

In the present investigation, an attempt has been made to prepare a formulation of Rebamipide as an oral gastro-rententive floating *in situ* gel using gellan gum and sodium alginate as gel-forming agents to control the release and further improve its absorption and bioavailability.

MATERIALS AND METHODS:

Materials: Rebamipide was gift sample from Yarrow chemicals, Mumbai, India. sodium alginate, gellan gum, sodium benzoate and sodium citrate were procured from HIMEDIA, Mumbai, India. Sodium bicarbonate, propylene glycol was purchased from Chemdie Corporation. Sodium methyl paraben, sodium propyl paraben was purchased from Sisco Research Laboratories. Fructose and Calcium chloride were purchased from SD Fine Chemicals Ltd, Mumbai. All the ingredients and reagents used are of analytical grade.

PREFORMULATION STUDIES:

Preformulation Study:

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a drug as well as stability in the presence of other excipients. The primary objectives of this investigation are the identification of stable storage conditions for a drug in the solid state and the identification of compatible excipients for a formulation.

Chemical Compatibility Studies by FT-IR:

To identify any feasible incompatibility between drug-excipient interaction, FTIR spectrum (FTIR-8400S, Shimadzu, Japan) of pure drug and formulated containing drug were carried out by using spectrum. Scanning range was from 400 to 4000 cm^{-1}. FTIR spectroscopy of samples was obtained by KBr press pellet technique.

Solubility Studies

Drug solubility was determined in 0.1 N HCl by employing the equilibrium solubility method. The addition of an excess amount of drug to various solvents in volumetric flasks. After shaking the contents in for 48 hours at room temperature on a gyratory shaker at 300 rpm, the contents were transferred into Eppendorf tubes and centrifuged for 20 minutes. The supernatant was passed through a 0.22 µm membrane (syringe) filter. The filtrate was diluted with methanol and measured for absorbance by UV- Visible spectrophotometer at λ_{Max} 227nm. The corresponding drug concentration was estimated from the standard graph.[13].

Formulation development of Rebamipide *In-situ* Gel:

Preparation of oral Rebamipide solution to act as in-situ gel. Different polymers were used to prepare Rebamipide to act as an in-situ gelling preparation, as shown in Table 1. Sodium benzoate and sodium citrate were dissolved in distilled water to prepare mixed solubilised solution. The mixture was heated to 37°C while stirring. Then add 0.5 mL glycerine and 2 mL propylene glycol was added with continuous

stirring and heating until all ingredients are dissolved and mixed completely. At the same time, the polymer (Na alginate/Gellan gum) was dissolved at different concentrations, each one separately, in distilled water containing sodium citrate and calcium chloride, heating to 60°C while stirring. Then mixed solubilised solution was added to the polymer solution with continuous stirring. Finally, various amounts of sodium bicarbonate were added, then Rebamipide was dispersed in the resulting solution after cooling. [14].

Table 1: Formulation of *in-situ* floating gel of Rebamipide (F1-F13)

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Rebamipide (%w/v)	1	1	1	1	1	1	1	1	1	1	1	1	1
Sodium benzoate (%w/v)	1	1	1	1	1	1	1	1	1	1	1	1	1
Sodium citrate (%w/v)	1	1	1	1	1	1	1	1	1	1	1	1	1
Glycerine (mL)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene glycol (mL)	3	3	3	3	3	3	3	3	3	3	3	3	3
Calcium chloride (%w/v)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
$NaHCO_3$	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium alginate (%w/v)	1	1	1	1	1	1	1	1		-	0.5	1	0.5
Gellan gum (%w/v)	-	-	-	-	-	-	-	-	0.5	1	0.5	0.5	1
HPMC K4M (%w/v)	0.5	1	1.5	2	-	-	-	-	1.5	1.5	1.5	1.5	1.5
HPMC K100M (%w/v)	-	-	-	-	0.5	1	1.5	2	-	-	-	-	-
Na+methyl paraben (%w/v)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Sodium propyl paraben (%w/v)	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018
Fructose (%w/v)	1	1	1	1	1	1	1	1	1	1	1	1	1
Distilled water Q.S (mL)	100	100	100	100	100	100	100	100	100	100	100	100	100

EVALUATION PARAMETERS OF REBAMIPIDE *IN-SITU* GEL:

Gel strength of *In-situ* gel

The method to measure gel strength of gelled mass was measured by using fabricated gel strength apparatus and it was done in triplicate. Solution of 5 mL was taken in the cylinder followed by addition of 25 mL of 0.1N HCl (pH 1.2) for gelation. After gelation, the HCl was drained off leaving the formed gel mass and then the device was rested on the surface of the gel. At the free end of the device, a light weight pan (4 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. [15].

Gelation time determination

Gelation time was evaluated visually. It was measured by placing 5 mL of 0.1 N HCl (pH 1.2) in test tube and maintained at 37 ± 1°C. One mL of each formula was taken with pipette and transferred slowly on the surface of the fluid, as the solution came in contact with gastric fluid solution, it was

immediately converted into gel-like structure. The gelation time was evaluated in triplicate on basis of time period for which gel formed.[16].

Determination of drug content

Accurately, 5 mL of liquid solution (containing 20 mg of the drug) from all formulations was taken and to which 70 mL of 0.1N HCl was added, then the sample was sonicated for 30 min until clear solution was made. The volume was made up to 100 mL and filtered using Whatman filter paper No. 41. From this solution, 1 mL sample was withdrawn and diluted to 10 mL with 0.1N HCl. Contents of Rebamipide was determined spectrophotometrically at λ_{Max} 227 nm using double beam UV-Visible spectrophotometer.[17].

***In-vitro* Buoyancy study**

The *in-vitro* buoyancy study is characterized by floating lag time and total floating duration. *In-vitro* buoyancy study was carried out in 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°C. Accurately 10 mL of the prepared in-situ gel formulation was drawn up using disposable syringe and placed into the petri dish (4.5 cm internal diameter) and finally the petri dish containing the formulation was placed carefully in the dissolution vessel. 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 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.[15].

pH Measurement

The pH of the prepared solution for all formulations was measured by digital pH meter at 25° ± 0.5°C, after it is calibrated using standard buffer solutions of pH 4, 7 and 9. Then the measurements of pH were recorded. [18].

Density Measurement of the Gel

The prime requirement for stomach-specific floating drug delivery system is the density; which is an important parameter and it should be less than the stomach fluid density (<1.004 g/cm³). The densities of all formulations were measured by forming gel of known volume (5 mL) in a petri dish containing 0.1N HCl. The weight of this gel was measured by using calibrated balance and accordingly the densities of formulations were calculated. Density measurement for each formulation was done in triplicate.

Swelling Index

The percentage of swelling index of in-situ gel of the formulations was determined. In-situ gel formed by putting 5 mL of each formula in a petri dish and 40 mL of 0.1N HCl (pH 1.2) was added. Then 0.1N HCl solution was removed from the gel and the excess of 0.1N HCl solution was blotted out with Whatman filter paper. The initial weight (W_o) of the gel was recorded, to this gel 10 mL of distilled water was added and after 60 minutes the water was decanted and the final weight (Wt) of the gel was recorded, this process was repeated for 5 hr and the difference in the weight was calculated and reported.[15]

The % weight gain (swelling index) for formulations is calculated by the following equation:

$$\% \text{ Swelling index} = (Wt - W_o / Wt) \times 100$$

Where, W_o = Initial weight of the gel, Wt = weight gain by the gel

Viscosity measurements

The viscosity of the prepared solutions was measured out using sample of 100 mL. Measurements were performed using suitable spindle number 64 and sheared at a rate of 3, 4, 5, 6, 10, 12, 20, 30, 50, 60 and 100 rpm, and the temperature was maintained at 37°C. The viscosity was read directly after 30 seconds. All measurements were made in triplicate. The rheological velocity was explained by plotting viscosity against angular velocity. [19].

Table 5 and Figures 3,4,5 illustrate a significant ($p>0.05$) increase in the viscosity of the formulations (F1-F13) as the concentration of HPMC increases, with a significant ($p>0.05$) effect on the viscosity with shear thinning behaviour due to an increase in polymer network cross-linking with strong elastic behaviour of the highly concentrated polymer. This result is in agreement with reported data.

***In-Vitro* Drug Release Study**

The *in-vitro* release of Rebamipide from buoyant in-situ gel solutions was studied using USP type II (paddle type) dissolution test apparatus. 5 mL (containing 50 mg of Rebamipide) from each formulation was transferred using disposable syringe, the needle was wiped clean and excess formulation was removed from needle end. The syringe plunger depressed slowly to extrude 5 mL into a petri dish with an internal diameter of 4.5 cm 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 5 hrs at a temperature

37 ± 0.5°C. This speed was slow enough to avoid the breaking of gelled formulation and was maintaining the mild agitation conditions believed to exist *in-vivo*. Five mL samples were withdrawn from dissolution medium with disposable syringe at predetermined time intervals of 5, 10, 15, 20, 30, 60, 120, 180, 240 and 300 min and replenished with 5 mL of pre-warmed fresh medium. Samples were filtered using Whatman filter paper No. 41 and Rebamipide contents in the aliquots was determined spectrophotometrically using double beam UV-Visible spectrophotometer at a wavelength of λ_{max} 227 nm after suitable dilution. The experiments were conducted in triplicate at each time interval and the average was recorded.[15].

Evaluation of accelerated stability studies for best formulation

Stability studies for *In-situ* gel of REB was carried out as per ICH guidelines. Stability studies are conducted for optimised formulations was 40º ± 2º C with 75± 5% RH for a period of 3 months. The physical condition and drug content was measured.

RESULTS AND DISCUSSION

FTIR:

The IR spectral analysis of the Rebamipide, polymer and other excipients was carried out by using the KBr pellet method, and the spectra are shown in the Fig 1. All the characteristic peaks appear for the pure Rebamipide and its physical mixture, indicating no interaction between Rebamipide and excipients as shown in Table 2

Table 2: FTIR Spectra of drug and Excipients

S.No	Rebampide	Optimised formulation
CH_3	2938	2956
N-H	3276	3306
C=O	1725	1736
$C=ONH_2$	1643	1644
C-N	1338	1347
C-H (Aromatic ring)	**759**	**758**

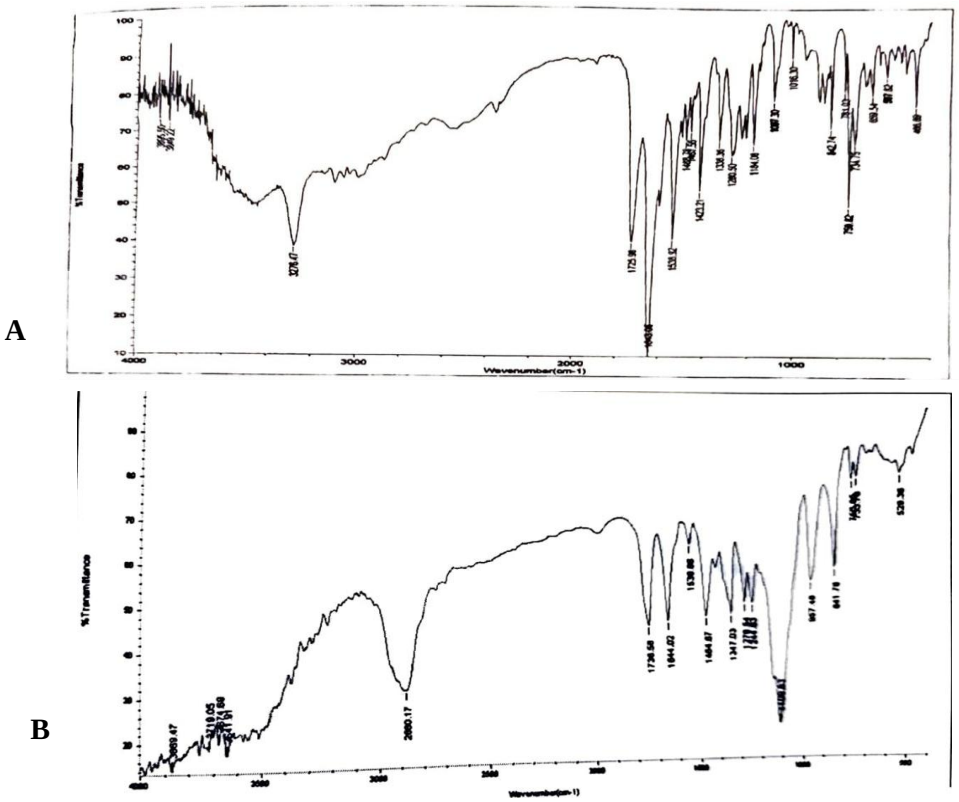

Figure 1: A) FTIR spectrum of pure Rebamipide
B) FTIR spectrum of optimised formulation (F12)

Solubility studies:

From the solubility studies, it is understood that Rebamipide is mostly soluble in a pH 7.4 buffer solution and has the least solubility in 0.1 N HCl. Solubility of Rebamipide in various solvents are given in Table 3 and Fig. 2

Table 3: Solubility studies of Rebamipide

Solvents	Solubility (mg/mL)
Water	**0.0231**
Ethanol	**0.322**
Methonol	**0.770**
pH 6.8	**1.295**
pH 7.4	**3.688**
0.1 N HCl	**0.0018**

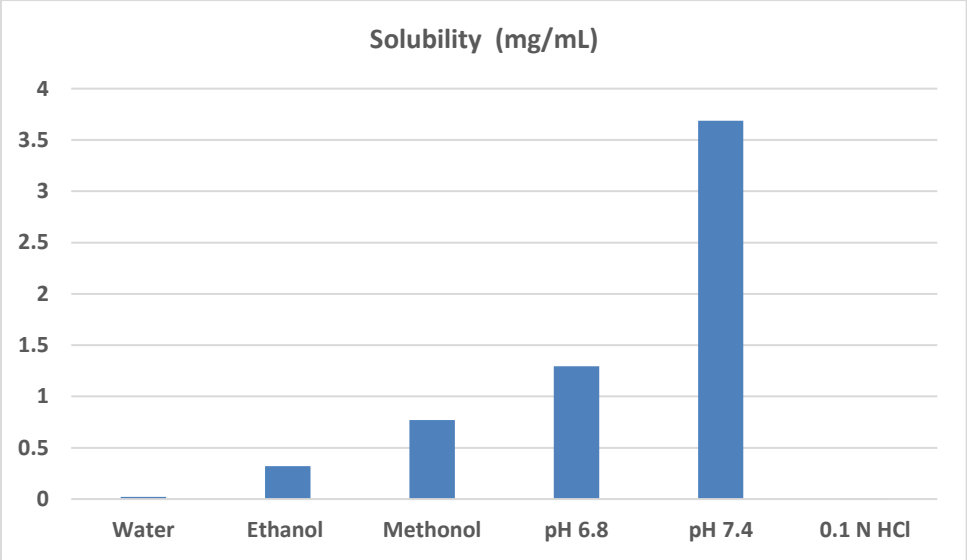

Figure 2: Solubility studies of Rebamipide

Evaluation of Rebamipide Floating *In-situ* Gel

All the formulations (F1-F13) prepared were evaluated for different parameters like: gel strength, gelation time, content uniformity, floating lag time, floating duration, pH measurement, density and swelling index. The results are summarised in Table 4.

Table 4: Evaluation parameters of Rebamipide Floating *In-situ* Gel (F1-F13)

CODE	Gel strength (N/m2)	Gelation Time (sec)	Drug Content (%)	Floating Lag time (sec)	Floating Duration (hr)	pH	Swelling Index (%)	Density (g/cm^3)
F1	11.94	11	95	23	>6	6.95	43.5	1.14
F2	16.14	15	96	26	>6	6.94	48.3	1.23
F3	20.18	18	91	28	>6	6.93	54.4	1.36
F4	12.18	20	93	30	>6	6.85	60.3	1.05
F5	10.20	7	96	36	>6	6.91	57.2	1.18
F6	17.76	4	98	37	>6	6.90	63.2	1.42
F7	9.45	2	94	39	>6	7.2	65.2	0.91
F8	10.20	0	91	43	>6	7.1	68.6	0.96
F9	17.76	12	95	34	>6	7.0	48.5	0.99
F10	7.89	14	92	33	>6	7.0	47.8	0.89
F11	13.02	11	97	36	>6	7.2	50.4	0.92
F12	**16.05**	**13**	**98**	**35**	**>6**	**7.1**	**49.1**	**0.94**
F13	10.96	11	96	33	>6	7.5	48.4	1.09

Gel strength:

Gel strength of the F1 to F13 was measured using a fabricated gel strength apparatus using 0.1N HCl (pH 1.2), and values are presented in Table 4. Gel strength has increased from F1 to F3 with an increase in the concentration of sodium alginate and HPMC K4M, and decreased with F4 with further increase in concentration. In F5 to F6, gel strength increased with an increase in concentration of HPMC K100M and decreased with further increase in concentration in F7 and F8. Optimum gel strength is shown in F12, which is 16.05 N/m^2.

Gelation time:

The gelation time determination is performed in 0.1N HCl (pH 1.2). The gelation time increased from F1 to F4 and decreased from F5 to F8 with a change in polymer in formulation from HPMC K4M to HPMC K100M, respectively. From formulation F9 to F13, gelation time has shown optimum gelation time, which are depicted in Table 4.

Drug content:

The drug content of F1 to F13 was described in Table 4. The percentage drug content of F1 to F13 ranges from 91% to 98%.

***In-vitro* buoyancy study:**

The *In-vitro* buoyancy of the formulations was performed in the USP dissolution apparatus type II using 900 mL medium of 0.1N HCl (pH 1.2). Two studies were performed, i.e. floating lag time (sec) and floating duration (hr). Floating lag time (sec) has from F1 to F4 (sodium alginate and HPMC K4M) and also in case of F5 to F8 (sodium alginate and HPMC K100M), and the optimum floating lag time (sec) was observed in F9 to F13. The floating duration (hr) of F1-F13 was observed to be >6 hours.

pH of *in-situ* gel formulations:

All the formulations pH was found to be neutral and slightly acidic. The pH value of all prepared *in-situ* gel formulations was found in the range of 6.85 to 7.5 and is shown in Table 4. This indicates the prepared gel formulations does not cause any irritation and discomfort to the oral cavity.

Swelling index:

The swelling index of the *in-situ* gelling solutions was performed in 0.1N HCl (pH 1.2), and the results of the swelling index are represented in Table 4. From the study results it is observed that with increase in HPMC K4M and HPMC K100M the swelling index increased, and formulations (F5 to F8) containing HPMC K100M showed maximum swelling index compared to other formulations. It is observed that it directly impacted the % drug release. The formulations F9 to F13, which are prepared in a combination of polymers (sodium alginate, gellan gum and HPMC K4M), showed optimum % swelling index.

Viscosity Measurement

The Rheological properties of the solutions are of importance in 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. The effect of shear stress on the viscosity of formulations are given in Table 5.

Table 5: Effect Of Shear Stress on Viscosity of Formulations

CODE	VISCOSITY (Pas/cps)										
	Shear speed (RPM)										
	3	4	5	6	10	12	20	30	40	50	100
F1	1800	1500	1300	1200	840	750	690	540	460	408	290
F2	1850	1500	1300	1200	940	850	790	640	470	438	320
F3	2700	2100	1700	1350	1200	1150	980	780	690	500	490
F4	2800	2200	1800	1400	1300	1150	990	800	750	610	500
F5	2800	2500	2300	2100	1920	1850	1770	1640	1580	1520	1460
F6	3400	3100	2900	2700	2400	2250	2160	2080	1900	1820	1640
F7	6800	6700	6500	6300	6120	5900	5700	5520	5230	3280	2160
F8	9000	8200	7900	7500	6540	6300	5520	4900	4340	4200	3580
F9	2300	2140	1935	1734	1446	1248	1104	1050	830	640	550
F10	2500	2100	1700	1350	1200	1150	980	780	690	500	600
F11	2600	2200	1800	1450	1300	1250	1180	1080	890	700	650
F12	**2100**	**1900**	**1700**	**1350**	**1200**	**1150**	**1080**	**980**	**790**	**610**	**500**
F13	2600	2200	1800	1550	1350	1250	1100	1000	850	700	650

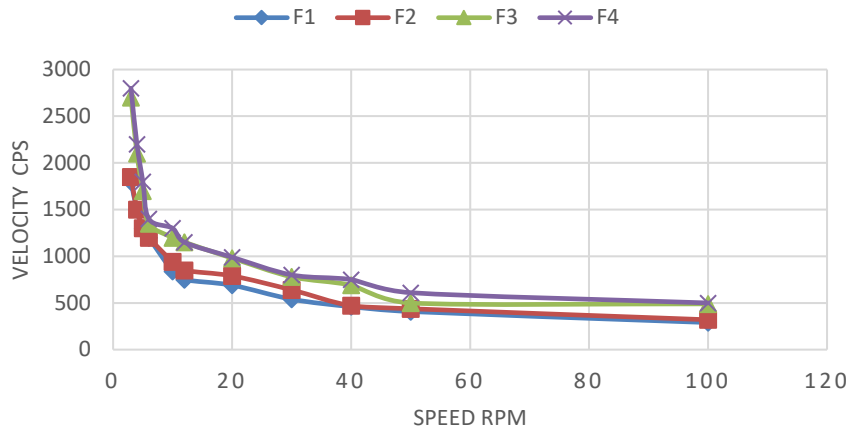

Figure 3: Rheological properties of Na Alginate + HPMC K4M formulations (F1-F4)

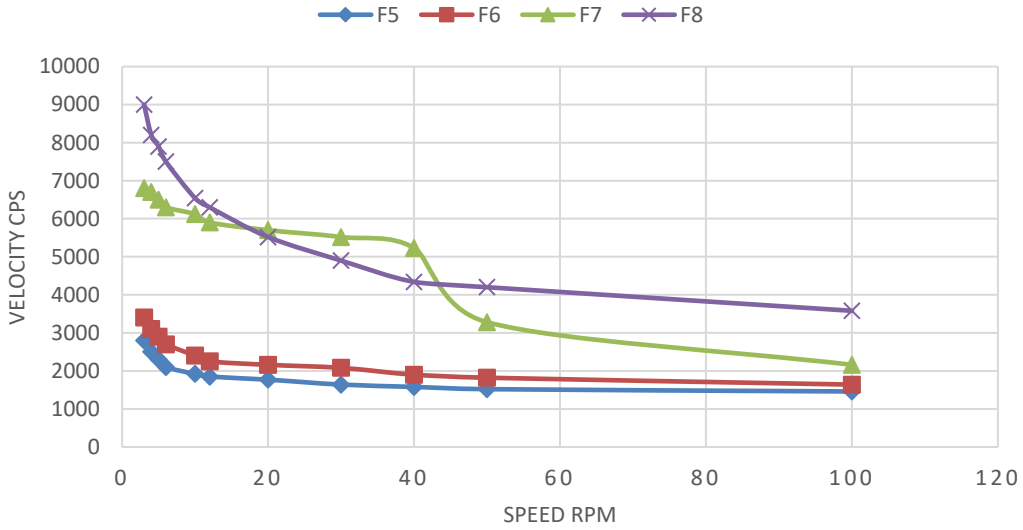

Figure 4: Rheological properties of Na Alginate + HPMC K100M formulations (F5-F8)

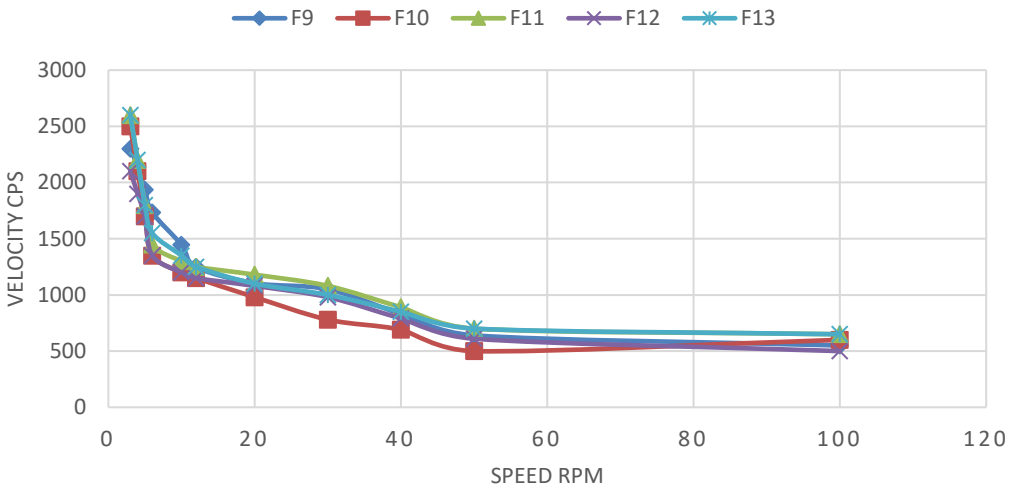

Figure 5: Rheological properties of a) Gellan Gum +HPMC K4M and HPMC K100M combination solutions (F9-F10) b) Na Alginate + Gellan Gum + HPMC K4M (F11-F13)

Table 5 and Figures 3,4,5 illustrate a significant ($p>0.05$) increase in the viscosity of the formulations (F1-F13) as the concentration of HPMC increases, with a significant ($p>0.05$) effect on the viscosity with shear thinning

behaviour due to an increase in polymer network cross-linking with strong elastic behaviour of the highly concentrated polymer. This result is in agreement with reported data.

***In-vitro* Drug Release Studies:**

In-vitro dissolution studies of all the formulations of the floating in-situ gel of Rebamipide were carried out in acidic buffer (0.1 N HCl). The study was performed for 5 hours, and cumulative drug release was calculated at different time intervals which are shown in Table 6.

The Formulations F1, F2, F3, and F4 were prepared using sodium alginate and HPMC K4M with increasing concentration. The Formulations F1, F2 and F3 has released a drug with increasing the concentration of polymer HPMC K4M as the drug content of 87.1%, 91.8% and 94.5% in 5 hrs, respectively, as shown in Fig. 6

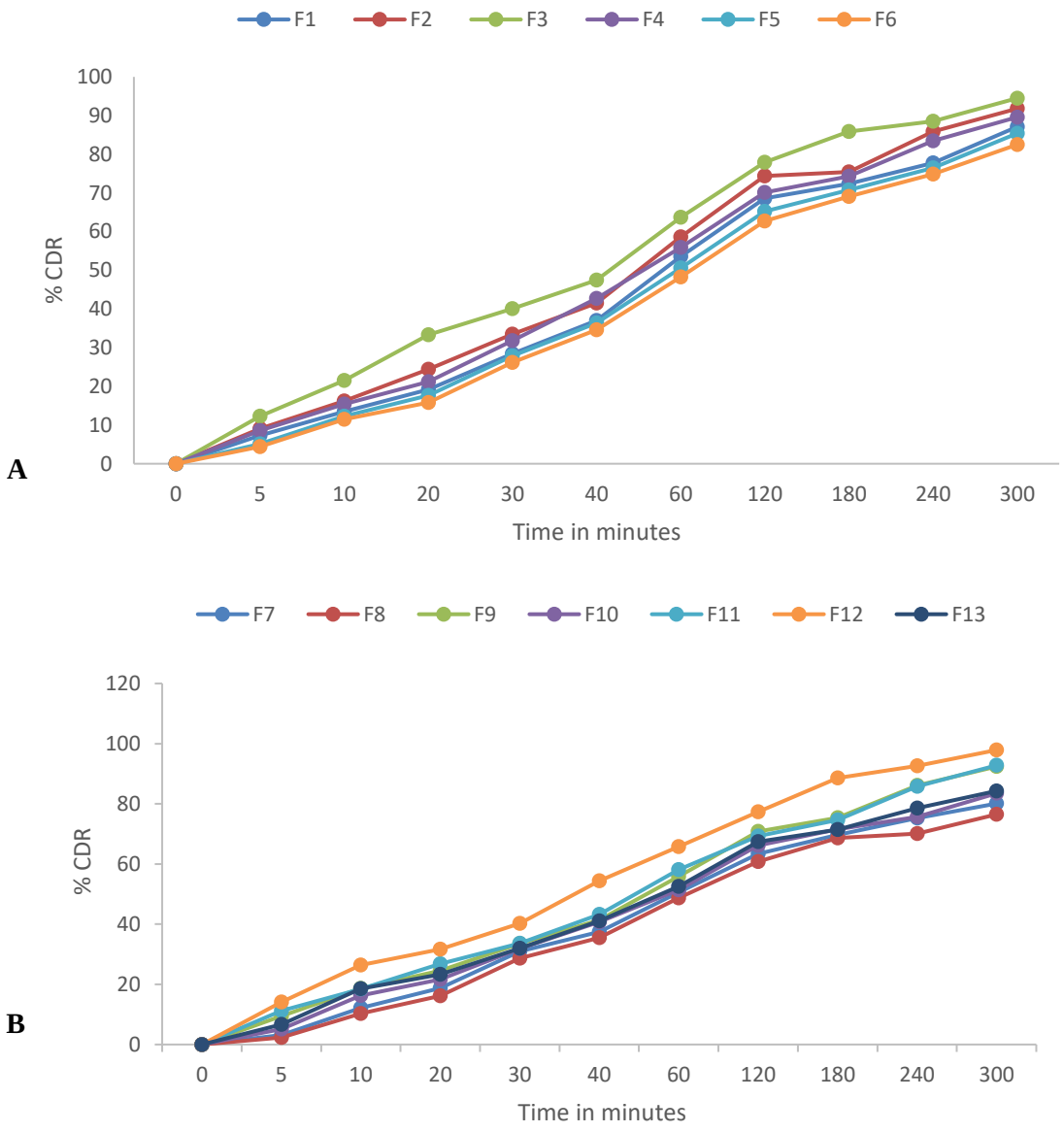

Figure 6: *A) In vitro* release data of Rebamipide *In-situ* gel F1-F6
***B) In-vitro* Release data of Rebamipide *In-situ* gel F7- F13**

The Formulation F4 showed a decrease in % of drug release compared to F3. In this case, the drug release is in optimum concentration of the polymer, as further increasing the polymer concentration, the viscosity also increases, thereby the polymer gets further swollen in the medium, thus decreases the

pore size and drug gets difficult to diffuse into the medium. Sameis seen in the formulations F5, F6, F7 and F8, which released the drug at 85%, 82%, 80% and 76% respectively.

Table 6: *In- vitro drug* release by dissolution method (F1-F13)

Time (min)	Formulation	0	5	10	20	30	40	60	120	180	240	300
Percentage of cumulative release F1-F13	**F1**	0	7.3	13.5	19.2	28.4	37	53.6	68.6	72.4	77.8	87.1
	F2	0	9.1	16.2	24.4	33.5	41.5	58.6	74.4	75.4	85.9	91.8
	F3	0	12.3	21.5	33.3	40.1	47.5	63.7	77.9	85.9	88.5	94.5
	F4	0	8.6	15.4	21.2	31.8	42.7	55.9	70.1	74.3	83.5	89.6
	F5	0	5.1	12.3	17.7	27.9	36.4	50.6	65.2	70.8	76.5	85.4
	F6	0	4.4	11.5	15.8	26.2	34.6	48.3	62.7	69.1	74.9	82.5
	F7	0	3.2	12.1	18.8	30.9	37.5	50.6	63.4	69.7	75.3	80.1
	F8	0	2.3	10.3	16.2	28.7	35.5	48.7	60.8	68.7	70.1	76.5
	F9	0	9.5	18.7	24.5	33.5	41.4	55.8	70.8	75.4	86.1	92.4
	F10	0	5.1	16.3	21.7	31.9	40.8	51.4	66.2	71.6	75.7	83.5
	F11	0	11.2	18.4	26.8	33.6	43.2	58.1	69.3	74.7	85.8	92.8
	F12	**0**	**14.1**	**26.4**	**31.7**	**40.2**	**54.4**	**65.8**	**77.3**	**88.6**	**92.6**	**97.9**
	F13	0	6.7	18.5	23.3	32	41.1	52.5	67.4	71.4	78.6	84.3

When comparing the formulations made from polymers like HPMC K4M and HPMC K100M, the maximum drug release was found in formulations made from HPMC K4M. Here, the viscosity of the polymer HPMC K100 M is more than HPMC K4M, thereby drug release is slower.

Kinetic mathematical modelling of drug release profile

In-vitro release data were fitted to various mathematical models such as zero order, first order, Higuchi, and Korsmeyer–Peppas model in order to understand the mechanism of drug release and the release rate from dosage forms.

Table 7: *In-vitro* kinetic model for the *in- situ* Rebamipide Gel (F1-F13)

Formulation	Zero order	First order	Higuchi model	Korsemayer-Peppa's model	
	R^2	R^2	R^2	R^2	n
F1	0.6528	0.9521	0.9613	0.9596	0.467
F2	0.5875	0.9624	0.9573	0.9627	0.438
F3	0.4278	0.9680	0.9336	0.9674	0.386
F4	0.6103	0.9560	0.9613	0.9644	0.446
F5	0.6865	0.9532	0.9660	0.9630	0.482
F6	0.7093	0.9522	0.9665	0.9629	0.494
F7	0.6266	0.9259	0.9540	0.9533	0.458
F8	0.6384	0.9124	0.9467	0.9434	0.467
F9	0.6064	0.9603	0.9711	0.9774	0.440
F10	0.5772	0.9208	0.9548	0.9612	0.434
F11	0.5689	0.9472	0.9656	0.9771	0.425
F12	**0.4000**	**0.9681**	**0.9292**	**0.9704**	**0.378**
F13	0.5573	0.9217	0.9567	0.9673	0.426

Table 7 illustrates the correlation of dissolution data to different models of release kinetic wear best fitting to the Higuchi Model was observed for most formulations, indicated by highest regression value (r^2). This result indicated that most formulation exhibits a diffusion mechanism in drug release, accompanied by an acceptable regression value for zero order. A kinetic model which best fit zero order and Higuchi's diffusion equation were most suitable for control release formulation.

For the Korsmeyer-Peppas model, the value of the release exponent (n) defines the release mechanism; the n value of all formulations is found to be less than 0.5. Hence, it can be concluded that drug release occurred via Fickian diffusion release, as shown in Table 8; this mathematical model, also known as the

power law, from which the rate of diffusion is much less than that of relaxation modes of the polymer penetrant system.

Table 8: *In-vitro* kinetic model of optimised *in-situ* Rebamipide gel (F12)

Formulation code	R^2 value				Best fit model
	Zero-order	First-order	Higuchi(diffusion)	Peppas	
F12	0.4000	0.9681	0.9292	0.9704	First and Higuchi

Evaluation of accelerated stability studies of the best formulation (F12)

Stability studies were carried out using a selected formulation, i.e., F12. The formulation was kept under accelerated stability conditions at 40°C/75% relative humidity for a period of 3 months as per International Conference on Harmonization guidelines. Samples were withdrawn at 3-month intervals, and evaluations were carried out for parameters such as pH, Floating lag time (sec), floating duration (hr), Viscosity (cp) at 100 rpm, and Drug Content (%) shown in Table 9.

Table 9: Stability studies of optimized formulation (F12)

Formulation parameters	Initials	After 3 months
pH	8.1	8.0
Floating lag time (sec)	35	34
Floating duration (hr)	>6	>6
Viscosity (cp) at 100 rpm	500	505
Drug response (%)	97.9	96.6

CONCLUSION

The oral floating *In-situ* gel formulations were prepared using sodium alginate polymers, gellan gum and changes in amounts of secondary polymers, HPMC K4M (0.5-2%w/v) and HPMC K100M (0.5-2%) have been used in different formulations, based on their effects on release trends and contingent reactions HPMC K4M (1.5%w/v) levels were set. Based on the assessment criteria, such as rheological tests, drug content, and gel strength, sodium alginate and gellan gum in combination were chosen as most adequate polymers for optimised results. The optimization batch composition F12 (sodium alginate 1% + Gellan Gum 0.5% + HPMC K4M 1.5%) had a maximum drug release rate of 97.9% in 5 hours. It was observed that the best-fit model for the optimised formulation F12 was the Higuchi (diffusion) coefficient (R^2 = 0.9892), and the n value was 0.378, which implies that the optimised formulation's release pattern was preceded by Fickian diffusion. Based on the FTIR studies, we conclude that there are no drug excipient interactions. Stability of Rebamipide optimised formulation F12, as solution improves in appearance, drug content, viscosity and floating time was observed, that Rebamipide *In-situ* floating gelling method was stable at 40ºC/ 75% RH for 3 months. Thus, incorporation of Rebamipide in floating *In-situ* gel resulted in sustaining the drug release, increasing gastric retention time and improving the bioavailability of the drug.

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