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Formulation and Evaluation of Gastro Retentive Floating In-Situ Gel Drug Delivery System of Proton Pump Inhibitor For Gerd

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ABSTRACT
The aim of this study was to develop and evaluate an oral floating in situ gel of Omeprazole using natural polymers such as Gelrite and sodium alginate. Omeprazole is a proton pump inhibitor that is used to treat gastrointestinal and oesophageal disorders (such as acid reflux, ulcers). It functions by lowering the level of acid secretion in the stomach. It alleviates symptoms including heartburn, trouble swallowing, and a constant cough, among others.
This research involved the development of an omeprazole oral solution that gels upon direct contact with an acidic atmosphere with a pH of 1.2 and then floats. Ion sensitive gelation occurs in the floating oral in situ gel. These floating in situ gel formulations were created using differing amounts of Gelrite (F1 to F3) and sodium alginate (F4 to F6).pH, in vitro gelling capability, gelling time, water uptake, viscosity, floating lag time, floating length, drug content uniformity, and in vitro drug release studies were performed on the prepared formulations.
Formulation F5 (1.5 percent w/v Gelrite) was chosen as the best formulation based on percent CDR, in vitro gelling capability, viscosity, and other considerations.
Higuchi's release is followed by Formulation F5, and the flow is Fickian.
In conclusion, the current research shows that Omeprazole floating in situ gel could be used for stomach specific managed drug delivery system.
Key Words: Omeprazole;Proton Pump Inhibitor; In situ gel; Gelrite; sodium alginate.

I. INTRODUCTION

Over the last few years, there has been a lot of focus on the development of in-situ gel systems. The advantages of in situ forming polymeric delivery systems, including as ease of administration and reduced frequency of administration, increased patient compliance and comfort, have sparked attention. Following administration, they gel in the stomach, aiding in bioavailability.

Omeprazole is a proton pump inhibitor that belongs to the substituted benzimidazoles class of anti-secretory drugs that do not have anticholinergic or histamine H2-receptor antagonist characteristics, but instead decrease stomach acid secretion by inhibiting the (H+-K+) ATPase enzyme system.[1,2]

It's also used to treat gastroesophageal reflux disease (GERD)[2] It is also used in the treatment of Gastro esophageal reflux disease (GERD), Helicobacter Pylori infections and stomach ulcers.

This medicine has a daily dose of 15-30 mg and requires numerous doses because of its shorter half-life, which frequently leads in dose-related side effects and poor patient compliance. To overcome a sustained medication delivery, 10ml of the formulation should be taken 3 or 4 times day in commercial formulations. At 2 hours after a single dose, there is a significant reduction in stomach acid output, which improves with subsequent treatment. Depending on the illness being treated, the peak response can take anywhere from 1 to 8 weeks. The tablet form of the medicine is difficult for geriatric and paediatric patients to take. [3,4]

The potential of sodium alginate, gellan gum, and guar gum mixture as a vehicle for sustained delivery of Omeprazole, which is delivered in liquid form and converts to gels in the stomach's acidic environment, is investigated in this study.[5]

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II. MATERIALS AND METHODS

Table 1 Materials:

SI No.	Materials	Source
1	Omeprazole	Gift Sample from Ce-Chem laboratories Bangalore
2	Gellan gum	SD Fine Chem., Mumbai..
3	Sodium alginate	SD Fine Chem., Mumbai.
4	Sodium citrate	Thomas Baker (chemicals) Pvt. limited, Mumbai
5	Calcium Carbonate	SD Fine Chem., Mumbai.
6	Methyl paraben	SD Fine Chem., Mumbai.
7	Bentonite powder	SD Fine Chem., Mumbai.
8	Sodium Saccharin	SD Fine Chem., Mumbai.
9	Sunset Yellow	SD Fine Chem., Mumbai.

III. METHODOLOGY

PREPARATION OF INSITU GELS:[6,7]

Polymeric solution of different concentration (1% w/v, 1.5% w/v and 2% w/v) were prepared in around 30 ml deionized water containing 1.5% w/v of Guar gum & sodium citrate (0.3% w/v). Then the solution was heated to 90°C with stirring individually and cooled below 40°C.

Appropriate amounts of calcium carbonate (2.5% w/v) was added. In another beaker Omeprazole (200 mg) was dissolved in deionized water with continuous stirring and finally poured into above solution with continuous stirring. Preservative Methyl paraben (0.02% w/v), Anti-caking agent bentonite powder (0.3%), along with sweetening agent Sodium Saccharin (0.5% w/v), and Sunset yellow as colouring agent were added to above solution. Then final volume was adjusted to 100 ml with deionized water with constant stirring.

The resulting in situ gelling solution containing Omeprazole was finally stored in amber coloured narrow mouth bottle until further use.

Sl.No.	Ingredients	Formulation					
		F1	F2	F3	F4	F5	F6
1.	Omeprazole	200	200	200	200	200	200
2.	Guar Gum	150	150	150	150	150	150
3.	Sodium Alginate	100	150	200	-	-	-
4.	Gellan Gum	-	-	-	100	150	200
5.	Calcium Carbonate	250	250	250	250	250	250
6.	Sodium Citrate	30	30	30	30	30	30
7.	Bentonite	30	30	30	30	30	30
8.	Sodium saccharin	50	50	50	50	50	50
9.	Methyl Paraben	2	2	2	2	2	2
10.	Sunset yellow	QS	QS	QS	QS	QS	QS

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11.	Water	100	100	100	100	100	100

Table 2: Formulation of In-situ Gel

Evaluation of Sol:

The following parameters were assessed for the developed in situ gel solutions. [8]

1. Physiochemical Characteristics: The formulated sols were examined visually. The sols were found to be devoid of dispersed particles. [8,9,10]

2. Viscosity of sols: The viscosity was determined with a Brookfield DV-II+ viscometer equipped with an LV-2 spindle. The formulation was placed in a sample holder, and the angular velocity was steadily increased from 10 to 100 rpm, with a wait time of 30 seconds at each speed. The highest torque value was discovered to be at 30 rpm for the spindle LV-2, which was chosen for the entire analysis. The viscosity was measured at room temperature.
[11,12]

3. Drug Content Determination: A known quantity of the prepared sols was agitated for 6 hours in 100ml of buffer solution (pH 6.8).The sample was then filtered, and the filtrate was measured at --------- nm using a spectrophotometric technique.[9,10]

4.**Invitro -Gelling time[11]**

Each formulation was mixed with 0.1 N HCl (approximately 50 ml) pH 1.2 in a beaker to evaluate gelling time, and the gelation was measured visually. The time it took to detect gelation using an in situ gelling system was recorded as gelling time, and the gel's integrity was also verified.

5.**Gel strength[12]**

In a 100 ml graduated cylinder, 50 ml of the formulation was put and gelled with pH 1.2 buffer. For the purpose of calculating gel strength, a 50 gm weight was put on the gel surface. The gel strength, which is an indicator of the formed gel's ability to preserve its integrity, was then measured in seconds. The time taken by the weight to penetrate 5 cm down through the gel was recorded as gel strength.

5..In vitro gelling capacity[12,13]

The formulations' in vitro gelling potential was determined by putting 5 ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube held at 37 ±1°C. The formulation (1 ml) was progressively added by inserting the pipette at the surface of the fluid in the test tube. As the solvent falls in contact with gelation solution, it is automatically turned into a stiff gel like structure.

6. Determination of Water Uptake[14]

To assess the water absorption by the gel in the current study, a basic procedure was used. For this analysis, an in situ gel formed in 500 ml of 0.1N HCl (pH 1.2) was used. The gel was isolated from the buffer solution and blotted with tissue paper; all formulations were taken out in the same manner and measured. It is regarded as the gel's initial weight. 10 mL of purified water was added to this gel. After 30 minutes decanted the water and re-weighed the gel.It was taken into account as the gel's final weight. Water uptake was determined using the formula below.

- **Water uptake** = $\frac{W_2 - W_1}{W_1} \times 100$

7. Floating behaviour (Buoyancy)[15]

0.1 N HCl was used to do a floating analysis on prepared in situ gel (pH 1.2). Without much disruption, 10 ml of the formulation (in situ gelling solution) was added to a dissolution vessel containing 500 ml 0.1 N HCl. The time it took for the formulation to appear on the medium's surface (floating lag time) and the amount of time the formulation floated on the medium's surface continuously (floating time)

8. In vitro dissolution study[16,17]

The drug release analysis was conducted using a USP-type II apparatus (rotating paddle type) at 37±0.2 °C and 75 rpm with a dissolution medium of 500 ml of 0.1 N HCl. For the analysis, an in situ gelling solution containing 20 mg of Omeprazole (10 ml) was used. At fixed time intervals, 5 ml of sample solvent was withdrawn.

Following sufficient dilution, samples were spectrophotometrically analysed at 301 nm. Following the removal of the test sample, an equal volume of fresh dissolution medium was replaced.

8. Drug Release Kinetics[18,19,20]

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Various mathematical models (zero order, first order, Higuchi's square root, Hixson-Crowell cube root law, and Pappas equation) were used to study drug release kinetics. Based on the correlation coefficient (R) value in different models, the one that best matches the release data is chosen. The model with the highest 'R' value is regarded as the best match to the release results.
The slope of the relevant plots was used to quantify the release constant, and the regression coefficient (R^2) was estimated.

IV. RESULTS & DISCUSSIONS

1. **Physiochemical Properties:** The sols formed were clear and viscous with a pleasant appearance.. With sodium alginate, Guar gum and calcium carbonate soft & Fragile gels were formed as compared to the ones obtained by the combination of Gellangum,guar gum & Calcium carbonate. Addition of sodium citrate to the solutions helps to form a complex with the calcium ions present in the formulation maintaining the fluidity of gel.
2. **Rheological behaviour of sols :** Table 3shows that all formulations displayed a substantial decrease in viscosity with increasingspindle rotation speed during viscosity evaluation. This decrease in viscosity is very noticeable, and itmay be attributed to the expansion of the polymeric chains as shear increases. This decrease inviscosity with increasing speed denotes shear thinning behaviour. The formulations with the highestcontent of polymer have the highest viscosity compared to all other formulations.

Formulation Code	Viscosity at 30 rpm (cps)	Viscosity at 60rpm (cps)	Viscosity at 100 rpm(cps)
F1	49.46±0.55	38.2±0.56	30.1±0.35
F2	79.46±0.83	70.2±0.36	57.4±0.98
F3	101.96±0.81	97.1±0.45	92.1±0.35
F4	46.36±0.28	37.1±0.45	29.1±0.79
F5	75.7±0.53	68.5±1.2	54.1±0.64
F6	91.33±0.36	87.2±0.64	81.6±0.56

Table 3: Viscosity determinations of floating in situ gel formulations
*Mean ± Standard deviation, n=3

5. Gelling Time: When the formulations were put in a pH 1.2 buffer, the findings revealed an instant sol to gel transformation. Almost all of the sol-gels responded to the sample. In the analysis, formulations F3 and F6 had shorter gelation times of 6 and 5 seconds, respectively, whereas formulations F1 and F4 had overall gelation times of 10 and 9 seconds, respectively. The concentrations of the polymers, sodium alginate and gellan gum, are responsible for the fast gelation of formulations.
The gelation time decreased as the concentration of polymer increased;
5.1 **Gelling Time:** The gelation time decreased as the concentration of sodium alginate increased;
Formulations **F1 and F3** had gelation times of **10sec and 6sec,** respectively. A drop of 4 seconds may be due to a rise in sodium alginate concentration from **1% (F1) to 2.0% (F4)** while keeping the concentration of other ingredients constant.
A similar pattern was found for gellan gum; as the concentration of gellan gum increased, the time required for gelation decreased dramatically.
Gelation times **of 9 seconds for formulation F4 (1 percent gellan gum) and 5 seconds for formulation F6 (2.0 percent gellan gum)** were observed.
5.2 **In-Vitro Gel Capacity & Gel- Strength:**
After mixing the formulation with 0.1 N HCl, (500ml) the gel strength of each formulation was calculated Gelation happens as divalent calcium ions participate in the interchain ionic binding of G-blocks in the polymer chain, resulting in a three-dimensional network. These ions serve as cross-linkers, stabilising polymeric chains and forming a gel matrix that incorporates cross-linked chains interspersed with more easily movable chains that join and entrap vast amounts of water. The gelification mechanism is characterised by a reorganisation of the gel network and the removal of water.
Formulation F1 with 1% Sodium alginate was softer and more fragile, with perhaps lower

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porosity. A similar pattern was found in **formulation F4, which contained 1% Gellan gum**. This is because the polymer chains have a lower binding strength and the molecules are more flexible. The concentration of gelification ions in the polymer network has a large impact on the gelification process.

Hence concentration of the polymer plays a pivotal role in the formation of the In-Situ gelling system.

Formulation code	Water Uptake %	Floating lag time (sec)	Floating duration (hrs)
F1	13.5	5	7
F2	6.9	3	7.5
F3	3.4	1	7.8
F4	11.2	4	7.3
F5	5.5	2	7.7
F6	4.2	1	7.9

Table no.4. Evaluation of pH, gelling time, gelling capacity,gel strength of in situ gelling formulations batch F1 to F6

6.**Measurement of water uptake**

The amount of water in the system influences drug release from the polymer matrix. The drug's release may involve the penetration of water into the matrix as well as the simultaneous release of the drug through diffusion or dissolution.

According to the findings, **F1 had the highest water uptake of at the end of 2 hours and F3 had the lowest water uptake of at the end of 2 hours.**

If the system absorbs more water, the drug is released from the system at a faster rate. As a result, it is preferable for a sustained release device to have less water uptake, which would enable the drug to be released for a longer period of time.

Table no.5 shows the data

Formulation code	Gelling time* (sec)	In vitro gelling Capacity	Gel Strength
F1	10	++	Poor
F2	8	++	Good
F3	6	+++	Excellent
F4	9	+	Poor
F5	6	++	Good
F6	5	+++	Excellent

Table 5:Evaluation of Floating lag time,floating duration and %Water Uptake Of in situ gelling formulations batch F1 to F6

7. **Floating lag time**

The in vitro floating experiment was performed in 500 ml of 0.1N HCl (pH 1.2) at 37^0C. Without disturbing the medium, a 10mL mixture was introduced into the dissolution vessel.

When the formulation was inserted in the medium, the CO2 released from it was entrapped in the gel network, resulting in a buoyant formulation. Furthermore, when calcium ion reacted with polymers, it formed a cross-linked 3-D gel network that swelled and entrapped more CO2. Because of the entrapment in the network system, there was buoyancy and flotation for an extended period of time.

The floating lag time was extremely limited in all formulations. The majority of the formulations floated within one minute after placing them in the dissolution medium.

8. Floating Duration

The period is calculated from the time the formulation forms on the surface before it falls

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back into the dissolution medium. This test is critical for an in situ floating formulation since the formulations must be floating before the drug release from the system is complete. The study lasted 8 hours and extended accumulation of dosage type in the stomach is not intended because they could be pulled away to the small intestine. All formulations under the study were found to be in the floating state for more than 7hours.

8. Invitro release studies

Time (Min)	%Cumulative Release					
	Formulation Code					
	F1	F2	F3	F4	F5	F6
0	0.0	0.0	0.0	0.0	0.0	0.0
60	53.2±0.182	25.6±0.228	13.6±0.339	61.2±0.384	42.0±0.271	14.3±0.159
120	64.5±0.319	37.1±0.352	23.7±0.358	73.3±0.225	45.5±0.144	22.7±0.371
180	76.5±0.121	49.2±0.271	43.7±0.375	86.5±0.291	57.7±0.347	36.2±0.273
240	88.4±0.175	60.1±0.339	51.4±0.158	94.3±0.214	67.8±0.169	45.6±0.338
300	98.3±0.141	74.0±0.277	63.5±0.171	99.5±0.397	87.6±0.251	57.3±0.374
360	100.0±0.25	82.5±0.223	70.8±0.391	100.0±0.248	96.2±0.27	69.9±0.318
420	100.00±0.254	88.50±0.37	71.20±0.247	100.00±0.289	96.40±0.225	70.50±0.223

Table 6: in vitro drug release studies of in situ gelling formulations batch F1 to F6

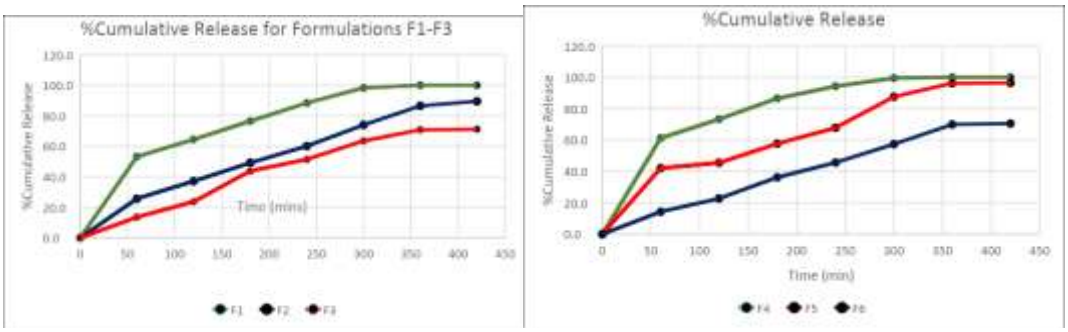

Figure :1Comparative in vitro drug release profile of F4 formulations.

Release Kinetics:

Release Model		Formulation Code					
		F1	F2	F3	F4	F5	F6
Zero Order	R^2	0.8021	0.9738	0.921	0.802	0.9201	0.932
First Order	R^2	0.94	0.959	0.968	0.89	0.9342	0.974
Higuchi's Model	R^2	0.968	0.992	0.942	0.979	0.973	0.912

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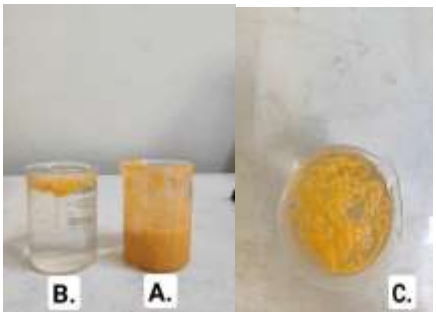
Hixon Crowell's Model	**R^2**	0.966	0.965	0.91	0.96	0.89	0.88
Korensmeyer-Peppa's Plot	**n**	0.3494	0.3966	0.3894	0.3352	0.3957	0.3875

Table no. 7 : Release Kinetics Studies of prepared In-situ gel Formulations F1-F6

To evaluate the best-fit model, data from in vitro release studies of floating in situ gels were fitted into different mathematical models.Formulations F1,F2, F4 &F5 obeyed Higuchi's equation i.e., the drug release was by Diffusion and time dependent.While formulations F4 & F6 containing highest concentration of polymer showed First order release i.e., the drug release was by matrix diffusion and depended on the concentration of polymers.

The value of 'n' in Peppa's model was in the range of 0.33-0.45 indicating that the flow is Fickian.



Photograph A. – In-Situ gelling system before administration

Photograph B. – In-Situ floating gel formed on surface of 0.1N HCl Solution

Photograph C – Closer look of In-Situ floating gel formed on surface of 0.1N HCl Solution

Selection of best formulation

The best batch is chosen based on viscosity, drug quality, gelling ability, and percent total drug release, as well as the composition. **Formulation F5** could be chosen as the best batch. In comparison to other formulations, it has a high gelling potential and optimal viscosity. **F5 indicates that the drugcontent was 98.65** percent, which was below the limit (not < 94% and not > 106%) as stated in U.S.P. **The viscosity of batch F5 was 75.7cps at 30rpm and 54.1cps at 100rpm,** which is ideal for swallowing and gelation. After **7 hours, cumulative drug release was 96.4 percent**, implying that full release could occur by the 8th hour. As a result, F5 was chosen as the optimal formulation.

V. CONCLUSION

This study has demonstrated the feasibility of forming gels in stomach by the oral administration of aqueous solution of sodium alginate, Gellan gum, and Guar gum containing calcium ions in a complex form. Furthermore, a sustained release of Omeprazole is achievable from gel vehicles over a period of at least 7 hours

Because of its strong gelling capability, optimum viscosity, and reasonable percent cumulative drug release after 7 hours, formulation F5 was chosen as the best formulation. It followed Higuchi's kinetic model with R2=0.97 and demonstrated Fickian flow with a Peppa's constant n=0.39 for drug release from the formulation.

The different properties of the prepared gelling method were discovered to be proportional to the concentration of polymer used in the formulation by analysing the results. If the polymer concentration increases, properties such as gel strength and viscosity are observed to increase, whereas percent cumulative drug release from the formulation decreases. In contrast to Gellan gum - based formulation, sodium alginate-based formulation has higher viscosity, lower gel strength, andslower rate of drug release. Thus in situ gels are suitable for oral sustained site specific delivery of omeprazole and recommended for further studies.

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