> Turkish Online Journal of Qualitative Inquiry (TOJQI) Volume 12, Issue 9, August 2021: 8085-8099

## Development of Novel Floating In-Situ Gelling System for Stomach Specific Drug Delivery System of the Narrow Absorption Window Drug Loratadine

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#### Abstract

The present investigation deals with the formulation, optimization and evaluation of sodium alginate based in situ gel of Loratadine. Sodium alginate is used as polymer and calcium carbonate was used as a cross linking agent. In situ forming polymeric formulation drug delivery systems is in sol form before administration in the body, but once administered, undergoes gelation In-Situ to form a gel. The formulation of gel depends upon factors like temperature, pH, presence of ions and ultra-violet irradiation, from which drug gets released in sustained and controlled manner. The objective of this study to develop a novel In-Situ gel system for sustained drug delivery using natural polymer. The system utilizes polymers that exhibit sol-to-gel phase transition due to change in specific physico-chemical parameters. In-Situ gel was formed at a biological pH. In vitro release studies were conducted in simulated gastric fluid and cumulative amount of drug release was analyzed by spectrophotometry. From designed set of experiments, it was evident that formulation containing 1.5% of sodium alginate control the release of drug for longer duration. The In-Situ gel exhibited the expected viscosity, pH, drug content, in-vitro gelling capacity, in-vitro floating ability, water uptake ability and sustained drug release.

#### **Key Words**

In-Situ gel, Loratadine, pH, 0.1N HCl, polymer, simulated gastric fluid.

#### Introduction:

In-Situ gel forming systems have been widely investigated as vehicles for sustained drug delivery. This interest has been sparked by the advantages shown by In-Situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. In-Situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. So, In-Situ gelling system via different route such as oral, nasal, ophthalmic etc. can be formulated. Various natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and polycaprolactone are used for formulation development of In-Situ forming drug delivery systems. Gastro retentive In-Situ gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. The gels formed from In-Situ gelling system, being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract. This review attempts to discuss stomach specific In-Situ gelling system in detail including formulation factors to be considered in the development of In-Situ drug delivery system. Also, different types of smart polymers, their mechanisms of gel formation from the sol forms.<sup>[1]</sup>

The stomach floating In-Situ gel of environmentally sensitive can be affected by many stimulus, these are: temperature, ionic concentration, electrical field, inflammation, solvent concentration, and glucose concentration. According to the mechanism by which sol-gel phase transition occur, the following three types of systems can be recognized

- 1- pH triggered systems.
- 2- Temperature sensitive system.
- 3- Ion activated system.

From the point of view of patient compliance, a liquid dosage form that can sustain drug release and remains in contact for extended period of time, improving the bioavailability, decreasing the dose concentration and frequency may be achieved by In-Situ gelling formulations. Gelation of the orally administered liquid formulations (Ion activated system) was ensured by the inclusion of calcium ions in the formulation as a soluble complex designed to break down to release free calcium ions on encountering the acidic environment of the stomach. The gelation was takes place after the orally administered solution reached the stomach by complexing the calcium with sodium.<sup>[2]</sup>

#### Materials and Methods

#### Materials

Loratadine was obtained from Aarti Drugs Ltd, Sodium alginate, Calcium carbonate, Hydrochloric acid all are of analytical grade.

### Methods

### Determination of $\lambda$ max in 0.1 N Hydrochloric acid

Dilute solution of Loratadine ( $10\mu g/ml$ ) prepared from the above stock solution using solution and its maximum absorption identified through UV hydrochloric acid (0.1N) spectrophotometer by scanning within the wavelength region of 200–400 nm against hydrochloric acid (0.1N) blank. Obtained spectra showing the peak with a highest absorbance (Wavelength 275nm) is considered as absorbance maximum of the drug.

## Drug excipient compatibility study FTIR

Compatibility study was carried out by using Fourier transform infrared spectrophotometer (Shimadzu). FTIR study was carried on pure drug. Physical mixture of drug and polymers were prepared and samples kept for 1 month at  $40^{0}$ C. The infrared absorption spectrum of physical mixture of drug and polymerswas recorded using KBr disc over the wave number 4000 to 650 cm<sup>-1</sup>.<sup>[4,14]</sup>

### **Preparation of floating gel of loratadine** [19,20,21,22]

Sodium alginate suspension of fixed concentration were prepared by adding ultrapure water containing sodium citrate heated to  $60^{\circ}$ C with constant stirring on magnetic stirrer. Allowed to cool below  $40^{\circ}$ C. Then an appropriate amount of calcium chloride was added with stirring. In another beaker drug was dissolved in 0.1 N hydrochloric acid this is added to above suspension. Calcium carbonate was also added. Methyl paraben is used as preservative. To neutralize above suspension 0.1 N sodium hydroxide was added.

#### Formulation optimization

 $3^{2}$ full factorial design was applied to the formulation that showed the satisfactory results. To see the effect of concentration of variables Sodium alginate (X1) and Calcium carbonate (X2) on various responses like % drug release. For Sodium alginate lower, middle and higher level were 0.5,1.5 and 2.5 gm respectively. Similarly for the Calcium carbonate lower, middle and higher level were 0.16, 0.33 and 0.50 gm respectively. Composition of all batches is shown in table no.1<sup>[9,16]</sup>

Formulation code Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loratadine (mg)	50	50	50	50	50	50	50	50	50
Sodium alginate (gm)	0.5	1.5	2.5	0.5	1.5	2.5	0.5	1.5	2.5

Sodium citrate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
(gm)									
Calcium chloride									
(gm)	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016
Methyl paraben									
(gm)	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
NaOH (0.1N)	q.s.								
Distilled water (up to ml)	50	50	50	50	50	50	50	50	50

**Table 1: Composition of formulation** 

## Evaluation of floating gel

## 1. Appearance:

The developed formulation met all the pre-requisite to become an In-Situ gelling floating system, gelled and floated instantaneously at the pH condition of the stomach. <sup>[8]</sup>

## 2. pH:

The pH of the in situ solution of Loratadine was measured using calibrated digital pH meter at 37°C. All measurement of pH was made in triplicate.<sup>[6]</sup>

## **3.Viscosity Determination:**

The viscosity of the prepared hydrogel formulations were measured at room temperature by Brookfield viscometer (DV-II +) attached with spindle 61. The spindle was rotated at varying rpm and readings were recorded to study the effect of shearing stress on viscosity.<sup>[11]</sup>

## 4. Determination of Drug content<sup>[3,20]</sup>:

The In-Situ solution was dissolved in HCL (0.1N) under sonication and filtered. The drug content was assayed using UV-spectrophotometer (V-630, Shimadzu Co Ltd., Japan) at 275 nm after suitable dilution with 0.1NHCl. Percent drug content was determined using formula

$$Percent Drug Content = \frac{Actual Drug Content}{Total Drug Amount Taken} \times 100$$

## 5. In vitro floating duration:

The in vitro floating study was determined using USP dissolution apparatus II having 900 ml of simulated gastric fluid (pH 1.2). The medium temperature was kept at  $37^{0}$  C. 10 ml prepared In-Situ gel formulations were drawn up using disposable syringe and placed into the petri dish (4.5mm internal diameter) and finally petri dish containing formulation was kept in the dissolution vessel containing medium without much disturbance. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the dissolution medium surface (duration of floating) were noted.<sup>[10]</sup>

### 6. Floating lag time:

The floating lag time is defined as time taken by the gel to reach the top from bottom of the dissolution flask. The floating lag time is determined by visual inspection a USP (Type II) dissolution test apparatus containing 900 ml of 0.1N HCl at  $37^{0}$ C.<sup>[7]</sup>

### 7. In vitro drug release study:

The release of Loratadine from sustained release suspension was determined using XXIV dissolution apparatus I (basket covered with muslin cloth) at 50 rpm. This speed was slow enough to avoid the breaking of gelled formulation and was maintained the mild agitation conditions believed to exist in-vivo. The dissolution medium used 900 ml of 0.1 N HCl, and temperature was maintained at 37°C. A sample (1 ml) of solution was withdrawn from the dissolution apparatus at 0 min., 30 min., 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr of dissolution. The samples were filtered through whatman filter paper and analyzed using UV method. Cumulative % of drug release was calculated and observed.<sup>[12]</sup>

### 8. Drug release kinetics:

To examine the drug release kinetics, the release data were fitted to models representing zero order, first order, Higuchi's square root of time kinetics and KorsemeyerPeppas kinetics. The coefficient of determination ( $r^2$ ) values were calculated from the plots of CDR vs. t for zero order, log %CDR remaining vs. t for first order, %CDR vs.  $t^{1/2}$  for Higuchi model and log %CDR vs. log t for Korsemeyer Peppas model, where %CDR is the amount of drug released at time t. The data obtained from study of diffusion kinetics of the optimized formulation was studied to obtain the best fit model. The best fitted model is the one which gives the highest  $R^2$  value and least slope value.

## 9. Stability studies<sup>[13,15]</sup>:

Test Conditions					
Duration of study	3 months				
Temperature conditions	$40^{\circ}C \pm 2^{\circ}C$				
Relative humidity conditions	$75\%RH \pm 5\%RH$				
Frequency of testing	1 month, 2 month, 3 months				

Test conditions for stability studies are shown in table no.2

#### Table 2: Test conditions for stability studies

The formulations were evaluated mainly for their physical characteristics at 1, 2 and 3 months. Physical appearance in terms of appearance, pH, viscosity and drug content were evaluated.

#### Results and discussion Compatibility study FTIR

The IR spectra of loratadine, polymer and physical mixture were generated. The IR absorption bands observed in the IR spectrum of drug and polymers resembles with that of found in the physical mixture proves compatibility of drug with polymers.

### Appearance:

The developed formulation met all the pre-requisite to become an In-Situ gelling floating system, gelled and floated instantaneously at the pH condition of the stomach.<sup>[17]</sup>



Fig. 1: Floating In-Situ gel formulation

## pН

The pH of the in situ solution of Loratadine was measured using calibrated digital pH meter at 37°C. All measurement of pH was made in triplicate.<sup>[6]</sup>

Sr. no.	Formulation code	Observed pH (±SD)
1.	F1	$7.7 \pm 0.10$
2.	F2	$7.6 \pm 0.17$
3.	F3	8.1 ± 0.15
4.	F4	$7.9 \pm 0.10$
5.	F5	8.1 ± 0.15
6.	F6	$8.1\pm0.07$
7.	F7	$7.8 \pm 0.26$
8.	F8	7.7 ± 0.26

9.	F9	8.1 ±0.20

 Table 3: pH values of formulations

The pH of all the formulations from F1 to F9 was found to be in the range of 7.6 to 8.1.

#### **Viscosity Determination**

The viscosity values of formulations are shown in table no.4

			Visco	osity (cp)	at Room	Temper	ature		
Rpm	Formulation code								
	F1         F2         F3         F4         F5         F6         F7         F8         F9								
10	448.8	1120	1200	1201	840.1	1132	1342	3301	4780
20	309.2	1123	1144	1133	809.8	1023	948.2	2724	3659
50	300.4	1055	1094	992.4	777.3	948.8	663	2252	2456

**Table 4: Viscosity of formulations** 



Fig. 2: Viscosity profile of formulations

Viscosity v/s rpm plots for all formulations shows decrease in viscosity as shear rate (rpm) was increased. Concentration of Sodium alginate was a major factor affecting viscosity of formulations.

#### **Drug content**

The Drug content of formulations is shown in table no.5.

Sr. no.	Formulation code	Drug content (%) (±S.D.)
1.	F1	99.60± 0.00015
2.	F2	$99.96 \pm 0.00022$
3.	F3	$98.15 \pm 0.00010$
4.	F4	$99.48 \pm 0.00012$
5.	F5	99.00± 0.00022
6.	F6	99.24 ± 0.00012
7.	F7	$98.76 \pm 0.00022$
8.	F8	$100.2 \pm 0.00020$
9.	F9	99.48 ± 0.00010

Table 5:	Drug	content	of flo	ating gel
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The percentage drug content of all prepared formulations was found to be in the range of 98-100 %.

#### In vitro floating duration

Sr.no.	Formulation code	Floating time
1.	F1	>8 hr
2.	F2	>8 hr
3.	F3	>8 hr
4.	F4	>8 hr
5.	F5	>8 hr
6.	F6	>8 hr
7.	F7	>8 hr
8.	F8	>8 hr
9.	F9	>8 hr

Table 6: In vitro floating duration of floating gel

#### **Floating lag time**

Sr.no.	Formulation code	Floating lag time
1.	F1	>2 min
2.	F2	<1 min
3.	F3	<1 min
4.	F4	>3 min
5.	F5	<2 min

6.	F6	<2 min
7.	F7	>3 min
8.	F8	<2 min
9.	F9	<2 min

 Table 7: Floating lag time of floating gel

### In-vitro Drug Release Study

Time	Cumulative Drug Release (%) (±S.D.)							
	F1	F2	F3	F4	F5			
0 min.	0	0	0	0	0			
30	17.53 ±0.00007	18.61 ±	17.53 ±	17.53 ±	18.61 ±			
min.		0.0001	0.0001	0.00007	0.0001			
1 hr	20.56±0.00007	$20.68 \pm 0.0001$	20.56 ±	21.64 ±	27.17 ±			
			0.0001	0.0001	0.0001			
2 hr	23.70 ±0.0001	24.90 ±0.0001	24.79 ±	29.24 ±	32.84 ±			
			0.0001	0.00007	0.0002			
3 hr	28.05 ±0.00007	31.55 ±	31.43±	35.27 ±	39.47 ±			
		0.0001	0.0001	0.0001	0.0001			
4 hr	36.98 ±0.0001	39.74 ±	39.63 ±	48.17 ±	53.82 ±			
		0.0001	0.012	0.00007	0.0001			
5 hr	54.20 ±0.0001	49.63 ±	52.43 ±	55.65 ±	62.85 ±			
		0.0001	0.0001	0.00015	0.0001			
6 hr	$68.66 \pm$	52.66 ±	52.43 ±	71.06 ±	73.47 ±			
	0.00017	0.0001	0.0001	0.00007	0.0001			
7 hr	83.11 ±0.0001	75.05 ±	72.66 ±	79.02 ±	82.13 ±			
		0.0001	0.0001	0.0001	0.0001			
8 hr	90.95 ±0.0001	89.74 ±	87.11 ±	91.53 ±	96.72 ±			
		0.0001	0.0001	0.00026	0.00007			

Time (hrs)	Cumulative Drug Release (%) (±S.D.)				
( ~)	F6	F7	F8	F9	

0min.	0	0	0	0
30	18.61 ±	15.35 ±	17.53 ±	15.35 ±
min.	0.0001	0.00007	0.00007	0.00007
1 hr	28.26 ±	20.31 ±	21.64 ±	21.39 ±
	0.0001	0.00015	0.00015	0.0001
2 hr	32.25 ±	35.36 ±	32.48 ±	24.66 ±
	0.00017	0.00035	0.0003	0.0001
3 hr	39.61 ±	43.21 ±	47.53 ±	32.39 ±
	0.0001	0.00015	0.00007	0.00015
4 hr	51.78 ±	51.52 ±	55.26 ±	47.21 ±
	0.0063	0.0003	0.00015	0.0001
5 hr	62.75 ±	65.75 ±	68.75 ±	51.33 ±
	0.00017	0.0002	0.0001	0.0001
6 hr	74.44 ±	$75.62 \pm$	77.79 ±	69.14 ±
	0.0001	0.0001	0.0001	0.00026
7 hr	84.68 ±	84.92 ±	87.96 ±	78.05 ±
	0.0001	0.0001	0.00007	0.0001
8 hr	96.58 ±	95.64 ±	97.04 ±	89.51 ±
	0.0001	0.0007	0.00025	0.00015

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#### Table 8: Cumulative Drug release of formulations

From the dissolution study it can be said that maximum release is shown by F8 formulation. The data also suggests that gel formulations are capable to produce linear drug release for a longer period of time. The optimized formulation F8 gel shows 97.04% drug release respectively in 8hrs.



Fig. 3: In-vitro drug release profile of formulations F1 to F9

#### **Drug release kinetics**

The classical zero order release curve was found to be linear. The curves plotted according to first order and Higuchi release model were also found to be linear. For the Korsemeyer-Peppas release curves  $r^2$  was found to be  $\ge 0.75$  for all 9 formulations and n value was found to be  $\ge 0.5$  which indicates that all the formulations show anomalous (non-Fickian release i.e. swellable matrix). The drug release occurs probably by diffusion and erosion.<sup>[18]</sup>

#### Optimization

A  $3^2$  full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The percentage of Sodium alginate (X<sub>1</sub>) and Calcium carbonate (X<sub>2</sub>) were selected as independent variables and the dependent variable was % drug release. The data obtained were treated using Design expert version 8.0.7.1 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the interaction of Sodium alginate (X<sub>1</sub>) and Calcium carbonate (X<sub>2</sub>) on dependent variable. Table no 32 shows ANOVA for the dependent variable % drug release. The values of X<sub>1</sub> and X<sub>2</sub> were found to be significant at **p** <**0.05**, hence confirmed the significant effect of both the variables on the selected responses.From this data optimum concentration of Sodium alginate 2% w/v and Calcium carbonate 3% w/v was found.<sup>[5]</sup>



#### Fig.4: Counter plot of % drug release for 8hrs

In the above Fig. 4 the contour plot shows that as the concentration of sodium alginate increases % CDR decreases. Hence it can be concluded that the two factorssodium alginate and Calcium carbonate have a combined effect on % CDR



Fig.5: 3D Response curve of % cumulative drug release for 8 hrs

#### **Optimized formula**

After generating model, equations relating main effects and responses various gel formulations containing loratadine were optimized based on in vitro drug release at 8 hours. (The optimal values for responses were obtained by numerical analysis based on the criteria

of desirability and optimal batch was selected. Optimized batch (F8) having highest drug release. This revealed that mathematical model obtained by factorial design to produce optimized responses was well fitted.

#### Accelerated stability study

Results of the stability studies showed that there is no change in the physical parameters of the formulation. Drug content of the formulation was found to be same as that before stability testing.

#### Conclusion

By preparing the in situ gel of Loratadine the effect of different variables on gel was studied.pH of all the formulations were found to be in between the range (7.7-8.1).The viscosities of all the formulations were determined and it was observed that viscosity was increased due to increasing concentrations of Sodium alginate.The prepared gel was also evaluated for floating lag time, floating duration, % drug content, %CDR (In vitro drug release.)It is one of novel dosage formulations that delivers the drug slowly into the GI tract and provide desired therapeutic effect for long period of time.

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