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Development and characterization of novel in-situ floating gel of levocetirizine dihydrochloride for oral drug delivery system

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ABSTRACT

Floating in-situ floating gel system of Levocetirizine Dihydrochloride was prepared using sodium alginate as a gelling polymer and calcium carbonate as floating agent for potentially prevent the Belgaum formation and to offer extended release, associated with the itching, runny nose and sneezing or sometimes vertigo caused problems to inner ear. Floating in-situ gel was prepared by dissolving various concentrations of sodium alginate in deionized water to which various concentration of floating agent dispersed well. The formulation parameters like concentration of sodium alginate influenced the rate and extent of in-vitro drug release significantly from floating in-situ gel. the evaluation parameters was carried out with the help of various studies like physical appearance, pH, viscosity, drug content, floating duration ,floating lag time, in-vitro drug release study, kinetic models and stability studies. Floating In-Situ Gel had shown all the evaluation parameters to offer sustained release and better therapeutic effect.

Keywords: Oral In-situ Floating System, Controlled Delivery, Levocetirizine Dihydrochloride, Gastric Residence Time, Floating Drug Delivery.

INTRODUCTION

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration[1,2]. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal Many buoyant systems have been developed. Formulation of gastroretentive *In-situ* gel system involves the use of gelling agent which can form a stable sol/suspension system to contain the dispersed drug and other excipients. The gelling of this sol/suspension system is to be achieved in gastric environment, triggered by ionic complexation due to change in pH.[3,4,5]The formulation adopted is a sodium alginate solution containing calcium carbonate (as a source of $Ca2^{+}$) and sodium citrate, which complexes the free $Ca2^{+}$ ions and releases them only in the acidic environment of the stomach. Sodium alginate acts as a gelling agent. The free $Ca2^{+}$ ions gets entrapped in polymeric chains of sodium alginate thereby causing cross linking of polymer chains to form matrix structure. This gelation involves the formation of double helical junction zones followed by re-aggregation of the double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding with water. In this way, the formulation remains in liquid form until it reaches the stomach, where gelation of sodium alginate is instantaneous [6,7].

MATERIALS AND METHODS

Materials

The sample of Levocetirizine Dihydrochloride was gifted from Granules India ltd. Aurangabad (M.S.), sodium alginate obtained from Mylochem, Indore (M.P.) and other polymers are obtained from Research Lab Fine Chem. Industries, Mumbai (M.S.) India.

Method

LevocetirizineDihydrochloride suspension was prepared using various polymers, complexion agent and suspending agents Sodium alginate solution of different concentrations (0.50-1.5%w/v) was prepared in deionized water containing sodium citrate (0.25%w/v) and calcium chloride (0.016%w/v). The sodium alginate was dispersed in deionized water, heated up to 90^0C with stirring continuously on magnetic stirrer .and then cools below 40^0C various concentrations of calcium carbonate and drug was added after cooling the solution below 40^0C with continuous stirring to form uniform dispersion [8,12,13,14].

A. Process variables and process optimization [22-23]

1. **Factor:** It is the variables which affect the result of the experiment. The determination of factor for particular experiment depends mainly on the objectives of the experiment and it needs to be determined after careful evaluation of results.

2. **Level:** It is the limit of the variable below or beyond which an experiment cannot give significant change in result. A 3^2 full factorial design was constructed where the amounts of sodium alginate (X_1) and calcium carbonate (X_2) were selected as the independent variables. The levels of the two variables were selected on the basis of the preliminary studies carried out before implementing the experimental design. The quantity of drug release at12 hrs selected as response (dependent) variables. All other formulations and processing variables were kept invariant throughout the study and summarize the experimental, their factor combinations and the translation of the coded levels to the experimental units used in the study.

Table 1: Variable in optimization study

Variables	Factors
Independent	
X_1	Sodium alginate.
X_2	Calcium carbonate.
Dependent	
Y_1	In vitro drug release.

Table 2: Combinations of two independent factors having three levels

Batches	Independent variables		Actual values	
	X1	X2	X1%	X2%
F1	-1	-1	0.50	0.25
F2	0	-1	1.0	0.25
F3	1	-1	1.50	0.25
F4	-1	0	0.50	0.75
F5	0	0	1.0	0.75
F6	1	0	1.5	0.75
F7	-1	1	0.50	1.5
F8	0	1	1.0	1.5
F9	1	1	1.5	1.5

Table 3: Formulation as per factorial design

Formulation code → Ingredients % ↓	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Levocetirizine Dihydrochloride.(mg)	25	25	25	25	25	25	25	25	25
Sodium alginate.(%w/v)	0.50	1.0	1.5	0.50	1.0	1.5	0.50	1.0	1.5
Tri-sodium citrate.(%w/v)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Calcium chloride.(%w/v)	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016
Calcium carbonate.(%w/v)	0.25	0.25	0.25	0.75	0.75	0.75	1.5	1.5	1.5
Methyl paraben	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water q.s. (ml.)	50	50	50	50	50	50	50	50	50

B. Evaluation and characterization of Floating In-Situ Gel [7-12]

1. Physical appearance

All the prepared in-situ formulations of Levocetirizine Dihydrochloride were checked for their type of solution formed, time required for gel formation, duration of floating, and type of gel formed.

2.pH of *In-Situ* solution

The pH of the In-situ solution of Levocetirizine Dihydrochloride was measured using calibrated digital pH meter at 37ºC and all measurements of pH were made in triplicate.

3. Viscosity

The viscosity of different *In-situ* gel formulation was determined at room temperature using a Brookfield viscometer type DV-II+PRO (LV1 Spindle).

4. Determination of drug content

The In-situ solution was dissolved in 0.1N Hydrochloric acid under sonication and filtered. The drug content was analyzed by using UV-spectrophotometer (V-630, Shimadzu, Japan) at 231 nm after suitable dilution with 0.1N Hydrochloric acid and percent drug content was determined using formula:

$$\text{Percent Drug Content} = \frac{\text{Actual drug content}}{\text{Total drug amount taken}} \times 100$$

5. In vitro floating duration

The in vitro floating study was determined using USP dissolution apparatus II having 900 ml of Hydrochloric acid (pH 1.2). The medium temperature was kept at 37^0C and 10 ml prepared In-situgel formulations were drawn up by 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. Time for 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) was noted.

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 Hydrochloric acid at 37 ^{0}C.

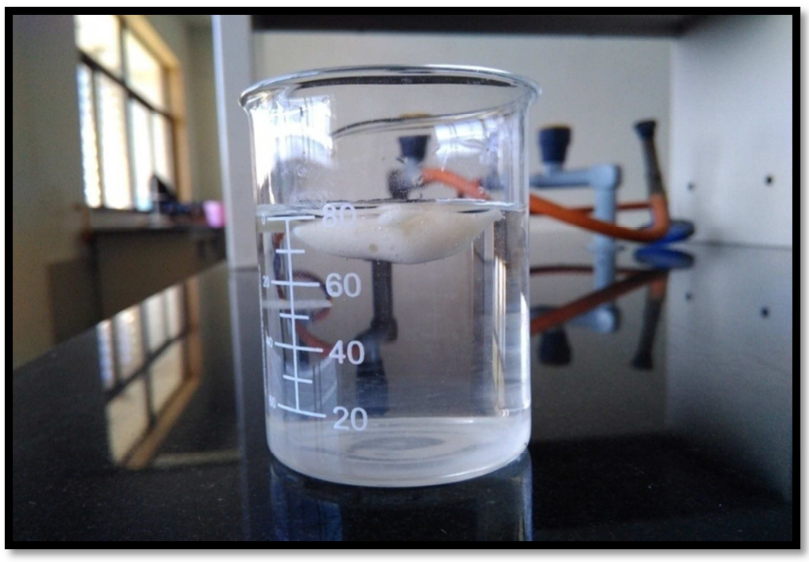

Fig. 1: Floating behavior of the gel

7. *In vitro* drug release study

The release of Levocetirizine Dihydrochloride from sustained release suspension was determined using dissolution apparatus I (basket covered with muslin cloth) at 50 rpm. The rotation 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 Hydrochloric acid and temperature was maintained at 37^0C.A sample (1 ml) of

solution was withdrawn from the dissolution apparatus at 0 min,30 min,1hr, 2hrs,3hrs,4hrs,5hrs,6hr,7hrs, 8hrs ,10hrs 12hrs of dissolution. The samples were filtered through Whatman filter paper and analyzed using UV method. Cumulative % of drug release was calculated and observed.[2, 4, 8, 9, 16, 21.]

8. Best fit kinetic model for optimized formulation:
The data obtained from study of diffusion kinetics of the optimized formulation was studied to obtain the best fit model. The best fitted model was the one which gave the highest R^2 value and least slope value.

RESULTS AND DISCUSSION

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.

2. pH of In-Situ solution:
The pH of the In-situ solution of drug was measured using calibrated digital pH meter at 37°C. All measurements of pH were made in triplicate and recorded.

Table 4: pH of the formulation (n=3).

Sr no.	Formulation code	Reported pH (±S.D.)
1.	F1.	7.8±0.09
2.	F2.	7.7±0.014
3.	F3.	7.6 ± 0.054
4.	F4.	7.8±0.24
5.	F5.	7.9±0.29
6.	F6.	7.9±0.0091
7.	F7.	7.6±0.0091
8.	F8.	7.8±0.5
9.	F9.	7.7±0.17

3. Viscosity
The viscosity of different In-situ gel formulation was determined at room temperature using a Brookfield viscometer type DV-II+PRO (LV1-Spindle)at fixed RPM.

Table 5: Viscosity of formulations (F1-F9).

Sr. No.	Formulation code	Spindleno. (LV1)	RPM	Viscosity (cps)
1.	F1.	60.	50.	398.2
2.	F2.	60.	50.	418.3.
3.	F3.	60.	50.	511.7.
4.	F4.	60.	50.	421.9.
5.	F5.	60.	50.	478.9.
6.	F6.	60.	50.	519.9.
7.	F7.	60.	50.	459.9.
8.	F8.	60.	50.	546.9.
9.	F9.	60.	50.	561.9.

4. Determination of drug content:
The In-situ solution was dissolved in 0.1N Hydrochloric acid under sonication and filtered. The drug content was assayed using UV-spectrophotometer (V-630, Shimadzu, Japan) at 231 nm after suitable dilution with 0.1N Hydrochloric acid. The percent drug content was determined using formula: [7]

$$\text{Percent drug content} = \frac{\text{Actual drug content}}{\text{Total drug amount taken.}} \times 100$$

5. *In vitro* floating duration
The in vitro floating study was determined using USP dissolution apparatus II having 900 ml of 0.1N Hydrochloric acid (pH 1.2). The temperature of medium was kept at 37^0C. Total 10 ml prepared 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 [17,18,19].

Table 6: Drug content of the formulation (n=3)

Sr. No.	Batch	Contents
1.	F1.	92.95 ± 0.00015
2.	F2.	92.33 ± 0.00022
3.	F3.	91.55 ± 0.00010
4.	F4.	93.70 ± 0.00012
5.	F5.	92.48 ± 0.00022
6.	F6.	93.62 ± 0.00012
7.	F7.	92.55 ± 0.00022
8.	F8.	93.37 ± 0.00020
9.	F9.	93.74 ± 0.00010

The percentage drug content of all prepared formulations was found to be in the range of 92.25-93.74%. Therefore uniformity of content was found to be maintained in all formulations.

Table 7: Floating duration of the formulations (F1-F9).

Sr no.	Batch.	Floating time. (Hrs)(Min)	
1.	F1.	10 hrs	3 min.
2.	F2.	10 hrs	5 min.
3.	F3.	10 hrs	9 min.
4.	F4.	10 hrs	21 min.
5.	F5.	10 hrs	18 min.
6.	F6.	10 hrs	28 min.
7.	F7.	11 hrs	32 min.
8.	F8.	11 hrs	43 min.
9.	F9.	11 hrs	51 min.

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 Hydrochloric acid at 37^0C.For F1-F9 batches Floating lag time was found to be in the range of 1-3 minutes.

Table 8: Floating lag time of formulation

Sr no.	Batch	Floating lag time(Min).
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.

7. In vitro drug release study

The In vitro drug release study of the formulation is shown in the following Table 9.

Table 9: Percent cumulative drug release of different formulations (F1-F9)

Time in hrs.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	7.6	6.53	4.13	15.46	12.13	10.02	5.61	1.06	8.13
2.	12.84	18.43	13.62	18.88	17.53	17.12	6.29	14.93	18.44
3.	21.44	20.27	21.69.	28.45	18.83	20.55	17.79	17.15	23.88
4.	23.69	27.45	29.68	33.54	31.33	27.06	27.76	28.58	31.34
5.	31.29	36.53	35.84	37.86	36.57	3254	31.78	31.14	35.51
6.	38.13	45.02	42.17	41.93	44.50	44.85	47.82	51.57	55.71
7.	47.17	47.78	47.21	46.03	4715	55.10	58.75	59.19	66.01
8.	65.80	66.04	51.21	55.05	57.00	58.20	56.94	62.85	69.58
9.	81.18 52min.	74.10 46min.	59.19 57min.	61.16	64.17	69.53	72.29	76.65	84.58
10.	87.69	81.60	78.10	81.57 21min.	79.24 18min.	78.35 28min.	81.76	81.21	87.47
11.	--------	--------	--------	89.32	84.76	82.92	85.57 32min.	85.87 43min.	89.68 51min.
12.	--------	--------	--------	--------	--------	--------	91.21	89.91	94.52

Maximum drug release shown by F9 batch and the data also suggests that gel formulations are capable to produce linear drug release for longer period of time. The drug release profile of formulation F1 to F9 shown in Fig.2. Dissolution profile of formulation F1 to F9 signified an extended drug release and out of nine formulations maximum release after 12 hrs was found for F9 formulation [15].

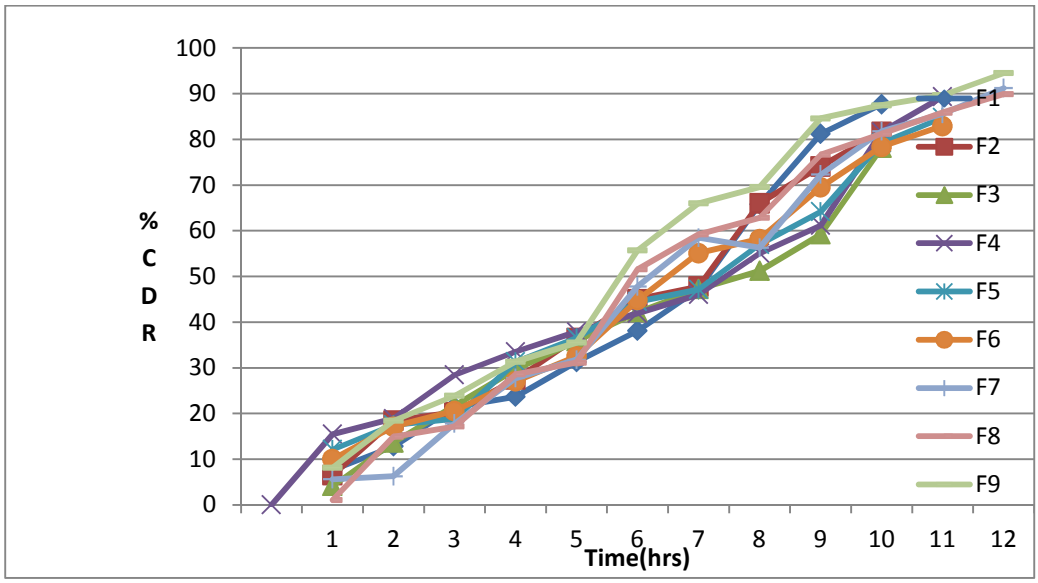

Fig.2: Drug release profile of all formulation F1-F9

Data Analysis

In order to investigate the mode of release from In-situ gel data were analyzed with following mathematical model [13, 14, 15, 26].

1. Zero-order kinetic

Fig.3: Zero order kinetic of formulation F8 batch

2. First-order kinetic

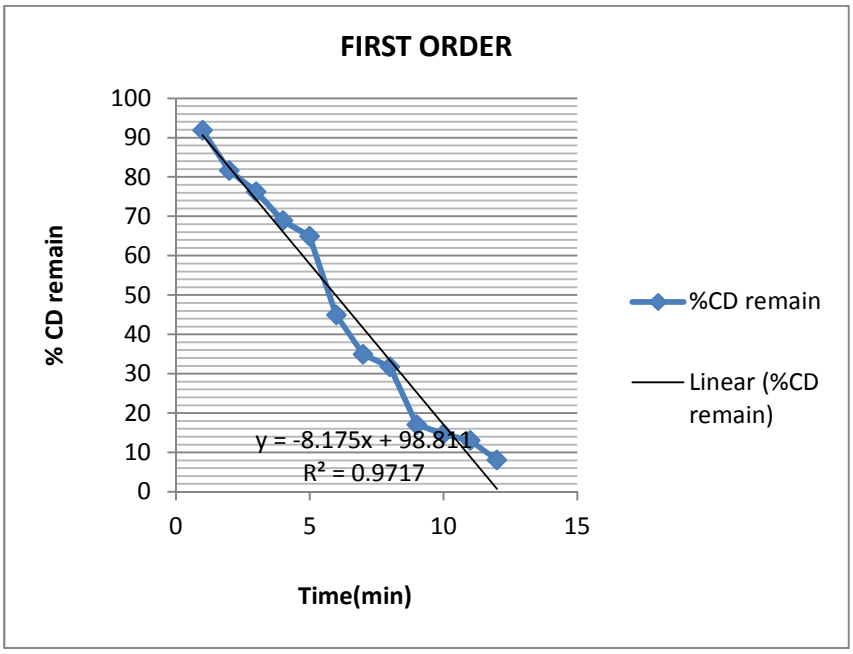

Fig.4: First order kinetic of formulation F9 batch

3. Higuchi equation

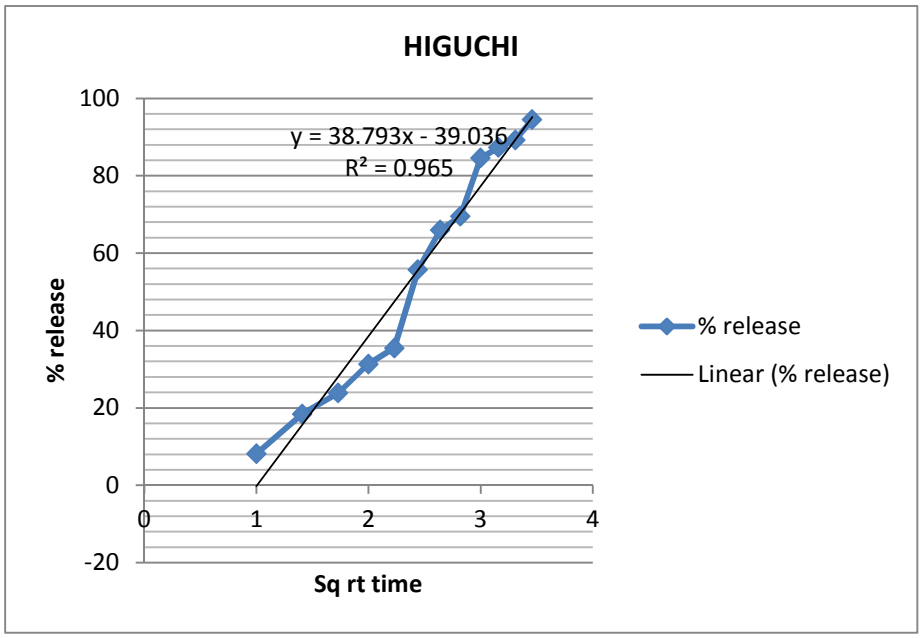

Fig.5: Higuchi model of formulation F9 batch

4. Korsemayer-peppas equation

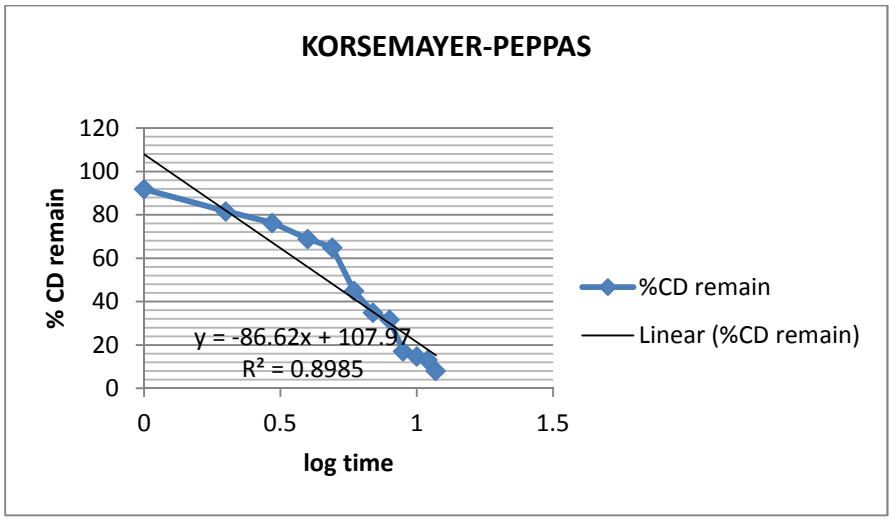

Fig. 6: Korsemayer-peppas equation of formulation F9 batch

Table 10: Drug release by using different models for F9 batch

Batch	Kinetic models				
	Zero order	First order	Highuchi	Korsemayer-Peppas	
F9	R^2	R^2	R^2	R^2	n
	0.974	0.971	0.965	0.898	8.429

Table 11: Drug release kinetics for optimized batch

Sr. no.	Model Fitting	R^2 Value	N
1	Zero order	0.974	8.429

The curves plotted according to first order and Higuchi model were also found to be linear. For the classical zero order release curve R^2 was found to be 0.974 for optimized formulation

CONCLUSION

Levocetirizine Dihydrochloride In-Situ gel evaluated for pH, viscosity, floating duration, floating lag time, % drug content and % drug release after 12 hrs. The concentration of Sodium alginate and Calcium carbonate had significant impact on viscosity and floating lag time. However the drug release was greatly retarded at higher concentration of sodium alginate, as the concentration increases from 0.5%w/v to 1.5 %w/v. Polymeric solution was too viscous to could not swallow. As the concentration of calcium carbonate increased from 0.25%w/v to 1.5%w/v floating lag time was decreased and drug content was found in range of 91.55 to 93.74. The results of a 3^2 full factorial design revealed that the polymer Sodium alginate (X_1) and Calcium carbonate (X_2) significantly affected the dependent variables such as floating lag time, viscosity, and % drug release after 12 hrs. from the prepared formulations.After the evaluation parameter of In-Situgel, optimized formulation (F9) was selected because of better drug content, viscosity, and sustained release of the drug. Optimized formulation (F9) was evaluated for stability study, floating lag time, floating duration, pH and viscosity. This leads to increase the effectiveness in therapy, reduction of dosing frequency, to improve patient compliance.

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