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Design and Evaluation of Nizatidine Floating *In-Situ* Oral Gel

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HUMAN

Lavate GD[*1], Jedage HD[2], Velhal AB[3], Raskar SM[4], Patil PS[5], Gurav PB[6], Salunke PB[7], Kodalkar VN[8]

[1-6]Late Narayandas Bhawandas Chhabada Institute of Pharmacy (Degree), Raigaon, Satara – 415020 (Maharashtra) India.

[7]SVERI's College of Pharmacy, Pandharpur – 413 304 (Maharashtra) India.

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ABSTRACT

An *In-situ* gel-forming polymeric formulation was in solution form before administration in the body, but once administered, undergoes gelation *In-situ* to form a gel. The formulation of gel depends upon factor like temperature modulation, pH change, the presence of an ion, ultra-violet irradiation, form which drug gets released in a sustained and controlled manner. The objective of this study was to develop a novel *In-situ* gel system for sustained drug delivery of Nizatidine using natural polymers Sodium alginate (SA) and Carbopol (CP). These polymers exhibit *sol-to-gel* phase transition due to change in specific physio-chemical parameters in presence of calcium carbonate. Nizatidine *In-situ* gel formulation designed of varying concentrations of sodium alginate and guar gum, Sodium alginate act as a gelling polymer and guar gum plays a vital role in not only producing a viscous solution but also controlling the release longer duration. The formed *In-situ* gel subjected to *in-vitro* drug release studies, viscosity determination, *in-vitro* floating ability etc. *In-vitro* drug release studies were conducted in simulated gastric fluid and the cumulative amount of drug release was analyzed by a spectrophotometer. The optimized formulation (F3) Nizatidine: Guar gum: Sodium alginate 1:1:2 Showed 91.57% drug release at the end of 8 hr.

INTRODUCTION

In-situ gel forming drug delivery systems are capable of releasing the drug in a sustained manner maintaining relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. The present research is about gastro retentive drug delivery systems in the form of *In-situ* gels.

Here Special approaches on floating drug delivery systems meant for gastric retention, float on the surface of the gastric fluids, due to their low density and produce the prolonged effect by showing the release, while being Buoyant on the gastric fluid surface. This type of delivery system is of great value for drugs which get absorbed from the upper part of the stomach i.e. their absorption window resides in an upper part of the stomach.[1,2]

The *In-situ* gelling system being one among them is a type of mucoadhesive drug delivery system principally capable of releasing drug molecule in a sustained manner affording relatively consistent plasma profile. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or upon change in pH. These have a characteristic property of temperature dependent, pH-dependent and cation induced gelation. This gelation 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 cations and hydrogen bonding. Compared to conventional controlled release formulations, *In situ* forming drug delivery systems possess potential advantages like simple manufacturing processes and ease of administration. Even though the delivery system is widely applicable for ocular therapy and nasal delivery.[3]

Gastroretentive drug delivery is an approach to prolong gastric retention of drugs, thereby used as site-specific drug delivery for the gastrointestinal tract. This approach improves the gastric retention of drugs by which it helps in maintaining minimum effective concentration in the systemic circulation for longer time duration. Administration of a prolonged release floating dosage form tablet or capsule will result in the dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug is available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.[4]

MATERIALS AND METHODS

1 Materials

Here Nizatidine and other ingredient were taken for *in-situ* gel formulation. All components and their suppliers are given in Table No. 1.

Table 1:-List of chemical

Sr. No.	Name of Ingredient	Name of suppliers
1	Nizatidine	Dr. Reddy's lab, Hyderabad.
2	Sodium alginate	Glenmark, Mumbai
3	Guar gum	Glenmark, Mumbai
4	Calcium carbonate	Loba chemical, Mumbai
5	Methylparaben	Loba chemical, Mumbai
6	Propyl paraben	Loba chemical, Mumbai
7	Conc. hydrochloric acid	Loba chemical, Mumbai
8	Propyl paraben	Loba chemical, Mumbai
9	Conc. hydrochloric acid	Loba chemical, Mumbai

2. Preparation of *In-situ* gelling system:

Nizatidine was passed through sieve no 60, in order to break lumps. Other polymers sodium alginate (SA), guar gum (GG), and calcium carbonate were passed through sieve no. #40, to form a free-flowing powder. In order to protect the solution from microbial contamination and degradation, distilled water was boiled for a sufficient period at 80ºC. methyl, paraben, and propylparaben (in 9:1) were added in distilled water and allowed to cool or to attain room temperature. To accomplish mixing to form the final solution.

An accurately weighed quantity of Nizatidine was added to this polymer solution and stirred thoroughly for 10-15 min. then calcium carbonate was added with continuous stirring, and stirring was continued for 15-20 min further. The solution so formed was sonicated for 10 min. using bath sonicator.

In order to find the most suitable combination of GG and SA polymer, initial trials were done on individual polymers followed by a combination of the formulation. The amounts were increased until a thick, viscous solution was obtained.[5]

3 Formulation Table:

Table 2: Formulation Table

Ingredient	F1	F2	F3	F4	F5	F6
Nizatidine	400	400	400	400	400	400
Guar gum	200	300	400	500	600	700
Sodium alginate	400	600	800	1000	1200	1400
Calcium carbonate	500	500	500	500	500	500
Methylparaben	90	90	90	90	90	90
Propylparaben	10	10	10	10	10	10
Purified water	Q .S. 100ml	Q. S. 100ml	Q .S. 100ml	Q .S. 100ml	Q .S. 100ml	Q .S. 100ml

Q.S. Quantity Sufficient

RESULTS

Preformulation studies of drug

The Nizatidine oral *In-situ* gel was formulated and evaluated by various instrumental analyses i.e. Infra-Red Spectroscopy, Differential Scanning Spectrophotometer, Viscometer and Drug Release study by UV-Spectrophotometer, etc.

5.1.1 Calibration Curve

λ_{max} Determination for Nizatidine.

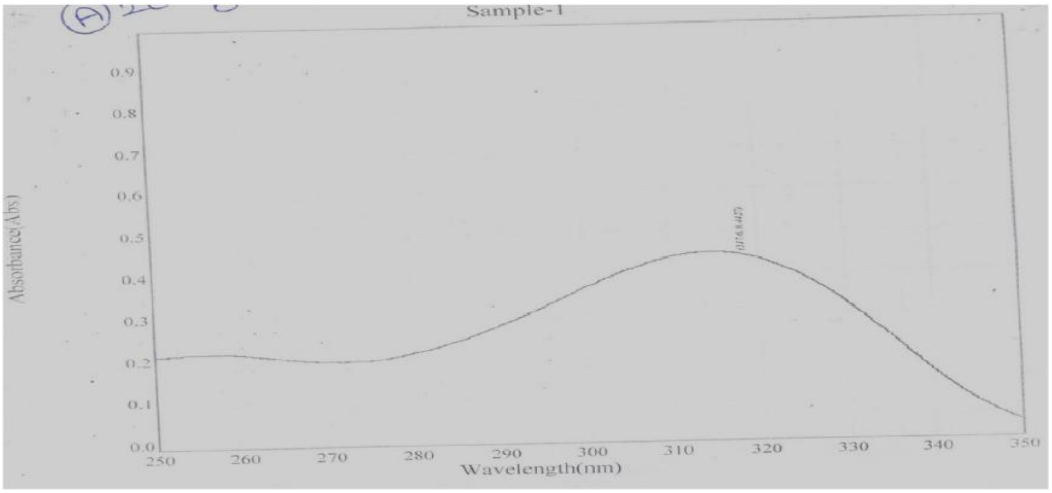

Fig 1: Wavelength scans measurement for Nizatidine.

Table 3: Absorption data of Nizatidine in 0.1 N HCl

Sr. No.	Concentration (µg/ml)	Absorbance	Slope	Intercept	R^2 Value
1	0	0.000	0.003	0.0022	0.998
2	5	0.0213			
3	10	0.0384			
4	15	0.0554			
5	20	0.0725			
6	25	0.0885			

*Average of three determinations.

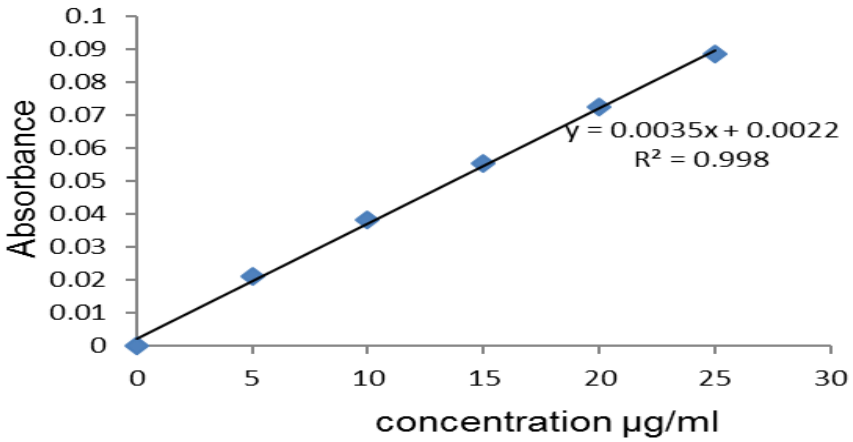

Fig 2: Calibration curve of Nizatidine in pH1.2

Evaluation of *in-situ* gel formulation.

Table 4: Viscosity of *in-situ* gel formulation:

Formulation code	20 rpm		60 rpm		100rpm	
	Viscosity (solution) (cps)	Torque (%)	Viscosity (solution) (cps)	Torque (%)	Viscosity (solution) (cps)	Torque (%)
F1	30	2.1%	32	6.5%	33	11.5%
F2	45	3.1%	48	13.1%	58	20.5%
F3	100	6.1%	105	19.6%	120	32.1%
F4	160	10.7%	140	28.1%	150	42.2%
F5	270	17.9%	265	52.1%	270	77.1%
F6	280	18.5%	275	52.5%	270	76.1%

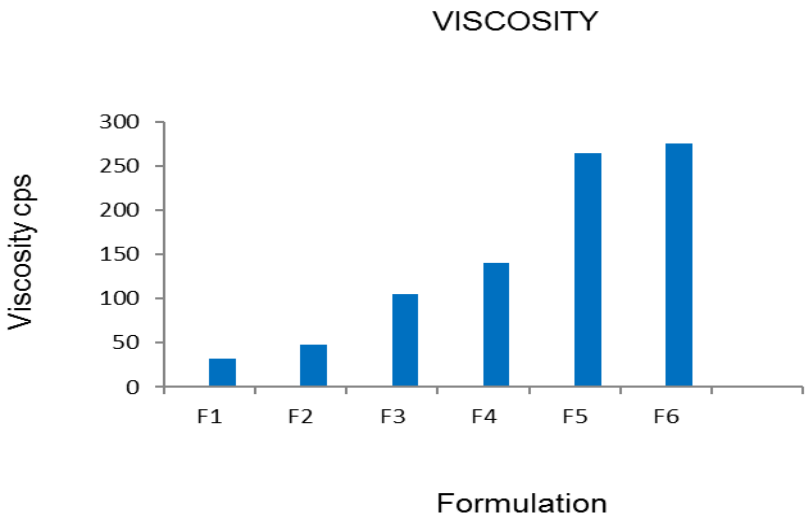

Fig 3: Viscosity of F1-F6 formulation at 20 rpm.

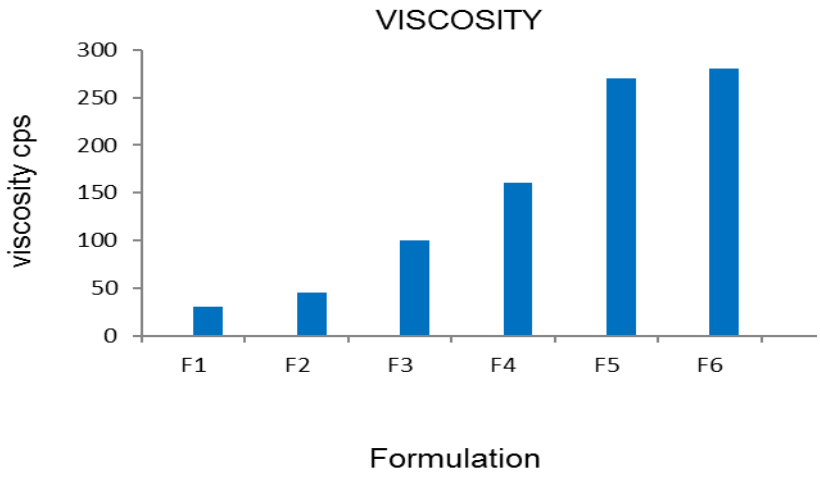

Fig 4: Viscosity of F1-F6 formulation in 60 rpm.

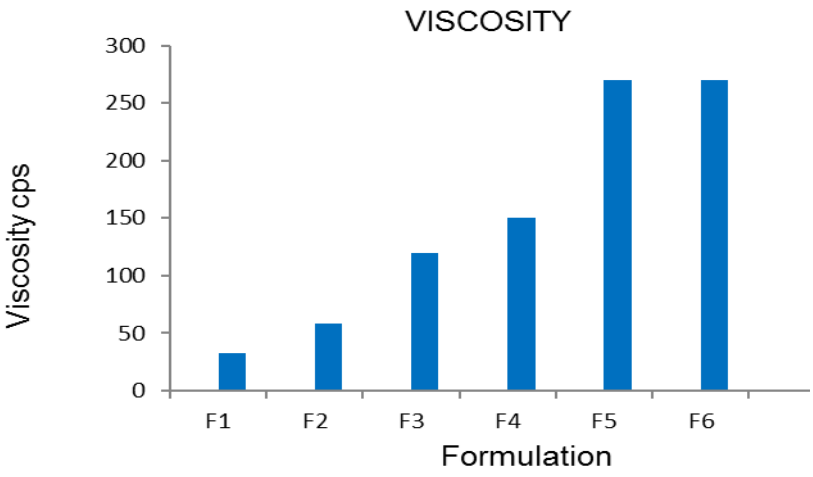

Fig 5: Viscosity of F1-F6 formulation in 100 rpm.

Table 5: *In-Vitro* gelling capacity, Gelling capacity of *In-situ* gel formulation:

Formulation code	Gelling capacity (sec.)	floating lag time (sec.)	Duration of floating lag time (hr)
F1	15	20	1
F2	16	25	3
F3	22	30	5
F4	25	40	8
F5	19	44	6
F6	18	48	7

F2 **F3**

Fig 6: In Vitro Floating and Gelling of *in-situ* gel formulation

Table 6: Drug content of *In-situ* gel formulation

Formulation Code	Drug Content (%) (±SD)
F1	95.00±27
F2	95.83±06
F3	98.32±07
F4	99.16±15
F5	97.05±13
F6	96.65±28

5.3.1 IR Spectrum:

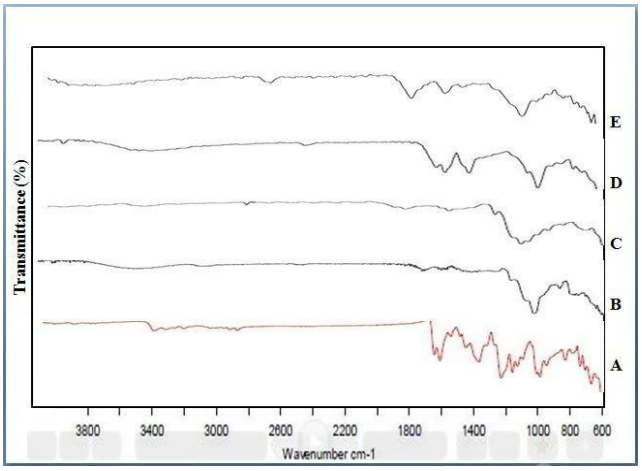

Fig 7: IR Spectra of (A) Nizatidine pure drug, (B) Sodium Alginate, (C)guar gum (D)Nizatidine+ Sodium Alginate + Guar Gum,(E) Nizatidine + sodium alginate.

IR Spectrum of Nizatidine

Table 7: IR Spectrum of Nizatidine

Sr. No.	Wave number(cm-1)		Functional groups
	Standard value of Functional group	Found value of functional group	
1	3280, 3210	3269, 3215	-NH stretch; two groups
2	3094	3091	-CH stretch in thiazole ring
3	2784	2776	-CH stretch in NHCH3
4	1622	1613	-C=C conjugated with NO2
5	1587	1579	-NO2 stretch
6	1521	1515	Thiazole ring
7	1422	1426	-CN stretch

5.3.2 Differential Scanning Calorimetry:

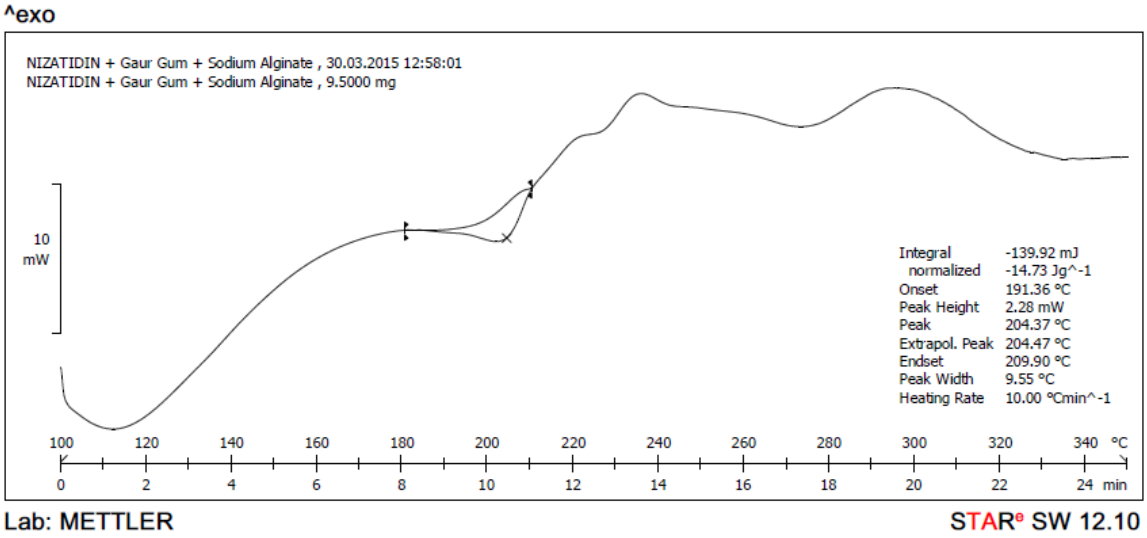

Fig 8: DSC Thermogram of F3 formulation (Nizatidine+ Guar gum +Sodium alginate)

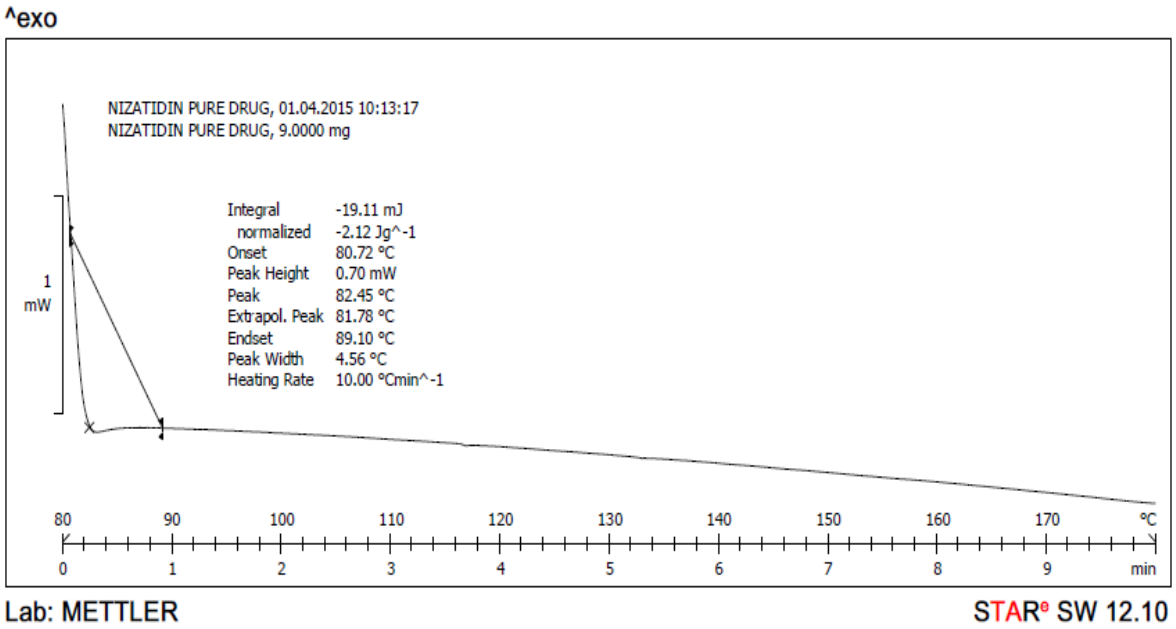

Fig 9: DSC Thermogram of pure drug Nizatidine

5.4 *In-vitro* drug release:

Table 8: *In-vitro* drug release profile F1 in 0.1N HCl

Time (min)	Concentration		Cumulative loss (mg)	The cumulative amount of drug release	
	900ml	5ml		mg	%
0	0	0	0	0	0
5	0.9	0.005	0.005	0.905	4.736842
15	3.6	0.02	0.025	3.625	18.94737
30	6	0.033333	0.058333	6.058333	31.57895
60	6.93	0.0385	0.096833	7.026833	36.47368
120	7.8	0.043333	0.140167	7.940167	41.05263
180	9.57	0.053167	0.193333	9.763333	50.36842
240	12	0.066667	0.26	12.26	63.15789
300	15	0.083333	0.343333	15.34333	78.94737
360	15.6	0.086667	0.43	16.03	82.10526
420	16.8	0.093333	0.523333	17.32333	88.42105
480	18.3	0.101667	0.625	18.92	96.31579

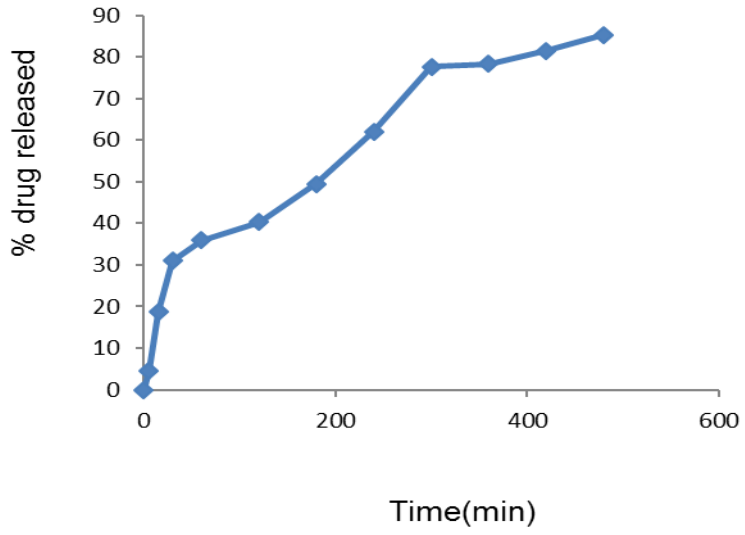

Fig 10: *In-vitro* drug release profile F1 Formulation in 0.1N HCl

Table 9: *In-vitro* drug release profile F2 in 0.1N HCl

Time (min)	Concentration		Cumulative loss (mg)	The cumulative amount of drug release	
	900ml	5ml		mg	%
0	0	0	0	0	0
5	1.2	0.006667	0.006667	1.206667	6.282723
15	2.7	0.015	0.021667	2.721667	14.13613
30	5.4	0.03	0.051667	5.451667	28.27225
60	6.9	0.038333	0.09	6.99	36.12565
120	7.8	0.043333	0.133333	7.933333	40.8377
180	11.1	0.061667	0.195	11.295	58.11518
240	13.5	0.075	0.27	13.77	70.68063
300	15.9	0.088333	0.358333	16.25833	83.24607
360	16.5	0.091667	0.45	16.95	86.38743
420	16.8	0.093333	0.543333	17.34333	87.95812
480	17.7	0.09833	0.62	18.32	93.15

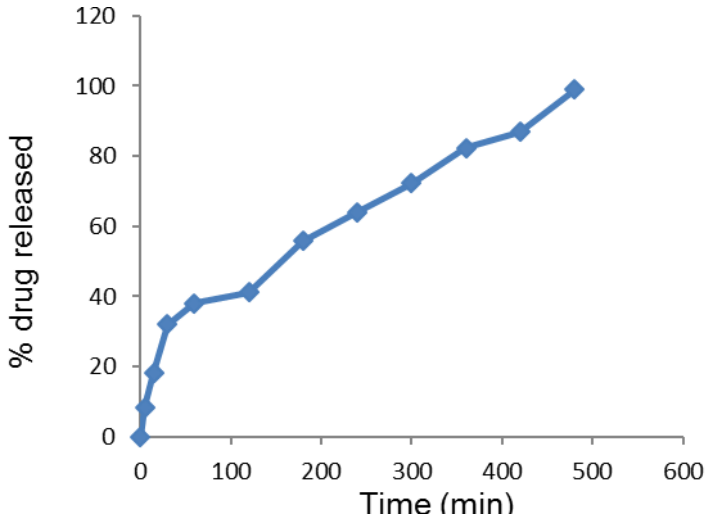

Fig 11: *In-vitro* drug release profile F2 Formulation in 0.1N HCl

Table 10: *In-vitro* drug release profile F3 in 0.1N HCl

Time (min)	Concentration		Cumulative loss (mg)	The cumulative amount of drug release	
	900ml	5ml		mg	%
0	0	0	0	0	0
5	1.65	0.009167	0.009167	1.659167	8.375635
15	3.6	0.02	0.029167	3.629167	18.27411
30	6.3	0.035	0.064167	6.364167	31.9797
60	7.5	0.041667	0.105833	7.605833	38.07107
120	8.1	0.045	0.150833	8.250833	41.11675
180	10.98	0.061	0.211833	11.19183	55.73604
240	12.6	0.07	0.281833	12.88183	63.95939
300	14.25	0.079167	0.361	14.611	72.33503
360	16.2	0.09	0.451	16.651	82.2335
420	17.1	0.095	0.546	17.646	86.80203
480	17.4	0.09666	0.62	18.02	91.57

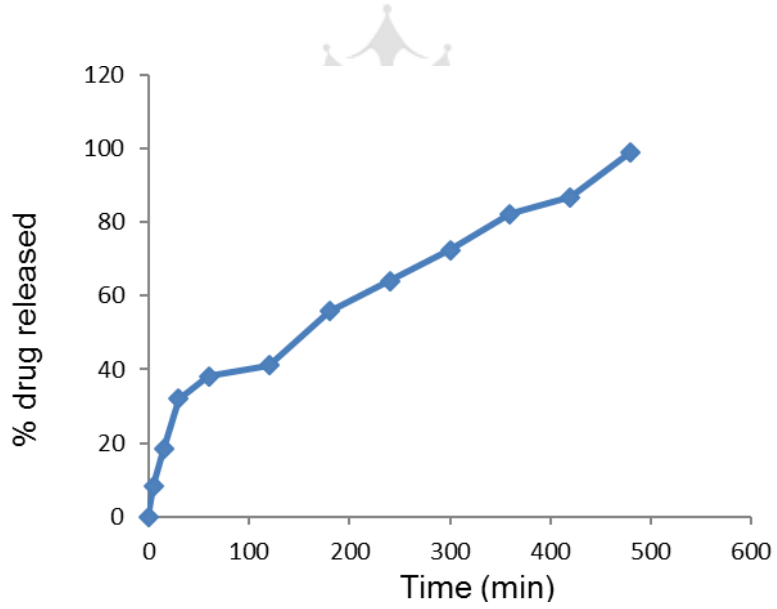

Fig 12: *In-vitro* drug release profile F3 Formulation in 0.1N HCl

Table 11: *In-vitro* drug release profile F4 in 0.1N HCl

Time (min)	Concentration		Cumulative loss (mg)	The cumulative amount of drug release	
	900ml	5ml		mg	%
0	0	0	0	0	0
5	1.92	0.010667	0.010667	1.930667	9.6823
15	3	0.016667	0.027333	3.027333	15.12859
30	6	0.033333	0.060667	6.060667	30.25719
60	7.2	0.04	0.100667	7.300667	36.30862
120	8.7	0.048333	0.149	8.849	43.87292
180	11.4	0.063333	0.212333	11.61233	57.48865
240	13.5	0.075	0.287333	13.78733	68.07867
300	14.1	0.078333	0.365667	14.46567	71.10439
360	16.2	0.09	0.455667	16.65567	81.6944
420	17.55	0.0975	0.553167	18.10317	88.50227
480	16.15	0.09416	0.6171	17.56	89.21

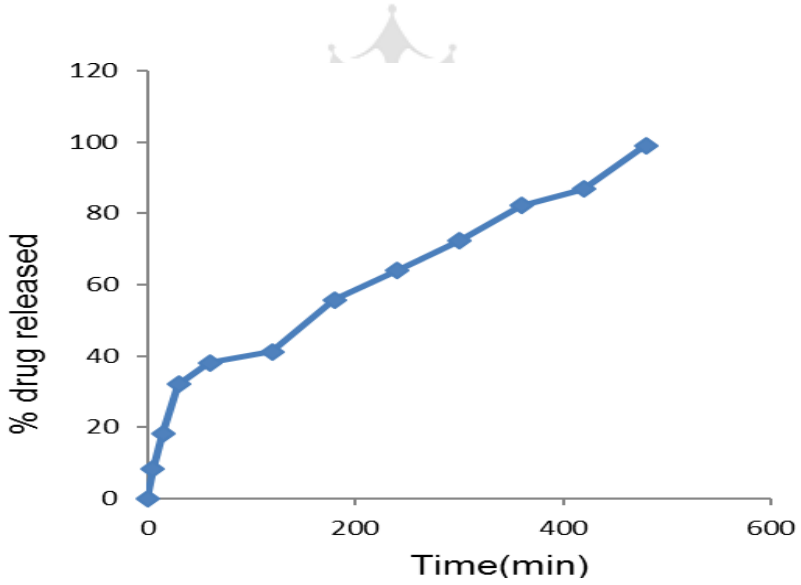

Fig 13: *In-vitro* drug release profile F4 Formulation in 0.1N HCl

Table 12: *In-vitro* drug release profile F5in 0.1NHCl

Time (min)	Concentration		Cumulative loss (mg)	The cumulative amount of drug release	
	900ml	5ml		mg	%
0	0	0	0	0	0
5	0.57	0.003167	0.003167	0.573167	2.923077
15	3	0.016667	0.019833	3.019833	15.38462
30	6	0.033333	0.053167	6.053167	30.76923
60	7.5	0.041667	0.094833	7.594833	38.46154
120	8.7	0.048333	0.143167	8.843167	44.61538
180	11.1	0.061667	0.204833	11.30483	56.92308
240	13.2	0.073333	0.278167	13.47817	67.69231
300	14.1	0.078333	0.3565	14.4565	72.30769
360	15.9	0.088333	0.444833	16.34483	81.53846
420	16.3	0.093333	0.538167	17.33817	86.15385
480	16.8	0.093667	0.614833	17.4183	88.42

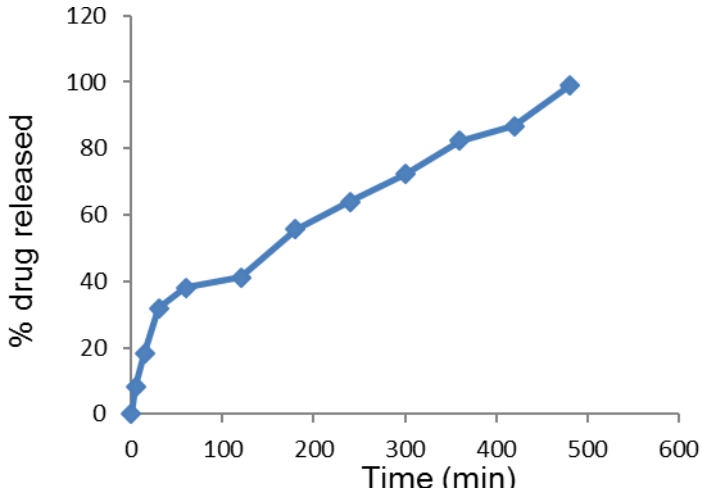

Fig 14: *In-vitro* drug release profile F5 Formulation in 0.1 N HCl

Table 13: *In-vitro* drug release profile F6 in 0.1 N HCl

Time (min)	Concentration		Cumulative loss (mg)	The cumulative amount of drug release	
	900ml	5ml		mg	%
0	0	0	0	0	0
5	0.63	0.0035	0.0035	0.6335	3.259183
15	2.7	0.015	0.0185	2.7185	13.96793
30	5.1	0.028333	0.046833	5.146833	26.38386
60	7.5	0.041667	0.0885	7.5885	38.79979
120	8.01	0.0445	0.133	8.143	41.43818
180	10.5	0.058333	0.191333	10.69133	54.31971
240	12.6	0.07	0.261333	12.86133	65.18365
300	14.25	0.079167	0.3405	14.5905	73.71961
360	15.15	0.08416	0.4275	15.5705	78.3755
420	15.75	0.0875	0.515	16.265	81.47
480	16.05	0.09166	0.6066	17.10	85.35

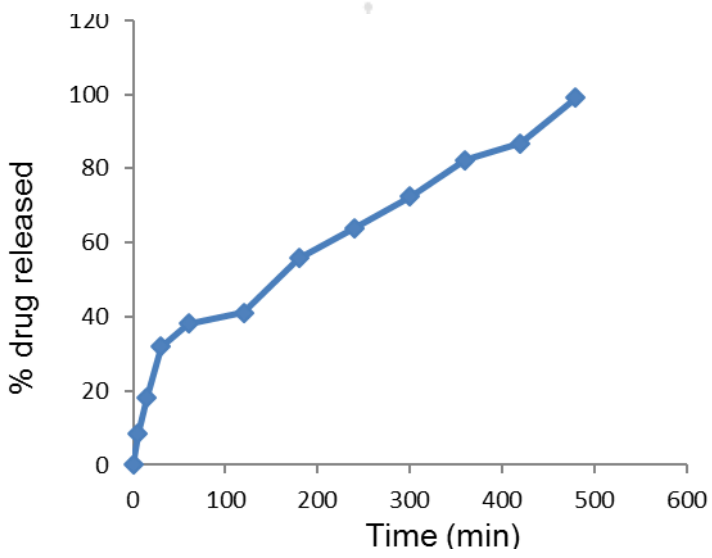

Fig 15: *In-vitro* drug release profile F6 Formulation in 0.1N HCl

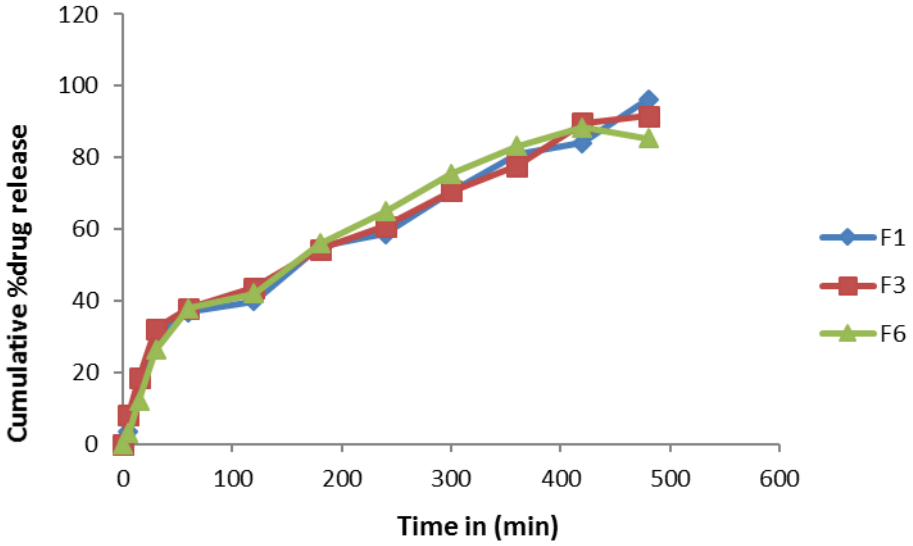

Fig 16: *In-vitro* drug release profile combined F1, F3 and F6 in 0.1N HCl

DISCUSSIONS

Preformulation study

Calibration Curve

Calibration curve of Nizatidine was performed in 0.1N HCl. Using Double beam UV-Vis spectrophotometer (Lab-India 3200). It was found at 317.6nm. The absorbance of all solutions was taken at wavelength 317.6 nm which showed in Table 5. Regression value was found to be 0.998 for Calibration curve.

Drug-Excipients compatibility study

IR study

The values of IR spectra showed in Table 7. That the characteristics peaks of NZ remain unaffected in the mixtures hence it can be concluded that Nizatidine is compatible with SA and GG indicating the absence of any significant chemical interaction.

DSC study

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and excipients in the formulation. Supporting evidence for compatibility between drug and excipients was obtained from DSC studies. As shown in the

figure, the DSC thermogram of Nizatidine showed an endothermic peak at 118^0 C which is close to the melting point of the drug. As observed in DSC thermogram of representative formulation, figure 5.8, no significant shift in the endothermic peaks of the drug was found (endothermic peak at 118^0 C). This indicated the absence of any interaction between drug and excipients.

Evaluation of *In-situ* gel formulation.

Determination of viscosity: The rheological properties of the solutions of important in view of their proposed oral administration in the selection of the concentration of the gelling polymer. A compromise is sought between a sufficiently high concentration for the formation of gels of satisfactory gel strength for use as a delivery vehicle, and sufficiently low concentration to maintain an acceptable viscosity for ease of swallowing.

The result of viscosity measurement of the formulation F1 toF6 tabulated in table no 5. The order of viscosity of all formulation was F6>F5>F4>F3>F2>F1respectively It was found that viscosity increased as the concentration of polymer increased attributed to a consequence of increasing chain interaction with polymer concentration. The formulations showed a marked increased viscosity on increased concentration of sodium alginate and guar gum.

***In-vitro* floating ability:** Time is taken by formulation to emerge on the medium surface well studies floating lag time and time during which formulation continuously floated duration of floating as shown in table-5.4 the released co_2 was entrapped in gel network producing buoyant formulation and then calcium ion reacted with SA producing a cross-linked 3-D gel network. The swelled structure that might further diffusion of co_2 and drug molecule resulted in an extended period of floating and drug release respectively fig-6.

As the expected higher concentration of SA and GG decrease drug release because of dense and compact gel formation which helps to slow drug release.

Drug content

The drug content uniformity was performed for Nizatidine containing *in-situ* gel formulations the average value and standard deviations of all the formulations were calculated The drug content *In-situ* gel was found to be in the range of 95.30±27 to 98.52±07 % as shown in table 7.

***In vitro* drug release studies:** The effect of polymer concentration on *in-vitro* drug release from *In-situ* gels was studied. As shown in fig- 8-16 significant decrease in rate and extent of drug release was observed with the increase in polymer concentration and it was attributed to an increase in the density of the polymer matrix and also a diffusion path length through which the drug molecules have to travel (Table 7. various release patterns of formulation can be judged. Formulations containing a lesser amount of guar gum showed initial burst release and dissolution were completed in the shorter period while a formulation containing a higher amount of SA and GG were released their content after a longer period of time at a sustained rate. Role of sodium alginate in formulations was primarily of the *sol-gel* phenomenon, it also did affect release from formulations with Guar Gum. Further it was found that formation F5 and F6 having SA:GG (1200:600) and SA: GG (1400:700) respectively were showed almost same amount of % drug release after 8hr it can be concluded that further increase in concentration of SA and GG will not have any effect on drug release.

CONCLUSION

The aim of this study was to design and evaluation of Nizatidine floating *In-Situ* oral gel by using guar gum and sodium alginate as the gelling polymer.

The following conclusion can be drawn from the results obtained,

1) Preformulation studies on Nizatidine performed in accordance with the reported literature limits.

2) The gel was found to be milky and having a uniform consistency.

3) The drug content was within an acceptable range which insured dose uniformity in the formulation.

4) FT-IR and DSC studies showed that Nizatidine was compatible with sodium alginate and guar gum.

5) Retard in drug release was observed with increase in the concentration of polymer.

6) On the basis of viscosity floating duration and better drug release, data F3 formulation was considered as optimized formulation.

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