

ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Floating Stomach Specific *In-Situ* Gel of Nizatidine

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ABSTRACT

This study reports the development and characterization of floating *in-situ* gel drug delivery system containing natural polymers was developed for stomach specific delivery of Nizatidine. Formulation and evaluation of *in-situ* gel by using different concentration of sodium alginate and sodium citrate with calcium chloride. Very little concentration of divalent cation was required for formulation. Optimization techniques have been applied in the present study to systemically study the influence of process variables on the formulation of dosage forms. These designs provide an effective means for studying the effect of various parameters on the dependent variables. Thus, factorial designs were applied to optimize the formulation and development of mucoadhesive microspheres and *in-situ* gel. Furthermore, a sustained release of the drug, Nizatidine is achievable from the gel vehicles over a period of at least 8 h. so we may conclude that sodium alginate may be a useful oral sustained release vehicle to improve patient compliance and bioavailability. Different formulation variables were studied and optimized to achieve the desired muco-adhesive or floating properties and release profiles. The stability of the formulations was evaluated after 3 months of storage at accelerated stability conditions.

Key words: Floating *in-situ* gel drug delivery system, Nizatidine, sodium alginate.

INTRODUCTION

Oral administration is the most convenient and preferred means of any delivery to the systemic circulation. Oral controlled release (CR) dosage forms (DFs) becoming an interesting topic of research for the past 3 decades due to their considerable therapeutic advantages to Oral controlled release drug delivery have recently been of increasing interest in Pharmaceutical field to achieve improved therapeutic advantages such as ease of dosing administration, patient compliance and flexibility in formulation^[1-3]. Drugs that are easily absorbed from gastro intestinal tract (GIT) and have short half life are eliminated quickly from systemic circulation. Frequent dosing of these drugs is required to achieve therapeutic activity. To avoid these limitations, the development of oral sustained controlled release formulation is an attempt to release the drug slowly into the gastro intestinal tract and maintain an effective drug concentration in the systemic circulation for long time. After oral administration, such a drug delivery would be retain in the stomach and release the drug in a

controlled manner so that the drug could be supplied continuously to its absorption site in gastro intestinal tract^[16-20].

The development of *in-situ* gel systems has received considerable attention over the past few years. In the past few years, increasing number of *in-situ* gel forming systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported. 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 formulations offers an interesting alternative for achieving systemic drug effects of parenteral routes, which can be inconvenient or oral route, which can result in unacceptably low bioavailability and passes the hepatic first-pass metabolism, in particular of proteins and peptides. This novel drug delivery system promotes the importantly ease and convenience of administration, deliverance of

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accurate dose as well as to prolong residence time of drug in contact with mucosa, that problems generally encountered in semisolid dosage forms. *In-situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered. From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulations. The advantages of using biodegradable polymers in clinical applications are apparent. Various natural and synthetic polymers are used for formulation development of *in-situ* forming drug delivery systems. This project attempts to discuss the newer developments and strategies for this drug delivery including physiological factors, physiochemical factors and 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, evaluation and characterization of *in-situ* polymeric formulations are discussed [4-10].

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 constant plasma profile. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. Compared to conventional controlled release formulations, *in-situ* forming drug delivery systems possess potential advantages like simple manufacturing processes and ease of administration [11-15].

Even though the delivery system is widely applicable for ocular therapy, it has several advantages as a dosage form for oral administration like maximum intimate contact of the drug at the absorption site, influenced rate of absorption, ease of preparation, homogeneity of drug distribution compared to other conventional suspensions, and mucoadhesive in nature which helps in coating of the ulcer lining once the sol comes in contact with the gastric pH.

It is also reported that oral treatment of gastric disorders with an H₂-antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs, also increases stomach wall receptor site bioavailability and increases the efficacy of drugs to reduced acid secretion.

Several approaches are currently used to prolong gastric retention time. Among them the principle of bioadhesive preparations offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [21-29].

MATERIALS AND METHODS

Materials:

Pectin (LM-104AS, DE = 31%, Lot 23001-7) was supplied by SANSHO Co., Osaka, Japan. Ambroxol hydrochloride (Lot YT-13) was supplied by YIA Co., Shiga, Japan and paracetamol (acetaminophen) was obtained from Yamanouchi Pharmaceutical Co., Tokyo. Caronal Syrup was from Showa YakuhinKako Co. Ltd., Tokyo. D-Sorbitol, xylitol, d-mannitol, sucrose and erythritol were obtained from Wako Pure Chemical Ind. Ltd., Osaka, Japan. All other reagents were of analytical grade.

Methods:

Preparation of *in-situ* gelling solution

Sodium alginate solutions of concentrations 1.0 and 1.5 % (w/v) were prepared by adding the alginate to ultra pure water containing 0.25% (w/v) sodium citrate and 0.075% (w/v) calcium chloride and heating to 60 °C while stirring. Famotidine was then dissolved in 10 ml of 0.1N hydrochloric acid solution (pH 1.2) and added in the resulting solution after cooling to below 40 °C. The solution was neutralized by 0.1N sodium hydroxide. A 1% (w/v) control solution (for use in the *in vitro* release experiments) was prepared by dissolving famotidine in a 0.6% (w/v) aqueous solution of sodium alginate. A 1% (w/v) solution of famotidine was prepared in ultra pure water. The resulting alginate *in-situ* gel solution containing famotidine was checked for viscosity and gelling property and finally stored in amber color narrow mouth bottles until further use.

Table 1: Composition of Optimization formulation G-1 to G-8

S. No	Formulation code	Nizatidine (mg)	Sodium alginate (g)	Sodium citrate (mg)	Calcium Carbonate (mg)	Sorbitol (gm)
1	G1	150	1	500	75	2
2	G2	150	1.5	500	100	2
3	G3	150	1	250	75	2

4	G4	150	1.5	500	75	2
5	G5	150	1	500	100	2
6	G6	150	1.5	250	75	2
7	G7	150	1.5	250	100	2
8	G8	150	1	250	100	2

EVALUATIONS:

The optimized formulation was subjected to different evaluation parameters listed below:

Physical evaluation:

The suspension was physically evaluated for appearance and taste.

Physical appearance and pH

All the prepared *in-situ* solutions of Nizatidine were checked for their clarity and the type of the solutions. The pH of each of the solution of sodium alginate based *in-situ* solutions of Nizatidine was measured using a calibrated digital pH meter at room temperature in triplicate.

Determination of Viscosity:

Viscosity of the samples was determined using *Brookfield Digital Viscometer* (Model No. DV II Pro). The formulation (100 ml) was taken in a beaker and maintained at room temperature. For determination of viscosity was used. Viscosities were determined at different shear rates from 00 to 100 rpm at room temperature.

In-vitro gelation study:

The gelation studies were carried out in gelation cells, fabricated locally using Teflon®. The cells were cylindrical reservoirs capable of holding 10 mL of simulated gastric fluid as gelation solution (0.1 N HCl, pH1.2). Within the cells located at the bottom is a transparent plastic cup to hold the gel sample in place after its formation. Two milliliters of the formulation was carefully placed into the cavity of the cup using a micropipette, and 6 mL of the gelation solution (SGF) was added slowly and the rate of gelation was detected by visual examination.

In-vitro floating ability:

The *in-vitro* floating study was carried out using 0.1N Hcl, (pH 1.2). The medium temperature was kept at $37 \pm 0.5^\circ\text{C}$. Ten milliliter formulation was introduced into 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 surface of the dissolution medium (duration of floating) were noted.

Determination of Drug Content:

Accurately, 10 ml of *in-situ gel* was measured and transferred to 100 ml of volumetric flask. To this

50-70 ml of 0.1N Hcl was added and shaken on mechanical shaker for 30 min, followed by sonication for 15 min. Complete dispersion of contents were ensured, visually and filtered using 0.45 membrane filter. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1N Hcl. Contents of Nizatidine was determine spectrophotmetrically.

In-vitro release studies:

The drug release studies was carried out in USP XXVI dissolution test apparatus using basket apparatus at $37 \pm 0.5^\circ\text{C}$ at 50 rpm using 900 ml of pH 1.2 buffer as a dissolution medium (n=6). *In-situ* gel equivalent to 20 mg of Nizatidine (13.5 ml) was used for test. 5 ml of aliquot was withdrawn at predetermined time intervals of 5, 10, 15, 20, 30, 60, 120, 180, 240, 300, 360, 420 and 480 min. The contents were filtered using 0.45 μ nylon filters and analyzed spectrophotmetrically. Same volume of dissolution fluid maintained at $37 \pm 0.5^\circ\text{C}$ was replaced immediately.

Accelerated Stability Study:

Optimized formulation was filled in suitable plastic container (well stoppered) bottle. Formulation was kept at suitable conditions (45°C temperature and $75 \pm 5\%$ RH) for six months. Periodically (initial, 1, 2, 3 and 6 months interval) samples were removed and characterized for viscosity, drug content, *in-vitro* gelling capacity, floating lag time, total floating time and *in-vitro* drug release study.

In-vivo study:

Male Wistar rats (200-250 gm each) were utilized for in vivo experiment study. All the animal studies were conducted in accordance with the protocol approval by the Institutional Animal Ethics Committee. The ulcer protective efficiency of Nizatidine in situ gel was compared with plain Nizatidine solution dissolved in PBS (pH 7.4). The animals were divided into five groups, each group containing five animals. The first group was treated as control and was fed with PBS (pH 7.4) by oral route. Second, third and fourth group was treated with immediate treatment of in situ gel, plain Nizatidine solution (equivalent to 30 mg/kg) and Nizatidine *in-situ gel*, respectively. The fifth group was fed with PBS (pH 7.4) and treated as blank.

One milliliter of 80% ethanol was used orally to induce gastric ulcer after 5 hrs except fifth group. The alcohol was given to dissolve the mucous coat of the stomach and so the condition was made to allow gastric acid to act on gastric walls. After 8 hrs, the animals were sacrificed (second group the animals were sacrificed after 20 min to observed whether gel is form or not) and stomachs were removed and dissected carefully to observe the ulcer protective function of Nizatidine in-situ gel as compared to plain Nizatidine solution. The incised stomachs were first washed with running tap water and placed on the watch glass and examined for severity of ulceration. The ulcer index was determined using the formula:

$$\text{Ulcer index} = 10/X$$

Where;

X = Total mucosal area/Total ulcerated area.

The results of *in vivo* study are depicted in (Table 5 & Fig 5).

RESULTS AND DISCUSSIONS

Appearance and pH:

All the prepared alginate in-situ solutions of Nizatidine were checked for their clarity and the time required for gel formation. Clarity of all the formulations was found to be satisfactory. The pH was measured of in-situ solutions of Nizatidine using a calibrated digital pH meter at 25°C. The pH of the formulations was found to be satisfactory as depicted in table 2 and was in the range of 6.5 - 7.5. The formulations were liquid at room temperature and at the pH formulated.

Viscosity

The formulation should have an optimum viscosity that will allow ease of administration as a liquid (drops), which would undergo a rapid sol-to-gel transition. (Table 2) shows the viscosity (cp) of formulations from G1 to G8. The viscosity increased in proportion it gelling agent.

Gelling studies:

Gelling studies were carried out using stimulated gastric fluid pH 1.2. In these studies the gelling

capacity (extent and speed of gelation) for all formulations were determined. The *in-situ* gel so formed should preserve its integrity without dissolving or eroding so as to localize the drug at absorption site for extended duration. Gelation characteristic was assessed on an ordinal scale ranging between + (gels after few minutes and dissolves rapidly), ++ (gelation immediate, remains for few hours only) and +++ (gelation immediate, remains for extended period).as shown in (Table 2). After ingestion, the liquid polymeric solution should undergo a rapid *sol-to-gel* transition by means of ionic gelation. The composition of SGF is rich in Cl ions; hence on interacting with CaCO₃, cross-linking agent was generated *in-situ* along generation and entrapment of gas (CO₂). As presented in table, formulations containing higher concentrations of SA were under went gelation instantly and formed good gel.

In-Vitro Floating Ability

Time taken by formulation to emerge on the medium surface (floating lag time) and time for which formulation continuously floated (duration of floating) are shown in (Table 2). The released CO₂ was entrapped in gel network producing buoyant formulation and then calcium ion reacted with SA produced a cross linked 3-D gel network and swelled structure that might further diffusion of CO₂ and drug molecule and resulted in extended period of floating and drug release respectively.

Drug content

This is one of an important requirement for any type of dosage form. Amount of the drug present in the formulation should not deviate beyond certain specified limits from the labeled amount. All formulations were found to having drug content in the range of 91-100 %, indicating homogenous distribution of drug throughout gel (Table 2).

(Figure 1 & Table 2) shows the percent drug content for formulations. The drug content was found to be in acceptable range for all the formulations indicating uniform distribution of drug.

Table 2: Evaluation of *in-situ* gel formulations

Formulation	pH	Viscosity(cp)	Gelling time (sec)	Floating time (hrs)	<i>In-vitro</i> Gelation Studies	Drug Content
G1	7.0	79	34	>6	++	93
G2	7.2	173	21	>10	+++	91
G3	6.9	63	29	8	+	95
G4	6.9	89	27	>8	+++	92
G5	7.0	159	25	8	++	97
G6	7.3	149	28	>10	++	96
G7	7.1	160	25	>10	+++	93
G8	7.1	72	37	>9	+	94

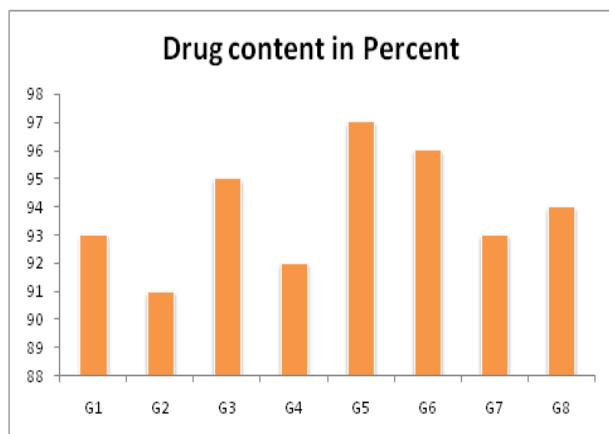


Figure 1: Drug content of Sodium alginate based in-situ gels batch F1-F8

In-vitro drug release

The effect of polymer concentration on *in-vitro* drug release from *in-situ* gels is shown in (Fig 2).

Table 3: *In-Vitro* dissolution of *in-situ* gel formulations (FG-1 to FG-5)

Time(min)	G1	G2	G3	G4	G5	G6	G7	G8
15 min	05.83	02.17	07.45	05.11	10.12	02.11	02.61	09.11
30 min	08.39	05.93	10.01	09.13	17.82	09.01	06.59	15.17
45 min	15.72	09.12	12.12	15.81	22.11	14.15	11.49	22.97
60 min	22.91	12.91	19.49	21.47	27.15	20.89	22.91	37.49
120 min	40.21	20.22	30.11	30.42	40.19	32.19	29.45	42.61
180 min	52.82	22.72	44.89	47.47	56.61	49.02	45.39	57.12
240 min	67.19	41.81	72.55	57.09	73.29	55.33	50.01	69.81
360 min	80.11	55.89	80.11	63.11	82.11	69.60	65.92	78.01
480 min	92.07	67.68	95.34	79.88	96.49	74.84	73.55	89.12

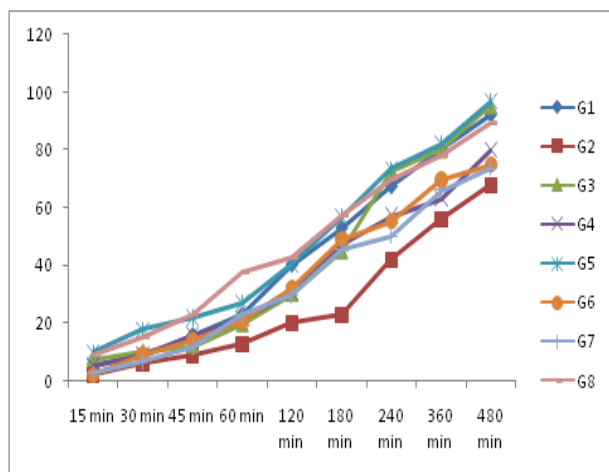


Figure 2: *In vitro* drug release study of sodium alginate based *in-situ* gelling system

Optimization of formulation by factorial design

For the purpose of optimization, drug release at the end of 8 hrs and the apparent viscosity were selected as dependent variables. The experiments aimed at sustaining as much drug as possible upto 12 hrs.

The viscosity is an important variable because it affects the gelation of the solutions, the flow of

A significant decrease in the rate and extent of drug release was observed with the increase in polymer concentration and is attributed to increase in the density of the polymer matrix and also an increase in the diffusional path length which the drug molecules have to traverse. (Table 3) shows various release patterns of formulations can be judged. Formulations containing lesser amount of SA showed initial burst of release and dissolution was completed in shorter period. While, formulations containing higher amounts of SA were released their contents for longer period of time at slower rate. Role of SA was primarily in formations of *sol-gel* phenomenon, but it also did affected release from formulations to some extent. From all above mentioned information, FG-5 was considered to the optimized formulation.

the formulation and time required for the gelation. The viscosity is dependent on the concentration of the polymer and concentration of the calcium carbonate. The viscosity of the sodium alginate solutions varied from 72 cp to 173 cp which was measured at 0 to 100 rpm (Table 2).

As seen from (Fig 3), the apparent viscosity increases as concentration of sodium alginate and calcium carbonate increase. The results also indicated that the effect of concentration of sodium alginate was as significant as that of the effect of concentration of calcium carbonate. Due to viscosity of formulation particle settling rate was decreased which would ensure uniformity of dose. Results of the equation indicate that the effect of X1 (concentration of sodium alginate) is more significant than X2 (concentration of sodium citrate) X3 (concentration of Calcium Carbonate). Moreover, volume of CaCO₃ had a negative effect on the viscosity, i.e. as the volume of cross-linking agent increases, the viscosity increases and has no significant effect on drug release.

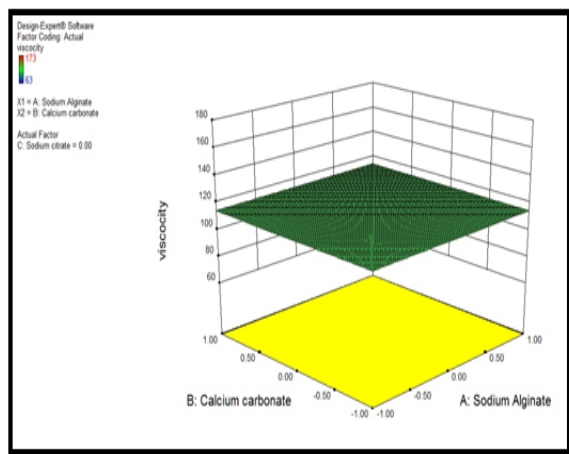


Figure 3: Surface response plot for apparent viscosity

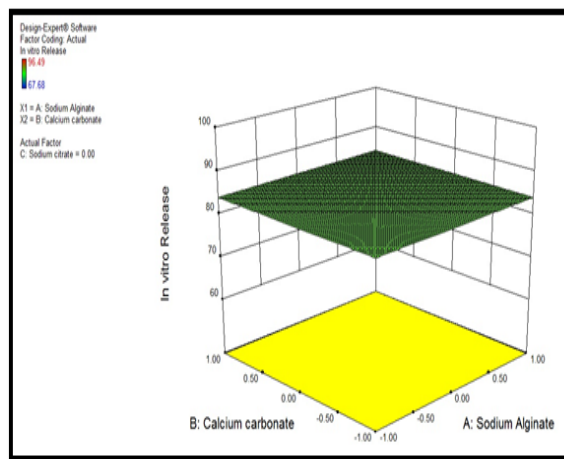


Fig 4: Surface response plot for % drug release at 8hrs

Table 4: 2³ full factorial design layout for *in-situ* gel of Nizatidine

2 ³ full factorial design layout for <i>in-situ</i> gel of Nizatidine					
Batch No	Variables levels Batch in coded form			Viscosity (cp)	% Release
	X ₁	X ₂	X ₃		
G1	-1	+1	-1	79	92.07
G2	+1	+1	+1	173	67.68
G3	-1	-1	-1	63	95.34
G4	+1	+1	-1	143	79.88
G5	-1	+1	+1	89	96.49
G6	+1	-1	-1	149	74.84
G7	+1	-1	+1	160	73.55
G8	-1	-1	+1	72	89.12
Variables level				Low (-1)	High (+)
Concentration of sodium alginate (X1)				1g	1.5g
Concentration of sodium citrate (X2)				250 mg	500mg
Concentration of Calcium Carbonate (X3)				75mg	100 mg

As seen from (Fig 4) the surface response plot revealed that a corresponding decrease in the drug release at 8 hrs was observed with increase in concentration of sodium alginate and calcium carbonate. This may be due to increase in the gel strength with increase in the concentration of both excipients. An increase in the concentration of calcium carbonate causes increase in the cross linkage of sodium alginate which ultimately increases the strength of gel, resulting in sustained release of drug through gel.

Results of *in-vivo* study

The present *in vivo* investigations demonstrated that there was a marked difference in the reduction of ulcer index from the Nizatidine *in-situ* gel (batch F5 drug content of 97 and the viscosity of 159 cp) when compared with the plain Nizatidine solution (P < 0.05). It was observed that the formulation under study not

only decreased the ulcer index to a significant larger magnitude but also sustained this magnitude (Table 5). In case of ethanol treated group, the ulcer index was found to be 2.47± 0.14 (Fig 5a). In case of immediate treatment group, the gel was formed but the ulcers were also identified to be 2.91±0.09 (Fig 5b). While in case of Nizatidine *in-situ* gel, the ulcer index was found to be only 0.35±0.02 after 8 hrs of dosing (Fig 5d). However, for plain drug the ulcer index was found to be 1.11± 0.04 after 8 hrs of dosing. The possible reason for this result may be the drug concentration in the body that was maintained for a longer duration in case of Nizatidine *in-situ* gel as compared with that of plain Nizatidine. The gel formation was checked in collected gastric juice of the rats and results showed immediately formation of gel in gastric juice of the rats.

Table 5: Effect of Nizatidine *in-situ* gel on ulcer index

Treatment Group	Ethanol treated	Immediate Treated	Nizatidine	Nizatidine <i>in-situ</i> Gel	Control
Ulcer index	2.47±0.14	2.91±0.09	1.11±0.04	0.35±0.02	No detectable

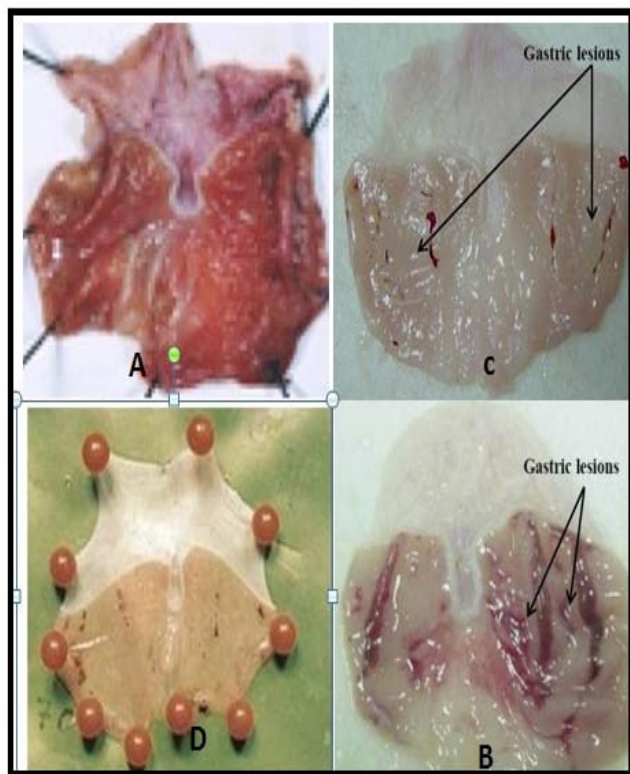


Fig 5: (a) Ethanol treated group (b) Immediate treatment of alginate based *in situ* gel group (c) Plain Nizatidine treated group (d) Nizatidine *in situ* gel treated group.

CONCLUSION

This study reports the development and characterization of a novel *in-situ* delivery system. A floating *in-situ* gel drug delivery system containing natural polymers was developed for stomach specific delivery of Nizatidine. This study has demonstrated the feasibility of forming gels in the stomach by the oral administration of aqueous solutions of sodium alginate containing Ca^{++} ions in a complexed form. Sodium alginate based *in-situ* gelling system undergoes sol-gel transition under influence of acidic pH in presence of calcium ion. Sodium citrate helps maintain fluidity before administration by complexation of calcium chloride which becomes free at acidic pH. Very little concentration of divalent cation was required for formulation. Furthermore, a sustained release of the drug, Nizatidine is achievable from the gel vehicles over a period of at least 8 h. so we may conclude that sodium alginate may be a useful oral sustained release vehicle to improve patient compliance and bioavailability and which may be most useful for pediatrics and geriatrics patients.

It was concluded that Sodium alginate is important for *in-situ* gel behavior along with

calcium carbonate, and sodium citrate is vital for controlling and extending the release from formulations. Lastly, formulations containing higher and moderate amount of sodium alginate were considered as optimized formulation.

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