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Research Article

DEVELOPMENT AND OPTIMIZATION OF RAFT-FORMING FORMULATION OF H_2BLOCKERS

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ABSTRACT

Objective: The present research work is focused to develop *in situ* raft gel of Nizatidine. sodium alginate (SA) is one of the critical components for the development *in situ* raft system.

Methods: The formulation was prepared using polymers such as SA and gellan gum. The formulations were subjected to evaluation characteristics such as pH, *in vitro* gelling capacity, viscosity, gel strength, and *in vitro* release studies.

Results: The pH of all the prepared batches was found in the range of 6.4–7.2 for S1–S9, and 6.3–7.2 for G1–G9. S1–S9 formulations showed viscosity in the range of 253.7–400.9 cps, and G1–G9 formulations showed viscosity in the range of 253.4–399.8 cps. Formulation S6 containing SA and G6 containing gellan gum gave the highest drug content of 99.58% and 99.5%, respectively. The highest gel strength 4.6 is exhibited by S6 and G6 formulations. Formulation S6 containing SA gave the highest drug release of 95.62% and also showed sustained and controlled release for up to 12 h.

Conclusion: Gastric raft formulation is a better choice for drugs such as Nizatidine which enhances the drug release for a prolonged time by remaining buoyant in the stomach for more than 12 h.

Keywords: *In situ* gel, Nizatidine, Raft, Controlled release.

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INTRODUCTION

Oral administration is the preferred method of delivering drugs to the systemic circulation. Its convenience and flexibility have led to the increasing interest in the development of new drug delivery methods. Delivering a drug through the oral route has become more challenging as several alternate advanced systems are available. However, the bioavailability issue of drugs administered orally has still to be improved. The concept of a controlled-release gastroretentive dosage form was developed to provide continuous distribution of formulation to the upper GI tract while minimizing the limitations of poor colon absorption [1]. Gastroretentive is one such approach to delivering the drug. In the gastroretentive system, the formulation is allowed to remain in the gastric region for the desired time and the formulation is fabricated to release the drug in a controlled manner to achieve the objective. By stopping the dosage form from flowing through the pyloric sphincter, gastric retention is achieved. Raft-forming systems are preparations that in contact with acidic pH undergo gelation to produce a thick layer that floats on gastric content. The gastroretentive raft system stays in the stomach for a long time to improve drug bioavailability [2].

Nizatidine belongs to the class of antihistaminic. An H2 receptor antagonist which has ulcer healing properties and is commonly used in the treatment of gastroesophageal reflux disease. The anti-ulcer property of the drug is due to decreased stomach acid secretion in parietal cells. Nizatidine is having an absorption window in the stomach as well as in the upper part of the intestine. The drug needs frequent dosing due to its short half-life (1–2 h) due to which the drug is having only 37% oral bioavailability. Moreover, the drug is subjected to metabolism in the colonic region. These properties of the drug make it an appropriate choice for preparing a raft-forming gastroretentive system, where the drug release is confined to the gastric region for a longer time in a controlled manner. Thus, it helps to overcome the problem associated with conventional preparations [3]. Sodium alginate (SA) is one of the hydrophilic polymers which have the unique property of undergoing gelation in contact with acidic pH. The formed gel has a density less than that of gastric juice. In the present work, an attempt is made to develop *in situ* raft system of Nizatidine to increase its bioavailability. The combined effort of retaining the drug in the gastric region and controlling the release of the drug made to attain the objective [4].

MATERIALS AND METHODS

Materials

Nizatidine was purchased from Yarrow Chem Product, Mumbai. SA, gellan gum, sodium bicarbonate, and calcium chloride were purchased from Loba Chemie, Mumbai, India.

Methodology

Pre-formulation evaluation

A pre-formulation study is the first step in the preparation of any formulation. The pre-formulation study confirms the formulation under consideration.

Organoleptic properties

The drug under consideration is examined for its physical appearance to confirm its physical stability [5].

Melting point

Determination of the melting point helps to investigate the purity of the drug. The study was carried out using a melting point apparatus with the help of a capillary tube. The obtained results were confirmed as a standard reference [6].

λ_{max} by UV-visible spectroscopy

UV spectroscopic method was used to identify Nizatidine. Standard solutions of Nizatidine were prepared by diluting a known amount

of the drug in 0.1N HCl (10, 20, 30, 40, 50, and 60 µg/mL). The solutions were subjected to UV spectroscopic scanning to identify λ max of Nizatidine. The spectrum was recorded at the 200–400 nm range [7].

Differential scanning calorimetry

Thermal analysis of the lafutidine sample was carried out using a differential scanning calorimeter (DSC). To carry out the study, the sample was placed in an aluminum pan and heated at a rate of 10°C/min over a range of 30–300°C under a nitrogen environment. The DSC spectrum will help to identify the sample purity [8].

Fourier transformer infrared (FTIR) spectroscopy

To conduct FTIR study, 5 mg of the drug sample is mixed with 500 mg KBr (IR grade) in an agate mortar pestle to get a uniform mixture. This mixture is then pressed in a disc by applying 10-ton pressure using a hydraulic press. The disc was then subjected to FTIR scanning over a wave number range of 4000–400 cm^{-1}. The spectrum was then studied to identify various functional groups to identify the drug [9].

Selection of polymers

The literature survey was carried out to identify various polymers to prepare formulation. From the survey, it was found that gelling polymer SA is one of the key components to prepare *in situ* raft system. Sodium bicarbonate was used as a gas-generating agent. Sodium ethylparaben and sodium propylparaben were used as a preservative [10].

Method of preparation of *in situ* raft system

Nizatidine and other ingredients were passed through sieve numbers 60 and 40, respectively. Prepare homogeneous dispersion by adding the drug gradually into the above-prepared solution using a magnetic stirrer operated at 150 RPM. Add SA or gellan gum to purified water containing sodium bicarbonate, sodium ethyl, and sodium propylparaben by heating at 60°C to obtain a gelling solution [11]. The formulation of *in situ* gelling solutions of SA and gellan gum is shown in Table 1.

Evaluation of Nizatidine *in situ* raft system

The prepared *in situ* raft formulations were examined for various evaluation parameters [12].

Physical appearance

The prepared all formulations were subjected to physical evaluation to observe their physical integrity [13].

pH

The hydrogen ion concentration (pH) of the formulations was evaluated using a digital pH meter (previously calibrated) at 37°C [14].

Viscosity

The resistant flow property (viscosity) of *in situ* gel formulations was determined at room temperature using a Brookfield viscometer (LV1 Spindle) in triplicate [15].

Measurement of gel strength

50 g weight was taken and placed on the surface of the 30 g gel, making it centric, where penetration occurs through the gel. The whole process is done in a 50 mL beaker. The time taken to penetrate 5 cm down through the gel by 50 g weight was recorded for all the formulations [16].

Drug content

The drug content of the formulation was measured by taking 5 mL of formulation into 50 mL of dissolution media 0.1N HCl (pH 1.2) maintained on a magnetic stirrer at 37°C for 1 h. on contact with 0.1N HCL; the formulation undergoes gelation to form a gel. The formed gel along with the solution was subjected to sonication for 10 min and filtered through Whatman filter paper. The absorbance of the solution was measured using UV spectrometer at 313 nm using 0.1N HCL as blank and drug content was calculated [17].

***In vitro* gelling capacity**

To evaluate *in vitro* gelling capability, accurately measured 10 mL of formulation was added to 100 mL of 0.1N HCl at 37°C in a beaker with gentle agitation that avoids breaking of farmed gel. The *in vitro* gelling capability was categorized into four classes on the idea of the stiffness of farmed gel, gelation time, and period that the gel remains intrinsically including [-] no gelation, (+) gels after few minutes dispersed rapidly using an FTIR (M/s Shimadzu, Model: IR Spirit) by the KBr disc method [11]. (++) Gelation immediately remains for few hours (+++) gelation immediate remains for an extended period [18].

***In vitro* drug release study**

A paddle-type apparatus, i.e., Type II USP dissolution apparatus was used to conduct the study. 900 ml of 0.1N HCl (pH 1.2) was used as a dissolution medium maintained at 37°C. 10 mL of the formulation was introduced into the dissolution medium and allowed for gelation to convert into a gel. After the formation of gel at the predetermined time, 10 mL of the dissolution sample was withdrawn and restored with fresh dissolution media to maintain proper sink condition. The sample was diluted was analyzed using UV spectrometer at 313 nm [19-21].

RESULTS AND DISCUSSION

Organoleptic properties of Nizatidine

Nizatidine was found to be white-to-off-white crystalline powder.

Melting point of Nizatidine

The melting point of Nizatidine was found to be 131°C, which confirms its identity and purity.

Determination of λ_{max} by UV-visible spectroscopy

The Nizatidine shows its absorbance peak at 313 nm in 0.1N HCl from the concentration of Beer's law ranging from 10 to 50 µg/mL (Fig. 1).

FTIR study of Nizatidine

The major peaks for pure Nizatidine were seen as 3207.77 for–NH stretching, 2570.84, 3094.40 for C-H stretching in NO_2-CH, 2941.97 for C-H stretching of thiazole ring, 1436.97 for C-H stretching in-NCH3,

Table 1: Formulation of *in situ* gelling solutions of sodium alginate

Ingredients (%W/V)	Composition (%W/V)								
	S1	S2	S3	S4	S5	S6	S7	S8	S9
Nizatidine	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Sodium alginate	2.5	2.5	2.5	3	3	3	3.5	3.5	3.5
Calcium chloride	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Sodium citrate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium bicarbonate	1	1	1	1.5	1.5	1.5	2	2	2
Sodium methylparaben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sodium propylparaben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Sodium saccharine	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Water q.s	100	100	100	100	100	100	100	100	100

*Sodium alginate was replaced by gellan gum for G1 to G9 formulation

1618.93 for C=C conjugated with-NO_2 group, and 1589.40,1438,1527 for C-H deformation in-NCH_3which confirms the important functional group Nizatidine (Fig. 2).

DCS study of pure Nizatidine

The thermogram of pure Nizatidine shows a sharp endothermic peak at 130.2°C corresponding to the melting of pure Nizatidine (Fig. 3).

Physical appearance of formulation

All the formulations were observed to have a creamy-white color with a smooth uniform consistency.

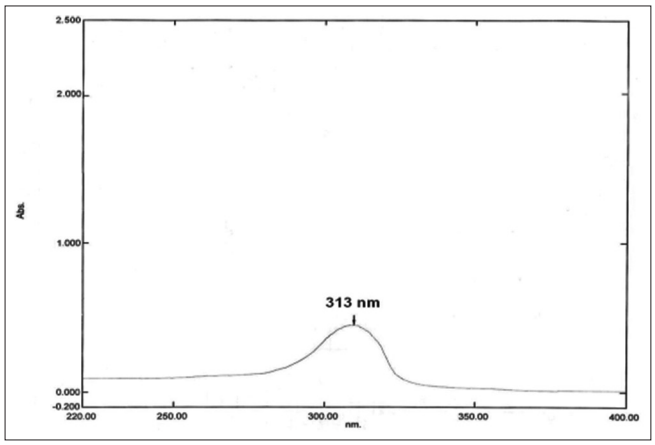

Fig. 1: UV spectrum of Nizatidine in 0.1 N HCl

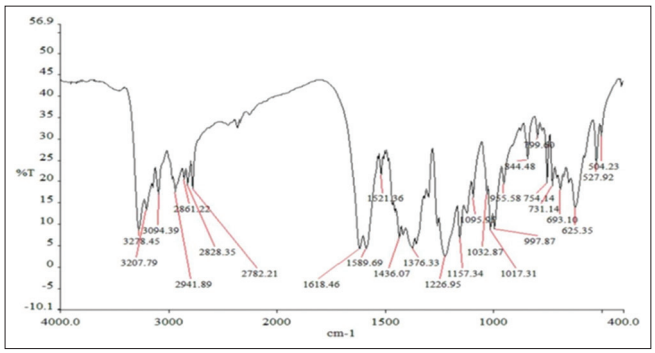

Fig. 2: FTIR of Nizatidine

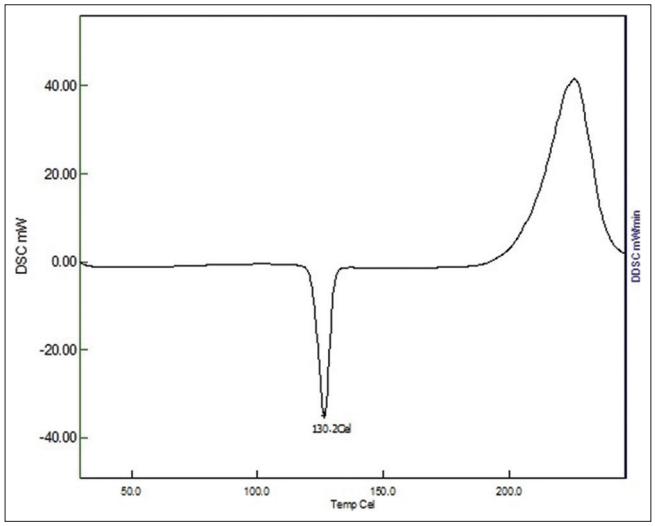

Fig. 3: Differential scanning calorimeter thermogram of Nizatidine

pH of formulation

The pH of S1–S9 and G1–G9 batches was found in the range of 6.4–7.2 and 6.3–7.2, respectively (Table 2).

Viscosity

The viscosity of S1–S9 and G1–G9 batches was found in the range of 253.7–400.9 cps and 253.4–399.8 cps, respectively (Table 3). From the above viscosity value, it can be concluded the preparations are easily pourable in nature, which leads to easy administration of dosage form.

Table 2: pH of formulations containing sodium alginate (S1–S9) and gellan gum (G1–G9)

Formulation	pH	Formulation	pH
S 1	6.4	G 1	6.3
S 2	6.5	G 2	6.5
S 3	6.6	G 3	6.7
S 4	6.7	G 4	6.7
S 5	6.8	G 5	6.8
S 6	6.8	G 6	6.9
S 7	6.9	G 7	7.0
S 8	7.1	G 8	7.2
S 9	7.2	G 9	7.2

Table 3: Viscosity of formulations containing sodium alginate (S1–S9) and gellan gum (G1–G9) mean±SD (n=3)

Formulation	Viscosity (cps)	Formulation	Viscosity (cps)
S1	253.7±0.7527	G 1	253.4±1.775
S2	260.8±0.8168	G 2	257.5±4.668
S3	282.7±2.136	G 3	279.2±2.684
S4	311.4±2.343	G 4	308.7±2.041
S5	331.5±1.873	G 5	324.6±9.392
S6	371.2±0.8947	G 6	370.1±2.759
S7	400.9±0.8168	G 7	399.8±1.965
S 8	280.4±0.5478	G 8	279.5±2.339
S 9	319.5±0.7526	G 9	315.5±4.888

Table 4: Gel strength of formulations containing sodium alginate (S1–S9) and gellan gum (G1–G9) mean±SD (n=3)

Formulation	Gel strength (g/cm^2)	Formulation	Gel strength (g/cm^2)
S1	4.1	G1	4.3
S2	4.3	G2	4.4
S3	4.4	G3	4.4
S4	4.3	G4	4.5
S5	4.4	G5	4.5
S6	4.6	G6	4.6
S7	4.4	G7	4.5
S8	4.5	G8	4.6
S9	4.5	G9	4.6

Table 5: Drug content of formulations containing sodium alginate (S1–S9) and gellan gum (G1–G9) mean±SD (n=3)

Formulation	Drug content (%)	Formulation	Drug content (%)
S 1	97.2±0.5317	G1	97.4±0.5200
S 2	97.54±0.3322	G2	98.55±0.3666
S 3	98.10±0.3443	G3	98.11±0.3367
S 4	99.37±0.3323	G4	99.36±0.3363
S 5	99.03±0.2135	G5	99.05±0.2162
S 6	99.58±0.2137	G6	99.5±0.2023
S 7	99.0±0.2543	G7	99.3±0.2685
S 8	98.5±0.3443	G8	99.47±0.3682
S 9	98.65±0.2323	G9	98.69±0.2383

Table 6: *In vitro* gelling capacity of formulations containing sodium alginate (S1 to S9) and gellan gum (G1 to G9)

Formulation	Sodium alginate (%w/v)	*In vitro* gelling capacity	Formulation	Gellan gum (%w/v)	*In vitro* gelling capacity
S1	1	- - -	G1	1	- - -
S2	1.5	+ + -	G2	1.5	+ - -
S3	2	+ + +	G3	2	+ + -
S4	2.5	+ + +	G4	2.5	+ + +
S5	3	+ + +	G5	3	+ + +
S6	3.5	+ + +	G6	3.5	+ + +
S7	4	+ + +	G7	4	+ + +
S8	4.5	+ + +	G8	4.5	+ + +
S9	5	+ + +	G9	5	+ + +

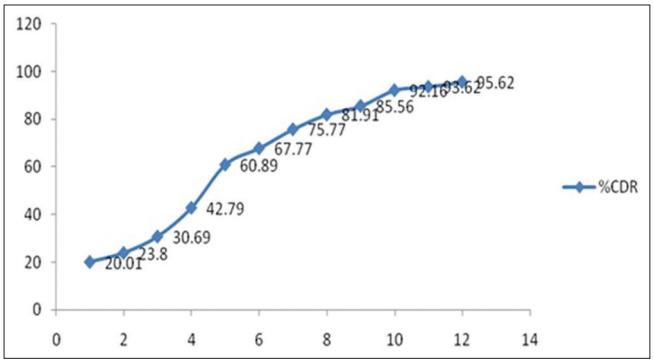

Fig. 4: Drug release profile of optimized batch S6 (X-axis: Time in hours, Y-axis: % CDR)

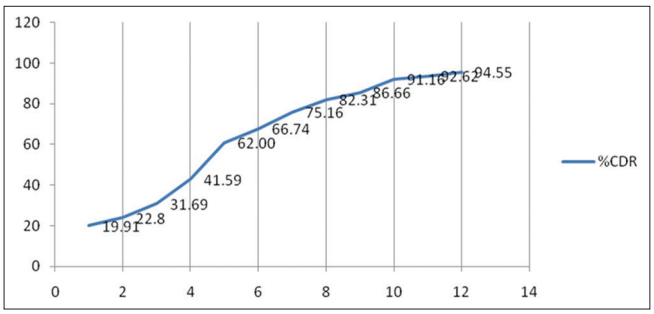

Fig. 5: Drug release profile of optimized batch G6 (X-axis: Time in hours, Y-axis: % CDR)

From the viscosity measurement, it has been observed that increasing concentrations of polymers enhanced the viscosity of preparations.

Measurement of gel strength

The gel strength of S1–S9 and G1–G9 batches was found in the range of 4.1–4.6 g/cm^2 and 4.3–4.6 g/cm^2, respectively (Table 4). The highest exhibited by S6 and G6 formulation. This is due to the fact of increasing polymer concentrations, which results in rigid three-dimensional network formation with double helical cross-linking with adjacent polymer chains.

Drug content

The drug content of S1–S9 and G1–G9 batches was found in the range of 97.54–99.58% and 97.4–99.5%, respectively (Table 5), which indicates that the distribution of the drug is uniform in all the formulations as per the monograph.

***In vitro* gelling capacity**

Gelling studies were carried out using 0.1N HCl (pH 1.2), and the obtained data are represented in Table 6. Gelation occurs when the insoluble sodium bicarbonate solubilizes when it comes in contact with an acidic medium releasing carbon dioxide and ions. The ions interact with the gelling polymer such as SA or gellan gum in the formulation causing instantaneous gelation and provide a gel barrier that restricts drug release. As the concentration of the polymer and sodium bicarbonate increases the *in vitro* gelling capacity also increases. S1, S2 and G1, G2, G3 formulations had somewhat fewer stiff gels when compared to other formulations.

***In vitro* drug release study**

The *in vitro* drug release study of prepared Nizatidine raft gel formulation was carried out by USP type II dissolution apparatus containing 900 mL of 0.1N HCl at 37±0.5°C at 50 rpm for 12 h, and the result is shown in Figs. 4 and 5. *In vitro,* drug release study of an optimized formulation S6 of SA and G6 of gellan gum was found to be 95.62% and 94.55% after 12 h.

DISCUSSION

Gastroretentive *in situ* raft formulation of Nizatidine was successfully done with all the evaluation tests performed and all the formulations were able to float instantaneously and kept floating for more than 12 h and all the test's values were observed within range with sustained and controlled release up to 12 h. Formulation S6 containing SA and G6 containing gellan gum gave the highest drug content therefore S6 and G6 were selected as optimized formulations. Formulation S6 containing SA shown higher drug release as compared to formulation G6 containing gellan gum. Hence, it is proved that gastro retentive raft formulation is a better choice for drugs such as Nizatidine which enhances the drug release for a prolonged time by remaining buoyant in the stomach for 12 h which is useful in the treatment of gastric ulcers.

CONCLUSION

The raft-forming system which is a gastro-retentive drug delivery system is designed to increase this gastric retention time, some of the problems we have with other methods of taking medication, as therapeutic efficacy will improve, floating of dosage forms faster than others administration into the patient is easy. As a result, it is concluded that manufactured SA containing Nizatidine raft formulation can be delivered to a specific location for more than 12 h showing sustained drug delivery over an extended period (95.62% CDR). It can be concluded that raft floating dosage forms containing SA serve the best system as compared to other gastroretentive approaches in the treatment of diseases related to the GIT.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none.

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