ISSN 2582 – 6050

Available Online at www.ijpba.info
International Journal of Pharmaceutical & Biological Archives 2021; 12(3):126-134

RESEARCH ARTICLE

Formulation and *In Vitro* Evaluation of Ranitidine Oral *In Situ* Gels

Mungara Meghana, Matti Bhargavi

Department of Pharmaceutical Analysis and Quality Assurance, Vallabaneni Venkatadri Institute of Pharmaceutical Sciences, Seshaadri Rao Knowledge Village, Gudlavalleru, Andhra Pradesh, India

Received: 10 June 2021; Revised: 20 July 2021; Accepted: 19 August 2021

ABSTRACT

Introduction: In the present study, formulation and evaluation of floating oral in situ gelling system of ranitidine was investigated using various polymers. **Material and Method:** The objective of the present research study was to formulate, develop, and optimize in situ gelling systems for oral administration. The development of in situ gelling systems has received considerable attention over the past few years. **Result:** In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. The drug content was found to being the range of 95–102% for all the formulations indicating uniform distribution of drug. Ranitidine was chosen as the model candidate for the development of oral in situ gel, since them possesses near ideal characteristics that these drugs must have formulating sustained drug delivery system. **Conclusion:** The results of study demonstrate that xanthan gum was suitable to develop sustained release oral in situ gels.

Keywords: Ranitidine, *in situ* gels, *in vitr*o

INTRODUCTION

In-situ Gel

The development of *in situ* gelling systems has received considerable attention over the past few years. *In situ* gel forming drug delivery systems are principle, capable of releasing 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. These have a characteristic property of temperature-dependent, pH-dependent, and action-induced gelation. Compared to conventional controlled release formulations, *in situ* forming drug delivery systems possess potential advantages such as simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance, and comfort.[1,2] *In situ* gel forming drug delivery is a type of mucoadhesive drug delivery system. In contrast to very strong gels, they can be easily applied in liquid form to the site of drug absorption. At the site of drug absorption, they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of *in situ* gels. *In situ* gel formation occurs due to one or combination of different stimuli such as pH change, temperature modulation, and ionic cross-linking.[3-5] Hence, *in situ* gels are administered by oral, ocular, rectal, vaginal injectable, and intraperitoneal route Recent advances in *in situ* gels have made it possible to exploit the changes in physiological uniqueness in different regions of the gastrointestinal (GI) tract for the improved drug absorption as well as patient's convenience and compliance.

Advantages of *In Situ* Gels[6]

- Ease of administration
- To increase local bioavailability

***Corresponding Author:**
Mungara Meghana
E-mail: meghanamungara@gmail.com

- Reduced dose frequency
- Improved patient compliance
- Its production is less complex and so lowers the investment.

Drug and Excipients Profile

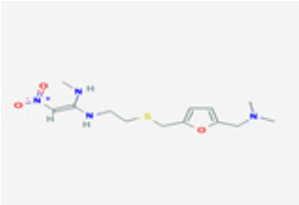
Drug profile

Ranitidine

Description

Ranitidine is a commonly used drug, classified as a histamine H2-receptor antagonist, and belongs to the same drug class as cimetidine and famotidine. This drug helps to prevent and treat gastric acid associated conditions, including ulcers, because of its ability to decrease gastric acid secretion. Ranitidine is often referred to as Zantac and is available in various forms, including tablet, injection, and effervescent tablet preparations. The prevalence of gastroesophageal reflux disease (GERD) is thought to be 10–20% in Western countries. Ranitidine has proven to be an effective treatment for relieving uncomfortable symptoms of gastric acid associated conditions and is, therefore, widely used in GERD and other gastric acid-related conditions.

Structure



CAS number: 66357-35-5
Average weight: 314.4
Monoisotopic: 314.141261758
Chemical formula: $C_{13}H_{22}N_4O_3S$
IUPAC Name: [1-({2-[({5-[(dimethylamino) methyl] furan-2-yl} methyl) sulfanyl] ethyl} amino)-2-nitroethenyl] methyl amine

Excipients Profiles

Sodium alginate

Sodium alginate is a natural hydrophilic polysaccharide derived from sea weed. It is the sodium salt of alginic acid, a high molecular weight linear polymer consisting of D-mannuronic acid and L-glucuronic acid residues that are arranged in the polymer chain in blocks.

Empirical formula: $(C_6H_7O_6Na)n$

Description

Sodium alginate occurs as a white or buff color coarse or fine powder which is odorless and tasteless. Aqueous solutions form gel on the addition of small amount of soluble calcium salt.

Solubility

Sodium alginate is slowly soluble in water, forming a viscous colloidal solution. It is insoluble in alcohol and in hydroalcoholic solutions in which the alcohol content is >30% by weight. It is also insoluble in other organic solvents and in acids where the pH of the resulting falls below 3.

Gel properties

Alginate forms gels with monovalent, divalent, and multivalent cations. Monovalent cations form soluble salts with alginate where as divalent and multivalent cations (except Mg^{2+}) forms gels or precipitates. Hydration of alginic acid leads to the formation of a high viscosity "acid gel" due to intermolecular binding. After gelation, the water molecules are physically entrapped inside the alginate matrix, but are still free to migrate. This is great importance in many applications, for example, alginate gels for cell immobilization/microencapsulation. The various cations show different affinity for alginate and selective ion binding in the basis for the ability of alginate to form ionotropic hydrogels. Alginate is easily gelled in the presence of a divalent cation as calcium ion. The gel strength will depend on the guluronic content and also of the average number of G-units in the G-blocks.

Viscosity

Various grades of sodium alginate are available yield in aqueous solutions of varying viscosity within a range of 20–400 centipoise (0.02– 0.4 Pa.S) in 1% solution at 20°C. Viscosity decreases of sodium alginate solutions above pH of 10.

MATERIALS AND METHODS

Materials

All materials (AR Grade) used were obtained from different sources and all instruments used in work that is as given in table, respectively [Tables 1 and 2].

Experimental Work

Pre-formulation studies

Solubility studies

Solubility of ranitidine was carried out in different solvents such as 0.1 N HCl, methanol, ethanol, 7.4 pH buffer, and 6.8 pH buffer. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 h at 25°C under constant vibration. Filtered samples (1 ml) were diluted appropriately with suitable buffer and solubility of ranitidine was determined spectrophotometrically at 230 nm.[6-15]

Fourier-transform infrared (FT-IR) spectroscopy

The physical compatibility between the pure drug and polymers used in the research was tested by infrared (IR) spectroscopy. FT-IR absorption spectra for pure drug and physical mixture were recorded in the range of 400–4000 cm^{-1} by KBr disc method using FT-IR spectrophotometer.

Table 1: Instruments used

Instruments	Companies
UV–visible spectrophotometer	T60 PG INSTRUMENTS
Weighing balance	Essae-Teraoka Ltd., DS-852j
Overhead stirrer	Techno Scientific Products, Bangalore
pH meter (pH Tutor)	Techno Scientific Products, Bangalore
Rheometer (DV-E)	Brookfield Viscometer
Magnetic stirrer	MB Instruments, MB575, Delhi
Mechanical stirrer	MBI Instruments, MB575, Delhi
Dissolution apparatus	DS 8000 Lab, India

Table 2: Materials used

S. No.	Materials	Sources
1	Ranitidine	Hetero Labs Ltd., Hyderabad.
2	Sodium alginate	Colorcon Asia Ltd., Verna, Goa.
3	Calcium carbonate	MJ Biopharmaceuticals, Mumbai
4	Sodium citrate	MJ Biopharmaceuticals, Mumbai
5	HPMC K15M	MJ Biopharmaceuticals, Mumbai
6	Xanthan gum	MJ Biopharmaceuticals, Mumbai
7	HPMC K100M	MJ Biopharmaceuticals, Mumbai
8	Water	Narmada Chemicals

Determination of absorption maxima by UV spectrophotometer

Ten milligrams of ranitidine were dissolved in 10 ml of buffers so as to get a stock solution of 1000 µg/ml concentration. From this, 1 ml solution was withdrawn and diluted to 10 ml to get a concentration of 100 µg/ml (SS-II). From this stock solution pipette out 1 ml of the solution and makeup the volume to 10 ml using buffer to get the concentration of 10 µg/ml concentration, this solution was scanned under UV spectroscopy using 200–400 nm.

Preparation of calibration curve of ranitidine

Ten milligrams of ranitidine were dissolved in 10 ml of 0.1 N HCl by slight shaking (1000 µg/ ml). One milligram of this solution was taken and made up to 10 ml with 0.1 N HCl, which gives 100 µg/ ml concentration (stock solution). From the stock solution, concentrations of 4, 8, 12, 16, 20, and 24 µg/ ml in 0.1 N HCl were prepared. The absorbance of diluted solutions was measured at 267 nm and a standard plot was drawn using the data obtained. The correlation coefficient was calculated.

Method of preparation of in situ gel

Floating *in situ* gel formulations of ranitidine were prepared using compositions given in Table 3. Take 100 ml beaker, in that beaker take sodium alginate and add with polymer, then mix with 60 ml distilled water, now heat the mixture at 60°C till solution occurs using a heating magnetic stirrer. Take another 100 ml beaker, in this add sodium citrate along with calcium carbonate, then mix with 30 ml distilled water, heat the mixture at 60°C till solution occurs. Now take another beaker, add 5 ml methanol with drug, then three mixtures are mixed at 60°C. After cooling this solution below 40°C, keep the above mixture in mechanical stirring for 30 min, well to get the final preparation which was stored in amber color bottles until further use.

Evaluation Parameters of Oral *In Situ* Gels

Visual appearance and clarity

Visual appearance and clarity were done under fluorescent light against a white and black

Table 3: Formulation of ranitidine oral *in situ* gels

Ingredients (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ranitidine	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Sodium alginate	1	1	1	1	1	1	1	1	1	1	1	1
Calcium chloride (%w/v)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium citrate (mg)	170	170	170	170	170	170	170	170	170	170	170	170
HPMC K15M	0.2	0.4	0.6	0.8	--	--	--	--	--	--	--	--
Xanthan gum	--	--	--	--	0.2	0.4	0.6	0.8	--	--	--	--
HPMC K100M	--	--	--	--	--	--	--	--	0.2	0.4	0.6	0.8
Water (ml)	100	100	100	100	100	100	100	100	100	100	100	100

background for the presence of any particulate matter.

pH measurement

The pH of the prepared *in situ* gelling system after addition of all the ingredients was measured using pH meter.[10,16-26]

Determination of drug content

Accurately, 5 mL of formulation from different batches was measured and transferred to 100 ml volumetric flask. To this, 50–70 ml of 0.1 N HCl was added and sonicated for 30 min. Volume was adjusted to 100 ml. Complete dispersion of contents was ensured visually and the dispersion was filtered using Whatman filter paper. From this solution, 1 ml of sample was withdrawn and diluted to 10 ml with 0.1 N HCl. Contents of ranitidine were measured at maximum absorbance at 230 nm using UV–visible spectrophotometer.

In vitro floating study

The *in vitro* floating study was carried out by introducing 5 ml of formulation into a beaker containing 100 ml of 0.1N HCl (pH 1.2) at 37°C without much disturbance. The time the formulation constantly floated on surface of the dissolution medium (duration of floating) were recorded.

In vitro gelation study

To evaluate the formulations for their *in vitro* gelling capacity, accurately measured 5 ml of formulation was added to 100 ml of 0.1 N hydrochloric acid (HCl, pH 1.2) at 37°C in a beaker with mild agitation that avoids breaking of formed gel.

The *in vitro* gelling capacity was graded in three categories on the basis of stiffness of the formulation.

(+) Gels after few minutes, dispersed rapidly (++) gelation immediate remains for few hours (+++) gelation immediate remains for an extended period.

Measurement of viscosity of in situ gelling system

Viscosity of the dispersion was determined using a Brookfield digital viscometer. The samples (5 ml) were sheared at a rate of 10 rpm/min using spindle number 2 at room temperature. Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30 s.

In vitro release studies

The drug release study was carried out using USP type II paddle-type apparatus at 37 ± 0.5°C and at 50 rpm using 900 ml of 0.1 N HCl (pH 1.2). *In situ* gel equivalent to 25 mg of ranitidine was used for the test. Sample solution (5 ml) was withdrawn at predetermined time intervals, filtered through a 0.45 μm membrane filter, diluted, and suitably analyzed by UV spectrophotometric LAB INDIA 8000 at 230 nm. Fresh dissolution medium was replaced immediately after withdrawal of the test sample to maintain sink condition. The dissolution studies were carried out for a period of 12 h.

Release Kinetics

In the present study, data of the *in vitro* release were fitted to different equations and kinetic models to explain the release kinetics of ranitidine from the *in situ* gels. The kinetic models used were zero-order equation, first order, Higuchi release,

and Korsmeyer–Peppas models. Kinetic Studies: Mathematical models:

Different release kinetic equations (zero-order, first-order, Higuchi's equation, and Korsmeyer–Peppas equation) were applied to interpret the release rate of the drug from matrix systems for the optimized formulation. The best fit with higher correlation (r^2) was calculated.

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation,

$$Qt = Q0 + K0t$$

Where, Qt is the amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution (most times, Q0 = 0), and K0 is the zero-order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time.

Application

It is used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as tablets with low soluble drugs in coated forms, osmotic systems, etc.

First-order model

The first-order equation describes the release from systems where the dissolution rate is dependent on the concentration of the dissolving species.

Release behavior generally follows the following first-order equation: Log C= Log Co-kt/2.303, where C is the amount of drug dissolved at time t, C_o is the amount of drug dissolved at t=0, and k is the first-order rate constant. A graph of log cumulative of % drug remaining versus time yields a straight line.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drugs in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

The first example of a mathematical model aimed to describe drug release from a system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then sustained to different geometrics and porous systems. This model is based on the hypothesis that,

- Initial drug concentration in this is much higher than drug solubility
- Drug diffusion takes place only in one dimension (edge effect must be negligible)
- Drug particles are much smaller than system thickness
- Swelling and dissolution are negligible
- Drug diffusivity is constant and
- Perfect sink conditions are always attained in the release environment.

In a general way, the Higuchi model is simply expressed by the following equation

$$Q = K_H - t^{1/2}$$

Where, K_H is the Higuchi dissolution constant.

The data obtained were plotted as cumulative percentage drug release versus square root of time.

Korsmeyer–Peppas model

Korsmeyer *et al*. (1983) derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer–Peppas model,

$$Mt/M\infty = Kt^n$$

Where, Mt/M∞ is a fraction of drug released at time t, k is the release rate constant, and n is the release exponent. The n value is used to characterize different release for cylindrical-shaped matrices.

In this model, the value of n characterizes the release mechanism of drug as described in Table 4.

Table 4: Drug transport mechanisms suggested based on "*n*" value

S. No.	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	t − 0.5
2	0.45 < *n* = 0.89	Non-Fickian transport	t n − 1
3	0.89	Case II transport	Zero-order release
4	Higher than 0.89	Super case II transport	t n − 1

The results of *in vitro* release profiles obtained for the *in situ* gels formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model)
2. Log cumulative percent drug remaining versus time (first-order kinetic model)
3. Cumulative percent drug released versus square root of time (Higuchi's model)
4. Log cumulative percent drug released versus log time (Korsmeyer–Peppas equation).[27-29]

RESULTS AND DISCUSSION

Saturation Solubility of Ranitidine

Solubility of ranitidine was determined in water, 0.1 N HCl, and 6.8 phosphate buffer and values obtained were noted in Table 5.

Discussion

From the above solubility data, we can say that ranitidine has more solubility in 0.1 N HCl.

Compatibility Study of Ranitidine

Compatibility between the drug and polymers was studied by FT-IR method. Pure ranitidine and optimized formulation were subjected for FT-IR spectroscopic analysis, to as certain any interaction between the drug and polymers used. The position of characteristic peaks of pure ranitidine was compared with those peaks obtained for optimized formulation. These characteristic bands for ranitidine were identifiable and there was no major shift or disappearance in the peak positions. This indicated that the drug was intact and has not reacted with the excipients used in the formulation and hence they are compatible. Hence, it can be concluded that the drug is in free state and can release easily from the polymeric network in the free form [Figures 1-4].

Table 5: Solubility studies of ranitidine in various solvents

Solvents	Solubility (µg/ml)
0.1 N HCl	0.756
Water	0.439
6.8 pH buffer	0.628

Determination of Absorption Maximum (λmax) of Ranitidine

Determination of ranitidine λ-max was done for accurate quantitative assessment of drug dissolution rate [Table 6].

Discussion

Ranitidine Beer's range concentration was found to be in the range of 5–30 µg/ml using 0.1 N HCl buffer as buffer solution. The regression value was closer to 1 indicating the method obeyed Beer-Lamberts' law as it was linear [Figure 5].

Discussion

The drug content was found to being the range of 95–102% for all the formulations indicating uniform distribution of drug [Table 7].

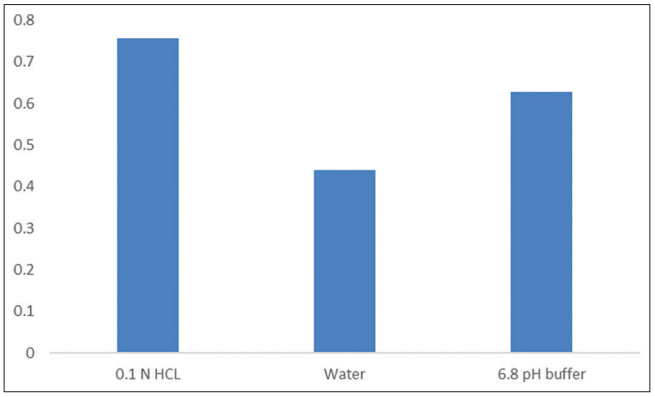


Figure 1: Solubility studies

Table 6: Calibration curve data ranitidine in 0.1 N HCl

Concentration (µg/ml)	Absorbance
0	0
5	0.132
10	0.264
15	0.397
20	0.524
25	0.651
30	0.782

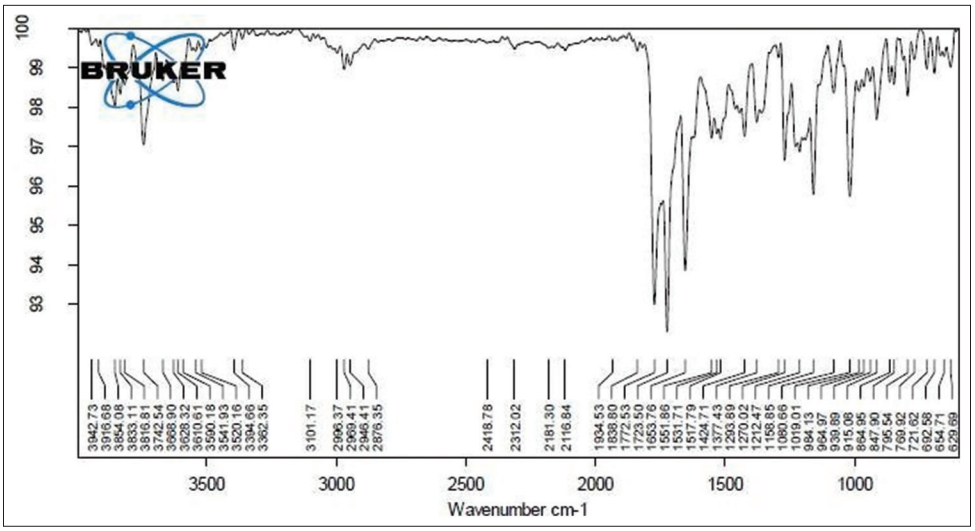


Figure 2: Fourier transform infrared graph of pure ranitidine

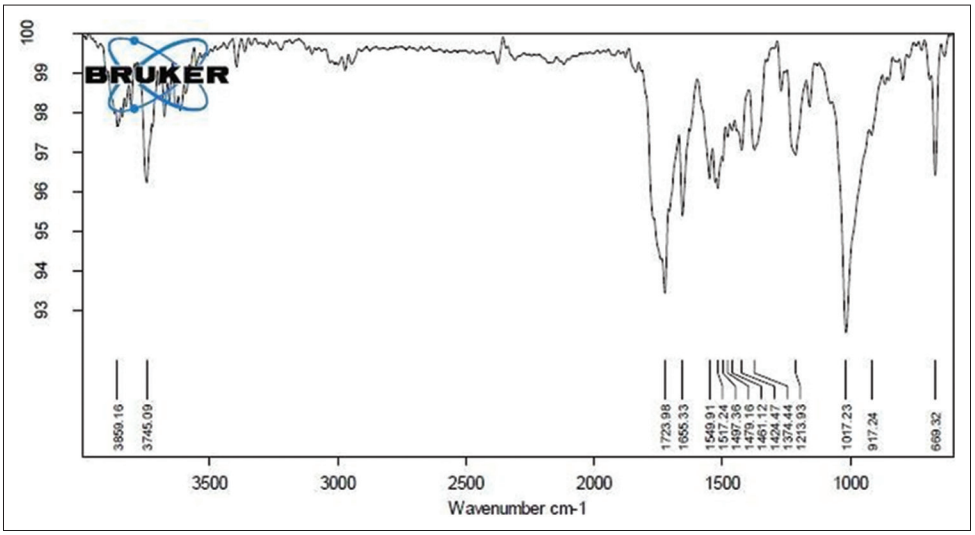


Figure 3: Fourier transform infrared graph of optimized formulation

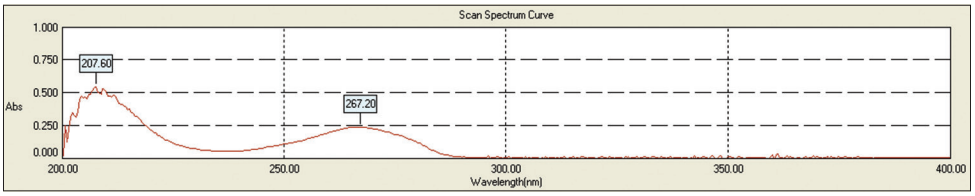


Figure 4: Absorption maximum (λ_{max}) of ranitidine 230 nm

SUMMARY AND CONCLUSION

Ranitidine oral *in situ* gelling systems were prepared using polymers such as xanthan gum, HPMC K15M, HPMC K100M, sodium citrate, calcium carbonate, and sodium alginate. A total of 12 (F1– F12) formulations were prepared and F8 was found to be the best formulation xanthan gum. Drug and polymers were subjected for compatibility study using FTIR studies, which revealed that there was no interaction between drug and polymers. The prepared formulations were evaluated for drug content, floating lag time, total floating time, viscosity, gelling nature, visual appearance, and *in vitro* release studies which were also performed. The *in vitro* release studies of all the formulations among them F8 formulation containing xanthan gum show drug release of 98.08% by the end of 12 h.

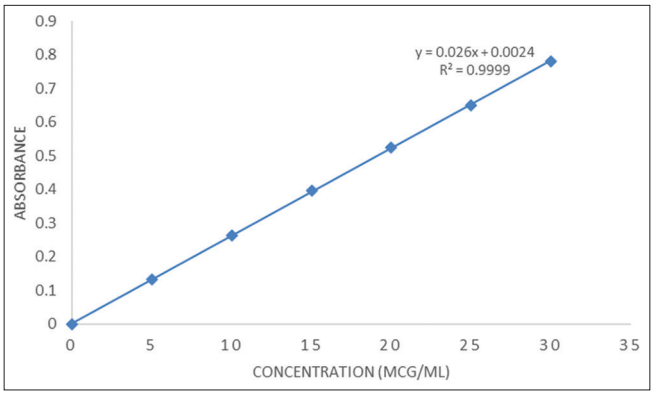


Figure 5: Calibration curve of ranitidine in 0.1 N HCl

Table 7: Percentage drug content of ranitidine *in situ* gels

Formulation code	Drug content (%)
F1	97.52
F2	98.26
F3	96.15
F4	99.42
F5	101.26
F6	98.04
F7	97.36
F8	99.04
F9	98.46
F10	95.48
F11	97.34
F12	96.82

The release kinetics of the optimized formulation was best fitted into Higuchi model ($R^2 = 0.973$) and showed zero-order ($R^2 = 0.985$) drug release with super case II transport mechanism. From the above experimental results, it can be concluded that ranitidine was chosen as the model candidate for the development of oral *in situ* gel, since they possess near ideal characteristics that these drugs must have formulating sustained drug delivery system.

The results of study demonstrate that xanthan gum was suitable to develop sustained release oral *in situ* gels.

REFERENCES

1. Rao GU, Murari P. Buoyant sustained release drug delivery systems current potentials advancements and role of polymers: A review. Int J Clin Pract 2012;2:1-7.
2. Rabadia N, Tiwari A, Patel G, Virani V. The floating drug delivery system and its impact on calcium channel blocker: A review article. Int J Pharm Res Dev 2011;3:107-31.
3. Jain NK. Progress in Controlled and Novel Drug Delivery Systems. New Delhi: CBS Publishers; 2003. p. 76-97.
4. Babu VB, Khar RK. *In-vitro* and *in-vivo* studies of sustained release floating dosage forms containing salbutamol sulphate. Pharmazie 1990;45:268-70.
5. Kikani HN. A Thesis on Floating Drug Delivery System. Patan: The North Gujarat University; 2001. p. 11-2.
6. Cohen S, Lobel E, Trevgoda A, Peled Y. A novel *in-situ* forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J Control Release 1997;44:201-8.
7. Srividya B, Cardoza RM, Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered *in-situ* gelling system. J Control Release 2001;73:205-11.
8. Miyazaki S, Kawasaki N, Endo K, Attwood D. Oral sustained delivery of theophylline from thermally reversible xyloglucan gels in rabbits. J Pharm Pharmacol 2001;53:1185-91.
9. Miyazaki S, SuzukiS, Kawasaki N, Endo K, Takahashi A, Attwood D. *In-situ* gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int J Pharm 2001;229:235.
10. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. Int J Pharm Technol Res 2009;1:623-33.
11. Bhardwaj L, Sharma PK, Malviya R. A short review on gastro retentive formulations for stomach specific drug delivery: Special emphasis on floating *in-situ* gel systems. Afr J Basic Appl Sci 2011;3:300-12.
12. Tripathi P, Ubaidulla U, Khar RK, Vishwavibhuti V. Floating drug delivery system. Int J Res Dev Pharm Life Sci 2012;1:1-10.
13. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics a Treatise. New Delhi: Vallabh Prakashan; 2008. p. 337.
14. Patel GM, Patel HR, Patel M. Floating Drug Delivery System: An Innovative Approach to Prolong Gastric Retention. Pharm Rev 2007;5:315.
15. Nayak AK, Maji R, Das B. Gastro retentive drug delivery systems: A review. Asian J Pharm Clin Res 2010;3:2-10.
16. Hardenia SS, Jain A, Patel R, kaushal A. Floating drug delivery systems: A review. Asian J Pharm Life Sci 2011;1:284-93.
17. Harrigan RM. Drug Delivery Device for Preventing Contact of Undissolved Drug with the Stomach Lining. United States: US Patent; 1977. p. 4055178.
18. Dhiman S, Singh TG, Sood S. Gastro retentive: A controlled release drug delivery system. Asian J Pharm Clin Res 2011;4:5-13.
19. Mishra J, Dash AK. Recent advances in gastro retentive

drug delivery system: A review. Mintage J Pharm Med Sci 2013;2:25-7.
20. Mishra A, Gupta P. Gastro retentive drug delivery system: A review. Int J Drug Dev Res 2012;4:28-39.
21. Swetha S, Allena RT, Gowda DV. A comprehensive review on gastro retentive drug delivery systems. Int J Pharm Biomed Res 2012;3:1285-93.
22. Yeole PG, Khan S, Patel VF. Floating drug delivery system: NEDDS and development. Indian J Pharm Sci 2005;67:265-72.
23. Chandel A, Chauhan K, Parashar B, Kumar H, Arora S. Floating drug delivery systems: A better approach. Int Curr Pharm J 2012;1:110-8.
24. Gopalakrishnan S, Chenthilnathan A. Floating drug delivery system: A review. J Pharm Sci Technol 2011;3:548-9.
25. Vedha H, Chaudhary J. The recent developments on gastric floating drug delivery system: An overview. J Pharm Technol Res 2010;2:524-34.
26. Arunachalam A, Kishan GK. Floating drug delivery system: A review. Int J Res Pharm Sci 2011;2:76-83.
27. Wilson CG, Washington N. The stomach: Its role in oral drug delivery. In: Rubinstein MH, editor. Physiological Pharmacetical: Biological Barriers to Drug Absorption. Chichester, UK: Ellis Horwood; 1989. p. 47-70.
28. Desai S, Bolton S. A floating controlled release drug delivery system: *In vitro-in vivo* evaluation. Pharm Res 1993;10:1321-25.
29. Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63:235-59.