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Developement and Characterization of Floating Tablets of Nizatidine for Peptic Ulcer

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Authors' contributions

This work was carried out in collaboration among all authors. Authors Ravindra B. Kumbhar and MS designed the study, performed the statistical analysis, wrote the protocol. Authors STG and SGK wrote the first draft of the manuscript. Author PJS and managed the analyses of the study. Author Rushikesh B. Katakar managed the literature search and above all mentioned authors read and approved the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The objective of the present research work is to develop an ideal floating drug delivery system of nizatidine to increase the gastric residence time in stomach. To overcome the short half life and lower bioavailability of drug in tablet form we developed the drug in the form of effervescent floating tablet containing HPMC K100 and sodium bicarbonate by direct compression methodology. The prepared effervescent floating tablets were characterized by thickness, weight variation, hardness, friability, drug content uniformity, *in vitro* buoyancy time, swelling test, *in vitro* study and stability study and found that all formulations showed satisfactory results with enhanced half life and bioavailability that is among all formulations F1 formulation exhibited good drug release of 95.03%

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& has shown floating lag time 55 sec. Finally, it was concluded that formulations of nizatidine floating tablet were successfully prepared and found prolonged drug release for 12 hours thereby getting enhanced bioavailability, patient compliance by reducing dose frequency and gastric residence time.

Keywords: Hardness; friability; duodenal ulcer; bioavailability.

1. INTRODUCTION

A peptic ulcer is a break in the inner lining of the esophagus, stomach, or duodenum. A peptic ulcer of the stomach is called a gastric ulcer. Peptic ulcer leads to decrease the p^H and mainly acetylcholine and histamine is responsible for development of peptic ulcer (Because of sensation of food). Peptic ulcers can be broadly classified into gastric ulcers and duodenal ulcers. Normally the stomach wall is protected by the mucosa against irritation of gastric acid. When the mucosa is damaged or when the stomach produces so much gastric acid that the protective lining is eroded with subsequent inflammation or necrosis, a local ulcer will develop. Peptic ulcer is usually caused by pepsin and acid a digestive stomach enzyme. The commonest symptom of peptic ulcers is intermittent abdominal pains, especially in the middle of the night.

1.1 Causes of Peptic Ulcers Are

1. Congenital hyperacidity.
2. Mental strain and emotional stress that make the nervous system stimulate the excessive production of gastric acid.
3. Undesirable eating habits, irregular meals or overeating.
4. Smoking and excessive alcohol are direct causes of increased morbidity.
5. Drugs such as aspirin and painkillers for rheumatism irritate and damage gastric mucosa [1].

Nizatidine is used for the treatment of acid-reflux disorders, peptic ulcer disease, active benign gastric ulcer and active duodenal ulcer. Nizatidine is H_2blocker Antihistamine. Nizatidine is a competitive, reversible inhibitor of histamine at the H_2-receptors, particularly those in the gastric parietal cells. By inhibiting the action of histamine on stomach cells, Nizatidine reduces stomach acid production. Nizatidine had no demonstrable anti androgenic action [2]. It has been demonstrated that treatment with a reduced dose of Nizatidine is effective as maintenance therapy following healing of active duodenal ulcers. Nizatidine was susceptible to metabolism by colonic bacteria, which in turn has ramifications for drug delivery and absorption. Thus, it is logically way to improve the therapeutic efficacy of the drug if the gastric residence time of the dosage form is increased at the absorption site [3].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract [4]. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability reduces drug waste and improves solubility of drugs that are less soluble in high pH environment. Gastric retention to provide new therapeutic possibilities and substantial benefits from patients [5]. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents, that delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs [6].

So, to overcome all problems of nizatidine, the dosage form of drug has been developed in the form of effervescent floating tablet, to improve the bioavailability and gastric retention time of drug.

2. MATERIALS AND METHODS

2.1 Materials

Nizatidine was a gift sample from Watson Pharma, Goa. Polymer HPMC K100 were recieved as gift sample from Hemedia Lab., Mumbai. Talc, Magnesium Stearate, Sodium bicarbonate, PVP K-30 is from Ozone International, Mumbai.

2.2 Methodology

2.2.1 Compatibility studies

2.2.1.1 Fourier transform infrared Spectroscopy (FTIR) [7]

In development of formulation drug and polymer are in close contact with each other and stability of developed formulations depends on these interactions. Proper care was taken while selecting the suitable polymers for formulations. Drug sample or polymer sample mixed with potassium bromide and FTIR spectra was taken. The spectrum of drug was compared with combined spectra of polymer and drug. Shifting or disappearance of drug peak was studied.

2.2.1.2 Differential Scanning Calorimetry (DSC) [8]

Thermo grams of drug, mixture of drug and polymers were recorded using a differential scanning calorimeter and were compared. 5 mg sample was sealed in aluminium pans which are flat bottomed and heated at temperature range of 100-300°C at a rate of 10°k/min using alumina as a reference standard.

2.2.2 Preparation of nizatidine floating tablet [9]

The formulation chart for formulating floating tablet is shown in following table. Floating tablet of nizatidine is prepared by direct compression method using 13.2 mm punch and die. Magnesium stearate, talc were added to the above blend as flow promoters. In all the formulations, the amount of nizatidine was kept constant at 150 mg and PVP K30 used as binder and thickener alos different polymers like HPMC K100M were used in different quantity with respect to drug.

3. EVALUATION OF FLOATING TABLET

3.1 Hardness [10]

The hardness of the 5 tablet was determined by using dr schleuniger hardness tester. And expressed in Kg / cm^2.

3.2 Weight Variation [11]

Twenty tablets were used randomly and weighed individually to check for weight variation. According to USP limit for weight variation is 130-324 mg ± 7.5% and more than 324 mg ± 5%.

Percent deviation = (Individual weight – Average weight / Average weight) X 100

3.3 Thickness [10]

The thickness of 05 the tablets was measured by varnier calliper scale-AAS Aerospance manual vernier caliper. It is expressed in mm.

3.4 Friability [12]

Friability of the tablets was determined by using Rolex friability tester. The chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. 6.5 gram sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) it was calculated by the following formula.

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

Table 1. Formulation table of Nizatidine loaded floating tablet [7]

Formulation	Drug (mg)	HPMC K100	Sodium bicarbonate (mg)	PVP K 30 (mg)	Magnesium stearate (mg)	Talc (mg)	Diluent mg
F1	150	100	150	100	20	20	00
F2	150	100	75	100	20	20	75
F3	150	100	50	100	20	20	100
F4	150	150	100	100	20	20	00
F5	150	75	100	100	20	20	75
F6	150	50	100	100	20	20	100

3.5 Drug Content [11]

The drug content was carried out by weighing five tablets and their average weight was calculated. These tablets were triturated to get fine powder. The weighed powder equivalent to 100 mg of nizatidine and dissolved in a 100 ml volumetric flask containing 50 ml of 0.1 N HCL and volume was made up to 100 ml with same solvent. The volumetric flask was shaken using sonicator for 1 hr. and after suitable dilution with HCl the drug content was determined using UV-spectrophotometer (Shimadzu UV-1800, Tokyo) at 314 nm.

3.6 Swelling Studies [13]

The extent of swelling was measured in terms percent of weight gained by the tablet. One tablet from each formulation was weighed and kept in Petri dish containing 50 ml of 0.1 N HCl. At the end of specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed. The percent swelling index of tablet was calculated by using following formula:

$$\text{Swelling Index (\%)} = \frac{M_t - M_0}{M_0} \times 100$$

Where, M_t – weight of tablets at time't'; M_0 – weight of tablets at time '0'

3.7 Buoyancy Lag Time Determination and Total Floating Time [14]

The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observation.

3.8 *In vitro* Dissolution Study [14]

In vitro drug release studies for the prepared floating tablets were conducted for a period of 24 hours using USP XXIV type-II (Paddle) dissolution test apparatus (Electro lab, Mumbai.) at 37±0.5^{o}C and 75 rpm speed using 900 ml of 0.1N HCL as dissolution medium. At predetermined interval of time, 10 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the sink condition. After filtration and appropriate dilution, the samples were analyzed for nizatidine by UV spectrophotometer at 314 nm. The amount of drug present in the samples was calculated.

Release kinetics was studied with different models such as Zero order model, First Order model, Pappas Model and Higuchi model with help PRISM 5.0 Software.

3.9 Stability Studies [15]

Stability is defined as the capability of particular drug or dosage form in a specific container to persist with its physical, chemical, therapeutic and toxicological specifications. Stability studies carried out at 4°±1°C, 25°±2°C and 60% RH±5% RH and at 37°±2°C and 65% RH±5% RH using Stability chamber-Hally Instruments Mumbai.

The purpose of stability testing is to make available information on how the quality of a drug product varies with time under the influence of variety of environmental factors such as temperature, humidity and light, and to establish a shelf life for the drug product at recommended storage conditions.

4. RESULTS AND DISCUSSION

4.1 Preformulation Studies

4.1.1 Description

The received sample of nizatidine was found to bewhite, odourless, amphorphous powder.

4.1.2 Melting point determination

The melting point of nizatidine in literature is 130°-132°C, after estimation it was found to be 126°-128°C which indicates purity of the drug sample.

4.1.3 Solubility determination

The received sample of nizatidine was found to be freely soluble in water and sparingly soluble in acetic acid and ethanol.

4.2 Identification of Drug

The IR spectral analysis identifies the characteristic functions present in substances. To identify given drug sample fourier transform infrared spectroscopy (FTIR) spectra of drug sample was recorded and was compared with standard reference spectra of drug from literature. For obtained sample of nizatidine

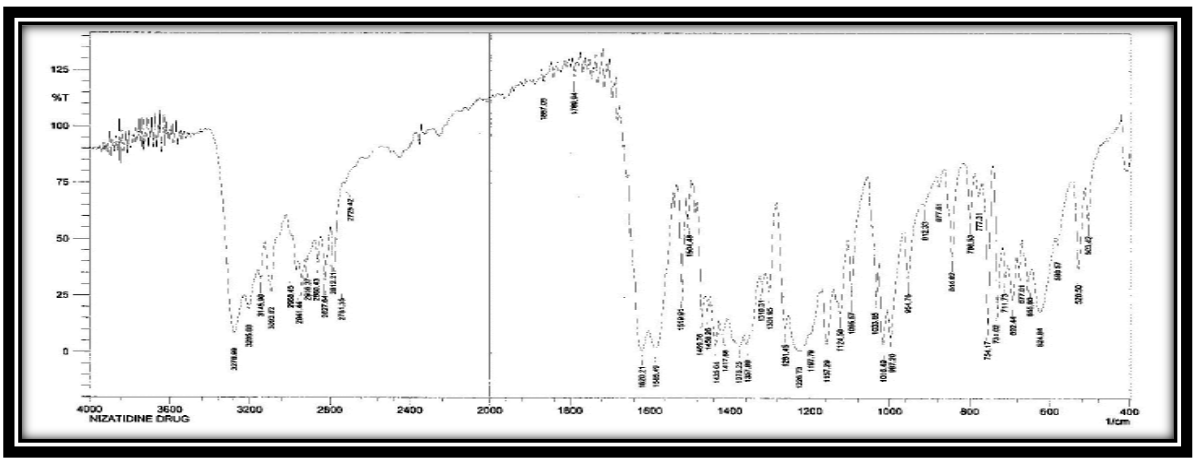


Fig. 1. FTIR spectra of pure Nizatidine

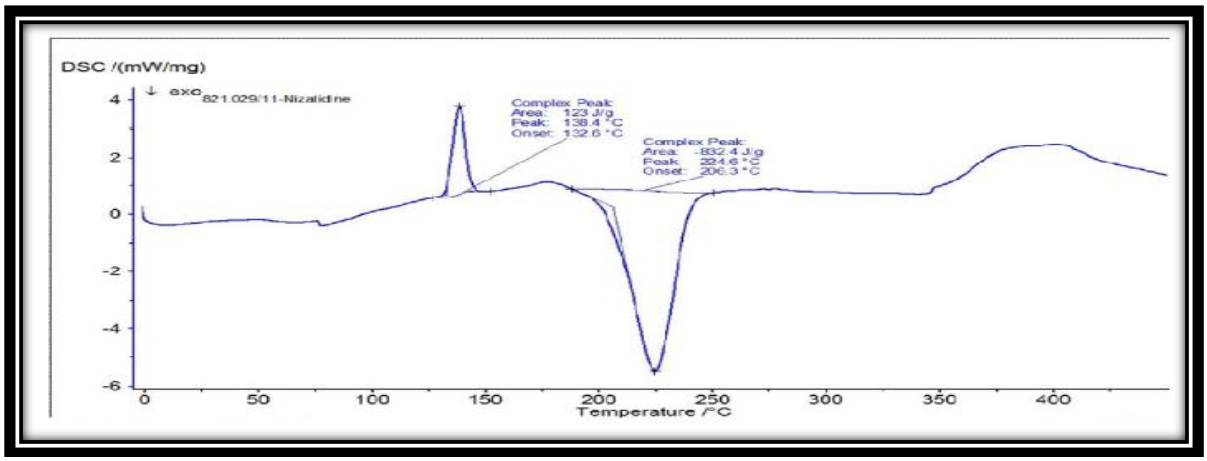


Fig. 2. DSC of pure Nizatidine

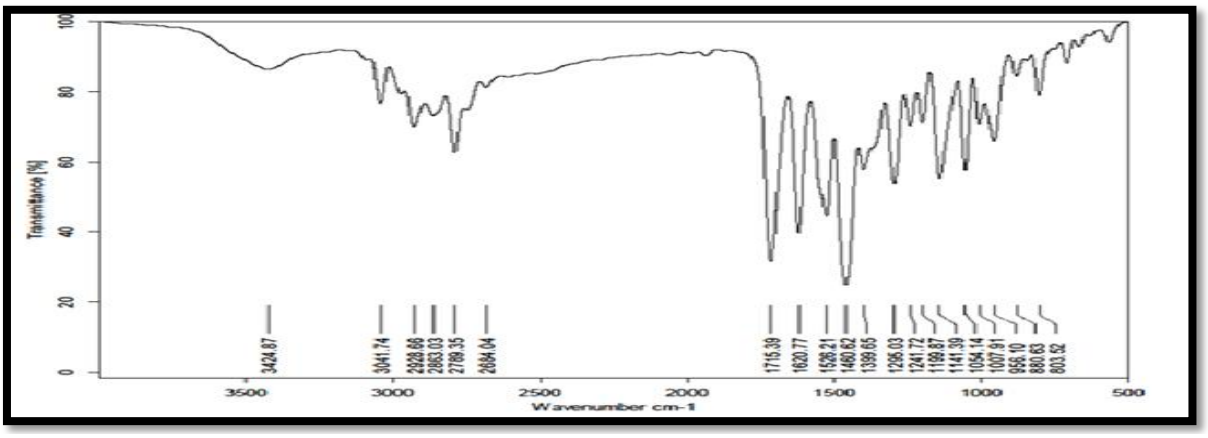


Fig. 3. FT-IR spectra of physical mixture of Nizatidine, sodium bicarbonate, Talc,PVP K 30, HPMC K100 and magnesium stearate

fourier transform infrared spectroscopy (FTIR) study was counducted. After comparing fourier transform infrared spectroscopy (FTIR) peaks of nizatidine with standard, it is confirmed that the obtained sample is nizatidine.

4.3 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) gives information about transition temperature. The

DSC technique provides qualitative physicochemical status of drug which is reported in endothermic or exothermic process. The resulted thermal transition includes melting, decomposition and out gassing for change in heat capacity.

4.4 Drug-polymer Compatibility Studies

Compatibility studies of nizatidine with polymers were carried out prior to the formulation of floating tablet. All the characteristic peaks of nizatidine were present in spectra at respective wavelengths. It indicate compatibility between drug and polymers. It shows that there was no significant change in the chemical integrity of the drug.

5. EVALUATION OF FLOATING TABLET

5.1 Compatibility Study

FTIR study was conducted between pure nizatidine and its physical mixture with its excipients was recorded and compared. All the characteristic peaks of nizatidine were retained in the spectra of drug and physical mixture indicating no chemical interreaction between drug and excipients are compatible. IR spectra of drug and polymers were obtained shown in Fig. 3 and hence the results of fourier transform infrared spectroscopy (FTIR) analysis showed that the integrity of drug was unaffected when developed in floating tablet formulation. Fourier transform infrared spectroscopy (FTIR) results indicates compatibility between drug, polymer and processing conditions.

5.2 Differential Scanning Calorimetry (DSC)

The DSC patterns of pure nizatidine showed a sharp endotherm at 138°C corresponding to its melting point and physical mixture was found to be 174°C which shows a slight change in attributed indicating no chemical interaction of drug with excipients. The DSC studies indicates that the integrity of nizatidine is unaffected in the presence of excipients.

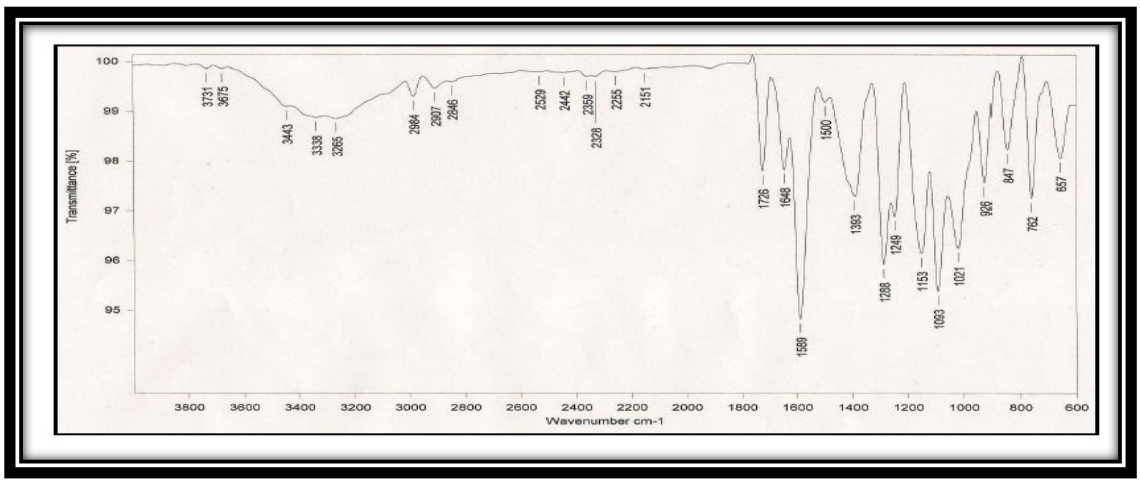


Fig. 4. FT-IR Spectra of formulation of Nizatidine

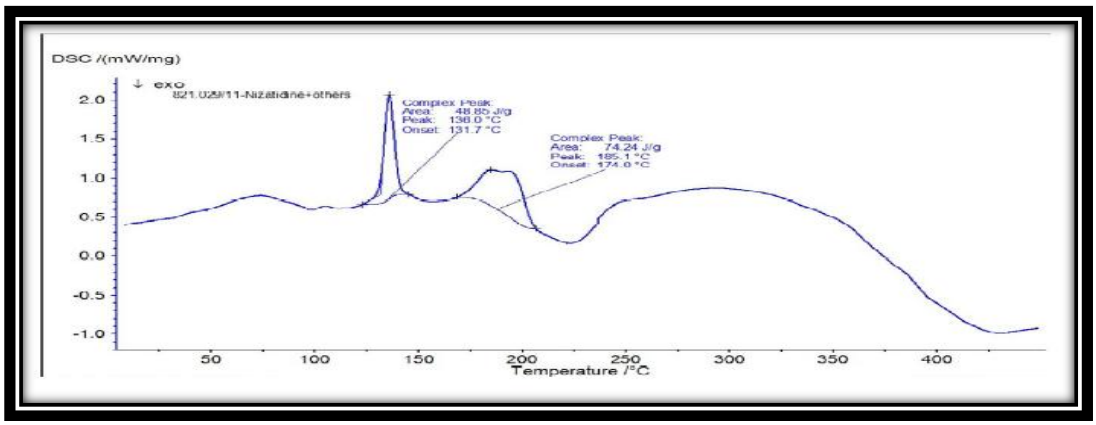


Fig. 5. DSC of Nizatidine formulation

Table 2. Physico-chemical evaluation of Nizatidine floating tablets

Code	Hardness Kg/cm^2	Thickness mm	Friability %	Drug content %	Weight variation%
F 1	4 ± 0.42	2.5 ± 0.12	0.55 ± 0.16	96.37 ± 0.68	1.38 ± 0.57
F 2	4.5 ± 0.24	2.5 ± 0.08	0.91 ± 0.12	97.05 ± 0.41	1.28 ± 0.36
F 3	4.4 ± 0.46	2.5 ± 0.06	0.78 ± 0.13	98.83 ± 0.26	1.46 ± 0.57
F 4	4.5 ± 0.51	2.1 ± 0.17	0.91 ± 0.08	97.74 ± 0.24	1.55 ± 0.39
F 5	4.5 ± 0.26	2.2 ± 0.23	0.77 ± 0.09	97.57 ± 0.41	1.43 ± 0.17
F 6	4.3 ± 0.39	2.4 ± 0.06	0.93 ± 0.06	98.58 0.26	1.89 ± 0.16

**All values are expressed as mean ± SD. n=3*

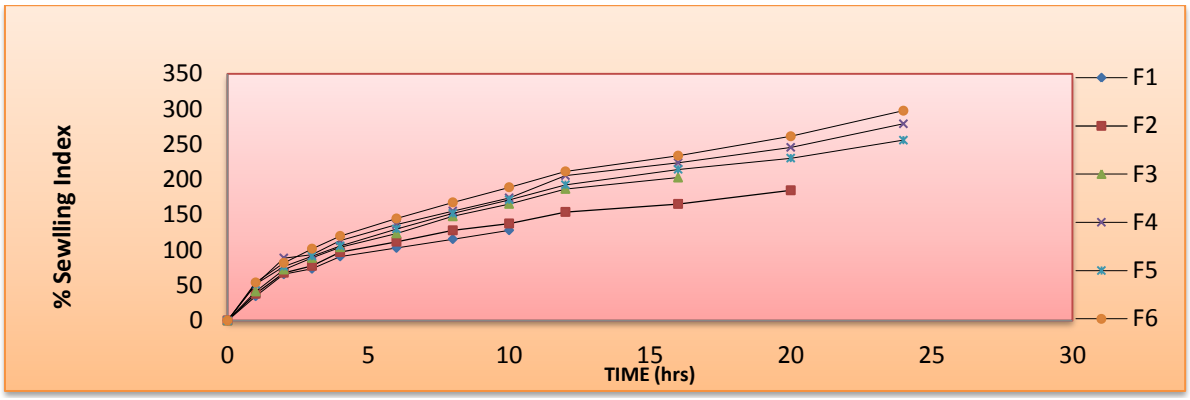


Fig. 6. Comparative swelling study of all formulations of floating tablet of Nizatidine

Table 3. Floating behavior of different floating tablets of Nizatidine in 0.1 N HCl

Sr. no.	Formulation code	Floating lag time (sec)	Total floating time (hrs)
1	F 1	55	18
2	F 2	50	19
3	F 3	59	21
4	F 4	80	18
5	F 5	54	17
6	F 6	58	15

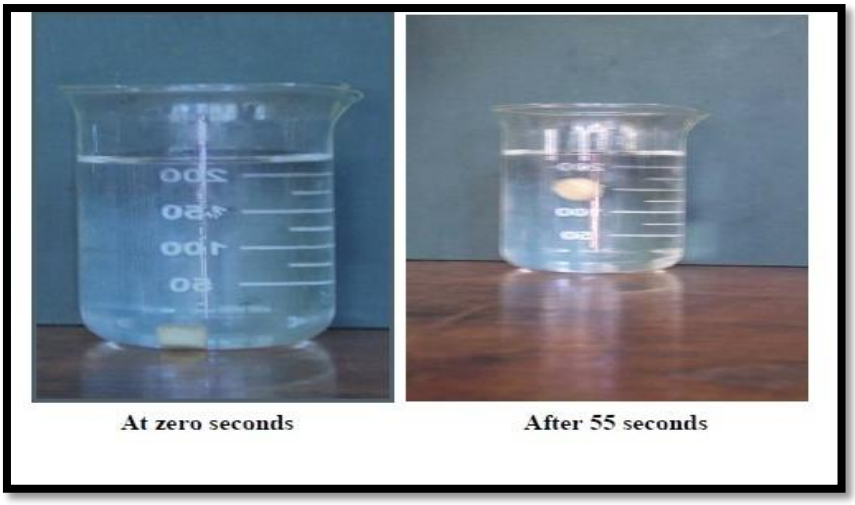


Fig. 7. Photographs indicating the floating lag time of optimized formulation

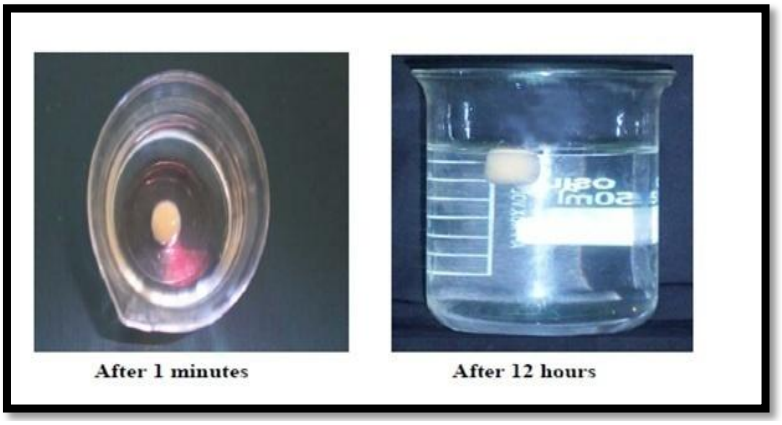


Fig. 7a. Photographs indicating the floating lag time of optimized formulation

5.3 Physico-chemical Evaluation of Nizatidine Floating Tablets

The physicochemical evaluation revealed highest hardness in formulation F2, F4 and F5 whereas highest weight variation found in F6. The drug content found to be minimally significant between the formulations.

5.4 Swelling Study

From the results of swelling study Formulation F6 having highest and Formulation F1 having lowest swelling index.

5.5 Floating Study

From floating study indicates formulation F3 has highest floating time and formulation F6 has lowest floating time results shown in Table 3.

5.6 *In vitro* Dissolution Study

***In vitro* Drug Release of floating tablet of nizatidine using USP type II (paddle type) dissolution test apparatus:** *In vitro* release profile is an important tool that predicts in advance how a drug will behave *in vivo*. Release studies are required for predicting the reproducibility of rate and duration of drug release. *In vitro* drug release studies of all the floating tablet formulations were carried out in 0.1 N HCl using USP type II (paddle type) dissolution test apparatus. The study was performed for 12 hrs, and cumulative drug release was calculated at different time intervals. The formulations F1, F2, F3, F4, F5 and F 6 containing have shown the drug release of 95.03%, 94.02%, 97.21%, 92.66%, 95.01% and 98.21% respectivelyafter 12 hrs.The data were plotted for cumulative percentage drug release vs time in as shown in Fig. 8 and Table 4.

5.7 Stability Studies

From the results of stability studies indicates that selected formulation is stable and no impact of variation in temperature and RH on drug release pattern of formulation results shown in Table 5 Fig. 9 and Fig. 10.

Table 4. *In vitro* dissolution study of different floating tablets of Nizatidine

Time (hrs)	% CDR					
	F 1	F 2	F 3	F 4	F 5	F 6
0	0	0	0	0	0	0
1	12.74	11.99	10.01	12.74	16.1	13.12
2	22.25	21.18	19.12	22.54	21.12	21.16
3	29.48	28.18	27.24	30.12	33.32	30.77
4	35.57	34.4	35.4	35.46	36.44	40.04
5	43.04	39.04	39.1	40.04	48.01	50.13
6	51.50	40.09	47.12	51.09	53.45	55.84
7	60.64	49.19	58.33	61.11	62.09	62.16
8	73.07	54.13	68.14	71.09	71.09	71.19
9	80.11	65.03	83.43	78.83	77.78	83.33
10	87.09	75.11	93.87	87.19	82.39	90.06
11	90.03	83.16	95.12	87.96	86.96	94.22
12	95.3	93.41	97.21	92.66	95.01	98.21

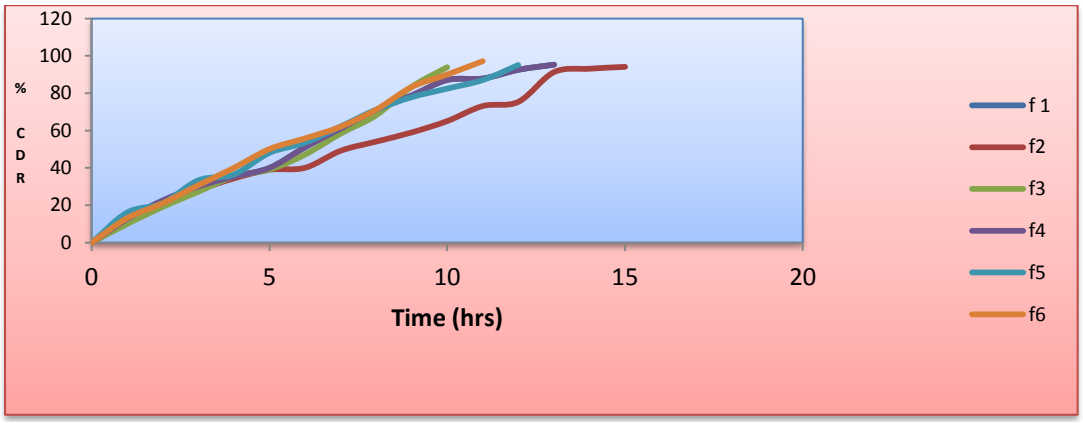


Fig. 8. Comparative *in-vitro* release of Nizatidine floating tablet from all formulation

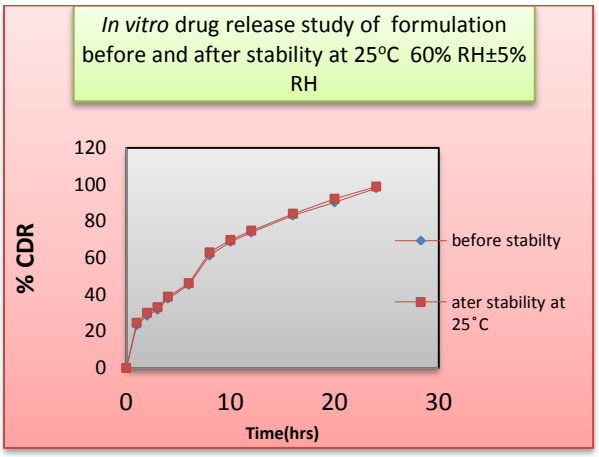


Fig. 9. *In vitro* drug release of formulation before and after stability at 25°C

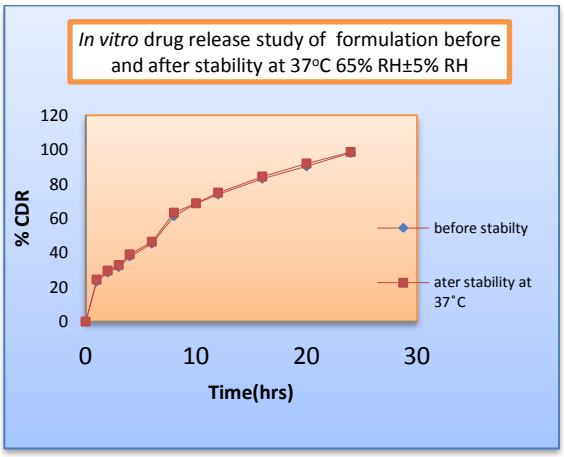


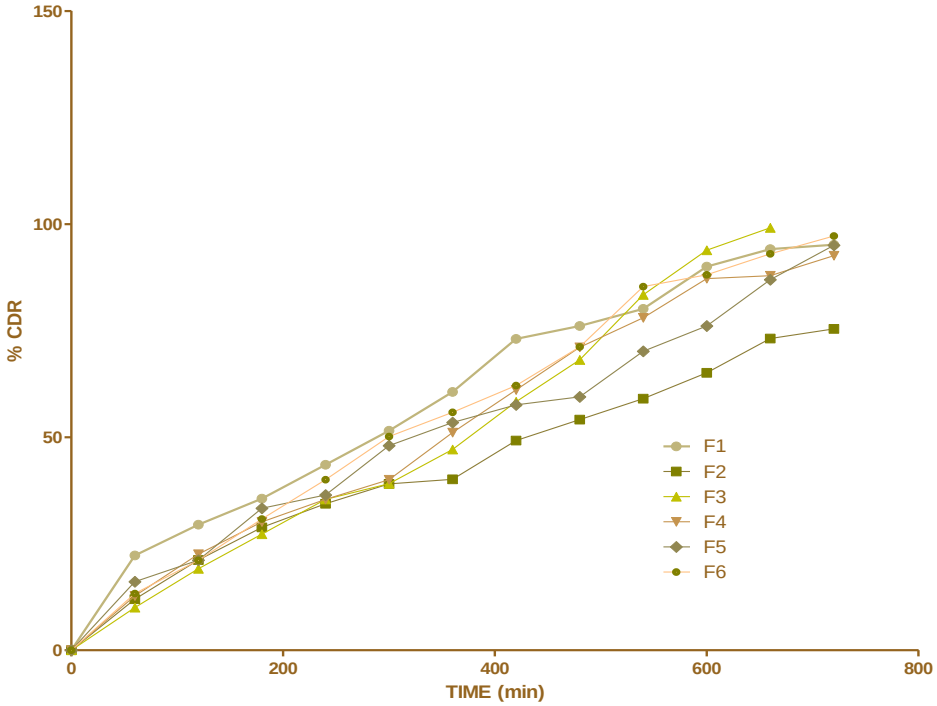
Fig. 10. *In vitro* drug release of formulation before and after stability at 37°C

Table 5. Stability studies – *in vitro* release studies of selected formulation F 1

Time	Before stability studies	%CDR at 4°±1°C	%CDR at 25°±2°C and 60% RH±5% RH	%CDR at 37°±2°C and 65% RH±5% RH
1	23.37	24.17	24.67	24.44
2	28.54	29.04	30.14	29.64
3	31.78	32.48	33.17	32.88
4	37.91	38.11	38.91	39.12
6	45.36	45.89	46.26	46.43
8	61.35	62.25	63.05	63.35
10	68.80	69.28	69.80	68.80
12	73.90	74.60	74.90	75.00
16	83.14	83.94	84.14	84.37
20	90.31	91.51	92.31	91.97
24	98.10	98.54	98.92	98.69

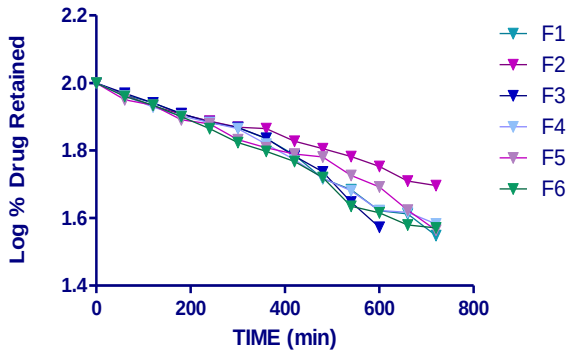
5.8 Release Kinetic Data for All Formulations

Higuchi's Classical Diffusion model describes the release from system where the rate of drug release is related to the rate of diffusion. The data obtained from *in vitro* drug release studies were fitted to zero-order, first-order, Higuchi's equations and Peppas model and it is represented in Figs. 11, 12, 13 and 14



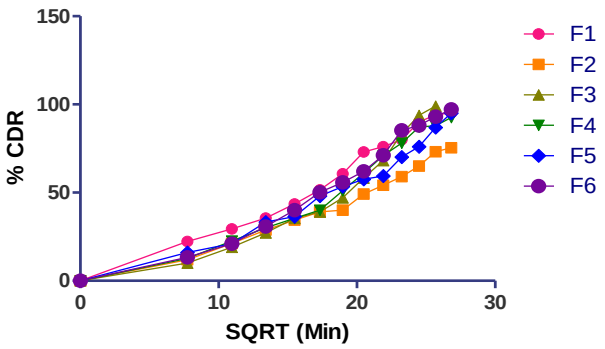
(First order kinetic model)

Fig. 11. % Cumulative drug release V/S. time. drug remaining v/s. time



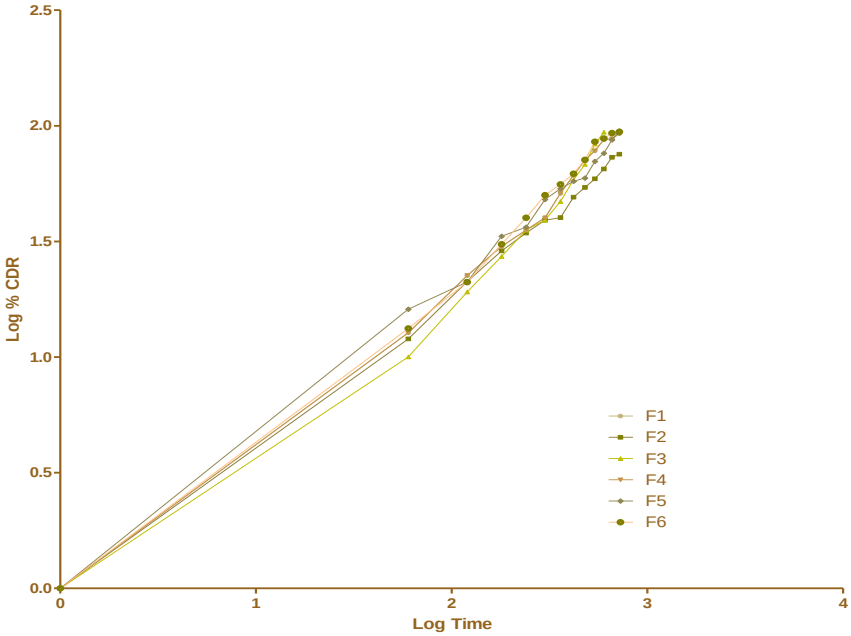
(Zero order kinetic model)

Fig. 12. Log % cumulative



(Higuchi's Classical diffusion model)

Fig. 13. % Cumulative drug released v/s. square root of time



(Peppa's model)

Fig. 14. Cumulative drug release v/s. Log time

respectively. After performing statistical analysis done for release study data the coefficient of correlation was found to favour for first order type of release.

From the results it seen that the drug release mechanism from the formulation was found to be follows first order kinetics. The dissolution process is purely defined as the total concentration of the drug is present in developed formulation indicating the total drug payload plays an important role in contributory factor in the release.

6. CONCLUSION

Finally, it was concluded that formulations of nizatidine floating tablet was successfully prepared and it may improve the drug bioavailability, that remains to be demonstrated**.** Hence, floating tablets of nizatidine containing HPMC K100 and sodium bicarbonate can be effectively increasing residence time showed promising results.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Satoskar RS, Bhandarkar SD, Ainapure SS. Pharmacology and Pharmaco-therapeutics. S. Chand. 2003;6(1):602-609.
2. Morton DM. Pharmacology and toxicology. Scandinavian Journal of Gastroenterology. 1987;22(136):1–8.
3. Mark G. Papich DVM, MS, DACVCP, Nizatidine Saunders Handbook of Veterinary Drugs (Fourth Edition); 2016.
4. Ujjwala Nautiyal, Meenashki Jassal. A review gastroretentive durg delivery system. IJPBR. 2015;3(1):82-92.

5. Devakant Sharma, Anjali Sharma. Gastroretantive drug delivery system: A mini review. Asian Pac. J. Health Science 2014;1(2):80-89.
6. Barar FSK. Essential of Pharmaco-theraputics. S. Chand. 2006;495-507.
7. Imaankhan Bhaishaikh: Floating microsponges as gastro retentive drug delivery system containing lafutidine to treat gastric ulcer. Acta Scientific Pharmaceutical Sciences. 2019;32:3-12.
8. Sunil T. Galatage, Killedar SG. Development and characterization of micro sponge of Amphotercin B for topical drug delivery RJPBCS. 2019;10:1288-1300.
9. Saritha D, Satish D. Formulaiton and evaluation of gastroretentive floating tablets of Domperidone maleate. Journal of Applied Pharmaceutical Sciences. 2012;2 (3):68-73.
10. Gupta AK. Introduction to pharmaceutics. 2nd Ed. New Delhi: CBS Publications. 1993;1:270.
11. Lakade SH, Bhalekar MR. Formulation and evaluation of sustained release matrix tablets of anti-anginal drug, influence of combination of hydrophobic and hydrophilic matrix former. Research Journal Pharmacy and Technology. 2008; 1(4):410-13.
12. Banker GS, Anderson NR. Tablets In: Lachman N, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Bombay: Varghese Publication House. 1987;286-300.
13. Nerurkar J, Jun HW, Prince JC, Park MO. Controlled release matrix tablets of ibuprofen using cellulose ethers and carrageenans: Effect of formulation factors on dissolution rate. European Journal of Pharmacy Biopharmaceutics. 2005;61:56-68.
14. Puneeth KP, Kavitha K, Tamizh MT. Development and evaluation of rosiglitazone maleate floating tablets. International Journal of Applied Pharmaceutical Sciences. 2010;2(2): 6-10.
15. Available:http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1150.html evaluation of a multiple-unit floating drug delivery system.

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