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PECTIN AS A RELEASE RETARDANT IN GAS GENERATING FLOATABLE SYSTEM OF NIZATIDINE - PREPARATION AND EVALUATION

Kiran Orugonda, Vasavi Devireddy and Srinivas Reddy Devireddy*,

Department of Pharmaceutics & Industrial pharmacy, Vaageswari College of Pharmacy, Ramakrishna colony, Karimnagar, 505481 India.

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ABSTRACT

Nizatidine hydrochloride is a histamine (H_2) receptor antagonist. It is widely prescribed in the treatment of gastric ulcer and duodenal ulcers. It has short biological half-life and susceptible to metabolize by colonic bacteria. The current investigation concerns formulation of nizatidine gastro retentive tablets by effervescent technique to increase the gastric retention time and control the drug release up to 12 h and also to improve bioavailability. In this attempt, the concentration of gas generating agent was optimized to 10%w/w of total tablet weight. Influence of pectin as release retardant was compared with other release retarding agents including xanthan gum, pectin, sodium alginate and HPMC K100M. Each polymer was used in the concentration range of 20% to 40% to achieve controlled drug release. Prepared tablets were characterized for drug content, density, swelling and *In-vitro* release. *In vitro* drug release studies reveals that formulations contained pectin shown better drug release than other polymers. Drug release kinetics of all formulations was shown that they follow non Fickian diffusion mechanism to release the drug from prepared matrix tablets. *In-vivo* X-ray Radiographic images were taken at different time intervals to describe the floatability of the dosage form.

INTRODUCTION:

Oral route of administration is most convenient way of drug delivery in terms of better patent compliance as compared with other route of administration and more than 60% of marketed pharmaceutical products are administered through oral route (1). Most of orally administered sustained release dosage forms cross the gastrointestinal tract before releases the drug from dosage form due to faster gastric emptying. The real dispute in designing of oral controlled release dosage forms is not just to retard the drug release for prolonged period of time also retain the dosage form in gastrointestinal tract until the drug is completely release from dosage forms (2). In order to overcome this kind of adversities, a significant interest is attained to develop gastro retentive dosage forms from past few years (3). Gastro retentive dosage forms can able to prolong the gastric residence time and avoid the problem of short gastric residence time by buoyant the dosage form in stomach for prolonged time period (4). Gastric ulcers and duodenal ulcers are most commonly acquired acid related disorders in human beings. Current days most of the patients are suffering from these diseases due to increased gastric acid production in stomach. In order to overcome this kind of disorders, different proton pump inhibitors and H_2 receptors blockers were used. Among all H_2 receptors blockers, Nizatidine is extensively prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastro esophageal reflux disease (GERD) due to its reducing nature of

gastric acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells (5). Nizatidine is able to suppress 24-hour gastric acid secretion by about 70%. It does not induce any anti-androgenic effects and drug interactions in patients as compared to any other class of H_2 Receptor Antagonists (6). Nizatidine (NZT) was known to metabolize by colonic bacteria, which reduces the therapeutic efficiency of Nizatidine and it also suffers from short biological Half life. Thus, it is reasonably better way to improve the therapeutic efficacy of the drug when it is formulated as sustain release gastro retentive dosage form (7).

MATERIALS AND METHODS

Materials

Nizatidine was generously gifted by Shasun chemicals and drugs, Chennai, India. Xanthan gum, pectin and HPMC K100M were purchased from Sigma Aldrich. Sodium bicarbonate, magnesium stearate, lactose and talc were purchased from S.D. Fine Chemical Pvt. Ltd., India. All other chemicals used were of analytical grade and were used without further purification.

Methods

Drug - excipient compatibility studies

The infrared spectra of pure drug nizatidine, xanthan gum, pectin, sodium alginate, HPMC K100M and optimized formulation (F5) were recorded between 400 and 4000 cm^{-1} by FT-IR spectrometer using KBr pellet technique.

Preparation of tablets

The tablet excipients were chosen after comprehensive drug–excipient interaction studies. All the tablets were prepared by direct compression method. Formulations were prepared by varying drug to polymer ratio and keeping other ingredients in required quantities to make the final weight of 400 mg per tablet. Briefly, preparation of tablets involved, passing all the ingredients except magnesium stearate and talc through sieve #40 and mixing the blend in an octagonal blender for 10 min. Magnesium stearate and talc were then passed through sieve #60 and were used to lubricate the blend. The lubrication was done for 5 min. The lubricated blend was compressed into tablets using 10 mm flat faced punches. The detailed composition of formulations is presented in Table 1.

Fourier transform infrared (FTIR) spectroscopy.

FTIR spectra were recorded by FTIR spectroscopy (Jasco FTIR spectrometer, USA). Samples (2 mg) were mixed with potassium bromide at 1:1 ratio before analyses. Spectra were recorded within the range of 4000–400 cm-1 at a spectral resolution of 2 cm^{-1} in a dynamic reflectance sample holder.

Differential scanning calorimetry (DSC)

Differential scanning calorimeter (DSC 60, Shimadzu, Japan) was used to study the thermal transitions of pure nizatidine, pectin and optimized formulation. Sample of 2 mg was placed in aluminum pan and sealed with a lid using a press. Thermograms were recorded at a heating rate of 10 ^oC per minute from ambient temperature up to 200 ^oC.

Evaluation of prepared tablets

The prepared tablets were tested for weight variation, thickness, drug content, hardness, friability, water uptake, in vitro drug release, in vitro floating lag time and total buoyancy.

Drug content

Accurately weighed 150 mg of Nizatidine was transferred into a 50 ml volumetric flask containing methanol to dissolve completely. The solution was filtered through whatman filter paper and diluted suitably with methanol, then measured the absorbance by using UV visible spectrophotometer at λ_{max} at 320nm.

In vitro buoyancy study

The *in vitro* buoyancy was determined by measuring floating lag time and duration of buoyancy The tablets were placed in a 100 ml beaker containing 100 ml 0.1 N HCl. The time required for the tablet to rise to the surface and float was taken as the floating lag time. The time for which tablets kept floating was termed as 'buoyancy time' of the tablets which was determined for all the formulations (8).

Tablet density

Density of prepared tablets was determined by placing in 0.1N HCl for predetermined time and the swollen tablet was carefully removed. Tablet density was measured by measuring mass and volume (height and width) of tablet using Vernier caliper (9).

Swelling studies

A Tablet was weighed (W1) and placed in a glass beaker, containing 200 mL of 0.1 N HCl. At regular time intervals, the tablet

were displaced and the excess surface liquid was carefully removed by a filter paper. The swollen tablet was then reweighed (W2). The swelling index (SI) was calculated using below formula (10).

$$\text{Swelling index} = \frac{W2 - W1}{W1} \times 100$$

Water uptake study

The swelling behavior of dosage form can be measured by studying its dimensional changes, weight gain or water uptake ability. The water uptake study for the dosage form was conducted by using Type II USP dissolution apparatus in 900 ml of distilled water which was maintained at 37 ±0.5 ^{0}C and rotated at 50 rpm. At selected intervals, the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU) calculated from following equation (11).

In vitro drug release studies

In vitro drug release studies were carried out using USP Type II dissolution apparatus containing 0.1 N HCl as dissolution media maintained at 37 ± 0.5°C with rotation speed of 50 rpm. Aliquots of 5 mL were withdrawn from dissolution apparatus at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h time intervals. At each time of withdrawal, 5 mL of fresh medium was replaced into the dissolution apparatus. Samples were analyzed using UV-Visible spectrophotometer at 228 nm. The results were expressed as mean±S.D. (n =3).

Drug release kinetics

In order to study the kinetics of drug release, the obtained data was analyzed by fitting in to different kinetic models like zero order, first order, Higuchi, and Hixson–Crowell model. To establish the mechanism involved in drug release from the tablets, data of percentage drug release versus log time were plotted according to Korsmeyer–Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight line.

Tablet preparation for In vivo studies

Tablets prepared for *in-vivo* studies contained 30% pectin, 5% PVP K30, 2% talc, 1% magnesium stearate and 12% barium sulphate ($BaSO_4$). $BaSO_4$ is a radio opaque agent and most often used in imaging of the gastro intestinal tract. Because of its high density, only 12% was used as it has high density (4.4777 gm /cm^3) and poor floating property. All the ingredients used in preparation of Nizatidine gastro retentive tablets were transparent to X-rays. In order to opaque the administered tablet in stomach by X-rays, incorporation of radio contrast agent is necessary. Barium Sulphate ($BaSO_4$) is most often used in imaging of the GI tract. but it has high density (4.4777 gm /cm^3) and poor floating property. So, 12% concentration of $BaSO_4$ is enclosed in tablet on behalf of 12% of Nizatidine to ensure the tablet float on stomach. In addition to $BaSO_4$, 30%pectin, 5% PVP K30, 2% Talc, 1% magnesium stearate were accurately weigh and mix to form uniform blend then compress by using tablet compression machine. *In vivo* studies were carried out in five healthy male human volunteers. Human subjects were allowed to fast for overnight. Tablets prepared with $BaSO_4$ were given orally and radio graphs were obtained using X-ray equipment after time intervals of 0.5, 2, 4 and 6 h. During the period of study, volunteers were allowed free access to only water (12, 13).

RESULTS AND DISCUSSION

Matrix tablet characterization

Physical properties of the compressed floating tablet systems

The results of the physical characteristics of floating tablets are shown in Table 2. The physical evaluation of the tablets revealed uniform thickness (3.0±0.05 to 3.4±0.46) and weight (399.27±3.09 to 402.6±2.91) for all the tablets. The hardness values between (3.8±0.96 to 4.4±0.17) kg/cm2 and low friability values (below 0.45%) across all formulations indicated that the tablets had sufficient mechanical strength. The drug content uniformity studies revealed that drug content between (97.5±0.12) and (99.9±0.57) % is acceptable.

FTIR spectroscopy

Pure nizatidine showed characteristic peaks 1017, 1228 (C-N stretch), 1354, 1588,3425 (N-H stretch). Pectin showed characteristic peaks 1051, 1351, 1592 (C-O stretch), 3406 (O-H stretch) optimized formulation showed characteristic peaks 1017, 1156, 1228, 1377, 1620, 3279

Differential scanning calorimetry (DSC)

In figure 2, the thermograms of Nizatidine, Pectine and best formulation from pectin were depicted. Therewere no significant

interactions were obeserved between the drug and excipients.

In vitro buoyancy studies

In all formulations optimized concentration (10%) of sodium bicarbonate used as effervescent agent which induces buoyancy to prepared tablets without effecting matrix integrity for up to 12 hrs, with minimum possible lag time. In acid environment sodium bicarbonate release carbon dioxide gas which was trapped and protected with gel barrier formed by swelling of hydrated barrier, thus the tablet density decreased to below 1.004gm/cm^3. As decreases in the tablet density tablet become buoyant (figure 3). Buoyancy study values of all formulations are mentioned in table. Formulations prepared with Xantane gum, pectin, and HPMC K100Mshows buoyancy lag time <1 minuet with standard deviation range of <2 minutes and retain the matrix integrity almost 12 hrs. But formulation prepared with sodium alginate shows floating lag time 1 to 2 minutes and failed to retain matrix integrity up to 12 hrs as low swelling rate of polymer unable to form gel barrier.

Tablet density

In all formulations the prepared matrix tablet density was found to be more than 1.004gm/cm^3 (Gastric fluid density). After placing the tablet in to 0.1N HCl medium tablet get swell in axial and radial direction. So, the tablet volume gets increases and density was decreases to less than 1.004gm/cm^3. Among all formulations, tablets prepared with sodium alginate shown higher tablet density near to 1.004gm/cm^3 was observed. Because of low swelling ability of sodium alginate which was observed on swelling studies slight increase in tablet volume was attained due to this reason these formulation shown high floating lag time. In case of formulations prepared with xanthan gum shown tablet density within the range of 0.68±1.35 to 0.83±1.22. In spite of xanthan gum contains high swelling ability; poor gas entrapment efficiency Xanthan gum increase in the tablet density was observed as compare with pectin. Tablet density of formulations prepared with HPMC K100M shown significant decrease in tablet density due to its high swelling ability, tablet swells and the diameter of tablet was increased on axial and radial direction there by tablet volume was increased which leads to decreases the tablet density.

Swelling study

Swelling index is one of the foremost factors, which plays a meaningful role for a tablet to float. It is also responsible for maintaining matrix integrity up to desired period. Based on swelling nature of polymer the thickness of gel layer varies. Swelling index of formulation comprise Xanthan gum (F1-F3) show more swelling ability than formulation prepared with pectin and sodium alginate containing formulation due to the presence of large number of trysaccharides units. As expected, the increase in polymer concentration swelling index was increased from 20% to 40% in case of Xanthan gum. Formulations prepared with pectin (F4-F6), shown gradual increase in swelling ability up to 10 hours than slight decrease in swelling index was observed. In presence of acidic environment, carboxyl groups of pectin converted to unionized carboxylic acid, which results decrease in negative charge of molecule there by decrease in hydration behavior of pectin also lowers the repulsive force of pectin molecule. Thus, it has low swelling ability than xanthan gum. However, here also as increasing polymer concentration was resulted in higher swelling indices. Formulations prepared with sodium alginate have shown very slow swelling indices than any other polymers. Because it posses low swelling index latter on the swollen matrix will be eroded. Formulations prepared with HPMC K100M shown highest swelling ability than other polymers used. In these formulations swelling index values were gradually increases up to 12 hours, as increasing polymer concentration swelling index was increased due to the presence of rapid hydrated and swellable nature of cellulose groups. Swelling index of data of all formulations were expressed in Tables III.

In vitro dissolution study

Formulations prepared of 20%, 30% and 40% of xanthan gum were able to retard the drug release up to 12 hours. Which conclude that initial concentrations were not enough to obstruct the drug release from matrix. Whereas, in remaining concentrations, they have sufficient amount of polymer and it forms high viscous gel barrier to retard the drug release up to 12 hours. In formulations prepared with 20%, 30% and 40% of pectin

were able to compile desired sustain drug release profile. Inspite of pectin having low swelling ability it results better drug release profile. Which is explains by two main reasons. As it has solubility enhancing property it improves the solubility of sparingly soluble Nizatidine thereby improving the drug release rate and pectin forms porous structure in presence of sodium bicarbonate which helps to improve the floating ability as well as drug release (figure 4). Formulations prepared with sodium alginate failed to retard the drug release up to 12 hour because of its low swelling nature and erodible property in acidic medium. Formulation prepared with 20%, 30% and 40% of sodium alginate retard the drug release up to 7, 10 and12 hours respectively.

Formulations prepared with HPMC K100M exhibited too slow drug release than the other polymers used. As increase in the polymer concentration drug release was decreased substantially. HPMC K100 was high viscosity grade polymer (1, 00,000mPas) it forms tight gel which obstructs the drug release from dosage forms. As outer gel layer is fully hydrated and disassociated, new inner layer replace it and enough to retard the influx of water and control the diffusion. Due to this reason it fails to release 70% of drug in 8 hours. So, it was not suitable for preparing acceptable Nizatidine gastro retentive tablets.

Drug release kinetics

To understand the drug release mechanism from prepared tablets in vitro drug release data was fitted in to different kinetic model like zero order, First order, Higuchi, krosmeyer-peppas models. Regression coefficient (R^2) values obtained by kinetic models were illustrates in table 4. Dissolution profile of most of formulations follows zero order kinetics, formulation prepared with 40% of Xanthan gum, 30% of pectin regression values shows linear drug release profile. From the kinetic data of korsemeyer - peppas model, we can confirm the mechanism of drug release. As per the present work concerns, drug release profile of all formulations follows non Fickian transport to release the drug from prepared tablets.

Drug excipient interaction

Drug Excipient interactions are effectively analyzed by Fourier transforms infrared (FT-IR) spectroscopy (brukeralfa) (figure 1). FT IR spectra of Nizatidine pure drug display principal bands at wave number of 3425.10cm^{-1} for amino group (-NH_2), 1354.89cm^{-1} for alkane group (-C-H). FT- IR spectra of pectin display band at wave number of 1592.06cm^{-1} for carbonyl group, hydroxyl group of carboxylic acid display characteristic band at wave number of 3406.93cm^{-1}, –OH group in alcohol display band at wave number of 1051.93cm^{-1}, amine group display band at wave number of 1351.1 cm^{-1}. A FTIR spectrum of optimized formulations shows specific bands for functional group in Nizatidine and pectin. A spectrum illustrates bands at wave number 3425.10cm^{-1} (amino group), 1588.61cm^{-1} (nitro group), 1354.89cm^{-1} (alkane group) which are represents Nizatidine. Pectin contain functional groups shows bands at wave number 1620.70cm^{-1} (carbonyl group), 1156.89cm^{-1} (-c-o), 1228.72(-C-NH_2). So, there is no significant interactions are observed as per this FTIR studies.

In vivo floating behavior

In vivo floating behavior of prepared gastro retentive tablets were observed by radiographic imaging technique in five healthy human volunteers. X-ray images were taken at 15 minute time showed that the tablet was able to float in all five volunteers in vivo conditions also. X-ray images taken in 2nd hour showed that the administered tablet was able to retain in stomach region and alteration of tablet position reveals that tablet did not adhere to stomach mucosa. X-ray images taken at 4th hour represent that the tablet still being in stomach but displacement in tablet position was observed. This indicates that the tablet was moved on to next segment of GIT. In three volunteers tablets were appear in different regions of stomach because may be presence of different GI motility in three volunteers. X-ray images taken 6th hour failed to retain in stomach this may be due to up take of water move the tablet to intestine.

CONCLUSION

Nizatidine effervescent gastro retentive tablets were successfully prepared and evaluated. This study demonstrates that 10% w/w sodium bicarbonate was sufficient to produce effervescence and to float the tablets. Formulations prepared with sodium alginate failed to retain its integrity up to 12h in comparison to other polymers.

Table 1: Formulation composition of gastroretentive tablets of nizatidine. All formulations consist 2% of talc and 1% of magnesium stearate.

Formulation Code	Drug (mg)	Xanthan gum Gum(mg)	Pectin(mg)	Sodium alginate (mg)	HPMCK100M (mg)	Sodium bicarbonate (mg)	Spray dried lactose (mg)	PVP K30 (mg)
F1	150	80	---	---	---	40	98	20
F2	150	120	---	---	---	40	58	20
F3	150	160	---	---	---	40	18	20
F4	150	---	80	---	---	40	98	20
F5	150	---	120	---	---	40	58	20
F6	150	---	160	---	---	40	18	20
F7	150	---	---	80	---	40	98	20
F8	150	---	---	120	---	40	58	20
F9	150	----	---	160	---	40	18	20
F10	150	---	---	---	80	40	98	20
F11	150	---	---	---	120	40	58	20
F12	150	---	---	---	160	40	18	20

Table 2: Physical parameters of gastroretentive tablets of nizatidine

Formulation Code	Weight Variation*	Thickness**	Hardness** (Kg/cm^2)	Friability** (%)	% Drug content**
F1	399.27±3.09	3.4±0.02	4.4±0.17	0.42±0.03	97.7±0.12
F2	400.27±3.77	3.0±0.06	4.4±0.115	0.38±0.08	98.87±0.43
F3	400.1±3.07	3.4±0.08	4±0.41	0.36±0.12	98.7±0.08
F4	400.16±2.83	3.06±0.04	4.3±0.8	0.32±0.91	98.2±0.09
F5	399.71±2.61	3.2±0.18	4.1±1.02	0.46±0.05	97.5±0.12
F6	399.9±1.82	3.4±0.46	4.3±0.115	0.36±0.1	98.6±0.68
F7	401.8±3.05	3.1±0.08	4.2±0.18	0.28±0.66	99.9±0.57
F8	402.6±2.91	3.2±0.5	3.8±0.96	0.35±0.92	98.91±0.62
F9	399.6±2.02	3.4±0.16	4.4±0.06	0.42±0.36	99.2±0.51
F10	399.68±3.39	3.2±0.18	4.1±0.112	0.42±0.1	98.3±0.18
F11	399.8±2.85	3.0±0.05	4.2±0.05	0.38±0.42	97.7±0.15
F12	402.1±2.68	3.2±0.1	4.4±0.115	0.42±0.06	98.9±0.28

Table 3: Floating behavior, swelling index and tablet density of gastroretentivenizatidine tablets.

Formulation Code	Floating Lag Time (sec)	Floating Duration Time (hr)	Swelling Index (At 12^{th}hr)	Tablet density After floating
F1	41±1.0	>12	188.6±1.23	0.72±0.67
F2	50±1.15	>12	205.1±1.02	0.75±0.49
F3	67±1.45	>12	216.7±2.44	0.83±1.22
F4	22±1.52	10	67.4±1.16	0.65±1.64
F5	30±2.0	>12	78.9±1.47	0.66±0.76
F6	45±1.25	>12	95.3±1.14	0.69±0.66
F7	58±.87	6	42.7±1.87	0.90±1.73
F8	120±1.3	10	72.8±1.73	0.92±0.57
F9	152±1.4	>12	84.8±1.28	0.95±2.06
F10	25±1.52	>12	225.1±2.25	0.52±1.23
F11	36±1.4	>12	248.3±1.59	0.68±1.22
F12	43±1.52	>12	265.3±3.4	0.69±0.78

Table 4: Drug release kinetics of all prepared formulations.

Formulation code	Regression coefficient(R^2)				Diffusion Exponent 'n'
	Zero Order	First order	Higuchi	Peppas	
F1	0.9702	0.8810	0.8729	0.7925	0.666
F2	0.9803	0.9450	0.8928	0.8959	0.716
F3	0.9893	0.9685	0.896	0.9334	0.685
F4	0.9715	0.8832	0.8652	0.9224	0.572
F5	0.9833	0.8906	0.8575	0.9091	0.543
F6	0.9493	0.8831	0.8294	0.9061	0.511
F7	0.8274	0.8454	0.9125	0.9843	0.691
F8	0.9667	0.9511	0.9447	0.9329	0.742
F9	0.9809	0.9448	0.9463	0.9564	0.677
F10	0.9557	0.9008	0.8345	0.8140	0.625
F11	0.9555	0.9090	0.8292	0.8390	0.641
F12	0.9450	0.8979	0.8120	0.7728	0.586

Figure 1: FT-IR spectra of a) Nizatidine pure drug, b) pectin and c) optimized formulation.

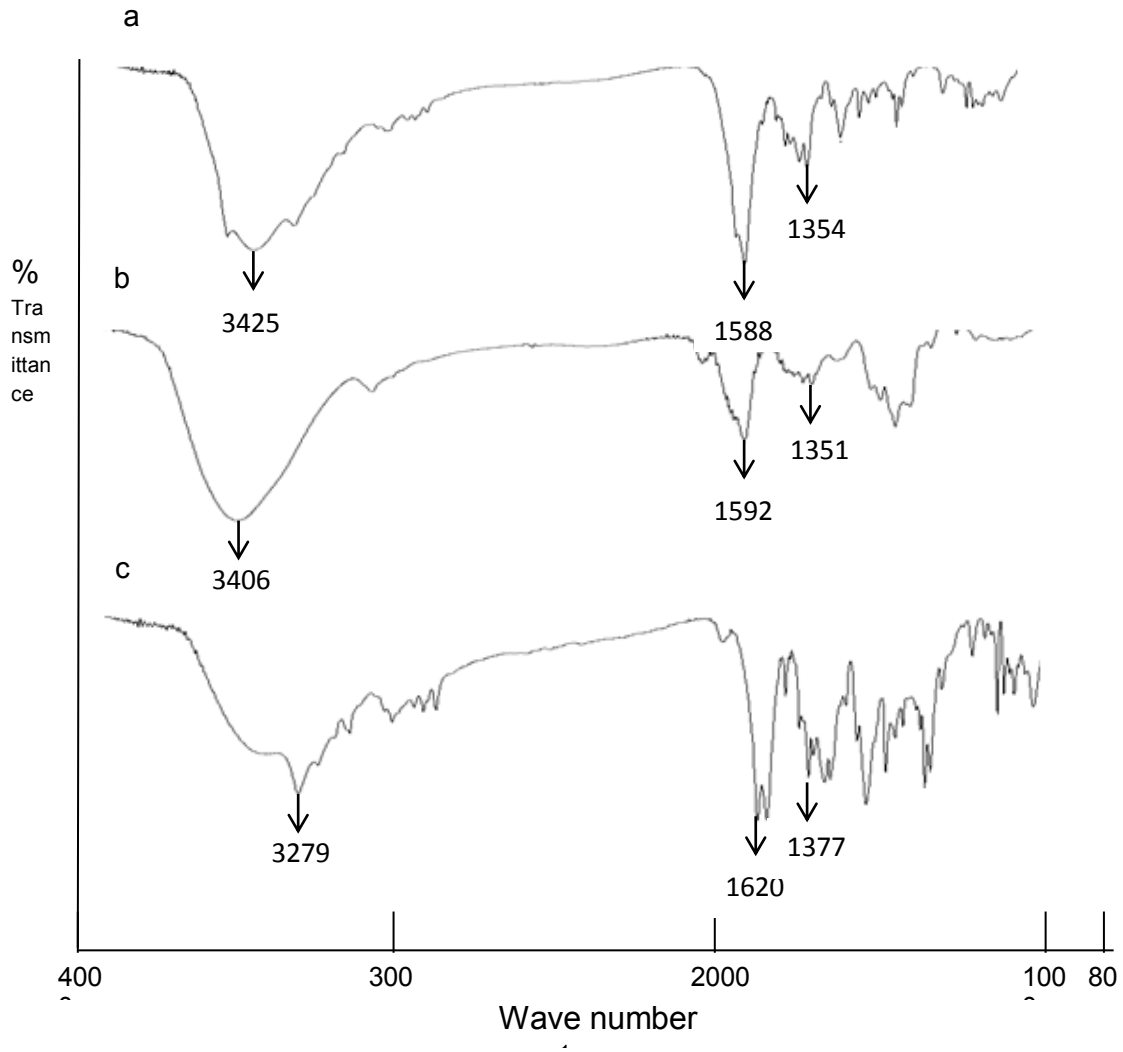


Figure 2: DSC thermograms of pure drug, pectin and optimized formulation.

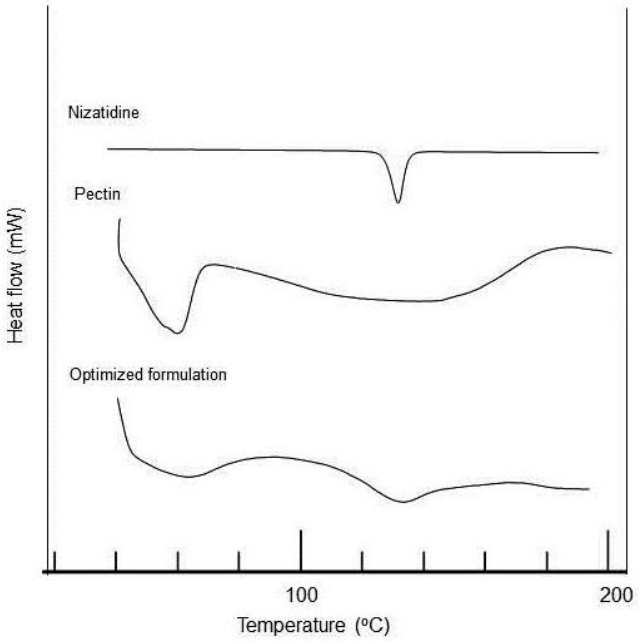
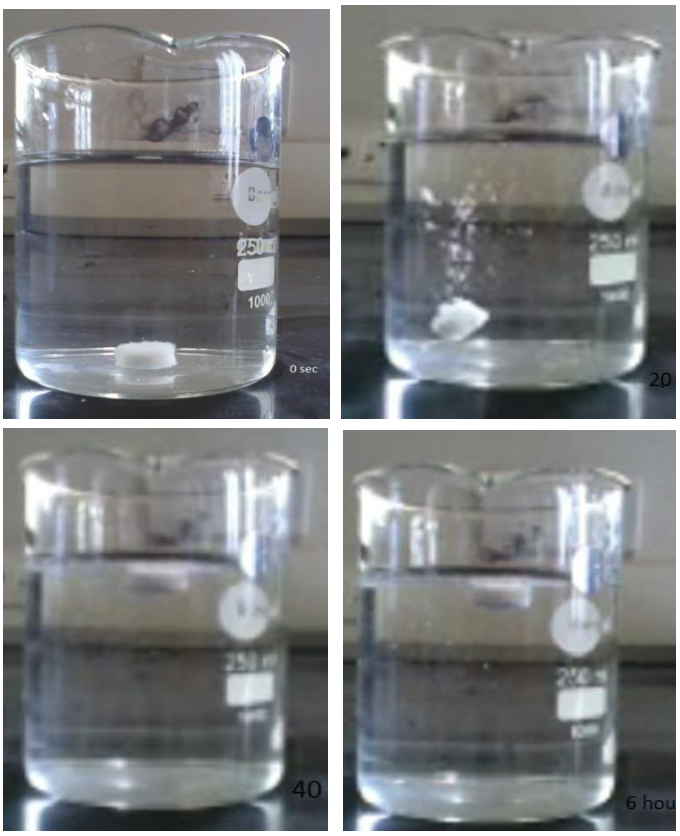


Figure 3*: In vitro* buoyancy study of optimized formulation.



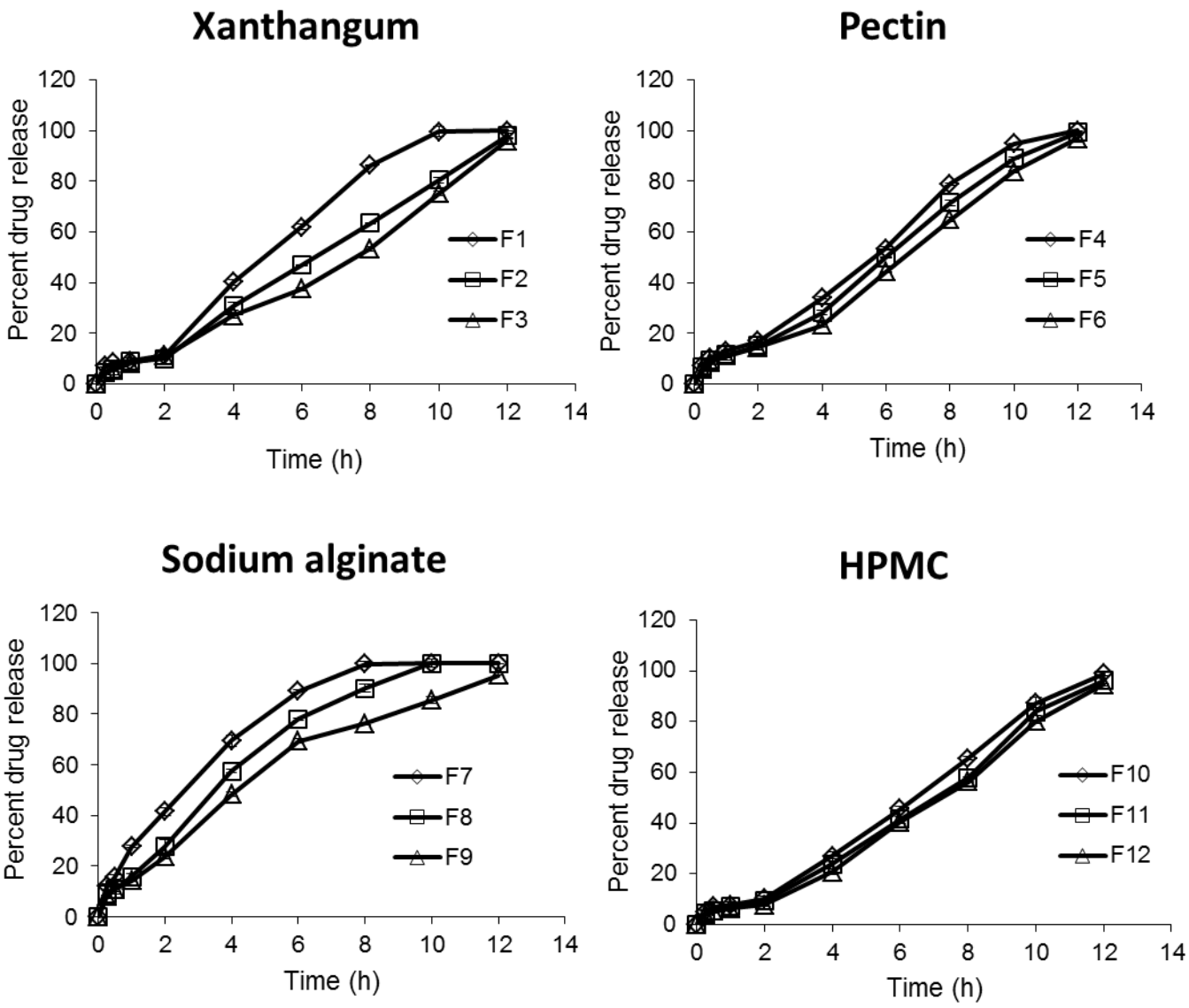


Figure 4: Drug release profiles: (a) drug release profiles of nizatidine floating tablets with xanthan gum (a), pectin (b), sodium alginate (c) and HPMC (d).

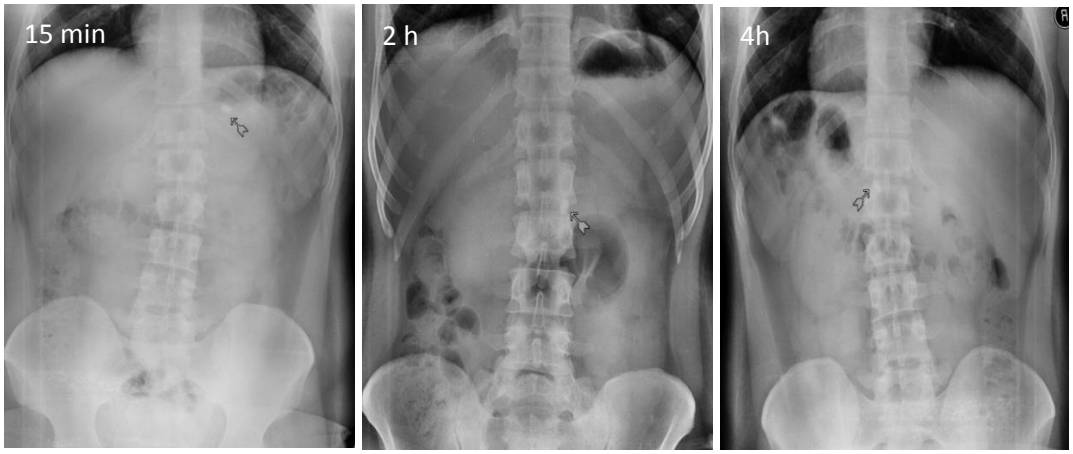


Figure 5: Representative x-ray photographs of *in-vivo* floating behaviour of gastro-retentive tablet at 0.25, 2 and 4h.

In vitro drug release study reveals that as increase in polymer concentration drug release decreased. Formulation with 30% pectin showed better release. Formulation F5 gave better sustained drug release in comparison to other formulations. These formulations best fitted to Korsmeyer–Peppas model and zero-order kinetics. In vivo x-ray radiographic studies indicated that tablets remained in the stomach for about 4 h, which indicates the increase in the gastric residence time due to floating and swelling principle.

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REFERENCES

1. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, et al. (2011) Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. Drug delivery 18: 97–110.
2. Dixit N (2011) Floating Drug Delivery System. Journal of Current Pharmaceutical Research 7: 6–20.
3. Prajapati VD, Jani GK, Khutliwala TA, Zala BS (2013) Raft forming system-an upcoming approach of gastroretentive drug delivery system. Journal of controlled release: official journal of the Controlled Release Society 168:151–165.
4. Raja Sekhar Reddy P, Chandrasekhara Rao G. Development of buoyant controlled release drug delivery systems of atazanavir sulphate: Effect of various diluents and lubricants on drug release. Pharmanest Int J Adv Pharm Sci 2014; 5:1947‑57.
5. Goodman & Gilman: laurenL.bruton, Jonu S. Lazo, KeiyhL.parker (Eds.). The pharmacological basics of therapeutics. 11ed. the pharmacological basis of therapeutics, 2006.
6. Gande S, Rao Y. Sustained release effervescent floating matrix tablets of baclofen: Development, optimization and *in vitro‑in vivo* evaluation in healthy human volunteers. Daru 2011; 19:202‑9.
7. Putta RK, Hiremath D, Raje S. Design and evaluation studies on novel floating tablets for peptic ulcer treatment. J Adv Pharm Edu Res 2011; 2:159‑76.
8. Argoff CE, Chen C, Cowles VE. Clinical development of a oncedaily gastroretentive formulation of gabapentin for treatment of postherpetic neuralgia: an overview. Expert Opin Drug Deliv. 2012; 9(9):1147–60.
9. Thakar K, Joshi G, Sawant KK. Bioavailability enhancement of baclofen by gastroretentive floating formulation: statistical optimization, in vitro and in vivo pharmacokinetic studies. *Drug Dev Ind Pharm*. 2013; 39(6):880–888.
10. Chen C, Han CH, Sweeney M, et al. Pharmacokinetics, efficacy, and tolerability of a once-daily gastroretentive dosage form of gabapentin for the treatment of postherpetic neuralgia. J Pharm Sci. 2013;102(4):1155–64.
11. Safaa S, Gamal E, Viviane FN, Ahmed NA: Optimization of Acyclovir oral tablets based on gastroretention technology: Factorial design analysis and physicochemical characterization studies. Drug Dev Ind Pharm 2011,37(7):855–867.
12. Johnson P, Becker L, Halpern R, et al. Real-world treatment of post-herpetic neuralgia with gabapentin or pregabalin. Clin Drug Investig. 2013; 33(1):35–44.
13. Baumgartner, S.; Kristl, J.; Vrecer, F.; Vodopivec, P.; Zorko, B.Optimisation of floating matrix tablets and evaluation of their gastric residence time. *International Journal of Pharmaceutics* (abbreviation), v.195, p.125-135, 2000.