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DEVELOPMENT AND IN VITRO- IN VIVO EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY OF NIZATIDINE USING NATURAL AND SEMI- SYNTHETIC POLYMERS

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ABSTRACT

Nizatidine is a competitive reversible inhibitor of histamine H_2 receptors, particularly in the gastric parietal cells. Floating modified release nizatidine tablets were prepared using the direct compression method. Tablets were formulated using natural polymers tamarind seed polysaccharide, semi-synthetic polymer Hydroxypropyl methyl cellulose (HPMC K4M). The pre formulation and post formulation parameters such as Angle of repose, Bulk density, tapped density thickness, hardness, friability and drug content were evaluated. *In vivo* study was performed by using the rabbits by X-ray imagining technique, radiological evidences suggest that a formulated tablet was well floated more than 10h in rabbit‟s stomach. Statistical data analysis revealed that tablets containing a composition of tamarind polysaccharide 15% w/w and HPMC K 15%w/w produced the most favourable formulation to develop 12 hours controlled release tablets with optimum floating behaviour and satisfactory physicochemical characteristics. Furthermore, F8 *in vitro* release study revealed that the formulated floating tablet had significantly lower buoyancy lag time and higher total floating time compared to the other formulations. Comparative kinetic model obtained for the tablet of F8 depends on r^2 in zero order kinetics and mechanism was fit to Korsmeyer –Peppa‟s model. It can be concluded that the combination of tamarind seed polysaccharide and HPMC in the ratio of 1:1 it can be used to develop controlled release floating tablets of nizatidine.

KEYWORDS Tamarind seed polysaccharide, Floating drug delivery, Nizatidine, HPMC and Controlled release.

INTRODUCTION

Peptic ulcer disease (PUD) is one of the most common chronic infections which affecting nearly 10% of world population. It is disease continues to be major health care problem, costing billions of dollars each year. Approximately about 5, 00,000 new cases are reported every year. India is 53rd in World‟s health ranking peptic ulcer diseases with 5.79% rate incidence of morbidity and mortality.[1,21]

Gastro retentive drug delivery is an approach to prolong gastric residence time (GRT), there by targeting site- specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effect.[2] Floating drug delivery system have emerged as an efficient means of enhancing the bioavailability and a promising formulation technique in the management of ulcer by opening a new therapeutic dimension.[3]

Nizatidine is a histamine (H_2) receptor antagonist. By inhibiting the action of histamine on stomach cells, nizatidine reduces stomach acid production. Conventional nizatidine tablets produce rapid and relatively high peak blood levels and require frequent administration to keep the plasma drug level at an effective range. This might cause side effects, reduced effectiveness and poor therapeutic management. It is widely prescribed in the treatment of Peptic ulcer, duodenal ulcer and gastro oesophageal reflux (GERD). It has short biological half-life of 1-2 hr and low absolute oral bioavailability >70%. The drug is prescribe as 150mg twice daily for acute duodenal ulcer.[4] It comes under the Biopharmaceutical classification Class III.[4,5]

The present research endeavour involves the development and characterization of newer floating controlled release tablet of nizatidine using tamarind seed polysaccharide and Hydroxy propyl methyl cellulose K4 M (HPMC K4 M) and investigation of the combined effect of these polymer on the floating behaviour and *in vitro* release pattern of the drug.

2. METERIALS AND METHODS

2.1 Materials

Nizatidine, (Central Drug Laboratory, Chennai), HPMC K4M (Hi Media Laboratories limited, Mumbai), Micro Crystalline Cellulose, $NaHCO_3$, Citric acid, Magnesium stearate,

Talc, (SD Fine chem. Ltd, Mumbai), Tamarind Seed (Local market, Trichy).

2.2 Methodology

The Nizatidine floating tablets were prepared by effervescent technique used the hydrophilic polymers (HPMC K4M, and Tamarind seed polysaccharides). Sodium bi carbonate & citric acid used as gas generating agent MCC are used as a binder by direct compression method. Nizatidine with the other excipients are in concentration & ratio are used for the preparation of tablet were shown in Table.1.

Table 1: Formulation of Nizatidine floating tablets.[6]

INGREDIENTS	FORMULATION CODE								
	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg	F8 mg	F9 mg
Nizatidine	150	150	150	150	150	150	150	150	150
Tamarind polysaccharide (1:0.5, 1:1, 1:1.5)	75	150	225	-	-	-	37.5	75	112.5
HPMC K4 (1:0.5, 1:1, 1:1.5)	-	-	-	75	150	225	37.5	75	112.5
Sodium bicarbonate (10%)	35	35	35	35	35	35	35	35	35
Citric acid (1%)	4	4	4	4	4	4	4	4	4
Talc (1.7%)	6	6	6	6	6	6	6	6	6
Magnesium stearate (4%)	4	4	4	4	4	4	4	4	4
Microcrystalline cellulose (14%)	50	50	50	50	50	50	50	50	50
Lactose (q. s)	176	101	26	176	101	26	176	101	26
Total weight	500	500	500	500	500	500	500	500	500

2.2.1. Isolation of Tamarind seed polysaccharide[7,8]

The seeds of Tamarinds indica are washed in water

↓

By heating seeds in sand ratio of 1:4

Tamarind seed: sand

↓

Reddish Testa of the seeds is removed

↓

Seeds are crushed lightly

↓

Crushed seeds are soaked in water for 24h & Boil for 1h

Removed Testa

↓

Kept aside for 24hr for the release of mucilage into water

↓

Soaked seeds are squeezed in a muslin bag to remove marc

Testa Removed Seeds

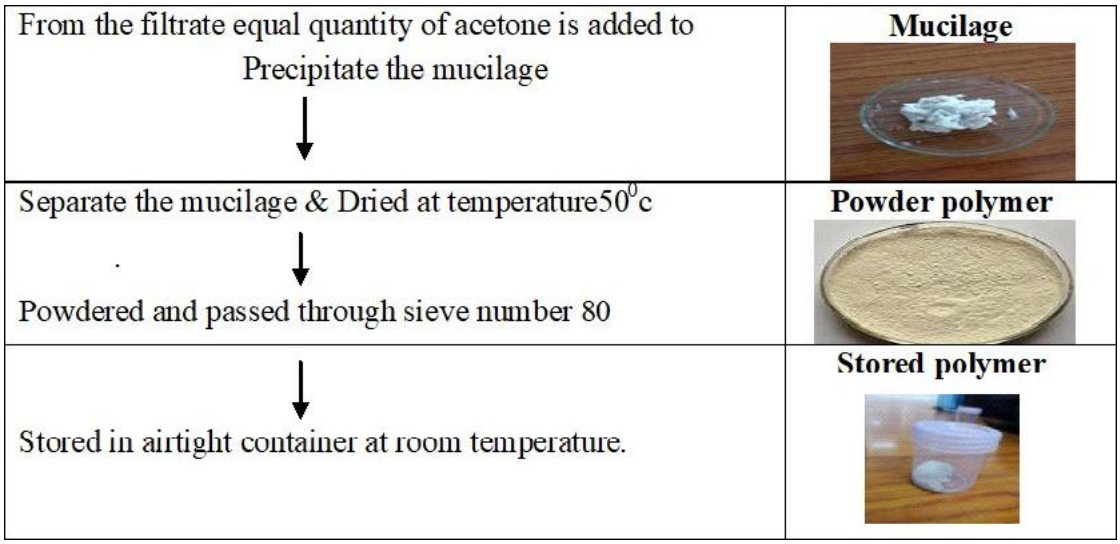


Fig 1: Isolation of Tamarind seed Polysaccharide.

2.2.2. Formulation of Nizatidine Floating Tablet

Steps involved in preparation of floating tablet by direct compression

Drug (Nizatidine) + Different polymers in various ratios + NaHCO3+ Citric acid + Talc

↓+Magnesium stearate

Were mixed in mortar with the help of pestle & add MCC and triturate well

↓

Blended materials compressed based on flat round punches & corresponding dies are used

↓

The Total weight of the prepared tablet was maintained as 500mg[9,10]

2.2.3. PRE – FORMULATION

a. Chemical incompatibilities

Infrared spectroscopic analysis was performed to check out the compatibility between the drug (Nizatidine) and the hydrophilic polymers HPMC K4M and Tamarind seed polysaccharides used in the formulation of floating tablets. IR spectrum of the pure drug and the physical mixtures of drug with polymers of formulations were studied.[11]

b. General appearance: Evaluate all the tablets should be good in appearance such as color, odour, shape of the tablet[14]

c. Angle of repose

It is define as the maximum angle possible between the surface of the pile of powder and the horizontal plane.[11] The angle of repose is designated **θ** is given by equation is.

$\theta = \tan^{-1}(h/r)$

Where, h is height of pile in cm, r= radius of pile, cm

c. Bulk density

It was the ratio of total weight of powder to the bulk volume of powder

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk volume of powder}} \text{ (g/ml)}$$

d. Tapped density

It was the ratio of the total mass of the powder to the tapped volume of the powder.

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped density of powder}} \text{ (g/ml)}$$

e. Carr's Index

The compressibility index indicates powder flow properties. It expressed in percentage

$$\% \text{ Compressibility index} = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100$$

f. Hausner ratio

It is the number that is correlated to the flow ability of the powder to be compressed.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.2.4. POST EVALUATION

a. Thickness and Diameter

They are measured by using Vernier caliper. Three tablets were selected randomly from each batch and thickness and diameter were measured.[12] It was expressed in mm.

b. Hardness

They measure the hardness of a tablet which may undergo chipping or breakage during transportation and handling. That three tablets were selected randomly and hardness of each tablet are measured by using Monsanto tester.[12,14] (Thermo lab, Mumbai, India).

c. Friability

Tablet strength was tested by Roche friabilator. Per weighed tablets were allowed for 100 rpm in 4 min were de-dusted. The % weight loss was calculated by reweighing the

tablets.[12,14]

d. Weight variation

20 tablets weighed individually weighed. The average weighs and S. D of 10 tablet variation is not more than for 250 mg are have deviation is (± 5%).[14]

e. Drug content

10 tablet are weight and taken in mortar and crushed to make powder form. A quantity of powder weight equivalent to 150mg of drug in volumetric flask & acid buffer pH 1.2 is added. The absorbance was measured at 314 nm using UV visible spectrometer. The amount of drug present in one tablet is calculated using Standard graph.[14]

2.2.5. IN VITRO BUOYANCY DETERMINATION

a. Floating Lag Time (FLT) The time between the introduction of the tablet into the Stimulated Gastric Fluid (SGF) with 37°C and its rise to upper surface and float was taken as the floating lag time.[13]

b. Total Floating Time (TFT) The time taken by the tablet to float constantly on the surface of the SGF medium was taken as total floating time.[13]

a. Swelling Index

Swelling of tablet excipient particles involves the absorption of a liquid resulting in an increase in weight and volume. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet.[15]

Swelling Index (S.I.) = $(W_t-W_o)/W_o$

Where,

S.I. = Swelling index, W_t = Weight of tablet at time t, W_o = Weight of tablet before placing in the beaker.

2.2.6. *IN VITRO* RELEASE STUDIES

Apparatus	**:** USP type II dissolution apparatus
Dissolution Medium	**:** 0.1 N HCl with pH 1.2
Temperature	**:** 37± 0.5C
RPM	50
Vol. With drawn and replace	**:** 1 ml

λ_{max} 314

Blank Solution **:** 0.1 N HCl with pH 1.2

Dissolution profile of the formulations were analysed by plotting drug release versus time for all models.[14,16]

2.2.7. *IN VITRO* KINETICS DRUG RELEASE STUDIES

The *in vitro* release kinetics studies were Studies done by software "DD Solver@". The release data (1- 12hrs) was analyzed as per Zero order, First order, Higuchi"s and Kormeyer - Peppa"s equation models to know the pattern of drug release and mechanism of drug release from the tablet. Equation are, $M_t = M_o - K_o t$ (1)

$\ln M_t = \ln Mo - K_1 t$ ..... (2)

$Q_t = K_H t^{1/2}$ ..... (3)

where M_t = quantity of drug remaining undissolved at time (t), M_o = quantity of drug remaining un- dissolved at time (t) = 0, t = time of sampling, Q_t = quantity of drug remaining undissolved at time (t), and K_o, K_1 and K_H are the release rate constant for zero-order, first-order and Higuchi models, respectively.[17]

2.2.8. *IN VIVO* RADIOGRAPHY STUDIES Animal and diet

The male albino rabbit (2 - 2.5kg) are housed in the polypropylene cages at temperature 22 ± 2 c. The animal is fasted overnight but allowed to take water ad libitum. Then 30 ml of 5% dextrose solution is given immediately before administering the tablet by using stomach tube (No. 12 French Catheter) and 20 ml syringes. The experiment protocol of the study was approved by Institutional Animal Ethical Committee (Registration No. KMCRET/M. Pharm/01/2018-2019).

After performing physicochemical characteristics, evaluate the gastro-retentive behaviour for the best formulation *in vivo,* incorporation of barium sulphate ($BaSo_4$) was required to visualize the tablet under X-ray but not to change the tablet buoyancy, therefore 200mg tablet was prepared with same formulation and 25% of the drug was replaced with barium sulphate with no change in other ingredients.[20]

2.2.9. STABILITY STUDIES

The stability are done according to the ICH Guide lines. The Promising formulation was tested for Accelerated stability testing under the condition (40°C ± 2°C /75% RH ±5%) for two months for their drug content and other parameters.[18,19]

3. RESULTS AND DISCUSSION

a. Chemical Incompatibility

Fourier Transform Infrared (FTIR) Spectroscopy

From the Fig. No.2,3,4 the majors peaks were obtained at 765, 1226, 1393 and 3000-2968/ cm-1 for pure drug of some functional groups of N-H, C-N, C=C, CH_3 of respectively. Ranges were shown in Table.3.

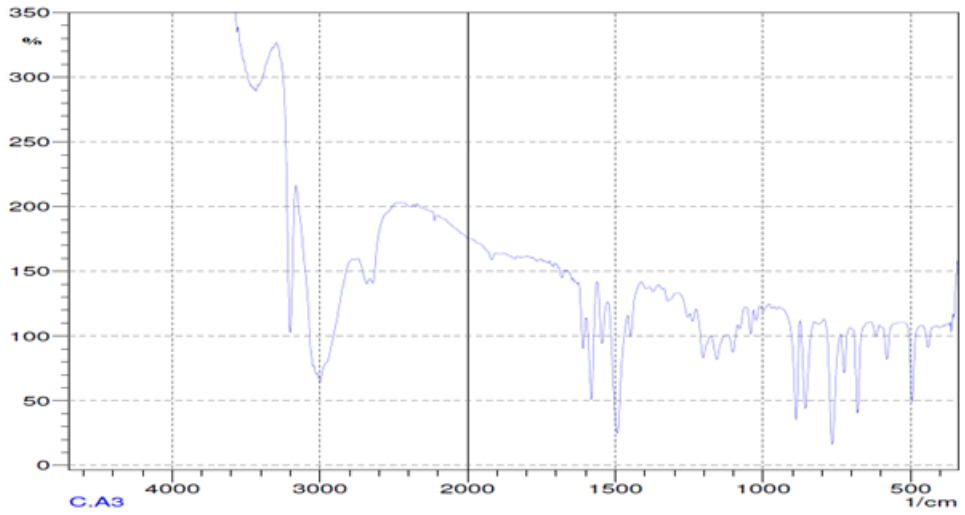


Fig. 2 FT-IR Spectra of Nizatidine pure drug.

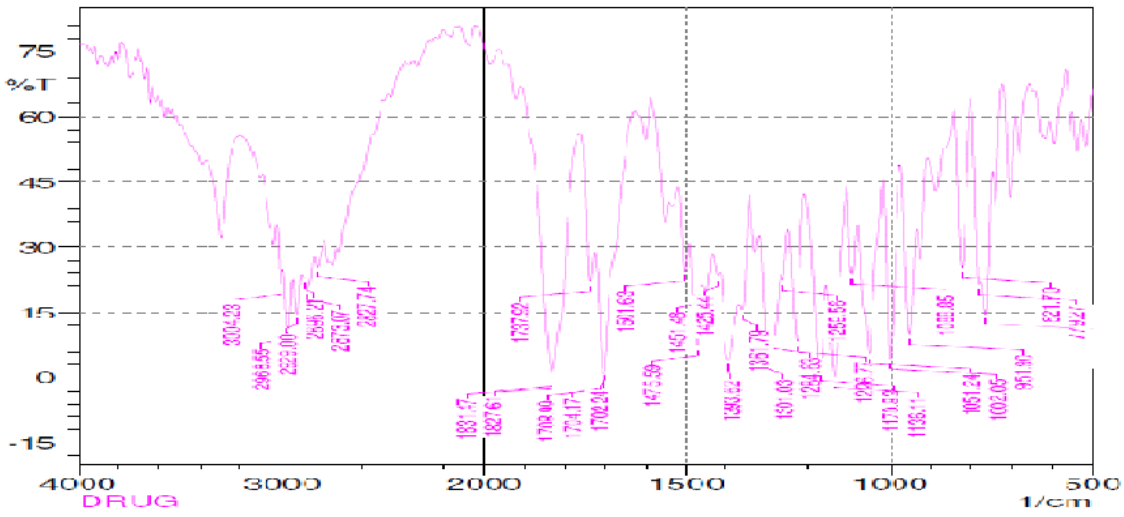


Fig 3: FT-IR Spectra of Nizatidine + Tamarind polysaccharide.

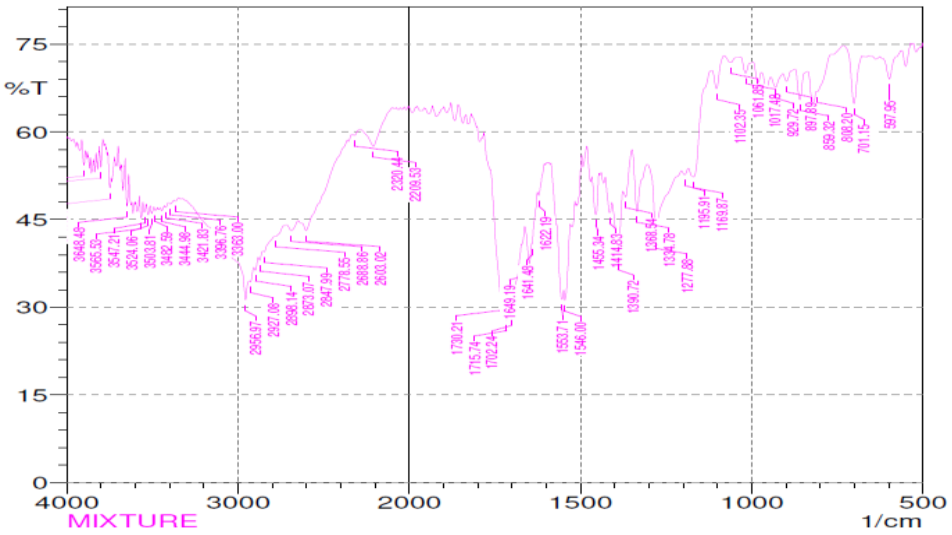


Fig 4: FT-IR Spectra of Nizatidine + HPMC K4M.

Table 2: Ftir Spectra of Drug And Excipients.

Specified functional group	Nizatidine Pure drug	Nizatidine + Tamarind	Nizatidine + HPMC
CH3	2968	2956	2968
NH	3300	3306	3300
N-O	1393	1390	1395
C-S	765	751	769
C-N	1301	1334	1330
C=C	1393	1390	1380

The major peaks obtained a pure drug in the same characteristic bands drug in excipients also shown, without any significant spectral changes thus there is no interaction between the drug and excipients used in the formulations.

3.1 PRE-FORMULATION PARAMETERS

The formulation shows good flow property and Carr‟s index (**Table.3**) Angle of repose ranged from 25042‟ to 28072‟, Bulk density ranged from 0.66 to 0.74 gm/cc, Carr‟s index ranged from 9.2 to 11.96%, and the Hausner‟s ratio ranged from 1.102 to 1.135.

Table 3: Pre-Formulation Studies for (F1-F9).

Formulations	Angle of repose(θ) ± SD	Bulk density (gm/ml) Avg ±S.D	Tapped density(gm/ml) Avg ±S.D	Carr's index (%)	Hausner's ratio
F1	25042‟ ± 1.11	0.742± 0.002	0.818± 0.002	9.24	1.102
F2	25069‟ ± 1.51	0.660± 0.002	0.740± 0.002	10.810	1.121
F3	27047‟ ± 1.63	0.731± 0.003	0.821± 0.003	10.962	1.123
F4	26094‟ ± 0.56	0.714± 0.004	0.789± 0.003	10.504	1.105
F5	26005‟ ± 1.48	0.740± 0.003	0.823± 0.002	10.085	1.112
F6	28068‟ ± 1.82	0.721± 0.002	0.818± 0.002	11.858	1.134
F7	26029‟ ± 0.51	0.734± 0.002	0.810± 0.002	9.382	1.103
F8	25060‟ ± 0.92	0.728± 0.004	0.826± 0.002	11.86	1.134
F9	28072‟ ± 1.48	0.736± 0.004	0.836± 0.002	11.96	1.135

3.2 POST-COMPRESSION PARAMETERS

The shape of all formulation shows dull white with smooth, flat faced circular with no visible cracks. All the tablet were passed in the weight variation within Pharmacopeial limits. The thickness and diameter were ranged 4.12 to 4.29mm and 11mm respectively. The hardness ranged between 6.26 to 7.2 kg/cm2. The friability was found to be 0.82 to 0.89%, which shows satisfactory mechanical resistance of the tablet. The drug content estimated value in range of 9.18±0.35 to 98.59±0.35% which shows good uniformity content in different formulations. The results were shown in **Table.4.**

Table 4: POST FORMULATION STUDIES (F1-F9).

Formulations	Average Weight(mg)	Thickness (mm)	Hardness kg/cm2	Friability (%w/w)	Diameter (mm)	Drug Content uniformity (%)
F1	472.3±0.862	4.12±0.11	6.66±0.378	0.829±0.03	11	97.18±0.35
F2	470.1±0.340	4.13±0.08	6.76±0.251	0.853±0.02	11	98.39±0.34
F3	483.5 ±0.055	4.20±0.12	6.79±0.264	0.826±0.13	11	98.39±0.34
F4	482.5 ±0.068	4.18±0.13	6.62±0.458	0.895±0.12	11	98.19±0.34
F5	480 ±0.0529	4.16±0.14	6.86±0.378	0.833±0.06	11	97.39±0.34
F6	472.5 ±0.155	4.23±0.11	6.96±0.321	0.826±0.04	11	98.29±0.6
F7	481.5 ±0.570	4.16±0.10	6.92±0.350	0.84±0.03	11	97.19±0.34
F8	485.5 ±0.755	4.25±0.11	7.01±0.251	0.856±0.02	11	98.59±0.35
F9	480 ±0.895	4.29±0.11	7.0±0.251	0.896±0.03	11	97.19±0.34

3.3 *IN VITRO* BUOYANCY DETERMINATION

a. Floating Lag Time(FLT)

All the formulation (F1-F9) shows the floating lag time were less than one minute Table.5. F8 were shows least Floating lag time when compare to the other formulations with 50 sec are shown in Fig.5.

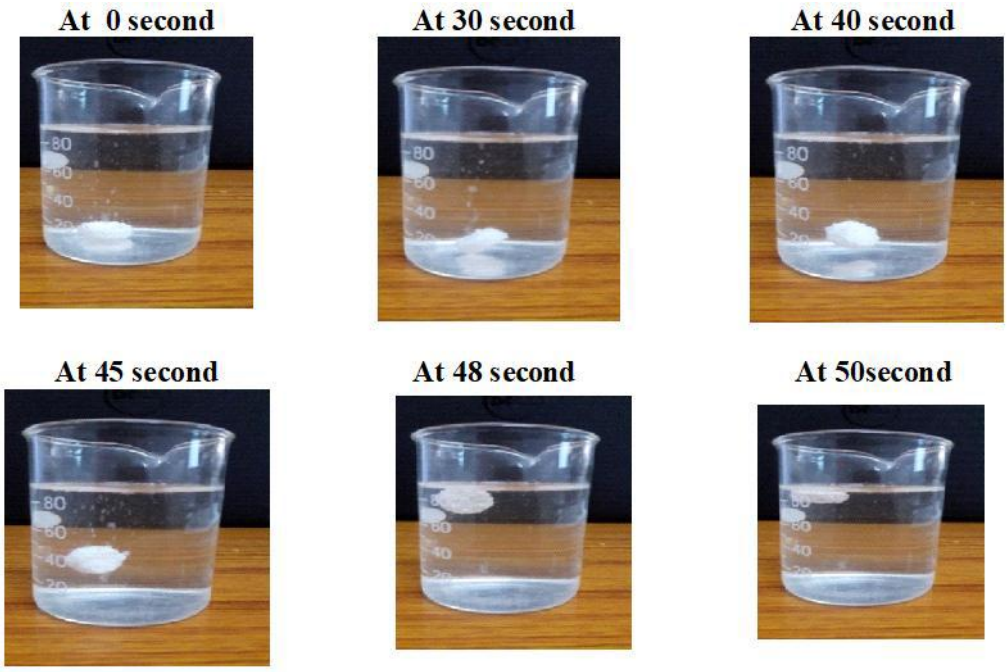


Fig 5: Floating lag time of F8 formulation.

b. Total Floating Time (TFT): All the formulation shows the total floating time of more than 10 h in **Table.5**. F8 formulation are shown **Fig.6.**

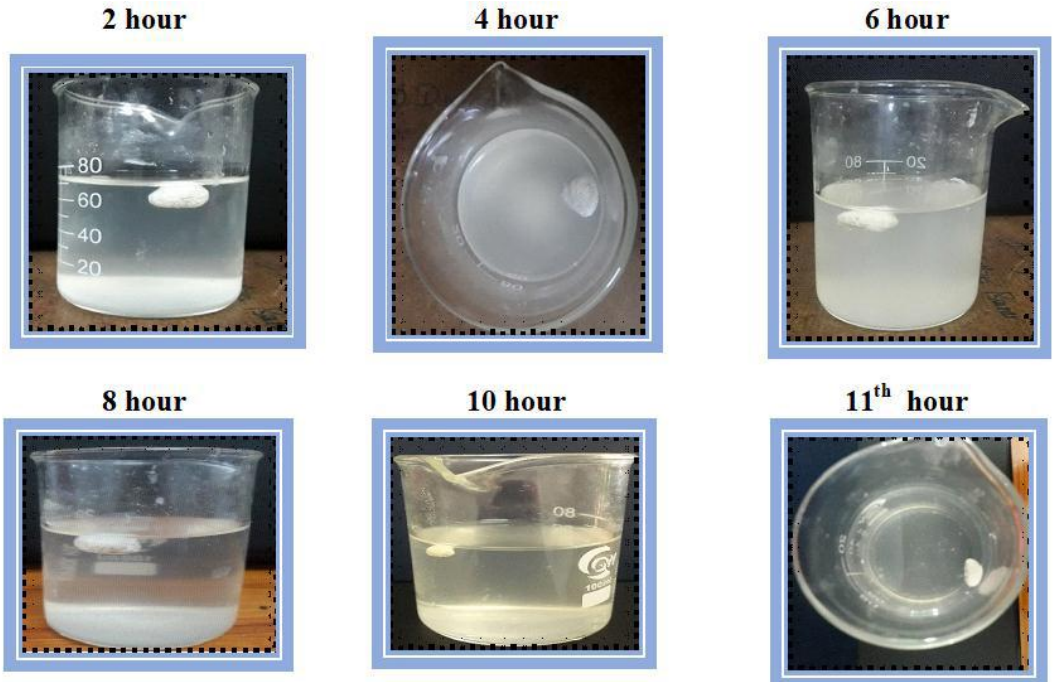


Fig 6: Total Floating time of F8 formulation.

Table 5: *In Vitro* Buoyancy Determination (F1- F9).

Formulation	Floating lag time (sec) Avg ± S.D	Total floating time (h)	Swelling index In 8 hr
F1	59 sec	Upto 10 h	44.21
F2	52 sec	Upto 12h	45.91
F3	69 sec	Upto 12h	47.64
F4	58 sec	Upto 10h	41.24
F5	57sec	Upto 12h	47.56
F6	56 sec	Upto 12h	49.57
F7	70 sec	Upto 10h	42.82
F8	50 sec	Upto 12h	48.97
F9	58 sec	Upto 12 h	46.51

3.4 *IN VITRO* DRUG RELEASE STUDIES

The *in vitro* drug release was observed that as the concentration of polymer is increased in formulations (F1 to F9) the time of drug release was decreased.

The release profiles were observed in the following order, Tamarind seed polysaccharide and HPMC K4M > Tamarind seed polysaccharide > HPMC K4M irrespective of the type of polymer. Among all the formulation, F8 was found to be optimal formulation it contain Tamarind Seed Polysaccharide 15% & HPMC 15% (1:1 in ratio), the FLT of these formulation was found to be 50 sec and 98% of the drug had been released in 12h when compare with other formulations. The rate of drug release was prolonged for a long time due to the better gel- forming ability of TSP& HPMC that slowed down the rate of diffusion of medium into the tablet. The results are shown in **Table.6** With graphical representation in **Fig.7.**

Table 6: *In vitro* Release data of Nizatidine floating tablets.

Time (Hrs)	Percentage of cumulative release F1 – F9 (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	20.28	17.4	18.99	19.12	16.94	18.21	16.42	15.22	14.96
2	27.52	20.24	17.91	25.12	21.42	23.15	24.63	19.98	21.93
3	28.64	29.54	26.87	33.92	29.54	33.12	32.84	23.16	30.24
4	35.97	37.95	35.83	46.23	31.54	37.45	41.05	37.93	42.65
5	42.63	49.42	40.79	55.12	38.54	42.15	49.27	48.69	55.12
6	56.29	60.23	53.74	59.22	46.15	55.72	56.15	52.13	62.82
7	62.94	68.57	62.70	67.42	52.19	61.21	65.69	58.92	67.31
8	68.26	75.42	71.66	79.12	58.49	66.15	73.90	64.52	73.75
9	77.64	82.24	80.62	83.52	78.21	70.43	82.29	71.57	78.24
10	94.12	88.5	89.57	96.99	80.23	78.12	94.11	85.94	82.92
11	94.12	93.12	91.53	96.99	85.29	87.65	94.11	90.41	90.87
12	94.12	96.21	95.21	96.99	96.21	95.92	94.11	98.28	95.25

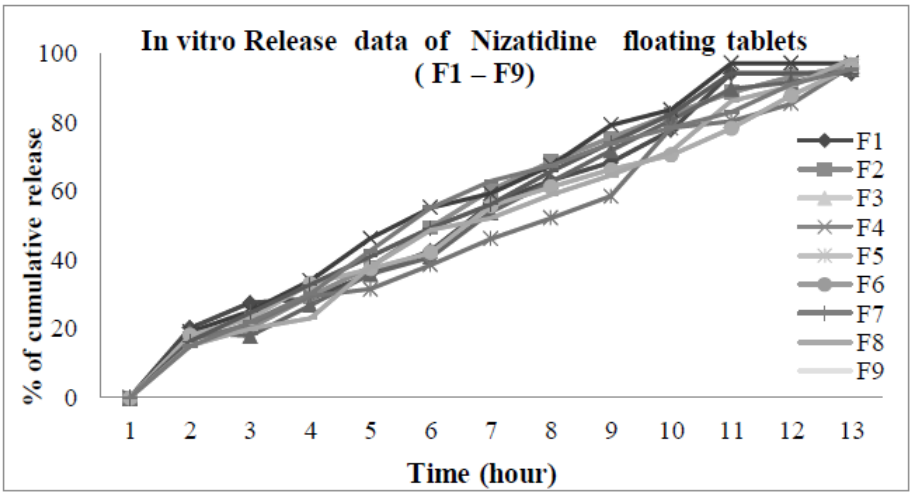


Fig 7: *In vitro* Release data of Nizatidine floating tablets F1 – F9.

3.5 *IN VITRO* RELEASE KINETICSSTUDIES

The kinetic studies of all the formulations showed that the Zero order plots were fairly linear as indicated by their high regression values (0.991 to 0.997) compared to first order plots. The „n" value of Koresmeyer-Peppas model of all formulations was between 0.929 to 0.998. Therefore, the most probable mechanism that the release patterns of all formulations followed was Non-fickian diffusion. Thus, the best formulation F8 Kinetic model values were shown in Table.7 & Fig.8,9.

Table 7: Comparative kinetic model for F8 is best fit to Korsmeryer -peppa's model kinetics.

Formulation	Zero order	First order	Higuchi model	Korsmeryer -peppa's model	
	r2	r2	r2	r2	N
F8	0.9951	0.9747	0.8911	0.9909	0.8898

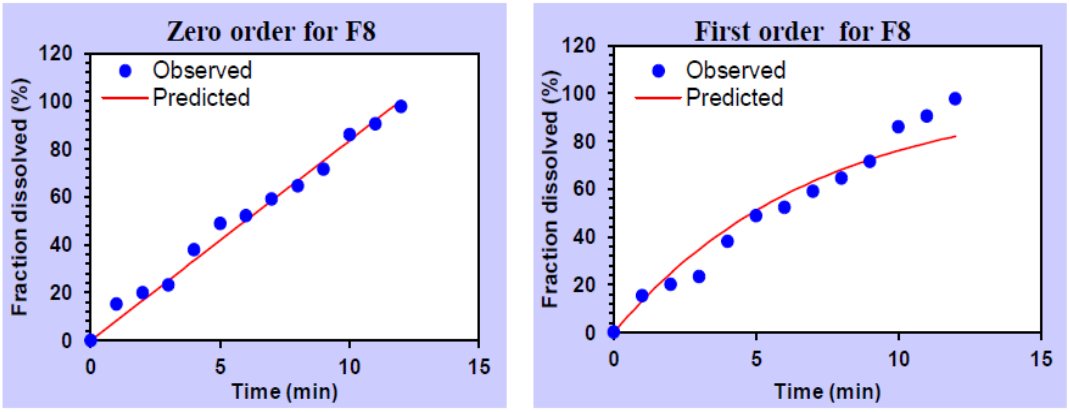


Fig 8: Comparative kinetic model for the Formulation F8 is best fit to Zero order kinetics.

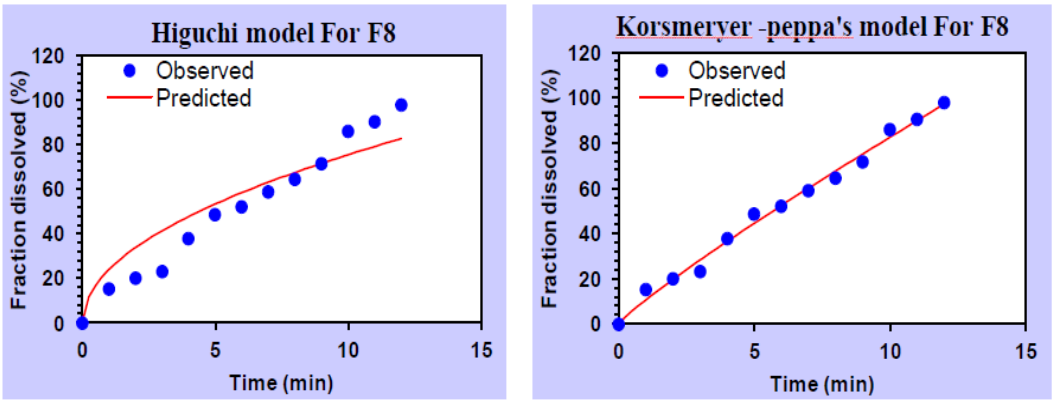


Fig 9: Comparative kinetic model for F8 is best fit to Korsmeryer -peppa's model kinetics.

3.6 SELECTION OF BESTFORMULATION

From the above results, F8 was selected the best formulation based on following character,

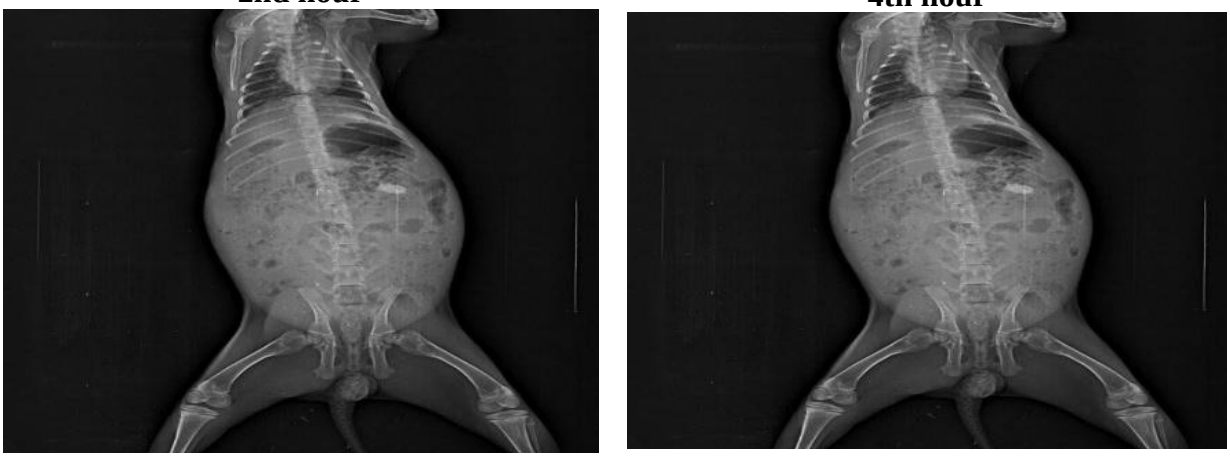
i. Floating lag time : 50 seconds.
ii. Total floating time : up to 12hrs.
iii. Swelling index : 65.57% (8hrs).
iv. *In-vitro* release profile : 98.28% (12hrs).
v. *In-vitro* release kinetics : Zero order kinetics (r^2=0.996).

3.7 *IN-VIVO* X-RAY STUDIES

***In vivo* X-ray for optimized formulation**

The appearance of the F8 formulated tablet can be visualized in the upper part of the stomach confirms its *in-vivo* floating behavior were the tablet can be visualized in 2nd hour, 4th hour, 6th hour, 8thhour, 10th hour, & 11th hour, X-rays were shown in **Fig.10.**

2nd hour **4th hour**



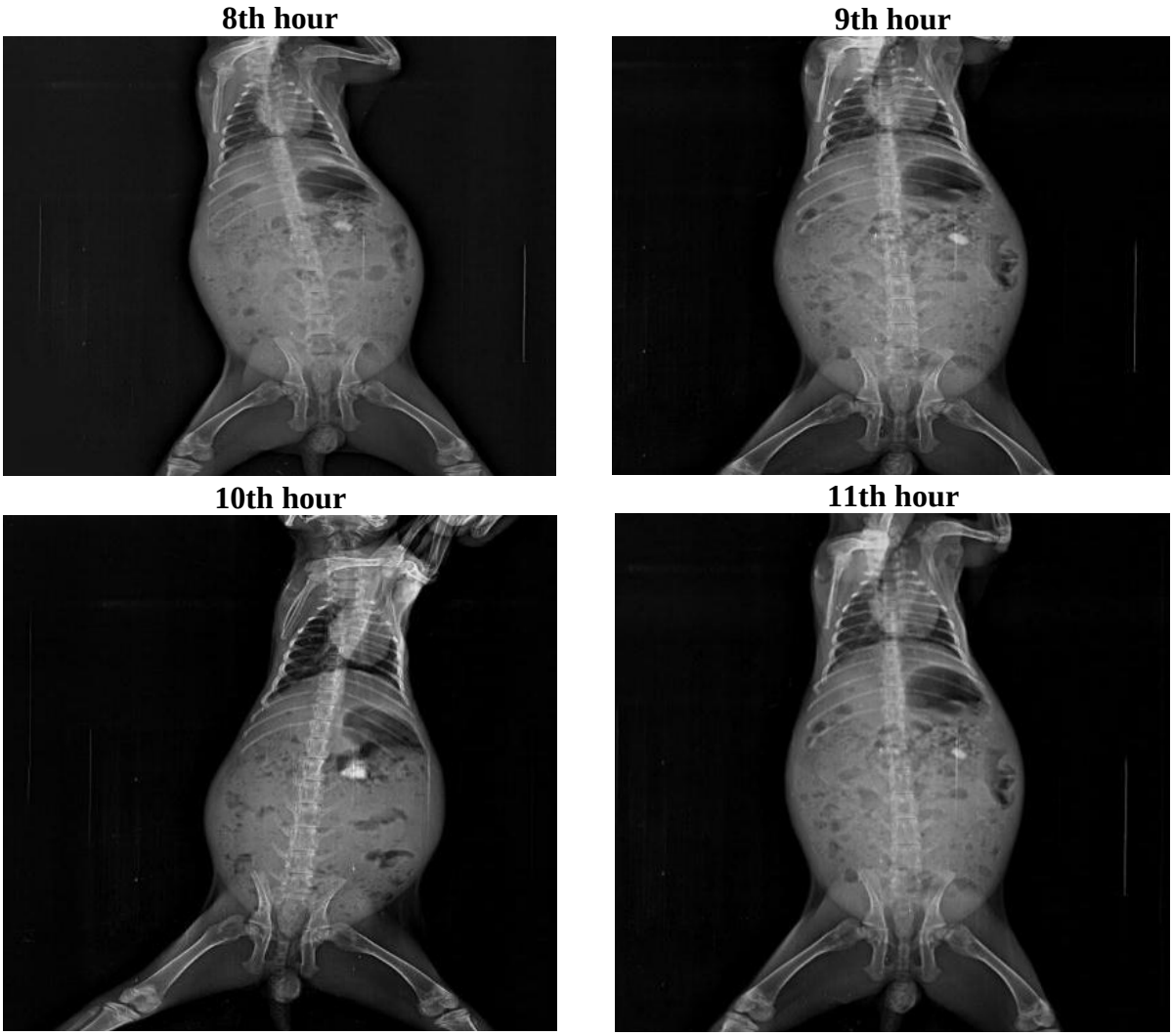


Fig 10: *In-Vivo* X-Ray Studies of Floating Tablet Of Nizatidine (F8).

10. EVALUATION OF SHORT TERM STABILITY STUDIES

Stability studies were carried out by using selected formulation F8 on the basic of in vitro drug dissolution studies. Form the data, the formulation found to be stable under the condition (40°C ± 2°C /75% RH ±5%) there was no significant change in the percentage of drug content **(Fig.11)** Thus the floating tablet remains stable under the condition for two months.

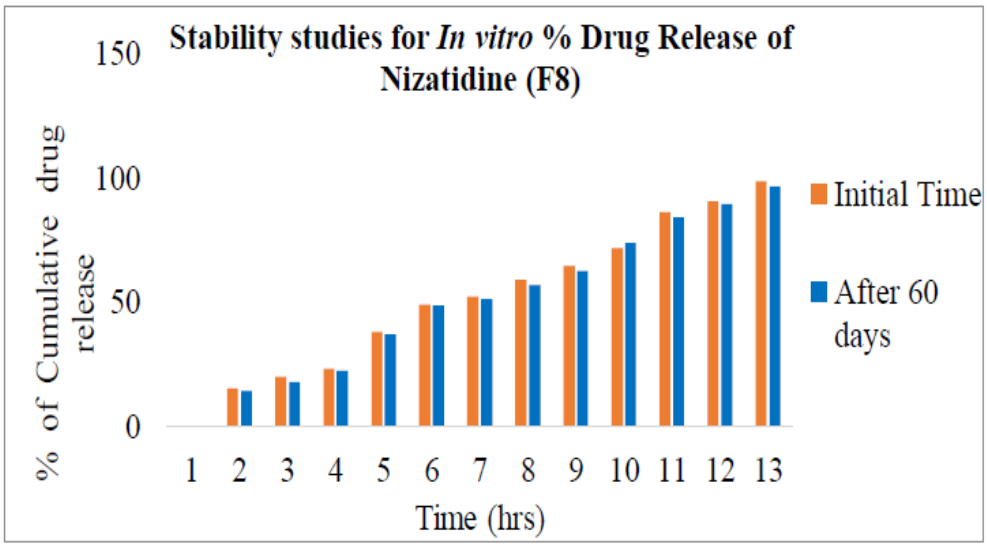


Fig 11: *In vitro* % drug Release of Nizatidine (F8) after 3 months stability studies.

CONCLUSION

Nizatidine floating tablets were successfully prepared with hydrophilic polymers Tamarind seed polysaccharide and HPMC K4M individually and in combinations in some ratio. It can be concluded that the combination of tamarind seed polysaccharide and HPMC in ratio of (1:1) can be used to develop controlled release floating tablets of nizatidine by incorporating sodium bicarbonate and citric acid for gas generation. However, clinical experiment on the human should be concluded with optimized formulation F8 in order to correlate *in vivo* performance with its *in vitro* behaviour. Use of Tamarind seed polysaccharides enhanced the floating lag time, maintained the Controlled release of drugs.

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