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FABRICATION, CHARACTERISATION AND *IN-VITRO* EVALUATION OF CONTROLLED RELEASE ORAL FLOATING DOSAGE FORM CARRYING ANTIULCER DRUG

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ABSTRACT

The aim of the present project is to design gastroretentive floating dosage form of Antiulcer drug. The tablets were formulated using direct compression technology by employing semi synthetic polymers like various grades of Methocel and natural polymers like xanthan gum and kondagogu gum. The FTIR and DSC study revealed that there is no drug-excipient interaction. The prepared tablets were evaluated for various physicochemical parameters such as flow properties, hardness, weight variation, friability, *in vitro* buoyancy (floating lag time, total floating time), swelling studies, drug content and *in-vitro* drug release. The in vitro drug release pattern of Nizatidine floating tablets was fitted to different kinetic models which showed highest regression for zero order kinetics with non fickian diffusion mechanism. Out of all formulations the one prepared with combination of HPMC K4M and K15M was optimized based on desired sustained release time (12hrs) and acceptable floating properties.

Key Words: Direct compression, Floating tablet, Floating lag time, Gastroretentive dosage form, *Invitro* release.

INTRODUCTION

Nizatidine is a H_2 receptor antagonist used for the treatment of gastric ulcer, peptic ulcer disease, and active duodenal ulcers. It does not show any demonstrable anti-androgenic effects and drug interactions compared to any other class of H_2Receptor Antagonists [1,2]. It is having applications in the field of local delivery of drug to the stomach and proximal part of small intestine and importantly in treating microorganisms(Helicobacter pylori [3,4]. Hydrochloric acid secreted by gastric parietal cells is majorly damaging and most consistent component form of refluxate. For this reason, current GRDDS pharmacotherapy focuses mainly on minimizing gastric acidity, either by neutralizing acid or by blocking major stimulator of this pump histamine (H2 receptor antagonist) [5]. Gastroretentive Drug Delivery Systems (GRDDS) would be retained in the stomach and release the drug there in a sustained manner, so that the drug would be supplied continuously to its site of absorption in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs for these drugs [6,7].

In recent years, several gastroretentive approaches like i) Floating drug delivery system [8] ii) expandable systems [9] iii) bioadhesive systems [10] and iv) High density systems [11], have been designed and evaluated with great success. Floating systems are of two types: A) effervescent systems B)Non- effervescent systems.

The delivery of drug to a human body can be achieved through several routes like oral, transdermal,

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topical and parenteral administration. Among this the oral ingestion is the predominant and most preferable routefor drug delivery [12]. Oral route is the most convenient and extensively used for drug administration [13]. Oral route has high patient acceptability, primarily due to ease of administration.

MATERIALS AND METHODS

Materials: Nizatidine is obtained as gift sample from Dr.Reddy's pharma Pvt Ltd, Hyderabad, Xanthan gum, Kondagogu gum, Lactose was obtained as gift sample from Cipla Pharma, Bangalore. Hydroxy Propyl Methyl Cellulose K-4M, K-15M, K-100M, was obtained as gift sample from A-Z Pharmaceuticals, Chennai. And all other chemicals used in formulations are Analytical Grade.

Formulation of Floating Tablets Of Nizatidine:

The composition of different formulations of Nizatidine floating tablets are shown in Table no 1**.** Nizatidine, HPMC K4M, HPMC K15M, HPMC 100M, Xanthan gum, Kondagogu gum were passed through sieve no. 80 separately. Sodium bicarbonate was passed through sieve no. 44. All the ingredients were mixed in the proportions shown in Table no.1. The powder blends were lubricated with Magnesium stearate (1% w/w) and Talc (2% w/w) and mixed for two to three minutes. These lubricated blends were compressed into tablets using 9 mm flat faced round tooling on a multiple punch tablet machine (Rimek mini press II). The compression force was adjusted to obtain tablets with hardness in the range of 4.5 to 5.5 kg/cm^2. Each tablet contained 150 mg of Nizatidine. Twenty one formulations were prepared and these were coded from F1 to F21.

Evaluation of Foating Tabets of Nizatidine

Prepared tablets were evaluated for post compression parameters like various quality control tests such as Tablet thickness and Diameter, Hardness, Friability, uniformity of weight, content uniformity of drug, drug release and other specific evaluation tests for GFDDS like floating lag time and total floating time. All the studies were performed in triplicate, and results were expressed as mean ± SD. In vivo studies in rabbit using x-ray method was carried out to determine the in vivo floating property of the developed formulation.

Tablet thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers.

Hardness

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this six tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability:

The friability test was carried out to evaluate the hardness and stability instantly. In Roche friabilator in which twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations i.e., 25 rpm for 4 minutes, the tablets were again weighed (w). The percent loss in weight or friability (F) was calculated by the formula

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

Where, F = friability
Wo = initial weight
W = final weight

Weight variation

Twenty tablets of each formulation were weighed using an electronic balance and average weight of twenty tablets and standard deviation were calculated.

Content Uniformity

This test is performed by taking twenty tablets were selected randomly, weighed and powdered. A quantity of powdered tablet equal to 150 mg of Nizatidine was dissolved in 0.1 N HCL in 100ml volumetric flask. The so formed sample was diluted and the absorbance was measured at 314 nm using 0.1 N HCl as blank and the % drug content was estimated using the following formula.

$$\% \text{ Drug content} = \frac{\text{Drug content (mg)}}{\text{Label claim (mg)}} \times 100$$

In Vitro Buoyancy Determination:

Floating Lag Time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium, at pH 1.2, temperature 37 ± 1˚C, paddle rotation at 50 rpm. It is measured using stopwatch. Shown in (figure.1)

Total Floating Time: The time taken by the tablet to float constantly on the surface of the simulated gastric fluid without pepsin, at pH 1.2, temperature 37 ± 1˚C, paddle rotation at 50 rpm. It is measured using stopwatch. Shown in (figure.1).

In vitro dissolution studies

Dissolution test was carried out using USP XXIV rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium (900ml). It was maintained at 37 ± 1˚C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with

dissolution fluid, wherever necessary and were analyzed for the Nizatidine at 314 nm by using a double beam UV spectrophotometer. Each dissolution study was performed for three times and the mean values were reported.

RESULTS AND DISCUSSION

Fourier Transform Infrared spectroscopic studies (FTIR):

A standard concentration of Nizatidine was prepared in 0.1N HCl and the absorbances were measured at 314 nm. Nizatidine is showing good linearity between 25-250 µg/ml with a correlation coefficient of 0.999.

The floatation was accomplished by incorporating gas generating agent, sodium bicarbonate into a swellable polymer.

FTIR and DSC studies of the pure drug Nizatidine and formulations showed that there was no drug polymer interaction.

Floating matrix tablets were formulated by using semi synthetic polymers such as HPMC K4M, HPMC K15M, HPMC K100M and natural polymers like Xanthan gum, Kondagogu gum.

The physico-chemical properties of all the formulations were found to be within the prescribed official limits.

Floating tablet formulations containing HPMC polymer showed less floating lag time than the formulations containing Xanthan gum.

The increase in polymer concentration and viscosity causes retarding of the drug release. Formulations containing higher polymer concentration had slower drug release when compared to formulations with lower concentration of polymers. Comparing the three different grades of methocel (K4M, K15M and K100M), it was found that combination of polymers containing HPMC K4M with less concentration of HPMC K15M provided better-controlled release characteristics with excellent drug release and in-vitro buoyancy. To study the effect of sodium bicarbonate on floating lag time and drug release xanthan gum formulations were selected as these showed increased floating lag time. It was observed that as the concentration of sodium bicarbonate increased drug release was increased to certain extent. Formulations with Xanthan gum, Kondagogu gum gave sustained release characteristics for 12 hours. Of the two natural polymers Kondagogu gum formulations showed desired release. Formulation F20 gave better-controlled drug release with desired loading dose in comparison to the all other formulations. Hence F20 formulation is optimized. The drug release pattern from the optimized formulations followed zero order kinetics with non fickian diffusion mechanism.

Table 1. Composition of different floating tablet formulations of Nizatidine

FC	Ingredients in mg							
	Drug	**HPMC (K100M))**	**HPMC (K4M)**	**HPMC (K15M)**	**Xanthan gum**	**Kondagogu gum**	**Sodium bicarbonate**	**Lactose**
F1	150	90					35	79.5
F2	150	120					35	42
F3	150		90				35	79.5
F4	150		120				35	42
F5	150		150				35	4.5
F6	150		180				40	18
F7	150			90			35	79.5
F8	150			120			35	42
F9	150			150			35	4.5
F10	150			180			40	18
F11	150				150		35	4.5
F12	150				120		35	34.5
F13	150				120		42	27.5
F14	150				120		52.5	17
F15	150				120		70	-
F16	150					150	35	4.5
F17	150					120	35	34.5
F18	150		75	75			35	4.5
F19	150		75	100			40	23
F20	150		100	75			40	23
F21	150		100	75			60	3

Table 2. FTIR peak positions (cm^{-1}) and assignments for Nizatidine drug and its combinations with Excipients

Nizatidine drug	Optimized formulation	Frequency range	Mode of vibration
2941.44	2939.52	2950-2800	CH
1469.76	1469.76	1454-1475	CH_2
2827.64	2827.64	2850-2815	CH_3
1469.75	1469.75	1475	C=C
1261.45	1261.45	1360-1250	C-N
3278.99	3278.99	3500-3180	N-H
1375.25	1377.17	1380-1360	NO_2
_	3404.36	3400-3300	OH
_	2351.23	2800-2340	OH
_	1072.42	1260-1000	CO
_	1058.92	1300-1000	C-O-C

Table 3. DSC melting points of the selected formulations

Formulations	DSC melting point in °C
Pure drug Nizatidine	138.4
Optimized formulation	136

Table 4. Results of Physiochemical properties of Nizatidine Floating Tablets

Formulation Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm2)	Friability (%)	Drug content(%)	Weight variation(mg)
F1	4.15±0.05	8.9±0.09	4.76±0.25	0.503	99.89±1.75	349.6±1.17
F2	4.15±0.03	8.9±0.1	5.23±0.25	0.543	99.93±2.71	350±1.13
F3	4.2±0.04	8.8±0.15	6.16±0.28	0.488	102.63±2.1	349.8±0.78
F4	4.16±0.036	8.9±0.11	5.03±0.05	0.644	99.56±0.75	349.8±0.73
F5	4.19±0.025	8.9±0.05	5.06±0.11	0.488	99.96±0.56	349.7±1.08
F6	4.25±0.025	8.9±0.11	5±0.2	0.689	98.5±1.00	399.8±0.8
F7	4.17±0.092	8.9±0.05	5.16±0.35	0.472	101.7±1.60	350.05±1.14
F8	4.2±0.025	8.8±0.11	5.83±0.28	0.644	101.51±0.75	349.85±1.11
F9	4.03±0.134	8.9±0.05	5.3±0.17	0.555	102.03±1.5	350±0.62
F10	4.32±0.39	8.9±0.17	4.66±0.28	0.687	99±0.54	399.9±1.11
F11	4±0.20	9.03±0.11	5.33±0.28	0.517	98.1±1.21	349.9±1.16
F12	4.1±0.108	8.9±0.05	5.23±0.25	0.538	98.26±0.8	349.9±0.5
F13	4.15±0.15	8.9±0.11	5.16±0.28	0.661	99.4±1.01	350±0.99
F14	4.18±0.02	9±0.1	5.33±0.28	0.743	99.93±0.51	350±0.72
F15	4.12±0.18	8.9±0.1	4.83±0.28	0.593	100.66±1.74	349.4±1.21
F16	4.13±0.15	9±0.05	4.93±0.11	0.484	98.9±0.45	349.9±1.11
F17	4.1±0.03	8.9±0	5±0.2	0.638	100.46±0.96	349.6±0.98
F18	4.2±0.31	8.83±0.05	5.33±0.28	0.592	103.03±0.45	349.17±1.48
F19	4.2±0.31	9±0	4.83±0.28	0.76	99.7±1.31	399.75±0.98
F20	4.2±0.09	8.93±0.05	4.66±0.28	0.561	102.83±0.35	399.6±1.02
F21	4..25±0.09	8.93±0.05	5.5±0.3	0.503	98.6±1.4	398.9±1.39

Table 5. Results of *In vitro* Buoyancy study of Nizatidine Floating Tablets

Formulation code	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
F1	140	8
F2	190	>12
F3	88	6
F4	82	>8
F5	95	>12

F6	110	>12
F7	90	6
F8	82	>8
F9	104	>12
F10	195	>12
F11	756	>24
F12	540	>16
F13	375	>12
F14	268	>12
F15	240	>12
F16	140	>12
F17	105	>12
F18	98	>12
F19	150	>12
F20	110	>12
F21	100	>12

Table 6. *Invitro* drug release of Nizatidine from formulations with HPMC K100M

Time(min)	Formulation code	
	F 1	**F 2**
0	0	0
60	19.85±0.377	16.55±0.75
120	29.5±0.75	27.58±0.38
180	35.86±0.38	36.69±0.76
240	41.76±0.532	41.89±0.83
300	49.29±0.988	48.51±0.615
360	56.86±1.3	55.39±0.47
420	61.77±1.0	63.94±0.85
480	71.86±1.66	74.59±1.63
540	79±1.31	80.45±0.28
600	93.06±1.42	86.67±0.583
660	99.58±0.29	92.86±0.74
720		95.51±0.54

Table 7. In vitro drug release profile of Nizatidine from formulations with HPMC K4M

Time (min)	Formulation code			
	F3	**F4**	**F5**	**F6**
0	0	0	0	0
60	58.05±0.75	44.1±0.39	39.7±0.45	31.1±0.9
120	66.77±0.45	50.24±0.37	43.47±0.82	35.01±0.382
180	77.24±0.83	55.92±0.67	58.16±0.68	44.81±0.66
240	90.22±0.54	64.83±0.68	68.43±0.69	51.15±0.291
300	95.61±0.68	71.54±0.91	74.03±1.47	59.09±0.6
360	97.33±0.69	78.83±1.51	79.61±0.85	63.42±0.75
420	102.01±0.39	83.70±0.87	83.44±0.85	68.55±0.56
480		93.51±1.78	90.95±1.08	79.57±0.37
540		99.56±0.32	94.94±0.69	85.61±1.06
600			97.4±0.412	91.77±1.05
660			99.97±0.27	95.35±0.46
720				98.42±0.361

Table 8. In vitro drug release profile of Nizatidine from formulations with HPMC K15M

Time (min)	Formulation code			
	F7	F8	F9	F10
0	0	0	0	0
60	47.1±0.6	38.5±0.52	34.5±0.6	28.1±0.82
120	56.66±0.45	48.91±0.53	43.24±0.905	33.6±0.45
180	58.87±0.68	55.28±0.53	45.38±0.76	38.58±0.605
240	65.5±0.53	61.09±1.14	52.53±0.53	44.75±0.455
300	75.61±0.45	65.97±0.69	58.96±1.21	49.64±0.836
360	82.22±0.74	68.98±0.46	62.94±1.45	57.49±0.94
420	91.21±0.54	72.66±0.47	69.93±0.49	59.49±0.77
480	96.16±1.66	86.3±1.3	79.78±0.75	64.46±0.85
540	99.58±0.47	91.97±0.63	87.89±1.01	73.32±1.46
600		97.96±0.49	93.07±0.86	80.24±0.49
660		101.39±0.53	97.17±0.63	89.44±0.35
720			101.89±0.41	96.18±1.04

Table 9. In vitro drug release profile of Nizatidine from formulations with combination of HPMC K4M and HPMC K15M

Time (min)	Formulation code			
	F11	F12	F13	F14
0	0	0	0	0
60	34.6±0.826	18.09±0.83	24.75±0.6	29.55±0.45
120	44.08±0.372	29.34±0.6	31.63±0.75	35±0.531
180	51.83±0.377	34.7±1.13	40.05±0.46	50.2±0.38
240	58.31±0.305	46.99±0.66	46.22±0.52	59.58±0.44
300	60.93±0.773	50.8±0.67	52.83±0.39	61.95±1.357
360	67.82±0.46	56.33±0.44	60.57±1.02	70.99±1.41
420	77.54±0.76	60.12±0.37	65.5±0.75	76.13±0.462
480	90.66±0.47	64.27±2.25	71.5±0.53	78.44±1.94
540	96.85±1.15	73.82±0.62	78.29±1.12	83.06±0.685
600	98.83±0.347	79.51±0.69	85.51±0.4	93.85±1.345
660	99.87±0.985	89.74±2.15	92.73±0.61	99.67±0.9
720	102.94±0.376	94.07±0.51	98.03±0.3	102.8±0.22

Table 10. In vitro drug release profile of Nizatidine from formulations with xanthan gum and kondagogu gum

Time (min)	Formulation code		
	F15	F16	F17
0	0	0	0
60	14.5±0.62	18.24±1.05	21.3±0.3
120	17.02±0.829	25.84±1.44	32.31±0.52
180	22.46±0.697	30.23±0.73	41.09±0.45
240	30.42±0.6	38.6±0.6	50.12±0.76
300	34.31±0.826	45.5±1.67	59.45±0.54
360	37.7±0.305	54.96±0.83	64.37±1.49
420	43.35±0.372	62.37±1.49	73.14±0.37
480	48.19±0.45	72.3±0.91	81.02±0.37
540	54.55±1.24	78.39±0.16	87.71±0.82
600	55.64±0.29	82.1±0.59	90.98±0.54
660	59.8±0.54	89.07±0.52	96.13±0.26
720	64.77±0.62	93.64±0.31	99.93±0.14

Table 11. In vitro drug release profile of Nizatidine from formulations with xanthan gum Using increasing concentration of sodium bicarbonate

Time (min)	Formulation code			
	F12	F13	F14	F15
0	0	0	0	0
60	15.45±0.6	16.95±0.3	21.5±0.904	22.9±0.45
120	22.88±0.54	21.48±0.372	28.26±0.37	26.27±0.61
180	28.96±0.52	26.58±0.408	33.96±0.61	32.51±0.6
240	32.62±0.68	34.1±0.6	38.6±0.487	43.4±1.13
300	42.2±0.97	38.33±0.74	43.72±0.697	48.33±0.83
360	47.23±0.37	47.56±0.6	53.56±0.58	57.04±0.53
420	51.04±0.67	53.75±0.52	58.8±1.42	63.9±0.6
480	57.32±3.04	57.49±0.53	61.27±0.606	67.75±0.54
540	62.38±0.62	61.7±0.466	65.4±1.65	72.57±0.388
600	66.27±0.706	67.99±0.54	72.35±2.29	76.61±0.31
660	71.37±0.58	74.5±0.6	79.49±0.378	82.07±0.66
720	75.61±0.51	81.51±0.38	83.32±0.612	84.62±0.305

Table 12. Different kinetic models for Nizatidine floating tablets

Formulation code	Zero order	First order	Higuchi	Korsemayer peppas		Hixon crowell
	R^2	R^2	R^2	R^2	n	R^2
F1	0.991	0.641	0.953	0.978	0.665	0.833
F2	0.992	0.913	0.984	0.995	0.713	0.968
F3	0.943	0.973	0.975	0.986	0.813	0.839
F4	0.997	0.693	0.971	0.984	0.745	0.872
F5	0.953	0.683	0.985	0.97	0.701	0.946
F6	0.991	0.867	0.98	0.969	0.508	0.954
F7	0.988	0.785	0.969	0.947	0.355	0.924
F8	0.985	0.815	0.965	0.964	0.402	0.746
F9	0.992	0.838	0.96	0.949	0.457	0.752
F10	0.989	0.799	0.947	0.948	0.503	0.895
F11	0.992	0.990	0.981	0.976	0.65	0.994
F12	0.993	0.988	0.989	0.993	0.653	0.996
F13	0.996	0.953	0.973	0.976	0.664	0.978
F14	0.994	0.957	0.978	0.98	0.562	0.980
F15	0.982	0.986	0.985	0.972	0.586	0.995
F16	0.993	0.926	0.977	0.981	0.700	0.973
F17	0.982	0.668	0.995	0.998	0.638	0.926
F18	0.97	0.807	0.969	0.969	0.469	0.867
F19	0.987	0.871	0.978	0.991	0.645	0.940
F20	0.998	0.812	0.981	0.984	0.571	0.926
F21	0.976	0.741	0.986	0.983	0.521	0.772

Figure 1. Photographs showing *in vitro* buoyancy study of optimized formula F20 in 0.1 N HCl at different time intervals

At initial time

At 110 seconds

At 120 seconds

At 4 hours

At 6 hours

At 12 hours

Figure 2. FTIR spectra of Nizatidine

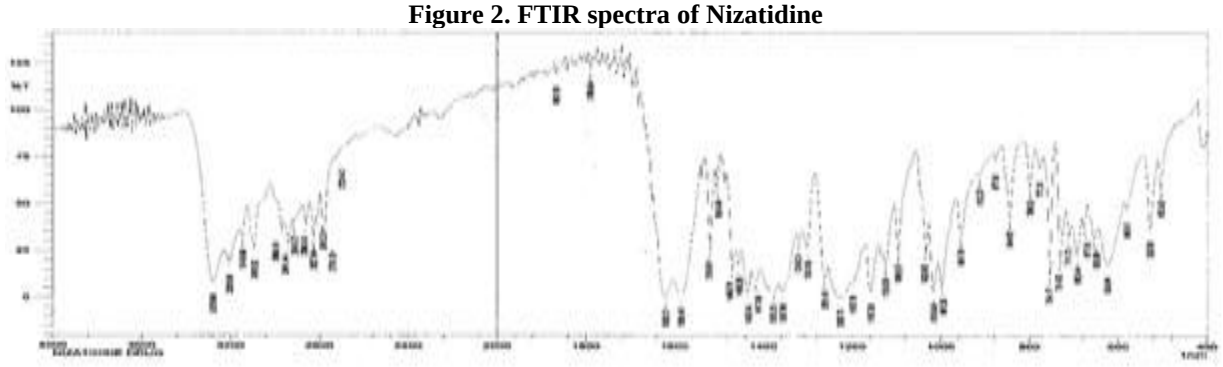


Figure 3. FTIR spectra of HPMC K4M

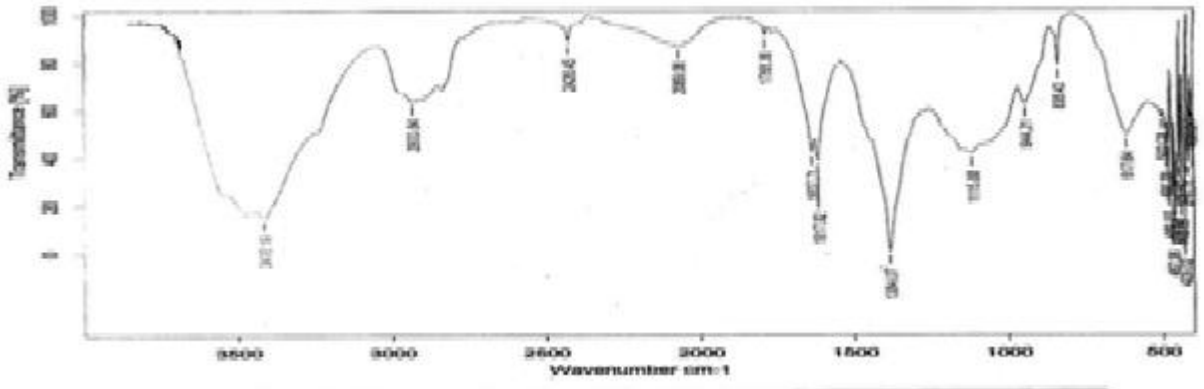


Figure 4. FTIR spectra of HPMC K15M

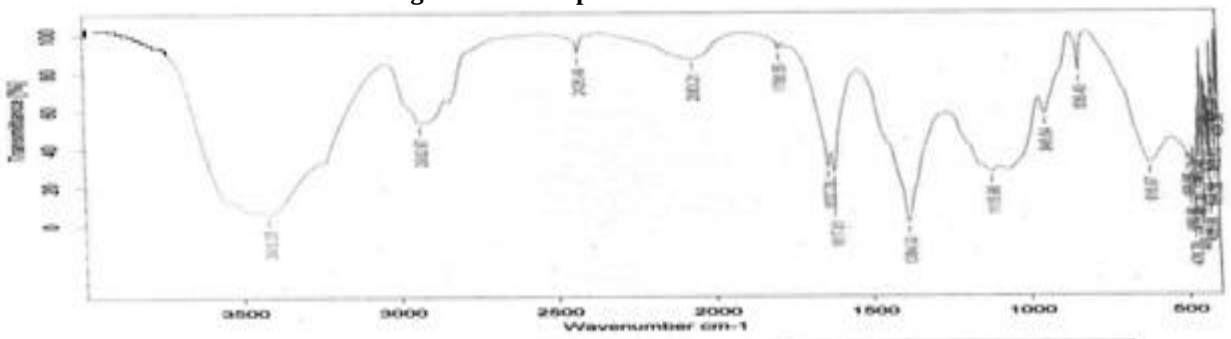


Figure 5. FTIR spectra of Nizatidine, HPMC K4M, HPMC K15M(optimized formulation)

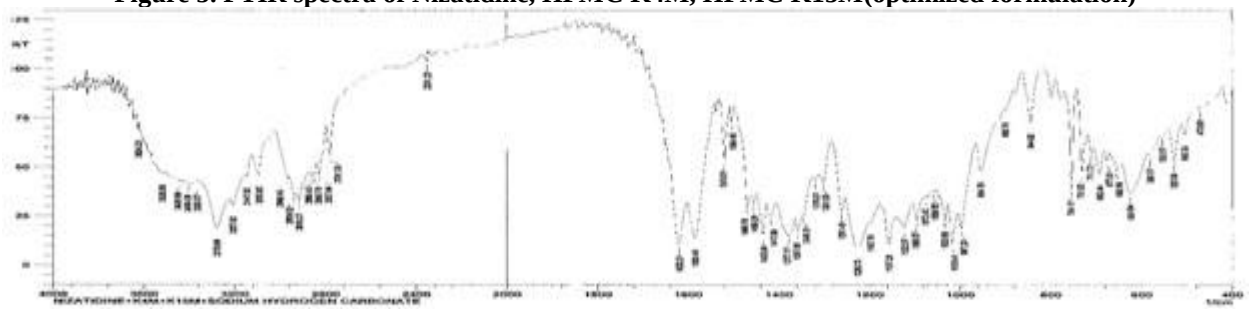


Figure 6. FTIR spectra of Xanthan gum

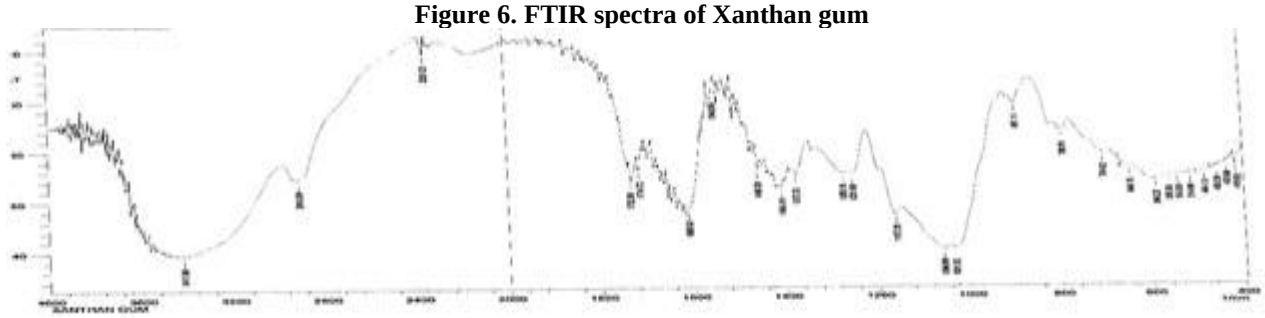


Figure 7. FTIR spectra of Nizatidine, Xanthan gum

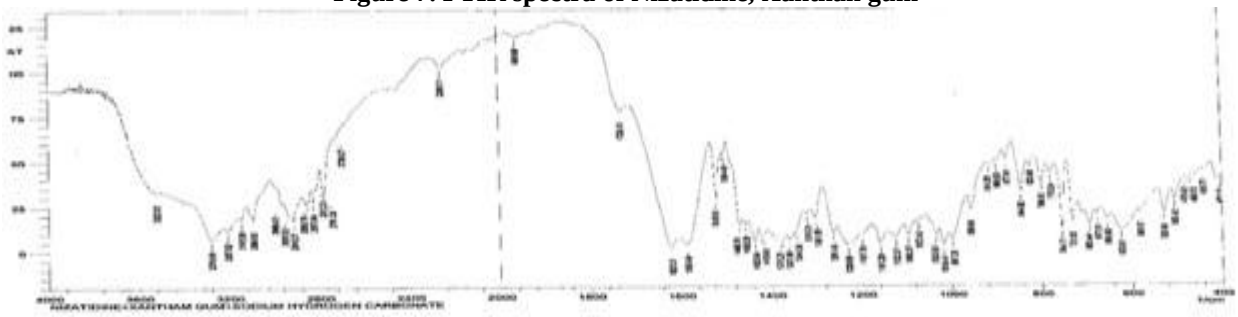


Figure 8. FTIR spectra of Kondagogu gum

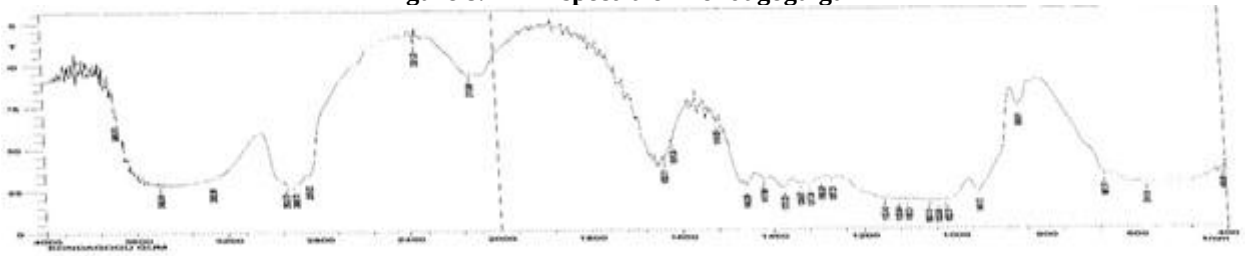
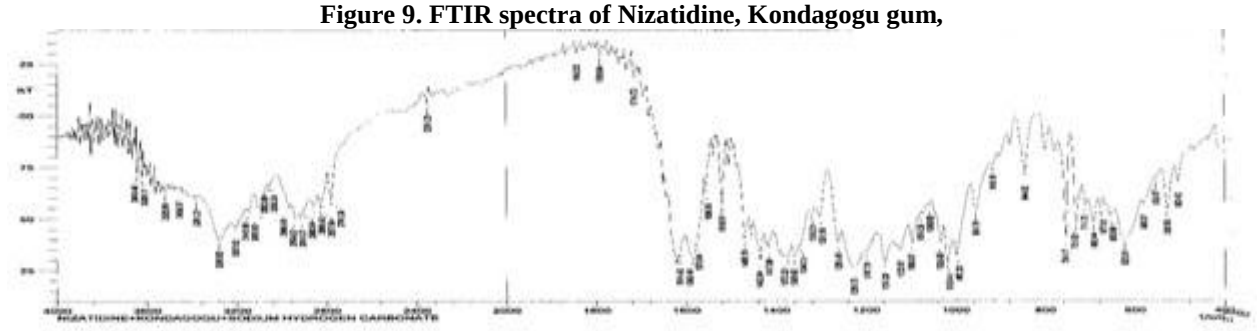


Figure 9. FTIR spectra of Nizatidine, Kondagogu gum,



Differential scanning calorimetric study (DSC):

Figure 10. DSC of pure drug Nizatidine

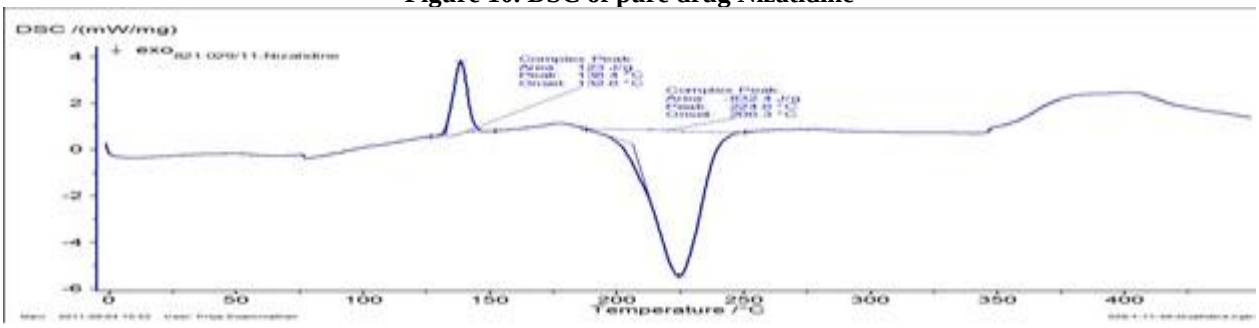
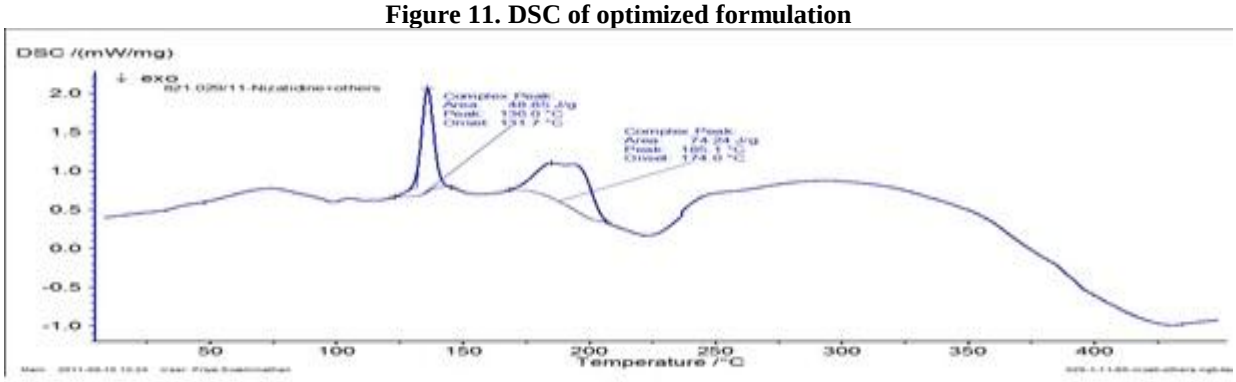


Figure 11. DSC of optimized formulation



CONCLUSION

In conclusion, Among the various GRDDS formulations studied, the formulation prepared with combination of HPMC K4M and HPMC K15 M showed the best result in terms of the required lag time (110 sec) and floating duration releasing 98.03 ± 0.3% of the drug in 12 h and is considered as the ideal formulation. The dosage form can control the release, avoid dose dumping and extend the duration of action of a drug with prolonged floating time. The present study demonstrates that Nizatidine could be successfully delivered to provide relief of gastric acidity by design of a floating formulation, where loading dose of Nizatidine will provide relief from acid secretion after meals while maintenance dose will provide controlled release for 12 hrs. The effervescent based GRDDS is a promising approach to achieve in vitro buoyancy for the effective treatment of gastric acidity and upper segment gastrointestinal disorders.

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