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Research article

DESIGN AND CHARACTERIZATION OF RAFT FORMING SUSPENSION OF RANITIDINE FOR GASTRO ESOPHAGEL REFLUX DISEASE

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ABSTRACT

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. Floating Rafts have been used in the treatment of Gastric esophageal reflux disease (GERD). The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids. The present study is to develop a formulation, optimization and evaluation of raft forming suspension of Ranitidine using different raft forming agents Sodium Alginate, Guar gum, Carbopol 974P, and Xanthan gum used in combination for good raft development and improve bioavailability. It starts with preliminary screening of raft forming agent and the design of the experiment done by 3^2 factorial designs optimized formulation. Later F3 selected for stability study as per ICH guidelines.

Key Words:- Ranitidine, Raft Forming Suspension, GERD.

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INTRODUCTION

Gastroesophageal reflux, also known as acid reflux, occurs when the stomach contents reflux or back up into the esophagus and/or mouth (Amit KN *et al*., 2010).

When we eat, food is carried from the mouth to the stomach through the esophagus, a tube-like structure that is approximately 10 inches long and 1 inch wide in adults. The esophagus is made of tissue and muscle layers that expand and contract to propel food to the stomach through a series of wave-like movements called peristalsis (Rabia Aslam *et al*., 2014). At the lower end of the esophagus, where it joins the stomach, there is a circular ring of muscle called the lower esophageal sphincter (LES). After swallowing, the LES relaxes to allow food to enter the stomach and then contracts to prevent the back-up of food and acid into the esophagus.

However, sometimes the LES is weak or becomes relaxed because the stomach is distended, allowing liquids in the stomach to wash back into the esophagus occasionally in all individuals. Most of these episodes occur shortly after meals, are brief, and do not cause symptoms. Normally, acid reflux should occur only rarely during sleep (Chaturvedi S *et al*., 2013).

MATERIALS AND METHODS

Table 1. List of Materials Used

S.No	Ingredients	Application	Manufacturers
1	Ranitidine	Active Pharmaceutical Ingredient	Orchid Pharmaceuticals
2	Sodium alginate	Raft forming agent	Protanal LFR5/60 Signet
3	Guar gum	Raft forming agent	Choltrol
4	Xanthan gum	Raft forming agent	Satiaxane
5	Carbopol 974p	Raft forming agent	Signet FMC polymer
6	Sodium bi carbonate	Gas forming agent	Signet FMC polymer
7	Calcium carbonate	Raft strengthening agent	Signet FMC polymer
8	Sodium chloride	Tonicity	Triveni chemicals
9	Sodium hydroxide	pH Neutralizer	Sigma-Aldrich
10	Glycerol	Co-solvent	Dhruvika chemicals trading Pvt.Ltd
11	Sodium Saccharin	Sweetening agent	Jay chem. Marketing
12	Sodium benzoate	Preservative	Nebula chemicals co., Ltd

PREFORMULATION STUDY

Physical appearance (Indian Pharmacopeia, 2014)

Ranitidine is a white to pale yellowish white crystalline powder.

Solubility study (Narashimha Swamy Lakka *et al*., 2012)

Solubility studies done by using shake flask method; An excess amount of Ranitidine was transferred to a 250 ml of conical flask containing 100ml of dissolution media. The solubility study was performed at a temperature of 25^0C. The flask was shaken for 24 hrs by keeping conical flask on rotary shaker at 200 RPM. A portion of drug solution dissolved in buffer solution was filtered and absorbance was measured at 265 nm using UV-visible double beam spectrophotometer. The amount of drug dissolved in dissolution medium were calculated and reported. The test was prepared in triplicate in the selected buffer (pH 1.2, 4.4, 6.8 and 7.4 buffer solutions).

Particle size determination (Manavalan R *et al*., 2005)

The size was determined by using eye piece micrometer. The eye piece micrometer was calibrated using stage micrometer. A smear of drug was prepared on a glass slide and the eye piece micrometer was used to determine the particle size.

Drug and excipients compatibility study

The drug and excipients chosen for the formulation were screened for compatibility study by using Fourier transformer infrared (FT-IR).

FT-IR Analysis for compatibility study

Drug excipients interactions were checked by comparing the FT-IR spectra of pure drug (Ranitidine) and FT-IR spectra of physical mixture of drug and excipients. In the present study potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromide crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded.

Preparation of standard calibration curve of Ranitidine:

I Stock solution: A weighed amount of Ranitidine (100 mg) was taken in a 100 ml volumetric flask and dissolved in 50 ml of 0.1N hydrochloric acid. Final volume was made up to the mark with 0.1 Hydrochloric acid.

II Stock solution: From the I stock solution 1 ml was withdrawn and diluted to 100 ml with 0.1N hydrochloric acid to get a concentration of 10 mcg/ml. From this standard stock solution samples of 2, 4, 6, 8, and 10 ml were pipette out into 10 ml volumetric flasks. The volume was made up to the mark with 0.1 N hydrochloric acid to get final concentration of 2, 4, 6, 8, and 10 mcg/ml. The absorbance was measured at 265 nm using UV-visible double beam spectrophotometer.

Formulation of Raft Forming Suspension

Steps Involved in Preparation of Raft Forming Suspension of Ranitidine (Faizanurrab *et al*., 2015)

Step 1: Drug and other ingredients were weighed accurately. The formulas for the different preliminary batches are shown Table 3.

Step 2: Required vessels were sterilized in hot air oven at 60^oC.

Step 3: Mucilage of gums were prepared by hydration using a part of vehicle. Carbopol 974P [64] was dispersed in distilled water and the pH neutralized with 1% sodium chloride. Guar gum[65] and Xanthan gum were dispersed in glycerol. Sodium Saccharin was dissolved in water.

Step 4: Drug was dispersed in purified water.

Step 6: Solid components like sodium alginate, sodium bicarbonate, sodium chloride and calcium carbonate of the formulation were finely triturated with aid of mortar and pestle.

Step 7: Sodium alginate, sodium bicarbonate, sodium chloride and calcium carbonate were placed in a beaker containing water and stirred for 1 h. After one hour of stirring drug dispersion was added and vigorously stirred in the mechanical stirrer for 5 min.
Step 8: Guar gum or Xanthan gum or Carbopol dispersion was added to above mixer. Sodium Saccharin solution was added with continuous mixing. Sodium benzoate and pepper mint flavor were added.
Step 9: Finally the suspension was transformed into amber color bottle.

Preliminary Screening (Mitul Patel *et al*., 2014)

Preliminary screening was carried out to select a good raft-forming agent, which has good *in-vitro* gelation time, raft weight and Acid neutralizing capacity. Four different raft forming agents like sodium alginate, guar gum, xanthan gum and Carbopol 974P were used in combination to get good raft development. A totally six formulations were prepared and evaluated for *in-vitro* gelation time, floating time and Acid neutralizing capacity. From the preliminary results, guar gum chosen for further studies using 3^2 factorial designs.

Optimization by 3^2 Full Factorial Designs

A 3^2 randomized full factorial design was used in the present investigation. In this design three factors were evaluated, each at two levels, and experimental trials were performed at all nine possible combinations. Amount of sodium alginate and amount of Guar gum (GG2) were chosen as independent variables in 3^2 full factorial design, While dependent variable were selected as per below.
1) *In-vitro* gelation time
2) Raft weight
3) Acid neutralization capacity
Different levels and their respective values are depicted in Table 1. The formulation layout of the factorial batches F_1 - F_9 shown in Table 4.

Evaluation of Raft Forming Suspension of Ranitidine
***In Vitro* Gelation Time/Floating Lag Time**

The time required to convert suspension into raft is referred to as floating lag time. For determination of floating lag time, 10 ml of suspension was added to 250 ml beaker containing 100 ml of 0.1N hydrochloric acid. The time required to develop raft and clears the lower portion of the beaker was noted as floating lag time or in vitro gelation time.

Determination of Sedimentation Volume

Sedimentation volume was recorded as ultimate settled volume relative to the total volume expressed as a percentage after allowing the suspension to stand for 10 days. In some cases on the top of the suspension as well as settled and here combined volumes were taken for the ultimate settled volume.

Sedimentation Volume = $F = Vu / Vo$
Vu – Final or ultimate volume of sediment
Vo – Original volume of suspension before settling

Floating Time

It is used to describe total time to which the raft remains floating on the liquid. For this 250 ml beaker was used in which 100 ml of 0.1N hydrochloric acid was added. 10 ml of suspension was added to it and time to which raft floated on the liquid was noted.

Raft Weight

For this study, 250 ml of beaker was used in which 100 ml of 0.1N hydrochloric acid was added. To this, 10 ml of suspension was added; raft was allowed to develop completely. For complete raft development, the beaker kept aside for 30 minutes. After raft development, the remaining liquid was decanted carefully. The raft was placed on a butter paper and the liquid was soaked by using tissue paper. Finally the dried raft was weighed directly and the raft weight was noted.

Raft Volume

For determination raft volume the following steps are applied. The empty beaker was completely dried and weighed and noted as W1. In this beaker 100 ml of 0.1N hydrochloric acid was added as raft developing liquid, and the weight was noted as W2. At this point the level to which raft developing liquid was added was marked. To this beaker 10 ml of suspension was added. For complete raft development it was kept aside for few minutes. After raft development, the remaining liquid was decanted and the raft was dried by using tissue paper. The dried raft was weighed and noted down as W3. This dried raft was added to a beaker used for raft development and filled with purified water up to the mark made while 100 ml of raft developing liquid was added. After filling with water, beaker was again weighed and noted down as W4. After noting all four weights, the raft volume was calculated by using following formula.
Raft volume = (W4-W1)-(W2-W1-W3)

***In Vitro* Drug Release Studies**

The in vitro dissolution study was determined by using USP dissolution testing apparatus. The paddle shaft was used which was rotated at 50 rpm and system was maintained at 37^0C. For this study 500 ml of 0.1N hydrochloric acid was added to the beaker. The paddle shaft was moved down and 10 ml of raft forming suspension was added to beaker and raft was allowed to develop for 5 min. Then shaft was started to rotate at 50 rpm and 1 ml of sample was withdrawn in 10 ml volumetric flasks at interval of 1 h. To maintain sink condition 1ml of 0.1N hydrochloric acid was added after sampling. After sampling, the volume was made up to mark with 0.1N hydrochloric acid. Then absorbance was taken at 265 nm by

using UV visible Double beam spectrophotometer to determine the concentration. By, applying dilution factor concentration in mg/ml was obtained.

Acid Neutralization Capacity (Patel M *et al*., 2014)

10 ml of suspension was taken in a 250-ml beaker. Water was added to make a total volume of about 70 ml, heated to 37°C and stirred continuously by maintaining the temperature at 37°C. 30 ml of 1M hydrochloric acid (previously heated to 37°C) was added and mixture was maintained at 37°C for 15 minutes with continuous stirring. The excess acid was titrated with 1M sodium hydroxide to a pH of 3.5. The number of meq of acid consumed by the tablet tested was calculated by the following formula:

Total mEq = $(V_{HCl} * N\ HCl) - (V_{NaOH} * N_{NaOH})$

Where, M HCl = molarity of hydrochloric acid
M NaOH= molarity of sodium hydroxide
V NaOH= volume of sodium hydroxide

Content Uniformity

Accurately about 1.700 gm of suspension containing 20 mg of Ranitidine was weighed in 100 ml volumetric flask and the volume was made up with 0.1N hydrochloric acid.The above solution was centrifuged and the supernatant liquid was collected. From this 5 ml was taken and made up the volume with 0.1N hydrochloric acid. Then absorbance was taken at 265 nm by using UV visible spectrophotometer to determine the concentration.

Viscosity of Suspension

The viscosity of the suspension was determined by using Brookfield viscometer. For determination of viscosity, spindle of various numbers are used and rotated at different speed in ascending order. Then, torque experienced by the spindle was used as a function to determine the viscosity.

Stability Studies (Shailesh T Prajapati *et al*., 2012)

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess drug and formulation stability, short term stability studies were done for 1 month. The stability studies were carried out for GG2 and F6 formulations. The formulations were sealed in amber color bottle and kept in a stability chamber maintained at 40 ± 2°C/75 ± 5% relative humidity (RH) and 30 ± 2^0C/55 ± 5% RH for 1 month. The optimized formulation sealed in amber color bottle was also kept at room temperature and humidity condition. At the end of the storage time, the samples were analyzed for floating lag time, in vitro drug release and % drug content. The in vitro drug release profiles for both formulations (initial and after storage at 40 ± 2°C/75 ± 5% RH and 30 ± 2^0C/65 ± 5% RH for 1 month) were compared by the similarity factor.

RESULTS AND DISCUSSION

Table 2. **Solubility Profile of Ranitidine at Different** pH

S. No	Buffer (pH)	Solvent in ml used to dissolve 1g solute	Solubility profile
1	pH 1.2	25.32	Soluble
2	pH 4.4	42.13	Sparingly soluble
3	pH 6.8	1006.7	Very slightly soluble
4	pH 7.4	877.3	Slightly soluble

Table 3. Formula for Suspension of Rafting Technology

Ingredients (mg)	GG1	GG2	C3	C4	XG5	XG6
Ranitidine	20	20	20	20	20	20
Sodium alginate	500	250	500	250	500	250
Guar gum	65	100	-	-	-	-
Carbopol 974p	-	-	65	100	-	-
Xanthan gum	-	-	-	-	65	100
Sodium Bicarbonate	250	250	250	250	250	250
Calcium carbonate	150	150	150	150	150	150
Sodium chloride	5	5	5	5	5	5
Sodium Saccharin	5	5	5	5	5	5
Sodium Benzoate	10	10	10	10	10	10
Flavouring agent	q.s	q.s	q.s	q.s	q.s	q.s
Purified water	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml

Table 4. Optimization of Batch (GG2) using 3^2 Factorial Designs

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ranitidine	20	20	20	20	20	20	20	20	20
Sodium Alginate	225	225	225	250	250	250	275	275	275
Sodium bicarbonate	250	250	250	250	250	250	250	250	250
Calcium carbonate	150	150	150	150	150	150	150	150	150
Guar gum	90	100	110	90	100	110	90	100	110
Sodium Chloride	5	5	5	5	5	5	5	5	5
Sodium Saccharin	5	5	5	5	5	5	5	5	5
Sodium Benzoate	10	10	10	10	10	10	10	10	10
Flavouring Agent	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Purified Water	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml

Preliminary Screening

Table 5. Measurements of pH of the Formulation

S. No	Formulation	pH
1	GG1	8.24±0.8
2	GG2	8.41±0.4
3	C1	7.60±0.1
4	C2	7.76±0.6
5	XG1	8.10±0.1
6	XG2	8.02±0.3

Trials were done by triplicate

Table 6. Measurements of *In-Vitro* Floating Lag Time

S. No	Formulation	Floating lag time in sec
1	GG1	31±0.3
2	GG2	20±0.6
3	C1	46±0.2
4	C2	52±0.6
5	XG1	66±0.5
6	XG2	62±0.3

Trials were done by triplicate

Table 7. Measurement of Sedimentation Volume

S. No	Formulation	Sedimentation volume		
		Initial volume (10ml)	Final Volume	F=Vu/Vo
1	GG1	10	9.9	0.99
2	GG2	10	10	1
3	C1	10	9.8	0.98
4	C2	10	9.8	0.98
5	XG1	10	9.8	0.98
6	XG2	10	9.8	0.98

Table 8. Measurement of Raft Weight

S. No	Formulation	Raft weight in gm
1	GG1	2.421±0.4
2	GG2	2.741±0.8
3	C1	2.610±0.4
4	C2	2.772±0.9
5	XG1	2.660±0.7
6	XG2	2.475±0.7

Table 9. Measurement of Raft Volume

S. No	Formulation	Raft volume in ml
1	GG1	2.661±0.8
2	GG2	3.112±0.5
3	C1	2.760±0.4
4	C2	2.860±0.8
5	XG1	2.962±0.2
6	XG2	2.691±0.3

Trials were done by triplicate

Table 10. Measurement of Acid Neutralizing Capacity

S. No	Formulation	$V_{HCl}*N_{HCl}$	$V_{NaoH}*N_{NaOH}$	ANC in mEq
1	GG1	30	46.1	6.95±0.3
2	GG2	30	45.7	7.15±0.4
3	C1	30	49.5	5.35±0.8
4	C2	30	48.9	5.55±0.6
5	XG1	30	51.2	4.4±0.3
6	XG2	30	50.7	4.65±0.7

Trials were done by triplicate

Table 11. Measurement of Viscosity

S. No	Formulation	Viscosity (cp)
1	GG1	1310±2
2	GG2	1420± 5
3	C1	1275±3
4	C2	1325±2
5	XG1	1295±4
6	XG2	1390±2

Trials were done by triplicate

FACTORIAL BATCHES

Table 12. Measurements of pH of Factorial Batches

S. No	FORMULATION	pH
1	F1	7.92±0.4
2	F2	8.21±0.7
3	F3	7.99±0.8
4	F4	8.01±0.5
5	F5	7.92±0.9
6	F6	7.89±0.1
7	F7	8.36±0.1
8	F8	7.96±0.0
9	F9	8.15±0.3

Trials were done by triplicate

Table 13. Measurements of Sedimentation Volume of Factorial Batches

S. No	Formulation	Sedimentation volume Final Volume F=Vu/Vo
1	F1	0.96
2	F2	0.98
3	F3	1
4	F4	0.95
5	F5	0.97
6	F6	0.96
7	F7	0.99

8	F8	0.94
9	F9	0.94

Trails were done by triplicate

Table 14. Measurements of *In-Vitro* Floating Lag Time of Factorial Batches

S. No	Formulation	*In-vitro* gelation study in sec
1	F1	30±0.5
2	F2	33±0.4
3	F3	20±0.5
4	F4	21±0.4
5	F5	25±0.3
6	F6	27±0.2
7	F7	40±0.7
8	F8	47±0.5
9	F9	44±0.8

Trials were done by triplicate

Table 15. Measurements Raft Weightof Factorial Batches

S. No	Formulation	Raft weight in gm
1	F1	2.310±0.4
2	F2	2.462±0.6
3	F3	2.520±0.9
4	F4	2.610±0.1
5	F5	2.690±0.3
6	F6	2.890±0.1
7	F7	2.420±0.8
8	F8	2.732±0.2
9	F9	2.680±0.4

Trials were done by triplicate

Table 16. Measurements Raft Volumeof Factorial Batches

S. No	Formulation	Raft Volume in ml
1	F1	2.602±23
2	F2	2.662±28
3	F3	2.694±27
4	F4	2.901±22
5	F5	3.032±25
6	F6	3.291±22
7	F7	2.873±28
8	F8	2.799±31
9	F9	2.857±24

Trials were done by triplicate

Table 17. Measurements Viscosityof Factorial Batches

S. No	Formulation	Viscosity in centipoise
1	F1	1420±4
2	F2	1470±2
3	F3	1475±6
4	F4	1480±3
5	F5	1425±5
6	F6	1460±3
7	F7	1430±4
8	F8	1420±1
9	F9	1440±2

Table 18. Measurements Acid Neutralizing Capacity of Factorial Batches

S.No	Formulation	$V_{HCl}*N_{HCl}$	$V_{NaOH}*N_{NaOH}$	ANC in mEq
1	F1	30	22.905	7.095±0.3
2	F2	30	22.915	7.085±0.6
3	F3	30	22.91	7.59±0.2
4	F4	30	22.58	7.42±0.6
5	F5	30	22.54	7.46±0.4
6	F6	30	22.56	7.44±0.3
7	F7	30	22.725	7.275±0.5
8	F8	30	22.765	7.235±0.2
9	F9	30	22.78	7.22±0.4

Trials were done by triplicate

Table 19. Comperative Study of *In-Vitro* Drug Release Profile

Time in Hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	7.56 ±0.21	6.58±0.53	7.96±0.46	7.20±0.31	8.30±0.21	6.71±0.46	6.41±0.21	6.17±0.18	7.21±0.45
2	12.75±0.47	12.97±0.22	15.54±0.53	13.65±0.40	15.54±0.47	12.20±0.53	11.25±0.24	13.12±0.35	14.37±0.32
3	20.89±0.61	19.03±0.28	21.76±0.49	17.95±0.23	21.82±0.29	18.39±0.49	20.32±0.23	21.53±0.16	23.56±0.36
4	25.68±0.21	25.23±0.47	26.85±0.37	23.48±0.53	26.12±0.34	24.17±0.37	24.15±0.26	27.32±0.23	28.72±0.38
5	32.61±0.23	31.63±0.38	32.66±0.33	30.42±0.49	31.57±0.51	32.41±0.33	32.66±0.29	33.24±0.28	34.38±0.21
6	39.43±0.53	39.72±0.61	40.95±0.26	38.20±0.68	37.95±0.62	40.65±0.26	37.63±0.22	38.95±0.26	40.72±0.32
7	44.00±0.36	45.33±0.55	49.57±0.61	43.76±0.37	46.61±0.36	46.20±0.37	44.30±0.32	44.57±0.14	47.02±0.27
8	49.90±0.51	49.84±0.42	58.27±0.45	51.86±0.25	53.21±0.20	52.45±0.25	50.85±0.25	53.72±0.34	54.72±0.18
9	55.70±0.32	56.50±0.37	65.37±0.27	61.73±0.30	61.76±0.17	63.15±0.30	61.76±0.36	61.62±0.11	63.30±0.25
10	61.82±0.28	62.00±0.46	74.32±0.21	70.74±0.61	71.82±0.36	71.22±0.61	68.71±0.31	71.21±0.36	73.17±0.36
11	68.03±0.41	71.24±0.21	83.24±0.53	77.80±0.30	78.24±0.24	80.52±0.30	75.21±0.27	77.33±0.10	79.85±0.21
12	78.23±0.25	79.32±0.12	92.40±0.07	86.38±0.41	87.24±0.28	88.72±0.41	83.74±0.20	85.17±0.29	86.89±0.19

Trials were done by triplicate

Table 20. Stability Studies for Factorial Batch F3:

Parameters	Initial	After One Month	
		$40^0 \pm 2°C$/ 75 ± 5% (RH)	$30^0 \pm 2^0C$/ 65 ± 5%(RH)
pH	8.41	8.45	8.42
In-vitro gelation time	20 sec	25 sec	22sec
ANC	7.44meq	7.32meq	7.39meq
In-vitro drug release study	92.40±0.07	91.86±0.3	91.96±0.2

Trials were done by triplicate

Fig. 1. Formulation of raft forming suspension

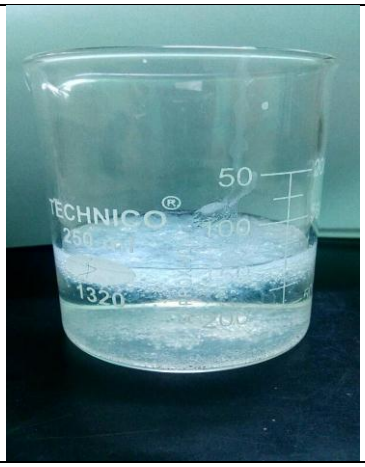
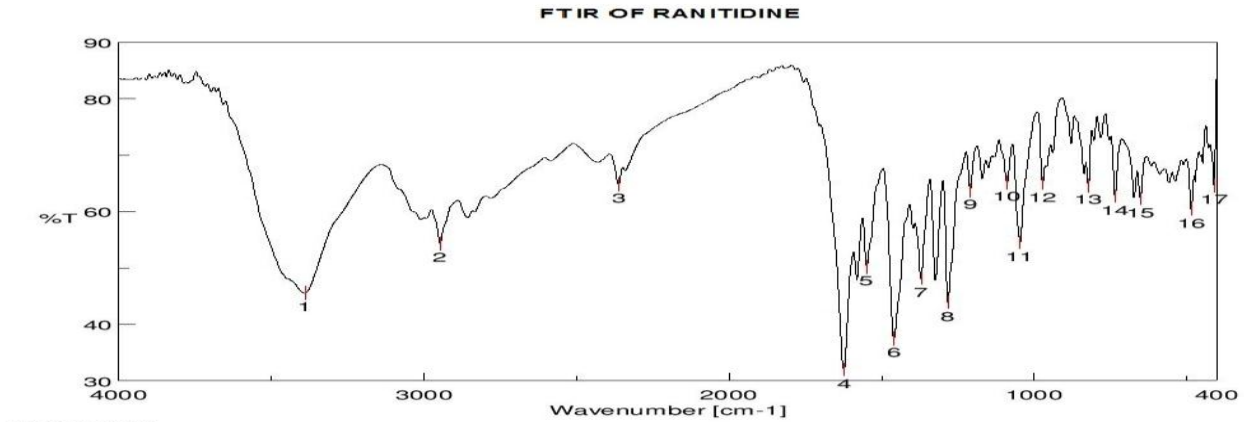


Fig. 2. FTIR of Ranitidine

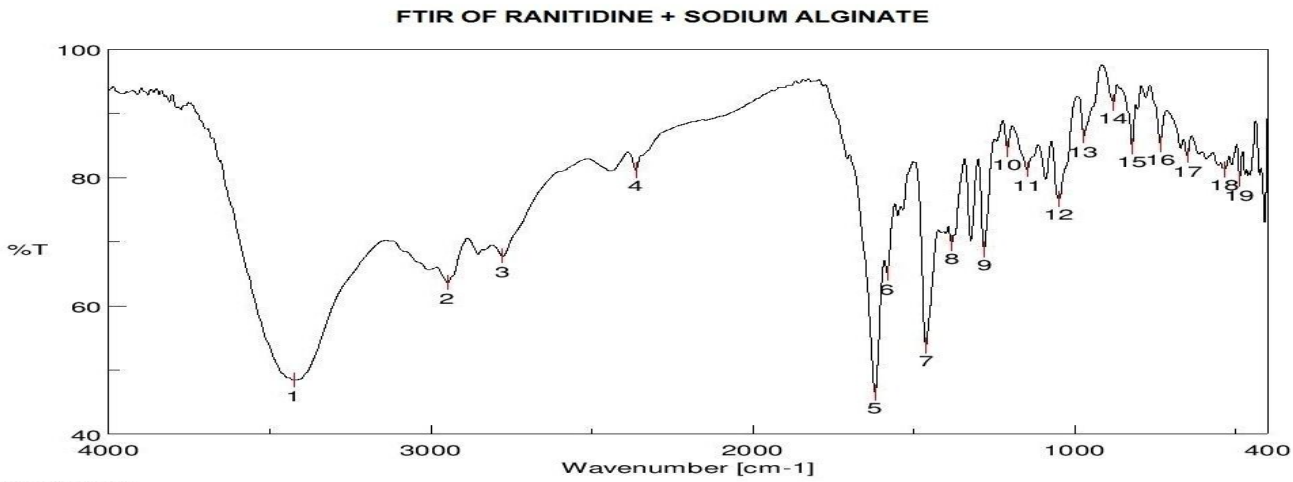


[Comments]
Sample name RANITIDINE
Comment FTIR SPECTRUM
User
Division
Company SRIPMS

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3390.24	45.5888	2	2946.7	54.299
3	2361.41	64.7885	4	1622.8	31.9705
5	1548.56	50.1763	6	1459.85	37.4567
7	1370.18	48.1253	8	1282.43	43.8463
9	1209.15	63.7086	10	1088.62	65.1457
11	1045.23	54.4804	12	971.947	64.9594
13	821.527	64.5854	14	734.746	62.6518
15	651.822	62.2171	16	485.974	60.3918
17	410.763	64.6134			

Fig. 3. FTIR of Ranitidine and Sodium Alginate

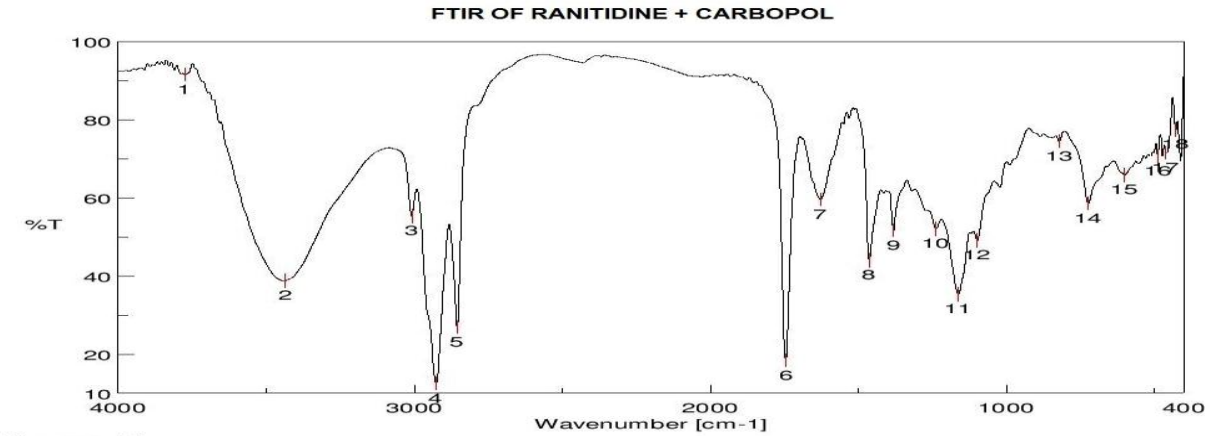


[Comments]
Sample name RANITIDINE + SODIUM ALGINATE
Comment FTIR SPECTRUM
User
Division
Company SRIPMS

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3423.99	48.4029	2	2947.66	63.5815
3	2776.99	67.7497	4	2362.37	81.145
5	1620.88	46.5093	6	1582.31	65.0505
7	1462.74	53.8377	8	1382.71	69.7666
9	1281.47	68.7943	10	1209.15	84.439
11	1148.4	81.186	12	1049.09	76.6788
13	971.947	86.4588	14	881.309	91.6717
15	822.491	84.8498	16	734.746	85.2213
17	650.858	83.4132	18	534.185	81.2875
19	488.866	79.6736			

Fig. 4. FTIR of Ranitidine and Carbopol

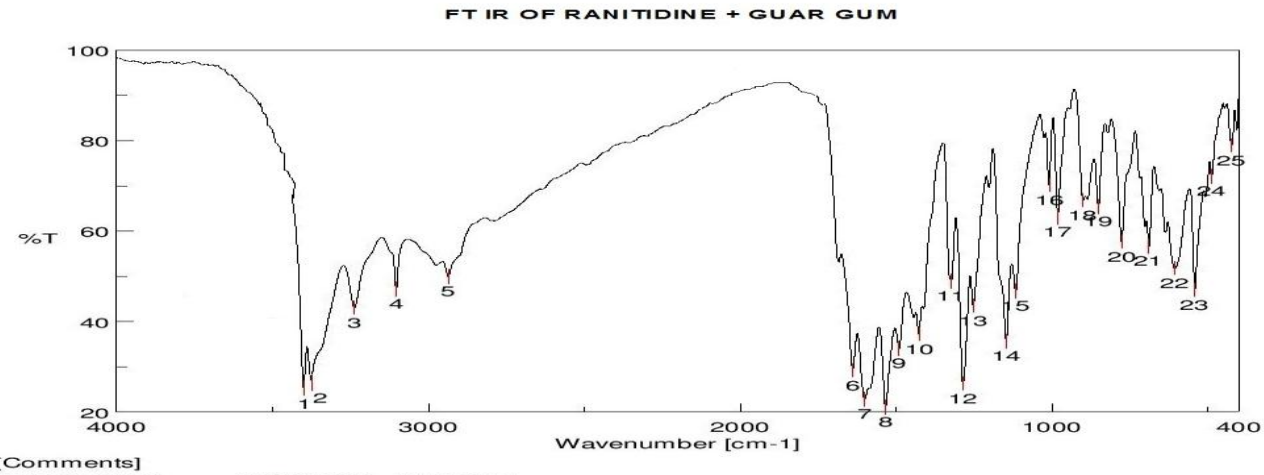


[Comments]
Sample name RANITIDINE + CARBOPOL
Comment FTIR SPECTRUM
User
Division
Company SRIPMS

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3774.97	91.4552	2	3436.53	38.7991
3	3008.41	55.2877	4	2926.45	12.4522
5	2855.1	26.8369	6	1745.26	18.3791
7	1628.59	59.4877	8	1463.71	44.0447
9	1381.75	51.6762	10	1238.08	52.0355
11	1162.87	35.3497	12	1099.23	49.0685
13	822.491	74.4222	14	724.139	58.4959
15	601.682	65.8531	16	489.831	70.5544
17	461.868	71.4725	18	428.12	77.4554

Fig. 5. FTIR of Ranitidine and Guar Gum

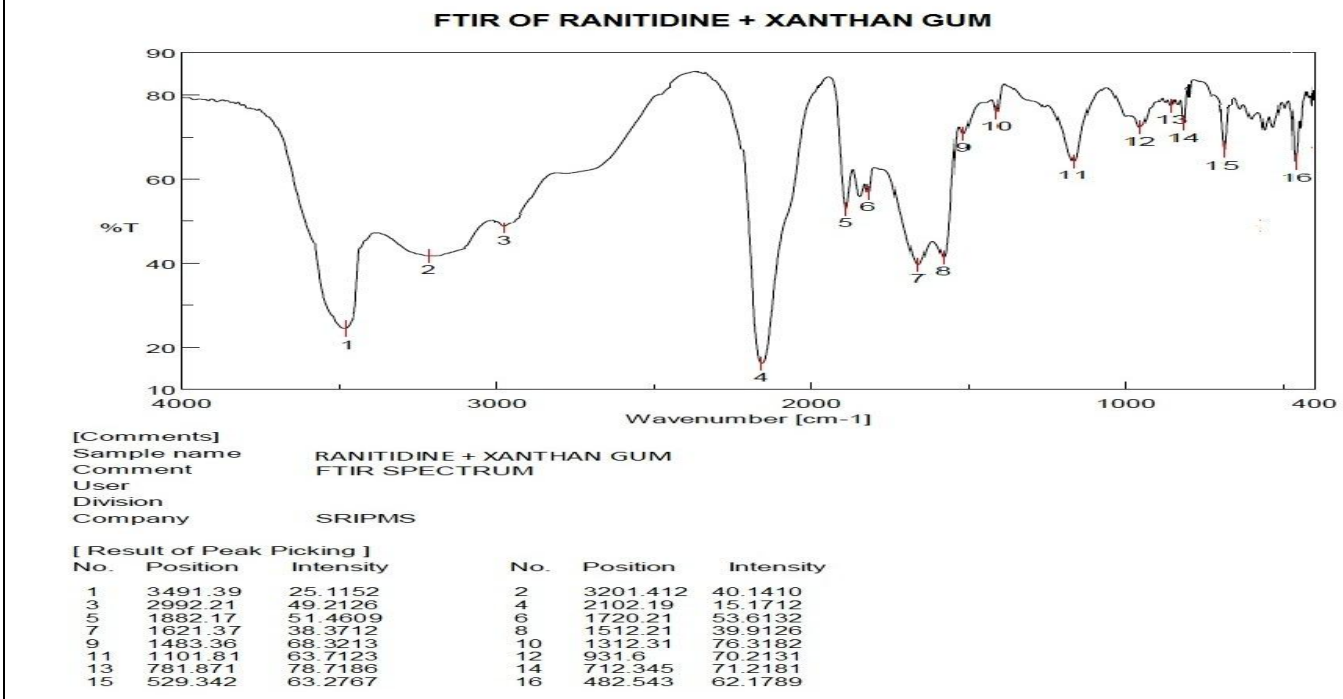


[Comments]
Sample name RANITIDINE + GUAR GUM
Comment FTIR SPECTRUM
User
Division
Company SRIPMS

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3404.99	21.0741	2	3399.89	25.3365
3	3236.93	43.0416	4	3102.9	47.2003
5	2936.09	49.9704	6	1639.2	29.1507
7	1601.59	22.8233	8	1534.1	21.0741
9	1490.7	34.021	10	1427.07	37.1624
11	1323.89	48.896	12	1285.32	26.2266
13	1252.54	43.4812	14	1146.47	35.6714
15	1116.58	46.723	16	1009.55	70.1103
17	981.59	63.0554	18	900.594	66.7829
19	851.418	65.4267	20	777.172	57.6141
21	689.427	56.6582	22	607.467	51.7717
23	541.899	46.9806	24	488.866	72.0888
25	424.263	78.9006			

Fig. 6. FTIR of Ranitidine and Xanthan Gum



[Comments]
Sample name RANITIDINE + XANTHAN GUM
Comment FTIR SPECTRUM
User
Division
Company SRIPMS

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3491.39	25.1152	2	3201.412	40.1410
3	2992.21	49.2126	4	2102.19	15.1712
5	1882.17	51.4609	6	1720.21	53.6132
7	1621.37	38.3712	8	1512.21	39.9126
9	1483.36	68.3213	10	1312.31	76.3182
11	1101.81	63.7123	12	931.6	70.2131
13	781.871	78.7186	14	712.345	71.2181
15	529.342	63.2767	16	482.543	62.1789

Fig. 7. Calibration Curve of Ranitidine

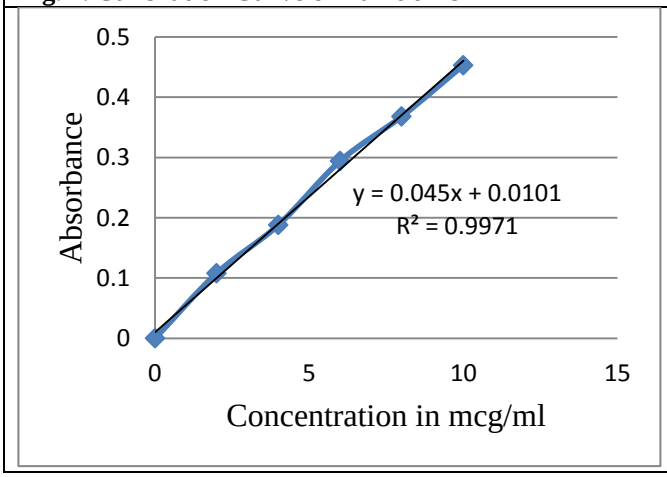
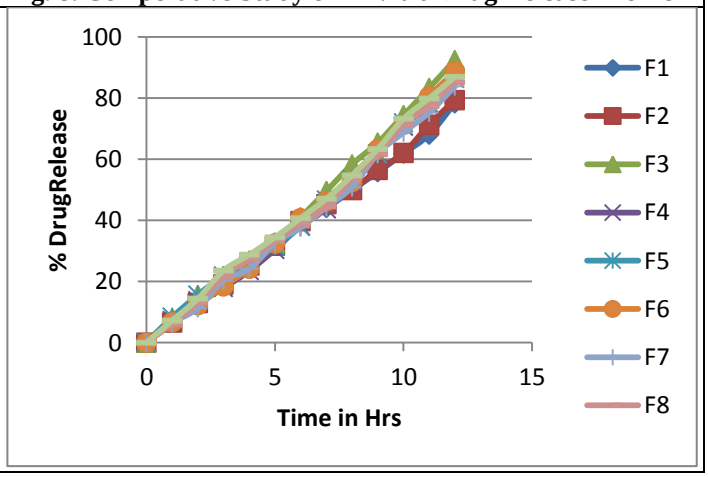


Fig. 8. Comperative Study of *In-Vitro* Drug Release Profile



Raw Material Analysis

The given drug Ranitidine was tested as per I.P standards and limits. The assay value obtained by procedure as per I.P showed a purity of 101.23% which was found to be in the range of I.P standard 97.5-102%. Thus the evaluation ensures the quality as per standard of the Indian Pharmacopeia and thus it can be included for further study of the formulation.

Particle Size Analysis

The average particle size of Ranitidine was found to be 2.132 µm.

Drug and Excipients Compatibility Study

The I.R spectrum of Ranitidine exhibits a peak at 3390.24 CM^{-1} due to the N-H stretching an d peaks at 1548.56 CM^{-1} and 1622.8 CM^{-1} due to N=O and C=C stretching, and C-S stretching at 734.746 confirms the structure of the drug shown in Fig. 2-6. The FTIR spectrum of the pure drug was found to be similar to the standard spectrum of Ranitidine. It was observed that all the characteristic peaks of Ranitidine were present in combination spectra which indicates the compatibility of the drug with the polymers used.

Calibration Curve

The calibration curve obtained in 0.1 N hydrochloric acid was shown in Fig.7. Statistical analysis of the curve the regression coefficient obtained was 0.997

which shows a better correlation between both axis. The line equation obtained y =0.0445x + 0.010.

Preliminary Batches

In preliminary batches, gaur gum (GG2) shows better in-vitro floating lag time, raft weight and ANC than other formulation.

In vitro floating time of guar gum shows less compare to other as shown in Table 6; and the raft was developed completely. So this gives immediate relief on acid reflux of GERD. The sedimentation volume of the guar gum shows better sediment sediment volume than other formulations as shown in Table 7. It was seen that when raft weight increased the anti reflux effect also increases GG2 formulation showed better raft weight than other formulations shown in Table 8. The acid neutralizing capacity of GG2 gives better results than other formulations shown in Table10. The combination of sodium alginate with guar gum produced a better raft formation of in-vitro floating lag time, raft weight and ANC. The raft formed with carbopol and xanthan gum has a longer floating lag time and the raft formed was not uniform. Hence guar gum in combination with sodium alginate was chosen for further studies.

pH: The pH of all the formulation was found to be between 7.60 to 8.41. This complies with the IP limits of 7.5 to 8.5 for antacids shown in Table 5.

Floating time: According to the results, floating period of raft was more than 24 hrs. So this reduces the frequency of dosing and patient compliance.

Viscosity: The viscous fluid increases the raft weight. All the formulations show 1290 to 1490 cps shown in Table 11.

Optimized Batch

All the results for physicochemical parameters like raft weight, raft volume, *in-vitro* gelation time and ANC are shown in Tables and Figures. All the results were found to be satisfactory and within a normal range.

The pH of all the optimized formulations shows within the range of 7.92±0.4 to 8.36±0.1 shown in the Table 12. Batch F3 was found to be minimum *in-vitro* gelation time of 20±0.2 sec shown in Table 14. Batch F3 shows sedimentation volume range as per limits as shown in Table 13. All factorial batches had raft weight and raft volume in the range of 2.310±0.4 to 2.890±0.1gm shown in Table 15 and 3.291±22 to 2.602±23 ml shown in Table 16 respectively. All batches had ANC in the range of 7.09±0.2 to 7.46±0.4 mEq shown in Table 18, which was as per the limits described in USP 28. Viscosity of all optimized formulation had within the range of 1420±2 to 1480±3 cps shown in Table 17. It was concluded that amount of sodium alginate and guar gum cross linking with calcium chloride and produce uniform raft development and the amount of sodium bicarbonate for critical floating (porous structure formation) of raft and neutralisation. F3 show better raft development and acid neutralizing capacity. The *in-vitro* drug release study show that more than 90% of the drug released at 12 hr. The *in-vitro* drug release profiles of all the factorial batches shown in Table 19. All parameters were found to be satisfactory for all factorial batches, so the batch with maximum raft weight, raft volume, ANC and *in-vitro* drug release study that is F3, was selected as optimized batch.

Stability Studies

The optimized formulation (batch F3) stored at 40 ± 2°C/75 ± 5% RH and 30 ± 2^0C/55 ± 5% RH for one month was found stable. After storage at 40 ±2°C/75 ± 5% RH and 30 ± 2^0C/55 ± 5% RH, pH, percentage *in-vitro* of drug release, ANC and *in-vitro* gelation time were nearly similar to the initial results were shown in Table 20. So, it was clear that the drug and the formulation were thermally stable as well as not affected by the high humidity at 40 ± 2°C/75 ± 5% and 30 ± 2^0C/55 ± 5%. The comparative dissolution profile of batch F3 before and after stability.

CONCLUSION

The raft forming suspension of Ranitidine were successfully formulated by sodium alginate combined with guar gum as raft forming agent and raft forming polymer respectively. The calcium carbonate was used as antacid and sodium bicarbonate as gas forming agent can form a floating raft in the presence of 0.1N hydrochloric acid within the range of 20 ± 0.2 to 45 ± 0.7 sec.

The formulation was optimized using three factors, two levels full factorial design. The amount of sodium alginate and guar gum showed significant effect on good *in-vitro* gelation time, raft weight; raft volume sufficient acid neutralising capacity and the *in-vitro* drug release concluded 12 hr of dissolution, the maximum release was observed for F3. It can be evidently said that in raft forming suspension of Ranitidine has increased the gastro retentive time period in stomach there by improved bioavailability. The drug was also compatible with all the excipients used in the formulation. The controlled release of Ranitidine by sodium alginate combined with guar gum. The formulation was also stable at accelerated conditions of temperature and humidity. The development of raft forming suspension of Ranitidine with sodium alginate combined with guar gum have a positive impact in bioavailability improvement of gastro retentive time provide maximum effects on Gastric ulcer and GERD.

It was concluded that rafting technology had better impact on bioavailability when sodium alginate combined with guar gum. The drug retained on longer period of time in stomach because of mucilaginous nature of guar gum. So the raft forming suspension of Ranitidine effective on Gastric ulcer and Gastro esophageal reflux disease with neutralize the acidity, reduce acid secretion by block H_2 receptor and prevent the acid reflux by floating raft on gastric fluid which prevent esophageal damage and heartburn.

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