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Research Article

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Formulation and evaluation of raft forming sustained release tablet containing Ranitidine

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ABSTRACT

Now a days, acidity, heart burning and gastro esophagus reflux disease are the most common problems which is seen in the patients. So this type of the problems can be overcome by the raft forming tablets containing combination of H_2 receptor blocker (Ranitidine) as well as raft forming agents (Sodium alginate and Pectin). The tablet was prepared by wet granulation method and evaluated for raft strength, raft volume, acid neutralization capacity and in vitro drug release. The highest raft strength is obtained by that tablets which are having sodium alginate and pectin in their appropriate amount. Mainly sodium alginate and pectin, a raft forming agents are playing important role in formation of raft formation. F5 batch was shown maximum raft strength, raft volume and raft weight. Same batch was shown in vitro drug release up to 5 hour. So by various evaluation test it can be conclude that raft forming tablet containing ranitidine could be an effective dosage form for treatment of peptic ulcer, heart burning, GERD (Gastro esophageal reflux).

Keywords: Ranitidine, raft forming tablet, sodium alginate, pectin, acid neutralization capacity, GRDDS

INTRODUCTION

For maximizing therapeutic effects of drug and for reduction of side effect, drug delivery system play very much important role in formulation. Oral route is very popular for administration of drug because of highest patient compliance and low cost therapy. More than 62% of drug is administered orally. Such effective parameters such as gastric empting time, gastrointestinal transit time, site of absorption as well as drug release from the dosage form.

Various gastric problems such as gastro esophageal reflux, peptic ulcer as well as heart burning are very common today. Symptoms of these diseases are shown after eating or at night. Sometimes hoarseness and raspiness in our sound can be done by these types of diseases. To overcome this type of problems, mainly following approaches are useful:

- H_2 receptor blocker
- Antacids
- Proton pump Inhibitors

Basic approach of above preparation is to maintain appropriate acidic condition in stomach and prohibit acid going up to the esophagus.

Raft forming agents are one of the best approaches to overcome all the problems. Mostly these types of agents are used to treat GRED, peptic ulcer, heartburn and esophagitis. Raft-forming anti-reflux preparations forms a viscous, gelatinous neutral layer or barrier on the top of the gastric acid contents. So this type of rafting barrier remains at the lower esophageal sphincter (LES) and prohibits the moment acidic content in upward position in esophagus and also

by the acid neutralizer contents of the formulation, maintain appropriate acidic condition in the stomach. This type of formulation creates gelling substances by coming contact with acidic environment and floats at upper surface oh gastric fluid so they are known as "RAFT FORMING FORMULATION".

As a raft forming agent's alginic acid, alginates as well as pectin are widely used. Some other raft forming agents are as follows:

- Guar gum
- Locust bean gum
- Carrageenan
- Isapgol

In this formulation, Sodium Bicarbonate as well as Calcium Carbonate are also helpful as gas generating agents. Just by coming contact with acidic fluid of the stomach, they starts to generates gas of carbon dioxide which is entraps in the formed raft and allow the raft to float on the surface and also provides mechanical strength.[2]

So this way by formation of raft as well as using acid neutralizers, this formulation overcome various gastric problems with higher patient compliance as well as without any side effects.

EXPERIMENTAL SECTION

Material used for study

The most important and vital components which are used for preparation of this formulation were Ranitidine, Sodium alginate and pectin. All other excipients used to prepare tablets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Method used for study

- Drug, polymer and other ingredients were weighed accurately.
- All ingredients except the binder, volatile ingredients and lubricant were mixed thoroughly.
- HPMC K100M was dissolved in sufficient quantity of isopropyl alcohol and added to a powder mixture to prepare a dough wet mass.
- The prepared wet mass was passed through a 20# sieve.
- The granules were allowed to dry in a hot air oven and then resifted through a 40# sieve.
- The granules were collected and other ingredients were added and lubricated.
- Tablets were compressed by a 12-mm diameter at punch with the help of a rotary tablet compression machine.

Table 1: Different formulation for optimization of sodium alginate and pectin

Ingredients (mg)	Formulations				
	F1	**F2**	**F3**	**F4**	**F5**
Ranitidine	10	10	10	10	10
Sodium alginate	127.5	255	-	85	170
Pectin	127.5	-	255	170	85
NaHCO3	28	28	28	28	28
CaCO3	85	85	85	85	85
Mannitol	80	80	80	80	80
HPMC K100M	16	16	16	16	16
Aspartame	11	11	11	11	11
Talc	10	10	10	10	10
Mg-Stearate	5	5	5	5	5
Total	500	500	500	500	500

Evaluation of all above formulations

TABLET DIMENSIONS[3, 4]

- Thickness and diameter of five tablets randomly selected were measured using vernier calipers.
- The Pharmacopoeia states that the extent of deviation in a batch of tablet should not exceed the limit of ± 5 % of their determined standard values.

HARDNESS TEST[5, 6, 7]

- The crushing strength kg/cm^2 of prepared tablets was determined for tablets of each batch by Monsanto tablet hardness tester.
- Hardness indicates the ability of a tablet to withstand mechanical shocks while handling.

FRIABILITY TEST[8, 9]

- The friability of tablets was determined using Roche friabilator.
- It is expressed in percentage (%) 13 tablets randomly selected were initially weighed (W_0 initial) and transferred into friabilator.
- As per IP 2007, for this test, take that numbers of tablets which are sufficient enough to make 6.5 gm of weight.
- Since our tablet weight was 500 mg so 13 tablets were taken to evaluate same test.
- The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions.
- The tablets were weighed again (W final). The percentage friability (%F) was then calculated by following equation:

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

Where, W_o = weight of tablet before test,
W = weight of tablet after test.

WEIGHT VARIATION TEST[5]

- Twenty tablets were selected randomly from each batch and weighed individually using electronic balance to check for weight variation.
- Pharmacopoeial parameters are displayed in Table 2.

Table 2. IP standards of percentage of weight variation

Percentage deviation allowed under weight variation test.	
Average weight of tablet	**Average weight of tablet**
80 mg or less 10	10
More than 60 mg but less than 250 mg 7.5	7.5
250 mg or more 5	5

Since, the average weight of the tablets is 500 mg; the percentage deviation is taken as ± 5

DRUG CONTENT ESTIMATION[6, 10, 11]

- Ten tablets were randomly selected and powdered.
- A quantity of powder equivalent to 10 mg of ranitidine was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in 0.1 N HCl and the volume was made with 0.1 N HCl (pH 1.2).
- The solution was filtered through Whattman filter paper.
- 1 ml of the above solution was transferred to a 100 ml volumetric flask and diluted to 100 ml with 0.1 N HCl and the absorbance was measured at 225 nm using UV / visible spectrophotometer.
- The percentage of ranitidine hydrochloride was determined using calibration curve.

RAFT STRENGTH MEASUREMENT[1]

- A tablet powder equivalent to unit dose was transferred to 150 ml of 0.1 N HCl and maintained at 37°C in a 250 ml glass beaker.
- Each raft was allowed to form around an L-shaped wire probe(Height 9 cm and wide at bottom surface 2 cm) held upright in the beaker throughout the whole period (30 min) of raft development.
- Raft strength was estimated using the modified balance method.
- Water was added drop wise to the left sided beaker and the weight of water required to break the raft was recorded.

RAFT WEIGHT AND RAFT VOLUME MEASUREMENT[2]

- Raft volume and raft weight Rafts were calculated by taking unit dose for 30 min in glass beakers of 150 ml 0.1 N HCl but without the inclusion of a wire probe.
- Each beaker used for raft formation was preweighed(W1).
- Note the volume of beaker before formation of raft. (M1).
- The position to which the top of each raft reached was marked on the outside of the beaker.
- The total weight of the beaker and contents was obtained after raft development (W2).
- The weight of each raft was then calculated from the formula:

Raft weight = Total weight of the beaker and contents was obtained after raft development (W2) – Preweighed beaker used for raft formation (W1).

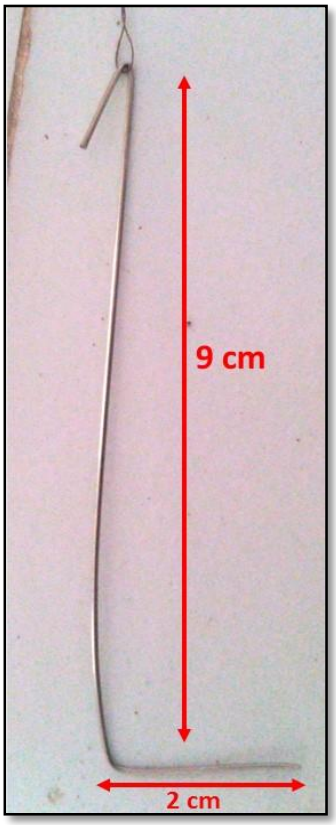

Figure 1: Wire probe for raft strength measurement

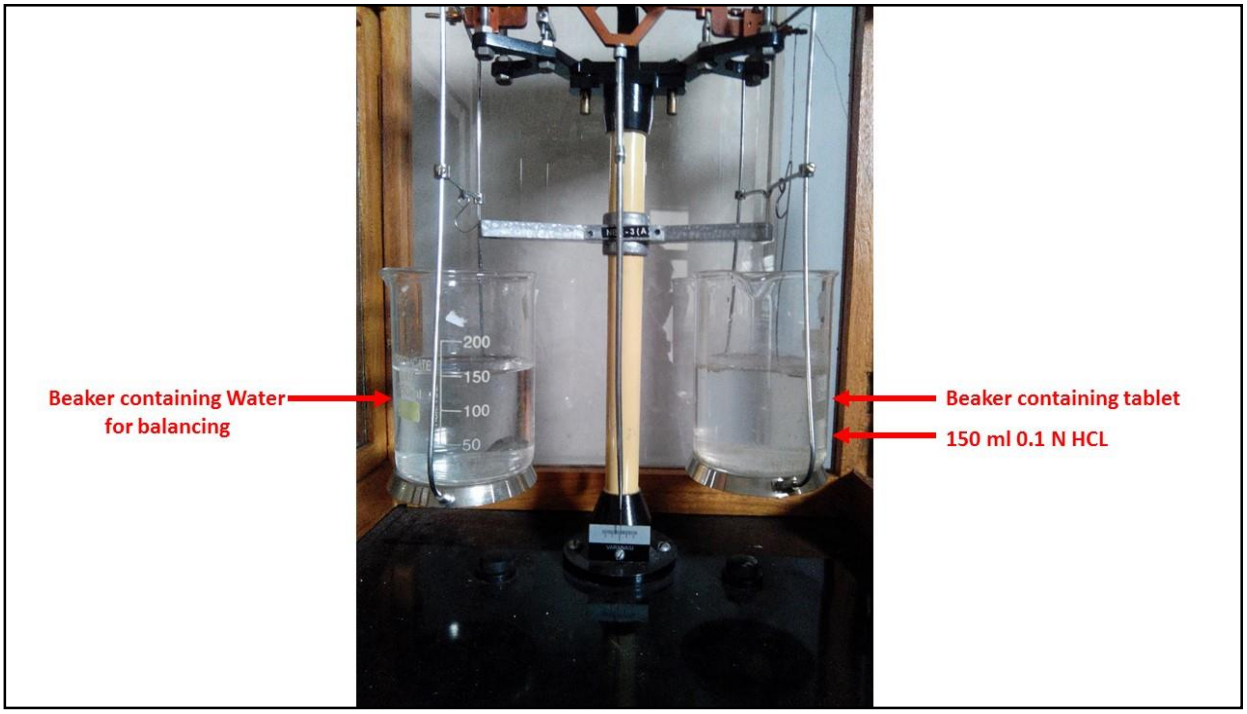

Figure 2: Modified apparatus for raft strength measurement

- The raft was then removed from the beaker by carefully decanting off the liquid and tipping the raft into a pre-tarred plastic weighing petri plate.
- This was left to stand for 30 s, excess subnatant liquid was drained off and the raft was weighed (W3).
- Remaining liquid was removed from the inside of the beaker with a paper towel and it was then refilled with water to the marked position (M2).

- Finally beaker was weighed (W4).
- The volume of each raft was then calculated from the formula:

Raft volume = Final volume of 0.1 N HCl after formation of raft (M2) –Initial volume of 0.1 N HCl before formation of raft (M1)

Where raft volume is measured in ml. and all weights are measured in gm.

- The formula assumes that the density of the subnatant liquid is the same as that of water.

ACID NEUTRALIZATION CAPACITY[1]

- A tablet powder equivalent to unit dose was transferred to a 250 ml beaker; 50 ml of water was added to it and was mixed on a magnetic stirrer for 1 min.
- A 30-ml volume of 1.0 N HCl was added with continued stirring on the magnetic stirrer for 10 min after addition of the acid.
- Stirring was discontinued briefly and the gum base was removed using a long needle without delay.
- The needle was promptly rinsed with 20 ml of water, and the washing was collected inthe beaker; stirring was resumed for 5 min.
- Titration was begun immediately. Excess HCl was titrated against 0.5 N sodium hydroxide to attain a stable pH of 3.5.
- The number of mEq of acid consumed by the tablet tested was calculated by the following formula:

Total mEq = (30×N HCL) – (V NaOH×N NaOH)

Where, N HCI = Normality of HCl; V NaOH = Volume of NaOH required; and N NaOH = Normality of NaOH.

***IN VITRO* DRUG RELEASE STUDY[1]**

- *In vitro* drug release study of Ranitidine tablets was performed using USP (United States Pharmacopoeia) apparatus II fitted with a paddle (50 RPM) at 37 ± 0.5°C using a simulated gastric fluid (pH 1.2; 900 ml) as a dissolution medium.
- The tablet was added to the dissolution medium.
- At pre-determined time intervals, 5 ml samples were withdrawn, filtered through a 0.45-µm membrane filter and analyzed at 225 nm using a double-beam spectrophotometer.
- Cumulative percentage drug release was calculated using an equation obtained from a calibration curve, which was developed in the range 2-20 µg/ml for 0.1 N HCl.

RESULTS

General parameters

- Tablets prepared by wet granulation are evaluated for hardness, friability, weight variation, drug content, and acid neutralization capacity. Results obtained are described in table no 3.

Table 3: Post compression parameter of all formulation

No.	Parameter	F1	F2	F3	F4	F5
1	Diameter(mm)	12 ± 0.02	12 ± 0.01	12 ± 0.03	12 ± 0.01	12 ± 0.01
2	Thickness(mm)	4 ± 0.01	4 ± 0.02	4 ± 0.02	4 ± 0.01	4 ± 0.03
3	Hardness(kg/cm2)	2.5 ± 0.20	2.5 ± 0.40	3 ± 0.20	3 ± 0.20	3 ± 0.20
4	Friability (%)	0.9846	0.9923	0.9954	0.9923	0.9969
5	Drug Content (%)	99.49 ± 0.2	99.75 ± 0.1	99.12 ± 0.2	99.49 ± 0.1	99.75 ± 0.1
6	Weight variation	Pass	Pass	Pass	Pass	Pass
7	ANC(mEq)	5 ± 0.2	3.5 ± 0.1	6 ± 0.3	4 ± 0.4	6 ± 0.5

- According to post compression parameter all criteria has been pass according to their specific standards.

Raft strength, raft volume and raft weight

- All the parameters are evaluated using 0.1 N HCl in specific procedure taking 10 tablets for evaluation of both the evaluation parameter.

Table 4: Raft Strength, Raft Volume and Raft Weight of all formulation

Formulation	Raft Strength (gm)	Raft Volume (ml)	Raft Weight (gm)
F1	8 ± 0.2	4 ± 0.1	0.21
F2	10 ± 0.1	5 ± 0.2	0.21
F3	13 ± 0.2	7 ± 0.1	0.23
F4	12 ± 0.1	6 ± 0.1	0.22
F5	15 ± 0.1	7 ± 0.1	0.24

- According to data of both specific evaluation parameter of the raft forming formulation, F5 batch was having maximum raft strength, raft volume as well as raft weight.
- So it was selected as an ideal formulation as raft formation tablet.

***In vitro* drug release profile**

- Data for *in vitro* drug release are shown in the table below.
- It was conclude that optimum amount of sodium alginate and pectin is able to release the drug in sustained manner (90%) up to 5 hour.

Table 5: In vitro drug release of all formulation

Time (Hour)	% Cumulative Drug Release				
	F1	F2	F3	F4	F5
0.5	15.25± 1.2	13.74± 1.1	16.75± 0.8	9.73± 1.5	9.73± 0.8
1	25.87± 2.1	29.87± 0.4	20.36± 1.1	18.81± 1.8	25.33± 1.2
1.5	33.53± 0.6	35.55± 0.6	33.51± 1.5	32.42± 1.9	30.99± 0.8
2	39.24± 1.1	42.27± 1.2	40.22± 1.1	47.19± 1.4	43.25± 1.3
2.5	47.48± 1.5	51.54± 1.3	47.96± 0.5	54.47± 1.1	48.96± 0.9
3	59.78± 1.7	64.86± 0.9	59.77± 0.8	58.28± 0.9	62.77± 1.1
3.5	68.13± 1.2	74.75± 0.5	68.12± 1.2	74.15± 0.8	69.14± 0.5
4	77.03± 0.9	84.69± 1.1	77.52± 1.5	81.58± 0.5	72.02± 1.2
4.5	86.99± 0.8	97.69± 0.8	90.99± 1.7	93.06± 0.3	82.95± 1.3
5	96.49± 1.2	99.89± 1.1	99.51± 1.9	99.09± 0.2	92.93± 0.9

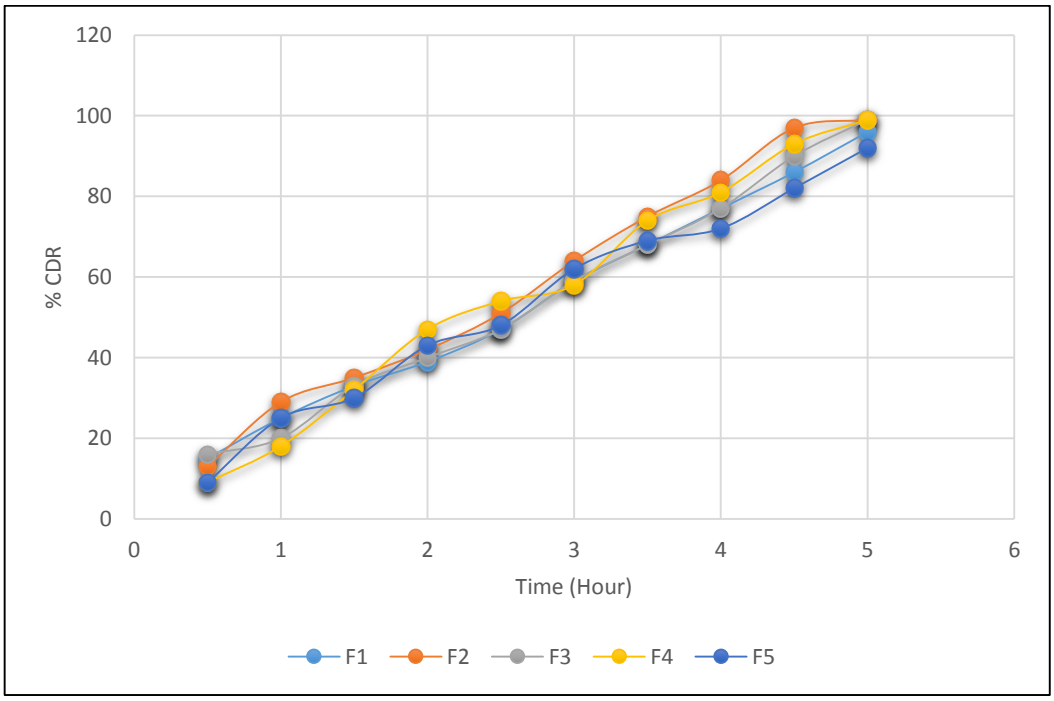

Figure 3: *In vitro* drug release profile of all formulation

- From above all formulations, F5 formulation was showing comparative sustained release among all formulations.
- So F5 formulation was selected as an ideal formulation.

DISCUSSION

As gastric problems now a days becoming often problem to the patient, can be easily treat by raft forming tablets. The principle of this treatment is formation of raft which is generated by sodium alginate and pectin as raft forming agent in appropriate amount i.e. 2:1. Apart from above calcium carbonate act as antacid and sodium bicarbonate act as gas generating agent play vital role to maintain optimum acidic condition and prevent excess acidity in stomach. From all the formulation, F5 formulation was considered to be an ideal one because it was having higher raft strength, raft volume, raft weight, acid neutralization capacity as well as % cumulative drug release up to 5 hour (90%) compare to all the formulation. The drug was also compatible with other ingredients used in formulation.

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