Research Article CODEN: IJPRNK IMPACT FACTOR: 1.862 ISSN: 2277-8713
Mitul Patel, IJPRBS, 2014; Volume 3(2): 580-597 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

FORMULATION AND EVALUATION OF RAFT FORMING CHEWABLE TABLET CONTAINING PANTOPRAZOLE SODIUM

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Accepted Date: 19/04/2014; Published Date: 27/04/2014

Abstract: Many of patients are suffering from severe acidity and heart burning and gastro esophagus reflux disease problem which can be overcame by formulating raft forming chewable tablet containing antacid and proton pump inhibitor. The main objective of this research is to formulate and evaluate raft forming chewable tablets of proton pump inhibitor (Pantoprazole sodium) along with raft forming agents sodium alginate and pectin and antacid ($NaHCO_3$). The tablet was prepared by wet granulation method and evaluated for raft strength, acid neutralization capacity ,*in vitro* drug release. The tablet containing appropriate amount of sodium alginate with pectin having highest raft strength. Raft strength was affected by amount of sodium alginate and pectin, and sodium bicarbonate. A 3^2 full factorial design was used in present study of optimization. Amount of sodium alginate, amount of sodium bicarbonate was used as an independent variable and raft strength, acid neutralization capacity and Q30 was used as dependent variable. Acid neutralization capacity and in vitro drug release of all batches was found to be satisfactory. F8 batch was optimized on based on maximum raft strength and good neutralization capacity and *in vitro* drug release within 1 hr. Stability study of optimized formulation showed that tablets were stable at accelerated condition. It can be conclude that raft forming chewable tablet containing pantoprazole sodium could be an efficient dosage form for treatment of heart burning, GERD, erosive esophagitis and peptic ulcer.

Keywords: Pantoprazole ,raft, chewable, sodium alginate ,pectin

PAPER-QR CODE

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Mitul Patel, IJPRBS, 2014; Volume 3(2): 580-597

INTRODUCTION

Gastro esophageal reflux occurs commonly in normal persons. Patients who have either symptoms or tissue damage resulting from reflux are said to have gastro esophageal reflux disease (GERD).The gastro oesophagul reflux is also called as heart burning.[1,2] Heartburn may happen many times a week, especially after eating or at night. GERD can also cause cough or have asthma symptoms. It can also make your voice sound hoarse and raspy. Various treatment options available for GERD are taking medicines like antacids, H_2 antagonist, proton pump inhibitor, etc.; surgery to strengthen the barrier between the stomach and the oesophagus may be a treatment option for acid reflux and endoscopic treatments help strengthen the muscle that keeps food and acid from going up into the oesophagus.[3-4]

Raft forming anti reflux preparation is one of the upcoming new approach to overcame the problem of sevearity of acidity, Peptic ulcer and gastritis problems. They are generally used in the treatment of gastric acid-related disorders, especially GERD, heartburn and oesophagitis.5

Raft-forming anti-reflux preparations forms a viscous, gelatinous neutral layer or barrier on the top of the gastric acid contents. The floating barrier remains located at the lower oesophageal sphincter (LES) and prevents the acidic gastric content from getting refluxed into the oesophagus and provides symptomatic relief to GERD patients. Since this barrier floats on the surface of the stomach content like a raft on water, the barrier is called a raft and the formulations are called as “raft-forming anti-reflux preparations”. The unique mechanism of action to provide relief in symptomatic GERD separates raft-forming anti-reflux preparations from traditional antacids and other therapeutic classes for treatment of GERD.[6]

Alginic acid, alginates and pectin are the most widely used raft-forming agents.7 Other polysaccharides are also being used, which include guar gum, locust bean gum, carrageenan, pectin and isapgol. Raft forming preparation includes raft forming agent which forms floating raft on contact with gastric fluid , antacids and gas generating agent like calcium carbonate and NaHCO3.Here calcium carbonate also used for raft strengthening agent. All recent treatments available for GERD either have one or more problems like side effects, costly or painful. Hence the objective of the present investigation was to formulate a chewable raft-forming tablet containing pantoprazole as proton pump inhibitor. It acts by inhibit Na^+/K^+ ATPase pump. And by that decrease gastric secration.

MATERIALS AND METHODS

Materials used for study

Pantoprazole sodium is obtained from suvik hiteck pvt ltd.(Gandhinagar, India). Sodium alginate was obtained from zydus cadila healthcare ltd.(Ahmedabad, India). All other excipients used to

prepare chewable tablets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

METHODS

Drug, polymer and other ingredients were weighed accurately. All ingredients except the binder, volatile ingredients and lubricant were mixed thoroughly. PVP K_{30} M 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 22# 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 flat punch with the help of a rotary tablet compression machine.

Preliminary screening for optimization of pectin

Sodium alginate is the main core ingredient for raft formation. It is necessary to check the effect of change in the amount of sodium alginate and pectin on raft strength. In experimental work combination of sodium alginate and pectin are useful for drug release and raft formation and its strength. So various combinations of sodium alginate and pectin has been incorporated on trial and error basis for raft formation and drug release upto 1 hr.

Table 1 composition of different batches for optimization of pectin

Ingredients (mg)	Formulations									
	PB1	PB2	PB3	PB4	PB5	PB6	PB7	PB8	PB9	PB10
Pantoprazole sodium	20	20	20	20	20	20	20	20	20	20
Sodium alginate	**125**	**150**	**100**	**150**	**200**	**250**	**300**	**325**	**325**	**425**
Pectin	**125**	**100**	**150**	**150**	**150**	**150**	**150**	**125**	**100**	**-**
$NaHCO_3$	50	50	50	50	50	50	50	50	50	50
$CaCO_3$	150	150	150	150	150	150	150	150	150	150
Mannitol	343	343	343	293	243	193	143	143	168	168
$PVPK_{30}$	30	30	30	30	30	30	30	30	30	30
Aspartame	20	20	20	20	20	20	20	20	20	20
Talc	18	18	18	18	18	18	18	18	18	18
Mg-Stearate	9	9	9	9	9	9	9	9	9	9

Subtotal (mg)	**900**	**900**	**900**	**900**	**900**	**900**	**900**	**900**	**900**	**900**

Optimisation by 3^2 full-factorial design

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 sodium bicarbonate were chosen as independent variables in 3^2 full factorial design, While dependent variables were selected as per below.

1) Raft strength

2) Acid neutralization capacity

3) Cumulative percent release at 30 min (Q30)

Table 2. Formulation layout of factorial batches

3^2full factorial design		
Independent variables		**Dependent variables**
X_1	**X_2**	**Y**
Sodium alginate	NaHCo3	Raft strength
		Acid neutralization capacity
		% drug release(Q30)

Coding value of full factorial batches

Coding value	**-1**	**0**	**+1**
Amount of sodium alginate	275	300	325
Amount of $NaHCO_3$	50	75	100

Formulation layout of factorial batches F1-F9

Table 3 Optimization of batch using 3^2 full factorial design

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pantoprazole sodium	20	20	20	20	20	20	20	20	20
Sodium Alginate	275	275	275	300	300	300	325	325	325
Pectin	100	100	100	100	100	100	100	100	100
$NaHCO_3$	50	75	100	50	75	100	50	75	100
$CaCO_3$	150	150	150	150	150	150	150	150	150
Mannitol	327	327	327	277	227	177	127	127	152
PVP K30	30	30	30	30	30	30	30	30	30
Aspartame	20	20	20	20	20	20	20	20	20
Talc	2	2	2	2	2	2	2	2	2
Mg-stearate	1	1	1	1	1	1	1	1	1
Vanilla flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s	q.s.
Total	**900**	**900**	**900**	**900**	**900**	**900**	**900**	**900**	**900**

Batch	X1	X2
F1	-1	-1
F2	-1	0
F3	+1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Evaluation of factorial batches

General evaluation parameters for tablets8-11

Weight variation test

Twenty tablets were selected at random, weighed and average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10%.

Friability

For each formulation, a pre-weighed tablet sample (six tablets) was placed in a Roche friabilator (Electrolab, Mumbai, India), which is then operated for 100 revolutions. The tablets were de-dusted and reweighed. Conventional compressed tablets that lose < 0.5 to 1% of their weight are considered acceptable.

Hardness

Hardness of tablets was determined using a Pfizer hardness tester (Campbell Electronics, Mumbai, India).

Content uniformity

Twenty tablets were weighted and powdered in a mortar. Accurately weighted a quantity of the powder equivalent to about 20 mg of pantoprazole sodium, diluted to 100 ml wit 0.1 N Hcl in 100 ml volumetric flask. It was shaken for 15 minutes and filtered. 1 ml of the filtrate was

diluted to 0.1 N Hcl. The absorbance of the resulting solution was measured at λmax 282 nm and the content pantoprazole sodium of was calculated from the absorbance obtained.

Raft strength measurement by in-house method12

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 (diameter: 1.2 mm) 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 dropwise to the pan and the weight of water required to break the raft was recorded.

Note: A double-pan dispensing balance was modified for raft strength measurement. One pan of the dispensing balance was replaced with an L-shaped wire probe as shown in Figure 1.

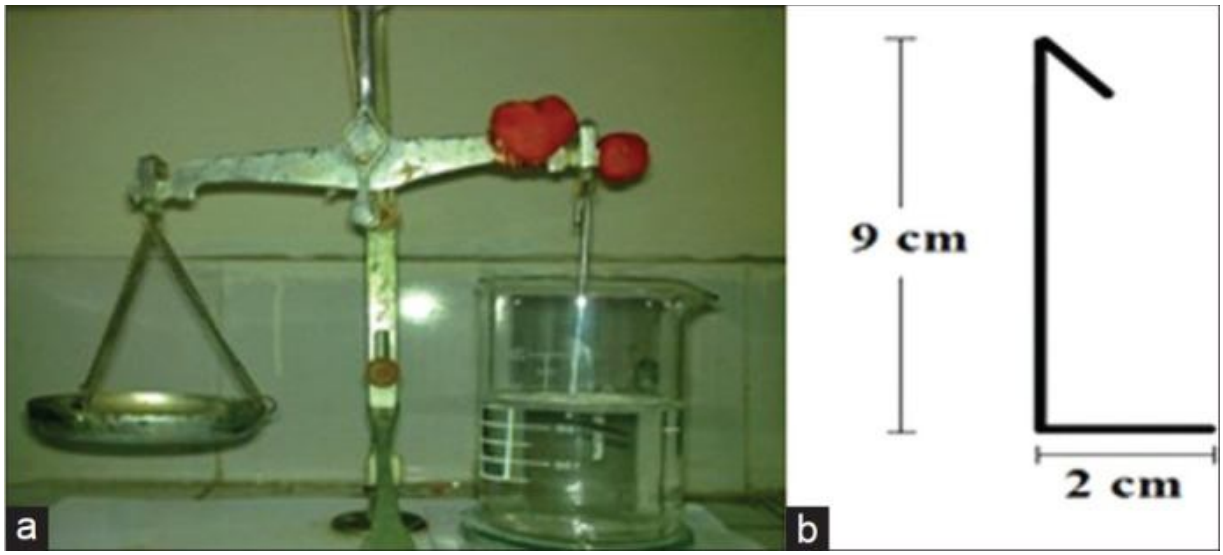

Figure 1

(a) Modified balance method. (b) Wire probe for raft strength measurement

Acid neutralisation capacity13

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 in the 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:[

$$\text{Total mEq} = (30 \times \text{N HCl}) - (\text{V NaOH} \times \text{N NaOH}) \quad (1)$$

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

In vitro drug release study

In vitro drug release study of Pantoprazole sodium chewable tablets (*n* = 3) was performed using USP (United States Pharmacopoeia) apparatus II (TDT-08T; Electrolab) fitted with a paddle (50 r.p.m.) at 37 ± 0.5°C using a simulated gastric fluid (pH 1.2; 900 ml) as a dissolution medium. The tablet was powdered and then added to the dissolution medium. At pre-determined time intervals, 10-ml samples were withdrawn, filtered through a 0.45-µm membrane filter and analysed at 265 nm using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve, which was developed in the range 5-25 µg/ml for 0.1 N HCl.

Raft strength measurement by Texture Analyzer

The raft strength of the most satisfactory formulation (batch F_5) was determined by a sophisticated instrument called Texture Analyzer (Brookfield QTS).

Powder of tablets 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. The raft was allowed to form around an L-shaped wire probe (diameter: 1 mm) held upright in the beaker throughout the whole period (30 min) of raft development. After 30 min of raft development, the probe was pulled vertically up through the raft at a rate of 30 mm/min. The force required to pull the wire probe up through the raft was recorded by the Texture Analyzer.

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Drug–excipient compatibility study

Fourier transform infrared spectrophotometry

A drug–excipient interaction plays a vital role in the release of drug from the formulation. Fourier transform infrared (FTIR) spectroscopy has been used to study the physical and

chemical interactions between drugs and excipients. The FTIR spectra of Pantoprazole sodium and a mixture of Pantoprazole sodium with major excipients were recorded using the KBr mixing method using an FTIR instrument (FTIR-8400S; Shimadzu).

Differential scanning calorimetry study

Differential scanning calorimetry (DSC) study was carried out using the Shimadzu DSC-60 (Shimadzu) instrument to check drug–excipient compatibility. The DSC thermograms of the pure drug Pantoprazole sodium and of the physical mixtures of Pantoprazole sodium with excipients were obtained. DSC aluminium cells were used as a sample holder and a blank DSC aluminium cell was used as reference. A 2- to 3-mg weight of sample was used for analysis. Thermograms were recorded over the range 50-300°C.

Stability studies of the optimised formulation

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 on the most satisfactory formulations (batch F_5). The most satisfactory formulations were sealed in aluminium packaging and kept in a humid chamber maintained at 40 ± 2°C/75 ± 5% relative humidity (RH) for 1 month. The optimised formulation sealed in aluminium foil was also kept at room temperature and humid condition. At the end of the storage time, the samples were analysed for raft strength, *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 for 1 month) were compared by the similarity factor (f_2).

RESULTS AND DISCUSSION

Table 4. Results of preliminary screening

Batch No	Amount of Sodium alginate	Amount of Pectin	Raft strength	Cumulative % drug release(1hr)
PB1	125	125	Not developed	-
PB2	150	100	Not developed	-
PB3	100	150	1.6±0.15	112.21
PB4	200	150	2.0±0.12	96.70
PB5	250	150	3.3±0.01	106.31

PB6	100	150	4.6±0.05	102.45
PB7	300	150	4.7±0.05	103.70
PB8	**325**	**125**	**4.8±0.08**	**98.13**
PB9	**325**	**100**	**4.8±0.33**	**101.27**
PB10	425	-	3.4±0.41	114.47

According to result it was found that sodium alginate was main agent of raft formation. Raft strength is increased with combination of pectin and sodium alginate. According to that pectin is also useful for improving raft strength. Raft strength is gradually decreased in absence of pectin and drug release is drastically affect without pectin. So pectin along with sodium alginate is required for good raft strength and accurate drug release upto 1 hr. According to trials PB1 to PB10 batches has been evaluated for further study.

Table 5 Acid neutralization capacity of batch PB1-PB10

Batch No	ANC mEq
PB1	-
PB2	-
PB3	6.60±0.02
PB4	6.53±0.05
PB5	6.66±0.09
PB6	6.54±0.12
PB7	6.73±0.15
PB8	6.68±0.02
PB9	6.85±0.28
PB10	6.80±0.21

Data for *in vitro* drug release are shown in the table below. It was conclude that optimum amount of pectin is necesory to release upto 1 hr.

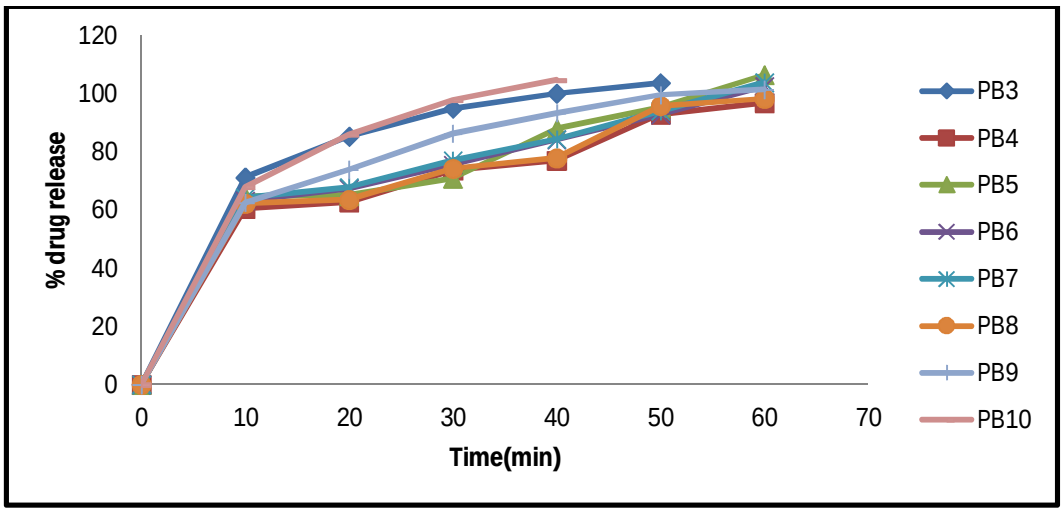


Figure : 1 *in vitro* drug release profile of preliminary batch PB3-PB10

Table 6. *In vitro* drug release profile of PB3-PB10.

Time (min)	% cumulative release							
	PB3	PB 4	PB5	PB6	PB7	PB8	PB9	PB10
0	0±.0.0	0±0.0	0±0.00	0±0.0	0±0.0	0±0.0	0±0.0	0±0.0
10	71.12±2.14	60.42±1.65	64.57±0.53	63.15±0.70	64.12±0.27	62.45±0.12	63.65±2.12	67.81±1.76
20	85.17±0.87	62.66±0.62	64.93±0.6	67.18±0.07	67.66±1.1	73.76±1.2	69.98±1.87	85.78±
30	94.767±0.76	73.56±0.12	70.83±0.8	75.46±0.25	76.87±1.73	86.15±0.89	74.67±0.95	97.12±2.54
40	99.94±1.20	76.91±0.70	87.83±	84.12±1.21	84.24±0.03	93.19±1.2	81.98±1.54	104.12±1.74
50	110.154±0.66	92.73±2.1	95.24±	92.67±1.78	93.87±0.87	99.45±1.18	92.57±0.97	-
60	-	96.70±0.78	106.31	102.45±1.5	103.7±1.23	101.27±0.9	100.48±1.41	-

Results of factorial batch

According to results obtained Carr's index for all the batches ranges from 11.11-16.04. Hausner's ratios for all the batches were found to be between 1.125-1.191. Values for angle of repose were in the range of 18.43-22.20. It was concluded that all the batches were having good flow characteristics.

Formulation code	Bulk density* (gm/ml)	Tapped density* (gm/ml)	Carr's index*(%)	Hausner's ratio*	Angle of repose*(^{O})
F1	0.345	0.399	12.56	1.144	21.01
F2	0.321	0.401	11.11	1.124	18.45
F3	0.340	0.382	11.87	1.135	21.12
F4	0.350	0.408	14.21	1.16	21.42
F5	0.329	0.421	21.75	1.27	27.9
F6	0.343	0.398	13.82	1.17	20.87
F7	0.328	0.388	15.46	1.18	23.91
F8	0.339	0.387	12.40	1.14	21.96
F9	0.354	0.398	11.05	1.13	22.13

Results of raft strength and ANC

Post compression parameter of factorial tablets

Tablets prepared by wet granulation are evaluated for hardness, friability ,weight variation, drug content, acid neutralization capacity. Results obtained are described in table 5.12

Table 7 Post compression parameter of 3^2 factorial batches F1-F4

Parameters	F1	F2	F3	F 4
Thickness(mm)	6.12±0.014	6.23±0.017	6.14±0.01	6.16±0.01
Diameter(mm)	11.95±0.01	11.98±0.01	11.98±0.01	11.97±0.00
Hardness(kg/cm^2)	6.1±0.40	5.15±0.35	5.50±0.014	4.65±0.0.17
Friability(%)	0.60±0.10	0.57±0.15	0.70±0.10	0.68±0.20
Acid neutralization capacity(mEq)	6.85±0.2	8.2±0.5	9.5±0.15	5.7±0.18
Weight variation	PASS	Pass	Pass	Pass
Drug Content (%)	98.50±0.32%	104.32±0.55%	101.12±0.12%	98.15±0.17

Table 8 post compression parameter of factorial batch of 3^2 batch F5-F9

Parameters	F5	F6	F7	F8	F9
Thickness(mm)	6.42±0.014	6.40±0.017	6.20±0.01	6.16±0.03	6.15±0.02
Diameter(mm)	11.98±0.00	11.95±0.0	11.98±0.0	11.98±0.00	11.97±0.00
Hardness(kg/cm^2)	6.1±0.40	5.15±0.35	5.50±0.014	4.65±0.0.17	4.60±0.13
Friability(%)	0.58±0.10	0.59±0.15	0.56±0.10	0.58±0.20	0.70±0.50
ANC(mEq)	8.45±0.2	10.2±0.5	5.4±0.15	7.0±0.21	10.3±0.16
Weight variation	Pass	Pass	Pass	Pass	Pass
Drug Content (%)	101.50±0.32	99.32±0.55	97.12±0.12	103.15±0.17	101.40±0.15

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

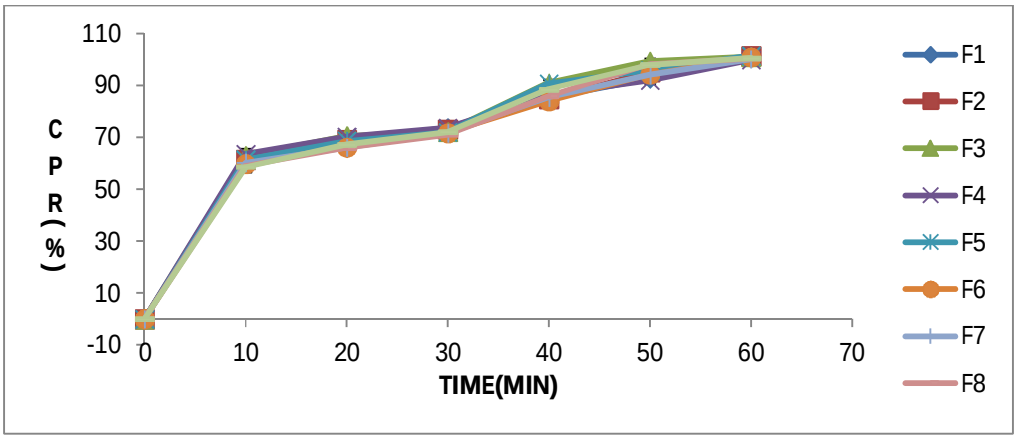
Raft strength of factorial batch F1-F9

Table 9 Raft strength of factorial batches

Batch No	Raft strength
F1	3.5±0.15
F2	3.7±0.10
F3	3.8±0.21
F4	4.3±0.12
F5	4.32±0.25
F6	4.98±0.10
F7	5.6±0.21
F8	5.8±0.05
F9	5.7±0.15

All values are mean ±SD

According to data batch F8 was having maximum raft strength.So It was selected as an optimized batch



RAFT STRENGTH MEASUREMENT BY TEXTURE ANALYZER

Raft strength of the most satisfactory formulation was determined by Texture Analyzer (Brookfield QTS). The graph of load vs time is shown below.

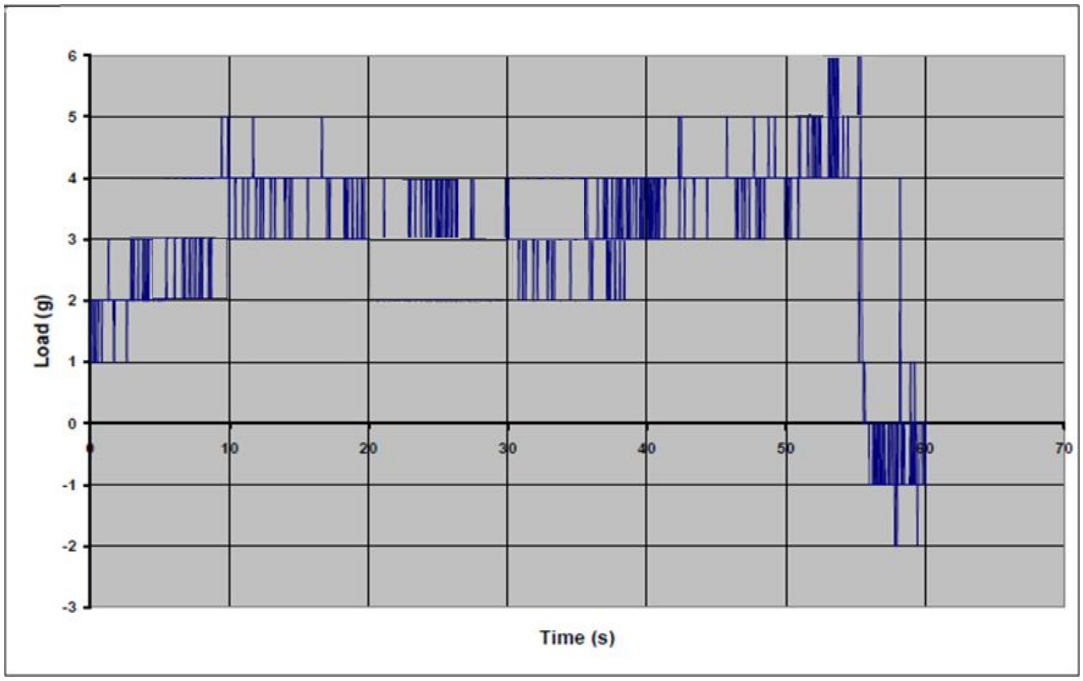


Figure 2 graph of load vs time for Batch F8

Initially load was increased with time, it showed maximum load when raft was broken and then it decreased sharply. The maximum raft strength observed at the breaking (rupture) point of the raft was found to be 5.0 gm.

The stability studies were carried out on the most satisfactory formulations (Batch F8) as per ICH guidelines Q1C. The stability studies were performed at 40 ± 2 °C / 75 ± 5 % RH conditions for 1 month. At the end of studies, samples were analyzed for the % drug content, in vitro drug release, raft strength and acid neutralization capacity.

Table 10 *In vitro* drug release profile of batch F8 after stability study and comparison with initial

Time (min)	CPR	CPR after storage at 40^0C ± 2 °C / 75 ± 5 % RH)
0	0	0
10	59.06	58.04
20	66.03	64.67
30	70.89	68.95
40	92.03	91.06
50	98.21	97.45
60	100.37	99.92

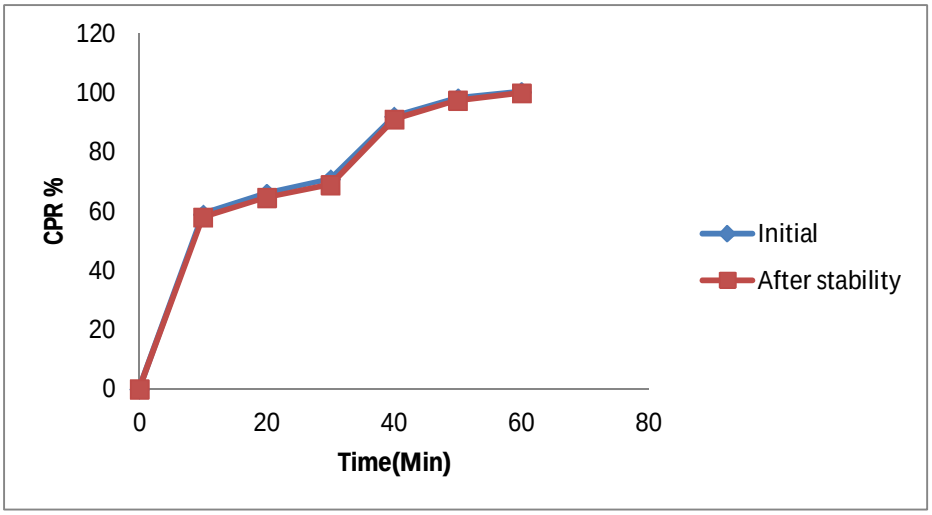


Figure 3 In vitro drug release profile of optimized batch after stability study and compare with initial

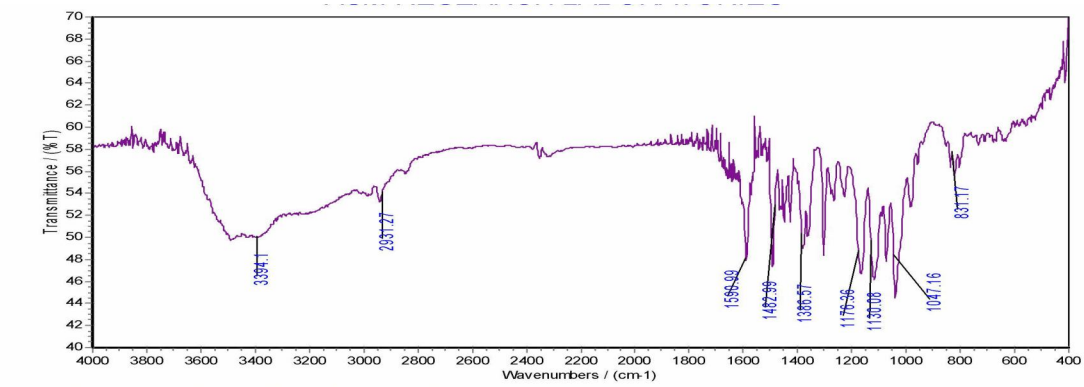
Table 11 Evaluation of batch F8 after stability study and comparison with initial

	Raft strength	ANC	% drug content
Initial	5.8±0.15	7±0.21	103.15±0.17
After stability	5.6±0.20	6.97±0.10	101.78±0.13

The optimized formulations (Batch F8) stored at 40 ± 2 °C / 75 ± 5 % were found stable. After storage at 40 ± 2 °C / 75 ± 5 % cumulative percentage drug release, raft strength, acid neutralization capacity and % drug content were nearly similar to the initial results. So, it was clear that drug and formulation were thermally stable as well as not affected by high humidity at 40 ± 2 °C / 75 ± 5 %. Similarity factor of the batch after stability study, was found to be 78.83 when compared with initial drug release profile.

Results of fourier transform infrared spectrophotometry

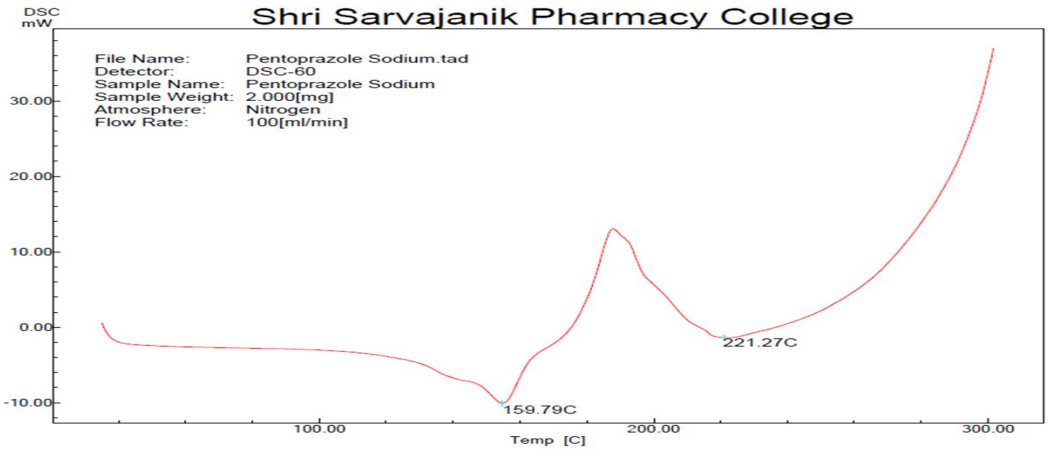
The IR spectra of pure drug Pantoprazole sodium and of the physical mixtures of the drug with excipients are as shown in Figure 4. Pure drug pantoprazole exhibited various peaks due to the presence of specific functional groups. Peaks of the major functional groups of the drug were obtained at 2931.27, 1590.99, 3394.10, 1130.08, 1047.00 and 3394.48. It was observed that the same peaks of drug functional groups were present in the IR spectra of the drug–excipients mixture and other peaks of excipients were present. Hence it was concluded that no interaction was found between the drug and excipients.

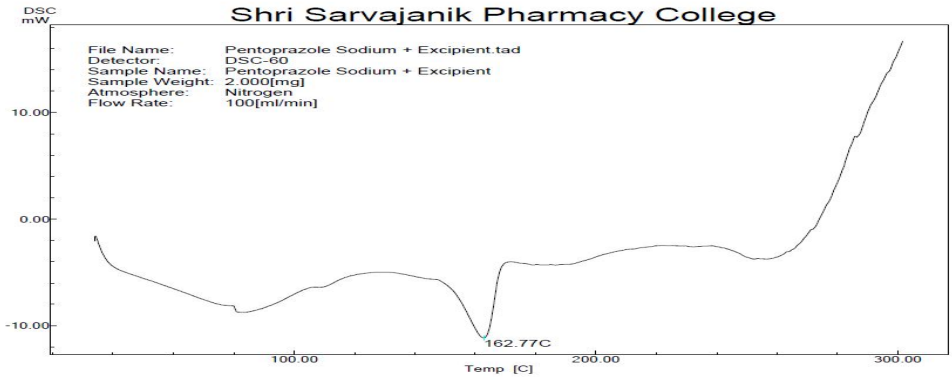


Results of DSC study

DSC thermograms were obtained for pure Famotidine and chewable tablet containing pantoprazole sodium and other excipients. Pure powdered pantoprazole sodium showed a melting endotherm at 159.23°C. The DSC thermogram of chewable tablet showed a melting peak of the drug at 161.21°C. There was no significant difference in melting point of drug in

both samples. It indicated that the drug was present in its characteristic physical and chemical form. It was compatible with all excipients present in the tablet and there was no major interaction of drug with excipients.





CONCLUSION:

• Many of patients are suffering from severe acidity and heart burning and gastro easophagul reflux disease problem which can be overcame by formulating raft forming chewable tablet containing antacid and proton pump inhibitor. It was conclude that chewable tablet was prepared by sodium alginate and pectin(raft forming agent) and sodium bicarbonate and calcium carbonate (antacid) which can form a floating raft in the presence of 0.1 N HCl .Raft strength is directly proportional to amount of sodium alginate. A 3^2 full factorial design was used for optimization. An optimized batch shows good raft strength, acid neutralization capacity and satisfactory *in vitro* drug release in 1 hr. The drug was also compatible with other ingredients used in formulation. Formulation was also stable at various conditions of temperature and humidity after stability study as per ICH guidelines.

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