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FORMULATION AND EVALUATION OF RAFT FORMING TABLET CONTAINING ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

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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 tablet containing antacid and proton pump inhibitor. The main objective of this research is to formulate and evaluate raft forming tablets of proton pump inhibitor(Esomeprazole magnesium trihydrate) along with raft forming agents sodium alginate and pectin and antacid(NaHCO3). 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, and amount of sodium bicarbonate was used as an independent variable and raft strength, acid neutralization capacity and Q_{30} was used as dependent variable. Acid neutralization capacity and in vitro drug release of all batches was found to be satisfactory. F6 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 tablet containing esomeprazole magnesium trihydrate could be an efficient dosage form for treatment of heart burning, GERD, erosive esophagitis and peptic ulcer.

Keywords: Esomeprazole Magnesium Trihydrate, Raft, Sodium Alginate, Pectin

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INTRODUCTION

Gastro retentive drug delivery system is the system in which a drug can remain in the gastric region for several hours in order to prolong its gastric residence time. Rapid gastrointestinal transit of convectional GRDDS can prevent complete drug release at gastric region and reduce the efficacy of the administered dose of drugs as the majority of drugs are absorbed in the stomach or the upper part of small intestine.

GRDDS are beneficial with reference to their bioavailability, therapeutic efficacy and possible pharma environment. Apart from these advantages; these systems offer various pharmacokinetic advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels. Gastric residence will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also prolonged gastric retention time in the stomach could be advantageous for local action in the upper part of the small intestine.

Materials and Methods

Esomeprazole magnesium trihydrate was received as gift from west coast pharmaceutical, Sodium alginate was received as a gift from siddhi vinayak industries, Pectin was received as a gift from Gujarat general pvt ltd., $NaHCo_3$ received from Karan chemicals, $Caco_3$ received from divine pharmaceutical, starch received from Shreeji industries, cross povidone received from Octavius pharma and talc and magnesium stearate received from Finar chemicals.

Preparation of raft forming tablet of esomeprazole magnesium trihydrate

Weigh accurately drug, polymer and other ingredient separately. All the ingredients except binder, volatile ingredient and lubricant were mixed thoroughly. PVP K30 M was dissolve in sufficient quantity of isopropyl alcohol and added to powder mixture to prepare dump mass. The prepared wet mass was passed through # sieve. Granules were allowed to dry in hot air oven then resifted through 40 # sieve. Granules were collected and other ingredient were added and lubricated. Tablets were compressed by 12mm diameter flat punch with the help of rotator tablets compression machine.

Table 1:- Preliminary batches

Ingredient (mg)	Formulations									
	PB1	PB2	PB3	PB4	PB5	PB6	PB7	PB8	PB9	PB10
Esomeprazole magnesium trihydrate	20	20	20	20	20	20	20	20	20	20
Sodium alginate	**150**	**125**	**100**	**150**	**200**	**175**	**275**	**175**	**200**	**100**
Pectin	**100**	**150**	**150**	**150**	**100**	**150**	**100**	**100**	**150**	**100**
$NaHCO_3$	90	90	90	90	90	90	90	90	90	90
$CaCO_3$	30	30	30	30	30	30	30	30	30	30
PVPK30	30	30	30	30	30	30	30	30	30	30
Starch	135	140	135	85	85	60	10	110	35	185
Cross povidone	30	30	30	30	30	30	30	30	30	30
Talc	6	6	6	6	6	6	6	6	6	6
Mg- stearate	9	9	9	9	9	9	9	9	9	9
Subtotal(mg)	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**

Optimization of raft forming tablet:

A 3^2 randomized full factorial design was used in the present investigation. In this design two factors were evaluated, each at three levels, and experimental trials performed at all eight possible combinations. A statistical model incorporating interactive and polynomial term was used to evaluate the response.

Amount of Sodium Alginate, Calcium carbonate and sodium bicarbonate where 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. (Q_{30})

Table 2:- Formulation layout of factorial batch

3^2 Full factorial design		
Independent variable		**Dependent variables**
X_1	**X_2**	**Y**
Sodium Alginate	Sodium Bicarbonate	Raft strength
		Acid neutralization capacity
		% drug release (Q30)

CODING OF VARIABLES

Coding value	**-1**	**0**	**+1**
Amount of sodium alginate	150	90	15
Amount of $NaHCO_3$	210	126	30

Formulation layout of factorial batches

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

Ingredients	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Esomeprazole magnesium trihydrate	20	20	20	20	20	20	20	20	20
Sodium alginate	150	210	150	150	210	210	150	210	150
Pectin	100	100	100	100	100	100	100	100	100
$NaHCO_3$	90	90	90	126	90	126	126	30	90
$CaCO_3$	15	15	15	15	15	15	15	15	15
PVP K30	30	30	30	30	30	30	30	30	30
Starch	150	90	150	144	90	210	114	80	150
Cross povidone	30	30	30	30	30	30	30	30	30
Talc	6	6	6	6	6	6	6	6	6
Mg-stearate	9	9	9	9	9	9	9	9	9
Total	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**

Table 4:-Formulation layout of factorial batches F1-F9

Batch	X_1	X_2
F_1	-1	-1
F_2	-1	0
F_3	-1	+1
F_4	0	-1
F_5	0	0
F_6	0	+1
F_7	+1	-1
F_8	+1	0
F_9	+1	+1

Evaluation of factorial batches

Thickness and diameter

The thickness and diameter of the tablet were measured using Vernier callipers. Three tablets were selected randomly from individual formulations, thickness and diameter was measured using Vernier callipers. It was measured in mm. results shown in table.

Hardness

The Pfizer hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in kg/cm^2.

Weight variation

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. not more than two tablets deviate from the percentage given below from the average weight and none deviate by more than twice the percentage shown.

Friability

Friability of the tablet determined using Friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighted sample of tablet was placed in the loss in the weight of tablet is the measure of friability and is expressed in % as,

% Friability = Initial weight of tablets – final weight of the tablet ×100

Initial weight of tablet

Raft strength measurement by in-house method

Tablet powder equivalent to unit dose was transferred to 150 ml of 0.1 N HCL, maintained at 37^0 C in a 250 ml glass beaker. Each raft was allowed to form around an L- shaped wire probe held upright in the beaker throughout the whole period of raft development. Raft strength was estimated using modified balance method. Water was added drop wise to the pan and weight of water required to break the raft was recorded.

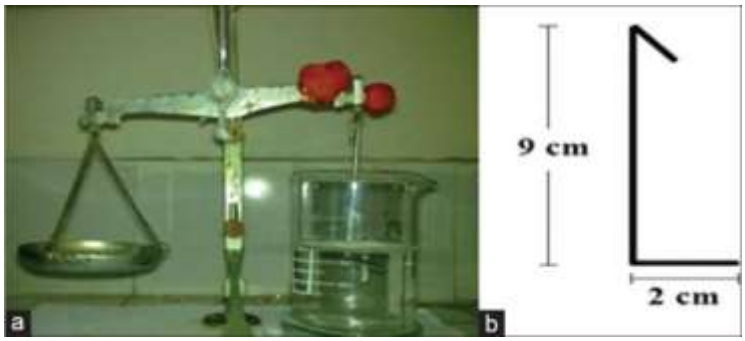

Figure 1: a) Modified balance method, b) wire probe for raft strength measurement

Acid neutralization capacity

Tablet powder equivalent to unit dose was transferred to 250 ml beaker, 50 ml of HCL was added while continued to stir on magnetic stirrer for 10 min after the addition of the acid. Stirring was discontinued briefly and gum base was removed using a long needle without delay. Needle was promptly rinsed with 20ml water, and washing was collected in the beaker, stirring was resumed for 5 min. titration was began immediately. Excess HCL was titrated against 0.5 N NaoH to attain a stable P^H 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 HCL = Normality of HCL

V NaoH = Volume of NaoH required

N NaoH = Normality of NaoH

***In vitro* drug release**

The in vitro drug release study of esomeprazole magnesium trihydrate was performed using USP apparatus II fitted with paddle (50 rpm) at 370C ± 0.50C using simulated gastric fluid (pH 1.2; 900ml) as a dissolution medium. Tablet was powdered and then added to dissolution medium. At the predetermined time intervals, 10ml samples were withdrawn, filtered through a 0.45 µm membrane filter and analyzed at given nm using a shimadzu UV 1800 double beam spectrophotometer. Cumulative % drug release was calculated using an equation obtained from a calibration curve which is developed in the range of µg/ml for 0.1 N HCL.

Raft strength measurement by Texture Analyzer

The raft strength of the most satisfactory formulation (batch F6) 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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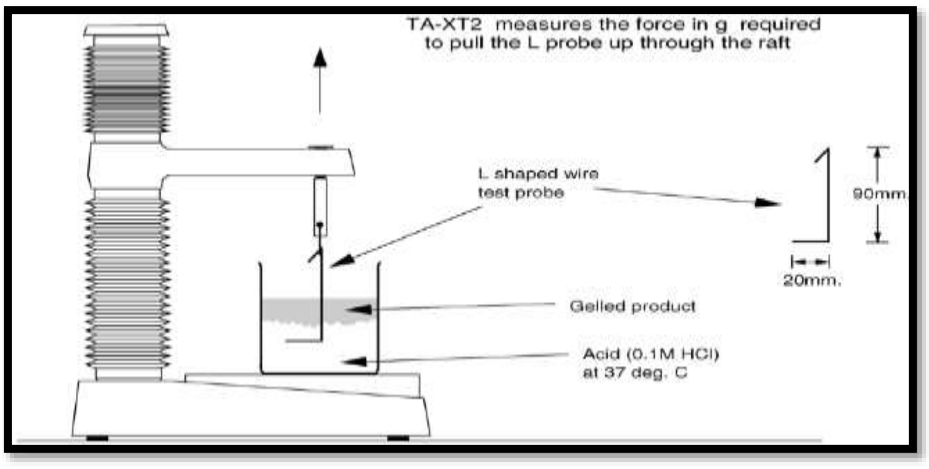

Figure 2 Raft strength measurement by texture analyser

Drug excipients compatibility study

By FTIR spectroscopy

IR spectra of pure drug esomeprazole magnesium trihydrate and physical mixture of drug with excipients are as shown in fig. 5.5 the pure drug esomeprazole magnesium trihydrate exhibited various peaks due to presence of specific functional groups. Peaks of major functional groups of drug are describe in table. It was observed that there were no changes in these major peak in the IR spectra of a mixture of drug and excipients.

Stability studies of the optimized 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 F6). 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 optimized formulation sealed in aluminium foil was also kept at room temperature and humid condition. At the end of the storage time, the samples were analyzed for raft strength, *in vitro* drug release and % drug content.

RESULT AND DISCUSSION

Table 5:- Result of preliminary screening

Batch no.	Amount of sodium alginate	Amount of pectin	Raft strength	Cumulative %drug release(mg)
PB1	150	100	1.3	104.21
PB2	125	150	1.6	103.65
PB3	100	150	1.4	114.13
PB4	150	150	2.0	98.54
PB5	200	100	3.3	101.57
PB6	175	150	4.6	97.76
PB7	275	100	4.7	98.43
PB8	**175**	**100**	**4.8**	**99.87**
PB9	**200**	**150**	**4.8**	**96.45**
PB10	100	100	3.4	98.69

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 6:-Acid neutralization capacity of batch PB1-PB10

Batch no.	ANC mEq
PB1	6.60±0.18
PB2	6.90±0.02
PB3	6.53±0.09
PB4	6.68±0.02
PB5	6.56±0.12
PB6	7.11±0.15
PB7	6.48±0.28
PB8	7.55±0.12
PB9	6.47±0.24
PB10	6.82±0.17

According to USP acid neutralization capacity must be ≥5 mEq. So acid neutralization capacity of PB1-PB10 was given in table and it was satisfactory.

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

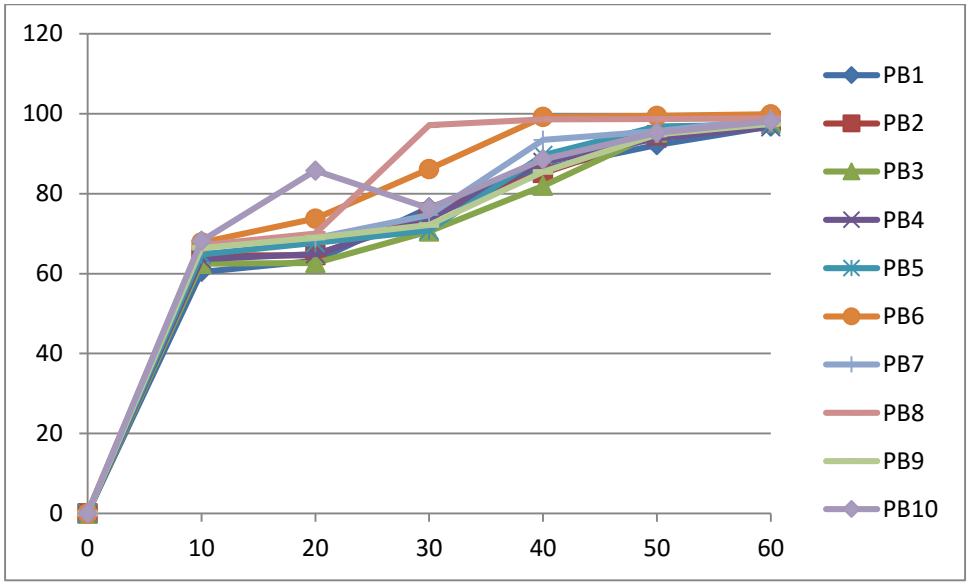

Figure : 3 In vitro drug release profile of preliminary batch PB1-PB10

Table 7*:- In vitro* drug release profile

Time(min)	PB1	PB2	PB3	PB4	PB5	PB6	PB7	PB8	PB9	PB10
0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
10	60.42±0.59	64.57±0.08	62.45±0.53	63.65±0.70	64.81±0.27	67.81±0.12	66.91±0.76	67.12±0.63	66.42±1.12	68.21±2.14
20	63.21±0.07	64.61±1.2	62.66±1.2	64.93±0.87	67.66±0.08	73.76±0.07	68.86±0.62	69.98±0.87	68.98±0.6	85.78±1.2
30	76.54±0.12	75.23±0.8	70.56±0.8	73.81±0.12	70.83±0.90	86.15±0.73	74.67±1.12	97.12±0.25	72.15±0.25	76.37±1.73
40	86.24±0.70	85.15±0.20	81.98±1.2	87.83±0.03	89.62±1.21	99.19±0.70	93.46±1.74	98.63±0.76	85.43±0.08	88.62±1.21
50	92.18±2.1	94.61±1.81	95.24±2.1	93.87±0.63	96.86±0.87	99.45±1.18	95.66±0.97	98.69±1.78	94.83±2.1	95.26±1.7
60	96.82±0.78	98.26±0.09	97.82±0.78	96.68±1.23	97.24±0.09	99.86±0.08	98.73±0.02	98.85±1.41	97.46±0.75	98.14±1.3

Table 8 In-vitro release profile of factorial batch

Time (min)	**Cumulative % release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0.±0.00	0. ±0.00	0. ±0.00	0. ±0.00	0. ±0.00	0. ±0.00	0. ±0.00	0. ±0.00	0.00± 0.00
10	58.63±1.15	61.53±2.2	62.84±1.65	60.36±1.80	59.06±1.72	64.32±2.51	63.15±2.11	60.34±2.06	59.62± 2.34
20	62.24±1.23	64.86±1.3	63.89±1.82	66.11±1.78	66.25±1.91	66.39±1.84	64.53±1.83	62.46±1.23	60.73± 1.43
30	73.5±1.63	73.12±1.76	72.15±1.2	73.56±1.8	72.05±2.2	71.61±1.7	71.87±1.63	71.04±1.15	72.08± 1.6
40	84.86±1.41	90.81±1.30	85.60±1.58	85.35±1.73	90.09±1.39	83.86±1.41	85.42±1.86	87.01±1.1	86.67± 1.22
50	90.60±1.30	97.21±1.85	98.36±1.18	89.86±1.28	96.75±1.80	94.28±1.30	94.18±1.85	99.11±1.40	96.98± 1.56
60	98.43±0.8	97.39±0.64	99.46±0.97	99.86±0.83	100.91±0.72	98.37±0.80	97.45±1.01	99.37±0.8	99.23± 0.7

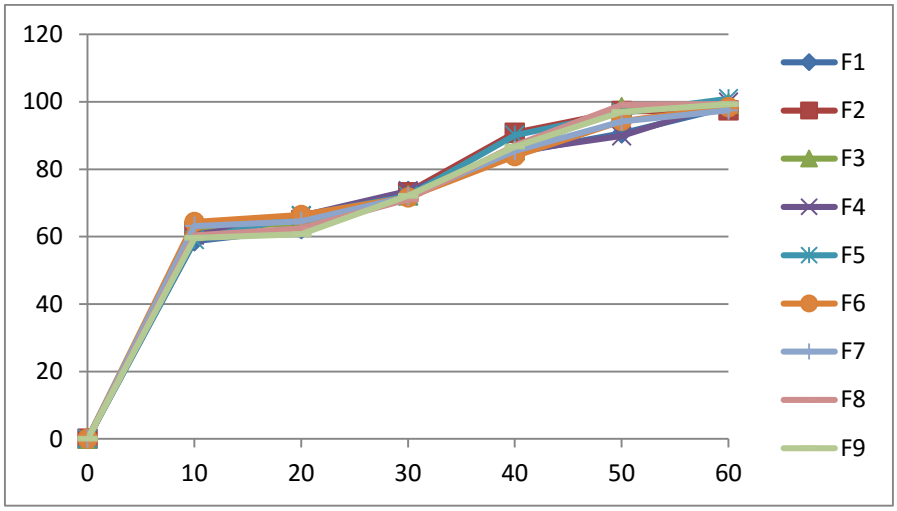

Figure 4 In vitro drug release profile of factorial batches

Results of factorial batch

According to results obtained Carr's index for all the batches ranges from 13.1-19.5

Hausner's ratios for all the batches were found to be between 1.27-1.34. Values for angle of repose were in the range of 22.1-24.2. It was concluded that all the batches were having good flow characteristics

Table 9:- Precompression parameter of 3^2 full factorial batches

Formulation code	Bulk density*(gm/ml)	Tapped density*(gm/ml)	Carr's index*(%)	Hausner's ratio	Angle
F1	0.48	0.62	15.4	1.29	22.2
F2	0.44	0.59	15.5	1.34	23.2
F3	0.45	0.58	19.5	1.28	22.2
F4	0.44	0.59	15.5	1.34	22.1
F5	0.43	0.58	16.1	1.34	22.7
F6	0.48	0.63	13.1	1.31	23.7
F7	0.48	0.62	15.4	1.29	24.2
F8	0.47	0.60	18.3	1.27	23.7
F9	0.45	0.58	19.5	1.28	23.1

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

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

Table 10:- Post compression parameters of factorial tablets

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness(mm)	4±0.04	4±0.06	4±0.01	4±0.01	4±0.02	4±0.02	4±0.07	4±0.02	4±0.01
Diameter(mm)	12±0.02	12±0.03	12±0.01	12±0.06	12±0.02	12±0.01	12±0.01	12±0.01	12±0.05
Hardness(k/cm²)	3.5±0.18	3.9±0.20	4.3±0.12	3.9±0.15	4.2±0.11	4.5±0.20	3.8±0.13	4.6±0.16	4.2±0.09
Friability (%)	0.81±0.41	0.72±0.18	0.79±0.29	0.86±0.02	0.72±0.17	0.89±0.07	0.76±0.42	0.88±0.18	0.85±0.09
Acid neutralization capacity	5.8±0.3	6.3±0.2	5.6±0.3	5.9±0.1	5.4±0.5	5.5±0.6	6.1±0.1	5.4±0.1	5.5±0.06
Weight variation	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
Drug content	96.67±0.08	96.46±0.22	96.49±0.12	97.75±0.01	96.56±0.18	99.63±0.02	98.69±0.12	97.0±0.01	97.01±0.015

Table 11:-Raft strength of factorial batch

Batch no.	Raft Strength
F1	3.2±0.11
F2	3.4±0.9
F3	3.7±0.18
F4	4.1±0.10
F5	4.3±0.21
F6	5.2±0.8
F7	5.1±0.19
F8	5.0±0.03
F9	4.9±0.06

All values are mean ±SD

STABILITY STUDY OF OPTIMIZED FORMULATION

The stability studies were carried out on the most satisfactory formulations (Batch F6) 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 12:- *In vitro* drug release profile of batch F6 after stability study and comparison with initial

Time (min)	CPR	CPR after storage at 40^{0}C ± 2^0 C/ 75±5 % RH)
0	0	0
10	54.01	53.06
20	59.15	57.01
30	62.03	60.12
40	71.09	70.26
50	92.09	91.32
60	98.05	97.11

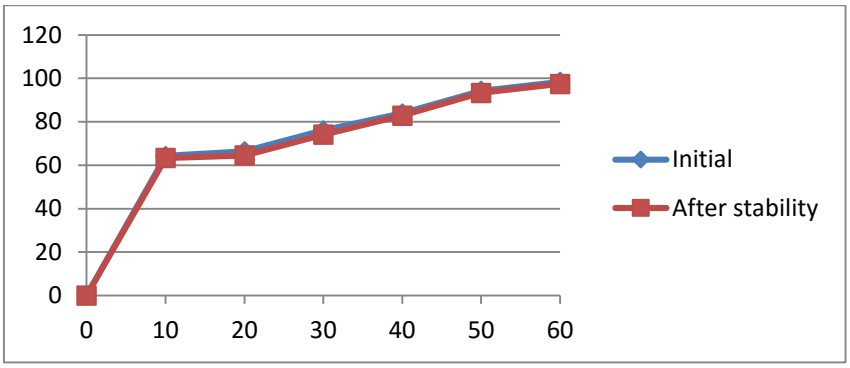

Figure: 4 In vitro drug release profile of optimized batch after stability study and compare with initial

Table 13:- Evaluation of batch F6 after stability study and comparison with initial

	Raft strength	ANC	% Drug content
Initial	5.4±0.12	9.6±0.23	101.12±0.15
After stability	5.2±0.18	7.62±0.13	99.32±0.10

The optimized formulations (Batch F6) 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%.

Fourier transforms infrared spectroscopy

The peak of esomeprazole magnesium trihydrate as shown in figure 8.1 and table 2 matches with the peaks mentioned in the literature, which conforms identification group.

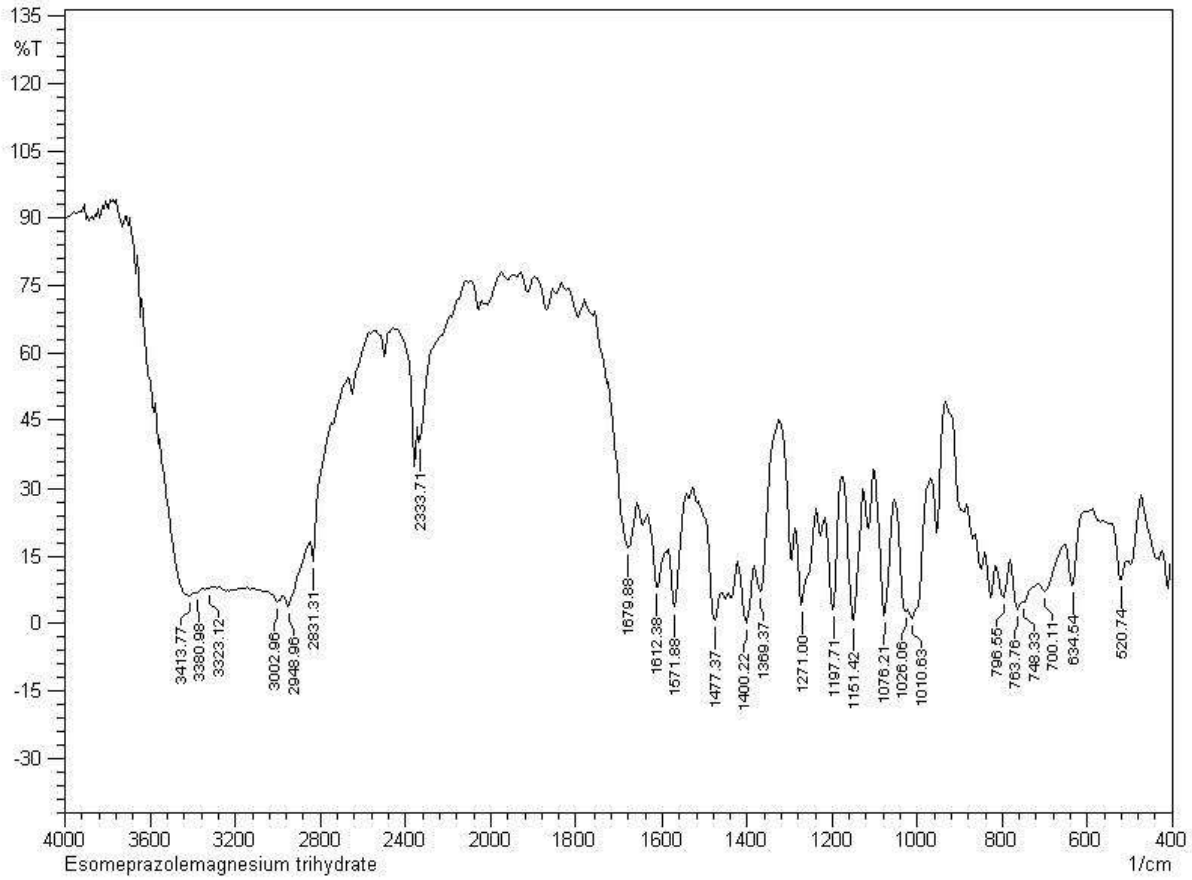

Figure:- 5 FTIR spectrum of esomeprazole magnesium trihydrate

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