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FORMULATION DEVELOPMENT AND EVALUATION OF RAFT FORMING DRUG DELIVERY SYSTEM OF FAMOTIDINE

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ABSTRACT

The objective of the present study is to formulate and evaluate raft forming chewable tablets of Famotidine for the treatment of gastroesophageal reflux diseases. The purpose of this research work was to formulate raft-forming tablets of Famotidine using a raft-forming agent along with an antacid- and gas-generating agent. Tablets were prepared by direct compression and evaluated for raft strength, acid neutralization capacity, weight variation, % drug content, thickness, hardness, friability and in vitro drug release.A 3^2 full-factorial design was used in the present study for optimisation. Tablets containing sodium alginate were having maximum raft strength as compared with other raft-forming agents. Acid neutralisation capacity and *in- vitro* drug release of all factorial batches were found to be satisfactory. The F9 batch was optimised based on maximum raft strength and good acid neutralisation capacity. Drug–excipient compatibility study showed no interaction between the drug and excipients. It was concluded that raft-forming tablets prepared using an optimum amount of sodium alginate and sodium bicarbonate could be an efficient dosage form in the treatment of gastro esophageal reflux disease.

KEYWORDS: Famotidine, raft, gastroesophageal reflux disease, sodium alginate, raft strength, acid neutralization capacity.

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. Various treatment options include for GERD are antacids, H2 antagonist, proton pump inhibitor etc.[3,4]

Famotidine is a histamine H_2-receptor antagonist. It is prescribed widely in Active Duodenal ulcers, Gastric ulcers, Zollinger-Ellison syndrome, Gastro Esophageal Reflux Disease (GERD) and Erosive Esophagitis. It has a low biological half-life of 2.5-4.0 h. The current recommended adult oral dosage of Famotidine is 20 mg twice daily or 40 mg once daily.[5] The low bioavailability (40-45%) and short biological half life (2.5-4.0 hours) of Famotidine following oral administration favors development of a sustained release formulation.[6] Controlled release formulation describes sustained action along with its predictability and reproducibility of release of drug ingredients from the drug delivery system.[7]

The raft forming system is one of the most feasible & preferred approach for achieving a prolonged and predictable drug delivery in the GI tract. This system releases drug in a sustained manner which results in constant plasma profiles.[8]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 CO_2. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents into the esophagus by acting as a barrier between the stomach and esophagus.[9]

MATERIALS AND METHODS

Material

Famotidine is obtained from Macleods Pharmaceuticals Pvt. Ltd. Sodium alginate is obtained from modern science laboratory. All other excipients used to prepare raft forming tablets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Method

Drug, polymer and other ingredients were weighed accurately. All the ingredients were passed through mesh no. 60. All the Ingredients were co-ground in a pestle

mortar for 5 minutes. The mixed blend of excipients was directly compressed using an 8 mm round flat punches on Tablet compression machine to produce tablets weighing 650 mg each.

Preliminary screening

Preliminary screening was carried out to select a good raft-forming agent, which has good raft strength. Five different raft-forming agents, viz., sodium alginate, HPMC K4 M, Locust bean gum, Pectin and Chitosan were used in the study. The formulas of the different preliminary batches (batch PB1-PB5) are shown in Table 1.

Table 1: Composition of different preliminary batches.

Ingredients	PB1	PB2	PB3	PB4	PB5
Famotidine	20	20	20	20	20
Sodium alginate	300	-	-	-	-
HPMC K 4 M	-	300	-	-	-
Locust bean gum	-	-	300	-	-
Pectin	-	-	-	300	-
Chitosan	-	-	-	-	300
Sodium bicarbonate	50	50	50	50	50
Calcium carbonate	100	100	100	100	100
PVP K 30	50	50	50	50	50
Talc	10	10	10	10	10
Magnesium stearate	15	15	15	15	15
Aspartame	20	20	20	20	20
Mannitol	95	95	95	95	95

Optimisation by 3^2 full-factorial design

A 3^2 randomized full factorial design was used in the present investigation. In this design, 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 % drug release and raft strength were selected as dependent variables.

Table 2: Formulation layout of factorial batches.

Independent variables		Dependent variables
X_1	X_2	Y
Sodium alginate	Sodium bicarbonate	% drug release Raft strength

Table 3: Coding value of full factorial batches.

Coding value	-1	0	+1
Amount of sodium alginate	200	250	300
Amount of sodium bicarbonate	30	40	50

Table 4: Optimization of batch using 3^2 full factorial designs.

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidine	20	20	20	20	20	20	20	20	20
Sodium alginate	300	300	250	250	200	250	200	200	300
Sodium bicarbonate	50	30	40	30	50	40	30	40	30
Calcium carbonate	100	100	100	100	100	100	100	100	100
PVP K30 M	50	50	50	50	50	50	50	50	50
Talc	10	10	10	10	10	10	10	10	10
Magnesium stearate	15	15	15	15	15	15	15	15	15
Aspartame	20	20	20	20	20	20	20	20	20
Mannitol	65	65	65	65	65	65	65	65	65
Total	650	650	650	650	650	650	650	650	650

Evaluation of Factorial Batches
General evaluation parameters for tablets.[10-13]

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, which is then operated for 100 revolutions. The tablets were dedusted 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.

Content uniformity
Twenty tablets were weighted and powdered in a mortar. Accurately weighted a quantity of the powder equivalent to about 20 mg of famotidine, 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 265 nm and the content famotidine of was calculated from the absorbance obtained.

Raft strength measurement by in-house method[14]
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.

Acid neutralization capacity[15]
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 NaOH to attain a stable pH of 3.5. The number of mEq of acid consumed by the tablet tested was calculated by the using formula.

***In vitro* drug release study**
In vitro drug release study of famotidine chewable 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 for 1 hour. The tablets were added to the dissolution medium. At pre-determined time intervals, 10-ml samples were withdrawn, filtered through a 0.45-µm membrane filter and analyzed at 265 nm using a Shimadzu UV 1800 double-beam spectrophotometer. 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 was determined by 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 held upright in the beaker throughout the whole period 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.

Drug–excipient compatibility study
Fourier transform infrared spectrophotometry
The FTIR spectra of famotidine and a mixture of famotidine with major excipients were recorded using the KBr mixing method using an FTIR instrument.

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 Famotidine and of the physical mixtures of Famotidine 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
To assess drug and formulation stability, accelerated stability studies were done for 3 months. The stability studies were carried out on the most satisfactory formulations (batch F9). 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 3 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 *in vitro* drug release and % drug content.

RESULT AND DISCUSSION

Results of preliminary screening

Tablets prepared using different raft-forming agents were tested for raft strength in 0.1 N HCl. Among all five batches prepared with five different raft-forming agents, tablets prepared using sodium alginate had maximum raft strength. So sodium alginate was selected as the raft-forming agent for further studies. All results are shown in Table 5.

Table 5: Evaluation Parameters of Preliminary screening batches.

Formulations	Raft strength
PB1	5.82
PB2	4.73
PB3	4.15
PB4	3.26
PB5	2.88

Evaluation parameters of Factorial batches:

Before compression the formulation powder blend was subjected for various evaluation parameters. The powder blend was evaluated by the measurement of Bulk density, Tapped density, Angle of repose, Carr's index (Compressibility index) and Hausner's ratio which is shown in Table 6.

Table 6: Pre compression parameters for factorial batches.

Formulation Code	Bulk density (gm/ml) ± SD	Tapped density (gm/ml) ± SD	Hausner's ratio	Carr's index	Angle of repose
F1	0.517±0.02	0.625±0.03	1.29±0.04	22±2.00	40.23
F2	0.500±0.01	0.625±0.02	1.24±0.01	20±2.64	40
F3	0.480±0.06	0.582±0.03	1.20±0.07	17±5.17	40.03
F4	0.503±0.05	0.662±0.02	1.30±0.17	22±5.89	35.53
F5	0.513±0.10	0.635±0.07	1.24±0.09	18±5.85	37.18
F6	0.508±0.01	0.592±0.05	1.16±0.10	13±7.82	39.8
F7	0.418±0.03	0.546±0.01	1.04±0.26	22±8.62	37.19
F8	0.547±0.04	0.682±0.02	1.25±0.15	18±4.50	37.18
F9	0.535±0.01	0.652±0.02	1.21±0.04	13±2.64	38.41
Broad range	0.418-0.547	0.546-0.682	1.04-1.29	13-22	35.53-40.23

Results of 3^2 full-factorial design

All results for physicochemical parameters like hardness, weight variation, thickness, % drug content and friability are shown in Table 7. All results were found to be satisfactory and within a normal range. Batch F9 was found to have maximum raft strength of 6 g. All batches had acid neutralisation capacity in the range of 6.9 to 9.5. The in vitro drug release profiles of all factorial batches are shown in Figure 2. All parameters were found to be satisfactory for all factorial batches, so the batch with maximum raft strength, that is batch F9, was selected as the optimized batch.

Table 7: Post compression parameters of factorial batches.

Formulation Code	Weight (mg) ±SD	Hardness (kg/cm^2) ± SD	Thickness (mm) ±SD	Friability ± SD%	% Drug content	Acid neutralization capacity (mEqui)
F1	649±4.7	6.0±0.5	5.52±0.02	0.504±0.2	97.04±3.3	7.9
F2	649±3.3	6.2±1.0	5.54±0.04	0.580±0.2	99.30±3.6	8.9
F3	649±4.4	6.4±1.1	5.55±0.01	0.547±0.04	94.45±3.0	7.7
F4	648±2.8	5.7±0.5	5.56±0.01	0.706±0.08	101.54±6.8	9.2
F5	649±3.4	6.0±0.5	5.55±0.02	0.630±0.19	95.36±1.7	6.9
F6	647±3.8	5.9±1.2	5.55±0.05	0.601±0.09	98.48±4.5	8.5
F7	648±4.1	5.8±1.1	5.58±0.03	0.541±0.12	102±5.03	8.4
F8	648±2.5	6.2±1.5	5.61±0.04	0.734±0.09	99.04±9.7	7.3
F9	648±3.8	6.1±1.7	5.57±0.05	0.857±0.08	100.61±4.0	9.5
Broad range	647-649	5.7-6.4	5.52-5.61	0.50-0.857	94.45-10	6.9-9.5

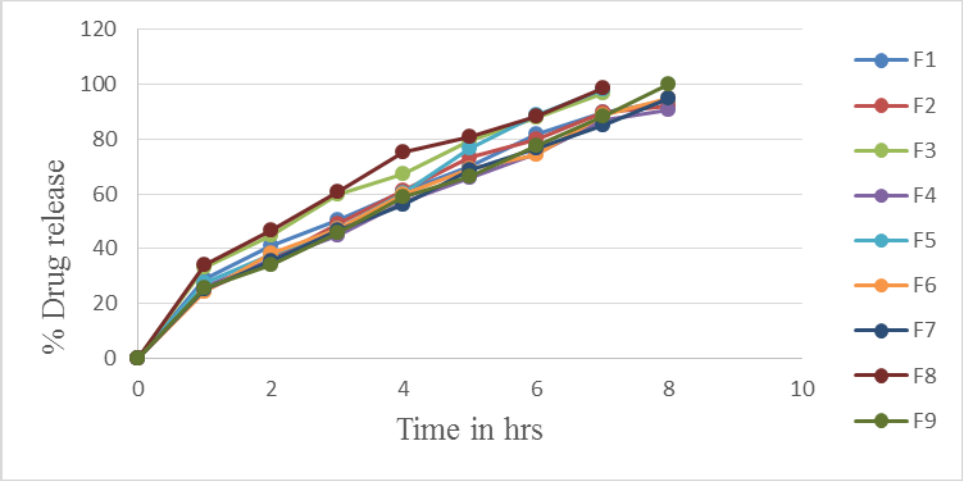

Figure 2: Percent Drug Release profile graph of Formulations.

Result of raft strength

The raft strength of the optimised formulation (batch F9) was measured by the Texture Analyzer. Raft strength of optimized formulation i.e. F9 was determined by using Texture analyzer and is found to be 6 which is shown in Figure 3.

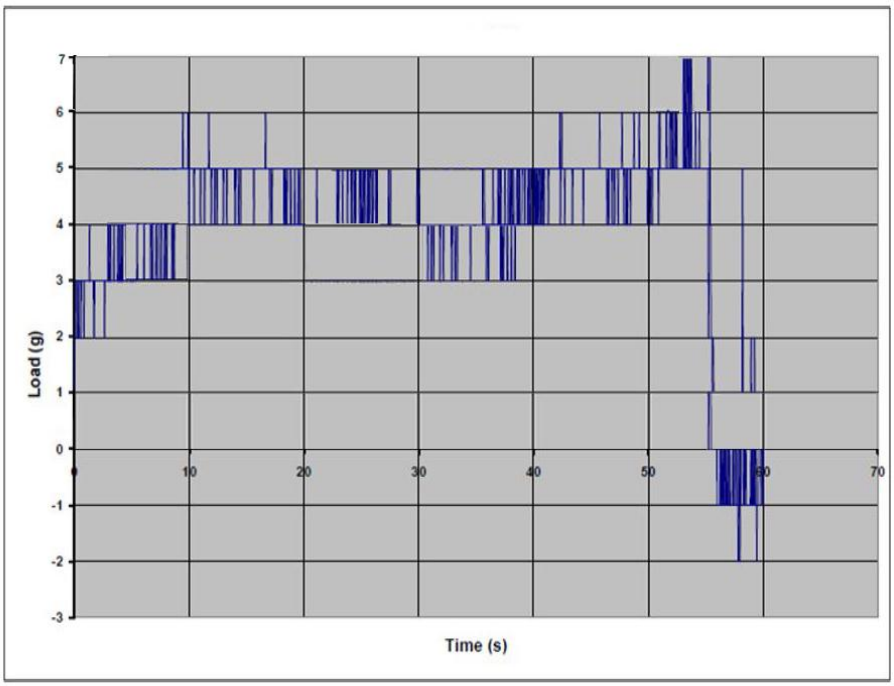

Figure 3: Graph of load Vs time for batch F9

Result FTIR spectra of Famotidine

The FTIR spectrum of Famotidine exhibited characteristic signals as shown in Figure 4. The absorption bands shown by Famotidine are characteristic of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Famotidine & absence of well-defined unaccountable peaks is a confirmation of the purity of the drug sample.

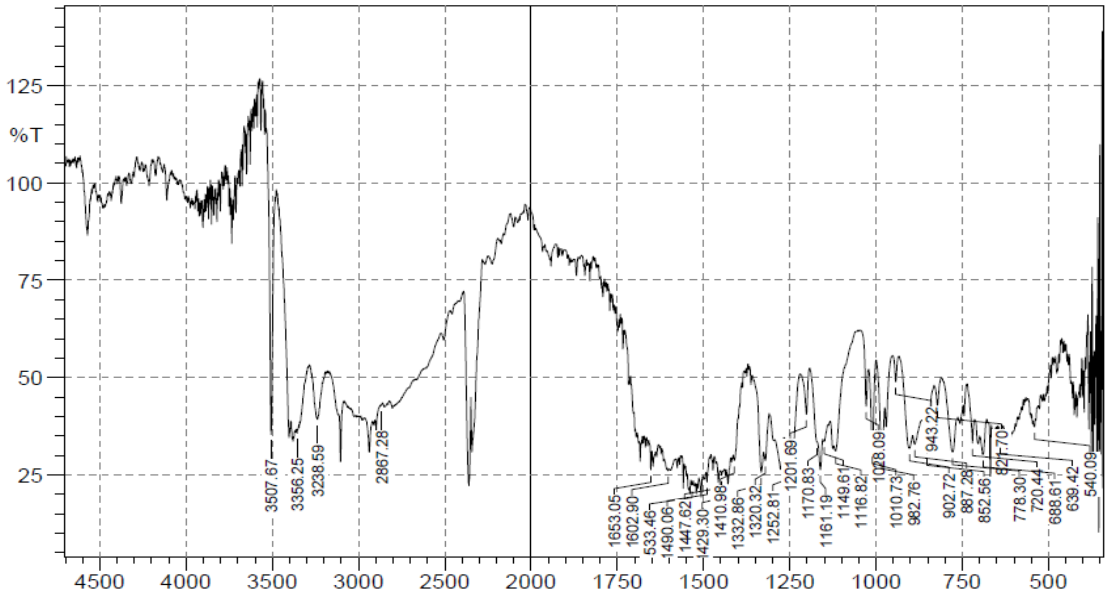

Figure 4: FT-IR spectrum of pure drug Famotidine.

Result of DSC study

Thermal analysis of drug was carried out using DSC. The DSC curve of Famotidine profiles endothermic peak at 160.65ºC corresponding to its melting point & indicates its purity & shows that it's not crystalline in nature. The heat required is -155.67J.

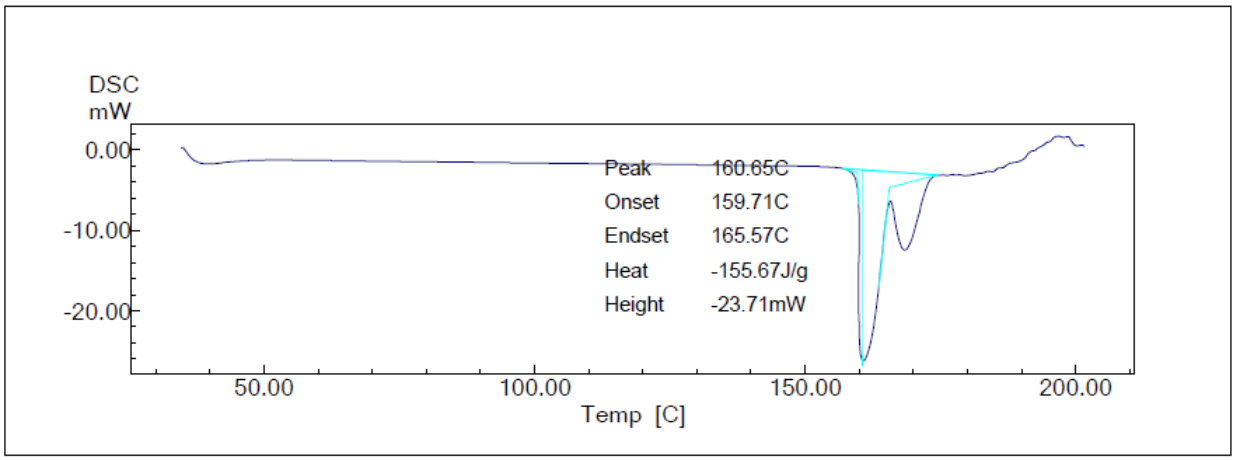

Figure 5: DSC of Famotidine.

Results of stability study

At the time of stability studies the tablets of the optimized batch F9 was subjected to evaluate for the physio-chemical parameters, for three month. The result showed that there is no change in the physio-chemical properties of the tablets. The results are shown in table 8.

Table 8: Stability study of raft forming Famotidine tablet.

Parameters	After 1 month observation	After 2 month observation	After 3 month observation
Physical appearance	No change	No change	No change
Weight variation (mg)	648±0.060	646 ± 0.059	646 ± 0.060
Thickness (mm)	5.57± 0.05	5.59 ± 0.15	5.54 ± 0.15
Hardness(Kg/cm²)	6.2 ± 0.57	6.0 ± 0.57	6.3 ± 0.57
Friability	0.775 ± 0.030	0.687 ± 0.030	0.618 ± 0.0030
Drug content (mg/tab)	99.36 ± 0.25	99.62 ± 0.20	102.8 9± 0.21
In-vitro Dissolution (8 hrs)	96.31	98.24	99.47

From the Table 8, hardness of formulation F9 for 30,60,90 days was found to be 6.2,6.0,6.3 resp. The % friability of the formulation was also found to be 0.775,0.687,0.618. resp. The % drug content of the

formulation was found to be 99.36,99.62,102.89% resp. In vitro drug release study of optimized formulation kept for stability was found to be 99.47%.As there is no negligible change in drug release profile of optimized batch, that indicates the development formulation was stable.

CONCLUSION

Preformulation study FT-IR and DSC showed that there is no strong interaction between drug and excipients used in formulation.Sodium alginate was selected from the preliminary batches for further formulation as it showed maximum raft strength. A formulated tablet with either method complies with official tests like weight variation, content uniformity, friability. It was concluded that raft forming tablet prepared by sodium alginate in combination with calcium carbonate and sodium bicarbonate can form a floating raft in the presence of 0.1 N HCl. Raft strength was directly proportional to the amount of sodium alginate in the tablet. The amount of sodium bicarbonate in the tablet were critical parameter in the formulation development. From the all formulations, the optimized formulation was found to be F9 as it had good raft strength, sufficient acid neutralization capacity and satisfactory *in vitro* drug release. The formulation was stable at accelerated conditions of temperature and humidity.

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