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FORMULATION DEVELOPMENT AND EVALUATION OF BILAYER TABLET FOR EFFECTIVE TREATMENT OF GASTRIC ULCER

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ABSTRACT

The aim of this study was to establish Gastro retentive bilayer drug delivery systems containing Sucralfate and clarithromycin for the treatment of H. pylori-induced gastric ulcers in order to reduce the frequency of drug administration and mitigate side effects. The tablet is distinguished by a Sucralfate immediate release layer and a clarithromycin gastroretentive layer. HPMC K 15, HPMC K4, and PVP K30 were used as floating agents, and sodium bicarbonate and citric acid were used as gas-generating agents in the formulation containing Gastroretentive layer. Crospovidone, sodium starch glycolate and croscarmellose sodium was used as superdisintegrant for the preparation of immediate release layer. Precompression parameters, physical characteristics such as stiffness, friability, uniformity of weight, uniformity of drug material, swelling index, in-vitro floating studies, and in-vitro drug release were all evaluated on the prepared Gastroretentive tablets.

KEYWORDS: Sucralfate, Clarithromycin, Bilayer floating tab, Crospovidone, Superdisintegrant.

INTRODUCTION

The oral route has long been the most common and convenient method of drug delivery. Because of the versatility in developing dosage forms and the lack of problems like sterility and possible damage at the site of administration, the oral route of administration has gained more publicity than any other dosage form in the pharmaceutical industry and research sector. Oral drug delivery systems account for about half of all drug delivery systems on the market. Drugs that are easily absorbed from the gastrointestinal tract and have a short half-life are quickly removed from the bloodstream, necessitating repeated dosing. To address this

problem, the oral sustain controlled release formulation was created in an effort to slowly release the medication into the gastrointestinal tract while maintaining therapeutic drug concentration in the serum for a longer period of time. The oral controlled-release mechanism is distinguished by a traditional pattern of drug release in which the drug concentration is retained in the therapeutic window for a long time, ensuring long-term therapeutic effect.[1] Peptic ulcer can be defined as any sore in the linings of GIT particularly stomach or duo-denum. There are two most common types of peptic ulcers called "gastric ulcers" and "duodenal ulcers". Peptic ulcer occurs as a result of imbalance between the aggressive (acid, pepsin, bile and H. pylori) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells) factors. Helicobacter pylori are an important cause of duodenal and gastric ulcers. Greater than 90% of duodenal ulcers and 70% of gastric ulcers are associated with H. pylori. H. pylori are a gram-negative, motile, micro-aerophilic, curved bacillus that is found in the mucus layer overlying the gastric epithelium.[2] The treatment for eradication of H. pylori is complicated, requiring a combination of an antibiotic with gastric acid inhibitors. Therefore, a well designed drug delivery system is required to overcome the troubles of conventional therapy and to enhance the therapeutic efficacy of given drug regimens. Gastroretentive drug deliveries locate the drug within the stomach and prolong ultimate contact with the absorbing membrane and increases efficacy. This is particularly important in the treatment of microorganisms which colonize in the stomach because the three main fraction reducing luminal delivery of drug to them are gastric emptying, gastric acidity and epithelial mucus layer.[3] In particular, H. Pylori lives deep within the gastric mucus layer and prolonged local application is needed for sufficient to diffuse to the bacteria. Sucralfate has traditionally been classified as a topical site-protective or cytoprotective agent of ulcer-healing drugs with a high affinity for the gastric mucosa.[4] Clarithromycin is a broad spectrum antimicrobial new generation macrolide active against most Gram positive aerobic cocci and Gram positive bacilli.[5] The activity of clarithromycin is enhanced by its extensive tissue distribution and by formation of the 14-(R)- hydroxyclarithromycin metabolite. Clarithromycin and 14-(R)-hydroxyclarithromycin have a minimum inhibitory concentration of 0.03 and 0.06 μg/ml for h. pylori, respectively. The clarithromycin is reported that it has activity against h pylori bacteria that causes peptic ulcer.[6] The current investigation aims at the development of Gastroretentive Bilayer floating tablets with different release patterns of **Sucralfate** and clarithromycin. Clarithromycin is an antibiotic to treat H. Pylori and esomeprazole is proton pump inhibitor to reduce gastric acid secretion.

MATERIALS AND METHODS

Sucralfate and Clarithromycin were gifted by Pharmaceutical Company. HPMC K4M, K15M, PVP K30 was obtained from Hi media. Sodium bicarbonate, citric acid, magnesium stearate and talc were obtained from Loba Chemical Pvt Ltd (Mumbai, India). Crospovidone, Sodium starch glycolate, Croscarmellose sodium obtained from Danmed Pharmaceuticals Pvt Ltd, Hyderabad. Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Formulation development

Formulation of immediate release (IR) layer

Fast dissolving tablets of Sucralfate were prepared by direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. All the ingredients given in table 1 were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Nine formulations of Esomeprazole granules were prepared and each formulation contained one of the three disintegrate in different concentration. Each tablets weighing 100 mg, were obtained. Composition of tablets is mentioned in Table 1.

Table 1: Composition of Sucralfate Fast Dissolving Tablets.

Ingredients(mg)	Formulation code								
	SIF1	SIF2	SIF3	SIF4	SIF5	SI 6	SIF7	SIF8	SIF9
Sucralfate	100	100	100	100	100	100	100	100	100
Sodium Starch glycolate	10	15	20	_	_	_	_	_	_
Croscarmellose sodium	_	_	_	10	15	20	_	_	_
Crospovidone	_	_	_	_	_	_	10	15	20
Microcrystalline cellulose	79	74	69	79	74	69	79	74	69
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	200	200	200	200	200	200	200	200	200

Formulation of floating sustained release (SR) layer

Direct compression was followed to manufacture the gas generating floating tablets of Clarithromycin. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers selected, drug and excipients were passed

through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table 2 and all the formulation were used for further evaluations parameters.

Table 2: Various formulations of clarithromycin gastro retentive tablet.

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clarithromycin	250	250	250	250	250	250	250	250	250
HPMC K 15	_	_	_	100	120	140	50	60	70
HPMC K 4	100	120	140	_	_	_	50	60	70
PVP K30	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	15	15	15	15	15	15	15	15	15
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	60	40	20	60	40	20	60	40	20
Total Weight	450	450	450	450	450	450	450	450	450

Formulation of bilayer tablet

Optimized formulation SIF8 of Instant release layer (Sucralfate) and optimized formulation of F-8 (clarithromycin) for control release used for formulation of Bi-layer tablet.

Evaluation of Precompression Parameter

Angle of Repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation**.**

$\theta = \tan\text{-}1(h/r)$

Where, h and r are the height and radius of the powder cone respectively.

Bulk Density/Tapped Density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index**.**

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula.[7-9]

Hausner's ratio = Tapped density/Bulk density.

Evaluation of post compression Parameter

Shape and color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) and measured in terms of kg/cm^2.

Weight variation

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. The friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

%Friability= (Loss in weight/ Initial weight) x 100

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

Uniformity of drug content for IR tablet

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 244.0nm for Esomeprazole.

Drug content for SR tab

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N Hcl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and react with dye and analyzed for drug content by UV spectrophotometer at a λ max of 416.0 nm using of 0.1 N HCL as blank.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 25 mg of clarithromycin was transferred to 100ml standard flask. The powder was dissolved in 25 ml of 0.1 N HCL and made up to volume with 0.1 N HCL. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.1 ml to 10 ml suitably (10 ppm of clarithromycin) and prepares individually 10 ppm solution of Sucralfate determine the Conc. of both drugs using 282 nm and 416nm for Sucralfate and clarithromycin respectively.

***In vitro* buoyancy studies**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were placed separately in a 100 ml glass beaker containing simulated gastric

fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Dissolution rate studies of SR tab

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50c and rpm of 75. One Clarithromycin tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCL, react with dye (methyl orange) and extract with chloroform and take the absorbance at 416.0 nm using spectroscopy.

Dissolution rate studies of Bilayer tab

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs periods for clarithromycin SR and 1 hr for Sucralfate IR, using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested. The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5◦C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Ultraviolet Labindia 3000+) spectrophotometer at λmax 282nm for Esomeprazole and 416 nm for clarithromycin respectively.

RESULTS AND DISCUSSIONS

The powdered blends of different formulations of sustained release floating tablets were evaluated for angle of repose, bulk density (BD), tapped density (TBD) and compressibility index. The results of SR floating tablets are summarized in Table. The formulation of immediate release tablet prepared by using the superdisintegrants exhibited the LBD, TBD, angle of repose, compressibility index and Hausner's ratio of within the range, which shows good flow properties of the powdered blend. The prepared tablets were evaluated for different physico-chemical properties and the results are summarized in Table. The tablets were white, circular in shape and were found to be uniform with respect to weight variation, hardness; thickness, friability and content uniformity of different batch of tablets were found within

acceptable range and the distribution of drug in all the formulations was uniform. The *in-vitro* drug release of GRF tablets was found in range of 98.15% after 12 hrs table 6.

Table 3: Result of Pre-Compression Properties of Sucralfate FGR Tablets.

Formulation code	Parameters			
	Loose Bulk density*(gm/ml)	Tapped bulk density*(gm/ml)	Carr's Index (%)	Hausner's Ratio
SIF1	0.49±0.01	0.56±0.02	12.500	1.143
SIF2	0.49±0.02	0.55±0.02	10.909	1.122
SIF3	0.52±0.02	0.59±0.01	11.864	1.135
SIF4	0.48±0.01	0.58±0.02	17.241	1.208
SIF5	0.48±0.01	0.59±0.03	18.644	1.229
SIF6	0.49±0.02	0.59±0.02	16.949	1.204
SIF7	0.51±0.02	0.59±0.02	13.559	1.157
SIF8	0.52±0.03	0.61±0.01	14.754	1.173
SIF9	0.49±0.01	0.62±0.02	20.968	1.265

Table 4: Result of Pre-Compression Properties of Clarithromycin FGR Tablets.

F. code	Angle of repose(Degree)	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	31	0.458	0.565	18.938	1.234
F2	32	0.469	0.554	15.343	1.181
F3	34	0.482	0.565	14.690	1.172
F4	33	0.487	0.572	14.860	1.175
F5	34	0.475	0.569	16.520	1.198
F6	34	0.476	0.572	16.783	1.202
F7	32	0.485	0.571	15.061	1.177
F8	32	0.478	0.573	16.579	1.199
F9	33	0.465	0.568	18.134	1.222

Table 5: Results of Post-Compression parameters of immediate release.

F. Code	Hardness Test* (kg/cm^2)	Friability* (%)	Weight variation * (%)	Thickness * (mm)	Drug content* (%)	Disintegration Time (sec.)
SIF1	3.4±0.1	0.989±0.012	pass	2.8±0.2	98.89±0.12	140±5
SIF2	3.3±0.1	0.965±0.011	pass	2.7±0.3	98.45±0.15	135±4
SIF3	3.3±0.2	0.965±0.013	pass	2.6±0.1	97.85±0.32	122±3
SIF4	3.4±0.1	0.956±0.012	pass	2.8±0.2	98.95±0.15	132±2
SIF5	3.4±0.2	0.856±0.011	pass	2.7±0.3	98.98±0.45	125±1
SIF6	3.3±0.2	0.841±0.012	pass	2.8±0.1	98.85±0.32	120±3
SIF7	3.4±0.2	0.865±0.012	pass	2.9±0.3	99.56±0.42	99±4
SIF8	3.4±0.1	0.862±0.013	pass	2.8±0.2	98.98±0.32	88±6
SIF9	3.3±0.1	0.865±0.014	pass	2.8±0.2	98.78±0.32	102±5

Table 6: Results of Post Compression Properties of Clarithromycin FGR Tablets.

F. code	Thickness* (mm)	Hardness* (kg/cm2)	Weight variation* (mg)	Friability* (%)	Drug content* (%)	Total floating Duration* (h)	Floating lag times (sec)
F1	3.2±0.2	5.1±0.3	pass	0.658±0.012	98.12±0.25	MT 12	22±2
F2	3.1±0.1	5.2±0.2	pass	0.552±0.015	98.96±0.32	MT 12	25±2
F3	3.3±0.3	5.2±0.4	pass	0.658±0.023	98.78±0.14	MT 12	32±3
F4	3.4±0.4	5.3±0.2	pass	0.547±0.021	99.12±0.25	MT 12	30±2
F5	3.2±0.2	5.4±0.3	pass	0.654±0.032	98.65±0.36	MT 12	26±5
F6	3.3±0.4	5.3±0.4	pass	0.854±0.21	98.78±0.32	MT 12	21±2
F7	3.4±0.2	5.2±0.5	pass	0.785±0.032	99.45±0.14	MT 12	33±3
F8	3.3±0.1	5.2±0.2	pass	0.741±0.025	98.98±0.21	MT 12	30±2
F9	3.4±0.2	5.3±0.3	pass	0.658±0.028	99.23±0.32	MT 12	28±3

Table 7: *In-vitro* Drug Release Study of GRF Tablets.

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	45.56	40.25	35.56	32.23	29.98	25.56	23.01	20.12	18.89
1	65.56	60.32	48.89	40.25	35.45	30.12	29.89	25.65	22.32
1.5	79.98	71.12	65.56	55.56	50.12	48.89	45.56	40.23	35.65
2	98.78	86.65	89.98	64.45	59.98	61.12	58.45	52.14	42.12
3	-	98.78	98.23	89.89	85.56	75.45	73.12	65.45	58.98
4	-	-	-	97.56	90.25	85.56	80.23	75.65	65.65
6	-	-	-	-	98.12	91.12	89.98	80.23	70.12
8	-	-	-	-	-	97.89	98.78	89.98	80.23
12	-	-	-	-	-	-	-	98.15	85.65

The prepared bilayer tablets were evaluated for different physico-chemical properties and the results are summarized in Table. The tablets were found to be uniform with respect to weight variation and hardness. The thickness and friability of optimized batch of tablets were found within acceptable range. Content uniformity of formulations was found to be 98.95 and 98.25% for Sucralfate and Clarithromycin respectively. Where the distribution of drug in all the formulations was uniform. The Instant layer of sucralfate release Approx 89.95 percent drug within 15 minutes and control floating layer Clarithromycin shows release up to 12 Hours Approx 98.98percent.

Table 8: Post-compressional parameters of bilayer tablets.

Formulation code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)	Sucralfate	Clarithromycin
1.	5.13 ± 0.21	0.8217± 0.01	Passes	5.42 ±0.03	98.95	98.25

Table 9: Results of Dissolution rate studies of Floating layer.

Time (Hour)	% CDR	
	% Drug Release of Instant layer	% Drug Release of Control layer
0.5	86.65	19.89
1	98.95	24.65
1.5	-	38.85
2	-	50.12
4	-	63.12
6	-	74.65
8	-	82.32
10	-	93.23
12	-	98.98

CONCLUSION

The Experiment relates to formulation and development of oral pharmaceutical bilayer tablet of sucralfate and clarithromycin for administration of therapeutically and prophylactically effective amount of drug substance to obtain both a relatively fast or quick onset of therapeutic effect and maintenance of a therapeutically active plasma concentration for relatively long period of time. Experiment conclude that Bi-layer tablet is suitable for delivering drugs with different release pattern like one layer of drug as immediate release to get quick relief and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose. Development formulations give synergistic effect due to presence of sucralfate as ulcer protective and clarithromycin as ulcer healing (Effective against *Helicobacter pylori*). A dissolution study shows the release of Sucralfate and Clarithromycin. The Instant layer of Sucralfate release Approx 98.98 percent drug within 60 minutes and control floating layer Clarithromycin shows release up to 12 Hours Approx 98.98 percent of drug release in 12 hours.

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