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FORMULATION DEVELOPMENT AND EVALUATION OF BILAYER TABLETS FOR EFFECTIVE TREATMENT OF ULCER

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ABSTRACT

The objective of the present study was to develop bi-layer tablets of Esomeprazole and Levosulpiride, a highly potent drug with short half-life that are characterized by initial burst drug release in the stomach and comply with the release requirements of sustained-release products. Each of the proposed bi-layer tablets is composed of an immediate-release layer of Levosulpiride and a sustained-release layer of esomeprazole. Bi-layer tablets of Esomeprazole and Levosulpiride were prepared using direct compression method. The granules of different formulations were evaluated with respect to bulk density, tapped density, compressibility index, and drug content. Dissolution study data of Levosulpiride SR tablets demonstrated that increased concentration of HPMC K4 and K15 lead to the decreased release of Levosulpiride. Taking into consideration of above results optimized formulation IF6 of Instant release layer (Esomeprazole) and optimized formulation of F6 (Levosulpiride) for control release used for formulation of Bi-layer tablet. Esomeprazole and Levosulpiride bilayer tablet has a promising potential as an alternative to the conventional dosage form. This new dosage form has commercial marketing potency as no such delivery systems are presently available in market.

KEYWORDS: Esomeprazole, Levosulpiride, Bilayer tablets, formulation development, Evaluation.

INTRODUCTION

Bilayer tablet is new era for successful development of controlled release formulation along with various features to provide successful drug delivery system. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles. The manufacture of bi-layer

tablets, produced by sequential compaction of loose powder layers has become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as loading dose and second layer is maintenance dose. In case of bilayered tablets drug release can be rendered almost unidirectional if drug can be incorporated in the upper non adhesive layer its delivery occurs into the whole oral cavity.

The immediate release layer of bilayer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time. This article explains why development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bilayer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be the best approach in producing a quality bilayer tablet under GMP-conditions, especially when high production output is required.[1]

Esomeprazole is inactive at neutral pH, rearranges to two charged cationic forms (asulphenic acid and a sulphenamide configurations) that react covalently with SH groups of the H+K+ATPase enzyme and inactivate it irreversibly, especially when two molecules of omeprazole react with one molecule of the enzyme. Its bioavailability is 89% and has a plasma elimination half life of 1.5 h 4. Esomeprazole reduces the production of digestive acids, thus minimizing their effect on the esophagus.[2] Levosulpiride is a prokinetic which works by increasing the release of acetylcholine (a chemical messenger). This increases the movement of stomach and intestines, and prevents reflux (acid going up to the food pipe). Esomeprazole is a proton pump inhibitor (PPI). It works by reducing the amount of acid in the stomach which helps in the relief of acid-related indigestion and ulcers.[3]

The objective of the present study was to develop bi-layer tablets of Esomeprazole and Levosulpiride, a highly potent drug with short half-life that are characterized by initial burst drug release in the stomach and comply with the release requirements of sustained-release products. Each of the proposed bi-layer tablets is composed of an immediate-release layer of Levosulpiride and a sustained-release layer of esomeprazole.[4,5,6]

MATERIAL AND METHODS

Preparation of Instant Layer of Esomeprazole

Fast dissolving tablets of Esomeprazole 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.[7] The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #40.

Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio.

The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Eight formulations of esomeprazole granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 40mg, were obtained. Composition of tablets is mentioned in Table 1.

Table 1: Composition of Esomeprazole Fast Dissolving Tablets.

Ingredients(mg)	Formulation code								
	IF1	IF2	IF3	IF4	IF5	IF6	IF7	IF8	IF9
Esomeprazole	40	40	40	40	40	40	40	40	40
Sodium Starch glycolate	10	20	30	_	_	_	_	_	_
Croscarmellose sodium		_	_	10	20	30	_	_	_
Crospovidone		_	_	_	_	_	10	20	30
Microcrystalline cellulose	39	29	19	39	29	19	39	29	19
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	100	100	100	100	100	100	100	100	100

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.[8-10]

Thickness test

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).

Weight variation test

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.

Hardness test

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

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

The test complies if tablets not loose more than 1% of their weight

Uniformity of drug content

The test is mandatory for tablets with 40mg 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 282.0nm for esomeprazole.

Method for Preparation of Levosulpiride Floating tablet

Direct compression was followed to manufacture the floating tablets of Levosulpiride. 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 No. 2 and all the formulation were used for further evaluations parameters.[11]

Optimization of Gastro retentive floating tablets of Levosulpiride Floating tablets

Table 2: Various formulations of Levosulpiride Gastro retentive tablets.

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levosulpiride	75	75	75	75	75	75	75	75	75
HPMC K 4	75	100	125	-	-	-	37.5	50	62.5
HPMC K 15	-	-	-	75	100	125	37.5	50	62.5
PVP K30	10	15	20	10	15	20	10	15	20
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	105	75	45	105	75	45	105	75	45
Total Weight	300	300	300	300	300	300	300	300	300

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes[12-14];

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

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 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 226.0 nm using of 0.1 N HCl as blank.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

***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

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±0.5^{0}C and rpm of 55. One Levosulpiride tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 12hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^{0}C) 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 and take the absorbance at 226.0 nm using spectroscopy.

Formulation development of bilayer tablet

Optimized formulation IF6 of Instant release layer (Esomeprazole) and optimized formulation of F6 (Levosulpiride) for control release used for formulation of Bi-layer tablet.

Evaluation of bilayer tablets

All the tablets were evaluated for following different parameters which includes;

1. General Appearance

Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually.

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

2. Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

3. Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

4. Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

5. Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

6. 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 Levosulpiride 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 Levosulpiride) and prepares individually 10 ppm solution of esomeprazole determine the Conc. of both drugs using 282nm and 226nm for esomeprazole and Levosulpiride respectively (simultaneous estimation).

7. Dissolution rate studies

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12hrs periods for Levosulpiride SR and 1 hr for esomeprazole IR, using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested.[15-17]

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 λ_{max} 282nm for esomeprazole and 226nm for Levosulpiride respectively.

RESULTS AND DISCUSSION

In present work bi-layer tablets of Esomeprazole and Levosulpiride were prepared using direct compression method. The granules of different formulations were evaluated with respect to bulk density, tapped density, compressibility index, and drug content.

Drug content was found to be uniform among different batches and was more than 98%. The compressed tablets were evaluated for weight variation, thickness, hardness, friability, disintegration time (for esomeprazole IR tablets) and content. The weight of tablets from all the formulation batches was found within acceptable range of weight variation (±5%) as per USP. The hardness of the tablets was found in the range of 2.5±0.37 to 2.9±0.5 kg/cm^2. The disintegration time obtained for the esomeprazole IR tablets was less than 1 min which was well below the limit of disintegration time of uncoated IR tablets as per the USP (i.e. not more than 15 min). The tablets containing crospovidone were disintegrated at faster rate as compared to the other disintegrants used. Since the disintegration time observed with crospovidone containing tablets was minimum, the batches (IF6) were considered for further studies. The tablets were assayed and the drug content was found within the range of 90-100% and also the tablets complied with the friability test.

From the in vitro drug release data (Levosulpiride SR tablets), it can be seen that the drug release profile of tablets from F7 batch showed 99.45% in 12 Hrs. However, the C8 batch released drug at control rate. Hence, F7 batch formulation was considered as optimized and was used further for the development of bilayer tablets.

Dissolution study data of Levosulpiride SR tablets demonstrated that increased concentration of HPMC K4 and K15 lead to the decreased release of Levosulpiride. Taking into consideration of above results optimized formulation IF6 of Instant release layer (esomeprazole) and optimized formulation of F6 (Levosulpiride) for control release used for formulation of Bi-layer tablet.

The dissolution study of bi-layer Tablets shows the release of esomeprazole and Levosulpiride. The Instant layer of esomeprazole release Approx 56.65 percent drug within 15 minutes and control floating layer Levosulpiride shows release up to 12 Hours Approx 99.65 percent of drug release in 12 hours.

Table 3: Results of Post-Compression parameters of all formulations.

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	Disintegration time (sec.) Mean ± SD
IF1	2.7±0.1	0.765±0.005	102±3	1.25±0.12	98.85±0.36	56±4
IF2	2.8±0.2	0.852±0.005	103±4	1.26±0.15	98.65±0.25	52±6
IF3	2.6±0.1	0.658±0.004	98±2	1.45±0.32	98.78±0.14	48±5
IF4	2.7±0.3	0.795±0.007	100±3	1.25±0.14	99.12±0.32	50±3
IF5	2.9±0.2	0.852±0.003	99±4	1.32±0.16	95.65±0.54	48±4
IF6	2.8±0.1	0.862±0.004	101±5	1.26±0.14	99.45±0.32	32±2
IF7	2.9±0.5	0.842±0.002	102±2	1.45±0.23	99.78±0.74	59±4
IF8	2.53±	0.895±0.005	103±4	1.25±0.41	99.65±0.35	55±3
IF9	2.6±0.4	0.785±0.004	101±3	1.21±0.25	99.21±0.56	48±2

Table 4: Results of Post Compression Properties of Levosulpiride FGR Tablets.

F. code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration (h)	Floating lag times (sec)
F1	1.74±0.105	5.21±0.45	305±4	0.845±0.005	99.12±0.45	>12	65±5
F2	1.70.065±	5.33±0.32	303±5	0.789±0.008	98.85±0.32	>12	69±4
F3	1.76±0.02	5.25±0.45	306±4	0.856±0.003	97.98±0.25	>12	72±6
F4	7.68±0.04	5.28±0.32	305±3	0.745±0.004	96.65±0.15	>12	75±2
F5	1.69±0.03	5.38±0.35	300±4	0.795±0.006	98.45±0.14	>12	69±3
F6	1.72±0.04	5.45±0.41	302±3	0.785±0.012	99.12±0.23	>12	79±4
F7	1.75±0.05	5.35±0.32	304±4	0.741±0.010	98.98±0.35	>12	82±3
F8	1.72±0.04	5.32±0.41	301±3	0.854±0.021	99.65±0.45	>12	85±4
F9	1.71±0.03	5.25±0.32	298±4	0.985±0.041	98.32±0.41	>12	90±5

Table 5: *In-vitro* drug release study of FGR tablets.

Time	% Cumulative drug release								
(hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	45.65	43.32	41.32	36.65	35.65	33.56	30.45	20.32	18.89
1	65.58	56.98	50.32	49.98	43.32	40.32	42.65	36.65	24.56
1.5	86.65	75.65	58.95	55.65	59.98	55.65	51.45	42.12	36.65
2	98.85	88.89	69.98	63.32	71.32	69.98	63.32	56.58	43.32
3	-	98.25	85.65	82.74	81.65	79.95	75.45	65.45	55.58
4	-	-	98.12	89.98	92.32	89.98	83.32	73.32	62.45
6	-	-	-	98.65	99.2	99.45	89.98	82.45	76.65
8	-	-	-	-	-		92.98	88.89	82.23
12	-	-	-	-	-	-	99.45	92.45	88.98

Table 6: Post-Compressional Parameters of Optimized Formulation of bilayer floating tablets.

Formulation code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.58	0.853	Pass	3.65

Table 7: Results of Drug content analysis of bilayer floating tablets.

Formulation	Esomeprazole (% Label Claim)	Levosulpiride (% Label Claim)
In-house Bilayer floating tablet	98.95	99.45

Table 8: Results of Dissolution rate studies of bilayer tablets.

Time (Hour)	% Drug Release of Bi-layer Tablets	
	Esomeprazole	Levosulpiride
0.25	56.65	12.25
0.5	89.98	29.98
1	99.12	41.65
1.5	-	52.32
2	-	65.56
4	-	76.65
6	-	84.65
8	-	89.98
10	-	94.65
12	-	99.65

CONCLUSION

Thus from the result, it can be concluded that the bilayer tablets containing 40mg of esomeprazole as immediate release component and 75mg Levosulpiride as sustained release component has successfully developed. Also, the release from the developed formulations was comparable and the results of current study clearly show that bilayer tablet was

developed as a stable dosage form. Esomeprazole and Levosulpiride bilayer tablet has a promising potential as an alternative to the conventional dosage form. This new dosage form has commercial marketing potency as no such delivery systems are presently available in market.

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