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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF BI-LAYER TABLET FOR TREATMENT OF GASTRIC

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Abstract

Aim of the study: The main objective of this study is to prepare a gastro retentive bilayer floating tablet of Lafutidine by direct compression and optimize concentration of polymer to give maximum retentive effect with good drug release profile. Lafutidine having biological half-life (1.92 ± 0.39 hours), selected model drug as it is competitive inhibition of histamine at H2-receptors of the gastric parietal cells resulting in reduced gastric acid secretion, gastric volume and hydrogen ion concentration reduced having first pass metabolism, low oral bioavailability, maximum absorption in the upper part of GIT hence it is suitable for gastro retentive system.

Results: In this study, a gastro retentive bilayer floating tablet was prepared which contains an immediate release portion and a floating layer. Immediate release layer prepared by superdisintegrant sodium starch glycolate, Crosspovidone and microcrystalline cellulose and Sustain release layer prepared by using hydrophilic & hydrophobic polymers. The tablets were characterized by lag time, floating time, weight variation, drug content and dissolution profile.

Keywords: Lafutidine, bilayer floating tablet, biological half-life, direct compression, superdisintegrant

Introduction

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolong gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GIT is to control the Gastric Residence Time (GRT), i.e. Gastro Retentive dosage Form(GRDF).

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Floating systems or hydro dynamically balanced systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time and a better control of the fluctuations in plasma drug concentrations. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow micro spheres. Floating drug delivery systems are designed to prolong the study of the dosage form in the gastro intestinal tract and aid in enhancing the absorption Floating drug delivery system (FDDS) is the main approach to prolonging the gastric residence time in the stomach in which the bilayer floating tablet has the main role. It is more suitable for the treatment of local infections such as peptic ulcer, gastritis, Zollinger-Ellision syndrome, indigestion, and other local infections related to the gastrointestinal tract and also used for systemic applications. FDDS provides protection for those drugs which are acid labile and have a short half-life. It also improves bioavailability, reduces drug waste, and enhances the residence time of drugs. Nowadays, various technologies are being used for the development of FDDS. Novel drug delivery systems incorporation into bilayer floating tablets have also broadened the role of FDDS. Polymers have the main role in the development of FDDS, which serve as carriers for the drug and determine the gastric retention time and drug protection. FDDS is also an easy, cheap, and more convenient method for dual drug delivery of drugs[2].

Material and Methods

Preparation of Instant Layer of Lafutidine hydrochloride 4-7

Fast dissolving tablets of Lafutidine hydrochloride 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. The ingredients given below were weighed and mixed in

geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh # 60.

- 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 Lafutidine hydrochloride granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 100 mg, were obtained. Composition of tablets is mentioned in Table 1.

Table 1: Composition of Lafutidine hydrochloride Fast DissolvingTablets

Ingredients (mg)	Formulation code								
	IF 1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Lafutidine hydrochloride	5	5	5	5	5	5	5	5	5
Sodium Starch glycolate	10	20	30	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	20	30	-	-	-
Crospovidone	-	-	-	-	-	-	10	20	30
Microcrystalline cellulose	85	85	85	85	85	85	85	85	85
Talc	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight	100	100	100	100	100	100	100	100	100

Evaluation of post compressionparameter

1. Shape and color oftablets

Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets inlight.

2. Thicknesstest

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).

3. Weight variationtest

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. The following percentage deviation in weight variation is allowed (Table 2).

Table 2: Percentage deviation in weight variation

S. No.	Average weight of a tablet	Percentage deviation
1.	130 mg or less	10
2.	More than 130 mg and less than 324 mg	7.5S
3.	324 mg or more	5

In all the formulations the tablets weight is more than 130 mg and less than 324 mg, hence 7.5% maximum difference allowed.

4. Hardnesstest

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg / cm2

5. 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, deducted and reweighted

and% friability was calculated. The friability was determined as the mass loss in percent according to Equation: -

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

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

6. Uniformity of drugcontent:

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 anddrugequivalentto10mgofdrugdissolvedin10ml 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 what man 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 284.0nm for Lafutidinehydrochloride.

Method for Preparation of Lafutidine hydrochloride SR Floating tablet 8-13

Direct compression was followed to manufacture the gas generating floating tablets. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers selected, drugs and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drugs and polymers were weighed as per given in table no. 3 and all the formulation were used for further evaluations parameters.

Polymers selected for tablets are:

• HPMC K 15,

• HPMC K4,

• PVP K30

Optimization of Gastro retentive floating tablets of Lafutidine hydrochloride

Table 3: Various formulations of Lafutidine hydrochloride Gastro retentive tablets

Excipients (mg)	**Formulation code**								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lafutidine hydrochloride	5	5	5	5	5	5	5	5	5
HPMC K 4	80	100	120	-	-	-	40	50	60
HPMC K 15	-	-	-	80	100	120	40	50	60
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
NaHCO3	20	20	20	20	20	20	20	20	20
Mg(C18H35O2)2	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	65	45	25	65	45	25	65	45	25
Total Weight	200	200	200	200	200	200	200	200	200

Excipients like sodium bicarbonate, citric acid anhydrous, magnesium stearate were selected for the study. Sodium bicarbonate and citric acid were used as gas generating agent. Citric acid was also used as an antioxidant. Steps involved in the manufacture of tablets, first the drug; polymer and other excipients selected were passed through 40-mesh sieve. Required quantity of drug, polymer and excipients were weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5min.

Evaluation of tablets:

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

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 284.0 nm using of 0.1 N HCl asblank.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) and the data is given in table4.

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. Weight visible results are mentioned in table 4**.**

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 2simulated 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 lagtime.

Dissolution rate studies (IP,2007)

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 causing the temperature of 37 ± 0.5ºC and rpm of 75. One Lafutidine hydrochloride tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring5mlwerewithdrawnafterevery1hourupto 10 hours using 10ml pipette. The fresh dissolution medium (370C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute upto10mlwith0.1NHClandtaketheabsorbanceat 284.0 nm using spectroscopy**.**

Formulation development of bilayer tablet14-16

Optimized formulation IF-3 of Instant release layer (Lafutidine hydrochloride) and optimized formulation of F-7 (Lafutidine hydrochloride) for control release used for formulation of Bi-layertablet

Evaluation of bilayer tablets

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

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 (--).

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.

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.

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 Lafutidine hydrochloride 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 (10ppm of Lafutidine hydrochloride) the Conc. of drug determined using UV Vis. spectroscopy at 284nm.

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 12 hrs periods for Lafutidine hydrochloride SR and 1 hr for Lafutidine hydrochloride IR, using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch weretested.

The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37 ± 0.5ºC. 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 wasdeterminedusingU.V.(UltravioletLabindia3000+) spectrophotometer at λmax 284nm for Lafutidine hydrochlorid.

Result and Discussion

Results of Post-compression parameters ofLafutidine hydrochloride of Instant Layer

Post compression parameter like hardness test, friability, weight variation, thickness and drug content have been given in table 4 along with then respective values. Further pre & past compression study instant are given in table 4,5 &6.

Table 4: Results of Post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	2.9±0.2	0.658± 0.012	102± 2	1.52± 0.08	98.89± 0.45
IF2	2.8±0.3	0.745± 0.015	103± 1	1.51± 0.07	98.85± 0.25
IF3	2.6±0.4	0.623± 0.65	105± 1	1.53± 0.06	98.45± 0.23
IF4	2.5±0.3	0.689± 0.36	103± 2	1.53± 0.03	98.65± 0.32
IF5	2.8±0.2	0.652± 0.45	99±1	1.51± 0.04	98.45± 0.14
IF6	2.4±0.4	0.675± 0.32	102± 1	1.52± 0.05	98.47± 0.56
IF7	2.8±0.3	0.725± 0.45	103± 2	1.52± 0.06	99.12± 0.58
IF8	2.5±0.1	0.785± 0.36	104± 1	1.53± 0.04	99.45± 0.41
IF9	2.9±0.5	0.698± 0.35	103± 2	1.53± 0.08	99.65± 0.32

Table 5: Results of post-compressional parameters of all formulations

Formulation code	*In vitro* Disintegration Time (sec.) (n=3) Mean ± SD
IF1	85±5
IF2	78±4
IF3	60±6
IF4	88±2
IF5	75±5
IF6	65±4
IF7	102±6

IF8	95±4
IF9	80±6

Hardness test:

The hardness of all the tablets prepared was maintained within the 2.00 kg / cm2 to 4.00 kg / cm2. All the tablets maintained hardness in the range 5.73 ± 0.29 kg / cm2 to 5.23 ± 0.42 kg / cm2 for formulations were almost uniform.

Friability test:

The study results tabulated in Table No. 8. Was found to be well within the approved range (<1%) in all designed formulations. The formulations TM-1 and TM-8 showed slightly higher than the other. This might be due to excess fines or due to improper granulation, but the values were found to be within the limit. Thus tablets possess good mechanical strength.

Weight variation test:

The weight variation test is done to ensure the tablet contains the proper amount of drug. All the tablets passed weight variation test as the average percentage weight variation was within the pharmacopoeial limits of ± 7.5%.

Thickness test:

Thickness of the tablets was measured by dial caliper by picking randomly from all the batches. The mean thickness was (n = 3) almost uniform in all the formulations and values ranged from 2.52 ± 0.05 mm to 2.59 ± 0.05 mm. The standard deviation values indicated that all the formulations were within the range.

Uniformity of drug content:

The content uniformity was performed for all the nine formulations and results are tabulated in Table No.9. Three trials from each batch were analyzed spectrophotometrically. The average value and standard deviations of all the formulations were calculated. The drug content in different formulation was highly uniform and in the range of 98.51 ± 0.75% to 99.65 ± 0.42%. The results were within the acceptable range and that indicated uniformity of mixing. The cumulative percentage drug released by each tablet in the in vitro release studies was based on the average drug content present in thetablet.

Table 9: Results of Drug content analysis

Formulation	Lafutidine hydrochloride (% Label Claim)
In-house Bilayer floating tablet	99.12

Dissolution rate studies of Instant layer:

Table 10: Results of Dissolution rate studies of Instant layer

Time (min)	% Drug Release of Instant Layer
15	95.65%

Table 11: Results of dissolution rate studies of floating layer

Time (Hour)	% Drug Release of Floating layer
0.25	46.56±0.32
0.5	21.32±0.45
1	35.65±0.56
1.5	43.32±0.52
2	58.89±0.32
4	73.36±0.74
6	82.32±0.85
8	90.23±0.65
10	95.65±0.85
12	98.89±0.52

Dissolution rate studies of floating layer

A dissolution study shows the release of Lafutidine hydrochloride and Amoxicillin Trihydrate. The Instant layer of Lafutidine hydrochloride release Approx 46.56 percent drug within 15 minutes and control floating layer of Lafutidine hydrochloride shows release 98.89 ± 0.52 percent of drug release in 12 hours.

Conclusion

The experiment relates to formulation and development of oral pharmaceutical bilayer tablet of Lafutidine

hydrochloride for administration of therapeutically and prophylactically effective amount of non-steroid antiinflammatory drug substance to obtain both a relatively fast or quick onset of therapeutic effect and mainatainence of a therapeutically active plasma concentration for relatively long period of time. The experiment concluded that the bi-layer tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick relief from pain and second drug as sustained release of drug which gives effect of drug for sufficient long time nd reduce frequency ofdose.

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Table 6: Results of Post Compression Properties of Lafutidine hydrochloride FGR Tablets

F. code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration (h)	Floating lag times (sec)
F1	3.52	5.2	450	0.856	98.89	>12	65
F2	3.42	5.3	455	0.898	98.12	>12	69
F3	3.44	5.4	460	0.854	99.12	>12	72
F4	3.53	5.6	449	0.862	99.45	>12	75
F5	3.55	5.5	445	0.869	99.65	>12	69
F6	3.51	5.6	452	0.856	99.58	>12	79
F7	3.53	5.6	448	0.821	98.85	>12	82
F8	3.55	5.5	450	0.822	99.32	>12	85
F9	3.54	5.4	452	0.836	99.65	>12	90

In vitro drug release study of Gastro retentive floating tablet

Percent cumulative drug release (in-vitro) drug release of all the developed and optimized formulation shown in table 7.

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	42.34	40.23	39.65	35.25	32.23	28.89	25.65	20.23	15.56
1	69.98	65.45	60.23	46.65	43.32	42.23	36.65	25.56	20.23
1.5	85.65	73.23	65.56	69.98	62.23	56.65	43.36	32.23	26.65
2	99.12	89.89	75.56	73.32	70.23	69.98	55.56	42.23	39.98

3	-	99.12	85.65	80.23	75.65	75.65	76.65	52.23	43.36
4	-	-	99.12	99.23	89.89	83.32	80.32	61.45	59.98
6	-	-	-	-	99.12	95.65	89.98	65.56	63.32
8	-	-	-	-	-	99.32	90.32	73.32	70.32
12	-	-	-	-	-	-	98.89	80.21	78.56

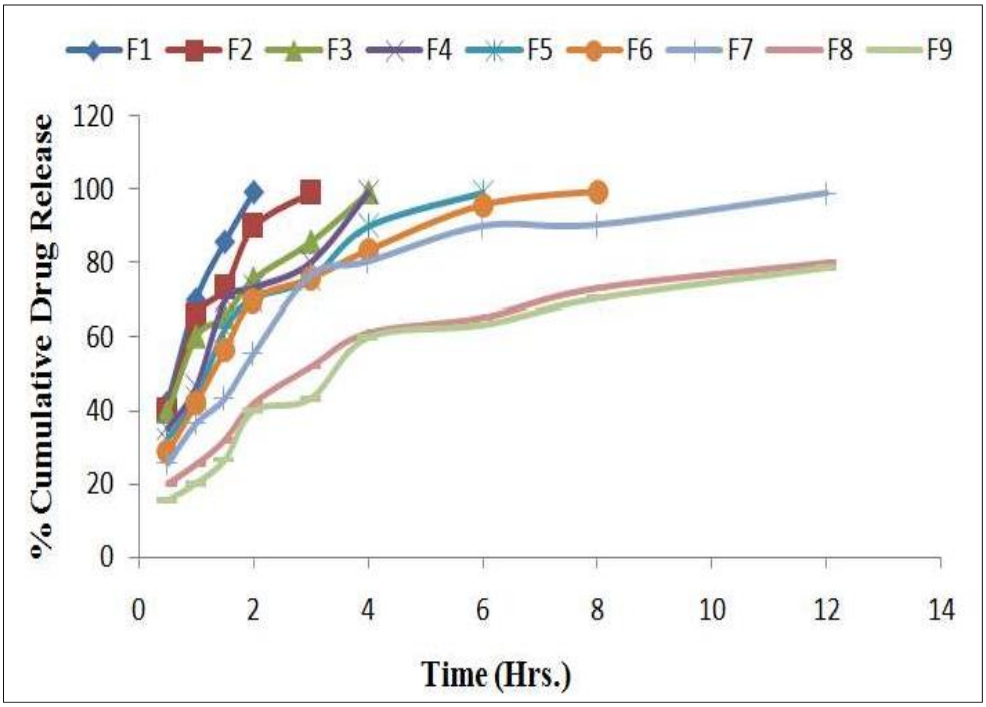

Figure 1: In-vitro Drug Release Study of GRF Tablets

Table 8: Post-Compressional Parameters of Optimized Formulation

Formulation code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	**5.23**	**0.895**	**Passes**	**4.23**