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Hydrodynamically Balanced Drug Delivery System Of Lafutidine: Formulation and Evaluation.

Burhan Ali[1], Jisu Das[2] Mr. Merajul Islam[3], Dr. Bapan Sarkar[4]

Dept. of Pharmacy, Huda Group of Institutions, Nagaon Assam[1,2,4].
Dept. of Pharmacy, North East Frontier Technical University [3]
E. mail. **burhanalia123@gmail.com** Ph. No. 7002976767

ABSTRACT :

The present investigation concerns the development of Hydrodynamically Balanced Systems (HBS) of Lafutidine, which are designed to increase the gastric residence time, thus prolonging the drug release with localized drug action. Hydroxy propyl methyl cellulose (HPMC) of different viscosity grades and at three different drug to polymer ratios were used to prepare HBS by wet granulation technique. The prepared HBS were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content, drug-polymer interaction studies, in vitro floating studies, in vitro drug release and short term stability studies. The drug-polymer ratio, viscosity grades of HPMC, different diluents and gas generating agents were found to influence the drug release and floating properties of the prepared HBS. The floating properties and drug release characteristics were determined for the prepared HBS in 0.1N HCl as dissolution media. All the HBS formulations showed good in vitro floating properties with an optimum concentration of gas generating agents, sodium bicarbonate and citric acid. The rate of drug release decreased with increased polymer concentration. It was found that HPMC viscosity had a significant impact on the drug release from the prepared HBS. The decrease in the release rate was observed with an increase in the polymeric system. Among the three viscosity grades of HPMC (K4M, K15M and K100M), HPMC K4M along with microcrystalline cellulose as diluent was found to be beneficial in improving the drug release rate and floating properties. Regression analysis of drug dissolution profiles on the basis of Higuchi's and Korsmeyer's model indicated that diffusion is the predominant mechanism controlling the drug release.

Key words: Hydrodynamically Balanced System (HBS), Lafutidine, Hydroxy propyl methyl cellulose, In vitro floating,

INTRODUCTION:

For the past three decades, oral controlled release dosage forms have been developed due to their important therapeutic advantages. By the introduction of a variety of controlled delivery systems, the inconvenience of conventional tablets or capsules that resulted in a transient overdose, followed by a long period of under dosing was overcome. The current controlled release technology had made it possible to release drugs at a constant release rate for longer periods of time ranging from days to years. However, this benefit was not satisfied a variety of important drugs that (i) are locally active in the stomach, (ii) have an absorption window in the stomach or in the upper small intestine, (iii) are unstable in the intestinal or colonic environment, or (iv) exhibit low solubility at high pH values. These limits promoted the development of gastro retentive drug delivery systems.

Objective:

The objective of the present study was to formulate HBS containing Lafutidine, which would remain in stomach for prolonged period of time in view to maximize bioavailability of the drug and increased patient compliance.
Thus there is a need to design and formulate a dosage form for gastric ulcers which attempts to overcome the disadvantage of variable bioavailability of Lafutidine.
The objectives of the research include:

1. To develop analytical method for the estimation of the drug in the formulations.
2. To carryout preformulation studies for possible drug and polymer interactions by FT-IR.
3. To formulate HBS tablets by using HPMC of different viscosity grades

Materials and methods:

The following materials that were either AR/LR grade or the best possible Pharma grade available were used as supplied by the manufacture.

Table 4.1: List of chemicals with grade and suppliers

Drug:

Sl. No.	Materials	Grade	Suppliers
1.	Lafutidine	Pharma	Shodhana Laboratories Ltd.

Polymers:

Sl. No.	Materials	Grade	Suppliers
1.	HPMC K4 M	LR	SD Fine Chem., Mumbai
2.	HPMC K15 M	LR	SD Fine Chem., Mumbai
3.	HPMC K100 M	LR	SD Fine Chem., Mumbai

Other excipients:

Sl. No.	Materials	Grade	Suppliers
1.	Sodium bicarbonate	LR	SD Fine Chem., Mumbai
2.	Micro crystalline cellulose	LR	SD Fine Chem., Mumbai
3.	Polyvinyl pyrrolidone K30	LR	SD Fine Chem., Mumbai
4.	Talc	LR	SD Fine Chem., Mumbai
5.	Magnesium Stearate	LR	SD Fine Chem., Mumbai
6.	Isopropyl alcohol	AR	SD Fine Chem., Mumbai
7.	Hydrochloric acid	AR	SD Fine Chem., Mumbai

Table 4.2: List of instrument used with manufacturer

Sl. No.	Equipment	Manufacturer
1.	Tablet compression machine	Shakti Engeenering ltd. Ahmedabad
2.	UV-Vis spectrophotometer	Shimadzu UV-1700
3.	Electronic Balance	Acculab ALC-210.4
4.	Tablet dissolution tester USP XXIII	Electrolab TDT-08L
5.	Hardness tester	Monsanto
6.	Friability test apparatus	Macro scientific works, Delhi
7.	Oven	Tempo industrial corporation
8.	Digital melting point apparatus	Analab scientific pvt.ltd.
9.	IR spectro photometer	Shimadzu 8400
10.	Digital pH meter	Hanna instruments, Italy.
11.	Digital micrometer	Mitu toyo

4.1 PREFORMULATION STUDIES:

Pre formulation testing is the first step in the rational development of dosage forms of the drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavaliable dosage forms, which can be mass-produced.

A thorough understanding of physicochemical properties may ultimately provide a rational for formulation design or support the need for molecular modification or merely confirm that there are no significant barriers to the compounds development. The goals of the program therefore are:

To establishment the necessary physicochemical characteristic of a new drug substance.

- To determine its kinetic release rate profiles.
- To establish its compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include physical tests and compatibility studies.

4.1.1 Melting point determination[48]:

Melting point of drug sample was determined by taking small quantity of drug in a capillary tube sealed at one end and was placed in digital melting point apparatus and temperature range at which the drug melts was noted.

EXPERIMENTAL METHOD:

- **Preparation of 0.1N HCl:**

  8.5ml of conc. HCl was taken in 1000ml of beaker and final volume was made up to 1000ml with distilled water to get 0.1N HCl.

- **Determination of λmax:**
  Most drugs absorbs light UV wavelength (200-400nm), since generally they aromatic contain double bond. The solution containing 10µg/ml of Lafutidine was prepared and scanned over the range of 200-400nm against 0.1N HCl as blank using double beam UV spectrophotometer. The maximum wave length obtained in the graph was considered as λmax for the pure drug.

PREPARATION OF CALIBRATION CURVE IN 0.1N HCL:

- **Standard solution:**
  Accurately weighed 100 mg of Lafutidine was dissolved in 10 ml of methanol and the final volume was made up to100 ml with 0.1N HCl, to get a solution containing 1000 µg/ml.
- **Stock solution**:
  From the standard solution, a stock solution was prepared to give a concentration of 50µg/ml in 0.1N HCl. Aliquots of 1, 2, 3, 4, and 5 ml of stock solution was pipetted out into 10 ml volumetric flasks. The volume was made up to the mark with 0.1N HCl. These dilutions give 5, 10, 15, 20 and 25 µg/ml concentration of Lafutidine respectively.
  The absorbance was measured using UV spectrophotometer.

4.6 METHOD OF FORMULATION OF FLOATING TABLETS:

Preparation of HBS of Lafutidine:

In this present work, wet granulation method has been employed to prepare HBS of Lafutidine with Hydroxypropyl methyl cellulose (HPMC) of different viscosity grades, (viscosities 4,000cps, 15,000cps and 1,00,000cps) at three different drug to polymer ratios as per the composition given in table No.-4.3 Microcrystalline cellulose was used as diluents along with sodium bicarbonate as gas generating agents. PVPK30 dissolved in sufficient isopropyl alcohol was used as a granulating agent, magnesium stearate was used as lubricant and talc as a glidant.

All the ingredients were accurately weighed and sieved through sieve No 60. In order to mix the ingredients thoroughly, drug and all the excipient except the lubricants (magnesium stearate and talc) were blended geometrically in mortar and pestle for 15minutes and granulated using PVPK30 dissolved in sufficient isopropyl alcohol by passing through sieve No. 12. Granules were dried at 60°C for 4 hours. The dried granules were sized through sieve no 18 and lubricated by adding magnesium stearate and talc. Tablets were compressed on a single punch tablet machine using flat surfaced, round shaped punches of 10mm diameter. Hardness of the tablet was maintained around 5kg/cm^2.

Table 4.3: Formulation of HBS tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lafutidine	10	10	10	10	10	10	10	10	10
HPMC K4M	40	80	100	-	-	-	-	-	-
HPMC K15M	-	-	-	40	80	100	-	-	-
HPMC K100M	-	-	-	-	-	-	40	80	100
Microcrystalline Cellulose	76	34	12	76	34	12	76	34	12
Sodium bicarbonate	10	10	10	10	10	10	10	10	10
PVP K30	08	10	12	08	10	12	08	10	12
Talc	02	02	02	02	02	02	02	02	02
Magnesium stearate	04	04	04	04	04	04	04	04	04

Total Wt of tablet	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

*All quantities in mg/tablet.

EVALUATION PARAMETERS:

4.7.1 Precompressional parameters: [49]

1. Bulk density **2.** Tapped density **3.** Carr's consolidation index **4.** Angle of repose

1) Bulk density and tapped density:

It is the ratio of total mass of powder to the bulk volume of powder. Accurately weighed 5 g of the granules was placed in a 10 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 200 times from a distance of 14 $\pm$ 2 mm. The tapped volume was measured to the nearest graduated unit. Again the tap volume was measured to the nearest graduated unit. The D_b and D_t were calculated in g/ ml using following formulae,

$$D_b = M/V_b \quad \text{.....(1)}$$
$$D_t = M/V_t \quad \text{.....(2)}$$

Where M = mass of the powder
V_b = bulk volume of powder
V_t = tapped volume of the powder
D_b = bulk density
D_t = tapped density

2) Carr's consolidation index:

Carr developed an indirect method of measuring powder flow from bulk densities. The % compressibility of the powder was direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated using the given formula.

Carr's index (%) = $[(D_t - D_b) \times 100]/D_t$ …….. (3)

Table 4.4: Flow property related to Carr's index.

CARR'S INDEX	TYPE OF FLOW
5-15	EXELLENT
12-16	GOOD
18-21	FAIR TO PASSABLE
23-35	POOR
33-38	VERY POOR
>40	EXTREMELY POOR

3) Angle of repose:

Good flow properties are critical for the development of any pharmaceutical tablets, capsule or powder formulations. Angle of repose is defined as the maximum angle possible between the surface of the pie of powder and horizontal plane. It is performed to determine the flow property of powder done by the funnel method. The powder mass was allowed to flow through the funnel orifice, kept vertically to a plane paper kept on horizontal surface, giving a heap angle of powder on a paper. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\Theta = \tan^{-1}(h / r) \text{.....(4)}$$

Where, h and r are the height and radius of the powder cone, respectively. Flow properties for different values of angle of repose were given below

Table 4.5: Comparison between Angle of Repose and Flow Property

Angle of Repose	Flow
< 25	Excellent
25 – 30	Good
30 – 40	Moderate (addition of 0.2% glidant required)
> 40	Poor

Post compression parameters:

1) Appearance:

The tablets were checked for presence of cracks, depressions, pinholes etc if any, uniformity of the color and the polish of the tablets.

2) Hardness:[50]

This test is used to check the hardness of the tablet, which may undergo chipping or breakage during storage, transportation, and handling. In this five tablets were selected randomly and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2. The mean values are given in table no.

3) Friability test[51]:

Friability test was carried out to evaluate the hardness and stability instantly. In roche friabilator, 10 tablets were weighed (W_0) initially and put in a tumbling and rotating apparatus drum. Then they were subjected for completion of 4 min or 100 rpm, the tablets were again weighed. The % loss in weight or friability (F) was calculated by the formula given below.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

4) **Weight variation[51]:**

This test was performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range. This was done by weighing 10 tablets at random and average weight was calculated. Not more than two of individual weight deviates from the average weight. The weight data from the tablets were analyzed for sample mean and percent deviation. IP limit for weight variation in case of tablets weighing 130 - 324 mg ± 7.5 % and more than 324 mg ± 5%.

5) Thickness:

Thickness of tablet was important for uniformity of the tablet size. Thickness was measured using digital screw gauze (mitu toyo).

6) Uniformity of drug content:

The content uniformity was mandatory for tablets. This test was performed by taking five tablets were selected randomly, weighed and powdered. A tablet triturate equivalent to 10 mg of drug weighed accurately, dissolved in 0.1N HCl and diluted to 100ml with the same. Further dilutions were done suitably and absorbance was measured at 240nm using UV spectrophotometer.

6) *Invitro* buoyancy determination:[52]

The floating characteristics are essential, since they influence the *in-vivo* behaviours of the drug delivery systems. However, there seems to be threshold value for the floating system to remain float under physiological conditions.

a) Buoyancy lag time determination:

The floating lag time of the tablets was studied at 37±0.5 ◦C, in 100 ml of simulated gastric fluid of 0.1N HCl. The time of duration of tablet floatation was observed visually and recorded.

b) ***In vitro* floating studies[53]:**

Duration of buoyancy was observed simultaneously, when the dissolution studies were carried out.[7] The duration of floating (floating time) of tablet in the dissolution medium (including floating lag time, which is the time required for the tablet to rise to the surface) was measured as total floating time by visual observation.

7) *In vitro* dissolution studies:[54]

The *invitro* dissolution of Lafutidine from floating tablets was determined by using Dissolution apparatus USP XXIII by rotating paddle method. The dissolution test was performed in 900ml 0.1N HCl solution at 37°C ± 0.5ºC at 50 rpm. At every 1 hour interval, 5ml of sample was withdrawn from the dissolution medium and the same amount was replaced to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl solution. The absorbance of the solution was measured at 240nm using UV-Visible spectrophotometer (Shimadzu 1700). Each dissolution studies were performed three time and the mean values were taken.

4.8 Release kinetics:

The results of *in vitro* release profiles obtained for all the HBS formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time. (First-order kinetic model).
3. Cumulative percent drug released versus square root of time (Higuchi's model).
4. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).

1) **Zero Order Kinetics:** A zero-order release would be predicted by the following equation.

$$\mathbf{A_t = A_0 - K_0 t} \quad \text{.....(6)}$$

Where:

A_t = Drug release at time 't'

A_0 = Initial drug concentration

K_0 = Zero-order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0 [55].

2) **First Order Kinetics:** A first-order release would be predicted by the following equation

$$\mathbf{Log\ C = Log\ C_0 - 303.2Kt} \quad \text{.....(7)}$$

Where:

C = Amount of drug remained at time 't'

C_0 = Initial amount of drug

K = First-order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant 'K' can be obtained by multiplying 2.303 with slope values[55].

3) Higuchi's Model:

Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = \left(\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t\right)^{1/2} \quad \text{..... (8)}$$

Where,

Q = Amount of drug released at time't'

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

t = Time (hrs) at which 'Q' amount of drug is released.

Equation-8 may be simplified if one assumes that D, C_S and A are constant. Then equation-8 becomes:

$$Q = Kt^{½} \text{ ..... (9)}$$

When the data is plotted according to equation-4 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism[56]. The slope is equal to 'K'.

4) Korsmeyer and Peppas Model:

The release rates from controlled release polymeric matrices can be described by the equation (10) proposed by korsmeyer et al[57].

$$Q = K_1 t^n \text{ ..... (10)}$$

Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism[58].

For Fickian release, n=0.45 while for anomalous (Non-Fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.89[57].

***Stability studies:*[59]**

Stability of a dosage form has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

4.9.1 Objective of the study:

The purpose of stability studies is to provide evidence that the quality of drug substance or drug product varies with time under the influence of a verity of environmental factors such as temperature, humidity and light enables recommended storage conditions, re-testing periods and shelf-lives to be established.

Accelerated stability study was carried out as per the ICH guidelines.

4.9.2 Procedure:

In the present study, the stability studies were carried out for a specific time upto 30 days for selected formulations. The selected formulation were analysed for the physical appearance, drug content and floating ability [60].

:Result and Discussion

HBS tablets of Lafutidine were developed with a view to deliver the drug in to local effect in a sustained manner. The details of result and discussion are given in the following section.

PREFORMULATION STUDIES:

5.1.1 Identification test:

- **Melting point determination:**

Melting point of carvedilol was found to be 96ºC-99ºC which is within the reported range of 96ºC-99ºC, indicating purity of the drug sample.

- **Standard Calibration Curve: (method developed)**

Suitable analytical method was developed for carvedilol using UV spectrophotometer. Analytical wavelength of λ_{max} 288 nm for Lafutidine was identified in 0.1N HCl solution. Calibration curve was constructed, the method have shown reproducibility with the R^2 value was found 0.999 has shown in fig. no.5.2

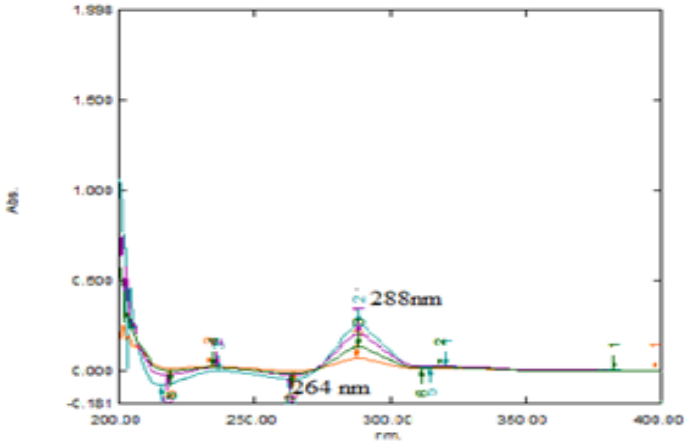
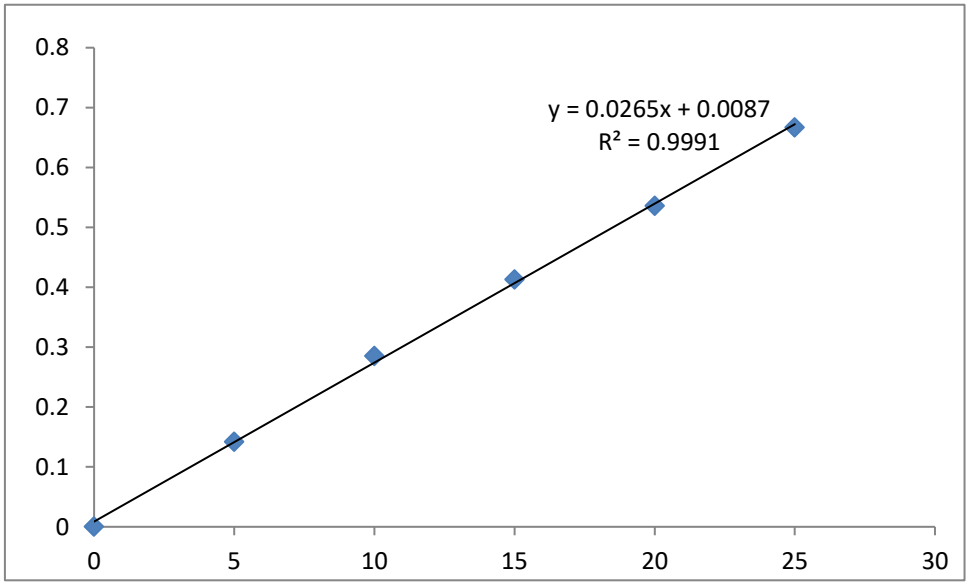


Fig. 5.1: Analytical Spectrum of Lafutidine in 0.1 N HCl

Table 5.1: Calibration data of Lafutidine in 0.1N HCl.

Sr. No.	Concentration (µg/ml)	Avg of absorbance at 288 nm	Standard deviation(SD)
1	0	00	0.00
2	5	0.242	0.012
3	10	0.355	0.017
4	15	0.433	0.017
5	20	0.536	0.015
6	25	0.667	0.034

Fig 5.2: Calibration curve of Lafutidine in 0.1N HCl



5.3 EVALUATION PARAMETERS:

5.3.1 Precompressional parameters:

1. **Bulk density and tapped density:**

   Interparticulates interactions that influence the bulking properties of powder flow, a comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder. Such a comparison obtained was used as the index of the ability of the powder to flow. The bulk density and tapped density values were shown in the table no 5.2.

2. **Carr's consolidation index:**

   The results of the Carr's consolidation index of all the formulations ranges from 10.36 - 19.10. Results of Carr's consolidation index of all the formulations were shown in the table no 5.2. results clearly showed that the flow ability of all the formulations was good and also the granules had good compressibility.

3. **Angle of repose (θ):**

   The data obtained for angle of repose for all the formulations were tabulated in the table no 5.2.The values indicated that all the formulation showed acceptable flow properties with low standard deviation value. In the preliminary formulations, all formulations showed excellent flow properties and gum formulations also showed excellent flow properties.

Table 5.2: Precompressional parameters of all HBS formulations

Formulation Code	Parameters			
	Bulk density (gm/ml)	**Tapped density (gm/ml)**	**Carr's index (%)**	**Angle of repose**
F1	0.472±0.05	0.480±0.021	13.00	26º69'±1.013
F2	0.521±0.05	0.525±0.07	18.47	28º85'±2.327
F3	0.626±0.17	0.519±0.021	18.13	24º28'±1.236
F4	0.446±0.01	0.498±0.017	19.10	28º21'±0.655
F5	O.462±0.05	0.450±0.006	16.72	25º97'±2.220
F6	0.482±0.08	0.601±0.020	13.84	27º72'±0.683
F7	0.512±0.010	0.571±0.013	15.60	24º64'±2.711
F8	0.481±0.015	0.461±0.009	17.30	26º49'±1.647
F9	0.453±0.013	0.498±0.005	10.36	27º66'±1.582

5.3.2 POST COMPRESSION PARAMETERS:

All HBS formulations of Lafutidine with HPMC in different concentration were prepared. All the formulation batches were prepared by wet granulation technique.

Nine formulations of Lafutidine with Hydroxypropyl methyl cellulose (HPMC) of different viscosity grades were prepared. All the HBS tablets were prepared by wet granulation technique.

The prepared tablets were evaluated for hardness, friability, uniformity of weight, uniformity of drug content, floating lag time, in vitro floating time, *in vitro* dissolution and short term stability.

Hardness

Hardness of all floating tablets was maintained within 3.5 to 6 kg/cm^2. The mean hardness values were measured for all the formulation using Monsanto hardness tester. The result were tabulated in table no 5.3

Friability (F)

Another measure of tablet strength is friability. The values of friability test were given in the table no 5.3. The % friability for all the formulations was below 1% indicating that the friability was within the prescribed limits the results of friability test indicates that the tablet possesses good mechanical strength.

Weight variation

The weight variation for all the formulations were shown in table no 5.3. All the tablets were passed weight variation test as the average weight variation was within the pharmacopoeial limit ±7.5%. The weight of all the tablets was found to be uniform with low standard deviation value.

Thickness

The thickness of the tablets was reported in the micrometer (mm). The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (150mg). The value of thickness ranges between 2.60-2.80 mm.

Uniformity of drug content

The % drug content of Lafutidine in all the HBS tablets were found within the limits. % drug content value of Lafutidine was within 95.54- 98.44%. The results within the range indicate uniform of mixing. The table no 5.3. showed the % drug content in each formulation.

Buoyancy lag time determination:

In this work, the floating strategy taken consideration in the design of drug delivery system. For all formulations, lag time is in the range of 20 sec to 150 sec, values were given in table no 5.3. All the formulations contained same concentration of gas generating agent but the results showed that the concentration of HPMC and viscosity of polymer were effect the buoyancy lag time. From this study, it was concluded that as the viscosity of HPMC and concentration increases, the buoyancy lag time also increases.

Table No 5.3: Postcompressional parameters of HBS formulationss

Formulation code	Parameters					
	Hardness (kg/cm^2)	**Friability (%)**	**Weight Variation (mg)**	**Thickness (mm)**	**Buoyancy Time(hr)**	**Drug Content (%)**
F1	4.12±0.20	0.88	153.00±0.76	2.76±0.012	More than 12hrs	97.81±0.001

F2	4.8±0.54	0.79	151.51±0.13	2.81±0.006	More than 12hrs	95.11±0.003
F3	4.38±0.34	0.63	150.22±0.98	2.68±0.009	More than 12hrs	95.11±0.003
F4	4.72±0.45	0.76	151.23±1.75	2.75±0.003	More than 12hrs	94.94±0.003
F5	3.98±0.66	0.86	151.00±0.46	2.56±0.022	More than 12hrs	98.10±0.06
F6	4.2±0.44	0.88	150.66±0.51	2.32±0.086	More than 12hrs	96.6±0.013
F7	4.31±0.45	0.72	151.50±0.18	2.66±0.09	More than 12hrs	96.21±0.014
F8	4.33±0.28	0.82	150.55±1.10	2.20±0.13	More than 12hrs	96.99±0.89
F9	4.21±0.23	0.87	152.10±0.87	2.18±0.31	More than 12hrs	95.71±0.93

All values are reported as mean ± SD with three times

***In vitro* floating studies:**

In vitro floating studies were performed by placing tablets in USP XXIII dissolution the apparatus-II containing 900 ml of 0.1N HCl maintained at a temperature of 37±0.5ºC. The time of duration of tablet floatation was observed and noted visually. All the designed formulations have floated more than 24 hrs.

Table No. 5.4: floating lag time of all the formulations

Sr. No.	Formulation code	Floating lag time (sec)
1	F1	40 sec
2	F2	55 sec
3	F3	70 sec
4	F4	90 sec
5	F5	125 sec
6	F6	145 sec
7	F7	180 sec
8	F8	190 sec
9	F9	210 sec

***In vitro* dissolution studies:**

In vitro drug release study was performed using USP XXIII dissolution test apparatus-II at 50rpm using 900 ml of 0.1 N HCl maintained at 37±0.5ºC as the dissolution medium.

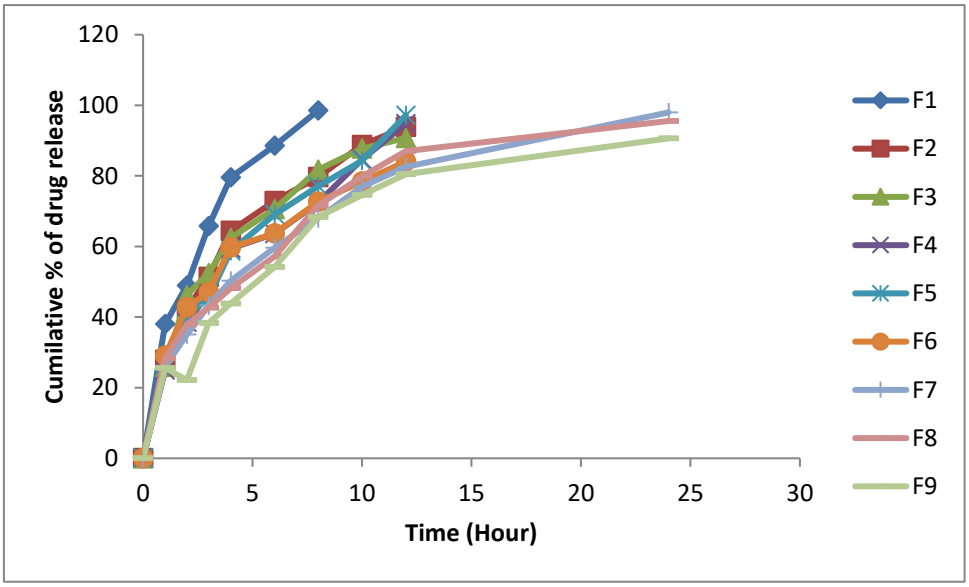
***In vitro* dissolution studies of all HBS formulation**

- Formulations F1, F2 and F3 containing drug : polymer ratio 1:1, 1:2 and 1:2.5 prepared with HPMC K4M exhibited 98.54, 98.9 and 97. 74% of drug release in 8, 12 hours respectively and the data is given in table 5.5 and drug release profiles are shown in figure- 5.3
- Formulations F4, F5 and F6 containing drug : polymer ratio 1:1, 1:2 and 1:2.5 prepared with HPMC K15M exhibited 97.8, 95.17 and 94.08 % of drug release in 12, hours respectively and the data is given in table 5.5 and drug release profiles are shown in figure-5.3
- In vitro drug release data for formulations F7, F8 and F9 are given in table 5.5 and drug release profiles are shown in figure-5.3 The formulations F7, F8 and F9 were prepared with HPMC K100M in drug polymer ratios 1:1, 1:2 and 1:2.5 exhibited 97.98, 94.56 and 90.65% drug release rates after 24 hours respectively.
- In the above results, it was observed that as the concentration of the polymers increased, there is a decrease in the drug release rates. An increase in polymer concentration causes increase in viscosity of the gel as well as the gel layer with longer diffusional path. This could cause a decrease in effective diffusion coefficient of the drug and a reduction in drug release rate.
- Formulations containing higher HPMC viscosity grades have slower drug release rates when compared to formulations with lower HPMC viscosity grades i.e. formulations F1, F2, F3 containing HPMC K4M have showed the fastest and formulations F7, F8, F9 containing HPMC K100M showed the slowest drug release rates. The amount of drug released for a particular drug polymer ratio was found to be in the order of K4M > K15M> k100M.

Table No. 5.5. Drug Release Data of Batches F1 To F9 of Lafutidine HBS Tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	38.02	27.84	25.88	25.00	26.46	29.1	26.01	28.32	25.59
2	48.91	42.22	46.22	38.48	40.33	42.74	35.05	37.94	22.20
3	65.77	51.35	52.43	46.65	45.5	47.09	43.29	42.63	38.34
4	79.59	64.45	62.43	59.4	58.73	59.74	50.25	48.19	43.87
6	88.52	72.83	70.62	63.66	69.08	63.68	59.64	57.18	54.19
8	98.54	79.68	81.71	72.4	77.08	72.71	67.99	71.56	68.35
10	-	88.73	87.73	84.67	84.26	78.44	76.92	75.85	74.59
12	-	98.9	97.74	97.8	95.17	94.08	82.61	80.02	80.45
24	-	-	-	-	-	-	97.98	94.56	90.65

FigureNo. 5.3. Drug Release Data of Batches F1 To F9 of Lafutidine HBS Tablets



5.4 Drug Release Kinetics:

In vitro drug release data of all the HBS formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release.

The curve fitting results of the release rate profile of the designed formulations gave an idea on the release rate profile and mechanism of drug release. The regression co-efficients for different drug release kinetics models were shown in table no 5.6. Models with highest regression co-efficients were judged to be the most appropriate model for the dissolution rate.

The data of various models reviewed that formulations followed peppas model with n value more than 0.5 and thus release can be concluded as non Fickanian diffusion. All the formulations followed higuchi matrix with first order release kinetic

Table no 5.6: Release kinetics data of all the formulations

Formulation code	Zero order	First order	Higuchi	Korsmeyer peppas	
	R^2	R^2	R^2	n	R^2
F1	0.979	0.888	0.879	0.809	0.937
F2	0.926	0.838	0.794	0.755	0.908
F3	0.888	0.930	0.869	0.709	0.939
F4	0.896	0.947	0.891	0.717	0.952

F5	0.866	0.901	0.866	0.748	0.915
F6	0.851	0.897	0.881	0.718	0.937
F7	0.833	0.890	0.877	0.736	0.940
F8	0.814	0.914	0.894	0.696	0.950
F9	0.849	0.896	0.849	0.770	0.910

Stability studies:

Short-term accelerated stability study was performed on the promising formulation F9 by storing the samples at 40±2ºC with 75±2 RH for 30 days. The samples were tested for any changes in physical appearance, drug content and *in vitro* floating ability studies after month. The results of stability studies did not show any significant change in the physical appearance, drug content and floating lag time of above formulation as shown in the table 5.7

Table no 5.7: Stability study of formulation F9

Time (month)	Drug content (%)	Floating behaviour	
		FLT (sec)	Floating duration (hr)
Zero	95.71±0.93	210	More than 24hrs
One month	95.22±0.45	214	More than 24hrs

CONCLUSION

The following conclusions can be drawn from the results obtained in this study:

- Hydrodynamically Balanced Systems offers a simple and practical approach to achieve increased gastric residence and to modify drug release profiles essential for sustained, site specific and localized drug action.
- The HBS of Lafutidine were developed by using different viscosity grades of HPMC by wet granulation technique. MCC were used as diluents. Sodium bicarbonate used as gas generating agent.
- All the prepared tablets prepared were found to be good without chipping, capping and sticking.
- The drug content was uniform and well within the accepted limits with low values of standard deviation indicating uniform distribution of drug within the HBS.
- The prepared HBS of Lafutidine showed excellent in vitro floating properties. Addition of gas generating agent sodium bicarbonate resulted in the reduction of floating lag time. All the HBS system have showed a floating time of 24 hours. The floating lag time is depended upon the concentration of HPMC with different viscosity grade were found to be essential to achieve an optimum in vitro floating.
- The in vitro dissolution profiles of all the prepared HBS formulations of Lafutidine were found to extend the drug release over a period of 8 to24 hours and the drug release decreased with increase in polymer concentration as well as viscosity of polymer.
- Among the various HBS formulations studied, formulation F9 containing drug-polymer ratio (1:2.5) prepared with HPMC K100M showed promising results releasing ≈ 90% of the drug after 24 hours with a floating lag time of 120 sec and floating time of 24 hours has been considered as an ideal formulation and subjected to further short term stability studies.
- Optimized HBS of Lafutidine (F9) was found to be stable at 40^{0} C following a one month stability study.
- Finally, it may be concluded that this novel drug delivery system i.e HBS offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The HBS of Lafutidine provides a better option for increasing the bio availability and reliability for peptic and duodenal ulcers by allowing a better control of fluctuations observed with conventional dosage forms.

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