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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF LAFUTIDINE

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ABSTRACT

The purpose of this research was to develop a novel gastroretentive drug delivery system based on wet granulation technique for sustained delivery of active agent. Quick GI transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to decreased efficacy of the administered dose and thus less patient compliance. Gastroretentive floating tablets, which was designed to provide the desired sustained and complete release of drug for prolonged period of time. Gastroretentive floating tablets of lafutidine were prepared by wet granulation technique using different concentrations of Gum Kondagagu, Gum olibanum and Locust bean Gum. The optimized formulation (LF14) exhibited 99.54% drug release in 12 hrs, while the buoyancy lag time was 33 sec. In-vitro drug release kinetics was found to follow both the Zero order and the possible mechanism of lafutidine release from the optimized formulation might be attributed to super case II transport mechanism. The Optimized formulation (LF14) showed no significant change in physical appearance, drug content, floating lag time, *in vitro* dissolution studies after 75%±5% RH at 40±2^{0}C relative humidity for 6 months.

Keyword: Wet granulation, Floating lag Time, Gastroretentive, Lafutidine

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INTRODUCTION

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action .Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that are locally active in the stomach, have narrow absorption window in gastrointestinal tract, are primarily absorbed from stomach and upper part of GIT, are unstable in the intestinal or colonic environment, disturb normal colonic bacteria and exhibit low solubility at high pH values. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients [1,2].

Lafutidine has newly developed 2nd generation H_2 antihistaminic blocker. It is exceedingly helpful in gastric and duodenal ulcers. It prevents the gastric mucosal lesions in both acute and chronic gastritis. The lafutidine penetrates the stomach wall and binds the H_2

receptors. The lafutidine also increases the blood flow to gastric mucosa. It shows protective action in an experimental model [3].

MATERIALS AND METHODS

Materials:

The Lafutidine was obtained as a gift sample from splendid laboratories, Pune. Gum Kondagogu, Gum Olibanum and Locust Bean Gum were obtained from Girijan Co-operative corp. Ltd, Hyderabad. Sodium bicarbonate, Citric acid, PVP-K30 was gifted from MSN Labs Ltd, Hyderabad. All other chemicals used were of analytical grade.

Methods:

Wet Granulation Method [4]

Gastroretentive floating tablets of lafutidine were prepared by wet granulation technique using different concentrations of Gum Kondagagu, Gum olibanum and Locust bean Gum. All the ingredients were passed through sieve no 85# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in isopropyl alcohol). The wet mass was passed through sieve no 12# and dried at 45^{0}C for 2 hr. Dried granules were sized by sieve no.18# add magnesium stearate and talc. Granules obtained were compressed with 8 mm flat punch (Cadmach, Ahmedabad, India).

Table 1: Formulation trials of floating tablets of Lafutidine using Locust bean gum

Ingredients	LF1	LF2	LF3	LF4	LF5	LF6	LF7	LF8
Drug	10	10	10	10	10	10	10	10
Locust bean gum	30	40	50	60	30	40	50	60
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	150	140	130	120	135	125	115	105
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table 2: Formulation trials of floating tablets of Lafutidine using Gum Kondagogu

Ingredients	LF9	LF10	LF11	LF12	LF13	LF14	LF15	LF16
Drug	10	10	10	10	10	10	10	10
Gum Kondagogu	50	70	90	110	50	70	90	110
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	130	110	90	70	115	95	75	55
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table 3: Formulation trials of floating tablets of Lafutidine using Locust bean gum

Ingredients	LF17	LF18	LF19	LF20	LF21	LF22	LF23	LF24
Drug	10	10	10	10	10	10	10	10
Gum Olibanum	65	75	85	95	65	75	85	95
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	105	95	85	75	80	70	60	50
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Evaluation Parameters

Precompression parameters [5,6]

Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hausner's ratio were calculated. While the flow properties of the powder bled were accessed from the angle of repose [4].

Evaluation of Floating Tablets [7,8]

Post compression parameters: The prepared tablets were evaluated for quality control tests like weight variation, hardness, thickness, friability and content uniformity.

Weight variation: Ten tablets were selected randomly from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this; percentage weight difference was calculated and then checked for USP specifications.

Hardness and friability: Hardness of tablet was determined by Monsanto hardness Tester. Ten tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated. Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were de-dusted and reweighed. The percentage friability was calculated.

In vitro buoyancy studies: The in vitro buoyancy was determined floating lag time, as per the method described by Rosa et al. The tablets were placed in a 250 ml beaker, containing 200 ml of 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up which the tablet remained buoyant is determined as Total Floating Time (TFT).

In vitro Dissolution Studies: The In vitro dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at $37^{o}C \pm 0.5^{o}C$. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 12 hrs and the same volume was replaced with pre -warmed fresh dissolution media. The samples were filtered through a whattman filter paper and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 220 nm using a UV spectrophotometer.

Stability studies: The optimized formulation of lafutidine were packed in strips of 0.04 mm thick aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 ^{0}C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for their floating lag time, content uniformity and for in vitro drug release [9].

RESULTS AND DISCUSSION

In the present work, lafutidine used in the treatment of ulcer has been utilized as an active drug and considered to be good candidate for reducing dose frequency, for solid oral sustained release formulation as well as more compliance in ulcers. The present it in the form of gastroretentive floating tablets to provide the desired sustained and complete release for prolonged period of time.

Precompression Parameters

The results of precompression evaluation parameters are shown in (Table 4). All the precomression evaluation parameters were within the USP Pharmacopoeia limits.

Postcompression Parameters

The results of postcompression evaluation parameters are shown in (Table 5). The Weight variation of all formulations witnessed to be in the limit allowed that is ± 5% of total tablet weight. The suitable hardness for compressed tablets is considered as a vital function for the end user. The deliberated crushing strength of fabricated tablets of formulations F1-F24 trended between 4.0-5.0kg/cm^2. The thickness of all the formulations ranges from 4.1-4.5 mm. The friability of all prepared formulation between 0.53-0.79 percent, the friability properties limits are in between 0-1%. The drug content of all formulation is in between 94.23-99.68%, drug content depends on the angle of repose since the angle of repose indicates uniform flow nature of powder blend which makes the drug to evenly distribute in all the formulation and to maintain content uniformity in all batches. Tablets of all batches had floating lag time below 60 seconds regardless of viscosity and content of polymers because of evolution of CO_2 resulting from the interaction between sodium bicarbonate and dissolution medium, entrapment of gas inside the hydrated polymeric matrices enables the dosage form to float by lowering the density of the matrices. Total Floating time for the natural polymers formulations were more than 12 hrs.

Table 4: Physical properties of prepared powder blends of Floating tablet

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose(Ɵ)	Carr's index (%)	Hausner's ratio
LF1	0.56±0.02	0.54±0.01	24.34±0.4	10.23±0.8	1.13±0.02
LF2	0.58±0.12	0.58±0.04	23.67±0.3	10.23±1.0	1.11±0.07
LF3	0.59±0.04	0.64±0.05	26.54±0.1	10.12±0.7	1.13±0.09
LF4	0.50±0.04	0.68±0.04	23.89±0.2	11.34±0.6	1.14±0.03
LF5	0.65±0.02	0.59±0.02	22.56±0.1	11.23±0.8	1.11±0.05
LF6	0.50±0.21	0.66±0.12	23.30±0.1	10.23±0.5	1.12±0.06
LF7	0.52±0.06	0.64±0.03	25.56±0.2	10.34±1.0	1.14±0.06
LF8	0.53±0.01	0.68±0.03	24.67±0.3	10.11±0.8	1.12±0.03
LF9	0.57±0.01	0.61±0.01	25.56±0.3	10.45±0.7	1.13±0.02
LF10	0.58±0.13	0.67±0.06	22.66±0.2	11.45±0.5	1.15±0.01
LF11	0.53±0.09	0.68±0.12	25.34±0.2	10.23±0.5	1.13±0.01
LF12	0.57±0.06	0.64±0.21	22.99±0.5	11.34±0.5	1.12±0.01
LF13	0.54±0.01	0.67±0.04	25.14±0.3	10.67±0.4	1.11±0.02
LF14	**0.51±0.04**	**0.66±0.07**	**21.09±0.2**	**09.23±0.4**	**1.10±0.03**
LF15	0.53±0.01	0.63±0.04	22.78±0.4	10.45±0.3	1.10±0.02
LF16	0.54±0.02	0.61±0.07	22.45±0.4	10.68±0.2	1.13±0.02
LF17	0.59±0.21	0.68±0.03	25.09±0.3	11.47±0.8	1.12±0.02
LF18	0.58±0.03	0.67±0.08	23.05±0.2	11.99±0.3	1.14±0.02
LF19	0.56±0.02	0.61±0.12	25.06±0.2	11.45±0.6	1.13±0.01
LF20	0.59±0.06	0.64±0.1	24.78±0.1	10.12±0.5	1.15±0.01
LF21	0.59±0.07	0.63±0.03	25.34±0.4	11.09±0.4	1.16±0.02
LF22	0.56±0.15	0.63±0.04	24.12±0.3	10.34±0.2	1.14±0.03
LF23	0.58±0.13	0.66±0.13	24.45±0.3	10.67±0.4	1.14±0.02
LF24	0.56±0.12	0.68±0.05	25.56±0.2	09.68±0.6	1.14±0.05

Table 5: Physicochemical parameters of lafutidine floating tablets

F. No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	#Content uniformity (%)	Floating lag time (sec)	Total floating time (hrs)
F1	249.65±1.2	4.4±0.12	4.3±0.12	0.57±0.01	95.23±0.63	55	>12
F2	251.69±0.8	4.3±0.06	4.1±0.06	0.55±0.02	97.04±0.06	52	>12
F3	248.04±0.5	4.3±0.06	4.1±0.06	0.63±0.03	95.56±0.14	50	>12
F4	250.05±0.0	4.2±0.12	5.2±0.12	0.72±0.01	98.11±1.01	47	>12
F5	251.54±0.4	4.3±0.00	4.3±0.00	0.62±0.02	94.23±1.08	44	>12
F6	250.78±0.4	4.3±0.10	5.1±0.06	0.66±0.01	95.45±0.31	42	>12
F7	252.65±0.3	4.1±0.10	4.3±0.10	0.53±0.02	98.91±0.49	40	>12
F8	249.57±0.2	4.3±0.25	5.3±0.40	0.69±0.01	97.23±0.51	57	>12
F9	250.76±0.3	4.3±0.06	5.3±0.06	0.58±0.00	96.13±0.56	55	>12
F10	248.49±0.2	4.2±0.20	4.2±0.42	0.79±0.02	95.23±0.24	52	>12
F11	251.53±0.4	4.2±0.06	5.3±0.06	0.76±0.01	97.97±0.21	49	>12
F12	250.58±0.3	4.2±0.00	4.4±0.06	0.73±0.02	98.45±0.76	46	>12
F13	251.34±0.2	4.3±0.26	4.8±0.35	0.72±0.02	97.45±0.48	43	>12
F14	**250.67±0.3**	**4.1±0.21**	**5.4±0.21**	**0.54±0.03**	**99.68±0.23**	**33**	**>12**
F15	249.65±0.2	4.4±0.06	5.0±0.23	0.65±0.02	96.45±0.36	58	>12
F16	250.65±0.3	4.2±0.25	4.4±0.23	0.68±0.01	96.45±0.69	55	>12
F17	251.79±0.4	4.5±0.15	5.8±0.32	0.59±0.01	96.34±0.35	53	>12
F18	251.87±0.1	4.4±0.25	4.7±0.35	0.68±0.01	97.56±0.23	50	>12
F19	249.65±0.2	4.4±0.06	4.0±0.23	0.75±0.02	96.45±0.36	47	>12
F20	249.32±0.2	4.2±0.12	5.5±0.20	0.63±0.03	97.18±0.81	45	>12
F21	250.16±0.8	4.0±0.10	4.2±0.81	0.52±0.89	95.23±0.13	51	>12
F22	251.33±0.2	4.3±0.15	5.3±0.25	0.61±0.23	97.59±0.65	48	>12
F23	249.58±0.7	4.1±0.33	4.8±0.12	0.58±0.55	96.38±0.33	54	>12
F24	250.11±0.4	4.5±0.28	4.5±0.45	0.71±0.67	98.42±0.27	49	>12

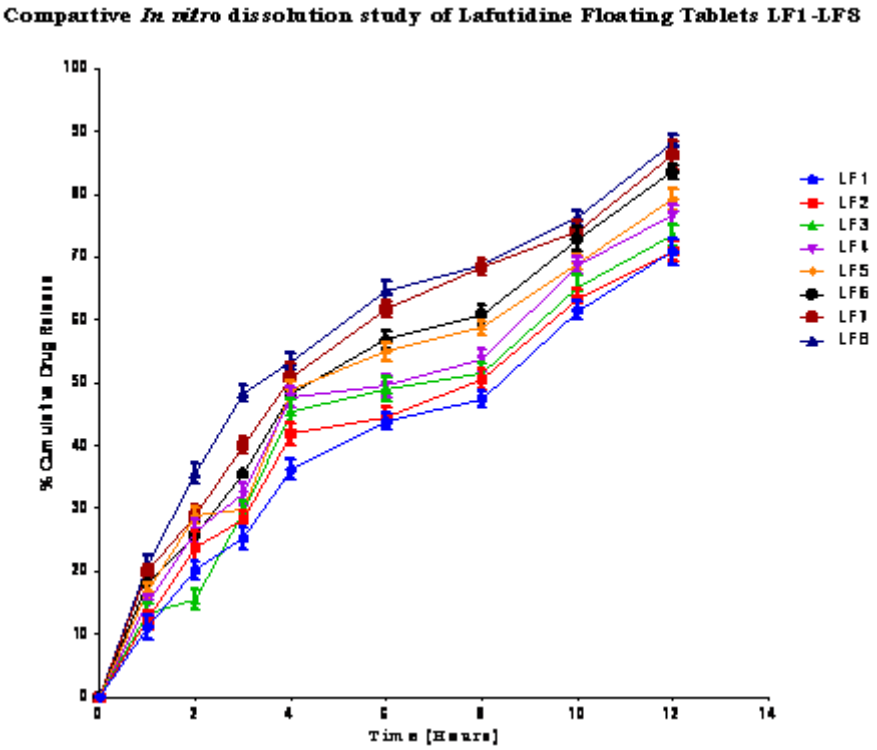

Figure 1: Comparison of *in vitro* Percentage drug release of lafutidine floating tablet formulations LF1-LF8

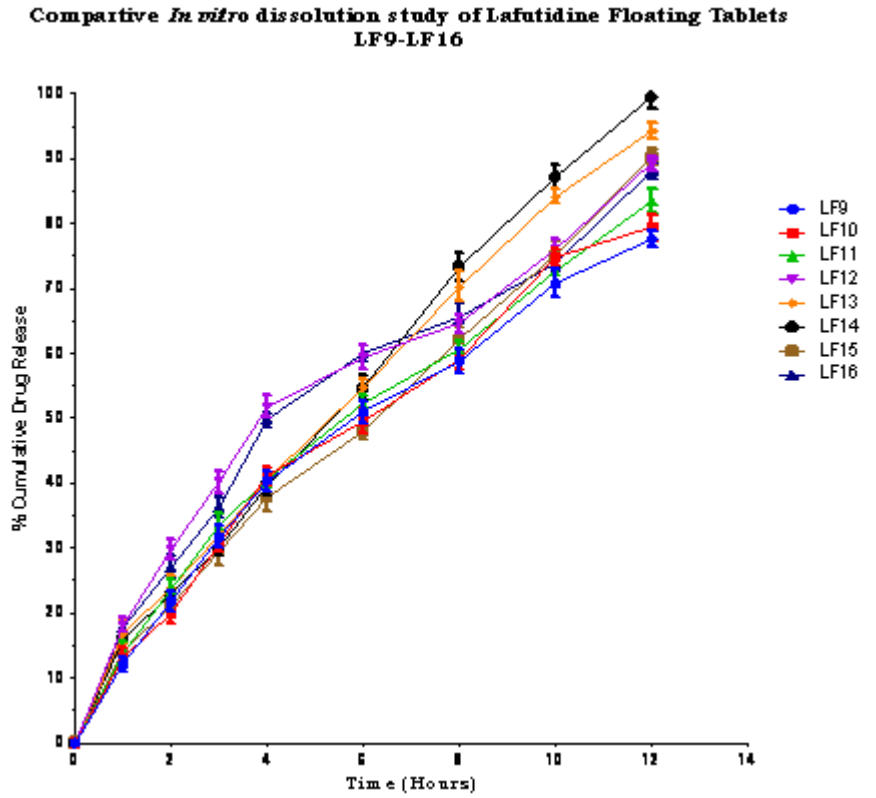

Figure 2: Comparison of *in vitro* Percentage drug release of lafutidine floating tablet formulations LF9-LF16

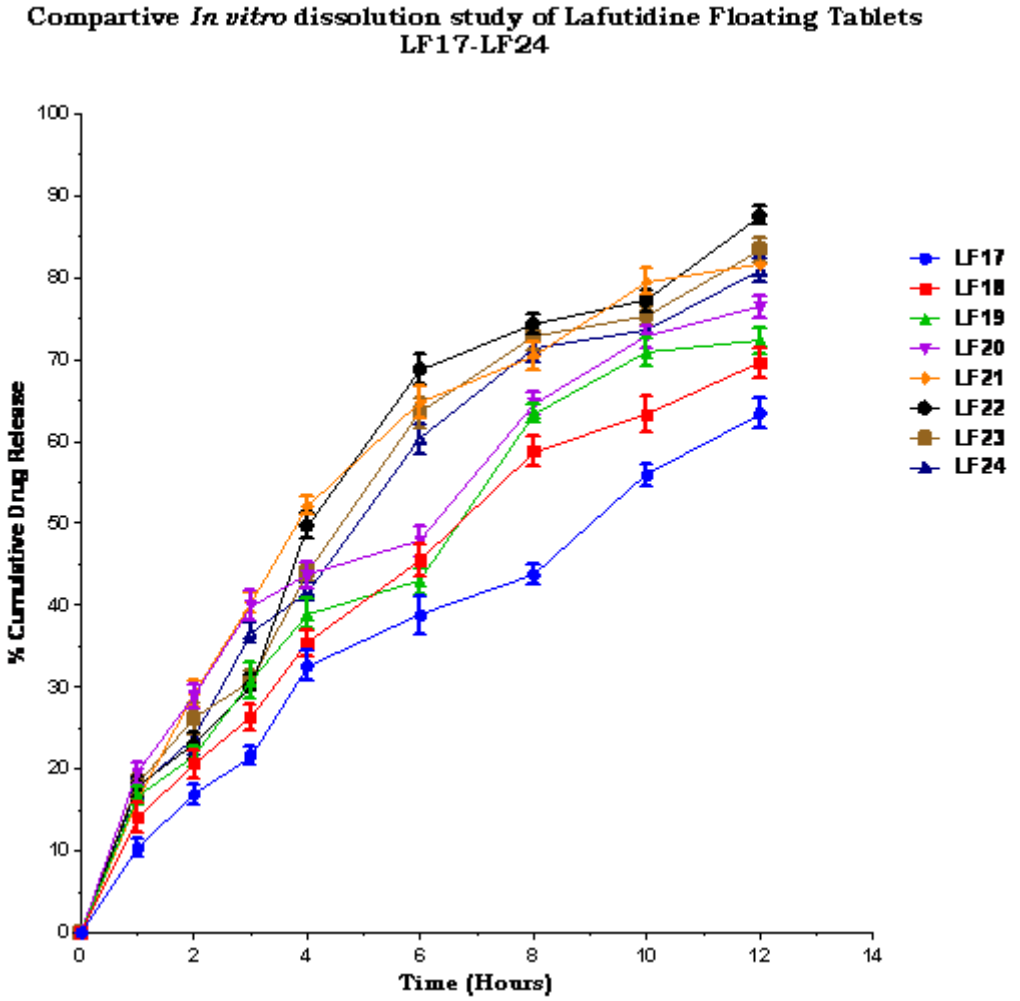

Figure 3: Comparison of *in vitro* Percentage drug release of lafutidine floating tablet formulations LF17-LF24

From the above figures (**Figure 1, 2 and 3**) it can be observed that the polymer Gum Kondagogu has sustaining effect on the release of drug from the floating matrix tablet of lafutidine compared to Locust bean gum and Gum olibanum. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of natural polymers. The concentration of polymer was added in increasing order to check its drug release retarding ability and LF14 was considered as best formulation among the all the formulations. LF14 showed good buoyancy properties and sustained the drug release for desired period of time (12hrs). The release profiles from all these formulations followed diffusion controlled release, complying with higher correlation coefficient values of Higuchi and Peppas equations.

Mathematical treatment of optimized formula of lafutidine floating tablets

In vitro dissolution has been identified as a vital part of drug development. It could be used for assessment of bioequivalence. There are several models to represents the drug dissolution profiles where it is a function of time associated with the amount of drug dissolved in distinction to the dosage form. The quantitative interpretation of the values collected in the dissolution assay is facilitated by the usage of a generic equation that mathematically interprets the dissolution curve in the function of some parameters related to the formulations.

A water soluble drug assimilated in a matrix is mainly liberated by diffusion, while for a low water- soluble drug the self-erosion of the matrix will be the principal release mechanism. Mathematical modeling of the release kinetics of specific classes of controlled-release systems may be used to predict solute release rates from and solute diffusion behavior through polymers and elucidate the physical mechanisms of solute transport by simply comparing the release data to mathematical models.

In the view of the establishment of the release mechanism and quantitatively interpreting and translate mathematically the dissolution date being plotted.

CONCLUSION

In the present work, it can be concluded that the lafutidine floating tablets can be an innovative and promising approach for the delivery of lafutidine for the treatment of gastric ulcers. The optimized formulation **LF14** containing Gum Kondagagu and a gas-generating agent. In-vitro release profile of lafutidine and marketed product when compared, the optimized formulation **LF14** showed drug release of 99.54±1.26 % within 12h

whereas 99.54 % of the drug was released from the marketed product within 12h. The major mechanism of drug release follows zero order kinetics and non fickian transport by coupled diffusion and erosion. This means that water diffusion and also the polymer rearrangement have an essential role in the drug release. The release rate constant of optimized formulation **LF14** was low enough prolonging drug delivery. This result is encouraging, because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the prolonged or sustained release dosage forms.

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