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FORMULATION DEVELOPMENT OF FLOATING DRUG DELIVERY SYSTEM (FDDS) FOR CEFIXIME

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Abstract:

The objective of the present study was to develop floating tablets of lafutidine in order to achieve an extended retention in the upper GITwhich may enhance the absorption and improve the bioavailability.The tablets were prepared by gas generation technique using differentratio and concentrations of natural gums like guar gum, gum karaya, hupu gum. Lafutidine a newly developed histamine H2-receptor antagonist wasretained in the stomach and assist in improving the oral sustaineddelivery of drugs in the gastrointestinal tract. The prepared tablets ofvarious formulations were characterized for a total floating time, buoyancy lag time, andpercentage drug released. The blend was characterized for determination ofangle of repose, Hausner's ratio, compressibility, bulk density and tapped density. The floating tablets wereevaluated for determination of weight variation, hardness, friability, content uniformity,floating lag time, total floating time, in–vitro drug release study, stability studies. The flowproperties of prepared floating tablets were found to be excellent. Tablets showed satisfactory characteristics with respect to weight, hardness and friability data. The formulation code F10 showed superior results it may be constructive for prolongeddrug release in the stomach to get better the bioavailability and abridged the dose frequency. Optimized floating tablets showed no significant changes in the physicalappearance, drug content, total buoyancy time, and also in vitro dissolution pattern afterstorage at 40°C/75% relative humidity for 3 months.

Key words: *Gastro retentive drug delivery system, lafutidine, stability studies, in-vitro drug release study.*

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INTRODUCTION

Drug absorption from gastrointestinal tract (GIT) is a complex process influenced by many variables. It has been reported that the extent of drug absorption from the GIT is related to contact time with gastro intestinal mucosa [1]. Floating drug delivery systems are good promising options for drugs which show good absorption in the stomach and which are degraded, less efficient in the intestine. These drug delivery systems are beneficial to achieve the more local action in the gastric environment. Floating systems are one type of gastro retentive drug delivery systems (GRDDS) which are retained in the stomach for longer period of time and there by improve the bioavailability, local action of drugs that are preferentially absorbed from upper GIT [2]. These floating systems will improve the contact time of drug with gastric mucosa and there by provide the beneficial results.Floating drug delivery system has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period oftime. While the system is floating on the gastric content, the drug is released slowly at adesired rate from the system, which results in increased gastric retentive time and reducesfluctuation in plasma drug concentration [3,4].

Lafutidine, (±)-2-(furfurylsulfinyl)-N-(4-[4-[piperidinomethyl]-2-pyridyl] oxy-(Z)-2-butenyl)acetamide is a newly developed second generation histamine H2-receptor antagonist [5]. It is usedin the treatment of gastriculcers, duodenal ulcers, and gastric mucosal lesions associated withacute gastritis and acute exacerbation of chronic gastritis [6,7]. It is absorbed in the smallintestine, reaches gastric cells via the systemic circulation, and rapidly binds to gastric cellhistamine H2 receptors, resulting in immediate inhibition of gastric acid secretion [8] Lafutidine has been shown to increase the gastric mucosal blood flow [9]and gastric mucus secretion [10,11] also accelerates sepithelial restitution in rats. Lafutidine has areceptor binding affinity, which is 2-80 times higher than famotidine, ranitidine and cimetidine [12]. The aim of the present study was to formulate lafutidinefloating tablets using guar gum, hupu gum, gum karaya, sodium bi carbonate and citric acid,and to select the best among them, based on the floating time.

MATERIALS AND METHODS

Materials

Lafutidine was a gift sample from Dr. Reddy'sLaboratories Limited, Hyderabad, India. Guar gum, Hupu gum, gum karaya were purchased from local market. Sodium bicarbonate, Aerosil, Citric acid, Magnesium stearate was procured from Merckspecialties private Ltd. Mumbai, India. Other excipients were procured from S.D. Fine Chemicals, Mumbai, India and reagents were analytical grade and used as received.

Methods

Preparation of Lafutidine floating tablets

Each tablet containing about 10 mg of Lafutidine was prepared by direct compressionmethod.Accurately weighed quantities of Gum karaya, Guar gum, Hupu gum, sodium bicarbonate, citric acid and micro crystalline cellulose were taken in amortar and mixed geometrically; to this mixturerequired quantity of Lafutidine was addedand mixed slightly with pestle. The powder ispassed through sieve no 60 and the whole mixturewas collected in a plastic bag and mixed for 3minutes. To this magnesium stearate was added and mixed for 5 minutes, later aerosil was added andmixed for 2 minutes. This mixture was compressed into tablets using a 12-station punching machine (Cadmach, CMD3-15) with flat shapedpunches. The drug and polymer ratio was varied toget floating tablets of varying polymerconcentrations as shown in Table 1.

Evaluation of blends

The floating tablets were characterized by their micromeritic properties such as particle size, bulk density, tapped density, hausner's ratio and angle of repose [13,14,15]

Table 1: Composition of Gastro Retentive Drug Delivery Systems of Lafutidine

Formulation code	Lafutidine (mg)	$NaHCO_3$ (mg)	Citric Acid (mg)	Guar gum (mg)	Gum Karaya (mg)	Hupu gum (mg)	Aerosil (mg)	Mg stearate (mg)	MCC (mg)	Total (mg)
F1	10	60	60	40	-	-	5	5	70	250
F2	10	60	60	50	-	-	5	5	60	250
F3	10	60	60	60	-	-	5	5	50	250
F4	10	60	60	70	-	-	5	5	40	250
F5	10	60	60	80	-	-	5	5	30	250
F6	10	60	60	90	-	-	5	5	20	250
F7	10	60	60	-	40	-	5	5	70	250
F8	10	60	60	-	50	-	5	5	60	250
F9	10	60	60	-	60	--	5	5	50	250
F10	10	60	60	-	70	-	5	5	40	250
F11	10	60	60	-	80	-	5	5	30	250
F12	10	60	60	-	90	-	5	5	20	250
F13	10	60	60	-	-	40	5	5	70	250
F14	10	60	60	-	-	50	5	5	60	250
F15	10	60	60	-	-	60	5	5	50	250
F16	10	60	60	-	-	70	5	5	40	250
F17	10	60	60	-	-	80	5	5	30	250
F18	10	60	60	-	-	90	5	5	20	250

Characterization of Tablets

Weight Variation

Twenty tablets were randomly selected from each batch and individuallyweighed. The average weight and standard deviation of 20 tablets was calculated.

Thickness

Thickness was determined for twenty pre-weighed tablets of each batch using a digital vernier scale (Mitutoyo- Digital) and the average thickness was determined in mm.The tablet thickness should be within a ± 5% variation of a standard.

Hardness

The hardness of ten tablets was measured using Monsanto Hardness tester. Meanand standard deviation were computed and reported. It was expressed as kg/cm.

Friability

The friability of the tablets was determined using Roche friabilator. It wasexpressed in percentage (%). 10 tablets were initially weighed and transferred to thefriabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes thetablets were weighed again. The tablets were found to pass the friability test, if the percentage weight loss was found to be less than 1%.

$$\% \text{ Friability} = (W_0 - W)/W_0 \times 100$$

Where, W_0=initial weight of twenty tablets, W= weight of 20 tablets after 100 revolutions

Physico-Chemical Characterization of Tablets of Lafutidine

FT-IR Spectroscopy Study

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation.1-2 mg of fine powder of Lafutidine and 200-300 mg of dry powder of KBr (IR grade) were taken ina mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400 cm^{-1} by FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

Drug Content

For drug content, the one tablet was crushed and transferred to 1000 ml volumetric flask and add small quantity of acetic acid then make up to 1000 ml with 0.1 N HCl. The solution was filtered through Whatman filter paper (0.45µm pore size), Lafutidine was analyzed at 272nm using double beam UV/Visible spectrophotometer after suitable dilution. The content of drug was calculated from standard curve.

In-vitro Buoyancy studies

The time taken for tablet to emerge on surface of medium is called the floating lag time(FLT) and duration of time the dosage form constantly remain on surface of medium is calledthe total floating time (TFT). The tablets were placed in a beaker containing 0.1Nhydrochloride solution (200 ml). The time required for the tablet to rise to the surface andfloat was determined as floating lag time [16].

***In vitro* Drug Release Study**

Drug release was studied using six station dissolution apparatus *United States Pharmacopeia*(USP) Dissolution Testing Apparatus 2 (paddle method)in 900 ml of 0.1 N hydrochloric acid at 37± 0.5°C and 75 rpm.Tablets were placed in the vessels and the apparatus was operated for 24 hours. 5 ml of thesample was withdrawn at regular intervals and the same volume of pre-warmed (37± 0.5°C)fresh dissolution medium was replaced. The samples withdrawn were filtered and drugcontent in each sample was analyzed after suitable dilution by using double beam UV/Visible spectrophotometer at 272nm.

Accelerated Stability Studies

Drug decomposition or degradation occurs during storage, because of chemical alteration of the active ingredients or due to product instability, leading to lower concentration of the drug in the dosage form, hence the stability of pharmaceutical preparation need to be evaluated. The objective of stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and relative humidity (RH) conditions. Stability studies were carried out at 40±2 °C and 75± 5% relative humidity for 90 days.

RESULTS AND DISCUSSION

The floating tablets of Lafutidine were prepared by direct compression method using gas forming agents such as sodium bicarbonate and citric acid. A total of 18 formulations were prepared. The powder blend of eighteen formulations (F1-F18) was evaluated for Angle of repose, Bulk density, Tapped density, Compressibility and Hausner's ratio, which showed the pre-compressed blend, has good flow property. The results are shown accordingly in Table 2.

The Bulk density values were found to be within the range of 0.39±0.001- 0.52±0.04. Tapped density values were found to be within the range of 0.44±0.06 - 0.637±0.20. Compressibility index values for most of the batches were good and some

are passable, Hausner's ratio values were good for the most, fair for the rest batches and Angle of repose values were good for all the batches have shown good flowing and compressibility nature.

FTIR study was carried out to determine if there is any potential interaction between the drug and the carrier used, which is indicated by the disappearance of important functional group of the drug. The FTIR spectra of pure Lafutidine drug and Lafutidine floating tablet were shown. From these spectra we can conclude that there is no potential chemical interaction between the drug and the excipients used and the molecular structure of Lafutidine was retained.

Post formulation studies, including weight variation, hardness, friability and % drug content, of Lafutidine floating tablets were performed and the observations were shown in table 3. All the tablets met the specifications for weight variation as per IP. The friability was less than 1% for all batches. Drug content was not more than 99±0.054and not less than 97±0.012, Hardness and thickness were found to be within the limits. The least buoyancy lag time was taken by F10 formulation and the most was taken by F17 formulation.

Table 2: Results of Pre-formulaiton Studies for Lafutidine Floating Tablets

Formulation code/Parameter	Bulk density	Tapped density	Angle of repose	Hausners ratio	Compressibility index
F1	0.721±0.04	0.87± 0.01	27.12	1.206±0.06	26.62±0.21
F2	0.710±0.04	0.873±0.04	29.71	1.251±0.04	27.46±0.11
F3	0.41±0.04	0.483±0.53	25.11	1.178±0.08	28.32±0.31
F4	0.45±0.04	0.52 ± 0.09	25.60	1.15±0.02	28.06±0.31
F5	0.45±0.04	0.50 ± 0.07	28.23	1.11±0.04	27.58±0.15
F6	0.44±0.04	0.50 ± 0.09	27.58	1.13±0.08	28.44±0.11
F7	0.45±0.04	0.50 ± 0.06	26.42	1.12±0.08	27.48±0.13
F8	0.44±0.04	0.50 ± 0.08	27.38	1.13±0.06	27.43±0.15
F9	0.42±0.04	0.50 ± 0.06	25.37	1.13±0.07	27.42±0.12
F10	0.40±0.04	0.50 ± 0.07	26.34	1.12±0.08	27.43±0.14
F11	0.39±0.04	0.50 ± 0.07	25.36	1.12±0.07	27.58±0.15
F12	0.40±0.04	0.50 ± 0.07	28.35	1.12±0.08	27.58±0.15
F13	0.380±0.01	0.500±0.02	27.28	1.310±0.06	23.91±0.05
F14	0.710±0.02	0.873±0.07	26.14	1.251±0.12	19.714±0.05
F15	0.371±0.03	0.483±0.05	25.41	1.299±0.35	23.188±0.06
F16	0.483±0.06	0.681±0.06	28.35	1.409±0.42	29.03±0.05
F17	0.461±0.05	0.608±0.07	26.24	1.32±0.36	24.177±0.04
F18	0.453±0.01	0.583±0.06	26.65	1.288±0.28	22.299±0.06
F19	0.710±0.02	0.873±0.07	25.45	1.251±0.41	19.714±0.03
F20	0.461±0.02	0.608±0.06	28.26	1.32±0.64	24.177±0.04

Table 3: Results of Physicochemical properties of Lafutidine Floating Tablets

Formulation code/Parameter	Avg. Weight (Mean± S.D) (n=20)	Hardness (kg/cm^2) (n=3)	Friability (Mean±S.D) (n=20)	%Drug content (mg)	Buoyancy Lag time (min)	Total floating Time (hrs)
F1	198±0.6	3.4±0.4	0.587	98±0.012	16	24
F2	199±0.9	3.5±0.4	0.612	98±0.025	20	24
F3	198±0.3	3.4±0.6	0.522	99±0.054	13	24
F4	197±0.4	3.7±0.1	0.543	98±0.018	15	24
F5	198±0.8	3.7±0.6	0.589	99±0.036	19	24
F6	201±0.8	3.3±0.4	0.578	98±0.062	22	24
F7	199±0.9	3.6±0.6	0.556	98±0.034	12	24
F8	201±0.8	3.4±0.4	0.590	99±0.052	14	24
F9	203±0.8	3.4±0.6	0.533	98±0.019	16	24
F10	200±0.9	3.2±0.6	0.511	99±0.012	10	24
F11	202±0.9	3.5±0.4	0.576	99±0.026	15	24
F12	196±0.6	3.3±0.4	0.537	97±0.012	13	24
F13	198±0.9	3.8±0.4	0.602	98±0.05	19	24
F14	201±0.3	3.4±0.6	0.501	99±0.012	17	24
F15	198±0.4	3.9±0.1	0.598	97±0.018	11	24
F16	199±0.8	3.6±0.6	0.577	99±0.036	19	24
F17	200±0.8	3.5±0.4	0.589	98±0.062	23	24
F18	199±0.9	3.7±0.6	0.566	98±0.043	14	24

In-vitro drug release studies for all 18 Lafutidine floating tablet formulations using 0.1N HCl as dissolution media and USP-II dissolution apparatus was performed. The dissolution process was done for 24 hrs. The dissolution data obtained was represented in table 4,5. Graphical representations of percent cumulative lafutidine release from floating tablets vs. time were shown in Fig 1 (A, B). The extended drug release for 24 hrs. was observed only in F10 of lafutidine floating tablets. Least release profile was observed by F11 i.e., total drug was released only in 4 hrs. The extended drug release for 24 hrs in F10 formulation may due to the presence of optimum levels of gum karaya, sodium bi carbonate and citric acid.

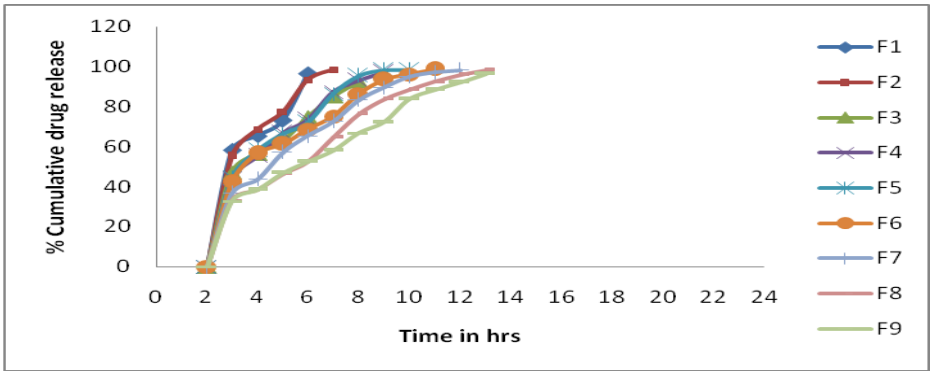
Table 4: Results of *In-vitro* drug release Studies of Lafutidine Floating Tablets (F1-F9)

Formulation code/Parameter → / Time ↓	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
1 hr	58.17	55.24	47.22	43.56	44.18	42.15	36.54	33.21	32.63
2 hr	65.38	68.62	56.54	55.24	58.16	56.78	43.62	38.50	38.54
4 hr	73.14	77.37	63.29	66.87	66.21	61.36	57.18	46.43	46.76
6 hr	96.36	93.25	74.55	73.55	72.20	68.54	65.34	52.39	52.54
8 hr		98.56	85.26	87.25	86.39	75.12	72.66	64.67	58.15
10 hr			92.65	93.21	95.54	86.39	83.34	76.26	66.65
12 hr				97.36	98.23	93.65	89.62	83.81	72.23
14 hr					98.36	96.21	94.87	88.54	83.69
16 hr						98.78	96.96	92.33	88.45
18 hr							98.27	95.86	92.16
20 hr								98.20	96.36
22 hr									
24 hr									

Table 5: Results of *In-vitro* drug release Studies of Lafutidine Floating Tablets (F10-F18)

Formulation code/Parameter → / Time ↓	F10 (%)	F11 (%)	F12 (%)	F13 (%)	F14 (%)	F15 (%)	F16 (%)	F17 (%)	F18 (%)
1 hr	24.84	49.28	45.62	37.55	33.28	30.28	32.54	30.63	28.42
2 hr	32.62	63.15	67.34	53.17	54.64	44.25	47.37	55.55	36.55
4 hr	44.36	94.78	77.38	67.52	63.25	57.64	56.18	67.53	47.45
6 hr	53.17		96.19	78.37	77.37	68.27	79.67	74.61	53.69
8 hr	61.52			93.16	83.28	74.38	83.14	79.66	74.34
10 hr	68.98				97.24	88.47	89.96	86.73	82.28
12 hr	74.45					96.98	94.56	92.77	86.51
14 hr	79.87						96.62	96.95	91.60
16 hr	84.63							98.24	96.53
18 hr	89.18								98.18
20 hr	94.63								
22 hr	98.54								
24 hr	99.17								

A)



B)

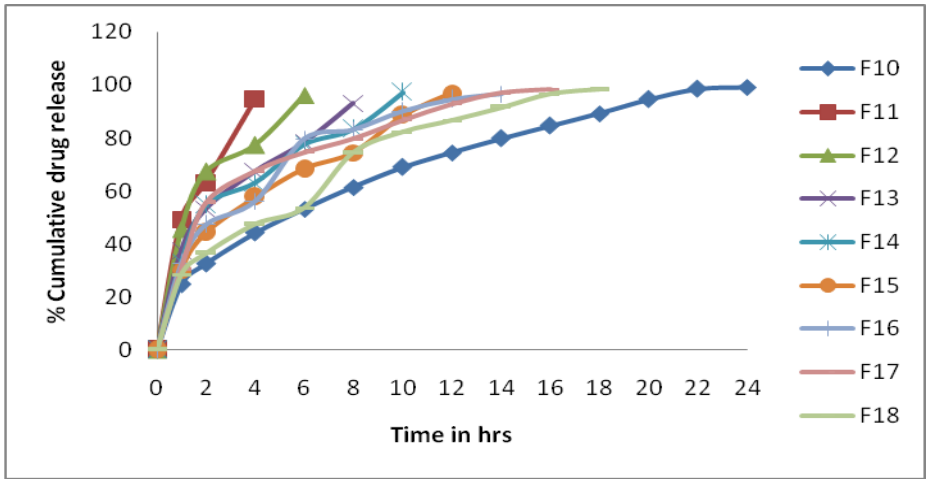


Fig 1: Percentage Cumulative Drug Release from Lafutidine Floating Tablets A) From F1 to F9 B) From F11 to F18

Stability studies were conducted to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and RH. Lafutidine (F10) optimized formulation was subjected to stability studies carried out by storing at 40ºC/75% RH for 3months (climatic zone IV condition for accelerated testing) to assess their stability. These samples were analyzed and checked for changes in physical appearance and drug content at regular intervals. The obtained data is presented in Table 6. From the table, it is clear that the formulations did not undergo any chemical changes/interaction during the study period.

Table 6: stability study for drug content of lafutidine floating tablets

Stability condition	Sampling (days)	Lafutidine Drug content (%)
40°C/75% RH	0	97.95±5.7
	7	97.83±2.4
	15	97.63±3.2
	30	96.98±1.6
	60	96.81±3.2
	90	96.26±1.3

CONCLUSION

The Lafutidine gastro retentive tablets were prepared by direct compression method by using different natural gums such as gum karaya, hupu gum, guar gum and along with gas forming agents such as sodium bicarbonate and citric acid. These tablets were evaluated for morphological characteristics, physical characteristics, chemical characteristics and stability. The results obtained were satisfactory and within specified limits as per Pharmacopoeias. Formulation F10 fulfills our objective of formulating a floating tablet of Lafutidine.

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