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RESEARCH ARTICLE

Development and Evaluation of Gastro Retentive Floating Tablets of Lafutidine: A Novel H_2-Receptor Antagonist

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ABSTRACT

The purpose of present investigation was to develop and evaluate floating drug delivery system of Lafutidine; a novel H_2 receptor antagonist. The floating tablets of Lafutidine were prepared by effervescent technique using HPMCK15, Pectin, and Carbopol 940 polymers. The precompression and post compression evaluation were performed as per pharmacopoeial standards. The tablets were prepared by direct compression method. Dissolution measurements were carried out in a (USP) dissolution testing apparatus II. Compatibility study was performed by FTIR. The compatibility study of the prepared Lafutidine floating tablets confirms that there is no interaction between the drug and polymers used. The release data were subjected to different models in order to evaluate their release kinetics and mechanisms. The drug release kinetics was observed by Non-fickian diffusion mechanism. The floating lag time were found to be significantly increased with the increasing concentration of the polymers. After the dissolution study of prepared Lafutidine floating tablet by effervescent technique it was concluded that the formulation with HPMC K15 shows better sustained release effect. The release kinetic data implies that the release mechanism of all the formulations was Non-fickian. The developed floating tablets of Lafutidine may be used to prolong drug release for at least 12h, thereby improving the bioavaibility and patient compliance.

KEYWORDS

Lafutidine, Gastroretentive, Floating Drug Delivery, Sustained Release

INTRODUCTION

From the recent scientific and patent literatures that an increased interesting novel oral controlled release dosage forms that designed to be retained in the GIT for a prolonged and predictable period of time exists today. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS), low-density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high-density systems, super porous hydrogels and magnetic systems. The FDDS is one of the most leading methodologies in gastroretentive drug formulations[1].

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient 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. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of

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drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration[2].

Lafutidine,(±)-2-(furfuryl sulfinyl)-N-(4-[4-[piperidino- methyl]-2-pyridyl]oxy-(Z)-2-butenyl) acetamide is a newly developed second generation histamine H2-receptor antagonist.[3] It is used in the treatment of gastric ulcers, duodenal ulcers and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis.[4] The Gastroretentive drug delivery system can improve oral bioavailability by controlled delivery of various drugs.[5,6] The formulation development to rate controlled oral drug delivery systems may overcome physiological adversities like short gastric residence and gastric emptying time.[6,7]

The aim of the present study was to design and evaluate the FDDS of Lafutidine by effervescent technique using effervescent compounds such as citric acid, sodium bicarbonate and polymers like HPMC k15, pectin, carbopol 940, etc. for optimum deliver.

MATERIAL AND METHODS

Lafutidine was obtained as a gift sample from Spectrum Pharma labs Hyderabad. Hydroxy propyl methyl cellulose K15, pectin from Spectrum Pharma labs Hyderabad. Carbopol 940, MCC, Mg-Stearate, Talc from Shreeji chemicals Mumbai. Sodium bicarbonate, Citric acid were gift samples from S.D. Fine Chemicals (Mumbai, India). All other chemicals were of analytical grades as required.

Drug Excipients Compatibility Study

Fourier Transformation-Infrared Spectroscopy (FTIR)

FTIR is used to identify the drug excipients interaction. FTIR studies were performed on drug, polymer and optimized formulation at 40^0C/75% relative humidity for 4 weeks. Sample preparation involved mixing the samples with potassium bromide (KBr), triturating in glass mortar and placing in sample holder. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (FTIR 8001, Shimadzu, Japan) in the region between 4200 and 400 cm^{-1}.[8]

Preparation of Lafutidine Floating Tablets by Direct Compression Method

Lafutidine floating tablets were prepared by direct compression technique using drug and variable concentration of polymers like HPMC K15, pectin, carbopol 940 and gas generating agents like Sodium Bicarbonate, Citric acid and additives like MCC, Mg-stearate, and Talc were used. The respective powders & optional additives (composition listed in table-1) were blended thoroughly with a mortar and pestle. The powder blended was then lubricated with Mg-stearate and purified talc and then compressed on a tablet punching machine.

Evaluation of Lafutidine Floating Tablets

Pre Compression Evaluation

The flow properties of powdered blend was characterized in terms of angle of repose,[9] bulk density, tapped density,[10] carr's compressibility index and Hausner's ratio.[11]

Post Compression Parameters

The prepared floating tablets were evaluated for weight variation[12] (Indian Pharmacopoeia 1996), hardness (Monsantotester), friability (Rochetype friabilator), thickness and diameter, drug content estimation, floating lag time and total floating time.

In-vitro Buoyancy Studies

In- vitro buoyancy studies were performed for all the twelve formulations as per the method described by Rosa *et al (*1994*).*[13] The in vitro floating behavior of the tablets were studied by placing them in 100 ml beaker containing 100 ml of 0.1 N HCl (pH 1.2, 37^0C). The time, tablet required for the emerge on the surface is floating lag time (FLT) or buoyancy lag time (BLT). And the time, tablet constantly float on the surface of the medium is called total floating time (TFT).

Drug Content Estimation

Powdered tablets extraction was carried out using 0.1 N HCl. The concentration was determined

spectrophotometrically against appropriate blank. Calculate the content of Lafutidine with specific absorbance at 279 nm.

In-Vitro Dissolution Studies

The release rate of Lafutidine from floating tablet was determined using the United States Pharmacopoeia (USP) dissolution testing apparatus II. The dissolution test was performed using 900ml of 0.1 N HCL, at 37 ± 0.5ºC and at 50 rpm. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution medium.[14,15] The samples were analysed by using UV spectrophotometer at 279nm.

Kinetic Modelling of Drug Release

The dissolution profile of all the batches were fit to zero order, first order[16], Higuchi[17], Korsmeyer–Peppas model[18,19]. The data obtained from dissolution kinetics studies were analyzed using PCP Disso v2.08 software.

RESULTS AND DISCUSSION

The drug and excipients studies reveal that there were no physical changes in drug and excipients mixtures. Spectral observation indicated that the principal IR absorption peaks observed in spectra of drug were close to those in spectra of excipients indicated that there was no significance interaction between drug and excipients (Figure 1a and b).

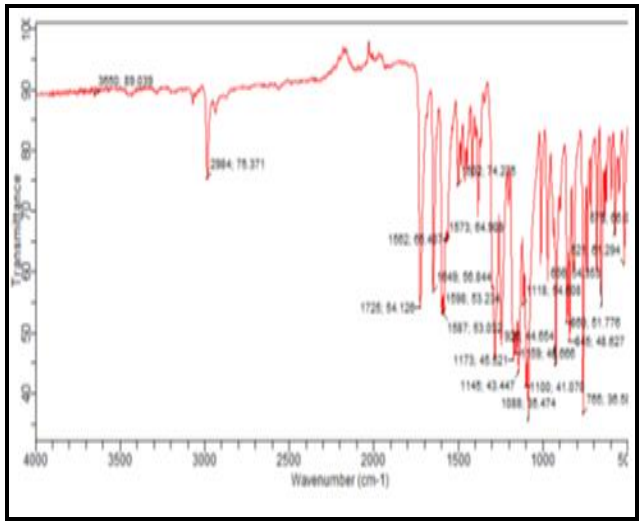

Figure 1(a): FTIR spectrum of Lafutidine

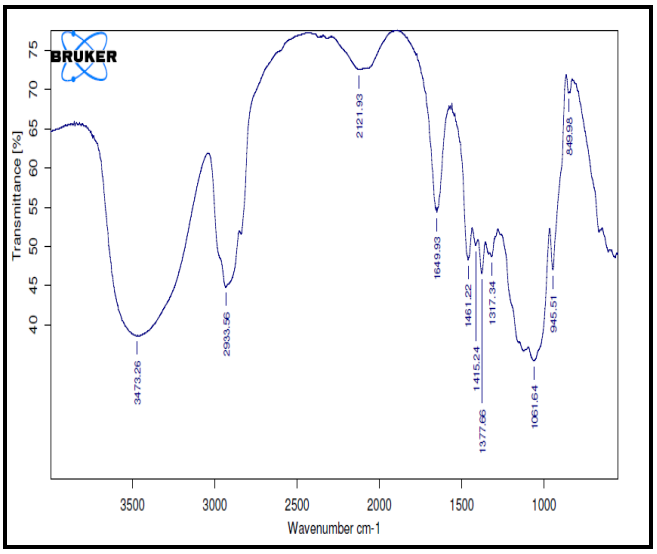

Figure 1(b): FTIR spectrum of HPMC K15

Pre compression Evaluation of Lafutidine Floating Tablets

Prepared powder blend of all formulations of the lafutidine (F1 to F12) were evaluated for their physical properties such as angle of repose, bulk density, tapped density, Carr's compressibility index and Haunser's ratio. Haunser's ratio was found in the range of 1.12 to 1.20 indicates better flow properties. So it can be clearly concluded that the powder blend with different formulations components were having good flow properties, good compressibility which allow these formulations to be directly compressed into tablets. Results of Precompression evaluations of formulations were shown in Table 2.

Post Compression Evaluation of Lafutidine Floating Tablets

Lafutidine floating tablets (F1 to F12) were evaluated for average weight, thickness, hardness, friability and drug content. The results were shown in Table 3. Physicochemical parameters of all the formulations were within the acceptance limit.

The Percentage of drug content for formulation F1 to F12 was found 95.09±2.15 to 101.14±1.45, it complies with Pharmacopoeial specifications. The floating lag time studies showed that batch containing HPMC K15 had less floating lag time compare to those containing pectin and Carbopol 940.

Table 1: Composition of Lafutidine floating tablets

S. NO	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Lafutidine	10	10	10	10	10	10	10	10	10	10	10	10
2	HPMC K15	10	20	30	40	-	-	-	-	-	-	-	-
3	Pectin	-	-	-	-	10	20	30	40	-	-	-	-
4	Carbapol 940	-	-	-	-	-	-	-	-	10	20	30	40
5	MCC	165.5	155.5	145.5	135.5	165.52	155.5	145.5	135.5	165.5	155.5	145.5	135.5
6	Mg Stearate	4	4	4	4	4	4	4	4	4	4	4	4
7	Citric Acid	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8	Sodium Bicarbo-nate	6	6	6	6	6	6	6	6	6	6	6	6
9	Talc	2	2	2	2	2	2	2	2	2	2	2	2

Table 2: Pre compression evaluation of Lafutidine Floating tablets

Formulation code	Angle of repose (θ) ±SD	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)
F1	24º6´±2	0.566	0.646	12.38
F2	27º7´±2	0.576	0.676	14.79
F3	28º12´±2	0.564	0.680	17.05
F4	23º11´±2	0.577	0.645	10.54
F5	24º25´±2	0.566	0.682	17.01
F6	26º39´±2	0.579	0.644	14.28
F7	25º19´±2	0.576	0.646	10.09
F8	23º19´±2	0.581	0.656	11.43
F9	27º31´±2	0.564	0.644	12.42
F10	24º12´±2	0.566	0.642	12.34
F11	23º39´±2	0.571	0.651	10.56
F12	26º09´±2	0.581	0.672	14.12

Table 3: Post compression evaluation of Lafutidine floating tablets

Formulation code	Mean Hardness Kg/cm^2	Thickness (mm)	Friability % w/w	Average weight (mg) ± SD	Mean drug content % ± SD
F1	4.5	2.93	0.63	199.5±5	99.42±1.59
F2	4.52	2.8	0.5	198.1±5	98.12±1.10
F3	4.3	3.01	0.5	198.2±5	95.90±0.90
F4	4.4	3.16	0.6	198.5±5	99.77±0.10
F5	4.25	3.2	0.5	197.3±5	101.14±1.45
F6	4.5	3.2	0.6	198.9±5	95.44±0.70
F7	4.35	3.3	0.63	199.3±5	95.09±2.15
F8	4.43	2.8	0.66	199.1±5	98.18±0.90
F9	4.35	2.9	0.5	199.3±5	96.87±0.20
F10	4.3	3.2	0.51	197.3±5	96.37±0.10
F11	4.5	2.98	0.61	199.2±5	99.53±0.59
F12	4.41	3.1	0.54	198.6±5	96.25±1.40

Table 4: Determination of cumulative % drug released, floating lag time and total Floating time of Lafutidine tablets

Formulation Code	Floating lag time (min) ± SD	Total floating time (hr)	Cumulative % drug release at 12 Hrs ± SD
F1	0.54±0.045	>24	82.346±0.182
F2	1.27±0.976	>24	78.812±0.135
F3	1.38±0.098	>24	75.624±0.219
F4	1.56±0.098	>24	96.083±0.457
F5	2.26±0.096	>12	91.542±0.782
F6	2.49±0.096	>12	88.812±0.314
F7	3.17±0.076	>12	88.621±0.414
F8	3.55±0.075	>12	82.356±0.306
F9	2.11±0.086	>12	79.521±0.423
F10	2.29±0.076	>12	92.354±0.864
F11	2.59±0.076	>12	85.624±0.367
F12	3.11±0.096	>12	83.731±0.537

The total floating time for the formulations containing HPMC K15 was more than 24 hours and for the formulations containing pectin and Carbopol 940 was more than 12 hours which is sufficient to be consider as buoyant drug delivery systems. In general it can also be concluded that with an increase in the polymer concentration there was an increase in floating lag time. The results were shown in table 4.

In-vitro Dissolution Studies

In vitro dissolution studies were performed for all the formulations of Lafutidine using USP XXIII dissolution test apparatus II at 50 rpm, 900ml of 0.1N HCl used as dissolution media. Different polymers such as HPMC K15 (F1, F2, F3, F4), Pectin (F5, F6, F7, F8) and Carbopol 940 (F9, F10, F11, F12) were used to prepare the gastroretentive floating tablets of lafutidine and their individual % cumulative drug released profile was evaluated and showed in Figure 2.

Among the various formulations studied, formulation F4 containing drug-polymer ratio (1:4) prepared with HPMC K15 showed promising results releasing ≈ 96.083% of the drug in 12 hours with a floating lag time of 1.56±0.098min and floating time of 24 hours has been considered as an ideal formulation. The Lafutidine floating tablets formulations (F1 to F12) exhibited cumulative % drug released were shown in Table 4.

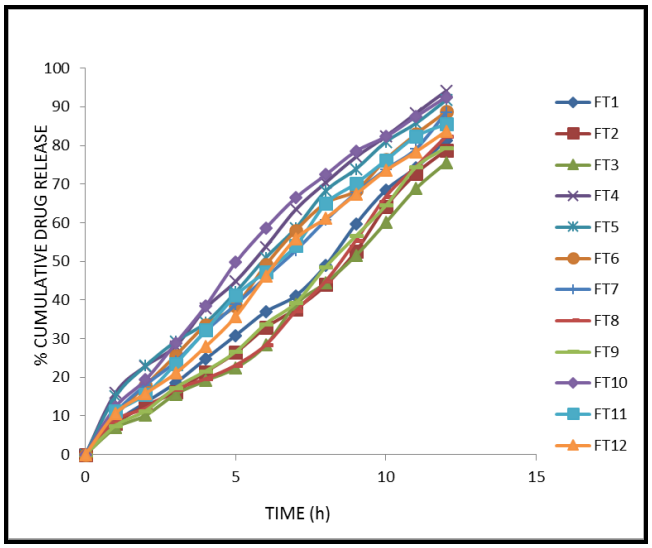

Figure 2: *In-vitro* drug release profile of Lafutidine floating tablets (F1 to F12)

Drug Release Kinetics

The data obtained from in vitro dissolution studies were fitted to zero-order; first- order, Higuchi and Korsmeyer–Peppas equations. The data were analysed, and the n value was found to be in the range of 0.767 to 0.993 indicating that the drug release is by Non-Fickian diffusion mechanism.

CONCLUSION

Buoyant delivery systems are promising dosage forms which could be a better alternative to the conventional oral dosage forms in order to improve bioavailability by increasing the gastric retention time of the drug.

From the compatibility studies, it is concluded that, HPMC K15, carbopol 940, pectin, were compatible with drug Lafutidine and thus suitable for the formulation of Lafutidine floating tablets. Lafutidine tablets were fabricated by direct compression method. *In-vitro* buoyancy studies were performed for all the formulations, F1 to F12 by using 0.1 N HCL solutions at 37^0C. Tablet containing HPMC k15 (F4) showed good buoyancy with very short lag time and long floatation time of more than 12 hrs in 0.1 N HCL. *In-Vitro* release study is performed for 12 hrs. Optimized formula containing (F4) showed better release compare to other formulations and it followed zero order kinetics. The non-Fickian diffusion was confirmed as the drug release mechanism from this formulation. From this study, it was concluded that HPMC K15 can be used in formulation of Lafutidine sustained release gastro retentive floating drug delivery system. Overall, this study concludes that viscosity of the polymer is a major factor affecting the drug release and floating properties of FDDS.

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