Available Online at www.jddt.in

ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 2 (24) 2014, 01-08

RESEARCH ARTICLE

Design and evaluation of lafutidine floating tablets for controlled release by using semi-synthetic and natural polymer

D. Lohithasu*[1], D. Midhun kumar[2], Hemasundara Rao. I[3]

[1]GITAM Institute of Pharmacy, GITAM University, Visakhapatnam- 530045, India.

[2]A.U. College of Pharmaceutical Sciences, Visakhapatnam- 530003, India.

[3]Sri Sai College of Pharmacy, Seetharampuram, Vizianagaram- 535005, India.

Received 25 November 2014; Accepted 7 December 2014

ABSTRACT

Purpose: Lafutidine is H2-receptor antagonist. The prepared tablets of various formulations were evaluated for a total floating time, buoyancy lag time, and percentage drug released. Guar gum is an efficient matrix forming agent in floating tablets by generating gas. Drug release from the prepared tablets was slowed over more 12 h and depended on the composition of guar gum and sodium bicarbonate. Lafutidine release was diffusion controlled and follows zero order kinetics. In case of F3 formulation non-fickian diffusion was the drug release mechanism from the prepared lafutidine floating tablets.

Methods: Floating tablets containing 10 mg of lafutidine could be prepared by wet-granulation technique employing guar gum of different grades as floating polymer and release retardant, methocel K100LVCR, methocel K15M as floating enhancers and sodium bicarbonate as a gas generating agent.

Results: The influence of various process parameters on physic-chemical properties and drug release potential have been studied. Different formulation ratios of blend affect the physical appearance of the tablets and micromeritic properties were observed. The measured tapped density was 0.501 to 0.643(g/cm^3), bulk density 0.421 to 0.540 (g/cm^3), Carr's index(I) 10.88 to 23.04%, thickness 4.33 to 4.38(mm), hardness 4.26 to 5.06 (Kg/cm^2), friability 0.24 to 0.46(%) were well within the limits, which indicates good flow potential of the prepared tablets. Angle of repose (θ) values for the granules was in the range 24.19 to 26.95^0 indicating good flow potential for the tablets.

Conclusion: Although the tablets with guar gum were able to float for more than 12 h. Resultant tablets blend did not have any incompatibilities showed in FT-IR studies.

Keywords: *Floating drug delivery system, in vitro, lafutidine and controlled release.*

INTRODUCTION

The design of floating drug delivery system (FDDS) should be aimed that to achieve more predictable and increased bioavailability of drugs [1]. Floating drug delivery is one of the approaches for gastroretention. FDDS or hydrodynamically balanced system shave a bulk density lower than gastric fluids and thus, 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, drug is released slowly at a pre-determined rate [2]. Lafutidine possesses a potent and long lasting gastric antisecretory effect mediated by H2-receptor blockade in animals. Lafutidine has a receptor binding affinity which is 2-80 times higher than other representative H2-receptor antagonists (e.g. famotidine, ranitidine, and cimetidine). In addition, lafutidine exerts gastroprotective effects independent of its antisecretory action. Lafutidine is freely soluble in acetic acid, slightly soluble in methanol, very slightly soluble in diethyl ether and practically insoluble in water. When 10 mg of lafutidine is orally administered to normal adult males, fasting plasma concentration of unchanged drug observed as T_{max}: 0.8±0.1 h; C_{max}: 174±20 ng/ml; $T_{1/2}$: 3.30 h. The total execration rate of lafutidine in urine is approximately 20% of given dose. Lafutidine is absorbed in the small intestine, reaches gastric cells via the systemic circulation, and rapidly binds to gastric cell H2 receptors, resulting in immediate inhibition of gastric acid secretion [3].

In the present study an attempt will be made to formulate and evaluate hydrodynamically balanced drug delivery system of lafutidine for the treatment of ulcer,

*Corresponding author: D.Lohithasu || E-mail: lohithasu@gmail.com

which attempts to increase the gastric retention time of lafutidine. The present research work is with lafutidine along with polymer, i.e. guar gum, which attempts to increase the gastric retention time of the lafutidine and developed for the controlled release.

MATERIALS AND METHODS

Materials

Lafutidine was gift sample from Suven Life Sciences. Guar gum, methocel K 100LVCR , methocel K 15 were purchased from Yarrow Chemicals, Mumbai. PVP-K-30 was purchased from Basf Corporation. Sodium bicarbonate was purchased from Qualigens Fine Chemicals, Mumbai. Citric acid was purchased from Finar Chemicals Limited, Ahmedabad.

Drug Excipient Compatibility Studies

The FT-IR spectra of lafutidine and lafutidine-guar gum are shown. The characteristic FT-IR bands of lafutidine at 3279 cm^{-1} –N-H- stretched, 3094 cm^{-1} CH stretched at thiazole ring, 2861 cm^{-1} at CH_2CH_2 Stretch, 1620 cm^{-1} at C=C bond conjugated with NO_2, 1520 cm^{-1} at thiazole ring, 1436 cm^{-1} CN Stretched were both observed in the FT-IR spectra of both lafutidine and lafutidine-guar gum.

Preparation of Standard Solution

Lafutidine (10mg) was dissolved in acetic acid in 10 ml of volumetric flask and diluted quantitatively with acetic acid to obtain a solution having a known concentration of 1000 µg/ml.

Procedure

The standard solution of lafutidine was subsequently diluted with 0.1N hydrochloric acid (HCl) to obtain a series of dilutions containing 2, 4, 6, 8 and 10 µg of lafutidine per ml of solution. The absorbance of these solutions was measured in analytical technologies Limited, UV-Visible Spectrophotometer at 286 nm using 0.1N HCL as blank.

Validation of the UV spectrophotometric method

Reproducibility

Reproducibility of the above method was studied by analyzing six individually weighed samples of lafutidine. The percent relative standard deviation (RSD) of the determinations found to be less than 1.0%.

Interference Study

The interference in the above method by the other excipients used in the present investigation was studied by testing their effects individually. Accurately weighed amounts of lafutidine, guar gum, methocel K 100 LVCR and methocel K15M or other excipients in 1:1 ratio were mixed thoroughly. From each mixture, an accurately weighed powder equivalent to 100 mg of lafutidine was assayed by the method described above.

Preparation of lafutidine floating tablets

Lafutidine tablets were prepared by wet granulation method. All the ingredients of the formulation were accurately weighed and the coherent mass was formed using water as a granulating fluid. The coherent mass was passed through mesh No. 16 and the granules obtained were air dried. The lubricants, talc (2%) and magnesium stearate (2%) were passed through mesh No. 60 onto the dry granules and blended in a closed polyethylene bag.

Evaluation of lafutidine floating tablets

The various physical properties of tablet blend like bulk density, tapped density, compressibility index and angle of repose were determined [4].

Bulk and tapped density

Bulk and tapped densities were measured by using 10 ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated.

Tapped density = Mass of formulation/tapped volume

Hausner ratio

Tapped density and bulk density were measured and the Hausner ratio was calculated using the formula,

Hausner ratio = ρ_t / ρ_o

Where, ρt = tapped density, ρo = bulk density

Compressibility Index

The bulk density and tapped density was measured and Compressibility index was calculated using the formula,

% Compressibility index (C.I.) = $\{(\rho_t - \rho_o)/\rho_t\} \times 100$

Where, ρ_t = tapped density, ρ_o = bulk density

Angle of repose (θ)

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. Angle of repose of different formulations was measured according to fixed funnel standing method (n = 3). The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper. The angle of repose was calculated by substituting the values of base radius 'r' and pile height 'h' in the following equation, where, θ is the angle of repose, h is the height and r is the radius

Tan θ = h/r

Drug content and percentage yield

Ten milligrams of lafutidine drug was dissolved in small quantity of acetic acid and then made up to 10 ml with 0.1N hydrochloric acid. The lipid was solidified and the drug solution was filtered through whatman filter paper. The sample was analyzed for drug content by UV spectrophotometry at 286 nm after suitable dilutions. Drug stability in the dissolution medium was checked for

a period of more than 12 h. The percentage yield of each formulation was calculated.

Floating lag time

In vitro buoyancy was determined by floating time as per the method described by Dave B.S.et al [5]. The randomly selected tablets from each formulation were kept in a 250 ml beaker containing 150 ml simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time.

Floating time

The floating behavior of the formulated floating controlled release tablet of lafutidine was studied. The floating time was determined using a USP XXIV type II (paddle) apparatus at 37 ± 0.5 ^{0}C containing 900 ml of 0.1N HCl and at 50 rpm. The time for which the tablet remains a float on the surface of the medium was measured as total floating time (TFT).

***In-vitro* dissolution rate studies**

The release rate of lafutidine from floating tablets was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml at 37±0.5 ^{0}C at 50 rpm in 0.1N HCl . Aliquot volume was withdrawn from the dissolution apparatus at the time intervals of 1 to 24 h and the samples were replaced with fresh dissolution medium. After filtration, the amount of drug released was determined from the standard calibration curve of pure drug.

The dissolution profiles of all the batches was fitted to various models like zero-order, first order, korsmeyer and peppas, and higuchi models to ascertain the kinetic modeling of drug release.

RESULTS

Preparation of lafutidine floating tablets

Table 1: Preparation of lafutidine floating tablet

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lafutidine	10	10	10	10	10	10	10	10	10
Guar gum	30	60	90	---	---	---	---	---	---
Methocel K100 LVCR	---	---	---	30	60	90	----	---	---
Methocel K15M	---	---	---	---	---	---	30	60	90
PVP-K-30	10	10	10	10	10	10	10	10	10
Sodium bicarbonate	30	30	30	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5	5	5	5
Lactose	113	83	53	113	83	53	113	83	53
Talc	6	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6	6

The Lafutidine floating tablets were prepared by using guar gum, methocel K100 LVCR and methocel K15M. Guar gum is an efficient matrix forming agent for floating tablets by generating gas. The lafutidine floating tablets were prepared by wet-granulation technique employing guar gum of different grades as floating polymer and release retardant, methocel K100LVCR, methocel K15M as a floating enhancer and sodium bicarbonate as gas generating agent.

Amount of lafutidine estimated in interference studies by UV spectrophotometric method

The UV spectrophotometric method obeys Beer's law in the concentration range of 2–10 µg/ml. Thus the method was found to be suitable for the estimation of lafutidine content.

Table 2: Amount of lafutidine estimated in interference studies

Excipients	Amount of lafutidine added (mg)	Amount estimated (mg)	Percent estimated (Recovery)
Guar gum	10	9.95	99.90
Methocel K 100 LVCR	10	9.90	99.67
Methocel K 15M	10	9.89	99.63
PVP K30	10	9.62	99.23
Sodium bicarbonate	10	9.74	99.18
Citric acid	10	9.80	99.42
Lactose	10	9.62	99.30
Talc	10	9.56	98.53
Magnesium stearate	10	9.88	99.78

Physical Properties

Different formulation ratios of blend affects the physical appearance of the tablets and micromeritic properties were observed. The measured tapped density was 0.501 to 0.643 (g/cm^3), bulk density 0.421 to 0.540 (g/cm^3), Carr's index(I) 10.88 to 23.04%, thickness 4.33 to 4.38(mm), hardness 4.26 to 5.06 (Kg/cm^2), friability 0.24 to 0.46(%) were well within the limits, which indicates good flow potential for the prepared tablets. Angle of repose (θ) values for the granules was in the range 24.19 to 26.95° indicating good flow potential for the tablets.

Table 3.Physical properties of prepared blend

Formulation	Tapped density (g/cm^3)	Bulk density (g/cm^3)	Compressibility index (%)	Angle of repose (θ)
F1	0.520±0.023	0.479±0.071	15.78±1.50	25.10±0.29
F2	0.638±0.037	0.526±0.034	18.02±1.85	26.55±0.82
F3	0.643±0.039	0.534±0.016	23.04±3.16	27.22±1.35
F4	0.513±0.016	0.443±0.012	15.29±1.72	24.36±0.23
F5	0.614±0.025	0.514±0.065	15.96±1.49	26.02±0.34
F6	0.638±0.038	0.540±0.028	19.34±1.32	26.95±1.06
F7	0.501±0.0018	0.421±0.020	10.884±1.63	24.19±0.23
F8	0.576±0.034	0.491±0.076	15.79±1.68	25.46±0.34
F9	0.627±0.035	0.517±0.089	16.90±1.44	26.39±0.42

Table 4: Thickness, Hardness, Friability, Drug content, Buoyancy Lag time and Total floating time of lafutidine floating tablets.

Formulation	Thickness in (mm)	Hardness (Kg/cm^2) ± S.D	Friability (%) ± S.D	Drug content (mg/tab) ± S.D	Buoyancy lag time (sec)	Total floating time (h)
F1	4.35±0.083	5.0 ± 0.01	0.31 ± 0.011	98.34± 0.12	18 ± 11	15 ± 0.011
F2	4.36±0.012	5.03 ± 0.02	0.24 ± 0.012	99.21 ± 0.47	19 ± 10	20 ± 0.021
F3	4.38±0.026	5.06 ± 0.04	0.24 ± 0.015	99.97 ± 0.08	19 ± 20	24 ± 0.052
F4	4.34±0.109	4.89 ± 0.41	0.34 ± 0.014	98.17 ± 0.45	18 ± 09	13± 0.451
F5	4.35±0.134	4.76± 0.33	0.28 ± 0.018	98.86 ± 0.23	15 ± 40	18 ± 0.014
F6	4.38±0.016	4.91± 0.32	0.24 ± 0.018	99.92 ± 0.69	13± 03	22 ± 0.051
F7	4.33±0.095	4.26± 0.34	0.46 ± 0.010	97.42 ± 0.70	15± 30	09 ± 0.024
F8	4.35±0.081	4.55 ± 0.46	0.29 ± 0.013	98.54 ± 0.71	16± 07	16 ± 0.077
F9	4.36±0.116	4.82± 0.22	0.25 ± 0.016	99.91 ± 0.43	12± 40	19 ± 0.085

Table 5: Correlation Coefficient (R^2) Values in the analysis of release data as per zero order, First order, higuchi, and peppas equation models.

Formulation	Zero order Model	First order Model	Higuchi Model	Peppas Model
F1	0.910	0.977	0.990	0.991
F2	0.922	0.986	0.986	0.993
F3	0.998	0.963	0.986	0.923
F4	0.972	0.952	0.932	0.992
F5	0.975	0.971	0.948	0.989
F6	0.992	0.983	0.986	0.966
F7	0.975	0.990	0.966	0.980
F8	0.937	0.993	0.982	0.983
F9	0.997	0.972	0.976	0.987

Table.6.Release characteristics of lafutidine floating tablets prepared employing guar gum, methocel K 100 LVCR, methocel K 15M

Formulation	% Release in 24 h ± SD	K_O (mg/h)	$K_1(h^{-1})$	'n' in Peppas equation
F1	99.63	6.58	0.3823	0.524
F2	100.09	16.90	0.4709	0.885
F3	100.01	2.70	0.2029	0.553
F4	99.12	1.70	0.0992	0.563
F5	99.46	11.30	0.4749	0.649
F6	99.81	14.60	0.8745	0.653
F7	100.28	1.90	0.8745	0.574
F8	99.86	6.90	0.1860	0.767
F9	100.11	6.60	0.2277	0.686

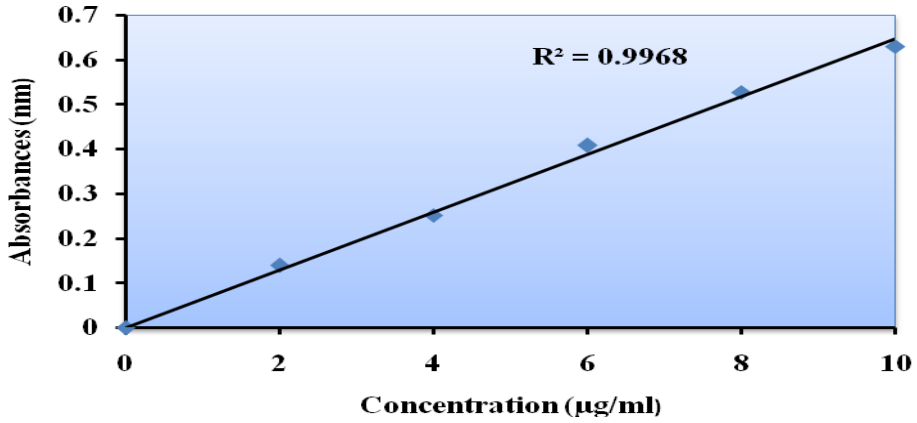

Figure 1. Calibration curve for the estimation of lafutidine

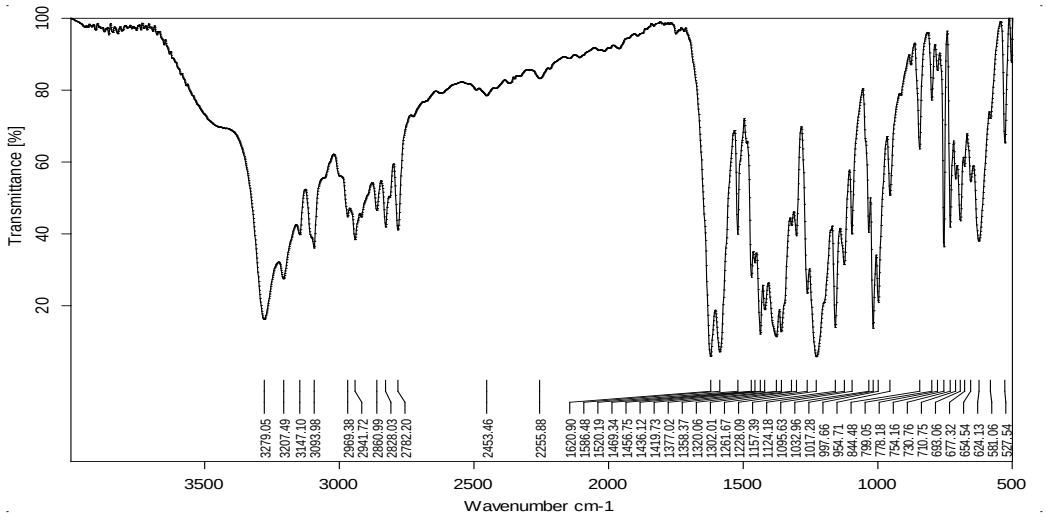

Figure 2: FT-IR spectra of lafutidine

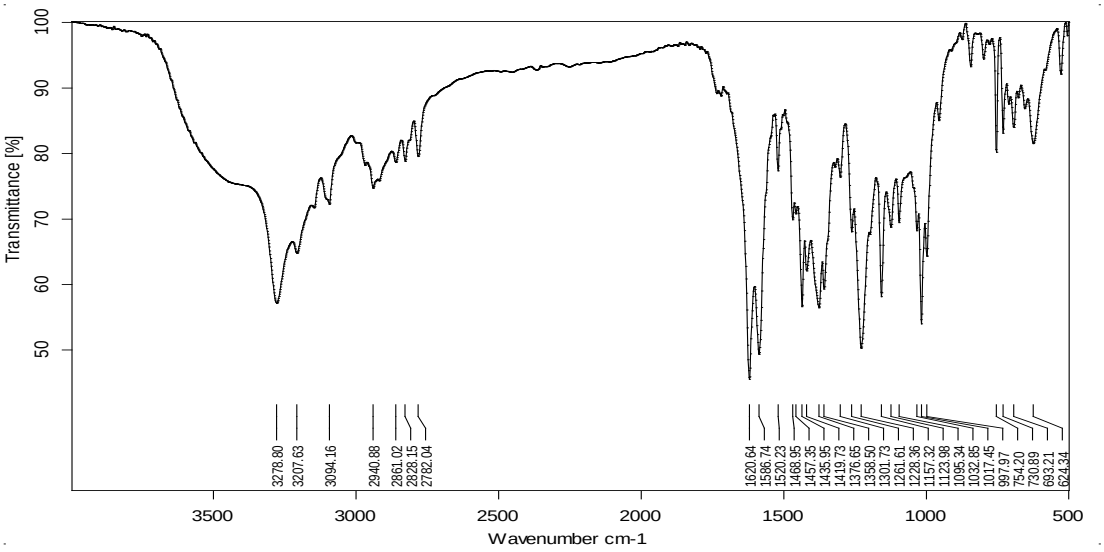

Figure 3: FT-IR spectra of mixture of lafutidine and guar gum

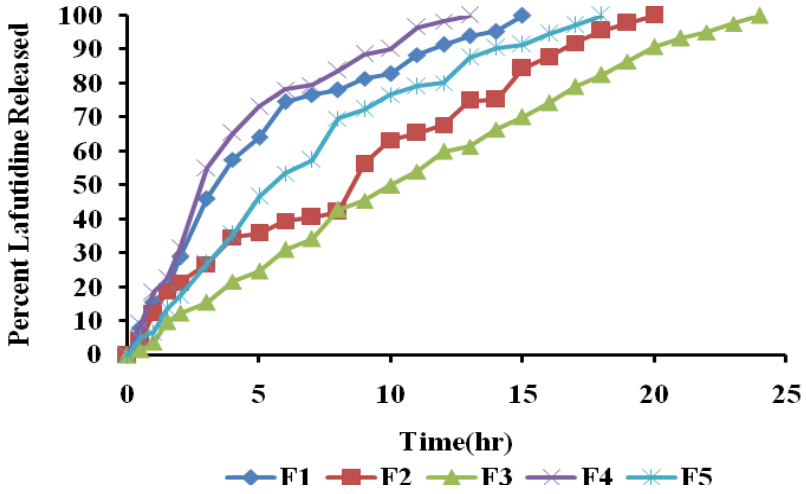

Figure 4: Release profiles of lafutidine floating tablets (F1-F5)

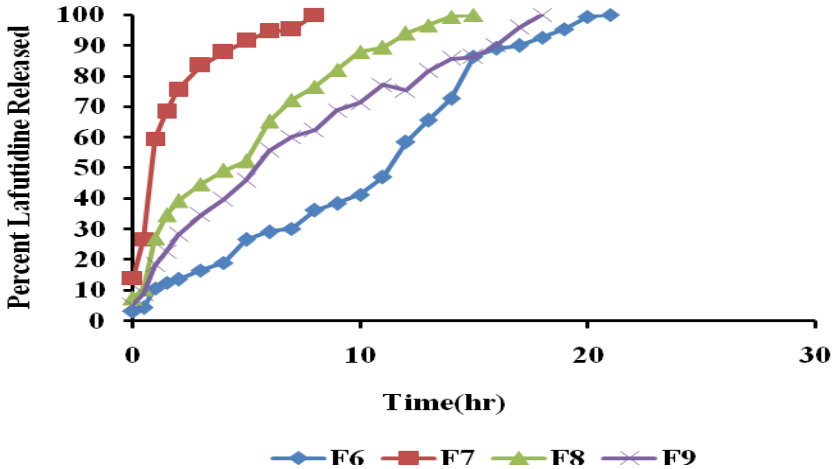

Figure 5: Release profiles of lafutidine floating tablets (F6-F9)

CONCLUSION

The evaluation results for *in-vitro* drug release showed that guar gum was able to retard the drug release more than 12 h. All the floating tablets prepared contained lafutidine within 100 ± 5% of the labeled claim. As such the prepared floating tablets were of good quality with regard to drug content , angle of repose, bulk density and tapped density. In the *in-vitro* buoyancy study varieties were observed in the floating lag time and floating time. In the *in-vitro* buoyancy study varieties were observed in the floating lag time and floating time of ideal formula F3.Lafutidine release from floating tablets was shown and spread over 12h depended on the composition of the matrix it concentration of guar gum, methocel K100LVCR, methocel K15M, sodium bicarbonate and PVP-K-30.The dissolution data of tablets F1 to F9 was fitted to zero order, first order, korsmeyer and peppas and Higuchi models. The results of correlation coefficient (R^2) were used to select the most appropriate model. The release profiles of formulations F3 fitted best to zero order model. Percent drug released verses square root time were found to be linear indicates that the drug release from the floating tablets prepared was diffusion controlled. The release data was also analyzed by the korsmeyer and peppas equation shown below in order to assess the release mechanism.

ACKNOWLEDGEMENTS

The authors are thankful to Sri Sai college of pharmacy, GITAM University and A.U.College of pharmaceutical sciences, Visakhapatnam-530003 for necessary support.

REFERENCES

1. Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63: 235-59.
2. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. AAPS Pharm Sci Tech 2005;6: E372-90.
3. Yamagishi H, Koike T, Ohara S, Horii T, Kikuchi R, Kobayashi S, *et al*. Stronger inhibition of gastric acid secretion by lafutidine, a novel H2 receptor antagonist, than by the proton pump inhibitor lansoprazole. World J Gastroenterol 2008;14:2406-10.
4. Patil SH, Talele GS. Formulation development and *in vitro* and *in vivo* evaluation of gastroretentive floating drug delivery system of Lafutidine. Asian J Pharm 2013;7:68-74.
5. Dave, B.S., Amin, A.F., Patel, M.M., “Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evaluation”, AAPS Pharm. Sci.Tech., 2004, 5, E34