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Research Article

FORMULATION AND INVITRO EVALUATION OF GASTRORETENTIVE BILAYER FLOATING TABLETS OF CLARITHROMYCIN AND LAFUTIDINE

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Abstract

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Usual treatment for Helicobacter pylori-induced peptic ulcer includes a 'triple therapy' consisting of two antibiotics (amoxicillin and clarithromycin) and a proton pump inhibitor (omeprazole). The aim of the present investigation was to develop a bilayer floating tablet (BLFT) of Clarithromycin (a macrolide antibiotic) and Lafutidine (a newly developed 2nd generation H2-receptor antagonist) for effective treatment of peptic ulcer.

BLFT was formulated using direct compression and wet granulation technique and it consists of two layers, i.e. IR layer containing Clarithromycin and floating SR layer containing Lafutidine. Optimization of the best formulation among the six formulations prepared for both IR and SR layer was done on the basis of their dissolution profiles. IR layer tablets F6 containing 12.5% of Crospovidone was found to be optimum and released 83.52% of Clarithromycin in 45mins. The floating SR layer tablet of Lafutidine (F6) containing HPMCK15M (10%) and Guar gum (30%) showed 43.53% in 8 hrs.

The Optimized immediate release (F6) & sustained release (F6) formulation was combined and made into bilayer floating tablet. The optimised BLFT of Clarithromycin and Lafutidine was formulated and evaluated for various evaluation parameters i.e. Hardness – 5.6 kg/cm^2, Friability 0.19%, Floating lag time 2mins 56 sec and floating time of 24 hrs. All the results of evaluations was found to be within limits and the final Optimised bilayer formulation released

83.52% of Clarithromycin in 45min and 86.78% of Lafutidine in 12hrs. The optimised formulation followed first order and the release mechanism was Case II Non- fickian.

Keywords: Lafutidine, Clarithromycin, floating, peptic ulcer, HPMC, Guar gum, cros povidone.

1. Introduction

Oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has several physiological problems, including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The main mechanism involved in this system is the production of carbon-dioxide gas due to reaction between sodium bicarbonate, citric acid & tartaric acid. The gas produced results in the reduction of density of the system thereby making it to float on the gastric fluids. Drugs that are easily absorbed from gastro intestinal tract and have short half life are eliminated quickly from systemic circulation. GRDFs extend significantly the period of time over which the drugs may be released. The objective of this project work was defined with a view to retain the drug in stomach for better antiulcer activity.

Lafutidine is a newly developed 2^{nd} generation histamine H2-receptor antagonist. 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. Lafutidine has a receptor binding affinity, which is 2-80 times higher than famotidine, ranitidine and cimetidine. It has multimodal mechanism of action. It not only suppresses gastric acid secretion, but also has cytoprotective properties by virtue of its property to induce the collagen synthesis in the gastric mucosa. Hence lafutidine is considered as a suitable candidate for the formulation of gastroretentive floating tablet.

Clarithromycin, a semisynthetic macrolide antibiotic derived from erythromycin, inhibits bacterial protein synthesis by binding to the bacterial 50S ribosomal subunit. Clarithromycin may be given to eradicate *H. pylori* in treatment regimens for peptic ulcer diseases. The terminal half-life of Clarithromycin is reportedly about 3-4 hours. Clarithromycin possesses greater acid stability, improved pharmacokinetic properties, and fewer gastrointestinal side

effects. Hence an attempt has been made to formulate Gastroretentive Bilayer floating tablets of clarithromycin and lafutidine for eradication of H.pylori infections effectively and in order to prolong the drug release and to increase the gastric residence time for localization of drug action.

2. Materials and Methods

2.1) Materials: Clarithromycin and Lafutidine drugs are obtained from Aurobindo Pharma Ltd, Hyderabad. HPMC grades, PVP, ethyl cellulose,xanthum gum, guar gum, cros povidone, croscarmellose sodium were received from MYLAN Chemicals Mumbai . Other materials were purchased from S.D Fine chem. Ltd.

2.2.1) Preformulation Studies:

2.2.1.1) Analytical method for Estimation of Clarithromycin IR by HPLC:

Preparation of mixed Phosphate buffer: 1.36 gm of potassium di- hydrogen phosphate (KH2PO4) was weighed and dissolved in 100ml of water and volume was made up to 1000ml with water. Adjust the pH to 5.0 using ortho phosphoric acid. The buffer was filtered through 0.45µ filters to remove all fine particles and gases.

Mobile Phase: A mixture of 30 volumes of Phosphate buffer (KH2PO4) pH 5.0, 40 volumes of Methanol and 30 volumes of Acetonitrile. The mobile phase was sonicated for 10min to remove gases.

Preparation of standard curve by HPLC: The analysis was carried out on a BDS Hypersil C18column using a mobile phase consisting of 0.3% TEA (pH adjusted to 5.0 with ortho-phosphoric acid) and acetonitrile in the ratio (78:22v/v). Before delivering the mobile phase into the system, the sol-vent was degassed and filtered through 0.45 µm PTFE filter using vacuum. The flow rate was kept constant at 1.0 mL/min and the column maintained at 40ºC. The injection volume was 20 µL. The prepared standard solutions were ranging from 5-15µg/ml. The detection was performed at 210 nm using a photo-diode array detector.

2.2.1.2) Analytical Method for Estimation of Lafutidine SR By HPLC

Preparation of Buffer: 30Mm Ammonium acetate buffer. Adjust pH to 3.8 with acetic acid.

Mobile phase: A mixture of Ammonium acetate Buffer: Methanol: acetonitrile (30:30:40). The mobile phase was sonicated for 10min to remove gases.

Preparation of standard curve: Before delivering the mobile phase into the system, the sol-vent was degassed and filtered through 0.45 µm PTFE filter using vacuum. The flow rate was kept constant at 1.0 mL/min and the column

maintained at 40ºC. The injection volume was 20 µL. The prepared standard solutions were ranging from 5-15µg/ml. The detection was performed at 282 nm using a photo-diode array detector.

2.2.1.3) Angle of repose: The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flowability of powder/granules.

A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula

$$\theta = \tan^{-1} (h/r) = \tan^{-1} (\text{height of pile}/0.5\text{base})$$

Where, θ = Angle of repose; h = Height of the pile; r = Average radius of the powder cone

2.2.1.4) Bulk density: Bulk Density of a compound varies substantially with the method of crystallization, milling or formulation. Usually, bulk density is of great importance when one considers the size of a high-dose drug product or homogeneity of a low-dose formulation. The homogeneity of a low-dose formulation in which there are large differences in drug and excipient could lead to segregation)

Apparent Bulk density (gm/ml) of the drug was determined by pouring (preseived 40-mesh) gently 4 gm of sample through a glass funnel into a 10 ml graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density was calculated by following formula.

$$\text{Bulk density} = \text{Weight of powder} / \text{Bulk volume}$$

2.2.1.5) Tapped density: Tapped densities the drug was determined by pouring gently 4 gm of sample through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. In USP TAP DENSITY TESTER, Tap density is measured in 500taps, 750 taps & 1250taps with drop/time-299-302. Volume occupied by the sample after tapping were recorded and tapped density was calculated.

$$\text{Tapped density} = \text{Weight of powder} / \text{Tapped volume}$$

2.2.1.6) Compressibility Index (CARR'S INDEX): Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density.

Carr's index = (Tapped density – Bulk density / Tapped density) X 100

2.2.1.7) Hausner's Ratio: Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa.

Hausner's Ratio = Tapped density /Bulk density

2.3) Formulation Development:

2.3.1) Formulation of Immediate Release Layer Clarithromycin Tablets

Procedure: Direct compression: Accurately weighed amounts of drug, super disintegrants, binder and diluents were mixed geometrically in a mortar. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate for 2 minutes and compressed into tablets using 9 mm round, flat-faced punches.

Table-1: Formulation table for immediate release layer of Clarithromycin tablets.

INGREDIENTS	F_1	F_2	F_3	F_4	F_5	F_6
Clarithromycin (mg)	250	250	250	250	250	250
PVP K30 (%)	5	5	5	5	5	5
CCS (%)	5	7.5	--	--	12.5	--
CP (%)	--	--	5	7.5	--	12.5
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium(%) stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc (%)	4	4	4	4	4	4
Total weight	400	400	400	400	400	400

CP- crospovidone, CCS- Cross Carmellose Sodium, PVP- Poly vinyl pyrrolidine, MCC- Micro crystalline cellulose

2.3.2) Formulation of Sustained Release Lafutidine Tablets.

By wet granulation method: The sustained release tablets of lafutidine were prepared by wet granulation method, using various concentrations of HPMC K4M, K15M, xanthum gum, guar gum,and ethyl cellulose along with half of

sodium bicarbonate and citric acid. Microcrystalline cellulose, povidone and remaining sodium bicarbonate were passed through #40 mesh and added to the above granular material and blended for 5 min and prepare damp mass and finally pass through #24 mesh and allow the granules at 40˚C, Magnesium stearate were passed through 60#and added to the above blended material. Compress the blend into tablets with punch size 9 mm

Table 2: Formulation table for SR layer (lafutidine) tablets

INGREDIENTS	F_1	F_2	F_3	F_4	F_5	F_6
Lafutidine (mg)	10	10	10	10	10	10
HPMC K4M (%)	30	30	--	--	--	
HPMC K15M (%)	--	--	--	--	30	10
Guar Gum (%)			20	20	--	30
Xanthum Gum (%)	--	--	--	20	--	--
EC(%)	--	10	10	--	--	--
Sodium bicarbonate (%)	15	15	15	15	15	15
Citric acid (%)	2	2	2	2	2	2
PVP K30 (%)	10	10	7.5	10	10	10
Magnesium stearate(%)	2	2	2	2	2	2
MCC(mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight (mg)	**300**	**300**	**300**	**300**	**300**	**300**

MCC: Micro crystalline cellulose; EC: Ethyl cellulose; PVP: Poly vinyl pyrrolidine; HPMC: Hydroxy Propyl methyl cellulose.

2.3.3) Formulation of Optimised Bilayer Tablets of Clarithromycin and Lafutidine.

Procedure: The Gastroretentive Bilayered Floating Tablets were prepared by the direct compression method and by wet granulation method. The immediate release layer granules were prepared by direct compression technique and the controlled release layer is prepared by wet granulation technique. The controlled release layer mixture was compressed in 8mm flat faced punches on a Rimek tablet press. Before final compression immediate release layer poured on sustained release layered.

Table-3: Formulation table of optimised gastroretentive bilayer floating tablets of clarithromycin and lafutidine.

S.NO.	INGREDIENTS	IR FORMULATION BATCH (IF6)	SR FORMULATION BATCH (SF6)	OPTIMISED BLFT
1.	Clarithromycin (Mg)	250	--	250
2.	Lafutidine (Mg)	--	10	10
3.	Crospovidone (%)	12.5	--	12.5

4.	PVP K30 (%)	5	10	15
5.	Microcrystalline Cellulose (%)	Q.S.	Q.S.	Q.S.
6.	Magnesium Stearate (%)	2.5	2	4.5
7.	Talc (%)	4	--	4
8.	HPMCK15M (%)	--	10	10
9.	Guar Gum (%)	--	30	30
10.	Sodium Bicarbonate (%)	--	15	15
11.	Citric Acid (%)	--	2	2
12.	Iron Oxide	--	Q.S.	
13.	Total Weight (Mg)	400	300	700

2.4) Evaluation of Gastroretentive Bilayer Floating Tablets of Clarithromycin and Lafutidine

a) **Thickness:** The thickness of the tablets was measured by Vernier calipers. It is expressed in **mm**.

b) **Hardness Test:** Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm2.

c) **Friability Test**: The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W) and transferred in to the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W) final. The % friability was then calculated.

d) **Weight Variation Test**: Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of tablet by U.S. Pharmacopoeia.

e) **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 called the total floating time (TFT).The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al.* The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

f) **Drug content uniformity:**

For sustained release lafutidine tablets:

Tablet containing drug is dissolved in 100 ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1 ml of filtrate was taken in 50 ml of volumetric flask and diluted up to mark with 0.1N HCl and analyzed spectrophotometrically at 282nm for sustained release layer of Lafutidine.

For ir layer clarithromycin tablets

Ten tablets were weighed and powdered and 250mg equivalent weight of Clarithromycin was accuarately weighed and transfered in 100ml volumetric flask. It was dissolved and made up the volume with 0.1N HCl pH- 1.2. Subsequently the solution was filtered and suitable dilution were made and analyzed at 275nm using UV-Visible spectroscopy.

g) Disintegration test: By using disintegration apparatus, tablets were tested for disintegration time at 37± 0.5^0C taking distilled water as medium.

h) **Swelling characteristics:**

The swelling properties of tablets were determined by placing the tablet in dissolution test apparatus in 900 ml of 0.1N HCl at 37 ± 0.5. The tablets were removed periodically from the dissolution medium. After draining the tablets were measured for weight gain. Swelling characteristics were expressed in terms of % water uptake (WU %).

$$WU\% = \frac{\text{Weight of swollen tablets} - \text{Initial Weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

2.5) In Vitro Dissolution Study:

For immediate release layer (clarithromycin):

Dissolution Parameters: Apparatus: Dissolution Apparatus USP Type – II (Paddle), Speed: 50 RPM, Medium: 900 ml of 0.1N HCl, Temperature: 37°C ± 0.5°C, Time: 45 Minutes

Preparation of sample solution: Apparatus was set as per above conditions, one tablet was placed in each of the six dissolution vessel and the dissolution test was started. After regular intervals of time the samples were collected i.e. 5, 15, 30, 45 mins and were analysed using HPLC at 210nm.

Chromatographic conditions: Apparatus: HPLC, Column: Stainless steel column (250×4.6mm) packed with Octa decyl silane (C18) bonded to porous silica, Flow rate: 1.0 ml/min, Column oven temperature: 50 ^{0}C, Injection volume: 50µL, Wave length: 210 nm

Procedure: 50 microlitres of filtered portion of the standard solution and sample solution were separately injected into the HPLC system. The chromatogram was recorded and the responses were measured for the major peaks. The amount of drug released was calculated in percentage with respect to label claim by using the following expression.

Dissolution studies of sustained release layer (lafutidine): In-vitro release studies were carried out USP II paddle type dissolution test apparatus. 900 ml of 0.1 N HCl (PH 1.2) was filled in dissolution vessel and the temperature of the medium were set at 37° C ± 0.1°C.The speed was set at 50 rpm. 5 ml of sample was withdrawn at predetermined time intervals for 8 hrs and same volume of fresh medium was replaced. The samples were analyzed for % drug released at λmax 282nm using HPLC.

Dissolution studies of bilayered tablets were carried out in HPLC (agilent) at 230nm which is the isobestic point of two drugs. Samples were mixed and injected into the column and these are being compared with the standard.

Dissolution Parameters: Apparatus: Dissolution Apparatus USP Type – II (Paddle), Speed: 50 RPM, Medium: 900 ml of 0.1N HCl, Temperature: 37°C ± 0.5°C, Time: 45 Minutes

Chromatographic conditions: Apparatus: HPLC, Column: Stainless steel column (250×4.6mm) packed with Octa decyl silane (C18) bonded to porous silica, Flow rate: 1.0 ml/min, Column oven temperature: 50 ^{0}C, Injection volume: 50µL, Wave length: 230 nm.

Procedure: 50 microlitres of filtered portion of the standard solution and sample solution (mixture of clarithromycin and lafutidine) were separately injected into the HPLC system. The chromatogram was recorded and the responses were measured for the major peaks. The amount of drug released was calculated in percentage with respect to label claim by using the following expression.

Formula for calculating % drug release by HPLC method:

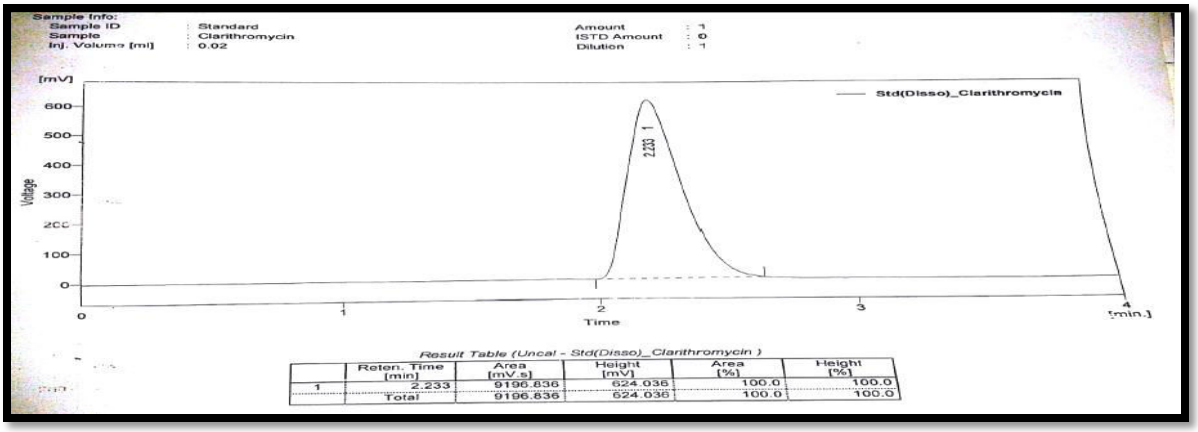
Percentge drug released can be calculated by the following expression given below:

% Drug released = Sample area/Standard area × Std. weight/Std.dilution×900/Wt. of tablet× Avg. weight of tablet/Label claim × Standard purity.

3) Results and Discussion

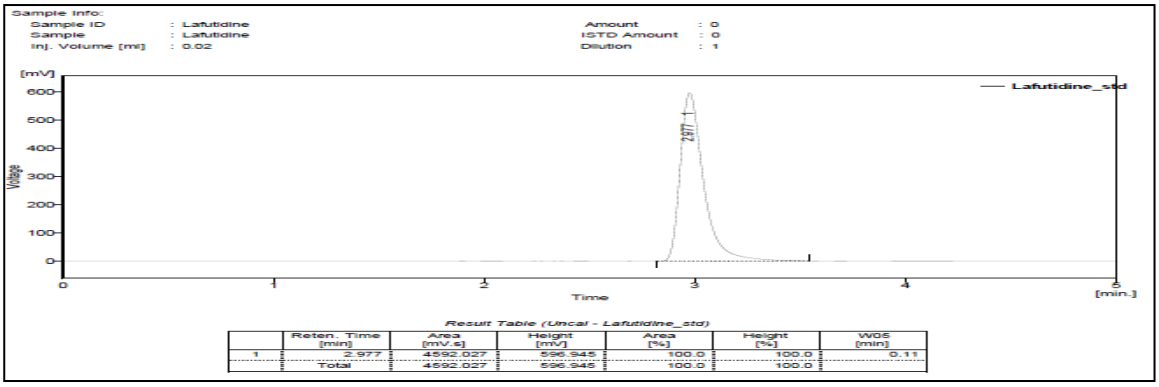
3.1 Preformulation characteristics:

Figure 1: standard graph of clarithromycin.



INFERENCE: Standard area = 9196.836

Figure 2: standard graph of Lafutidine.



INFERENCE: standard area = 4592.027

3.2 Drug: Excipient Compatibility studies- FTIR:

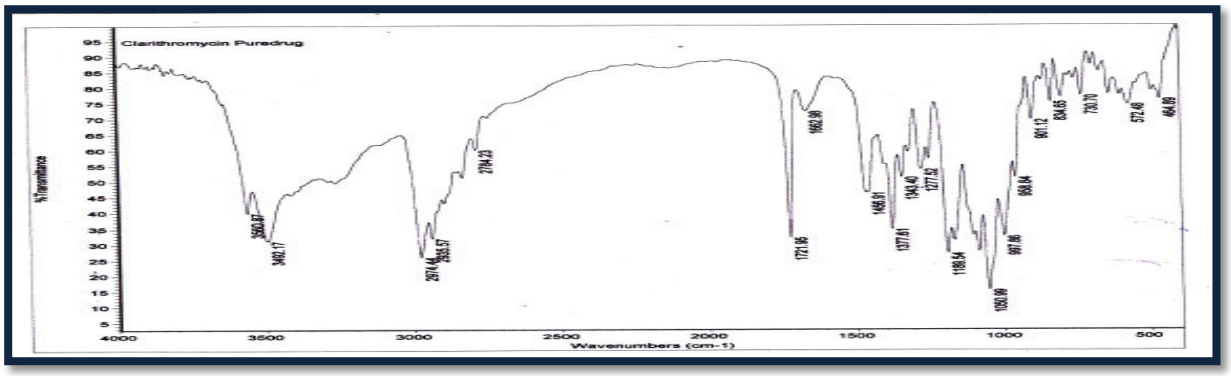


Figure 3: FTIR Spectrum of Clarithromycin Pure Drug.

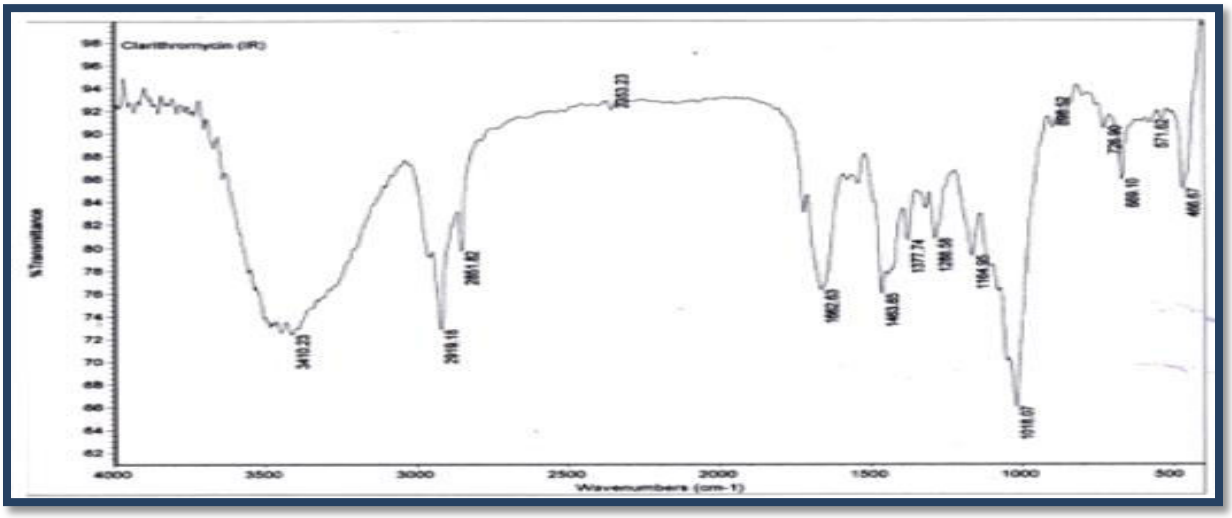


Figure 4: FTIR Spectrum of Immediate Release Clarithromycin Layer.

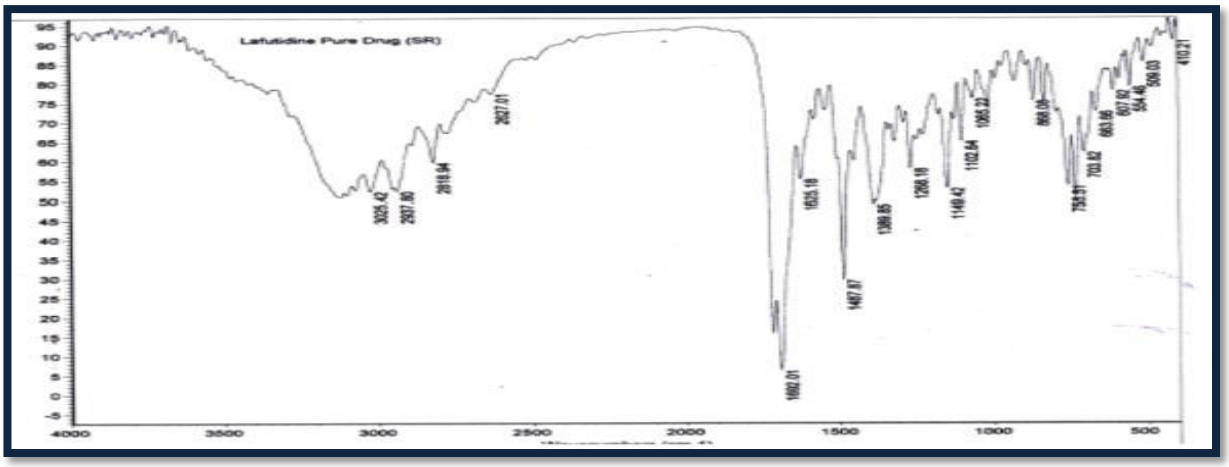


Figure 5: FTIR Spectrum of Lafutidine Pure Drug.

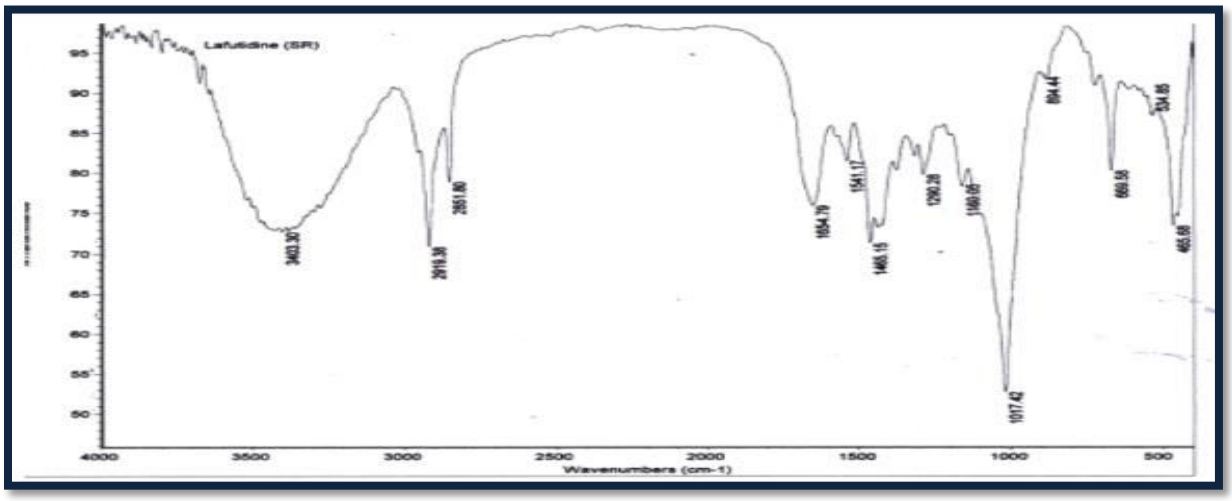


Figure 6: FTIR Spectrum of Lafutidine SR Formula.

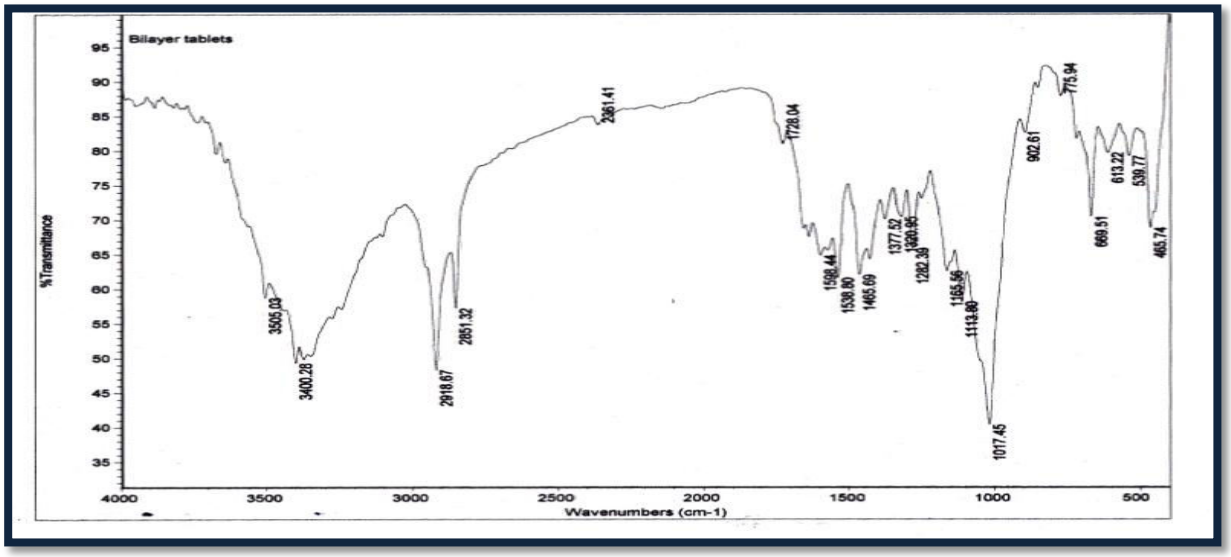


Figure 7: FTIR Spectrum for Bilayer Floating Tablets of Clarithromycin and Lafutidine.

Inference: There is no significant change in the shift of major peaks of drug in the above graphs, hence there were no drug and excipient interactions found in either IR, SR, OR Bilayer tablets.

Table-5: Precompression parameters of immediate release layer of clarithromycin:

Formulation Code	Angle of repose(Θ)	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Hausener's ratio	Flow
F1	25.6	0.475	0.546	15.3621	1.149325	Good
F2	26.6	0.782	0.881	11.23723	1.126598	Good
F3	21.0	0.689	0.777	11.32561	1.127721	Good
F4	25.9	0.741	0.855	13.33333	1.153846	Good
F5	27.8	0.792	0.888	10.81081	1.121212	Good
F6	26.6	0.38	0.45	15.55556	1.184211	**Good**

Discussion: All the formulation blends of IR layer were subjected to preformulation studies and the flow was found to be good. The optimised batch F6 has good flow properties.

Table 6: Precompression parameters for the sustained release layer of lafutidine:

Formulation Code	Angle of repose(Θ)	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Hausener's ratio	Flow
F1	21.0	0.323	0.403	19.85112	1.247678	Fair
F2	25.6	0.321	0.398	19.34673	1.239875	Fair

F3	25.9	0.41	0.483	15.113	1.178	Good
F4	27.8	0.45	0.52	15.60	1.15	Good
F5	25.6	0.229	0.285	19.64912	1.1244541	Good
F6	25.2	0.255	0.302	15.56291	1.184314	**Good**

Discussion: All the formulation blends of SR layer were subjected to preformulation studies and the flow was found to be fair to good. The optimised batch F6 has good flow properties

Table -7: Postcompression evaluation tests of immediate release layer of clarithromycin.

Formulation Code	**Weight Variation (mg)**	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Friability (%)**	**Disintegr-ation time in sec**	**Drug Content (%)**
F1	397 ± 3.13	5.1 ± 0.010	3.83 ± 0.055	0.15	20	98.6
F2	398 ± 3.33	5.04 ± 0.035	3.93 ± 0.042	0.16	25	99.25
F3	396.4± 2.31	5.05 ± 0.016	3.94 ± 0.055	0.20	15	99.52
F4	399± 2.64	5.13 ± 0.032	3.83 ± 0.047	0.30	38	98.94
F5	401± 2.34	5.34 ± 0.014	3.73 ± 0.058	0.12	10	99.53
F6	**404 ± 1.11**	**6.05 ± 0.019**	**3.64 ± 0.038**	**0.03**	**7**	**99.87**

Discussion: All the formulations of IR layer tablets were evaluated for various physicochemical parameters and they were found to within limits. The optimised formula is F6.

Table-8: Post compression evaluation tests of sustained release layer of lafutidine.

Formulation Code	**Weight Variation (mg)**	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Friability (%)**	**%Drug Content**
F1	302± 2.34	4.73 ± 0.030	3.53 ± 0.035	0.14	97.6
F2	296 ± 2.33	4.64 ± 0.025	3.63 ± 0.032	0.16	99.25
F3	299.4 ± 2.31	5.35 ± 0.029	3.44 ± 0.025	0.16	99.52
F4	301± 1.14	4.73 ± 0.017	3.53 ± 0.017	0.19	98.94
F5	305 ± 2.13	4.74 ± 0.018	3.43 ± 0.028	0.20	99.53

F6	**298 ± 1.11**	**4.85 ± 0.030**	**3.54 ± 0.018**	**0.24**	**99.87**

Discussion: All the formulations of SR layer tablets were evaluated for various physicochemical parameters and they were found to within limits. The optimised formula is F6.

Table-9: Swelling Index

Time(hrs)	F1	F2	F3	F4	F5	F6
1	12	9	16	9	18	**14**
2	22	18	32	19	39	**29**
4	38	30	42	25	44	**38**
6	56	46	50	36	65	**49**
8	60	55	55	48	75	**62**
10	64	62	62	56	78	**66**
12	68	66	74	63	88	**76**

Table-10: In-vitro floating studies of lafutidine.

Formulation Codes	Formulation Lag Time (Sec/Min)	Floating Time (hrs)
F1	1min 24 seconds	12hrs
F2	2min 20seconds	12hrs
F3	1 minute12 seconds	24hrs
F4	1minutes 40 seconds	24hrs
F5	1 minute 02 seconds	24hrs
F6	**2 minute 20 seconds**	**24hrs**

Discussion: In vitro Floating studies of Lafutidine SR tablets were performed and the optimised formula F6 has a floating lag time of 2 mins 20 secs and floating time was 24 hrs.

Table-11: Comparative in vitro dissolution study of IR layer clarithromycin tablets.

S.No.	Time (Mins)	%Drug Release					
		F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	5	10.05	12.06	28.06	35.3	19.6	28.5
3.	15	20.06	25.14	54.3	46.2	35.5	54.5

4.	30	28.6	38.08	60.02	65.3	53.6	80.3
5.	45	33.26	43.36	63.15	70.2	61.4	86.8

Discussion: Among all the formulations, F6 containing 12.5 % of Cros Povidone showed highest % of drug release i.e. 86.6% in 45 mins highest among all formulation. Hence F6 was optimised.

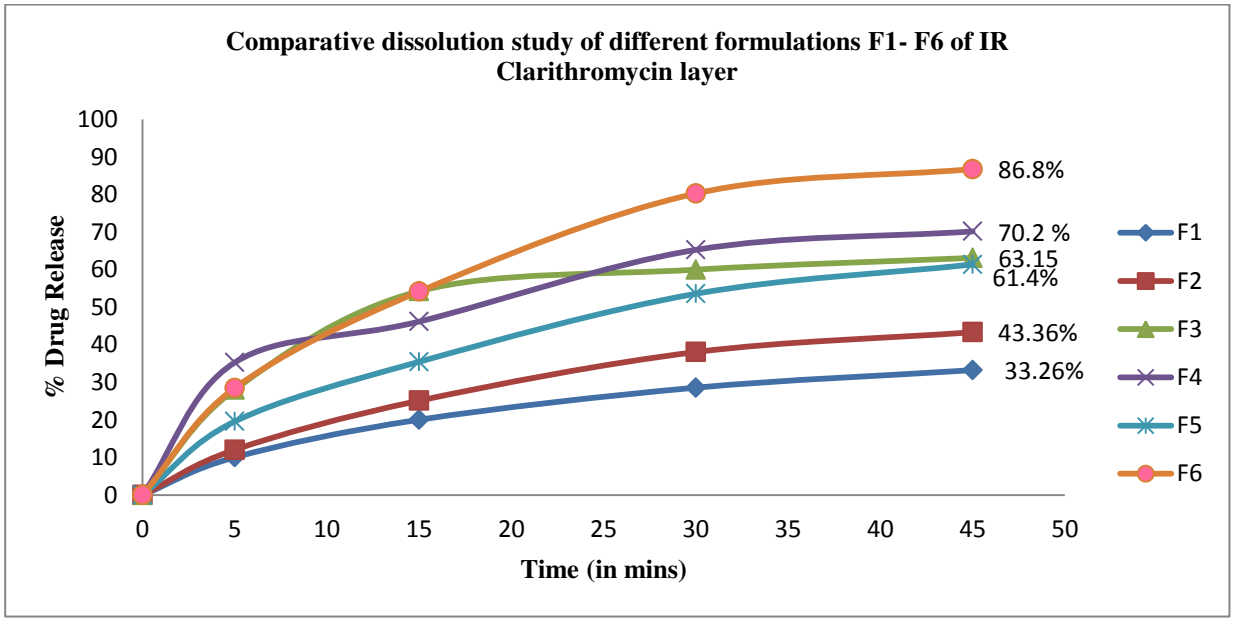


Figure 8: Comparative In vitro dissolution study of IR layer Clarithromycin.

Table-12: Comparative Invitro dissolution studies of lafutidine SR layer tablets.

S.no.	Time (mins)	% drug release					
		F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	60	50.30	70.04	46.85	25.13	21.14	24.98
3.	120	56.25	75.96	58.44	33.01	31.05	28.98
4.	300	76.1	77.28	65.70	46.37	44.64	40.53
5.	480	85.55	90.93	78.23	50.27	48.91	43.53

Discussion: Among all the formulations studied F6 containing combination of natural and synthetic polymer i.e, 30% Guar Gum and 10%HPMCK15M showed excellent release retardant property with 43.53% of drug release in 8 hrs. Hence F6 was optimised.

Figure 9: Comparative In vitro dissolution studies of Lafutidine SR layer tablets.

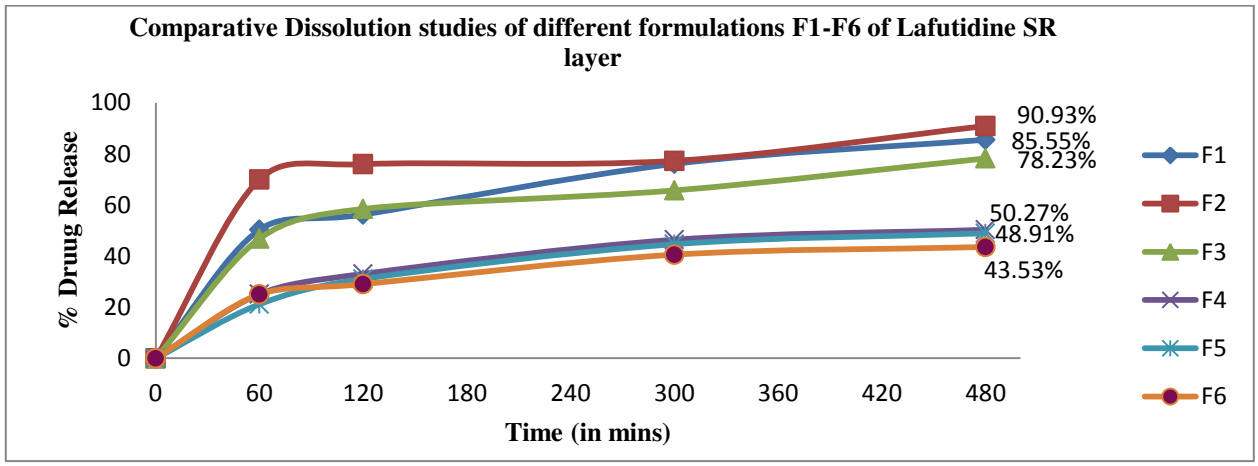


TABLE- 13: Post compression parameters for optimised bilayer floating tablet

S. NO.	Evaluation parameters	Bilayer tablet values
1.	Hardness (Kg/Cm^2)	5.6 ±0.45
2.	Thickness (mm)	4.96±0.02
3.	Friability (%)	0.19±0.02
4.	Disintegration Time for IR layer (Secs)	56±2
5.	Content Uniformity (%)	99.8±0.2
6.	Floating Lag Time (Mins/Secs)	2 Mins 56 Secs
7.	Floating Time (Hrs)	24Hrs

Discussion: The optimised Bilayer floating tablets were evaluated for various post compression parameters Hardness, Thickness, Friability, drug content, disintegration time, lag time and floating time. All the parameters were found to be well within limits of IP norms.

Table 14: % Swelling Index of Bilayer Tablet.

S.no	Time (hr)	% Swelling Index
1	1	11
2	2	14
3	4	29
4	6	38
5	8	49
6	10	62
7	12	74

% Swelling index of optimized bilayer tablet.

Discussion: % Swelling index of optimized bilayer tablet after 12 hr was found to be 74%.

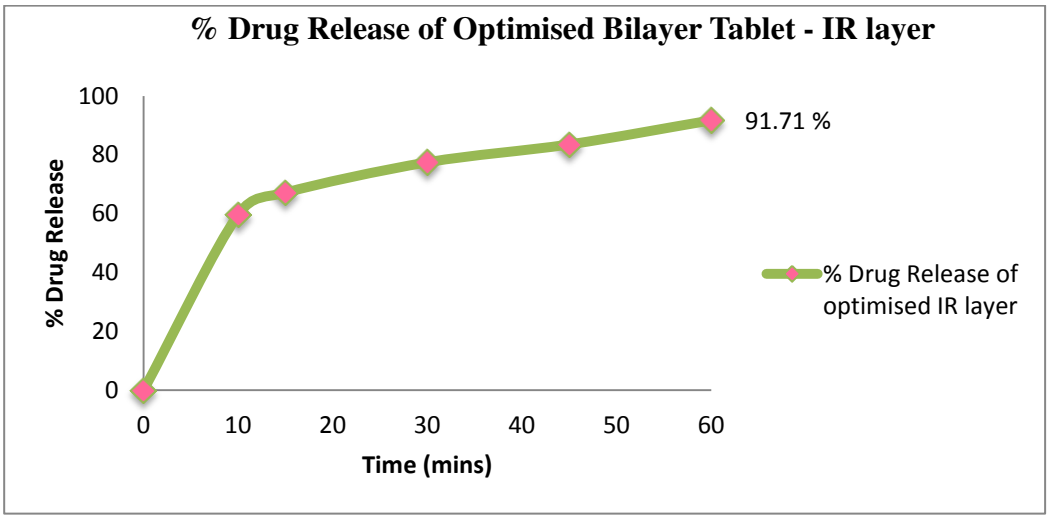


Figure-10: Dissolution Graph of Optimised Bilayer Tablet - Clarithromycin IR Layer.

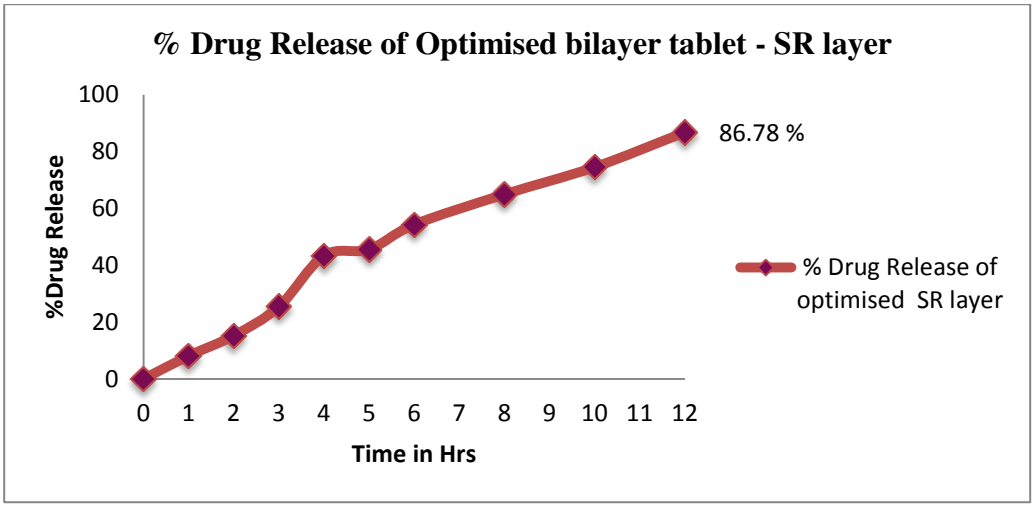


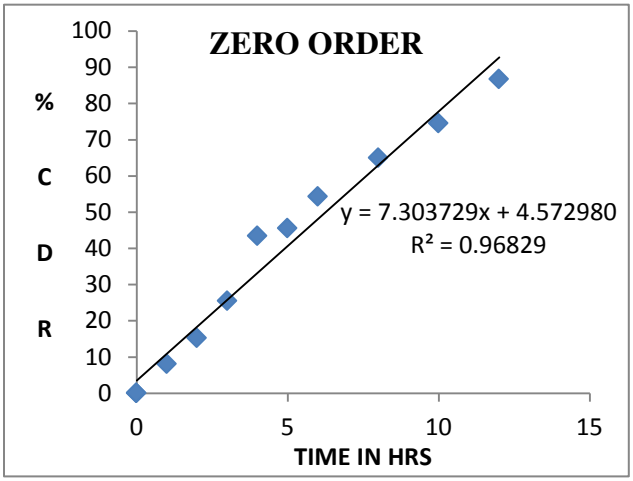
Figure 11: Dissolution Graph Of Optimised Bilayer Tablet - Lafutidine SR Layer.

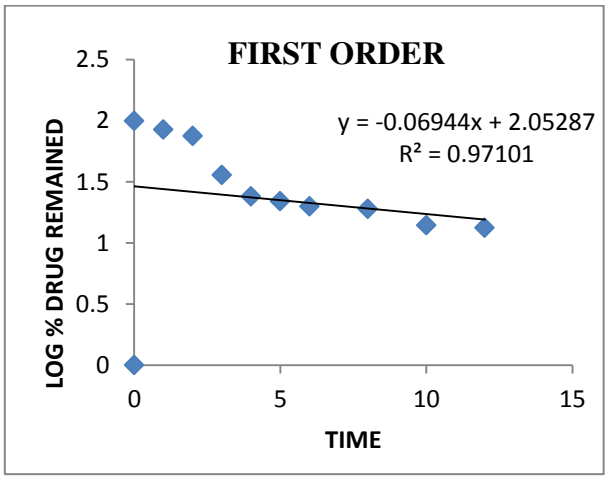
Discussion: The dissolution profile of optimised bilayered tablet of Clarithromycin and Lafutidine showed a % drug release of Clarithromycin 91.71% in 60 mins and 86.78% of drug release in 12hrs.

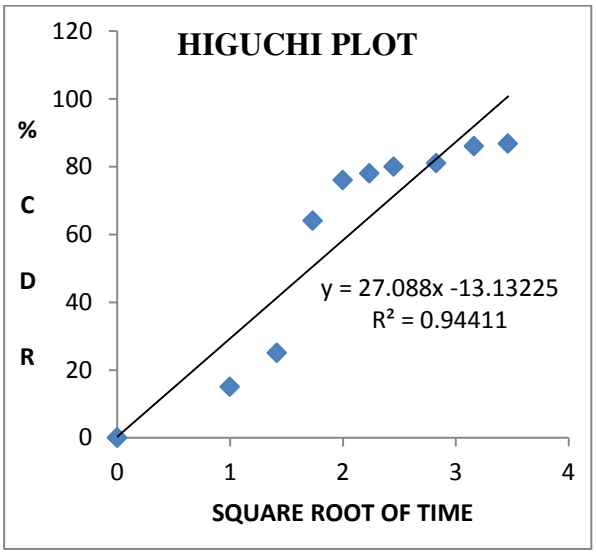
3.4 Release Kinetics of optimized Bilayer formulation:

Discussion: The optimised formula followed first order and Non fickian release.

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.303729302	-0.069446614	27.08890326	1.38232066
Intercept	4.572980562	2.052870394	-13.13225166	0.607900757
Correlation	0.984017979	-0.985401832	0.971655895	0.901130685
R 2	0.968291384	0.97101677	0.944115178	0.812036512







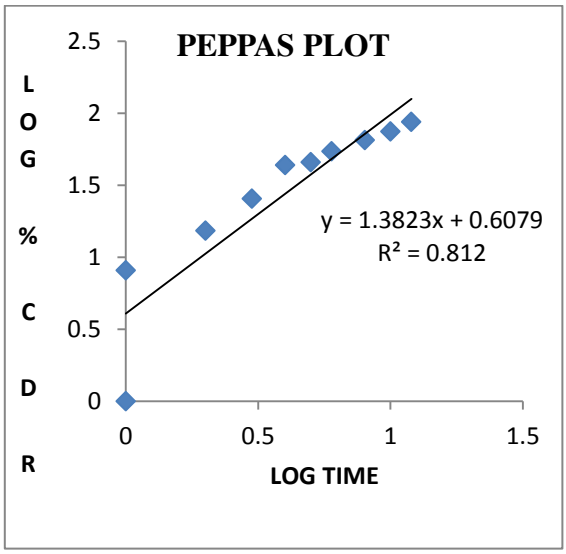


Figure 12: Graphs indicating drug release kinetics.

Conclusion:

The optimised Bilayer tablet of Clarithromycin and Lafutidine was formulated and evaluated for various evaluation parameters i.e. Hardness – 5.6 kg/cm^2, Friability 0.19%, Floating lag time 2mins 56 sec and floating time of 24hrs. All the results of evaluations was found to be within limits and the final Optimised bilayer formulation released 91.71% of Clarithromycin in 60 mins and 86.78% of Lafutidine in 12hrs. The optimised formulation was fitted in kinetic models and it followed first order and the release mechanism was Case II Non- fickian refers to a combination of both diffusion and erosion controlled-drug release. Thus the optimised Bilayer floating tablets of Clarithromycin and Lafutidine appears suitable for further pharmacodynamic and pharmacokinetic studies to evaluate the clinical safety of these Bilayered Floating tablets in suitable animals and human models.

Finally, it may be concluded that this novel drug delivery system that is Bilayered Floating Tablet offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The BLFT'S of Clarithromycin Lafutidine provides a better option for increasing the Bioavailability and Reliability for treating peptic and duodenal ulcers by following a better control of fluctuations observed with the conventional dosage form.

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