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Gaurav Kumar
NRI Institute of Pharmacy, Bhopal, Madhya Pradesh, India

Vivek Jain
NRI Institute of Pharmacy, Bhopal, Madhya Pradesh, India

Shradha Shende
NRI Institute of Pharmacy, Bhopal, Madhya Pradesh, India

Prabhat Jain
Scan Research Laboratories, Bhopal, Madhya Pradesh, India

Correspondence
Gaurav Kumar
NRI Institute of Pharmacy, Bhopal, Madhya Pradesh, India

Formulation and evaluation of bilayer tablets of clarithromycin and omeprazole against *Helicobacter pylori* infection

Gaurav Kumar, Vivek Jain, Shradha Shende and Prabhat Jain

Abstract
In the current study a successful attempt was made to formulate bilayer floating tablets of clarithromycin and omeprazole by direct compression method containing loading dose, superdisintegrants in immediate release layer and maintenance dose, rate controlling polymers and gas generating agents in floating layer. The extended release was prepared by direct compression method using HPMC K15, HPMC K4, PVP K30, as sustained release polymer and sodium bicarbonate as gas generating agent to reduce floating lag time. Immediate release layer were prepared by direct compression using sodium starch glycolate, Croscarmellose sodium, crospovidone as super disintegrant. Gastro retentive floating drug delivery systems have been designed to increase its residence time in the stomach. The granules were evaluated for bulk density, tapped density, compressibility index, and hausner's ratio. The granules showed satisfactory flow properties. The optimized tablets were compressed to obtain bilayer tablets. The tablets were evaluated for various physicochemical parameters and dissolution study. Further, the bilayer tablets were subjected to accelerated stability study. The omeprazole tablet showing more than 99.45 % release in 15 min and clarithromycin tablet showing more than 99.76 % release at the end of 12 h of initial lag time were compressed one above the other to obtain bilayer tablet. The similar release pattern was observed with the bilayer tablets as that of individual tablets. The bilayer tablets were found to be stable at the end of 6 months storage period as per ICH guidelines. Both the layers of the bilayer formulation showed desired drug release at the end of time period.

Keywords: Bilayer tablet, clarithromycin, omeprazole, HPMC, physicochemical parameters

Introduction
The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration [1]. Fixed dose combination therapy has various advantages over conventional monotherapy such as simpler dosage schedule leading to improved patient compliance and therefore improved treatment outcomes, reduced side effects and potentially lower cost of manufacturing, handling, packing and shipping compared to the costs of producing separate products [2]. The conventional dosage form produces wide fluctuation in drug concentration in the blood stream which led to the concept of sustained drug delivery. Gastro-retentive drug delivery is a novel approach of drug delivery which prolong the gastric emptying time. Many techniques such as floating drug delivery, low density, raft systems, mucoadhesive systems and high density systems are under research. Floating drug delivery remains buoyant in the gastric content for a prolonged period of time. This improves bioavailability of drugs with narrow absorption window and poor solubility or stability in alkaline pH [3, 4]. A bilayered tablet is made up of two separate layers, with each layer intended for a specific result, layers can be formulated to separate physically or chemically incompatible ingredients or to produce repeat action or to dissolve at different times or to deliver the product to different locations or to give different pharmacological effects [5, 6]. Helicobacter pylori (H. pylori) are a gram-negative bacillus responsible for one of the most common infections found in humans worldwide [7]. H. pylori cause's gastric diseases, such as peptic ulcer, gastric mucosa associated lymphoma. One reason for the incomplete eradication of H. pylori is probably due to the short residence time of antimicrobial agents in the stomach so that effective antimicrobial concentration cannot be achieved in the gastric mucous layer or epithelial cell surfaces where H. pylori exists [8]. The main objective of this work is to formulate and evaluate the floating bilayer tablets containing clarithromycin and omeprazole as an anti- H. pylori agents that will remain in vicinity of absorption site for prolonged period of time.

Material and Methods

Materials

Hydroxypropyl methyl cellulose (HPMC K15, HPMC K4), Polyplasdone XL (Crospovidone) and Glycolys (sodium starch glycolate) were generously gifted by Colorcon Asia Pvt. Ltd. (Goa, India), International Specialty Product Ltd. (Mumbai, India) and Roquette India Pvt. Ltd. (Mumbai, India) respectively. Ac-Di-Sol (Croscarmellose sodium) and (Microcrystalline cellulose) were supplied by Signet Chemical Corporation Pvt. Ltd. (Mumbai, India). Talc, lactose, citric acid, $NaHCO_3$, was purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). All other chemicals and reagents were of analytical grade.

Methods

Preformulation studies

Organoleptic properties

Clarithromycin and omeprazole were tested for organoleptic properties such as appearance, colour, odour, taste etc.

Melting point determination

A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus (Chemline) containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

Solubility

Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1N HCL, 0.1N NaOH and chloroform) shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

FTIR Spectroscopy

To check the drug-drug and drug-excipient interactions, preformulation studies were performed. Drugs alone, in combination and along with excipients proposed to be used were filled in amber colored vials sealed with bromo butyl rubber stoppers and kept in environmental stability chamber (Remi Lab, Mumbai, India) for accelerated stability condition at 40 ± 2ºC temperature and 75 ± 5 % relative humidity for a period of 30 days. Infra-red spectra of samples were obtained with FT-IR spectrophotometer (Brukers Alpha) with IR solution software and compared with the initial spectra of drugs.

UV Spectroscopy

Accurately weighed 10 mg of drugs was dissolved in 10 ml of 0.1 N HCL solutions in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 0.1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 0.1 N HCL solution to make it to a concentration of 10µg/ml for clarithromycin (react with methyl orange and extract with chloroform) and omeprazole. The spectrum of this solution was run in 200-800 nm range in U.V. spectrophotometer (Labindia-3000+).

Preparation of instant layer of omeprazole

Fast dissolving tablets of omeprazole were prepared by direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included angle of repose, bulk density, tap density, Carr's index and hausner's ratio. The blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Nine formulations of omeprazole granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablet weighing 100 mg was obtained. Composition of tablets is mentioned in Table 1.

Method for preparation of clarithromycin floating tablet

Direct compression was followed to manufacture the gas generating floating tablets of clarithromycin. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table 2 and all the formulation were used for further evaluations parameters. Excipients like sodium bicarbonate, citric acid, magnesium stearate were selected for the study. Sodium bicarbonate and citric acid were used as gas generating agent. Citric acid was also used as an antioxidant. First the drug; polymer and other excipients selected were passed through 40- mesh sieve. Required quantity of drug, polymer and excipients were weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5min. The blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine.

Formulation development of bilayer tablet

Optimized batch of IF-6 of instant release layer (omeprazole) and F-8 (clarithromycin) was selected for formulation of the bilayer tablet. As a previously reported procedure, both layers were compressed to form bilayer tablet through direct compression by using the 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine.

Table 1: Composition of omeprazole fast dissolving tablets

Ingredients (mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Omeprazole	40	40	40	40	40	40	40	40	40
Sodium Starch glycolate	5	7.5	10	_	_	_	_	_	_
Croscarmellose sodium	_	_	_	5	7.5	10	_	_	_
Crospovidone	_	_	_	_	_	_	5	7.5	10
Microcrystalline cellulose	44	41.5	39	44	41.5	39	44	41.5	39
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	100	100	100	100	100	100	100	100	100

Table 2: Composition of clarithromycin gastro retentive tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clarithromycin	250	250	250	250	250	250	250	250	250
HPMC K 15	_	_	_	160	170	180	80	85	90
HPMC K 4	160	170	180	_	_	_	80	85	90
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	40	30	20	40	30	20	40	30	20
Total Weight	500	500	500	500	500	500	500	500	500

Pre compression parameters

To assess physicochemical properties of the granular blend, all formulations are subjected to pre-formulation studies like bulk density, tapped density, angle of repose, compressibility index, Hausner's ratio and particle size distribution [9].

Angle of Repose

This is the maximum angle possible between the surface of a pile of granules and the horizontal plane.

$$\theta = \tan^{-1} (h / r)$$

Where, θ = angle of repose h = height of the heap r = radius of the heap

Particle size distribution of granules

The particle size distribution was measured using sieve analysis method.

Bulk Density (BD) & Tapped Density (TD) of granules

The bulk density and tapped bulk density were determined and calculated by the following formulas.

BD = weight of the powder / initial volume

TD = weight of the powder / final volume

Compressibility of granules

The compressibility index was determined by Carr's compressibility index and Hausner's ratio.

Carr's index = TD – BD X 100 / BD

Hausner's ratio = TD / BD

Evaluation of Compressed Tablets

The prepared tablets were evaluated for general appearance, weight variation, disintegration test, dissolution test, thickness, hardness, uniformity of drug content, *In vitro* buoyancy studies and friability [10].

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. The friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated. The weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10 mg of omeprazole and clarithromycin was transferred to 100ml standard flask. The powder was dissolved in 25 ml of 0.1 N HCL and made up to volume with 0.1 N HCL. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 1 ml to 10 ml suitably (10 ppm of clarithromycin) and prepares individually 10 ppm solution of omeprazole determine the conc. of both drugs using 306nm and 416 nm for omeprazole and clarithromycin respectively. *In vitro* buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were placed separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time [11].

***In- vitro* Drug Release**

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs periods for clarithromycin SR and 1 hr for omeprazole IR, using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested. The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5◦C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Ultraviolet Labindia 3000+) spectrophotometer at λmax 306 nm for omeprazole and 416 nm for clarithromycin respectively [12].

Stability Studies

The optimized formulation was subjected for two month stability study according to ICH guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at Room Temperature 40ºC / 75% RH for 2 months and evaluated for their permeation study.

Results and Discussion

The melting point of clarithromycin and omeprazole was 220-221ºC and 155-157 ºC respectively and The UV absorption of 10µg/ml for clarithromycin (react with methyl orange and extract with chloroform) and omeprazole in 0.1N HCL in the range of 200-800 nm exhibit maximum at 306 nm in case of omeprazole and at 416 nm in case of clarithromycin using U.V. spectrophotometer (Labindia-3000+) table 3 & fig 1, 2.

Table 3: Stastical data for linearty

S. No.	Parameter	Clarithromycin	Omeprazole
1.	Linearty Range	10-50 µg/ml	5-25 µg/ml
2.	Regression Equation	0.015x+0.024	0.023 x+0.001
3.	Correlation Cofficient	0.990	0.999

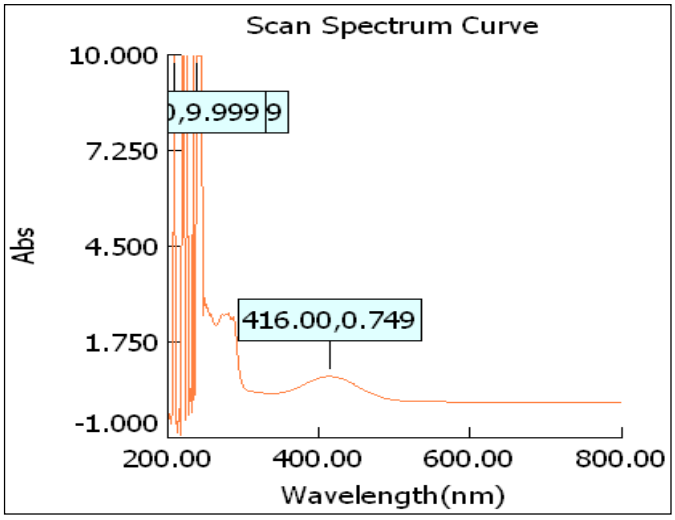


Fig 1: Determination of λ_{max} of clarithromycin

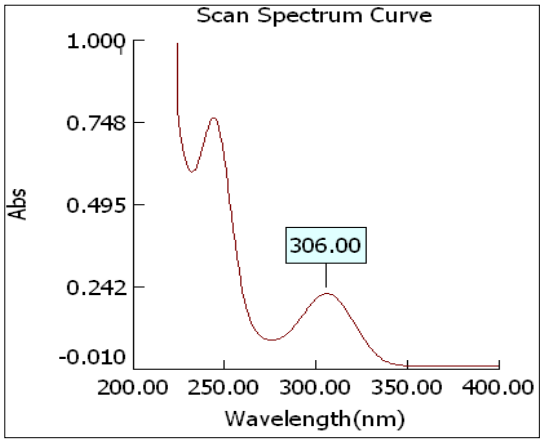
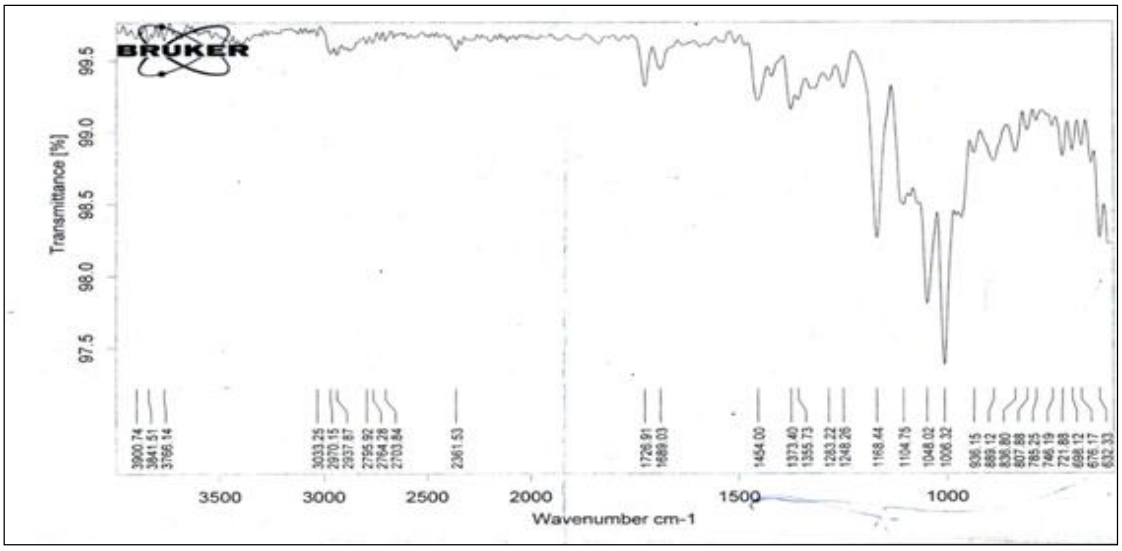
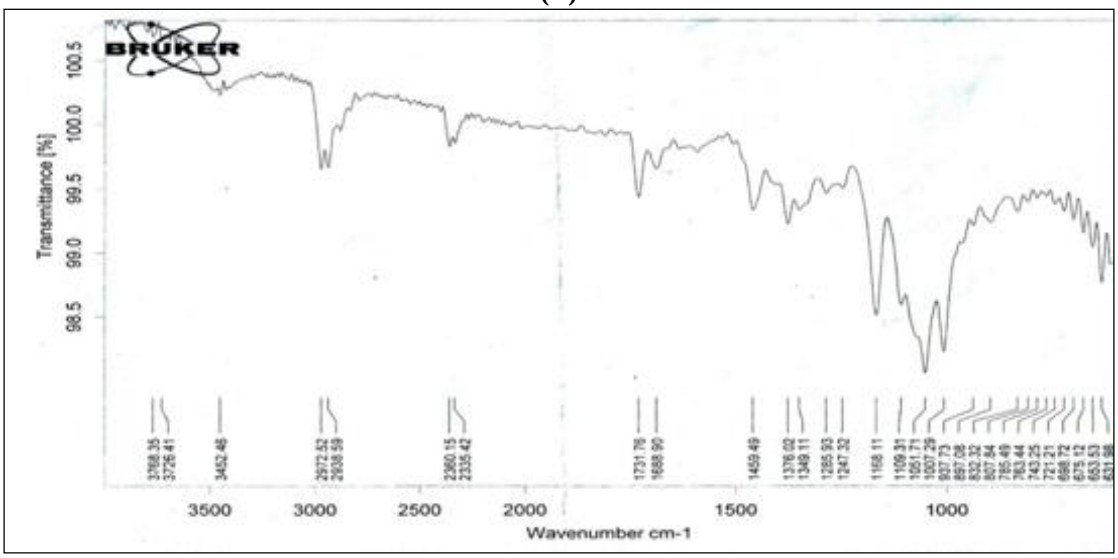


Fig 2: Determination of λ_{max} of omeprazole

The FT-IR spectra of physical mixture of drugs and drugs with excipients after 30 days of accelerated stability were compared. The spectra showed no additional peaks compared to their individual IR spectrum of initial conditions. Also the physical appearance of the samples was not changed. The FT-IR spectra of clarithromycin and omeprazole have shown the presence of peaks which are characteristics of the drugs structures fig 3.



(A)



(B)

Fig 3: FT-IR spectrum of (A) omeprazole (B) clarithromycin

The micro meritic properties such as of bulk density, tapped density, angle of repose, compressibility index, Hausner's ratio and particle size distribution of omeprazole instant release layer blend and clarithromycin gastro retentive layer were studied. The all the blends/ granules have shown good compression properties. The value of bulk density indicates good packing characteristics. Drug content was found to be uniform among different batches and was more than 95%. Other parameters for granules were found to be in the acceptable range. The compressed tablets were evaluated for weight variation, thickness, hardness, friability, disintegration time (for omeprazole IR tablets) and content table 4 and 5. The weight of tablets from all the formulation batches was found within acceptable range of weight variation (±5%) as per USP. The hardness of the tablets was found in the range of 3.10-4.05 kg/cm^2. The disintegration time obtained for optimized omeprazole IR tablets was less than 1 min which was well below the limit of disintegration time of uncoated IR tablets as per the USP (i.e. not more than 15 min). The floating lag time of optimized formula was 95secs compared to the other formulations where the time was extended to a maximum of about 110 secs and the total floating time was more than 12 hrs for all formulations. The results of swelling index are given in Table 5, from the results it can be concluded that swelling increases with time because polymer gradually absorbs water due to its hydrophilicity. The *in vitro* drug releases of gastro retentive floating tablet from different formulations are shown in table 6. Maximum drug release was observed in F8 with 99.76% for 12 hrs and for omeprazole the drug release was 99.45% at 15 min. The in-vitro dissolution characteristics of bilayer tablets are shown table 7 and fig 4. optimized formulation showed better drug release, which was achieved by increasing the polymer concentration by combining two polymers such as HPMC K15, HPMC K4 which release the drug in a controlled rate at regular time intervals in appropriate concentrations as per the limits. The post-compression parameters of optimized formulation was given in table 8 was found in acceptable limits.

Table 4: Results of Post-Compression parameters of omeprazole

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	*In vitro* Disintegration Time (sec.) (n=3) Mean ± SD
IF1	3.13 ± 0.21	0.8217± 0.01	Passes	1.42 ±0.03	99.41±0.42	120±1
IF2	3.10 ± 0.30	0.7262 ±0.05	Passes	1.45 ±0.05	99.77±0.51	100±2
IF3	3.11 ± 0.50	0.5314 ±0.03	Passes	1.41 ±0.03	98.53±0.71	80±1
IF4	3.13 ± 0.29	0.6425 ±0.11	Passes	1.40±0.06	99.41±0.49	100±2
IF5	3.11 ± 0.51	0.6346 ±0.05	Passes	1.44 ±0.03	99.33±0.66	70±2
IF6	3.21 ± 0.40	0.7114 ±0.16	Passes	1.46 ±0.05	98.51±0.75	50±2
IF7	3.26 ± 0.29	0.5612 ±0.07	Passes	1.40 ±0.04	99.57±0.42	110±1
IF8	3.27 ± 0.71	0.8554 ±0.11	Passes	1.43 ±0.05	98.33±0.62	80±2
IF9	3.12± 0.42	0.7377 ±0.15	Passes	1.42 ±0.04	99.65±0.48	75±2

Table 5: Results of post compression properties of clarithromycin

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration (h)
F1	3.53±0.05	4.8	500.19± 2.94	0.58 ± 0.10	98.33± 0.92	8
F2	3.94± 0.10	4.4	500.18 ± 3.77	0.51 ± 0.08	97.20 ± 0.34	10
F3	3.96± 0.05	4.5	500.33 ± 1.50	0.38 ± 0.12	99.60 ± 1.39	>12
F4	3.95± 0.05	4.7	500.30 ± 3.30	0.16 ± 0.04	98.14 ± 1.69	>12
F5	3.93± 0.10	5.2	500.13 ± 2.83	0.31 ± 0.07	97.21 ± 1.07	>12
F6	4.03± 0.06	5.3	500.16 ± 2.33	0.27 ± 0.05	97.50± 1.81	>12
F7	4.05± 0.05	4.8	500.18 ± 3.11	0.29 ± 0.08	98.34 ± 0.37	>12
F8	3.98± 0.05	4.5	500.04 ± 2.56	0.34 ± 0.12	98.31± 0.91	>12
F9	3.69±0.06	4.9	500.02±2.11	0.32±0.09	97.83±0.59	>12

Table 6: *In-vitro* Drug Release Study of GRF Tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	08.23	07.14	07.24	08.23	07.23	07.45	08.32	07.26	07.28
1	12.32	10.23	11.45	10.45	10.45	11.23	12.23	11.87	12.56
1.5	26.23	22.42	24.23	23.76	31.23	38.23	32.13	26.28	18.58
2	42.45	40.32	45.23	44.23	48.23	46.32	47.14	38.21	40.28
3	76.34	66.11	67.21	65.71	50.56	67.02	71.13	68.24	56.98
4	82.23	77.33	75.11	82.34	55.00	88.13	91.23	89.12	73.98
6	82.55	97.13	87.13	83.00	56.00	99.13	92.00	99.25	84.16
8	83.00	97.10	94.23	83.21	57.25	99.99	93.00	99.56	89.26
12	84.21	97.23	99.26	83.50	57.85	97.67	94.56	99.76	94.56

Table 7: Results of Dissolution rate studies of Floating layer

Time (Hour)	% Drug Release of Floating layer
0.5	7.98
1	10.65
1.5	18.51
2	25.25
4	36.23

6	52.25
8	76.26
10	85.25
12	98.23

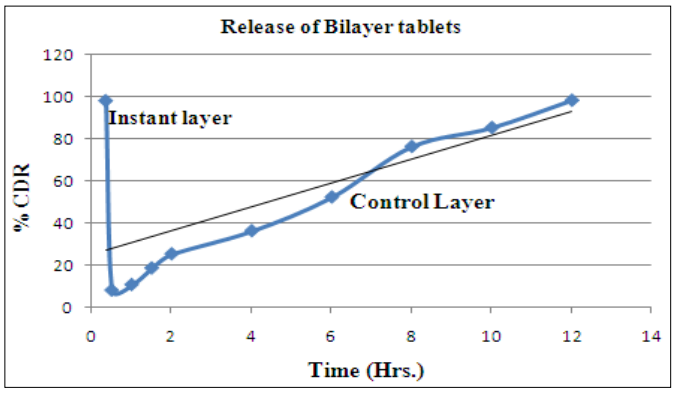


Fig 4: Graph of release of bilayer tablets

Table 8: Post-compressional parameters of optimized formulation

F. code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	5.13 ± 0.21	0.8217± 0.01	Passes	5.42 ±0.03

Conclusion

The optimised Bilayer tablet of clarithromycin and omeprazole was formulated and evaluated for various evaluation parameters i.e. Hardness-5.13 kg/cm^2, Friability 0.82%, Thickness 5.42 mm and floating time of 12hrs. All the results of evaluations was found to be within limits and the final Optimised bilayer formulation released 98.23 % in 12hrs. Thus the optimised Bilayer floating tablets of clarithromycin and omeprazole 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 and omeprazole provides a better option for increasing the Bioavailability and Reliability for treating *H. pylori* by following a better control of fluctuations observed with the conventional dosage form.

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