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Formulation and Evaluation of Bilayer Floating Tablet of Clarithromycin and Rabeprazole Sodium

Sachin Kumar[1], Garima Verma[2*], Charu Saxena[2], Ajay Kumar Shukla[3], Prasanjit Paul[2], Kunal Arora[2]

[1]Research Scholar, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University Meerut, UP, INDIA
[2]Kharvel Subharti Collage of Pharmacy, Swami Vivekanand Subharti University Meerut, UP, INDIA
[3]Institute of Pharmacy, Dr. Rammanohar Lohia Avadh Universiy, Ayodhya, INDIA
Email: garima.srivastava2111@gmail.

In the current work, A bilayer tablet is being developed that has Clarithromycin in the sustained release layer and Rabeprazole Sodium in the quick release layer, Optimized, and evaluated in vitro. SSG(sodium starch glycolate) is being used as a superdisintegrant for the quick release layer, and floating polymers such as HPMC K100M and PVP (polyvinyl pyriiodine) are being used for the sustained release layer. The bilayer tablet demonstrated an initial burst effect, supplying a dose of immediate release layer Rabeprazole Sodium to regulate the degree of acid secretion and a sustained release of Clarithromycin for a duration of twenty-four hours. Because the blends had good flow properties, immediate and sustained release tablets were formulated using the direct compression method. In-vitro floating studies, in-vitro drug release, hardness, friability, uniformity of weight, uniformity of drug content, swelling index, and precompression characteristics were tested for the manufactured bilayer tablet. Rabeprazole Sodium was reported to have released 98.85% of its contents from the immediate release layer in 60 minutes. The sustained release floating layer's Clarithromycin release was measured to be 98.67 % over the course of 12 hours. The action of Clarithromycin is enhanced by Rabeprazole Sodium. To increase patient compliance with the efficient treatment of ulcers, Rabeprazole Sodium and Clarithromycin bilayer tablet were thus utilized.

Keywords: Bilayer tablet, Clarithromycin, Rabeprazole Sodium.

1. Introduction

Oral drug delivery system: The most popular and practical method of drug administration is oral administration. The most popular and practical method of drug administration is oral administration.. The pharmaceutical industry and research have focused a lot of attention on it because of its versatility in dosage form design and lack of issues like sterility and potential injury at the administration site.[1] Oral medication delivery systems make for around half of the available market. Drugs with a short half-life and rapid absorption from the gastrointestinal system are quickly removed from the blood circulation, requiring regular doses. Oral formulations with continuous controlled release have been created in order to address this problem.[2]

Gastro-retentive drug delivery system: Gastro-retentive systems are drug delivery devices intended to stay in the stomach for lengthy periods of time. These systems are intended to provide continuous drug release in the upper gastrointestinal tract and have shown to be advantageous for specific types of medications.[3]The extended presence of drugs in the stomach can also improve their solubility, especially if they are less soluble in the higher pH environment of the intestine. Some drugs, such as metronidazole, ranitidine hydrochloride, and captopril, may deteriorate in the colon. Medications with short half-lives typically exit the systemic circulation quickly.[4] The gastro-retentive drug delivery system offers several benefits, including a more straight forward dosage schedule, enhanced patient compliance, leading to improved treatment results, decreased gastrointestinal side effects, more consistent pharmacological effects, and an improved efficacy/safety ratio.[5]

Floating drug delivery systems: Drugs with limited solubility in the intestines or reduced stability are meant to be delivered to the stomach by floating drug delivery systems, which float above the low-density gastric fluid.[6] The pills are made of sodium bicarbonate and citric acid, hydroxypropyl cellulose, gas-relasing agents that, when in communication with stomach fluid,, release co_2, which makes the tablets float.[7] Floating drug delivery systems should use medications with a shorter half-life, enhanced bioavailability, a dissociation constant larger than 2.5, a partition constant more than 1, and resistance to acidic conditions.[7] These systems enable the prolonged release of drugs in a regulated manner, maintaining the dosage at the absorption site, thus enhancing bioavailability.[7]

Clarithromycin, a macrolide antibacterial, disrupts protein synthesis by attaching to the 50s sub-units of the ribosomal microorganism. Clarithromycin is the preferred medication for the treatment of ulcers and bacterial infections in the gastrointestinal tract. Because of its ability to remain stable in acidic pH levels and be easily absorbed in the stomach, this antibiotic provides a different option for eradicating H. pylori in comparison to other macrolides.9 Utilizing a long-term drug delivery system ensures optimal drug release over an extended period, with minimal fluctuations in plasma drug concentration. Clarithromycin displays a clearance half-life of 3.3 to 4.9 hours, making it suitable for creating a sustained drug delivery system.[10]

PPIs are derivatives of Benzimidazoles: the most commonly prescribed are omeprazole, esomeprazole, and rabeprazole.[11]

The final stage of stomach acid production is permanently inhibited by proton pump

inhibitors of H+-ATPase and K+-ATPase. PPIs are triggered when stomach acid falls below 4.0 pH. They do this by crossing the secretory canaliculus and the parietal basement membrane. Subsequently, The proton pump's cysteine group is bound by the sulfenamide form, thereby permanently inhibiting acid secretion.6 PPIs are thought to be the most efficient medication therapy for gastroesophageal reflux disease (GERD), despite the fact that the condition is frequently treated with a variety of medications, such as H2RA and P-CAB. [12]

2. Material and method

Material

Clarithromycin, Rabeprazole Sodium, HPMC, Sodium Bicarbonate, MCC(Micro crystalline cellulose), PVPK30 (polyvinyl pyrilidone), Magnesium Stearate, Citric Acid , Sodium Starch Glycolate. Talc, Lactose.

Methods

Preformulation studies

Organoleptic properties

The organoleptic qualities of Clarithromycin and Rabeprazole Sodium, including appearance, color, odor, and taste, were examined.[13]

Melting point determination

A fusion tube contained a little amount of powder. The tube was put in the Chem line, a device that measures melting points, along with castor oil. The castor oil's temperature was automatically raised step by step while monitoring the point at which the point at which the powder melted entirely and started to melt.[14]

Solubility

The drug's solubility was evaluated by placing a tiny amount (approximately 1-2 mg) of the drug in a test tube alone, adding five ml of the solvent (H_2O, CH_3CH_2OH, 0.1N HCL, CH_3OH, 0.1N NaOH, and chloroform), shaking violently, and letting it sit for a while. Take note of how soluble the medication is in different solvents (at room temperature).[15]

FTIR Spectroscopy

Preformulation investigations were performed to confirm the interactions between pharmaceuticals and the excipients that make them up. The drugs were added to amber-colored vials, both individually and in combination with the recommended excipients, and closed with rubber stoppers made of bromo butyl. After that, the vials were stored for thirty days under accelerated stability conditions in an environmental stability chamber (Remi Lab, Mumbai, India) with a temperature of 42 degrees Celsius and a relative humidity of 75%. Using IR solution software and an FT-IR spectrophotometer (Brukers Alpha), infrared spectra of the samples were obtained and compared to the original medicine spectra.[16]

U.V. Spectroscopy

Take a volumetric flask of 10-milliliter, 10 mg of precisely weighed medicines and Ten milliliters of 0.1 N HCL solution were used to dissolve the medications. This solution yielded a 1000µg/ml concentration. A 10 ml volumetric flask was filled with 0.1 ml of this solution, which was pipetted out. The concentration was then increased to 10µg/ml for rabeprazole and clarithromycin. This solution's spectrum was measured using a UV spectrophotometer (Labindia-3000+) in the 200–800 nm range.[17,18]

PRECOMPRESSION PARAMETER

Angle of repose

The funnel method was used to measure the powder's angle of repose. The powder blend was carefully weighed and then poured through a funnel. The funnel's height was modified so that, at 2.0 cm above the hard surface, The top of the powder pile was barely touched by the funnel's tip. Through the funnel, the powders were allowed to freely pour onto the surface.[19]

The following equation was used to estimate the powder cone's diameter and determine its angle of repose:

Angle of Repose $\theta = \tan^{-1} H/R$

Where H = Height of the powder cone

R = Radius of the powder cone

Bulk density

The process of measuring the total volume and powder weight after adding the power mix to the measuring cylinder allowed for the determination of bulk density.[20]

formula.7

$$\text{Bulk density (BD)} = \frac{\text{weight of powder(M)}}{\text{volume of bulk(vb)}}$$

Tapped density

The bulk density instrument has been filled with a precisely calculated amount of powder. The cylinder was struck every two seconds, beginning at a height of 2.5 cm, up until the volume plateau. The taped density was calculated using the formula below.[20]

(t).9

:ρt= m

Compressibility index (CI) / Carr's index

It was acquired by tapping and bulk densities. The following formula was used to calculate it: [21]

$$\%\ \text{Carr's index} = \left(\text{Tapped density} - \frac{\text{Bulk density}}{\text{tapped density}}\right) \times 100$$

Where T.D =Tapped density

B.D= Bulk density

Hausner's ratio

The Hausner's ratio quantifies a powder's flowability. The ratio of tapped density to bulk density is used to measure it.[22]

$$Hausner's\ ratio\ =\ (\frac{Tapped\ density}{Bulk\ Density})$$

POST COMPRESSION PARAMETERS

Appearance

The Prepared tablets were identified visually by checking the difference in colour. And found elegant. We examined the shape using a magnifying lens.

Weight variation

A random selection of twenty tablets was made from the formulated tablet. It was calculated to find the average weight and standard deviation. The table shows the most % weight fluctuation that tablets can have in accordance with USP. Consequently, if the tablet weighs between 130 and 324 mg, a maximum variance of ±7.5% is permitted.[23]

Hardness

Using the procedure outlined, the hardness of each clarithromycin and Rabeprazole pill was measured. It was discovered that the produced bilayer tablets containing rabeprazole and clarithromycin varied in hardness between 6 and 8 kg/cm2 across all batches.[24]

Friability

Using the Roche friabilator, the friability test was conducted.. A batch of twenty tablets was weighted, put in a friabilator chamber, and given 100 revolutions to spin. These tablets experience shock when they fall from a six-inch height during each spin. Tablets were weighed again after 100 revolutions, and the weight reduction showed the friability.[25]

Disintegration time

One tablet was placed into a beaker of buffer (0.1N HCl or phosphate buffer solution with a pH of 6.8) in each test tube disintegration apparatus, and the test was conducted at 37°C. The disintegration phase of the medicine is referred to as its disintegration time.[26]

In vitro dissolution studies

With the aid of the USP paddle apparatus, the dissolution test was carried out by maintaining a temperature of 37ºC for 50 rpm (rpm) of rotational speed. After that, 0.5 ml of the sample was extracted at various intervals, and 5 ml of the buffer solution was used in place of the 5 ml solution.[27]

In vitro Buoyancy studies

These tablets contained material that created gas, and when they came into touch with water, the CO2 inside the tablets caused them to float on the surface. Tablet buoyancy/floating was evaluated using paddle method, USP Method-II. The apparatus flask was filled with 0.1 N

HCl (900 mL) and rotated at 50 rpm for 24 hours, maintaining a temperature of 37 ± 0.5 ◦C. The tablets' total floating time and floating lag time were calculated.[28]

Formulation of immediate release layer

The bilayer tablet formulation was produced using the direct compression method.. A variety of super disintegrants, including sodium starch glycolate, were used to create the immediate release layer. The medication and super disintegrants above were run through a 40# sieve before being transferred to a polybag and mixed for three minutes. Next, incorporate more excipients into the mixture mentioned before. Lastly, incorporate (glidant) talc into the mixture.

A second layer was also created by direct compression.. The medication and polymer (HPMC k4M) were combined thoroughly for three minutes after passing through a 40# sieve and being transferred into a polybag. After thoroughly blending the other excipients, magnesium stearate was added to the mixture and stirred for two minutes.

At last, the batch blends that were optimized above were compressed using a rotating tablet compression machine.

Table 1 Compositions of floating bilayer tablet for immediate release

Ingredients	Product code (quantity in mg)					
	IF1	IF2	IF3	IF4	IF5	IF6
Rabeprazole Sodium	40	40	40	40	40	40
MCC	45	42.5	40	37.5	35	32.5
Sodium Starch Glycolate	5	7.5	10	12.5	15	17.5
Mg Sterate	4	4	4	4	4	4
Talcum	6	6	6	6	6	6
Total weight	100	100	100	100	100	100

Table 2 Compositions of floating bilayer tablet for sustain release layer

INGREDIENTS	Formulation code					
	SF1	SF2	SF3	SF4	SF5	SF6
Clarithromycin	250	250	250	250	250	250
PVP-k3	25	25	25	25	25	25
HPMC K100M	40	50	60	70	80	90
$NAHCO_3$	10	10	10	10	10	10
Citric acid	10	10	10	10	10	10
Lactose	60	50	40	30	20	10
Talcum	5	5	5	5	5	5
Total weight	400	400	400	400	400	400

MICROBIOLOGICAL ASSAY

Procedure

For the bacterial experiment, standard medications utilized in the investigation included streptomycin at a dosage of 1 mg/ml. Using a sterile Pasteur pipette, standardized innocula (0.1x 108 cell/ml) were added to the petriplates holding 25 ml of sterile nutritional agar. A steel borer was used to create 8 mm-diameter wells in the center of each plate. 0.2 ml of different test and standard chemical solutions were aseptically dispensed into each of these

wells. The extracts were let to infuse into the medium at room temperature for one hour. For seven days, the plates were cultured for microorganisms at 37°C ±1°C for 18 hours. The mean diameter of The area of inhibition encircling the wells served as the foundation for determining the test compound's antimicrobial capability. The average values were recorded after the experiment was conducted three times. Minimal inhibitory concentrations of several test substances were also examined since notable results in the form of a significant zone of inhibition were observed.[30]

3. Results and Disscusion

UV spectroscopy

Table 3 Absorbance of Clarithromycin in 0.1 N HCL

Concentration	Absorbance
0	0
10	0.072
20	0.141
30	0.162
40	0.218
50	0.272
60	0.310

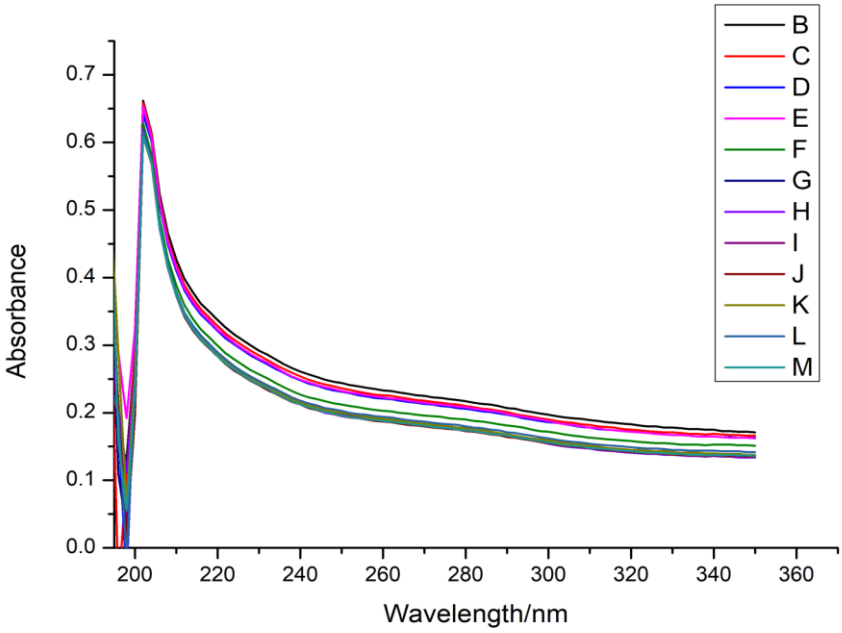

Fig 1 Spectrum of Clarithromycin

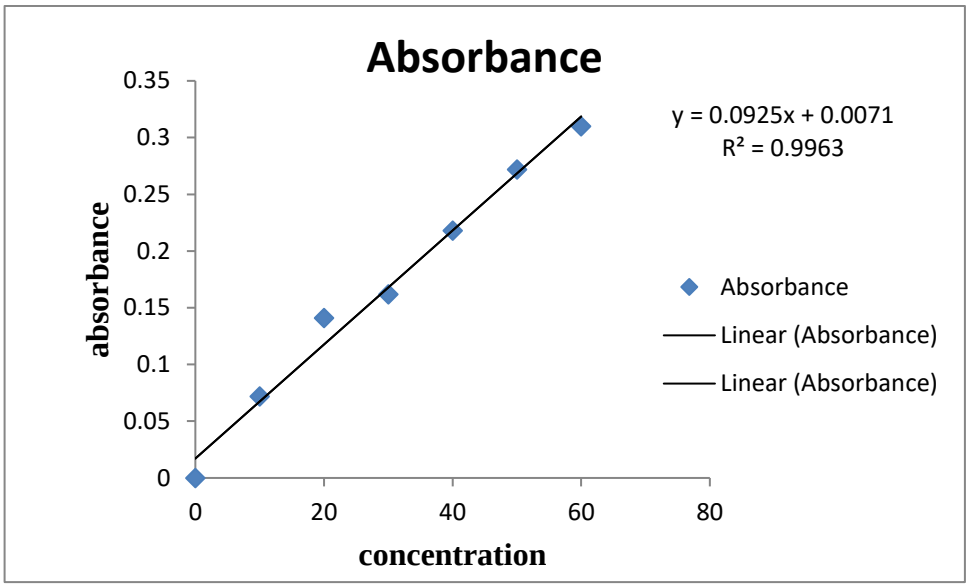

Fig 2 Standard calibration curve of clarithromycin in 0.1N HCL

Clarithromycin solution was scanned from 400nm to 200nm, highest absorption was detected at 211nm as showed in fig 2 was verified using the clarithromycin UV spectrum.

Table 4 Absorbance of Rabeprazole Sodium

Conc	Absorbance
0	0
1	0.092
2	0.16
3	0.214
4	0.412
5	0.482
6	0.544

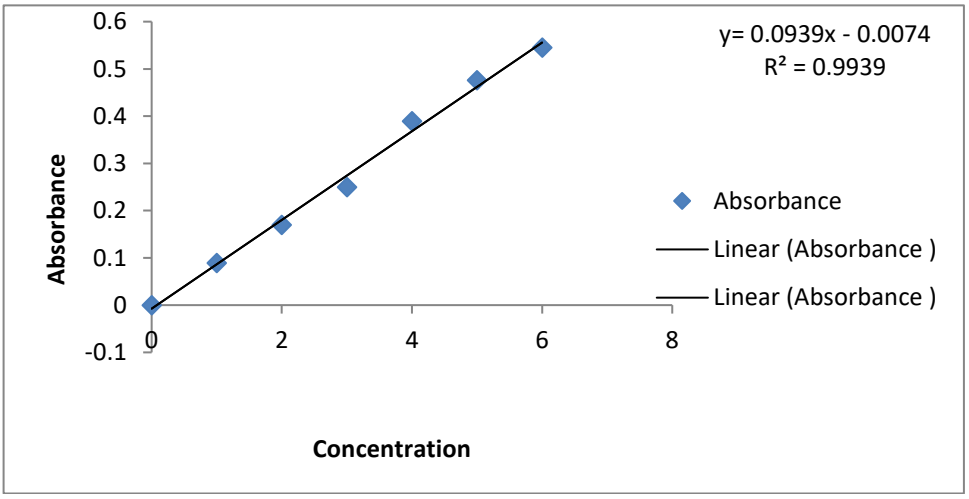

Fig 3. Standard calibration curve of Rabeprazole Sodium in 0.1N HCL

When the Rabeprazole Sodium solution was scanned from 400 nm to 200 nm, the reported rabeprazole sodium UV spectrum was verified. As seen in fig., the maximum absorption was measured at 276 nm.

IR spectroscopy

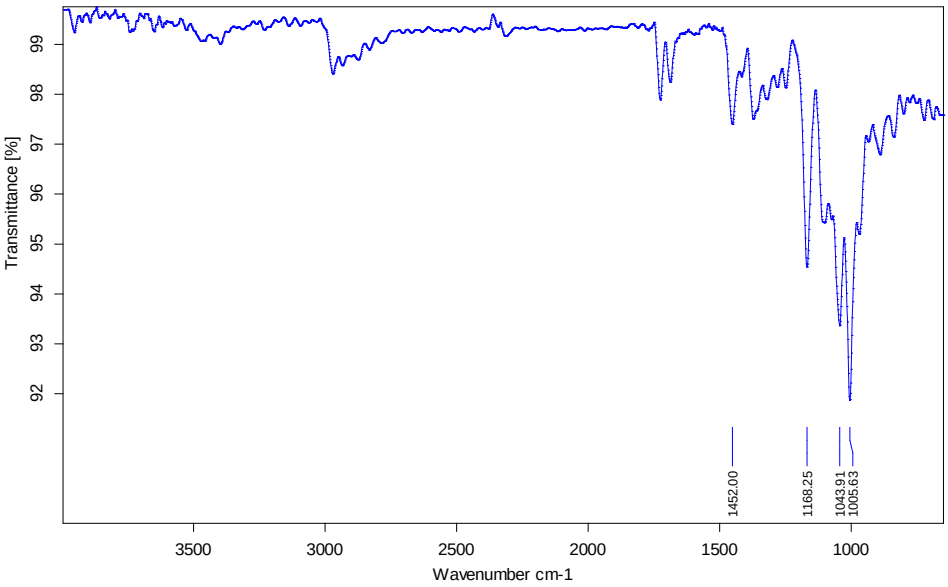

Fig 4 IR spectrum of Clarithromycin

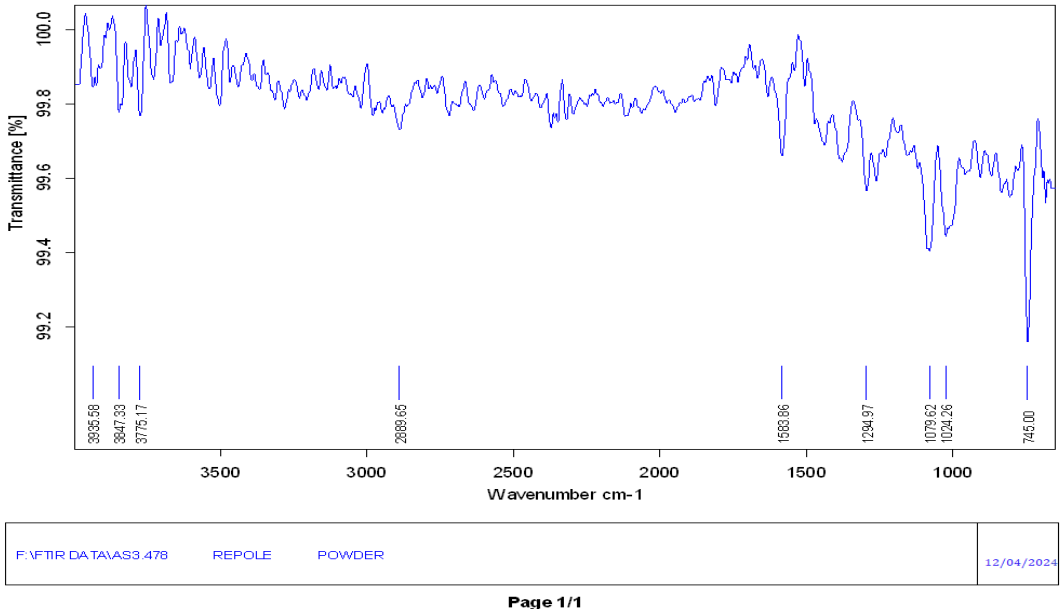

Fig 5 IR Spectrum of Rabeprazole Sodium

Table 5 IR peaks of Rabeprazole sodium and Clarithromycin

Clarithromycin cm^{-1}	Rabeprazole Sodium cm^{-1}
1005.63,1043.91,1168,25,1452	745,1024,1079.62.1294.97.1583.86,2869.65,3775.17.3847.33,3935,58

In the solid state, Potassium Bromide dispersion was used to measure the infrared spectrum. Figures representing the IR spectra of Clarithromycin and Rabeprazole Sodium are respectively. Table displays the detected peaks for both Rabeprazole and Clarithromycin, which are comparable to the peaks reported for Clarithromycin and Rabeprazole Sodium.

Table 6 Solubility data of Clarithromycin and Rabeprazole Sodium in various buffers

Clarithromycin		Rabeprazole Sodium	
Medium	Solubility	Medium	Solubility
1.2 pH buffer	0.131	Ethanol	25mg/ml
4.0 pH buffer	0.175	Distilled water	10 mg/mL
7.4 pH buffer	0.155	Solvent	solubility
Distilled water	0.083	Methanol	Very soluble
methanol	0.142	Chloroform	insoluble

Table 7 Melting point of Clarithromycin and Rabeprazole sodium

S.No	Melting point	Average point	Melting point	Average point
1	221^0C	221.33^{0}C	141^0C	141.33^{0}C
2	223^0C		140^0C	
3	220^0C		142^0C	

Melting point of clarithromycin was also evaluated in laboratory and found to be shown in table 9 the average 221.33 and Rabeprazole Sodium melting found to be in the average range 141.33^{0}C table9 The melting point that was reported served as confirmation of Clarithromycin and Rabeprazole sodium.

Table 8 Precompression parameter of powder blend

Formulation code	Parameters				
	Angle of repose	Bulk density gm/cm^3	Tapped bulk density gm/cm^3	Hauser's ratio (H_R)	Compressibility index(%)
IF1	29.38±1.4	0.29±0.01	0.35±0.03	1.28±0.30	24.03±1.10
IF2	28.24±1.5	0.28±0.05	0.37±0.02	1.30±0.24	27.32±1.22
IF3	27.23±1.4	0.23±0.07	0.34±0.03	1.32 ±0.15	28.40±1.25
IF4	28.3±1.5	0.26±0.04	0.36±0.03	1.31 ±0.17	24.26 ±1.20
IF5	28.20±1.5	0.30±0.03	0.34±0.05	1.28±0.02	31.24±1.25
IF6	31.88 ±1.2	0.18±0.01	0.32±0.03	1.35±0.40	30.02±1.42
SF1	27.32±1.2	0.32±0.05	0.39±0.40	1.38±0.38	29.75±1.44
SF2	29.48±1.4	0.26±0.04	0.38±0.05	1.32±0.40	27.86 ±1.13
SF3	27.05±1.2	0.26±0.06	0.42±0.05	1.39±0.04	28.43±1.44
SF4	26.65±1.4	0.26±0.03	0.40±0.03	1.40±0.16	31.12±1.26
SF5	30.78±1.5	0.29±0.02	0.42±0.02	1.42±0.13	30.15±1.73
SF6	29.43±1.3	0.30±0.04	0.44±0.04	1.41±0.12	33.34±1.25

For both the immediate release powder blend and the sustain release powder blend, the following physical properties were characterized: hauser's ratio, angle of repose, bulk density, tapped bulk density, and compressibility index.. Blends can be compressed directly, as demonstrated by the result shown in table 10

Table 9 Post compression parameter of floating bilayer tablet

Formulation	Parameters					
	Hardness (kg/cm^2)	Friability	Uniformity of weight	Drug content	Thickness	Diameter(mm)
Specified limit	4 - 6	Not more then 1.0%	703 - 707	90-100%	2.5 – 3.5	4.5 – 5.5
F1	5.56 ±0.80	0.65 ±0.24	755.35 ±0.85	94.25 ±0.75	2.76 ±0.68	5.3 ±0.35
F2	5.45 ±0.45	0.55 ±0.31	765.28 ±0.25	97.45 ±0.45	2.80 ±0.45	5.2 ±0.46
F3	5.20 ±0.55	0.35 ±0.12	754 .34±0.35	98.44 ±0.50	2.30 ±0.35	4.8 ±0.32
F4	4.80 ±0.35	0.80 ±0.32	730.37±0.40	98.80 ±0.80	2.50 ±0.70	4.8 ±0.40
F5	4.60 ±0.75	0.65 ±0.33	750.60±0.50	97.85 ±0.74	3.14 ±0.65	4.4 ±0.40
F6	5.80 ±0.34	0.75 ±0.45	780.43±0.38	96.86 ±0.50	3.16 ±0.50	4.9 ±0.15

Table 10 In vitro Dissolution study of immediate release

time (min)	IF1	IF2	IF3	IF4	IF5	IF6
0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	46.26	74.10	76.10	76.40	75.20	74.10
10	51.56	823.15	84.15	84.45	83.15	80.15
15	56.74	82.45	89.55	90.60	89.40	86.45
20	61.45	90.60	91.20	92.60	90.60	88.60
25	64.15	92.35	92.35	92.35	92.35	90.35
30	66.34	93.89	94.70	94.89	94.89	93.89
35	73.40	95.25	95.75	95.25	95.25	94.25
40	78.39	95.60	96.60	95.50	95.50	95.10
45	81.25	96.40	97.15	96.30	96.30	96.20
50	84.45	97.05	98.10	97.20	97.20	96.80
55	87.46	97.30	98.64	97.80	97.80	97.30
60	92.45	97.40	98.85	98.45	98.45	97.34

IF= Immediate release layer

Table: 11 In vitro dissolution for sustained release by direct compression

Time (hrs)	SF1	SF2	SF3	SF4	SF5	SF6
0	0.0	0.0	0.0	0.0	0.0	0.0
1	28.35	27.15	28.63	29.45	25.37	24.58
2	37.42	31.84	35.32	37.48	35.43	28.87
3	43.78	37.84	42.74	45.32	44.43	44.04
4	55.64	44.28	46.64	68.34	51.67	45.67
5	64.72	51.32	58.63	65.13	55.32	56.32
6	68.64	57.82	65.75	71.64	61.46	68.12
7	71.43	62.29	72.35	78.43	63.02	69.34
8	74.83	71.02	79.45	83.32	66.57	75.78
9	79.05	76.93	86.37	88.60	69.83	82.35
10	85.32	83.24	91.54	92.35	73.12	86.34
11	89.62	88.94	95.15	94.45	78.34	88.52
12	92.15	94.42	98.67	98.40	84.65	89.45

SF= Sustain release layer

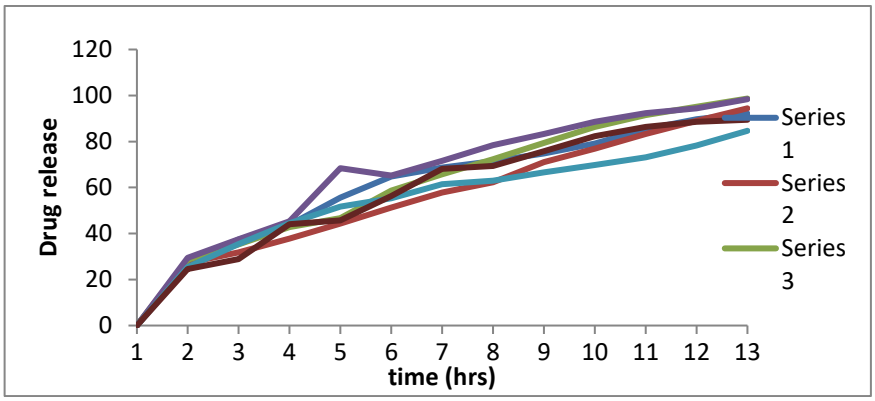

Fig 6 Sustained drug release

In vitro- drug release data is reported and formulation F3 in -vitro showing in-vitro drug release 98.56 and formulation F4 showing 98.30 within a period of 60 min was chosen as optimized formulation.

Table 12 In vitro buoyancy studies

Formulation (F)	Floating lag time(sec)	Total Floating time (hr)
1	240	5.55
2	230	6.15
3	260	10.50
4	270	12.40
5	250	8.40
6	280	6.30

The drug floating lag time & floating time data is reported in table 12 and the best result was shown in formulation F3 & F4.

Table 13 Microbiological assay of Clarithromycin and Rabeprazole Sodium

Organism	diameter of zone inhibition (mm)	
	Standard solution (1mg/ml) Streptromycin	Sample solution (Clarithromycin 1mg/ml)
s.aureus (MTCC3160)	32	29
E.coli(NCIM 20650)	30	26
V. cholera(MTCC 3906)	32	28

1.s.aureus= Staphylococcus aureus,; 2.V. cholera: Vibrio cholera; 3E. coli: Escherichia coli; Testing was done on three bacterial strains to determine the antimicrobiologic activity of the formulated optimum tablet in terms of zone of inhibition and lowest inhibitory concentration. And the result found the Clarithromycin is more effective against s.aurus and v.cholera.

Table 14 Drug release after and before stability

Time (hr)	Cumulative drug release	
	Initial	After three months
0	0	0
1	27.45	26.04
2	36.48	36.54
3	43.32	42.32
4	57.34	56.30

5	64.13	63.21
6	70.64	70.89
7	76.43	77.65
8	81.32	80.43
9	87.60	87.50
10	90.35	91.32
11	95.45	96.40
12	98.30	97.80
FLT (Sec)	11.06 hrs	11hrs

Tablet 14 show that there are no major difference in drug release after storage formulation.

4. Conclusion

Rabeprazole Sodium increases clarithromycin's effectiveness. Consequently, the usage of Rabeprazole Sodium and Clarithromycin bilayer tablets was implemented to enhance patient compliance to the efficient treatment of ulcers. Therefore, based on the results, it can be said that the bilayer tablet that contain 400 mg of clarithromycin for sustained release and 100 mg of Rabeprazole Sodium for quick release have been developed successfully. The current study's findings unequivocally demonstrate that bilayer tablets were created as a stable dose form. The bilayer tablet containing Clarithromycin and Rabeprazole Sodium shows great promise as a replacement for the traditional dose form. Given that there are currently no similar delivery devices on the market, this new dosage form has substantial marketing potential.

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