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A NOVEL TRIPLE THERAPY FORMULATION APPROACH FOR TREATMENT AND MANAGEMENT OF H.PYLORI INFECTION

***M. Anushiya, Dr. G. Selvi, V. Deepa Kumari and R. Priya Darshini**

CL Baid Metha College of Pharmacy, Chennai-600097.

***Corresponding Author: M. Anushiya**

Research Associate, 5/96 Harisana Street, Kulithalai, Tamil Nadu, India, 639104.

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ABSTRACT

A novel triple therapy comprising of an antibiotic, anti-ulcer drug and a prostaglandin analogue in modified release dose form that would be an effective treatment for eradication of h. pylori infection. Considering bilayer tablet technology as a representation for drug delivery system, Misoprostol, Metronidazole and Esomeprazole were chosen as model drugs for the current study. Initially the process variables like concentration of the super disintegrates Crospovidone, sodium starch glycolate, cross carmellose sodium in immediate release layer, polymers HPMC K15M and carbopal, Xanthan gum in sustained layer were tablets formulated by direct compression technique. FTIR studies indicated that the drug is compatible with all the excipients the standard calibration curves for Misoprostol, Metronidazole and Esomeprazole were plotted by UV spectrometer individually. The physical mixtures of both the layers were evaluated for pre compression parameters. Tablets were prepared by direct compression technique. Post compression parameters weight variation, hardness, friability assay and dissolution profile were carried out which were within the limits. The immediate release layer of the bilayer tablet releases within 45min and other layer sustains for 12 hrs. And release 98% of drug. The results of the release kinetics study for SR layer indicates that the First order Kinetics (R2 0.900-0.9750) and it fit into higuchi's model (R2 0.920 - 0.989). The bilayer tablets were subjected to short term stability study as per ICH guidelines. The data for stability studies revealed that no considerable differences in physical and chemical parameters. The proposed triple therapy with bimodal release of three drugs could prove an effective treatment strategy for h. pylori infection in which the Misoprostol reduces the inflammation and pain, Metronidazole inhibits the bacterial growth and Esomeprazole supresses the acid secretion in stomach.

KEYWORDS: Bilayer tablet, Misoprostal, Metronidazole, Esomeprazole, Immediate Release, Sustained Release.

INTRODUCTION

Bilayer tablets have some key advantages compared to conventional mono layer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profile by combining slow release with immediate release layer. Bilayer tablet is suitable for sequential release of two drug in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.[1,2]

SCOPE OF BILAYER TABLETS[2,3,4]

1. For the administration of fixed dose combinations of different active pharmaceutical ingredients (APIs)
2. To prolong the drug product life cycle,
3. To fabricate novel drug delivery systems like buccal /mucoadhesive delivery systems, chewing device and floating tablets for gastro-retentive drug delivery.
4. Controlling the delivery rate of either single or two different API.
5. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable /erodible barriers for modified release.
6. To separate incompatible APIs from each other,
7. To control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).

IDEAL CHARACTERISTICS OF BILAYER TABLETS

1. A Bilayer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.

2. It should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing
3. It should have the chemical and physical stability to maintain its physical attributes over time .the bi layer tablet must be able to release the medicinal agents in predictable and reproducible manner.
4. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agent.

ADVANTAGES OF THE BILAYER TABLET DOSAGE FORM

1. Bilayer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.
3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Flexible Concept.

DISADVANTAGES OF BILAYER TABLET DOSAGE FORM ARE

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bio availability.

NOVELTY WITH TRIPLE THERAPY

Currently existing triple and quadruple therapy consists of a combination of two antibiotics, one Proton pump inhibitor (PPI) or two antibiotics with one PPI and bismuth compound of high dose resulting in pronounced adverse effects.

Innovations in triple therapy with a sustained release layer for esomeprazole, metronidazole, and immediate-release layer for misoprostol offer several advantages, especially in the treatment of Helicobacter pylori infection or peptic ulcers.

HELICOBACTER PYLORI INFECTION

Helicobacter Pylori is a gram negative micro aerophilic spiral (helical) bacterium usually found in the stomach. Helicobacter pylori (H. pylori) infection is a prevalent global bacterial infection that can potentially exaggerate symptoms of other serious infections like SARS-CoV-2 (COVID-19), H. pylori infection has been associated with gastritis, duodenal ulcer, gastric ulcer, and the epidemic form of gastric carcinoma. Eradication of H. pylori infection has proven to be difficult. Most people with H. pylori never have symptoms. But the bacteria can damage the inner protective lining of the stomach and cause other diseases, like a peptic ulcer. Symptoms of a peptic ulcer from H. pylori include: dull or burning stomach pain (especially when you have an empty stomach), bloating, nausea, unexplained weight loss, vomiting, burping and poor appetite. While rare, stomach cancer is also an increased risk for people with H. pylori. (H. pylori) resides in the stomach, colonizes gastric epithelium, and causes several digestive system diseases.[5]

The cchronic infection generates a state of inflammation, which however is asymptomatic in the majority of the subjects. In brief, the stages of the H. pylori colonization are the following: crossing of the gastric mucus layer, adhesion to the gastric epithelium, and then obtaining nutrients while avoiding to be defeated by the host immune response. For some H. pylori colonization/virulence factors a specific role has been suggested in the development of the inflammation and in the impact on the host immune system. In other words, both bacterial action and host response contribute to the pathogenesis.[6,7]

Direct Compression

The international pharmaceutical excipients council (IPEC) defines excipients as "Substances, other than the Active Pharmaceutical Ingredients (API) in finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing or aid manufacture, product, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use". Solvents used for the production of dosage form but not contained in the final product are considered to be excipients, i.e. the granulation fluids, which might be dried off later, should comply with relevant requirements of Pharmacopoeia unless adequately justified. Excipients no longer maintain the initial concept of "inactive support "because of the influence they have both over biopharmaceutical aspects and technological factors.

The desired activity, the excipients equivalent of the active ingredients efficacy, is called its functionality[8] **figure 1** indicating the direct compression process of tablet manufacturing[9] and **TABLE 1** shows indicating the ideal requirements ,advantages and limitation of direct compression.

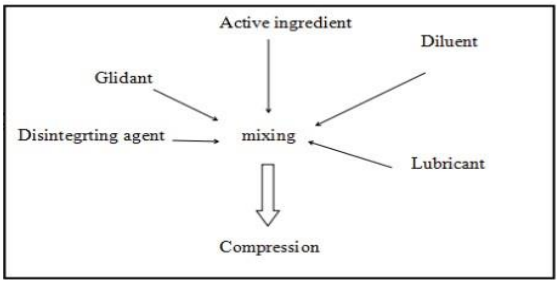

Figure 1: Direct compression method.

MATERIALS AND METHODS

Metronidazole, Misoprostol, Esomeprazole Magnesium, Sodium starch glycolate, Croscarmellose sodium, Crospovidone, Lactose anhydrous, Magnesium sterate, Carbopol, Talc, and HPMC K 15All over chemical purchased from Fourrts India laboratories Pvt. Ltd. Chennai.

Preformulation studies

The drug substances of Metronidazole, Misoprostol, Esomeprazole magnesium was characterized for their identity and purity. The following studies were performed.

Preparation of standard calibration curve of Misoprostol

Stock solution

25 mg of Misoprostol was solubilized by 20 ml of water in a 500 ml volumetric flask, and sonicated for 30 minutes. This solution was further diluted with water was added to make up the volume.

Standard solution

10 ml of stock solution was diluted to 100 ml with water. Similarly, 20 ml, 30 ml, 40 ml, and 1 ml of standard solution was taken and further diluted with the 10 ml water to the volume. UV absorbance was taken at the wavelength of 208nm in UV-Visible spectrophotometer UV-1601, Shimadzu.

Preparation of standard calibration curve of Metronidazole

Stock solution

25 mg of Metronidazole was solubilized by 20 ml of water in a 250 ml volumetric flask, and water was added to make up the volume.

Standard solution

1 ml of stock solution was diluted to 25 ml with water. Similarly, 2 ml, 3 ml, 4 ml, 1 ml of standard solution was taken and further diluted with the 25 ml water to the volume. UV absorbance was taken at the wavelength of 277nm in UV-Visible spectrophotometer UV-1601, Shimadzu.

Preparation of standard calibration curve of Esomeprazole

Stock solution

25 mg of esomeprazole was solubilized by 25 ml of DMF in a 250 ml volumetric flask, and water was added to make up the volume. The standard drug solution was prepared by dissolving 25 mg of esomeprazole in 25 mL DMF taken in a 25 mL standard flask. This stock solution was suitably diluted with 50:50 v/v of DMF: Distilled water solvent to get a standard drug solution of 100mcg/mL

Standard solution

1-5 mL standard drug solution was transferred to a series of 10 mL volumetric flasks. To each of these flasks were made up to the volume with 50:50 v/v of DMF: distilled water and the UV absorbance was taken at the wavelength of 275 nm in UV-Visible spectrophotometer UV-1601, Shimadzu.

Chemical Compatibility study by FTIR

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of a mixture there by we can study incompatibility with two compounds. Compatibility in between pure drug and compatibility in between both drug and excipient has been investigated by FTIR. The IR spectra of the test samples were obtained by Pressed Pellet technique using excipients.

Evaluation of bilayer tablets

Precompression Studies

Tapped Bulk Density

It was determined by pouring gently 2 g of the powder blend from each formula through a glass funnel into 10 ml measuring cylinder. The cylinder was tapped gently on to a hard surface from the height of 2 inches at second interval until a constant volume was obtained. Volume occupied by the sample after tapping was noted. Tapped density was expressed in (g/ml) and calculated by using following formula.

Tapped Density = (Weight of the Granule / Tapped volume)

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of the pile of the Granule and the horizontal plane. Angle of repose of different formulations was measured according to fixed height funnel standing method.

$$\tan \theta = h / r \; ; \; \theta = \tan -1 \; h / r) \; , \; d)$$

Carr's Index

Compressibility index (CI) or Carr's index value of micro particles was computed according to the equation: Carr (%) = [(Tapped density – Bulk Density) / Tapped Density] × 100 e)

Hausner's Ratio

Hausner's ratio of micro particles was determined by comparing the tapped density to the bulk density using the equation: Hausner ratio = tapped density/bulk density.

Postcompression Studies

a) Weight Variation: It was performed as per the method given in the Indian Pharmacopoeia (1996). 20 Tablets were selected randomly from the formulation and the average weight was determined. Then individual Tablets were weighed and the individual weight was compared with the average weight.

Following are the formulas

%Deviation= (Average Weight – Individual Weight) / Average Weight. X 100

b) Hardness: This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five Tablets were selected at random and the hardness of each Tablets formulation and marketed Tablets was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm2.

c) Friability: The friability test was carried out to evaluate the hardness and stability instantly. The Tablets friability was measured according to the Indian Pharmacopoeia. In this, 10 Tablets were weighed initially and put in a rotating apparatus drum (Roche friabilator). Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, loose dust particles were removed from the Tablets after the test and the Tablets were again weighed. The Tablets friability was expressed in (%). The percentage friability of the Tablets formulation was calculated by using following formula is given below
%Friability= Initial Wt. of Tablets – Final Wt. of Tablets x 100 Initial Wt. of Tablets

d) Tablets Thickness and Size: Thickness and size of Tablets were important for uniformity of Tablets size. Thickness and size of the Tablets formulation was measured using Vernier caliper and is expressed as (mm).

e) Assay: Ten tablets were randomly selected from each formulation batch, weighed, crushed and finely powdered. Equivalent weight of drug was taken and dissolved in 10 ml 6.8 phosphate buffer; make up the volume into 25 ml. After suitable dilutions it is estimated for the drug content separately for metronidazole & misoprostol of IR layer and esomeprazole of SR layer. it was done using UV – spectrophotometer at 277 nm & 271nm and 302nm respectively for IR layer of metronidazole & misoprostol and SR Layer of esomeprazole.

F) In vitro Dissolution Test: The in vitro dissolution study of esomeprazole SR layer, Metronidazole & misoprostol Of IR layer were performed according to USP apparatus I(Paddle type). The following parameters are considered for the dissolution study Tab.

The in vitro dissolution profile was conducted in 500 ml 0.1 N HCL, pH 1.28 for all the prepared IR batches are dissolved in this medium The samples were withdrawn simulteneously at respective intervels 10, 15, 30 and 45 mins and the rotation speed of the paddle was 100 rpm, and the temperature of the medium was maintained at 37.0 ± 0.5 °C. For the acid resistance of bilayer tablet, after 45 mins pH of dissoution medium were increased by adding 0.086 M dibasic sodium Phosphate buffer pH 6.8 to make it. SR formulations was dissolved in this dissolution medium. Samples were withdrawn at 1, 2, 4, 6, 8, 10, 12, 16 hours in USP Type II apparatus. An samples will be analysed by UV separatelyand different spectrophotometer. Percentage drug release will be determined for each formulation.

2.4 FORMULATION OF IMMEDIATE RELEASE LAYER

Fast dissolving tablets of Metronidazole and Misoprostal was prepared by direct compression method. After incorporating different super disintegrants such as SSG, CCM, CP, in different concentration. all the ingredients given in table were weighed and mixed in geometric progression in a drug and clean mortar. then the ingredients were passed through mesh #60. The blend was compared on 9.1 mm shallow cancave punches on a ‘Rimek mini press 10 station rotary compression machine.

2.5 FORMULATION OF SUSTAINED RELEASE LAYER

Sustained release tablets were prepared by direct compression method, the drug and all other excipients except magnesium stearate and talc were weighed appropriately and were passed through sieve No. 4 Esomeprazole was mixed with different ratios of xanthan gum, carbopal 934, PVP. These three different types of polymers must be used together to achieve a sustained release rate of the selected drug. Such a combination of polymers facilitates manufacturing processes and improves drug release and absorption profiles.

Table 2: Formulation chart of Triple therapy.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
	Immediate release layer							
METRONIDZOLE	125	125	125	125	125	125	125	125
MISOPROSTAL	20	20	20	20	20	20	20	20
SSG	6	7	5	6	5	7	-	-
CCM	-	-	-	6	7	-	6	8
CP	6	5	7	-	-	5	-	-
LACTOSE ANHYDROUS	15	15	15	15	15	15	15	15
MG ST	2	2	2	2	2	2	2	2
COLOUR	1	1	1	1	1	1	1	1
	Sustained release layer							
ESOMEPRAZOLE	20	20	20	20	20	20	20	20
HPMC K 15	10	20	40	60	-	-	-	-
CARBOPAL 934	-	-	-	-	20	30	10	-

XANTHAN GUM	-	-	-	-	-	-	-	20
MCC-112	63.9	53.9	33.9	13.9	53.9	43.9	63.9	53.9
PVP K30	5	5	5	5	5	5	5	5
TALC	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MG ST	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6

3.0 RESULTS AND DISCUSSION

Determination of Absorption Maxima of APIs

- The absorbance maximum of Metronidazole was found to be at 277 nm.
- The absorbance maximum of Misoprostol was found to be at 271 nm.
- The absorbance maximum of Esomeprazole was found to be at 302 nm.

Drug and Excipient Compatibility Studies

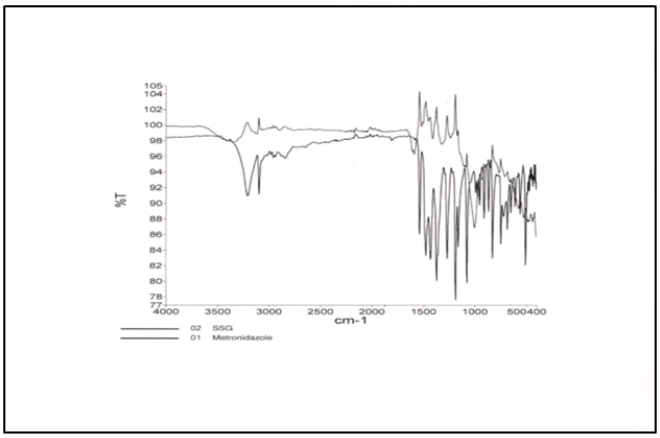

Figure 2: **FT IR Studies of Drug and excipients (METRONIDAZOLE+SSG).**

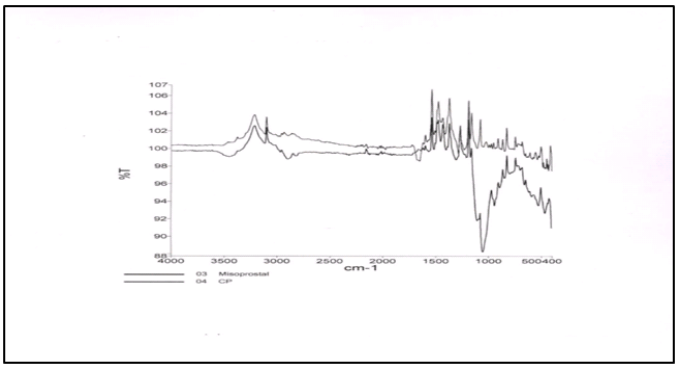

Figure 3: FT IR Studies of Drug and excipients (MISOPROSTAL+CP).

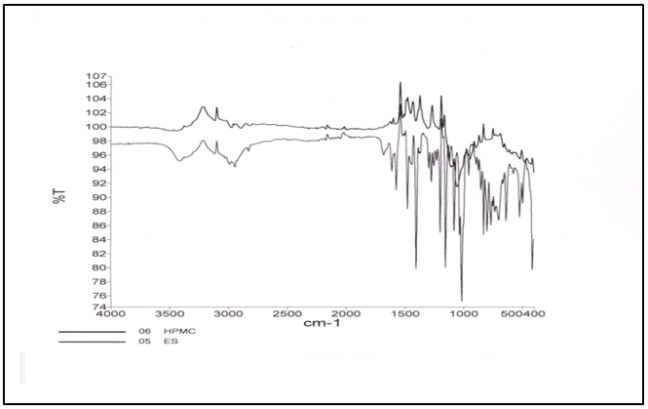

Figure 3: FTIR Studies of Drug and excipients (ESOMEPRAZOLE+HPMC).

Pre Compression Parameters for Immediate Release Layer

Table 2: Pre Compression Parameters for Immediate Release Layer.

S.NO.	Parameters	IR formulation
1	Bulk Density	0.922
2	Tapped Density	1.254
3	Compressability index	26.00
4	Hausner's ratio	1.254
5	Angle of repose	25.79

Pre Compression Parameters for Sustained Release Layer

Table 3: Pre Compression Parameters for Sustained Release Layer.

S.NO.	Parameters	IR formulation
1	Bulk Density	0.410
2	Tapped Density	0.470
3	Compressability index	12.76
4	Hausner's ratio	1.140
5	Angle of repose	21.94

3.1 Post Compression Parameters for bilayer tablet

Table 4: Post Compression Parameters for bilayer tablet.

Trial	Weight Variation (%)(±SD)	Thickness (mm) (±SD)	Diameter (mm) (±SD)	Hardness (kg/cm^2) (±SD)	Friability (%)	Disintegration(min) (±SD)
F1	275±1.52	4.5±0.10	9.1±0.003	7.7±0.08	0.69±0.015	4.40±0.05
F2	278±2.51	3.9±0.06	9.1±0.002	7.6±0.06	0.51±0.017	3.54±0.02
F3	275±1.52	4.2.±0.30	9.1±0.002	8.7±0.12	0.48±0.014	4.17±0.02
F4	277± 2.00	4.13±0.06	9.1±0.003	8.4±0.15	0.64±0.015	4.40±0.10
F5	275±1.52	3.6±0.05	9.1±0.002	8.2± 0.05	0.71±0.016	3.00±0.25
F6	275±1.52	3.9±0.03	9.1±0.001	8.3±0.03	0.54±0.026	2.52±0.01
F7	276±1.52	4.6±0.15	9.1±0.03	8.9±0.16	0.68±0.026	3.55±0.02
F8	275±1.52	4.8±0.05	9.1±0.03	8.0±0.10	0.49±0.025	3.30±0.01

Determination of drug content

Table 5: Determination of Drug Content.

Content Uniformity (%) (Misoprostol)	Content Uniformity (%) (Metronidazole)	Content Uniformity (%) (Esomeprazole)
96.75±0.15	98.03±0.2	99.17±1.5
93.65±0.25	99.46 ±1.2	99.44±1.2
94.25±0.12	98.98 ±0.6	99.89±4.2
98.54±0.26	99.96 ±1.1	99.97±3.2
93.47±0.23	99.98 ±1.2	99.62±1.2
94.56±0.14	99.24 ±2.0	99.64±2.6
98.27±0.45	98.64 ±0.3	99.24±2.0
96.25±0.12	99.24 ±1.2	99.44±2.0

In-vitro dissolution study of different formulations of Misoprostol immediate released tablet (F1-F8)

Table 6: In-vitro dissolution study of Misoprostol immediate released Layer.

Time (min)	Cumulative drug release (%)							
	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
0	0	0	0	0	0	0	0	0
5	26.90±0.01	15.73±0.48	29.34±0.02	23.04±0.58	29.34± 0.18	26.90±0.02	20.70±0.01	20.78±0.01
10	45.26±0.1	58.88±0.02	39.15±0.53	40.32±0.84	41.59±0.03	41.59±0.15	29.36±0.1	31.80±0.20
20	67.3±0.15	67.52±0.29	70.96±0.58	64±0.05	64.86±0.04	64.86±0.02	39.17±0.02	53.80±0.01
30	77.6±0.41	73.13±0.08	85.70±1.0	72.66±0.02	77.15±0.01	75.93±0.01	59.98±0.01	66.11±0.04
45	89.41±0.24	76±1.52	93.13±0.16	80±0.08	89.46±0.05	88.23±0.06	72.27±0.1	84.52±0.03

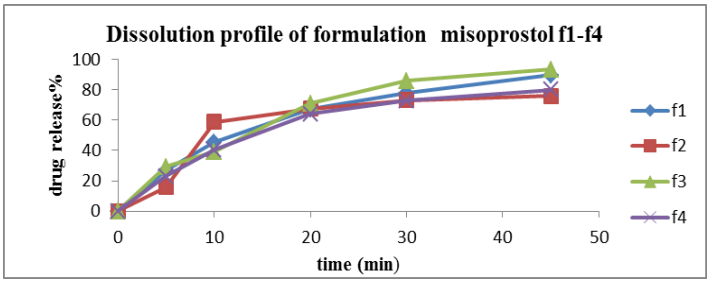

Figure 6: Dissolution profile of formulation misoprostol f1-f4.

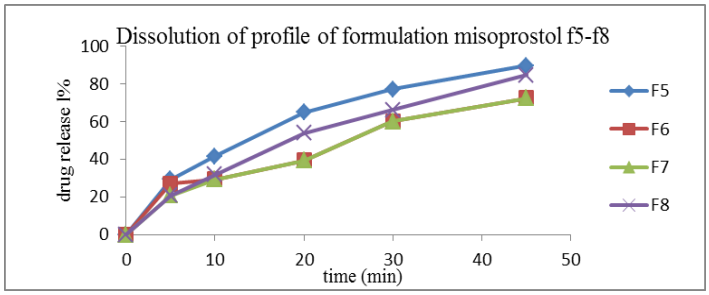

Figure 7: Dissolution profile of formulation misoprostol f5-f8.

Determination of In-vitro dissolution study of different formulations of metronidazole Immediate released tablet (F1-F4)

Table 7: In-vitro dissolution study of Metronidazole immediate released Layer.

Cumulative drug release (%)								
Time (min)	**F1 (%)**	**F2 (%)**	**F3 (%)**	**F4 (%)**	**F5 (%)**	**F6 (%)**	**F7 (%)**	**F8 (%)**
0	0	0	0	0	0	0	0	0
5	18.32±0.01	16.69±0.15	23.27±0.20	17.62±0.1	20.38±0.22	20.38±0.22	20.38±0.22	20.38±0.22
10	53.25±0.02	52.45±0.02	55.21±0.25	49.04±0.2	45.18±0.09	45.18±0.09	45.18±0.09	45.18±0.09
20	70.25±0.14	73.19±0.01	74.75±0.15	57.26±0.5	55.26±0.01	55.26±0.01	55.26±0.01	55.26±0.01
30	83.52±0.17	84.26±0.25	88.25±0.07	78.81±0.5	75.61±0.03	75.61±0.03	75.61±0.03	75.61±0.03
45	90.02±0.03	91.45±0.02	93.20±0.11	88.54±0.1	85.23±0.12	85.23±0.12	85.23±0.12	85.23±0.12

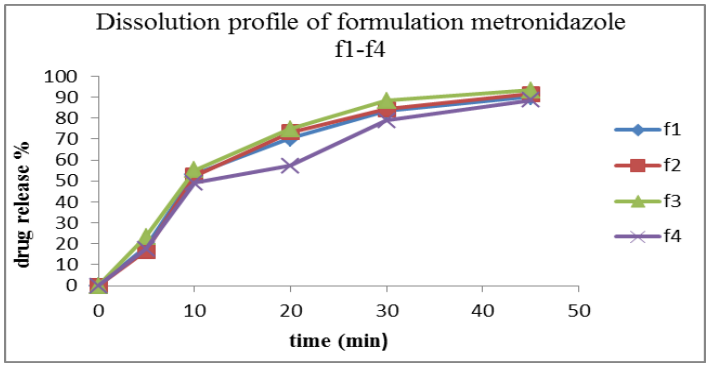

Figure 8: Dissolution profile of formulation metronidazole f1-f4.

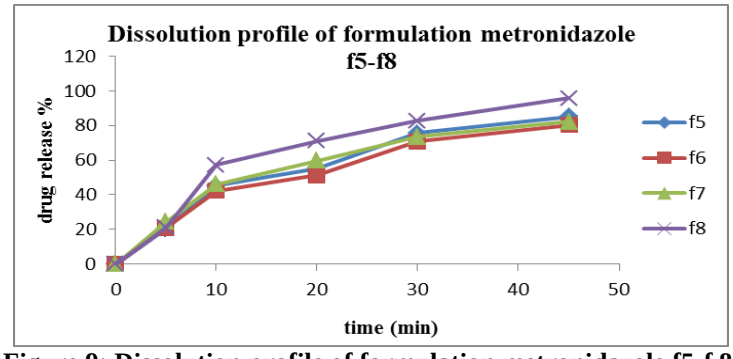

Figure 9: Dissolution profile of formulation metronidazole f5-f 8.

Table 8: Determination of In-vitro dissolution study of different formulations of esomeprazole Sustained released tablet (F1-F4).

TIME (hrs)	Cumulative drug release (%)			
	F1 (%)	F2 (%)	F3 (%)	F4 (%)
1	42±1.2	43±2.2	33±2.1	44±1.0
2	54±1.0	54±2.8	43±2.0	58±1.1
3	65±3.1	61±2.2	57±4.8	66±1.3
4	72±2.9	69±2.6	65±3.2	72±2.2
6	86±2.2	76±2.4	72±2.1	86±2.8
8	92±1.1	84±2.9	83±2.2	95±3.1
10	97±3.2	93±3.0	89±3.5	98±2.1
11		98±3.8	94±3.3	
12			98±3.2	

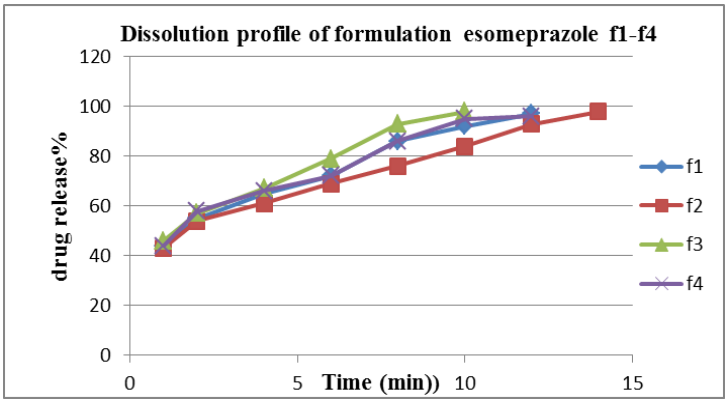

Figure 10: In vitro Dissolution Studies of Esomeprazole sustained Release f1-f4.

Table 9: Determination of In-vitro dissolution study of different formulations of esomeprazole sustained released tablet (F5-F8).

Cumulative drug release (%)				
Time(hrs)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
1	42±2.4	26±1.5	36±2.4	46±1.9
2	56±3.3	38±1.7	43±1.7	57±2.2
3	61±3.4	46±1.1	55±1.3	67±3.3
4	68±3.3	52±1.2	67±2.4	79±3.1
6	75±3.9	64±2.1	74±3.2	93±1.8
8	86±3.5	76±2.9	85±3.8	98±1.2
10	93±2.2	83±2.7	94±0.8	
11	98±0.1	88±2.2	98±1.8	
12		92±21		

In vitro Dissolution Studies of esomeprazole sustained Released Tablets

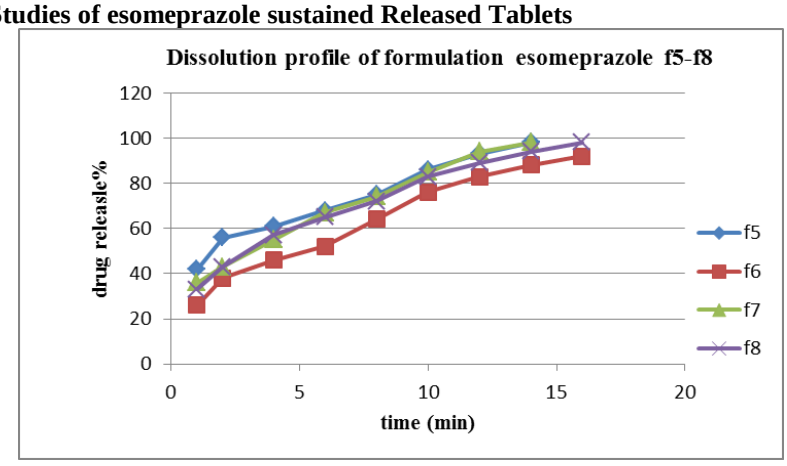

Figure 11: Dissolution profile of formulation esomeprazole f5-f8.

Table 10: kinetic studies of esomeprazole.

FORMULATION CODE	KINETIC MODELS		
	Zero order R^2	First order R^2	Higuchi R^2
F1	0.496	0.959	0.949
F2	0.417	0.900	0.924
F3	0.609	0.973	0.982
F4	0.449	0.94	0.931
F5	0.417	0.905	0.921
F6	0.705	0.975	0.989
F7	0.589	0.977	0.979
F8	0.529	0.925	0.948

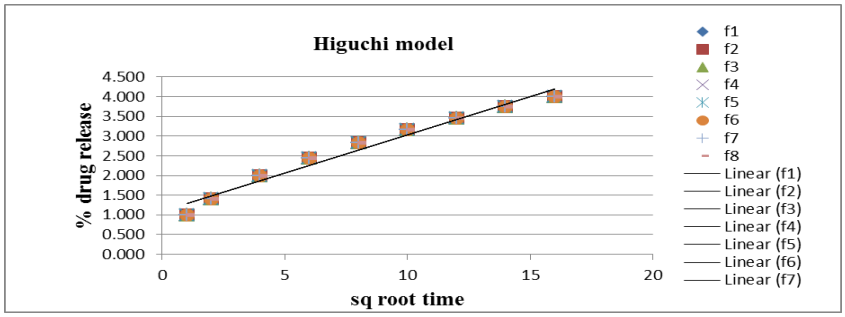

Figure 11: Kinetic studies of Higuchi model.

ZERO ORDER KINETICS

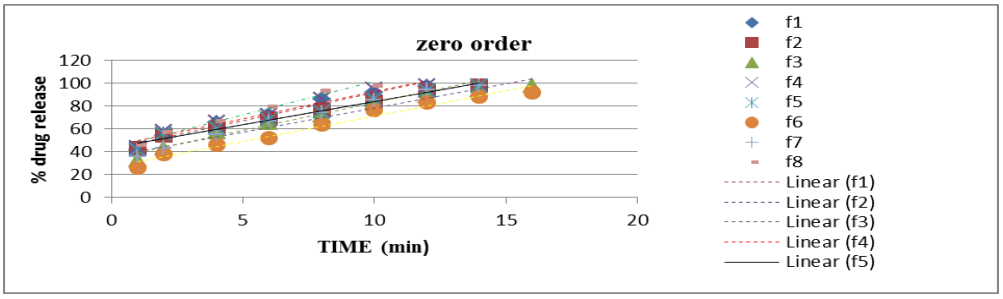

Figure 12: Kinetic studies of zero order.

FIRST ORDER

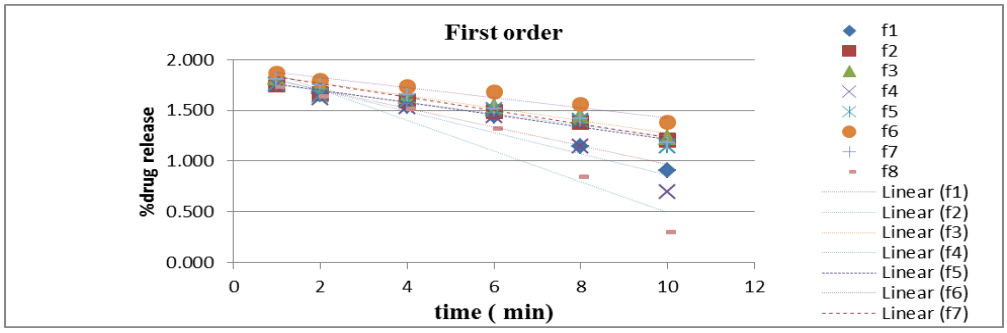

Figure 13: Kinetic studies of first order.

4.0 Stability studies

Stability of a drug in a dosage form t different environmental conditions is important as it determines the expiry date of that particular formulation. Changes in the physical appearance, colour, odour, taste, or texture of the formulation indicate the drug instability. Among the three formulations, Formulation f3 was selected for stability studies based on the physicochemical characterization of bilayer tablet and release characteristics.

The stability studies were carried out at 40 ± 2˚C, 75 ± 5% RH with which shown table. There were no significant changes in their physical appearance, average weight of tablets and hardness. It was observed that the initial drug content and the drug contents of the samples analyzed after 1 month of storage were similar. The release profile also not showed any significant changes indicating that there were no significant changes in the physical as well as chemical characteristics of the formulation. Hence, it can be conculed from the results

that the developed tablets were stable and retain their pharmaceutical properties over a period of 1 month.

Table 11: Stability studies.

Evalution parameters	Observation in month		
	Initial	15 days	1st month
Physical appearance	White & yellow colour	No changes	No changes
Hardness (kg /cm^2)	8.7±0.12	8.7±0.56	8.7± 0.26
Drug content (%)	99.89±4.2	99.89±4.8	99.89±4.15

CONCLUSION

In this present research work a novel triple therapy for treatment of H pylori infection as a bilayer tablet was formulated. The first layer is an immediate release layer comprised of two different drugs; one is an anti-inflammatory drug Misoprostol, a prostaglandin analogue that shall protect the inner surface of the stomach to reduce pain induced by gastric erosion and second drug is Metronidazole, an antibiotic to treat to H Pylori infection with maximum potency. The second layer consists of proton pump inhibitor Esomeprazole which is designed to release in a sustained manner to reduce excess acid secretion. Simultaneously advising the infection and also to treat the condition.

Super disintegrates and polymers were used in first and second layer respectively in different ratios. The layer which consists of metronidazole and misoprostol was made to release immediately. The next layer esomeprazole sustains for 12 hours. The formulation which satisfies both of these criteria is selected as the best one and it is formulation 3. All the formulations were evaluated for the pre compression and post compression parameters. The drug content was estimated for all the batch and the results obtained were within I.P limits. The results of release kinetics of the selected formulations follow first order kinetics. Stability studies were done for the best formulation according to the ICH guidelines. The results indicated no significant changes in physical and chemical characteristics of the drug indicating good stability. The results of the current research work suggests that the triple therapy consisting of Esomeprazole, Misoprostol and Metronidazole formulated as bilayer tablet for bimodal release could be a novel approach in the treatment of H pylori infection with better efficacy and good patient compliance.

Conflicts of interest

It is hereby stated that this paper has no conflict of interest.

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REFERENCES

1. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of Metoclopramide hydrochloride and Ibuprofen. AAPS Pharm Sci Tech, 2008; 9(3): 818-27.
2. Pranjal Kumar Singh, Sanjoo Kumar Bilayer and Floating Bio adhesive Tablets: Innovative approach to Gastroretention, Journal of Drug Delivery & Therapeutics, 2011; 1(1): 32-35.
3. Kulkarni A, Bhatia M. Development and evaluation of bilayer floating tablets of atenolol and lovastatin for biphasic release profile. Iran. J. Pharm. Res; 2009; 8: 15–25.
4. Nirmal J, Saisivam S, Peddanna C, Muralidharan S, Nagarajan M, et al. Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. Chem. Pharm. Bull, 2008; 56: 1455–1458, 26-102-1PB.
5. http://ijrrpas.com/wp-content/uploads/2013/09/Bilayer-Tablet-A-Review.pdf.
6. http://www.jgtps.com/admin/uploads/2gGmHN.pdf.
7. https://www.healthline.com/health/helicobacter-pylori#symptoms.
8. Salam, W. Dumitru L. Directly compressible Adujvants –A Pharmaceutical Approch. Farmacia, 2008; Vol LVL 6: 591-593.
9. Rabia B, Muhammad H; Nousheen A. Formulation Development and Optimization of Ibuprofen tablets By Direct Compression Method pak. J. PHARM. SCI; April 2008; 21(2): 113.
10. Ruggiero, Paolo Current Bentham Science Publishers Pharmaceutical Design Helicobacter Pylori and Inflammation, 2010; 16(38): 4225-4236(12).
11. Ashutosh Gupta[a], Shiran Shetty[b], Srinivas Mutalik[c], Raghu ChandrashekarH[d], NandakumarK[e], Elizabeth Mary Mathew Treatment of H. pylori infection and gastric ulcer: Need for novel Pharmaceutical formulation Heliyon, 2023; 9: e20406.
12. Gupta YK, Ramachandran SS. Fixed dose drug combinations: Issues and challenges in India. Indian J Pharmacol. 2016 Jul-Aug; 48(4): 347-349. doi: 10.4103/0253-7613.186200. PMID: 27756941; PMCID: PMC4980918.
13. Ayaskanta Singh1*□, Jimmy Narayan1 □ and Shivaram Prasad Singh 2 Helicobacter pylori Infection: Challenges in India Singh et al. J Pure Appl Micro biol, June 2019; 13(2): 715-723. Article 5531 https://dx.doi.org/10.22207/JPAM.13.2.07.
14. Brown L. M. Helicobacter pylori: epidemiology and routes of transmission. Epidemiologic Reviews, 2000; 22(2): 283-97.

15. Marshall B. J., Warren J. R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet, 1984; 1: 1311-1315.
16. Gill H. H., Majumdar P., Shankaran K., Desai H. G. Agerelated prevalence of H. pylori antibodies in Indian subjects. Indian J. Gastroenterol, 1994; 13: 92-4.
17. RJ, Dai YY, Qin C, Li XH, Qin YC, Pan Y, Huang YY, Huang ZS, Huang YQ. Treatment strategies and Lpreventive methods for drug-resistant Helicobacter pylori infection. World J Meta-Anal, 2020; 8(2): 98-108. [DOI: 10.13105/wjma.v8.i2.98.
18. Liu WZ, Xie Y, Lu H, Cheng H, Zeng ZR, Zhou LY, Chen Y, Wang JB, Du YQ, Lu NH; Chinese Society of Gastroenterology, Chinese Study Group on Helicobacter pylori and Peptic Ulcer. Fifth Chinese National Consensus Report on the management of Helicobacter pylori infection. Helicobacter, 2018; 23: e12475. [Cited in This Article: 2] [Cited by in Crossref: 187] [Cited by in F6Publishing: 166] [Article Influence: 33.2] [Reference Citation Analysis (0)].