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RESEARCH ARTICLE

PREPARATION AND EVALUATION OF BI-LAYER TABLETS OF PANTORAZOLE AND CLARITHROMYCIN

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ABSTRACT:

The objective of the present investigation was to develop a Bi-layer floating tablet of Clarithromycin and Pantoprazole. it consists of two layers, The immediate release layer containing comprised super disintegrating agent and pantoprazole and floating SR layer containing HPMC of various grade as the release retarding polymers and Clarithromycin. Optimization of the best formulation among the nine formulations prepared for both IR and SR layer was done on the basis of their dsinrigation and dissolution profiles. IR layer tablets IF8 containing Crospovidone was found to be optimum of pantoprazole. The floating SR layer tablet of Clarithromycin (F6) containing HPMCK15M was found optimum. The Optimized immediate release (IF8) & sustained release (F6) formulation was combined and made into Bi-layer floating tablet. The optimised Bi-layer tablets of Clarithromycin and pantoprazole was formulated and evaluated for various evaluation parameters. All the results of evaluations was found to be within limits and the final Optimised Bi-layer formulation released up to 12hrs. This formulation are used for effective treatment of peptic ulcer.

Keywords: Clarithromycin, Pantoprazole; floating; *H. pylori*; peptic ulcer.

INTRODUCTION

Clarithromycin (CLA) is a macrolide antibiotic widely prescribed in H.pylori mediated peptic ulcers, Upper Respiratory Tract Infections.[1] The recommended adult oral dosage of clarithromycin is 500 mg twice daily for the effective treatment of H.pylori caused peptic ulcer. As the drug is effective when the plasma fluctuations are minimized, sustained release dosage form of clarithromycin is desirable. The short biological half life of drug (~3–5 h).[2]

Proton pump inhibitors (PPIs) suppress gastric acid secretion by specific inhibition of the H+/K+- ATPase in the gastric parietal cell. This process starts with absorption of the PPI in the parietal cell. PPIs are weak bases, so protonation takes place in the acidic region of the secretory canaliculus of the parietal cell. In the secretory canaliculus, the methylsulfinylgroup shifts to a highly reactive sulfenamide. The final step is covalent binding of the reactive sulfenamide to 2 cysteine moieties of the catalytic subunit of the H+/K+- ATPase of the proton pump.[3]

There are two major reasons for the failure of H. pylori eradication with conventional dosage forms of antibiotics. One of the reasons for incomplete eradication may be the degradation of antimicrobial agents such as Clarithromycin by gastric acid.[4] In an effort to overcome this problem, concomitant administration of antimicrobial agents and drugs which inhibit gastric acid secretion such as H2 receptor antagonists and proton pump inhibitors (PPI) have been tried such as pantoprazole.

Material and method

Materials

Clarithromycin and Pantoprazole were generously gifted by Alembic Pharma Vadodra. Crude Fenugreek purchased from local farmer of Bhopal (M.P.). HPMCK4M and HPMCK15M, lactose, magnesium stearate and talc, Citric acid, and Sodium bi carbonate were purchased from S.D fine chemicals, Mumbai.

Method

Preparation of Immediate Release pantoprazole Tablets [5]

Immediate release layer of Pantoprazole were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the

ingredients were passed through mesh #40. Magnesium stearate as lubricant and talc as glidant were throngh mesh 40#. All the above were mixed in geometric proportion in a poly bag for 15 minutes., 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. Eight formulations of Pantoprazole granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 100 mg, were obtained. Composition of tablets is mentioned in [Table-1].

Table 1. Composition of Pantoprazole Fast Dissolving Tablets

Ingredients(mg)	**Formulation code**								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Pantoprazole	40	40	40	40	40	40	40	40	40
SodiumStarch glycolate	5	7.5	10	_	_	_	_	_	_
Croscarmellose sodium	_	_	_	5	7.5	10	_	_	_
Crospovidone	_	_	_	_	_	_	5	7.5	10
Microcrystalline cellulose	24	21.5	19	24	21.5	19	24	21.5	19
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	80	80	80	80	80	80	80	80	80

Preparation of Sustained Release clarithromycin [5]

Tablets Sustained release layer of clarithromycin was prepared direct compretiom technique. Clarithromycin and HPMC were passed through sieve no # 40. All the above were mixed in geometric proportion in a poly bag for 15 minutes. Then Talc as glidant and magnesium stearate as lubricant were passed through sieve no # 60. All the excipients were mixed in geometric proportion in a poly bag for 5 minutes.

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.

Table-2 various formulation of Clarithromycin Gastro retentive Floating tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clarithromycin	500	500	500	500	500	500	500	500	500
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
Sucralfate	100	100	100	100	100	100	100	100	100
Lactose	40	30	20	40	30	20	40	30	20
Total Weight	850	850	850	850	850	850	850	850	850

Evaluation of IR/SR Tablets [6]

The prepared tablets were subjected to various evaluation tests like thickness, hardness, weight variation, friability, and drug content.

Thickness of the tablets

Thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets were selected and used for determination of thickness.

Hardness

Hardness is termed as the tablet crushing strength and it is the force required to break a tablet diametrically. Hardness of tablets was measured by selecting 6 tablets randomly and the

hardness of each tablet was measured with Monsanto hardness tester. The hardness was noted. The hardness is usually measured in terms of kg/cm2.

Weight Variation

Twenty tablets were weighed collectively and individually. Average weight was calculated and based on the obtained weights % weight variation was calculated using the formula,

$$\% \text{ Weight Variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

Friability; The tablet friability is a measure of loss due to abrasion. The pre weighed tablets were exposed to repeated shocks in Roche friabilator in which they are initially weighed ($W0$) and kept in a tumbling and rotating apparatus drum and were subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were reweighed (W) and the percent loss in weight or friability (f) was calculated by the formula given below.

$$\%\text{Friability} \frac{\text{Initial weight} - \text{Final}}{\text{Initial weight} \times 100}$$

Drug Content

Twenty tablets were selected randomly and average weight was calculated. The tablets were crushed in a mortar and accurately weighed amount of average tablet weight was taken from the crushed blend and transferred in to a 100mL volumetric flask. To this little amount of methanol was added to dissolve the drug and volume was made up to the mark with concerned medium. The content was shaken periodically and kept for 1 hour to allow the drug to dissolve completely. Then it was filtered and appropriate dilutions were made. Finally dilutions were observed using spectrophotometer to determine % drug content. The drug content should bewithin the range between 90 and 110% of standard amount.[7]

Disintegrating Time

The disintegration test is carried out in an apparatus (Electro lab, Mumbai) containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28–32 times per minute in a medium of 900mLwaterwhich is maintained at 37 ± 2^0C. Six tablets were

placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (#10) was considered as the disintegration time of the tablet.

***In Vitro* Dissolution Studies**

The release of drug from different batches of prepared tablets was studied using USP dissolution apparatus type II. The dissolution medium used was 500mL of 0.1N HCl for first 30minutes for immediate release layer and then 900mL of 0.1N HCl with 0.5% w/v SLS was used up to 12 hours for sustained release layer. The temperature was maintained at 37 ± 0.5^0C and the stirring rate was 50 rpm. The samples were withdrawn at regular intervals and this withdrawn volume was replaced with fresh medium. The collected samples were filtered using Whatman filter paper and observed using spectrophotometer at respective λmax against a blank (respective medium).

Kinetic Data Analysis

The drug release kinetic studies were carried out for bi-layer tablets of Clarithromycin and pantoprazole and were evaluated using the linear regression method

(1) Zero order kinetic models—cumulative % of drug released versus *T*
(2) First order kinetic model—log cumulative percent drug remaining versus *T*
(3) Higuchi's model—cumulative percent drug released versus square root of *T*
(4) Korsmeyer equation/Peppa's model—log cumulative percent drug released versus log

Formulation development of Bi-layer Tablet [8,9]

Optimized formulation IF-8 of Instant release layer and optimized formulation of F-6 for control release used for formulation of Bi-layer tablet.

Evaluation of Bi-layer Tablet [10-12]

Evaluation parameters of bi-layer tablet were performed according to I.P. specifications. Parameters such as weight variation were performed by taking average weight of 20 tablets and hardness test was performed by Monsanto hardness tester. Thickness of the tablet was measured using vernier caliper. Friability test was performed by taking 6 tablets in Roche friabilator and % friability was calculated. *In vitro* drug release studies of bi-layer tablets were carried out using USP dissolution apparatus type II in 900mL of 0.1NHCl up to 12 hours. Samples were collected at regular intervals of time and filtered. The collected samples were filtered and observed in UV spectrophotometer.

Result & Discussion

In all immediate release formulations (IF1 to IF9), the weight variation of all formulation was passed according to pharmacopeia limit, hardness test of tablets was rang between (2.12± 0.42 to 2.812±0.51), Friability (0.5314 ±0.03 to 0.8554 ±0.11), Thickness test of tablets was rang between (1.42 ±0.03 to 1.46 ±0.05), Drug content test of tablets was rang between (98.33±0.62 to 99.41±0.42), Disintegration time of tablets was rang between (1.03±0.69 to 33.34±1.23). This result is giving in table no 3.

Table-3 Results of Post-Compression parameters of Pantoprazole IR Tablets.

F. Code	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	*In vitro* Disintegration Time(sec.) (n=3) Mean ± SD
IF1	2.13 ± 0.21	0.8217± 0.01	Passes	1.42 ±0.03	99.41±0.42	3.48±0.56
IF2	2.70 ± 0.30	0.7262 ±0.05	Passes	1.45 ±0.05	99.77±0.51	6.40±0.71
IF3	2.51 ± 0.50	0.5314 ±0.03	Passes	1.41 ±0.03	98.53±0.71	5.34±0.41
IF4	2.73 ± 0.29	0.6425 ±0.11	Passes	1.40±0.06	99.41±0.49	12.00±0.22
IF5	2.81 ± 0.51	0.6346 ±0.05	Passes	1.44 ±0.03	99.33±0.66	33.34±1.23
IF6	2.50 ± 0.40	0.7114 ±0.16	Passes	1.46 ±0.05	98.51±0.75	1.50±1.53
IF7	2.66 ± 0.29	0.5612 ±0.07	Passes	1.40 ±0.04	99.57±0.42	1.54±0.96
IF8	2.77 ± 0.71	0.8554 ±0.11	Passes	1.43 ±0.05	98.33±0.62	1.03±0.69
IF9	2.12± 0.42	0.7377 ±0.15	Passes	1.42 ±0.04	99.65±0.48	32.45±1.15

The immediate release formulation of pentaprazole (IF1 to IF9) having Croscarmellose sodium, Crospovidone showed drug release in 12min. It was observed F8 formulation gave better result with cross povidone as super disintegrating agent in the concentration 7.5mg. The low concentration of super disintegrate agent gave less release, the concentration increase with increase release.

In all sustained release formulations (IF1 to IF9), the hardness test of tablets was range between (4.4 to 5.3), Friability test of tablets was range between (0.27 ± 0.05to 0.58 ± 0.10), weight variation test of tablets was range between (850.19± 2.94 to 851.04 ± 2.56), thickness test of tablets was range between (3.53±0.05 to 4.05± 0.05), drug content test of tablets was

range between (98.33± 0.92 to 99.60 ± 1.39), floating time (>12). These results are giving in table no 4.

Table-4 Results of Post Compression Properties of Clarithromycin FGR(floating gastroretentive) Tablets.

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	850.19± 2.94	0.58 ± 0.10	98.33± 0.92	8
F2	3.94± 0.10	4.4	850.18 ± 3.77	0.51 ± 0.08	97.20 ± 0.34	10
F3	3.96± 0.05	4.5	850.33 ± 1.50	0.38 ± 0.12	99.60 ± 1.39	>12
F4	3.95± 0.05	4.7	852.30 ± 3.30	0.16 ± 0.04	98.14 ± 1.69	>12
F5	3.93± 0.10	5.2	853.13 ± 2.83	0.31 ± 0.07	97.21 ± 1.07	>12
F6	4.03± 0.06	5.3	849.16 ± 2.33	0.27 ± 0.05	97.50± 1.81	>12
F7	4.05± 0.05	4.8	850.18 ± 3.11	0.29 ± 0.08	98.34 ± 0.37	>12
F8	3.98± 0.05	4.5	851.04 ± 2.56	0.34 ± 0.12	98.31± 0.91	>12
F9	3.69±0.06	4.9	851.02±2.11	0.32±0.09	97.83±0.59	>12

The sustained release formulation F1-F9 having Clarithromycin and HPMC K15 and HPMC K4 used in various ratio were showed drug release in 12hrs. It was observed F6 formulation gave better result with HPMC k_{15} polymer in the concentration 180mg. The higher concentration of polymer gave long time release of drug.

In-vitro buoyancy study of Clarithromycin layer of all formulation (F1- F9). floating time of all 9 formulation were obtained (30s- 110s) and total floating time were obtained (>8 - >12 hrs)).

In vitro drug release studies of GRF tablets of all 9 formulation were optimizes in 12 hrs. In the % Cumulative Drug Release of Formulation (F1- F9) were obtained (84.21- 99.76). This result are giving in table no 5.

Table-5 *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	99.87	94.56	99.76	94.56

A dissolution study shows the release of Clarithromycin and Pantoprazole. The Instant layer of Pantorazole release Approx 99.5 percent drug within one hour and control floating layer Clarithromycin shows release up to 12 hours Approx 99.23 percent of Drug release in 12 hours.

Table 6: Post-Compressional Parameters of Optimized Formulation

Formulation code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)	Clarithromycin (%Label Claim)	Pantorazole (%Label Claim)
1.	5.13 ± 0.21	0.821±0.01	Passes	4.542 ±0.03	99.56	99.56

Conclusion

The experiment relates to formulation and development of oral pharmaceutical Bi-layer tablet of Pantoprazole and Clarithomycin for administration of therapeutically and prophylactically effective amount of anti ulcer drug substance to obtain both a relatively fast

or quick onset of therapeutic effect and mainatainence of a therapeutically active plasma concentration for relatively long period of time. Experiment conclude that Bi-layer tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick relief from pain and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

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