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# Formulation and Evaluation of Cytoprotective Gastroretentive Floating tablets of Clarithromycin

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## Abstract

The fundamental object of study is to achieve a site-specific or local effects of the drug for prolong duration of time. The oral route has achieved the most concentration and is quite successful. This is because of the ease of administration as well as the fact that gastrointestinal (GI) physiology offers more elasticity in the design of dosage-form than the other routes. This study is a scientific approach for preparing a floating tablets which is a serves as combination therapy of a Cytoprotective drug i.e. Sucralfate and an anti *H. pylori* drug i.e. Clarithromycin. In the present study nine formulations with variable concentration of polymers (HPMC K15, HPMC K4) were prepared by direct compression method and evaluated for physicochemical properties, buoyancy lag time, total floating time, and *in-vitro* drug release. The result indicated that optimized formulation **F6** on immersion in 0.1N HCL at 37±0.5° C tablets immediately starts drug release and buoyant upto 12 hours without disintegration. These two factors are essential for the tablet to acquire bulk density < 1, so that it remains buoyant on the gastric fluid.

Key-Words: GI, Floating tablets, Clarithromycin

## Introduction

A peptic ulcer is a wound in the lining of abdomen (duodenum or stomach. The peptic ulcers which are found in the stomach are called gastric ulcers. The peptic ulcers which are found in the duodenum are called duodenal ulcers. Peptic ulcers can be treated successfully. Peptic ulcers are the areas of degeneration and necrosis of gastro intestinal mucosa exposed to acid peptic secretion. Peptic ulcer is a lesion in the lining of stomach or duodenum due to attack by acid & pepsin. Though they can occur at any level of the alimentary tract that is exposed to HCL and pepsin, they occur most commonly (98-99%) in either the duodenum or the stomach. The immediate cause of peptic ulcer disease is disturbance in normal protective mucosa barrier by acid pepsin. (Klaussner E.A., 2002).

Classified of Peptic ulcers:

a) Acute Peptic (Stress) ulcer
b) Chronic peptic ulcer

The common symptom of peptic ulcer is burning pain in the gut. This pain is not regular; it comes and goes for a few days or for several weeks. It starts after 2 to 3 hours a meal, comes in the mid-night when the stomach is empty and generally goes away just after meal. This pain naturally occurs in empty stomach and in the early morning, but it can also occur at other times. The duration of such pain may be from minutes to hours depends on severity and it may be overcome by eating or by taking antacids. The other symptoms include loss of appetite, nausea and vomiting. In the chronic stages bleeding is also seen, due to prolonged bleeding anemia may occurs.Other symptoms are losing weight, not feeling like eating, having pain while eating, and Feeling sick to your stomach and vomiting (Hunt R.H., 1998).

Peptic ulcers are mainly caused by the bacteria called *Helicobacter pylori*. Other causes of peptic ulcers include Nonsteroidal anti-inflammatory drugs (NSAIDs), smoke, alcohol and diet, genetic factors, stress and or present of other diseases (Klaussner E.A., 2002).

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*Helicobacter pylori* are the etiologic factor for the peptic ulcer disease in most patients and may develop gastric carcinoma in many individuals. *H. pylori* colonize in the human stomach. Still it is not cleared that how *H. pylori* transmitted, but it seems that it spread via a faecal and oral route. The occurrence of *H. pylori* in adults seems to be inversely associated to the social and economical status. It is also considered that water acts as reservoir for transmission of *H. pylori* (Lewis 2002; Wang 2010).

*H. Pylori* is a gram-negative bacterium. It is spiral shaped organism with a smoother outer coat with four to six bulbous tipped sheathed flagella at one end, which help to penetrate the mucosa and colonize on the surface of the gastric ant rum. This is able to stay alive in stomach by taking benefit of the protective mucus layer and living in it. *H. pylori* are able to survive in the gastric acid due to present of enzyme urease, which breaks urea into bicarbonate and ammonia. This forms a strong base which neutralizes the gastric acid and other chemicals presents around the *H. pylori*. In the mid 1980's the *H. pylori* was discovered by Warren and Marshall and its ethiological association with peptic ulcer disease was established (Marshall 1984). Eradication therapies against *Helicobacter pylori* infection together with effective antisecretory proton pump inhibitors (PPI), introduced in the late 1980's, have made most peptic ulcers possible to treat merely with pharmacological therapy. The need for elective ulcer surgery has therefore diminished to almost zero and hospitalization rates for uncomplicated ulcer disease has declined.

## Material and Methods

The following materials that were procured from different sources some of which were analytical grade and best possible Laboratory Reagent were used as supplied by the manufacturer without further purification or investigation.

Clarithromycin was obtained as a gift sample from Alembic Pharma Vadodra. Sucralfat, HPMC K 4, HPMC K 15, Sucralfate, PVP K30, Talc, Magnesium sterate, Sodium bi carbonate, Citric acid and Lactose was obtained from Mapromax, Life sciences Pvt. Ltd., Dehradun for the preparation of floating tablet

**Formulation and Evaluation:**

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 No.1 and all the formulation were used for further evaluations parameters. Excipients like Sucralfate, Sodium bicarbonate, citric acid anhydrous, 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. Steps involved in the manufacture of tablets, 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 (Lachman L., 2009).

**Evaluation of tablets:**

All the tablets were evaluated for following different parameters which includes (Lachman L., 2009, I.P. 2007);

**General Appearance:**

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated.

Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -) (Lachman L., 2009).

**Thickness and diameter:**

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated (Lachman L., 2009).

**Drug content:**

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 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N Hcl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and react with dye and analyzed for drug content by UV spectrophotometer at a λ max of 414.0 nm using of 0.1 N Hcl as blank (Lachman L., 2009).

**Hardness:**

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) (Lachman L., 2009).

**Friability:** (Lachman L., 2009)
The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated (Lachman L., 2009).

**Uniformity of weight:**
Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated (Lachman L., 2009).

***In vitro* buoyancy studies:**
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.
In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50c and rpm of 75. One Clarithromycin tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (370c) was replaced every time with the same quantity of the sample from this take 0.5 ml and dilute up to 10 ml with 0.1 N HCL. Take 2 ml of this solution add 1 ml of methyl orange and separate with chloroform collect the lower layer and take the absorbance at 414.0 nm using spectroscopy (I.P. 2007).

## Results and Discussion

In the present study nine formulations with variable concentration of polymers (HPMC K15, HPMC K4) were prepared by direct compression method and evaluated for physicochemical properties, buoyancy lag time, totol floating time, and *in-vitro* drug release. The result indicated that optimized formulation **F6** on immersion in 0.1N HCL at 37±0.5° C tablets immediately starts drug release and buoyant upto 12 hours without disintegration. These two factors are essential for the tablet to acquire bulk density < 1, so that it remains buoyant on the gastric fluid.
The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of higuchi was maximum i.e. **0.977** hence indicating drug release from formulations was found to follow higuchi kinetics.

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**Table No. 1 various formulations 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 |

**Table No. 2 Results of *in-vitro* buoyancy study of Clarithromycin FGR Floating time**

| Formulation Code | Floating lag times (sec) | Total Floating Time (hrs) |
|---|---|---|
| F1 | 55s | >8 |
| F2 | 35s | >10 |
| F3 | 30s | >12 |
| F4 | 75s | >12 |
| F5 | 60s | >12 |
| F6 | 80s | >12 |
| F7 | 110s | >10 |
| F8 | 95s | >10 |
| F9 | 106s | >8 |

**Table No. 3 *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 |
| 1.0 | 12.32 | 10.23 | 11.45 | 1045 | 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 |
| 2.0 | 42.45 | 40.32 | 45.23 | 44.23 | 48.23 | 46.32 | 47.14 | 38.21 | 40.28 |
| 3.0 | 76.34 | 66.11 | 67.21 | 65.71 | 50.56 | 67.02 | 71.13 | 68.24 | 56.98 |
| 4.0 | 82.23 | 77.33 | 75.11 | 82.34 | 55.00 | 88.13 | 91.23 | 89.12 | 73.98 |
| 6.0 | 82.55 | 97.13 | 87.13 | 83.00 | 56.00 | 99.13 | 92.00 | 99.25 | 84.16 |
| 8.0 | 83.00 | 97.10 | 94.23 | 83.21 | 57.25 | 99.99 | 93.00 | 99.56 | 89.26 |
| 12.0 | 84.21 | 97.23 | 99.26 | 83.50 | 57.85 | 99.87 | 94.56 | 99.76 | 94.56 |

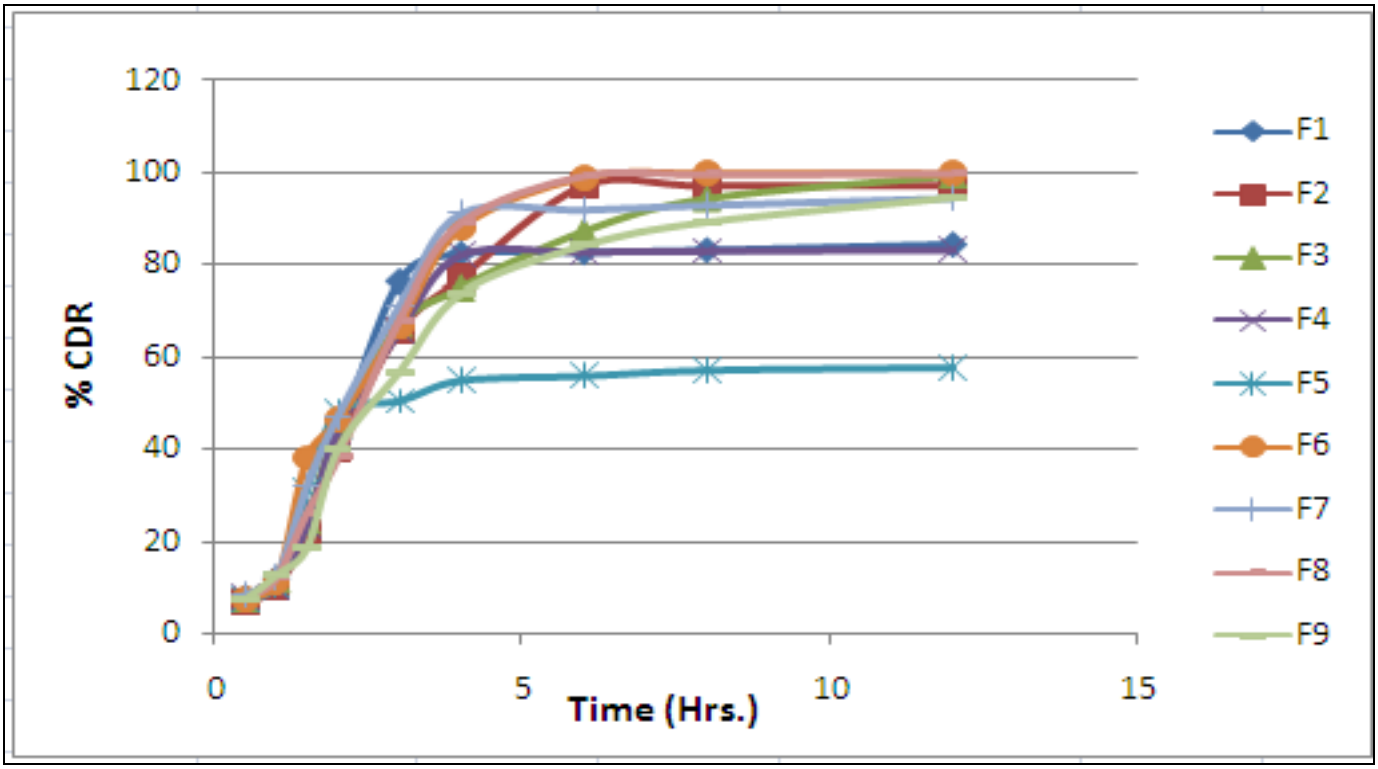


**Fig. No.01 *In-vitro* Drug Release Study of GRF Tablets**

**Table No. 4 Kinetic data of Clarithromycin floating Tablet in comparison with All Formulation**

| Formulation | | Zero Order | First order | Higuchi | Korsmayer papas | Best fitted Model |
|---|---|---|---|---|---|---|
| F1 | r2 | 0.441 | 0.631 | 0.810 | 0.849 | Korsmayer Papas |
| F2 | r2 | 0.668 | 0.858 | 0.868 | 0.898 | Korsmayer Papas |
| F3 | r2 | 0.675 | 0.981 | 0.896 | 0.896 | First Order |
| F4 | r2 | 0.496 | 0.678 | 0.828 | 0.852 | Korsmayer Papas |
| F5 | r2 | 0.154 | 0.333 | 0.762 | 0.755 | Higuchi |
| F6 | r2 | 0.581 | 0.797 | 0.873 | 0.860 | Higuchi |
| F7 | r2 | 0.512 | 0.793 | 0.847 | 0.859 | Korsmayer Papas |
| F8 | r2 | 0.632 | 0.909 | 0.857 | 0.899 | First Order |
| F9 | r2 | 0.708 | 0.969 | 0.894 | 0.916 | First Order |

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