



Formulation and Evaluation of Gastroretentive Bilayer Tablets

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Abstract

Gastroretentive bilayer tablets were designed to prolong the gastric residence time after oral administration and to achieve immediate release of lansoprazole and controlled release floating layer of clarithromycin to treat gastric ulcers. Instant release layer has a combination of super disintegrating agents. A combination of effervescent mechanism is used. HPMC K5 was used as swelling polymer and citric acid, sodium bicarbonate as gas generating agent to reduce the floating lag time. Bilayer floating tablets were prepared with varying proportions of instant layer and sustained release floating approaches. The prepared formulations were evaluated for various tablet and floating parameters. Tablet properties were found to be within the limits according to procedures prescribed in USP. They had a floating lag time around 3-7 seconds and floating time more than 24 hours. The cumulative % drug release in simulated gastric fluids after 10 hours was 70% - 95%. The mechanism of drug release was analyzed by fitting the release data into various kinetic models. It was found that all the formulations best fit the Higuchi's model.

Keywords: Gastroretentive drug delivery system; Bilayer tables, Instant release layer, Floating layer, Lansoprazole, Clarithromycin.

INTRODUCTION

Rapid gastrointestinal transit could result in incomplete drug release from the device beyond the absorption zone leading to diminished efficacy of the administered dose. Relatively brief gastric residence time in major absorption window results in incomplete drug release from the dosage form. Floating systems float over the gastric contents and remain buoyant in stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. Floating drug delivery also has the applications in site specific drug delivery, sustained drug delivery and also in enhancement of absorption ¹.

Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include bio-adhesive systems, swelling and expanding systems, and floating systems ². The swelling and expanding systems may show hazard of permanent retention. Bioadhesive systems may cause problems such as irritation to the mucous layer owing to high localized concentration of the drug. Hydrodynamically balanced systems, designed using effervescent mixtures alone have achieved commercial success but require a high drug: excipients

ratio, and are unsuitable for drugs degrading in basic pH due to the alkaline microenvironment ³. In the present study, we have prepared the floating system with swelling polymer in combination with the effervescent mixture. Lansoprazole is a proton pump inhibitor with a bioavailability of 80% or more and protein binding of 97%. Its metabolism is mainly by liver (CYP3A4 and CYP2C19 mediated) and excretion by renal and fecal. Its dose is usually 30 mg. It acts by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system of the gastric parietal cell ⁴. Previously Lansoprazole micropellets were prepared by using the non-effervescent polymers like HPMC, Methyl cellulose and chitosan without the incorporation of gas liberating agent⁵. Its half life is 1-1.5 hours with poor absorption may be because of poor solubility or degradation. It can be assumed that the solubility and absorption can be improved with an increase in the gastric residence time and also by creating basic pH due to the alkaline microenvironment with the release of sodium bicarbonate. Our main aim of the study was to prepare the gastric retentive drug delivery system for the drug Lansoprazole and at the same time to sustain the drug release for longer time to overcome the short half life of the drug ⁵. Clarithromycin is a semisynthetic macrolide antibiotic derived from erythromycin. It inhibits bacterial protein synthesis by binding to the bacterial

50S ribosomal subunit. Clarithromycin may be bacteriostatic or bactericidal depending on the organism and drug concentration. Clarithromycin is rapidly absorbed from the gastro intestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. The elimination half-life of clarithromycin was about 3 to 4 hrs and use as sustained release approaches ⁶.

MATERIALS AND METHODS

Preparation of instant layer of lansoprazole: The instant release layer of drug containing lansoprazole were prepared by direct compression with using different superdisintegrating agents such as,

crosscarmellose sodium (Ac-Di- Sol), crospovidone and sodium starch glycolate in various concentrations. The ingredients were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh size no # 40. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend. The blend was compressed on 8 mm (diameter) flat punches on a single station compression machine. A number of formulations of lasonoprazole 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.

Table 1: Composition of instant release layer of lansoprazole

Ingredients (mg)	Formulation code								
	LIR1	LIR2	LIR3	LIR4	LIR5	LIR6	LIR7	LIR8	LIR9
Lansoprazole	50	50	50	50	50	50	50	50	50
Sodium Starch glycolate	5	10	15	–	–	–	–	–	–
Croscarmellose sodium	–	–	–	5	10	15	–	–	–
Crospovidone	–	–	–	–	–	–	5	10	15
Microcrystalline cellulose	35	30	25	35	30	25	35	30	25
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight	100	100	100	100	100	100	100	100	100

Preparation of floating layer of clarithromycin: The drug clarithromycin gas generating floating layer (CFL1, CFL2, CFL3, CFL4, CFL5, CFL6, CFL7, CFL8, CFL9) 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 5.2 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 single station compression machine Table 2.

Table 2: Composition of floating layer of clarithromycin

Ingredients (mg)	Formulation code								
	CFL1	CFL2	CFL3	CFL4	CFL5	CFL6	CFL7	CFL8	CFL9
Clarithromycin	250	250	250	250	250	250	250	250	250
HPMC K 15	90	90	90	90	90	90	90	90	90
Citric acid	10	20	30	40	40	30	20	10	25
Sod. bicarbonate	40	30	20	10	10	20	30	40	25
Mag. stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total Weight	400	400	400	400	400	400	400	400	400

Formulation development of bilayer tablet: All the 9 batches of instant release layer (lansoprazole) and floating release layer (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 on 8 mm (diameter) fat punches on a single station compression machine Table 3⁷.

Table 3: Composition of bi layer tablets

Ingredients (mg)	Formulation code								
	LCBLT1	LCBLT2	LCBLT3	LCBLT4	LCBLT5	LCBLT6	LCBLT7	LCBLT8	LCBLT9
Instant layer	LIR1	LIR2	LIR3	LIR4	LIR5	LIR6	LIR7	LIR8	LIR9
	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Floating layer	CFL1	CFL2	CFL3	CFL4	CFL5	CFL6	CFL7	CFL8	CFL9
	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
Lactose anhydrous	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg

Characterization of bilayer tablets:

Thickness: Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Weight variation: The weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The average weight by more than the percent shown below and none deviates by more than twice that percent.

Hardness: Hardness of tablet is defined as the force required to break a tablet in a diametric direction. A tablet was placed between two anvils. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing. The hardness was measured in terms of kg/cm².

Friability: Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches and allowed to rotate for 100 revolutions. The difference in the weigh is calculated and the weight loss should not be more than 1%. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated⁸.

Drug content study: 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 lansoprazole 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 lansoprazole determine the conc. of both drugs using 279 nm (figure 1) and 416 nm (figure 2) for lansoprazole 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 time⁹.

In-vitro drug release study: In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5°C temperature over a 12 hrs periods for clarithromycin SR and 1 hr for lansoprazole 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 shimadzu 1800) spectrophotometer at λ_{max} 279 nm for lansoprazole and 416 nm for clarithromycin respectively. The release rate of bilayer floating tablet was determined by using USP dissolution test. Where Mt is the amount of drug released in time t. M0 is the initial amount of the drug. K0 is the Zero order release constant, KH is the Higuchi rate constant, Kk is a Korsmeyer – Peppas release constant and n is the release exponent that characterizes the mechanism of drug release¹⁰.

Model fitting for drug release: The suitability of several equations that are reported in the literature to identify the mechanisms for the release of drug was tested with respect to the release constraints between 20 to 80% of cumulative % drug release. The data was evaluated according to the following equations¹¹:

Zero order model: $M_t = M_0 + K_0t$

Higuchi model: $M_t = M_0 + K_H$

Korsmeyer - Peppas model: $M / M_{\infty} = K_{tn}$

RESULTS AND DISCUSSION:

In the present study floating bilayer tablets of Lansoprazole and clarithromycin were prepared in order to increase the gastric residence time and also to sustain the drug release rate. The maximum absorption (λ-max) of drug sample lansoprazole in 0.1 N HCl solutions were found to be at 279 nm and the maximum absorption (λ-

max) of drug sample clarithromycin in 0.1 N HCl solutions were found to be at 416 nm. The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.99. Evaluation parameters like weight variation, hardness, friability and disintegration were evaluated. The % deviation from the mean weight of all the formulations, disintegration time and % weight loss in friability (less than 1%) were found to be within the prescribed limits of USP. Disintegration time was found to be increased with the increase in the HPMC content. The cumulative % drug release of the formulation was at the order of 90-95% and was found to be sustained with the content of HPMC. This indicates the formation of swollen gelatinous mass by HPMC which slows down the drug release. For all the formulations the floating lag time was found to be between 3-7 seconds. This lag time was decreased with an increase in the sodium bicarbonate content. All formulations have shown a floating time more than 24 hours. The swelling index which was in the order of 185% - 200% also increased with increase in the HPMC content. Among the prepared formulations both LCBT4 were found to have the optimum properties of floating lag time, and sustained property. In this study in vitro release profiles of all the formulations could be best expressed by Higuchi's matrix model as they showed a good linearity with 'R' value of 0.9996 to 0.9946. The 'n' value for the Korsmeyer and Peppas model were between 0.5- 0.9 which indicates, that non- fickian diffusion is the dominant mechanism of drug release.

Characterization of floating bilayer tablets

Floating bilayer tablets were prepared by the direct compression method, using swellable polymers with citric acid and sodium bicarbonate as floating agent. The effect of the nature of polymers was studied by preparing various formulations of buoyant tablets. In all these formulations, a constant amount of drug (150 mg) was maintained and it was initially characterized for flow

properties and all other parameters. The different characterization as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio includes angle of repose (28.71), bulk density (0.254 g/cm³), tapped density (0.263 g/cm³), Carr's index (25.71 %) and Hassner's ratio was found to be (1.18). The other characterization includes thickness, hardness, friability, weight variation, drug content, buoyancy lag time and in-vitro drug release. The average weights of the entire prepared tablet were 240.17 mg to 240.71 mg which was within the specified limit. The thickness of all the tablets was in the range of 4.01 to 4.09 mm. The hardness of all the formulated tablets was found to be in the range of 5.04 to 5.36 kg/cm². Friability was found to be 0.31 to 0.38 %. Citric acid and sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium resulted in immediate tablet floatation with a lag time in between 140 to 180 seconds. Total buoyancy time of all the prepared formulation was found between 1.12 h to 1.31 h. Citric acid and sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium resulted in immediate tablet floatation with a lag time in between 140 to 180 seconds. Total buoyancy time of all the prepared formulation was found between 1.12 h to 1.31 h. From the in vitro drug release studies, it was found that in formulations LCBLT4 showed best sustained release profile. Cumulative drug release of all the prepared formulation was found to be in between 95.5% to 99% in 12 h. The prepared formulation LCBLT4 was found to be the best formulations in terms of sustained drug release for retarding drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer-Peppas and Higuchi's equation. The regression coefficient (r²) value of various models was found to be non-fickian drug release diffusion mechanism and followed supercase II transport mechanism respectively.

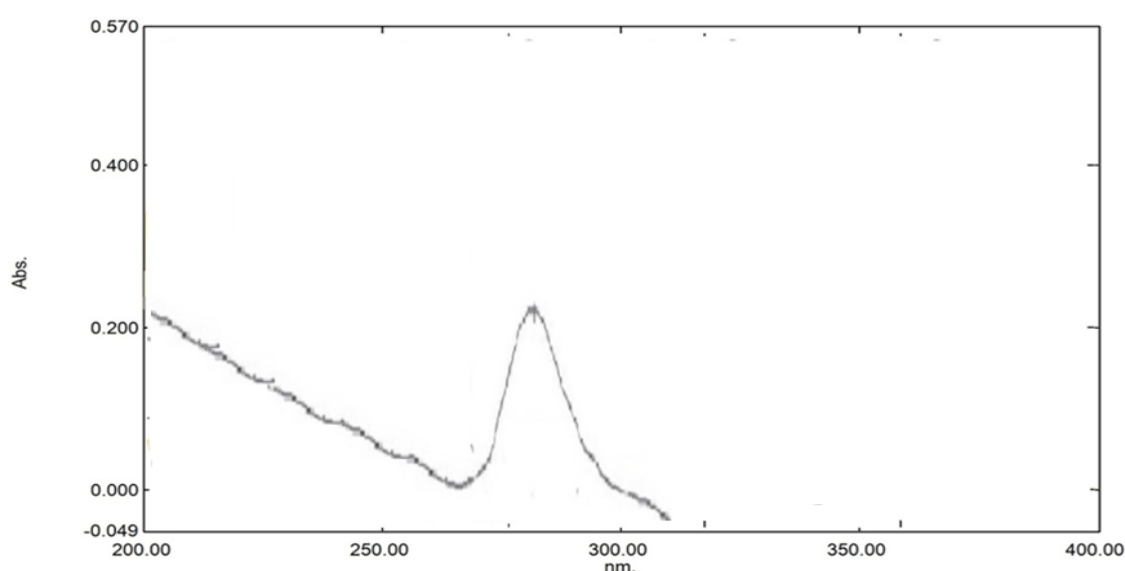


Figure 1: Maximum Absorption wavelength (λ -max) of lansoprazole drug in 0.1N HCl solution (10 μ g/ml)F

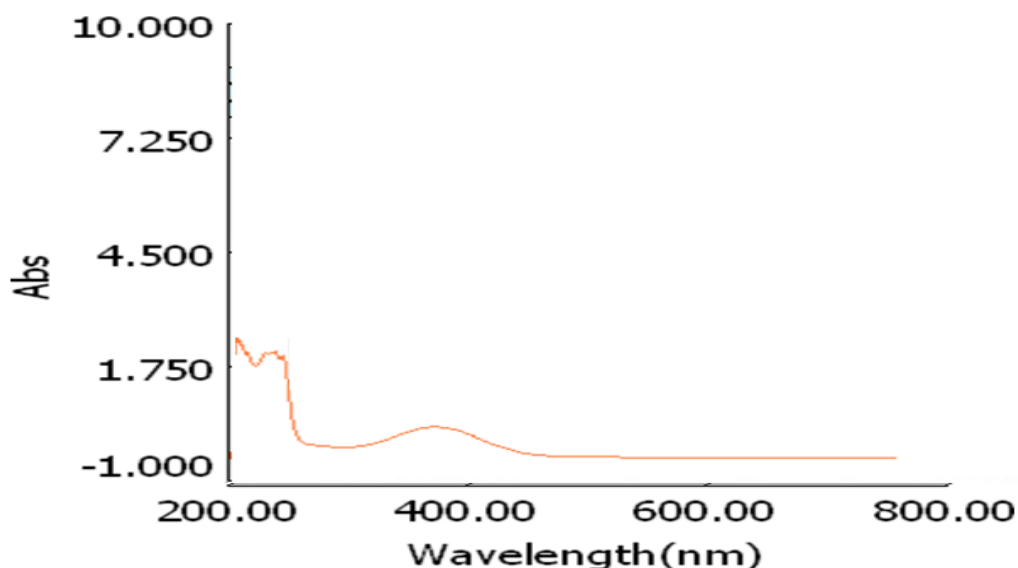


Figure 2: Maximum Absorption wavelength (λ -max) of clarithromycin drug in 0.1N HCl solution (10 μ g/ml)

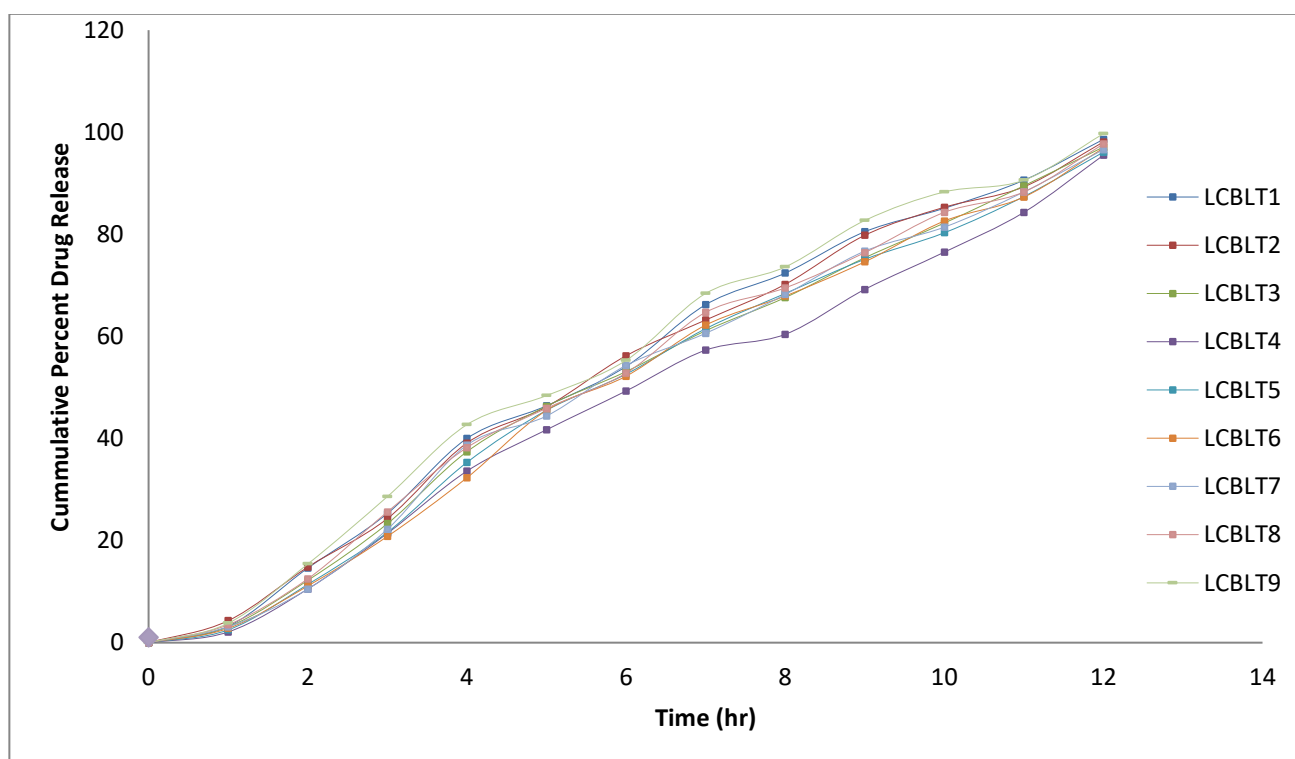


Figure 3: Zero-order kinetic plot of prepared floating bilayer tablets (LCBLT1-LCBLT9)

SUMMARY AND CONCLUSION:

In the present study an attempt was made to develop a floating bilayer tablet of lansoprazole and clarithromycin with variation in polysaccharide polymeric combination with different ratios to increase floating ability at gastric mucosa. Such type of proposed formulations increases the gastric residence time, thus increase the bioavailability. A major problem in gastric delivery is the attainment of an optimal concentration at site of action with maximum bioavailability of drugs. The problem is associated with the conventional dosage form for peptic ulcer diseases is frequent dosing due to the low half-life. The bioavailability of an instilled compound is generally low from 1.5 – 3.0 h and low solubility, with only a small

fraction reaching the target site. The preliminary and screening studies were performed using different superdisintegrating polymers and gas generating agents, the final batches were prepared by direct compression method of both instant release layer and floating layer and were evaluated for various parameters buoyancy lag time and total buoyant time, drug content, in-vitro dissolution study. The formulation LCBLT4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. The regression coefficient (r^2) value of various models was found to be non-fickinon drug release diffusion mechanism and followed supercase II transport

mechanism respectively. Antimicrobial sensitivity against marketed antibiotics drugs is dynamic and alters with the development of resistance in microorganisms. The current study revealed that the prepared bilayer solid dosage form of pharmaceutical dosage forms showed reasonable antimicrobial activity except for the eyedrops dosage forms which showed slightly lower inhibition zone in comparison to standard. There was a slight difference between the studied brands which may be related to the differences in the manufactures production procedures. The poor-quality antibiotics are not only the developing countries' health-related issues but rather have global dimensions due to widespread of resistant bacteria globally.

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