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FORMULATION AND EVALUATION OF FLOATING-MUCOADHESIVE TABLET OF CLARITHROMYCIN

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ABSTRACT

The objective of the present study was to formulate and evaluate Floating–mucoadhesive tablets of clarithromycin for the treatment of Helicobacter pyloric (*H.pylori)* infection. Tablets were prepared by direct compression using directly compressible polymers such as HPMC K4M, HPMC K15M and carbopol 974P and were evaluated for drug - excipient compatibility, density, buoyancy test, mucoadhesion force, swelling study, drug content and *in-vitro* release profile. Sodium bicarbonate and citric acid were used for producing effervescent base for buoyancy of tablets. Analysis of drug release from tablet indicates drug release by zero order rate kinetics. No significant change was observed in physical appearance, drug content, floatability or *in vitro* dissolution pattern after storage at 45 °C / 75% RH for three months.

KEYWORDS

Floating mucoadhesive, clarithromycin, floating lag time, release kinetics.

INTRODUCTION

Helicobacter Pylorus (H.Pylori) is a Gram-negative, motile, microaerophilic spiral bacterium .Helicobacter species cause peptic ulcer disease. Gastric (mainly peptic) ulcer is one of major aliments affecting about 60% of human adults and nearly 80% of child population, all H.Pylori species cause some degree of persistent inflammation[1]. Treatment of H.Pylori remain a challenging position although H.Pylori is highly sensitive to most antibiotics, eradication of H.Pylori from patient is difficult, even with the current best therapies[2, 3]. Conventional tables and capsules are , in general used for eradication therapy not remain in stomach for a long time hence the present study was carried out to formulate and evaluate Floating – mucoadhesive tablets of clarithromycin for prolonged residence in stomach for the treatment of Helicobacter pyloric (*H.pylori)* infection.

Clarithromycin (CL) is broad spectrum antibiotic used in treatment of the *H.pylori* infection in stomach[1]. Clarithromycin is acid stable drug and easily absorb from the stomach[2]. Clarithromycin is the drug of choice as H. pylori resistance rates are much lower for Clarithromycin as compared to other antibiotics like

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amoxicillin and tetracycline. Complete removal of *H.pylori* is possible by the optimum concentration of CL at the site of infection. Hence to achieve maximum drug concentration at the site of infection, targeted drug delivery system like floating mucoadhesive tablet is required[3, 4].

The present study involves the design and development of Clarithromycin floating mucoadhesive tablet for prolonged residence in stomach for the treatment of Helicobacter pyloric (*H.pylori)* infection.

MATERIAL AND METHOD

MATERIAL

Clarithromycin was obtained from Biochem pharmaceutical, Daman, India. HPMC K4M, HPMC K15M were obtained as gift samples from colorcorn company, Mumbai, India; Carbopol-974 was obtained noveon, Mumbai, India; other ingredients used were of analytical grade.

METHOD

Preparation of Floating-Mucoadhesive Tablets

CL, HPMC K4M, HPMC K15M, carbopol 974P (F8-F10) and lactose were blended homogeneously in mortar (Table 1). Blended mixture was passed through Sieve 60, finally $NaHCO_3$: citric acid (10 % in ratio of 1:08) and magnesium stearate 1% was added and blended. The homogeneously blended mixture was compressed in rotary tablet press with the 13.7 mm flat punch. The tablet hardness was in the range 5-6 kg/cm^2 tested on Monsanto tablet hardness tester.

Table 1.
Formulations composition of CL tablet

Formulation*	HPMC K4M (mg)	HPMC K15M (mg)	Carbopol 974P (mg)	$NaHCO_3$:citric acid (mg)	Magnesiiun stearate (mg)	Lactose (mg)
F 1	* *	-	-	-	-	-
F 2	110	-	-	45	4.5	40.5
F 3	125	-	-	45	4.5	25.5
F 4	140	-	-	45	4.5	10.5
F 5	-	110	-	45	4.5	40.5
F 6	-	125	-	45	4.5	25.5
F 7	-	140	-	45	4.5	10.5
F 8	100	-	10	45	4.5	40.5
F 9	90	-	20	45	4.5	40.5
F 10	80	-	20	45	4.5	30.5

* All formulation contains 250 mg of CL

** Marketed conventional tablet of CL (Maclar-250)

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Density Measurement of Tablet

Density of tablets was calculated from their volumes and masses in triplicate. The volume V of the cylindrical tablets were calculated from their height h and radius r (both determined with a verniar caliper) using the mathematical equation for a cylinder ($V = \pi \times r^2 \times h$). The tablets with ~1 g/cm3 density or less were chosen for further studies.[6]

Buoyancy Test

Formulations F 1 to F 10 were subjected to buoyancy test. Buoyancy test was done by using USPXXII apparatus-2 at 100 rpm maintaining 37±0.5 ^{0}C temperature. Tablets were placed in jar containing HCL buffer of pH 1.2. The time between introduction of the dosage form and its buoyancy on the acidic buffer pH 1.2 and the time during which dosage form remain buoyant were measured.[7]

Table 2.
Physical properties of Floating-Mucoadhesive tablets.

Formulation	Density of tablet (g/cm^3)*	Floating-lag time (s)*
F 1	1094 ± 0024	0
F 2	1054 ± 0018	58 ± 596
F 3	1009 ± 0007	35 ± 616
F 4	1074 ± 0014	30 ± 402
F 5	1073 ± 0004	151 ± 872
F 6	1089 ± 0019	114 ± 1550
F 7	1086 ± 0034	109 ± 1041
F 8	1055 ± 0040	177 ± 1206
F 9	1028 ± 0004	213 ± 1361
F 10	1023 ± 0018	384 ± 1931

*±Standard deviation (n=3)

Mucoadhesive Force Measurement

Mucoadhesive force measurement of tables was done by modifying balance method [8].The right pan was replaced with a glass beaker container and on the left side beaker with a copper wire. Teflon block of 1.5 cm diameter and 3 cm height was adhered strongly with the glass beaker. The

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two sides were then adjusted, so that the left hand side was exactly 5 gms heavier than the right. Stick the stomach on the teflon block with help of the cynoacrylate glue and fill the beaker with acidic buffer till the tissue remains in a moist condition. Stick the tablet to beaker and put on the tissue for a 15 minute. After 15 minute add water slowly in to right beaker until the tablet detaches. Weight the water required for the tablet detachment. Calculate Actual weight for detachment and force of adhesion in dyne by following equation

Actual weight for detachment (W) = weight for detachment (g) – 5

Swelling Study

Formulations F 2 to F 10 were subjected to swelling study for 10 hours. Swelling study was done by using USPXXII apparatus at 37± ^{0}C temperature using HCl buffer having 1.2 pH. Initially weighted tablet was placed in each jar filled with 900 ml of HCl buffer; tablets were weighed at time interval of 1 hour to 10 hour. % swelling of the tablets was determined by the following equation [9].

$$Force\ of\ mucoadhesion\ in\ dyne = Mucoadhesion\ in\ gm \times 0.0981$$

$$\%\ Swelling = \frac{Weigh\ of\ tablet\ after\ swelling - Initial\ weight\ of\ tablet}{Initial\ weigh\ of\ tablet} \times 100$$

In-Vitro Release Study of Floating - Mucoadhesive Tablet

In-vitro release study of tablets was done using USPXXII dissolution test apparatus. Jar was filled with HCl buffer of pH 1.2 and temperature was maintained at 37±0.5 ^{0}C. Paddle was revolved at 100 rpm speed. Five ml of sample was withdrawn after interval of 1 hour and replaced with 5 ml of fresh dissolution medium to maintain sink condition. Samples were then analyzed spectrophotometrically for drug content at 485 nm. The release data obtained were fitted to Zero order, fist order, higuchi and Korsemeyer and Peppas equation to determine the corresponding release rate and mechanism of drug release from the floating-mucoadhesive tablet.

FT-IR Spectroscopy

The pure drug and Tablet (F 10) was mixed with IR grade potassium bromide in a ratio of (1:100) and pellets were prepared by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over range of 4000-400cm^{-1} in FTIR instrument.

DSC Study

The possibility of any interaction between CL and excipients used in formulations during tablet processing was assessed by carrying out the thermal analysis on pure drug and formulation F 10 using differential scanning calorimetry.The thermograms of samples were obtained at a scanning rate of 10^0 C / min conducted over range of 50-300^{0}C.

Stability Study

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To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. Optimized formulation was sealed in aluminum packaging coated inside with polyethylene, and then kept in stability chamber maintained at 45 °C and 75% RH for 3 months. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, floating behavior and other physicochemical parameters [10-11].

RESULT AND DISCUSSION

Buoyancy Test

Buoyancy test of all formulations was performed in acidic buffer pH 1.2 at 37 ± 5 ^{0}C for 10 hour. Marketed tablet was unable to float while formulations F 2 to F10 float for 10 hour without disintegration. Buoyancy of tablet was due to the density of prepared formulation (density ≈1) which is equivalent to gastric fluid density. Floating lag time was varied in all formulation as shown in Table. 2. Increase in concentration of polymer decreases the floating lag time. Formulation F 4 was having lowest lag time 30 ± 4.02 second while the F 10 was having lag time of 384 ± 19.31 second. Higher lag time in formulation F 10 was due to high density polymer carbopol 974P. During buoyancy study of the tablet there was no change in shape in case of formulation containing HPMC while formulation F 8 to F 10 shows change in shape due to the carbopol 974P [12].

Mucoadhesive Force Measurement

Adhesion was reported to be effected by hydration. Hydration of the mucoadhesive polymer is essential to initiate the mucoadhesive bonding process. In case of tablets applied in the dehydrated state, which is most convenient, it is essential that sufficient water is available so that rapid hydration takes place, and a flexible rubbery state occurs. The capillary force arises when water from the space between the mucosa and the polymer was taken up by a dry system. Once the bond is formed, reduction in the rate of swelling due to water uptake from the tissue surface may only prolong the association of the tablet with the mucosa. Removal of water from the underlying mucosa layer by the hydrating polymer may increase the cohesive forces of mucus; this plays a vital role in the establishment of an effective mucoadhesive bond.[13]

Modified balance method was used for the measurement of mucoadhesive force. During measurement of mucoadhesive force 15 min contact time was kept constant. Mucoadhesive force depends on the viscosity and concentration of the polymer. Formulation F2 was having lowest mucoadhesive force because the HPMC K4M having lower viscosity. While formulation (F 7) containing HPMC K15M shows higher mucoadhesion force due to higher viscosity (Fig. 2)

In order to increase the mucoadhesive strength of low viscosity polymer containing HPMC K4M was combined with carbopol 974P having good mucoadhesive property. This combination results in good mucoadhesive properties as seen in F 8 to F10. From the above results it was found that polymers having high molecular weight and high viscosity exhibited higher adhesion. HPMC K15M and Carbopol 974P were found to be having good mucoadhesive strength. HPMC and carbopol possesses hydroxyl and carboxyl groups respectively required for bioadhesion.

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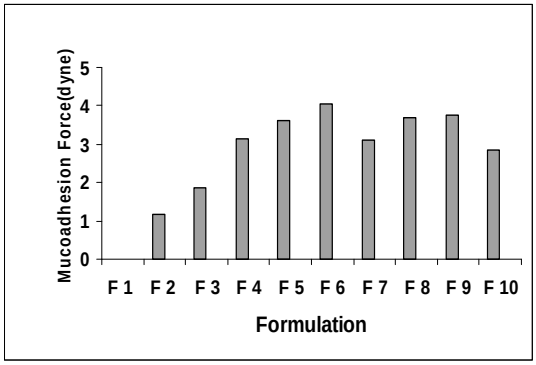

Fig 2. ***Mucoadhesion Force Study***

Swelling Study

Results showed that polymers with higher concentration had lower swelling this was due to the fact that polymers concentration restricts the movement of the polymers (Fig. 2). Formulations containing HPMC K 4 M i.e. F2, F3 and F4 had higher % Swelling than formulations containing HPMC K 15 M i.e. F5, F6 and F7. Polymers HPMC K4M and Carbopol 974P have higher cross linking this indicates that polymers having cross linking constrain and therefore the polymer did not open up easily. Fabergas and Gareia have reported a correlation between % Swelling and mucoadhesive strength. Initial swelling due to hydration aided bioadhesion but further swelling induced over-extension of hydrogen bonds and other forces this resulted in lower bioadhesion. % Swelling decreased with polymer concentration because high concentration of the polymer restricts its movement.

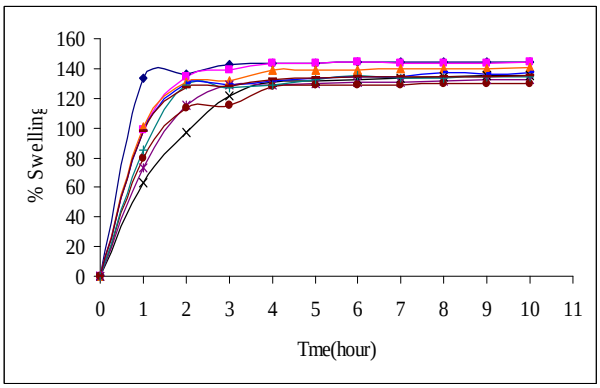

Fig 3. ***Swelling study of all formulation, (♦)F 2, (■) F 3, (▲)F 4, (×)F 5,(*) F 6 (•)F 7,(ו)F 8(–),F 9 and (—) F 10***

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In-Vitro Release Study of Floating-Mucoadhesive Tablet

In vitro drug release shows that except the conventional tablets, all formulations tested showed controlled release for 10 hours. All formulations (F 2 to F10) remained floating and swelled during dissolution test. Marketed conventional tablet remain sink and completely releases the drug within 2 hour. As expected, the drug release rate was dependent on the viscosity grade and the concentration of the polymers used. In formulation F 2 to F 4 HPMC K4M was used which having low viscosity while in formulation F 5 to F 7 HPMC K15M was used having higher viscosity than the HPMC K4M, so formulation F 2 to F 4 gave higher release than the formulation F 5 to F 7. HPMC K4M combined with carbopole-974P shows drug release retardation as seen in formulation F8 to F 10. Formulation F 2 has given 95.93±3.95 % release after the 10 hour, as the increase in polymer concentration retard the release rate of CL. Several kinetic models are described for drug release from floating mucoadhesive tablets. The model that best fits the release data was evaluated by correlation coefficient (r). The r - value was found to be higher in zero order models as compared to first order model which indicates the formulations follows zero order release kinetic mechanisms (F 2 and F 10 optimized formulation). The n-value of the korsmeyer-peppas is greater than 0.5 that indicates formulation followed non-fickian release. So the drug release from floating-mucoadhesive tablets was found to be diffusion controlled and followed zero order kinetics.[14-15]

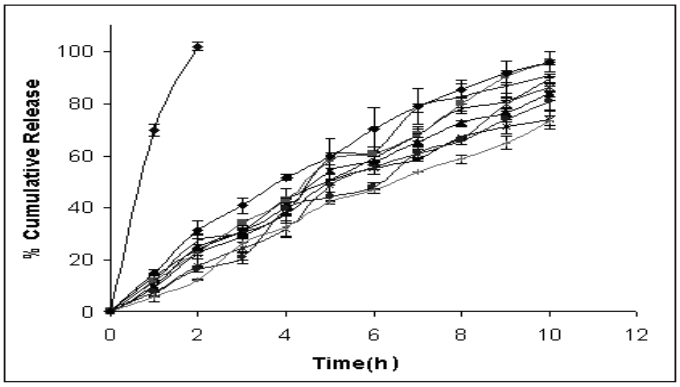

Fig 1. ***Cumulative drug releases from tablet, F 1 (♦)F 1, (■) F 2, (▲)F 3, (×)F 4,(*) F 5 (•)F 6, (ǀ)F 7(–),F 8 , (—) F 9 and(♦)F 10***

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FT-IR Spectroscopy

Pure drug and formulation were characterized for drug – excipient interaction using FT-IR study. Drug shows characteristics peaks such as –CH- stretch (2929.6 cm−1), C=O stretch (1635.53 cm−1), C-N bend (1278.72 cm−1), C-OH, stretch (3384.84 cm−1). The characteristic peaks of CL were not altered after encapsulation, indicating no chemical interaction between drug and polymer

DSC Study

Result of DSC study shown in Fig. 4. CL shows thermal peak at 220 ^{o}C and the tablet formulation also given the same characteristic peak at 220.31^{o}C indicates no endothermic degradation of CL in the formulation.

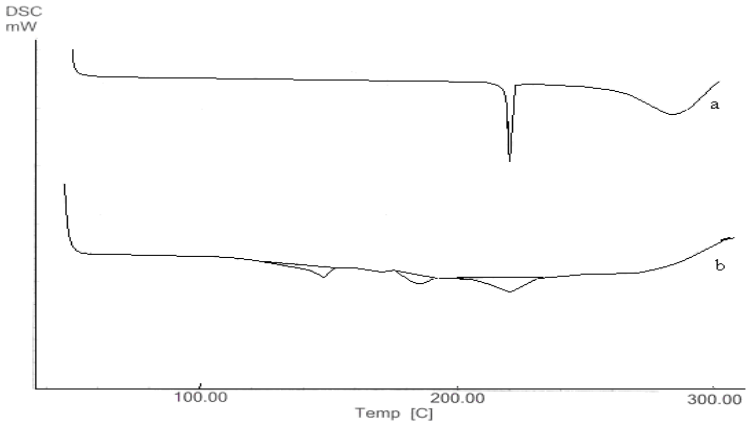

Fig 4. ***DSC Thermogram, (a) clarithromycin (b) Tablet Formulation***

Stability Study

In view of the potential utility of the formulations, stability studies were carried out at 45°C and 75% RH for three months (climatic zone IV condition for accelerated testing) to assess their long-term (2 years) stability. The protocols of stability studies were in compliance with the guidelines in the WHO document for stability testing of products intended for the global market. The analysis of the parameters such as dissolution floating behavior, mucoadhesion, drug content (Table.3) and efficiency of dissolution data (Fig. 5) after storage at 45 °C and 75% RH for three months was done. Hardness of tablet remains remaining constant between 5-6 kg / gm^{3}.

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Table 3.
Comparison Mucoadhesion, floating lag time and % Drug content of F 2 before and after Stability Study.

Formulation	Mucoadhesion force (dyne)	Floating lag time (s)	Percentage Drug Content
After 3 month F 2	1079	6174±379	98.11
F 2	1778	5843±596	99.52

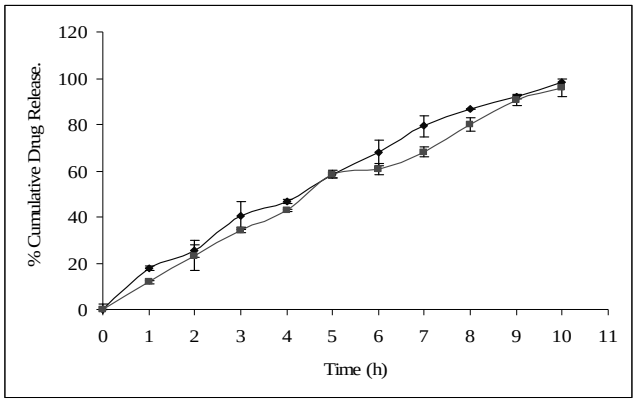

Fig 5. ***Graph of Time Vs % cumulative Drug Release F 2 and after Stability Study of F 2, (♦) Formulation F 2 and (■) After stability study F 2***

CONCLUSION

CL is the drug of choice as H. *pylori* resistance rates are much lower for CL as compared to other antibiotics like amoxicillin and tetracycline. Stomach-specific antibiotic drug delivery would be highly beneficial in the treatment of H. pylori infection in peptic ulcer disease. Floating - Mucoadhesive tablets of CL are potential dosage form due to prolonged residence in stomach for complete removal *H.Pylori* as compared to conventional marketed tablet.

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