WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 8, 1920-1932. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF MUCOADHESIVE TABLETS OF ANTIBIOTIC USED IN THE TREATMENT OF *HELICOBACTER PYLORI* INFECTION

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Article Received on
09 June 2020,

Revised on 29 June 2020,
Accepted on 19 July 2020,

DOI: 10.20959/wjpr20208-18254

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ABSTRACT

The main aim of this investigation was to optimize and develop mucoadhesive formulations using the combination of Almond gum (AG) and Carbopol 940 (CP) with Clarithromycin as a model drug and their evaluation. Direct compression technique was employed for the preparation of mucoadhesive tablets. A 3^2 full factorial design (FFD) was constructed where the amounts of AG (X_1) and CP (X_2) were selected as the independent factors. All formulations were tested for pre and post-compressional parameters. Physical characterization of drug shows good agreement with literature values. FTIR studies showed no evidence of interactions between drug, polymers and excipients. The hardness, friability, weight variation, drug content, mucoadhesive strength, *in vitro* release were uniform and reproducible. However, the AG and CP markedly affected the mucoadhesion strength and the release profile. As amount of polymers increases mucoadhesive strength increases and drug release decreases. Statistical experimental design and data analysis using response surface methodology is also illustrated. The *in vitro* release kinetics studies reveal that all formulations fits well with Korsmeyer-Peppas model and the mechanism of drug release is non-Fickian diffusion. The investigation results clearly

indicated that, combination of AG and CP be capable of mucoadhesive polymer for drug delivery.

KEYWORDS: Clarithromycin, mucoadhesion, Almond gum, Carbopol 940.

INTRODUCTION

Helicobacter pylori (H. pylori) is a type of bacteria. These germs can enter your body and live in your digestive tract. After many years, they can cause sores, called ulcers, in the lining of your stomach or the upper part of your small intestine. For some people, an infection can lead to stomach cancer.[1] During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached.[2-4]

Although some important applications, including oral administration of peptide and protein drugs, can be used to prepare colonic drug delivery systems, targeting drugs to the colon by the oral route. More often, drug absorption is unsatisfactory and highly variable among and between individuals, despite excellent in vitro release patterns. The reasons for this are essentially physiological and usually affected by the gastrointestinal (GI) transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability.[5-7]

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the GI tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems.[8-9]

Stomach specific (Gastric retention) will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.[10] Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.[11]

Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the

stomach. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.[12,13]

Helicobacter pylori is a prevalent human specific pathogen, which is now believed to be the causative bacterium for chronic gastritis, peptic ulcer and adenocarcinoma, one of the most common forms of cancer in humans and its eradication requires high concentration of drug within the gastric mucosa for long duration. Thus, mucoadhesive drug delivery system is expected to remain attach to gastric mucosa in a lasting way upon the gastric contents and enhance bioavailability of all drugs which are well absorbed from the GI tract.[14]

The present study was aimed at the development of stomach site specific drug delivery system using approach like mucoadhesive matrix tablets of Clarithromycin.

MATERIALS AND METHODS

Clarithromycin (CLM) was obtained as a gift sample from Ajanta Pharma, Aurangabad. Almond gum (AG) samples were purchased from the Paccha Wholesale Supermarket Chennai, Tamil Nadu, India. Carbopol 934 (CP), Dibasic calcium phosphate (DCP), Magnesium Stearate (MS) and directly compressible lactose (DCL) were purchased from Rajesh Chemicals, Mumbai. All other chemicals used in study were of analytical grade.

Preformulation studies

Preformulation study is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rationale development of dosage forms.[15]

Preparation of Standard Calibration Curve of Clarithromycin (CLM)[16]

Preparation of stock solution: Accurately weighed 100 mg of Clarithromycin was transferred to the 100 mL volumetric flask. Then approximately 50 mL of phosphate buffer solution (PBS) of pH 6.8 was added and resulting solution was sonicated for 5 min. Further required quantity of PBS pH 6.8 was used to adjust volume of solution to 100 mL and the resulting solution obtained was 1000 µg/mL.

Preparation of serial dilution: From the stock solution pipette out 10 ml solution, make up to 100ml. prepared 10,20,30,40, 50, 60µg/mL using 1,2,3,4,5,6 ml of above stock solution respectively. Finally the absorbance of prepared solutions was measured against blank (PBS pH 6.8) at 210 nm by using UV visible Spectrophotometer and calibration was plotted.[41]

Drug excipients compatibility studies[17]

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote consistent release improve bioavailability of the drug and protect it from degradation. The FT-IR spectrum of pure drug and physical mixture of polymers were analyzed to verify the compatibility between the pure drug and polymers using by KBr disc method. The procedure consisted of dispersing a sample (drug alone or mixture of drug and polymers in 1:1 ratio) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained to identify functional group and bond of drug or its mixture.

Preparation of Mucoadhesive tablets

Table 1 lists the composition of different mucoadhesive formulations prepared using varying amounts of Almond gum (AG), Carbopol 940 (CP), Direct Compressible Lactose (DCL) along with a fixed quantity of Mg. Stearate, Talc and dibasic calcium phosphate (DCP). Mucoadhesive tablets were prepared by a direct compression method. In the beginning, drug, polymers (AG and CP) and diluents were mixed homogeneously. This mixture was grinded in morter and pestle and then passed through the sieve. Finally lubricant was added and mixed for 5 minutes. The mixture was then compressed on 10 station tablet punching machine using 13 mm punches at a pressure of approximately 6-7 kg /cm^2.

Table 1: Composition of different mucoadhesive formulations.

Sr. No.	Ingredients*	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	CLM	500	500	500	500	500	500	500	500	500
2	AG	40	40	40	80	80	80	120	120	120
3	CP	40	60	80	40	60	80	40	60	80
4	DCP (3%)	24	24	24	24	24	24	24	24	24
5	DCL	180	160	140	140	120	100	100	80	60
6	Mg. stearate and Talc 1:2 (2%)	16	16	16	16	16	16	16	16	16
Total weight		**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**

*All values are in mg

Evaluation of Prepared Mucoadhesive Tablets

All formulations were evaluated for uniformity in tablet weight and thickness. Diameter and thickness of tablets were determined by using vernier caliper (Mitutoyo, Japan). Each formulation was also examined for friability using a Roche-type friability apparatus and hardness using a Monsanto-type hardness tester and drug content determination.[17-19]

Determination of Mucoadhesive Strength

The mucoadhesive strength of each formulation (n=3) was determined by using the apparatus which was locally assembled and was a modification of the one described and applied by Gupta A *et al* as shown in Fig. 1 Stomach mucosa was obtained from the local slaughterhouse. A load of 5.0 gm was placed as the initial pressure on the upper rod for three minutes. After 3 min, water was added into container present on the right pan through the burette at constant flow until the complete detachment of tablets from mucosa takes place. The water collected in the container was measured and expressed as weight (g) required for the detachment. Mucoadhesive strength was assessed in terms of weight (g) required to detach the tablet from the membrane.[20-22]

Fig. 1: Modified Mucoadhesion Test Apparatus.

***In-vitro* dissolution study of Clarithromycin mucoadhesive tablet[23]**

The *In vitro* release of formulated tablets was carried out in USP-type II dissolution apparatus using 900 mL dissolution medium (0.1 N hydrochloric acid solution, pH 1.2) maintained at

37 ± 0.5^0C at stirring speed of 50 rpm. Three tablets from each formulation were tested individually in a 0.1 N hydrochloric acid for eight hour. Simultaneously, samples measuring 5 mL were withdrawn periodically at different time intervals. The samples were filtered and analyzed for drug content in a U.V. Spectrophotometer at 210 nm. Sample of 5 mL of dissolution media from a drug devoid tablet, run simultaneously under similar condition, was used as a blank. The same volume was replenished into dissolution chamber to maintain sink condition.

Kinetics of Drug Release

The dissolution profile of the batches were fitted to Zero order kinetics, First order kinetics, Higuchi, Korsmeyer and Peppas to ascertain kinetics modeling of drug release by using a manually calculations on computer.[23,24]

Korsmeyer- Peppas equation: $\% R = Kt^n$

$\text{Log } \%R = \log k + n \log t$

Where, n= release exponent.

This model is widely used; when the release mechanism is not well known or when more than one type of release phenomena could be involved.

RESULTS AND DISCUSSION

Physical characterization of drug sample

The received sample of Clarithromycin was found to be white crystalline and odorless powder. The average melting point of Clarithromycin was determined by thiel's tube method in triplicate and was found to be 218^0C, which is in good agreement with reported melting point range $217\text{-}220^0$C.

Construction of calibration curve of Clarithromycin

Standard calibration curve of Clarithromycin in 0.1 N hydrochloric acid (HCl) solution (pH 1.2) was plotted by using the observation in shown in Fig. 2.

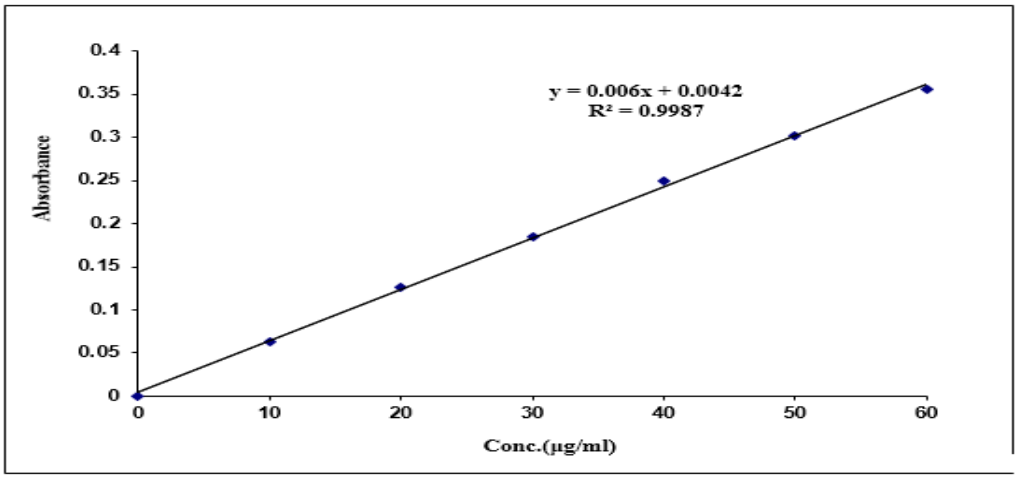

Fig. 2: Standard calibration curve of Clarithromycin.

Drug Polymer Compatibility Studies

FT-IR Spectra of Clarithromycin, polymer and formulation containing different excipients were recorded. The characteristic peaks due to pure Clarithromycin shows IR absorption at 3398.57cm^{-1} (NH, stretching), 3053.32cm^{-1} (CH stretching), 1629.85 cm^{-1}(asymmetric C=O, stretching), 1270.88 (C-C stretching).

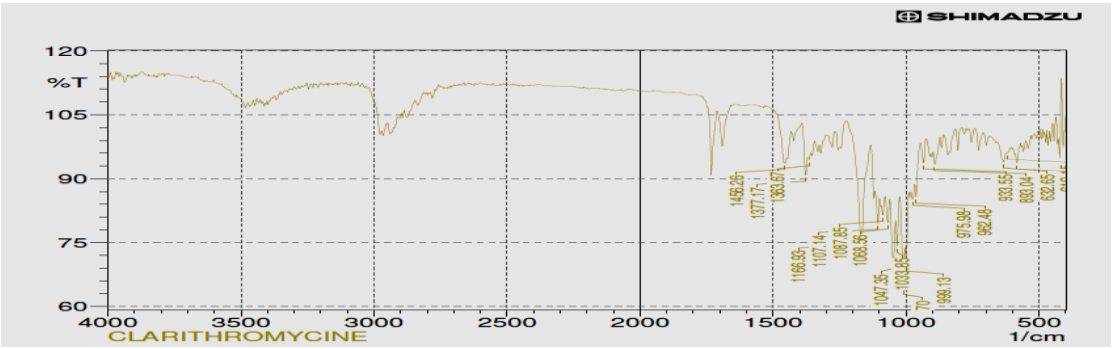

Fig. 3: IR spectra of Clarithromycin.

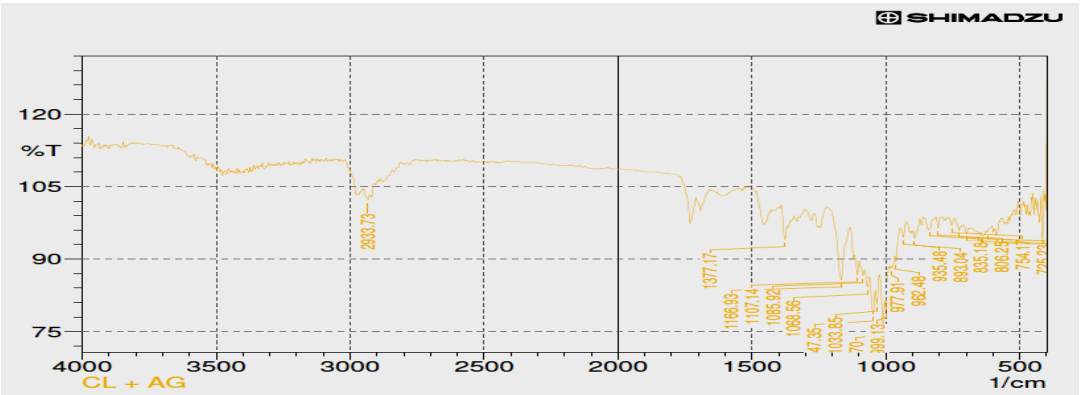

Fig. 4: IR spectra of mucoadhesive formulation.

Evaluation Precompression parameters of powder blend

Powder blends of all formulations were evaluated for Angle of repose, Bulk density, Tap density, Compressibility index and Hausner's ratios were computed from the data. The values are given in Table 2 (n=3).

Table 2: Rheological properties of powder blend of F1 to F9.

Batch	Angle of repose(θ)	Bulk density(g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner's ratio
F1	30.10±0.60	0.483±0.015	0.568±0.011	14.96±0.01	1.17±0.01
F2	32.43±0.68	0.487±0.005	0.554±0.007	12.09±0.05	1.13±0.04
F3	32.33±0.27	0.510±0.015	0.585±0.015	12.82±0.10	1.14±0.02
F4	31.40±0.73	0.532±0.015	0.610±0.035	14.66±0.02	1.14±0.01
F5	30.44±0.51	0.532±0.001	0.595±0.013	10.58±0.02	1.11±0.01
F6	30.33±.34	0.534±0.012	0.603±0.011	11.44±0.03	1.12±0.10
F7	34.54±0.29	0.577±0.025	0.647±0.062	12.17±0.02	1.12±0.08
F8	33.61±0.15	0.575±0.013	0.662±0.023	13.14±0.01	1.15±0.06
F9	32.51±0.11	0.576±0.014	0.656±0.016	12.19±0.01	1.13±0.03

*Average of three values (n=3) ±Standard Deviation

Evaluation Post compression parameters of formulations

Tablets of all batches were evaluated for thickness, hardness, friability, weight variation, drug content uniformity and results were tabulated in Table 3.

Table 3: Evaluation parameters of formulations.

FC	Diameter* (mm) ± S.D.	Thickness* (mm) ± S.D.	Hardness* (kg/cm^2) ± S.D.	Friability (%)	Average weight (mg) ± S.D.	Drug content* (%) ± S.D.
F1	12.99 ±0.04	5.16 ±0.01	6.5 ±0.47	0.41	800.65 ±1.29	98.73 ± 0.383
F2	12.98 ±0.01	5.15 ±0.02	6.4 ±0.1	0.40	800.41 ±1.12	98.74 ± 0.379
F3	12.98 ±0.06	5.14 ±0.01	6.4 ±0.32	0.36	800.50 ±1.74	98.84 ± 0.445
F4	12.98 ±0.07	5.16 ±0.01	6.3±0.42	0.38	800.05 ±1.37	98.72 ± 0.395
F5	12.98 ±0.04	5.15 ±0.03	6.2±0.41	0.37	801.10 ±1.13	99.07 ± 0.866
F6	12.99 ±0.06	5.12 ±0.06	6.1±0.54	0.38	799.55 ±1.18	98.53 ± 0.890
F7	12.98 ±0.05	5.16 ±5.15	7.2±0.32	0.42	799.85 ±1.65	99.05 ± 0.470
F8	12.99 ±0.06	5.15 ±0.02	7.3±0.65	0.38	800.03 ±1.11	97.97 ± 0.078
F9	12.98 ±0.02	5.16 ±0.03	7.4±0.41	0.39	800.68 ±1.35	99.33 ± 0.75

*Average of three values (n=3) ±Standard Deviation

Mucoadhesive Strength

The mucoadhesive strength of prepared mucoadhesive tablet**s** was studied using goat gastric mucosa. Mucoadhesion is considered to occur in four major stages wetting, interpenetration,

adsorption and formation of secondary chemical bonds between mucus membrane and polymer.

The Mucoadhesive Strength (expressed in gm) of Clarithromycin was calculated for all the formulations of mucoadhesive tablets. The study was carried out in triplicate. Table 5 shows the results of the Mucoadhesive Strength in each formulation with S.D. values.

The highest mucoadhesive strength was due to pronounced swelling upon hydration of these polymers, the maximum mucoadhesive strength shown by formulation F9 i.e. 29.58±0.24g (Table 4). The lowest mucoadhesive strength was 11.50±0.22 g observed with formulation F1 which containing less amount of Almond gum and Carbopol 940 because of low swelling and rapid detachment upon hydration. Mucoadhesive strength was found in the following order: F9 > F8 >F7>F6>F5>F4>F3>F2>F1.

Table 4: Mucoadhesive Strength of Clarithromycin mucoadhesive tablets.

Formulation code	Mucoadhesive strength (g)*
F1	11.50±0.22
F2	13.63±0.22
F3	15.41±0.15
F4	14.68±0.24
F5	17.47±0.19
F6	22.52±0.23
F7	20.76±0.18
F8	25.55±0.21
F9	29.58±0.24

*Average of three values (n=3) ± Standard Deviation

***In-vitro* drug release Study**

The *In vitro* release of formulated tablets was carried out in USP-type II dissolution apparatus using 900 mL dissolution medium (0.1 N hydrochloric acid solution, pH 1.2) maintained at 37±0.5^{0}C at stirring speed of 50 rpm.

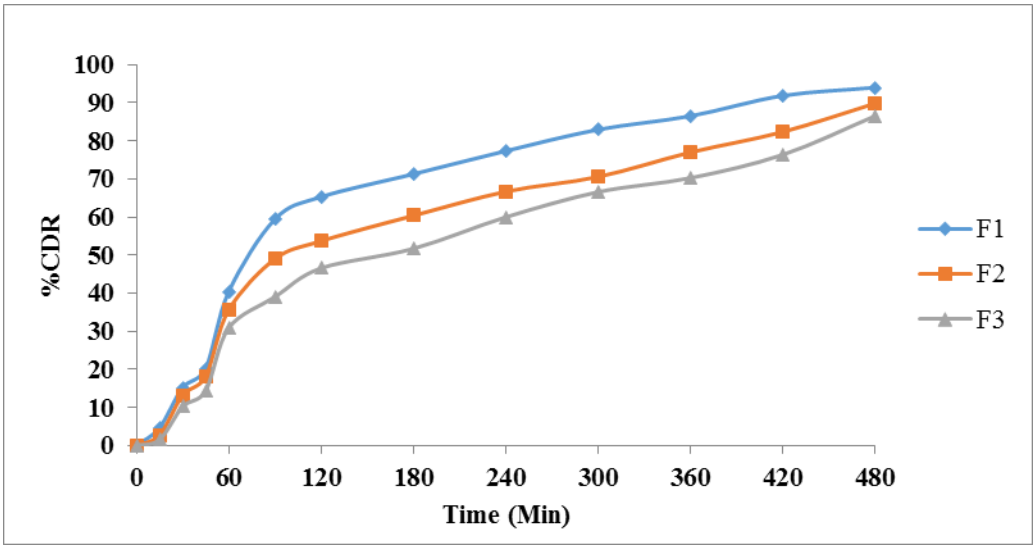

Fig. 5: Percent Cumulative Drug Release F1-F3.

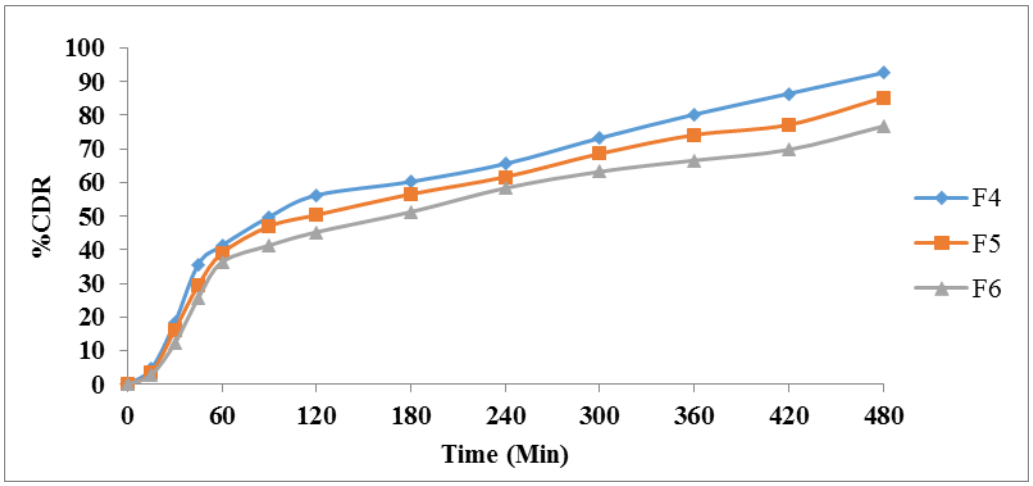

Fig. 6: Percent Cumulative Drug Release F4-F6.

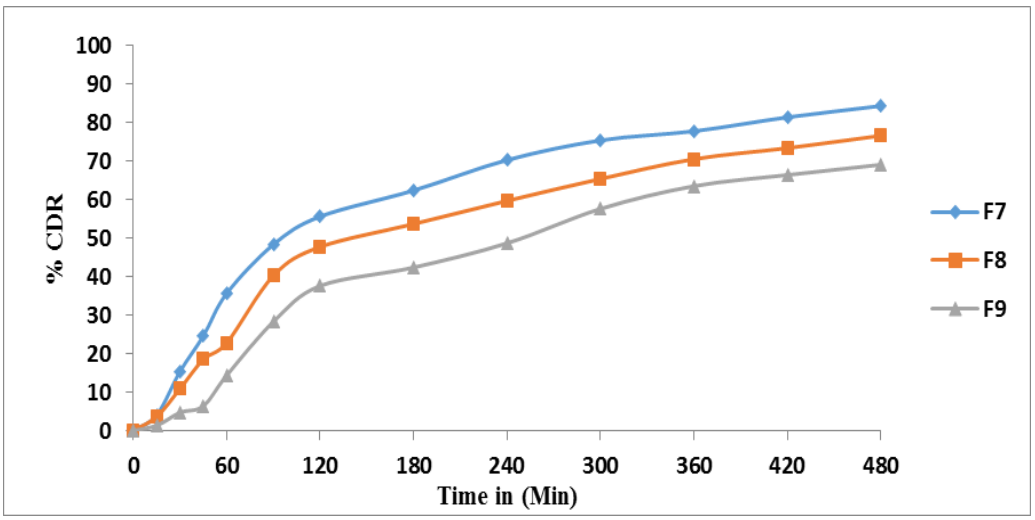

Fig. 7: Percent Cumulative Drug Release F7-F9.

The release rate was found to be decreasing with increasing amounts of either Almond gum or Carbopol 940. *In vitro* release data obtained was statistically analyzed by ANOVA at p <0.05 and found that the data at any point of time are significant.

7.11 Drug release kinetics[24]

In order to know the drug release mechanism, the data was further analyzed by Korsmeyer-Peppas equation and the value of n i.e. release exponent was calculated. The drug release data was analyzed by the following simple power equation:

Log % R= log k + n log t

Table 5: Drug release kinetics.

Formulation Code	'n' value	Drug transport mechanism
F1	0.79138	Non-fickian diffusion or Anomalous transport. (0.45< n < 0.89)
F2	0.75409	
F3	0.72145	
F4	0.75541	
F5	0.71076	
F6	0.67174	
F7	0.7147	
F8	0.68055	
F9	0.65738	

The n values were found to be between 0.65738-0.79138, indicating non-fickian diffusion or anomalous transport. The n (0.45< n < 0.89) value also revealed the drug release mechanism via diffusion coupled with erosion.

CONCLUSIONS

In the present study mucoadhesive matrix tablets of Clarithromycin was developed as stomach site specific drug delivery system. However the AG and CP markedly affected the mucoadhesion strength and the release profile. Mucoadhesive strength and drug release was found to be a function of amount of polymers. As amount of polymers increases mucoadhesive strength increases and drug release decreases. All experimental data obtained was statistically analyzed by ANOVA at p< 0.05 and found that the data at any points are significant.

Based on the results obtained so far, it was concluded that, the objectives of the investigation was fulfilled. The investigation so far has indicated that, stomach site specific drug delivery systems using approach like mucoadhesive matrix tablets of Clarithromycin containing AG

and CP can showed good mucoadhesion and drug release. Therefore, these polymer combinations, AG and CP have potential for consideration for drug delivery as mucosal dosage forms.

ACKNOWLEDGEMENTS

The authors are thankful to The Management of HSBPVT's, GOI, College of Pharmacy, Kashti for permitting to carry out the research work in the laboratories. The authors are also thankful to Ajanta Pharma, Aurangabad for providing the gift sample.

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