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ORIGINAL ARTICLE

Formulation and Evaluation of Sustained Release Mucoadhesive Oral Dosage Form Containing Clarithromycin Using Natural And Synthetic Polymer

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ABSTRACT
Formulation and Evaluation of mucoadhesive tablets of Clarithromycin using Guar gum as natural polymer and carbopol as synthetic polymer to impart mucoadhesion. Clarithromycin is a macrolide antibiotic used in treatment of peptic ulcer and works by stopping the growth of causing bacteria 'Helicobacter pylori'. The short biological half-life of drug favours development of sustained release formulation. And for this, guar gum and carbopol is used as sustained release mucoadhesive polymer and lactose, talc and magnesium stearate is used as remaining excipients. Direct compression method is used for the tablet formulation. Tablets were evaluated by various precompression and postcompression parameters such as, compatibility study, hardness, thickness, In vitro drug release, swelling index etc. Total 6 batches was formulated among this F6 batch was found to be the optimised batch with uniformity weight 349 mg, thickness 3.5, hardness 6.3, friability 0.52, drug content 98.99, drug release 84.48, swelling index 48.64, bioadhesion strength 33.2. This research includes that mucoadhesive tablets of clarithromycin can be a good way to bioadhesion properties and improve the bioavailability of clarithromycin.
Keywords: *Clarithromycin, natural and synthetic mucoadhesive polymer, evaluation, matrix tablet, In vitro drug release.*

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INTRODUCTION

Mucoadhesion describes the attractive forces between a biological material and mucous membrane [1]. Mucous membranes adhere to epithelial surfaces such as the gastrointestinal tract (GI-tract), the vagina, the lung, etc. They are generally hydrophilic as they contain many hydrogen macromolecules due to the large amount of water (approximately 95%) within its composition. However, mucin also contains glycoproteins that enable the formation of a gel-like substance [1]. Understanding the hydrophilic bonding and adhesion mechanisms of mucus to biological material is of most importance in order to produce the most efficient applications. For example, in drug delivery systems, the mucus layer must be penetrated in order to effectively transport micro or Nano sized drug particles into the body [2].

Mucoadhesion involves various types of bonding mechanisms, and it is the interaction between each process that allows for the adhesive process such as wetting theory, adsorption theory, diffusion theory, electrostatic theory, and fracture theory [3]. Specific processes include mechanical interlocking, electrostatic, diffusion interpenetration, adsorption and fracture processes [4].

Mucoadhesive tablets are the oral and most convenient dosage form.The present research was aimed to formulate and evaluate oral sustained release mucoadhesive matrix tablets of clarithromycin which is completely absorb by gastrointestinal tract.

Clarithromycin is a macrolide antibiotic used in treatment of peptic ulcer and works by stopping the growth of causing bacteria '*Helicobacter pylori'*. The short biological half-life of drug favors development of sustained release formulation [5].

Helicobacter pylori is a pathogen act as a causative agent for chronic gastritis, peptic ulcer etc [6]. Therefore it become necessary to formulate oral dosage form to deliver clarithromycin to increase the efficiency of drug and provide sustain action.

MATERIAL AND METHODS

Material

Clarithromycin was received as gift sample from Flemingo Pharmaceuticals, Thane, India, Guar gum (Research lab fine chem. Mumbai, India), Carbopol 934 (Research lab fine chem. Mumbai, India),), Magnesium stearate (HILAB chemicals, Shrirampur, India), Talc (Thermosil fine chem. Khed, Pune, India), Lactose (G.S. lab, India).

Method

Sustained release mucoadhesive tablet of clarithromycin was prepared by direct compression method. Sustained release layer was prepared by using natural and synthetic polymer at different concentration.
Clarithromycin mucoadhesive tablets was prepared by direct compression method. Clarithromycin, Carbopol 934, Guar gum, lactose was weigh accurately and mixed and blended in mortar. Then the mixture was passed through 60 sieve, then add talc and magnesium stearate. Then the mixture was compressed in rotary tablet compression machine (make-CREATE INDUSTRIES, MODEL-LP-8GMP).

Table 1. FORMULATION TABLE FOR DEVELOPMENT OF MUCOADHESIVE TABLETS.

Ingredients	F1 (Mg)	F2 (Mg)	F3 (Mg)	F4 (Mg)	F5 (Mg)	F6 (Mg)
Clarithromycin	250	250	250	250	250	250
Guar gum	50	70	90	-	-	-
Carbopol	-	-	-	50	70	90
Lactose	40	20	-	40	20	-
Talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5

Preformulation study:-

Identification by U.V. visible spectropthotometer

50 mg of clarithromycin Hcl was weighed accurately and transferred it into 50 ml volumetric flask. Dissolve it into 0.1N HCL1.2 pH and make the volume up to 50 ml with respective solvent. This was a stock solution (1000mcg/ml). Further dilutions were made by using this stock solution and scanned in the range of 400-200 nm using U.V. spectrophotometer (SHIMADZU U.V.1800) [6].

Melting point

Melting point of clarithromycin was determined by using melting point apparatus by capillary method [7].

Solubility [9]

The solubility of drug was done by dissolving 10 mg of drug in 10 ml of solvent such as acetone, methanol, ethanol, acetonitrile, distilled water etc.

Compatibility study by FT-IR [6, 7, 8]

The compatibility study of clarithromycin with excipients was studied by FTIR spectroscopy. The method used for study is pressed KBr pellet method and the ratio of sample is should be 1:100, where 1 is a part of drug sample and 100 is a part of KBr. The scanning range was 4000-400 cm^{-1} at ambient temperature. (Perkin Elmer Spectrum-65).

Precompression study [7, 8]

Bulk density and tapped density

The measured quantity of drug was introduced into the measuring cylinder and initial volume was noted. Then the cylinder was allow to tap. The tapping was continue until no any change in volume was observed.
The bulk density and tapped density was determined by using formula,
Bulk density= mass/ bulk volume
Tapped density= mass/ tapped volume

Hausner's ratio

Hausner's ratio was calculated by formula, tapped density/bulk density. It is the number that is correlated to the flowability of powder.

Carr's index [6]
Carr's index was calculated by formula:

$$Carr's index = \frac{Tapped\ density - Bulk\ density}{tapped\ density} X\ 100$$

Table 2. Relationship between carrs index and their type of flow

SR.NO.	Carr's index	Type of flow
1	5-15	Excellent
2	12-18	Good
3	18-23	Satisfactory
4	23-35	Poor
5	36-38	Very poor
6	>40	Extremely poor

Angle of repose [6,7]
The angle of repose was determined by fixed funnel method, the funnel was fixed at certain height and allow powder to flow through it. Then measure the height and radius of cone.
Angle of repose was calculated by applying formula
Angle of repose= $\tan^{-1} h/r$
Where,
h= height of cone,
r= radius of cone.

Table 3.The relationship between angle of repose and powder flow is given as follows,

Sr.no	Angle of repose	Powder flow
1	< 25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Post compression evaluation [6, 7,10]
Weight uniformity
The weight uniformity of tablet was determined by selecting 10 tablets. Then each tablet weigh individually and compared with average weight of tablet.
Thickness
The Vernier calliper is used to measure the thickness of tablet. 5 tablets selected randomly and thickness was measured in mm.

Table 4. Limits for tablet weight variation

Average weight of tablet (mg)	Allowed % difference
130 or less	10%
From 130 to 324	7.5%
>324	5%

Hardness
Hardness is the important parameter and it indicates the ability that resistance of tablet to break under the condition of handling, storage and transportation. The hardness was measured by using Monsanto hardness tester and expressed in terms of kg/cm^2.
Friability
Friability testing is performed to determine the weight loss of tablets during friction and shock. 6 tablets are weighed and placed in a Roche friabilator. The tablets are falls from 6 inches in each turn. After 100 resolutions the tablets are weighed and compared with initial weight of tablets to determine percentage loss in tablet weight.

$$\%\ loss = \frac{Initial\ weight\ of\ tablet - final\ weight\ of\ tablet}{initial\ weight\ of\ tablet} X\ 100$$

Drug content

Ten tablets were weighed and powdered in mortar and 50 mg equivalent weight of clarithromycin was weighed and transferred into a 100 ml volumetric flask. Then it was dissolved and made up the volume with 0.1 N HCl. This was filter and suitable dilutions were made and analysed at 275 nm using U.V. Visible spectrophotometer (SHIMADZU U.V.1800)

Swelling Index

Swelling of tablet involves the absorption of a liquid resulting in an increase in volume and weight. The swelling index can be measured in terms of % weight gain by the tablet. For that one tablet from each formulation batch was weighed and placed in a petri plate containing 0.1N HCL of 1.2 pH buffer solution. After 8 hours tablet was removed from plate and remove excess buffer by using filter paper and weigh again.

Swelling index can be calculated by the formula:

$$\text{Swelling index} = \frac{\text{Final weight of tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \text{X } 100$$

Bioadhesive strength determination [11]

In vitro mucoadhesion studies were carried out using rat stomach mucosa. The apparatus used for testing bioadhesion was assembled in laboratory. The mucoadhesion strength of tablet was measured on modified physical balance using rat stomach mucosa. A double beam physical balance used for this method. The left pan was removed and to the left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass vial of 30ml capacity with uniform surface was tied. A clean glass beaker of 500ml was placed below hanging glass vial within which another glass beaker of 100 ml capacity was placed in inverted position. The solution of pH 1.2 was added until it grazed of mucosal surface. The buffer was maintained at 37°c.

The sides of balance were then balanced so that right hand side was exactly 5 g heavier than left.

***In-vitro* drug dissolution studies**

In-vitro drug release was studied using USP type II paddle apparatus with 900 ml of 0.1N HCL of pH 1.2 at 37±0.5°c for 8 hours and 50rpm for study. Aquilot volume of 5 ml was withdrawn at specific intervals. Then the samples were replaced with fresh dissolution medium. The samples were analysed by U.V. Visible spectrophotometer at 275nm.

RESULTS AND DISCUSSION

Pre-compression studies

The absorption maxima of clarithromycin was found to be 265.50nm in acetone.

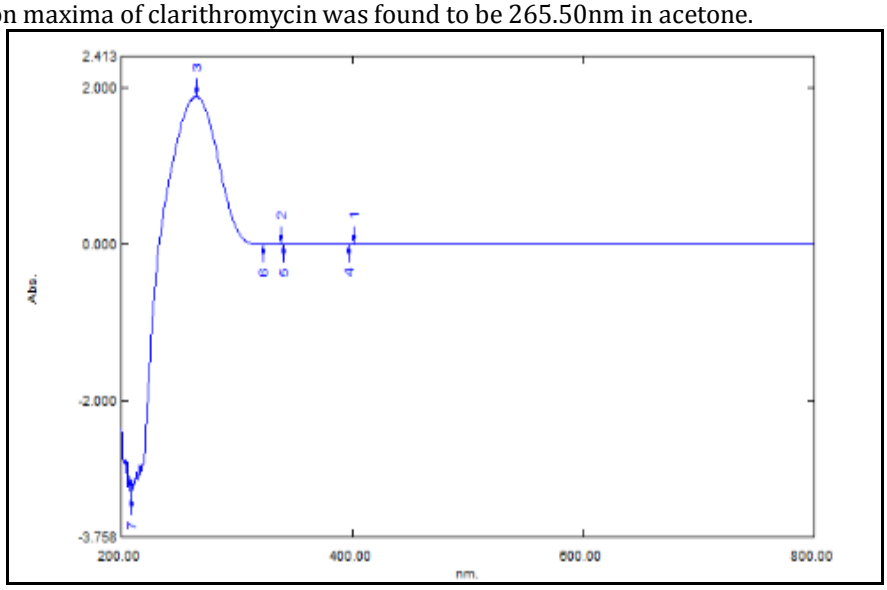

Figure 1. ABSORBANCE MAXIMA OF CLARITHROMYCIN

Identification by U.V. visible spectrophotometer

The samples of different concentrations was analysed at 275 nm using U.V. spectrophotometer against 0.1N HCL at pH 1.2.

Table5. Identification by U.V. visible spectrophotometer

Sr.No	CONCENTRATION	ABSORBANCE
1	2	0.232
2	4	0.339
3	6	0.437
4	8	0.549
5	10	0.671

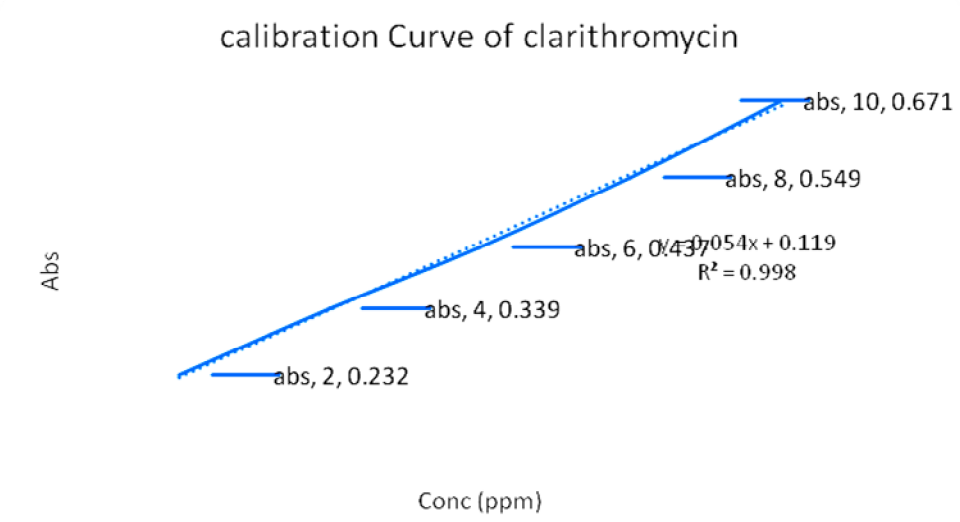

Figure 2. Calibration curve of clarithromycin

Compatibility study by FTIR

Drug polymer interaction was studied by FTIR spectroscopy. The spectra were recorded for pure Clarithromycin and with polymer mixture.The spectra were recorded for Clarithromycin and physical mixture of drug with polymers using FTIR. And polymers are found compatible with the drug.

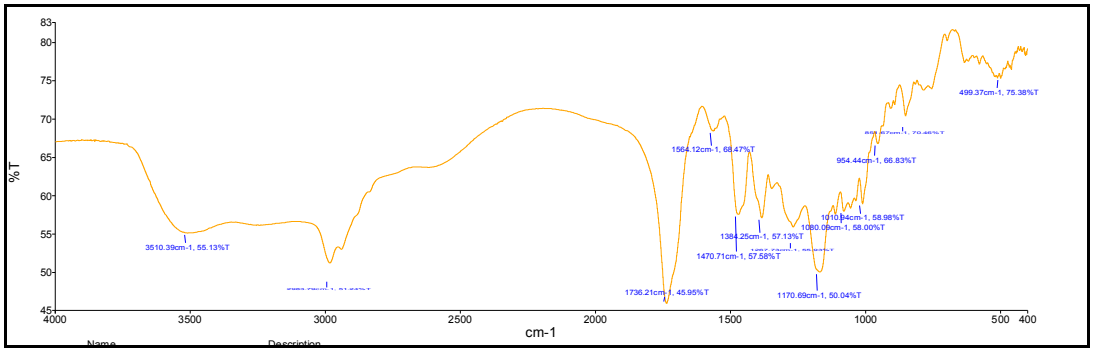

Figure 3. FTIR of Pure drug

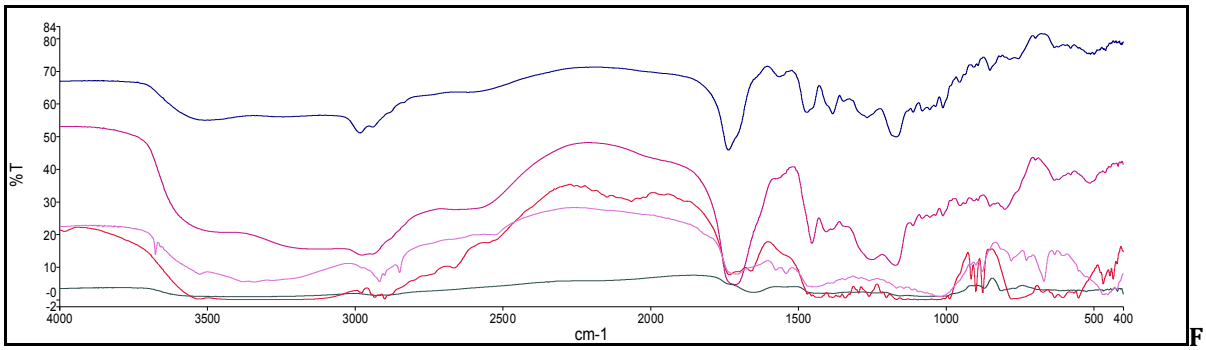

Figure 4. FTIR of Pure drug along with excipients

Table 6. Preformulation study of clarithromycin

Sr.No.	Parameter	Clarithromycin
1	Identification by UV vis. spectrophotometer	275 nm
2	Melting point	220^{o}c
3	Solubility	Soluble in acetone, slightly soluble in ethanol, methanol, acetonitrile, practically insoluble in water
4	Compatibility study	Compatible

Precompression evaluation of powder blend

Precompression parameters such as bulk density, tapped density, angle of repose, compressibility index, and Hausner's ratio of sustained release mucoadhesive powder were studied. And overall results are shown in following table.

Table 7. Precompression evaluation of powder blend

Parameter	F1	F2	F3	F4	F5	F6
Bulk density (g/ml)	20.64	25	21.84	20.64	24.92	20.58
Tapped density (g/ml)	27	31.81	26.88	25.07	29.08	23.33
Compressibility Index (%)	23.55	21.40	18.75	17.67	14.30	11.78
Hausner's ratio	1.30	1.27	1.23	1.21	1.17	1.13
Angle of repose (^{o})	27.2	28.6	30.1	20.5^{o}	22.7^{o}	24.1^{o}

Post compression evaluation of sustained release mucoadhesive tablet

Prepared tablets was evaluated for weight variation, dissolution test, hardness, thickness, friability, drug content etc . And overall results are shown in following table.

Table 8. Post compression evaluation of sustained release mucoadhesive tablet

Parameter	F1	F2	F3	F4	F5	F6
Uniformity weight (mg)	351.4	348.1	352	351.3	348	349
Thickness (mm)	3.6	3.2	3.4	3.3	3.6	3.5
Hardness (kg/cm^2)	4.5	5.2	4.9	6.1	6.6	6.3
Friability (%)	0.92	0.81	0.73	0.62	0.58	0.52
Drug content	98.79	99.58	98.86	99.42	99.89	98.99
% Drug release	91.85	93.54	94.48	88.13	86.36	84.48

Bioadhesion strength

The in vitro bioadhesion study was performed using modified balance and the force required to detach the tablet from mucous membrane (gm) was noted. The bioadhesion characteristics was affected by the concentration of bioadhesive polymer used [10].

Table 9. Bioadhesion strength

Parameter	F1	F2	F3	F4	F5	F6
Bioadhesion strength (gm)	19.8	20.9	22.4	30.6	31.9	33.2

Swelling study

Polymers with higher concentration had lower swelling and this is due to polymers concentration restricts the movement of polymers. Formulation containing guar gum shows more swelling.

Table 10. Swelling study of prepared mucoadhesive tablets of clarithromycin

Formulation code	Time (hours) 1	2	3	4	5	6	7	8
F1	24.28	27.54	31.12	34.86	37.64	41.10	45.26	49.31
F2	25.99	28.39	32.46	35.97	38.47	42.53	47.14	51.32
F3	27.29	30	33.21	36.18	39.43	43.78	48.86	52.67
F4	21.18	24	26.76	30.88	34.59	37.58	40.17	42.86
F5	23.36	26.67	30.37	35.12	38	41.62	43.21	45.78
F6	25.40	30.18	34.59	37.98	41	43.14	45.89	48.64

Table 11. Post compression evaluation of mucoadhesive sustained release tablet of F6 optimized batch

Sr.No	Parameter	F6
1	Uniformity weight (mg)	349
2	Thickness (mm)	3.5
3	Hardness (kg/cm^2)	6.3
4	Friability (%)	0.52
5	Drug content	98.99
6	Drug release	84.48
7	Swelling Index	48.64
8	Bioadhesion strength (gm)	33.2

***In-vitro* drug dissolution studies**

In-vitro drug release was studied using USP type II paddle apparatus with 900 ml of 0.1N HCL of pH 1.2 at 37±0.5^{o}c for 8 hours and 50rpm for study. Aquilot volume of 5 ml was withdrawn at specific intervals. Then the samples were replaced with fresh dissolution medium. The samples were analysed by U.V. Visible spectrophotometer at 275nm.From the in vitro dissolution data it was found that the release of clarithromycin from the prepared formulations was analyzed by plotting cumulative percentage drug release vs time as shown in figure. From all formulations, over 20% of the clarithromycin was release within the first hour of dissolution study. In the present study the formulation F6 (carbapol) has shown cumulative percent drug release of about 84.48% in 08 h as shown in figure.

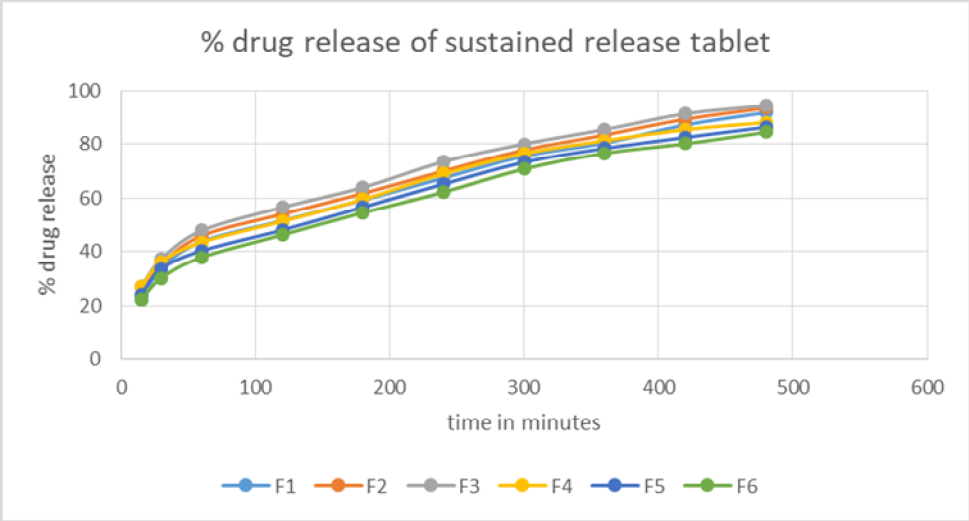

Figure 5. % drug release of sustained release tablets

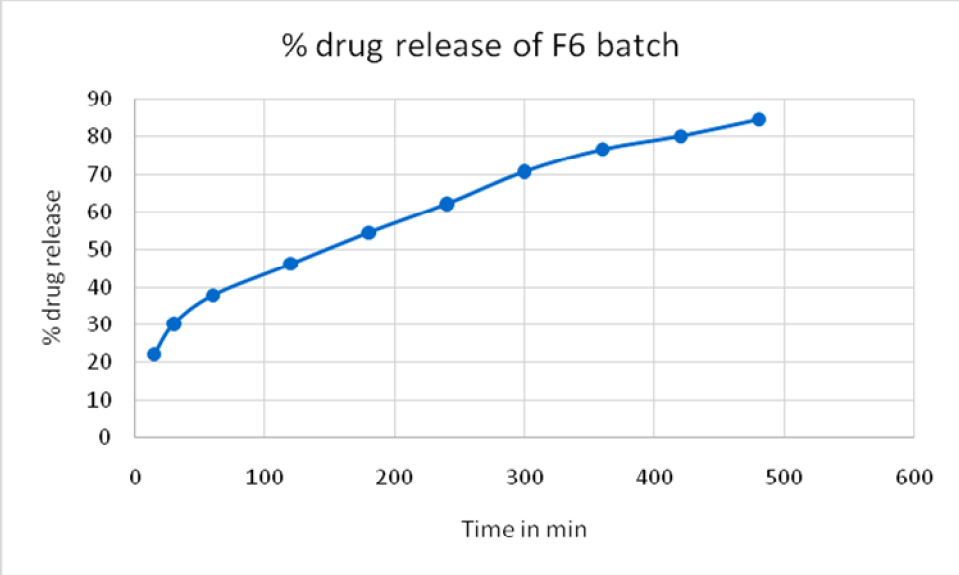

Figure 6. % drug release of optimized formulation F6

Table 12. Drug release kinetics of sustained release mucoadhesive tablet of clarithromycin

Time (Min)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt.)	Wo-Wt.
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
15	22.23	77.77	3.873	1.891	1.176	1.347	22.23	4.268	0.374
30	30.23	69.77	5.477	1.844	1.477	1.480	8	4.117	0.525
60	37.88	62.12	7.746	1.793	1.778	1.578	7.65	3.960	0.682
120	46.32	53.68	10.954	1.730	2.079	1.666	8.44	3.772	0.870
180	54.64	45.36	13.416	1.657	2.255	1.738	8.32	3.566	1.076
240	62.24	37.76	15.492	1.577	2.380	1.794	7.6	3.355	1.287
300	70.79	29.21	17.321	1.466	2.477	1.850	8.55	3.080	1.562
360	76.64	23.36	18.974	1.368	2.556	1.884	5.85	2.859	1.783
420	80.16	19.84	20.494	1.298	2.623	1.904	3.52	2.707	1.935
480	84.48	15.52	21.909	1.191	1.000	1.927	4.32	2.494	2.148

Kinetic Models

Dissolution data of above sustained release mucoadhesive tablet was fitted in First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

CONCLUSION

It is proved from this study that mucoadhesive tablet of antibacterial drug clarithromycin can be formulated to increase the gastric residence time and thereby improve its bioavailability. Formulation F6 containing carbapol in higher quantity which prolonged the release (84.48 % up to 08 hours) of the drug as compared to other prepared formulations. Thus the objective of formulating a sustained release mucoadhesive dosage form of clarithromycin has been achieved. And it is proved that mucoadhesive property of synthetic polymer carbapol is better than natural polymer guar gum.

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REFERENCES

1. Smart, John D. (2005). "The basics and underlying mechanisms of mucoadhesion". Advanced Drug Delivery Reviews. 57 (11): 1556–1568. Doi:10.1016/j.addr.2005.07.001. PMID 16198441
2. Grießinger, Julia; Dünnhaupt, Sarah; Cattoz, Beatrice; Griffiths, Peter; Oh, Sejin; Gómez, Salvador Borrós i; Wilcox, Matthew; Pearson, Jeffrey; Gumbleton, Mark; Abdul Karim, Muthanna; Pereira de Sousa, Irene; Bernkop-Schnürch, Andreas (2015). "Methods to determine the interactions of micro- and nanoparticles with mucus"(PDF). European Journal of Pharmaceutics and Biopharmaceutics. 96: 464–76. Doi:10.1016/j.ejpb.2015.01.005. PMID 25641005
3. Amit, Alexander; Charma, Sharad; Khad, Mohammed (2010). "Theories and Factors Affecting Mucoadhesive Drug Delivery Systems: A Review". Journal of Advanced Pharmaceutical Technology and Research. 1 (4): 381–387. Doi:10.4103/0110-5558.76436. PMC 3255397. PMID 22247877
4. Shaikh, Rahamatullah; Raj Singh, Thakur Raghu; Garland, Martin James; Woolfson, A. David; Donnelly, Ryan F. (2011). "Mucoadhesive drug delivery systems". Journal of Pharmacy and Bioallied Sciences. **3** (1): 89–100. doi:10.4103/0975-7406.76478. PMC 3053525. PMID 21430958
5. Https://go.drugbank.com/drugs/DB01211
6. Pranjal K Singh , V. K. Shukla , T.S. Easwari , Sanjoo Kumar , Ramkumar Chaudhary , Alok Nath Sharma , Saurabh Saraswat (2012). Formulation development and evaluation of mucoadhesive oral dosage form containing clarithromycin using different mucoadhesive polymers, international journal of pharmaceutical science and health care issue 2, volume 2:22-25
7. Padekar, h., and o. Lohote. (2019). "Formulation and evaluation of bilayer tablet containing diclofenac sodium as sustained release and aloe vera gel powder as immediate release". International Journal of Current Pharmaceutical Research, 11, no. 4, pp. 70-78, doi:10.22159/ijcpr.2019v11i4.34923
8. Gurdeep R Chatwal, Sham K Anand. (2011). Instrumental methods of chemical analysis. 3rd ed Himalaya Publishing House, Mumbai; P. 244.
9. Lachman L, Lieberman HA, Kanig JL.(2009). The theory and practice of Industrial pharmacy, Varghese Publishing House Bombay; special Indian edition.
10. Balaji A, Radhika V and Goud V: (2014). Formulation and evaluation of mucoadhesive buccal tablets by using natural polymer. Int J Pharm Sci & Res ; 5(11): 4699-08. Doi: 10.13040/IJPSR.0975-8232.5(11).4699-08