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COMPARITATIVE *IN-VITRO* AND *EX-VIVO* EVALUATION STUDIES OF NATURAL POLYMERS ON BIOADHESIVE CLARITHROMYCIN TABLETS

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ABSTRACT

The present investigation was to formulate controlled release of muco adhesive tablets of clarithromycin followed by it's evaluation studies. The tablets were formulated by using clarithromycin as drug, used for the treatment of H.pylori infection in peptic ulcer. The natural polysaccharides like, Tamarind Seed Polysaccharide (TSP), obtained from *Tamarindus indica* and chitosan were used as polymer material for controlled drug release. The formulated tablets of such different polymer were compared for different evaluation studies. The pre formulation studies were performed by using FTIR, DSC studies. The tablets were evaluated for in-process, *in-vitro* studies. The bioadhesive strength of tablets and polymers were comparatively determined by *ex-vivo* methods. The selected formulation were subjected to stability studies, the study concluded that Tamarind polysaccharide loaded tablets are more adhesive than chitosan loaded tablets. TSP is the best natural polymer for mucoadhesive due to biodegradability and controlled release mechanism.

KEYWORDS

Clarithromycin, Mucoadhesion, Tamarind seed polysaccharide, Chitosan and *Ex- vivo* methods.

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INTRODUCTION

The term mucoadhesion makes a bond between two biological surface or biological surface with bio adhesive materials. Muco adhesive drug delivery is topic of current interest in design of drug delivery system for prolonged control release mechanisms. It can be design on different formulations like, Tablets microsphere, liposphere, etc¹. The mechanics of muco adhesion describes the adherence of polymeric materials to epithelial surface, and makes gel like structure which enhances hydrophilic bonding and adhesion mechanism of materials with mucus and makes prolonged drug adhesion and in controlled manner. Bonding mechanism include

adsorption theory, Diffusion theory, electronic theory etc².

Clarithromycin is a macrolide antibiotics, which are consider as first line drugs for treatment of bacterial infection in peptic ulcer³. The half-life of (3-4 hours) of clarithromycin suitable for once daily dosage form. Present study aims to develop controll release muco adhesive tablets by dry granulation method. The natural polysaccharides like TSP and chitosan are natural polymers. The pre-formulation studies where performed and compatibility tests where done using FTIR and DSC techniques. These different formulated tablets where subjected to different comparative evaluation studies. Release rate where confirmed by *in-vitro* dissolution study. The binding capacity of these polymers and tablets were determine by different *ex-vivo* methods. The stability studies were performed as per ICH guidelines for the optimized formulations.

MATERIAL AND METHODS

Materials

Plant material was authenticated by KFRI, Nilambur, Kerala. Chemicals used in the present study were of analytical reagent grade.

Clarithromycin was procured by Biochem Pharmaceutical (Daman, India), Microcrystalline cellulose, mannitol by Colorcon Asia pvt., Goa, India. Lactose, talc, Mg-stearate and chitosan was gifted by Loba Chemie Pvt Ltd, Mumbai, India.

Isolation and Purification tamarind seed polysaccharide from *Tamarindus Indica*

Seeds of *Tamrindus Indica* were collected from surrounding place of Calicut .Kerala in April month .Seeds were washed with purified water to remove the adhering materials. The seeds were crushed and powdered. The powders were soaked in water for 24 hours and boiled for 1.5 hours. The boiled preparation was kept aside for 4 hours to release the mucilage. The mucilage were separated, to the mucilage ethyl alcohol were added to precipitate the polysaccharide. Which was filtered, dried and sized⁴

Preformulation studies

Micromeritic properties

The TSP and chitosan powder was examined for different physicochemical studies. The

clarithromycin pure drug and drug mixtures evaluated for powder characteristic studies.

Drug-excipient compatibility studies:

Infrared (IR) spectroscopy was conducted using a FTIR Spectrophotometer (Jasco FT-IR 410) and the spectrum was recorded in the wavelength region of 1600 to 400 cm⁻¹. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressed 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^{5,6}.

Differential Scanning Colorimetric Studies (DSC)

DSC analysis was performed (by DSC-60, Shimadzu, Japan) for clarithromycin and clarithromycin - tamarind seed polysaccharide mixture (1:1) and clarithromycin-chitosan. The sample was heated between 40 to 400^oC. Heating rate of 20^oC/minute was used and thermo gram obtained. It was reviewed for the determination any intractions⁷.

X-RAY diffraction studies of clarithromycin:

X-RAY diffraction studies was performed by X-ray diffractometer to investigate the effect of cristallinity of clarithromycin, using 45KV, 30ma by Cu-K α replication method⁸.

Formulation of clarithromycin-TSP mucoadhesive tablets.

Formulation of tablets using tamarind seed polysaccharide (TSP)

The component of each formulation made to the preparation of 250 tablets as shown in the tables. All the components were sifted through mesh no (#40). Clarithromycin was mixed with polymer and followed by diluents. The powder mixture were subjected to lubrication with half portions of lubricants and compressed with oblong shape punches (slugging). Which were made into size reduction and sieved through mesh no #16 and added remaining portion of lubricants. The powder were compressed using oblong shape punches.

Evaluation of Clarithromycin Mucoadhesive tablets

Physical properties of tablets the optimized formulation were selected for different physical property tests. Results are discussed in Table No.2

Thickness: 20 tablets were selected and the thickness was measured by Vernier calipers. The average diameter and thickness were calculated.

Hardness of tablets: Monsanto hardness tester determined the hardness of tablets. The test was performed in 6 tablets.

Friability test: 20 tablets were examined to determine the %of friability in friabilator. The speed was adjusted for 25rpm 4 minits. The tablets weighed and % of friability calculated.

$$\%F = (W_0 - W) / W_0 \times 100$$

Weight variation test: since average wt of tablets is more than 250mg, the weight variation of tablets is not less than 95% and not more than 105%.

Test for content uniformity

Determination of λ max was done by UV spectrophotometric method. The amount of drug, which is present in the tablets, were determined by UV spectrophotometric method using 0.1M H₂SO₄.

In- vitro dissolution study

The cumulative drug release was determined by dissolution test. The Clarithromycin release rate was performed by using USP dissolution test apparatus Type II (paddle method) using 900 ml of 0.1N HCl at 37 ± 0.5°C at 50 rpm. This study was done for 12 hrs. A sample of 5 ml were withdrawn at an interval of 15min, 30min, 1hr, 2hr, 4hr, 6hr, 8hr, 10hr and 12hr. The samples were replaced with fresh dissolution medium each time⁹.

Determination of adhesive strength of polymer (ex- vivo)

Study of mucoadhesive strength for polymers

Wihelmy method

Take a small slide of (2×5 cm) length. Which is coated by 1% W/V solution of mucoadhesive agent. The slide were dipped in the mucin solution in beaker by maintaining the temperature 30°C. The one end of the slide is connected to nylon thread and the other end is to keep the weights. The slides were withdrawn in different time interwels of 5,10,15,30 minutes. The experiments were performed for selected formulation¹⁰.

Shear stress method

Glass plates were taken and mucoadhesive polymer were kept inside. The experiment were performed for HPMC-K100 and cheto-TSP natural polymers. Different concentration like 1%, 2% and 3% were

made and arranged 3 sets of glass plates. 100gm wt rolled over the plates to improve the adhesion uniformly. The time taken to move the distance from the initial point in 15, 30, 60 minutes were determined¹¹.

Study of mucoadhesive strength for tablet

Detachment force measurement

This is the method used to measure *in vitro* mucoadhesive capacity of different polymers. It is a modified method developed by Martti Marvola to assess the tendency of mucoadhesive materials to adhere to the oesophagus. The assembly of this apparatus consists of two glass slides, one modified physical balance, weights, thread, goat intestine, tyrode solution, distilled water and a beaker to hold the water¹².

Method

Immediately after slaughter, the intestines was removed from the goat and transported to laboratory in tyrode solution is (g/litre); (sodium chloride 8 gm; potassium chloride 0.2 gm; calcium chloride 2H₂O 0.134 gm; sodium bicarbonate 1.0 gm; sodium dihydrogen phosphate 0.05 gm and glucose H₂O 1gm). During this experiment take the intestine in a specified area and place it on one glass slide and tie it. The glass slide with the intestine was affixed on one side floor below the modified physical balance¹³.

Already prepared 200 mg plain polymer tablet was pasted in another glass slide and it balanced in the assembled physical balance with a beaker in other side which is used to hold the water. Now the balance was calibrated.

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-testing for the drug substance or a self-life for the drug product and recommended storage conditions¹⁴.

So, formulation No. F6 was subjected to determine its shelf life i.e. stability study by using accelerated stability chamber. The tablets were packed and stored in the stability chamber under desired

temperature and humidity given below for six month.

RESULTS AND DISCUSSIONS

Micromeritic properties of clarithromycin

The results of Micromeritic properties were performed. The results indicate that the clarithromycin raw material showing passable flow ability with the angle of repose value of 32.92° . All granules ready for compression showing fair to good flow ability with the angle of repose values like 28.76° and 29.26° respectively. According to angle of repose graph readings and are better than that of powder drug. The bulk density, tapped density, compressibility index and Hausner ratio were observed. It reveals that all the formulation blend having good flow characteristics and flow rate than raw material. Degree of compression is characteristic of compression capability of the granules and the results obtained exhibited good compression capability of the granules.

Compatibility studies

X-RAY diffraction studies of clarithromycin

An X-ray diffraction (XRD) study of clarithromycin was carried out on X-ray diffractometer. The XRD spectra of clarithromycin showed characteristic peaks at (2θ values) 11.25, 12.62, 15.01, 17.52 and 19.11 (Figure No.3). This data indicated that the drug is in the crystalline and stable form.

Drug Excipient Compatibility Studies

FTIR compatibility studies

Drug excipient compatibility studies were carried out by IR spectrophotometer. The FTIR spectra of pure clarithromycin and its polymers were shown there was no interaction between drug and polymer.

Differential Scanning Calorimetric studies

The DSC thermogram of clarithromycin drug and TSP polymer isolated from *Tamrindus indica*. L was performed in the temperature range between 40°C - 400°C and presented in fig:. The clarithromycin and mixture showed endothermic peaks at 220.15°C , 221.42°C and 250°C . In all these cases the endothermic and exothermic peaks of mixture in comparison with drugs showed overall results of DSC studies confirmed almost similar physical state of clarithromycin.

Physical evaluation of tablets

The in-process evaluation studies of all the formulation of TSP and chitosan shown good results. All the results were within the limit.

Test for content uniformity

λ max of clarithromycin was determined by UV spectrophotometric method. The percentage purity of drug was found to be 97.16%W/W. The amount of drug present in the selected formulation (F6) was found to be 100.15%W/W for TSP loaded tablet and 98.45%W/W for chitosan loaded tablets.

In -vitro dissolution study of Clarithromycin mucoadhesive tablets

The % of cumulative drug release of F1 to F6 for both tablets for 24 hours were showed below. F6 showed better release than other formulation,

Dissolution data clarithromycin mucoadhesive Tablet formulated by TSP polymer

The formulation 6 shows better release compare to other formulations which were prepared by TSP in 24 hours

Dissolution data clarithromycin mucoadhesive tablet using chitosan polymer

The formulation 6 shows better release compare to other formulations which were prepared by chitosan in 24 hours

Determination of Adhesive Strength of Polymers Wihelmy's method

The comparative mucoadhesive strength for Chitosan and TSP polymer were performed up to 60 minutes. It shows that when time continuing the adhesive strength of polymer increases. The TSP (Tamarind seed polysaccharide) polymer shows more adhesive strength than chitosan polymer.

Shear stress method

Shear stress method was performed for different polymers in different time intervals. The comparative studies were performed for both chitosan and TSP polymers. The weight required to pull the glass plate in each time interval increases with increase in time. The TSP polymer shows more adhesive strength than chitosan polymer.

Determination of adhesive strength for tablets

Detachment force method Selected formulation (F6)

Detachment force method performed for to determine the adhesive strength and adhesive force.

The test was carried out for different time intervals 5, 10, 15 and 30 minutes respectively. The weight required to detach the tablet from gastric mucosa is different in different time intervals. Hence, more time contact increases the adhesion strength and adhesion force.

In-vitro wash off test

In-vitro wash of test were performed by using disintegration test apparatus. Test were carried out for last four formulations like F4, F5, F6 and F7. The detachment fore varies with different time (720 to 1080 minutes). The formulation F6 tablet shows maximum time of contact (1080 minutes) with mucus layer till detachment.

Stability studies

The stability studies were performed for selected formulation (F6) of Clarithromycin mucoadhesive tablet as per the guidelines. All the results evaluation studies were resembles with initial tablets. Hence stability studies confirmed that, the selected formulation (F6) has very good stable condition.

Table No.1: Formulation of tablets using tamarind seed polysaccharide (TSP)

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Clarithromycin	500	500	500	500	500	500
2	Lactose	20	30	40	35	35	30
3	TSP	160	152	150	160	165	170
4	MCC	34	48	40	35	30	30
5	MS	10	10	10	10	10	10
6	Talc	10	10	10	10	10	10
Av weight / tablet(mg)		750	750	750	750	750	750

Table No.1: Micromeritic properties of clarithromycin

S.No	Materials	Angle of repose	Bulk density	Tapped density	Compressibility index	Hausner ratio
1	Clarithromycin	32.92	0.652	0.833	21.73	1.270
2	Clarithromycin+TSP	28.76	0.75	0.80	18.36	1.225
3	Clarithromycin+ chitosan	29.26	0.40	0.65	20.15	1.34

Table No.2: Formulation of tablets using chitosan polymer

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Clarithromycin	500	500	500	500	500	500
2	Lactose	66	47	62	66	61	56
3	Chitosan	130	135	125	130	138	142
4	MCC	34	48	43	34	34	32
5	MS	10	10	10	10	10	10
6	Talc	10	10	10	10	10	10
Av weight / tablet(mg)		750	750	750	750	750	750

Table No.3: In-process evaluation of clarithromycin with TSP and Chitosan loaded tablets

S.No	Tablets	Formulation	Wt.variation mg	Thickness mm	Diameter mm	Hardness Kg/cm ²	Friability (%)
1	Clarithromycin with TSP	F1	750	5.42	13.10	5.2	0.98
		F2	751	5.40	13.20	5	0.76
		F3	748	5.41	13.03	4.9	0.70
		F4	748	5.42	13.05	5.6	0.90
		F5	750	5.40	13.05	4.5	0.70
		F6	750	5.39	13.04	5.0	0.80
2	Clarithromycin with chitosan	F1	752	5.30	13.06	5.2	0.97
		F2	748	5.32	13.04	5.2	0.80
		F3	751	5.32	13.01	4.8	0.75
		F4	748	5.34	13.05	5.3	0.92
		F5	751	5.33	13.05	4.7	0.78
		F6	750	5.31	13.04	5.1	0.85

Table No.3: Data for dissolution of various formulations

S.No	Time	F1	F2	F3	F4	F5	F6
1	2	14.05	18.02	21.02	21.32	22.03	24.52
2	4	55.02	22.05	25.48	28.25	35.25	29.32
3	6	60.23	30.15	35	30.25	40.21	35.65
4	8	63.25	40.15	38.54	34.65	45.65	42.35
5	10	70.21	49.25	48.25	40.15	52.01	55.26
6	12		52.15	59.24	49.65	59.65	62.96
7	16		57.23	64.28	56.21	61.023	70.25
8	20		62.58	78.25	62.98	74.23	79.26
9	24		70.25	82.35	70.23	86.23	91.235

Table No.4: Data for dissolution of various formulations

S.No	Time	F1	F2	F3	F4	F5	F6
1	2	18.05	21.03	23.21	20.51	19.62	24.52
2	4	56.25	30.21	27.48	31.54	38.25	36.87
3	6	70.81	40.85	32.56	44.52	46.24	44.2
4	8	95.25	52.64	39.54	52.35	55.45	53.6
5	10	102.23	63.27	44.87	59.54	63.21	64.18
6	12		70.78	49.78	67.03	69.76	73.59
7	16		74.87	53.29	78.15	75.18	81.24
8	20		78.25	59.54	84.21	84.54	89.35
9	24		80.14	66.32	90.56	92.35	95.26

Table No.4: Mucoadhesive strength of different polymers

S.No	Time (minutes)	Mucoadhesive strength (gm),n=3	
		Chitosan	TSP
1	05	0.85	0.96
2	10	0.91	1.34
3	15	1.21	1.62
4	30	1.55	1.89
5	60	1.90	2.10

Table No.5: Mucoadhesive strength of different polymers

S.No	Time (minutes)	Wt required (adhesion strength, gm)	
		Chitosan	TSP
1	05	0.85	1.63
2	10	0.91	1.76
3	15	1.19	1.98
4	30	1.38	2.21

Table No.6: Mucoadhesive strength by detachment force method

S.No	TIME	5 minutes	10 minutes	15 minutes	30 minutes
1	Adhesion strength (gm)	26.55	50.15	73.28	95.24
2	Adhesive force (N)	0.255	0.4905	0.7161	0.9343

Adhesive force= (adhesive strength/1000) ×9.81

Table No.7: Detachment time of last four formulations

S.No	Formulations	Time of detachments (minutes)
1	F4	720
2	F5	910
3	F6	1080
4	F7	950



Figure No.1: Wilhelmy's Method to Measure Mucoadhesive Strength

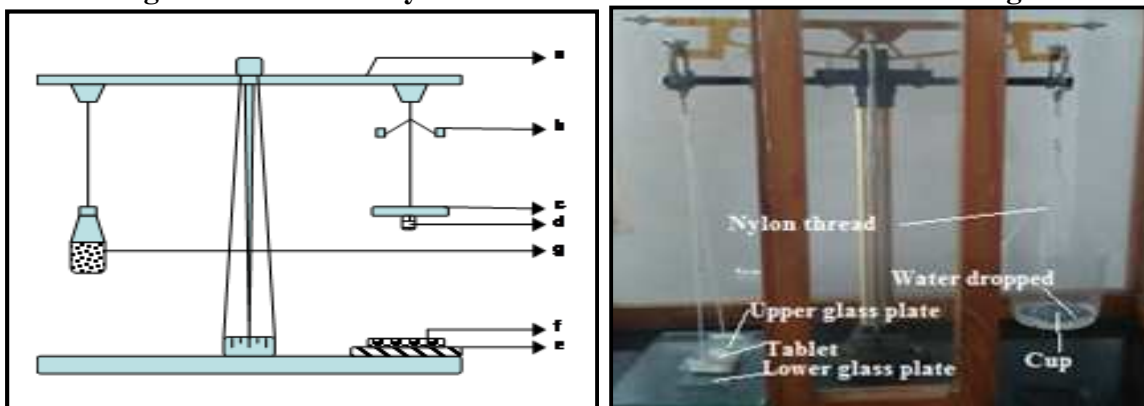


Figure No.2: detachment force measurement method

a → Modified physical balance b → Weights c → Upper Glass Slide d → Tablet
 e → Lower glass slide f → Goat intestine g → Beaker which hold water

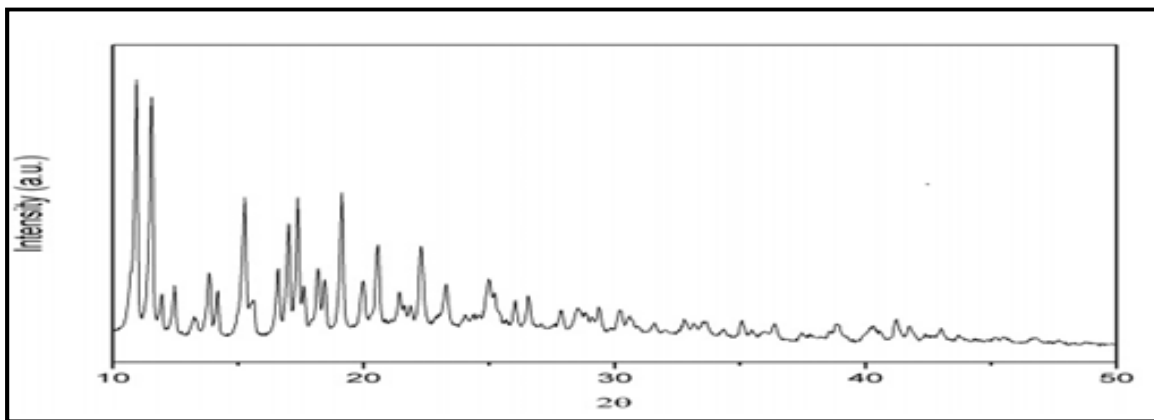


Figure No.3: X-RAY diffraction spectrum of clarithromycin standard

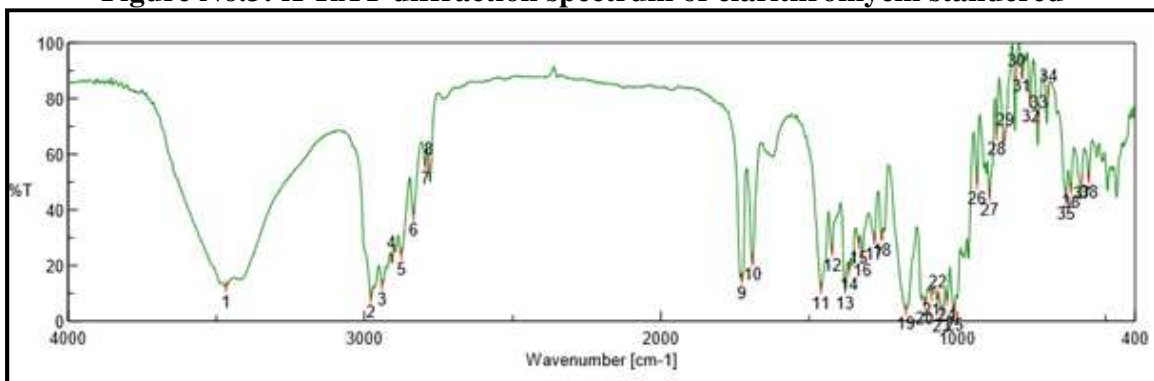


Figure No.4: FTIR spectra of Clarithromycin standard

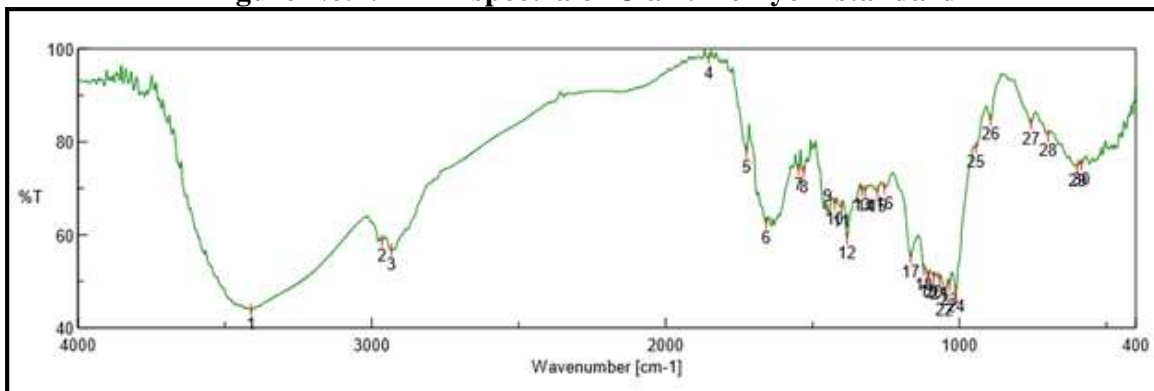


Figure No.5: FTIR spectra of Tamrarind seed polysaccharide

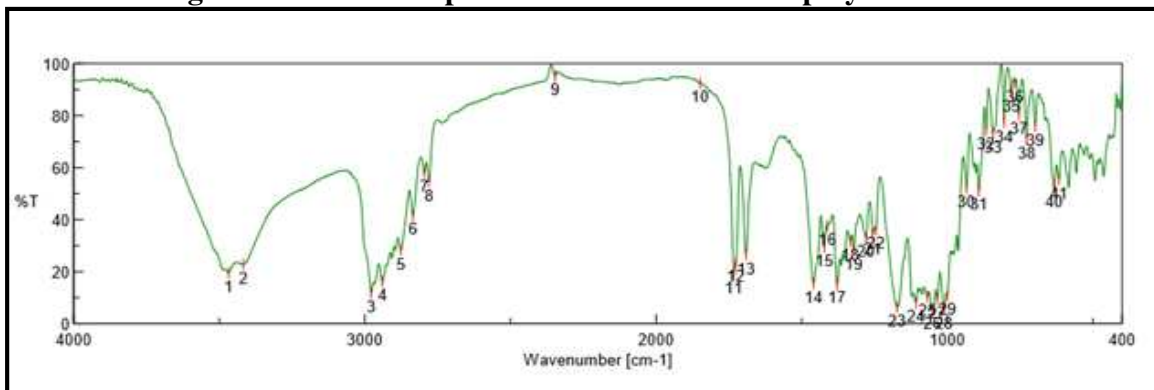


Figure No.6: FTIR spectra of Clarithromycin with Tamrarind seed polysaccharide

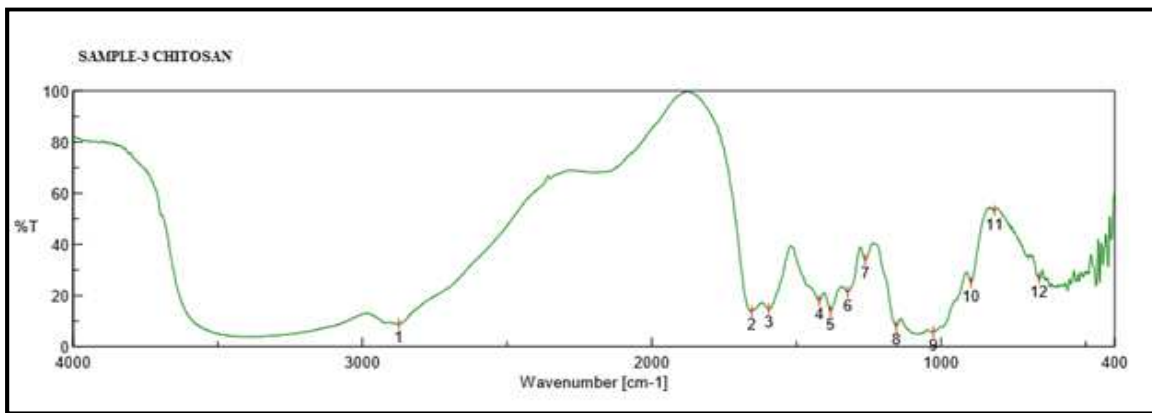


Figure No.7: FTIR spectra of Chitosan

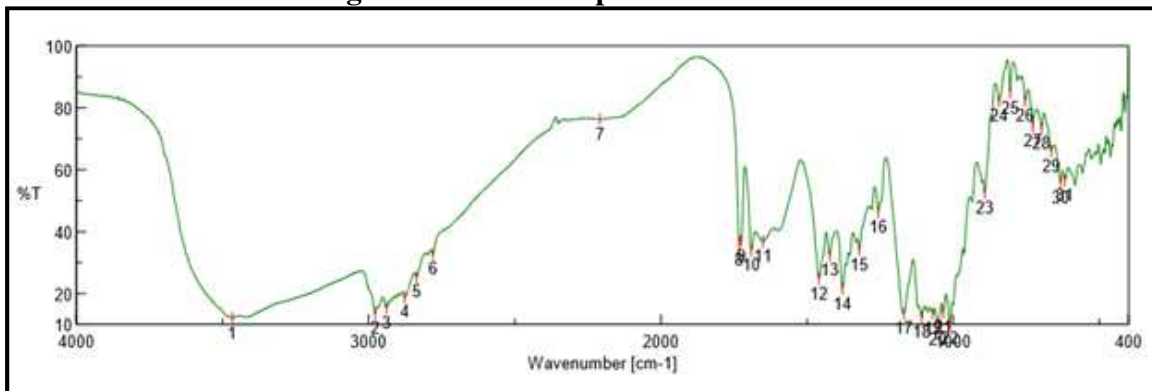


Figure No.8: FTIR spectra of Clarithromycin with chitosan Clari+ che

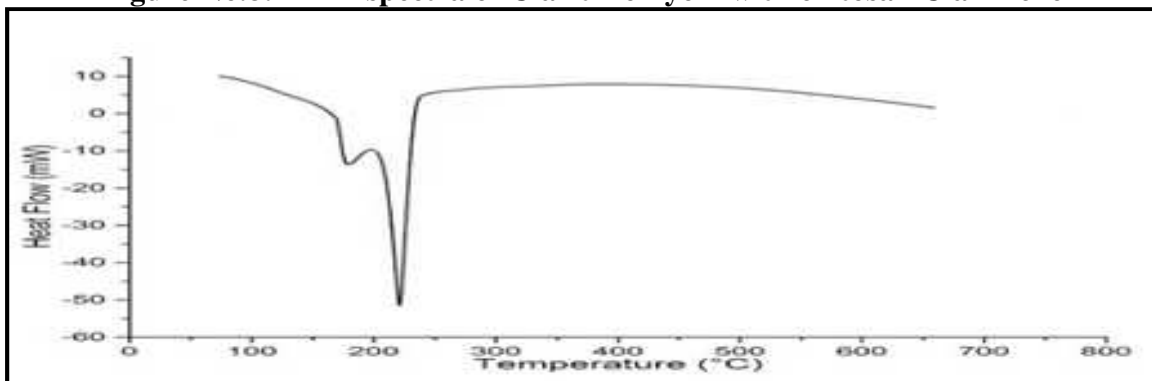


Figure No.9: DSC thermogram of Clarithromycin standard

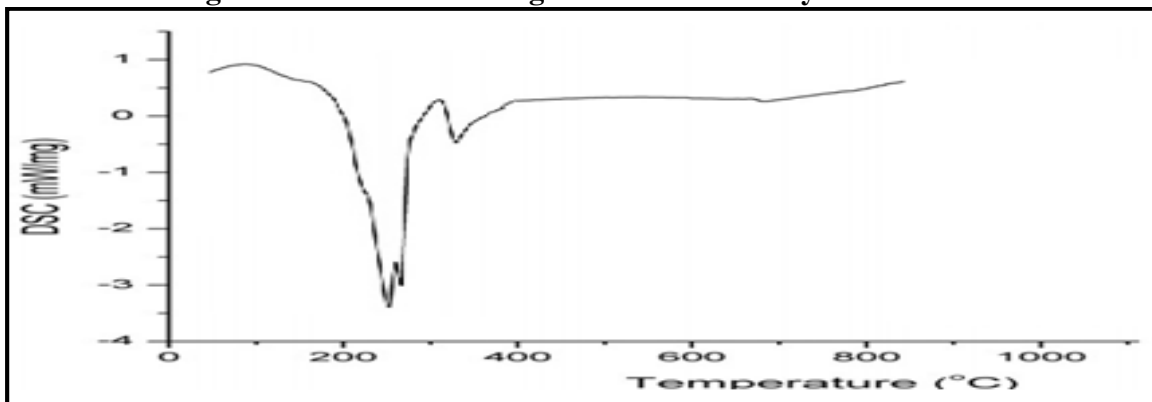


Figure No.10: DSC Thermogram of Clarithromycin standard and tamarind seed polysaccharide

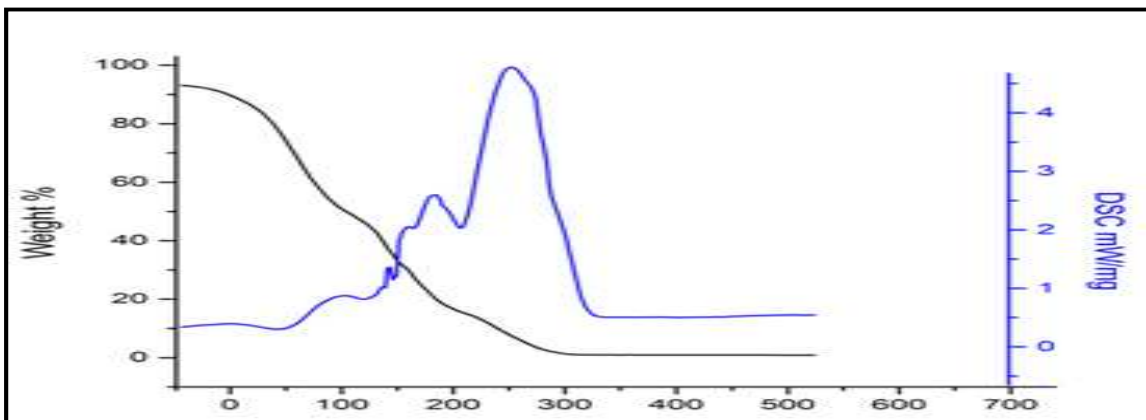


Figure No.11: DSC Thermogram of Clarithromycin standard and chitosan

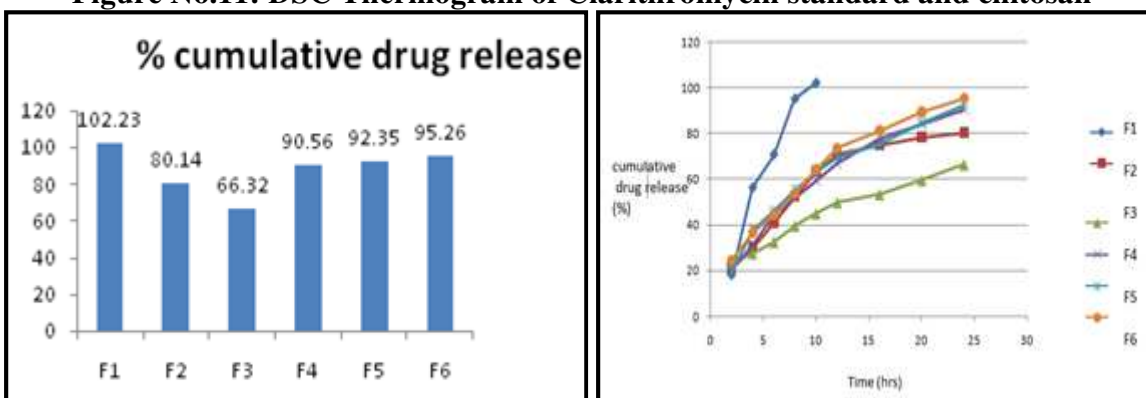


Figure No.12 and 13: % cumulative drug release profile of clarithromycin tablets

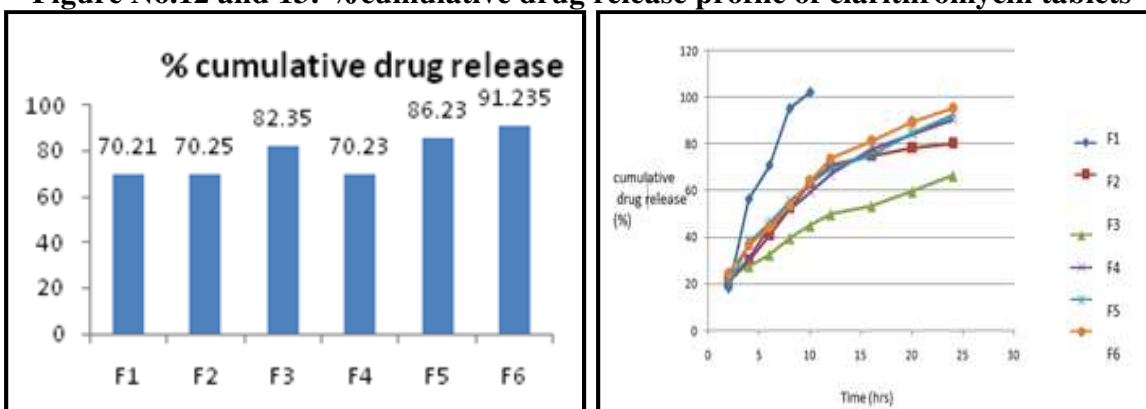


Figure No.14 and 15: % cumulative drug release profile of clarithromycin tablets

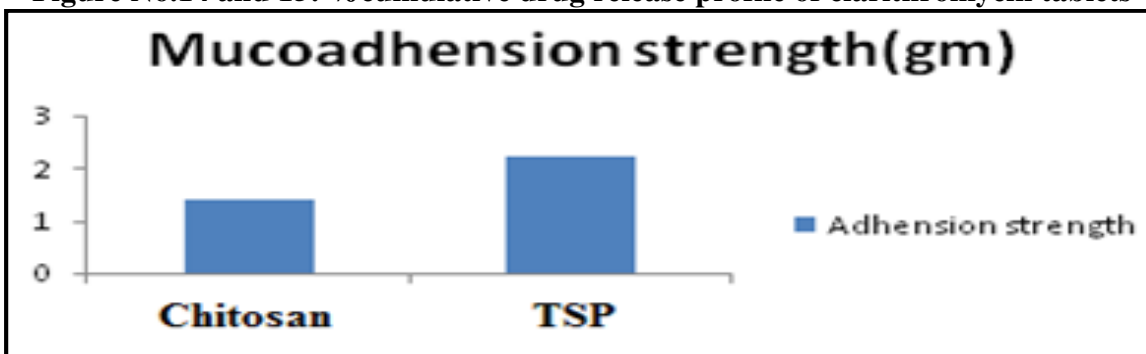


Figure No.16: Muco adhesion strength at 60th minute

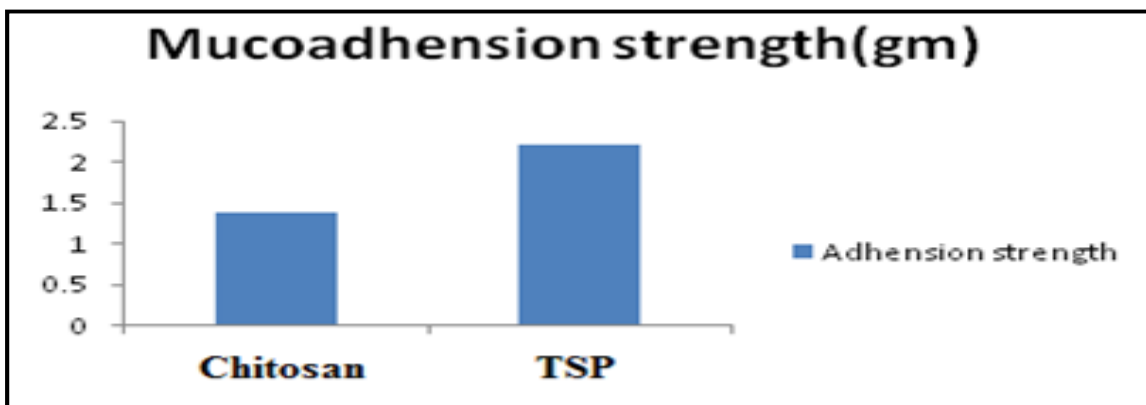


Figure No.17: Muco adhesion strength at 30th minute

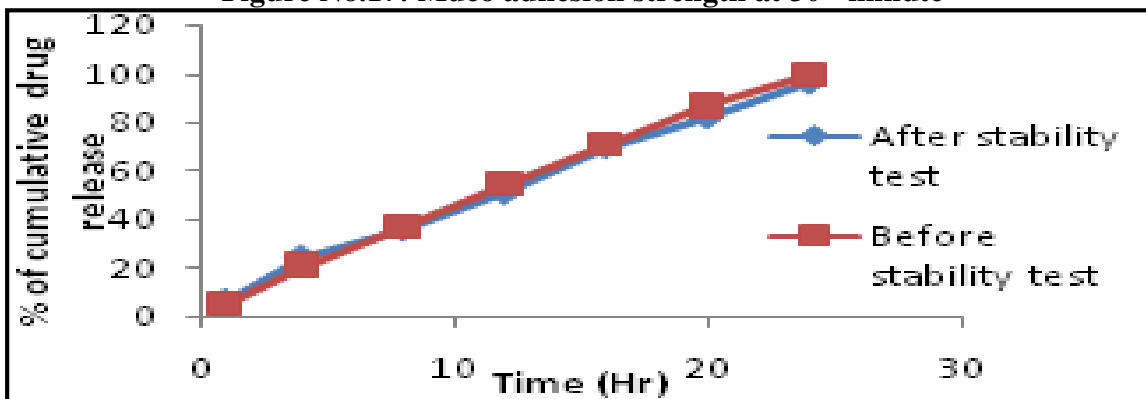


Figure No.18: In-vitro release profiles of F6 before and after stability test

CONCLUSION

The study was undertaken with the aim of comparative study of binding property of natural polymers like polysaccharide and its tablets on mucoadhesion. By formulating the tablets with Tamarind polysaccharide and chitosan. The *in-vitro* studies shown that the release character of TSP loaded tablets is more better than chitosan loaded tablets. The various *ex-vivo* methods for polymers and tablets assured the good bioadhesive property of TSP compared to chitosan. Hence the study can be concluded that tamarind seed polysaccharide (TSP) is a best natural polymer for the bioadhesion and encourages the controlled release action as well as good biodegradability.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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