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Formulation and *In Vitro* Evaluation of Mucoadhesive Buccal Tablets of Azithromycin

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ABSTRACT

The present investigation aimed to Formulate and Evaluate the mucoadhesive buccal tablet of Azithromycin to study the effect of different polymers on release profile of drug for prolonged release. In this study mucoadhesive, buccal tablet was prepared by direct compression method. Azithromycin is a macrolide antibiotic used to treat many types of bacterial infections. Various rheological characteristics of the powder bed like bulk density, compressibility index, and angle of repose were evaluated and studied. Mucoadhesive buccal tablets were compressed on an 8-station mini press using 8 mm flat faced punches and were all assessed for weight variation, hardness, thickness, percent swelling index, mucoadhesive strength and in vitro release of the drug by using USP dissolution testing apparatus method II using a paddle at 50 rpm. Ex vivo mucoadhesion time, mucoadhesive strength and ex vivo permeation studies results were satisfactory for optimized formulation F7. The stability studies showed that there is no deviation in the drug content of all formulations for 3 months.

INTRODUCTION

Oral delivery has been the most common and preferred route of administration for most of the therapeutic agents. The popularity of the oral route has been attributed to the patient acceptance, ease of administration, accurate dosing, cost-effective manufacturing method, least sterility constraints, flexible design of dosage forms and generally improved shelf-life of the product.

Mucoadhesive drug delivery systems are delivery systems that utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods. Mucoadhesive controlled drug delivery systems are beneficial since they give a controlled drug release over some time and can also be utilized for localizing the drug to a specific site in the body. Mucoadhesive substances could also be used as therapeutic agents in their own right, to coat and protect and soothe the injured tissues (gastric ulcers or lesions of the oral mucosa) or as lubricants (in the oral cavity, eye and vagina).

Bioadhesion is defined as an ability of a material to adhere to a biological tissue for an extended period. In case of polymer, it attaches to the mucin layer of mucosal tissue, the term mucoadhesion is used. Adhesion may be defined simply as a process of “fixing” of two surfaces to one another. The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for extended periods by the help of interfacial forces.

Therefore, adhesive mucosal dosage forms were suggested for oral delivery, which include adhesive tablets, adhesive gels and adhesive patches. So, buccal route is an attractive site for the administration of drugs. These buccal tablets are small, flat and are intended to be held between the cheek and teeth or in the cheek pouch and an ideal buccal adhesive system must have the following properties: should adhere to the site of attachment for few hours, should release the drug in controlled manner and should provide the drug release in a unidirectional way in to the mucosa.

In the Present research work, buccal tablet of Azithromycin Dihydrate is formulated using direct compression technique. Azithromycin is an advanced generation; broad-spectrum antibiotic approved for the treatment of acute bacterial exacerbation of chronic bronchitis (AECB), group-A beta-hemolytic streptococcal pharyngotonsillitis and uncomplicated skin/skin structure infections in adult and adolescent patients. Azithromycin has a slightly bitter test and has a half-life of 68 hrs and has poor water solubility. So, in case of acute bacterial exacerbation of chronic bronchitis (AECB) group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections it requires immediate release of drug from the dosage form, which make Azithromycin suitable candidate for buccal tablets.

Azithromycin have activity against gram-positive organisms also offers increased gram-negative coverage over erythromycin and clarithromycin. It also shown good activity against H. influenzae. However, it has variable activity against the family Enterobacteriaceae. Nonetheless, Salmonella and Shigella species are susceptible, as have other diarrheal pathogens such as Yersinia and Campylobacter. Its unique feature is an excellent activity against sexually transmitted pathogens, especially Chlamydia trachomatis and can use also in the patients with weak immune response like in children then in HIV, gonorrhea, non - gonococcal urethritis. An azithromycin is generally used in middle ear infections, tonsillitis, throat infections, laryngitis, throat infections, bronchitis, pneumonia, typhoid etc. But instead of all these positive effects to patients, azithromycin is having some side effects also. When, the patient is frequently taking azithromycin (in case of weak immune system diseases and sexually transmitted diseases) it shows some side effects like nausea, loose stool-diarrhea, abdominal pain, headache, vomiting, unexplained rashes, pilling of skin, abnormal swelling, blood in stool etc. and all these side effects are related with upper GI tract. Therefore, the present work aimed to develop a new bioadhesive sustain-release tablets for buccal delivery of Azithromycin.

MATERIALS AND METHODS

MATERIALS:

Azithromycin dihydrate was obtained as gift sample from, Kniss pharmaceuticals, gerugambakkam, Chennai. Carbopol 934, HPMC K4M, HPMC K100M, Mannitol, Talc, Magnesium sterate were obtained from Mahaveer Chemicals, Nyniappa Street, Chennai.

METHODS:

The compatibility studies of drug and excipients were determined by FTIR studies. Both pure drug and excipients were individually analysed and further the physical mixture and formulations were also studied.

Preparation of Mucoadhesive buccal tablets of Azithromycin by direct compression method:

Mucoadhesive buccal tablets of Azithromycin were prepared by direct compression method by using as carbopol 934, HPMC K4M, HPMC K100M as mucoadhesive polymers. Mannitol as diluents, magnesium stearate as lubricant, talc used as glidants. Before going to direct compression all the ingredients were screened through sieve no.60, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 2-3 min. Before compression, hardness was adjusted and compressed into 400mg each tablets using tablet compression machine equipped with 8 mm flat faced beveled edge punches on 8 station rotary tablet machine (the Cadmach compression machine) and same hardness was used for the required number of tablets. The various formulations designed were shown in Table 1.

Table 1: Formulation development of Mucoadhesive buccal tablet of Azithromycin

INGREDIENTS	**F_1** **(mg)**	**F_2** **(mg)**	**F_5** **(mg)**	**F_7** **(mg)**	**F_9** **(mg)**
Azithromycin	250	250	250	250	250
Carbapol	100	-	80	90	70
HPMC K_4 M	-	100	20	-	-
HPMC K_{100}M	-	-	-	10	30
Mg Sterate	5	5	5	5	5
Talc	5	5	5	5	5
Mannitol	40	40	40	40	40
Total Weight	**450**	**450**	**450**	**450**	**450**

EVALUATION OF MUCOADHESIVE BUCCAL TABLETS

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Pre-compression parameters

ANGLE OF REPOSE: The angle of repose of granules was determined by the fixed funnel and free-standing cone method, weighed blend (5gm) was carefully poured through the funnel with its tips at 2cm height (h) until the apex of conical heap so formed just reached the tip of funnel. The mean diameter (r), of the base for the powder cone was measured and angle of repose (θ) was calculated using the following equation.

$$\text{TAN } \theta = h/r$$

$$\theta = 1/\tan (h/r)$$

Were,

θ = angle of repose, h = height, r = radius.

BULK DENSITY: Bulk density was determined, (20gm) of the blend from each formula was weighed, previously lightly shaken to break any agglomerates cylinder. After the initial volume was observed, the cylinder was allowed to full. Volume was noted LBD (loose bulk density) and calculated using the following formula.

$$\text{LBD} = \text{weight of powder} / \text{volume of packing}$$

TAPPED DENSITY: The tapped density was calculated by tapping the measuring cylinder 100 times. The volume of TBD was measured and calculated using the formula,

$$\text{TBD} = \text{weight of powder} / \text{tapped volume of packing.}$$

HAUSNER'S RATIO: it indicates the flow properties of the powder and it measured by the ratio of TD to the BD.

$$\text{Hausner's ratio} = \text{tapped density} / \text{bulk density}$$

COMPRESSIBILITY INDEX: Carr's index was calculated based on the LBD and TBD. The compressibility index of the blend was determined by Carr's index.

$$\text{Carr's Index (\%)} = 100 (\text{TBD} - \text{LBD} / \text{TBD})$$

POST COMPRESSION PARAMETERS

Tablet thickness and diameter

The thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier callipers.

Hardness

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this, five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Uniformity of weight

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated.

Friability test

The friability of tablets was determined using Roche friabilator. It is expressed in percentages (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into a friabilator. The friabilator was operated at 25rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W_{final} Content uniformity). The % friability was then calculated by:

$$\% \text{ loss} = 100(\text{initial weight-final weight/initial weight})$$

Weight variation

10 tablets of each formulation were weighed using an electronic balance and the test was performed according to the USP official limits of percentage deviation of tablets are presented in the table. The batches passes the test if not more than two of the individual tablet weights deviate from average weight by more than the percentage shown in below table and none deviate by more than twice the percentage ±5.

Table 2: Weight variation limits

Maximum % of weight difference limit	Average weight of the tablet	
	USP	IP
10	< 130	<80
7.5	130-324	80 -250
5	>324	>250

Content uniformity

Three tablets were crushed into powder, the quantity of powder equivalent to average weight of formulation was weighed and taken in a volumetric flask dissolved in 15ml methanol, the solution is filtered through whatman filter paper, from this 1ml of solution is withdrawn and diluted to 10ml. Again, from this, 1ml of solution is withdrawn and diluted to 10ml, absorbance is taken at 275nm and % drug content is calculated by the formula,

Drug content= (absorbance/slope) dose× dilution factor×1/1000

% Drug content= (drug content/ dose of formulation) × 100

Swelling studies

Six buccal tablets were individually weighed (W_1) and placed separately in petri dishes with 5 ml of phosphate buffer of pH 6.8. At the time intervals of 1,2,4,6 and 8 hrs tablets and excess water was removed from petri plate carefully using the following formula,

$$\text{Percentage hydration} = [(W_2 - W_1) / W_1] \times 100$$

Surface pH studies

Tablet was taken in a petridish which contains 1ml of distilled water. Tablet was allowed to swell for 2 hours at room temperature pH was noted down by bringing the electrode in contact with the surface of the tablet, allowing it to equilibrate for 1 min.

IN-VITRO DRUG RELEASE STUDIES:

Invitro dissolution study

Dissolution rate was studied using USP type II apparatus at 50 rpm (USP XXIII dissolution test apparatus) using 1000ml of Phosphate buffer pH 6.8 as dissolution medium. Temperature of dissolution medium was maintained at 37±0.5ºC, aliquot of dissolution medium was withdrawn at every 2 hours interval and filtered. The absorbance of filtered solution was checked by UV spectrophotometric method at 275 nm and the concentration of drug was determined from standard calibration curve. Dissolution rate was studied for all designed formulations and the results are shown in table with graphical representation.

Drug release kinetics studies

Further the cumulative amount drug released from the formulations at different time intervals were subjected to various kinetic models such as Zero order, first order, Higuchi and Korsmeyer-peppas model to characterize the mechanism of drug release.

Mucoadhesive Strength

The mucoadhesive forces of tablets were determined by means of mucoadhesive measuring device as shown in figure. The sheep buccal mucosa was cut into stripes/ pieces and washed with phosphate solution. At the time of testing a section of sheep buccal mucosa was secured keeping the mucosal side out, on the upper glass vial using rubber band and aluminium cap. The diameter of each exposed mucosal membrane was 1cm. the vial with sheep buccal mucosa was stored at 37ºC for 10 min. Then one vial with section of sheep buccal mucosa and another vial were fixed on height adjustable pan. To the lower vial a tablet was placed with the help of bilayered adhesive tape, the adhesive side facing downward. The height of lower vial was adjusted so that a tablet could adhere to the sheep buccal mucosa of upper vial. A constant force was applied on upper vial for 2mins, after which it was removed and upper vial was then connected to the balance. Then the weight on right side pan was slowly added in an increment of 0.5g, till the two vials just separate from each other. The total weight (g) required to detach two vials was taken as a measure of mucoadhesive strength. From the mucoadhesive strength the force of adhesion was calculated.

Force of adhesion (N) = (mucoadhesive strength (g)/1000) 9.81

Ex vivo drug permeation studies

Tissue isolation

The objective of this study was to investigate the permeability of buccal mucosa to Azithromycin. Buccal tissue was taken from a local slaughterhouse. It was collected within 10 min after the slaughter of the sheep and tissue was stored in Krebs buffer solution. It was transported immediately to the laboratory and was used within 2 hours of isolation of buccal tissue. The buccal epithelium was carefully separated from the underlying connective tissue with surgical technique, and then the remaining buccal mucosa was carefully trimmed with the help of surgical scissors to a uniform thickness. Sufficient care was taken to prevent any damage to the buccal epithelium. Finally, the membrane was allowed to equilibrate for approximately 1 h in receptor buffer to regain the lost elasticity.

Procedure

Ex vivo permeation study of azithromycin was performed through the buccal mucosa using Franz diffusion cell. The isolated buccal epithelium was carefully mounted between the two compartments of a modified Franz diffusion cell, and the membrane was allowed to equilibrate for approximately 1 h. After the buccal membrane was equilibrated for 1 h with pH 6.8 phosphate buffer solution between both the chambers, the receiver compartment was filled with 50 ml fresh phosphate buffer solution (pH 6.8), and the donor compartment was charged with 4ml (1 mg/ml) of drug solution. The entire setup was placed over a magnetic stirrer at 50 rpm, and the temperature was maintained at about 37°C. The 5 ml of samples were collected at predetermined time intervals 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6.0 h from receptor compartment and replaced with an equal volume of fresh buffer solution and stored under refrigerated conditions till the analysis was carried out. All the experiments were performed in triplicates. Finally, the amount of drug permeated through the buccal mucosa was determined by measuring the absorbance at 275nm using a UV-visible spectrometer. The studies were repeated in triplicate (n=3), and the mean was calculated.

Stability studies

Stability can be defined as the capacity of drug product to remain within specifications established to ensure its identity, strength, quality, and purity. The product is subjected to

accelerated stability studies at 40℃ ± 2℃ / 75 % ± 5 % RH in a stability chamber for 3 months.

Table 3: Stability storage conditions

S. No	Storage condition	Test period (3 months)	
		Initial	Final
1	40℃ ± 2℃ / 75 % ± 5 % RH	1st day	90th day

RESULTS AND DISCUSSION

The compatibility studies revealed both drugs and excipients were compatible after FT IR studies, the results shown in Figure 1.

Pre-compression evaluation parameters

For each type of formulation blends of active pharmaceutical ingredients and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.41-0.43 g/cm3 and the tapped density was between 0.55 - 0.58 g/cm^3. Using the above two density data, Carr's compressibility index were calculated. The compressibility index was found between 21.80- 29.25 % and the compressibility and flowability data indicated good flow properties of all powder blends. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 20º 55´ to 24º 34´. Angle of repose below 30º indicates good flow property. In the present study all powder blends showed good flow properties. The results are shown in Table 4.

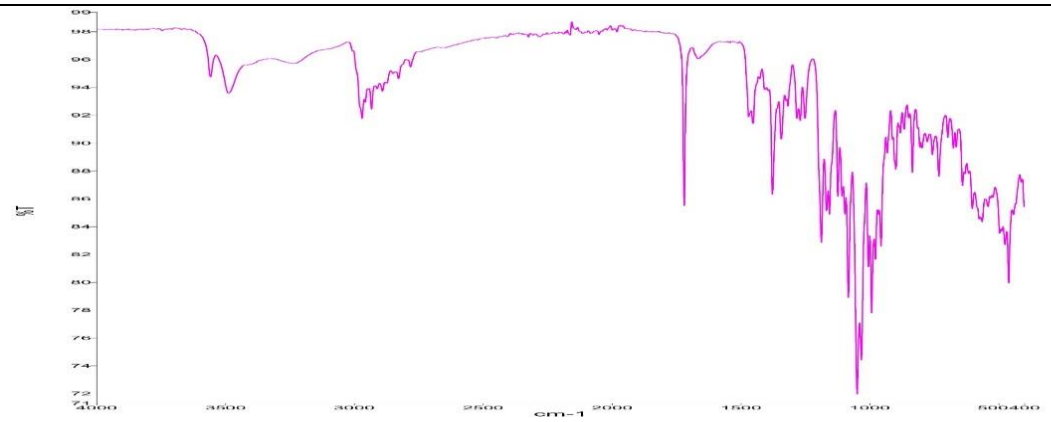
Table 4: Pre-compression parameters

FORMULATION CODE	ANGLE OF REPOSE	BULK DENSITY	TAPPED DENSITY	HAUSNERS RATIO	CARR'S INDEX
F1	20.55±0.332	0.416	0.588	1.41	29.25%
F2	21.49±0.364	0.434	0.588	1.35	26.19%
F3	22.10±0.328	0.434	0.555	1.27	21.80%
F4	22.37±0.378	0.434	0.588	1.35	26.19%
F5	23.38±0.385	0.434	0.555	1.27	21.80%
F6	22.39±0.387	0.416	0.588	1.41	29.25%
F7	23.17±0.429	0.434	0.555	1.27	21.80%
F8	24.34±0.485	0.416	0.555	1.33	25.04%
F9	23.01±0.394	0.434	0.588	1.35	26.19%

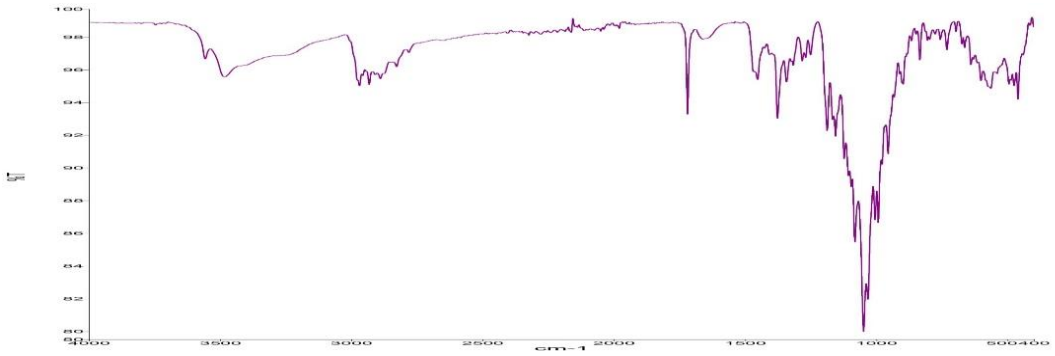
COMPATIBILITY STUDIES

Compatibility studies were performed using FT-IR spectrophotometry. The spectrum of pure drug and physical mixture of drug and excipients were studied. The peak obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicated that the drug was compatible with formulation components. The spectra for all formulations were shown in **Fig : 1**. The azithromycin absorption band owing to the C=O group, detected at 1729 cm^{-1}, 1188 cm^{-1} and 1052 cm^{-1}, offered sufficient sensitivity and selectivity for the identification of the active principle. The interpretation of azithromycin with HPMC K4M showed peaks at 1729 cm^{-1}, 1188 cm^{-1} and 1052 cm^{-1} which is characteristics of azithromycin. Similarly, a peak was observed at 2900 cm^{-1} for HPMC K4M. Hence no interaction was found between the azithromycin and HPMC K4M. The major IR peaks of HPMC K100 M were observed, 3431.71 (3300-3500) (N-H), 2886.92 (2850-3000) (C-H), 1451.17 (1430 - 1470) -CH3, 1075.12 (1000-1300) (C-O) cm^{-1}. These peaks were distinct and reveals that there is no interaction between HPMC K100M and azithromycin. The four main peaks were observed at 1708 cm^{-1}, 1431 cm^{-1}, 1346 cm^{-1} and 1101 cm^{-1} which is a characteristic peak for carbopol. The peak at 1729 cm^{-1} reveals the C=0 group of azithromycin. This shows that there is no interaction of azithromycin with carbopol. These principal peaks of the drug 1729 cm^{-1}, 1188 cm^{-1} and 1052 cm^{-1} were seemed to be unaffected in all the physical mixtures of drug & HPMC K4M, drug & HPMC K100M, drug

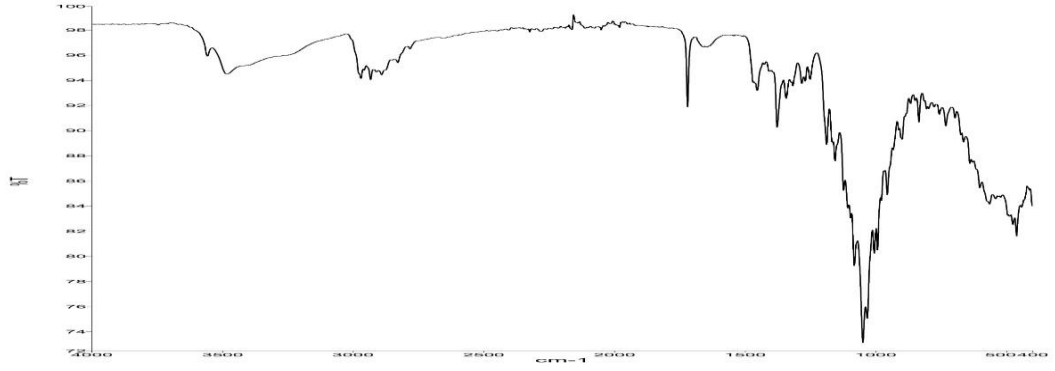
& carbopol. The peaks of respective polymers have also appeared in their respective spectra. No new peaks were found in addition to the drug and polymer. The FTIR study revealed no interaction between the drug and polymers confirms their compatibility.



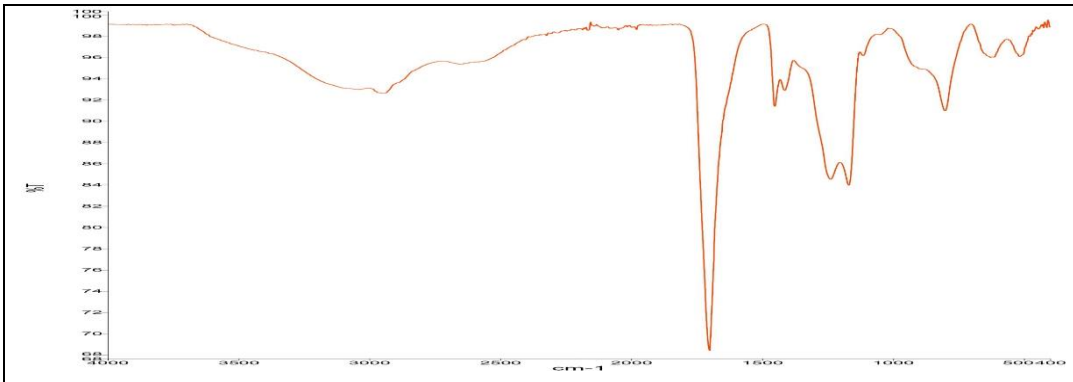
A: Pure drug Azithromycin



B: Drug with HPMC K4M



C: Drug with HPMC K100M



D: Drug with Carbapol 934

Figure 1: FTIR studies of pure drug, with excipients and formulation

POST-COMPRESSION EVALUATION PARAMETERS

Organoleptic characters

Various organoleptic properties viz. taste, colour and odour were performed on all the formulations, the results found that all the formulations were sweet in taste, white in colour and odour less.

Thickness and Hardness

The hardeness of different formulation of Azithromycin ranges from 3.8±0.23 - 4.4±0.18 kg/cm^2 The thickness of tablets of Azithromycin are ranged from 0.32±0.03 - 0.40±0.07 mm as shown in the table no: 5.

TABLE 5: HARDNESS AND THICKNESS OF THE TABLETS

FORMULATION CODE	HARDNESS OF THE TABLET (kg/cm^2)	THICKNESS OF THE TABLET (mm)
F1	4.4± 0.18	0.32± 0.03
F2	4.3± 0.15	0.37± 0.02
F3	4.1± 0.15	0.39± 0.04
F4	3.9± 0.26	0.38± 0.03
F5	3.8± 0.23	0.35± 0.02
F6	4.0± 0.35	0.36± 0.04
F7	4.2± 0.38	0.40± 0.07
F8	3.9± 0.42	0.38± 0.06
F9	3.8± 0.18	0.39± 0.05

All values are mean ± SD, n=3

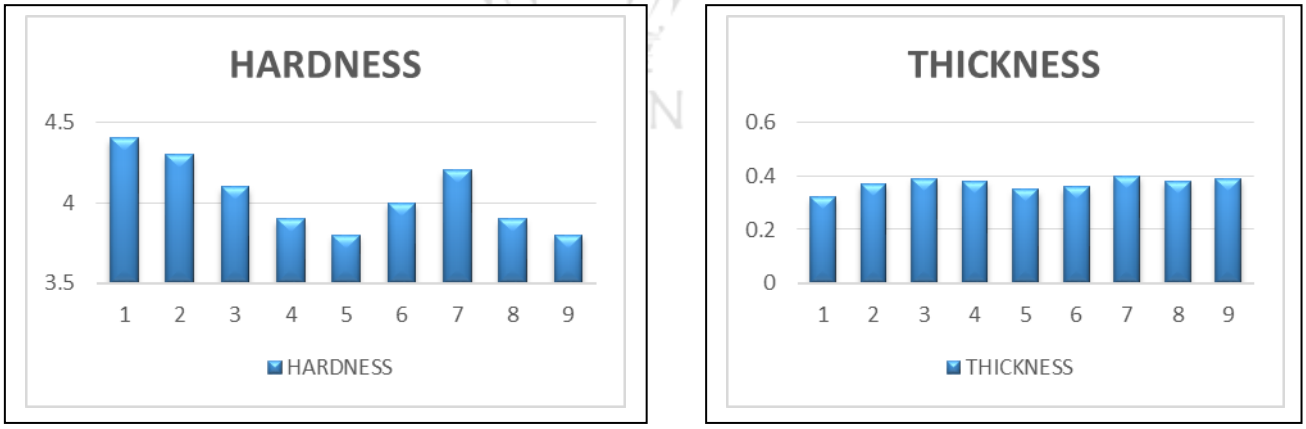


Figure 2: Hardness andThickness of Azithromycin tablets

FRIABILITY TEST: All the formulations exhibited less than 1% friability, which was within limit.

WEIGHT VARIATION TEST: The percentage weight variation for all formulations is performed. All the tablet formulations were within limits.

DRUG CONTENT: The content uniformity test for Azithromycin was performed. The results were found to be 96.52-98.65 %. The results were found to be within the USP specification limits (90%-110%). It found that the drugs were distributed uniformly.

TABLE 6 : RESULTS OF POST-FORMULATION STUDIES

FORMULATION CODE	FRIABILITY(%)	WEIGHT VARIATION (mg)	DRUG CONTENT (%)
F1	0.68± 0.01	450.25± 0.57	97.41± 0.66
F2	0.66± 0.03	450.38± 0.99	98.28± 0.53
F3	0.68± 0.07	450.42± 0.78	98.45± 0.55
F4	0.65± 0.06	450.38± 0.46	96.52± 0.62
F5	0.64± 0.04	449.44± 0.68	97.65± 0.78
F6	0.70± 0.09	450.12± 0.34	98.22± 0.73
F7	0.62± 0.04	450.19± 0.33	98.65± 0.50
F8	0.66± 0.05	449.76± 0.48	98.45± 0.26
F9	0.68± 0.06	450.06± 0.52	97.33± 0.15

All values are mean ± SD, n=3

SWELLING STUDY

Table 7: In vitro swelling study of prepared mucoadhesive tablets of Azithromycin.

FORMULATION CODE	1 (hrs)	2 (hrs)	3 (hrs)	4 (hrs)	5 (hrs)
1	0.54± 0.015	0.78± 0.02	1.05± 0.05	1.24± 0.04	1.56± 0.07
2	0.58± 0.013	0.76± 0.04	1.02± 0.06	1.22± 0.05	1.52± 0.06
3	0.62± 0.057	0.75± 0.03	1.10± 0.03	1.26± 0.04	1.48± 0.09
4	0.56± 0.024	0.82± 0.05	0.98± 0.04	1.31± 0.06	1.47± 0.08
5	0.55± 0.019	0.76± 0.06	1.13± 0.06	1.38± 0.08	`1.54± 0.05
6	0.59± 0.026	0.78± 0.04	1.14± 0.02	1.36± 0.07	1.56± 0.06
7	0.63± 0.043	0.85± 0.05	1.06± 0.04	1.25± 0.08	1.61± 0.05
8	0.55± 0.036	0.72± 0.06	1.11± 0.06	1.27± 0.06	1.58± 0.04
9	0.58± 0.026	0.69± 0.05	1.09± 0.05	1.32± 0.04	1.57± 0.06

All values are mean ± SD, n=3

***IN VITRO* DRUG RELEASE**:

The percentage of drug release from buccal tablet were shown in table no:8,

TABLE 8: DISSOLUTION TEST RESULTS.

TIME (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.6 ±0.14	12.2 ±0.02	12.14 ±0.45	14.12 ±0.26	15.35 ±0.31	14.86 ±0.47	15.26 ±0.39	16.09 ±0.36	16.75 ±0.27
2	28.9 ±0.13	30.14 ±0.24	30.75 ±0.26	32.4 ±0.19	32.42 ±0.25	35.36 ±0.24	33.86 ±0.35	34.12 ±0.29	34.96 ±0.16
3	42.3 ±0.24	44.6 ±0.05	44.65 ±0.35	48.7 ±0.32	51.32 ±0.35	52.76 ±0.26	47.75 ±0.46	49.85 ±0.35	51.36 ±0.35
4	54.9 ±0.28	58.48 ±0.06	59.24 ±0.14	67.42 ±0.28	69.28 ±0.28	71.23 ±0.35	68.74 ±0.48	67.21 ±0.41	70.82 ±0.26
5	73.26 ±0.18	74.96 ±0.45	74.23 ±0.27	76.32 ±0.16	77.22 ±0.18	81.67 ±0.38	79.08 ±0.33	78.43 ±0.38	80.80 ±0.32
6	82.33 ±0.35	83.42 ±0.08	82.86 ±0.38	86.46 ±0.33	85.40 ±0.36	88.43 ±0.27	84.53 ±0.47	85.93 ±0.39	85.26 ±0.42

All values are mean ± SD, n=3

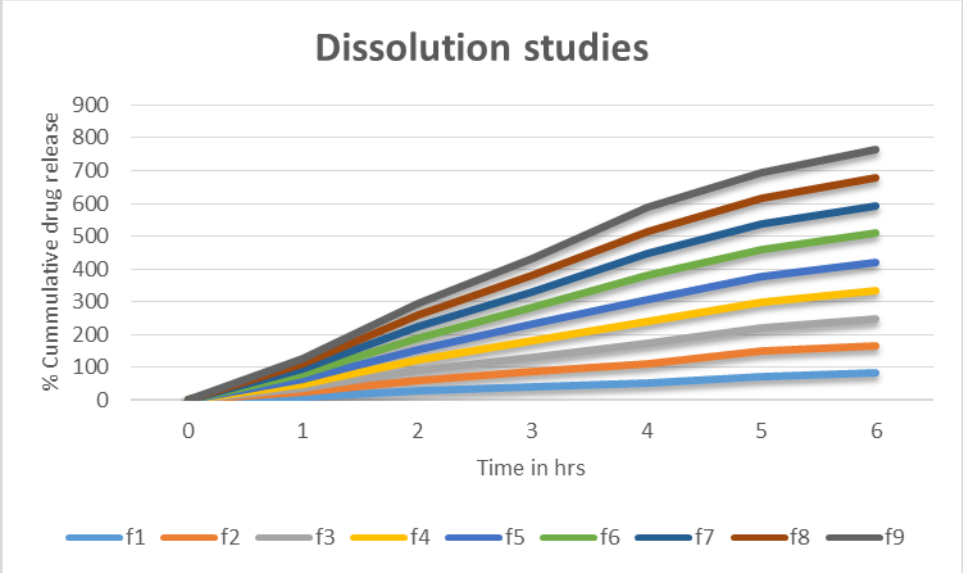
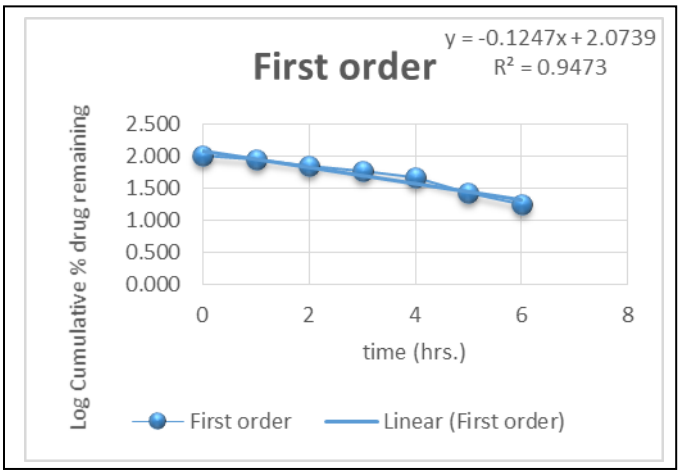


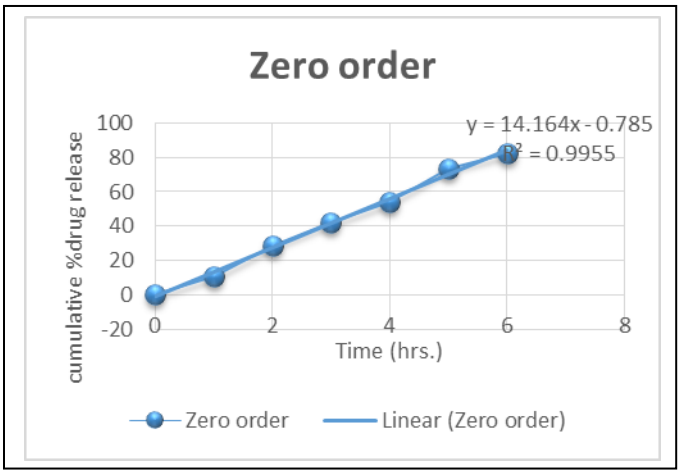
Figure 3: Results of dissolution study

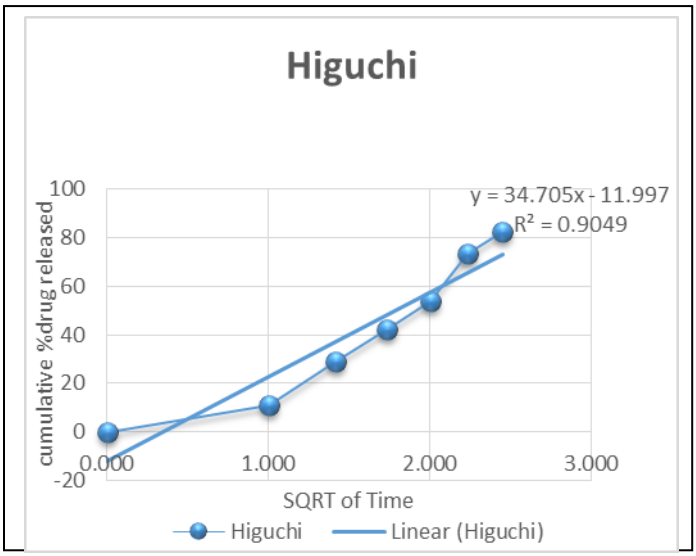
DRUG RELEASE KINETIC STUDY:

TABLE 9: RESULTS OF *INVITRO* RELESE KINETICS

S.NO.	ZERO ORDER ($R^{2)}$	FIRST ORDER ($R^{2)}$	HIGUCHI ($R^{2)}$	HIXON CROWELL ($R^{2)}$	KORSMEYER-PEPPAS ($R^{2)}$
F1	0.955	0.947	0.904	0.975	0.964
F2	0.995	0.958	0.915	0.983	0.971
F3	0.988	0.962	0.919	0.986	0.974
F4	0.994	0.968	0.929	0.990	0.976
F5	0.980	0.981	0.937	0.993	0.979
F6	0.981	0.934	0.934	0.992	0.978
F7	0.986	0.976	0.932	0.988	0.971
F8	0.976	0.974	0.942	0.993	0.973
F9	0.989	0.980	0.940	0.989	0.971







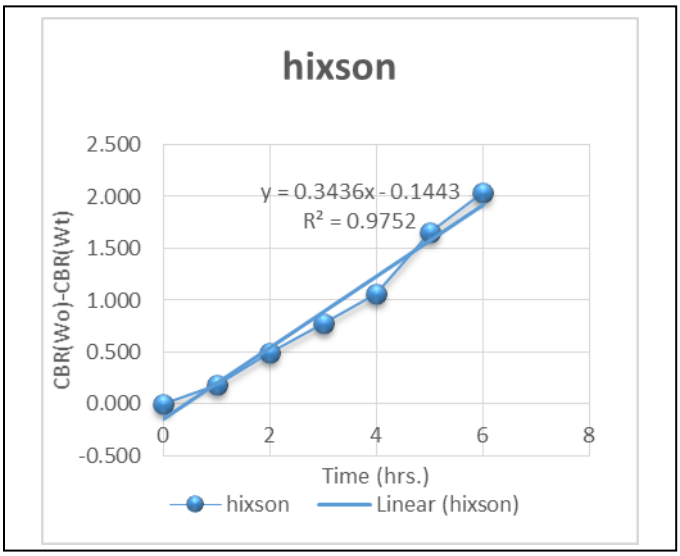


Fig. 4: Release kinetic plots for formulation Azithromycin

SURFACE pH STUDIES:

Tablet was taken in a Petri dish which contains 1ml of distilled water. Tablet was allowed to swell for 2 hours at room temperature pH was noted down by bringing the electrode in contact with the surface of the tablet, allowing it to equilibrate for 1 min, enlisted in table 10.

***EX VIVO* MUCOADHESION TIME**

The mucoadhesive time on goat buccal mucosa ranged from 3.23 to 5.48 hours.

BIOADHESIVE STUDIES :

Table 10: Results of Mucoadhesive strength, Exvivo residence time, Surface pH of prepared buccal tablets of Azithromycin

FORMULATION CODE	MUCOADHESIVE STRENGTH(gm)	MUCOADHESION TIME(hr)	SURFACE pH
F1	39.80 ± 1.39	5 hr 48 min	6.98± 0.05
F2	20.83 ± 0.62	3 hr 32 min	6.08±0.09
F3	21.00±1.63	4 hr 20 min	6.67±0.26
F4	38.11 ± 0.55	4 hr 50 min	6.45±0.04
F5	30.23 ± 0.50	3 hr 30 min	6.65±0.07
F6	23.40 ± 1.04	3 hr 23 min	6.32±0.37
F7	40.83 ± 0.84	5 hr 12 min	6.87±0.05
F8	31.11 ± 1.00	4 hr 45 min	6.86±0.08
F9	35.53 ± 0.41	3 hr 27 min	7.35±0.12

All values are mean ± SD, n=3

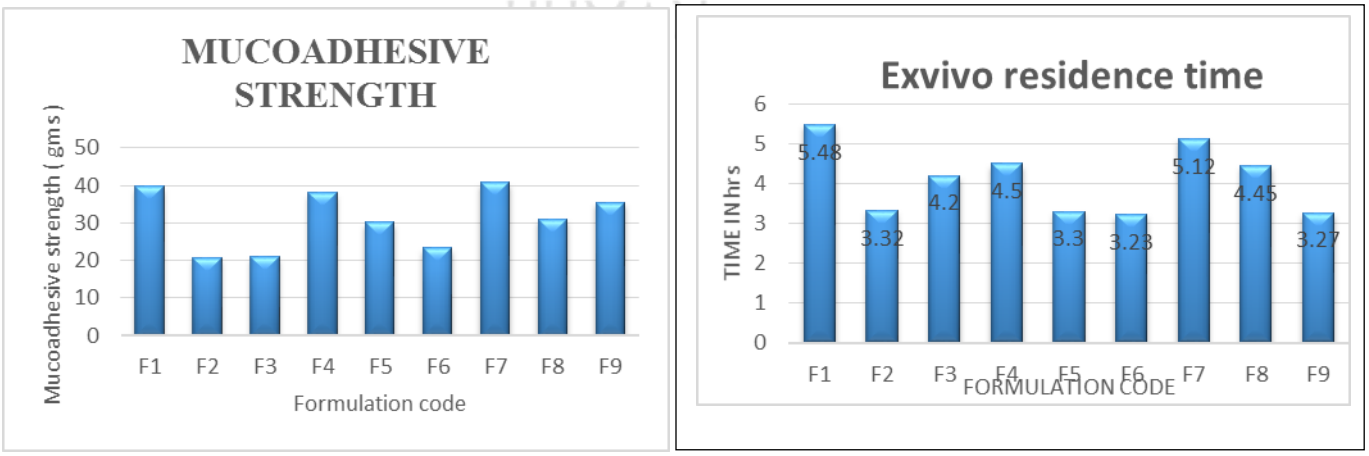


Fig 5: Mucoadhesive strength and Mucoadhesion time

EX VIVO PERMEATION STUDIES

Table 11: Ex- vivo permeation studies of Azithromycin buccal formulations F4 and F7

Time (hrs)	F4	F7
1	12.6±0.35	16.8±0.94
2	29.8±0.09	33.45±0.75
3	38.5±0.05	43.56±0.05
4	62.5±0.45	69.45±0.09
5	75.3±0.08	80.23±0.06
6	90.23±0.23	95.2±0.59

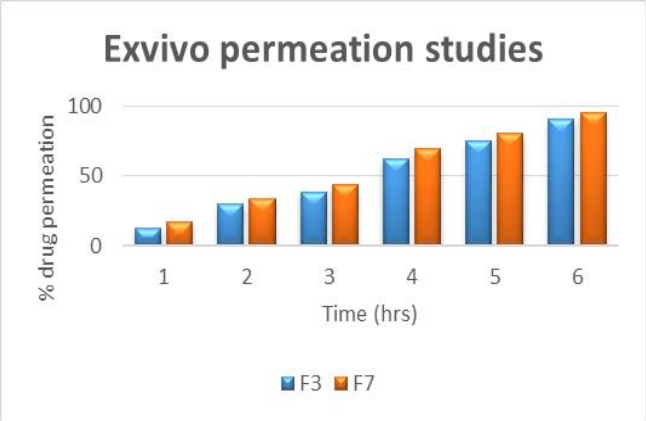


Fig 6 : Exvivo Permeation Studies

STABILITY STUDIES

The product is subjected to accelerated stability studies at 40℃ ± 2℃ / 75 % ± 5 % RH in a stability chamber for 3 months.

Table 12 A: Stability studies of optimized formulation F7

S.no.	Parameters Tested	Storage Conditions	
		Initial	40℃ ± 2℃ / 75 % ± 5 % RH (3rd. month)
1	Description	White color	No change
2	Average weight(mg)	452	452
3	Thickness (mm)	0.42	0.42
4	Hardness (Kp)	4.2	4.2
5	Friability (%)	0.62	0.62
6	Drug Content (%)	98.65	98.65

Table 12 B: *In – vitro* Dissolution of Formulation F7 after stability studies

Invitro dissolution after 90 days at 40℃ ± 2℃ / 75 % ± 5 % RH		
Dissolution medium	Time in hours	Cumulative % drug release
Phosphate buffer pH 6.8	1	15.25
	2	33.80
	3	47.56
	4	68.50
	5	80.35
	6	85.54

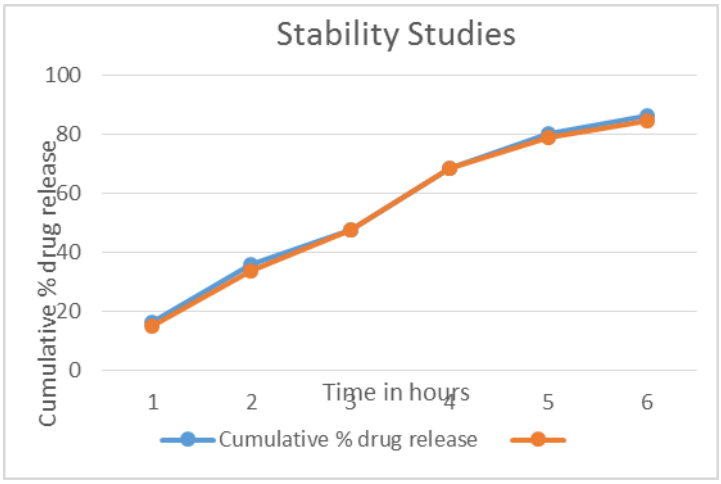


Fig 7: *Invitro* dissolution of formulation F7 after stability

CONCLUSION

The development of mucoadhesive buccal tablets of Azithromycin is one of the alternative routes of administration to avoid high gastric irritation and direct access to systemic circulation. In this present study F7 formulation comprises of Azithromycin with Carbapol 974P and HPMC K4M showed optimum drug release and satisfactory bioadhesive properties. Thus, the study revealed that the Azithromycin buccal tablets showed good mucoadhesion time with sustained release of drug for more than 6 hours. The optimized formulation also showed satisfactory surface pH and physical parameters, effective ex vivo permeation, satisfactory stability and comfortability in the oral cavity. A result of the study of individual polymers shows that the, HPMC K4M, HPMCK100M and Carbopol 974P, alone was also able to control the release in 6 hours. Release of Azithromycin, from combination of HPMC K4M with Carbopol 974P, Combination of HPMC K100M with Carbapol 974P, gave the good results compared to employing individual polymers. Tablets of batch F7 selected as an optimum batch.

From the results of present investigation, it can be concluded that Azithromycin can certainly be administered through the oral mucosa and it is suitable for the development of buccoadhesive system. The above study demonstrated the possibility of making a Mucoadhesive drug delivery system for Azithromycin which will be more efficacious and acceptable than the conventional drug delivery of Azithromycin and it could be a drug delivery of choice in the treatment of bacterial infections. Hence, this study concludes that the Azithromycin could be delivered through the buccal route. Further work is recommended to

support its efficacy claims by pharmacodynamic and pharmacokinetic studies in human beings.

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