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DEVELOPMENT AND *IN VITRO* EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF GLIPIZIDE

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ABSTRACT

The objective of present study is to prepare mucoadhesive buccal tablets of Glipizide using the bioadhesive polymers Carbopol 974P (CP) in combination with cashew nut tree gum, Aegle marmelos gum, Moringa Oleifers gum as binding agent and Ethyl cellulose (EC-50 mg) as impermeable backing layer. Nine formulations of mucoadhesive buccal tablets of Glipizide were prepared, which contain the polymers in various combinations. Tablets were prepared by direct compression method and characterized for swelling studies, surface pH, bioadhesive properties, in-vitro drug dissolution and in-vitro diffusion studies. All the formulations show the satisfactory results in terms of bioadhesive performance. The swelling index was proportional to polymer content. The surface pH of all tablets was found to be satisfactory, close to neutral pH; the Glipizide released and drug diffusion from these tablets was depended on the ratio and type of the natural polymers used in the formulation. All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeia limits. As the amount of polymer in the tablets increase, the drug release rate decreases, whereas swelling index and mucoadhesive strength increases Drug polymer interaction were evaluated by Fourier Transform Infrared Spectroscopy and Differential Scanning Calorimetry.

KEY WORDS

Glipizide, Buccal tablets, Natural Polymers.

INTRODUCTION

Mucoadhesive drug delivery systems is defined as drug delivery systems which utilize the property of bioadhesion of certain water-soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. Mucoadhesives are synthetic or natural polymers which interact with the mucus layer covering the mucosal epithelial surface and mucin molecules constituting a major part of mucus. They render the treatment more effective and safer, not only for topical disorders but also for systemic problems[1].

Glipizide is the most rapidly and short acting oral hypoglycemic agent belonging to the sulphonylurea group.[8] Glipizide is one of the most potent antidiabetic drugs. Its peak level is rapidly obtained and activity appears in 40 to 60 minutes. After its administration, the effect on blood glucose is prompter and immuno reactive insulin levels higher.[2] Glipizide upregulates insulin receptor in the periphery, which seems to be the primary action. It has a special status in the treatment of non-insulin dependent diabetes mellitus because it is effective in many cases which are resistant to all other oral hypoglycemic drugs. It was the first oral

hypoglycemic drug shown to thin a diabetes-thickened endothelial basement membrane and hence to reverse diabetic angiopathy. About 90% of Glipizide is metabolized in the liver to several inactive metabolites. The half-life is about 2 to 4 hr.[3] So an attempt has been made to develop a buccal mucoadhesive dosage form of Glipizide for improving and enhancing bioavailability in controlled release fashion. It may be possible to bypass first pass hepatic metabolism by administering it through the buccal mucosa. Hence, Glipizide has been selected as a suitable candidate for preparing buccal mucoadhesive dosage form. In this study, muccoadhesive tablets of Glipizide have been developed using bioadhesive polymers Carbopol 974P (CP) in combination with cashew nut tree gum, Aegle marmelos gum, Moringa Oleifers gum as binding agent and Ethyl cellulose (EC-25mg) as impermeable backing layer.

MATERIALS AND METHODS

Glipizide was a gift sample Alembic Limited, Vadodara, Gujarat, India. Aegle marmelos gum, Cashew nut tree gum and Moringa Oliefera gum procured from Local Area. Carbopol-934P and Ethyl Cellulose purchased from Qualigens fine chemicals, Mumbai. Microcrystalline cellulose, Magnesium stearate and Talc purchased from SD fine chemicals, Mumbai. All other chemicals and reagents used were of analytical reagent grade and purchased from Himedia, Hyderabad.

Methods of preparation of Natural gums

Aegle marmelos gum

The fresh fruits of *Aegle marmelos* were soaked in distilled water and boiled for 5 h in a water bath until slurry was formed. The slurry was cooled and kept in refrigerator overnight. so that most of the undissolved portion was settled out. The upper clear solution was decanted off and centrifuged at 500 rpm for 20 min. The supernatant was concentrated on a water bath until the volume reduced to one third of its original volume. The solution was cooled down to the room temperature and was poured into thrice the volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried at 500C under vacuum drier. The dried gum was powdered and stored in a tightly closed container for further usage[4].

Cashew nut tree gum

The collected crude *cashew nut tree gum* about 100g was crushed by using mortar and pestle. The crushed gum was dissolved in water about 300ml. The solution was filtered through muslin cloth and the filtrate was collected. To the filtrate, alcohol (90% v/v) was added in 1:1 ratio and the precipitate were obtained. The precipitate was filtered and dried in a hot air oven at 450C. 100 g of powder obtained was dissolved in 100 ml water, filtered through several folds of muslin cloth. Then the filtrate was centrifuged at 3000 rpm for 10 minutes and the supernant layer was collected, evaporated and dried to obtain solid mass. This mass was passed through sieve no. 80 and stored in an airtight container for further studies[5].

Moringa oleifera tree gum

The gum was collected from incisions of trees. The gum was dried and crushed by using mortar and pestle. It is passed through sieve no.100. Dried gum was stirred in distilled water (300ml) for 4 – 5 hours at room temperature. The supernant layer was obtained by centrifugation. The residue was washed with water; this procedure was repeated for three times. Finally, the supernant layer was made up to 500ml and treated with twice the volume of acetone by continuous stirring. The precipitate material was washed with water and dried at 50 – 60^{0}C under vacuum[6].

Preparation of Glipizide buccal tablets

Buccal tablets were prepared by direct compression procedure involving two consecutive steps. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 Mins. Microcrystalline cellulose, Magnesium stearate and talc were added in the blended material and mixed. The blended powder was then lightly compressed on 9 mm flat punched using tweleve station tablet compression machine, the upper punch was then removed and backing material ethyl cellulose was added over it and finally compressed at a constant compression force. All ingredients were dried, passed through 100 mesh sieve and mixed manually in mortar. The tablets were compressed by using tweleve station tablet machine fitted with flat faced punches and ratios of drug and all ingredients were shown in table 1[7]

Table 1: Formulations of Glipizide Tablets (in mg) by direct compression

Sr.No.	Name of Ingrident	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Glipizide	50	50	50	50	50	50	50	50	50
2	Cabopol -934P	30	30	30	30	30	30	30	30	30
3	Cashew nut tree gum	30	40	50	---	---	---	---	---	---
4	Aegle marmelos gum	---	---	---	30	40	50	---	---	---
5	Moringa Oleifers gum	---	---	---	---	---	---	30	40	50
6	Microcrystalline cellulose	85	75	65	85	75	65	85	75	65
7	Magnesium stearate	3	3	3	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2	2	2	2
9	Ethyl Callulose	50	50	50	50	50	50	50	50	50

Total Wright= 250 mg

EVALUATION STUDIES

Drug Excipient Compatibility

Infrared Spectral Analysis

Glipizide and individual polymer (in 1:1 ratio) were mixed well. This mixture was then triturated with KBr and the disk was prepared for identification by I.R. spectra. The I.R. spectra of the drug-polymer mixtures were compared with that of pure drug[8].

Differential Scanning Calorimetry Study

Differential Scanning Calorimetry of Glipizide and optimized formulations was recorded between 30.0°C to 300.0°C at the rate of 20.0°C per minute under the environment of nitrogen[9].

Standard Curve for Glipizide

The standard curve for Glipizide was prepared in phosphate buffer pH 6.8. An accurately weighed quantity of 10 mg Glipizide was dissolved in 500 ml of phosphate buffer pH 6.8 in order to get a stock solution of 20 µg/ml, from this stock solution aliquots of 5, 10, 15, 20, 25 ml was withdrawn and volume was made up to 25 ml in a volumetric flask with phosphate buffer pH 7.4, in order to get a concentration range of 4, 8, 12, 16 and 20 µg/ml. The absorbance was measured at 224 nm[10].

Evaluation of tablets

Hardness

For this test Monsanto Hardness Tester was used. This tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring was compressed, a pointer ride along a gauge in the barrel to indicate the force. The force of fracture was recorded, and the zero-force reading was deducted from it[11].

Weight variation

Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percentage of weight variation was calculated by using the following formula[12].

%Weight variation= (Average weight) -(Individual weight)/(Average weight)X100

Friability

The Roche friabilitor apparatus was used to determine the friability of the tablets. About 20 tablets were selected, dedusted and weighed. Then they were placed in a drum and rotated at 25 rpm for 4 minutes. Then tablets were dedusted to remove dust and reweighed. The percentage friability was calculated by the given formula[12].

%Friability= (Initial weight) -(Final weight)/(Initial weight)X100

Drug content

Twenty tablets were collected and powdered. The powder equivalent to 50mg of the drug was weighed accurately, dissolved in 100ml of phosphate buffer pH 6.8. The solution was filtered, suitably diluted and an aliquot was analyzed at 224nm by using Uvspectrophotometer[13].

In-vitro dissolution test

The release of Glipizide from the tablet was studied using USP – Type II paddle apparatus. The drug release profile was carried out in 500 ml of 6.8 pH phosphate buffer maintained at 37±0.5°C temperature at 50 rpm. 5 ml of sample was withdrawn at regular time intervals. The samples were analyzed at 224 nm by UV spectrophotometer[14].

Surface pH study

The tablet was allowed to swell by keeping in contact with 1 ml of distilled water for 2hrs at room temperature. The pH measured was by bringing the

electrode in contact with the surface of the tablet an allowing to equilibrate for 1 min[15].

Swelling study

Three buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates at 37±1oC. After every 2h time interval until 6h the tablet was removed from the Petri dish and excess surface water was removed carefully with blotting paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the formula given in equation[16].

Swelling index = (W2-W1)/W1 X 100

Where, W1 = initial weight of the tablet,

W2 = final weight of the tablet

Ex-vivo mucoadhesive time

The ex-vivo mucoadhesion time was examined after application of the buccal tablet on freshly excised goat buccal mucosa which was obtained from the slaughter house. The fresh goat buccal mucosa was tied on the glass slide and buccal tablet was pasted to the goat buccal mucosa by applying a light force with a fingertip for 30sec. The glass slide was then dipped down in the beaker, which was filled with 200ml of the phosphate buffer pH 6.8 maintained at 37±1°C. After 2min, stirring was applied by a magnetic stirrer slowly to stimulate the buccal cavity environment and tablet adhesion was maintained for 10h. The time for the tablet to detach from the goat buccal mucosa was recorded as the mucoadhesion time[17].

I. *Ex-vivo* Bioadhesive strength:

Ex-vivo bioadhesive strength of the buccal tablets was measured by the modified physical balance method. The fresh goat buccal mucosa was obtained from the slaughter house was cut into pieces and washed with the phosphate buffer pH 6.8. The tablet was stick to the lower side of the second glass slide with glue. The both pans were balanced by adding an appropriate weight on the left-hand pan. The glass slide with mucosa was placed with appropriate support, so that the tablet touches the mucosa. Previously weighed beaker was placed on the right-hand pan and water equivalent to weight was added slowly to it until the tablet detach from the mucosal surface. The weight equipped to detach the tablet from the mucosal surface gave the bioadhesive

strength. The experiment was performed in triplicate and the average value was calculated[18].

Force of adhesion (N)= (Mucoadhesive strength) X (9.1)/ (1000)

RESULTS AND DISCUSSION

Drug Excipient Compatibility

Infrared Spectral Analysis

The FT-IR spectrum did not show the presence of any additional peaks for new functional groups, indicating no chemical interaction between drug and polymers.

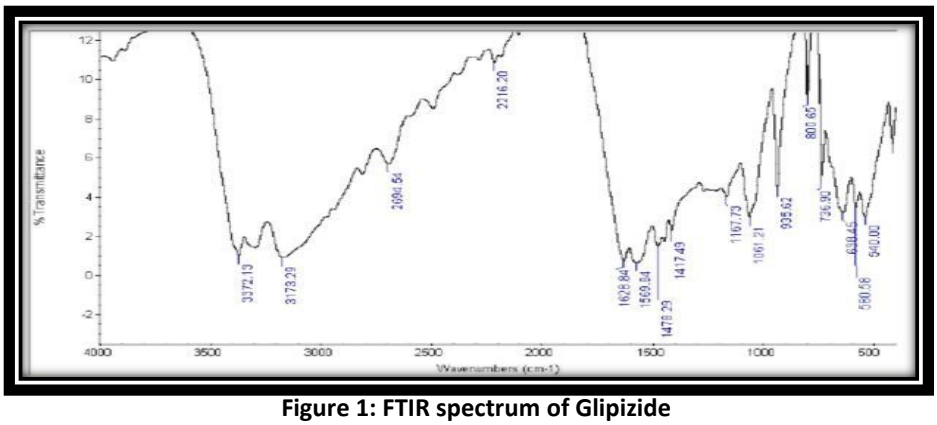

Figure 1: FTIR spectrum of Glipizide

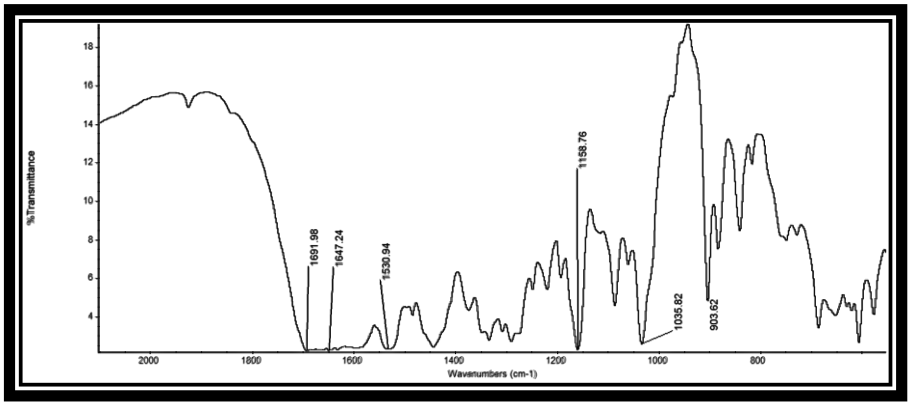

Figure 2: FTIR spectrum of Glipizide with Carbopol-934P

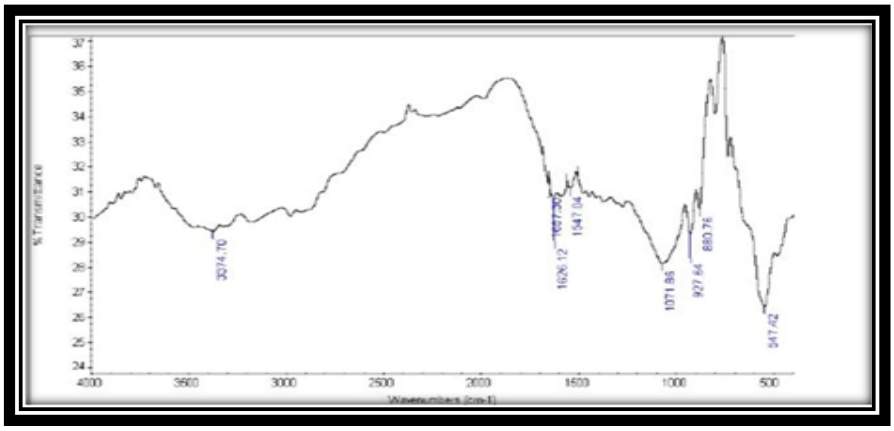

Figure 3: FTIR spectrum of Glipizide buccal tablets prepared with Aegle marmelos gum

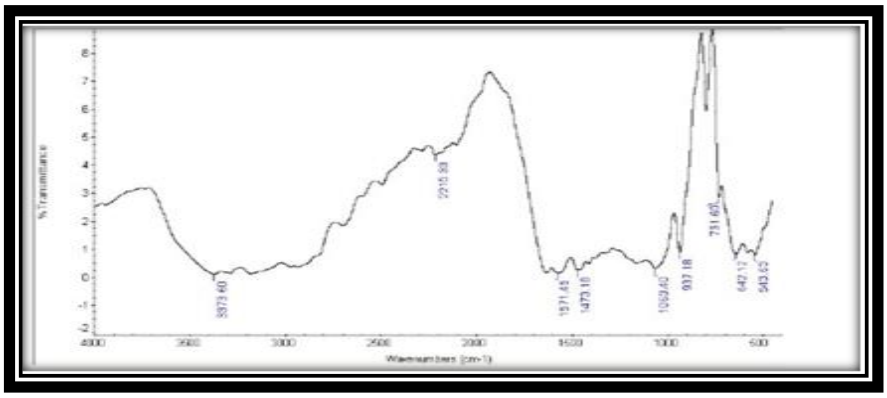

Figure 4: FTIR spectrum of Glipizide buccal tablets prepared with Cashew nut tree gum

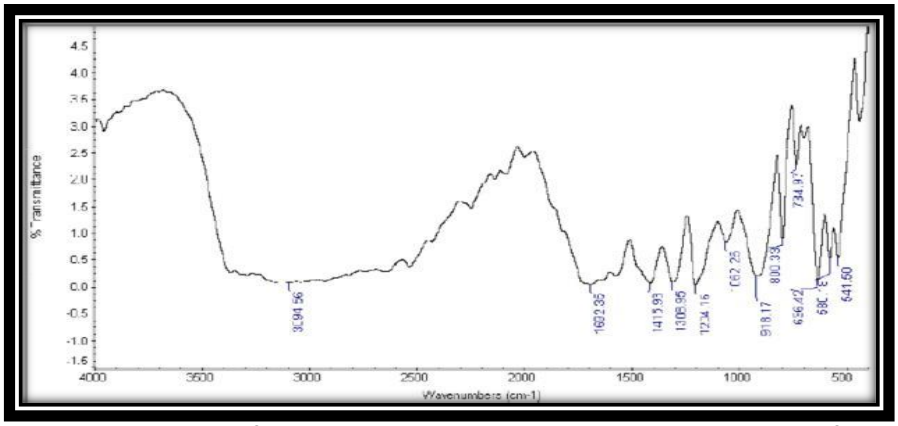

Figure 5: FTIR spectrum of Glipizide buccal tablets prepared with Moringa oleifera gum

Differential Scanning Calorimetry Study

DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug thermogram results are shown in figure numbers 6-7. No interaction was found between drug and polymers.

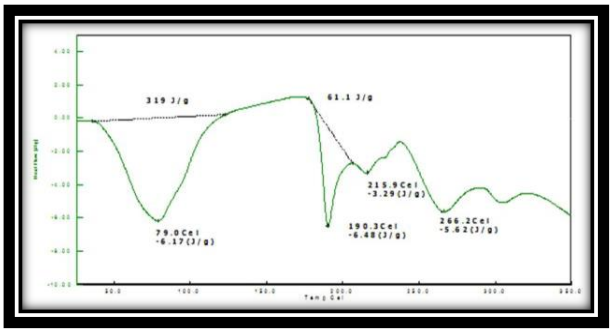

Figure 6: DSC thermogram of Glipizide

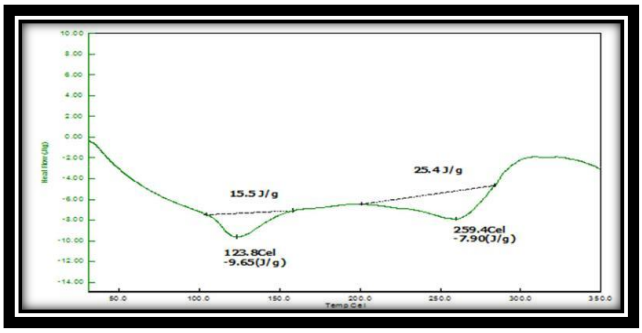

Figure 7: DSC thermogram of the Glipizide+ Polymer mixer

Standard Curve for Glipizide

Table No. 2 shows the absorption reading of Glipizide standard solutions containing 4-20 µg/ml of drug in phosphate buffer pH 6.8. Figure No.8 shows the standard calibration curve for Glipizide with slope of 0.023. The calculation of drug content, *in-vitro* dissolution and in-vitro diffusion rate studies are based on this standard curve.

Table no. 2 standard curve determination

Sr. No.	Concentration (µg/ml)	Absorbance
1	4	0.096
2	8	0.186
3	12	0.280
4	16	0.370
5	20	0.464

Medium: Phosphate buffer pH 6.8; Wavelength: 224nm

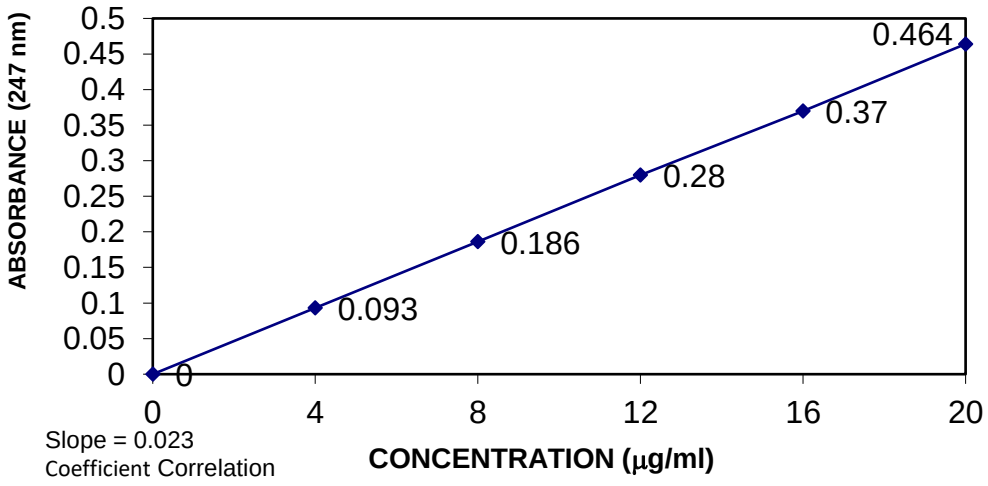

Figure 8: standard calibration curve for Glipizide

EVALUATION OF TABLETS

Table 3: Physical properties of Glipizide buccal tablets formulated

All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeia limits.

Formulation code	Evaluation parameter			
	Hardness (kg/cm2)	Average weight variation (mg)	Friability (%)	Drug content (%)
F1	4.21±0.06	250±1	0.44	99.15
F2	4.36±0.02	250±3	0.49	99.47
F3	4.24±0.01	250±1	0.52	98.50
F4	5.36±0.06	250±2	0.50	99.21
F5	4.46±0.05	250±2	0.53	99.28
F6	4.38±0.06	250±2	0.66	99.48
F7	5.26±0.03	250±3	0.51	99.10
F8	4.32±0.03	250±1	0.54	98.35
F9	4.22±0.07	250±1	0.58	98.60

The swelling behavior is important for bioadhesion. Water sorption increases with an increase in the concentration of polymers. Swelling index, Mucoadhesive strength and *Ex-vivo* residence time were shown in Table 4. The *Cashew nut tree, Aegle marmelos and Moringa Oleifers* gum swells slowly and dissolves in the presence of water. As hydrophilicity of the hydrogel increases, the interaction between water and hydrogel will increase too this facilitates water diffusion and leads to greater swelling. The surface pHwas determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH was bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 6.2 to 6.8 which were nearer to the salivary pH 6.8. Hence it was assumed that these formulations do not cause any irritation to the mucous layer of the oral cavity. Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion. All nine formulation shows good mucoadhesive strength. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum. This improves the consolidation step that increases the mobility of molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases. F6 shows maximum mucoadhesive strength.

Table 4: Mucoadhesion strength, swelling index, retention time, and surface pH of tablets

Formulation code	Evaluation parameter			
	Swelling index	Ex-vivo mucoadhesion time	Ex-vivo bioadhesive strength	Surface pH
F1	8.21±0.06	7 hours 34 minutes	15.20±0.43	6.3±0.03
F2	9.36±0.02	8 hours 49 minutes	16.78±0.58	6.6±0.06
F3	10.24±0.01	9 hours 54 minutes	17.32±1.43	6.8±0.05
F4	8.36±0.06	6 hours 47 minutes	16.38±0.74	6.4±0.03
F5	9.46±0.05	8 hours 34 minutes	17.47±0.67	6.7±0.07
F6	10.38±0.06	10 hours 14 minutes	18.27±1.17	6.8±0.04
F7	8.26±0.03	6 hours 23 minutes	15.21±0.63	6.2±0.05
F8	9.32±0.03	8 hours 48 minutes	16.10±0.78	6.6±0.02
F9	9.42±0.07	9 hours 27 minutes	16.90±1.45	6.7±0.03

The ex-vivo residence time was determined using USP disintegration apparatus. Among the nine formulations subjected for this study F6 showed maximum residence time of 10.14 Hrs. It was found that an increase in concentration of the polymer increases the residence time. This was mainly due to the strong mucoadhesion nature of the polymer used. The results of in vitro drug release studies of different formulation were shown in Table 5.

Table 5: *In vitro* release data of Glipizide buccal tablets

Time (hrs.)	Percent drug release at time (hr)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	16.20±0.9	10.22±0.6	08.31±0.3	17.20±0.8	11.21±0.6	6.13±0.3	17.12±0.2	10.11±0.3	08.56±0.3
2	33.10±0.3	24.21±0.2	16.20±0.9	35.10±0.4	22.23±0.5	13.21±0.5	34.32±0.2	20.23±0.3	15.78±0.6
3	49.01±0.34	39.01±0.1	28.23±0.3	48.01±0.37	36.32±0.4	24.25±0.5	49.23±0.1	31.25±0.3	24.78±0.6
4	64.87±0.32	51.02±0.69	39.35±0.2	59.87±0.23	48.24±0.2	37.36±0.5	63.32±0.2	39.32±0.4	33.36±0.3
5	78.58±0.7	63.58±0.6	48.21±0.7	75.58±0.77	61.25±0.2	45.87±0.6	77.23±0.2	48.24±0.5	41.63±0.1
6	86.58±0.7	74.71±0.1	61.03±0.9	84.58±0.4	71.58±.0.5	54.21±0.4	88.54±0.6	59.36±0.4	55.36±0.3
8	98.54±0.4	86.15±0.52	70.8±0.1	96.54±0.3	84.21±	67.89±0.4	98.86±0.2	75.61±0.5	67.21±0.3
9	------	96.14±0.3	80.74±0.3	99.14±0.2	96.25±0.5	74.54±0.4	------	86.23±0.2	80.89±0.2
10	------	99.23±0.2	91.69±0.5	------	99.72±0.3	82.31±0.4	------	99.86±0.6	93.63±02.
11	------	------	99.58±0.2	------	------	92.01±.012	------	------	99.54±0.6
12	------	------	------	------	------	99.41±0.74	------	------	------

CONCLUSION

Glipizide buccal tablets were prepared using the bioadhesive polymers Carbopol 974P (CP) in combination with natural polymers such as, *Cashew nut tree* gum, *Aegle marmelos gum* and *Moringa oleifera* gum has shown the prolonged release. Among the three polymers, *Aegle marmelos* shows more prolonged release compared with other polymers. Glipizide buccal tablets F6 formulation shows more prolonged drug release compared with the other polymers. The prepared Glipizide buccal tablets compile with the Indian Pharmacopeia standards.

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