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

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ABSTRACT

The aim of study was to prepare and characterize mucoadhesive buccal tablets of glipizide using different Mucoadhesive polymers such as Carbopol 940, Sodium alginate and HPMC K15M in combination. Twenty one formulation were developed with different concentration of mucoadhesive polymers in each formulation.The formulated buccal tablets were tested for surface pH,*in vitro* drug release and moisture absorption. The prepared tablets also evaluated for bioadhesive strength, ex-vivo residence time and drug permeation through porcine buccal mucosa. *In vitro* bioadhesive strength, ex-vivo residence time and *in vitro* release studies showed that formulation F5 containing 1:8 ratio of drug and polymer combination showed satisfactory bioadhesive and exhibited optimum drug release (72.35±0.04 after 12hrs). DSC results showed no evidence of strong interaction between the drug and polymers. The results indicated that suitable bioadhesive buccal tablets with desired permeability could be prepared. Stability of glipizide mucoadhesive buccal tablets was determined in natural human saliva; it was found that both glipizide and buccal tablets were stable in human saliva.

KEYWORDS: **Glipizide, mucoadhesive buccal tablets, Formulation, Evaluation**

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INTRODUCTION

The oral cavity is an attractive site for the administration of drugs because of ease of administration and overcoming deficiencies associates with oral route of drug administration.[1-3] In recent years delivery of therapeutic agents through buccal mucosa has gained significant attention and it is a potential site for the delivery of drugs to the systemic circulation. Buccal delivery involves administration of drug through the buccal mucosal membrane lining of oral cavity.[4,5] Among the various trans mucosal routes the buccal mucosa is an attractive alternative to the oral route of drug administration later mode undergoes degradation in the gastrointestinal track or hepatic first pass metabolism.[6]Therapeutic agents administered through buccal mucosa enters directly to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability.[7] Buccal drug delivery is the safer method of drug utilization because; drug absorption is terminated in case of toxicity by removing the dosage form from the buccal cavity.[8,9] The buccal mucosa also have other advantages includes, excellent accessibility, an expanse of smooth muscle, immobile mucosa, moderate permeability, less enzymatic activity, suitable for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless drug administration, possible to include the permeation enhancer/enzyme inhibitor or pH modifier in the formulation and suitable for the administration of retentive dosage forms.[10,11]. It is also possible to administer therapeutic agent to patients who cannot be dosed orally to prevent accidental swallowing.[12]Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site.[13] In addition, there is excellent acceptability and the drug can be applied, localized and may be removed easily at any time during the treatment period.[14] During the past decade, bioadhesive polymers have received considerable attention for platforms of buccal controlled delivery because of their ability to localize the dosage form in specific regions to enhance drug bioavailability and control the release rate of the drug.[15,16]Glipizide is widely used sulphonyl urea antidiabetic agent, for the treatment of patients with type II diabetes [17]. It is a weak acid (pKa = 5.9) practically insoluble in water and acid solution but as per biopharmaceutical Classification System (BCS) it is highly permeable [18]. The oral absorption is uniform, rapid and complete with an elimination half-life of 2- 4 hours. Glipizide having a short biological half-life (3.4 ± 0.7 h) requiring it to be administered in 2 to 3 doses of 2.5 to 10 mg per day [19]. SR formulations that would maintain plasma levels of drug for 8 to 12 hrs might be sufficient for once a day dosing for glipizide. Hence, in the present work an attempt was made to formulate mucoadhesive buccal tablet for glipizide using different combination of polymers in order to avoid first pass metabolism and prolonged effect.

2. MATERIALS AND METHODS

2.1. Materials

Glipizide was a gift sample from Micro labs ltd, Bangalore. HPMC K15M, Sodium alginate, Carbopol 940 was received as gift sample from AET lab, Hyderabad, India. Micro crystalline cellulose (MCC) was gift sample from Vilin Bio med Ltd. Roorkee,India. Talc from S.D. fine chemicals Pvt. Ltd. Magnesium Stearate was from Himedia Pvt. Ltd. All other ingredients used were of analytical grade

2.2 Methods

2.2.1 Mucoadhesive buccal tablets preparation

Glipizide Mucoadhesive buccal tablets were prepared by direct compression technology. The Compositions of buccal tablet formulations are given in Table 1. All the powders passed through a 60 mesh sieve. The required quantity of drug, various polymer mixtures and fillers were mixed thoroughly. The blend was lubricated with

magnesium stearate for 3-5mins and talc was added as glidant. The blend was directly compressed (6 mm diameter, round flat faced punches) using multiple punch tablet compression machine (Cad mach Machinery Ltd., Ahmedabad, India). Each tablet contained 5 mg of glipizide. All the tablets were stored in airtight containers for further study.

Table 1
Composition of Glipizide Buccal tablets

Formulation code	Drug	Sodium alginate	carbopol 940	HPMCK 15	Talc	Magnesium stearate	Micro crystalline cellulose
F1	5mg	10mg	10mg	--	1mg	1mg	73mg
F2	5mg	20mg	10mg	--	1mg	1mg	63mg
F3	5mg	30mg	10mg	--	1mg	1mg	53mg
F4	5mg	40mg	10mg	--	1mg	1mg	43mg
F5	5mg	10mg	20mg	--	1mg	1mg	63mg
F6	5mg	10mg	30mg	--	1mg	1mg	53mg
F7	5mg	10mg	40mg	--	1mg	1mg	43mg
F8	5mg	10mg	--	10mg	1mg	1mg	73mg
F9	5mg	20mg	--	10mg	1mg	1mg	63mg
F10	5mg	30mg	--	10mg	1mg	1mg	53mg
F11	5mg	40mg	--	10mg	1mg	1mg	43mg
F12	5mg	10mg	--	20mg	1mg	1mg	63mg
F13	5mg	10mg	--	30mg	1mg	1mg	53mg
F14	5mg	10mg	--	40mg	1mg	1mg	43mg
F15	5mg	--	10mg	10mg	1mg	1mg	73mg
F16	5mg	--	20mg	10mg	1mg	1mg	63mg
	5mg	--	30mg	10mg	1mg	1mg	53mg
F18	5mg	--	40mg	10mg	1mg	1mg	43mg
F19	5mg	--	10mg	20mg	1mg	1mg	63mg
F20	5mg	---	10mg	30mg	1mg	1mg	53mg
F21	5mg	--	10mg	40mg	1mg	1mg	43mg

Evaluation of buccal tablets

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of ten randomly selected glipizide buccal tablets from each batch was measured using Pfizer Hardness tester (Secor Scientific Eng Corporation India) and expressed in Kg/cm^2. The mean and standard deviation values were calculated and reported.

Weight variation test[20]

All prepared buccal tablets were evaluated for weight variation as per USP monograph. Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance. The average weight was calculated and percent variation of each tablet was calculated.

Friability

Roche type friabilator was used for testing the friability using the following procedure. Previously weighed 10 tablets from each batch were taken in Roche friabilator (Pharma labs, Ahmedabad, India) apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 100 revolutions, the tablets were weighed and the percentage loss was determined.

Thickness

Ten randomly selected glipizide buccal tablets from each formulation were used for thickness determination. Thickness of each tablet was measured in mm using a digital Vernier Caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) .The average values were calculated.

Drug content estimation[21]

Twenty tablets from each formulation were taken, crushed and mixed. From the mixture quantity equivalent to 5mg of glipizide was accurately weighed and extracted thoroughly with100 ml of pH 7.4 phosphate buffer on rotary shaker overnight. The solution is filtered through Whatman filter paper the amount of drug present in each extract was determined using UV spectrophotometer (Elico, India) at 276 nm. Each measurement was carried out in triplicate and the average drug content in the buccal tablet was calculated.

Determination of surface pH [22]

The Surface pH of the prepared muco-adhesive glipizide tablets was determined to evaluate the possible irritation effects on the mucosa. The buccal tablets were placed in glass tubes and allowed to swell in contact with pH 7.4 phosphate buffers (12ml) and the pH was measured at one hour intervals up to 8 hrs by placing the electrode in contact with the microenvironment of the swollen tablets.

Moisture absorption study [23]

Agar (5% w/v) was dissolved in hot water, transferred into Petri plates and allowed to solidify. Six glipizide buccal tablets from each formulation were placed in vacuum over night prior to the study to remove moisture if any and weighed initially, laminated on one side with water impermeable backing membrane. Then they were placed on the surface of the agar and incubated at 37^0C for one hour. Then the tablets were removed and reweighed and the percentage moisture absorption was calculated using the following formula.

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

In vitro drug release study[24]

The in vitro release of glipizide from the buccal tablets was determined using a dissolution apparatus (Electrolab Pvt. Ltd., India) according to USP method II (paddle).Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed one side of the tablet and the tablets were immersed into dissolution media. The dissolution test was performed using 500 ml of phosphate buffer pH 7.4, at 37 ± 0.5°C and 50 rpm. Five ml of samples were periodically withdrawn and replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically after suitable dilution at 276 nm using UV-Visible spectrophotometer (Elico, Ahemadabad, India).

Release kinetic studies [25,26]

To find out the mechanism of drug release from glipizide buccal tablets, the *in vitro* release data was treated with different kinetic models, namely zero order, first order, Higuchi and Korsemeyer-Peppas. A criterion for selecting the most appropriate model was based on goodness of fit, high regression coefficient value.

Ex-vivo mucoadhesive strength [27]

Ex vivo mucoadhesive strength of glipizide buccal tablets was measured by using modified physical balance using the method described by Kashappa Goud et.al.Fresh porcine buccal mucosa was obtained from the local slaughterhouse and stored in phosphate buffer pH7.4 and the experiment was performed within 2 h of procurement of pig mucosa. The porcine buccal mucosa was fixed to the stainless steel piece with an adhesive and placed in a beaker; then pH 7.4 phosphate buffer was added into the beaker up to the upper surface of the porcine buccal mucosa to maintain buccal mucosal viability during the experiment. Then the tablet

was attached to the upper clamp of the apparatus and the beaker was raised slowly to establish contact between porcine buccal mucosa and the tablet. A preload of 50 gm was placed on the clamp for 5 mins to establish adhesive bond between the tablet and porcine buccal mucosa. After completion of preload time, preload was removed from the clamp and water was added into the beaker from burette at a constant rate. The weight required to detach the tablet from the mucosal surface gave the measure of mucoadhesive strength in gm (total weight of water in beaker). Experiments were carried out triplicate and the averages of them are noted down.

Ex vivo residence time [28]

The *Ex vivo* residence time for glipizide mucoadhesive buccal tablets was determined using a modified USP dissolution apparatus. The dissolution medium was composed of 500 ml of phosphate buffer pH 7.4 maintained at 37°C. A segment of porcine buccal mucosa each of 3 cm length was glued to the surface of glass slab which was then vertically attached to the apparatus. Three tablets of each formulation were hydrated using phosphate buffer pH 7.4 and hydrated surface was brought into contact with mucosal membrane. The tablets secured on the glass slab were completely immersed in the buffer solution. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded.

Ex vivo permeation studies [29]

Ex vivo permeation study of glipizide mucoadhesive buccal tablet was carried out on porcine buccal mucosa using modified Franz diffusion cell. Phosphate buffer pH 7.4 was used as receptor solution. A semi permeable membrane (porcine buccal mucosa) was clamped between the donor and acceptor compartments. The assembly
of drug permeated through the membrane was determined by removing samples periodically and replaced with an equal volume of phosphate buffer pH 7.4. These aliquots after filtration were diluted suitably and analyzed spectrophotometrically (Elico, India) at 276 nm.

DSC Studies

The DSC analysis of pure drug, drug+ Sodium alginate & HPMC K15, drug+ HPMC K15& Carbopol 940, drug+ sodium alginate & Carbopol 940 and drug+ HPMC K100, were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer interaction. Accurately weighed 5-6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10^{o}C/min over a temperature range of 40 to 300 ^{o}C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min.

Stability of buccal tablets [27]

Stability studies of glipizide mucoadhesive buccal tablets were performed for optimized formulation in normal human saliva. The human saliva was collected from human healthy volunteers and filtered through filter paper. Buccal tablets were immersed in separate petri dishes containing 5 mL of human saliva and placed in a temperature-controlled oven for 6 hr at 37°C ± 0.2°C. At predetermined time interval the buccal tablets were evaluated by observing change in color, shape, collapse of the tablet. The experiments were repeated in triplicate (n = 3).

RESULTS AND DISCUSSION

All the tablets with different proportion of polymer composition were within the weight range of 99.91± 1.01 mg to 100.74 ± 0.75 mg .The tablets thickness of the various formulations was found to be in the range of 2 .51 ± 0.02 to 2.55 ± 0.03 (Table 2). The mass and thickness of all compressed tablets were within the limit as per USP. The hardness of tablets was optimized on the basis of trail preparation of tablets. The hardness of all prepared tablet were in the range of 6.3±0.16 to 7.4±0.33 kg/cm^2.Hardness increased as the amount of concentration of the

polymers increased. The friability of all tablets was less than 1% i.e., in the range of 0.43 – 0.81 % which is in the acceptable limits which indicates formulations have good mechanical strength.

Table 2
Physico chemical properties of Glipizide Buccal tablets

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	% Friability	Weight variation	% Drug content
F1	6.8±0.60	2.55 ± 0.03	0.55	100.74 ± 0.61	99.15 ± 0.44
F2	6.3±0.16	2.55 ± 0.02	0.63	100.04 ± 0.80	99.53 ± 0.75
F3	7.0±0.30	2.54 ± 0.03	0.66	100.38 ± 0.71	99.18 ± 0.92
F4	6.8±0.16	2.55 ± 0.02	0.58	100.42 ± 0.75	98.77 ± 0.04
F5	6.6±0.16	2.55 ± 0.02	0.64	100.45 ± 0.64	100.96 ± 0.44
F6	7.4±0.33	2.51 ± 0.02	0.47	99.91 ± 1.01	98.81 ± 0.92
F7	6.6±0.16	2.52 ± 0.01	0.66	99.98 ± 0.82	99.77 ± 0.72
F8	6.8±0.16	2.55 ± 0.03	0.65	100.42 ± 0.61	99.81 ± 0.44
F9	7.1±0.16	2.55 ± 0.02	0.43	100.38 ± 0.80	99.15 ± 0.75
F10	6.9±0.16	2.54 ± 0.03	0.66	100.04 ± 0.71	99.53 ± 0.92
F11	7.3±0.16	2.55 ± 0.02	0.58	100.74 ± 0.75	98.69 ± 0.67
F12	7.1±0.16	2.55 ± 0.02	0.67	100.45 ± 0.64	98.96 ± 0.44
F13	6.8±0.30	2.51 ± 0.02	0.61	99.91 ± 1.01	100.77 ± 0.92
F14	6.8±0.16	2.52 ± 0.01	0.65	99.98 ± 0.82	99.81 ± 0.72
F15	6.8±0.33	2.55 ± 0.03	0.50	100.74 ± 0.61	99.84 ± 0.44
F16	6.3±0.16	2.55 ± 0.02	0.43	100.54 ± 0.80	99.15 ± 0.75
F17	7.1±0.33	2.54 ± 0.03	0.56	100.38 ± 0.71	99.53 ± 0.92
F18	6.3±0.16	2.55 ± 0.02	0.58	100.47 ± 0.75	100.47 ± 0.01
F19	6.8±0.33	2.55 ± 0.02	0.81	100.42 ± 0.64	98.96 ± 0.44
F20	6.6±0.16	2.51 ± 0.02	0.41	99.98 ± 1.01	98.7 ± 0.92
F21	6.8±0.16	2.52 ± 0.01	0.68	99.91 ± 0.82	99.91 ± 0.02

The content uniformity of the entire tablet (F1 to F21) was evaluated and the results are presented in Table 2.The drug content in various formulations varied between 98.69 ± 0.67 % to 100.96 ± 0.4 %. The low values in standard deviation indicate uniform drug content in all the formulations.Drug dissolution profile of various formulation prepared are shown in figures 1 and 2.Formulation prepared with batches F1 to F7 containing sodium alginate and carbopol 940 (different ratios) as matrix forming agent. Formulations F1 to F7 released the drug 90.58, 88.82, 83.94, 77.35, 72.35, 64.47 and 55.58 % respectively after 12 hours. Formulation prepared with batches F8 to F14 containing sodium alginate and HPMC K15M (different ratios) as matrix forming agent. Formulations F8 released the drug completely after 9 hours, where as formulation F9 to F14 released the drug 87.64, 69.11, 51.76, 81.47, 61.47and 57.64 % respectively after 12 hours. Formulation prepared with batches F15 to F21 containing Carbopol 940 and HPMC K15M (different ratios) as matrix forming agent. Formulations F15 to F21 released the drug 66.28, 57.32, 47.51, 25.2, 72.64, 38.82 and 39.25% respectively after 12 hours. The possible reason for observed reduction in total drug release may be the interaction between two charged bioadhesive polymers i.e. Sodium alginate (anionic) and Carbopol 940 (anionic) in formulations F1 to F7 , Sodium alginate (anionic) and HPMC K15 M (non ionic) in formulations F8 to F14, Carbopol 940 (anionic) and HPMC K15 M (non ionic) in formulations F15 to F21.

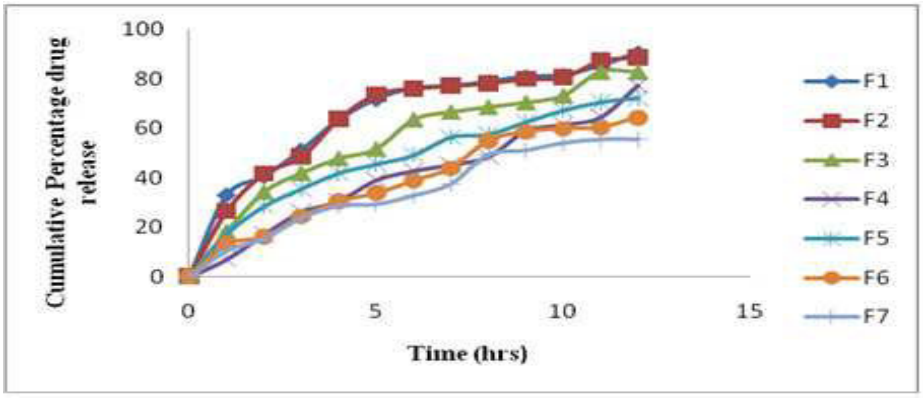

Figure1.1
Comparative release profile of formulation F1 to F7

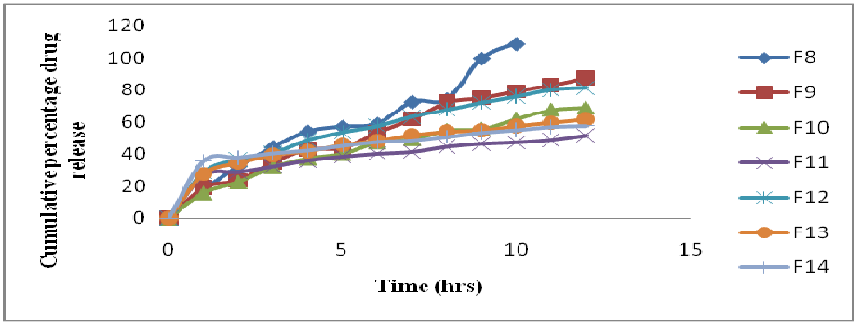

Figure 1.2
Comparative release profile of formulation F8 to F14

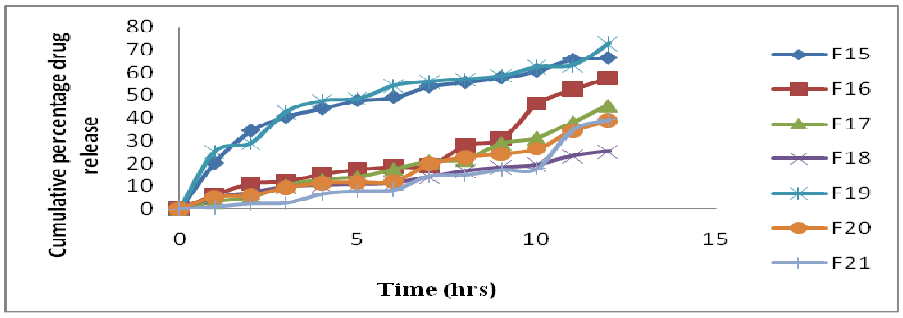

Figure 1.3
Comparative release profile of formulation F15 to F21

In vitro drug release studies revealed that the release of glipizide from different formulations varied according to the type and ratios of the matrix forming polymers. As increase in the polymer concentration increases the viscosity of the gel as well as the formation of gel layer with longer diffusional path. This could cause a decrease in the effective diffusion co-efficient of drug and therefore reduction in drug release rate. *In-vitro* drug release data of F1 to F21 were fitted to zero order, first order, Higuchi and Korsmeyer-Peppas equations to ascertain the pattern of drug release (Table 3).In case of F5 formulation the r^2 value indicated that the highest r^2 (0.9903) value was found for first order. According to n value it is between 0.5-1, so it follows non-fickian diffusion with first order release.

Table.3
Kinetic parameter of Glipizide buccal tablets

Formulation code	Zero order	First order	Higuchi	Korsemyer pepas	n-value	Hixon crowel
F1	0.5398	0.8117	0.4751	0.828	0.16	0.8281
F2	0.6351	0.8788	0.9274	0.8966	0.22	0.8643
F3	0.7134	0.9741	0.682	0.9028	0.29	0.8964
F4	0.813	0.9616	0.782	0.9819	0.36	0.9242
F5	0.9287	0.9903	0.876	0.9747	0.54	0.9776
F6	0.9001	0.9537	0.8775	0.9115	0.6	0.9564
F7	0.9491	0.9794	0.9752	0.9231	0.86	0.984
F8	0.9832	0.9728	0.8787	0.9791	0.97	0.9917
F9	0.9837	0.9759	0.8469	0.9669	0.93	0.9792
F10	0.9954	0.9866	0.8585	0.981	0.95	0.9904
F11	0.7134	0.9741	0.682	0.9028	0.29	0.8964
F12	0.5398	0.8117	0.4751	0.828	0.16	0.8281
F13	0.6351	0.8788	0.9274	0.8966	0.22	0.8643
F14	0.9001	0.9537	0.8775	0.9564	0.6	0.9115
F15	0.813	0.9616	0.782	0.9819	0.36	0.9242
F16	0.9287	0.9903	0.876	0.9776	0.54	0.9747
F17	0.6351	0.8788	0.9274	0.8966	0.22	0.8643
F18	0.9491	0.9794	0.9752	0.9231	0.86	0.984
F19	0.9954	0.9866	0.8585	0.981	0.95	0.9904
F20	0.9837	0.9759	0.8469	0.9669	0.93	0.9792
F21	0.9491	0.9794	0.9752	0.9231	0.86	0.984

The values of the mucoadhesive strength of glipizide mucoadhesive buccal tablets are given in table 4. The mucoadhesive strength were influenced by the nature and proportions of the bioadhesive polymers used in the formulations .In all the formulations, as the polymer mixture concentration increased, the mucoadhesive strength also increased. The order of mucoadhesive strength of bioadhesive polymer mixtures used in the formulations can be given as carbopol 940 and sodium alginate < sodium alginate and HPMCK15M < HPMCK15M and Carbopol 940. Very strong mucoadhesion could damage the epithelial lining of the buccal mucosa. Mucoadhesive strength exhibited by the formulation F5 tablets can be considered satisfactory for maintaining them in the oral cavity for 12hrs. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity. An acidic or alkaline pH may cause irritation to the buccal mucosa. The surface pH of the formulation depends on the nature and composition of polymers. Surface pH of the all the formulation were found to be in the range of 6.3±0.16, 7.1±0.33. This pH is near to the neutral, so the formulation does not cause any irritation on the mucosa. Surface pH values for all the formulations shown in Table 4.

Table 4
Physico chemical properties of Glipizide Buccal tablets

Formulation code	Surface pH	Moisture absorption	Mucoadhesive strength	*Ex vivo* residence Time
F1	6.3±0.16	25.41 ± 1.96	12.81 ± 0.30	5 hours 15 min
F2	6.8±0.6	35.57 ± 0.41	14.31± 0.31	6 Hours 30 min
F3	7.0±0.3	44.08 ± 0.30	15.38 ± 0.06	7 Hours 15 min
F4	6.8±0.16	59.31 ± 0.56	16.18 ± 0.25	7 Hours 45 min
F5	6.6±0.16	38.29 ± 1.41	17.28 ± 0.25	Above 8 Hours
F6	6.8±0.33	62.05 ± 0.07	18.04 ± 0.26	Above 8 Hours
F7	6.6±0.16	65.31 ± 1.07	23.60 ± 0.26	Above 8 Hours
F8	6.8±0.16	23.13 ± 1.96	8.46 ± 0.30	3 Hours 15 min
F9	7.1±0.16	32.16 ± 0.41	11.12 ± 0.31	4 Hours 45 min

F10	7.1±0.16	38.42 ± 0.30	13.2 ± 0.06	6 Hours 45 min
F11	7.1±0.16	46.57 ± 0.56	14.32 ± 0.25	Above 8 Hours
F12	7.1±0.16	29.34 ± 1.41	12.41 ± 0.25	5 Hours 30 min
F13	6.8±0.3	34.71 ± 0.07	13.95 ± 0.26	7 Hours 45 min
F14	6.8±0.16	43.83 ± 1.07	15.41 ± 0.26	Above 8 Hours
F15	6.8±0.33	34.62 ± 1.96	10.32 ± 0.30	4 Hours 15 min
F16	6.3±0.16	35.57 ± 0.41	13.13 ± 0.31	7 Hours 15 min
F17	7.1±0.33	44.08 ± 0.30	15.93 ± 0.06	Above 8 Hours
F18	6.3±0.16	57.05 ± 0.56	19.21 ± 0.25	Above 8 Hours
F19	6.8±0.33	43.83 ± 1.41	9.01 ± 0.25	4 Hours 30 min
F20	6.6±0.16	49.76 ± 0.07	11.23 ± 0.26	5 Hours 45 min
F21	6.6±0.16	62.5 ± 1.07	13.68 ± 0.26	Above 8 Hours

Moisture absorption studies give an indication of the relative moisture absorption capacities of polymer mixtures and whether the formulations maintained their integrity after its absorption. Moisture absorption was increased from formulation F1 to F7, F8 to F14 and F15 to F21. The increasing moisture absorption of formulations may be due to the increased concentration of polymer mixture from formulation F1 to F7, F8 to F14 and F15 to F21.The moisture absorption was more in formulations containing carbopol 940 and sodium alginate group when compared to all other formulation.The order of increasing mois ture absorption was of carbopol 940 and sodium alginate < HPMCK15M and Carbopol 940 < sodi um alginate and HPMCK15M (Table 4). This may be due to the more hydrophilic nature of Carbopol. Among all the formulations the F5 formulation showed minimum matrix erosion and optimum moisture absorption 38.29 ± 1.41% at the end of 8 hrs. The *Ex vivo* residence time was determined by using specially designed apparatus. Formulations F8 to F14 showed lower residence time when compared to the formulations F1 to F7 & F15 to F21 (Table 4 & figure 2.1 to 2.3). As the concentration of mucoadhesive material increased, the *ex vivo* residence time also increased. This test reflects the adhesive capacity of polymers used in formulations. The results revealed that the mixture of carbopol 940 and sodium alginate containing formulations showed better residence time than the mixture of sodium alginate and HPMC K15M &HPMC K15 M and carbopol formulations.

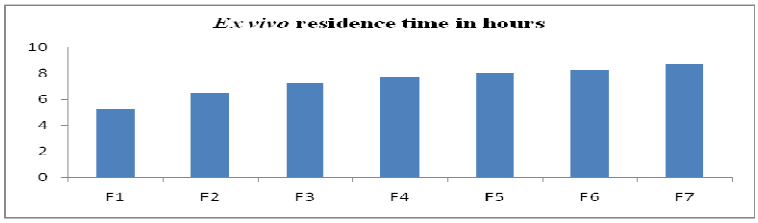

Figure 2.1
Ex vivo residence time of formulation F1 to F7

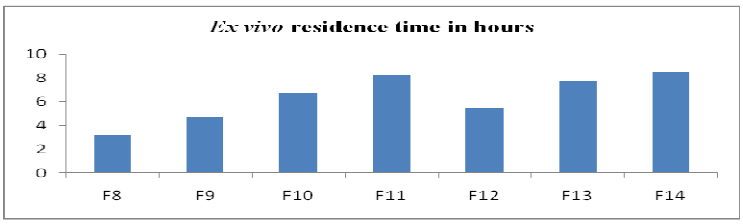

Figure 2.2
Ex vivo residence time of formulation F8 toF14

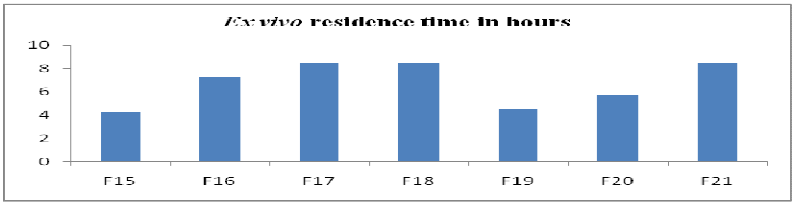

Figure 2.3
Ex vivo residence time of formulation F15 to F21

Based on ex *vivo* mucoadhesion, *ex vivo* residence time and in-*vitro* release studies formulation F5 was selected for ex vivo permeation study. Pigs buccal mucosa resembles that of humans more closely than any other animal in terms of structure and composition and therefore porcine buccal mucosa was selected for drug Permeation studies.

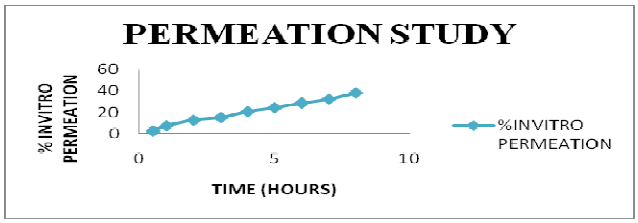

Figure 3
In vitro permeation study of formulation

The results of drug permeation from buccal tablets through the porcine buccal mucosa revealed that glipizide was released from the tablet and permeated through the porcine buccal membrane and could possibly permeate through the human buccal membrane. The drug permeation was slow and steady (fig 3) and 38.23 % of glipizide could permeated through the buccal membrane in 8 hours. The stability studies performed in normal human saliva would be more accurate to mimic the stability of the glipizide mucoadhesive buccal tablet in oral cavity *in vivo*. Hence the stability of buccal tablet was examined in natural human saliva.

Based on the results of *ex vivo* mucoadhesion, *in-vitro* release studies, moisture absorption, formulation F5 was selected for stability study. Stability studies in normal human saliva showed no change in the color of buccal tablets, which would have happened if drug was unstable in human saliva. This reveals that the tablets are having sufficient stability in the human. The thickness and diameter of tablets slightly changed due to swelling of the polymers in human saliva but tablets did not collapse till the end of studies confirming that the device strength was sufficient. The results were shown in table.5.

Table 5
Stability study data of F5 formulation in human saliva

Time	Color change	Thickness (mm)	Change in surface area (Cm^2)	Collapsing+
0	No change	2.55 ± 0.02	No	No change
1	No change	2.59 ± 0.05	0.25	No change
2	No change	2.75 ± 0.05	0.48	No change
3	No change	2.89 ± 0.05	1.19	No change
6	No change	3.24 ± 0.05	1.93	No change

DSC studies were performed to investigate the physical state of the drug in the tablets and to know the interactions of drug with polymers in the formulations. Pure Glipizide showed a single sharp endothermic melting peak at 216.4º C (figure 4.1), which was slightly shifted in the thermogram of different polymer composition formulations (figure 4.2 to 4.4) evidencing there was no strong chemical interactions.

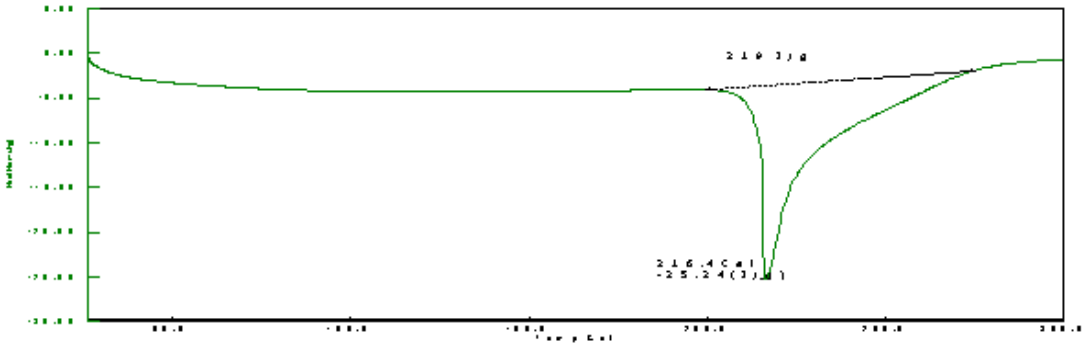

Figure 4.1.
DSC study of Pure Drug Glipizide

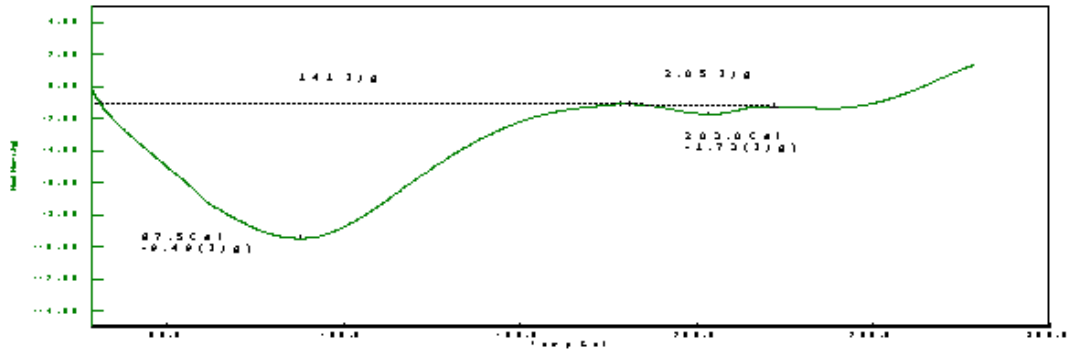

Figure 4.2.
DSC study of Formulation containing Carbopol 940 & HPMC K15M

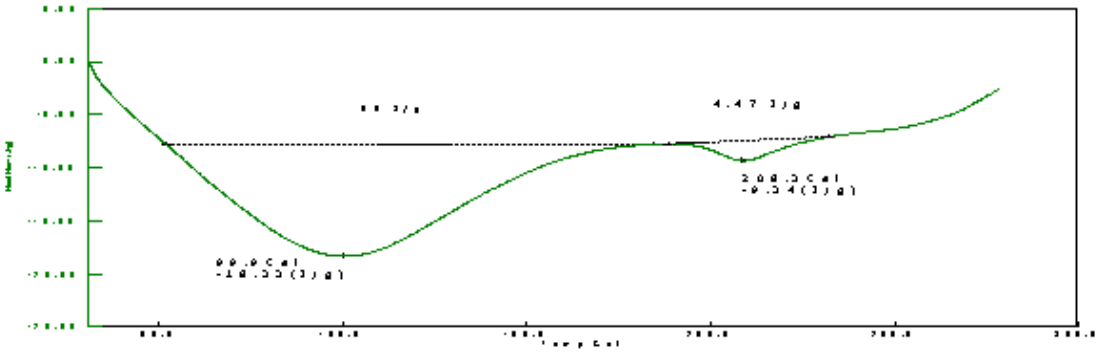

Figure 4.3.
DSC study of Formulation containing sodium alginate & HPMC K15M

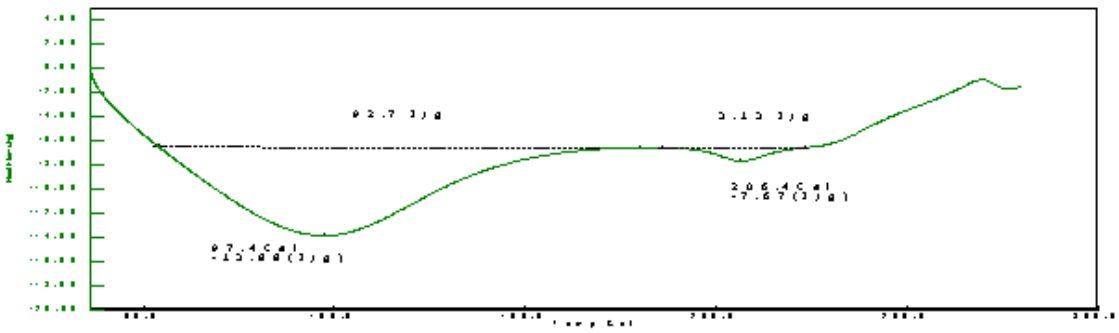

Figure 4.4.
DSC study of Formulation containing sodium alginate & carbopol 940

CONCLUSION

The overall results indicated that the polymers Carbopol 940 and Sodium alginate in the ratio of 1: 8 showed satisfactory mucoadhesive properties. Among all the formulations, the F5 formulation using these polymers in the above ratio with drug exhibited significant moisture absorption properties with optimum release profile. The optimized formulation F5 also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability in human saliva. Hence it can be concluded that the formulation F5 will be useful for buccal administration of glipizide .So, the mucoadhesive buccal tablets of glipizide may be a good choice to bypass the hepatic first pass metabolism with an improvement in the bioavailability of glipizide through Buccal mucosa .Further work is recommended to support its effic acyclaims bypharmacodynamic and pharmacokinetic studies in human beings.

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