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RESEARCH ARTICLE

Preparation and Evaluation of Bilayered Buccal Tablet of Glipizide

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ABSTRACT

The main objective of the present work was to design a bucco-adhesive bilayered tablet which has potential use in the treatment of Diabetes mellitus. A Bi-layered tablet (Core layer+ Backing layer) containing hypoglycemic agent Glipizide, was formulated. A significant reduction in dose and dosing frequency can be achieved, thereby reducing dose-dependent side effects, patient compliance & prolong the duration of action. Tablets of Glipizide (20 mg) were prepared by direct compression method using bioadhesive polymers like Sodium alginate, Carbopol 934P, HPMC K 100M, Polyvinylpyrrolidone (PVP) in a different ratio. The core layer constituents were Glipizide (20mg), sodium alginate, HPMC K100M, Carbopol 934P, Polyvinylpyrrolidone, Mannitol, Aspartame, Magnesium stearate. Ethyl cellulose acts as backing layer which helps in preventing the back flow of the drug. Buccal tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, and content uniformity, surface pH, ex vivo bioadhesive strength, in vitro drug release, and further studies. The modified in vitro assembly was used to measure the bioadhesive strength of tablets with fresh sheep buccal mucosa as a model tissue. The tablets were evaluated for drug release in pH 6.8 phosphate buffer for 10 hr in standard dissolution apparatus. In order to determine the release kinetics; the data was subjected to Zero order, First order, Korsmeyer and Peppas diffusion model. The mechanism of drug release was found to follow zero order kinetics with regression coefficient value 0.988.

KEYWORDS

Mucoadhesive buccal tablets, bilayered tablets, Glipizide, Carbopol 934P; Sodium alginate, HPMC K 100M, Polyvinylpyrrolidone (PVP), Mannitol, Zero order release.

INTRODUCTION

The oral route is perhaps the most preferred route among patient and the physician among various drug delivery route. However, oral route has several disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Therefore absorptive mucosa is considered as potential sites for drug administration.

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Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages such as possible bypass of first pass effect, avoidance of pre-systemic elimination within the GI tract over oral administration for systemic delivery.

The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). In view of the systemic transmucosal drug delivery, the buccal mucosa is a most preferred region as compared to the sublingual mucosa. One of the reasons is that buccal mucosa is less permeable and is thus not able to elicit a

rapid onset of absorption and hence better suited for formulations that are intended for sustained release action. Further, the buccal mucosa being relatively immobile mucosa and readily accessible, it makes it more advantageous for retentive systems used for oral transmucosal drug delivery[1].

Over the past few decades, the concept of use of bioadhesive polymers to prolong the contact time has gained remarkable attention in transmucosal drug delivery. Adhesion as a process is simply defined as the "fixing" of two surfaces to one another. Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion[2].

To accomplish site-specific drug delivery, a lot of interest has been turned on to the concept of mucoadhesion, which encompasses a pharmaceutical formulation incorporating mucoadhesive hydrophilic polymers along with the Active Pharmaceutical Ingredient (API). The rationale being that the formulation will be 'held' on a biological surface for localized drug delivery and the release of API will be close to the site of action leading to enhanced bioavailability[3,4]. Over the years, mucoadhesive polymers were shown to be able to adhere to various other mucosal membranes. The capability to adhere to the mucus gel layer which covers epithelial tissues makes such polymers very useful excipients in drug delivery[5,6]. Mucoadhesion is known to increase the intimacy and duration of contact between drug- containing a polymer and a mucous surface. It is believed that the mucoadhesive nature of the device can increase the residence time of the drug in the body. The bioavailability of the drug is improved because of the combined effects of the direct drug absorption and the decrease in excretion rate. Increased residence time and adhesion may lead to lower API concentrations and lower administration frequency to achieve the desired therapeutic outcome[7,8].

MATERIALS AND METHOD

Drug Glipizide was procured from BAL Pharma Ltd, Bangalore whereas other excipients such as Carbopol 934P, HPMC K100M, Sodium alginate, PVP K 30, Mannitol, Ethyl Cellulose, Magnesium stearate, Aspartame were procured from KAPL, Bangalore. All reagents were procured from S.D fine chemicals Ltd Mumbai and were of analytical grade.

2.1. Identification:

Characterization of Glipizide was carried out using following tests.

2.1.1. Study of Organoleptic properties:

A small quantity of pure Glipizide powder was taken on a butter paper and viewed in well-illuminated place for appearance and colour[9, 10].

2.1.2. Determination of Melting point: Melting point of Glipizide was determined by taking a small amount of drug separately in a capillary tube closed at one end and placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplicates and average value was reported.[11]

2.2. Drug-excipient compatibility study

Drug and excipient were thoroughly mixed in a predetermined ratio and passed through the 40# sieve. The blend was filled in transparent glass vials and closed with gray rubber stoppers and sealed with aluminum and kept into condition at 40°C/75 % RH for 4 weeks. Drug-excipients compatibility studies were carried out using FT-IR infrared spectrum. The study was carried out on individual pure drug and its physical mixture with the excipients used in the study. The spectrum obtained was compared with the reference spectrum of glipizide[12].

2.3. Formulation of Glipizide buccoadhesive tablets: Buccal tablets composed of two layers a core layer and backing layer. Core layer contains drug Glipizide, different mucoadhesive polymers and magnesium stearate as a lubricant. For the preparation of core layer's mixture all ingredients such as Glipizide, polymers and magnesium stearate as a lubricant and mannitol were mixed

well by using mortar and pestle. The mixture (100mg) was then compressed using an 8-mm-diameter die in a single stroke multistation machine. The upper punch was raised and the backing layer of Ethyl Cellulose was placed on the above compact; the two layers were then compressed into a buccoadhesive bilayer tablet[12, 13]. Each tablet weighed 150 mg and the compositions of Glipizide bilayer buccal tablets were given in Table no.1

Table no 1: Composition of Glipizide buccoadhesive tablets

Ingredients (mg)	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Glipizide	20	20	20	20	20	20	20	20
Carbopol 934 p	8	6	4	2	8	6	4	2
Sodium alginate	32	34	36	38	-	-	-	-
HPMC K100M	-	-	-	-	32	34	36	38
PVP K 30	35	35	35	35	-	-	-	-
Mannitol	-	-	-	-	35	35	35	35
Aspartame	2	2	2	2	2	2	2	2
Mg. Stearate	3	3	3	3	3	3	3	3
EC	50	50	50	50	50	50	50	50
Total weight in mg	150	150	150	150	150	150	150	150

*** Mg.- Magnesium; PVP-Polyvinylpyrrolidone; EC- Ethyl Cellulose; HPMC-Hydroxypropylmethyl Cellulose**

2.4. PRE-COMPRESSION STUDIES:

2.4.1. Angle of Repose [12]**:** Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically to a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated using the formula.

$$\theta = \mathrm{Tan}^{-1}\left(\frac{h}{r}\right)$$

Where θ is the angle of repose, h is the height of pile; r is the radius of the base of the pile.

2.4.2. Bulk Density [12, 13]**:** Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (*Vb*) and weight of powder (*M*) were determined. The bulk density was calculated using the formula.

$$\rho b = M / V0$$

Where ρb = bulk density,

M = weight of sample in grams

V0 = Apparent unstirred volume

2.4.3. Tapped Density [12, 13]**:** The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (*Vt*) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (*ρt*) was calculated using the following formula.

$$\rho t = M / Vf$$

Where, ρt = Tapped density

M = weight of sample in grams

Vf = final volume

2.4.4. Porosity [13]**:** % Porosity is determined from the ratio of the difference between bulk volumes to true volume to that of bulk volume. The result is reported in table

$$\text{Porosity} = [(Vb - Vp)/ Vb] \times 100.$$

Where Vb is the bulk volume and

Vp is the true volume.

2.4.5. Carr's index[13]: The Carr's index is determined from the tapped density and poured density (bulk density) The Carr's Index was calculated as per the formula.

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Where TBD is the total bulk density and LBD is the loose bulk density

2.4.6. Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

Hausner's ratio = ρt/ ρd

Where ρt is tapped density and ρd is bulk density. Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (>1.25).

2.5. POST COMPRESSION EVALUATION PARAMETERS FOR FORMULATED TABLETS[12, 13, 14]:

2.5.1. Weight variation test: Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%).

The percentage deviation was calculated using the following formula

$$\%\ \text{Weight variation} = \frac{\text{Actual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

2.5.2. Uniformity of thickness: The tablet thickness was measured by placing tablet between two arms of the digital vernier calipers. Five tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. It is expressed in mm.

2.5.3. Hardness: The hardness of the tablet from each formulation was determined using Monsanto hardness tester.

2.5.4. Friability: Friability of the tablets was determined using Electro lab-EF 2 Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. A pre-weighed sample of tablets was placed in the friability and was subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$\%\ \text{Friability} = \frac{WO - W}{WO} \times 100$$

Where,

W_0 = weight of the tablets before the test.

W= weight of the tablets after the test.

2.5.5. Uniformity of drug content: Five tablets from each formulation were powdered individually and a quantity equivalent to 100 mg of Glipizide was accurately weighed and extracted with a suitable volume of phosphate buffer 6.8 pH. Each extract was suitably diluted and analyzed spectrophotometrically at 274 nm.

2.5.6. Surface pH Study: The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects *in vivo*. Highly acidic or alkaline pH may cause irritation to the buccal mucosa. It was determined to keep the surface pH as close to neutral as possible. The tablet was allowed to swell by keeping it in contact with 5 ml of phosphate buffer containing agar medium (pH 6.8±0.01) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min.

2.5.7. In vitro swelling studies: Tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing phosphate buffer pH 6.8. At regular intervals (0.5, 1, 2, 3, 4 h), samples were removed from the Petri dish and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (W_2). The swelling index of each system was calculated using the following formula:

Swelling Index (S.I) = $[(W_2-W_1)/W_1] \times 100$

Where, W_1- initial weight of Tablet, W_2- weight of tablet at time t

2.5.8. In-Vitro Release Studies:

The USP type II rotating paddle method was used to study the drug release from the bilayer tablet. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of the buccal tablet was attached to the glass slide with cyanoacrylate adhesive. The tablet was placed at the bottom of the dissolution vessel. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, with appropriate dilutions with phosphate buffer pH 6.8 and were analyzed spectrophotometrically at 274 nm.

2.5.9. Data Analysis (Curve fitting analysis)

The results of in vitro release profiles obtained for all the BDDS formulations were fitted into four models of data treatment as follows:

a. Cumulative percent drug released versus time (zero order kinetic model).

b. Log cumulative percent drug remaining versus time (First-order kinetic model).

c. Cumulative percent drug released versus square root of time (Higuchi's model).

d. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).

2.6. Ex vivo Bioadhesive strength[15]: A modified physical balance method was used for determining the *ex vivo* buccoadhesive strength. Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2h of slaughter.The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8. The two sides of the balance were made equal before the study, by keeping a 5 g saliva solution at 37°C. The Sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer.

The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37±1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive and add weight to the right-hand pan. A weight of 5 g was removed from the right-hand pan which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly to an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of then buccal tablet in grams.

Force of adhesion (N) = (Bioadhesive strength (g) ×9.8)/1000

Bond strength (N m^{-2}) = Force of adhesion/surface area.

2.7. Ex vivo mucoadhesion time[14,15]: The *Ex vivo* mucoadhesion time was examined after applying mucoadhesive tablet on the freshly cut bovine oral mucosa. The fresh bovine oral mucosa was tied on the glass slide and a mucoadhesive core side of each tablet was wet with 1 drop of phosphate buffer (pH 6.8) and posted to the bovine oral mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer and kept at 37^0C ± 0.5^0C. After 2 minutes, a slow stirring rate was applied to stimulate the oral mucosal cavity environment and tablet adhesion was monitored for 20 hours. The time for the tablet to detach from the bovine mucosa was recorded as the mucoadhesion time.

2.8. Stability studies[15]

- Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.
- 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,

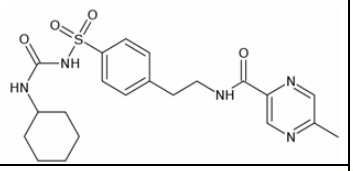
humidity and light and enables recommended storage conditions, re-test periods and shelf lives to be established.

The present study, stability studies were carried out at 40°C /75 % RH for a specific time period up to 3 months for the selected formulations.

RESULTS AND DISCUSSION

3.1.1 Description data of Glipizide:

Table No 2: Description of Glipizide

Name	Glipizide
Formula and Structure	$C_{21}H_{27}N_5O_4S$ 
Molecular Weight	445.54
Appearance	Amorphous solid
Color	White
Odour	Odourless
Taste	Characteristic taste

3.1.2 Melting point determination of Glipizide

Melting point of Glipizide was found to be 209^0c

3.2: Drug-excipients compatibility study:

A.)

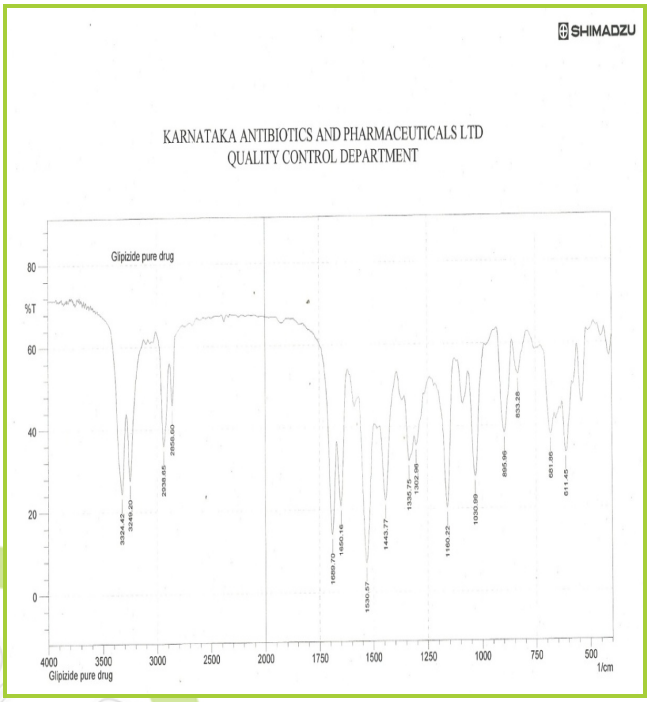


Figure No. 1: FTIR spectrum of Glipizide

3.4 Evaluation of mucoadhesive tablets of Glipizide:

a.) Pre-compression Evaluation:

Table No 3: List of pre-compression parameters for F1 to F8

* All values are expressed as mean ± standard deviation, n=3.

Formulation Code	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's Ratio
F1	0.433±0.02	0.496±0.03	25.94±0.73	12.65±2.25	1.145±0.03
F2	0.420±0.01	0.463±0.006	25.25±0.36	9.32±3.16	1.103±0.04
F3	0.453±0.025	0.536±0.025	28.21±0.29	15.54±1.19	1.184±0.02
F4	0.450±0.01	0.51±0.017	27.87±0.40	11.69±3.61	1.126±0.05
F5	0.410±0.01	0.457±0.025	25.17±0.34	10.87±2.84	1.113±0.04
F6	0.443±0.015	0.517±0.032	26.78±0.63	14.21±1.11	1.165±0.01
F7	0.406±0.02	0.47±0.01	29.93±0.46	13.47±2.48	1.156±0.03
F8	0.413±0.02	0.477±0.015	28.21±0.27	14.23±3.22	1.154±0.02

3.4.1. Angle of repose: Flow property of the powder, and resistance offered to the movement of the particle can be judged by angle of repose. The angle of repose provides a qualitative and quantitative assessment of internal cohesive and frictional force under low level of external load applied during mixing and tableting. The data obtained from the angle of repose for all the

formulations were found to be in the range of 25.17° and 29.93°. All the formulations showed the angle of repose less than 30° which reveals good flow property.

3.4.2. Bulk density & tapped density: Bulk density and tapped density for the blend was performed. Bulk density was found in the range of 0.406 gm/cm^3 to 0.453 gm/cm^3. Tapped density is between 0.457 gm/cm^3 to 0.517 gm/cm^3.

3.4.3. Carr's consolidation index: The results of Carr's index or compressibility index (%) for the entire formulation blend ranged from 9.32 % to 15.54 %. Hence the prepared blends possessed good flow properties and these can be used for tablet manufacture.

3.4.4. Hausner's Ratio: The powder blends for the formulations from F1 to F8 had Hausner's factor values which were in the range of 1.10 to 1.18 indicating good flowability. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

3.5. Post compression parameters evaluation:

Table No 4: List of post-compression parameters for F1 to F8

Formulation Code	Thickness * [mm]	Hardness * [kg/cm^2]	Friability** [%]	Weight variation [mg]	Drug content (%)*
F1	2.08 ± 0.05	3.58±0.728	0.65±0.05	148.1± 0.85	100.63±0.37
F2	2.03 ± 0.10	4.25± 0.155	0.72±0.08	149.7 ± 1.74	98.91±0.43
F3	2.06 ± 0.15	4.56± 0.114	0.81±0.03	150.03±0.02	101.34±0.95
F4	2.04 ± 0.16	4.9± 0.138	0.82±0.01	148.02±0.36	99.63±0.37
F5	2.07 ± 0.14	3.41± 0.121	0.66±0.08	150.05±1.51	97.1±0.69
F6	2.06 ± 0.20	3.82± 0.143	0.71±0.06	149.08±1.18	98.55±0.37
F7	2.04±0.08	4.24±0.545	0.76±0.02	148.06±0.95	98.5±0.02
F8	2.00±0.00	4.56±0.023	0.79±0.06	150.2±0.99	99.0±0.05

3.5.1. Weight variation: Prepared tablets were evaluated for weight variation and percentage deviations from the average weight are reported in table 4 and were found to be within the prescribed official limits.

3.5.2. Thickness test: The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch (8 mm) and the weight of the tablet (150 mg). The thickness of the tablets was measured by using by picking the tablets randomly. The mean values were shown in the Table no.4. The thickness of the tablets was found in the range from 2.00 mm to 2.08 mm.

3.5.3. Hardness test: Randomly picked tablets were subjected to test the hardness using Monsanto hardness tester. The results were given in Table no.4. Hardness for all formulation batches prepared by direct compression was found to be between 3.41 to 4.9 Kg / cm^2.

3.5.4. Friability test: Friability is needed for tablets to withstand the force of compression applied during the manufacture of tablets. The friability of all the formulated tablets of Glipizide was found to be between 0.65 to 0.82 are reported in Table no.4 and all the formulated tablets of Glipizide were shown the % friability within the official limits. (i.e., not more than 1%).

3.5.5. Drug content: The drug content of all the nine formulations of Glipizide tablets were found to be within the range of 97.1 to 100.6%. The

drug content of all the formulations of Glipizide buccoadhesive bilayered tablets was shown in Table no.4.

Table No 5: List of post-compression parameters for F1 to F8

Formulation code	Surface pH*	Swelling index(8hrs)	Bioadhesive strength(gm)	Mucoadhesive time(hrs)
F1	6.77±0.061	93.26	7.52	12.43
F2	6.73±0.030	86.81	6.84	12.02
F3	6.62±0.026	79.62	6.12	11.42
F4	6.79±0.040	71.10	5.71	10.74
F5	6.56±0.065	89.21	7.25	12.52
F6	6.77±0.066	86.41	6.68	12.21
F7	6.77±0.061	78.56	5.97	11.24
F8	6.56±0.066	70.65	5.45	10.14

3.5.6. Surface pH: Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the tablets was determined. The observed surface pH of the formulations was found to be in the range of 6.56±0.061 to 6.79±0.040. From the results, it was found that there is no significant difference of surface pH in all the formulations and the pH range lies within the range of salivary pH i.e. 6.5 to 6.8, hence do not cause irritation and achieve patient compliance. The results were shown in Table No: 5

3.5.7. Swelling index: Swelling index of all formulations of Glipizide tablets were found to be within the range of 70.65 to 93.26 (in 8 hrs). Swelling property of tablets increased with increase in Carbopol 934P concentration.The swelling index of all the formulations of Glipizide buccoadhesive bilayered tablets was shown in Table no. 5.

3.6. Ex vivo bioadhesive strength: Bioadhesion strength measurements of tablets were found to be within the range of 5.45 to 7.52 and it indicates that the bioadhesive strength was proportional to carbopol content. The bioadhesion strength of all the formulations was shown in Table no.5.

3.7. Mucoadhesion time: Mucoadhesion time of all formulations of Glipizide tablets were found to be within the range of 10.14 to 12.43 hrs. The mucoadhesive time for all the formulations of Glipizide buccoadhesive tablets was shown in Table.no.5.

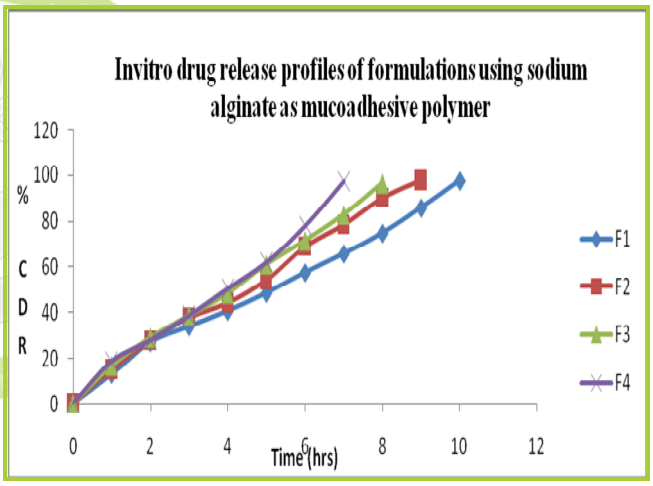


Figure No. 2: Release profile of Glipizide buccal tablets containing Sodium Alginate as a Mucoadhesive polymer

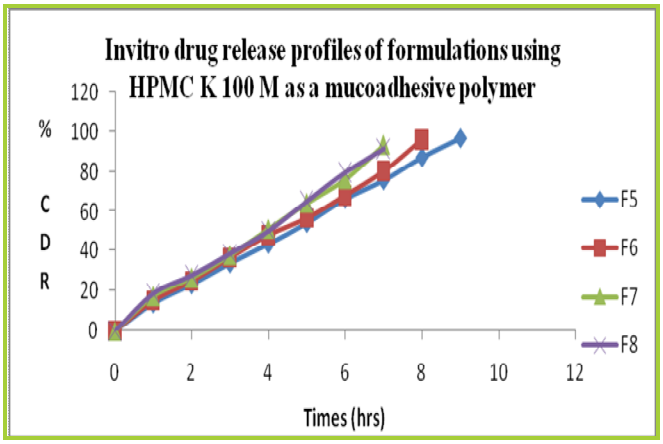


Figure No. 3: Release profiles of Glipizide buccal tablets containing HPMC K 100 M as a Mucoadhesive polymer

Table No 6: Release profile of Glipizide buccal tablets for all formulations F1-F8

Time [hrs]	Percentage cumulative drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	12.94	15.26	16.63	18.73	13.89	15.26	17.57	18.73
2	26.96	27.80	28.86	27.81	23.27	24.96	26.75	27.81
3	33.83	37.73	38.47	38.68	33.83	36.57	38.04	38.63
4	40.60	44.19	48.09	50.41	43.44	47.98	51.35	50.09
5	48.33	54.24	60.98	62.15	54.02	56.66	64.56	65.26
6	57.44	69.04	71.52	78.21	66.29	68.66	76.53	79.59
7	65.82	78.69	82.81	97.56	75.52	80.06	93.67	91.25
8	74.84	90.36	96.49	-	86.97	95.83	-	-
9	85.87	98.04	-	-	96.44	-	-	-
10	97.65	-	-	-	-	-	-	-

Table no.6

3.7.1 In vitro dissolution studies: Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of phosphate buffer pH 6.8 medium. The temperature of the dissolution medium was maintained at 37±0.5°C, an aliquot of dissolution medium was withdrawn at every 1 hr. interval. The absorbance of the solution was measured by UV spectrophotometric method at 274 nm and concentration of the drug was determined from the standard calibration curve.The results obtained in the *in vitro* drug release for the formulations F1 to F4 are tabulated in Fig. 2 and for the formulations, F5 to F8 are tabulated in Fig. 3 and all formulations F1-F8 were tabulated in Total Eight formulations were formulated F1 to F8 by using different polymers in varying concentrations i.e., in different ratios. The formulations F1-F4 were formulated using Sodium alginate and Carbopol 934p in different ratios. The formulations F5 to F8 were formulated using Carbopol 934p and HPMC K100M.

Among those eight formulations, F1 showed highest drug release of 97.65 %. The data for *in vitro* drug release of formulations was shown in Tables 6.

3.7.2 Drug Release Kinetic Models

Table No 7: Drug-release profile of the optimized formula F1

Time (Hrs)	√T	Log T	% Cumulative release	Log % cumulative release	% Drug Cumulative drug remaining	Log % drug Cumulative drug remaining
0	0	---	0	---	100	2
1	1	0	12.94	1.111	87.06	1.939
2	1.414	0.301	26.96	1.4307	73.04	1.863
3	1.732	0.477	33.83	1.529	66.17	1.820
4	2	0.602	40.60	1.608	59.4	1.773
5	2.236	0.698	48.33	1.684	51.67	1.713
6	2.449	0.778	57.44	1.759	42.56	1.629
7	2.645	0.845	65.82	1.818	34.18	1.533
8	2.828	0.903	74.84	1.874	25.16	1.400
9	3	0.954	85.87	1.933	14.13	1.150
10	3.162	1	97.65	1.989	2.35	0.371

Table No 8: kinetics of drug release

Formulation	Zero order	Higuchi Model	First order	Korsmeyer Peppa's Model
	R^2	R^2	R^2	R^2
F1	0.988	0.933	0.750	0.958

Kinetics modeling of drug dissolution profiles: *In vitro* release study data of optimized formulation F1 is fitted into various mathematical models i.e. Zero order, First order, Higuchi model, Korsmeyer Peppas to determine the best-fit model. The release was found to follow zero order with regression coefficient value 0.988.

3.8 STABILITY STUDIES:

The optimized formulation F1 was subjected to stability studies at 25 ± 2 ºC and 60 ± 5 % RH, 40ºC ± 2 ºC /75% RH ± 5% and 2-8 ºC for 3 months and analyzed for Physical appearance and physicochemical evaluation parameters like Thickness, Hardness, % Friability, Drug content, % CDR and Bioadhesive strength.

Table No 9: Physicochemical evaluation of formulation F1 after stability studies.

Time in days and Condition		Thickness (mm)	Hardness Kg/cm^2	% Friability	% Drug Content	% CDR	Bioadhesive strength
30	25 ± 2 ºC 60 ± 5 % RH	2.03	3.57	0.61	99.20	96.10	7.37
	40± 2 ºC 75 ± 5 % RH	2.06	3.54	0.63	98.64	95.95	7.48
	2-8 ºC	2.01	3.58	0.65	99.20	96.65	7.45
60	25 ± 2 ºC 60 ± 5 % RH	1.98	3.67	0.67	98.64	92.72	7.31
	40 ± 2 ºC 75% ±5 RH	1.96	3.71	0.71	98.06	91.54	7.39
	2-8 ºC	2.03	3.56	0.65	98.92	93.01	7.42
90	25 ± 2 ºC 60 ± 5 % RH	1.96	3.74	0.61	98.64	90.32	7.25
	40± 2 ºC 75 ± 5 % RH	1.97	3.41	0.59	97.20	88.12	7.36
	2-8 ºC	1.95	3.53	0.59	98.06	89.08	7.34

Stability studies: The promising formulation F1 was subjected to short-term stability study by storing the formulations at 25 ± 2 ºC and 60 ± 5 % RH, 40ºC ± 2 ºC /75± 5 % RH and 2-8 ºC for 3 months.

The tablets were withdrawn periodically and evaluated for different parameters like Thickness, Hardness, %Friability, % Drug content and Drug release studies and Bioadhesive strength. These parameters were evaluated at zero month, 1st month, and 2nd month and 3rd-month intervals.

The formulation showed there were no many significant changes in the values. The data obtained were tabulated in Table no.9. From those results, it was concluded that formulation F1 was stable and retained their properties.

CONCLUSION

The main objective of the present study was to develop buccal bilayered formulations containing 20 mg of Glipizide by using mucoadhesive polymers like Sodium alginate, Carbopol 934p, HPMC K100M, PVP K30, Mannitol by direct compression method which can enhance the bioavailability of the drug. The 8 batches of prepared buccal tablets were evaluated for various parameters and compared to all formulations, F1 containing Sodium alginate and Carbopol in the ratio of 4:1 showed the better mucoadhesive time, highest swelling index, better-controlled drug release and better bioadhesive strength.

On the basis of above result, the prepared bilayered buccal tablet can be used as a potential candidate for the treatment of diabetes mellitus.

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