Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 7s, https://carcinogenesis.com/

Formulation And Characterization of a Mucoadhesive Buccal Patch of Glipizide for Sustained Antidiabetic Action

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ABSTRACT

Worldwide, diabetes mellitus is becoming an increasingly serious health concern. Chronically elevated blood sugar levels due to insulin resistance, insulin ineffectiveness, or, more often than not, both, are the root cause of this condition. Significant macrovascular and microvascular consequences, including as cardiovascular disease, neuropathy, nephropathy, and retinopathy, can develop from this metabolic illness if it is not well controlled. These problems greatly diminish quality of life and raise death rates. To effectively treat diabetes, one must take a comprehensive approach that includes medication, physical activity, and dietary changes in order to keep blood glucose levels within a physiological range. The majority of people with Type 2 Diabetes Mellitus (T2DM) rely on oral hypoglycemic agents (OHAs) as their primary medication. Using the solvent casting process, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, carbopol-934P, and Eudragit RL-100 were utilised to create glipizide mucoadhesive buccal films. The films that were prepared were tested for in vitro residence duration, folding endurance, thickness, surface pH, swelling index, in vitro release, and permeation investigations, among other parameters. with consistent drug content. Over the course of more than six hours, the films demonstrated controlled release. Results showed that films containing 5 mg glipizide in a 4.9% w/v hydroxypropylmethylcellulose and 1.5% w/v sodium carboxymethylcellulose solution swelled adequately, had an ideal residence duration, and showed promise for drug release. Researchers determined that the formulation might be used to create buccal films with therapeutic potential.

Keywords: *glipizide, diabetic, mucoadhesive, bioingredients*

How to Cite: Anasuya Patil, Anamika kulshrestha, Suneel Kumar Niranjan, Payal N. Vaja, Payal Khamora, Shamna MS, Ramenani Hari Babu, Mahesh Madhavrao Thakare, (2025) Formulation And Characterization of a Mucoadhesive Buccal Patch of Glipizide for Sustained Antidiabetic Action, *Journal of Carcinogenesis*, *Vol.24, No.7s*, 324-334

1. INTRODUCTION

Diabetes Mellitus is a major and growing health problem around the world. It is caused by high blood sugar levels that last for a long time because of problems with insulin production, insulin action, or, most of the time, both.[1] This metabolic disorder, if inadequately managed, leads to significant macrovascular and microvascular complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, which substantially impair quality of life and increase mortality rates. Effective diabetes management requires meticulous regulation of blood glucose levels within a physiological range, demanding a holistic approach that encompasses diet, exercise, and pharmacotherapy. For individuals with Type 2 Diabetes Mellitus (T2DM), oral hypoglycemic agents (OHAs) are frequently the principal pharmacological treatment. The search for the best treatment plan is still going on. [2]Many current medications are difficult to use because they don't work well in the body, their dosing schedules are inconvenient, which makes it hard for patients to stick to them, and they often cause side effects like low blood sugar. The limitations underscore an immediate necessity for advanced drug delivery systems that can improve therapeutic efficacy, enhance safety profiles, and align with patient-centered treatment paradigms to achieve optimal glycaemic control and prevent long-term repercussions. Glipizide is a second-generation sulfonylurea that is often prescribed to help people with type 2 diabetes mellitus control their blood sugar levels. It works by making the active beta cells in the pancreas release more insulin, which lowers blood sugar levels.[3][4] Even though it has a strong effect on lowering blood sugar, the therapeutic use of regular immediate-release glipizide tablets is very limited because of their complicated pharmacokinetic properties. Glipizide has a lot of pre-systemic clearance, which means it goes through a lot of first-pass metabolism in the liver. After being taken by mouth and absorbed, the drug goes through the portal vein to the liver, where a large part of it is broken down before it enters the systemic circulation and has its therapeutic effect. This process greatly reduces its absolute bioavailability to about 80–100%, with a lot of variation between people, which makes it harder to predict the right dose. Second, glipizide has a relatively short half-life of about 2 to 4 hours. This makes it work quickly, but you need to take it many times a day (usually 2–3 times) to keep therapeutic plasma levels up all day. Patients find it hard to stick to this frequent dose schedule, which often leads to inconsistent blood glucose levels—periods of hyperglycemia followed by dangerously low levels that can cause hypoglycemia. These inherent limitations highlight the necessity for a novel delivery system capable of circumventing first-pass metabolism and guaranteeing sustained medication release. Buccal drug delivery, which means giving a drug through the mucosal membranes of the inner cheek (buccal mucosa), is a smart and logical way to solve the pharmacokinetic problems that come with glipizide. This method has a strong set of benefits that directly address its therapeutic flaws. [5][6]The main benefit is that it avoids first-pass metabolism. Substances absorbed through the highly vascular buccal mucosa directly enter systemic circulation via the jugular vein, thereby bypassing the hepatic portal system and the associated enzymatic degradation in the liver. This can greatly improve the bioavailability of drugs like glipizide, making sure that a larger percentage of the dose gets to its target location. This means that less medicine is needed and side effects may be less severe[6]. Also, the buccal route is non-invasive, which makes it much easier for patients to accept and stick with than parenteral methods. It makes it easy to stop therapy right away if something bad happens by just stopping the dosage form. For a drug like glipizide that has a small therapeutic index and a constant risk of hypoglycemia,[7][8] the buccal cavity is the best place to make a sustained-release device. Regulating the release rate from a mucoadhesive patch or film helps keep plasma levels stable within the therapeutic window. This reduces the peaks and troughs that are common with regular tablets and lowers the risk of hyperglycaemic and hypoglycemic episodes. The successful implementation of a buccal drug delivery system relies exclusively on its ability to persist at the absorption site for a designated duration, opposing the inherent clearance mechanisms of the oral cavity, such as saliva flow, swallowing, and tongue movement. Mucoadhesive polymers are the most important technological part here.[9][10] These are specialised hydrophilic macromolecules that interact with the mucin layer of the buccal epithelium, creating strong but reversible bonds that keep the dosage form in place. The mucoadhesion process typically consists of two phases: an initial contact phase, during which the polymer hydrates and swells in response to saliva, promoting close interaction with the mucus; and a consolidation phase, marked by the interpenetration and entanglement of polymer chains with mucin glycoproteins, enhanced by secondary chemical bonds, including van der Waals forces, hydrogen bonding, and electrostatic interactions. Choosing the right polymer is very important for a glipizide buccal formulation. The best polymers should be able to stick to mucus better than other materials, not be toxic, be compatible with living tissue, and not irritate the mucosa. Chitosan is a natural cationic polysaccharide that is known for its ability to improve permeation. [11][12] Cellulose derivatives include hydroxypropyl methylcellulose (HPMC) and sodium carboxymethyl cellulose (SCMC). Synthetic compounds include poly(acrylic acid) derivatives (e.g., Carbopol). These polymers not only ensure prolonged residence time but can also be engineered to control the drug release rate, forming the basis of a sustained-release buccal delivery system for glipizide. The idea of prolonged release is especially new for diabetes medicines like glipizide. The main goal of a sustained-release (SR) system is to release the drug at a set, controlled rate over a long period of time, usually 8 to 12 hours or more, in order to keep plasma drug levels stable. [13][14]This has a lot of therapeutic benefits for treating diabetes. SR formulations provide a steady, consistent supply of medicine, which helps to optimise the plasma concentration-time profile by reducing sharp peaks that could cause hypoglycemia and avoiding troughs that could make glycaemic control less effective. This makes blood sugar levels more stable throughout the day, which lowers the number of times people have hyperglycaemic or hypoglycemic episodes. This often means that the patient only has to take the medicine once a day instead of several times a day, which

makes it much easier for them to stick with it for a long time. Furthermore, improved pharmacokinetic regulation can enhance the drug's efficacy and potentially decrease the total daily dosage required, thus mitigating dose-dependent adverse effects. In the specific context of a buccal sustained release system for glipizide, these advantages are enhanced. [15]The method provides sustained release and enhances bioavailability by avoiding first-pass metabolism. This synergistic approach represents a transformative shift in oral hypoglycemic therapy, moving from conventional pulsatile dosing to a more physiological, continuous, and patient-centered method of drug delivery, which holds the potential for markedly improved clinical outcomes in Type 2 diabetes. Buccal drug delivery systems are designed to facilitate the localized or systemic absorption of drugs through the buccal mucosa, offering a promising alternative to conventional oral administration.

2. MATERIALS AND METHODS

Glipizide was generously provided as a gift sample by USV Ltd (Daman, India). The polymers hydroxy propyl methylcellulose (HPMC-E15), Carbopol-934P (CP-934P), Eudragit RL-100, and sodium carboxymethylcellulose, 1500-4000 cps (SCMC-H), were procured from Central Drug House, Mumbai. Propylene glycol was obtained from E. Merck (P) Ltd, Mumbai, and all other reagents used were of analytical grade. The mucoadhesive buccal films were prepared using the solvent casting method.

Preparation buccal film

The buccal films of glipizide were prepared by a solvent casting technique utilizing aluminum foil cups placed on a glass surface as a substrate. The composition for a single circular cast film for each formulation (F1 to F4) is detailed in Table 1. The formulations were designed using HPMC-E15 either alone (F1) or in combination with other mucoadhesive polymers: sodium CMC-H (F2), Eudragit RL-100 (F3), or CP-934P (F4). Propylene glycol was incorporated as a plasticizer and penetration enhancer at a concentration of 30% w/w of the polymer weight, and ethanol (95%) served as the solvent. In the preparation process, the calculated amounts of polymers were first dispersed in ethanol. Three hundred milligrams of glipizide was then incorporated into the polymeric solutions after being levigated with the propylene glycol. The resulting medicated gels were left overnight at room temperature to form clear, bubble-free mixtures. To prevent solvent evaporation, these gels were transferred to vials and sealed tightly with rubber closures. Subsequently, the gels were cast into aluminum foil cups (4.5 cm diameter) placed on a glass surface and allowed to dry overnight at room temperature (25°C) to form flexible films. The dried films were then cut into uniform sizes of 20 mm diameter, packaged in aluminum foil, and stored in a desiccator until further evaluation.

Physical evaluation

physical characterization, the film weight and thickness were determined. The weight was evaluated by individually weighing three films from each formulation on a digital balance (Fisher Brand PS-200), and the average was calculated. Similarly, the thickness of three films per formulation was measured at three different points using a micrometer screw gauge (Mitutoyo MMO-25DS), and the mean value was derived. The surface pH of the films was assessed by allowing three films from each formulation to swell for 2 hours on the surface of an agar plate. The pH was then measured by placing a pH paper on the surface of the swollen patch, and the mean of three readings was recorded.

Swelling index

swelling of the films was determined after establishing their original weight and diameter. The film samples were allowed to swell on the surface of an agar plate in an incubator maintained at 37 ± 0.2°C. The increase in weight of the films (n=3) was monitored at pre-set time intervals over 5 hours. The percent swelling (%S) was calculated using the equation: %S = [(Xt - Xo) / Xo] × 100, where Xt is the weight of the swollen film at time t and Xo is the initial film weight at time zero. The folding endurance, a measure of film flexibility, was evaluated by cutting three films from each formulation to a size of 2 x 2 cm. The test involved repeatedly folding a small strip of the film at the same place until it broke. The number of times the film could be folded without breaking was recorded as the folding endurance value, with the mean and standard deviation of three readings reported.

In vitro residence time

In this we indicates mucoadhesion performance, was determined using a disintegration apparatus. The medium consisted of 800 ml of phosphate buffer (pH 6.6) maintained at 37 ± 2°C. Segments of rat intestinal mucosa (3 cm length) were glued to a glass slab, which was vertically attached to the apparatus. Three films from each formulation were hydrated on one surface with pH 6.6 buffer and then brought into contact with the mucosal membrane. The glass slab was moved vertically up and down, immersing the film in the buffer at the lowest point. The time taken for the film to either completely erode or detach from the mucosal surface was recorded as the *in vitro* residence time (n=3).

Drug uniformity

Drug content uniformity was assayed by placing three film units (20 mm diameter) from each formulation into separate 100 ml volumetric flasks. Each flask was filled with pH 6.6 phosphate buffer and stirred continuously for 24 hours. The

solutions were then filtered, suitably diluted, and analyzed spectrophotometrically at 274 nm using a UV spectrophotometer (Thermospectronic UV-1). The average drug content from the three films was taken as the final reading.

Invitro drug release study

In vitro drug release studies were conducted using a USP XXIV six-station dissolution apparatus (Type 1, V Scientific Model No. DA-6DR). A single film from each formulation was fixed just above the basket of the central shaft using a cyanoacrylate adhesive. The dissolution medium was 900 ml of pH 6.6 phosphate buffer, maintained at 37 ± 0.5°C with a rotational speed of 50 rpm. The study was carried out over 6 hours, with 1 ml samples withdrawn from each station every hour and replaced with an equal volume of fresh medium to maintain sink conditions. Each withdrawn sample was filtered, diluted, and analyzed at 274 nm using UV spectrophotometry. The data presented are the mean of three determinations.

TABLE 1: COMPOSITION OF MUCOADHESIVE BUCCAL FILMS

Ingredients	Formulations F1	F2	F3	F4
Glipizide (g)	0.30	0.30	0.30	0.30
HPMC-E15 (g)	1.30	1.00	1.00	1.00
Sodium CMC-H (g)	-	0.30	-	-
Eudragit RL100 (g)	-	-	0.30	-
Carbopol -934P (g)	-	-	-	0.30
Propylene Glycol (ml)	0.48	0.48	0.48	0.48
Ethanol (95%) ml	20	20	20	20

3. RESULTS AND DISCUSSION

Spectroscopic studies:

Table : 3 UV spectroscopy

Concentration (mg/L or M?)*	Absorbance
0	0
2	0.0872
4	0.1280

The UV spectrum of Gliclazide in phosphate buffer pH 6.8 showed maximum absorption at 229.5 nm. Hence drug used in the formulation was found to be pure according to USP specification. The UV spectrum of the Gliclazide in phosphate buffer is given in figure below.

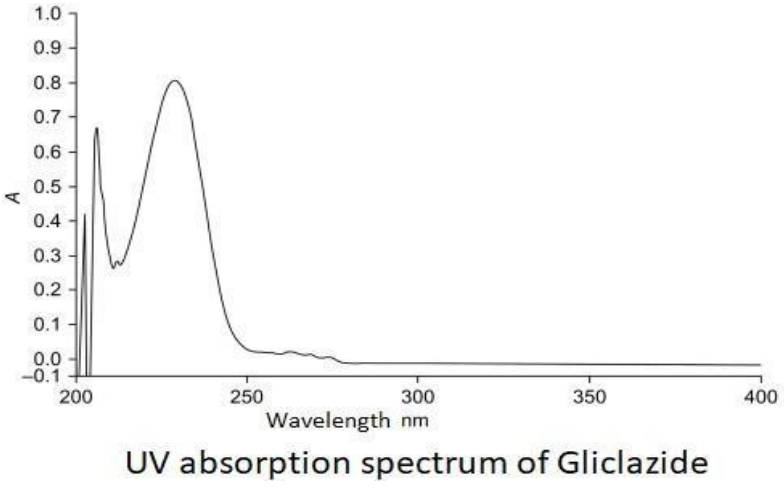

Fig: 1 UV absorption spectrum of gliclazide

Standard calibration curve of Gliclazide:

A standard curve was prepared by dissolving 10 mg of Gliclazide dissolved in required quantity of methanol and make up 100 ml with phosphate buffer pH 7.4 to get solutions in concentration range 2 to 8 µg/ml. The absorbance of these solutions were determined spectrophotometrically at 220 nm. The absorbance values were noted as shown in table 4 and figure shows standard calibration curves with slope 0.0814 and regression value of 0.9995. The curve was found to be linear in the range 2 to 8 µg/ml at 229.5 nm.

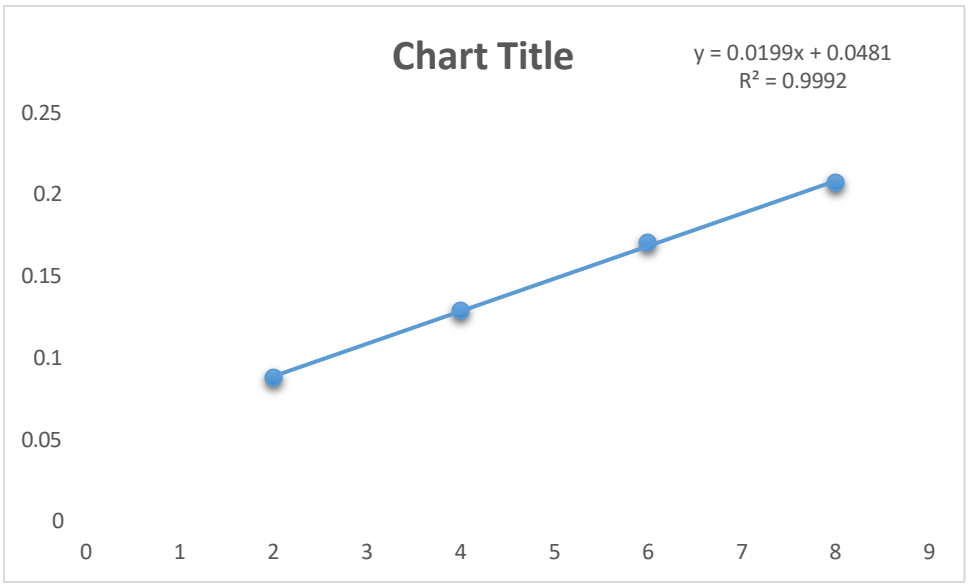

Fig: 2 Standard Calibration Curve of Gliclazide:

Fig: 3 FT-IR Spectra of Gliclazide

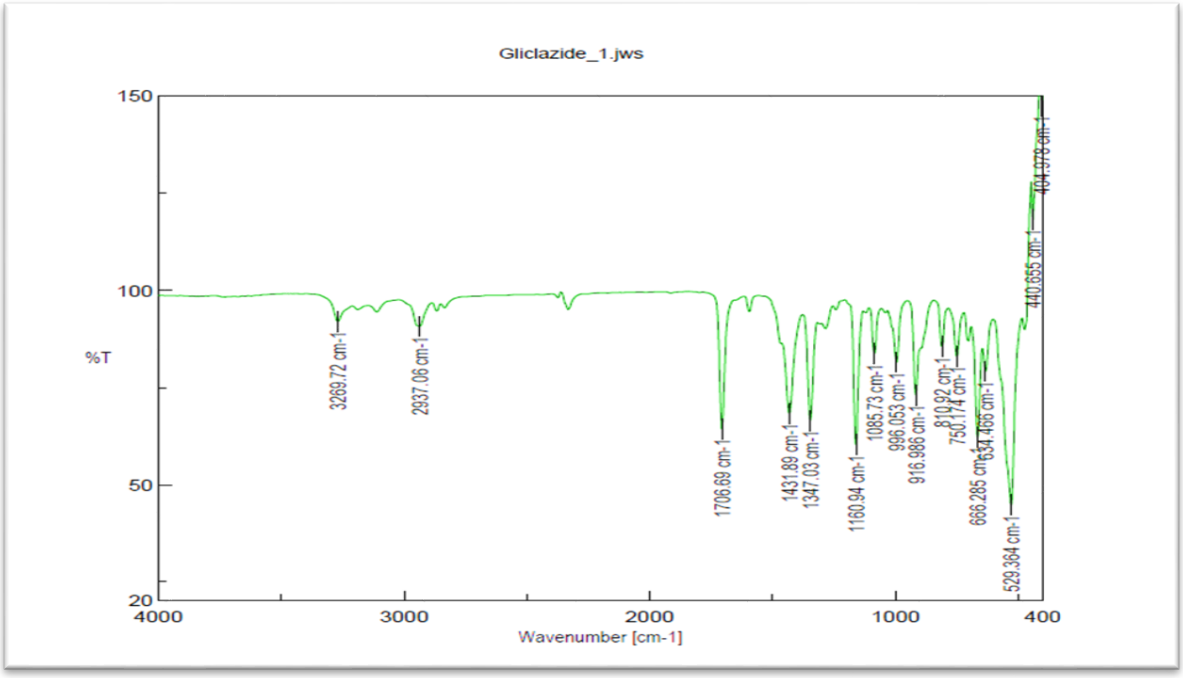

Fig: 4 FT-IR Spectra of Carbapol

Evaluation of Buccal Patches: Physicochemical Evaluations

Table: 4 Physical parameter evaluation

Formulation	Flexibility	Smoothness	Transparancy
F1	✓	✓	Opaque
F2	✓	✓	Opaque
F3	✓	✓	Opaque
F4	✓	✓	Opaque
F5	✓	✓	Opaque
F6	✓	✓	Opaque
F7	✓	✓	Opaque
F8	✓	✓	Opaque
F9	✓	✓	Opaque

Physical Appearance

Table : 5 Surface Ph, weight & Thickness Determination:

Formulations	Surface pH	Weight Uniformity	Thickness
F1	6.2 ± 0.06	157.61 ± 0.59	0.14 ± 0.006
F2	6.3 ± 0.06	159.62 ± 0.08	0.13 ± 0.006
F3	6.47 ± 0.06	161.64 ± 0.01	0.14 ± 0.006

F4	6.63± 0.06	163.61 ± 0.01	0.13 ± 0.006
F5	6.42 ± 0.06	163.26 ± 0.01	0.13 ± 0.006
F6	6.45 ± 0.06	158.61 ± 0.09	0.13 ± 0.006
F7	6.33 ± 0.06	157.26 ± 0.00	0.11 ± 0.006
F8	6.27 ± 0.06	157.83 ± 0.09	0.12 ± 0.006
F9	6.17 ± 0.06	157.63 ± 0.09	0.11 ± 0.006

Drug content uniformity:

The percentage drug content was determined by UV spectrophotometer at 229.5 nm method using thestandard calibration curve and the same procedure was repeated for three patches of each formulation. The drug content uniformity of superior batch was found to be in the range of 97.93% - 99.99%. As the drug content values of same formulation did not show a significant difference, it can be concluded that the drug was uniformly dispersed in buccal patches.

Folding endurance:

Folding endurance of patches was determined by repeatedly folding a film at the same place until it breaks**.** The number of folding required to break or crack a patch was taken as the folding endurance. The folding endurance was found to be increased with an increasing concentration of PVA and decreasing concentration of carbapol. Allthe patches showed good value of folding endurance (more than200 was considered to be good value). This confirms that there will be no breakage of patch till its use.

Table: 6 Folding Endurance

Formulation	**Content uniformity**	**Folding endurance**
F1	97.92±0.9	190.87±5
F2	95.98±0.9	197.87±0.9
F3	95.97±0.92	195.87±5
F4	98.98±0.21	193.87±0.32
F5	99.96±0.43	192.87±0.12
F6	98.95±0.42	199.87±0.5
F7	96.92±0.98	199.87±0.1
F8	99.91±0.87	198.87±0.9

Measurement of mechanical property:

Tensile streng Thetensile strength was found to be in the range of 10.12 to 15.68 kg/mm^2. As

the concentration of hydrophilic polymer carbopol 934 was increased the tensile strength was found to be increased. All film showed 100% flatness.

Table no. 7 Tensile strength

Formulation	**Tensile strength (N/mm2)**
F1	15.68
F2	12.74
F3	13.45

F4	11.98
F5	10.95
F6	12.14
F7	11.24
F8	12.10
F9	10.39

Swelling Index:

Thedegree of swellingof bio-adhesive polymer is an important factor affecting bioadhesion. All the patches showed maximum increase in swelling after 1 h. Figure below shows the comparative swelling index of different formulation of Gliclazide buccal patches. The formulated patches F1-F9 showed increase in the swelling index which indicates that as the concentration of the PVA increases the swelling of the patch increases.

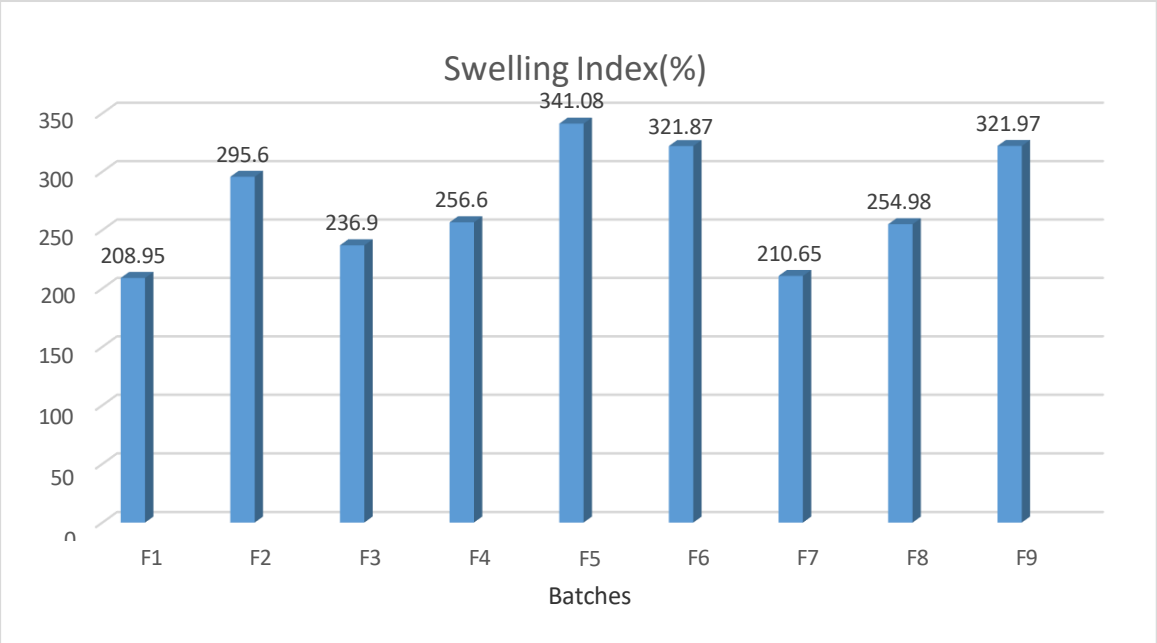

Fig: 5: Bar Graph Showing % swelling index of gliclazide buccal patches after 1

Table: 8 Bio adhesion time

Formulation	**Bio-adhesion Time (min)**
F1	256
F2	234
F3	237
F4	290
F5	286
F6	249
F7	298
F8	276
F9	287

Table.no. 9 Comparative Permeation Study

	0	1	2	3	4	5	6
F1	0	15.03	30.06	40.98	52.09	65.98	76.98
F2	0	16.87	32.76	44.98	56.98	69.986	79.87
F3	0	18.98	32.98	43.68	56.98	69.986	80.65
F4	0	13.089	26.87	42.87	56.98	69.986	81.89
F5	0	14.87	28.98	42.87	56.98	63.87	79.98
F6	0	16.87	28.98	42.87	53.98	67.88	79.98
F7	0	17.34	34.19	44.98	54.98	68.09	80
F8	0	18.04	32.98	44.98	55.87	68.09	78.98
F9	0	18.04	32.98	42.87	55.87	69.09	78.98

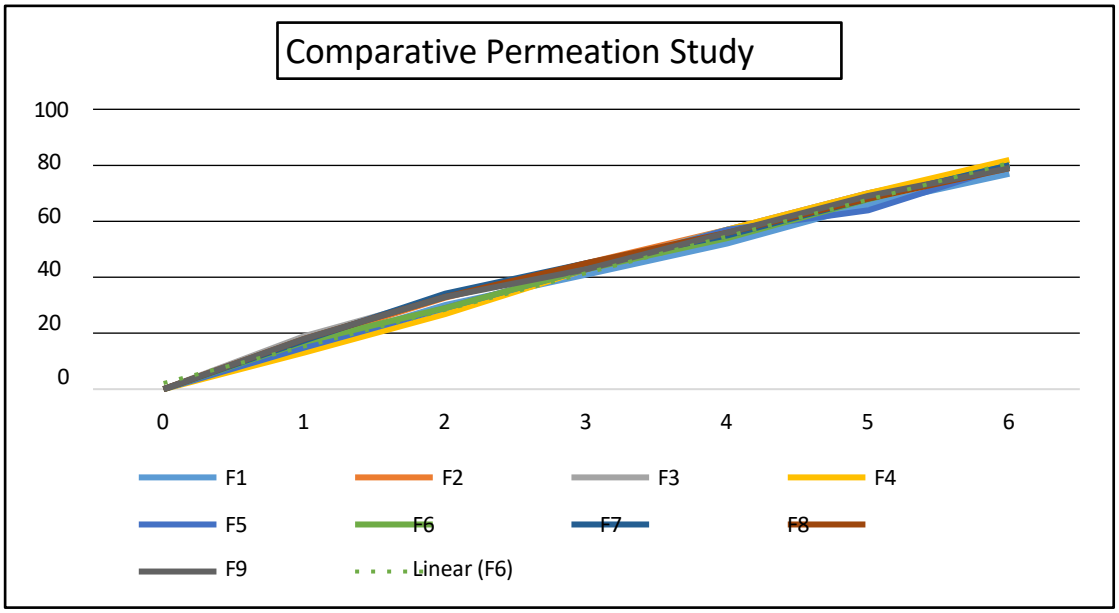

Fig: 5 Comparative permeation studies

Accelerated Stability Studies:

Stability was carried out on optimized buccal patch formulation for three months. It was found that formulation remained stable at temperature of $40^0C \pm 2^0C$ and relative humidity of 75%± 5 as per ICH guidelines. The results obtained are shown in Table. The results shown that there was no change in physical appearance of buccal patches. Drug content showed no marked change after three months. These results concluded that buccal patches were chemically and physically stable at different temperature and humidity conditions for three months.

Table: 9 Accelerated Stability Study

Parameter	0 day	30 days	60 days	90 days
Appearance	**No change**	**No change**	**No change**	**No change**
% Swelling Index	**No change**	**No change**	**Slightly change**	**Change**
% Drug Release	**No change**	**No change**	**Slightly change**	**Change**
Folding Endurance	**No change**	**Slightly change**	**Slightly change**	**Change**

Table: 10 Stability studies for drug diffusion of batch F1

Time	Cumulative %Drug Release At 0 Day	Cumulative %Drug Release At 30 Day	Cumulative %Drug Release At 60 Day	Cumulative %Drug Release At 90 Day
0	0	0	0	0
1	26.33	26.34	25.765	26.654
2	51.795	50.653	52.456	51.2621
3	66.15	63.65	65.876	64.44
4	74.64	70.12	70.982	71.57
5	85.529	84.21	84.34	84.2432

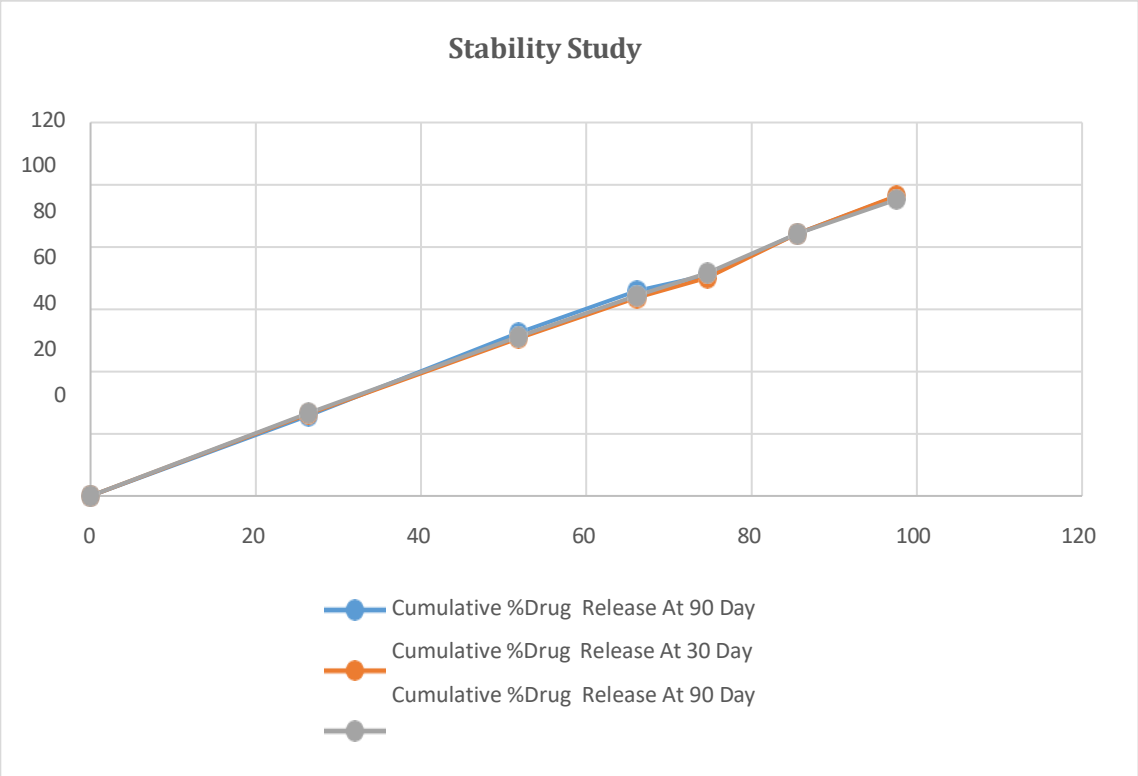

Fig: 6 Stability studies

4. CONCLUSION

Gliclazide buccal patches were the focus of this investigation. The organoleptic properties, solubility, and drug-polymer interaction tests were conducted using FT-IR prior to the formulation of the patches. The results were positive in all of the aforementioned studies, and no polymers and drugs do not mix.

At 3369.79 (N-H), 2930.96 (C-H), 2843.20 (O-H), 1444.75, 1543.12 (N=O), 1154.45 (C-N), and 1036.78 (C-O), gliclazide exhibited strong peaks. All of the main peaks of the Gliclazide drug were visible in the spectra of the physical mixture with all of the other excipients, including HPMC K4M, Carbopol934, PVA, and PG, suggesting that the drug remained stable throughout the process. There was no significant shifting or loss of functional peak appearance between the drug and excipient spectra in the FTIR analysis of pure drug, HPMC K4M, Carbopol934, PG, and PVA. Therefore, the medicine and the excipients are compatible. Subsequently, homogeneity of weight, swelling index, folding endurance, thickness, percentage of drug release, determination of muco-adhesion, diffusion study, and nine batches of Gliclazide matrix buccal patches containing different concentrations of polymer were created using the solvent casting method. Researchers used

Franz diffusion cells to study the spread of buccal patches. As a permeability barrier and phosphate absorber, the goat buccal membrane was utilised.

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