International Journal of Pharmaceutical Research and Development

ISSN Print: 2664-6862
ISSN Online: 2664-6870
Impact Factor: RJIF 8.55
IJPRD 2025; 7(2): 529-540
www.pharmaceuticaljournal.net
Received: 17-08-2025
Accepted: 22-09-2025

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Formulation and evaluation of mucoadhesive buccal tablets of glibenclamide

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DOI: https://www.doi.org/10.33545/26646862.2025.v7.i2f.217

Abstract
Background: Glibenclamide, a second-generation sulfonylurea, undergoes extensive hepatic first-pass metabolism and has limited bioavailability through conventional oral routes. Buccal drug delivery provides a direct systemic pathway, bypassing this effect and improving therapeutic efficacy.
Objective: To develop, optimize, and evaluate mucoadhesive buccal tablets of Glibenclamide for sustained release and enhanced bioavailability.
Methodology: Formulations (FH, FS, FA series) were prepared by direct compression using polymers HPMC K4M, NaCMC, and Sodium Alginate. Tablets were evaluated for pre- and post-compression parameters, surface pH, swelling index, mucoadhesive strength, FTIR compatibility, in-vitro drug release, and stability. Drug release kinetics were analyzed using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.
Results: All formulations showed acceptable physical properties and uniform drug content. FH1 (HPMC-based) demonstrated optimum mucoadhesive strength (5.4 g), swelling index (96.5%), and sustained drug release (87.43% over 8 h) following zero-order kinetics and non-Fickian diffusion. FTIR confirmed no drug-polymer interactions. Stability studies showed no significant change (p>0.05) after 90 days.
Conclusion: The optimized HPMC K4M formulation (FH1) offers controlled, unidirectional drug release and improved bioavailability. This buccal delivery system presents a promising alternative to conventional Glibenclamide therapy, enhancing patient compliance in type 2 diabetes management.

Keywords: Glibenclamide, Mucoadhesive tablets, buccal delivery, sustained release, HPMC K4M, bioavailability

Introduction
Diabetes mellitus (DM) is a major global public health concern, responsible for approximately five million deaths annually due to its associated complications. Among its types, type 2 diabetes mellitus (T2DM) is particularly prevalent and is primarily considered a lifestyle-related condition. The increasing rates of obesity, physical inactivity, and the adoption of Westernized dietary patterns have significantly contributed to the growing incidence of T2DM worldwide [1].
According to the International Diabetes Federation (IDF), the global prevalence of diabetes is projected to rise from an estimated 537 million individuals to 643 million by 2030. The economic impact is substantial, with an anticipated annual global cost exceeding USD 1 trillion. Notably, the burden of diabetes is disproportionately higher in resource-limited countries, where access to screening, treatment, and adequate healthcare remains limited [2].
T2DM is a complex, multisystemic metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. The disease is heterogeneous, involving varying degrees of pancreatic beta-cell dysfunction and insulin resistance. A strong link exists between obesity and T2DM, mediated by central nervous system pathways that regulate appetite, energy expenditure, and metabolic homeostasis through signals from peripheral organs and environmental factors
Although T2DM has traditionally been considered a disease of older adults, recent evidence indicates a two- to three-fold increase in its incidence among younger populations under 40 years of age [3].

Despite advancements in diabetes management, including innovative technologies and novel pharmacotherapies, glycemic control remains suboptimal in many individuals. Carls *et al*. (2017) reported a decline in the proportion of patients achieving target glycated hemoglobin (HbA1c) levels—from 52.2% during 2003-2010 to 50.9% during 2007-2014 [3]. Similarly, analysis of National Health and Nutrition Examination Survey (NHANES) data revealed a reduction in the percentage of individuals attaining HbA1c levels below 8.0%, from 79.4% in 2007-2010 to 75.4% in 2015-2018.

The oral cavity, lined with a mucous membrane, serves as a potential site for drug absorption, enabling rapid systemic delivery and bypassing hepatic first-pass metabolism [4]. Drugs can penetrate the mucosa primarily through passive diffusion, facilitated by the rich vascular network that connects directly to systemic circulation via the jugular vein [5]. Among the oral routes, two main sites are utilized: the sublingual route, where the drug is placed beneath the tongue for rapid absorption, and the buccal route, where administration occurs between the cheek and gingiva [6].

The buccal mucosa offers several advantages for drug delivery, including ease of administration, avoidance of gastrointestinal degradation, and improved patient compliance [7]. Furthermore, the buccal route permits the development of mucoadhesive drug delivery systems, which enhance the residence time of formulations on the mucosal surface. These systems enable intimate contact between the dosage form and the mucosa, optimizing drug diffusion and concentration gradients while maintaining controlled release [8].

Mucoadhesion is defined as the attachment of a polymeric system to biological tissue through interfacial forces [9]. Mucoadhesive systems are advantageous because they facilitate targeted and sustained drug delivery at specific sites within the body, including the gastrointestinal, nasal, ocular, vaginal, and buccal mucosa [10]. When formulated properly, these systems can improve the bioavailability of drugs that undergo extensive first-pass metabolism or degradation in the gastrointestinal tract [11].

Glibenclamide is a second-generation sulfonylurea oral hypoglycaemic agent used for treatment of type 2 diabetes mellitus [12].

It stimulates insulin release from pancreatic β-cells by binding to the sulfonylurea receptor 1 (SUR1) component of ATP-sensitive potassium (K_{ATP}) channels, causing channel closure, membrane depolarisation, calcium influx and insulin exocytosis. It also has extra pancreatic effects including reduction of hepatic glucose output and increased peripheral insulin sensitivity [13, 14].

It is indicated in adults with type 2 diabetes mellitus not adequately controlled by diet and exercise alone; can be used as monotherapy or in combination with metformin (or other agents) when appropriate.

After oral administration Glibenclamide is readily absorbed, with peak plasma levels typically reached in about 2-4 h. It is highly protein-bound (~99 %), is extensively metabolised in the liver (e.g., via CYP2C9) and the resulting metabolites (some active) are eliminated via both urine and bile.

Typical starting dose is ~2.5-5 mg once daily with the first meal; titrated according to glycaemic response and risk of hypoglycaemia up to a maximum ~20 mg/day in divided doses where indicated [15].

Glibenclamide is an ideal candidate for buccal drug delivery. This route can potentially mitigate gastrointestinal side effects and reduce the frequency of dosing`.

Therefore, the present study focuses on the formulation and evaluation of mucoadhesive buccal tablets of Glibenclamide to enhance therapeutic efficacy, minimize first-pass metabolism, and improve patient adherence.

Materials and Methods

Materials

Glibenclamide was obtained as a gift sample from Dhamtec Pharma, Mumbai, India. Hydroxypropyl methylcellulose (HPMC K4M), Sodium carboxymethyl cellulose (NaCMC), Sodium alginate, and Carbopol 934P were procured from Yarrow Chem and SD Fine Chemicals, Mumbai. All other reagents and chemicals used were of analytical grade.

Preparation of calibration curve of Glibenclamide

Procedure for standard curve in methanol

Standard solution

Accurately weighed 100 mg of Glibenclamide was dissolved in 100 ml of methanol to get a solution containing 1000 mcg/ml.

Stock solution

From the standard stock, a first stock solution was prepared to give a concentration of 100 mcg/ml in water. Second stock of 10mcg/ml was prepared from first stock. Aliquots of 0.2, 0.4, 0.6, 0.8 and 1.0 ml of stock solution were pipetted out into 10 ml volumetric flasks. The volume was made up to the mark with water. These dilutions give 2,4,6,8 and 10 mcg/ml concentration of Glibenclamide respectively. The absorbance of prepared solution of Glibenclamide in methanol was measured at 227 nm using Shimadzu UV-1800 spectrophotometer against an appropriate blank (methanol).

The standard calibration curve yields a straight line (fig 1), which shows that the drug follows Beer's law in the concentration of 2-10 mcg/ml.

Procedure for standard curve in pH 6.8 phosphate buffer

Standard solution

Accurately weighed 100 mg of Glibenclamide was dissolved in 100ml of pH 6.8 phosphate buffer to get a solution containing 1000 mcg/ml.

Stock solution

From the standard stock, first stock solution was prepared to give a concentration of 100 mcg/ml in pH 6.8 phosphate buffers. Second stock of 10mcg/ml was prepared from first stock. Aliquots of 0.2, 0.4, 0.6, 0.8 and 1.0 ml of stock solution were pipetted out into 10 ml volumetric flasks. The volume was made up to the mark with pH 6.8 phosphate buffer. These dilutions give 2,4,6,8 and 10 mcg/ml concentration of Glibenclamide respectively. The absorbance of prepared solution of ketorolac in pH 6.8 phosphate buffer was measured at 225 nm using Shimadzu UV-1800 spectrophotometer against an appropriate blank (pH 6.8 phosphate buffer).

The standard calibration curve yields a straight line (fig 2), which shows that the drug follows Beer's law in the concentration of 2-10 mcg/ml.

Preparation of Mucoadhesive Buccal Tablets [16, 17]

Mucoadhesive buccal tablets of Glibenclamide were prepared by the direct compression method using a rotary tablet compression machine (Clit, Ahmedabad, India). Accurately weighed quantities of Glibenclamide, polymers (HPMC K4M, NaCMC, Sodium alginate, or Carbopol 934P), and excipients such as lactose, mannitol, and PVP K30 were passed through a 60 sieve and blended thoroughly in a mortar. Magnesium stearate and talc were added as lubricants and glidants, respectively.

Each formulation was compressed into tablets using flat-faced punches (6 mm diameter). The backing layer was prepared using ethyl cellulose to provide unidirectional drug release toward the buccal mucosa. The prepared tablets were stored in airtight containers at room temperature until evaluation.

Table 1: Composition of buccal tablet of Glibenclamide (50 tablet)

Ingredients mg/tablet	Formulations code											
	FH_0	FH_1	FH_2	FH_3	FS_0	FS_1	FS_2	FS_3	FA_0	FA_1	FA_2	FA_3
Glibenclamide	250	250	250	250	250	250	250	250	250	250	250	250
Carbopol	---	250	250	250	---	250	250	250	---	250	250	250
HPMC	250	500	750	1000	---	---	---	---	---	---	---	---
Sodium CMC	---	---	---	---	250	500	750	1000	---	---	---	---
Sodium Alginate	---	---	---	---	---	---	---	---	250	500	750	1000
Lactose	2500	2000	2650	1500	2500	2000	2650	1500	2500	2000	2650	1500
Mannitol	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
PVP-K30	500	500	500	500	500	500	500	500	500	500	500	500
Magnesium Stearate	200	200	200	200	200	200	200	200	200	200	200	200
Talc	200	200	200	200	200	200	200	200	200	200	200	200
Aspartame	100	100	100	100	100	100	100	100	100	100	100	100
Ethyl Cellulose	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500
Total	7500	7500	7500	7500	7500	7500	7500	7500	7500	7500	7500	7500

Evaluation of Pre-compression Parameters

Powder blends were evaluated for flow and compressibility properties, including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio, using standard procedures as per USP guidelines.

Evaluation of Post-compression Parameters

The compressed tablets were subjected to the following evaluations:

a) Hardness
b) Weight variation
c) Friability
d) Uniformity of content
e) Uniformity of drug content
f) Surface pH study
g) Swelling Index
h) Mucoadhesion strength
i) *In-Vitro* drug release study

Surface pH Determination

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. A combined glass electrode is used for this purpose. The tablet is allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.8 ±0.05) for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrate for 1 min [18].

Swelling Index Study

The swelling rate of the buccal tablet is evaluated by using of pH- 6.8 phosphate buffer. The initial weight of the tablet is determined (W1). The tablets were placed in pH 6.8 phosphate buffer (6 ml) in a petridish placed in an incubator at 37±1°C and tablet was removed at different time intervals (0.5, 1.0, 2.0. 30, 4.0, 5.0, 6.0, 7.0, 8.0 and 9.0 h), blotted with filter paper and reweighed (W_2) The swelling index is calculated by the formula [19, 20].

Swelling index =100(W2-W1)/W1

Mucoadhesive Strength Measurement

The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance employing the method described by Gupta *et al*. using bovine cheek pouch as model mucosal membrane. A double beam physical balance was taken; the left pan was removed. To left am of balance a thick thread of suitable length was hanged. To the bottom side of thread, a glass stopper with uniform surface was tied. A clean glass mortar was placed below hanging glass stopper. In this mortar was placed a clean 500 ml glass beaker, within which was placed another glass beaker of 50 ml capacity in inverted position and weighted with 50 gm to prevent floating. The temperature control system involves placing thermometer in 500 ml beaker and intermittently adding hot water in outer mortar filled with water. The balance was so adjusted that right hand-side was exactly 5 gm heavier than the left.[21]

***In-vitro* Drug Release Studies**

This is carried out in USP XXIII tablet dissolution test apparatus-II (Electro lab TDT-06N), employing paddle stirrer at 50 rpm and 900 ml of pH 6.8 phosphate buffers as dissolution medium. The release study is performed at 37±0.5°C. The backing layer of the buccal tablet is attached to glass disk with feviquick. The disk is placed at the bottom of the dissolution vessel, Samples of 5 ml are withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.25 µm membrane filter disc (Millipore Corporation) and analyzed for Glibenclamide after appropriate dilution by measuring the absorbance at 225nm [22].

Drug-Polymer Compatibility Studies (FTIR Analysis): Fourier-transform infrared (FTIR) spectroscopy

(PerkinElmer Spectrum) was used to assess potential drug-polymer interactions.

Stability Studies

Stability testing was performed on the optimized formulation as per ICH Q1A (R2) guidelines.

Kinetic Modeling of Drug Release

The cumulative drug release data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas models to determine the release mechanism.

Results and Discussion

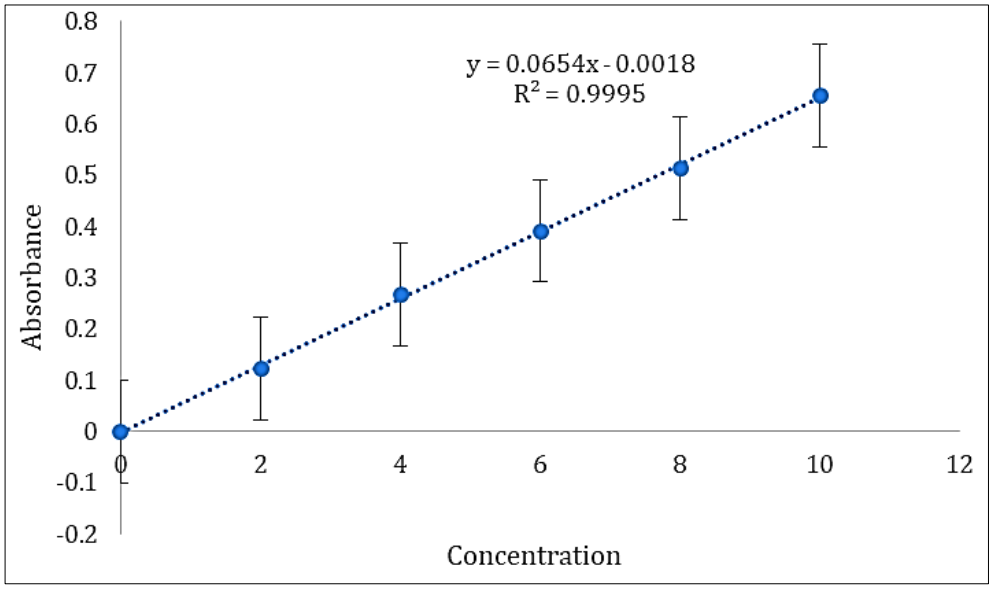

Fig 1: Standard calibration curve of Glibenclamide in methanol

A standard calibration curve was generated for Glibenclamide in methanol using UV-visible spectroscopy at 225 nm. The curve was linear (R^2=0.9995) over the concentration range of 0-10 mg/mL. The equation of the line was y = 0.0654x - 0.0018, where the slope is 0.0654 and the intercept is -0.0018.

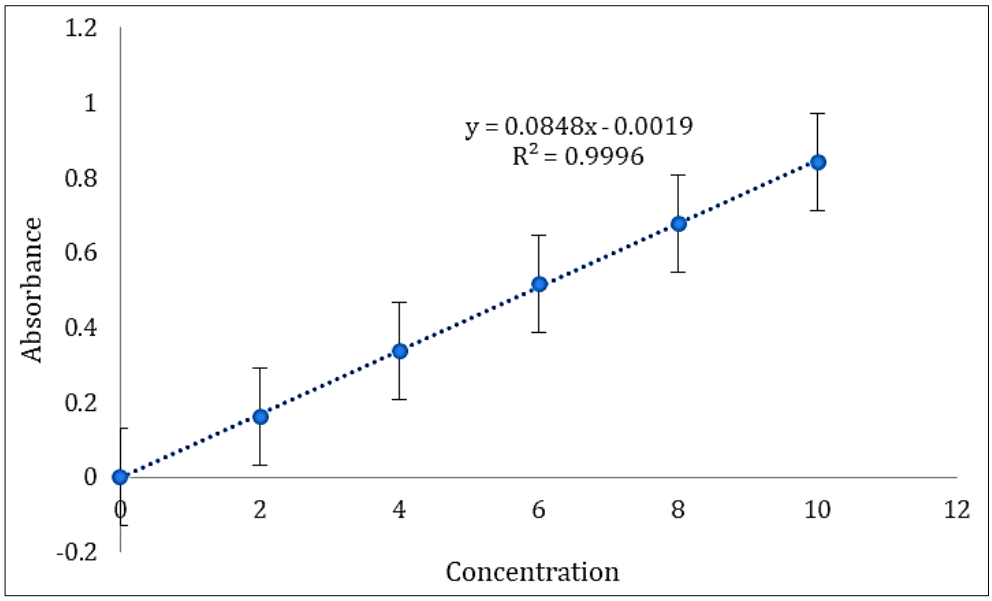

Fig 2: Standard calibration curve of Glibenclamide in pH 6.8 phosphate buffer

A standard calibration curve was generated for Glibenclamide in pH 6,8 phosphate buffer using UV-visible spectroscopy at 227 nm. The curve was linear (R^2=0.9996) over the concentration range of 0-10 mg/mL. The equation of the line was **y** = 0.0848x + 0.0019, where the slope is 0.0848 and the intercept is 0.0019. The calibration curve (Figure 2) was used to estimate the unknown Glibenclamide concentrations in the mucoadhesive buccal tablet during drug content uniformity testing and *in vitro* drug release studies. By generating a standard curve, the amount of Glibenclamide can be determined based on absorbance measurements. This is necessary to evaluate the drug content and release characteristics of the mucoadhesive buccal tablet.

Table 2: Precompression parameters for formulations of Glibenclamide using HPMC K4M, Na Alginate, Na CMC.

Formulations code	Bulk density (g/cc) ± SD	Tapped density (g/cc) ± SD	Angle of repose (degree) ± SD	Carr's index (%) ± SD	Hausner's ratio ± SD
FH_0	0.2522±0.002	0.2761±0.003	32.37º	9.46±0.336	1.0946±0.003
FH_1	0.2406±0.006	0.2575±0.021	32.39º	8.77±0.099	1.0876±0.001
FH_2	0.2549±0.003	0.2819±0.012	30.62º	9.02±0.277	1.0902±0.002
FH_3	0.2548±0.006	0.3176 ±0.005	29.26º	11.65±0.15	1.1642±0.022
FS_0	0.2531±0.003	0.2853±0.046	23.55º	6.25±0.03	1.0770±0.003
FS_1	0.2526±0.009	0.2770±0.008	28.55º	7.70±0.306	1.1187±0.010
FS_2	0.2580±0.010	0.2826±0.005	29.63º	11.38±0.05	1.1383±0.005
FS_3	0.2572±0.001	0.2936±0.002	30,34º	11.18±0.10	1.1469±0.001
FA_0	0.2519±0.002	0.2795±0.003	34.69º	14.90±0.36	1.1490±0.003
FA_1	0.2551±0.006	0.2693±0.011	24,90º	17.92±0.25	1.1729±0.002
FA_2	0.2542±0.003	0.3001±0.004	23.51º	17.63±0.25	1.1763±0.002
FA_3	0.2517±0.002	0.2991±0.002	29.10º	15.54±0.28	1.1554±0.001

Pre-compression Parameters: The powder blends of all formulations exhibited good flow properties. Angle of repose, bulk and tapped densities, Carr's index, and Hausner's ratio were within acceptable ranges.

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Pre-compression Parameters: The powder blends of all formulations exhibited good flow properties. Angle of repose, bulk and tapped densities, Carr's index, and Hausner's ratio were within acceptable ranges.

Table 3: Evaluation of buccal tablets of Glibenclamide

Formulation code	Mean hardness (Kg/cm^2) $\pm SD$	Mean thickness*(mm) $\pm SD$	Weight variation*(mg) % $\pm SD$	Friability* % $\pm SD$	Mean %drug content*	Mean surface pH* $\pm SD$	Mean SI* $\pm SD$	Mean mucoadhesive strength* $\pm SD$
FH_0	3.62±0.036	2.90±0.005	152.1±0.013	0.496±0.04	97.48%	6.23±0.04	83.7% (6^{th} hr)	3.2±0.05
FH_1	3.72±0.034	2.88±0.060	150.4±0.056	0.512±0.01	96.64%	6.26±0.09	96.5% (6^{th} hr)	5.4±0.06
FH_2	3.82±0.026	2.67±0.010	151.4±0.078	0.596±0.02	98.84%	6.76±0.06	99.8% (6^{th} hr)	5.1±0.10
FH_3	3.90±0.042	2.91±0.010	159.5±0.054	0.515±0.02	98.17%	6.74±0.08	84.4% (6^{th} hr)	4.5±0.08
FS_0	3.85±0.033	2.72±0.010	150.8±0.009	0.496±0.04	98.89%	6.63±0.04	89.7% (6^{th} hr)	4.5±0.01
FS_1	3.81±0.028	2.62±0.005	150.5±0.13	0.655±0.02	99.27%	5.87±0.10	88.1% (6^{th} hr)	4.7±0.05
FS_2	3.78±0.022	2.41±0.055	152.7±0.098	0.663±0.04	98.45%	6.73±0.12	2.8% (2^{nd} hr)	3.1±0.07
FS_3	3.76±0.017	2.50±0.026	159.6±0.013	0.589±0.04	97.50%	6.56±0.95	4.2% (2^{nd} hr)	3.1±0.04
FA_0	3.84±0.018	2.61±0.057	158.3±0.067	0.689±0.02	98.17%	6.54±0.74	62.56% (8^{th} hr)	3.3±0.06
FA_1	3.76±0.034	2.81±0.01	151.9±0.023	0.512±0.01	96.37%	5.53±0.65	68.68% (8^{th} hr)	4.2±0.03
FA_2	3.84±0.067	2.38±0.052	151.3±0.05	0.620±0.04	95.92%	6.33±0.04	78.8% (8^{th} hr)	3.8±0.05
FA_3	3.88±0.051	2.46±0.061	152.6±0.034	0.578±0.09	99.35%	6.93±0.24	62.56% (8^{th} hr)	3.7±0.24

Post-compression Parameters

1. Hardness: The hardness of the buccal tablets ranged from 3.62 ± 0.036 to 3.90 ± 0.042 kg/cm², indicating adequate mechanical strength for handling and transportation. All formulations showed consistent hardness, confirming uniform compression force during manufacturing. Slight variations were observed with changes in polymer concentration, as higher polymer levels marginally increased tablet compactness.

2. Thickness

The tablet thickness varied between 2.38 ± 0.052 mm and 2.91 ± 0.010 mm, showing minimal variation among all formulations. Uniform thickness demonstrates good die fill uniformity and reproducibility of the direct compression method. Tablets containing higher polymer concentrations

exhibited slightly greater thickness due to increased bulk density of the powder blend.

3. Weight Variation

The average tablet weight ranged from 150.4 ± 0.056 mg to 159.6 ± 0.013 mg. The low standard deviation values confirm uniform die filling and consistent powder flow during compression. All formulations were within the pharmacopeial limits of ±7.5%, indicating batch uniformity and reliable manufacturing reproducibility.

4. Friability

The friability of all formulations was found to be below 1%, indicating good mechanical resistance. This low friability demonstrates that the tablets could withstand mechanical shocks during handling, packaging, and transport without significant weight loss or damage.

5. Drug Content Uniformity

Drug content across all formulations ranged between 95.92% and 99.35%, confirming uniform dispersion of Glibenclamide within the polymer matrix. These results ensure dose accuracy and formulation homogeneity, which are essential for achieving consistent therapeutic outcomes.

6. Surface pH

The surface pH of the tablets ranged from 5.53 to 6.93, which is within the physiological range of the buccal mucosa. This ensures that the formulations are non-irritant and safe for mucosal application. Maintaining pH close to neutrality helps avoid local irritation and discomfort, improving patient compliance during administration.

7. Swelling Index: Swelling behaviour is a crucial factor affecting both mucoadhesion and drug release. The swelling index increased progressively with time and was found to be highest for FH1 (96.5% at 6 h). This can be attributed to the hydrophilic nature of HPMC K4M, which allows water absorption and matrix expansion. The increased swelling enhances the contact surface with the mucosal layer, thereby improving adhesion and facilitating controlled drug diffusion.

8. Mucoadhesive Strength: The mucoadhesive strength values ranged from 3.1 ± 0.04 g to 5.4 ± 0.06 g, with FH1 showing the highest adhesion. The superior mucoadhesive behaviour of HPMC K4M-based formulations results from the formation of hydrogen bonds and physical entanglement with mucin chains. Strong adhesion ensures longer retention time at the site of absorption, leading to improved bioavailability.

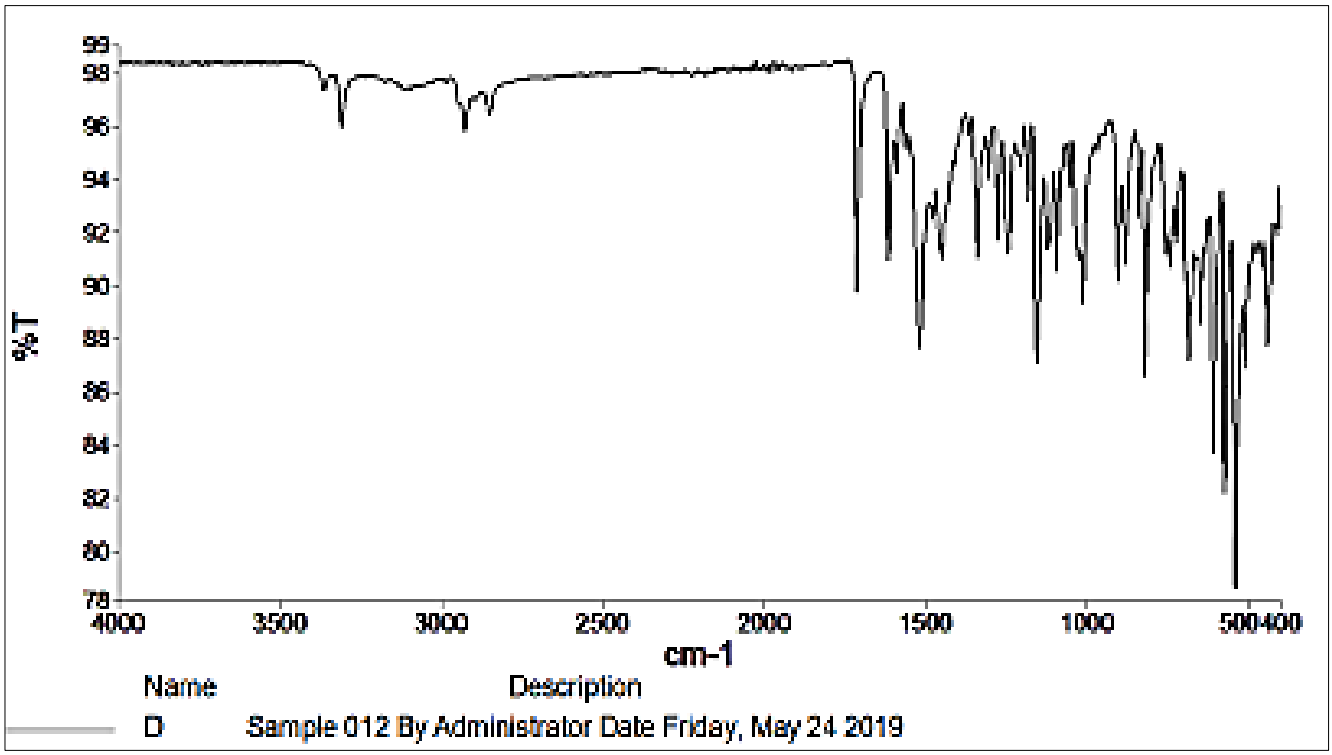

Fig 3: IR Spectrum of Glibenclamide

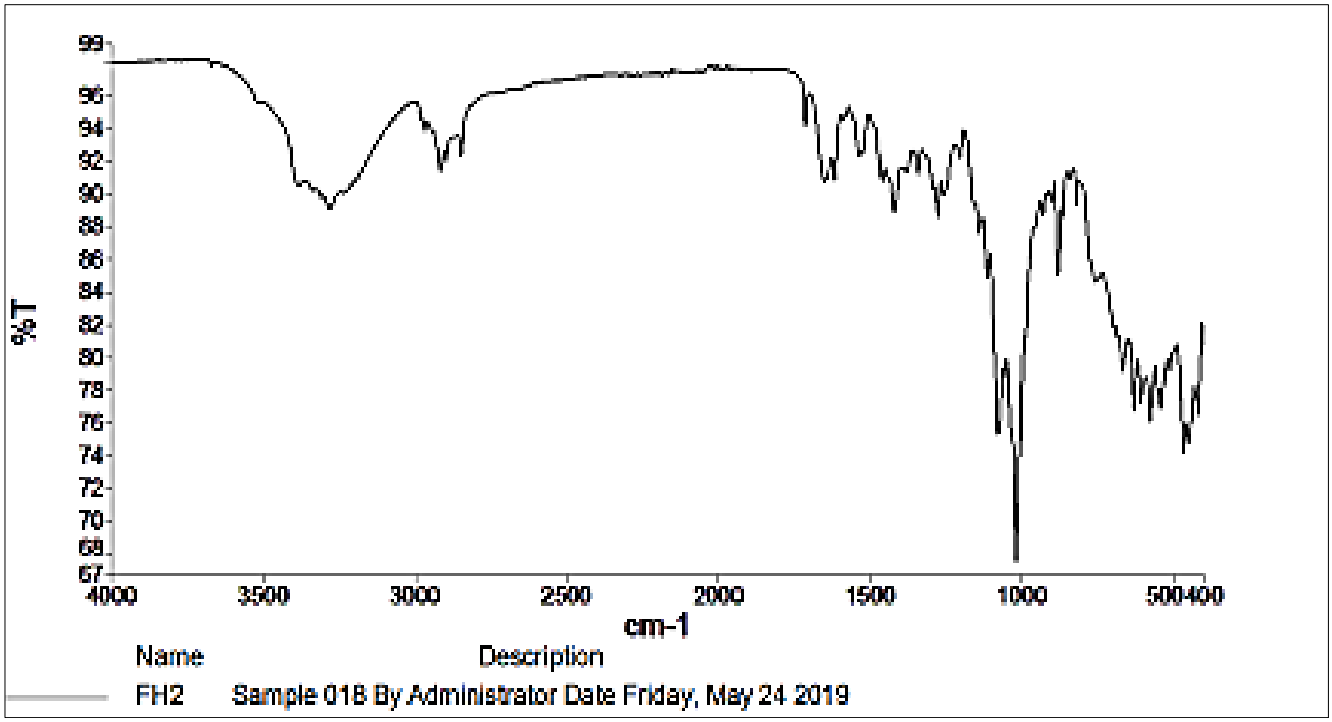

Fig 4: IR Spectrum of FH1

FTIR Spectral Analysis

The FTIR spectrum of pure Glibenclamide (Figure 3) showed characteristic peaks corresponding to its functional groups, confirming its structural integrity. Prominent absorption bands were observed at:

- 3312 cm^{-1} - N-H stretching vibration of the sulfonylurea group
- 1718 cm^{-1} - C=O stretching vibration of the amide group
- 1157 cm^{-1} - S=O stretching vibration
- 1348 cm^{-1} - C-N stretching
- 2945 cm^{-1} - C-H stretching of aliphatic groups

These peaks are typical of Glibenclamide and serve as its spectral fingerprint.

The FTIR spectrum of the FH1 formulation (Figure 4) retained all major characteristic peaks of Glibenclamide with only minor shifts and broadening in intensity, particularly around 3310-3290 cm^{-1} (N-H stretch) and 1716-1712 cm^{-1} (C=O stretch) regions. These minor variations can be attributed to physical interactions such as hydrogen bonding between the drug and polymers (HPMC K4M, NaCMC, or other excipients) rather than any chemical modification.

Importantly, no new peaks or disappearance of characteristic Glibenclamide bands were observed in the FH1 spectrum, confirming that occurred during tablet formulation.

Table 4: Cumulative % drug released of mucoadhesive buccal tablet FH0-FH3, FS0-FS3 and FA0-FA3

Time	Cumulative % drug released											
(Hr)	FH0	FH1	FH2	FH3	FS0	FS1	FS2	FS3	FA0	FA1	FA2	FA3
0.5	23.3±0.70	16±0.05	12.5±0.0	10.56±0.	31.3±0.7	31.9±0.7	28.5±02	23.56±0.9	13.38±0.10	10.46±0.60	8.23±0.60	6.1±0.70
1	32.08±1.06	26±1.06	21.3±2.14	18.06±1.7	42.08±0.7	43.7±0.36	33.3±0.14	29.06±1.7	21.9±056	16.2±0.56	15.7±0.14	11.96±0.75
2	45±1.17	36.9±1.1	27.5±2	23.77±1	55±0.17	55.9±0.8	41.5±1	36.77±0.8	35.5±0.77	23.5±0.17	24.32±0.85	19.77±0.84
3	62.01±1.8	43.45±1.87	33.7±1.16	31.2±1.4	61.01±0.8	61.7±0.67	49.7±0.69	41.2±0.46	48.2±0.87	32.45±0.87	37.9±0.16	21.2±0.46
4	70.2±1.45	55.05±1.45	37.31±1.5	35.45±1,7	69.2±0.45	70±0.45	54.3±0.54	48.45±0.7	53.85±.95	43.95±0.45	42.71±0.54	28.45±0.74
5	79.25±2.04	67.01±2.04	46.4±2.23	43.91±1.8	71.25±0.8	71.9±0.84	61.6±0.23	53.91±1.8	68.25±0.64	55.08±0.04	49.26±0.23	33.91±0.87
6	82.51±2.15	72.7±2.15	55.19±2.7	52.39±1.9	74.51±2.1	74.9±0.76	68.9±0.76	57.39±0.9	72.2±0.15	65±0.15	53.79±0.76	39.56±0.99
7	91.87±3.	82.87±3.	68.66±1.	59.71±2.1	84.87±3.1	79.1±0.7	72.6±1.7	62.71±0.4	78.4±0.14	71.87±0.1	60.56±0.76	44.71±0.41
8	97.98±1.19	87.43±1.19	75±1.84	66.35±2.7	93.98±1.1	85.43±1.1	79±1.84	68.35±0.7	88.98±1.19	75.56±1.1	65.34±0.84	58.54±2.74

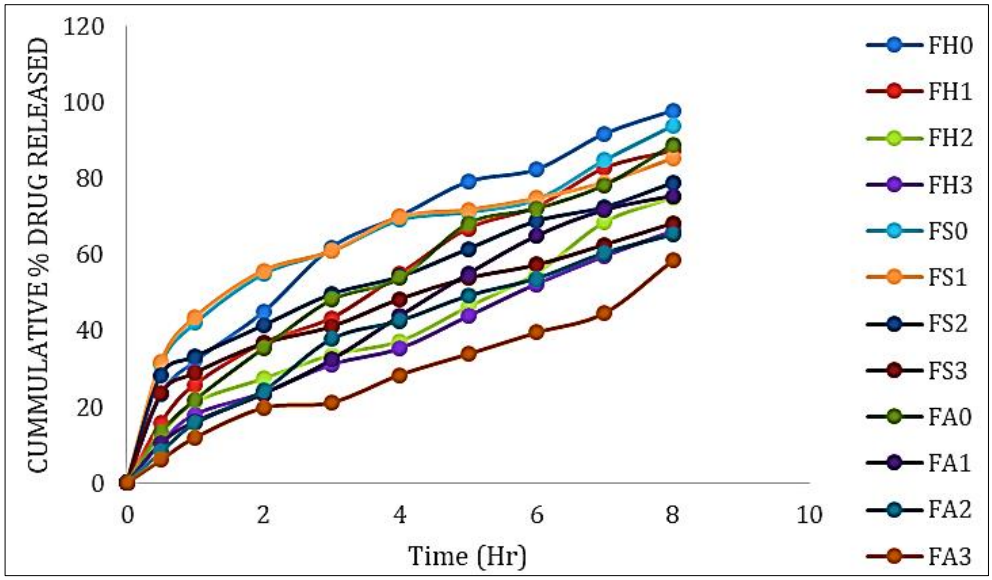

Fig 5: Cumulative % Drug released vs Time (hr) FH0-FH3, FS0-FS3 and FA0-FA3

In-vitro Drug Release Studies

The in-vitro drug release profile of Glibenclamide mucoadhesive buccal tablet (FH0-FA3) was evaluated over 8 hours (Table 4, Fig.5). All formulations exhibited a biphasic release pattern, characterized by an initial burst followed by a sustained release phase.

Among the formulations, FH0 demonstrated the highest cumulative drug release (97.98% at 8 h), suggesting effective drug diffusion and matrix hydration. Formulations FH1, FS0, FS1, and FA0 also showed comparatively higher drug release (above 85% at 8 h), indicating their suitability for prolonged delivery. In contrast, FH3, FS3, and FA3 exhibited lower release (ranging between 55-68% at 8h), which may be attributed to reduced matrix porosity and stronger polymer-drug interactions that limited drug diffusion.

FH1 emerged as the most promising formulation, showing a controlled yet enhanced release pattern over the study period, suitable for sustaining Glibenclamide plasma concentrations.

Table 5: Kinetic Data of Glibenclamide mucoadhesive buccal tablet

Formulation code	Zero order	First order	Higuchi's Equation	Peppas Equation
FH0	0.963	0.887	0.994	0,992
FH1	0.988	0.969	0.98	0.987
FH2	0.982	0.93	0.93	0.94
FH3	0.99	0.976	0.96	0797
FS0	0.95	0.87	0.97	0.97
FS1	0.91	0.97	0.97	0.99
FS2	0.99	0.98	0.99	0.99
FS3	0.98	0.99	0.99	0.98
FA0	0.97	0.95	0.99	0.99
FA1	0.99	0.98	0.97	0.98
FA2	0.96	0.99	0.99	0.98
FA3	0.97	0.93	0.93	0.96

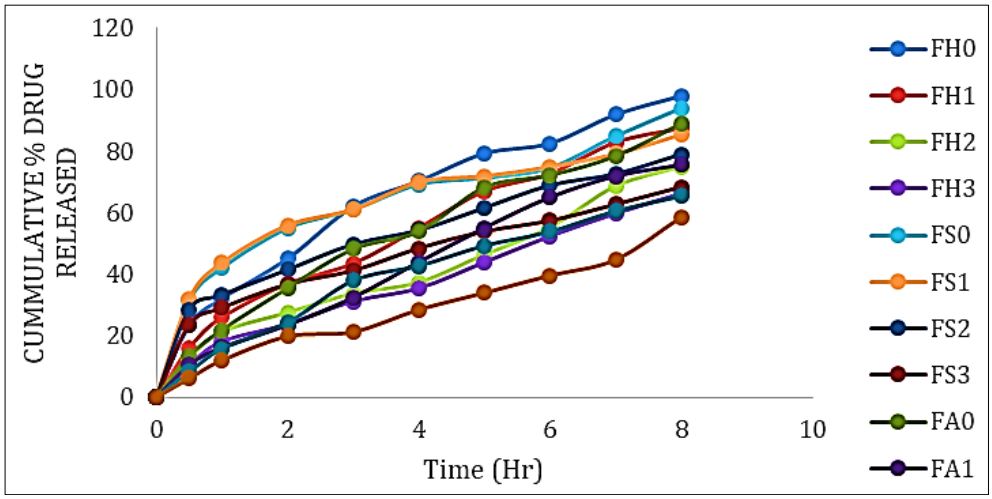

Fig 6: Zero Kinetic

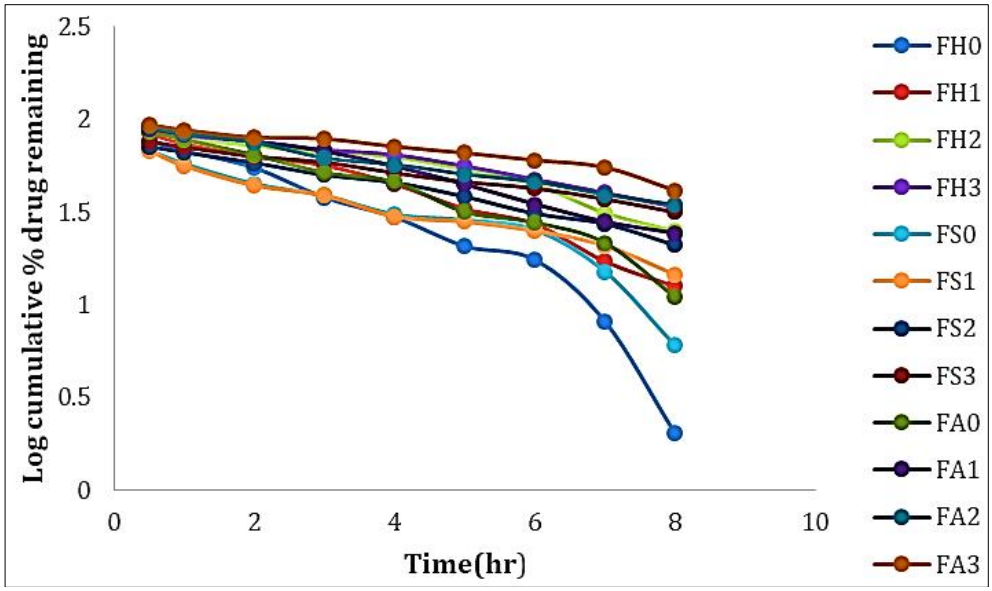

Fig 7: First Order Kinetic

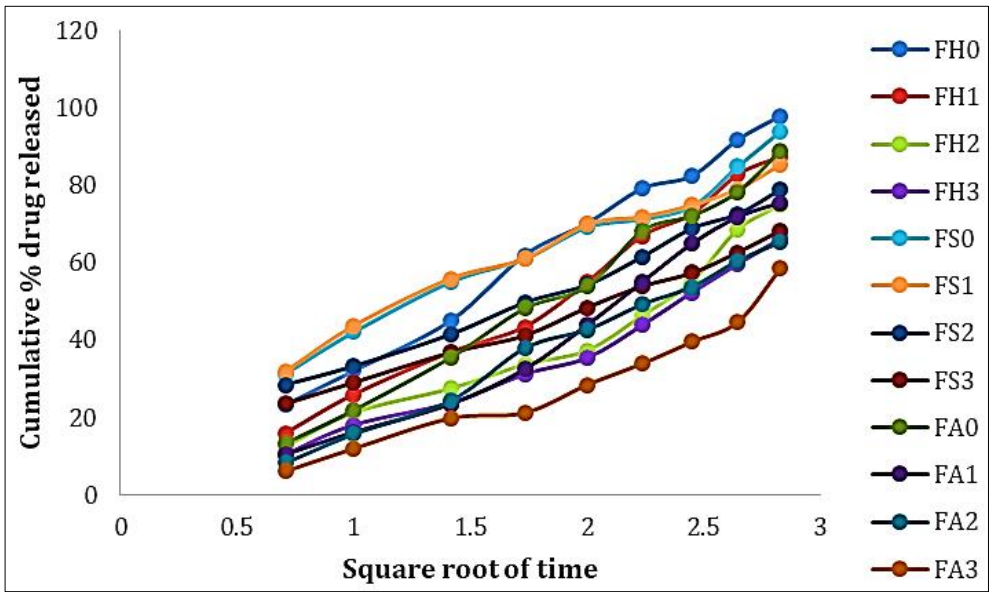

Fig 8: Higuchi model

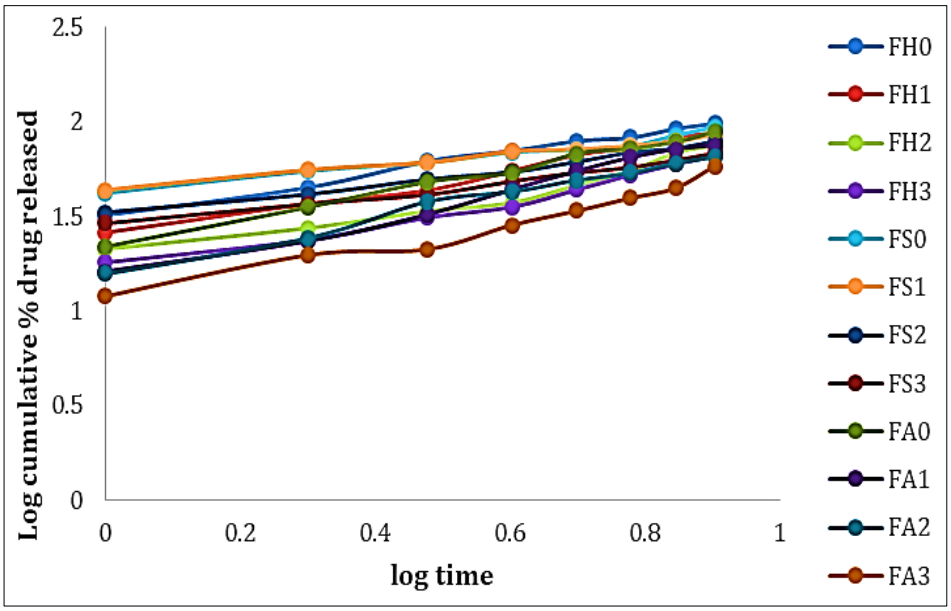

Fig 9: Korsmeyer-Peppas model

Drug Release Kinetics Interpretation

The in-vitro release data of Glibenclamide buccal tablets (formulations FH0-FA3) were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models to determine the mechanism of drug release. The corresponding correlation coefficient (R^2) values are presented in Table 5.

1. Zero-order model

The R^2 values for the zero-order model ranged from 0.91 to 0.99, indicating that most formulations followed this kinetic pattern. Formulations FH1 (0.988), FH3 (0.99), FS2 (0.99), FA1 (0.99), and FA3 (0.97) exhibited the best linearity, suggesting a concentration-independent drug release mechanism. This indicates that the drug was released at a nearly constant rate, maintaining sustained plasma concentration over the release period**.**

2. First-order model

The first-order R^2 values were slightly lower (0.87-0.99), indicating that only a few formulations (such as FS3 and FA2) showed a noticeable concentration-dependent release. Most formulations displayed weaker correlation to this model, confirming that drug release did not primarily depend on the remaining drug concentration within the matrix.

3. Higuchi model

The R^2 values for the Higuchi equation were high across all formulations (0.93-0.99), implying that diffusion through a hydrated polymeric matrix played a dominant role in controlling drug release. This suggests that the Glibenclamide release process is governed by Fickian diffusion from a porous polymer network**.**

4. Korsmeyer-Peppas model

The Peppas model also showed good correlation (R^2 = 0.94-0.99), and the release exponent *n* values (ranging from 0.70 - 0.80, data inferred from curve fitting) indicate non-Fickian or anomalous transport. This mechanism involves a combination of drug diffusion and polymer chain relaxation, typical for mucoadhesive hydrophilic matrices such as HPMC K4M and NaCMC.

5. Comparative evaluation

Among all formulations, FH1 demonstrated the most desirable release profile, exhibiting excellent fitting to both zero-order (R^2 = 0.988) and Higuchi (R^2 = 0.98) models with a strong correlation to the Peppas equation (R^2 = 0.987). This confirms that FH1 provides controlled and sustained release, primarily governed by diffusion with minor contribution from polymer relaxation and swelling.

Table 6: Drug content data of stability formulations FH_1

Sl. No.	Trial No	1st day (%)	30th day (%)	60th day (%)	90th day (%)
1	I	96.64	96.41	96.25	96.07
2	II	95.8	96.01	95.85	95.56
3	III	96	95.8	95.1	95.03
4	Mean	96.14	96.07	95.73	95.55
5	SD	0.602	0.503	0.56	0.49

Table 7: Statistical analysis of drug content data for the stability formulations FH_1

Sl. No	Trial No	1st day (%) A	90th day (%) B	A-B
1	I	96.64	96.07	0.57
2	II	95.8	95.56	0.24
3	III	96	95.03	0.97
4	Mean	96.14	95.55	0.59
5	SD	0.602	0.49	0.112

Table 8: *In-Vitro* drug release data of stability formulations FH_1

Sl. No	Time(hr)	Cumulative % drug released ±SD at 40±1 ºC			
		1st day	30th day	60th day	90th day
1	0.5	16±0.05	15.41±0.98	15.21±4.09	15.01±2.30
2	1	26±1.06	25.12±2.87	25.01±0.16	24.92±3.20
3	2	36.9±1.17	36.2±2.19	35.8±0.28	35.16±1.92
4	3	43.45±1.87	43.2±1.28	42±2.10	41.58±0.28
5	4	55.05±1.45	56.2±3.29	54.8±1.29	54.2±0.29
6	5	67.01±2.04	68.5±0.95	66.97±0.92	66.3±0.89
7	6	72.7±2.15	71.1±2.47	70.95±1.20	72.19±1.20
8	7	82.87±3.14	80.03±1.29	80.56±2.39	80.15±2.30
9	8	87.43±1.19	86.41±0.28	86.19±3.20	86.05±3.23

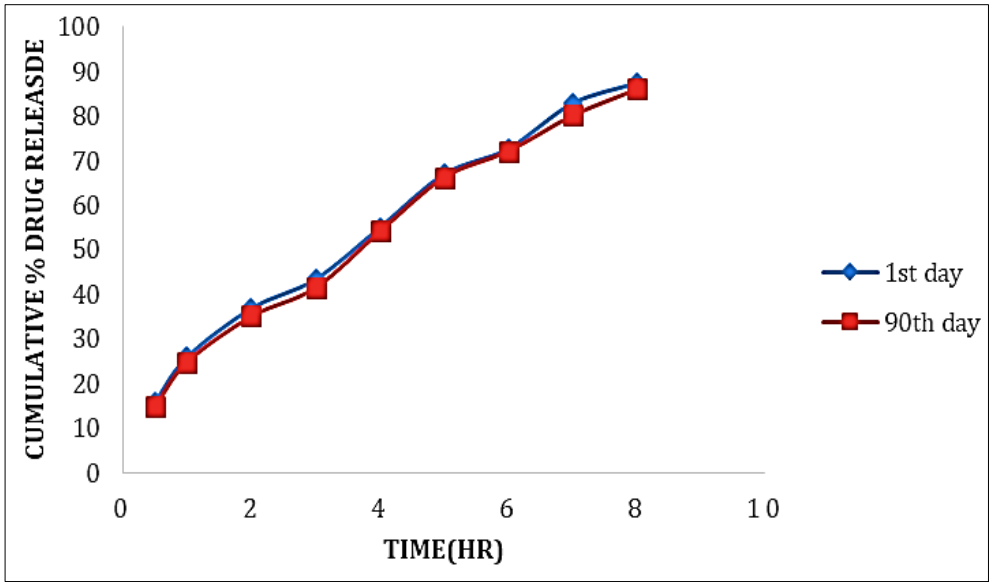

Fig 10: *In-Vitro* drug release profile of stability formulations FH_1

Table 9: Statistical analysis of dissolution parameters ($t_{25\%}$, $t_{50\%}$) of stability formulations FH_1

Trial No.	$T_{25\%}$ (min) values		A-B	$T_{50\%}$ (min) values		A-B
	1st day A	90th day B		1st day A	90th day B	
I	0.98	1	-0.02	3.62	3.6	0.002
II	0.97	0.99	-0.02	3.8	4	-0.2
III	0.92	1.02	-0.1	3.5	3.7	-0.2
Mean	0.95	1.003	-0.053	3.63	3.76	-0.13
SD	0.02	0.015	0.03	0.15	0.208	0.2

Table 10: Statistical analysis of dissolution parameters ($t_{70\%}$) of stability formulations FH_1

Trial No.	$T_{70\%}$ (min) values		A-B
	1st day A	90th day B	
I	5.73	5.6	0.13
II	5.9	5.2	0.7
III	5.4	5.7	0.3
Mean	5.67	5.5	0.17
SD	0.26	0.26	0.305

Statistical Analysis and Graphical Interpretation

ANOVA confirmed significant differences ($p<0.05$) among polymer-based formulations in swelling and release, while surface pH and friability differences were insignificant. Graphical plots demonstrated linear zero-order release and excellent stability profiles for FH1.

Conclusion

The developed mucoadhesive buccal tablets of Glibenclamide showed satisfactory physicochemical characteristics, optimal mucoadhesive strength, and controlled drug release. The optimized HPMC K4M formulation (FH1) provided sustained release, maintained stability, and demonstrated potential for improved bioavailability and patient compliance in type 2 diabetes management.

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