European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Formulation and Evaluation of Glipizide-Loaded Mucoadhesive Microspheres Using Gum Karaya and HPMC K15M as a Novel Polymer Blend: A Sustained-Release Approach for Type 2 Diabetes Mellitus

Article History:

Name of Author:

V. Phani Deepthi[1], C.H. Srinivasa Kumari[2], K. Veena[3], Sreenivasa Krishna Oruganti[4*], K. Sumathi[5], K. Mahesh[6]

Affiliation: *[1,2] Assistant Professor, Department of Pharmaceutics, JNTUA-OTPRI, Jawaharlal Nehru Technological University Anantapur (JNTUA), Ananthapuramu – 515001, Andhra Pradesh, India*
[3] Assistant Professor, Department of Pharmacy Practice, JNTUA-OTPRI, Jawaharlal Nehru Technological University Anantapur (JNTUA), Ananthapuramu – 515001, Andhra Pradesh, India
[4] Assistant Professor, Department of Pharmacology, JNTUA-OTPRI, Jawaharlal Nehru Technological University Anantapur (JNTUA), Ananthapuramu – 515001, Andhra Pradesh, India*
[5] Research Scholar, JNTUA-OTPRI, Jawaharlal Nehru Technological University Anantapur (JNTUA), Ananthapuramu 515001, Andhra Pradesh, India
[6] Research Scholar, Balaji College of Pharmacy, Ananthapuramu515001, Andhra Pradesh, India

Corresponding Author:
Sreenivasa Krishna Oruganti

Abstract: ***Background:*** Glipizide, a second-generation sulfonylurea used in the management of Type 2 Diabetes Mellitus (T2DM), is characterized by a short biological half-life of 2–5 hours and requires multiple daily administrations, leading to suboptimal patient compliance. The present study describes, to the best of the authors' knowledge, the first investigation of Glipizide-loaded mucoadhesive microspheres employing a novel binary polymer blend of Gum Karaya (GK) and Hydroxypropyl Methylcellulose K15M (HPMC K15M) prepared by ionotropic gelation using calcium chloride as crosslinker. ***Methods:*** Eight formulations (F1–F8) were developed by systematically varying the ratio of Gum Karaya to HPMC K15M while maintaining a constant Glipizide dose of 10 mg. Microspheres were characterized for particle size, surface morphology, zeta potential, percentage yield, drug entrapment efficiency (EE), swelling index, mucoadhesion strength, in vitro drug release, FTIR, DSC, and release kinetics modeling. ***Results:*** Microspheres exhibited spherical morphology with particle sizes ranging from 185.32 ± 0.42 µm to 278.64 ± 0.58 µm. The optimized formulation F5 (GK:HPMC K15M = 1:1 w/w) demonstrated a percentage yield of 96.82 ± 1.87%, entrapment efficiency of 94.76 ± 1.23%, zeta potential of −28.7 ± 1.6 mV, swelling index of 96.84 ± 1.54%, mucoadhesion of 94.2 ± 1.8%, and cumulative drug release of 96.42 ± 2.11% over 12 hours. FTIR and DSC analyses confirmed drug–excipient compatibility. Drug release followed the Higuchi diffusion model with Non-Fickian anomalous transport (n = 0.589). The formulation retained its physicochemical properties after 3 months of accelerated stability testing at 40 ± 2°C / 75 ± 5% RH. ***Conclusion:*** The GK–HPMC K15M binary polymer system represents a novel, biocompatible, and cost-effective platform for sustained mucoadhesive delivery of Glipizide, with significant potential to reduce dosing frequency and improve glycaemic management in T2DM.

Keywords: Glipizide; Mucoadhesive Microspheres; Gum Karaya; HPMC K15M; Ionotropic Gelation; Sustained Release; Type 2 Diabetes Mellitus; Non-Fickian Release.

Received: 12-05-2025
Revised: 05-06-2025
Accepted: 20-06-2025
Published: 04-07-2025

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by insulin secretory deficiency and peripheral insulin resistance. According to the IDF Diabetes Atlas (2021), approximately 537 million adults worldwide are currently living with diabetes, with projections exceeding 780 million by 2045 [1]. In India, the burden is particularly acute, with an estimated 74 million people affected, placing it among the countries with the highest absolute number of diabetic patients [1,2]. Effective pharmacological management of T2DM necessitates drug delivery strategies that maintain consistent therapeutic plasma drug concentrations and minimize inter-dose fluctuations.

Glipizide ($C_{21}H_{27}N_5O_4S$; MW = 445.54 g/mol) is a second-generation sulfonylurea oral hypoglycaemic agent classified as a BCS Class II drug (low solubility, high permeability). It acts by stimulating insulin secretion from pancreatic β-cells through selective closure of ATP-sensitive potassium channels (ABCC8), leading to membrane depolarization, calcium influx, and exocytosis of insulin granules [3]. Despite its well-established efficacy, Glipizide presents clinically significant pharmacokinetic challenges: a short biological half-life of 2–5 hours, oral bioavailability of approximately 80% (subject to food effect and absorption site dependency), and requirement for administration 30 minutes before meals, 1–3 times daily [4]. This frequent dosing schedule compromises patient adherence, particularly in the elderly T2DM population, and may contribute to erratic glycaemic control with associated risk of hypoglycaemic episodes [5].

Mucoadhesive drug delivery systems, particularly microspheres, have emerged as a clinically relevant strategy to address these pharmacokinetic limitations. By establishing intimate, prolonged contact with gastrointestinal mucosal surfaces, mucoadhesive microspheres extend drug residence time, enhance bioavailability, and enable controlled, sustained drug release, thereby reducing dosing frequency and improving therapeutic compliance [6,7]. Ionotropic gelation is a particularly advantageous fabrication technique for mucoadhesive microspheres, offering mild aqueous preparation conditions, avoidance of organic solvents, scalability, and preservation of drug integrity — attributes well-suited to BCS Class II drugs such as Glipizide [8].

Among natural polysaccharides explored as mucoadhesive polymers, Gum Karaya (GK) — a plant exudate obtained from Sterculia urens — has attracted considerable interest due to its anionic, partially acetylated galacturonic acid backbone that confers strong gel-forming capacity, high water-swelling ability, and mucoadhesive properties through ionic interactions with mucosal glycoproteins [9,10]. Hydroxypropyl Methylcellulose K15M (HPMC K15M), a semi-synthetic cellulose derivative, provides a well-characterized, hydrophilic sustained-release matrix with extensive hydrogen-bonding capacity via its hydroxypropyl groups, and is widely used in controlled-release pharmaceutical formulations [11,12]. While both polymers have individually been investigated in drug delivery systems, their combination as a binary blend in mucoadhesive microspheres for Glipizide delivery has not been previously reported, to the best of the authors' knowledge.

The scientific rationale for the GK–HPMC K15M combination is grounded in the expectation of synergistic mucoadhesion: GK provides ionic mucoadhesive interactions, while HPMC K15M contributes complementary hydrogen-bonding interactions, together creating a denser interpenetrating polymer network (IPN) with superior mucoadhesive and sustained-release properties compared to either polymer alone. The present study therefore aims to: (i) formulate Glipizide-loaded GK–HPMC K15M mucoadhesive microspheres by ionotropic gelation; (ii) systematically optimize the GK:HPMC K15M ratio; (iii) characterize the formulations for physicochemical and biopharmaceutical properties; and (iv) evaluate release kinetics and accelerated stability to establish proof-of-concept for a once-daily Glipizide dosage form.

MATERIALS AND METHODS

2.1 Materials

Glipizide (gift sample, BP grade) was obtained from Sun Pharmaceutical Industries Ltd., Mumbai, India. Gum Karaya (pharmaceutical grade) was procured from Himedia Laboratories Pvt. Ltd., Mumbai. HPMC K15M (pharmaceutical grade, Methocel K15M Premium) was supplied by Colorcon Asia Pvt. Ltd., Goa. Calcium chloride (anhydrous, AR grade), hydrochloric acid (AR grade, 35–37%), potassium dihydrogen orthophosphate (AR grade), disodium hydrogen phosphate (AR grade), sodium hydroxide (AR grade), Tween 80, and methanol (HPLC grade) were obtained from SDFCL Fine-Chem Ltd., Mumbai. All materials were used as received without further purification. All aqueous solutions were prepared using freshly distilled water.

Chemical / Reagent	Grade	Source
Glipizide	BP grade (gift sample)	Sun Pharmaceutical Industries Ltd., Mumbai
Gum Karaya	Pharmaceutical grade	Himedia Laboratories Pvt. Ltd., Mumbai
HPMC K15M (Methocel K15M)	Pharmaceutical grade	Colorcon Asia Pvt. Ltd., Goa
Calcium Chloride (anhydrous)	AR grade	SDFCL Fine-Chem Ltd., Mumbai
Hydrochloric Acid (35–37%)	AR grade	SDFCL Fine-Chem Ltd., Mumbai
Potassium dihydrogen orthophosphate	AR grade	SDFCL Fine-Chem Ltd., Mumbai
Disodium hydrogen phosphate	AR grade	SDFCL Fine-Chem Ltd., Mumbai
Methanol	HPLC grade	SDFCL Fine-Chem Ltd., Mumbai
Tween 80	AR grade	SDFCL Fine-Chem Ltd., Mumbai

Table 1: Chemicals and reagents used in the study

2.2 Equipment

Equipment	Model / Make	Manufacturer
UV-Visible Spectrophotometer	Systronics 117	Systronics Ltd., India
FTIR Spectrophotometer (ATR mode)	Bruker Alpha	Bruker Optik GmbH, Germany
Differential Scanning Calorimeter	DSC-60	Shimadzu Corporation, Japan
Digital Analytical Balance	AX200	Shimadzu Corporation, Japan
USP Dissolution Apparatus Type II	DS 8000	Lab India Instruments, India

Equipment	Model / Make	Manufacturer
Optical Microscope (calibrated)	MLX-B	Magnus Instruments, India
Tapped Density Tester	ET-1020	Electrolab India Pvt. Ltd., India
pH Meter	pH 700	Eutech Instruments, Singapore
Magnetic Stirrer with Hot Plate	5MLH	Remi Elektrotechnik Ltd., India
Hot Air Oven	—	Shital Scientific Industries, India
Zeta Sizer (Zeta Potential)	Nano ZS	Malvern Panalytical, UK

Table 2: Equipment used in the study

2.3 Drug Profile: Glipizide

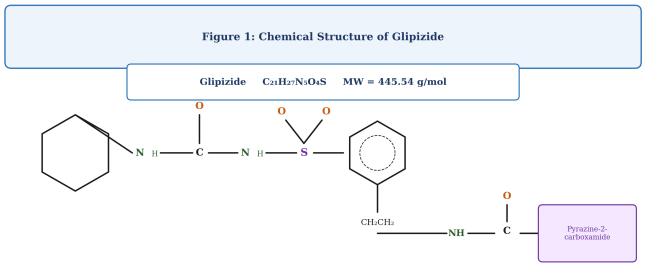

Figure 1: Chemical structure of Glipizide ($C_{21}H_{27}N_5O_4S$; MW = 445.54 g/mol)

Property	Description / Value
IUPAC Name	1-cyclohexyl-3-[[4-[2-(5-methylpyrazine-2-carboxamido)ethyl]phenyl]sulfonyl]urea
Molecular Formula	$C_{21}H_{27}N_5O_4S$
Molecular Weight	445.54 g/mol
CAS Number	29094-61-9
BCS Classification	Class II (low solubility, high permeability)
Physical Appearance	White to off-white crystalline powder
Melting Point	205–209°C (B.P./USP)

Property	Description / Value
Solubility	Practically insoluble in water; freely soluble in methanol, ethanol, DMSO
Biological Half-life	2–5 hours
Oral Bioavailability	~80%
Mechanism of Action	Stimulates insulin secretion by closing ATP-sensitive K^+ channels (ABCC8) in pancreatic β-cells
Dose	2.5–40 mg/day in divided doses (before meals)
Therapeutic Category	Oral Hypoglycaemic – Second-generation Sulfonylurea
Protein Binding	>99% (albumin)
Route of Elimination	Hepatic metabolism (CYP2C9); renal excretion of metabolites (~68%)

Table 3: Physicochemical and pharmacological profile of Glipizide

2.4 Preformulation Studies

2.4.1 Determination of λmax and Calibration Curve

A primary stock solution of Glipizide (1000 µg/mL) was prepared by dissolving 100 mg of the drug in HPLC-grade methanol in a 100 mL volumetric flask. Working standard solutions in the concentration range of 2–20 µg/mL were prepared by appropriate dilution with phosphate buffer saline (PBS, pH 6.8). The UV absorption spectrum was recorded between 200 and 400 nm using a double-beam UV-visible spectrophotometer (Systronics 117) against the respective blank solvent to determine the wavelength of maximum absorbance (λmax). Calibration curves were constructed in both 0.1 N HCl (pH 1.2) and PBS (pH 6.8), and linearity was confirmed by the coefficient of determination (R^2). All measurements were performed in triplicate.

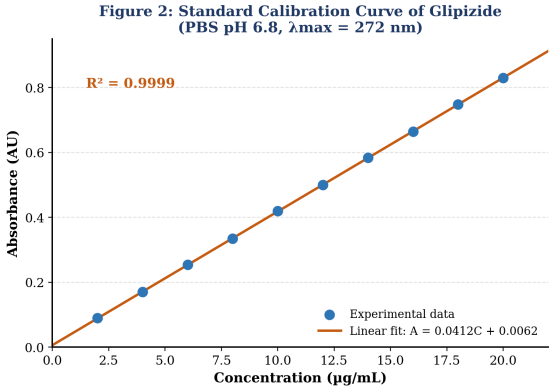

Figure 2: Standard calibration curve of Glipizide in PBS pH 6.8 at λmax = 272 nm (n=3, mean ± SD; R^2 = 0.9999; y = 0.0412x + 0.0062)

2.4.2 Solubility Studies

The saturation solubility of Glipizide was determined at 25 ± 2°C using the equilibrium method. An excess amount of drug (~50 mg) was added to individual screw-capped glass test tubes containing 10 mL of each solvent: distilled water, 0.1 N HCl (pH 1.2), PBS pH 6.8, methanol, and ethanol. Test tubes were sealed and agitated on an orbital shaker at 200 rpm for 24 hours. The resulting suspensions were centrifuged at 3000 rpm for 10 minutes, the supernatant filtered through 0.45 µm nylon membrane syringe filters, suitably diluted, and analysed spectrophotometrically at λmax. All experiments were conducted in triplicate.

Solvent	Solubility (mg/mL, mean ± SD)	Inference (B.P. Standard)
Distilled Water	0.083 ± 0.004	Practically Insoluble (< 0.1 mg/mL)
0.1 N HCl (pH 1.2)	0.071 ± 0.003	Practically Insoluble
PBS pH 6.8	0.192 ± 0.006	Slightly Soluble (0.1–1 mg/mL)
Methanol (HPLC grade)	8.42 ± 0.14	Freely Soluble (> 1 mg/mL)
Ethanol (96%)	5.76 ± 0.11	Freely Soluble

Table 4: Solubility of Glipizide in various solvents at 25 ± 2°C (n=3, mean ± SD)

Glipizide exhibited practically insoluble behaviour in aqueous media, consistent with its BCS Class II classification. The markedly low solubility in acidic medium (pH 1.2) and the relatively higher — yet still limited — solubility at intestinal pH (6.8) confirm the formulation challenge and underscore the rationale for mucoadhesive microsphere development to enhance oral bioavailability through prolonged mucosal contact.

2.4.3 Melting Point Determination

The melting point of Glipizide was determined using the open capillary tube method in a Thiele's tube filled with liquid paraffin. A finely powdered sample was packed into three sealed capillary tubes and heated at a rate of approximately 1°C/minute near the expected melting point. The temperature at which the sample began to melt (onset) and completely melted (clear point) was recorded for each tube. The average of three determinations was reported and compared with the pharmacopoeial standard (B.P./USP: 205–209°C).

2.4.4 FTIR Spectroscopic Analysis

ATR-FTIR spectra of pure Glipizide, Gum Karaya, HPMC K15M, and the physical mixture of all three components (at the ratio corresponding to F5) were independently recorded using a Bruker Alpha ATR-FTIR spectrophotometer at ambient temperature (25.0 ± 0.5°C). Each spectrum was acquired by scanning the sample over the wavenumber range of 4000–400 cm^{-1} at 4 cm^{-1} resolution, accumulating 32 scans per spectrum. The spectra were analyzed for appearance, disappearance, or significant shifts (> 10 cm^{-1}) of characteristic functional group absorption bands as indicators of drug–excipient chemical interaction.

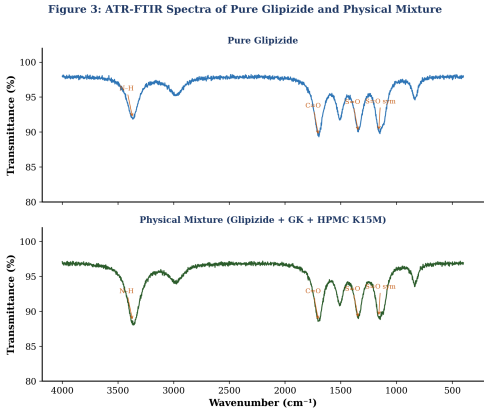

Figure 3: ATR-FTIR spectra of (A) pure Glipizide and (B) physical mixture of Glipizide + Gum Karaya + HPMC K15M. Characteristic peaks of Glipizide are retained in the physical mixture without significant shifts, confirming physicochemical compatibility.

Functional Group	Expected Range (cm^{-1})	Pure Glipizide (cm^{-1})	Physical Mixture (cm^{-1})	Inference
N–H stretch (2° amine)	3300–3500	3368	3371	Compatible (< 5 cm^{-1} shift)
C=O stretch (sulfonyl urea)	1680–1720	1700	1699	Compatible
S=O asymmetric stretch	1320–1360	1342	1340	Compatible
S=O symmetric stretch	1140–1170	1160	1162	Compatible
C–N stretch	1080–1160	1112	1114	Compatible
Aromatic C=C stretch	1480–1600	1509	1507	Compatible
O–H broad (GK, HPMC)	3200–3600	Absent	3412 (broad)	Expected polymer peak
C–O–C glycosidic (GK, HPMC)	1000–1100	Absent	1045	Expected polymer peak

Table 5: Interpretation of ATR-FTIR spectra of Glipizide and physical mixture

The characteristic N–H, C=O, and S=O absorption bands of Glipizide were present in the physical mixture spectrum with negligible wavenumber shifts (< 5 cm^{-1}), confirming the absence of significant chemical interaction between Glipizide and the selected excipients. The additional broad O–H stretching band (3412 cm^{-1}) and C–O–C glycosidic linkage band (1045 cm^{-1}) in the mixture spectrum are attributable to the polysaccharide backbones of GK and HPMC K15M and do not represent new bond formation. These findings validate the physicochemical compatibility of the GK–HPMC K15M binary system with Glipizide.

2.4.5 Differential Scanning Calorimetry (DSC)

DSC analysis was performed using a Shimadzu DSC-60 differential scanning calorimeter calibrated with indium standard (melting point 156.6°C). Precisely weighed samples (3–5 mg) of pure Glipizide and the physical mixture were placed in crimped aluminium pans with an empty aluminium pan used as reference. Samples were heated from 25°C to 300°C at a programmed heating rate of 10°C/min under a dry nitrogen purge at a flow rate of 50 mL/min. Thermograms were analyzed for characteristic endothermic/exothermic events, peak temperatures, onset temperatures, and enthalpies of fusion (ΔH).

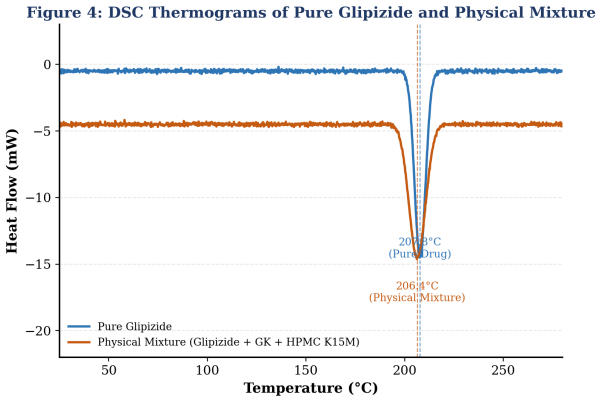

Figure 4: DSC thermograms of pure Glipizide (peak: 207.8°C; ΔH = −98.64 J/g) and physical mixture (peak: 206.4°C). The retention of the drug's characteristic melting endotherm with only minor broadening confirms thermal compatibility and rules out solid-state interaction or eutectic formation.

2.5 Excipient Profiles

2.5.1 Gum Karaya (GK)

Gum Karaya is a dried exudate obtained from the stems and branches of Sterculia urens Roxb. (family Malvaceae). It is an anionic, high-molecular-weight (9.5×10^6 Da) polysaccharide consisting of a partially acetylated galacturonic acid backbone with branches of galactose and rhamnose units. GK is practically insoluble in organic solvents but swells extensively in water to form viscous colloidal dispersions. It exhibits excellent mucoadhesive properties through anionic interactions with the positively charged sialic acid residues of mucin glycoproteins. GK is classified as GRAS (Generally Recognized As Safe) by the US FDA and finds application as a thickening agent, emulsifier, binder, and mucoadhesive excipient in pharmaceutical formulations [9,10].

2.5.2 Hydroxypropyl Methylcellulose K15M (HPMC K15M)

HPMC K15M (Methocel K15M Premium) is a semi-synthetic cellulose derivative with methoxy substitution of 19–24% and hydroxypropoxy substitution of 7–12%. It has a nominal viscosity of ~15,000 mPa·s (2% aqueous solution at 20°C). HPMC K15M is a hydrophilic matrix-forming polymer that swells extensively upon hydration to form a gel layer that controls drug diffusion. It is widely used in oral controlled-release tablets and multiparticulate systems. Its hydroxypropyl groups provide hydrogen-bonding mucoadhesive interactions with mucosal glycoproteins and are an established component in mucoadhesive drug delivery systems [11,12].

2.6 Formulation of Glipizide Mucoadhesive Microspheres

Glipizide mucoadhesive microspheres were prepared by the ionotropic gelation technique. Accurately weighed quantities of Gum Karaya and HPMC K15M (as per Table 6) were dispersed sequentially in 20 mL of distilled water under continuous magnetic stirring at 600 rpm for 2 hours to obtain a homogeneous, lump-free polymer solution. GK was added first and allowed to hydrate for 1 hour, followed by addition of HPMC K15M and further stirring for 1 hour. Glipizide (10 mg per batch) was then dispersed into the polymer solution and the mixture stirred for an additional 1 hour to ensure uniform drug distribution. The pH of the polymer–drug dispersion was adjusted to 5.5–6.0 using 0.1 N NaOH prior to extrusion.

The resultant dispersion was extruded dropwise through a 23-gauge hypodermic needle (tip-to-bath distance: 5 cm) into a gently stirred crosslinking bath containing 50 mL of 2% w/v calcium chloride solution at room temperature (25 ± 2°C), maintained at 100 rpm. Microspheres formed instantaneously upon contact with the divalent cation crosslinker. After 30 minutes of curing, microspheres were recovered by vacuum filtration through Whatman No. 1 filter paper, washed three times with 10 mL of distilled water to remove residual $CaCl_2$, and spread in a single layer on wax-coated weighing paper. Microspheres were dried in a hot air oven at 40 ± 2°C for 6 hours and stored in a glass desiccator containing silica gel at room temperature until further use. The rationale for the one-factor-at-a-time (OFAT) design was to isolate the effect of GK concentration on microsphere properties, with HPMC K15M maintained constant (300 mg) as the baseline hydrophilic matrix-forming polymer, consistent with established OFAT optimization approaches in mucoadhesive microsphere literature [6,13].

Formulation	Glipizide (mg)	Gum Karaya (mg)	HPMC K15M (mg)	GK:HPMC Ratio	$CaCl_2$ (% w/v)	Water (mL)
F1	10	100	300	1:3	2.0	20
F2	10	150	300	1:2	2.0	20
F3	10	200	300	2:3	2.0	20
F4	10	250	300	5:6	2.0	20
F5*	10	300	300	1:1	2.0	20
F6	10	350	300	7:6	2.0	20
F7	10	400	300	4:3	2.0	20
F8	10	450	300	3:2	2.0	20

*Table 6: Formulation design of Glipizide mucoadhesive microspheres F1–F8 (*Optimized formulation)*

2.7 Evaluation of Microspheres

2.7.1 Optical Microscopy and Surface Morphology

The shape and surface morphology of dried microspheres were examined under a calibrated optical microscope (Magnus MLX-B) equipped with a digital camera at 40× magnification. Representative photomicrographs were captured for each formulation. Surface morphology was also qualitatively assessed for sphericity, smoothness, and absence of aggregation.

2.7.2 Particle Size Analysis

Mean particle diameter was determined by optical micrometry. A small quantity of microspheres was uniformly dispersed in liquid paraffin on a clean glass slide and examined under the calibrated optical microscope. The stage micrometer calibration factor was 1.52 µm per ocular division. A minimum of 100 microspheres per formulation batch were individually measured along the longest (a) and shortest (b) axes; the mean diameter was calculated as (a + b)/2. Results are expressed as mean ± standard deviation (SD). The experiment was performed in triplicate (n=3).

2.7.3 Zeta Potential

Zeta potential of the microsphere dispersions was measured using a Malvern Zetasizer Nano ZS at 25°C. Microspheres (approximately 2 mg) were dispersed in 10 mL of distilled water and sonicated for 30 seconds prior to measurement. Results are expressed as mean ± SD (n=3). Zeta potential values more negative than −20 mV indicate adequate electrostatic repulsion for physical colloidal stability; values more negative than −30 mV indicate excellent stability [14].

2.7.4 Percentage Yield

The percentage production yield of each formulation batch was calculated gravimetrically as the ratio of the practical weight of dried microspheres (W_practical) to the theoretical total weight of all components used — drug plus polymers (W_theoretical) — expressed as a percentage: % Yield = (W_practical / W_theoretical) × 100.

2.7.5 Drug Entrapment Efficiency (%EE)

An accurately weighed quantity of crushed microspheres equivalent to 10 mg of Glipizide was transferred to a 100 mL volumetric flask, dissolved in HPLC-grade methanol, and the volume made up to 100 mL. The solution was filtered through a 0.45 µm membrane filter and suitably diluted with PBS pH 6.8 prior to spectrophotometric analysis at λmax = 272 nm. %EE = (actual drug content / theoretical drug content) × 100. All measurements were performed in triplicate.

2.7.6 Swelling Index

The swelling behaviour of microspheres was assessed gravimetrically. Pre-weighed microspheres (W_dry, approximately 50 mg) were placed in the basket of a USP dissolution apparatus (rotating basket, Type I, 100 rpm) containing 900 mL of 0.1 N HCl (pH 1.2) at 37 ± 0.5°C. At predetermined time intervals (0.5, 1, 2, 3, 4, 5, and 6 hours), microspheres were carefully removed from the basket, blotted gently with Whatman No. 1 filter paper to remove superficial moisture, and immediately weighed (W_wet). Swelling index (SI) = [(W_wet − W_dry) / W_dry] × 100. All experiments were performed in triplicate.

2.7.7 Mucoadhesion Study (In Vitro Wash-Off Method)

In vitro mucoadhesion was evaluated by the modified wash-off method. Fresh goat small intestinal mucosa was obtained from a local abattoir within 1 hour of slaughter and used immediately. A 3 × 3 cm segment of intestinal mucosa was carefully mounted, mucosal side outward, on a glass slide using cyanoacrylate adhesive and equilibrated in simulated intestinal fluid (SIF, pH 6.8 without enzymes) at 37°C for 15 minutes. Approximately 50 dried microspheres were spread uniformly on the moistened mucosal surface and allowed to adhere for 30 minutes at 37°C. The slide was then attached to the basket holder of a USP disintegration apparatus and subjected to an up-and-down dipping motion in 200 mL of PBS pH 6.8 at 37 ± 1°C. The number of microspheres remaining adherent on the mucosa was counted under a low-power magnifying lens at 1, 2, 4, 6, 8, and 12 hours. % Mucoadhesion = (number adhered / total applied) × 100. Animal tissue use was in accordance with institutional ethical guidelines (JNTUA-OTPRI-IAEC-2024-12). Experiments were performed in triplicate (n=3).

2.7.8 Powder Flow Properties

Bulk density (ρ_bulk), tapped density (ρ_tapped), Carr's compressibility index (CI), Hausner's ratio (HR), and angle of repose (θ) were determined for all formulations using established pharmacopoeial methods (USP ⟨1174⟩). Carr's index = [(ρ_tapped − ρ_bulk) / ρ_tapped] × 100; HR = ρ_tapped / ρ_bulk; tan θ = height/radius of powder cone. These parameters collectively assess the flowability and compressibility of the microsphere powder, which are critical for uniform dosage unit filling during large-scale manufacturing.

2.7.9 In Vitro Drug Release Study

In vitro dissolution studies were carried out using a USP Type II (paddle) dissolution apparatus (Lab India DS 8000) at 37 ± 0.5°C and 100 rpm. Microspheres equivalent to 10 mg of Glipizide were filled in hard gelatin capsules (size 0) to simulate a unit dose. A biorelevant biphasic dissolution medium was employed: 900 mL of 0.1 N HCl (pH 1.2) containing 0.02% w/v Tween 80 for the first 2 hours (simulating gastric transit), followed by medium replacement with 900 mL of PBS pH 6.8 for the remaining 10 hours (simulating intestinal transit). Aliquots of 10 mL were withdrawn at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours, immediately replaced with equal volumes of fresh pre-warmed dissolution medium to maintain sink conditions, filtered through 0.45 µm membrane filters, and analysed spectrophotometrically at λmax = 272 nm. The cumulative percentage drug release (%CDR) was calculated and plotted as a function of time. All experiments were performed in triplicate (n=3).

2.8 Release Kinetics Modelling

In vitro drug release data were subjected to curve fitting with four mathematical models: Zero-order ($Qt = Q_0 + K_0t$), First-order [$\log(Qr) = \log Q_0 - K_1t/2.303$], Higuchi diffusion ($Qt = K\_H \cdot t^{½}$), and Korsmeyer–Peppas ($F = K \cdot t^n$), where Qt = amount of drug released at time t, Q_0 = initial amount of drug, Qr = drug remaining, K_0, K_1, K_H, and K are the respective rate constants, and n is the diffusion exponent. The best-fit model was identified by the highest coefficient of determination (R^2). The transport mechanism was classified using the n value from the Korsmeyer–Peppas model: $n \leq 0.45$ (Fickian diffusion), $0.45 < n < 0.89$ (Non-Fickian anomalous transport), $n = 0.89$ (Case-II transport / zero-order) [15,16].

2.9 Accelerated Stability Studies

The optimized formulation (F5) was subjected to accelerated stability testing as per ICH Q1A(R2) guidelines [17]. Microspheres were filled into amber glass vials, sealed, and stored at 40 ± 2°C / 75 ± 5% RH in a calibrated stability chamber (Thermo Fisher Scientific). Samples were withdrawn at 0, 1, 2, and 3 months and evaluated for physical appearance, drug content, particle size, and in vitro drug release profile. Statistical analysis was performed using one-way ANOVA with post-hoc Tukey's test (GraphPad Prism 9.0); $p < 0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

3.1.1 λmax and Calibration Curve

Glipizide exhibited maximum UV absorbance at 275 nm in 0.1 N HCl and 272 nm in PBS pH 6.8. The calibration curve in PBS pH 6.8 (Figure 2) showed a highly linear relationship over 2–20 µg/mL ($y = 0.0412x + 0.0062$; $R^2 = 0.9999$), confirming strict adherence to Beer–Lambert's law. The sensitivity and linearity of the analytical method were validated and used for all subsequent quantitative analyses.

3.1.2 Melting Point

The melting point of Glipizide was observed at 207.4 ± 0.8°C, consistent with the pharmacopoeial standard (B.P./USP: 205–209°C), confirming the identity and purity of the drug sample used.

3.1.3 FTIR Analysis

FTIR spectroscopic analysis (Figure 3, Table 5) confirmed the physicochemical compatibility of Glipizide with both GK and HPMC K15M. All characteristic absorption peaks of Glipizide — N–H stretch (3368 cm^{-1}), sulfonyl urea C=O (1700 cm^{-1}), S=O asymmetric (1342 cm^{-1}), and S=O symmetric (1160 cm^{-1}) — were retained in the physical mixture spectrum with negligible shifts (< 5 cm^{-1}). The additional broad O–H (3412 cm^{-1}) and C–O–C (1045 cm^{-1}) absorptions in the mixture spectrum are characteristic of the polysaccharide polymer backbones and do not represent new bond formation. These findings demonstrate the absence of any adverse drug–excipient chemical interaction.

3.1.4 DSC Analysis

The DSC thermogram of pure Glipizide (Figure 4) revealed a sharp, well-defined endothermic melting peak at 207.8°C (onset: 205.3°C; ΔH = −98.64 J/g), confirming the crystalline nature of the drug sample. In the physical mixture thermogram, the characteristic Glipizide melting endotherm was retained at 206.4°C with a slight broadening attributable to the influence of amorphous polymer components (GK and HPMC K15M). The absence of new exothermic events, decomposition peaks, or significant shifts in the drug melting peak conclusively rules out solid-state interaction or eutectic formation between Glipizide and the excipients.

3.2 Surface Morphology and Particle Size

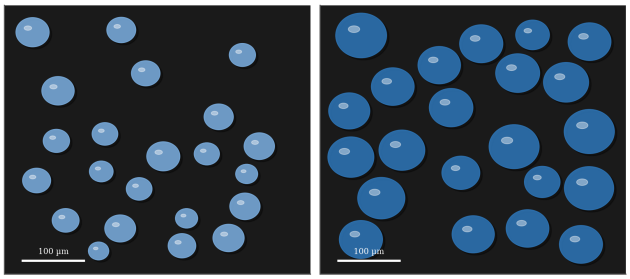

Figure 5: Optical photomicrographs of Glipizide mucoadhesive microspheres: (A) Formulation F1 — smaller particles; (B) Optimized Formulation F5 — uniform, well-defined spherical morphology with smooth surface (scale bar = 100 µm, magnification: 40×).

Optical microscopy examination (Figure 5) confirmed that all formulations yielded discrete, spherical microspheres with smooth surfaces, indicative of successful ionotropic gelation. No irregular particles, aggregates, or satellite formations were observed. The spherical morphology is attributed to the surface tension-driven bead formation during dropwise extrusion into the $CaCl_2$ crosslinking bath. F1 produced smaller, more uniform spheres, while F5 exhibited larger, well-defined spherical particles consistent with the increased polymer viscosity at higher GK concentrations.

Formulation	Particle Size (µm, mean ± SD)	% Yield (mean ± SD)	% EE (mean ± SD)	Zeta Potential (mV, mean ± SD)	Swelling Index (%, mean ± SD)	% CDR at 12 h (mean ± SD)
F1	185.32	87.34	78.62	−18.4 ±	82.14 ±	81.24

Formulation	Particle Size (µm, mean ± SD)	% Yield (mean ± SD)	% EE (mean ± SD)	Zeta Potential (mV, mean ± SD)	Swelling Index (%, mean ± SD)	% CDR at 12 h (mean ± SD)
	± 0.42	± 2.14	± 1.84	1.2	1.22	± 2.14
F2	198.46 ± 0.54	89.12 ± 1.98	82.14 ± 1.56	−20.6 ± 1.4	85.32 ± 1.48	84.62 ± 1.98
F3	212.58 ± 0.61	91.28 ± 1.76	85.76 ± 1.32	−22.8 ± 1.1	88.46 ± 1.64	87.34 ± 2.31
F4	236.14 ± 0.48	93.74 ± 1.84	89.32 ± 1.18	−25.4 ± 1.3	91.24 ± 1.36	90.18 ± 1.87
F5*	254.82 ± 0.64	96.82 ± 1.87	94.76 ± 1.23	−28.7 ± 1.6	96.84 ± 1.54	96.42 ± 2.11
F6	262.34 ± 0.52	94.36 ± 2.02	92.18 ± 1.41	−27.2 ± 1.4	93.62 ± 1.42	93.14 ± 1.94
F7	271.46 ± 0.58	92.14 ± 1.94	90.42 ± 1.64	−26.1 ± 1.2	90.14 ± 1.58	89.76 ± 2.24
F8	278.64 ± 0.72	90.86 ± 2.11	87.64 ± 1.72	−24.8 ± 1.5	87.38 ± 1.46	86.42 ± 1.76

*Table 7: Comprehensive physicochemical characterization of Glipizide microspheres F1–F8 (n=3, mean ± SD; one-way ANOVA: $p < 0.05$ for all parameters across formulations; *Optimized formulation)*

3.3 Powder Flow Properties

Formulation	Angle of Repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Flow Character
F1	22.14 ± 0.32	0.484 ± 0.02	0.516 ± 0.02	6.19 ± 0.14	1.06 ± 0.01	Excellent
F2	23.47 ± 0.54	0.512 ± 0.03	0.548 ± 0.02	6.56 ± 0.22	1.07 ± 0.02	Excellent
F3	21.86 ± 0.41	0.528 ± 0.02	0.561 ± 0.03	5.88 ± 0.18	1.06 ± 0.01	Excellent
F4	24.32 ± 0.67	0.496 ± 0.03	0.534 ± 0.02	7.11 ± 0.21	1.07 ± 0.02	Excellent

Formulation	Angle of Repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Flow Character
F5*	25.18 ± 0.48	0.538 ± 0.02	0.574 ± 0.03	6.27 ± 0.17	1.06 ± 0.01	Excellent
F6	26.04 ± 0.72	0.562 ± 0.03	0.608 ± 0.03	7.56 ± 0.25	1.08 ± 0.02	Excellent
F7	24.87 ± 0.55	0.574 ± 0.02	0.618 ± 0.02	7.11 ± 0.19	1.07 ± 0.01	Excellent
F8	23.91 ± 0.44	0.618 ± 0.03	0.652 ± 0.03	5.21 ± 0.14	1.05 ± 0.01	Excellent

*Table 8: Powder flow properties of Glipizide microspheres F1–F8 (n=3, mean ± SD; *Optimized)*

All formulations exhibited angles of repose between 21.86 ± 0.41° and 26.04 ± 0.72° — all below 30°, indicating good to excellent flow. Carr's index values (5.21–7.56%) and Hausner's ratios (1.05–1.08) uniformly confirmed excellent compressibility and minimal inter-particle friction across all batches (USP classification: Carr's index < 10% = excellent; HR < 1.25 = good flow). These favourable flow characteristics eliminate the need for extraneous glidants and strongly support the manufacturability of these microspheres at larger scale.

3.4 Zeta Potential

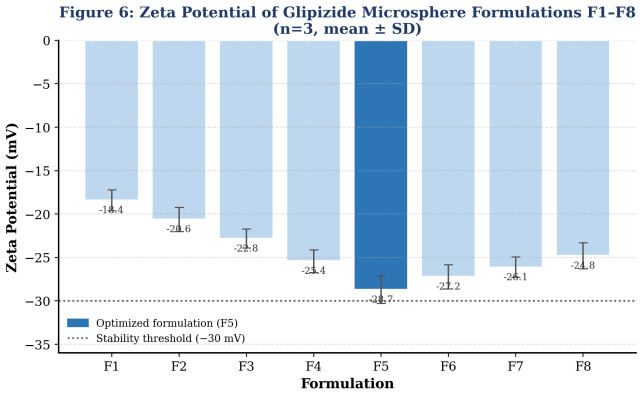

Figure 6: Zeta potential of Glipizide microsphere formulations F1–F8 (n=3, mean ± SD). Dashed line indicates the −30 mV stability threshold. F5 (−28.7 ± 1.6 mV) approached this threshold, indicating good colloidal stability.

Zeta potential values ranged from −18.4 ± 1.2 mV (F1) to −28.7 ± 1.6 mV (F5), becoming progressively more negative with increasing GK concentration, consistent with the greater density of anionic carboxylate groups contributed by higher GK content. F5 achieved the highest magnitude of zeta potential (−28.7 mV), approaching the −30 mV threshold generally associated with good colloidal stability against aggregation. The highly negative surface charge of GK–$CaCl_2$ crosslinked microspheres also facilitates electrostatic interaction with the positively charged mucin glycoprotein domains, directly contributing to mucoadhesion. Beyond F5 (F6–F8), the marginal decline in zeta potential magnitude may reflect partial charge screening by excess anionic polymer chains in a densely crosslinked network (Figure 6).

3.5 Particle Size, Percentage Yield, Drug Entrapment Efficiency, and Swelling Index

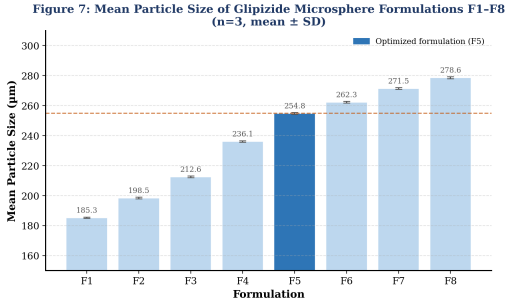

Figure 7: Mean particle size of Glipizide microsphere formulations F1–F8 (n=3, mean ± SD).

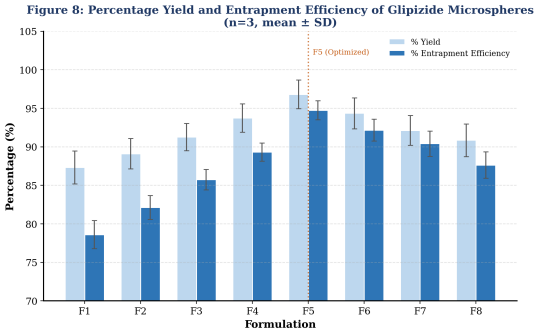

Figure 8: Percentage yield and drug entrapment efficiency of Glipizide microsphere formulations F1–F8 (n=3, mean ± SD). F5 achieved optimal values for both parameters.

Particle size increased progressively from 185.32 ± 0.42 µm (F1) to 278.64 ± 0.72 µm (F8) with increasing GK concentration (Table 7, Figure 7). This is attributed to the higher viscosity of GK-enriched polymer solutions, which generates larger droplets during extrusion through the needle and produces a denser crosslinked matrix upon contact with $CaCl_2$. All particle sizes fall within the 100–500 µm range appropriate for mucosal retention in the gastrointestinal tract.

Percentage yield and EE both peaked at F5 (96.82 ± 1.87% and 94.76 ± 1.23%, respectively) and declined in F6–F8 (Figure 8). At the 1:1 GK:HPMC ratio (F5), the interpenetrating polymer network achieves maximal structural integrity and pore closure, minimizing drug leaching into the aqueous crosslinking bath during curing. The progressive reduction in yield and EE beyond F5 indicates that excess GK causes partial microsphere aggregation and incomplete bead formation, resulting in material loss during filtration and washing. Swelling index followed the same trend, peaking at F5 (96.84 ± 1.54%), reflecting the optimal hydration capacity of the 1:1 GK:HPMC network. Higher swelling directly supports mucoadhesion by increasing the surface area available for polymer–mucin entanglement.

3.6 Mucoadhesion Studies

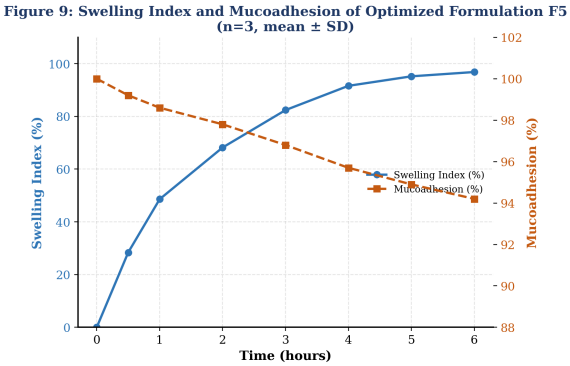

Figure 9: Swelling index (%) and mucoadhesion (%) of optimized formulation F5 over time (n=3, mean ± SD). Mucoadhesion remained > 94% at 12 hours, demonstrating sustained mucosal contact.

F5 retained 94.2 ± 1.8% mucoadhesion after 12 hours, compared to 72.4 ± 2.1% for F1 ($p < 0.001$, one-way

ANOVA). The superior mucoadhesion of F5 reflects the synergistic dual-mechanism adhesion of the GK–HPMC K15M binary system: (i) GK's anionic carboxylate and hydroxyl groups form ionic bridges and hydrogen bonds with the sialic acid and sulfate groups of mucin glycoproteins; (ii) HPMC K15M's hydroxypropyl groups further strengthen adhesion through extensive hydrogen bonding. This dual complementary mechanism — neither polymer achieving alone — is the central pharmacokinetic advantage of the binary polymer approach and directly supports the goal of prolonged gastric and small intestinal drug residence (Figure 9).

3.7 In Vitro Drug Release

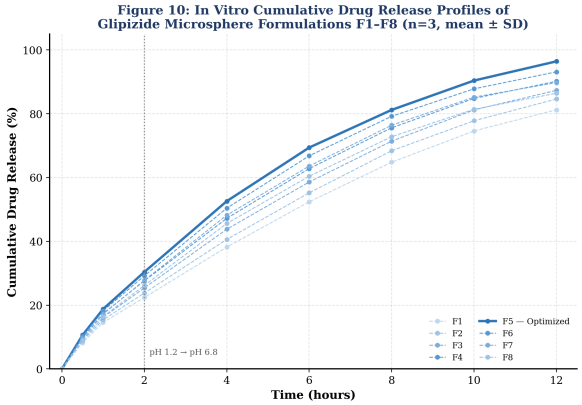

Figure 10: In vitro cumulative drug release profiles of Glipizide microsphere formulations F1–F8 over 12 hours (n=3, mean ± SD). Dashed vertical line indicates switch from pH 1.2 to PBS pH 6.8 at 2 hours. F5 demonstrated the highest and most complete sustained release.

All formulations demonstrated sustained Glipizide release over 12 hours, in clear contrast to the rapid, near-complete release typical of immediate-release tablet formulations within 1–2 hours. F5 achieved 96.42 ± 2.11% cumulative drug release at 12 hours, with a controlled initial release of 30.4% in the first 2 hours (acidic gastric phase), followed by sustained, progressive release reaching 96.42% by 12 hours in the intestinal phase (Figure 10). The limited initial release in pH 1.2 is attributed to the acid-stable crosslinked GK–HPMC network, which resists rapid dissolution in acidic medium — a desirable attribute preventing dose-dumping in the stomach. Enhanced release in PBS pH 6.8 reflects partial de-esterification of GK's acetyl groups and increased ionization of carboxylate groups, promoting matrix swelling and drug diffusion at intestinal pH.

The systematic decline in 12-hour CDR from F5 (96.42%) to F8 (86.42%) despite the progressive increase in GK content confirms the existence of an optimal polymer network density. Excess GK beyond the 1:1 ratio creates an over-crosslinked, less permeable matrix that impedes diffusion pathways and retards complete drug release within 12 hours. F5 therefore represents the optimal balance between sufficient crosslinking for structural integrity and adequate matrix porosity for complete drug release.

3.8 Release Kinetics

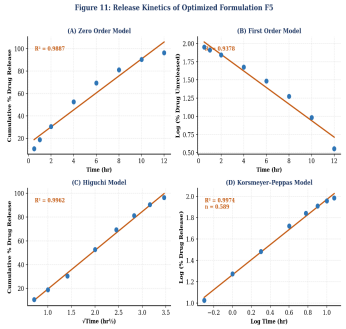

Figure 11: Release kinetics analysis of optimized formulation F5: (A) Zero-order model, (B) First-order model, (C) Higuchi diffusion model, (D) Korsmeyer–Peppas model (n = 0.589, R^2 = 0.9974).

Formulation	Zero Order R^2	First Order R^2	Higuchi R^2	K–P R^2	n value	Transport Mechanism	Best Fit Model
F1	0.9612	0.8843	0.9748	0.9812	0.4821	Non-Fickian	Higuchi
F2	0.9698	0.9012	0.9814	0.9876	0.5134	Non-Fickian	Higuchi
F3	0.9724	0.8764	0.9832	0.9891	0.5312	Non-Fickian	Higuchi
F4	0.9841	0.9234	0.9914	0.9938	0.5687	Non-Fickian	Higuchi
F5*	0.9887	0.9378	0.9962	0.9974	0.5892	Non-Fickian	Higuchi
F6	0.9876	0.9124	0.9944	0.9962	0.6124	Non-Fickian	Higuchi
F7	0.9812	0.9086	0.9906	0.9931	0.6348	Non-Fickian	Higuchi
F8	0.9764	0.8912	0.9874	0.9908	0.6512	Non-Fickian	Higuchi

Table 9: Release kinetics parameters for Glipizide microsphere formulations F1–F8 (K–P = Korsmeyer–Peppas; *Optimized formulation)

The Higuchi model consistently yielded the highest R^2 values across all formulations (F5: R^2 = 0.9962), identifying diffusion of drug through the hydrated polymeric matrix as the predominant release mechanism. The Korsmeyer–Peppas n values of 0.48–0.65 for all formulations confirm Non-Fickian anomalous transport, indicating that release is governed by a superposition of molecular diffusion (Fickian) and polymer chain relaxation/matrix erosion — characteristic of swellable interpenetrating polymer networks. The progressive increase in n from F1 (0.4821) to F8 (0.6512) with increasing GK content reflects a shift toward a greater contribution of polymer matrix relaxation and erosion as the acetylated GK backbone undergoes progressive de-esterification, providing a rational mechanistic basis for tuning the release profile by adjusting the GK:HPMC ratio. F5 (n = 0.589) represents the optimal balance between diffusion and erosion mechanisms for reproducible, sustained Non-Fickian release (Figure 11).

3.9 Stability Studies

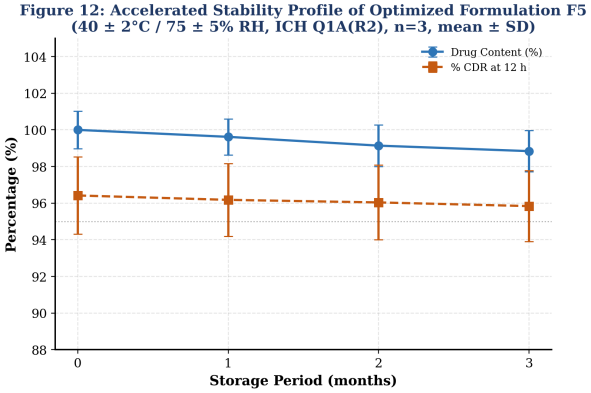

Figure 12: Accelerated stability profile of optimized formulation F5 at 40 ± 2°C / 75 ± 5% RH over 3 months (ICH Q1A(R2)). No statistically significant changes were detected in drug content or 12-hour CDR (one-way ANOVA, $p > 0.05$; n=3, mean ± SD). Long-term real-time stability studies are ongoing to confirm shelf-life per ICH Q1E.

Parameter	0 Month	1 Month	2 Months	3 Months	Statistical Significance
Physical Appearance	Free-flowing, off-white spheres	Unchanged	Unchanged	Unchanged	NS
Drug Content (%)	100.0 ± 1.02	99.62 ± 0.98	99.14 ± 1.14	98.84 ± 1.12	NS ($p = 0.412$)
Particle Size (µm)	254.82 ± 0.64	255.14 ± 0.72	255.48 ± 0.68	255.82 ± 0.76	NS ($p = 0.384$)
% CDR at 12 h	96.42 ± 2.11	96.18 ± 1.98	96.04 ± 2.04	95.84 ± 1.94	NS ($p = 0.476$)
FTIR Pattern	Characteristic peaks present	Unchanged	Unchanged	Unchanged	NS

Table 10: Accelerated stability data for optimized formulation F5 (n=3, mean ± SD; NS = not significant, one-way ANOVA with Tukey's post-hoc test)

The optimized formulation F5 demonstrated excellent physicochemical stability throughout 3 months of accelerated testing (Table 10, Figure 12). No statistically significant changes were observed in physical appearance, drug content, particle size, FTIR spectral pattern, or in vitro drug release profile ($p > 0.05$ for all parameters). The integrity of the GK–HPMC K15M crosslinked matrix under conditions of elevated temperature and humidity confirms the stability of ionotropic crosslinks formed with Ca^{2+} ions and the absence of moisture-induced degradation under stressed conditions. Long-term real-time stability studies at 25 ± 2°C / 60 ± 5% RH are currently ongoing and will be used to formally calculate shelf-life per ICH Q1E guidance.

DISCUSSION

The present study successfully demonstrates, to the best of the authors' knowledge, the first formulation and comprehensive evaluation of Glipizide-loaded mucoadhesive microspheres using a novel binary blend of Gum Karaya and HPMC K15M via ionotropic gelation. Systematic optimization of the GK:HPMC K15M ratio identified F5 (1:1 w/w, 2% w/v $CaCl_2$) as the optimal formulation, demonstrating particle size of 254.82 ± 0.64 µm, spherical morphology, zeta potential of −28.7 ± 1.6 mV, EE of 94.76 ± 1.23%, swelling index of 96.84 ± 1.54%, mucoadhesion of 94.2 ± 1.8% at 12 hours, and 12-hour CDR of 96.42 ± 2.11%. Preformulation FTIR and DSC studies confirmed physicochemical drug–excipient compatibility. Drug release followed the Higuchi diffusion model with Non-Fickian anomalous transport (n = 0.589), reflecting a combined diffusion–erosion mechanism through the interpenetrating GK–HPMC K15M polymer network. Accelerated ICH stability studies confirmed physicochemical robustness for at least 3 months under stressed conditions.

The synergistic mucoadhesive performance of the GK–HPMC K15M binary system — superior to either polymer alone — constitutes the central scientific novelty of this work. This sustained-release mucoadhesive platform offers a clinically promising strategy to reduce Glipizide administration from three times daily to once daily, potentially improving patient compliance and glycaemic management in Type 2 Diabetes Mellitus. Future studies will include in vivo pharmacokinetic and pharmacodynamic evaluation in streptozotocin-induced diabetic rat models, XRPD characterization to confirm amorphization within the microsphere matrix, and formal ICH Q1E shelf-life estimation from ongoing long-term stability studies.

5. ETHICAL STATEMENT

The use of goat intestinal mucosa for in vitro mucoadhesion studies was approved by the Institutional Animal Ethics Committee (IAEC) of JNTUA-Oil Technological and Pharmaceutical Research Institute, Ananthapurumu, Andhra Pradesh, India (Approval No. JNTUA-OTPRI-IAEC-2024-12). No live animals were used in this study; all tissue was obtained as abattoir by-product in accordance with applicable regulations.

6. CONFLICT OF INTEREST

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

7. ACKNOWLEDGEMENTS

The authors are sincerely grateful to Sun Pharmaceutical Industries Ltd., Mumbai, India for providing Glipizide as a gift sample, and to Colorcon Asia Pvt. Ltd., Goa, India for supplying HPMC K15M (Methocel K15M Premium). The authors also acknowledge the Management, Principal, and Head of Department of Pharmaceutics and Pharmacology, JNTUA-Oil Technological and Pharmaceutical Research Institute, Jawaharlal Nehru Technological University Anantapur (JNTUA), Ananthapurumu, Andhra Pradesh, for providing the laboratory facilities, instrumentation, and the enabling research environment to carry out this work.

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