RESEARCH PAPER

Formulation and Evaluation of Gelatinized Metroxylon sagu Oral Thin Films for the Controlled Systemic Delivery of Glimepiride

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ABSTRACT

Traditional oral solid dosage forms (macro-tablets, caplets, and dense hard-gelatin capsules) present deep clinical limitations within specialized patient demographics, particularly acute swallowing dysfunctions (dysphagia) in pediatric and geriatric populations. Moreover, high-clearance metabolic pathways, characterized by immediate gastric acid degradation and extensive hepatic first-pass pre-systemic clearance, radically decrease the absolute bioavailability of many critical therapeutic entities. Polymeric buccal oral thin films (OTFs) have surfaced as a highly advanced, non-invasive systemic delivery platform. Positioned against the non-keratinized mucosal lining of the oral cavity, these matrices absorb directly through the local vascular network into the internal jugular vein, ensuring rapid bioavailability while avoiding gastrointestinal and hepatic clearance pathways.

Objective

This extensive research documents the systematic design, molecular optimization, and physical-chemical evaluation of novel biopolymeric thin oral films utilizing a meticulously engineered blend of gelatinized sago starch (Metroxylon sagu) and Hydroxypropyl Methylcellulose (HPMC) to deliver the poorly water-soluble third-generation antidiabetic sulfonylurea, Glimepiride, over a controlled 6-hour period.

Keywords: Metroxylon sagu, Glimepiride, Buccal Oral Thin Films, Solvent Casting, Mucoadhesion, Controlled Drug Delivery, Polymer Blending, Dissolution Kinetics.

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1. Detailed Introduction and Theoretical Framework

1.1 The Clinical Landscape of Oral Drug Delivery

The historical trajectory of global drug manufacturing and clinical practice demonstrates that the administration of therapeutic entities via oral pathways remains the most widely adopted, commercially viable, and preferred approach across clinical settings [1]. This deep market penetration stems directly from its non-invasive nature, cost-efficient manufacturing scaling potential, formulation versatility, and high levels of patient compliance [1,2]. The human gastrointestinal tract presents a massive absorptive surface area designed to facilitate systemic uptake. However, traditional oral solid matrices, such as macro-tablets, compressed caplets, and hard gelatin encapsulated formulas, frequently exhibit severe physiological and psychological drawbacks [2,3]. Among these, acute swallowing difficulties, clinically classified as dysphagia, affect up to 40% of geriatric individuals and a significant percentage of pediatric patient demographics, leading to missed doses and compromised therapeutic regimens [3]. Furthermore, issues such as poor taste masking, accidental choking hazards, and localized esophageal irritation due to delayed tablet transit times present notable formulation challenges [4].

Beyond these patient-centric compliance limitations, traditional oral delivery faces major pharmacokinetic and biopharmaceutical challenges [2]. When a drug matrix is swallowed, it encounters the highly acidic environment of the stomach (pH 1.5 to 3.5), where many active pharmaceutical ingredients (APIs) face premature chemical degradation or enzymatic hydrolysis [3]. Following gastric transit, the dissolved therapeutic agents traverse the intestinal epithelium and enter the hepatic portal system via the mesenteric veins [5]. This pathway exposes the molecules to immediate, aggressive metabolic breakdown within the liver—a phenomenon known as the hepatic first-pass effect [6]. For many high-potency molecules, this pre-systemic clearance radically reduces absolute bioavailability, requiring higher oral doses that can

lead to increased systemic side effects and volatile plasma concentration profiles [5,6]. Liquid oral formulations, while partially mitigating dysphagia, introduce separate complications, including chemical stability issues in aqueous media, risk of dose inaccuracy when measured by patients, and bulky transport requirements [2,4]. Similarly, alternative delivery systems like parenterals bypass first-pass clearance but require trained clinical supervision, carry risks of needle-stick injuries or localized tissue inflammation, and introduce high manufacturing costs due to strict sterility mandates [1,2].

1.2 Evolution of Fast-Dissolving and Polymeric Film Systems

To overcome these clinical barriers, Fast-Dissolving Drug Delivery Systems (FDDS) were introduced during the late 20th century, representing a major advancement in oral drug delivery [3]. These early systems focused primarily on orally disintegrating tablets (ODTs), designed to rapidly break down within the oral cavity upon contact with saliva, eliminating the need for water [3,4]. However, ODT platforms possess inherent mechanical limitations, including low physical density, high friability, and poor resistance to ambient moisture, which require specialized, expensive packaging solutions like peelable blister packs [4]. Furthermore, manufacturing technologies for high-quality ODTs, such as lyophilization, spray-drying, and direct compression using complex superdisintegrant blends, involve significant operational expenses and technical constraints [4,6].

To address these limitations, polymer-based oral thin films have emerged as a highly sophisticated alternative [5]. Designed as ultra-thin, flexible, stamp-sized polymeric sheets, oral films dissolve rapidly when placed on or under the tongue, or against the buccal mucosal lining [6]. This rapid dissolution allows the active pharmaceutical ingredient (API) to dissolve in localized salivary fluids and pass directly across the highly vascularized oral mucosal borders [5]. By entering the systemic circulation via the internal jugular vein, the drug safely avoids the harsh gastric environment and bypasses first-pass hepatic metabolism entirely [5,6]. This direct systemic entry can accelerate therapeutic onset, lower the required clinical dose, and maintain stable plasma drug profiles [6].

1.3 Anatomical and Physiological Considerations of the Buccal Mucosa

The oral cavity contains three distinct physiological zones for drug delivery: sublingual, buccal, and local mucosal pathways [1]. The buccal mucosal membrane, representing roughly one-third of the total 100 cm^2 oral surface area, features an epithelial lining approximately 0.5 mm thick [7]. Although the buccal epithelium is non-keratinized and thicker than sublingual tissue, it exhibits up to a 4,000-fold increase in permeability relative to transdermal pathways, making it an excellent target for bioadhesive patches and thin films [7,8]. Permeation across this anatomical barrier operates via transcellular or paracellular passive diffusion mechanisms [9]. Hydrophilic molecules migrate primarily along intercellular spaces, while lipophilic entities traverse the lipid-rich cellular membranes [9,10].

Establishing long-term residence within this dynamic environment requires mucoadhesion—a multi-step phenomenon driven by polymer wetting, adsorption, chain interpenetration, and electronic double-layer attraction across the mucous gel surface [11]. The presence of a continuous salivary film layer, ranging from 10 to 100 micrometers in thickness, creates an interface where water molecules interact with hydrophilic polymer strands. As these strands hydrate, they untangle and interpenetrate into the glycoprotein networks of the mucus layer, establishing strong physical bonds that prolong the local residence time of the formulation [11,12].

1.4 Polymer Matrix Selection and Biopolymer Blending Strategies

A core challenge in buccal film engineering involves selecting a polymer matrix that achieves optimal mechanical strength, flexible folding endurance, biocompatibility, and controlled release [5,12]. While synthetic polymers like polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) are widely used, they can present concerns regarding environmental sustainability, production costs, or potential local tissue irritation during long-term use [12]. Consequently, research interest has shifted toward exploring altered natural biopolymers [13]. *Metroxylon sagu* (sago starch) represents an underutilized, highly stable, and abundant natural carbohydrate source [14]. Composed of a balanced structural blend of linear amylose and highly branched amylopectin fractions, sago starch displays unique properties when gelatinized [14,15]. Applying thermal energy disrupts the crystalline structure of the starch granules, causing them to absorb water, swell, and form a continuous polymer network [15]. This gelatinized sago starch forms clear, flexible thin films with excellent chemical stability [15,16].

However, pure natural starch films often exhibit rapid moisture absorption and lower mechanical resistance when exposed to salivary stress [16]. To address these issues, blending natural sago starch with semi-synthetic polymers like Hydroxypropyl Methylcellulose (HPMC) provides an effective optimization strategy [16,17]. HPMC, a cellulose derivative substituted with methoxyl and hydroxypropyl groups, provides excellent film-forming properties, strong mechanical resilience, and highly predictable swellable-matrix dissolution kinetics [17]. By adjusting the blending ratios between gelatinized *Metroxylon sagu* starch and

HPMC, the film's microstructure can be precisely tailored to modulate swelling capacity, mechanical flexibility, and drug release rates [16,17].

1.5 Glimepiride as a Model Therapeutic Candidate

Glimepiride, chemically identified as 3-ethyl-4-methyl-N-(2-(4-(N-((trans-4-methylcyclohexyl)carbamoyl)sulfamoyl)phenyl)ethyl)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide, is a potent third-generation sulfonylurea widely prescribed for managing Type 2 Diabetes Mellitus [17]. It functions by binding selectively to ATP-sensitive potassium channel receptors on pancreatic beta cells, triggering depolarization and stimulating insulin secretion [17,19]. Glimepiride is classified under the Biopharmaceutics Classification System (BCS) as a Class II drug, meaning it possesses high membrane permeability but extremely low aqueous solubility across physiological pH ranges [19]. This low solubility limits its dissolution rate in gastrointestinal fluids, resulting in variable oral absorption and a delayed therapeutic response [19]. Furthermore, conventional oral doses are subject to pre-systemic clearance, which causes fluctuations in plasma levels and increases the risk of side effects like sudden hypoglycemia [17,19]. Formulating Glimepiride into an ultra-thin buccal film using a blended gelatinized *Metroxylon sagu*/HPMC matrix offers a highly effective method to accelerate dissolution, enable direct systemic entry, and provide controlled release over an extended 6-hour period [18,19].

2. Comprehensive Literature Review

Modern pharmaceutical research heavily emphasizes exploring buccal architecture to overcome the bioavailability bottlenecks of conventional delivery methods. Pandian et al. [5] noted that buccal films utilize an intricate balance of natural or synthetic polymers, plasticizers, and absorption enhancers to optimize mechanical resilience against oral shear forces while maintaining an ideal drug release profile. Despite challenges like moisture sensitivity and constrained spatial loading capacities, recent advances in polymer blending have successfully expanded this platform to handle complex therapeutics, including macromolecules and small, low-dose compounds [5,6]. Nair et al. [6] highlighted that while cutting-edge fabrication tools like 3D printing and electrospraying are gaining traction, traditional solvent casting remains the baseline standard for evaluating novel excipient performance due to its processing reliability and precise thickness control.

Altering polymer compositions directly dictates the resulting film morphology and release dynamics. For instance, Najafi et al. [7] evaluated mucoadhesive films of glibenclamide fabricated via solvent casting using HPMC and Eudragit RL100. They observed that while pure HPMC formulations displayed poor visual appearance and uneven thickness, incorporating Eudragit delivered highly flexible, bubble-free matrices with optimized swelling kinetics and enhanced patient compliance. Similarly, Kansagra et al. [8] demonstrated that blending distinct polymers (Chitosan, Noveon, and Eudragit) successfully yielded a balanced, moderately swelling matrix for Sertaconazole Nitrate, ensuring safe, sustained intraoral delivery for over 10 hours.

The integration of natural, bio-safe materials has emerged as a key strategy to eliminate synthetic excipient toxicity. Balaji et al. [9] formulated Atorvastatin buccal films using a natural casein base blended with HPMC E15 and Sodium CMC. Their optimized batch achieved a smooth, biocompatible profile with an extended *ex vivo* permeation duration of 24 hours. To control release rates, Bhattacharjee [10] engineered HPMC-based mucoadhesive films for water-insoluble agents using different plasticizers, demonstrating a steady, matrix-controlled drug release extending over 6 hours. Furthermore, Ganaie et al. [11] confirmed through kinetic modeling that combining HPMC with PVP K-30 yields a zero-order release mechanism, providing highly uniform, predictable drug plasma levels.

Physical flexibility and mechanical strength are critical parameters for ensuring a film survives packaging and consumer handling. Gales et al. [12] observed that adding 20% propylene glycol to a 2% polyvinyl alcohol base significantly increased percentage elongation while preventing brittle fractures. For rapid-onset applications, Rani et al. [13] demonstrated that balanced polymer blending can achieve over 98% immediate release within 15 minutes, which is highly useful for managing acute painful conditions like arthritis. Conversely, for anti-infective or chronic metabolic management, long-term stability and sustained action are crucial. Rachh et al. [14] developed HPMC-based films for Ciclopirox Olamine that successfully maintained therapeutic concentrations above the minimum inhibitory limit for 8 hours.

Investigating antidiabetic treatments within buccal systems is supported by multiple successful studies. Bansal et al. [15] engineered fast-dissolving systems using polyvinyl alcohol and maltodextrin, achieving a neutral surface pH that avoids tissue irritation. Das et al. [16] evaluated Repaglinide buccal patches formulated with chitosan and PVP K-30, showing that smooth, neutral-pH matrices remained highly stable during accelerated stress storage. Furthermore, Vijayalakshmi et al. [17] worked directly with Glimepiride using an HPMC-E5 and maltodextrin blend, noting that low-dose drugs are exceptionally well-suited for oral film delivery, resulting in enhanced absorption profiles and superior *in vivo* plasma compliance. These foundational studies establish a clear rationale for optimizing a natural, gelatinized *Metroxylon sagu*

starch matrix to safely manage controlled Glimepiride kinetics.

3. Detailed Methodology

3.1 Materials and Reagents

Glimepiride was obtained as a gift sample from a pharmaceutical manufacturer, certified at $>99.2\%$ purity profile via HPLC assay. *Metroxylon sagu* (sago starch) was acquired from regional commercial suppliers and subjected to a multi-stage purification protocol: washing with 0.1M sodium hydroxide to extract residual proteins, neutralization with distilled water, filtering through a 100-mesh sieve, and drying in a hot-air oven at 40°C for 12 hours. Hydroxypropyl Methylcellulose (HPMC, K100M grade with a nominal viscosity of $100,000\text{ cPs}$), pure glycerol ($99.5\% \text{ w/w}$), analytical grade methanol, potassium dihydrogen phosphate (KH_2PO_4), and sodium hydroxide (NaOH) pellets were purchased from standard chemical suppliers. All solvent configurations, dilution banks, and dissolution media were prepared using freshly distilled, deionized water.

3.2 Pre-formulation Characterization of Glimepiride Powder

To optimize the handling parameters and processing kinetics of the active pharmaceutical ingredient (API) prior to solvent suspension, the raw Glimepiride powder underwent micromeritic testing following standard pharmaceutical compounding metrics [18].

3.2.1 Bulk Density and Tapped Density Evaluation

A precise mass ($m = 5\text{ g}$) of raw Glimepiride powder was carefully poured into a clean, dry 100 mL graduated glass cylinder. The uncompacted apparent volume (V_0) was noted immediately to define the starting bulk density profile. The cylinder was then placed onto a mechanical tapped density apparatus configured to execute localized tapping protocols ($1,250$ continuous cycles). The final compacted powder volume (V_f) was measured. The bulk density (ρ_b) and tapped density (ρ_t), measured in grams per cubic centimeter (g/cm^3), were calculated using the following equations:

$$\rho_b = \frac{m}{V_0}$$

$$\rho_t = \frac{m}{V_f}$$

3.2.2 Interparticulate Friction and Flow Mechanics

To predict the dispersion stability of the formulation, the internal friction and flow properties of the powder were determined using the Hausner Ratio, Carr's Compressibility Index percentage, and the Angle of Repose [18]. The Hausner Ratio was computed to gauge interparticulate friction levels via:

$$\text{Hausner Ratio} = \frac{\rho_t}{\rho_b}$$

The percentage compressibility of the powder matrix was quantified using Carr's Compressibility Index:

$$\text{Carr's Index } (\%) = \left(\frac{\rho_t - \rho_b}{\rho_t} \right) \times 100$$

The static internal friction angle was assessed using the fixed funnel technique. Powder samples were poured through a glass funnel suspended at a fixed height above a horizontal surface until the apex of the resulting conical pile touched the lower tip of the funnel. The average height (h) and baseline radius (r) of the conical heap were measured, and the angle of repose (θ) was calculated as:

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

3.3 Fourier-Transform Infrared (FT-IR) Spectroscopy Studies

FT-IR spectroscopic evaluations were performed to check for chemical compatibility and rule out potential covalent interactions between the model drug, the polymer matrix, and the selected plasticizer [19]. Pure Glimepiride powder, individual processed samples of sago starch and HPMC, and physical mixtures of the final formulation designs were analyzed. Samples were blended uniformly with pure potassium bromide (KBr) powder at a 1:100 weight ratio and compressed under high mechanical pressure (10 tons) to form thin, transparent analytical disks. The structural scans were gathered across a spectral window from 4000 cm^{-1} to 400 cm^{-1} at a resolution of 4 cm^{-1} using a calibrated FT-IR spectrophotometer.

3.4 Fabrication of Gelatinized *Metroxylon sagu*/HPMC Oral Films

The polymeric thin-film matrices were prepared using the solvent casting technique [20]. Six distinct formulation batches (F1 to F6) were designed with varying weight ratios of gelatinized *Metroxylon sagu* starch and HPMC as detailed in Table 1.

To initiate starch gelatinization, a precise quantity of purified sago starch was dispersed in distilled water under continuous magnetic stirring (300 rpm). The suspension was heated on a thermostatic water bath maintained at 75°C for 45 minutes, allowing the starch granules to swell, hydrate, and rupture to form a clear, viscous hydrogel core. Concurrently, the specified mass of HPMC was dissolved in an organic solvent mixture of methanol and water (80:20 v/v) under continuous stirring until fully hydrated. The plasticizer, glycerol (0.2 mL), was then added to the mixture along with 20 mg of Glimepiride. The gelatinized sago starch phase and the HPMC drug phase were combined under continuous magnetic stirring for 2 hours to ensure complete homogeneity and a bubble-free casting solution. The resulting mixture was cast into clean, structured Petri dishes (9 cm diameter) and dried in a hot-air oven at

45°C for 24 hours. After drying, the uniform films were carefully peeled from the dishes, cut into $2 \times 2\text{ cm}^2$ dosage units, wrapped in protective aluminum foil, and stored in a desiccator.

3.5 Evaluation of Post-Formulation Physical Parameters

3.5.1 Film Thickness and Weight Uniformity

The thickness of each $2 \times 2\text{ cm}^2$ film unit was measured at five random spots (one central point and four corners) using a calibrated digital micrometer screw gauge (0.001 mm accuracy) to confirm batch uniformity [21]. For weight uniformity testing, twenty individual film units from each casting batch were weighed on an electronic analytical balance, and the average values and standard deviations were calculated.

3.5.2 Surface pH Compatibility and Folding Endurance Mechanics

To ensure local tissue compatibility and prevent mucosal irritation, surface pH profiles were evaluated [22]. Individual film units were placed in a Petri dish and moistened with 0.5 mL of distilled water for 30 seconds. A calibrated digital pH electrode was placed in direct contact with the moistened film surface, and the stable reading was recorded. Folding endurance was assessed by repeatedly folding a film sample manually at the same line until it broke or showed structural tearing. The total number of folds completed without structural cracking defined the folding endurance value [21].

3.5.3 Fluid-Induction Swelling Kinetics

The water-binding capacity and swelling kinetics of the films were evaluated using a simulated salivary fluid model [21]. Film sections were weighed (W_1) and placed onto a pre-moistened stainless-steel mesh basket submerged in a phosphate buffer solution (pH 6.8) at room temperature. At regular intervals, the mesh basket was removed, surface moisture was carefully blotted away with filter paper, and the swollen film was re-weighed (W_2). The swelling index percentage was derived using the following equation:

$$\text{Swelling Index } (\%) = \left(\frac{W_2 - W_1}{W_1} \right) \times 100$$

3.5.4 Active Drug Content Uniformity

To determine the uniformity of drug distribution, individual $2 \times 2\text{ cm}^2$ film units were transferred into volumetric flasks containing 100 mL of phosphate buffer solution (pH 6.8). The flasks were subjected to vigorous mechanical shaking and sonication for 45 minutes to dissolve the polymer framework and release the encapsulated Glimepiride. The solution was filtered through a $0.45\ \mu\text{m}$ membrane filter, diluted appropriately with the buffer medium, and analyzed using a UV-Visible spectrophotometer at the maximum absorbance wavelength ($\lambda_{\max} = 228\text{ nm}$) against a blank film baseline [22].

3.6 In Vitro Dissolution and Release Studies

In vitro drug release testing was conducted using a modified USP Type II (Paddle) dissolution test apparatus to evaluate the controlled delivery profile over 6 hours [23]. The dissolution medium consisted of 900 mL of phosphate buffer solution (pH 6.8) maintained at a controlled physiological temperature of $37 \pm 0.5^\circ\text{C}$ with a paddle rotation speed of 50 rpm. Polymeric oral film units containing 20 mg of Glimepiride were secured to stainless steel disks and placed at the bottom of the dissolution vessels.

Aliquots of 5 mL were sampled at fixed intervals (15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes), and an equal volume of fresh, pre-warmed buffer medium was added immediately to maintain sink conditions. The collected samples were filtered and evaluated spectrophotometrically to calculate cumulative drug release percentages over 6 hours.

4. Comprehensive Results and Discussion

4.1 Micromeritic Evaluation and Pre-Formulation Flow Mechanics

The pre-formulation testing of raw Glimepiride powder yielded a bulk density of $0.42 \pm 0.02\text{ g/cm}^3$ and a tapped density of $0.54 \pm 0.03\text{ g/cm}^3$. These density profiles reflect the structural layout and high interparticulate void spaces typical of micronized hydrophobic active ingredients [18]. The computed Carr's Compressibility Index percentage was found to be:

$$\text{Carr's Index} = \left(\frac{0.54 - 0.42}{0.54} \right) \times 100 = 22.22 \pm 1.15\%$$

This score falls into the passable category, indicating a clear tendency for particle bridging and cohesive resistance during processing [18].

This observation was further supported by the calculated Hausner Ratio:

$$\text{Hausner Ratio} = \frac{0.54}{0.42} = 1.28 \pm 0.04$$

This value indicates notable interparticulate friction trends [18]. Additionally, the fixed funnel testing revealed a static angle of repose of $34.12^\circ \pm 1.22^\circ$. This threshold confirms the powder has passable to marginal flow regularities, indicating a high level of physical cohesiveness [18]. These combined micromeritic data points highlight that processing raw Glimepiride powder directly into conventional compressed matrices could present notable manufacturing challenges, such as weight variation or uneven content uniformity. This highlights the value of incorporating a structured liquid-blended polymer casting matrix to ensure highly uniform drug distribution during processing [18,20].

4.2 Structural Compatibility Characterization via FT-IR Spectroscopy

FT-IR spectroscopy confirmed that the molecular structure of Glimepiride remained stable and uncompromised within the blended polymer network [19]. The spectrum of pure Glimepiride displayed its characteristic functional group markers: a distinct sharp peak at 3288 cm^{-1} corresponding to the N-H stretching vibration, a high-intensity absorption band at 1705 cm^{-1} representing the C=O carbonyl stretching vibration, and a sharp peak at 1345 cm^{-1} associated with the asymmetric S=O sulfonamide stretching vibration [19].

FT-IR Transmittance Profile Overlap Analysis:

Sample Matrix	N–H Stretch (cm^{-1})	C=O Stretch (cm^{-1})	S=O Stretch (cm^{-1})	O–H Band (cm^{-1})
Pure Glimepiride	3288	1705	1345	—
Isolated Starch/HPMC Blend	—	—	—	3412
Optimized Blended Batch (F3)	3285	1702	1342	3416

In the spectra of the isolated processed polymers, sago starch and HPMC displayed a broad absorption band at 3412 cm^{-1} indicating extensive intra- and intermolecular O-H stretching from their polysaccharide frameworks, along with a sharp ether linkage stretch (C-O-C) at 1056 cm^{-1} [21,24]. In the spectra of the final blended formulations (F3, F4, and F5), all characteristic peaks of Glimepiride were observed with minor shifts within $\pm 5\text{ cm}^{-1}$ and no new covalent bands or peak disappearances. This confirms that the model drug dissolved uniformly within the gelatinized starch and cellulose network without undergoing structural decomposition or adverse chemical interactions during the thermal solvent casting process [19,20].

4.3 Evaluation of Post-Formulation Physical Profiles

4.3.1 Film Thickness and Gravimetric Weight Uniformity

The physical parameters evaluated across batches F1 through F6 are compiled in Table 2, confirming high reproducibility across all casting runs.

Formulation Code	Average Thickness (mm)	Weight Uniformity (mg)	Surface pH Profile	Folding Endurance	Swelling Index (%)	Drug Content (%)
F1	0.024 ± 0.001	32.4 ± 1.2	6.8 ± 0.05	112 ± 8	123.33 ± 25.16	93.11 ± 1.12
F2	0.082 ± 0.003	44.1 ± 1.8	7.1 ± 0.04	245 ± 12	210.45 ± 31.22	97.54 ± 0.88
F3	$0.0	$38.	$6.	$18	$17	$96

Formulation Code	Average Thickness (mm)	Weight Uniformity (mg)	Surface pH Profile	Folding Endurance	Swelling Index (%)	Drug Content (%)
	51 \pm 0.02$	2 \pm 1.5$	9 \pm 0.02$	9 \pm 10$	5.56 \pm 22.40$	.23 \pm 1.05$
F4	0.042 ± 0.02	36.0 ± 1.1	6.8 ± 0.06	142 ± 9	148.12 ± 19.35	94.87 ± 1.41
F5	$0.090 \p	$46.3 \pm	$7.2 \p	$284 \pm	$222.2	$98.43

Formulation Code	Average Thickness (mm)	Weight Uniformity (mg)	Surface pH Profile	Folding Endurance	Swelling Index (%)	Drug Content (%)
	m0.04$	2.1$	m 0.05$	15$	2 \pm 38.48$	\pm 0.65$
F6	0.033 ± 0.01	34.7 ± 1.4	6.9 ± 0.03	126 ± 7	136.40 ± 17.82	94.15 ± 1.20

***Table 2**: Physico-mechanical evaluation profiles of formulations F1 to F6.*

Average film thickness values ranged between $0.024 \pm 0.01\text{ mm}$ and $0.090 \pm 0.04\text{ mm}$, demonstrating a high degree of physical uniformity. A clear trend emerged where increasing the concentration of semi-synthetic HPMC led to a progressive increase in overall film thickness and weight parameters. This variation can be attributed to the high molecular weight and linear

structural configuration of the cellulose derivative compared to the branched nature of the starch fractions [24]. The low standard deviations across all measured spots confirm that the solvent casting parameters were well-controlled and that the liquid mass spread evenly across the casting surfaces before drying [20,21].

4.3.2 Surface pH Compatibility and Folding Endurance Mechanics

The surface pH across all formulations remained within a neutral physiological range (6.8 ± 0.05 to 7.2 ± 0.05). This confirms that the formulations are highly compatible with human oral mucosa, minimizing the risk of local irritation, redness, or tissue damage during clinical use [22].

Folding endurance testing revealed a clear correlation with polymer composition. Pure sago starch films (F1) exhibited lower mechanical resistance (112 ± 8 folds), while incorporating HPMC (F5) significantly enhanced structural flexibility, raising the value to 284 ± 15 folds. This improvement highlights a strong synergistic effect between the two polymers: the gelatinized starch provides a stable structural core, while the linear cellulose strands distribute mechanical stress more effectively across the polymer network [25]. The addition of glycerol further optimized this effect by locating between the polymer chains, increasing free volume and allowing the matrix to flex easily without breaking [12,25].

4.4 Fluid-Induction Swelling Kinetics and Drug Distribution

Swelling kinetics are critical for oral drug delivery as they directly control fluid penetration and subsequent matrix erosion [21]. Formulations containing higher proportions of HPMC (such as F5) showed maximum swelling indexes, reaching up to $222.22 \pm 38.48\%$. This behavior is driven by the abundant hydrophilic hydroxyl groups along the cellulose chains, which facilitate water binding and create a highly hydrated gel layer [26]. In contrast, pure gelatinized sago films (F1) exhibited a lower swelling capacity ($123.33 \pm 25.16\%$), which helps prevent rapid structure breakdown or premature dissolution in the mouth.

Drug content uniformity across the batches remained exceptionally stable, falling within a tight range between $93.11 \pm 1.12\%$ and $98.43 \pm 0.65\%$. This high uniformity confirms that the solvent casting parameters were well-controlled and demonstrates that the model drug dissolved evenly throughout the blended polymeric matrix without phase separation or particle aggregation during the drying phase [22].

4.5 In Vitro Controlled Dissolution Performance and Kinetics

The cumulative *in vitro* release data for Glimepiride from formulations F1 to F6 over a 360-minute evaluation period are detailed in Table 3.

Formulation Code	15 min	30 min	45 min	60 min	120 min	180 min	240 min	300 min	360 min
F1	28.12	44.30	58.45	72.10	89.44	92.15	94.12	94.15	94.15
F2	12.45	24.18	36.12	44.89	62.33	71.50	81.04	90.45	97.12	
F3	18.90	32.45	45.67	56.12	74.55	82.12	89.23	93.40	96.20
F4	22.34	38.12	51.20	63.45	81.90	87.55	92.45	94.80	95.10
F5	10.11	20.34	31.40	40.23	58.12	68.90	78.56	88.12	96.88
F6	25.67	41.20	54.89	68.12	85.34	90.11	93.18	94.25	94.65

Table 3: Cumulative percentage drug release profiles over a 360-minute time horizon.

The dissolution profiles showed a distinct two-phase release mechanism across all formulations:

1. **Initial Burst Release Phase:** All formulations exhibited a rapid initial release, with over 50% of the drug dissolving within the first 45 to 60 minutes for batches rich in sago starch (F1, F4, F6). This initial burst is highly advantageous for achieving rapid therapeutic blood concentrations, which is essential for managing acute hyperglycemic spikes [27].
2. **Controlled Sustained Release Phase:** Following the initial burst, the drug release rate slowed and stabilized, providing a steady, controlled release that extended up to 360 minutes, with cumulative release values reaching between 93.87% and 97.12%.

This biphasic behavior is directly regulated by the changing composition of the polymer matrix. As fluid enters the film, the highly soluble sago starch fractions dissolve rapidly, creating initial micro-channels that drive the burst release phase. Concurrently, the HPMC component hydrates to form a thick, cohesive viscous gel barrier. This gel layer controls further drug migration by forcing the remaining Glimepiride to diffuse slowly through the tortuous path of the swollen polymer matrix, maintaining a sustained delivery profile over 6 hours [28]. These findings demonstrate that adjusting the ratio of gelatinized *Metroxylon sagu* starch to HPMC allows for precise control over the drug release kinetics, making this biopolymeric system highly suitable for controlled oral applications.

5. Detailed Conclusion and Future Directions

This extensive research demonstrates the development, optimization, and characterization of controlled-release oral thin films utilizing a novel blend of gelatinized sago starch (*Metroxylon sagu*) and Hydroxypropyl Methylcellulose (HPMC). The eco-friendly solvent casting method produced uniform, mechanically resilient films. Incorporating HPMC into the natural sago starch matrix significantly enhanced the physicomechanical performance and folding endurance of the films, while maintaining a neutral surface pH compatible with human buccal tissues.

The *in vitro* dissolution behavior exhibited a highly desirable biphasic kinetic profile, characterized by an initial burst effect for rapid therapeutic onset followed by a sustained, matrix-controlled release extending up to 6 hours. This delivery profile makes the biopolymeric system a promising alternative for the administration of low-dose antidiabetic agents like Glimepiride, particularly for pediatric and geriatric patients facing compliance challenges with conventional solid oral dosages.

Moving toward clinical translation, future research directions will focus on:

1. **Ex Vivo Mucoadhesive Strength Evaluations:** Testing the formulation against isolated bovine or porcine buccal mucosa using a modified tax-balance or texture analyzer setup to measure the peak detachment force and total work of adhesion.
2. **Long-Term Stability Testing:** Evaluating the films under variable temperature and relative humidity profiles according to international ICH guidelines to confirm structural, chemical, and functional shelf-life stability.
3. **In Vivo Pharmacokinetic Profiling:** Testing the optimized formulations in animal models to determine absolute bioavailability parameters, map peak plasma times ($T_{\max}$), and establish reliable *in vitro-in vivo* correlations (IVIVC).

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