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Review Article

A Review of Rational Design of Once-Daily Glipizide Sustained-Release Matrix Tablets

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Abstract:
Type II diabetes mellitus affects over 537 million adults globally, with glipizide remaining a widely prescribed second-generation sulfonylurea. Despite 100% oral bioavailability, glipizide exhibits a short elimination half-life of 2–4.7 hours, high plasma protein binding of 98–99%, and pH-dependent solubility, necessitating 2–3 times daily dosing. This dosing frequency causes peak–trough plasma fluctuations, increasing hypoglycemia risk and reducing patient compliance. Sustained-release (SR) matrix tablets provide a rational solution by maintaining therapeutic plasma concentrations for 12–24 hours with once-daily dosing. This review critically evaluates the formulation and evaluation of glipizide SR matrix tablets, focusing on the mechanistic roles of HPMC K100M and Eudragit RSPO, excipient functionality (advantages and disadvantages), formulation optimization strategies, and recent advances from 2015–2025. Optimized HPMC K100M: Eudragit RSPO blends at 2:1 ratios combined with a 1:1 Lactose: DCP ratio achieve zero-order release over 12–16 hours with f_2 >50 against marketed Glucotrol XL. Challenges of burst release, over-lubrication, and IVIVC establishment are discussed.
Keywords: Glipizide; Sustained release; Matrix tablets; HPMC K100M; Eudragit RSPO; Type II diabetes; Hydrophilic matrix.

Introduction

Type II diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive β-cell dysfunction, affecting approximately 10.5% of the global adult population. Sulfonylureas like glipizide have been prescribed as first-line oral hypoglycemic agents for over four decades.

Glipizide stimulates insulin secretion by binding to the SUR1 subunit of ATP-sensitive K^+ channels on pancreatic β-cells, inducing channel closure, membrane depolarization, calcium influx, and insulin exocytosis. It also exerts extrapancreatic effects including enhanced peripheral glucose uptake and reduced hepatic glucose output. [1]

Despite proven efficacy, conventional immediate-release glipizide tablets present significant pharmacokinetic limitations. With a half-life of only 2–4.7 hours and rapid absorption producing peak plasma concentrations within 1–3 hours, patients require 2–3 doses daily. This results in

pronounced peak–trough fluctuations, hypoglycemic episodes, and poor compliance especially in elderly patients. Sustained-release hydrophilic matrix tablets address these limitations by providing zero-order drug input, reducing dosing frequency, and maintaining therapeutic plasma levels for 12–24 hours. Matrix systems using cellulosic polymers (HPMC) and acrylic polymers (Eudragit) have demonstrated success in achieving the desired extended release profiles for short-half-life drugs. This review critically synthesizes current knowledge on the formulation, evaluation, and optimization of glipizide SR matrix tablets with emphasis on excipient roles, formulation strategies, and translational challenges. [2]

Drug Profile: Glipizide

Pharmacology

Glipizide is a second-generation sulfonylurea insulin secretagogue. It binds with high affinity to SUR1 on pancreatic β-cell ATP-sensitive K^+ channels, inducing channel closure, membrane depolarization, opening of voltage-gated Ca^{2+} channels, and Ca^{2+}-mediated insulin granule exocytosis. Extrapancreatic actions include increased insulin receptor sensitivity, enhanced peripheral glucose utilization, and decreased hepatic glucose production. [3]

Physicochemical and Biopharmaceutical Profile

Glipizide is practically insoluble in water with pH-dependent solubility (higher in alkaline media, pKa 5.9–6.2), creating dissolution challenges in the acidic stomach but favoring absorption in the upper intestine.

With oral bioavailability approaching 100% but a short half-life (2–4.7 hours), extensive hepatic metabolism to inactive metabolites, and 98–99% plasma protein binding, SR formulation is strongly justified to maintain steady therapeutic plasma levels and avoid subtherapeutic troughs. [4]

Table 1: Physicochemical and Biopharmaceutical Profile of Glipizide

Property	Details
Drug Name	Glipizide
IUPAC Name	1-Cyclohexyl-3-[[p-[2-(5-methylpyrazine-2-yl)-2-oxoethyl]phenyl]sulfonyl]urea
Molecular Formula	$C_{21}H_{27}N_5O_4S$
Molecular Weight	~445.54 g/mol
Chemical Category	Second-generation sulfonylurea; insulin secretagogue
Physical Appearance	White or almost white crystalline powder
Dose Range (oral)	2.5–20 mg/day (divided or SR doses)
Solubility	Practically insoluble in water; soluble in alkaline media
pKa	~5.9–6.2 (weak acid)
Protein Binding	~98–99% to plasma proteins
Elimination Half-life	2–4.7 hours
Route of Administration	Oral (immediate and modified release tablets)
Biopharmaceutics	High bioavailability; short half-life; BCS Class II; suitable for SR

Mechanism of Drug Release from Matrix Tablets

Hydrophilic Matrix Mechanism

In hydrophilic matrix tablets, the polymer hydrates upon contact with GI fluid, forming a cohesive gel layer on the tablet surface. Drug release occurs by two simultaneous processes:

(i) diffusion of dissolved drug through the tortuous gel network, and (ii) erosion of the outer gel layer exposing fresh matrix. For glipizide (poorly water-soluble), diffusion predominates. Higher HPMC concentrations increase gel tortuosity, reducing release rate. HPMC alone at 20–40% w/w achieves 12–24 hour release but causes significant initial burst release due to rapid surface hydration. [5]

Hydrophilic–Hydrophobic Binary Matrix Mechanism

When HPMC K100M is combined with a hydrophobic polymer (Eudragit RSPO), both mechanisms operate simultaneously. HPMC forms the hydrated gel diffusion barrier, while Eudragit RSPO creates a rigid hydrophobic framework that: (i) reduces initial water penetration into the matrix, (ii) minimizes burst release, and (iii) prevents premature gel erosion. This dual mechanism produces more linear zero-order release than either polymer alone. Korsmeyer-Peppas exponent n = 0.60–0.75 confirms anomalous (non-Fickian) transport combining diffusion and erosion. Zero-order r^2 >0.98 is achieved with optimized HPMC:Eudragit RSPO (2:1) blends, compared to r^2 ~0.85 with HPMC alone a significant improvement in release linearity. [6]

Excipient Profile and Functional Role in Matrix Tablets

Polymers are the most critical components of glipizide SR matrix tablets. Both hydrophilic and hydrophobic polymers are commonly employed, individually or in combination, to achieve the desired controlled release profile. The following section provides a critical review of each excipient used, including its mechanism, advantages, disadvantages, and specific role in glipizide SR matrices. [7]

Hydroxypropyl Methylcellulose (HPMC K100M)

HPMC K100M is the most widely used hydrophilic matrix-forming polymer. It hydrates rapidly in GI fluid, forming a thick, cohesive gel layer (2% w/v viscosity ~100,000 mPa·s) that serves as the primary diffusion barrier. Drug release occurs by diffusion through the gel network and simultaneous outer gel erosion.

Advantages:

- Produces robust, consistent gel layer ensuring 12–24 hour release at 20–40% w/w
- Non-ionic; compatible with most drugs and excipients; pH-independent swelling
- Excellent safety profile; listed in all major pharmacopoeias (IP, USP, BP, EP)
- Suitable for both direct compression and wet granulation

Disadvantages:

- Causes significant initial burst release (~25–35% in 1 hour) when used alone
- Cohesive nature results in poor powder flow; requires glidant (colloidal SiO_2)
- IVIVC establishment is challenging for BCS Class II drugs without additional retardant
- High levels (>40% w/w) needed for very soluble drugs, increasing tablet weight [8]

Role in Glipizide SR: At 20–40% w/w, HPMC K100M forms the primary release-controlling gel. However, burst release (~25–35%) necessitates combination with Eudragit RSPO. The 2:1 HPMC:Eudragit blend provides the optimal balance between gel formation and burst release control.

Eudragit RSPO

Eudragit RSPO is a water-insoluble but water-permeable copolymer (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride).

In the matrix, it forms a rigid hydrophobic framework that restricts water penetration, reduces matrix porosity, and slows glipizide diffusion. It is pH-independent, ensuring consistent release throughout the GI tract.

Advantages:

- Reduces burst release from ~25–35% (HPMC alone) to <10% at 2 hours
- Reinforces matrix mechanical strength; prevents premature matrix disintegration

- pH-independent; consistent release from stomach to colon
- Allows reduction of total polymer load, improving blend processability

Disadvantages:

- Alone, gives incomplete release (<70% at 12 hours) due to excessive hydrophobicity
- Expensive compared to cellulosic polymers
- Requires careful blending; poor distribution causes uneven release
- At >20% w/w, causes under-release and sub-therapeutic drug levels. [9]

Role in Glipizide SR: Functions as the hydrophobic retardant at 10–20% w/w. Neither HPMC alone nor Eudragit alone achieves the target profile. At 2:1 HPMC:Eudragit ratio, the combination achieves zero-order release (r^2 >0.98) over 12–16 hours with f_2 >50 versus Glucotrol XL. [10]

Lactose Monohydrate: Lactose monohydrate is a crystalline, water-soluble diluent. In the HPMC matrix, it dissolves upon hydration, creating pores and channels that increase effective surface area for drug diffusion, modestly accelerating release.

Advantages: Improves compressibility; fine-tunes release rate as a pore-former; widely accepted; compatible with glipizide.

Disadvantages: Excessive levels (>30% w/w) cause burst release and loss of sustained action; the Lactose:DCP ratio is a critical formulation variable requiring careful optimization. [11]

Role in Glipizide SR: Used at 10–30% w/w. A 1:1 Lactose:DCP ratio provides optimal matrix porosity for 12-hour zero-order release (r^2 = 0.9959). Increasing lactose to 40 mg/tablet caused 25% burst release in 1 hour.

Dibasic Calcium Phosphate (DCP): DCP is a water-insoluble, slightly basic inorganic diluent. Unlike lactose, it does not dissolve during dissolution, remaining as an insoluble skeleton maintaining matrix integrity and lengthening diffusional pathways.

Advantages: Excellent compressibility; low hygroscopicity; insoluble skeleton maintains structural integrity; chemically inert; slightly basic microenvironment may aid glipizide solubility.

Disadvantages: Excess (>40 mg/tablet) extends release beyond 20 hours with incomplete drug release; cannot be used as sole diluent — must be balanced with lactose.

Role in Glipizide SR: At 10–30% w/w with 1:1 Lactose:DCP ratio, provides optimal structural balance. Increasing DCP to 40 mg/tablet extended release beyond 20 hours clinically unacceptable for once-daily dosing. [12]

Microcrystalline Cellulose (MCC PH 102)

MCC PH 102 is a directly compressible, partially depolymerized cellulose (mean particle size ~100 μm). It provides excellent compressibility through plastic deformation, ensuring adequate tablet hardness at low compression forces.

Advantages:

Outstanding compressibility; ensures hardness >5 kg/cm² even at 8 kN; chemically inert; promotes uniform drug distribution.

Disadvantages: May slightly accelerate water uptake through capillary action; higher cost than conventional diluents; does not contribute to release retardation.

Role in Glipizide SR: Used at 15–40% w/w as the mechanical backbone. Ensures hardness 5–7 kg/cm² and friability <0.8% without affecting the SR release profile. [13]

Colloidal Silicon Dioxide: 765dColloidal silicon dioxide (surface area >200 m²/g) functions as a glidant by coating excipient particles and reducing interparticulate friction, which is essential in cohesive HPMC-Eudragit blends.

Advantages: Highly effective glidant at 0.5–1.0% w/w; reduces angle of repose from ~38° to ~26°; prevents segregation; chemically inert.

Disadvantages: Over-glidation at >1% w/w may reduce tablet hardness; fine particles require GMP handling precautions.

Role in Glipizide SR: At 0.5–1.0% w/w, essential for acceptable die filling uniformity and tablet weight consistency in HPMC-Eudragit blends. [14]

Magnesium Stearate

Magnesium stearate is a hydrophobic lubricant used at 0.5–1.0% w/w to reduce die-wall friction. It forms a thin hydrophobic film on particle surfaces.

Advantages: Highly effective lubricant at low concentration; prevents sticking during compression; pharmacopoeially accepted.

Disadvantages: Over-lubrication (>1% w/w or mixing >3 min) creates hydrophobic barriers retarding wettability and reducing glipizide release by ~20%; blending time is a critical process parameter.

Role in Glipizide SR: Used at 0.5–1.0% w/w with strictly controlled blending time of 2–3 minutes a validated critical process parameter. [15]

Evaluation of Glipizide Sr Matrix Tablets

Pre-compression Parameters

Good powder flow is critical for uniform die filling. Target values for glipizide SR blends: angle of repose <30°, Carr's index 12–16%, Hausner ratio <1.25. Colloidal silicon dioxide (0.5–1.0% w/w) reduces angle of repose from ~38° to ~26° in HPMC-Eudragit blends. [16]

Post-compression Parameters

Required: hardness 5–7 kg/cm², friability <0.8%, weight variation ±5%, content uniformity 95–105%. MCC PH 102 ensures hardness >5 kg/cm² even at 8 kN compression force. [17]

Swelling, Erosion and In Vitro Dissolution

HPMC K100M matrices alone show 250–350% swelling and ~35% erosion in 8 hours. Addition of Eudragit RSPO reduces swelling to 180–220% and erosion to ~18%, confirming matrix reinforcement by the hydrophobic framework.

Dissolution testing: USP Apparatus II, 50 rpm, 900 mL (0.1 N HCl for 2 h, then pH 6.8 phosphate buffer). Target profile: <25% at 2 h, 45–65% at 6 h, >85% at 12 h. HPMC:Eudragit (2:1) blends with 1:1 Lactose:DCP ratio consistently meet this profile. Korsmeyer-Peppas exponent n = 0.60–0.75 confirms anomalous transport; zero-order r^2 >0.98 confirms near-ideal SR kinetics.

Recent Advances and Challenges

Recent Advances

Floating and Gastroretentive Systems:

Since glipizide absorption is primarily limited to the stomach and upper duodenum, floating matrix tablets using HPMC K100M + sodium bicarbonate have been developed to extend gastric residence to 6–8 hours, increasing bioavailability 1.8-fold.

Teja et al. (2025) reported floating glipizide tablets achieving zero-order release over 12 hours with f_2 = 71.3, demonstrating improved absorption compared to conventional SR systems.

Natural–Synthetic Hybrid Matrices: Xanthan gum combined with HPMC K100M reduces synthetic polymer use by 30% while maintaining 12-hour release with comparable f_2 values. Guar gum and alginate combinations provide cost-effective alternatives with acceptable SR profiles, particularly relevant for low-cost generic formulations. [18]

Conclusion and Future Prospects

This review critically evaluated the rationale, formulation strategies, and evaluation of once-daily glipizide SR matrix tablets based on HPMC K100M–Eudragit RSPO blends with optimized Lactose–DCP ratios.

Key conclusions:

1. HPMC K100M alone causes burst release; Eudragit RSPO alone gives incomplete release. Their combination at 2:1

ratio achieves zero-order release (r^2 >0.98) over 12–16 hours neither polymer is adequate alone.
2. A **1:1 Lactose: DCP ratio** provides optimal matrix porosity for 12-hour zero-order release with $r^2 = 0.9959$.
3. **Magnesium stearate blending time** (2–3 min maximum) is a critical process parameter that must be validated to prevent over-lubrication-induced dissolution failure.
4. **QbD-based factorial design** is the recommended optimization strategy for defining a robust formulation design space. [19]

Identified Research Gaps:

- Level A IVIVC for HPMC-Eudragit glipizide systems needs validation across multiple formulations
- In vivo pharmacokinetic studies in T2DM patients (not only healthy volunteers) are lacking
- Long-term physical and chemical stability studies of binary polymer blends under ICH accelerated conditions are underreported
- 3D-printed glipizide SR tablets using HPMC as the printing matrix represent a promising future direction for individualized dosing

Rational excipient selection guided by QbD principles will continue to drive development of robust once-daily glipizide SR matrices that improve glycemic control and patient adherence in T2DM management. [20]

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