



Review Article

Glipizide in Situ Gels: A Promising Approach for Gastroretentive Drug Delivery

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ABSTRACT

Glipizide, a second-generation sulfonylurea, is widely used to manage type 2 diabetes. However, it requires frequent dosing to its short half-life, low bioavailability, and site-specific absorption in the upper gastrointestinal tract. Gastroretentive drug delivery system (GRDDS), especially in situ gels, address these issues by extending gastric retention and allowing sustained drug release. These systems convert from liquid to gel in response to physiological triggers like pH, ions, or temperature. Key polymers such as sodium alginate, gellan gum, poloxamers, and HPMC are used to formulate these gels. Evaluation parameters include gelation capacity, drug release profile, mucoadhesive strength, and floating behavior. Research indicates that in situ gels can sustain drug release for 12-24 hours, enhancing therapeutic efficacy and patient compliance. Despite their promise, challenges remain, such as ensuring formulation consistency and scalability. Future studies should focus on optimizing polymer combinations, conducting in vivo studies for validation, and addressing regulatory requirements to ensure safe and effective clinical use.

INTRODUCTION

Technologies involving in situ gel formation have been extensively studied as a means of long-term medication administration. The benefits of in-situ reforming polyamide dosage forms, including their ease of drug use, decreased time spent on treatment, increased adherence from patients,

and comfort, have piqued enthusiasm^[1]. However, conventional oral formulations are limited by glipizide's short half-life (2–4 hours), pH-dependent solubility, and absorption confined to the upper gastrointestinal tract. These pharmacokinetic constraints lead to frequent dosing, poor bioavailability, and increased risk of hypoglycemia due to plasma level fluctuations^[2].

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In situ gel, as shown in the Table. 1 and 2, based on gastroretentive drug delivery systems (GRDDS), offer a promising alternative. These formulations are administered as liquids and form gels in the stomach in response to physiological

stimuli like pH, temperature, or ionic changes [3]. The gel adheres to the gastric mucosa or floats on gastric fluids, prolonging gastric residence and allowing site-specific, sustained drug release.

Table.1: Overview of In Situ Gel Systems for Glipizide

Attributes	Details	References
Advantages	<ul style="list-style-type: none"> • Improved bioavailability • Reduced dosing frequency • Minimized side effects • Enhanced patient compliance (especially chronic use) • Suitable liquid form for pediatric and geriatric patients 	[4]
Drawbacks	<ul style="list-style-type: none"> • Formulation complexity • Need for precise, reliable trigger–response mechanisms 	[5]
Limitations	<ul style="list-style-type: none"> • Patient-to-patient variability in gelation • Differences in gastric conditions affecting performance 	[6]
Importance	<ul style="list-style-type: none"> • Targeted, patient-friendly approach to optimizing glipizide therapy 	[7]

Table.1 Types of In Situ Gel System

Type of In Situ Gel System	Mechanism of Gelation	Examples	References
pH-Sensitive Gels	Gelation occurs in acidic pH (such as the stomach environment)	Gellan gum, Carbopol	[8]
Ion-Activated Systems	Gelation induced by ions (e.g., Ca ²⁺) present in gastric fluids	Gellan gum + calcium ions	[9]
Temperature-Sensitive Gels	Gelation occurs at body temperature (~37°C)	Poloxamers (e.g., Poloxamer 407)	[10]

Mechanism of In Situ Gels in Gastroretentive Drug Delivery Systems (GRDDS)

In situ gels are a promising approach within gastroretentive drug delivery systems (GRDDS), particularly beneficial for drugs like glipizide that have a narrow absorption window in the upper gastrointestinal tract. These formulations are administered as liquids and undergo a sol-to-gel transformation once they encounter physiological conditions in the stomach. The mechanisms through which they work can be categorized as physical, physicochemical, and biological [11].

1. Physical Mechanisms

The primary physical mechanisms include floating and mucoadhesion. Floating in situ gels are designed to have a lower density than gastric fluids, allowing them to float on the stomach contents. This buoyant property helps the formulation stay in the stomach longer, avoiding premature transit to the intestines [12]. Another physical mechanism is mucoadhesion, where the gel adheres to the gastric mucosa through weak physical interactions such as hydrogen bonding or van der Waals forces. This localized adhesion



prevents displacement by gastric motility, enhancing gastric retention time [13].

2. Physicochemical Mechanisms

These involve environmental triggers that induce gelation. pH-sensitive systems respond to the acidic pH of the stomach, where polymers like sodium alginate and Carbopol gel, upon exposure to gastric fluids [14]. Ion-sensitive gels use polymers like gellan gum or pectin, which undergo gelation in the presence of divalent ions (e.g., Ca^{2+} or Mg^{2+}) naturally present in the stomach. Thermosensitive gels, such as those made with poloxamers, remain liquid at room temperature but form gels at body temperature ($\sim 37^\circ\text{C}$), enabling temperature-triggered gelation after administration [15].

3. Biological Mechanisms

Less commonly used in GRDDS, enzyme-triggered systems rely on specific enzymes to initiate gelation. These are more applicable to site-specific delivery in the intestines rather than the stomach, but remain an area of research interest [16].

POLYMERS USED IN IN SITU GEL FORMULATIONS

1. Gellan Gum

Ion-activated polysaccharides form in situ gels in the presence of divalent cations like calcium (Ca^{2+}). The gelation occurs through ionic crosslinking between the polymer chains and the ions, providing structural integrity and prolonged gastric retention [17]. These polymers exhibit high gel strength and stability, making them suitable for sustained drug delivery. When combined with gas-generating agents, they offer excellent floating ability, enhancing gastric retention.

Additionally, they are biocompatible and well-tolerated, ensuring safety for long-term use [18].

2. Sodium Alginate

Natural polysaccharides, such as sodium alginate, form ion-sensitive in situ gels through interaction with calcium ions, creating an “egg-box” structure [19]. Polymers are mucoadhesive, non-toxic, and form soft yet stable gels. Increasing their concentration enhances gel strength, prolongs drug release, and influences gelation time and mechanical properties [20].

3. Carbopol

pH-sensitive synthetic polymers, such as Carbopol, swell and form gels in acidic environments through hydrogen bonding and chain entanglement [21]. They exhibit excellent thickening and mucoadhesive properties, making them suitable as primary or secondary gelling agents. Even at low concentrations, they significantly increase viscosity, while higher concentrations strengthen the gel network and may delay drug release [22].

4. HPMC (Hydroxypropyl Methylcellulose)

Semi-synthetic cellulose derivatives, such as HPMC (Hydroxypropyl Methylcellulose), primarily function as viscosity enhancers and drug release modulators. They possess good film-forming and stabilizing properties and are non-reactive, making them compatible with other polymers. Increasing their concentration enhances viscosity and mucoadhesiveness while slowing drug diffusion through the gel matrix, contributing to sustained release [23].

FORMULATION STRATEGIES FOR GLIPIZIDE IN SITU GELS



Developing an effective gastroretentive in situ gel system for glipizide requires precise formulation strategies to ensure prolonged gastric residence, consistent gelation, and controlled drug release [24]. Key considerations include:

1. Optimization of Polymer Concentration

- The choice and concentration of polymers such as gellan gum, sodium alginate, or poloxamer 407 directly influence the viscosity, gel strength, and drug diffusion rate.
- An optimal balance is necessary: too low may lead to weak gelation, while too high may hinder pourability and drug release [25].

2. Selection and Use of Gelling Agents

- Ion-induced gelation is commonly employed using:
 - Calcium carbonate (CaCO_3): Slowly releases calcium ions, promoting gradual and sustained gelation.
 - Calcium chloride (CaCl_2): Provides immediate and strong ionic crosslinking for quick gelation.
- The amount and form of calcium source affect the rate and uniformity of gel formation [26].

3. pH Adjustment

- Ensuring that the formulation gels specifically in the acidic pH of the stomach (~1.2) is critical.
- An acidic pH promotes gelation in pH-sensitive polymers, such as Carbopol, and helps maintain drug solubility and stability.
- Buffers or acidifiers may be added to maintain appropriate pH for triggering gelation post-administration [27].

Drug Loading and Compatibility

- Uniform dispersion of glipizide within the gel matrix is essential for consistent dosing and reproducible release profiles.
- Drug-polymer interactions must be studied to avoid precipitation, crystallization, or incompatibility that may affect performance.

These formulation strategies play a vital role in achieving the desired gastroretentive behavior, mucoadhesion, and therapeutic efficiency of glipizide in situ gel systems [28].

EVALUATION PARAMETERS OF GLIPIZIDE IN SITU GELS

Through evaluation of in situ gel formulations is essential to ensure their performance, stability, and therapeutic efficiency. The following parameters are commonly assessed:

IN VITRO GELATION STUDY

This study evaluates the ability of in situ gel formulations to undergo sol-to-gel transition under simulated gastric conditions, typically using simulated gastric fluid (pH ~1.2). Gelation may be triggered by pH change (e.g., Carbopol), ionic interaction (e.g., gellan gum, sodium alginate), or temperature shift (e.g., poloxamer 407) [29].

For ion-activated systems, divalent cations like Ca^{2+} (from calcium chloride or calcium carbonate) promote gel formation via ionic crosslinking [30].

Gelation is assessed based on:

- Time required for gelation
- Gel clarity and strength
- Stability of the formed gel

VISCOSITY AND RHEOLOGICAL BEHAVIOR

This parameter assesses the flow characteristics of the formulation before and after gelation using a viscometer or rheometer. Ideal in situ gels show



pseudoplastic (shear-thinning) behavior, allowing easy administration and strong gel formation in the stomach [31]. Viscosity directly influences pourability, Spreadability, and gastric retention, making it a critical factor in formulation performance [32].

FLOATING ABILITY AND GEL STRENGTH

Floating ability is assessed by measuring floating lag time and total floating duration in simulated gastric fluid, crucial for prolonged gastric retention. Gel strength is evaluated using a texture analyzer or penetration test, ensuring the gel can withstand gastric motility and sustain drug release. Together, these parameters enhance gastric retention and ensure localized, controlled drug delivery [33].

IN VITRO DRUG RELEASE AND KINETIC MODELING

Drug release is evaluated using a USP dissolution apparatus, and results are analysed using kinetic models like Zero-order, First-order, Higuchi, and Korsmeyer-Peppas. This helps determine the release rate and mechanism, assessing the formulation's capability for sustained drug delivery [34].

IN VIVO STUDIES

In vivo studies are essential for evaluating the pharmacokinetic profile and therapeutic efficacy of glipizide in situ gel formulations. These studies are typically carried out in appropriate animal models or human volunteers to determine key pharmacokinetic parameters such as C_{max} (maximum plasma concentration), T_{max} (time to reach C_{max}), and AUC (area under the plasma concentration-time curve). The performance of the in-situ gel is compared with that of conventional glipizide dosage forms to assess

improvements in drug delivery. Enhanced bioavailability, prolonged drug action, and reduced dosing frequency are primary indicators of formulation success [35]. These studies help establish the effectiveness of the gel in sustaining drug release and improving patient compliance. Additionally, therapeutic outcomes such as blood glucose regulation are monitored to confirm clinical efficacy. Overall, in vivo evaluations are crucial for translating in vitro performance into real-world therapeutic benefits [36].

FUTURE PERSPECTIVES

The development of glipizide in situ gels presents numerous opportunities for innovation in drug delivery. One promising direction is the formulation of combination therapies, such as co-delivery with metformin, to improve glycaemic control in type 2 diabetes. Furthermore, advances in smart in situ gels—responsive to multiple physiological stimuli like pH, temperature, or glucose levels—could enable controlled, site-specific drug release tailored to patient needs. Future research should also focus on clinical trials to establish long-term efficacy, safety, and patient compliance. In addition, this delivery platform can be extended to other drugs with narrow absorption windows, low solubility, or requiring sustained gastric residence, making it a versatile strategy in oral drug delivery.

CONCLUSION

Glipizide in situ gels represent a promising gastroretentive drug delivery system that enhances bioavailability, ensures prolonged therapeutic action, and enables reduced dosing frequency. With optimized formulation strategies and comprehensive evaluation, these systems can significantly improve the management of diabetes by providing sustained and targeted drug release. As research advances, further clinical validation



will be crucial to confirm their safety and efficacy, paving the way for personalized therapies and potential combination treatments. This innovative approach holds strong potential for broader application in oral delivery of drugs with similar absorption characteristics.

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CONFLICT OF INTEREST

All authors, including the guide and co-guide, declare that there are no conflicts of interest related to the publication of this review article.

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