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Review Article

In Situ Gel Based Smart Drug Delivery Systems: Chemical Insights and Application in Diabetes

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ABSTRACT

Stimuli-responsive *in situ* gel-based smart drug delivery systems represent an innovative approach to diabetes therapy that addresses the limitations of conventional formulations, such as poor bioavailability, short drug half-life, and frequent dosing. These systems undergo sol-to-gel transitions in response to physiological stimuli, including pH, temperature, ions, and enzymatic activity, enabling controlled and prolonged drug release. Synthetic polymers such as poloxamers, polyethylene glycol (PEG) derivatives, and poly(*N*-isopropylacrylamide) (PNIPAAm) allow the precise modulation of gelation behavior, stability, and physicochemical properties. Due to their biocompatibility and stimuli-responsiveness, *in situ* gels have been explored via oral, nasal, ocular, injectable, and transdermal routes for the delivery of insulin, oral hypoglycemics, and peptide-based drugs. Recent advances have integrated nanoparticles and glucose-sensitive components for feedback-regulated insulin release, closely mimicking pancreatic β-cell function, and improving therapeutic precision. Despite challenges, such as limited mechanical strength, gelation variability, and regulatory constraints, continued progress in polymer chemistry, nanotechnology, and biomaterial design is expected to overcome these barriers. Collectively, the *in-situ* gel-based delivery systems offer a promising, patient-friendly, and physiologically adaptive platform for next-generation diabetes management.

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Content

1. Introduction

Rapid diabetes mellitus (DM) is a significant metabolic condition in the 21st century and is characterized by persistent hyperglycemia due to impairment in insulin production, insulin action, or both. The incidence of diabetes has escalated to alarming proportions globally, propelled by aging demographics, inactive lifestyles, and poor nutritional practices [1]. The International diabetes federation (IDF) reports that more than 500 million individuals worldwide are affected by diabetes, with projections indicating a substantial increase in this population in the coming decades. The increasing disease burden not only threatens public health, but also imposes enormous economic and social costs on healthcare systems. Effective management of diabetes requires not only glycemic control, but also the prevention of associated concerns, including retinopathy, nephropathy, neuropathy, and cardiovascular disease [2]. Despite the availability of a wide range of pharmacological agents, clinical management of diabetes remains suboptimal for many patients. This is largely due to the limitations of conventional drug delivery systems, which often fail to provide sustained therapeutic efficacy, minimize adverse effects, or adequately address patient compliance. These challenges have created an urgent need for innovative therapeutic strategies, among which *in situ* gel-based smart drug delivery methods have attracted significant interest due to their potential to revolutionize diabetes treatment [3].

1.1. Diabetes: An overview

DM is broadly classified into type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes, with T1DM and T2DM being the most prevalent. T1DM, often diagnosed in children or young adults, results from autoimmune obliteration of pancreatic β-cells, culminating in complete insulin insufficiency. Conversely, T2DM, which is responsible for more than 90% of global diabetes cases, is characterized by insulin resistance in peripheral tissues and increased β-cell failure. The interaction of genetic susceptibility, obesity, lifestyle, and environmental variables facilitates the onset of T2DM. Gestational diabetes, while temporary, increases the risk of problems during pregnancy and predisposes both the mother and child to future metabolic conditions [4]. The long-term consequences of uncontrolled diabetes extend beyond glycemic imbalances. Persistent hyperglycemia triggers the development of advanced glycation end products (AGEs), oxidative stress, and chronic inflammation, which significantly contribute to both microvascular and macrovascular problems. These pathological consequences underscore the need for stringent and sustained glycemic control. Current pharmacological options include insulin therapy, oral hypoglycemic agents (such as sulfonylureas, biguanides, thiazolidinediones, and DPP-4 inhibitors), and newer classes of drugs such as GLP-1 receptor agonists and SGLT-2 inhibitors. Although these therapies target different aspects of glucose homeostasis, their efficacy is often hindered by

issues such as poor bioavailability, short half-life, systemic side effects, and patient noncompliance [5]. Another important consideration is the need for personalized medicine for diabetes management. Factors such as patient age, comorbidities, lifestyle, and genetic background influence the drug response, making it difficult to achieve universal therapeutic success with conventional treatment regimens. This complexity reinforces the demand for novel drug delivery platforms that can provide site-specific, controlled, and patient-friendly drug administration, while reducing dosing frequency and minimizing adverse effects [6]. **Figure 1** illustrates the mechanism of glucose uptake via insulin signaling. Under healthy conditions, insulin binds to its receptor, activating the glucose transporter (GLUT4) to facilitate glucose entry into cells. In T1DM, insulin is absent, preventing glucose uptake despite the presence of functional receptors and transporters. In T2DM, insulin is present, but its receptors are desensitized, resulting in impaired GLUT4 activation and reduced glucose entry.

1.2. Challenges in conventional antidiabetic drug delivery

Despite the diversity of available pharmacological options, traditional drug delivery methods for diabetes are far from ideal. The oral route, which is preferred for patient adherence, encounters significant challenges including enzymatic breakdown in the gastrointestinal tract, inadequate permeability across the intestinal epithelium, and substantial first-pass metabolism in the liver. Many peptide-based therapies, such as insulin, GLP-1, and amylin analogs, exhibit poor oral bioavailability, necessitating parenteral administration. Therefore, insulin injections remain the cornerstone of T1DM therapy and are increasingly required in patients with advanced T2DM. However, subcutaneous injections have significant drawbacks, including pain, local tissue reactions, risk of infection, needle phobia, and reduced adherence to therapy [7]. Conventional formulations typically provide pulsatile or immediate release of an active drug, which fails to mimic the physiological secretion profile of endogenous insulin. This pharmacokinetic mismatch often results in episodes of hyperglycemia and hypoglycemia, both of which are harmful to patients in the long-term. Sustained release systems have been developed, but many lack precision in drug release and do not respond dynamically to fluctuating blood glucose levels [8]. Another significant challenge is patient compliance. Diabetes management requires lifelong therapy, strict dosing schedules, and frequent monitoring of the blood glucose levels.

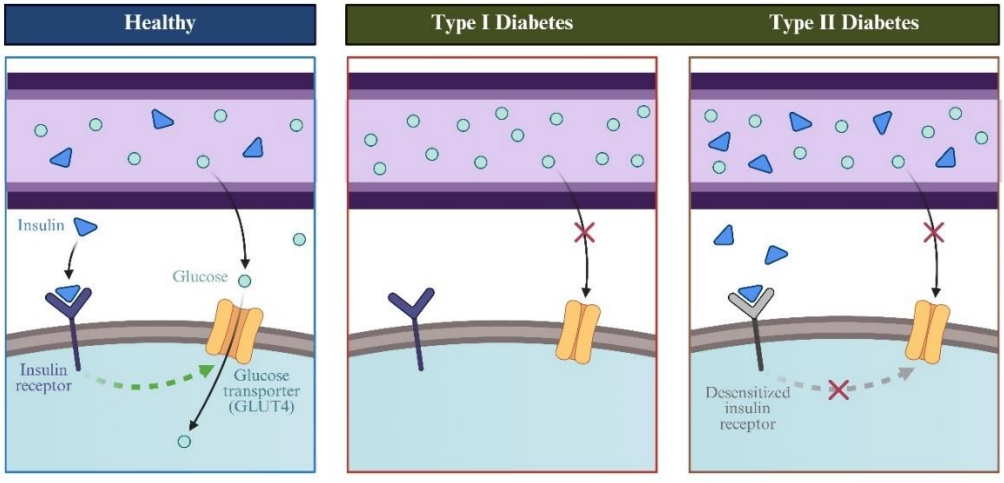

Figure 1. Mechanism of glucose uptake in healthy, type I, and type II diabetes. Insulin receptor activation promotes GLUT4-mediated glucose transport; its absence or desensitization causes impaired uptake

The burden of multiple daily injections or oral dosing regimens can compromise adherence, particularly in elderly and pediatric patients. Additionally, pharmacological management of diabetes often involves polypharmacy, as patients commonly require concomitant treatment for hypertension, dyslipidemia, or cardiovascular complications. The resulting pill burden further exacerbates compliance issues [9]. From a formulation perspective, antidiabetic drugs present challenges, such as poor aqueous solubility, instability in biological fluids, and limited permeability across biological membranes. For example, insulin is sensitive to enzymatic degradation and environmental stressors such as temperature, pH, and shear forces. These properties complicate the formulation into stable and effective dosage forms. Similarly, many oral antidiabetic agents have poor pharmacokinetics, necessitating frequent dosing or high doses that increase the risk of side effects [10]. Conventional delivery methods offer limited capacity for personalized or responsive therapies. Because blood glucose levels fluctuate throughout the day based on diet, activity, and hormonal changes, an ideal drug delivery system should adaptively respond to these variations. Unfortunately, most traditional formulations provide a static release profile, making it difficult to achieve precise and dynamic glycemic control [11].

1.3. Need for smart drug delivery systems

The constraints of traditional medication administration in diabetes control underscore the pressing need for new patient-centric and physiologically adaptive methods. Intelligent drug delivery systems have been designed to address the pharmacokinetic and pharmacodynamic limitations of conventional formulations using improved materials, stimuli-responsive mechanisms, and innovative administration methods. *In situ* gel-based systems are promising because they can generate gels under physiological conditions and maintain regulated drug release [12]. *In situ* gels are liquid mixtures that shift from a sol to a gel state when subjected to physiological stimuli, including temperature, pH, ionic strength, or enzyme activity. This unique property enables them to be easily administered through minimally invasive routes (oral, nasal, ocular, and injectable), after which they form a depot at the site of administration. The gel matrix provides prolonged residence time, controlled release, and protection of labile drugs from degradation, making it especially suitable for peptide- and protein-based antidiabetic agents, such as insulin [13]. One of the most compelling advantages of smart *in situ* gel systems is their ability to mimic physiological insulin secretion. By incorporating glucose-sensitive polymers or nanoparticles within the gel matrix, these systems can achieve feedback-regulated drug release, releasing insulin in response to hyperglycemia and reducing insulin release during normoglycemia. Such “intelligent” or self-regulated delivery has the potential to significantly reduce the risk of hypoglycemia, improve glycemic control, and enhance patient quality of life [14]. *In situ* gel formulations can improve patient compliance by reducing the dosing frequency and offering less invasive administration options. For instance, intranasal or oral *in situ* gels may provide noninvasive alternatives to injections, thereby addressing one of the most significant barriers to adherence to insulin therapy. From a pharmaceutical perspective, the flexibility of *in situ* gel systems allows for combination therapies in which multiple drugs can be co-delivered to target different pathways in the pathophysiology of diabetes. This is particularly relevant in T2DM, for which multidrug therapy is often required [15]. In addition to their therapeutic advantages, *in situ* gels offer formulation and commercial benefits. They can be formulated using both natural and synthetic polymers, providing adjustable characteristics such as gelation temperature, viscosity, and degradation rate. This versatility makes these materials appealing candidates for scale manufacturing and clinical translation. Regulatory interest in such advanced delivery systems is growing, and several *in situ* gel formulations have already been approved for non-diabetic indications, paving the way for their application in diabetes.

The urgent need for smart drug delivery systems for diabetes arises from the shortcomings of conventional therapies in terms of efficacy, safety, and patient adherence. *In situ* gel-based smart delivery platforms provide a versatile, adaptable, and physiologically responsive solution that holds great promise for addressing these challenges. The subsequent sections of this review explore the chemical principles underlying *in situ* gel systems, their formulation strategies, and their potential applications in diabetes management [16].

2. *In Situ* Gel Systems: Fundamentals

In situ gel systems have emerged as promising platforms in the field of advanced drug delivery, bridging the gap between conventional formulations and stimuli-responsive "smart" delivery technologies. These systems are unique in that they are administered in a liquid or low-viscosity form and subsequently undergo phase transition into a gel under physiological conditions. This transition creates a depot at the site of administration from which the drug is released in a controlled and sustained manner [13]. The fundamental principle of *in situ* gels lies in exploiting physiological triggers, such as pH, temperature, ionic strength, or enzymatic activity, to induce sol-to-gel transformation. Due to their minimally invasive administration, prolonged residence time, and capacity for stimuli-responsive drug release, *in situ* gels are highly relevant for diseases requiring long-term and precise pharmacological management, such as DM. Understanding the concept, mechanisms, and classification of *in situ* gels provides a foundation for exploring their chemical properties and therapeutic applications [17].

2.1. Definition and concept of in situ gels

The phrase "*in situ* gel" denotes polymeric formulations that exist as liquids before injection and later as gel at the delivery site in reaction to physiological cues. The word "*in situ*," meaning "in place," highlights the localized gelation process that occurs after administration rather than prior to administration. This property distinguishes *in situ* gels from preformed hydrogels, which exist as semi-solid matrices before administration and often require surgical implantation [18]. The fundamental advantage of *in situ* gels lies in their dual nature; they combine the ease of administration of liquid formulations (such as solutions or suspensions) with the drug release benefits of solid or semi-solid depots. For example, injectable *in situ* gels can be administered through a fine needle as a fluid, minimizing patient discomfort; however, once inside the body, they form a gel matrix that provides sustained drug release, improved bioavailability, and enhanced therapeutic efficacy [13]. The *in situ* gel concept has been successfully applied across multiple routes of administration, including ocular, nasal, oral, rectal, vaginal, and parenteral. Each route uses different physiological triggers to achieve gelation. In the context of diabetes therapy, injectable and oral *in situ* gels have attracted particular attention due to their potential to replace frequent insulin injections and enhance the bioavailability of poorly absorbed antidiabetic drugs [19].

2.2. Mechanism of sol-to-gel transition

The central feature of *in situ* gel systems is their ability to undergo sol-to-gel phase transition under physiological conditions. This process is driven by physicochemical changes in the polymer network, which result in the formation of a cross-linked three-dimensional structure capable of retaining water and encapsulating drug molecules [20].

The mechanisms underlying sol-to-gel transition vary depending on the type of trigger: *Thermodynamic interactions*: Temperature changes can alter the hydrophilic and hydrophobic interactions within polymer chains. For example, certain polymers undergo coil-to-globule transitions as the temperature increases, leading to aggregation and gelation [21]. *pH-driven ionization*: In pH-responsive polymers, changes in the ionization state of functional groups, such as carboxyl or amino

groups, lead to solubility changes, precipitation, or gel formation [22-24]. *Ionic crosslinking*: Polymers such as alginate and gellan gum undergo gelation in the presence of multivalent cations that form ionic bridges between polymer chains [25]. *Enzymatic reactions*: Enzyme-responsive gels rely on the enzymatic cleavage or crosslinking of polymeric precursors, leading to gelation at the site where the enzyme is present [26].

In most systems, gelation is a reversible process that allows the gel matrix to gradually degrade and release its drug payload over time. The release kinetics are influenced by factors such as the polymer composition, crosslinking density, molecular weight, and the physicochemical properties of the incorporated drug [27].

2.3. Classification of in situ gel systems

In situ gels were classified according to the triggering mechanism that initiates gelation (**Table 1**). The four most widely studied categories are pH-triggered, temperature-responsive, ion-activated, and enzyme-responsive systems. Each system offers unique advantages and limitations, making it suitable for different therapeutic applications [28].

Table 1. Classification of *in situ* gel systems and their key features

Type of *in situ* gel system	Triggering factor	Mechanism of gelation	Examples of polymers/Systems	Applications in diabetes drug delivery	Ref.
pH-Triggered systems	Change in physiological pH (e.g., stomach to intestine, ocular pH)	Ionization of functional groups leading to sol–gel transition	Carbopol, poly (methacrylic acid), chitosan derivatives	Oral and ocular delivery of antidiabetic drugs, controlled insulin release	[29]
Temperature-responsive systems	Change in body temperature (ambient 37 °C)	Reversible sol–gel transition due to polymer chain dehydration or micelle packing	Poloxamers (pluronics), pnipaam, PEG–PLGA	Injectable depot for insulin, sustained peptide/protein release	[30]
Ion-activated systems	Presence of physiological ions (ca^{2+}, Na^{+}, K^{+} in tear fluid, gastric fluids)	Ionic crosslinking between polymer chains and multivalent cations	Alginate, gellan gum, pectin	Ocular delivery, oral sustained-release formulations	[26]
Enzyme-responsive systems	Enzymatic activity at target site (e.g., esterases, amylases, proteases)	Enzyme-catalyzed cleavage of polymer backbone or side chains triggering gelation	Dextran-based systems, peptide-modified polymers	Site-specific delivery of insulin, peptide-based antidiabetic therapies	[31]

2.3.1. pH-triggered systems

pH-Sensitive *in situ* gels depend on polymers that experience ionization or structural alterations in response to pH variation. These polymers possess acidic or basic functional groups (such as carboxyl, sulfonic, or amino groups) that either receive or provide protons based on their surroundings [32]. Polymers, such as Carbopol and chitosan, are extensively used in pH-responsive systems. Carbopol, a derivative of poly (acrylic acid), remains in a collapsed state at acidic pH but expands and forms a gel following neutralization in physiological fluids. Chitosan is soluble in acidic environments due to the protonation of amino groups; however, at elevated pH levels, deprotonation diminishes its solubility, leading to gel formation [33]. In diabetes management, pH-triggered systems are particularly useful for the oral delivery of peptide drugs, such as insulin, which are degraded in the acidic gastric environment. By designing formulations that remain stable in the stomach, but gel in the intestinal pH range (6–7.4), drug release can be targeted to the absorption site. This approach protects insulin from gastric degradation and enhances its intestinal absorption [34].

2.3.2 Temperature-responsive systems

Temperature-sensitive in-situ gels represent the most extensively studied class of systems. These formulations exploit the difference between room temperature (where they remain liquid) and body temperature (where they gel). Such systems are based on polymers with lower critical solution temperatures (LCST) or upper critical solution temperatures (UCST) [35]. The most widely used example is the poloxamer (Pluronic®), a triblock copolymer of polyethylene oxide (PEO) and polypropylene oxide (PPO). Poloxamer solutions remain fluid at room temperature but undergo micellization and gelation at body temperature due to the dehydration of PPO blocks and increased hydrophobic interactions. By adjusting the polymer concentration and combining it with additives, the gelation temperature and drug release profiles can be finely tuned [36]. Temperature-responsive gels are particularly attractive injectable systems. For instance, an insulin-loaded poloxamer solution can be injected subcutaneously as a liquid; however, once inside the body, it forms a gel depot that slowly releases insulin. This approach reduces the frequency of injections and provides a more stable glycemic control than conventional formulations [37].

2.3.3. Temperature-responsive systems

Ion-sensitive *in situ* gels undergo gelation upon exposure to the ions present in physiological fluids. Such systems are particularly relevant for ocular, nasal, and oral drug delivery, where ionic triggers, such as sodium, potassium, or calcium, are abundant [38]. Polymers, such as gellan gum, alginate, and pectin, are classical examples. For instance, alginate gels in the presence of divalent cations such as Ca^{2+} form “egg-box” junctions between polymer chains. Similarly, in the presence of mono- or divalent cations, gellan gum gels form double helices that aggregate into a three-dimensional network [39]. Ion-activated systems are advantageous for ocular delivery of antidiabetic drugs, where formulations instilled as eye drops can rapidly gel upon contact with tear fluid (containing Na^{+} and Ca^{2+}). This prolongs the ocular residence time, improves drug absorption, and reduces the dosing frequency. Although ocular applications are less common in diabetes therapy, similar principles can be applied to nasal delivery, offering a non-invasive route for the systemic absorption of insulin and other antidiabetic agents [40].

2.3.4. Ion-activated systems

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between polymer chains. Similarly, in the presence of mono- or divalent cations, gellan gum gels form double helices that aggregate into a three-dimensional network [42]. Ion-activated systems are advantageous for ocular delivery of antidiabetic drugs, where formulations instilled as eye drops can rapidly gel upon contact with tear fluid (containing Na^+ and Ca^{2+}). This prolongs the ocular residence time, improves drug absorption, and reduces the dosing frequency. Although ocular applications are less common in diabetes therapy, similar principles can be applied to nasal delivery, offering a non-invasive route for the systemic absorption of insulin and other antidiabetic agents [43]. **Figure 2** illustrates the two key mechanisms by which ions cross cellular membranes: ion transporters (left) and ion channels (right). Ion transporters actively move ions against their concentration gradient by binding ions and translocating them across the membrane, thereby generating and maintaining ion concentration gradients that are essential for cellular homeostasis. In contrast, ion channels provide a selective pathway for ions to diffuse down their concentration gradient, allowing rapid and regulated ion flux across the membrane. Together, these ion-activated systems play a critical role in processes such as signal transduction, excitability, and energy metabolism, by establishing and controlling the ionic environment within the cell.

2.3.5. Enzyme-responsive systems

Enzyme-responsive *in situ* gels represent the most advanced category, and are designed to exploit local enzymatic activity as a trigger for gelation. These systems employ polymers or crosslinkers that are substrates for specific enzymes. Upon enzymatic action, chemical changes such as cleavage, crosslinking, or deprotection occur, leading to sol-to-gel transformation [44]. For example, systems incorporating phosphorylated polymers can undergo dephosphorylation by alkaline phosphatase at a target site, resulting in gelation. Similarly, peptide-based polymers can be cleaved by proteases to initiate gel formation [45,46]. In diabetes management, enzyme-responsive gels are particularly promising glucose-sensitive delivery systems.

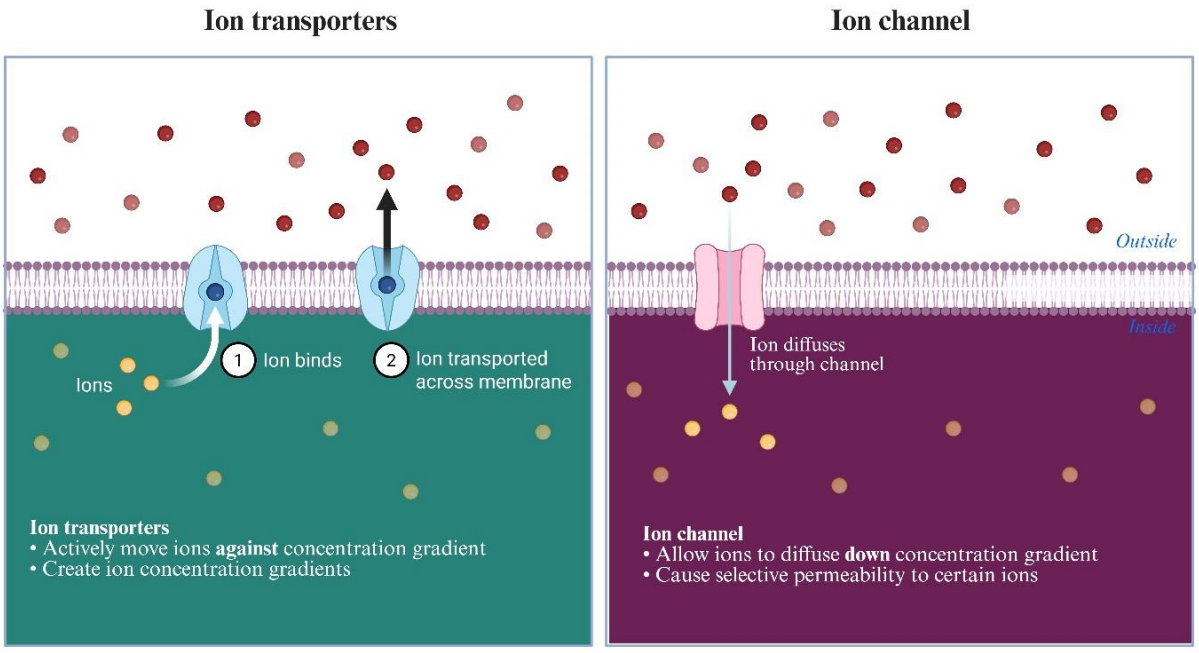

Figure 2. Comparison of ion transporters and ion channels in ion-activated systems. Ion exchange of Na^+, K^+, and Ca^{2+} regulates ionic crosslinking in polymers such as alginate and gellan gum for gel formation

By incorporating glucose oxidase into the gel matrix, the presence of elevated glucose levels leads to the enzymatic production of gluconic acid, which decreases the local pH and triggers gel swelling or degradation. This enables feedback-controlled insulin release, closely mimicking physiological insulin secretion by pancreatic β-cells [47]. The activation of enzyme-linked receptors by signaling molecules switches the receptor from an inactive to an active enzyme state. In enzyme-responsive *in situ* gel systems for diabetes, this principle is exploited, wherein specific enzymes (*e.g.,* glucose oxidase) respond to elevated glucose levels, initiating receptor-mediated or enzymatic pathways. This triggers gel transformation, controlled substrate release, and effector activation, enabling smart and sustained insulin or antidiabetic drug delivery (**Figure 3**).

3. Chemical Insights into *In situ* Gelling Polymers

The design of *in situ* drug delivery systems is fundamentally dependent on the chemical nature and properties of the polymers employed. Polymers serve as the structural backbone of these systems, dictating not only the gelation mechanism, but also the biocompatibility, biodegradability, and drug release behavior. For *in situ* gels, polymers must possess the unique ability to remain in the sol state under external conditions (such as room temperature) while undergoing a controlled phase transition into a gel matrix once exposed to physiological stimuli.

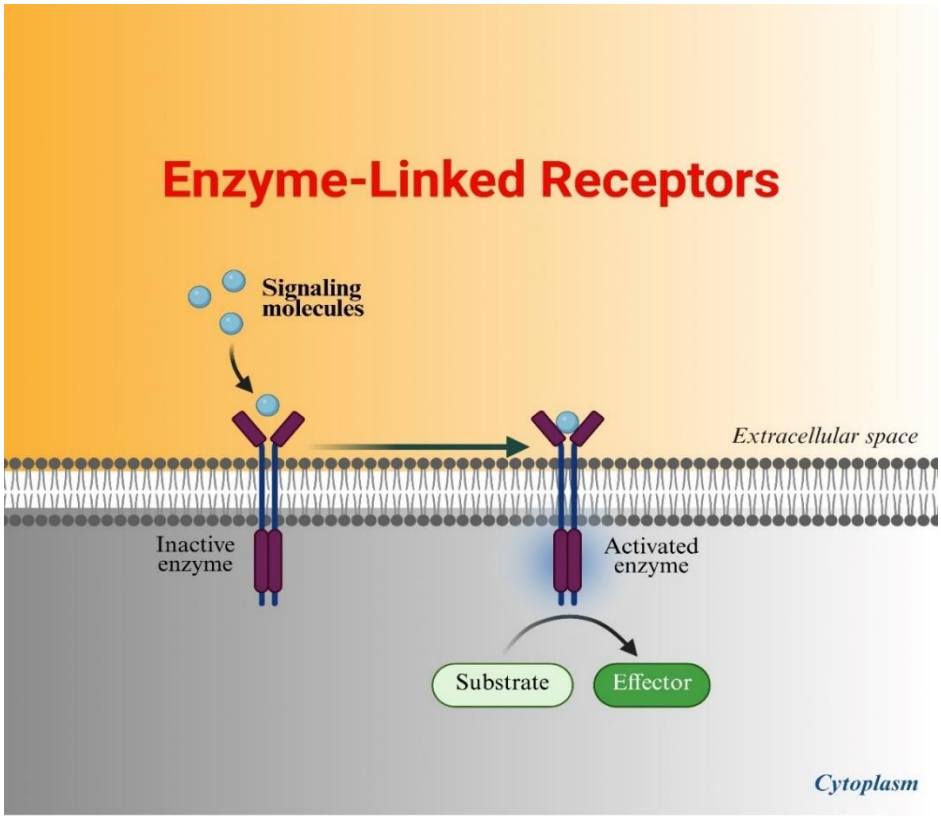

Figure 3. Enzyme-linked receptor signaling in enzyme-responsive *in situ* gel systems. Glucose oxidase (GOx) converts glucose to gluconic acid, lowering pH and triggering gelation for feedback-controlled insulin delivery

The chemical composition, functional groups, molecular weight, and structural configuration of these polymers are critical parameters that govern gelation kinetics, crosslinking density, and ultimately, therapeutic performance. Generally, polymers used in *in situ* gels can be classified into natural polymers derived from renewable biological sources and synthetic polymers engineered to provide tailored physicochemical properties. Furthermore, understanding the crosslinking mechanisms and physicochemical parameters influencing drug release is essential for the rational design of these systems for applications, such as diabetes management [48].

3.1. Natural polymers

Natural polymers are extensively employed in *in situ* gels because of their biodegradability, biocompatibility, and structural similarity to extracellular matrices. Their ability to undergo ionic or pH-induced gelation makes them attractive for pharmaceutical applications. Among the most widely studied are chitosan, alginate, and gellan gum [49]. Chitosan is a cationic polysaccharide derived from the deacetylation of chitin, which is abundant in the exoskeletons of crustaceans. Chemically, chitosan is a linear polymer composed of *β*-(1→4)-linked *D*-glucosamine and *N*-acetyl-*D*-glucosamine units. The free amino groups confer pH-sensitive solubility, making chitosan an excellent candidate for *in situ* gelation [50]. At low pH, the protonation of amino groups enhances solubility, while at physiological pH, deprotonation induces precipitation or gelation. The polycationic nature of chitosan also allows for electrostatic interactions with negatively charged biomolecules and drugs. In diabetes therapy, chitosan-based *in situ* gels have been investigated for oral insulin delivery, where the gel protects insulin from gastric degradation and enhances intestinal permeation by transiently opening tight junctions in the epithelial cells. Additionally, chemical modifications of chitosan, such as carboxymethyl chitosan or thiolated chitosan, further improve its solubility, mucoadhesion, and gelation properties [51].

Alginate, another widely studied polymer, is a naturally occurring anionic polysaccharide extracted from brown seaweeds. Structurally, alginate is composed of *β*-*D*-mannuronic acid (*M*-blocks) and *α*-*L*-guluronic acid (*G*-blocks) arranged in homopolymeric (MM or GG) and heteropolymeric (MG) sequences. Gelation of alginate occurs through ionic crosslinking with divalent cations such as Ca^{2+}, forming the characteristic “egg-box” structure, where G-blocks of adjacent chains are held together. Alginate-based gels are highly biocompatible, and their gelation kinetics can be controlled by adjusting polymer concentration, molecular weight, and cation availability. *In situ* gelling alginate formulations have been explored for the parenteral delivery of insulin, where subcutaneous injection of an alginate solution containing calcium salts leads to rapid gelation and formation of a depot. Moreover, alginate gels exhibit pH sensitivity and remain stable under acidic gastric conditions but swell under neutral intestinal conditions, making them useful for oral antidiabetic drug delivery [52].
Gellan gum is an anionic polysaccharide produced by Sphingomonas elodea. It consists of repeating tetrasaccharide units of glucose, rhamnose, and glucuronic acid. Gellan gum undergoes a sol-to-gel transition in the presence of mono- and divalent cations via double-helix formation and aggregation. Its unique property of requiring a low polymer concentration for gelation makes it advantageous for biomedical applications. Gellan-gum-based *in situ* gels have been widely investigated for ocular and nasal drug delivery due to their rapid gelation upon contact with physiological fluids rich in cations. For diabetes, intranasal delivery of insulin via gellan gum gels has shown promise in bypassing gastrointestinal degradation and hepatic first-pass metabolism, thereby offering a noninvasive alternative to injections [53]. Collectively, natural polymers have the advantages of biocompatibility and bioactivity; however, they often suffer from batch-to-batch variability, low mechanical strength, and limited control over gelation kinetics. These limitations have encouraged the exploration of synthetic

polymers with tunable chemical properties [54,55].

3.2. Synthetic polymers

Synthetic polymers offer distinct advantages over natural polymers primarily because their molecular weight, block composition, and functionalization can be precisely controlled during synthesis. This tunability allows the design of polymers with predictable gelation behavior, mechanical strength, and degradation profiles. Poloxamers and polyethylene glycol (PEG) derivatives are among the most extensively studied synthetic polymers for *in situ* gel systems [56]. Poloxamers, also known as Pluronics®, are amphiphilic triblock copolymers composed of poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO), arranged as PEO–PPO–PEO. A unique feature of poloxamers is their temperature-sensitive micellization and gelation. At low temperatures, poloxamers exist as individual unimers in solution, but as the temperature increases, the PPO blocks become hydrophobic and aggregate into micelles, with PEO chains forming a hydrophilic shell. At higher concentrations, micelle packing results in gel formation. The gelation temperature can be tailored by adjusting the polymer concentration or blending with other polymers. For drug delivery, poloxamer-based *in situ* gels are particularly useful for injectable formulations, where they remain liquid at room temperature but rapidly gel at body temperature, forming depots that sustain the drug release. In diabetes management, insulin-loaded poloxamer gels have shown potential to prolong release and reduce injection frequency [57].

PEG derivatives are another important class of molecules. PEG itself is highly hydrophilic, biocompatible, and FDA-approved; however, it does not inherently gel. By functionalizing PEG with hydrophobic or reactive groups, PEG-based copolymers can exhibit stimuli-responsive gelation. For instance, PEG–poly (lactic acid) (PEG–PLA) and PEG–poly(ε-caprolactone) (PEG–PCL) block copolymers form thermosensitive gels. Additionally, PEG can be modified with pH-sensitive or enzyme-cleavable linkers to impart smart responsiveness [58]. PEGylation also enhances protein stability, protects labile drugs from enzymatic degradation, and prolongs the systemic circulation time. In the context of diabetes, PEG-based gels have been investigated for glucose-sensitive insulin delivery, where PEG networks are cross-linked with glucose-responsive moieties, such as phenylboronic acid [59]. Other synthetic polymers, such as poly(*N*-isopropylacrylamide) (PNIPAAm), poly(vinyl alcohol) (PVA), and synthetic polypeptides have also been employed. In particular, PNIPAAm exhibits a sharp lower critical solution temperature (LCST) of approximately 32 °C, making it a classic thermoresponsive polymer. However, concerns regarding biodegradability have limited its clinical application [60].

Synthetic polymers provide a high degree of chemical versatility, enabling the design of tailored *in situ* gel systems with precise control over the gelation and release characteristics. However, their lack of inherent bioactivity compared to that of natural polymers sometimes necessitates hybrid formulations [61].

3.3. Crosslinking mechanisms and gelation chemistry

The sol-to-gel transition in polymeric systems is fundamentally governed by crosslinking mechanisms, which can be physical or chemical in nature (**Table 2**) [62]. Physical crosslinking relies on non-covalent interactions such as hydrogen bonding, ionic interactions, hydrophobic interactions, and van der Waals forces. These interactions are typically reversible and enable gels to dynamically respond to environmental stimuli. For example, ionic crosslinking of alginate with calcium ions is a physical process similar to the thermosensitive micellization of poloxamers. Physical gels are generally safer because they avoid chemical reagents or toxic crosslinkers, but may exhibit weaker mechanical strength and faster degradation [63]. Chemical crosslinking, on the other hand, involves covalent bond formation

between polymer chains, often initiated by chemical agents, photocrosslinking, or enzymatic reactions. Chemically cross-linked gels offer superior mechanical stability and prolonged drug release; however, residual crosslinkers may pose toxicity risks. Enzyme-mediated crosslinking, such as transglutaminase-induced peptide bonding, provides a biocompatible alternative [64]. The chemistry of gelation is crucial for tailoring drug delivery performance. For instance, reversible Schiff base linkages between aldehyde and amine groups provide pH-sensitive gelation, while disulfide crosslinks respond to redox conditions. In glucose-responsive gels, phenylboronic acid moieties form reversible complexes with diols (such as glucose), allowing smart, and self-regulated drug release. Thus, selecting the appropriate crosslinking chemistry requires a balance between mechanical strength, responsiveness, biocompatibility, and safety [65].

3.4. Physicochemical properties influencing drug release

Once formed, the gel matrix serves as a reservoir for controlling the drug diffusion and release kinetics.

Table 2. Crosslinking mechanisms and gelation chemistry of *in situ* gel systems

Crosslinking mechanism	Underlying chemistry	Representative polymers/Materials	Key features	Relevance in diabetes drug delivery	Ref.
Ionic crosslinking	Interaction between ionic groups of polymer and counter-ions (*e.g.,* Ca^{2+}, Na^{+}, and Mg^{2+})	Alginate, gellan gum, and pectin	Mild gelation, reversible, biocompatible	Oral and ocular gels for controlled insulin and hypoglycemic agents	[66]
Hydrogen bonding	Intermolecular *H*-bonds between functional groups (–OH, –COOH, $–NH_2$)	Poly (vinyl alcohol), chitosan, and carbopol	Thermoreversible, pH-sensitive, non-toxic	Enhances mucoadhesion for nasal and oral insulin delivery	[67]
Hydrophobic interactions	Self-assembly of amphiphilic blocks forming micelles and gels	poloxamers (pluronics), PEG–PLGA, and pnipaam	Temperature-sensitive, injectable sol–gel transition	Injectable depot systems for sustained insulin release	[68]
Covalent crosslinking	Formation of stable covalent bonds via chemical reactions (*e.g.,* click chemistry, photo-crosslinking)	PEG-diacrylate, polyurethane, acrylamide derivatives	Strong, durable gels; tunable degradation	Long-term, sustained antidiabetic drug release	[69]
Enzyme-mediated crosslinking	Enzymes catalyze bond formation or cleavage to initiate gelation	Dextran–tyramine (peroxidase-catalyzed), peptide-based gels	Site-specific gelation, responsive to biological signals	Targeted insulin delivery at responsive sites	[70]
Physical entanglement	Chain entanglement without chemical bonding	Hydroxypropyl methylcellulose (hpmc), peo	Simple, reversible gels; viscosity-dependent	Oral sustained-release matrices for hypoglycemic drugs	[71]

Several physicochemical properties of polymers influence this behavior, and the swelling behavior of hydrophilic polymers allows them to absorb water, increase the mesh size, and facilitate drug diffusion; however, this must be optimized to achieve controlled release by balancing drug retention and release. Crosslinking density plays a crucial role, as a higher crosslinking density restricts mesh size and slows diffusion, thereby prolonging release, whereas a lower crosslinking density accelerates release but compromises gel strength [72]. Biodegradable polymers, such as alginate or PEG–PLA, further contribute through gradual degradation, the rate of which is influenced by their chemical composition, crystallinity, and environmental conditions. The hydrophilic–hydrophobic balance, particularly in amphiphilic polymers such as poloxamers, supports the encapsulation of hydrophobic drugs within micelles, enhancing solubilization while dictating gel stability and strength. Similarly, the molecular weight of polymers affects gel viscosity and strength, with higher molecular weights typically slowing drug diffusion [73]. Drug-polymer interactions, including ionic, hydrogen bonding, or hydrophobic forces, strongly influence encapsulation efficiency and release behavior; for instance, cationic chitosan interacts with negatively charged insulin to improve its retention within the gel [74]. Diabetes therapy, achieving sustained yet responsive drug release, is crucial. By fine-tuning the polymer properties, gels can be designed to release insulin steadily over several hours or days, or even in a pulsatile manner in response to glucose levels. This optimization directly stems from the chemical and physicochemical insights into the polymer design [75].

4. Formulation Approaches for Antidiabetic Drug Delivery

The growing global prevalence of DM has driven extensive research into innovative drug delivery systems that enhance therapeutic efficacy, improve patient compliance, and minimize side effects. Traditional delivery routes, such as oral administration of tablets or repeated insulin injections, are often associated with limitations, such as poor bioavailability, short half-life, enzymatic degradation, and patient discomfort. These challenges necessitate advanced formulation strategies that allow sustained release, targeted delivery, and noninvasive administration. In particular, *in situ* gelling systems and polymeric carriers have gained significant attention due to their ability to provide controlled and site-specific drug release. Several delivery approaches have been explored, including oral, nasal, ocular, injectable, transdermal, and combination therapy (**Table 3**). Each of these approaches presents unique advantages and challenges, making their optimization crucial for the development of next-generation antidiabetic therapies [76].

Table 3. Formulation approaches of *in situ* gel systems for antidiabetic drug delivery

Route of administration	Formulation approach	Polymers	Model drugs/Antidiabetic agents	Mechanism of gelation	Research outcomes / Advantages	Ref.
Oral delivery	pH-sensitive *in situ* gels	Chitosan, carbopol, poly (methacrylic acid)	Metformin, glibenclamide, and insulin	pH-triggered sol–gel transition in gi tract	Protects drug from gastric degradation; enhances absorption	[77]

	Mucoadhesive hydrogels	Hpmc, sodium alginate, pectin	Insulin, sitagliptin	Ionic crosslinking, hydrogen bonding	Prolonged gastric retention; improved drug residence	[78]
Nasal delivery	Thermoresponsive gels	Poloxamers (pluronic f127), carbopol blends	Insulin, exenatide	Sol–gel transition at nasal temperature	Bypasses first-pass metabolism; rapid absorption	[79]
	Mucoadhesive in-situ gels	Chitosan, gellan gum	Insulin	Ion-activated gelation with nasal ions	Enhanced mucoadhesion and permeation	[80]
Ocular delivery	Ion-sensitive gels	Sodium alginate, gellan gum	Insulin, antioxidants for diabetic retinopathy	Ion-triggered gelation with tear fluid cations	Prolonged precorneal residence; reduced dosing frequency	[81]
	pH-sensitive gels	Carbopol, hpmc blends	Antidiabetic peptides	pH-triggered gelation in tear fluid	Sustained ocular drug delivery	[82]
Injectable systems	Thermoresponsive sol–gel formulations	Poloxamers, PEG–PLGA, pnipaam	Insulin, GLP-1 analogs (liraglutide, exenatide)	Temperature-induced micellization and gelation	Depot formation; sustained systemic release	[83]
	Covalently cross-linked injectable gels	PEG-diacrylate, polyurethane	Long-acting insulin analogs	Covalent bonding (photo-/chemical crosslinking)	Strong, durable depot; tunable release	[84]
Transdermal delivery	Hydrogel patches	PVA, chitosan, carbopol	Insulin, DPP-4 inhibitors	Physical entanglement, H-bonding	Non-invasive delivery; patient compliance	[85]
	Microneedle-loaded gels	Gelatin, PEG, hyaluronic acid	Insulin, GLP-1 analogs	Enzyme-responsive or thermoresponsive gels	Targeted delivery; rapid onset; painless administration	[86]
Combination therapy / Co-delivery	Nanoparticle-loaded in-situ gels	PLGA NPs, liposomes in poloxamer gels	Insulin + metformin, insulin + antioxidants	Thermoresponsive and ion-triggered gelation	Dual drug delivery; synergistic effects; enhanced stability	[87]

4.1. Approaches for oral delivery

Oral administration remains the most desirable and widely accepted route for antidiabetic drugs due to its convenience, patient compliance, and suitability for chronic therapy. However, the oral delivery of peptide-based drugs, such as insulin, glucagon-like peptide-1 (GLP-1) analogs, and

dipeptidyl peptidase-4 (DPP-4) inhibitors, is significantly challenged by enzymatic degradation in the gastrointestinal (GI) tract, poor permeability across the intestinal epithelium, and first-pass metabolism in the liver. To overcome these barriers, formulation scientists have developed advanced systems to enhance stability, permeability, and bioavailability [88]. One promising approach is the use of enteric-coated nanoparticles and microparticles, which protect insulin or other labile drugs from gastric acid and digestive enzymes, releasing them only in the intestinal environment. Additionally, mucoadhesive polymers, such as chitosan, carbopol, and alginate, have been widely employed to increase residence time in the intestinal mucosa and promote paracellular transport of hydrophilic drugs. Another innovation is the use of nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs), which improve drug solubility and stability while enabling controlled release [89]. Oral delivery systems have also incorporated permeation enhancers and enzyme inhibitors to facilitate the trans-epithelial transport of peptides. For instance, protease inhibitors can prevent enzymatic degradation, whereas surfactants such as sodium lauryl sulfate temporarily open tight junctions to enhance absorption. Advanced technologies such as self-emulsifying drug delivery systems (SEDDS) have also been applied to poorly water-soluble antidiabetic agents, significantly improving their dissolution and bioavailability [90]. Recent research has demonstrated the feasibility of oral *in situ* gelling formulations that undergo a sol-to-gel transition upon exposure to physiological conditions such as pH or ionic strength. These systems not only protect sensitive drugs from degradation, but also provide prolonged gastric retention, ensuring sustained drug release. Although clinical translation of oral insulin remains a challenge, continuous advancements in polymer science, nanotechnology, and formulation strategies have gradually made oral peptide delivery a more realistic possibility [91,92].

4.2. Nasal and ocular delivery systems

Nasal and ocular drug delivery systems have emerged as non-invasive alternatives for the administration of antidiabetic drugs, particularly peptides, such as insulin, which are otherwise degraded in the GI tract. The nasal route provides direct access to the highly vascularized nasal mucosa, enabling rapid absorption and bypassing the hepatic first-pass metabolism [93]. Similarly, the ocular route, though less conventional for systemic therapy, is being investigated for the localized delivery of antidiabetic agents to address diabetes-related ocular complications, such as diabetic retinopathy and macular edema [94]. Nasal formulations often employ mucoadhesive *in situ* gelling systems to overcome the challenges of mucociliary clearance and short residence times. Polymers such as gellan gum, poloxamers, and Carbopol have been widely used to design thermosensitive or ion-sensitive gels that solidify upon contact with the nasal mucosa, thereby prolonging drug retention and absorption. Additionally, nanoparticles and liposomes have been incorporated into nasal gels to further enhance permeability, protect labile molecules, and facilitate controlled release. Clinical studies have shown promising results for intranasal insulin, demonstrating its rapid onset of action and potential utility in postprandial glucose control. However, variability in absorption, irritation of the nasal mucosa, and dose limitations remain challenges for widespread adoption [95]. In the ocular route, the focus is primarily on managing diabetic eye complications, rather than systemic glucose control. Conventional eye drops often have poor bioavailability due to tear drainage, blinking, and limited corneal permeability. To address these limitations, *in situ* gelling ocular formulations have been developed using polymers, such as poloxamers, alginates, and cellulose derivatives. These gels undergo sol-to-gel transition upon instillation, increasing the precorneal residence time and enhancing drug penetration into ocular tissues. Encapsulation of antidiabetic drugs in biodegradable nanoparticles dispersed within gels further

improves the therapeutic efficiency. Such systems can be tailored to release drugs for extended periods, thereby reducing the need for frequent administration and improving patient adherence [96]. Both nasal and ocular delivery systems hold great promise for use in non-invasive antidiabetic therapy. Although nasal delivery is better suited for systemic action, ocular formulations offer targeted therapy for diabetic complications. Advances in bioadhesive polymers, nanocarriers, and *in situ* gelling systems are likely to accelerate the clinical translation of these approaches [97].

4.3. Injectable in situ gel systems

Injectable *in situ* gel systems are one of the most widely explored strategies for sustained antidiabetic drug delivery. This approach offers a less invasive alternative to conventional multiple daily insulin injections, providing controlled release and reducing the dosing frequency. Injectable *in situ* gels are typically administered as liquid formulations that undergo gelation under physiological conditions such as temperature, pH, or ionic interactions. Once injected subcutaneously, they form a depot that slowly releases the encapsulated drug over extended periods [98]. Several polymers have been investigated for use in injectable in-situ gel formulations. Thermosensitive polymers, such as poloxamers (Pluronic® F127), undergo sol-to-gel transition at body temperature, making them ideal for injectable systems. Similarly, biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), have been utilized to create long-acting depots for peptide delivery. Natural polymers such as chitosan and gellan gum also play important roles due to their biocompatibility and mild gelation mechanisms [67,99]. One of the key advantages of injectable *in situ* gels is their ability to provide prolonged drug release ranging from days to weeks, thereby reducing the burden of frequent injections. For example, insulin-loaded PLGA *in situ* gels can sustain release for up to several days, while GLP-1 analogs formulated in thermosensitive gels have demonstrated controlled release for over a week. Furthermore, such systems minimize fluctuations in plasma glucose levels by maintaining steady drug concentrations, thereby reducing the risk of hypoglycemia [100]. Recent advances have also included the incorporation of nanoparticles, liposomes, and microspheres into injectable gels to achieve dual-release kinetics or encapsulate multiple drugs for combination therapy. Biodegradable hydrogels with responsive properties, such as glucose-sensitive gels, are under investigation for their potential to release insulin in response to rising glucose levels, thereby mimicking physiological feedback mechanisms [101]. Despite their advantages, challenges remain in ensuring reproducible gelation, minimizing injection site irritation, and achieving large-scale manufacturing consistency. Nevertheless, injectable *in situ* gel systems remain a highly promising platform for long-acting antidiabetic therapy and are likely to play a major role in diabetes management in the future [102].

4.4. Transdermal applications

Transdermal drug delivery offers an attractive non-invasive alternative for antidiabetic therapy, enabling sustained drug release and improved patient compliance. However, the skin is a formidable barrier, particularly for macromolecules such as insulin, which have poor permeability through the stratum corneum. To address this limitation, several advanced transdermal strategies have been developed, including microneedle patches, iontophoresis, sonophoresis, and polymer-based *in situ* gelling systems [103]. Microneedle-based patches have gained significant attention because they can painlessly breach the stratum corneum to deliver insulin or other antidiabetic drugs directly into the dermis. These patches can be fabricated from biodegradable polymers, dissolvable sugars, or silicon, and can be designed to release drugs rapidly or in a sustained manner. Recent innovations include glucose-responsive microneedles, which release insulin in response to hyperglycemia, thereby providing a closed-loop control of blood glucose levels [104]. In addition to microneedles,

chemical permeation enhancers such as surfactants and fatty acids have been incorporated into transdermal gels to improve the skin penetration of smaller antidiabetic molecules, such as metformin or sulfonylureas. Iontophoresis and sonophoresis techniques use electrical currents and ultrasound, respectively, to transiently disrupt skin barriers and facilitate drug permeation [105]. Polymeric *in situ* gelling formulations for transdermal delivery are also being explored, wherein gels form a thin film on the skin that enhances adhesion and provides sustained release. Liposomes, ethosomes, and transfersomes incorporated into these gels further improve drug permeation and stability [106]. Transdermal systems are particularly advantageous in reducing the frequency of injections and improving adherence among patients with needle phobia. However, challenges include variability in skin permeability among individuals, potential irritation, and limited capacity to deliver large drug doses. With ongoing technological advances, particularly in smart microneedle patches, transdermal delivery is expected to become a key strategy for non-invasive antidiabetic therapy [107].

4.5. Combination therapies and co-delivery

Combination therapies are increasingly being recognized as essential for effective diabetes management, especially in patients with advanced disease who require multiple drugs to achieve glycemic control. Co-delivery systems aim to incorporate two or more therapeutic agents into a single formulation, providing synergistic effects, reducing pill burdens, and improving patient adherence [108]. One major area of interest is the co-delivery of insulin with oral hypoglycemic agents, such as metformin, sulfonylureas, and DPP-4 inhibitors, to target different pathophysiological pathways simultaneously. For instance, insulin lowers blood glucose levels by promoting cellular uptake, while metformin reduces hepatic glucose production. Delivering these agents together in a sustained-release system can optimize glycemic control while minimizing the side effects [109]. Advanced polymeric- and nanocarrier-based systems have been developed for co-delivery. Polymeric nanoparticles, liposomes, and hydrogels can encapsulate multiple drugs and release them at controlled rates or in response to specific stimuli. For example, glucose-sensitive hydrogels have been designed to release insulin and GLP-1 analogs in a feedback-regulated manner. Similarly, injectable *in situ* gels loaded with dual drugs can exhibit prolonged and synergistic effects [110]. Another promising strategy involves the combination of antidiabetic drugs with antioxidants or anti-inflammatory agents to address oxidative stress and inflammation associated with diabetes and its complications. Co-delivery systems targeting both glucose control and secondary complications, such as diabetic nephropathy or retinopathy, offer holistic therapeutic benefits [111]. Co-delivery can also be applied via different routes. For instance, microneedle patches have been designed to deliver both insulin and glucagon antagonists, while nasal formulations can co-deliver insulin with enzyme inhibitors. These innovative strategies not only improve therapeutic outcomes, but also reduce the complexity of treatment regimens [112]. Combination therapies face challenges such as drug–drug interactions, differing physicochemical properties of active ingredients, and ensuring synchronized release profiles. However, advances in nanotechnology, responsive polymers, and *in situ* gelling systems have provided solutions to these problems. The integration of combination therapies into clinical practice is expected to revolutionize diabetes management by offering more effective, patient-friendly, and personalized treatments [113].

5. Smart Features of *In Situ* Gel Systems'

In situ gel systems have emerged as highly versatile and intelligent drug delivery platforms that are particularly relevant in the management of chronic diseases, such as DM. Unlike conventional dosage forms, these systems exhibit the unique ability to undergo sol-to-gel

transitions upon exposure to physiological conditions, such as temperature, pH, or ionic composition. This transformation allows them to be administered as liquids and subsequently form semisolid depots at the site of administration, where they can sustain drug release for prolonged periods. Their "smart" behavior is attributed to several intrinsic features, including controlled and sustained release, stimuli-responsive mechanisms, site-specific targeting capabilities, and excellent biocompatibility. Collectively, these properties make *in situ* gels not only carriers of drugs, but also dynamic delivery platforms capable of improving therapeutic outcomes, minimizing adverse effects, and enhancing patient adherence [114].

5.1. Controlled and sustained release profiles

A defining characteristic of *in situ* gel systems is their capacity to provide a controlled and sustained release of therapeutic agents. For antidiabetic drugs, especially peptide-based molecules such as insulin and GLP-1 analogs, achieving stable plasma concentrations is crucial for effective glycemic management. Traditional dosage forms often lead to fluctuations in blood drug levels, resulting in poor glycemic control and an increased risk of complications, such as hypoglycemia or hyperglycemia. In contrast, *in situ* gels create a drug reservoir at the administration site, from which the drug diffuses gradually into systemic circulation [115]. The controlled release mechanism is influenced by the polymer network architecture, degree of crosslinking, and physicochemical interactions between the drug and gel matrix. For instance, highly cross-linked gels restrict diffusion, leading to slower release, while loosely cross-linked matrices allow for faster drug liberation. Additionally, hydrophilic polymers such as chitosan or alginate can imbibe water, swell, and thereby modulate drug diffusion rates. This tunability allows researchers to tailor the release kinetics according to therapeutic requirements, ranging from rapid onset of action to prolonged maintenance over days or even weeks [116]. Sustained release not only improves the pharmacokinetic profile of drugs, but also reduces the frequency of dosing, which is particularly important in chronic diseases such as diabetes, where lifelong therapy is required. Patients relying on daily insulin injections often face compliance challenges. However, a single injection of an *in-situ* gel depot capable of releasing insulin over a week could dramatically reduce the treatment burden. Moreover, maintaining steady-state drug levels minimizes sharp peaks and troughs in plasma concentrations, ensuring better metabolic control [117]. Another important advantage is the ability to incorporate multi-phase release profiles. Some *in situ* gels are designed to provide an initial burst release to quickly establish therapeutic levels, followed by a sustained-release phase to maintain efficacy. This dual-phase behavior is particularly valuable for drugs such as insulin, which require a rapid onset for postprandial glucose control along with long-acting basal support. Additionally, the incorporation of nanocarriers such as liposomes or microspheres within the gel matrix can further fine-tune release kinetics, providing multimodal delivery [118]. The controlled and sustained release properties of *in situ* gel systems represent a cornerstone of their smart functionality, addressing one of the biggest limitations of conventional drug delivery and maintaining consistent therapeutic levels without frequent dosing [119].

5.2. Stimuli-responsive behavior

One of the most fascinating aspects of *in situ* gels is their stimuli-responsive nature, which allows them to undergo a sol-to-gel transition in response to specific physiological triggers. These systems can be designed to respond to various stimuli such as temperature, pH, ionic strength, and even biological signals such as glucose concentration. This adaptability provides a powerful mechanism for achieving site-specific gelation and controlled release in real-time [120]. Thermosensitive gels are, perhaps, the most widely studied. Polymers such as poloxamers and PNIPAAm exhibit reversible

sol–gel transitions at the body temperature. When injected or applied at room temperature, they remain in the liquid form, facilitating easy administration. Upon exposure to physiological temperature (~ 37 °C), they rapidly form gels, entrap the drug, and establish a depot for sustained release. Such systems are particularly advantageous for the subcutaneous delivery of antidiabetic drugs, where minimally invasive injection of a liquid that solidifies *in situ* enhances patient comfort [121]. pH-sensitive gels exploit differences in pH across the body environment. For instance, polymers such as Carbopol or chitosan undergo ionization-dependent swelling or gelation in response to pH variations. This feature is particularly useful for oral formulations, in which the drug must survive in the acidic gastric environment and be released in a relatively neutral intestinal milieu. For antidiabetic agents prone to gastric degradation, pH-sensitive *in situ* gels act as protective carriers, ensuring drug release only at the appropriate sites [122]. Another important class is ion-sensitive gels, exemplified by alginate and gellan gum systems, which gel upon exposure to divalent cations, such as Ca^{2+}, present in biological fluids. Such gels have been applied in ocular and nasal delivery systems for antidiabetic drugs, where ionic interactions ensure rapid gelation and prolonged residence times [123]. It is possible that the most innovative development is glucose-responsive *in situ* gels. These smart systems are engineered to release insulin in direct response to rising blood glucose levels, thereby mimicking the physiological functions of pancreatic *β*-cells. They often incorporate glucose oxidase, which catalyzes the conversion of glucose to gluconic acid, altering the local pH and triggering drug release from the gel matrix. Alternatively, boronic acid-based polymers can form reversible complexes with glucose, thereby modulating gel swelling and drug diffusion. Such systems hold enormous promise for creating closed-loop insulin delivery devices, potentially eliminating the need for continuous patient monitoring and frequent dose adjustments [124]. By harnessing stimuli-responsiveness, *in situ* gels go beyond passive drug carriers to become active, adaptive systems capable of dynamically responding to the body's needs. This not only enhances therapeutic precision, but also minimizes the risks of over- or under-dosing, which is a major concern in diabetes management [125].

5.3. Targeted delivery to pancreatic or extra-pancreatic sites

Targeted drug delivery is another smart feature of *in situ* gel systems, which enhances therapeutic efficacy while minimizing systemic side effects (**Table 4**). While systemic insulin replacement remains the cornerstone of diabetes management, targeting drugs to specific tissues such as the pancreas, liver, muscle, or even ocular tissues (for diabetic retinopathy) can provide additional therapeutic benefits. *In situ* gels offer an effective platform for such site-specific delivery, due to their gelation-triggered localization and capacity for modification with targeting ligands [126]. Pancreatic targeting research has focused on developing systems that deliver drugs directly to the pancreas to enhance insulin secretion or to protect pancreatic *β*-cells from oxidative stress and apoptosis. Nanoparticles encapsulated in *in situ* gels can be functionalized with ligands, such as peptides or antibodies that recognize pancreatic receptors, thereby improving drug accumulation at the site. Such approaches not only enhance efficacy, but also reduce systemic exposure and minimize risks such as hypoglycemia [127]. Hepatic targeting is particularly important, because the liver plays a central role in glucose homeostasis. *In situ* gel systems can be designed to preferentially release metformin or other insulin sensitizers into the liver, thereby improving the suppression of hepatic glucose production. Similarly, muscle-targeted delivery can enhance glucose uptake, whereas adipose tissue targeting can modulate insulin sensitivity [128]. A particularly promising application of *in situ* gels is the management of diabetes-related ocular complications. Ocular gels formulated with antidiabetic or anti-angiogenic agents can be instilled as eye drops, where they undergo

sol-to-gel transition on the corneal surface, prolonging drug retention and enhancing penetration into intraocular tissues. Such localized delivery reduces the need for repeated invasive injections into the eye, thereby significantly improving patient comfort [129]. Targeted delivery is not limited to organs directly involved in the glucose metabolism. *In situ* gels have also been investigated for neuroprotective delivery in diabetic neuropathy and for renal protection in diabetic nephropathy. The ability to localize therapy to diseased tissues while sparing healthy tissues represents a major leap forward in personalized medicine [130]. The targeted delivery capability of *in situ* gel systems ensures that drugs act where they are most needed, enhancing therapeutic efficiency while reducing systemic toxicity, which is a truly smart feature that distinguishes them from conventional drug delivery approaches [131].

Table 4. Targeted delivery of antidiabetic agents via *in situ* gel systems

Target site	Delivery approach	Drugs	Mechanism of targeting	Therapeutic advantage	Ref.
Pancreas (β-cells)	Injectable thermoresponsive gels	Insulin, GLP-1 analogs	Depot formation near pancreatic tissue, sustained release	Maintains localized insulin concentration; reduces systemic fluctuations	[132]
	Ligand-modified *in-situ* gels	Insulin, exenatide	Receptor-mediated uptake at pancreatic β-cells	Enhanced site-specific uptake, improved bioavailability	[133]
Liver (extra-pancreatic site)	pH- or enzyme-responsive gels	Insulin, metformin	pH/Enzyme-triggered release in hepatic microenvironment	Direct regulation of hepatic glucose output	[134]
Adipose / Muscle tissue	Injectable depot gels	Insulin analogs	Temperature-responsive depot near muscle/adipose tissue	Improves peripheral glucose utilization	[135]
Intestinal L-cells (GLP-1 secretion)	Oral *in-situ* gels	GLP-1 mimetics, DPP-4 inhibitors	Mucoadhesion and controlled release in intestine	Stimulates incretin pathway, enhances insulin sensitivity	[136]
Ocular / Retinal sites (diabetic retinopathy)	Ion-activated ocular gels	Antioxidants, anti-VEGF agents	Ion-induced gelation in tear fluid with posterior segment penetration	Localized therapy, reduced systemic exposure	[137]

5.4. Biocompatibility and safety considerations

Regardless of the sophistication of the delivery system, its success depends on its biocompatibility and safety profile. *In situ* gel systems are typically designed using natural or synthetic polymers that are biodegradable, non-toxic, and well tolerated by the body. Their ability to form gels under mild physiological conditions without the need for harsh solvents or chemical cross-linkers contributes significantly to their safety [138]. Natural polymers such as chitosan, alginate, gellan gum, and hyaluronic acid are inherently biocompatible as they resemble components of the extracellular matrix. They degrade into non-toxic byproducts that can be safely metabolized or excreted. Synthetic polymers such as poloxamers, PEG derivatives, and PLGA are also widely used, many of which have FDA approval for biomedical applications. Importantly, these polymers allow precise control over the degradation rates, enabling formulations to be tailored for specific therapeutic durations [139]. Safety considerations can also be extended to local tissue compatibility. As *in situ* gels are often injected or applied directly to mucosal or ocular surfaces, it is critical to ensure that they do not cause irritation, inflammation, or immune reactions. Extensive preclinical studies have demonstrated that properly formulated gels are well-tolerated, producing minimal tissue responses. Thermosensitive gels, for instance, are liquid at room temperature and solidify only upon administration, thus minimizing mechanical stress during injection [140]. Another safety advantage of *in situ* gels is their ability to reduce dosing frequency and drug burden, which in turn decreases systemic side effects. For example, sustained-release insulin gels maintain steady plasma concentrations, reducing the risk of hypoglycemic episodes associated with sharp drug peaks. Similarly, ocular *in situ* gels release drugs slowly over days, avoiding the toxicity that may result from frequent high-concentration eye drops [102]. Nevertheless, careful attention must be paid to formulation additives, such as stabilizers, cross-linkers, or permeation enhancers, which may introduce toxicity if not appropriately chosen. Regulatory guidelines emphasize the importance of comprehensive biocompatibility testing, including cytotoxicity, genotoxicity, and immunogenicity assessments before clinical translation [141]. The inherent biocompatibility of *in situ* gel systems, combined with their safety-enhancing features such as reduced dosing frequency and localized release, makes them highly suitable for long-term antidiabetic therapy. These systems are expected to gain increasing clinical acceptance with ongoing improvements in polymer design and safety evaluation [142].

6. Applications in Diabetes Management

The versatility and "smart" behavior of *in situ* gel systems have made them attractive platforms for diabetes management. DM, a chronic metabolic disorder characterized by persistent hyperglycemia, requires continuous therapeutic intervention with insulin, oral hypoglycemic drugs, or newer biologics. Traditional drug delivery routes often have limitations such as rapid clearance, enzymatic degradation, short half-lives, and the need for repeated dosing. *In situ* gels, with their sol-to-gel transformation under physiological conditions and ability to sustain drug release, overcome many of these drawbacks. They have been successfully investigated for insulin delivery, oral hypoglycemic drugs, novel peptide- and protein-based therapies, and even nanoparticle-assisted delivery approaches. Together, these applications highlight the transformative potential of *in situ* gels in creating noninvasive, patient-friendly, and effective treatment strategies for diabetes [143].

6.1. Delivery of insulin via in situ gels

Insulin replacement therapy remains the cornerstone of type 1 diabetes management and is increasingly being used in the advanced stages of type 2 diabetes. Conventional insulin delivery through multiple subcutaneous injections often leads to patient discomfort, poor compliance, and variable pharmacokinetics. *In situ* gel

systems have emerged as promising alternatives by providing sustained and controlled insulin release, reducing dosing frequency, and mimicking physiological secretion patterns [144]. One of the most studied approaches involves injectable thermosensitive gels, where polymers such as poloxamers, chitosan, or PLGA derivatives remain liquid at room temperature but gel upon contact with the body temperature. These systems entrap insulin and gradually release it over days or weeks, creating a depot effect. By maintaining steady insulin levels, they minimize the glycemic fluctuations that are often associated with traditional injections. Importantly, reduced injection frequency improves patient adherence and quality of life [145]. More advanced systems incorporate glucose-responsive elements into a gel matrix. For instance, gels containing glucose oxidase can sense elevated glucose concentrations, producing gluconic acid, which triggers localized pH changes and accelerates insulin release. Similarly, boronic acid–based gels reversibly bind glucose molecules, modulating gel swelling and drug diffusion in real-time. Such systems aim to replicate the feedback-regulated insulin secretion of healthy pancreatic β-cells, offering a closed-loop delivery mechanism that minimizes the risk of both hyper- and hypoglycemia [146]. Insulin-loaded nasal and ocular *in situ* gels have also been explored as noninvasive alternatives. These systems exploit mucoadhesive and ion-sensitive polymers, such as gellan gum or carbopol, to increase the residence time at mucosal surfaces and enhance insulin absorption. Although systemic bioavailability remains lower than that of injectable routes, ongoing improvements in permeation enhancers and nanoparticle incorporation have shown promising results [147]. Despite the challenges in large-scale translation, insulin delivery via *in situ* gels has demonstrated substantial potential to revolutionize diabetes therapy by reducing patient burden, improving pharmacodynamics, and moving closer to physiologically responsive systems [148].

6.2. Delivery of oral hypoglycemic agents

While insulin therapy is indispensable for type 1 diabetes, type 2 diabetes is primarily managed with oral hypoglycemic agents (OHAs), such as metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and SGLT-2 inhibitors. However, conventional oral dosage forms face challenges, such as poor solubility, rapid metabolism, and variable gastrointestinal absorption. *In situ* gel systems, particularly those designed for oral and transdermal routes, have provided novel solutions for improving the bioavailability and sustained release of OHAs [149]. In the oral route, pH-sensitive *in situ* gels protect drugs from degradation in the stomach and release them in the intestine, where absorption is optimal. For example, metformin-loaded alginate or chitosan gels resist gastric acid, but swell and release the drug in neutral pH environments, ensuring prolonged drug availability. This not only improves bioavailability, but also reduces gastrointestinal irritation, a common side effect of metformin therapy [150]. Oral *in situ* gels can be engineered to increase gastric retention, forming a floating gel layer in the stomach that prolongs drug residence time. Such formulations are particularly beneficial for drugs with absorption windows in the upper intestines. By extending the contact time and providing controlled release, these systems enhance therapeutic efficacy while reducing dosing frequency [151]. In the transdermal domain, *in situ* gels and microneedle-assisted systems have been applied to deliver small-molecule OHAs through the skin, bypassing the hepatic first-pass metabolism. Polymers incorporated with permeation enhancers allow molecules such as glibenclamide and repaglinide to permeate efficiently, achieving stable plasma levels without oral side effects [152]. Combination gels that deliver two or more OHAs simultaneously are under investigation for targeting multiple metabolic pathways in type 2 diabetes. For instance, the co-delivery of metformin and sulfonylurea in an *in situ* gel system provides complementary mechanisms that reduce hepatic glucose output while enhancing insulin

secretion, leading to synergistic control of hyperglycemia [153]. The application of *in situ* gels for oral hypoglycemic drugs addresses key pharmacokinetic limitations, enhances patient comfort, and aligns with the chronic dosing requirements of type 2 diabetes management [154].

6.3. Emerging peptide and protein-based therapies

Beyond insulin and classical OHAs, new peptide- and protein-based therapies are transforming the diabetes management landscape. These include glucagon-like peptide-1 (GLP-1) receptor agonists, amylin analogs, and DPP-4-resistant peptides, all of which play critical roles in modulating glucose metabolism, appetite regulation, and insulin secretion. However, these biomolecules face challenges similar to those of insulin, such as enzymatic degradation, poor oral bioavailability, and short half-lives. In-situ gels provide an ideal platform for stabilization and sustained delivery [155]. GLP-1 receptor agonists, such as exenatide and liraglutide, have shown significant promise in improving glycemic control while promoting weight loss. Conventional formulations often require frequent injections, but encapsulation within injectable *in situ* gels can extend their release to weekly or monthly dosing. Thermosensitive or biodegradable gels made from PLGA or poloxamers have demonstrated controlled exenatide release in preclinical studies, reducing the need for repeated injections [156]. Amylin analogs such as pramlintide complement insulin therapy by slowing gastric emptying and suppressing postprandial glucagon secretion. *In situ* gels have been used to co-deliver pramlintide with insulin, ensuring the synchronized release of both hormones for optimal glycemic control. Such combination gels reduce the injection burden while addressing multiple metabolic pathways [157]. Emerging dual- and tri-agonist peptides that simultaneously activate GLP-1, GIP, and glucagon receptors are also being explored for their enhanced glycemic and weight management effects. *In situ* gels offer a means to stabilize these complex peptides, protect them from proteolytic enzymes, and provide sustained systemic exposure [158]. Protein-based therapies targeting inflammation and oxidative stress in diabetes are currently being developed. Encapsulating cytokine inhibitors, antioxidants, or growth factors in *in situ* gels ensures localized and prolonged release, particularly in tissues affected by diabetic complications, such as the retina, kidney, or nerves [159]. The sustained and protective delivery of fragile biomolecules *in situ* gels expands the therapeutic arsenal beyond insulin and OHAs, bringing next-generation peptide- and protein-based therapies closer to clinical translation [160].

6.4. Nanoparticle-loaded in situ gels for diabetes

The integration of nanotechnology with in-situ gel systems has opened new avenues for highly efficient diabetes management. Nanoparticle-loaded *in situ* gels combine the benefits of nanoscale carriers, such as enhanced drug solubility, stability, and targeted delivery, with the sustained release properties of the gels. This hybrid approach offers precise control over drug release kinetics, improved bioavailability, and the potential for multifunctional therapies [161]. Polymeric nanoparticles encapsulated within *in situ* gels protect sensitive molecules, such as insulin or GLP-1 agonists, from enzymatic degradation and provide dual-level release: an initial release from the gel matrix followed by sustained release from nanoparticles. This layered release profile ensures rapid therapeutic onset and long-term maintenance [162]. Lipid-based nanoparticles, such as SLNs and NLCs, further enhance drug solubility and membrane permeability. When dispersed within *in situ* gels, they create depot systems capable of delivering poorly water-soluble OHAs or hydrophobic antioxidants for diabetic complications [163]. Another promising application is the integration of stimuli-responsive nanoparticles integrated into *in situ* gels. For instance, glucose-sensitive nanoparticles that release insulin in response to hyperglycemia can be embedded within a

thermosensitive gel depot, resulting in a self-regulating, "smart" delivery system. Such hybrid systems bring us closer to the vision of an artificial pancreas by offering closed-loop glucose regulation [164]. Targeted delivery using ligand-modified nanoparticles within in-situ gels has also been investigated. For example, nanoparticles decorated with antibodies against pancreatic receptors can be incorporated into gels for pancreatic targeted drug release. Similarly, ocular *in situ* gels containing anti-VEGF-loaded nanoparticles have been designed for the treatment of diabetic retinopathy, prolonging drug residence in the eye and reducing the need for repeated injections [165]. From a safety perspective, the gel matrix prevents rapid nanoparticle clearance, minimizes systemic toxicity, and ensures localized drug retention. Combining the strengths of nanotechnology and polymeric gel systems, nanoparticle-loaded *in situ* gels represent one of the most advanced and promising strategies for diabetes therapy [166]. **Figure 4** shows a smart drug delivery strategy in which nanoparticles are encapsulated within an *in situ* gel formulation. Upon injection, the gel forms at the site of administration and provides sustained release of therapeutic agents. In diabetes therapy, this system enhances glucose regulation by promoting insulin receptor activation and GLUT4 function, thereby improving glycemic control through controlled and targeted delivery.

7. Challenges and Future Perspectives

Although *in situ* gel systems have emerged as a transformative approach in drug delivery for diabetes management, several challenges hinder their large-scale clinical application. These challenges stem from formulation complexities, physiological barriers, and translational hurdles that must be overcome to fully exploit the potential of these smart systems. On the other hand, recent advancements in polymer chemistry, biomaterials, and nanotechnology drive innovation toward more effective and patient-friendly therapies. Understanding these limitations, keeping track of technological breakthroughs, and envisioning the future

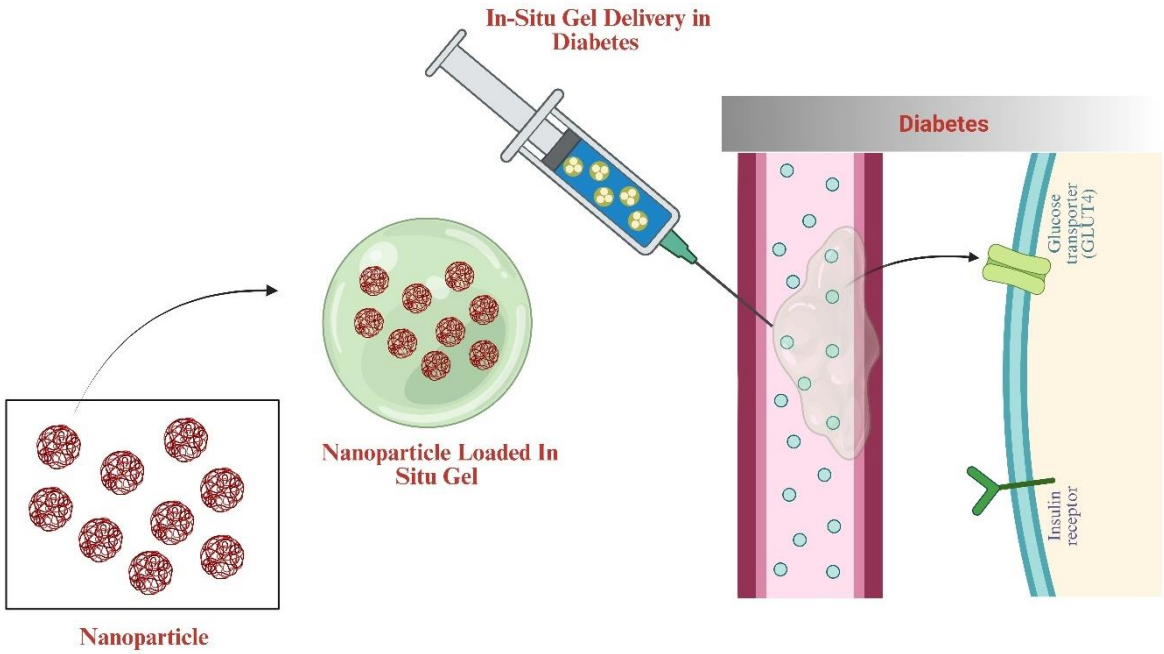

Figure 4. Nanoparticle-loaded *in situ* gel system for diabetes management. Embedded nanoparticles within thermosensitive gels provide sustained insulin or GLP-1 release, enhancing receptor activation and glycemic control

outlook are essential steps for realizing the full therapeutic potential of *in situ* gel systems in diabetes care.

7.1. Limitations of current in situ gel systems

Despite their promise, current *in situ* gel systems have several formulation and clinical limitations that restrict their widespread adoption. One major limitation is the incomplete control of drug release kinetics. While *in situ* gels provide sustained release, it is often difficult to achieve precise control over the release profiles, especially when multiple drugs or biomolecules are co-encapsulated. For example, a rapid initial burst release may occur because of loosely entrapped molecules at the gel surface, followed by a slower release from the gel core. Inconsistent release rates can lead to suboptimal therapeutic outcomes, particularly in diabetes, where steady-state plasma concentrations are critical for maintaining glycemic control. Another key challenge is the reproducibility of the gelation under physiological conditions. Gel formation depends on triggers such as temperature, pH, or ionic strength, which may vary between individuals and tissue sites. For instance, thermosensitive gels may form prematurely during injection if exposed to warm conditions, whereas pH-sensitive gels may not consistently gel in gastrointestinal environments due to fluctuating acidity. These variations introduce uncertainty into the performance and limit clinical predictability. Biocompatibility concerns persist. Although many polymers used in *in situ* gels are considered safe, additives such as crosslinkers, stabilizers, or permeation enhancers may cause local irritation, inflammation, or immune reactions. Long-term biocompatibility, particularly for chronic administration to patients with diabetes, requires thorough investigation. Moreover, polymer degradation products may interact with the encapsulated drug, thereby reducing its stability and efficacy. From a manufacturing and scalability perspective, *in situ* gel systems pose challenges in maintaining consistency, stability, and sterility. The large-scale production of injectable gels must meet stringent regulatory standards, which can be difficult to achieve for complex formulations involving sensitive biomolecules. Additionally, stability during storage remains a problem because some gels may undergo premature crosslinking or degradation, reducing their shelf life. Patient-related factors also limit their adoption. While injectable *in situ* gels reduce dosing frequency, they still involve needles, which may not fully address needle phobia in diabetic patients. Oral and nasal *in situ* gels, although more patient-friendly, often suffer from poor bioavailability due to enzymatic degradation or mucociliary clearance. Moreover, cost considerations may limit accessibility, especially in low- and middle-income countries, where the prevalence of diabetes is rapidly rising. Taken together, these limitations highlight the need for continuous research on optimizing gel formulations, ensuring reproducibility, enhancing safety, and developing scalable manufacturing processes.

7.2. Advances in polymer chemistry and nanotechnology

In recent years, polymer chemistry and nanotechnology have provided powerful tools to address many of the above limitations. These advances have paved the way for the next generation of *in situ* gel systems with improved performance and broader applications. The development of stimuli-responsive polymers has been a major breakthrough in polymer chemistry. Glucose-sensitive polymers, for example, can dynamically regulate insulin release in response to blood glucose fluctuations, mimicking the natural feedback mechanisms of the body. These polymers often incorporate boronic acid derivatives or glucose oxidase to achieve responsiveness, creating a "smart" drug delivery system capable of closed-loop regulation. Innovations in multifunctional polymers enable gels with tunable degradation rates, improved mechanical strength, and enhanced drug–polymer compatibility. For example, copolymers of PEG, PLGA, and poloxamers can be tailored. Natural–synthetic polymer hybrids combine the biocompatibility

of natural polymers such as chitosan or alginate with the mechanical robustness of synthetic polymers, offering the best of both worlds. Nanotechnology integration has further expanded the capabilities of in-situ gels. Nanoparticles, liposomes, dendrimers, and micelles incorporated into gels provide additional control over drug encapsulation and release. These carriers can protect sensitive biomolecules, enhance their solubility, and achieve targeted delivery. For example, insulin-loaded nanoparticles embedded in a thermosensitive gel can release insulin in a dual-phase manner: an initial burst from nanoparticles near the gel surface, followed by sustained release from deeper layers. Another exciting innovation is the design of multi-drug-loaded gels enabled by the nanocarrier technology. Nanoparticles containing different drugs can be dispersed within a single gel matrix, allowing the co-delivery of insulin with oral hypoglycemic agents or antioxidants. This approach offers synergistic therapeutic effects and simultaneously addresses the multiple pathological pathways in diabetes. Nanotechnology facilitates targeted drug delivery. Ligand-modified nanoparticles embedded in gels can preferentially accumulate in specific tissues, such as the pancreas, liver, or retina. For example, ocular *in situ* gels containing anti-VEGF-loaded nanoparticles have shown promise in treating diabetic retinopathy by prolonging the residence time and enhancing penetration into intraocular tissues. Advances in polymer crosslinking strategies have resulted in gels with improved reproducibility and stability. Physical crosslinking through ionic interactions or hydrogen bonding avoids the use of toxic chemical crosslinkers, thereby enhancing safety. Dynamic covalent bonds enable reversible gelation, allowing the gels to adapt to changing physiological environments. The convergence of polymer chemistry and nanotechnology is also driving the development of personalized gels, in which formulations can be tuned to individual patient needs, disease progression, and lifestyle. Three-dimensional (3D) printing technologies are being explored to fabricate custom-designed gel depots with precise geometry and drug distribution, further enhancing therapeutic precision. Collectively, these advances mark a paradigm shift in the design of *in situ* gel systems, moving from passive sustained-release formulations to intelligent, adaptive, and multifunctional drug delivery platforms.

7.3. Future outlook for diabetes therapy

Looking ahead, *in situ* gel systems are poised to play a central role in the future of diabetes management; however, their success will depend on overcoming existing limitations and integrating emerging technologies. One of the most exciting prospects is the development of fully glucose-responsive *in situ* gels that can act as an artificial pancreas. By combining glucose-sensing elements with controlled-release mechanisms, such systems can autonomously regulate insulin delivery, eliminating the need for continuous patient monitoring and frequent injections. These closed-loop systems, if clinically successful, would revolutionize diabetes therapy and significantly improve quality of life. The integration of nanomedicine with precision medicine is another promising approach. Future *in situ* gels may be designed to deliver not only insulin or OHAs, but also gene therapies, stem cell factors, or immunomodulators aimed at regenerating pancreatic β-cells or reversing disease progression. For instance, gels delivering CRISPR-Cas9 components or siRNA can target genetic pathways involved in insulin resistance or β-cell dysfunction, moving beyond symptomatic control toward disease modification. Digital health and smart devices are also expected to converge with in-situ gel systems. Wearable glucose monitors can communicate wirelessly with stimuli-responsive gels, triggering drug release when glucose levels exceed thresholds. Such an integration of biosensors, drug depots, and mobile applications could create a holistic diabetes management ecosystem. From a clinical translation perspective, a patient-centric design is crucial. Formulations that minimize the injection frequency, reduce side effects, and improve convenience will drive adoption. For

example, weekly or monthly injectable *in situ* gels can replace multiple daily insulin injections, dramatically simplifying the treatment regimens. Noninvasive gels for nasal, ocular, or transdermal delivery can further reduce the treatment burden. In terms of research, the future will focus on optimizing the scalability and regulatory approval. Standardized manufacturing methods, reproducibility across patient populations, and long-term safety data are necessary for its clinical adoption. Cost-effectiveness must also be addressed, ensuring that advanced gel systems remain accessible to patients in resource-limited settings where diabetes prevalence is highest. The future outlook emphasizes a multidisciplinary approach. Collaboration between polymer chemists, nanotechnologists, biomedical engineers, clinicians, and regulatory experts is essential to translate laboratory success into real-world therapies. The ultimate goal is not only better glucose control, but also holistic management of diabetes complications, including neuropathy, retinopathy, and nephropathy. Challenges remain; the trajectory of research suggests that *in situ* gel systems, enhanced by advances in materials science and nanotechnology, hold immense potential to redefine diabetes therapy. They represent a shift from conventional treatments to smart, adaptive, and patient-centered solutions that address both metabolic control and long-term complications. In the coming decades, *in situ* gels may evolve from experimental platforms to mainstream clinical tools, fundamentally changing the way diabetes is managed. Despite remarkable advancements in stimuli-responsive *in situ* gel systems, their clinical translation remains limited by regulatory and manufacturing challenges. The complex composition of smart polymers, including stimuli-sensitive cross linkers, nanoparticles, or bioactive agents, often raises concerns regarding reproducibility, scalability, and long-term biocompatibility. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), require extensive characterization, stability data, and safety evaluations before approval, which can prolong development timelines. Additionally, the lack of standardized testing protocols and predictive *in vitro–in vivo* correlation models complicate the assessment of these dynamic systems. Therefore, future research should integrate regulatory science early in the design phase, focusing on simplified formulations, well-characterized polymers, and cost-effective production methods to facilitate clinical translation. Addressing these regulatory and translational barriers is crucial for advancing smart polymer-based *in situ* gels from laboratory innovations to practical therapeutic applications in diabetes management.

8. Conclusion

In situ gel-based smart drug delivery systems represent a transformative approach to overcoming the limitations of conventional antidiabetic therapies. Their ability to undergo sol-to-gel transitions in response to physiological stimuli, such as pH, temperature, ions, or enzymes, allows for site-specific and sustained release of therapeutic agents. By tailoring the chemical composition, crosslinking density, and hydrophilic–hydrophobic balance of polymers, these systems enable controlled drug release, while maintaining biocompatibility and patient compliance. Synthetic polymers, such as poloxamers and PEG derivatives, as well as hybrid formulations, have demonstrated versatility in oral, nasal, ocular, injectable, and transdermal applications, extending their potential to a wide spectrum of antidiabetic drugs. In particular, *in situ* gels have shown promise for insulin delivery, oral hypoglycemic agents, and novel peptide-based therapies, with nanoparticle-loaded gels further enhancing their stability and bioavailability. Despite these advances, challenges remain, including the optimization of gelation kinetics, achieving precise targeting to pancreatic or extra-pancreatic sites, and ensuring reproducibility in large-scale manufacturing. Advances in polymer chemistry, nanotechnology, and stimuli-responsive design are expected to refine these systems, bridging the gap between laboratory innovations and

clinical translation. Overall, *in situ* gel-based platforms offer a promising and patient-friendly future for diabetes management, with the potential to revolutionize therapy by enhancing its efficacy, safety, and adherence.

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Conflict of Interest

Authors have declared that there is no conflict of interest exists.

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