INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Recent Advancements in Glucose-Modulated Insulin Delivery Systems

Rupali Chopade*, Sakshi Jatale, Pallavi Kandale, Dr. Shivshankar Mhaske, Shatrughna Nagrik

Satyajeet College of Pharmacy, Mehkar.

ARTICLE INFO

Published: 25 May 2025
Keywords:
Phytochemical, Neurodegenerative diseases, Natural neuroprotectants, Neuroinflammation
DOI:
10.5281/zenodo.15507328

ABSTRACT

The management of diabetes has expanded tremendously with the development of glucose-modulated insulin delivery systems to improve glycemic control and reduce the risk of hypoglycemia. Traditional insulin therapy requires regular monitoring and precise dosing by the patient which can then lead to discomfort or possible ramifications. New technologies such as smart insulin formulations and automated delivery systems that can react in real-time after blood glucose fluctuations have emerged. An important contribution is glucose-responsive insulin (GRI), which consists of insulin molecules that were chemically modified to release insulin in response to elevated glucose concentrations. These formulations include glucose-sensing moieties, which include phenylboronic acid, glucose oxidase, and polymer hydrogels, for controlled release of insulin. One of the key developments was the development of engineered insulin analogs that can independently modify their activity according to glucose concentrations to increase efficacy. In addition, smart insulin pumps and artificial pancreas systems that combine continuous glucose monitoring (CGM) and automated insulin delivery, where dosing is based on data from machine learning algorithms, have been developed. Novel nanotech-type carriers such as microneedles, hydrogels, and nanoparticles can improve stability of insulin and controlled release. These new technologies have common goals of improving patient adherence, reducing glucose variability, and minimizing the long-term and acute consequences associated with diabetes. Despite these advancements, challenges with biocompatibility, cost, and regulatory approvals still need to be addressed. Future studies plan to optimize these technologies for widespread use in clinical practice, as they offer a more physiological and patient-centered approach to diabetes management. The integration of nanomedicine, artificial intelligence, and biomaterial engineering will continue to push ahead in the field, getting us closer to an autonomous insulin delivery system.

***Corresponding Author:** Rupali Chopade
Address: *Satyajeet College of Pharmacy, Mehkar.*
Email ✉: rupalichopade688@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by either insufficient insulin production, insulin resistance, or a combination of both, leading to prolonged periods of hyperglycemia (American Diabetes Association, 2021). The International Diabetes Federation (IDF) estimated that in 2021, approximately 537 million people worldwide were living with diabetes (IDF, 2021), and the number is projected to increase significantly in the ensuing decades partly due to lifestyle changes and the aging population. Poor glycemic control among individuals living with diabetes often corresponds with major adverse complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy, resulting in an increase in morbidity and mortality (Sun et al., 2022). Optimal diabetes management requires maintaining blood glucose levels in a narrow physiological range, mainly by using insulin. More than 90% of people living with diabetes are treated with traditional insulin delivery systems, which may take the form of multiple daily injections, or continuous subcutaneous insulin infusion; however, these approaches rarely mimic endogenous insulin delivery. Insulin released from β-cells of the pancreas, leads to repeated episodes of hyperglycemia and hypoglycemia (Patel et al., 2020). In response to these challenges, glucose-modulated insulin delivery systems have emerged as a new way to achieve near-physiological glucose control (Yu et al., 2021). These systems are designed to dynamically respond to changes in blood glucose levels and provide automated insulin administration only as needed, reducing glycemic variability and the risk of complications (Zhang et al., 2023). To date, glucose-responsive insulin formulations, intelligent polymeric carriers, microneedle patches, and recombinant cell-based systems represent a transformative advance in diabetes management providing more efficacious and patient-friendly therapies (Chen et al., 2021). This positing offers a review of the progress made made in glucose-modulated insulin delivery systems, while evaluating their systems, advantages, shortcomings, and potential clinical applications. Conventional insulin therapy is the cornerstone of diabetes management, but it has serious limitations associated with multiple subcutaneous injections, hypoglycemia, weight gain, and issues with patient adherence (Owayez et al., 2024). Existing basal insulin formulations often demonstrate pharmacokinetic variability, which can lead to suboptimal glycemic control and an increased risk for nocturnal hypoglycemia (Rosenstock et al., 2024). Furthermore, insulin therapy cannot replicate physiological insulin secretion, leading to postprandial glucose variability and increased cardiovascular risk (Asaad et al., 2024). Recent advancements utilize a glucose-modulated manner in insulin delivery systems to improve treatment effect using non-invasive means, smart-routed insulin formulations, and closed-loop approaches. Oral and nasal routes of insulin delivery are endeavored to promote adherence while replicating the physiological nature of insulin secretion (Saghir et al., 2024). Inhaled insulin and insulin polymers that target the intestines via glucose-responsiveness have produced positive results in preclinical trials (Ying et al., 2024). New long-acting, once-weekly insulin analogs, such as icodec, have improved levels of adherence and glycemic control compared to daily basal insulin protocols (Rosenstock et al., 2024). Automated insulin delivery (AID) systems incorporating continuous glucose monitoring (CGM) with insulin pumps are developing toward a fully closed-loop system that similarly lowers the risk for postprandial hyperglycemia and hypoglycemia (Moscoso-Vásquez et al., 2024). The use of GLP-1 receptor agonists (GLP-1RA) as adjunct therapy

in AID systems leads to better metabolic outcomes (Shah et al., 2024). Despite these advancements, difficulties remain in ensuring consistent absorption, preventing immunogenicity, and improving real-time glucose tracking in smart insulin preparations (Zhang et al., 2024). Future work should focus on the incorporation of artificial intelligence-based algorithms and nanotechnology to develop personalized or self-adjusting insulin delivery systems (Akturk & Bindal, 2024). Glucose-responsive insulin (GRI) delivery systems also represent a major step in diabetes management; they can deliver insulin similar to normal physiological secretion and limit the risk of hypoglycemia (Høeg-Jensen et al., 2024). Typical insulin therapy requires precise dosing, often leading to blood glucose variability and patient non-adherence. GRIs, on the other hand, deliver insulin in response to immediate glucose changes, eliminating the need for continuous monitoring and multiple injections (Liu et al., 2024). Smart hydrogels, nanoparticles, and enzyme-based glucose sensors have been developed to enable controlled insulin delivery, increase patient adherence, and improve clinical effects related to long-term metabolic outcomes (Ying et al., 2024). New improvements in glucose-sensitive membranes have led to significant advancements in the accuracy of closed-loop insulin delivery and improved postprandial glucose control (Saranya et al., 2024). In addition, surface treatments of nanoceria could demonstrate utility as an insulin delivery and oxidative stress depressor for treatment of a frequent contributor to diabetes-related effects (Sharmah et al., 2024). Emerging modalities of insulin-containing collagen hydrogels loaded with insulin could represent an emerging approach to replacement therapy for beta cells, potentially as an alternative treatment for islet transplantation (Moon et al., 2024). Further, glucose-sensitive macromolecular conjugates, exemplified by NNC2215 currently in development, may enhance affinity toward insulin receptors in response to hyperglycaemia, while reducing hypoglycaemia (Høeg- Jensen et al., 2024). Oral insulin formulations utilizing glucose-responsive nanocarriers also improve bioavailability as a non-invasive alternative to conventional subcutaneous injections (Saghir et al., 2024). There are still challenges in improving sensor accuracy, increasing biocompatibility and reducing cost in order to make these advances clinically adoptable (Medina et al., 2024). There is tremendous opportunity for artificial intelligence-based closed-loop systems to improve the precision of glucose-responsive insulin delivery systems and tailor those systems to specific patients (Castañeda et al., 2024). The current publication provides an in-depth analysis of the progress with glucose controlled insulin delivery systems, through exploring assessment of safety, effectiveness, and potential for improved glycemic management as part if diabetes management. The increasing prevalence of diabetes mellitus shows the limitations of existing treatment options for patients using insulin (e.g. functions of daily injections, risk of hypoglycemia, non-compliance with requirements has led to exploration of new methods of delivery) (Fan et al, 2024). This review highlighted the importance of innovative biomaterials including hydrogels and nanoparticles synthesized to develop glucose-responsive insulin to produce a more physiological insulin release (Barkhordari et al., 2024). The consideration of AID systems in limited cohorts including pregnant women with type 1 diabetes and the need for individualized algorithm and glycemic targets was highlighted (Chillakanti et al., 2024). Finally, we explored the clinical perspective of new technologies for insulin delivery: recognising issues such as cost, accessibility and patient compliance (Kockaya et al., 2024). This review will serve as a comprehensive resource for researchers,

physicians, and policymakers that working towards improving diabetes care via novel methods of insulin delivery.

1. Enzyme-Based Systems

1.1 Glucose Oxidase-Mediated Insulin Release in Enzyme-Based Systems

Glucose oxidase (GOx)-mediated insulin delivery represents a new form of enzyme-based glucose-responsive insulin delivery systems which improves glycemic control for diabetes management. GOx utilizes glucose to catalyze the oxidation of glucose to gluconic acid and hydrogen peroxide (H2O2). Ulitmately, these mechanisms are the basis of controlled release of insulin, specifically at ambient blood glucose levels (Ma et al., 2024). Enzyme-based insulin delivery systems will have also incorporated GOx into either nanogels, hydrogels, or vesicles, all of which include insulin molecules for delivery. Increased glucose levels facilitates GOx converting glucose to gluconic acid which simultaneously decreases the local pH and subsequently triggers the insulin release from the degradation of polymeric encapsulation. Overall, the byproduct of H2O2 assists in the destabilizing insulin loaded nanoparticles and produces a controlled and sustained release of insulin (Sharmah et al., 2024). A recent demonstration that has occurred in GOx mediated insulins systems, is its application in conjunction with titanium dioxide (TiO2) nanoparticles which provide glucose sensitivity and increased bioavailability of insulin. TiO2-functionalized insulin carriers, have reported improved glucose responsiveness and duration of insulin release, providing a much less probability of hypoglycemia post-prandial (Liu et al., 2024). To increase enzyme stability, researchers have synthesized dually crosslinkednanogels to minimize enzyme leakage and sustain GOx activity in the system for longer durations, promoting insulin delivery efficiency and stability, ultimately making these systems more applicable (Romero-Carmona et al., 2024). The inclusion of phenylboronic acid (PBA) in functionalized systems with GOx (glucose oxidase) enhances glucose sensitivity as well and facilitates a faster and dynamic release of insulin (Xu et al., 2024). Despite its promising ability to mediate the delivery of insulin, hurdles such as enzymatic degradation, cytotoxicity from H2O2, and the precision of glucose threshold tuning, need to be targeted. Future work will assess the stabilization of enzyme activity, the minimization of cytotoxicity from oxidative stress, and the integration of AI-assisted real-time glucose monitoring for more precise and individualized insulin modulation for therapeutic treatment of diabetes.

1.2 .Peroxidase-Based Catalysis for Insulin Delivery in Enzyme-Based Systems

Peroxidase based catalysis is a new area of interest in glucose response delivery systems that provide diabetes management with a controlled means of delivering insulin. This enzyme-based system utilizes peroxidase enzymes (horseradish peroxidase, HRP, or artificial nanozymes) to trigger insulin release in response to oxidative signals to help improve glycemic control (Sharmah et al., 2024) Peroxidase-mediation when developing insulin-delivery systems typically uses hydrogen peroxide (H2O2) as the triggering agent. Glucose oxidase (GOx) can catalyze the oxidation of glucose resulting in H2O2. H2O2 then interacts with peroxidase enzymes resulting in structural changes within the insulin-loaded nanocarriers allowing for the controlled and sustained release of insulin which is reported as mimicking pancreas function (Xu et al., 2024). Advanced materials, in the form of functionalized titanium dioxide (TiO2) or cerium oxide (CeO2) base nanozymes, are combined with the peroxidase systems, improving

catalytic efficiency and stability. Nanozymes have intrinsic peroxidase-like reactivity while mitigating issues of enzyme degradation. This strategy leads to a vastly superior bioavailability of insulin being released while managing hypoglycemia (Romero-Carmona et al., 2024) One of the primary advantages of peroxidase-catalyzed processes is its biocompatibility and viability in physiological concentrations of glucose. Hydrogel carriers designed with a hybrid composition and loaded with peroxidase enzymes can achieve prolonged insulin release suggesting relevance for prolonged glucose regulation. Furthermore, these formats could be modified with phenylboronic acid (PBA) groups to enhance specificity to glucose and quickness of response kinetics (Liu et al., 2024) While exciting progresses have been made, challenges remain, such as enzyme stability, potential cytotoxic effects from H2O2 products, and the need to tune glucose threshold pathways both precisely. Future studies have and will continue to examine hybrid enzyme-nanozyme systems to aid in insulin delivery while reducing degradation associated with peroxidase. Real-time glucose readings monitored through artificial intelligence in closed-loop systems that utilize an artificial pancreas, will further optimize this approach/the efficacy of this function/every intersection of this function, making insulin delivery via peroxidase a potential transformative innovation in diabetes (Ma et al., 2024).

2. Phenylboronic Acid-Based Systems

2.1 Boronate-based hydrogels for glucose sensing

Recently, boronate hydrogels based on phenylboronic acid (PBA) have garnered a lot of attention for use in glucose sensing and glucose-modulated insulin delivery systems. The interest in these hydrogels lies in the unique nature of PBA forming reversible covalent bonds with diols such as glucose, which means that the hydrogels can be used for both dynamic sensing of glucose and responsive drug release in response to changes in glucose. The use of glucose-responsive hydrogels that include PBA has come a long way with the growth of PBA as a material and the novel advances in material synthesis and crosslinking processes and hydrogel structure.474.48. Recently, novel routes have been explored for synthesizing glucose-responsive hydrogels, like 3D printing and other methods to enable the design of PBA-functionalized hydrogels that produce very specific drug release profiles. For example, Odent et al., developed a 3D printed phenylboronic acid-bearing hydrogel in which the authors provided a glucose-triggered drug release to provide on-demand insulin delivery via glucose-responsive mechanisms (Odent et al., 2024). In the same vein, developed in-situ forming multipolymeric glucose-responsive hydrogels, made from heterobifunctional formylphenylboronic acid (FPBA) crosslinkers, that held a compromise between injectability, self-healing properties, and insulin delivery control (Saha et al., 2024). Photonic crystal hydrogels (PCHs) are now being used to further enhance the visual monitoring of glucose levels. established smart photonic crystal hydrogels able to visually monitor glucose by displaying colorimetric sensing in relation to glucose-induced swelling and shrinkage. This offers a non-invasive, expedient means of glucose sensing with future potential impacts on diabetic wound healing (Yang et al., 2024). Beyond insulin delivery, boronate-based hydrogels will likely have biosensing applications beyond glucose monitoring. presented hydrogel grating sensors given boron affinity and molecular imprinting effects that gave rapid, highly selective imaging of tumor markers in serum. This technology was based on nanostructured hydrogel gratings with a dynamic

response to the concentration of biomarkers, which should inform glucose-responsive hydrogel-related future projects (Fu et al., 2024). There is clearly a bright future for the use of PBA-based hydrogels in the fields of glucose sensing and insulin delivery, provided that key issues such as biocompatibility, response time, and stability can be further developed. Regardless, the recent advances in designing biomaterials, or hybrid polymeric networks and nanostructured hydrogel systems that integrate biological molecules, are encouraging when seeking to optimize these systems for more direct clinical applications. With further modelling and technological advances, functionalized PBA-hydrogels will ultimately provide viable alternatives to continuous glucose monitoring and controlled insulin delivery, facilitating change in our day-to-day diabetes management.

2.2. Mechanism of pH-responsive insulin release

Due to their pH-responsive properties, phenylboronic acid (PBA)-based systems have been of great interest in glucose-modulated insulin delivery due to their ability to mediate controlled delivery of insulin via pH-responsive frameworks. Insulin delivery via PBA-based hydrogel systems arises from the diffusive interactions between PBA and diols, in particular glucose, which lead to changes in hydrogel swelling, and therefore, the drug release mechanism. PBA conjugated hydrogel networks build reversible boronate ester bonds with glucose, which may also be destabilized with some pH interactions, leading to controlled drug diffusion through network swelling. The pH-sensitive behaviour of these frameworks arises from the way PBA can exist in both a neutral and charged state depending on the local acidity, which promotes different solubility and network conformation. In normal physiological conditions involving pH ~7.4, PBA occurs predominantly in its neutral state, and therefore the hydrogel remains stable while retaining insulin. However, during a hyperglycemic response, the increased glucose-binding actives not only contribute to increased acidity but therefore increased availability of the charged boronate form of insulin-PBA polymer, expanding hydrogel swelling and releasing insulin. (Kao et al.,2025) This pH-dependent reaction provides an insulin delivery system that is self-regulating and responsive to feedback. In-situ forming multipolymeric glucose-responsive hydrogels were developed, which displayed improved glucose selectivity and pH responsiveness. These hydrogels are made from polyvinyl alcohol (PVA) and polyethyleneimine (PEI) and use formylphenylboronic acid (FPBA) crosslinkers, allowing for tunable release of insulin, while maintaining the native structure (Saha et al., 2024). A similar study was performed by Ying et al. (2024), who created a smart hydrogel with targeted intestinal delivery that had dual-glucose and pH responsiveness improving the efficacy of oral insulin delivery. This system is made from carboxymethyl agarose modified with 3-amino-phenylboronic acid; pro-drug insulin specifically at pH 6.8 regarding insulin release, simulating the gut conditions (Ying et al., 2024). Another the dependency of hydrogel architecture with dynamic insulin release rate kinetics has been explored through 3D-printing. Odent et al. (2024) developed 3D printed phenylboronic acid bearing hydrogels for glucose mediated triggering of drug release, able to fine tune the insulin drug release rates based on polymer cross-linking density and material composition control (Odent et al., 2024). These hydrogels showed enhanced stability and demonstrated responsiveness suggesting their potential with an implantable delivery system for insulin. Supramolecular peptide amphiphile (PA)-based hydrogels have also been studied for their assembly into nanofibrillar structures that act in a

glucose-dependent manner. Chen et al. (2024) synthesized PA-functionalized PBA hydrogels that demonstrated glucose-dependent assembly and pH-induced release of insulin, effectively inoculating insulin degradation while maintaining bioavailability (Chen et al., 2024). These results highlight the potential of PBA hydrogels to enable insulin delivery with glucose-mediated accuracy. The future focus of PBA-based pH responsive systems will be to improve biocompatibility, response kinetics and add additional stimuli responsive systems. The incorporation of molecular imprinting, nanoparticle conjugation and bioinspired polymers will further enhance the functionality of these hydrogels to allow for better efficiency and patient friendly diabetes management options.

3.Polymeric and Hydrogel-Based Systems

3.1 .Smart hydrogels for glucose-dependent swelling and insulin diffusion

Smart hydrogels have attracted considerable interest as a glucose-modulated insulin delivery platform due to their glucose-dependent swelling and insulin diffusion capacities. These polymeric networks can exhibit dynamic glucose responsive behaviors, thus enabling controlled insulin release that accounts for the requirements of the patient. The mechanism of action for glucose-responsive hydrogels is generally based on glucose oxidase (GOx)-mediated catalysis, PBA-diol interactions, or pH-sensitive swelling mechansms. Liu et al. developed a Dioscoreaopposita polysaccharide-calcium carbonate (CaCO3) microsphere-doped hydrogel that combines glucose-responsive insulin release and anti-inflammatory actions. This hydrogel system relies on borate ester bonds between polylysine-phenylboronic acids (PL-PBA), and poly(vinyl alcohol) (PVA), resulting in glucose-dependent swelling and the consequent insulin release (Liu et al., 2025) In a similar manner, Chaudhary et al. (2024) developed a semi-interpenetrating network hydrogel comprising microcrystalline cellulose and itaconic acid that was both pH-sensitive and improved oral insulin bioavailability. The hydrogel could swell more in an environment rich in glucose and release its insulin under diabetic conditions (Chaudhary et al., 2024). In addition, Chaudhary et al. (2024) developed a pH-responsive hydrogel composed of methacrylic acid that had glucose-sensitive swelling properties, making it suitable for oral insulin delivery. This hydrogel was stable in an acidic conditions, gave insulin bioavailability, but swelled profusely in neutral or alkaline pH allowing drug release in the intestine (Chaudhary et al., 2024) Other advances were the use of montmorillonite sodium nanocomposites in developing polymeric hydrogels, which increase hydrogel stability, and further enhance encapsulation of insulin and controlled release of insulin. Shabir et al.(2024) illustrated that the functionalization of hydrogel matrices with montmorillonite sodium was able to enhance the bioavailability of insulin, by attaining improved glucose-dependent insulin release (Shabir et al., 2024). By extending past the typical polymeric network, Ahmad et al. (2023) produced a hydrogel derived from psyllium-hyaluronic acid and collagen that contained pH-responsive properties for the oral administration of insulin. This hydrogel was able to uptake small amounts of water when exposed to acidic environments but swelled considerably at physiological pH facilitating the protection of insulin in the stomach and allowing controlled release in the intestine (Ahmad et al., 2023). The development of smart hydrogels as systems for glucose-responsive insulin delivery is appreciated in the optimization of polymeric composition, biocompatibility, and added stimuli responsiveness in conjunction with enzyme-functionalized networks and/or nanostructured carriers. A derived pH-sensitive,

glucose-responsive and bioactive hydrogel could usher an exciting future for diabetes treatment and management with non-invasive self-regulated insulin delivery.

3.2.Injectable and implantable hydrogel systems

Hydrogel systems designed for injection and implantation provide an essential platform for glucose-controlled insulin delivery. These systems use intelligent polymeric matrices to provide controlled, sustained, drug delivery through materials that are expected to respond to physiological glucose levels. A hydrogel can be delivered as an injectable product that is designed to spontaneously form after injection. Implantable hydrogels may serve as long-acting insulins for glucose regulation by their prolonged insulin retention due to biocompatibility or mechanical stability in the body. In the discussions with a polysaccharide-calcium carbonate microsphere hydrogel that would further enhance diabetic wound healing and utilize glucose-responsive insulin release property. The hydrogel crosslinking involved polylysine-phenylboronic acids (PL-PBA) in glucose-responsive insulin diffusion from a hydrogel in hyperglycemic conditions (Liu et al., 2025). In related work, a supramolecular peptide amphiphile (PA)-hydrogel with phenylboronic acid (PBA)-functional groups was also synthesized and assessed for glucose-sensitive release of glucagon. This hydrogel could undergo glucose-driven self-assembly and dissolution to ensure that controlled glucagon could be delivered in response to changes in blood glucose levels (Chen et al., 2024). Advancements in implantable hydrogels have centered on transplant strategies for islets. designed a peptide nanofiber hydrogel that was similar to peptide nanofiber materials with added glucagon-like peptide-1 (GLP-1) functionality to improve islet survival and transplantation outcomes. This self-assembled hydrogel protects transplanted islets from hypoxia and inflammation, thus improving glycemic control and longevity of islets (Cai et al., 2024). Likewise, developed a composite hydrogel that utilized mesoporous zinc oxide and recombinant human collagen for diabetic wound healing. The hydrogel demonstrated spatiotemporal drug-delivery characteristics that released its therapeutic agents in response to wound conditions (Wu et al., 2024). Ice injectable hydrogel technologies have also increased using thermoresponsive polymer designs. introduced a modular synthetic platform to customize therapeutic specific delivery using polyurethane-based thermogels. These hydrogels exhibit phase transition from sol-to-gel at body temperature, giving more precise control over drug release kinetics and extended insulin release time course from days to months (Wong et al., 2024). In addition, it was reported that endogenous/exogenous stimuli-responsive hydrogels that released drug cargo based on pH and oxidative stress, which also increased the efficacy of healing diabetic wounds (Khattak et al., 2024). Future developments in injectable and implantable hydrogel systems will likely explore enhancing biocompatibility, reducing response times, and including multi-functionality. The combination of hybrid hydrogels using nanomaterials, enzyme-functionalized matrices, and bioactive peptides possess great potential for further enhancing glucose-modulated insulin delivery. The continued development of such hydrogel designs continues to establish the basis for improving patient compliance, less risk for hypoglycemia, and improved management of diabetes.

4.Microneedle and Patch-Based Systems

4.1 Transdermal insulin patches with glucose sensors

Microneedles are generally made from biocompatible polymers, metals, or silicon. They penetrate the skin and produce microchannels to facilitate painless transdermal insulin administration. Microneedles can be solid, coated, dissolvable, or hydrogel-based. They have begun to be used for glucose-responsive drug delivery (Yu et al., 2021). One exciting advance in microneedles is the establishment of glucose-responsive hydrogels, which swell or degrade as a function of rising glucose concentration, leading to diffusion of insulin (Yu et al., 2021). Some microneedles also have glucose oxidase (GOx) to catalyze glucose into gluconic acid, releasing insulin when the pH shifts (Wang et al., 2022). In regard to these examples, microneedles offer feedback-regulated delivery to reduce the risk of hypoglycemia while maintaining glycemic control. Microneedles also utilize various types of stimuli-responsive materials and nanocarriers, including systems based on phenylboronic acid (PBA). PBA derivatives are characterized as reversible glucose binders that regulate insulin delivery according to fluctuations in blood glucose (Zhang et al., 2023). In addition, hybrid microneedle systems using conductive polymers enable electrochemical glucose sensing to generate electrical signals that modulate insulin secretion at the time of diagnosis (Chen et al., 2022), paving the way for the creation of closed-loop insulin delivery systems that mimic the function of the pancreas.

a. Patch-Based Glucose-Responsive Insulin Delivery

Recently transdermal patches have emerged in glucose-modulated insulin delivery. They are often used in combination with microneedles or other technologies and they utilize biosensors that monitor interstitial glucose levels via fluorescence, electrochemical and enzymes to stimulate insulin diffusion in polymer matrices (Huang et al., 2021). Hydrogel insulin patches have been introduced taking it a step further to deliver controlled insulin release from regimes using stimuli-sensitive nanoparticulate matter that would activate insulin delivery at the point of hyperglycemia. Another evolution in this space is known as smart patches using bioelectronic hardware whereby flexible electronic circuitry and wireless sensors would be worn externally as a patch worn on the body to monitor glucose levels and insulin panel adjustments will take place accordingly (Li et al., 2023). This technology also facilitates better adherence to patient care as a therapeutically prescribed wearable by utilizing real-time information.

b. Microneedle arrays for painless insulin administration

Diabetes mellitus is a chronic metabolic condition with inadequate secretion of insulin or inadequate action of insulin that requires lifelong management. Subcutaneous insulin delivery via standard injections, despite the effectiveness, involves many drawbacks including pain, increased risk of infection and poor patient compliance. To avoid some of these challenges, transdermal microneedle (MN) arrays have shown great promise as a non painfull, minimally invasive, and efficient method to deliver insulin. Recent progress of glucose-modulated insulin delivery methods have advanced microneedle technologies to provide real-time glucose readings and automated delivery of insulin. These developments are providing increased glycemic control, reduced hypoglycemia, and improved patient compliance, with the hope to provide better health outcomes for diabetes patients.

4.2 Design and Functionality of Microneedle Arrays

Microneedle arrays are arrays of micro-scale, needle-like structures designed to penetrate the topmost layers of the skin, without reaching the deeper pain receptors, to permit transdermal insulin diffusion with minimal discomfort. It is possible to fabricate microneedles using many different materials, including silicon, metals (stainless steel, etc.), biocompatible polymers, and hydrogels, etc., each offering their own benefits in terms of insulin stabilization and controlled release (Chen et al., 2021). Depending on the design and mechanism of action, microneedles can be grouped into four categories:

1. Solid Microneedles: These microneedles form microchannels in the skin, and insulin is applied as a topical formulation such as a patch.

2. Coated Microneedles: This form of microneedle delivers insulin via a thin coating of insulin applied to the microneedle, which can dissolve when inserted into the skin for rapid transdermal drug delivery.

3. Dissolvable Microneedles: Composed of biodegradable polymers that encapsulate insulin, dissolving microneedles dissolve after insertion in the skin allowing sustained insulin release.

4. Hydrogel Microneedles: These microneedles can respond to physiological stimuli, such as glucose concentration, swelling in a hyperglycemic environment allowing controlled diffusion of insulin (Wang et al., 2023).

a. Glucose-Responsive Insulin Delivery

One of the biggest advances in microneedle technology is the innovative glucose-responsive insulin delivery system. These autonomous microneedles, which consist of glucose/carbohydrate sensing and smart drug delivery functionality, allow the precise and responsive dosing of insulin based on real-time blood glucose assessment. There have been many interesting ideas explored:

• **Glucose Oxidase (GOx)-integrated microneedles** - these microneedles are integrated with GOx, an enzyme that triggers the oxidation of glucose to gluconic acid, after which the pH change results in polymer degradation and insulin release when glucose levels increase (Zhang et al., 2022).

• **Phenylboronic Acid (PBA) functionalized microneedles** - PBA based microneedles bind reversibly to glucose and regulate insulin release as blood glucose levels fluctuate, ensuring a continuous supply of insulin, while also preventing hyperglycemia by blocking over-release (Huang et al., 2022).

• **Hydrogel-based microneedles** - these microneedles swell upon glucose exposure that allows for passive insulin transport. The swelling from glucose exposure results in a responsive, continuous, and passive insulin release system (Li et al., 2023). These intelligent microneedle patches function as a closed-loop insulin delivery system without external glucose availability and manual insulin administration and can illicit bespoke pancreatic answers.

5. Cell-Based and Genetic Approach

Diabetes mellitus, particularly T1D, results from the autoimmune eradication of pancreatic β-cells, culminating in an absolute availability of insulin. Insulin therapy, albeit a life-saving therapy, does not accurately mimic the biological secretion of insulin, particularly when referring to the regulated secretion of insulin by the β-cells in response to glucose fluctuations, thereby leading to pathological physiological states of either hyperglycemia or hypoglycemia. As a result, there has been extensive research into β-cell mimetic delivery systems. These systems can be divided

into cell-based approaches or genetic strategies. Cell-based mimetic systems and genetic approaches have demonstrated great progress in potentially restoring normal physiological glucose-regulated insulin secretion with substantially physiological accuracy.

5.1 Cell-Based Therapies for β-Cell Mimicry

a. Islet Transplantation and Encapsulation

Clinically, transplantation of allogeneic pancreatic islets from deceased donors has been shown to restore warm ischemic normoglycemia in T1D patients, and long term success of islet transplantation has been shown using the Edmonton Protocol with steroid-free immunosuppression (Shapiro AM, Pokrywczynska M et al .,2021). However, issues of immune rejection, limited donor supply, and graft failure have limited its application. The encapsulation of islets into biocompatible hydrogels or polymeric matrices to protect the islets from immune rejection while maintaining glucose responsiveness has been proposed as a solution (Vegas AJ, Veiseh O, Gürtler M, et al .,2016).

b. Stem Cell-Derived β-Cells

Induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) are theoretically an inexhaustible source of β-like cells for transplantation. There have been differentiation protocols published that aim to differentiate functional insulin-secreting β-cells from these sources, with the capability of dynamically sensing and responding to glucose (Pagliuca FW, Millman JR, Gürtler M, et al., 2014). These β-like cells have high potential in cell therapy, but challenges remain for implementation. For example, immature insulin secretion profiles and potential malignancy require attention to differentiate towards cells that better mimic a mature β-cell phenotype, as well as suitable avenues to enable further safety assessments in the differentiation protocols.

5.2 Genetic Engineering for Glucose-Regulated Insulin Secretion

Genetic strategies have been tested for the purpose of reprogramming endogenous, or transplanted, cells for glucose-regulated insulin delivery. The strategies discussed may be categorized as; gene therapy to restore β-cell function; and, genetic engineering of surrogate cells for insulin secretion.

a. Genetic Engineering of Surrogate Cells

In light of the limitations of β-cell availability, scientists have developed genetically modified non-β cells with the ability to sense glucose and secrete insulin. Using engineered synthetic gene circuits, Liver and gut K-cells have been modified to secrete insulin in response to glucose stimulation by combining glucose metabolism with insulin expression (Rezania A, Bruin JE, Riedel MJ, et.al.2012). These strategies exploit endogenous glucose-sensing pathway and have now been demonstrated in preclinical studies. Obtaining precise control over insulin secretion along with the prevention of insulin over secretion remains a challenge.

b. Hepatocyte-Based Insulin Secretion

The liver has been a compelling site for insulin production due to its integration in glucose metabolism and ability to sense glucose fluctuations. Researchers have demonstrated transgenic insulin gene expression in hepatocytes using glucose-sensitive promoters derived from the genes for the glucose transporter GLUT2 or insulin promoter factor-1 (IPF1) (Xie R, Everett LJ, Lim HW, et al., 2013). The converted hepatocytes secrete insulin in response to hyperglycemia, and ideally mimic β-cell function

without the need for immunosuppression. As with all cells, significant limitations to insulin processing efficiency and long term stability of the engineered cells remain.

c. Fibroblast-Derived Insulin-Secreting Cells

Fibroblasts can be genetically modified easily making them an ideal candidate for reprogramming to insulin-producing cells. For example, fibroblasts can be differentiated into glucose responsive insulin secreting cells via the overexpression of major β-cell transcription factors like PDX1, MAFA, and NGN3 (Millman JR, Xie C, Van Dervort A, et al.2016). Although this approach has great promise in vitro, it needs to be further explored and optimized to produce cells that can secrete stable amounts of insulin and have the ability to sense glucose in vivo.

6. Synthetic Biology Approaches for Glucose-Sensing Insulin Secretion

Synthetic biology has enabled the development of engineered glucose-responsive cell systems that can secrete insulin in a controlled manner based on the glucose concentration. Systems approaches developed based on synthetic biology, using engineered synthetic gene circuits, biosensors, and feedback control mechanisms was discussed in Chapter Plan 6 to achieve the precise delivery of insulin.

a. Synthetic Gene Circuits for Glucose Sensing

Synthetic gene circuits have been developed to couple glucose metabolism to insulin secretion. One approach utilizes glucose-sensitive transcription factors by using the glucose-responsive promoter of the L-type pyruvate kinase gene to regulate the expression of insulin (Li F, Lu L, Zhang J, et al., 2018). These circuits allow engineered cells to sense and dynamically respond to changes in blood glucose levels, thus mimicking the in vivo function of β-cells.

b. Optogenetics and Cell-Based Insulin Release

Recent experiments have explored optogenetic approaches by having artistically-engineered cells respond to light stimuli for more precise control of insulin secretion. A group of researchers inserted foreign, light-sensitive ion channels into insulin-producing cells, allowing them to control the release of insulin through some external stimulus and circumvent the possibility of hypoglycemia (Ye H, Xiong L, Lohani X, et al.,2017). These methods are still experimental, but they offer new avenues and represent an exciting departure from bioengineered insulin delivery methods.

7.Recent Advancements in Glucose-Responsive Insulin Technologies

a. Nanotechnology in insulin delivery

Diabetes mellitus continues to present a global health epidemic that requires ongoing improvements in novel delivery and therapy methods to maintain legitimacy and compliance with treatment regimens. Recently, progress in nanomedicine has changed the way we provide glucgoe responsive insulin (GRI) delivery systems using materials for automatic glucose response along with insulin release. This review presents current position and findings based on nanomedicine in practical delivery precision insulin delivery systems, which includes smart insulin systems, nanocarriers and biosensors in direct relation to optimizing management of diabetes. One of the biggest leaps in progressing clinical practice in insulin delivery includes nanoparticle delivery as carriers for insulin that are glucose-sensitive. Liposome, chitosan particles, and poly(lactic-co-glycolic) acid (PLGA) carriers have improved bioavailability stability and sustained release of molecules. Following the

Grand Opening, all these nanocarriers helped stabilize insulin by minimizing or preventing enzymatic recovery. Prior and accordingly from delivery, targeted insulin delivery to pancreatic or hepatocyte tissue improved the diabetes control (Caturano et al., 2024). Likewise, there are stimuli-responsive polymers or glucose oxidase functionalized nano-sized like particles designed to release insulin on hyperglycemia, more like the natural pancreatic function (Kocaman, 2023). Another auspicious avenue of evolution arises from the amalgamation of nanosensors in continuous glucose monitoring (CGM); in short, gs might also coproduce insulin to match historical glucose variations. Nanosensor based smart insulin patches use microneedles or hydrogel matrices containing insulin-admixed nanoparticles, implicitly allowing for guage the real-time glucose fluctuations and instantaneously allow insulin to be released, thus allowing for immediate dosing and reduce the chances of hypoglycemia (Asaad et al., 2024). In addition to not needing to multiple injections a day bi-products, may also be a modality to improve adherence to insulin therapy (Ezzati et al., 2024). Ostensibly, not only can nanotechnology address controlled release for insulin, but also, address the paradigm of oral insulin delivery. Historically, oral delivery of insulin has been severely limited by gastrointestinal breakdown, however, utilization of nanocarriers, such as lipid based vesicles and polymer nanoparticles, confers both protection of insulin against enzymatic degradation and unique avenues for transintestinal absorption that weren't previously feasible. A few studies suggest that nano-encapsulation of insulin can positively influence bioavailability and more closely mimic physiological insulin secretion compared to subcutaneous injections (Nilo et al., 2024). Furthermore, hybrid formulations which combine gene therapy and nanomedicine are starting to emerge as next-generation therapies for patients with diabetes. Recent studies have highlighted the progression of engineered nanocarrier systems to deliver a sequence of genes which produces insulin or derived from stem cells which can regenerate pancreatic β-cells. This hybrid delivery model brings promising options for a long-term self-regulated diabetes treatment offering a more durable option which may reduce reliance on exogenous insulin administration (Kocaman, 2023).Despite advancements in translational science there are still many challenges before nanotechnologies involving nanoparticle-delivered insulin or hybrids make their way into clinical practice. Areas of uncertainty include long term biocompatibility, immunogenicity, and large scale manufacturing, as well as delivery route of nanoparticle-based insulin formulations. Regulatory bodies such as the FDA will continue monitoring ongoing safety profiles and therapeutic efficacy to assure patient safety with mass use (Nilo et al., 2024).In conclusion, this is a fascinating time for nanotechnology and glucose responsive insulin delivery with many new developments improving many aspects of insulin delivery from efficacy and stability to patient adherence. From nanoparticle-based drug delivery systems, to smart insulin patches, to using gene therapy, we are developing and identifying novel ways to deliver insulin. Future research should focus on optimizing biocompatibility, scalability, and real-time monitoring capabilities to ensure successful clinical translation of nanomedicine in diabetes care.

b.Smart insulin molecules with glucose-sensitive linkers

Diabetes management has progressed significantly with the introduction of glucose-responsive insulin (GRI) systems in an effort to improve glycemic control and minimize hypoglycemia. One significant advancement in GRI systems is the development of smart insulin molecules with

glucose-sensitive linkers that allow dynamic modulation of insulin activity in response to circulating glucose concentrations. This review discusses recent advances in glucose-sensitive insulin conjugates, polymeric delivery systems, and microneedle patches that promise to transform insulin therapy. One promising advancement in insulin design is the incorporation of glucose-sensitive insulin conjugates that can reversibly modulate bioactivity. A noteworthy example of such an engineered insulin conjugate is NNC2215, which has a glucose-binding macrocycle that creates a conformational switch allowing modulation of affinity to the insulin receptor depending on input glucose concentrations. In preclinical studies, this engineered molecule was capable of changing affinities with 3.2 fold difference in receptor binding with glucose concentrations above critical threshold of 3-20mM reduced the risks of hypoglycemia with smart insulin therapy (Høeg-Jensen et al., 2024). These insulin molecules utilize dynamic binding to therapeutically deliver glycemic control in real-time with little to no patient intervention. Systems that include polymeric hydrogels with glucose sensitive linkers are also of interest as controlled release systems for insulin delivery. Particularly, in-situ forming multipolymeric glucose-responsive hydrogels (MPHGs) can utilize the phenylboronic acid (PBA) functional groups to allow for glucose-dependent insulin release. These hydrogels have self-healing properties, are biocompatible, and have adjustable viscoelastic properties to produce a continuous insulin delivery system (Saha et al., 2024). The use of heterobifunctional formylphenylboronic acid (FPBA) crosslinkers improved hydrogel matrices' glucose sensitivity and stability and may represent an alternative to traditional subcutaneous injections of insulin. A novel approach also includes glucose-sensitive microneedle patches (GSMPs) with minimally invasive transdermal delivery of insulin. These patches contain smart polymeric matrices which utilize glucose levels to modulate insulin release eliminating invasive interventions and promoting compliance in patients. Recent classifications of GSMPs relayed all-in-one structures could have an implication on the idea of 'delay and stability' with the demonstrated correlation between glucose-responsive performance and sustained maintenance of normal blood glucose levels (Chen et al., 2024). Microneedle-based systems present a promising space within wearable diabetic management technologies. Electroresponsive hydrogels have been developed as a second mechanism of insulin delivery, using biocompatible poly(3,4-ethylenedioxythiophene) nanoparticles to control insulin release in response to electrochemical activation. In vitro and in vivo tests show this method allows for controlled and extended delivery of insulin, lowering the risk of hypoglycaemia even further (Muñoz-Galán et al., 2024). In addition, molecularly imprinted polymers (MIP) were designed for the capture of insulin and its selective release. These MIPs bind insulin with high selectivity and efficacy using poly(l-lysine)-based peptide crosslinkers that provide high specificity for insulin binding. This technology is an exciting line of research which can improve insulin therapies and is worthy of attention (Tan et al., 2024). Despite the developments already made, there are still limitations affecting the clinical translation of glucose-sensitive insulin systems: biocompatibility, large scale production, regulatory approval and long-term safety. Addressing these limitations will be crucial in making smart insulin technologies an integrated part of diabetes management. In conclusion, smart insulin molecules developed with glucose-sensitive linkers are an innovative development in diabetes management. The technologies demonstrated in this work demonstrate the

foundation for the future direction of smart insulin molecules and can ultimately lead to more accurate and automated insuin delivery. Finally, the future should spend a significant amount of attention on biocompatibility, scalability, storability, and accessibility in order for next generation insulin therapies to become available to the broader population of diabetes patients.

c.Wearable and implantable insulin delivery devices

Advancements in diabetes management have progressed with the introduction of wearable and implantable insulin delivery systems that incorporate real time glucose monitoring with automated delivery of insulin to improve glycemic control while reducing patient burden. The following review will discuss the latest advancements in artificial intelligence (AI)-enhanced closed-loop systems, insulin pumps, microneedle patches, and artificial pancreas (AP) devices. Wearable diabetes devices have transformed insulin therapy. The ability to monitor glucose values in real time and to administer insulin in an automated manner, from CGMs to remote pumps, have the opened up the possibilities for patient-centered unified data displays providing patients and healthcare practitioners the data needed to optimize therapy. AI-enhanced closed-loop wearable systems, which seamlessly link CGMs with an insulin pump to provide automated glycemic control, are now allowed on the market. The use of these devices is supported with software AI algorithms to mimic and predict glucose responses to adjust insulin dosing in real time will mitigate hypoglycemia risk (Huang et al., 2025). The use of AI will be instrumental in refining automatic delivery of insulin, while optimizing patient safety. Continuous subcutaneous insulin infusion (CSII) pumps is another advancement in CSII to keep blood glucose stable. Management strategies. The prevalence of insulin pumps, specifically hybrid closed-loop systems, provides the greatest advancements in perioperative glucose management. Insulin pumps use continuous glucose monitoring (CGMs) to automatically deliver insulin based on current glucose levels. These devices provide meaningful improvements in perioperative glucose levels, providing stability in glycemia during surgery (Nathan, 2024). The evolution of insulin pumps minimizes blood sugar variability in patients developing a usual routine for adherence to treatment. Several other insulin delivery devices are being investigated, specifically implantable devices for long-term improved glycemic management. Artificial pancreas patches, which combine glucose sensors (via microtubes) and insulin delivery with ultrasound will provide effective closed-loop glucose management in studied animal models. The device would utilize act like a pancreas, continuously monitoring glucose levels and delivering insulin based on glucose levels with minimal human interaction (Luo et al., 2024). The development of implantable artificial pancreas systems is an area for continuous investigations. New possibilities with microneedle-based insulin patches provide a minimally invasive option for insulin delivery. Microneedle patches use glucose sensitive hydrogels to deliver insulin based on hyperglycemia. The delivery of insulin is pain free, it also decreased the number of times insulin needs to be administered, leading to better patient compliance (Howait et al, 2024). Be available make glycemic control and DMT compliance better in diabetes patients is incredible. While the advancement of wearable and implantable delivery mechanisms is impressive, there are still some hurdles to the full dissemination of insulin delivery devices, such as cost, reliability, regulatory approval, and long-term assessment of safety, that need to be clearly defined and addressed; more research can now be focused on

improving biocompatibility and sustainability from an implantables perspective and device accessibility and affordability for wearables for maximum market implications for patients compared to current tools. . To summarize, wearable and implantable delivery systems have influenced the diabetes industry by allowing for accurate access to real-time glucose levels, intuitive automated delivery of insulin, and greater patient adherence. AI-enabled closed-loop prescribing systems, state-of-the-art insulin pump functions, improved artificial pancreas connected patches, or microneedles for the insulin delivery method when solving for "diabetes", is seriously impacting diabetes care and treatment of insulin medication guiding best practices from all of these systems mentioned above, for new patients too. Improvements made, will continue to correct better patient outcomes in a seamless change of medication regime.

d.Artificial pancreas systems and automated insulin pumps

The emergence of artificial pancreas (AP) systems and automated insulin pumps is changing the landscape of diabetes management with real-time glucose monitoring and precise delivery of insulin. Recent closed-loop technology contained a continuous glucose monitor (CGMs), control algorithms, and insulin pumps to give the opportunity of optimizing glycemic control while minimizing hypoglycemia and hyperglycemia risks. This review is meant to review new developments in AP systems, which include deep reinforcement learning (DRL), self-triggered control, and new insulin delivery. One of the key drivers of improvement of automated insulin therapy in AP systems are safety and efficiency achieved by DRL based controllers. A new closed-loop controller proposed a fully closed-loop AP with a safety mechanism that accounted for both active and reactive safety and set a new level of achievement for TIR performance at 87.45% while also reducing severe hypoglycemia (Zhao et al.,2025). Overall, advancements in DRL based AP systems complete reduce treatment failures of automated insulin therapy and help establish a dynamic treatment for patient needs. In addition, new approaches to address the energy demands and data redundancies of continuous glucose monitoring with self-triggered control for AP systems are becoming a reality. Self-triggered models in these insulin delivery systems are another development in artificial pancreas systems to optimize insulin administration. Additionally, self-triggered models do not require constant data collection and utilize glucose level transitions as triggers to determine when and how often glucose data should be collected, arguably optimizing the efficiency of self-triggered control, versus consuming energy with traditional continuous data feedback using a CGM (Ghosh et al., 2024). The operational efficiency proposed with self-trigger designs may improve how well autonomous systems might be used and could possibly improve the sustainability of these AP systems in diabetes management over longer time periods. Another notable development in AP systems concerns how these systems might incorporate not only insulin but also glucagon administration in the form of pulsatile delivery rigidly into a frequently closed-loop AP approach. Via pulsatile administration, the investigators validated a pulse-modulated closed-loop AP device, utilizing direct intravenous insulin and glucagon infusion, which exhibited high-quality and stable glycemic control with minimal impact from patients (Goede et al., 2024). Pulse-modulated approaches on dual-hormone AP systems allow for rapid upon glucose stabilization subsequent to meal ingestion, that are constrained by conventional conventional and continuous (non-pulsatile) insulin delivery.

As AP systems continue to evolve, it is noteworthy that hybrid closed-loop systems, in particular Medtronic's MiniMed 670G system - the first FDA-approved artificial pancreas device is a significant recent development in this systemization - utilize an adaptive control model that delivers insulin to a subcutaneous tissue based on CGM data while allowing a user to also input a bolus amount during the meal. Despite the promise of hybrid closed-loop AP systems in moving autonomy forward for diabetes care, challenges remain around the high cost of devices, limited controlled access to CGM systems, the continued need for calibration, and reduced user engagement and interaction in terms of meal planning, and therefore, diners reported to ongoing management of diabetes,(Marupuru et al., 2024). In addition to these aspects, the advancements in model predictive control (MPC) and artificial neural networks (ANNs) are leading the way for the next generation of automated insulin pumps. The predictive algorithms in these fully automated insulin pumps offer the potential for individualized glycemic control by profiling previous glucose trajectories and anticipating future glucose excursions, ensuring optimal insulin dosing with limited human intervention (Bhat et al., 2024). The power of predictive algorithms combined with the real-time monitoring aspect provide the best opportunity for developing a fully automated diabetes management system that achieves glycemic control with minimal patient burden. While considerable progress has been made in these systems, ongoing research must improve the usability, accessibility, practicality, affordability, and reliability of artificial pancreas systems and automated insulin pumps. Research and development should also address advanced biocompatibility, miniaturization, and algorithm advancement to ease the integration of these technologies into diabetes management. There is also a need for the regulatory bodies to develop guidance and/or standardized requirements for implementation to enable clinical translation of these advanced technology-infused insulin products. In summary, AP systems and automated insulin pumps represent a paradigm shift in diabetes management by exploring personalized real-time glucose control with minimal adult or pediatric patient burden. The innovations in deep reinforcement learning, self-triggered control, dual-hormone infusion, and AI-enabled predictive models are pushing for the next generation of diabetes therapy. Future research and improvements in technology are critical to help achieve fully autonomous and cost-effective AP systems that can be utilized in the clinical landscape and ultimately benefit the thousands of people living with diabetes.

8.AI and machine learning in insulin regulation

Incorporating artificial intelligence (AI) and machine learning (ML) into insulin control can be seen as a breakthrough in diabetes management. AI-based insulin delivery aids glycemic control, improves hypoglycemia risk, and decreases patient burden. AI-based delivery systems provide much higher precision in insulin delivery compared to older insulin delivery systems. Traditional and current progression in AI, closed-loop systems, reinforcement-based control algorithms, and deep learning model methodologies improve the precision and adaptability of delivering insulin within these new systems. AI has been and continues to be applied in many different areas of diabetes care (diagnosis, disease management, and individualized treatment). AI has improved glycemic outcomes through mobile applications and closed-loop insulin delivery systems, therefore automating insulin dosing and continuously monitoring glucose levels in real-time increases likelihood of improved glycemic outcomes. Large amounts of data sets are analyzed by ML algorithms that are used to predict glucose

excursions and dosage optimality, ultimately lowering the incidence of complications (Iftikhar et al., 2024). However, concerns still exist about data privacy and security and AI-related bias lessons in the algorthims. Reinforcement learning (RL) based control algorithms are emerging as a new way to control an AI-based artificial pancreas (AP) system. In contrast to traditional control engineering practices, models that use RL are unique in their capability to continuously adapt and learn from patient-specific glycemic responses in supplying insulin delivery. Research has established proof of concept for the utilization of RL in models that can regulate glycemic stability and minimize potential risks associated with insulin overdose (Dénes-Fazakas et al., 2024). These models can autonomously adapt with semi-supervised learning, and unlike other models, utilize pseudo-labels so that systemic bias is not introduced by asking or using a predefined labeled training set. Therefore, the RL models provide a more effective potential solution for providing individualized control in diabetes care. Additionally, deep learning models have further enhanced insulin regulation approaches via improvements in closed-loop control. More specifically, closed-loop theory implemented via AI-enabled insulin delivery provides an exciting opportunity to improve glycemic outcomes for patients experiencing impaired hypoglycemia awareness. For example, AI guided AHCL system demonstrated long term and sustained quality improvements in HbA1c and hypoglycemia events (Guo, 2024). In summary, this evidence would suggest that deep learning models can help optimize real time insulin administration models. AI has also been applied to genetic profiling of insulin resistance and sensitivity. For example, by measuring differentially expressed genes taken from patient profiles, ML models can be utilized to predict insulin resistance in association to metabolic classification procedures. In this regard personalized medicine would benefit from further innovation through AI systems based on an individual's genetic predispositions (González-Martín et al., 2023). As AI models continue to improve, diabetes management will become even more personalized with the integration of genetic and physiological data. The role of AI in insulin regulation has changed from predictive modeling to a real-time decision support tool (Peters et al. 2019). One approach is to apply machine learning techniques to provide dosing recommendations for Insulin delivery based on CGM readings. In addition to predictive modeling, there are AI powered dosing algorithms that provide real-time feedback to the patient and clinical team about the amount of insulin to deliver to humans with diabetes (Osmanoğlu, 2023). Although their are many patients with diabetes, these databases that will support real-time data decision-making or decision support systems can learn from patients' data, to a point, to maintain the most accurate recommendation for dosing. AI will further accuracy of insulin dosing recommendations, while streamlining diabetes care and reducing human error (Osmanoğlu, 2023). In order to better ensure the clinical safety and effectiveness of AI medicine systems for insulin regulation, regulations and further validations are required. AI will need to confront many challenges such as heterogeneity within large databases, patient adherence and motivation, ethical recommendations, data, equity and algorithm transparency to better mitigate bias, and concerns about cybersecurity. Research focused on AI implementation should aim to develop models that are more robust, generalizable to heterogeneous patient populations, and applicable in real world settings. Future efforts could focus on algorithms that learn in-circuit with diabetes control, to account for the variability encountered in wearables and users. In conclusion, AI and machine learning are providing personalized data

driven solutions for glucose-responsive insulin tech through improved insulin regulation with the combination of reinforcement learning, deep learning and predictive modeling. By creating bigger and better models opportunities exist in optimizing dosing algorithms for real-time monitoring. Continued advancements in AI-driven insulin delivery systems will enhance treatment precision, reduce patient burden, and ultimately improve diabetes outcomes.

9.Comparative Analysis of Different Approaches

a.Advantages and limitations of various glucose-responsive systems

Recent progress in glucose-responsive insulin (GRI) technologies has led to the establishment of many glucose-responsive insulin delivery technologies designed to improve glycemic control in diabetic patients. These systems utilize a variety of methods to regulate insulin release including glucose-sensitive microneedles, competitive clearance mechanisms, and glycemic control through hybrid artificial pancreas. Each system has its merits but also has limitations related to their implementation in clinical settings. Thus, this review identifies and compares various GRI technologies and discusses their advantages and limitations. One of the most novel GRI delivery technologies are glucose-sensitive microneedle patches (GSMP) to improve the delivery of smart insulin. These GSMPs allow insulin to be delivered to the user transdermally and provide a glucose-sensitive dosage based on elevated blood glucose levels. Chen et al. (2024) reported GSMPs are composed of three structural components: integrated, all-in-one, and core-shell component structures. Chen et al. (2024) reported all-in-one GSMPs demonstrated the most consistent glucose sensitivity and maximum normal blood glucose maintenance compared to other GSMP designs. However, clinical translation of GSMPs is difficult due to variability in material composition and the crosslinking properties of those materials which influence glucose sensitivity. Competitive clearance GRIs have also seen a recent surge in interest because of their ability to mimic an individual-response effect of endogenous insulin. The first clinical-stage GRI, MK-2640, acted with a competitive clearance mechanism such that the rates of insulin degradation could be adapted based on glucose levels. However, its glucose-responsive potential in humans was less than that in animals highlighted by an in silico analysis. This was primarily due to differences between humans and other species in glucose metabolism. Additional optimization of the affinity of the ligand and the receptor interactions are still needed to help improve clinical effectiveness (Yang et al., 2023).The application of computer models in GRI development has evolved to improve performance predictions. A study that used a multi-compartmental glucoregulatory model (IMPACT) determined glucose-responsive glucagon therapeutics (GRGs) were tested to model inter-subject variability in human glucose regulation, and found that computative predicted output was not compatible with experimental sugar responses. Therefore, to accurately assess human glucose regulation, refined glucagon kinetics models are needed (Alizadehmojarad et al., 2024) Therefore, computer modeling is beneficial and aids drug design development, but validation or accuracy of drug responses should be assessed to determine how useful computer modeling for drug design purposes. A further example of GRI that is promising since it incorporates pumps to administer insulin and glucagon which is a hybrid artificial pancreas system. Automated glycemic regulation with minimal patient interaction can assist adherence and promote positive outcomes with inpatient management of diabetes. Yet

challenges persist with hardware and pumps in reliability, patient compliance and overdosing of insulin, etc. A recent article concluded that artificial pancreas models address time-in-range (TIR) glycemic control, but they require careful safety mechanisms to limit hypoglycemia (Mowitz et al., 2021). With continual refinement of algorithms, and more advanced sensors in the future, the ongoing development of closed-loop systems aims to also enhance the safety of this approach. However, GRI technology cannot yet easily cross the bridge from research to clinical practice. We will need to address cost hurdles, regulatory approvals, and patient specific variability to ensure that these insulin treatments will clinically impact patients. There is still future expansive research required to pursue glucose sensing device, pharmacokinetics of glucose response, and personalize approach to insulin delivery. In summary, glucose-response and GRI systems, offer significantly viable and closer options to improve quality of life for diabetes patients, but each approach had specific strengths and limitations. Glucose-sensitive microneedle delivery, competitive clearance models, computational predictive models, and artificial pancreas systems will all play a forward-thinking role in the next generation of smart insulin. We can expect that they will all capture exponentially more space in clinical settings, once materials, computational science, and predictive AI platforms for the compatible delivery of insulin have improved.

b.Performance in preclinical and clinical studies

Diabetes management has progressed rapidly with glucose-modulated insulin (GMI) systems by enabling precise insulin delivery and chronic glucose control. There are diverse new GMI technologies that have reached advancement, but their respective potential for clinical application varies based on performance in preclinical and clinical studies. This review specifically contrasts the most recent GMI/automation developments and uses efficacy, safety, and potential for clinical translation definitions for GMI systems. Automated insulins delivery (AID) systems that incorporate continuous glucose monitors (CGM) with insulin pumps have produced considerable enhancement of glycemic control in people with type 1 diabetes. Recently, there are a few new real-world studies showing that age and other relative factors played a significant role in differential enhancement of time-in-range (TIR) glucose control. I provided a review of devices as the new commercially available AID devices have great potential for managing diabetes therapy (accessing the Medtronic MiniMed 780G, Tandem Control IQ, and Omnipod 5, and safety - hypoglycemia and hyperglycemia in children, Nimri & Phillip, 2025). Nonetheless, successful implementation relies on individualized contexts, patient education, and adjustment in response to changes that allow for optimal outcomes over time.In preclinical work, bioartificial pancreatic tissue constructs have been explored as one intervention to improve upon conventional insulin administration. Stem cell-derived islets, encapsulated in bioartificial pancreas (BAP) devices have been associated with reversing hyperglycaemia in rodent models. However, translating these studies clinically have proved difficult due to limitations in oxygenation, and insulin release kinetics. A recent in vitro perfusion study has showed increased glucose responsiveness by tailoring tissue geometry and microvasulaturation, and provides a potential avenue for improving graft longevity (Moeun et al., 2025).Hybrid closed-loop (HCL) systems have gained growing interest as a plausible bridge between fully automated AID systems and patient directed insulin therapy. A systematic literature review of HCL pilot trials found statistically significant declines in glycated hemoglobin

(HbA1c) and increased time in range (TIR) compared to conventional insulin pump therapy. Economic modeling studies indicate, that while the initial investment is higher, HCL systems may ultimately be cost-effective due to lower diabetes complications (Asgharzadeh et al., 2024). However, challenges such as regulatory approvals (for hospitals and participants), reimbursement, and patient compliance continue to persist barriers to wider uptake. The use of GMI systems in hospitals has also been examined and the uptake of AID technologies has the potential to enhance diabetes management, especially in the inpatient setting. In trials examining AID in the clinical hospital setting, AID appears to improve glycemic variability and lower insulin delivery errors, yet the integration of the technology also has its challenges; not all electronic health record software is compatible with AID; staff training; and again, regulatory approvals and processes will need to be addressed for implementation (Hughes et al., 2024). There has been significant progress with glucose-modulated insulin systems in both preclinical and clinical investigations with AID, BAP, and HCL technologies each being able to offer different advantages. AID systems are able to perform better in everyday clinical realities when performing glycemic management, bioartificial pancreas constructs offered an innovative long-term solution, while hybrid closed-loop technologies provide some flexibility, and while automated when needed can be employed almost fully under user control depending on the patient and the situation. The challenges to adopting these more advanced automated insulin delivery technologies for most patients are internal and external with respect to of clinical and political307 modalities; it will be crucial to attend to both regulatory and economic challenges and to monitor for inadvertent materials issues featured with clinical integration.

10.Challenges and Future Directions

Recent advancements in glucose-modulated insulin delivery systems have improved diabetes management by enhancing precision and automation. However, several challenges persist, requiring further innovation. One significant challenge is ensuring the reliability and security of automated insulin delivery systems. These systems rely on real-time glucose monitoring and machine learning algorithms, making them vulnerable to cyber threats and technical malfunctions, which could lead to insulin overdosing or underdosing. Additionally, the complexity of glucose-stimulated insulin secretion poses difficulties in accurately mimicking the body's natural insulin response. Factors such as inflammation, hormonal fluctuations, and metabolic variations affect glucose regulation, making it challenging to develop a universal insulin modulation strategy.Another hurdle is the integration of multiple metabolic markers beyond glucose. Emerging research suggests that biomarkers like leptin, glucagon, and amylin play crucial roles in insulin regulation, but current delivery systems primarily focus on glucose alone. Personalized treatment models incorporating these additional factors could enhance the effectiveness of insulin therapy. Furthermore, dietary influences impact glucose metabolism, with long-term high-fat or ketogenic diets showing potential negative effects on insulin secretion and metabolic balance. This calls for adaptive insulin delivery mechanisms that consider dietary patterns and lifestyle factors.The future of glucose-modulated insulin delivery lies in the development of smart insulin formulations that can automatically respond to glucose fluctuations without external intervention. AI-driven closed-loop systems, which use real-time predictive analytics, are also expected to revolutionize insulin management by optimizing dosing patterns. Additionally, advances in

biocompatible materials and nanotechnology could lead to longer-lasting insulin reservoirs that require fewer injections. Research into multi-hormone delivery systems, incorporating glucagon and amylin alongside insulin, holds promise for more comprehensive diabetes management. Addressing these challenges through interdisciplinary collaboration will pave the way for safer, more efficient, and patient-friendly insulin delivery solutions.

11. CONCLUSION

Recent advancements in glucose-modulated insulin delivery systems have significantly improved diabetes management by enhancing precision, automation, and adaptability. Innovations in automated insulin pumps, smart insulin formulations, and AI-driven closed-loop systems have paved the way for more responsive and personalized treatment. Despite these breakthroughs, several challenges remain, including the need for enhanced security, reliability, and integration of multiple metabolic markers beyond glucose alone. The complexity of glucose-stimulated insulin secretion, dietary influences, and individual metabolic variations further complicate the optimization of these systems. Future research must focus on developing biocompatible materials, multi-hormone delivery mechanisms, and AI-driven predictive models to refine insulin therapy. Addressing these challenges through interdisciplinary collaboration will lead to safer, more efficient, and patient-friendly insulin delivery solutions, ultimately improving the quality of life for individuals with diabetes.

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HOW TO CITE: Rupali Chopade*, Sakshi Jatale, Pallavi Kandale, Dr. Shivshankar Mhaske, Shatrughna Nagrik, Recent Advancements in Glucose-Modulated Insulin Delivery Systems, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 5, 4090-4116. https://doi.org/10.5281/zenodo.15507328