The Bioscan
AN INTERNATIONAL QUARTERLY JOURNAL OF LIFE SCIENCES
20(3): 804-815, 2025 www.thebioscan.com

Advances in Glucose-Responsive Drug Delivery Systems: Revolutionizing Diabetes Management through Intelligent Therapeutics

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DOI: 10.63001/tbs.2025.v20.i03.pp804-815

KEYWORDS
Glucose responsive insulin, glucose oxidase, phenylboronic acid, microneedle patches, hydrogels.

Received on:

14-08-2025

Accepted on:

10-09-2025

Published on:

16-10-2025

ABSTRACT

Diabetes mellitus is a widely spread chronic disease that is associated with poor insulin production or response and requires a consistent follow-up and supplemental doses of insulin. Conventional modes of delivery, in typography subcutaneous injections, are reported to cause distress and in some cases poor glycemia control. Present progress in the field of glucose-controlled insulin delivery has introduced encouraging options in the use of intelligent biomaterials that adapt insulin delivery to ongoing changes in glucose. The most recent advances in glucose-responsive drug delivery are reviewed through enzymatic-based technologies such as glucose oxidase-based hydrogel carriers and nanoparticles, protein carriers like concanavalin A, and protein-free carriers including phenylboronic-acid-based hydrogel carriers and acetylated dextran nanoparticles. They are focused on their glucose sensing mechanism, efficiency in encapsulation of insulin, release and their adaptability to be administered either by injection or orally. The possible combination of digital health, closed- loop artificial pancreas, and microneedle patches are also discussed, which are expected to imitate the insulin secretion process in vivo, provide patient comfort, and have fewer chances of hypoglycemia events and hyperglycemia. Whereas the preclinical results are promising, long-term biocompatibility, effective in-vivo responsiveness, and manufacturing in a scalable manner pose as primary tasks. Future applications are the personal and precision medicine to benefit with artificial intelligence, big data analytics, and 3D printing of a personalized formulation. The combination of these innovations seems to indicate a groundbreaking transition to patient-centric and more effective diabetes care.

INTRODUCTION

Diabetes mellitus is the most common chronic disease and is characterized by insufficient or ineffective insulin in the body (1). In diabetes mellitus, there is insufficient secretion of insulin from B islet Langerhans cells in the pancreas. Continuous monitoring and subcataneous injection of insulin are imperative for managing diabetes (2). According to international diabetes management, the number of adults aged 20--79 years suffering from diabetes is expected to increase by approximately 50% in 2021, and 783 million people will be affected by diabetes by 2045(3). Insulin injection is necessary for controlling blood glucose levels because of physical and mental pain(4). Importantly replacement therapy is achieved by stable control of blood glucose in a few cases, such as through intake, exercise, etc., through the hypoglycemic system to provide continuous patient care (self-monitoring, dietary restrictions, and insulin administration) This disease is dependent on several factors (eg ,stress, low physically activity unhealthy food habits , genetics age and inflammation) (5). There are two types of diabetes mellitus, type 1 diabetes and type 2 diabetes. Gestational diabetes and secondary type 2 diabetes develop through insulin independent of diabetes mellitus (6). Glucose-responsive insulin is designed to release the response of glucose concentrations to insulin when the blood glucose level is high and should continue to decrease to normalize glucose levels through the risk of hypoglycemic agents(7). Some diabetes patients respond well to insulin therapy because complications arise from poor inadequate system hypoglycemia through patient coma or death. Owing to diabetes resulting from patient care through life-time treatment of infected patients, iv injection or less invasive and noninvasive delivery systems have been developed for insulin therapy (8). In recent years, diabetes patient care has improved by focusing on enhancing the quality of life through oral, nasal, pulmonary, and transdermal drug delivery systems.there are majority divided two groups of closed loop insulin release system first type basis electronic devices which incorporated a subcutaneous latter implanted another body location another type of device is known as artificial pancreas device system. In diabetes mellitus, a Various forms of insulin closed-loop insulin delivery systems are available in diabetes mellitus that include a glucose- sensing compenent that mimics natural pancreatic function by releasing insulin in response to the body's glucose levels (9). Therefore, the second category of the loop of the insulin release system involves direct contact with patients receiving sub cardiac injections(9). glucose sensing and insulin involved in treating diabetics several closed loop system also known as feedback control device eliminate need for the patient intervention, These system sense glucose and insulin help treat diabetics also being able to change the amount of insulin release without pain in the responsive to rising the blood glucose level is crucial factor that can help negative effect of diabetes Moreover, the painless adjustment of insulin release in response to rising blood glucose levels is an important factor

that can help reduce the side effects associated with diabetes(10). The new multifunctional group of systems, which are designed with glucose-sensitive materials, can indicate blood glucose levels during insulin development (11). When insulin development is restored by normal blood glucose levels storage in the form glucose, such as that in muscles, adipose tissues and the liver, is normalized (12). The main goal of research and development is to monitor the level of glucose released. There is a new platform for treating diabetes insulin in desirable patients, and it's very helpful insulin delivery systems for the treatment of diabetes mellitus(13).To execute insulin release in blood needs to be determined focusing on the development of controlled insulin release deliver in the beneficial to reduce the drawbacks associated with traditional method which can achieve smart insulin release according to the blood glucose concentration glucose resposnive release system (3) . The significant example under is section is smart insulin originally designed by smart cells that was latterly then acquired later by merck and co. Smart insulin then changes its drug name to mk 2640 and then currently in early human trails at merck.

2.1 Enzymatic systems (glucose oxidase)

The immobilization of glucose oxidase (GOD) on polymers has been extensively studied for the development of novel glucose sensors (14). These studies have also investigated the use (GOD) or the stimulation of pH-responsive release from polymer matrices or membranes. Glucose oxidase has been used on a wide variety of polymers, such as polyacrylates. The presence of polyethylene, polypyrole, silica and poly(vinyl alcohol) hydrogels is an important parameter that affects the performance of hydrogel membranes. Glucose oxidase, which can enter the membrane, can be used as a sensitive drug delivery carrier. GOD–containing materials suffer from low mechanical strength, resulting in unexpected drug leakage(3,15). In general, sensitive hydrogels are based on the glucose levels present in the bloodstream; for example, high glucose concentrations (hyperglycemia) are necessary for quick insulin delivery systems, and these hydrogels can release insulin without requiring any type of patient input. Hydrogels can serve as self-monitor devices(3). In glucose oxidase hydrogels, networks of the matrices in polymers and crosslinking between polymers are needed to prevent the dissolution of networks before use. This type of crosslinking hydrogel synthesis is an important factor affecting hydrogel properties and must be determined according to the desired application (16). In 2017, this hydrogel formulation was combined with a catheter. The pores perpendicular to the long axis of the catheter served as the channel for communication between the internal insulin solution and glucose for the concentration in the outer interstitial fluid, whereas the gel space covering the pores functioned as the glucose responsive for insulin diffusion in the pores and then implanted this device under the skin type of diabetic mouse, and the blood levels decreased from approximately 500 mg/dL to 300 mg/dL. When the type 1 diabetic mouse was fed normally through glucose tolerance tests, it was also performed overnight and fasted to diabetic mice. The pores perpendicular to the long axis of the catheter served as the channel for communication between the internal insulin solution and glucose in the concentration in the outer interstitial fluid, whereas the gel space covering the pores functioned as the glucose responsive for insulin diffusion in the pores and then implanted this device under the skin type of diabetic mouse, the blood levels decreased from approximately 500 mg/dL to 300 mg/dL. When the type 1 diabetic mouse was fed normally through glucose tolerance tests were also performed overnight and fasted to diabetic mice. The hydrogel is beneficiary for sustained release and controlled drug delivery systems. Therefore, the hydrogel is thermosensitive in a free-flowing gel at body temperature (37c). In thermosensitive systems, insulin has also been loaded into hydrogels via new synthesized materials for sustained release(17).These materials to make biosenor that can sense things stimuli -responsive gels need to be used with a suitable read out that turns swelling caused stimuli into signals that can be read these sensors respond swiftly because the ultrathin materials inflate significantly faster than regular bulky gel forms. When the level of glucose oxidase in the blood glucose level increases (after eating, for example), glucose enters the hydrogel and its oxidase by generating hydrogen peroxide. The hydrogel system can release the insulin system only when necessary, and the peak blood glucose level increases, closely resembling that of the body in natural insulin. In recent days, ongoing research and development have focused on advanced hydrogel formation products that do not respond only to glucose and other factors, such as pH, temperature and light (18). In glucose oxidase studies, the goal has been to develop a microsphere formulation of glucose oxidase with high drug loading and the encapsulation efficiency of the bioactive gel loading encapsulation efficiency of the loaded material. The pH absorption medium is lower than the isoelectric point of GOX. Three types of insulin microspheres (IMS) are used to deliver insulin selectively in the intestinal tract via pH-dependent solubility. In IMS, more than 90% of the insulin is released within 60 min. In microspheres, the release of the insulin response to a change in local energy (e.g., pH or the presence of hydrogen peroxide) occurs (19). Glucose increases the production of hydrogen peroxide by the Gox enzyme. When the blood stream increases (e.g., after glucose enters the microspheres, when glucose oxidases in the microspheres), it results in hydrogen peroxide and lowers the pH of the microspheres in the local environment). These changes in the pH response to hydrogen peroxide can occur through the release of insulin from the microspheres. In glucose-responsive insulin, the release of insulin is needed when the blood glucose level is high (20). In particular, microspheres can achieve the controlled release of insulin in the body via natural responsiveness and are compatible with insulin injections for patients. In recent advances, studies have focused on glucose-responsive systems that require the use of the glucose oxidase insulin encapsulated in microspheres. Glucose oxidase nanoparticles can be used to form an encapsulated glucose-sensitive system to develop a signal that can trigger insulin release(21). Therefore, glucose oxidase nanoparticles are present when the glucose concentration increases, as diabetic glucose oxidase nanoparticles react with hydrogen peroxide. Glucose oxidase converts glucose into gluconic acid. GOD nanoparticles made from the dextran with high cyclic acetal content (94% of residues) release quickly ,while nanoparticles made from the dextran with a high cyclic acetal content (71% of residues) release insulin(22) .GOD nanoparticles promising materials that frequently empolyed to regulate medications over time . The speed and absorption efficiency of insulin injection via glucose-sensitive nanoparticles are high. Compared with microgels, hydrogels and microparticles, which have 3D structures, are used(22). Nanoparticles are integrated with the nanotechnology of medicine for better human health care. Nanoparticles detect protein or DNA molecules through insulin nanoparticles via nanotechnology, which are restricted to the lungs through the route of drug delivery systems for local treatment. The inhaled products can be divided into two major groups, dry powder formulations and solutions, which are transported through different inhalers. Most insulin molecules are encapsulated in the lungs by inhalation through dried powder formulations of insulin nanoparticles. A recent study focused on improving the efficacy and safety of glucose oxidase in nanoparticles via an insulin delivery system. This system cannot induce significant immune toxicity or response in the body. Improving GOX nanoparticles to target pancreatic cell tissues with high glucose levels is helpful for insulin. The future level of potential for more personalized medicine through the use of insulin in diabetic patients.

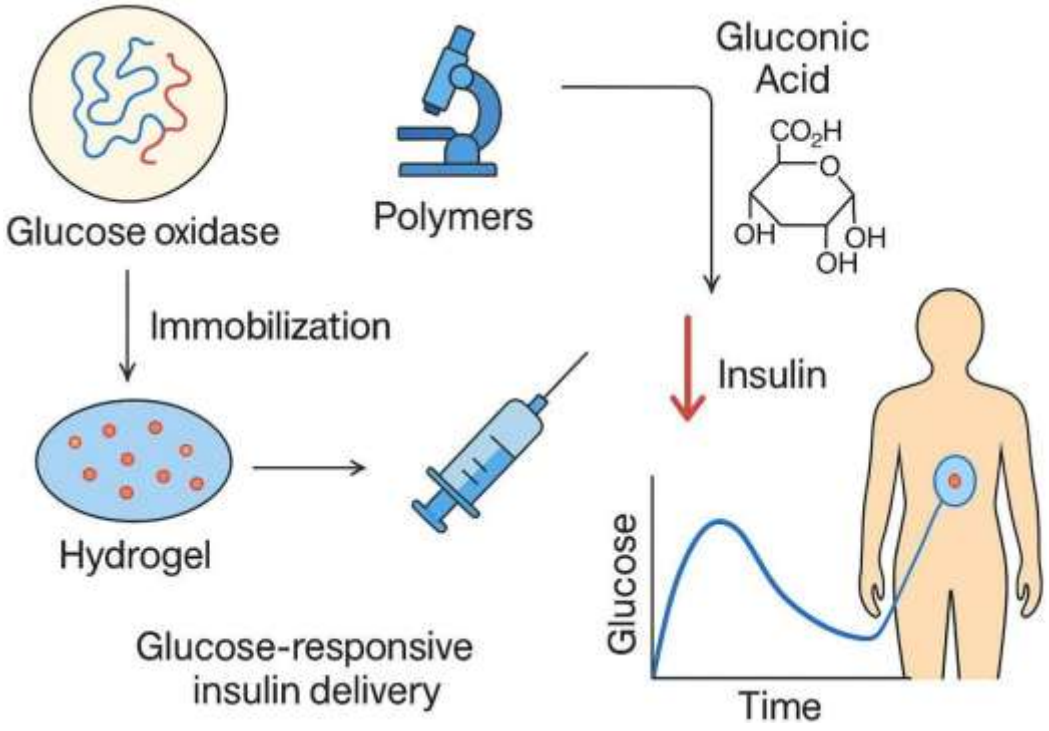

Fig 1: Glucose oxidase immobilized in polymers forms a hydrogel that releases insulin in response to glucose helping regulate blood sugar levels.

Table 1: Comparative analysis of the pH-responsive insulin delivery system based on the polymer and parameter type and release characteristics.

parameter	**Polymer type**	**Enzyme immobilization method**	**Drug /Active ingredient**	**Release profile**	**Release response** (23)
Hydrogel Formulation1	polyacrylate	Covalent Bonding	Drug released	Release kinetics	pH responsive (low pH)(23)
Hydrogel Formulation2	polyethylen e	Physical Entrapment	Insulin	Rapid release (fast)	PH responsive(lowp h) (24)
Microspheres (IMS)	Polylactic acid (PLA)	Encapsulation	Insulin	>90% released in 60 min	PH responsive (acid)(24)
Nanoparticles	Dextran	Encapsulation	Insulin	Controlled release	PH responsive (LOW PH)(25)
				(medium)	
Polymeric film(GOD Based)	Poly(vinyl alcohol)	crosslinking	Insulin	Sustained release (medium)	PH responsive (acidic)(23)

2.2 Glucose binding protein based concanavalin A

Glucose binding development of the system involves the binding affinity between Con A and glucose in hydrogel formation (26). In the past five years, Con A was developed to use smart Glucose-binding Concanavalin A (Con A) is a plant-derived lectin that specifically recognizes carbohydrate structures containing glucose and mannose. It is widely used in biochemical studies to investigate protein–carbohydrate interactions due to its strong affinity for these sugars. Con A is often employed to bind and isolate specific glycoproteins from complex protein mixtures. In experimental protocols Con A-binding proteins are typically incubated with Con A conjugated to horseradish peroxidase (HRP) for detection and analysis(27). Concanavalin A serves as an affinity-based biosensor for glucose monitoring in individuals with diabetes. Both in vitro and in vivo studies have demonstrated that such affinity sensors can accurately track glucose levels over extended periods. The glucose- binding protein concanavalin A is a promising method with chemical stability at body temperature. Therefore, research on sensor methods has been ongoing over the last 25 years (28).

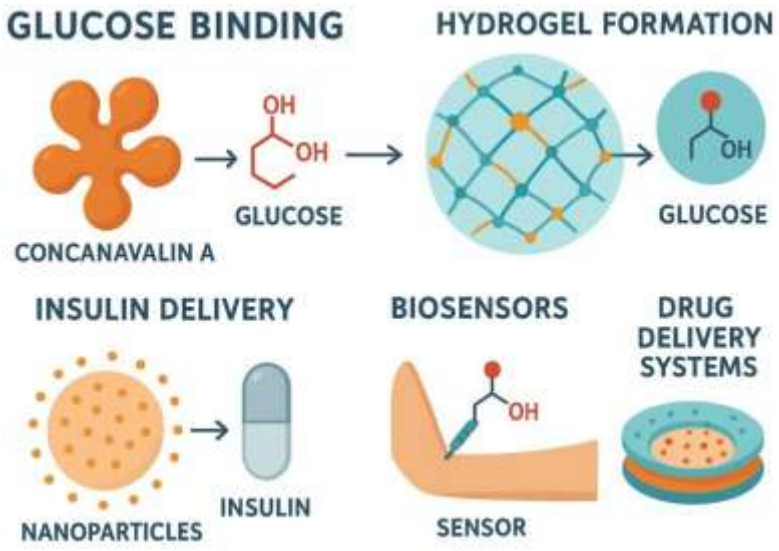

Fig 2: Concanavalin A and glucose interactions enable hydrogels, biosensors and drug delivery systems.

The most widely used lectins are concanavalin A and wheat germ agglutinin. polymers are silica that can be used to analyse glycoproteins. The high affinity of glycoproteins is a flexible immobilization method, and samples can be prepared from glycoproteins(29). Concanavalin A is defined as a tetrameric protein with its binding sites. These compounds are capable of interacting with specific terminal glycosyl residues of polysaccharide or glycoprotein chain ends (30). In concanavalin, polysaccharide and gel transformation occurs in the presence of free glucose. to control the insulin diffusion rate in diabetic patients(31). When glucose or mannose is an environmental factor that recognizes sites that bind primarily to hydroxyl groups, hydrogen bonding involves a glucose or a hydroxyl group and specific amino acids through its protein binding specificity. In a concanavalin study, a biopolymer was used to form nanoparticles through interactions between Con A and amylopectin. Therefore, insulin was encapsulated in the nanoparticles, and the encapsulation efficiency of insulin was approximately 69.73%.When a insert capacity of insulin was high in 17% of the insulin released in the nanoparticles in 3mg/ml glucose was 2.23 time greater than to nanoparticle concanavalin is the absence of glucose in nanoparticles (32) Therefore, nanoparticles play an important role in the development of systems. The utilization of nanoparticles in insulin delivery systems is a potential solution for bypass through complicated mucosal membrane barriers that have historically hundered the effects of nanoparticle oral insulin delivery systems on formulations (32). Therefore, these nanoparticles range in size from 100-300 nm. exhibit biodegradable properties suitable for carrying suitable or biological drugs such as peptides and oligonucleotides(33) when these approaches represent significant advancements in diabetes treatment by providing a more precise personalized insulin delivery system. To improve patient outcomes and healthy life(34). Glucose-sensitive hydrogels are reversible and involve specific interactions between polymers bound to glucose concanavalin A. The main aim of this study was to characterize the release model of proteins and insulin. The performance of the hydrogel membranes was dependent on the free glucose concentration, which was unchanged (35). When a glucose- binding protein interacts in a hydrogel network, it is a crosslinking agent(36). In glucose concanavalin A, the remaining glucose-binding moieties on the polymer chains are managed through the retention of insulin. When the blood glucose level increases, such as after a meal, free glucose molecules diffuse through the hydrogel and bind once glucose levels return to common free development materials including hydrogels, microgel and nanoparticles films to make bisosensors or systems for delivering drugs . These recent reviews were about con A which is a type of substance that can be used to find and treat diabetes patients(37).

Table 2,2 Overview of concanavalin A (Jack bean lectin) Structure , properties and Applications.

Aspect	**Details**
Source	Extracted from jack bean (canavalin ensiformis). (38)
Structure	Tetrameric protein with four sugar binding sites . forms pleated interactions create dimers and tetramers sheets(39)
Binding specificity	Binds specially to terminal D mannosyl and D glucosyl residues in polysaccharides(38)v
Applications	Used in affinity chromatograph to purify glycosylated macromolecules Biosensors for glucose monitoring in diabetics controlled insulin delivery through glucose responsive hydrogels and nanoparticles (38)
Mechanism of Binding	Recognizes hydroxyl groups in glucose and mannose via hydrogen bonding and specific aminoacid interactions(38)

Chemical stability	Demonstrates stability at body temperature . making it suitable for long term glucose systemsvalin (39)
Diabetics management	Forms glucose responsive hydrogels or nanoparticles that regulate insulin diffusion rate . with insulin encapsulation efficiency approximately 69.73%(40)
Interaction with horseradish peroxidase	Stabilizes protein structure upon binding, as observed through differential scanning calorimetry (38).
Therapeutic potential	Provides personliazed insulin delivery system (38).

2.3 Synthetic glucose sensor phenylboronic acid

Phenylboronic acid-based glucose sensors represent an innovative non-enzymatic approach for glucose detection, particularly useful in insulin delivery systems for diabetes management. The unique property of phenylboronic acid lies in its ability to bind glucose directly and continuously. These sensors enable real-time glucose monitoring in blood without relying on enzymatic reactions (41). Phenylboronic acid (PBA) based glucose sensors are typical formulated as a hydrogel through functional groups with PBA moieties that reversibly bind glucose (42). Owing to the response of insulin release to the glucose concentration, which enables smart insulin delivery (43), phenylboronic acid forms a reversible covalent bond (boronate) with the glucose concentration of the cis diol group, which is stable and potentially self-regulated on the demand of the insulin delivery system(44). A current study and development of PBAs revealed a suitable and sensitive form of glucose suitable for the formation of an insulin delivery system. These are future directions(45) for the use of glucose sensors, phenylboronic acid or functionalized nanoparticles in insulin delivery systems. The release of insulin in response to elevated glucose concentrations is an approach to managing diabetes. PBA enables glucose sensitivity in nanoparticles to swell and release insulin in a glucose-based manner. Moreover, the insulin encapsulation efficiency reached 15%, and the system demonstrated good cytocompatibility(46). When chitosan was functionalized with PBA, it was alkylated to make glucose-sensitive nanoparticles(47). Therefore, these nanoparticles are synthesized from N.vinylcaprolactam, and 3 acrylamidolphenylboronic acids are both glucose sensitive(48). For human insulin, PBA groups are on the nanoparticle surface and backbone of the polymer through covalent bonds with moieties that are connected through glucose insulin(49). The displacement of the nanoparticles through the PBA increased the number of negative and charged particles through density due to the presence of glucose-binding sensors, leading to the expansion of the nanoparticle network and the release of insulin. These studies confirmed that insulin release with minimal cytotoxicity to PBA nanoparticles(50). In advance, studies in recent years have made significant progress, such as the development of glucose- responsive insulin delivery systems in phenylboronic acid. These functions mimic pancreatic function, resulting in self-regulated insulin release and the response of blood to changes in the glucose level of insulin (51). A promising material based on hydrogels has emerged as a promising material for the response of smart insulin delivery systems, mainly through diabetes management. Therefore, hydrogels can utilize the reversible binding of PBA- containing molecules such as glucose, which plays an important role in the insulin release of hydrogels (52,53). These materials dissolve through acrylamide monomers and PBA- functionalized monomers in aqueous buffer at physiological pH (7.4) and add suitable polymers (e.g., N.N. -methylenebisacrylamido control networks). The hydrogel was washed to remove unwanted monomers and equilibrate in buffer. Then, the hydrogel was soaked in an insulin solution for physical loading because of its covalent bonds. PBA interacted with reversible covalent bonds with glucose, leading to changes in the hydrogel network through the volume of the network structure. These properties may hinder glucose detection of insulin release. Therefore, the dynamic nature of these bonds allows the response of the hydrogels to fluctuations in the glucose concentration(54). In glucose sensors, microneedles based on an insulin delivery system utilizing phenylboronic acid are involved in diabetes management. PBA involves dynamic covalent interactions that are highly suitable for glucose sensing through a drug delivery system. Therefore, glucose sensor microneedles can be coated with composites of materials consisting of PBA polymers, such as polystyrene block acids of acrylamidophenyboronic acid. These microneedles are self-regulated drugs that are promising for improving the treatment of diabetes-related insulin (55).

Fig 3: PBA polymers form hydrogels that swell with glucose, enabling smart insulin delivery.

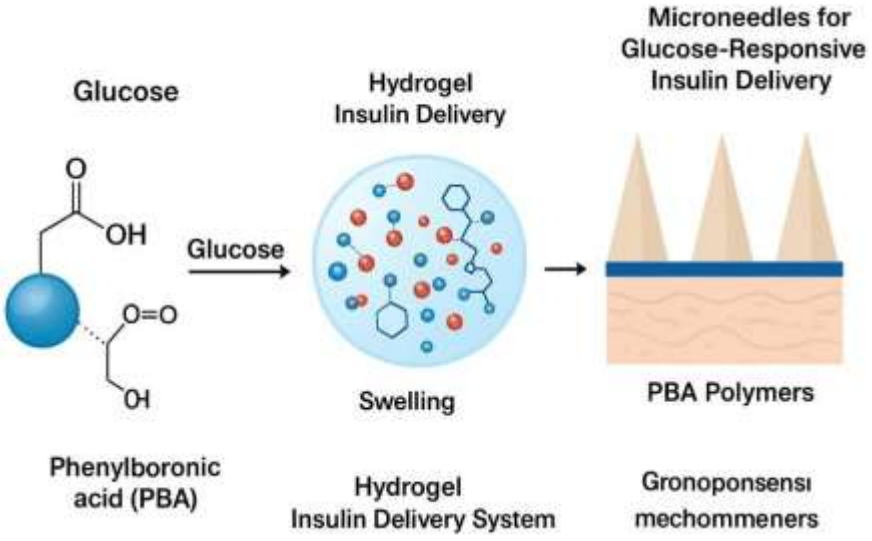

Table 3. Glucose-responsive drug delivery system features and descriptions

Feature/Aspect	Description	Ref.
Glucose sensors	Hydrogels , nanoparticles , microneedles ,	(41)
Insulin Release diabetic mechanism	Swelling/contraction through the network change in PBA based materials triggers the insulin level to form glucose responsive insulin.	(43)
Stability	High level , due to non enymatic mechanism through physical and	(44)
	chemically to long term use	
Glucose sensor selectivity	Enhanced formation chemical modification of PBA derivatives , selectivity for glucose over other sugar and lactae	(56)
Biocompatibility	Demonstrated good cytocompatibility in recent studies , for suitable clinical applications	(44)
Clinical potential	Smart self regulated insulin delivery system . continuous glucose sensing for diabetics management	(41)
Wearable/noninvasive Applications	Integrated into contact lenses and wearble devices for the point glucose care monitoring	(43)
Glucose sensing mechanism	Glucose binding causes volumertic changes through hydrogels , indicating diffraction colour of light transmission quantitative optical detections	(43)
Continous monitoring capability	PBA based for developing sensors enabling the measurement without need for recalibration , unlike enzymes based methods	(41)
Recent advances	The hydrogel flims for smart based detections selectivity and into minimally invasive detection, like microneedles .	(57) (41)

2.4 Protein free glucose responsive drug delivery systems.

Protein free drug delivery system that is responsive to glucose involve the release of drugs, such as insulin-responsive glucose to change the glucose concentration through biological proteins. When these systems utilize synthetic chemical moieties such as phenylboronic acid, PBA can reversibly interact with glucose-responsive proteins, offering stability (58).

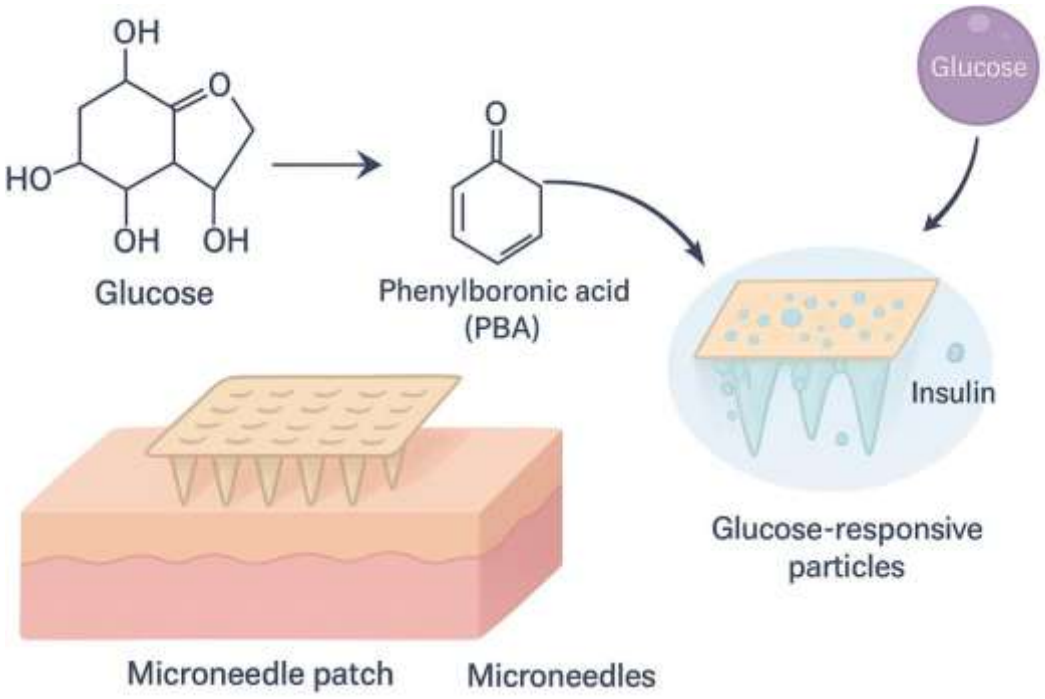

Fig 4: Phenylboronic Acid (PBA) -Based Glucose responsive Microneedle patch for smart insulin delivery using glucose triggered particles.

Glucose-responsive MN patches and transdermal drug delivery systems are designed to release insulin levels in the blood(59). In general, glucose-responsive polymers are alcohol (PVA). Polyvinylpyrrolidine (PVP) is crosslinked in glucose-sensitive systems(60). In the insulin system, glucose oxidase is incorporated to catalyze the generation of some chemical changes (e.g., H202 pH shift). Hypoxia triggers insulin release(5). The insulin should be loaded to encapsulate the MN matrix within the glucose-responsive particles, which are all incorporated into the MN patch. Therefore, moulding strategies are commonly used for microneedle patches with uniform morphology and high mechanical strength of skin penetration(61). In PBA-modified chitosan/PVA/PVP MNs. The presence of glucose leads to the binding of glucose PBA, causing the hydrogel to swell and release insulin(62). Microneedles are minimally painless invasive patches enabled through transdermal delivery pain without injection. These insulin molecules are only released when blood glucose levels are elevared ,therby minizing the likehood of hypoglycemia .There has been sustantail advancement in the development of glucose responsive microneedles that are equipped with an insulin delivery system in recent years.

Table 4. Comparison overview of glucose-responsive drug delivery systems

Type	Responsive Moiety/Mechanis m	Materials/component	Advantages/ Notes	Limitations / challenges
Protein base (GOX	Enzyme catalyzed oxidation of glucose (PH/H202	Glucose oxidase(GOX) PH responsive polymers	High glucose specificity , widely used in monitoring and delivery	Sensitive to pH , temperature oxygen dependent slow response (63)
Protein based (ConA , GBP)	Glucose – binding proteins/lectins	Concanavalin A (conA, GBPs	High glucose specificity dynamic sensing	Susceptible degradation competitive binding with other sugars (6)
Protein – free (PBA – based)	Reversible covalent binding with glucose	Phenylboronic ,acid (PBA) .hydrogels (PVA, PVP, chitosan	Rapid response. Chemical stability . versatile	Nonspecific at low PH potential cytotoxicity at high dose (64)(65)
Microneedl e (MN) patches (protein free or Hybrid	Glucose -triggered swelling/release via hydrogel or vesicles disintegration	PBA - modified chitosan/PVA/PVP smart vesicles microneedles	Minimally invasive painless responsive release reduces hypoglycemia	Manufacturi ng complexity mechanical strength requirement (66)

2.5. Acetalated dextran nanoparticles.

Acetalated dextran (AC-DEX) nanoparticles offer a flexible and glucose-responsive method to diabetes management because they combine the characteristics of biocompatibility-biodegradability and glucose triggered drug release to ensure effective control of diabetes and minimal side effects . Acetalated dextran is a chemically modified form of dextran a natural polysaccharide which is acetalated by the substitution of acid sensitive acetal groups in place of hydroxyl groups on dextran. This structural changes gives AC-DEX specfic acid degradable characterstics for best fit model controlled release drugs , particularly with insulin which is placed in vital peptide hormone included in maintaining the sugar level in body(67). The encapsulation of insulin into AC-DEX nanoparticles would have potential developing glucose controlled demand responsive system in similar to the natural pancreatic beta cell process for insulin secertion triggered by glucose . Nanoparticles act as carriers which may help insulin avoid enzyme based breakdown for sustained and controlled release and responsive act to high glucose availability in the body therefore giving better glycemic control as compared to the injection adminstration strategies usually performed with insulin . Nanoparticles which have a high acyclic acetal compostion have fast degraded as well as a release of insulin hence its offering a fast onset of action vital in the treatment of postprandial glucose control . when the acetal groups largely cyclic a slower degradation profile is providing a longer release of insulin and therefore euglycemia is extended form of longer basis (68) . This tunable degradation facilitates a flexible dosing protocol by particles varying acetal ratio can be co adminstered to offer a biphasic release formulation of insulin-a fast onset component to correct acute glucose changes and slow release profiles to occur sustained release basal insulin action . In such plan was specifically observed in streptozotocin induced type 1diabetic mouse models for single subcutaneous adminstration of AC-DEX nanoparticles loaded with insulin , GOX and catalase maintained between 16 hours compared to the same amount of insulin injected in free form , which accumalted less possiblity of hypoglycemia and enabled tight glucose control .Further evidence of the safety of AC-DEX nanoparticles is their negative result on biocompatibility studies in which minimal cytotoxicity ,neglibile hemolysis, and minimal inflammatory response were noted after the administration of AC-DEX nanoparticles in subcutaneous murine models. (69). In vivo imaging has been used to validate such nanoparticle retention at the site of injection with minimal migration, which is essential in delivering predictable pharmacokinetics of release of the drugs. In additional functional assays show evidence of insulin concentration of greater than increase elevated glucose in both healthy and diabetic animals giving direct evidence of this system has a glucose dependent functionality at some level in biologically systems . In comparison most of the nanoparticles formulations as insulin delivery system are targeted at enhancing bioavailability in the oral route of administration , enzyme resistance or ability to control release of the insulin drug but do not carry the being sensitive to glucose . An eg would be dextran sulfate or chiostan based nanoparticles enriched with zinc or topped with ligands, the purpose of which is mostly to protect insulin against the effects of gastrointestinal output on the basis of glucose concentration(70) . The goal to improve diabetes treatment by mimicking how the body naturally releases insulin.AC- DEX is a biopolymer that breaks down in acid . It is made by modifying dextran with cyclic and acetal groups . The quantities of these groups change the nanoparticles degrade in acidic conditions.When these nanoparticles are combined with insulin in glucose oxidase (GOX) and catalase they breakdown faster when glucose levels rise (71). These processes produce gluconic acid through GOX activity. Due to lower pH and triggers insulin release., Nanoparticles are contain more acyclic acetal breakdown quickly allowing for fast insulin release With more cyclic acetal break down more slowly providing a steady release. There are two types of particles it is possible to achieve both rapid and extended insulin release from one injection. This help to manage blood sugar levels for up to 16 hours in diabetic mouse .Additionally when the nanoparticles encapsulated in alginate microgels they create a system that stabilizes insulin and extends its release over several weeks (72) .Due to In vivo studies reveal that insulin levels in blood increase more over three times under high glucose condtions for conformation the glucose responsive release. This approach combines the benefits of controlled degradation speed and enzymatic glucose sensing offering a promising way to deliver smart insulin.(22) example would be dextran sulphate or chitosan nanoparticles enriched with zinc or topped with ligand the purpose of which mostly to protect insulin against the effects of gastrointestinal output on the basis of glucose concentration over the decade studies have extensively the scope of synthesis degradation and release of insulin patterns of AC-DEX nanoparticles.

3. Applications

Acetalated dextran nanoparticles (AC-DEX NPs) are one of most recent and potential developments in nanomedicine relating to insulin delivery with potential to revolutionize the management of diabetes by providing smart glucose responsive systems of delivery. Providing enhanced bioavailability (orally) and lowering the risks that regular insulin protocols often involve. They are relevant to the unique structural grafting of a naturally available polysaccharide known as dextran with acetal groups to its hydroxyl or residues to create an acid-bio friendly adjustable tunable biopolymer. The intensity and form of acetalation cyclic or acyclic will straightway determine how fast each AC-DEX degrades and eventually insulin kinetics. This properties enable formulators to fine tune drug delivery profiles nanoparticles in the abundance of acyclic acetals degrade quickly such that fast insulin release is achieved in response ***to*** glucose spikes where a nanoparticles with cyclic acetals have a longer release period (several hours) (73) .Which permits both prandial and bases treatment with a single blend shot. Preclinical use of such co-formulated systems has already had profound results with a seminal study showing that co injected rapid band prolonged – release AC-DEX NPs loded with insulin ,glucose oxidase and catalyse were responsive to ambient hyperglycemia conditions in diabetic mice increasing serum insulin levels up to threefold across glucose challenges and maintaining glycemia control over at least sixteen hours after bio distribution an achievement that could not be achieved via standard adminstration of free insulin notably these platforms provided not only an improved level glycemia control but also significantly lowered the risks of hypoglycemia which is one of the most urgent issues in diabetes care management. In addition of injectable AC-DEX nanoparticles are supporting the progress of oral insulin delivery extinguishing enzymatic degradation in the gastrointestinal tract and enhancing trans epithelial transport this makes them acid sensitive so that they can be manufacturing to deliver insulin only in gastric or intestinal conditions besides opening the intercellular tight junctions also recognised as a process which enhances further absorption through paracellular and bioavailability as confirmed by the cell model and the preclinical trails also a great benefit has been encapsulation ofAC-DEX in microgel alginate based systems which ensure NP localization and can be used to tailor release characteristics pf NP with microgel contained insulin nanoparticles causing glucose responsive insulin sufficient to effectively normalise glycemia in animal models without cytotoxic or inflammatory effects (74). AC-Dex Nps also are amenable to combination therapies since their chemistry is modular they could be used to co- deliver incretin mimetics stabilizing enzymes or targeting ligand openings pathway to precision medicine and multi-modal diabetes management . Even though more advanced surface modifications such as ligand conjugation to achieve target cellular uptake or coating with muco-adhesive polymers allow an even greater degree of control over tissue distribution and also increased resistance against physiological clearance mechanisms. safety is a priority with extensive studies on biocompatibilty demonstrating a low level of cytotoxicity less than 1 percent hemolysis at pertinent concentrations , and local inflammation does not persist long after subcutaneous dosing in murine models further support that AC-DEX NPs remain in place following injection sites and stay there more than several days a key aspect in maintaing long term therapeutic efficiency (75). However preclinical postive direction are still major

barriers to transition to humans all lie in the future. More recent developments in the chemistry of nanoparticles such as the development of ethoxy acetalated dextran derivatives. The idea of oral dosage forms inculding AC- DEX and smart tablets and thermoresponsive gels has tremendous potential to remove injection related pain and stigma and it will increase patient compliance to a large extent in both pediatric and elderly patient. Another way autonumous . just in time insulin delivery could be possible is through intergration between clinical innovation and digital health solution .Those patient specific closed loop system in te future incorporting glucose sensor, AC-DEX Np reservoirs that autonomous real time over insulin based on real time glycemic measurements and machine learning .overall acetalated dextran nanoparticles have revolutionized insulin delivery studies over the decades of research using their tunable glucose responsive and hypoglycemic and subcutaneous and orally active delivery (70). The vast preclinical body of evidence synthetic versatility and continued improvement of targeting encapuslation and scale make AC-DEX NPs next generation of treatment modalities in diabetics provided a few short coming can be translated to clinic and clinical performance can meet preclinical expectations (76).

4. Future directions

4.1 Personalized and precision medicine

In the future, personalized and precision medicine for diabetes mellitus in insulin therapy has been developed through the integration of big data, and artificial intelligence (AI) has been used for molecular research. The precise aim of medicine to develop highly developed individualized treatment plans is multidimensional patient data, including genetics metabolism environment lifestyle factors(77). In particular, powerful data are used to process the pathophysiology of the treatment of diabetes type 2 diabetes (T2DM). Insights into facilitating risk and prediction will enable clinicians to explore insulin regimens more precisely to improve glycemic control to minimize adverse effects. AI-driven analytics will allow for dynamic adjustment of insulin therapy on based on patient care for immediate enhancement of both efficacy and patient quality of life(78). Future research and development should focus on elucidating the molecular and genetic basis of insulin resistance to transition these frameworks to clinical applications of precision medicine in the treatment of diabetes through advancements in genomics metabolomics and machine learning. These technologies, which are based on the identification of biomarkers that predict individual responses to insulin and glucose lowering agents, allowing for the personalized treatment of patients, should be considered in terms of genetic variation, comorbidities and lifestyle preferences. Currently, innovations in insulin delivery systems, such as smart insulin pens, insulin pumps, and loop systems, exist. Future diabetes care will also emphasize patient empowerment through personalized lifestyle interventions involving real-time health management for recommendations by smart devices(34). When challenges related to cost accessibility and the implementation of these alternative technologies should be addressed broadly, patient benefits should be addressed. Currently, AI and advanced insulin delivery systems are promising technologies for diabetes management because they provide more effective, safer and patient-centered insulin therapy(79).

4.2 Patients in specific formulations in 3D printing

Current 3D printing technology has revolutionized patient approaches through specific formulations for diabetes management. In 3D printing, the creation of personalized medications involves the unique properties of the therapeutic needs of each diabetes patient to address critical challenges. Owing to dose regimens and variable drug responses, e.g., extraction based on fused design modelling (FDM), 3D printing techniques have been utilized to fabricate tablets that incorporate multiple active pharmaceutical glipizide into single-doses, which results in specific release kinetics for immediate sustained release for patients(80). This level of customization not only simplifies regimens of medication for improving adherence but also enhances therapeutic efficacy, minimizing side effects. Additionally, 3D printing allows the integration of poorly soluble drugs into optimized formulations for expandable therapy for individuals with diabetes. Currently, beyond oral dosage forms, 3D printing is also known as an innovative drug delivery system for diabetes, such as transdermal microneedle patches on implantable devices. This system can deliver insulin or other protein drugs in a controlled-on-demand manner to reduce the burden of frequent injections to improve patient comfort, e.g., 3D-printed multiunit implants loaded with insulin, as demonstrated by the release of the drug resulting from external stimuli and the fabrication of pancreatic tissue B-cell constructs, potentially enabling the restoration of insulin production by diabetic management(81). In personalized nutrition products such as high-fibre, sugar-free foods, further development of pharmaceutical interventions in diabetes care medicaments for 3D printing for patient specification and formulations in diabetes care is ongoing in research and development to ensure safety and efficacy.

CONCLUSION

Glucose-responsive drug delivery systems represent transformative steps involved in diabetes management, offering the potential to closely replicate the natural closed loop of insulin through pancreas exertion. Through protein-based systems, glucose oxidase and glucose- binding proteins are used to generate more stable and scalable protein forms of materials through the use of phenylboronic acid on the basis of hydrogels and MN patches. When smart systems dynamically release insulin, the blood glucose level of insulin fluctuates, thereby reducing the risk of both hyperglycemia and hypoglycemia and improving overall glycemic agents. Recent innovations such as painless microneedle patches and glucose responsive insulin . have demonstrated effective in blood glucose regulation in preclinical models . highlighting the promise of these technologies . Additionally advances in device integration of continuous glucose monitoring ,(CGM) with automated insulin delivery system support their potential as personalized medicine for high level diabetes care . In clinical perspectives and emerging clinical data indicate that CGM intergrated closed loop insulin delivery system also known as artificial pancreas system can signficantly improve glycemic control and reduce the incidence of hypoglycemia in patients with type 1 diabetes. Early stage clinical trails of microneedle patches and glucose responsive insulin formulations show promise for enchanced patient compliance more stable glycemic improve quality life due a minimal invasiveness and more physiologic insulin delivery system. Due to advances of several challenges remain before widespread clinical adopotion. Long term safety and biocompatiblity data for microneedles and novel polymers or biomaterials . Glucose responsive insulin systems must demonstrate and predictable responsiveness in variable physilogical environment of human patients. In device integration faces hurdles including cost, data , security , sensor accuracy , lag time , and need for substantital patient education. Additionally regulatory approval process and reimbursement policies may affect clinical accessibility and adoption .

5. Declaration of competing interest

The authors declare no competing interests.

6. Data Availability

The data will be made available on request.

7. CRediT authorship contribution statement

K.Barath: Writing-original draft, Writing-review & editing, Conceptualization, Data curation. **Farhath Sherin:** Investigation, Conceptualization, Project administration, Resources, Supervision, Validation, Writing-review & editing.

8. Acknowledgements

The authors are thankful to Department of Pharmaceutics, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu.

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