ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 2, 2022

Online - 2455-3891
Print - 0974-2441

Review Article

RECENT APPROACHES IN GLUCOSE RESPONSIVE INSULIN DELIVERY SYSTEM

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Received: 11 November 2021, Revised and Accepted: 01 January 2022

ABSTRACT

Diabetes mellitus is a chronic medical condition currently affecting 382 million people across the globe, caused due to increased blood glucose levels due to less insulin production or insulin resistance. Subcutaneous insulin administration for diabetes is the only most accepted therapy for maintaining blood glucose levels in diabetic patients. Many patients with advanced type II diabetes mellitus need to regularly monitor their blood glucose level to keep their blood glucose level in the target range. However long-term insulin therapy through an invasive route of administration causes problems with patient compliance and a sudden decrease in blood glucose levels. An artificial closed-loop insulin release system that mimics the glucose-responsive insulin secretion by β-cells of pancreas is one of the ways to overcome the problem faced with the conventional method of insulin administration. Many polymeric formulations showed an improved glucose-responsive release of insulin when incorporated with glucose-responsive catalysts such as glucose oxidase, phenylboronic acid, and glucose binding proteins, the release rate can be controlled by optimizing the concentration of glucose-responsive catalysts. This article is been focused on different mechanisms of glucose-responsive release by incorporation with glucose-responsive catalysts.

Keywords: Glucose oxidase, Gluconic acid, Phenyl boronic acid, Concanavalin A, Hydrogen peroxide.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i2.43572. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Diabetes mellitus is an autoimmune disorder in which glucose metabolism fails to maintain the normal glucose concentration in the body as a result of Wang *et al*. [1]. Insufficient production of insulin from pancreas due to destruction of β-cells of islets of Langerhans (type I diabetes) or [2] a combination of insulin resistance by cells and insufficient insulin secretion (Type II diabetes). Subcutaneous administration of insulin and regular monitoring of blood glucose is imperative for type I diabetes patients and some type II diabetes patients. However, conventional treatment of diabetes in which drug therapy and glucose sensing is not directly coupled, known as open-loop insulin delivery, does not tightly regulate glucose levels in patients [53, 54]. To obliterate this problem one of the approaches is an artificial pancreas like a closed-loop insulin delivery system that can release insulin in response to changing blood glucose levels [52, 57]. This would also eradicate the risk of insulin-induced hypoglycemia; the potential of insulin treatment for glycemic control is not realized in numerous people with diabetes [55, 56].

To formulate such a closed-loop system usually consist of a glucose-monitoring moiety and an insulin-releasing module as depicted in Fig. 1 [43, 44]. The current closed-loop system contains a glucose sensor and an external insulin infusion pump. However, the limitation in the application of such systems lies as the system lags in blood glucose feedback and biofouling [50, 51]. An alternative to this is a chemically controlled glucose-responsive system that has been widely scrutinized during the last few decades. Typically, insulin embedded matrix with a glucose-responsive molecule can control insulin release through structural changes such as swelling, shrinkage, degradation, or dissociation in response to glucose concentration [48]. The commonly investigated glucose-responsive molecules include glucose oxidase (GOx), phenylboronic acid (PBA), and glucose binding proteins (GBP).

GOX BASED MECHANISMS

$$Glucose + O_2 + H_2O \xrightarrow{GOx} Gluconic\ Acid + H_2O_2 \quad (1)$$

GOx is a flavin-containing glycoprotein that catalyzes glucose to produce hydrogen peroxide (H_2O_2) and gluconic acid by consuming oxygen [49]. Erosion of polymer and release of endogenous substance (insulin) triggered by varying physiological environment by the effect of gluconic acid, hydrogen peroxide (H_2O_2), and hypoxia condition [1-3]. Some of the research on GOX based insulin release system are summarized in Table 1.

pH-responsive systems

A common glucose-responsive moiety is GOx, which catalyzes the oxidation of glucose to gluconic acid and hydrogen peroxide. The pH-lowering effect that is derived from the generation of gluconic acid results in swelling of the GOx-entrapped pH-sensitive polymer, which subsequently releases insulin from the polymer matrix [4].

Conversion of glucose into gluconic acid causes a lowering in pH this will lead to cause conformational or structural change in the structure of the polymer to regulate the release of insulin [40, 42]. GOx enzyme is also sensitive to environmental changes and can be potentially denatured when it is entrapped in or covalently linked to a polymeric matrix shown in Fig. 2. Example of such strategies includes chitosan microgel [5], amphipathic 2-nitroimidazole–l-cysteine–alginate conjugates [6], and peptide hydrogel [2].

Hypoxia-responsive system

Glucoresponsive systems utilizing GOx as the responsive material for the release of insulin from the system generally consist of pH-sensitive polymers, which are either protonated or degraded with the reduction in environmental pH. But such pH-dependent releases are often compromised by moderate or slow responsiveness, particularly in a buffered physiological environment. A novel glucose-responsive delivery system consisting of hypoxia sensitive polymer can be used for the release of insulin that shows much faster release as compared to the pH-sensitive release mechanism [7, 41].

This novel system of drug release comprising hypoxia sensitive polymer that consists of GOx cause conversion of glucose to gluconic acid which takes place with consumption of oxygen, this cause induction of hypoxia

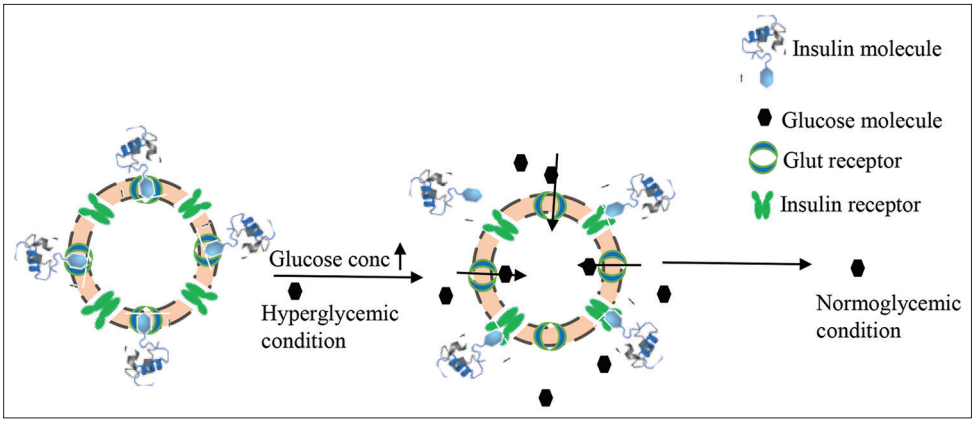


Fig. 1: Schematic representation of the dissociation of insulin glut complex in presence of free glucose and binding of insulin with insulin receptor and transport of glucose through glut

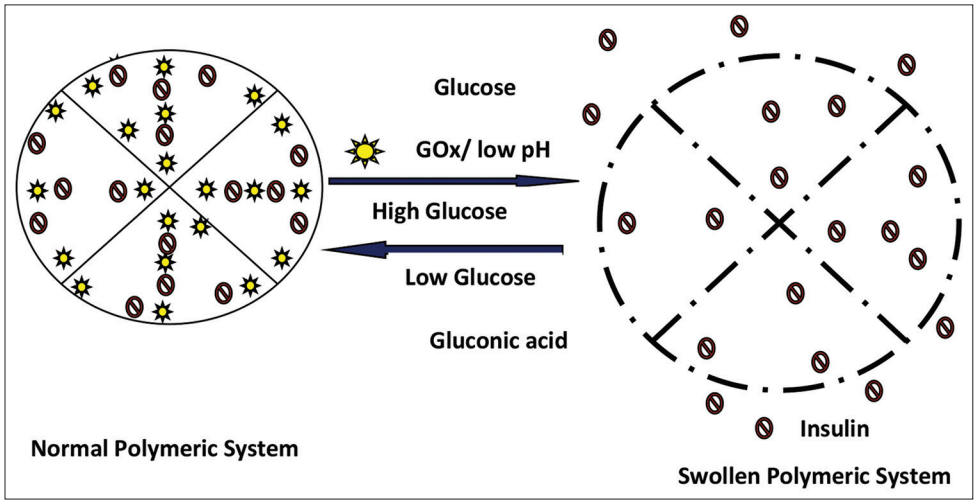


Fig. 2: Schematic representation of glucose triggered pH responsive insulin release system

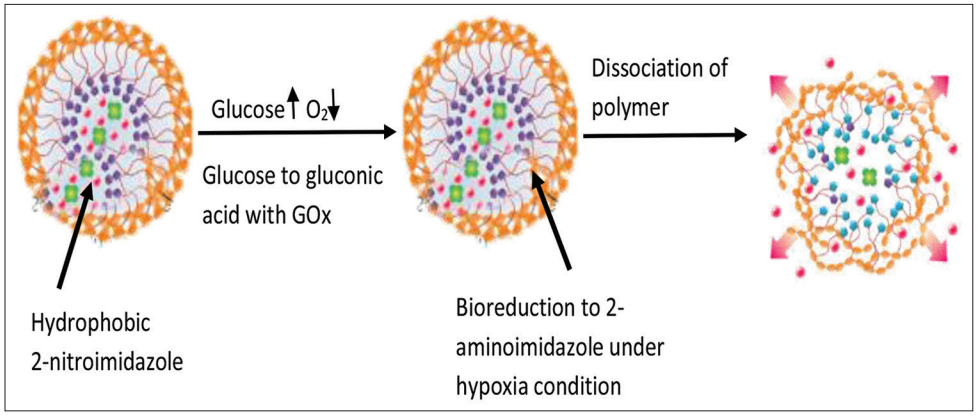


Fig. 3: Schematic representation of the dissociation of hypoxia mediated polymer and release of insulin

condition that causes degradation of polymer and release of the drug Fig. 3 [46, 47]. Examples of such hypoxia sensitive polymer include 2-nitroimidazole, a hypoxia sensitive polymer that is hydrophobic gets converted to 2-aminoimidazole and becomes hydrophilic due to which it gets dissolved in physiological fluid and release of the drug occurs [7,8].

H_2O_2 responsive systems

Novel glucose-responsive drug delivery system comprising GOx as the glucose-responsive enzyme that converts glucose to gluconic acid by utilizing oxygen also produces hydrogen peroxide in the reaction. This hydrogen peroxide remains in the system that raises the concern about the biocompatibility inside our body [44, 45]. However, this hydrogen peroxide can be used for the dissociation of the glucose-responsive system containing H_2O_2 responsive polymer such as co-block polymer polyethylene glycol (PEG) and phenylboronic ester (PBE)-conjugated polyserine (designated mPEG-b-P[Ser-PBE]) for the formation of the system [9].

Di-block copolymer employed for the glucose-responsive release comprises polymer containing H_2O_2 sensitive PBA pinacol ester that gets hydrolyzed in the presence of hydrogen peroxide formed during the conversion of glucose to gluconic acid [38, 39]. These polymers become water-soluble after hydrolysis and get dissolved in the physiological fluid causing the release of insulin as shown in Fig. 4. Many such polymers were used for the delivery of drugs-like diblock copolymer (mPEG-b-polyserine) [9], self-assembled polymeric vesicle from a triblock copolymer containing PEG, poly(PBA) (PPBA, glucose-sensitive block), and (PPBA pinacol ester) [10], and block copolymer PEG-b-PAPBE [11].

GBP BASED MECHANISM (CONCANAVALIN A-COMPLEX)

Recently, the glucose-binding capacities of glucose transporter, GBPs, and aptamer have moreover developed within the domain of glucose-sensing and insulin delivery systems. As depicted in Fig. 5. concanavalin A can bind specifically, reversibly and competitively to glucose and mannose molecule with high affinity. Concanavalin A can bind specifically, reversibly, and competitively to glucose and mannose molecules with a high affinity. Concanavalin A molecule can bind to the saccharide moiety and act as a cross-linker of macromolecule. Gels are a highly suitable type of formulation that can be used as a glucose-responsive system with Concanavalin A based insulin release. In the presence of increased glucose concentration Concanavalin A binds competitively with the free glucose moiety causing decrease in the crosslinking thickness of the gel [1]. Various other mechanisms that have been used for concanavalin A based insulin delivery are:

Responsive hydrogel cross-linked by Con A

The glucose-responsive moiety Concanavalin A in such a system acts as a cross-linker with the saccharide polymer to form a hydrogel. These concanavalin A moiety competitively binds with the free glucose group present in the body fluid causing gel to sol transformation and swelling of the polymeric system for the release of insulin.

Many such concanavalin A and polymeric complex have been used to formulate a system for glucose-responsive insulin delivery like complex formation between poly (glucosyloxyethy1 methacrylate) (poly[GEMA]) and Con. A [12], (Con A-copolymerized GEMA hydrogel by copolymerizing a monomer having pendant glucose with chemically-modified ConA having vinyl groups [13]. Allyl glucose copolymerized with acrylamide and crosslinked with concanavalin A. (Obaidat *et al*. 1996) Glucosyl-oxyethyl acrylate-Chitosan cross-linked with Concanavalin A [15]. ConA@poly(NIPAM) is comprised Concanavalin A, as the glucose recognition moiety, which is interpenetrated in a chemically-crosslinked network of poly(N-isopropyl acrylamide) (poly[NIPAM]) [16]. Many such concanavalin A based system are mentioned in Table 2.

Irresponsive gel immobilized with Con A

Concanavalin A reactivity toward d-mannose and d-glucose is much stronger as compared to other polysaccharide rings. This property of concanavalin A causes it to form competitive bonding with free glucose present in blood and causes dissociation of the polymeric complex of the vesicle to release insulin. However, this system is vulnerable to component loss, especially Con A loss, which could lead to weak glucose sensitivity and undesirable biocompatibility. Therefore, it is necessary to develop an efficiently crosslinked network and covalently immobilize Con A to the polymer matrix.

Therefore covalently bonded and efficiently crosslinked concanavalin A with the polysaccharide polymer is an effective method to prevent the leakage of concanavalin A. Researchers used different chemical modifications of Concanavalin A to immobilize it on the polymer-like concanavalin A covalently bounded on hydrogel using carbodiimide reaction, ring-opening reaction, and Schiff base reaction [17], an acrylic derivative of dextran was photo-polymerized with concanavalin A with the help of UV light to form cross-linkage [18]. Concanavalin A was covalently bonded to periodate oxidized dextran [19].

Endogenous lectin-targeted systems

Recently, glucose responsive insulin delivery systems have been developed by targeting mannose receptor C-type I, a lectin receptor that

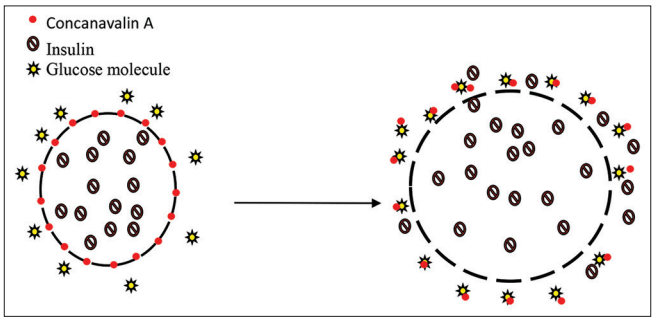


Fig. 5: Schematic representation of competitive binding of Concanavalin A with glucose and swelling of polymeric vesicle to release insulin

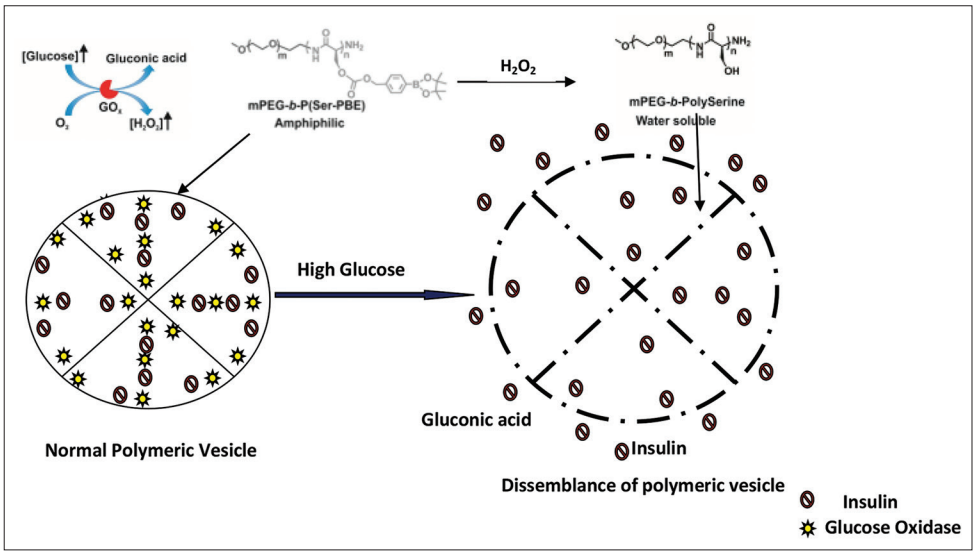


Fig. 4: Schematic representation of H_2O_2 responsive release of insulin

Table 1: Glucoresponsive insulin delivery system based on glucose oxidase

Bioresponsive system	Component	Route of administration	*In vitro* study	*In vivo*	Reference
Microneedles patch	Polymeric carrier positively charged amphiphilic diblock copolymer Enzyme Catalase Glucose Oxidase	Topical	Average size: 60 nm ζ-potential: 4.4±0.5 mV Loading capacity: 50 wt% Release rate: twofold faster at a glucose concentration of 400 mg dL^{-1} than that of 100 mg dL^{-1}	Lowering of Blood glucose levels by 100 mg dL^{-1} in 30 min post-administration and maintained below 200 mg dL^{-1} for almost 4 h, considerably longer than those of the mice subcutaneously injected with insulin	[1] 2018
Liposome	Lipid carrier hyaluronic acid (HA) Organic Reagent: Phenylboronic acid	Oral	Average size : 94 nm zeta potential: –6.6 to –28.1 mV encapsulation efficiency (EE): 20.7% loading capacity (LC): 17.1%	Lowering of Blood glucose levels during the first 12 h after treatment	[2] 2019
Dual-sensitive nanogels	Polymeric carrier: AHMDM (acryloyl [4-(5-[hydroxymethyl]-5-methyl-1,3,2- dioxaborinan-2-yl)phenyl] methanol) Enzyme: Glucose oxidase	Subcutaneous route	Particle size: 268 nm Loading efficiency: 9.7% for insulin 1.1% for GOx Encapsulation efficiency: 16.3% for insulin 10.3% for GOx Release rate: Absence of glucose 16% insulin release In 1 g/ml glucose solution 38% and 57% insulin release from nanogel without GOx and with GOx, respectively. 4 g/ml glucose solution 59% and 78% insulin release from nanogel without GOx and with GOx, respectively	PBS-insulin reduced BGL to the normoglycemic condition in 0.5 hr and returned to the hyperglycemic state in 3 h NG-Ins reduced BGL to the normoglycemic condition in 2 h and returned to the hyperglycemic state in 7 h NG-Ins-GOx reduced BGL to normoglycemic condition within 1 h and maintained below hyperglycemic condition for 16 h	[3] 2019
Metal-organic framework (MOF) integrated nanoparticles	Polymeric carrier: zeolitic imidazole framework-8 (Zinc nitrate hexahydrate[Zn[NO3]2・6H2O], 2- ethylimidazole) Enzyme: Glucose oxidase	Subcutaneous route	Average size: 320 nm Release Rate: 300 μg mL^{-1} insulin release at glucose conc 400mg mL^{-1} Structure degradation was observed in ZIF@Ins&GOx but no degradation in the structure of ZIF@Ins structure	ZIF@Insu&GOx reduced BGL in 1.5 h and maintained Normoglycemic condition (<200 mg dL^{-1}) for 3 days Free insulin reduced BGL in 0.5 h but returned to hyperglycemic (>400 mg dL^{-1}) with 24 h ZIF@Ins reduced BGL in 2 h but recovered above 200 mg dL^{-1} within 24 h	[4] 2020
Peptide hydrogel	Polymeric carrier: Self-assembling peptide hydrogel (peptide IA 0). Enzyme: Glucose oxidase Catalase	Subcutaneous route	Release Rate: The release rate of insulin increase to 4 fold in glucose-responsive hydrogel as compared to a normal hydrogel	BGL decreased in hydrogel without enzyme G (I) in the first 3 h up to 9 h A sharp decrease in BLG decrease in the hydrogel with enzyme G (I+E) and normoglycemic condition (<11 mmol/L) was maintained for 4 days.	[5] 2017
Hyaluronic acid microgels	Polymeric Carrier: Hydrophobic m-dextran Enzyme: Glucose Oxidase Catalase	Subcutaneous route	Particle size: 226.9±20.6 nm Loading capacity: 9.1±0.2 wt% Encapsulation efficiency: 66.8±7.2 wt%. Release rate: Insulin release increased to 2.3 folds when glucose concentration increased from 100 mg dL^{-1} to 400 mg dL^{-1}	Diabetic mice treated with HA(I+E), HA(I), and insulin. HA(I+E) maintained normoglycemic condition in mice for 8 days, HA(I) maintained normoglycemic condition for only 1 day due to burst release whereas in case of insulin injection BGL returned to hyperglycemic condition within 12 h	[6] 2015

(Contd...)

Table 1: ***(Continued)***

Bioresponsive system	Component	Route of administration	*In vitro* study	*In vivo*	Reference
Multiresponsive supramolecular Theranostic Nanoparticles	Polymeric carrier: Water-soluble pillar [5] arene. Enzyme: Glucose oxidase Phenyl boronic acid (−35.13 mV)	Intraperitonial route	Particle Diameter: 210 to 250 nm Zeta potential: -35.13 mV Loading Efficiency: 59.60% Release Rate: 5% release occurred in euglycemic condition (100 mg dL^{-1} glucose concentration) 40% release occurred in Glucose conc 250mg dL^{-1} The release was much higher when vesicles were incubated at much higher conc 400 mg dL^{-1}	Free insulin (I) and Vesicle with enzyme (V [E+I)] and insulin reduced BGL in 0.5 h Normoglycemic state maintained by (V [E+I]) for 2 h	[7] 2018
Hypoxia and H_2O_2 Dual-Sensitive Vesicles	Polymeric Carrier: Di block co-polymer PEG and polyserine modified with 2-nitroimidazole (PEG-polyserine) Enzyme: Glucose Oxidase Catalase	Transcutaneous patch	Average diameter: 94 nm found by DSC Loading efficiency: 3.2% Release rate: Quick insulin release occurred in high glucose concentration (400 mg dL^{-1}) as compared to low glucose concentration (100 mg dL^{-1}). Insulin release found to be 11.2 fold increase in high glucose concentration (400 mg dL^{-1}) as compared to low glucose concentration (100 mg dL^{-1})	d-GRP (E+I) containing enzyme and insulin caused a rapid decrease in BGL within 1h of administration and normal glycemic condition was maintained for 6 h No decrease was observed in BGL with MNs without enzyme (d-GRP [I]) and they remained stable for 24 h	[8] 2017
PLGA/ Chitosan based nanocomplex	Polymeric carrier: Chitosan and PLGA (Poly lactic co glycolic acid) Enzymes: Glucose oxidase Catalase enzyme	Subcutaneous route	Particle Size: 245 + 24 nm, PDI- 0.2 Zeta potential: +19±3.92 mV for Cs NPs and -25.5±2.1 for PLGA NPs. Encapsulation efficiency 50±5.3% for Cs NPs 59.3±1.5% for PLGA NPs Loading efficiency: 4.1±0.4% for Cs NPs 4.73±1.33% for PLGA NPs Release rate: NC-Ins-Enz in first 2 h release was 62% in pH4 and 36.6% in pH 7.4 In the first 4 h, the release was 72.4% in pH 4 and 41.8% in pH 7.4 At 112 h release was 100% in pH 4 and 60% in pH 7.4. Insulin release was much higher at glucose concentration 400 mg dL^{-1} as compared to 100 mg dL^{-1} and burst release occurred in the first 2 h independent of glucose concentration.	Ins SC reduced BGL to 100 mg dL^{-1} and returned to 400 mg dL^{-1} after 8 h Cs-Ins-2mg and Cs-Ins-4mg reduced BGL for 12 h and 24 h NC-Ins-2mg and NC-Ins-4mg reduced BGL for 48 h and 72 h	[9] 2019

(Contd...)

Table 1: ***(Continued)***

Bioresponsive system	Component	Route of administration	*In vitro* study	*In vivo*	Reference
Glucose responsive micro-devices	Carrier: PDMS (polydimethylsiloxane) Enzyme: Glucose oxidase Catalase	Intraperitonial implants	Insulin release rate increase in 2.5 h when glucose concentration increased from 5 mmol L^{-1} to 20 mmol L^{-1}. 49.7+11.1 µg amount of insulin released in 4 h	Normoglycemia was maintained in the group implanted with hydrogel for 7 days and BGL increase after day 10	[10] 2012
Microneedle-array patches	Polymeric Carrier: Hyaluronic acid + 2-nitroimidazole Enzymes: Glucose oxidase	Transcutaneous patch	Insulin release rate increased to 6.6 times when glucose conc increased from 100 to 400 mg dL^{-1} in 20 min. Whereas GRVs containing half amount of GOx showed slow release of insulin due to a decrease in consumption of oxygen for conversion of glucose to gluconic acid.	Insulin dose was 10mg/kg. BGL reduced to 200mg dL^{-1} and maintained <200 mg dL^{-1} for 4 h by GRV (I+E). BGL reduced to 350 mg dL^{-1} with GRV with half enzyme concentration. GRV without enzyme did not show any decrease in BGL.	[11] 2015
Erythrocyte-Membrane-Camouflaged Nanoparticles	Polymeric carrier: RBC membrane, Ethoxy acetal derivatized dextran Enzymes: Glucose oxidase Catalase	Intravenous injection	Particle size: 124.3 nm Zeta potential: −10.4 to −20.1 mV Release rate: Maximum insulin release occurred was 7.8+0.8 µg at 400mg dL^{-1} glucose solution. And release rate increased to 2.9 fold when glucose concentration increased from 100 mg dL^{-1} to 400 mg dL^{-1}.	STZ induced diabetic mice treated with NP(I), NP(I+E), RBCm/NP(I+E) and RBCmNP(I+E). NP(I) and NP(I+E) reduced BGL to hypoglycemic state within 1 hr and returned to hyperglycemic state within 12 h RBCm/NP(I+E) maintained normoglycemic condition for 4 h RBCmNP(I+E) slowly reduced BGL and maintained normoglycemic condition for 24 h and returned to hyperglycemic state slowly over 4 days	[12] 2018
Glucose-Responsive Microgels Integrated with Enzyme nanocapsules	Polymeric carrier: Chitosan Enzyme: Glucose oxidase catalase	Subcutaneous route	Particle size: 256 + 18 µm Loading efficiency: 44.6 + 2.8% Encapsulation efficiency: 59.7 + 3.4% Release rate: Insulin release rate increase to 2.5 folds when glucose concentration increased from 100 mg dL^{-1} to 400 mg dL^{-1} Particles showed 1.7 times increase in diameter and 5 fold increase in volume within 3 h of incubation with 400 mg dL^{-1}. Whereas no swelling occurred on incubation with 100 mg dL^{-1} glucose concentration	BGL was reduced in mice treated with MG (I+E) and MG(I) to normoglycemic condition within 2 h of administration through inj MG (I+E) maintained normoglycemic condition for 12 h and then gradually increased. Whereas MG (I) showed a rapid increase in BGL after 2 h of administration.	[13] 2013
Glucose responsive bioinorganic nano-hybrid membrane	Polymeric carrier: poly(Nisopropylacrylamide-co-methacrylic acid) (poly[NIPAM-MAA]) Bovine serum albumin Enzymes: Glucose oxidase Catalase	N.A	Insulin permeability increase 2 and 4 fold in membrane with MnO_2 when glucose increase from 100 to 200 mg dL^{-1} and 100 to 400 mg dL^{-1} respectively Insulin permeability increase only 2 fold in the membrane without MnO_2 when glucose increase from 100 to 400 mg dL^{-1}	N.A	[14] 2010

(Contd...)

Table 1: ***(Continued)***

Bioresponsive system	Component	Route of administration	*In vitro* study	*In vivo*	Reference
Subcutaneous Implant	Carrier: Micro device salinized by 3-aminopropyl trimethoxysilane and crosslinked with bovine serum albumin Enzyme: Glucose Oxidase	Implants	Release rate: Insulin release from the micro device increased 2.29 times when glucose concentration increased from 100 mg dL^{-1} to 400 mg dL^{-1}		[15] 2015
Glucose sensitive liposomes	Polymeric Carrier: Egg phosphatidylcholine (EPC) Enzyme: P(NIPAM-co-MAA-co-ODA) conjugated glucose oxidase	Subcutaneous route	Particle size: 100–300 nm Release rate: When glucose concentration was 50 mg dL^{-1} insulin release was 40% in 90 min When the concentration was 200 mg dL^{-1} insulin release was 56% in 90 min	N.A	[16] 2009
Glucose-Responsive Micelles	Polymeric carrier: (PEG-b-PDPA) Enzyme: Glucose oxidase	N.A	Particle size: 328.3±20.7 nm Loading efficiency: LE = 21.12% for insulin LE = 24.09% for GOx Encapsulation efficiency: EE = 91.53%for insulin EE = 86.08% for GOx Release Profile: Insulin release was 50% in absence of glucose concentration. Whereas the release was 80% in presence of 10 mg/ml glucose concentration	N.A	[17] 2016
Bioresponsive microneedle with a Sheath structure	Polymeric carrier: Poly(DMAEMA-PBA) Enzyme: Glucose Oxidase	Oral	Release rate: The release rate of insulin from Ins-NCs entrapped in the gel was twofold faster at a glucose concentration of 400 mg dL^{-1} than that of 100 mg dL^{-1}	N.A	[18] 2018
Dextran nanoparticles	Polymeric carrier: Nano-acryloyl crosslinked dextran dialdehyde (NACDD) Enzyme: Glucose oxidase	Subcutaneous route	Particle size: 48 nm to 74 nm Loading Efficiency: 48.68% Release Rate: Release was found to be 70% in pH 7.4 with NACDD, whereas release was found to be 90% with NACDD-GOx in pH 7.4 with a glucose concentration of 4 mg/ml	NA	[19] 2019
Mesoporous silica nanoparticles	Polymeric carrier: n-cetyltrimethyl ammonium bromide (CTAB). Enzyme: β-cyclodextrin-modified enzyme glucose oxidase (CD-GOx)	NA	Particle size: 426.1 ± 54.2 nm Zeta potential: -17.7 mV Release Rate: 3% FITC Insulin release in 20 h in absence of glucose 26% insulin released in solution with 50 mM of glucose	NA	[20] 2017
Self-Assembled Polyamine Nanoparticles	Polymeric carrier: Poly(allylamine hydrochloride) and Sodium phosphate monobasic monohydrate salt aggregate Enzyme Glucose oxidase	Oral route	Average size: 90 nm Release rate: 9% release in absence of glucose, 15% release in normoglycemic condition (5 mM), 40% release in glucose conc (10 mM) 100% release in hyperglycemic condition (15 mM and 20 mM)	NA	[21] 2019

is primarily expressed on hepatic sinusoidal endothelial cells, specific macrophages, and dendritic cells for the treatment of hyperglycemia.

Some of the researchers have targeted lectin receptors for the delivery of insulin through the small intestine by conjugating insulin with saccharide conjugate, like mannose conjugated with insulin forming MK-2640 novel insulin delivery that showed glucose-responsive release [20,21]. Fig. 6 describes the pathway about the delivery of insulin through lectin receptor targeting through small intestine. Disaccharide maltose bound to form semisynthetic sugar-insulin derivative complementary to the binding site of lectin Concanavalin A, where the release of maltose conjugated insulin release is proportional to the amount of glucose concentration present in the blood [22].

Table 2: Glucoresponsive insulin delivery system based on Concanavalin A

Bioresponsive system	Component	Route of administration	*In vitro* study	*In vivo*	Reference
Microhydrogel	Polymeric carriers: Glycidyl methacrylate modified dextran Enzyme: Ethylene glycol acrylate methacrylate modified concanavalin A	Oral	The release rate of insulin from Ins-NCs entrapped in the gel was twofold faster at a glucose concentration of 400 mg dL^{-1} than that of 100 mg dL^{-1}	NA	[29] 2018
Microgels	Polymeric carrier: Chitosan, Methyl α-d-glucopyranoside Enzyme: Concanavalin A	Oral	Particle size : 2.9 ± 1.0 Encapsulation efficiency (EE): 61.7% at pH 7.4 loading capacity (LC): 6.7% at pH 7.4 Release Rate: The release of insulin was found to be much higher in presence of glucose as compared to a solution without glucose. Even glucose-responsive insulin release was able to release insulin to longer extend	NA	[30] 2014
Nanoparticles	Polymeric carrier: Gelatinized Amylopectin Enzymes: Concanavalin A	Oral	Particle Size: 241.10–292.20 nm Encapsulation efficiency: 69.73%. Loading capacity: 17%. insulin-release rate for nanoparticles in 3 mg/ml Release study: Concanavalin A containing nanoparticles shows a much higher release due to more conjugation of glucose with concanavalin A as compared to nanoparticles without enzymes	NA	[31] 2018
Microhydrogel	Polymeic carrier Glucosyloxyethyl methacrylate (GEMA) N-(2-[dimethylamino] ethyl)-methacrylamide (DMAEMA) Enzyme Concanavalin A	Oral	Particle Size: 38 µm Release rate: Release of insulin from concanavalin A based microhydrogel show an increase in release rate with an increase in glucose concentration in the release medium	NA	[32] 2011
Microparticles	Polymeric carrier: Chitosan, Dextran Enzyme: Concanavalin A	Oral	Particle Size: 2.5 µm, Entrapment efficiency: 92.2%, Loading capacity: 9.1% Release rate: A slower release rate of insulin was detected in PBS (pH 7.4) with glucose 0 mg/mL when compared with that in PBS (pH 7.4) with glucose 4 mg/mL. However, a burst release profile within the first 20 min was displayed in both mediums	NA	[34] 2010
Microspheres	Polymeric carrier: Dextran conjugated glycidyl methacrylate Enzyme: Concanavalin A		Particle size: 5.23 µm Entrapment Efficiency: 94.6 % Loading capacity: 12.13% Release rate: Effect of light radiation was observed on the release rate of insulin. The light-irradiation could significantly reduce the average insulin release rate in the first cycle of bolus-basal release after the implementation of the first two times of light-irradiation, while no significant change happens on the third and fourth light-irradiation, which were attributed to the less remnant un-reacted photo-active groups and relatively high remained insulin concentration of irradiated samples compared with non-irradiated microspheres	NA	[35] 2019
Hydrogel	Polymeric carrier: Methacrylated dextran (Dex-G) Enzyme: Concanavalin A	Oral	NA	NA	[36] 2010

Glucose transporter-mediated insulin delivery

Recently many researchers have conceived the concept to use glucose transporter (Glut) to achieve glucose-responsive insulin release from the formulation for the mitigation of hyperglycemic conditions. In such type of release system, insulin is reversibly bound with glucose transporter present on the cells, and insulin is released mediated by the displacement of insulin from the glucose transporter due to competitive binding of free glucose present in the blood under hyperglycemia conditions.

Some of such formulations maneuvered by the researcher were conjugating insulin reversibly with Glut inhibitor. On reaching to blood circulation in hyperglycemic condition insulin analog-Glut complexes dissociate. The free insulin analog can subsequently bind to IR to trigger the translocation of Glut to cell membranes and enhance glucose clearance into muscle and fat. Meanwhile, the Glut, which is previously inaccessible to glucose as part of the insulin analog-Glut complex, can enhance the blood glucose clearance [23-25] formulated insulin F by conjugation of human recombinant insulin and glucose transporter

Table 3: Glucoresponsive insulin delivery system based on phenyl boronic acid

Bioresponsive system	Component	Route of administration	*In vitro* study	*In vivo*	Reference
Double-layered nanogel	Polymeric carrier: glycol chitosan (GC)/sodium alginate (SA)- poly(L-glutmate-co-N-3-L-glutamylphenylboronic acid) (PGGA) Enzyme: Phenyl boronic acid	Retro-orbital route	Particle Size: 767.9 nm Zeta potential: 5-12mV Loading efficiency: 71+3.5% Release rate: Insulin release from PBA conjugated nanogel showed increased release in insulin with the release medium containing glucose conc of 5mg/ml and 10mg/ml. The release was much higher as compared to the glucose conc with 0mg/ml and 1mg/ml	To confirm the controlled insulin release capability of GC/SA-PGGA nanogel *in vivo*, mice were treated with four different samples: blank GC/SA-PGGA, free insulin, insulin loaded GC/SA, and insulin-loaded GC/SA-PGLA. Compared to insulin-loaded GC/SA, insulin-loaded GC/SA-PGGA-treated mice showed that the blood glucose levels were more dramatically decreased until 60 min, meaning that GC/SA-PGGA nanogel can controllably release the encapsulated insulin by its glucose responsiveness	[33] 2015
Glucose-responsive insulin activity by covalent modification with aliphatic phenylboronic acid conjugates	Polymeric carrier: m 12-amino dodecanoic acid Enzyme: Phenyl boronic acid	Oral	NA	NA	[59] 2015
Nanoparticles	Polymeric carrier: Cyclodextrin conjugated with (5-ethyl-2-phenyl-1,3,2-dioxaborinan-5-yl) methyl 2-bromoacetate (EPDMB) Enzyme: Phenyl boronic acid	Oral	Release rate: Insulin release from nanoparticles formed by the conjugation of cyclodextrin with phenylboronic acid showed increased release of insulin in presence of glucose concentration as compared to the nanoparticles without phenylboronic acid	NA	[58] 2018
Microparticles	Polymeric carrier: A pseudopolyrotaxane (PPRX) comprising 3-carboxy-5-nitro phenylboronic acid modified γ-cyclodextrin (NPBA-γ-CyD) Enzyme: Phenyl boronic acid	Oral	NA	NA	[60] 2016
Polymeric complex	Polymeric carrier: Polymerized tert-butyl (2-acrylamido ethyl) carbamate (Boc-EDAA) Enzyme: Phenyl boronic acid	Sub-cutaneous	Release rate: Poly (EDAA0.7-FPBA0.3) –insulin complex exhibited a relatively slow insulin release rate. Moreover, the insulin release rate was steadily increased in response to glucose concentration variation (from 100 to 400 mg/dl), achieving a maximum of fourfold enhancement Poly (EDAA0.4-FPBA0.6) -insulin complex also achieved pulsatile insulin release for several cycles by alternating glucose concentrations between 100 and 400 mg/dl	Poly (EDAA0.7-FPBA0.3), Poly (EDAA0.4-FPBA0.6), a dose of 80 U/kg was administered. The BGLs of all treated groups decreased to below 200 mg/dl, indicating the retention of activity of complex insulin. Moreover, Poly (EDAA0.4-FPBA0.6), was shown to maintain BGLs within the normal range (<200 mg/dl) for 8 h, much longer than native insulin and Poly (EDAA0.7-FPBA0.3)	[61] 2019

BGL: Blood glucose level, MNs: Micro needle, d-GRPs: Dual sensitive, glucose sensitive polymersomes, P(NIPAM-co-MAA-co-ODA): Poly(N-isopropylacrylamide-co-methacrylic acid-co-octadecylacrylate), Poly(DMAEMA-PBA): poly(2- dimethylaminoethyl methacrylate)-block-poly(n-butyl acrylate) (PDMAEMA-b-PBA)

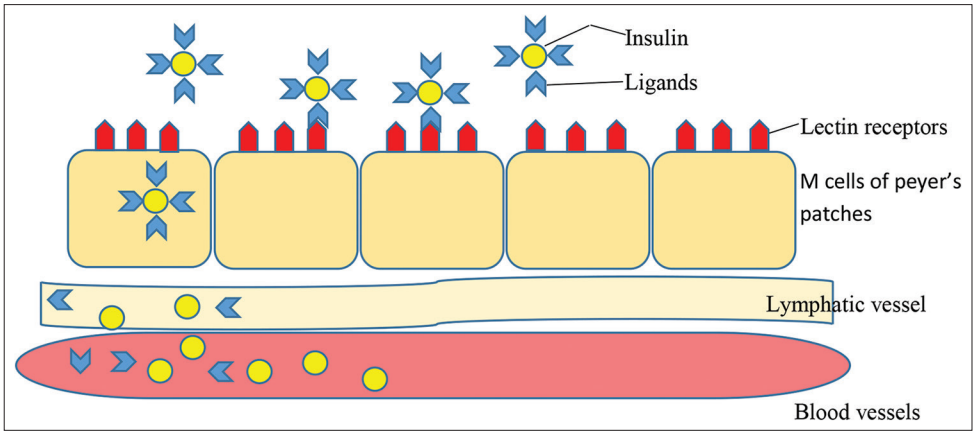


Fig. 6: Schematic representation of ligand target insulin delivery system

inhibitor, forskolin. The introduction of forskolin reduces the water solubility of insulin and prolongs its retention after subcutaneous injections, thereby providing sustained release of insulin-F from the injected depot.

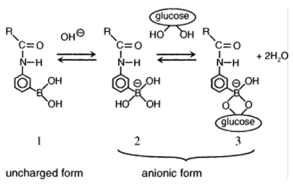
PBA

Various researchers have extensively studied the use of GOx and GBP for the formulation of glucose-responsive insulin delivery system; however, as compared to GOx and GBP-like concanavalin A, PBA is a highly stable glucose-responsive compound with high durability in the physiological environment [26]. Demonstrated the formation of an ester from aromatic boronic acids and a series of diol-containing compounds. It was subsequently found that a cis-1, 2- or 1, 3-diol compound favored the formation of esters with PBA. PBA found reversible complexation with other polymeric compounds that disrupt in presence of glucose concentration causing the release of insulin from the polymeric vesicles [37].

Different types of systems such as bulk hydrogels, micro/nanogels, and self-assembled micelles can be prepared from molecules with a PBA moiety or boronate ester. An increase in glucose concentration in physiological fluid dissociates the PBA- diol bond, causing swelling of the carrier and release of insulin. Insulin can be conjugated with PBA, competitive binding of glucose in the physiological fluid with PBA causes the release of insulin. Many of the studies conducted on such phenylboronic acid based insulin delivery system is summarized in Table 3.

Bulk hydrogels

3D structure of hydrogel contains a considerable amount of water and it is maintained via chemical or physically crosslinked 3D polymeric scaffold. The incorporation of PBA into the polymeric network provides glucose-responsive hydrogel in presence of increased glucose concentration in the physiological fluid. Increased free glucose concentration causes the formation of boronate ester inducing increased hydrophilicity of polymeric chain ultimately leading to dissociation of polymeric gel and release of insulin.



Examples of such bulk hydrogel are hydrogel matrix with major component poly (N-isopropylacrylamide) (PNIPAAm) derivatized with a definite fraction of a PBA group as the glucose-sensing moiety. A small amount of N,N′-methylene-bis-acrylamide was used as a cross-linker [27], polymeric gel composed of poly (N-isopropylacrylamide) (PNIPAAm), and 3-acrylamidophenylboronic acid (AAPBA) (9:1 in molar ratio: NB10 gel) [28,29]. Hydrogels with copolymerization of AAPBA and 2-hydroxyethyl methacrylate [30].

CONCLUSION

Diabetes is a chronic metabolic health disorder that is affecting a huge population all across the globe. Subcutaneous administration of insulin remains one the conventional and most used therapy in case of insulin deficiency related to diabetes. However, the use of subcutaneous injections for insulin leads to patient non-compliance due to pain, discomfort, and chances of local infections linked to it. An approach towards the use of oral administration of insulin through novel drug delivery systems can lead to patient acceptability as well as it can mimic the action of body physiological insulin. Along with that utilization of different glucose-responsive elements and their incorporation into various novel drug delivery systems help to produce glucose-responsive insulin delivery into the blood circulation giving a closed-loop insulin delivery. Emerging smart insulin delivery systems are based on a glucose-responsive insulin delivery system. Current researches with *in vitro* and *in vivo* data prove to improve the diabetes mellitus condition by proper maintenance of glucose concentration in the blood circulation. Glucoresponsive release can reduce the sudden decrease in blood glucose level that might result in some cases after the administration of insulin. Thus, glucose-responsive insulin release can prove to be an effective way of insulin delivery without frequent testing of blood glucose levels. Apart from the advantages of a glucose-responsive insulin delivery system, there are many problems linked to it that need to be solved. First, degradation of insulin at the gastric fluid due to the presence of peptidase enzymes, secondly the insulin loading capacity on the novel drug delivery systems. Since the release of insulin is controlled by the blood glucose level, the concentration of insulin should be optimum in the release system for a proper release. Further evidence is needed to prove the safety of smart insulin delivery systems in long-term usage. Systematic studies on the metabolic mechanisms of the monomers, polymers, and degradation compounds should also be carried out.

AUTHORS CONTRIBUTION

All the authors have contributed towards the preparation of review preparation and editing of the manuscript.

CONFLICTS OF INTEREST

All the authors have none to declare.

AUTHOR FUNDING

No funding received for the completion and publication of the article.

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