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**Title: Efficacy and safety of glucose sensors for delivery of insulin: A
Systematic Review**

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Declarations of interest

The authors declare no conflict of interest.

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Abstract:

Background: Diabetes is a widely spread chronic disease affecting about 463 million people in 2019. It is defined as chronic hyperglycemia caused by either an impaired action or an abnormal secretion of insulin. New diabetes medications based on glucose-sensitive delivery systems can offer better control of blood glucose levels without the need to worry about the patient diet control or the frequency of exercising. Such delivery systems are comprised of glucose-sensitive moieties such as glucose oxidase, Phenylboronic acid derivatives and Concanavalin A. These systems can be administered via different routes such as subcutaneous injections, implants, oral, transdermal and nasal. This systematic review discussed the most suitable insulin delivery system in terms of efficiency to maintain blood glucose levels in normal range, and safety in animals upon administration.

Method: The search was conducted using different databases such as Web of Knowledge, Pubmed, Europe PMC, Wiley Online Library, and Science direct.

Results: A total of 313 studies were collected and 64 studies were included after screening using inclusion and exclusion criteria based on PICOS model. The results indicated that subcutaneous implants incorporated with glucose oxidase are the most suitable and were able to maintain normal blood glucose for up to 1738 hours with a single administration. This was followed by PBA intraperitoneal implant, then oral GOx. Toxicity studies were conducted for all these dosage forms indicating good biocompatibility.

Conclusion: The GOx subcutaneous implant was found to be the most efficient and safe insulin delivery systems offering prolonged control of glucose in diabetic patients.

Keywords: Diabetes, glucose sensitive delivery system, glucose oxidase, Phenylboronic acid derivatives and Concanavalin A

Abbreviations List:

AAPBA: 3-Acrylamidophenyl boronic acid

ACDD: Acryloyl Crosslinked Dextran Dialdehyde

AM-co-AAPBA-co-CSMA: acrylamide-co-3-acrylamido phenylboronic acid-co-chitosan grafted maleic acid

BGLs: Blood Glucose Levels

BSA: Bovine Serum Albumin

β -CD-EPDME: phenylboronate group modified cyclodextrin

CAT: Catalase

CHEMS: cholesteryl hemisuccinate

Con A: Concanavalin A

CPUL: succinic anhydride carboxylated pullulan derivative

CSPBA: Chitosan PheynylBoronic Acid

DDOPBA: 4-(1,6-dioxo-2,5-diaza-7-oxamyl) phenylboronic acid

DMAEMA: N-2-(dimethylamino)ethyl methacrylamide

DOPE: Dioleoylphosphatidylethanolamine

EVAc: Ethylene- Vinyl acetate co-polymer

FAD: Flavin Adenine Dinucleotide

GA: Glutaraldehyde

GIP: Gastric Inhibitory Peptide

GLP-1: Glucagon-Like Peptide-1

GOx: Glucose Oxidase

HDL: High Density Lipids

HEMA: 2-hydroxyethyl methacrylate

HGB: Hemoglobin

IDF: International Diabetes Federation

IVGTT: Intravenous Glucose Tolerance Test

LAMA: 2-lactobionamidoethyl methacrylate

LbL: Layer-by-Layer

LDL: Low Density Lipids

NIPAM: N-isopropyl acrylamide

NIPAM-4-VP-PBA: N-isopropyl acrylamide-4-vinyl pyridine-3-acrylamidomethyl phenylboronic acid

OA-g-ACD: Oleic Acid- grafted- Aminated beta CycloDextrin

OGTT: Oral Glucose Tolerance Test

PACAP: Pituitary Adenylate Cyclase Activating Polypeptide

PBA: PhenylBoronic Acid

PCL-b-PPBDMA: p(ϵ -caprolactone)-b-p(2-phenylboronic ester-1,3-dioxane-5-ethyl)methacrylate

PCT: Platelet count

PEG: Polyethylene Glycol

PEGDA: polyethylene glycol diacrylate

PLGA: Poly Lactic-co-glycolic acid

PMS: polymersome

RBC: Red Blood Cells

ROS: Reactive Oxygen Species

RSA: Resistant starch acetate

SRA: Sulfonated Resorcinarenes

T1D: Type 1 Diabetes

T2D: Type 2 Diabetes

VIP: Vasoactive Intestinal Peptide

VLDL: Very Low Density Lipids

WBC: White Blood cells

1. Background:

Diabetes is a widely spread chronic disease that is characterized by the increase of blood glucose or blood sugar levels. It is defined as chronic hyperglycemia, it is caused by either an impaired action or an abnormal secretion of insulin [1]. In diabetic patients, the body is unable to regulate glucose levels in the blood, resulting in serious complications such as kidney failure, blindness, cardiovascular, lower limb amputation, and sometimes death. According to the International Diabetes Federation (IDF), diabetes has increased drastically in the last 3 decades, affecting about 463 million people in 2019, and it is expected to reach about 700 million people by 2045.

Diabetes is categorized into 2 types: type 1 diabetes (T1D) and type 2 diabetes (T2D). Type 1 diabetes which is characterized as an autoimmune disorder, the autoimmune destruction of the β pancreatic cells will lead to a complete insulin deficiency [2]. Type 2 diabetes, which is the more common type of diabetes, is characterized as insulin resistance, where different factors as age, obesity, and lifestyle can lead to a cumulative loss of the β pancreatic cells [2].

Extensive research has been done to discover the most suitable treatment and control measures of diabetes, there is a variation between different treatments depending on the different stages of the disease. Treatment strategies can vary from lifestyle interventions; healthy diet and regular physical activity at the early stages to the incorporation of different anti-diabetic drugs at the late chronic stages of the disease [2].

Healthy diet and nutritional management is a keystone in diabetes care and education [3,4]. People with type 2 diabetes are required to carefully manage their diet in order to achieve improved glycemic control alongside drugs. A diet with low-carbohydrates content may help control blood glucose levels [5]. However, emerging studies show that poor nutrient intake is also linked with type 2 diabetes[6,7]. For example, Low vitamin D status is associated with insulin resistance, impaired pancreatic β -cell function and type 2 diabetes risk [8,9]. Moreover, high magnesium status is associated with reduced

diabetes risk in individuals with prediabetes and improved blood glucose parameters in patients with type 2 diabetes [10].

Similarly, people with type 1 diabetes should also adjust their insulin doses to meal content, meal size, and activity levels to achieve near-normal glycemic control [11]. The consistency of carbohydrates in the daily diet has been advised to be quite important for individuals using fixed daily insulin doses [12,13]. The outcome of blood glucose levels among children and adults with type 1 diabetes is affected by consuming fruits and vegetables, fiber intake, saturated fat and added sugar, adjusting insulin dose to carbohydrate intake and adherence to a planned meal pattern [12–17].

Yet nutritional management might not be enough even during the early stages of type 2 diabetes, hence patients are subjected to oral hypoglycemics such as Metformin and/or glipizide [18,19]. In later stages, another intervention is added; amylin analogue or GLP-1 receptor analogue [2], pramlintide, and liraglutide, respectively [20].

Emerging technologies such as nanomaterial-based immunotherapy may help treating diabetes by immunosuppression of CD4+ and CD8+ T-cells and help preventing complications such as obesity [21]. However, Insulin is incorporated in the late stages of type 2 diabetes for treatment. It is used exclusively for managing type 1 diabetes currently [2]. Insulin, made of 51 amino acids and holds a molecular weight of 5808Da [22], is a peptide hormone that is secreted by the β -cells of the islets of Langerhans in the pancreas. Prior to insulin, the peptide hormone exists as proinsulin, it is comprised of chain A, chain B, and a connecting peptide (C-peptide) which is cleaved in later steps to give the free insulin [23] (Fig. 1).

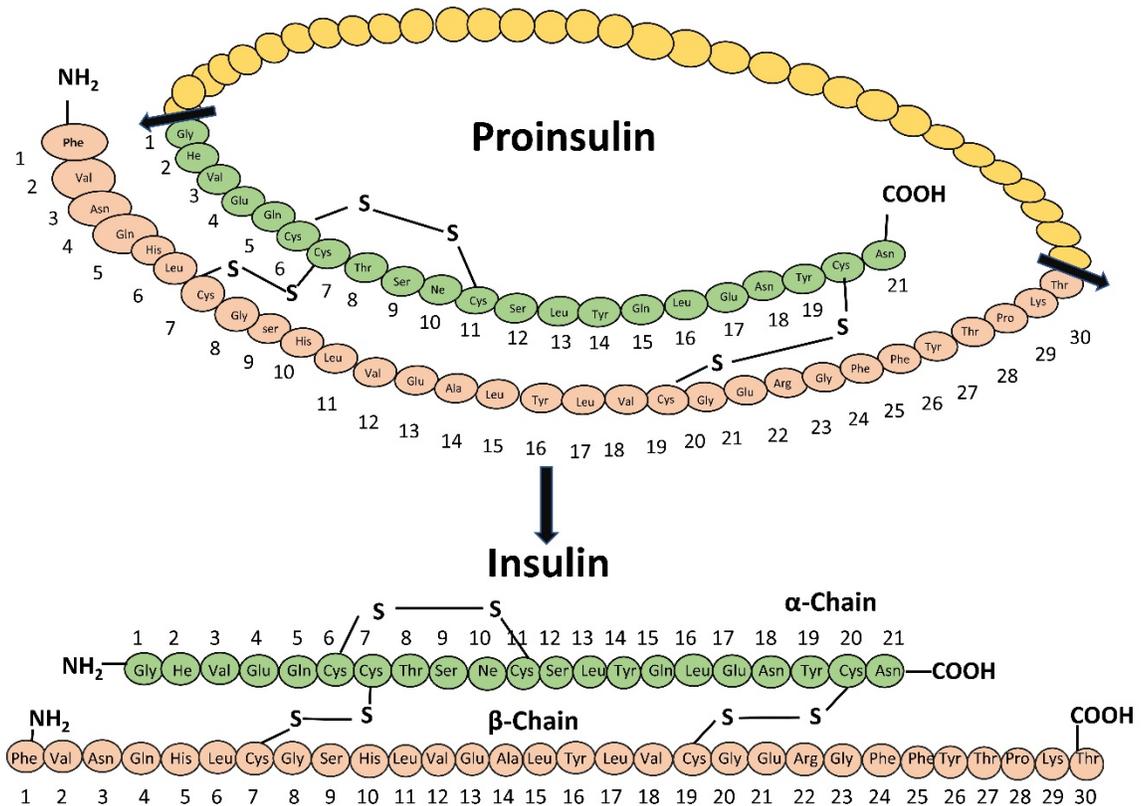


Figure 1: A diagrammatic representation of Proinsulin and Insulin

Subcutaneous injection (SC) is the most common route of insulin administration, this is due to the insulin sensitivity to high temperature, enzymatic degradation, and poor permeability across the body membranes [22]. SC injections have low cost, high absorption, and bioavailability profiles, however; the continuous SC injections can be considered painful, and can often lead to hypoglycaemic profiles, injection site infections, lipodatrophy, and lipohypertrophy [22,24]. Alternative delivery routes of insulin are being investigated. The transdermal route is cheap, non-invasive, has a large delivery area, and will avoid pre-systemic metabolism, but it has a limited permeation ability and can deliver small doses only [25]. Furthermore, the nasal route is painless, non-invasive, safe for the lungs, and it will avoid pre-systemic metabolism, however, this route has a large variability in bioavailability, and insulin will be eliminated by mucociliary [25]. Another route of delivery is the oral route, it is painless, non-invasive

and it avoids peripheral hyperinsulinemia, but insulin will be subjected to metabolism in the GI tract (pre-systematic metabolism) and poor permeability through the intestinal epithelial cells (9). Apart from this, the inhaled route avoids pre-systematic metabolism, and it has a large surface area for absorption, however, it can cause safety issues in the lungs, and it is not accurate in terms of dosages [25]. It has become necessary to develop new delivery systems for insulin with enhanced efficiency and safety profiles.

Poor glycaemic control in diabetic patients can lead to complications in the long-term [26], these complications include cardiovascular disease, nephropathy, nerve damage, blindness, non-healing wounds, coma, and particularly hypoglycemic profiles which can promote brain damage, unconsciousness, and even death. Hence, the development of a smart delivery system for insulin became necessary to maintain normoglycemic BGLs for longer durations. These delivery systems are comprised of the glucose-sensitive materials, mainly Glucose oxidase (GOx), Phenylboronic acid derivatives (PBA), and Concanavalin A (Con A) [27].

GOx is an enzyme produced by different microorganisms, plants and animals, it is a glycoprotein comprised of 2 subunits bonded by a flavin adenine dinucleotide (FAD) prosthetic group [22]. GOx transforms glucose into gluconic acid and hydrogen peroxide in the presence of oxygen [2] (Fig. 2). GOx can be formulated as nanogels [28], hydrogels [29,30] hollow nanospheres [31], vesicles [32], liposomes [33], and microcapsules [34]. It can be immobilized with pH-sensitive polymers to control the release of insulin. As glucose concentration in blood increases, it is transformed into gluconic acid, decreasing the surrounding pH. The pH-sensitive polymeric matrix will sense the drop in pH, leading to swelling or shrinking of the delivery system to release insulin [2]. A drawback of GOx is its by-product H_2O_2 which causes inflammation of human tissues. To overcome this issue, GOx systems are embedded with catalase (CAT), horseradish peroxidase (HRP), or other peroxidases that will break down or scavenge the by-product to H_2O and O_2 [22].

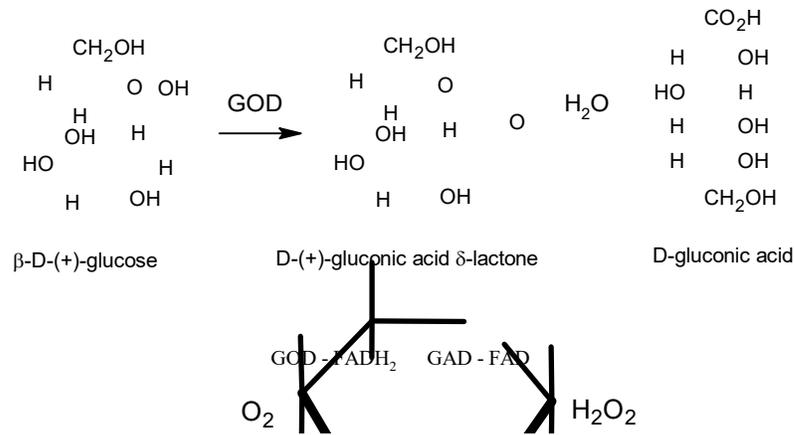


Figure 2: Conversion of glucose to gluconic acid by GOx in presence of oxygen.

Another glucose sensor that have been explored is Phenylboronic acid (PBA) and its derivatives (Fig 3A) PBA is a synthetic compound with high stability and durability under physiological conditions [27]. PBA and its derivatives are the most used synthetic compounds for glucose-responsive delivery systems [22]. PBA and its derivatives act as a Lewis acid with pKa value between 8.2-8.86 [2,35]. Besides, these compounds will form reversible covalent complexes with cis-diols like glucose [36], leading to the formation of cyclic boronic esters when dissolved in water [2]. When in an aqueous solution, PBA exists in 2 states; an uncharged trigonal planar state, and an anionic tetrahedral state [27] (Fig. 3B). Both states can form complexes with glucose, however, the complex formed with the uncharged hydrophobic state is less stable and more prone to hydrolysis than the hydrophilic charged state [2]. Hence, glucose will form a complex with the negatively charged form of PBA, shifting the equilibrium to form more of the charged state, leading to increased swelling of the matrix due to repulsive forces between similar charges [37]. In addition to the repulsive forces between the negatively charged matrix and insulin which has a negative net charge, and as a result, insulin will be released [38].

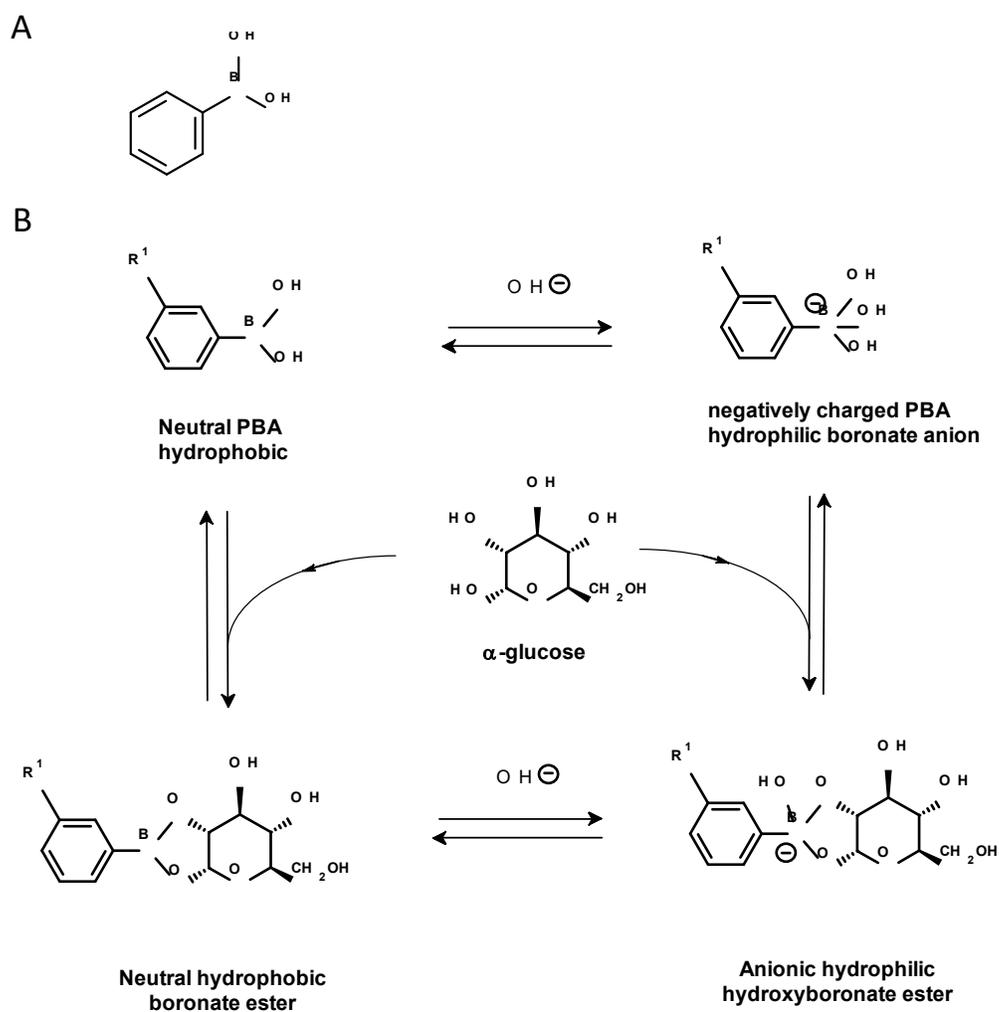


Figure 3: Chemical structure of Phenylboronic Acid (A), complexation between phenylboronic acid derivatives and glucose (B).

Another type of glucose-sensitive moiety is Con A, which is a lectin protein (carbohydrate binding protein) extracted from Jack Beans [2]. Con A has 4 binding sites to glucose and mannose, it can also bind to the modified insulin, or glycosylated insulin (G-insulin) where the glucose residue of G-insulin is attached to the carbohydrate specific binding subunit of Con A [39]. However, the priority of the carbohydrate binding site of Con A is for free glucose rather than glucose residue of G-insulin [27]. Thus, when

glucose is added to the system, Con A competitively binds to glucose and the G-insulin is released.

Unfortunately, it is quite difficult for diabetic patients to control their glucose levels with nutrition only, hence there is a need for a smart insulin delivery system that can sense blood glucose in fed and fasted states hence enabling the better control of diabetes.

The aim of this review is to identify the most suitable glucose-sensitive delivery system of insulin for the treatment of Type 1 and Type 2 Diabetes by evaluating the current efficacy and safety data in the literature. Our research question is “Which glucose-sensitive moiety is more suitable for insulin delivery for the treatment of diabetes?”.

2. Methods:

2.1) Search Strategy:

The search for relevant studies was done using Pubmed, Europe PMC, Web of Knowledge, Cochrane Library, Wiley Online Library, Science Direct, and ACS Publications databases, using a specific combination of keywords that are relevant to our topic. The searched terms were “Glucose responsive insulin delivery”, “Glucose sensitive insulin delivery”, “Glucose sensitive insulin delivery *in-vivo*”, “Glucose triggered insulin delivery”, “Phenylboronic acid for insulin delivery”, “Concanavalin A for insulin delivery”, “Glucose oxidase for insulin delivery”, “Phenylboronic acid for insulin delivery *in-vivo*”, “Concanavalin A for insulin delivery *in-vivo*”, and “Glucose oxidase for insulin delivery *in-vivo*”. Besides, repeated authors were also searched for more studies.

2.2) Selection of Studies:

Two independent screenings were carried out by two different reviewers. In the first screening, studies were selected according to the relevance to our topic from titles and abstracts. In the second screening, the studies included from the first screening were scanned, the results were studied to check whether the included studies fit the inclusion/exclusion criteria. A third reviewer was also available to open a discussion in

the case of a mismatch or a discrepancy between the two initial reviewers regarding the disagreed study.

2.3) Inclusion and Exclusion Criteria:

Inclusion and exclusion criteria is a way to limit our search for relevant studies so that the only studies included are the studies directly related to our topic of interest. Our criteria were based on a system suggested by Cochrane Library [40], this system proposes criteria for population, intervention, comparison, outcome, and study design (PICOS). Study subjects or population included are T2DM, and T1D animal models and induced diabetic animals using (STZ), studies without animal models were excluded. The intervention in our study was insulin, with one of the three glucose-sensitive moieties (GOx, Con A, and PBA) as comparisons. However, studies with anti-diabetic drugs other than insulin, and other delivery systems to GOx, Con A, or PBA were excluded from this review. Outcomes included in this study were efficiency in maintaining normoglycemic levels and the ability to lower blood glucose levels (BGLs), and toxicology studies to assess the safety of the candidates. Moreover, in the study design; *in-vivo* animal studies and both *in-vivo* and *in-vitro* studies were included, and studies with glucose sensing devices and *in-vitro* studies alone were excluded. Inclusion and exclusion criteria are presented in Table 1.

Table 1: Inclusion and exclusion criteria used in screening the primary literature

	Include	Exclude
Population	<ul style="list-style-type: none"> - Animal models with T2DM, and T1D. - Animals with induced diabetes 	<ul style="list-style-type: none"> - No animal models - Other types of diabetes
Intervention	<ul style="list-style-type: none"> - Insulin loaded glucose-sensitive moieties. 	<ul style="list-style-type: none"> - Anti-diabetic drugs other than insulin.
Comparison	<ul style="list-style-type: none"> - Phenylboronic Acid - Glucose Oxidase - Concanavalin A 	<ul style="list-style-type: none"> - Other delivery systems
Outcome	<ul style="list-style-type: none"> - Efficiency (maintaining normoglycemia, lowering BGLs) - Time of normoglycemia - Glucose tolerance test 	<ul style="list-style-type: none"> - No efficiency studies
Study Design	<ul style="list-style-type: none"> - <i>In-vivo</i> animal studies - Both <i>in-vivo</i> and <i>in-vitro</i> studies, 	<ul style="list-style-type: none"> - <i>In-vitro</i> studies only - No <i>in-vivo</i> studies - Glucose sensing devices.

2.4) Data Extraction:

Data were extracted from the included studies by one author only according to an extraction form. Data extracted included; type and number of animals used, group divisions, and the number of animals in each group, intervention, and comparison administered to each group, and the outcome of each group. Any missing information was obtained by contacting the authors, or the study was excluded.

2.5) Outcomes:

The primary outcome was the efficiency in maintaining BGLs in the normoglycemic range (for how long was normoglycemia maintained) together with the onset time of each dosage form, the secondary outcome was the toxicology profiles of each study.

3. Results:

3.1) Selection of Studies:

A total of 313 studies were collected in the first search according to the relevance of the title and abstract. A total of 130 studies were found using the Web of knowledge database, and another 104 and 42 studies were obtained from Pubmed and Europe PMC respectively (Figure 4A). 203 studies were excluded for not fitting the inclusion/exclusion criteria, where 48 studies were excluded for not including animal studies, 79 studies for not including *in-vivo* studies, 32 studies for not using insulin as an intervention, 41 studies for not using Con A, GOx, or PBA, 2 studies for using glucose-sensitive moieties for glucose sensing, and one study for not using the formulation for the treatment of diabetes. In the second screening, the results were scanned to check if the 74 included studies will fit the criteria. Another 10 studies were excluded (5 studies for not including animal studies, and 5 studies for not measuring the time the system can maintain normoglycemia). Therefore, a total of 64 studies were left to include in this review (Fig 4 and 5).



Figure 4: Number (%) of primary literature studies found per each database searched (A), number (%) of included and excluded studies (B).

130 Studies from Web of Knowledge	104 Studies from Pubmed	42 Studies from EuropePMC	21 Studies from Wiley Online Library	16 studies from other sources: ACS Pub, ScienceDirect, RSC
A total of 313 studies were collected				

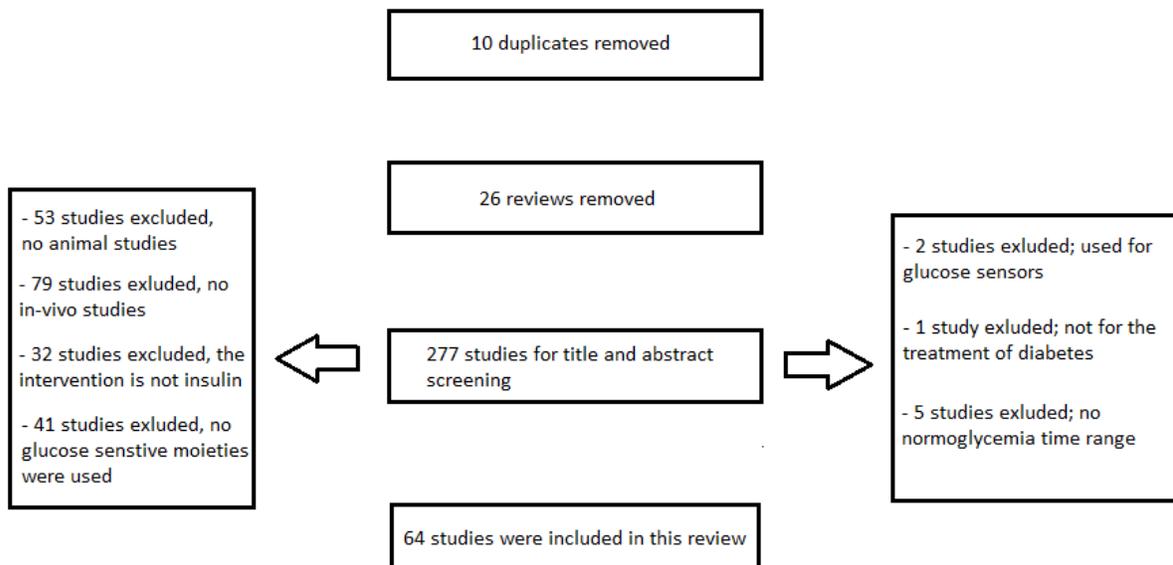


Figure 5: Flow chart showing the selection of articles included in the review

3.2) Included Studies:

According to the included studies in this review, only 7 studies were published between 1985 and 2011. There were another 6 publications in 2012 which then declined to only 2 studies that came out in 2013 followed by 2 studies in 2014. However, the research on glucose-responsive delivery systems has significantly increased over the last 6 years. Since 2015, 47 studies (about 73% of the included studies) have been published (Fig. 6).

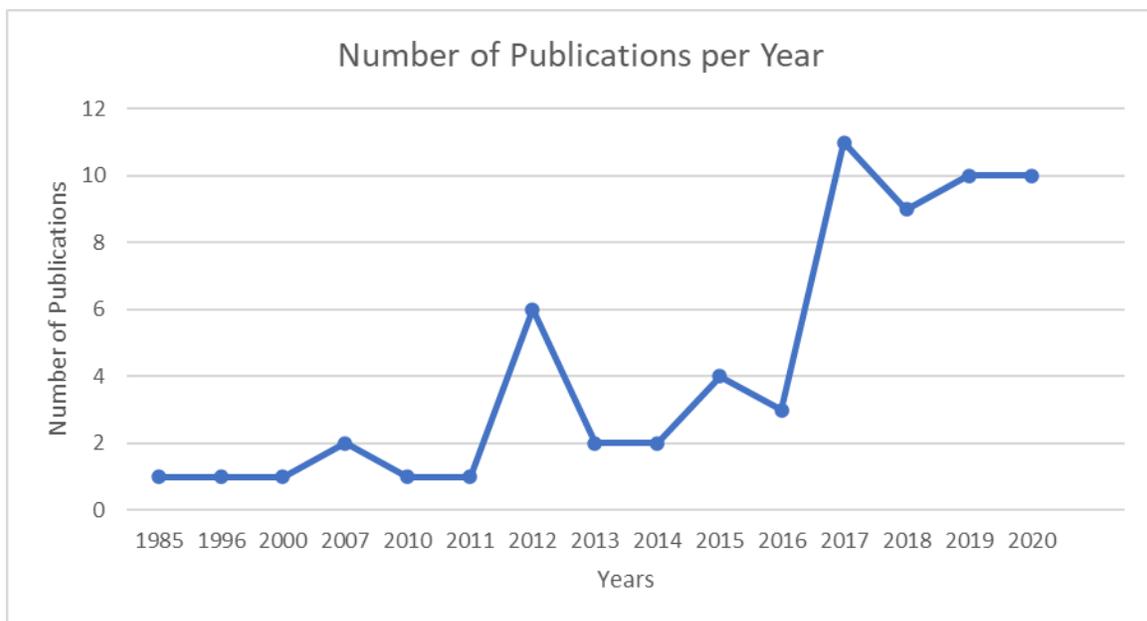


Figure 6: number of included research articles per year of publication

Among the 64 included studies, 30 studies (47%) were accessed from Pubmed database, 21 (33%) from the Web of Knowledge database, 4 (6%) from Europe PMC database and 9 (14%) from other sources (Figure 7A). With reference to glucose sensitive moieties, Con A was reported in 4 studies, 36 studies used GOx based sensors, whilst PBA was reported in 24 publications (Figure 7B).

The included studies were also stratified by the type of dosage forms used; including microneedles, subcutaneous (SC), intraperitoneal (IP), and

transcutaneous (TS) injections, implants (SC and IP), oral and nasal delivery systems.

For Con A, 3 studies were based on oral dosage forms and 1 study used a SC implant. Among the studies on GOx, 10 utilised microneedles as a dosage form, 16 investigated GOx efficiency in SC injections, 5 studies employed SC implants, 3 studies looked at GOx IP implants and 2 studies used GOx in oral dosage forms (Figure 8). For PBA, majority of the studies (n=11) used SC injections to deliver the sensors, this was followed by oral formulation, SC implants then IP implants. There was also a single study based on transcutaneous (TS) injection and another one on nasal dosage form (Figure 8). Moreover, the animal models used to evaluate the efficiency of the delivery systems *in-vivo*, were comprised of mice in 58% (n=38) of the studies, rats in 40% (n= 26) studies and dogs in only 2% of the studies (n= 1) as shown in Figure 8. Mice (58%, n= 38) followed by rats (40%, n=26) were the most common animal models used to study the efficacy and toxicity of the used glucose sensors (Figure 9)

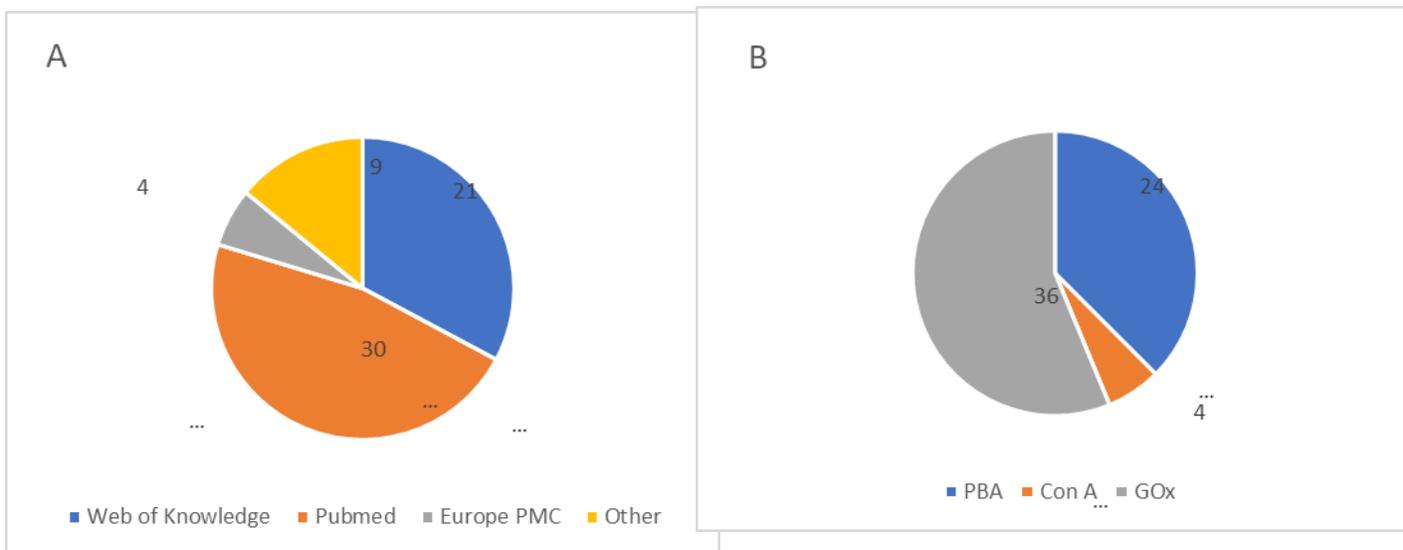


Figure.7: Databases used for included studies (A). Glucose sensitive moieties used in studies (B)

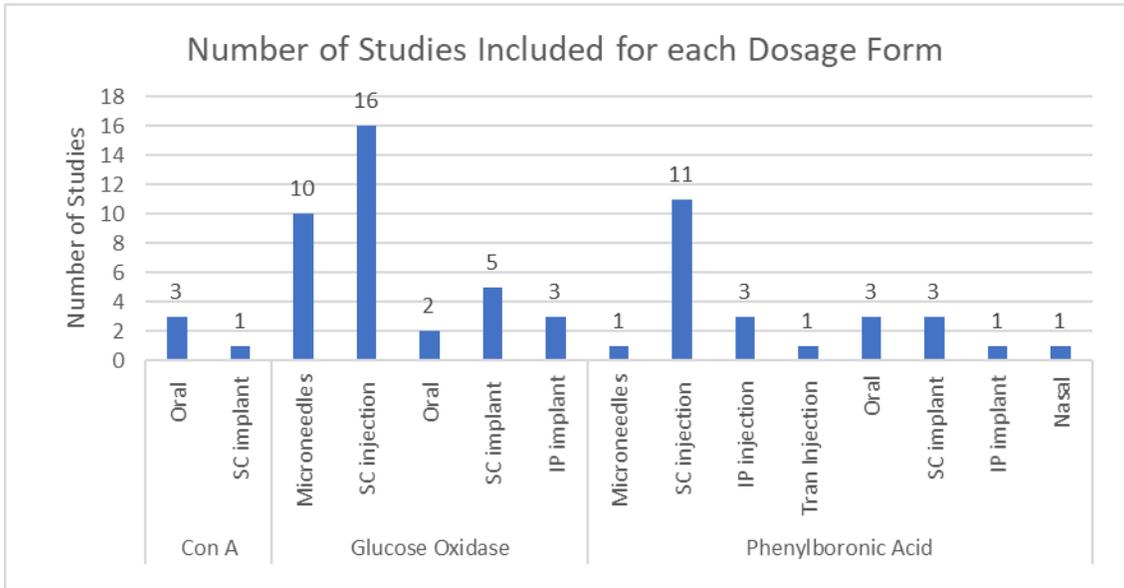


Figure.8: Type of dosage form used stratified by the type of glucose sensor; Con A, GOx and PBA.

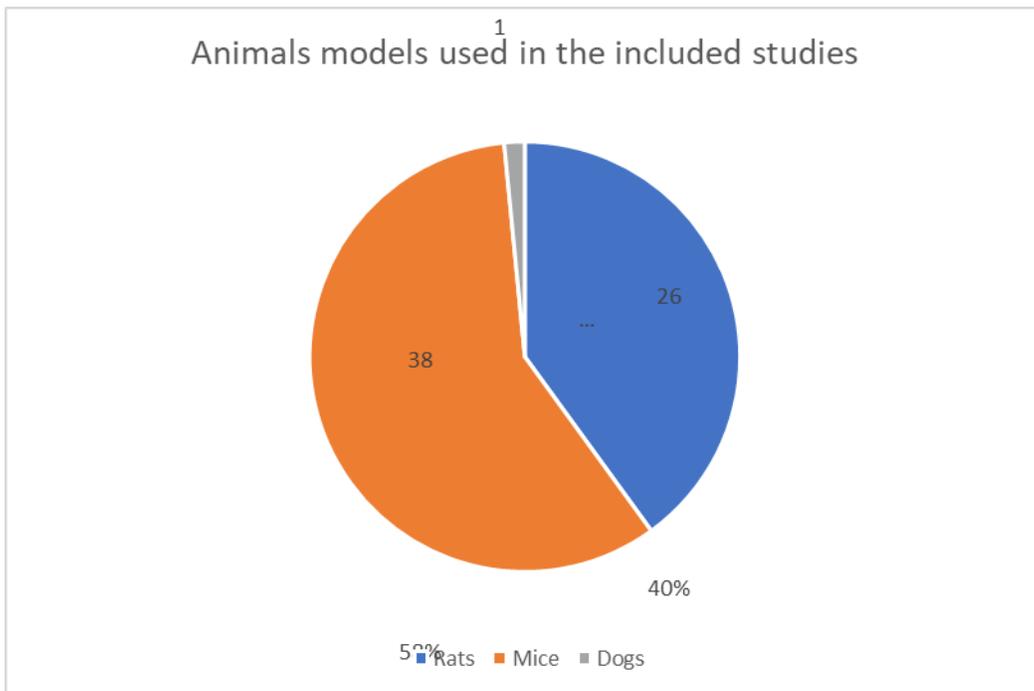


Figure 9: Type of animals used in testing the efficacy of the glucose sensors included in the review

3.3) Concanavalin A:

In this review, the 4 studies on Con A used oral and intravenous implants. It is interesting to note that there is a huge literature gap between the first study and the remaining 3 studies included in this review. The first study was performed in 1985 and in spite of the positive outcomes mentioned in this study, no further research on Con A was performed until 2015. After which three research articles have been published, all were based on oral dosage forms. Moreover, there is no evidence of any toxicological tests performed on Con A formulations. The small number of studies conducted on Con A as a glucose sensor could be attributed to the limited toxicity data and the need of chemical modification of the insulin molecules.

Three of the Con A sensors were administered orally, and one was studied as an implant. All the oral Con A formulations were tested on STZ induced diabetic rats to evaluate their efficiency. Two of these studies used 6 diabetic rats each with an equal insulin dose of 20 IU/Kg, and PLGA (Poly lactic-co-glycolic acid) nanoparticles as delivery vehicles. The third study used a total of 15 diabetic rats and subjected them to 3 different insulin doses (60, 80 and 100 IU/Kg) (5 rats for each dose) and RSA (Resistant starch acetate). All the oral dosage forms were able to maintain normal BGLs for at least 24 hours with an insulin onset of 1 hour [41–43].

The Con A implant was studied on 5 pancreatectomized dogs inserted using cellulose tubing pouch. The intravenous glucose tolerance test (IVGTT) showed that the implants managed to maintain the normoglycemic levels for 6hrs in all the dogs used with an insulin onset of 0.16 hours [44].

3.4) Glucose Oxidase:

In this review, 36 studies on glucose oxidase were included, different dosage forms were used including microneedles, SC injections, SC and IP implants, nasal and oral formulations.

Out of the three glucose sensitive materials, glucose oxidase was the most researched glucose sensor for insulin delivery. The oldest paper included in this review was published in 2000 but most of the investigations on glucose oxidase were performed after 2010 with a huge surge in interest in the last few years. Out of the included 36 studies, there were 8 (22%) studies with no evidence of toxicological data. The remaining 78% reported either acute or no inflammation in the various toxicological tests performed. The toxicological tests were based on detection of inflammation, wound healing and monitoring of cytokine levels after H&E staining in microscopic and histopathological models.

Ten GOx studies used microneedles to deliver insulin, STZ induced diabetic mice (total of 33 mice) were used in 70% of these studies, the rest used STZ diabetic rats (total of 12 rats). Different insulin doses were used, most doses ranged from 15 IU/Kg to 60 IU/Kg, and some studies used much larger doses of 10 mg/Kg and 50 mg/Kg. All the GOx studies were able to maintain blood glucose levels in the normal range from 2 hours to 6 hours, with an average insulin onset time of 0.34 hours, depending on the insulin dosage and type of microneedles used [45–52].

Sixteen studies used subcutaneous injections to deliver GOx formulations, 86% of the studies used induced diabetic mice (70 mice), and 14% used diabetic rats (23 rats). All studies but one (94%) induced diabetes by STZ injections. Moreover, the insulin doses used ranged from 0.8 IU/Kg to 40 IU/Kg, some other studies used much higher insulin doses that ranged from 2 mg/Kg to 60

mg/Kg. Normoglycemia was maintained in all the studies and was maintained for 12 to 240 hours, this broad variation was due to type and form of nano-material (nanogels, hydrogels, nano-capsules and polymeric micelles) used in the injection. Besides, the average insulin onset time for SC injections was about 0.44 hours.

It worth noting that two studies evaluated the ability of GOx SC injections to control blood glucose levels by glucose tolerance test. One study used 6 STZ diabetic rats, in which glucose was administered orally at 0 and 24 hours, and 3 IU/Kg insulin was injected. In this study, BGLs were maintained within the normal ranges for about 16 hours. In the second study, 5 STZ induced diabetic mice were injected with 14.4 IU/Kg insulin, and glucose was injected intraperitoneally every 3 hours, and BGLs were also maintained in the normal range for 16 hours [53–67].

The use of oral formulations to evaluate the ability of glucose oxidase to control blood glucose levels was not common and was limited to 2 studies only (around 5%). Both studies used STZ induced diabetic rats (16 rats were used), with different insulin doses. In the first study, 2.5 mg/Kg insulin formulation was orally administered, which could maintain BGLs in the normal range for up to 216 hours (9 days) with a 30 mins insulin onset time. Whereas in the second study, 100 IU/Kg insulin formulation was administered, followed by oral glucose administration after 6 hours (insulin onset time 15 mins), BGLs were maintained in the normal range in the first 6 hours which increased for 1 hour after OGTT, but it then decreased again to the normal range for up to 4 hours [68,69].

The most common types of implants used to deliver GOx are subcutaneous and intraperitoneal implants. A total of 8 were found; 5 studies used SC implants and 3 studies used IP implants.

Among the studies with SC implants, 4 studies used STZ induced diabetic rats (24 rats), implants were able to maintain BGLs in the normal range from 14 to 56 days (336 to 1344 hours) with an insulin onset of 1 hour. Moreover, one study used 7 STZ induced diabetic rats, but the implant did not affect BGLs [70–74]. Besides, studies with intraperitoneal implants used STZ induced diabetic rats (a total of 16 rats) within 3 studies using 3 different insulin doses. BGLs were maintained in the normal range from 21 hours up to 7 days with an average insulin onset of 15 hours [75–77].

3.5) Phenylboronic Acid derivatives:

In this review, 23 studies using phenylboronic acid derivatives for insulin delivery were included, with a variety of dosage forms such as oral forms, microneedles, implants, and different injection forms.

Phenylboronic acid and its derivatives have been frequently reported by researchers as a potential insulin carrier especially over the last four years as 17 Out the included 23 studies (74%), were conducted between 2016 and 2020. Majority of the studies (78%) conducted toxicological testing of PBA sensors. Around 61% of the studies (n=11) observed no or non-significant toxicity while 39 % (n=7) reported mild inflammation.

One study was found to use microneedle to deliver PBA derivative for insulin delivery. 5 STZ induced diabetic mice were administered with microneedles with 0.5 mg insulin, which were able to maintain BGLs in the normal range for up to 10 hours with an insulin onset of 30 mins [78].

Three types of injections were used to deliver PBA; SC, IP, and TS injections. Eleven studies used SC injection for insulin delivery. STZ induced diabetic mice were used in 10 studies (53 mice in total), 1 study used STZ induced diabetic rats (8 rats in total), and 1 study used 10 Type 2 diabetic mice. Insulin doses varied from 4 IU/Kg to 80 IU/Kg, and in some cases, it reached 1670 IU/Kg (equivalent to 58 mg/Kg). SC injection forms were able to maintain BGLs in the normal range from 2 hours to 408 hours with an insulin onset of 0.9 hours [79–89].

Besides, 3 studies used IP injections for insulin delivery, 19 diabetic mice were injected with different insulin doses; 1 IU/Kg and 10 IU/Kg and this enabled blood glucose control for 2 hours to 60 hours [90–92]. Moreover, 1 study used transcutaneous injection with 5 STZ induced diabetic mice and an insulin dose of 1.2 IU/Kg. BGLs were maintained in the normoglycemic range for up to 12 hours [93].

Oral delivery of PBA were reported in 3 studies; 2 of which used STZ diabetic rats (11 rats) and 1 study used STZ diabetic mice. Variations in insulin doses and efficiency in maintaining normoglycemia were obvious, with insulin doses ranging between 20 to 75 IU/Kg, and the time of normal glycemia ranged between 7 to 16 hours, in addition to an insulin onset of 2.8 hours [94–96].

Similarly, to GOx implants, implants incorporating PBA derivatives for insulin delivery include SC and IP implants. For SC implants, 3 studies used 7 STZ induced diabetic rats and 15 diabetic mice, with different insulin doses ranging between 1.4 mL and 1 mg, BGLs were maintained in the normal range from 24 to 168 hours with an onset of 1.25 hours [97–99].

For IP implants, 1 study used 5 STZ induced diabetic rats subjected to glucose tolerance test, where normoglycemia was achieved for 7 days [100].

One study used nasal administration to control blood glucose using PBA, 6 rats were nasally administered with 5 IU/kg insulin. BGLs were maintained at a low level for about 6 hours [101].

In Figure 10 the normoglycemic time for each dosage form was calculated as the average time (i.e. total normoglycemic time reported in all studies for the dosage form, divided by the number of studies for that dosage form). Huge variation can be observed in the normoglycemic times achieved by each glucose sensor and type of dosage form used to deliver the sensor together with insulin. The most efficient sensor was GOx SC implant, which was able to maintain normoglycemia for 1783 hours. Phenylboronic acid IP implant was the second most effective sensor type maintaining basal glucose levels for 168 hours.

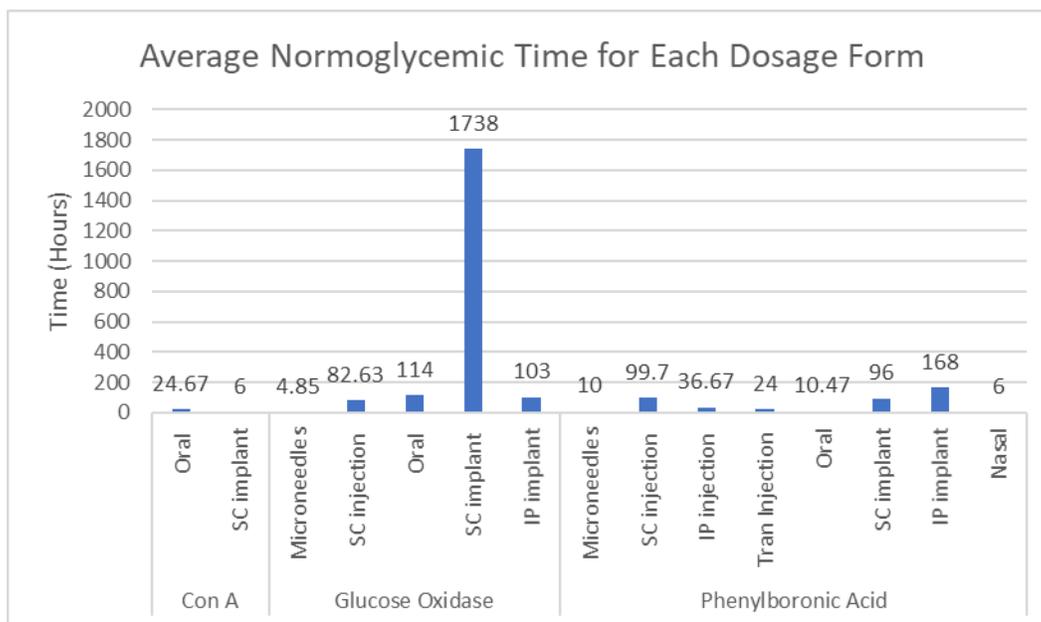


Figure 10: The average normoglycemia time achieved by the different glucose sensor stratified by the dosage form used.

Following the PBA IP implant, oral GOx was able to maintain BGLs in the normal range for 114 hours, then GOx IP implant for 103 hours, PBA SC injection for 99.7 hours then

PBA SC implant for 96 hours. BGLs were achieved for short times in oral PBA, PBA microneedles, nasal PBA and con A SC implant. From the results above, it can be deduced that GOx is the most efficient glucose-responsive moiety followed by PBA derivatives, then Con A.

4. Discussion:

From the results above, the most efficient dosage form for insulin delivery is the glucose oxidase subcutaneous implant which was able to maintain normoglycemia for up to 1738 hours [70–74] , followed by phenylboronic acid intraperitoneal implant which was able to maintain normoglycemia for 168 hours [100]. Although all the included studies tested the efficiency of the insulin delivery system *in-vivo*, there were large variations in terms of the number of studies for each dosage form, the number of animals used, insulin doses administered, and matrices used in the synthesis of the delivery system. To check whether a dosage form is suitable for the treatment of diabetes, toxicity studies for the corresponding system must be evaluated. Among the studies that delivered insulin by a subcutaneous implant, the multilayer film synthesized from the positively charged poly[2-(dimethylamino)ethyl methacrylate] (21-star PDMAEMA), insulin, and GOx by layer-by-layer (LbL) assembly method [60]. During the fabrication of the films, the first layer was the positively charged 21-star pDMAEMA followed by the negatively charged insulin and 4 bilayers of pDMAEMA/insulin, then another 4 bilayers of pDMAEMA/GOx, the system was enclosed with a layer of star pDMAEMA to prevent GOx leakage [71] (Fig.11a). The star pDMAEMA being a weak polyelectrolyte, it can show a pH-responsive behaviour, when subjected to a decrease in pH caused by the conversion of glucose to gluconic acid by GOx. Star pDMAEMA will get ionized and expanded, which will increase the permeability of the system to release more insulin [71]. Furthermore, cell viability was tested and the surviving percentage for cells was 97%, 120.5%, and 98.14%, after 2, 4, and 6 days, respectively. The wound caused by the implant was cured after 2 weeks [71]. Another film was synthesized using

the same materials; star pDMAEMA, insulin, and GOx [70]. The LbL assembly for this system was according to $(x+y)_n$, where x is the number of star pDMAEMA/insulin bilayers, y the number of star pDMAEMA/GOx bilayer, and n repeated units of x and y (Fig. 11b). It was proved that model $(2+2)_2$ had a better on/off transition of insulin release and it could sustain insulin release for a longer duration than $(1+1)_4$ and $(4+4)_1$. To further assess the suitability of this system, body weight which is an important health indicator for patients with diabetes, and toxicity profiles were evaluated. Diabetic rats had an initial weight loss after inducing diabetes and the weights of the rats were monitored for 40 days. Rats that did not administer LbL films did not recover the lost weight, where rats that administered LbL films had progressive weight gains. These weight gains in LbL films treated mice were highest in $(2+2)_2$ model. It was also indicated that the wound caused by implant was healed without any complications, and H&E staining showed no inflammation on tissues that were in contact with the implant according to the number of lymphocyte and macrophages (no macrophages were detected), making this system suitable for insulin delivery [70]. Similarly, a third study also fabricated a layer-by-layer (LbL) star pDMAEMA film, but it was incorporated with porcine insulin (P-SIA), GOx, and catalase [72]. Porcine insulin can undergo 2 oligomeric intermediates under the influence of decreasing pH and increasing temperature, the dominant form will have a pearl-like arrangement of monomers or dimers, which will then form mature amyloid fibrils that will aggregate and assemble as fibrils. The film was fabricated with 2 layers of pDMAEMA/P-SIA-22 h, then a layer of pDMAEMA/P-SIA-22 h, followed by 2 layers of pDMAEMA/GOx, and this layer assembly was repeated [72] (Fig. 11c). Three different films were synthesized with different amounts of P-SIA-22 h, film-1, film-2, and film-C. It was indicated that film-2 had the highest insulin release profile, in addition to the best efficiency in controlling blood glucose levels. Furthermore, the suitability of the system was tested in terms of wound healing, which was indicated without any complications or adverse effects, in addition to the toxicity profiles by H&E staining. This indicated some inflammatory cells that are not considered

as obvious inflammation according to the number of lymphocytes and macrophages. These results prove the suitability of this system for insulin delivery [72].

Poly(2-hydroxyethyl methacrylate- co- N,N-dimethylaminoethyl methacrylate) p(HEMA-co-DMAEMA) hydrogel, encapsulated with GOx, catalase, and insulin [63] is another example of the GOx subcutaneous implant that was studied. This hydrogel incorporates pH-sensitive properties from the cationic DMAEMA, which gets ionized under the effect of decreasing pH, while GOx and catalase enabled the glucose-sensing ability of the delivery system [73]. Different hydrogels were synthesized with different fractions of the polymers DMAEMA and HEMA, 2 formulations were chosen for the *in-vivo* studies with copolymer compositions of (59.51% HEMA and 40.49% DMAEMA) and (47.37% HEMA and 52.63% DMAEMA). Both these hydrogels were efficient in maintaining blood glucose levels in the normal range, in addition to being biocompatible [73]. The biocompatibility profile was evaluated by histopathological analysis, where no inflammation was observed in the site of the implant, and no fibrous tissues were formed. Moreover, a change was observed in serum creatinine, urea, cholesterol, triglycerides, HDL, and LDL, between animals treated with hydrogel and diabetic control animals. These histopathological results indicated the suitability of this GOx system [73]. It can be seen from the studies mentioned above that the GOx can be effective when incorporated with DMAEMA.

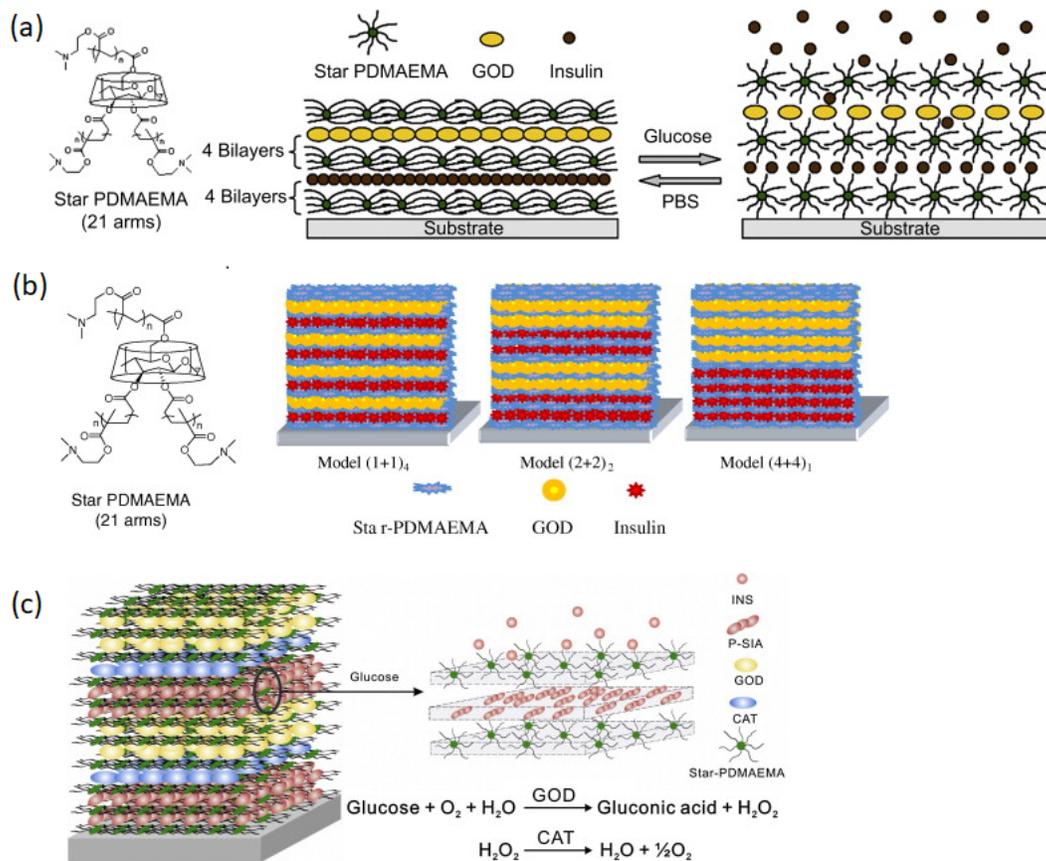


Figure.11: glucose sensitive multilayer films assembled from star p(DMAEMA) (a): [71], (b): [70], and (c):[72]

DMAEMA is a cationic polyelectrolyte and a pH-sensitive moiety that will get highly ionized under the effect of decreasing pH that is caused by the oxidation of glucose to gluconic acid by the glucose-sensitive moiety; GOx. It can also be indicated that this polymer is biocompatible with no toxicity reported [70–73]. Besides, the LbL assembly of the above implants can create a protective shield to prevent the release of insulin, and the degradation of the system under normoglycemic conditions, prolonging its effect to longer time ranges [70–72].

The last system incorporating GOx by subcutaneous implant was a polymeric matrix from ethylene-vinyl acetate co-polymer (EVAc) immobilized with GOx and insulin [74]. When the polymer matrix is subjected to an increase in blood glucose levels, glucose will

be oxidized to gluconic acid and thus decreasing the surrounding pH, this will lead to increased dissolution and diffusion of insulin incorporated in the matrix, and as a result, increased insulin release [74]. There was no effect on blood glucose levels in this study since a very large amount of glucose was injected (plasma glucose concentration of 1800mg/dL) which is a very high concentration to be controlled. In addition, the aim of the study was to evaluate the insulin response affected by increasing glucose concentration [74].

Following GOx subcutaneous implant, the phenylboronic acid IP implant was the next most efficient dosage form for insulin delivery, it was able to maintain blood glucose levels in the normal range for 168 hours. The glucose responsive system used for IP implant comprised of a hydrogel from the temperature-sensitive polymer, p(N-isopropylacrylamide-dextran maleic acid-3-acrylamidophenylboronic acid) p(AAPBA-DexMA-NIPAM) [101]. The rheological studies of the polymer indicated that at low temperatures, p(AAPBA-Dex-NIPAM) will exist as an aqueous solution, this flowing solution can be transformed into a gel when administered (at body temperature). In addition, as glucose concentration increases, the PBA will form a hydrophilic boronate anionic complex, this will increase the swelling ratio of the hydrogel due to the repulsive forces between the negatively charge insulin and the anionic complex. Moreover, the hydrogel exhibits a porous structure that will allow the formation of water reservoirs inside the hydrogel and will ease the process of entrapping and releasing the drug [101]. The cytotoxicity of the hydrogel was evaluated by MTT cell viability assay, the results exceeded 80% for 2 different formulations with different ratios of the incorporated polymers.

In addition, biomarker for macrophages (CD68) and macrophage products (TNF- α) were evaluated, which showed no significant increase from day 5 to 14. Also, only a slight inflammation was observed from H&E staining results [101]. When evaluating the

efficiency and safety of a delivery system to check the suitability, one study is not enough to generate results for a systematic evaluation.

Oral GOx was the third most efficient insulin delivery dosage form, it maintained blood glucose levels in the normal range for about 114 hours. Different systems were incorporated in the delivery systems, an erythrocyte modified GOx was used for insulin delivery [68] (Fig.12). Glucose oxidase was linked to the surface of erythrocyte, which was then loaded with insulin through different steps; hypotonic dialysis, hypertonic reannealing, and isotonic resealing. The GOx-INS-ERs system maintained its structure in a normoglycemic solution but when placed in a hyperglycemic solution the spherical structure was broken, leading to swelling of the system to release insulin [68]. The accumulation of H₂O₂ due to the oxidation of glucose to gluconic acid by the membrane GOx led to rupturing of the lipid bilayer membrane of the erythrocyte. The safety profile of the erythrocyte system was evaluated on healthy rats by performing H&E staining that did not indicate any inflammations. Also, a blood panel test (for red blood cells (RBC), white blood cells (WBC), platelet count (PCT) and hemoglobin (HGB)), a liver function markers test (for ALP, ALT, and AST), and a kidney function markers test (for BUN, CR, and GLB) were conducted at days 1, 3 and 7 post-administration, all the tests showed normal results with no disorders indicating biocompatibility of the system. The levels of TNF- α , IL-1 β , and IL-6 were tested in diabetic rats administered with GOx-INS-ERs, the results indicated lower levels when compared to control diabetic rats indicating the safety of the erythrocyte system [68]. Another system for oral insulin delivery was a peptide modified polymersome system that binds to the intestinal epithelium [69]. The polymersome (PMS) was synthesized from polyethylene glycol (PEG) and the polyamino acid (Met), the peptide that binds to ganglioside-monosialic acid (GM1) receptors was linked with PEG-PLGA (Pep), the Pep-PMS had a spherical cavity that was suitable for insulin and GOx entrapment (Fig.12). When blood glucose concentration increases, the H₂O₂ produced by the oxidation of glucose, led to the oxidation of the hydrophobic polyMet, making it hydrophilic and easing the dissolution of mPEG-PolyMet. This is due to the ability of the sulfide bonds to oxidize to sulfoxides and further to sulfones by the

impact of H_2O_2 [69]. To further check the suitability of this system, biodegradability and biocompatibility profiles were assessed by GPC, mass spectrometer (MS), and H&E staining. GPC and MS were used to characterize the degradation products of the Pep-PMS, the results suggested that the peptide modified polymersome was degraded into small and nontoxic molecules (according to molecular weights, products might be PEG and methionine). H&E staining was performed after 14 days of daily oral administration of Pep-PMS, the results showed no significant damage in tissues, indicating the biocompatibility of this system [69].

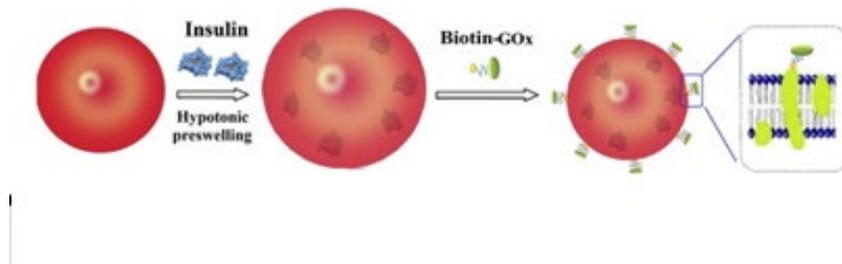


Figure 12: GOx modified erythrocyte entrapped with insulin (55)

5. Conclusion:

Stimuli responsive delivery systems can offer a better effectiveness and control of various diseases(102). This is a review on glucose-sensitive delivery systems for insulin, different glucose-sensitive moieties including concanavalin A, glucose oxidase, and phenylboronic acid derivatives were reviewed. The mode of action and the components of these systems were discussed. In addition, a meta-analysis was conducted to calculate the average time of normoglycemia for each sensor/dosage form. After efficiency and safety evaluation of different glucose-responsive insulin delivery systems, the most efficient dosage forms were GOx subcutaneous implant, PBA intraperitoneal implant, then oral GOx. These dosage forms were able to maintain blood glucose levels in the normoglycemic range for 1738, 168, and 114 hours, respectively. Also, toxicity studies were conducted for all these dosage forms indicating the biocompatibility of these systems and showing no signs of toxicity. From the results above, it can be

concluded that the GOx subcutaneous implant is the most suitable insulin delivery systems in terms of efficiency and safety and can offer prolonged control of glucose in diabetic patients. This will be reflected positively on the quality of life of these patients.

Some limitations were identified in the current review, As a limited number of studies meet the inclusion criteria, this led to a small sample size for some dosage forms such as Oral glucose oxidase and Nasal Phenylboronic acid. Another drawback was the use of different doses of insulin which can affect the onset time of normoglycemia. In addition, not all studies reported a plasma insulin concentration vs. time for the used glucose sensor.

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Author contribution statement

AAN designed and conducted the study. AE, MS, and IGB contributed to the study conceptualisation and design, and supported database searching and screening of records. AAN synthesised the findings. AAN, AE, MS, and IGB prepared the manuscript. All authors critically reviewed the manuscript and approved the final version.

Declarations of interest

The authors declare no conflict of interest.

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